

5-1-2011

# Cardiovascular risk scores do not account for the effect of treatment: A review

Su May Liew  
*University of Oxford*

Jenny Doust  
*Bond University, jenny\_doust@bond.edu.au*

Paul Glasziou  
*Bond University, paul\_glasziou@bond.edu.au*

Follow this and additional works at: [http://epublications.bond.edu.au/hsm\\_pubs](http://epublications.bond.edu.au/hsm_pubs)

 Part of the [Cardiovascular Diseases Commons](#)

---

## Recommended Citation

Su May Liew, Jenny Doust, and Paul Glasziou. (2011) "Cardiovascular risk scores do not account for the effect of treatment: A review" *Heart*, 97 (9), 689-697: ISSN 1355-6037.

[http://epublications.bond.edu.au/hsm\\_pubs/230](http://epublications.bond.edu.au/hsm_pubs/230)

# Cardiovascular risk scores do not account for the effect of treatment: a review

S M Liew,<sup>1,2</sup> J Doust,<sup>3</sup> P Glasziou<sup>2,3</sup>

► Additional material is published online only. To view this file please visit the journal online (<http://heart.bmj.com>).

<sup>1</sup>Department of Primary Care Medicine and Julius Center UM, University of Malaya, Kuala Lumpur, Malaysia

<sup>2</sup>Department of Primary Health Care, University of Oxford, Oxford, UK

<sup>3</sup>Centre for Research in Evidence-Based Practice, Faculty of Health Sciences, Bond University, Gold Coast, Australia

## Correspondence to

Dr Su May Liew, Department of Primary Health Care, University of Oxford, Rosemary Rue Building, Old Road Campus, Oxford OX3 7LF, UK; [su.liew@phc.ox.ac.uk](mailto:su.liew@phc.ox.ac.uk)

Accepted 21 January 2011

## ABSTRACT

**Objective** To compare the strengths and limitations of cardiovascular risk scores available for clinicians in assessing the global (absolute) risk of cardiovascular disease.

**Design** Review of cardiovascular risk scores.

**Data sources** Medline (1966 to May 2009) using a mixture of MeSH terms and free text for the keywords 'cardiovascular', 'risk prediction' and 'cohort studies'.

**Eligibility criteria for selecting studies** A study was eligible if it fulfilled the following criteria: (1) it was a cohort study of adults in the general population with no prior history of cardiovascular disease and not restricted by a disease condition; (2) the primary objective was the development of a cardiovascular risk score/equation that predicted an individual's absolute cardiovascular risk in 5–10 years; (3) the score could be used by a clinician to calculate the risk for an individual patient.

**Results** 21 risk scores from 18 papers were identified from 3536 papers. Cohort size ranged from 4372 participants (SHS) to 1591209 records (QRISK2). More than half of the cardiovascular risk scores (11) were from studies with recruitment starting after 1980. Definitions and methods for measuring risk predictors and outcomes varied widely between scores. Fourteen cardiovascular risk scores reported data on prior treatment, but this was mainly limited to antihypertensive treatment. Only two studies reported prior use of lipid-lowering agents. None reported on prior use of platelet inhibitors or data on treatment drop-ins.

**Conclusions** The use of risk-factor-modifying drugs—for example, statins—and disease-modifying medication—for example, platelet inhibitors—was not accounted for. In addition, none of the risk scores addressed the effect of treatment drop-ins—that is, treatment started during the study period. Ideally, a risk score should be derived from a population free from treatment. The lack of accounting for treatment effect and the wide variation in study characteristics, predictors and outcomes causes difficulties in the use of cardiovascular risk scores for clinical treatment decision.

## INTRODUCTION

For many years, the Framingham cardiovascular risk equation has been the preferred method of cardiovascular risk assessment. However, in February 2010, the National Institute for Health and Clinical Excellence (NICE) announced that the Framingham equation should be considered as just one of several acceptable methods.<sup>1</sup> The same guideline included a systematic review, which found 110 different cardiovascular risk-scoring methods. Clinicians are now able and expected to select, from these 110 cardiovascular risk scores,

## What is already known on this subject

- Guidelines advocate the use of cardiovascular risk scores to calculate global risk instead of focusing on single risk modification.
- Healthcare providers in the UK are expected to select a cardiovascular risk score appropriate for their requirements from the many existing risk assessment tools with the recent change in the NICE guidelines.

## What this study adds

- The existing risk scores vary widely in terms of study characteristics, predictors and outcomes.
- These cohort studies have not taken into account the effect of treatment on the study population and will therefore underestimate cardiovascular risk.

one that is appropriate for their patients. How should they decide which one is appropriate?

Despite guidelines advocating the use of cardiovascular risk scores to calculate global risk instead of focusing on single risk modification, adoption of cardiovascular risk scores has been slow.<sup>1 2</sup> One survey in three countries showed that only 48% of physicians regularly use cardiovascular risk scores.<sup>3</sup> In another survey in six European countries, 85% of respondents recognised the importance of global risk assessment; yet, the majority (62%) used a subjective assessment of cardiovascular risk rather than specific risk calculators in practice.<sup>4</sup> Subjective risk assessment often disagrees with assessment by cardiovascular risk scores.<sup>5 5</sup> Doctors who use cardiovascular risk scores can rate individual risk factors more accurately<sup>6</sup> and are more likely to correctly prescribe treatment in given scenarios than non-users.<sup>3</sup>

Why don't doctors use cardiovascular risk scores in practice? Many physicians do not trust the validity of the risk scores<sup>7</sup> and believe their own estimation to be more accurate.<sup>3</sup> Another reason may simply be that there is too much choice. The Framingham risk equations were first published in 1976.<sup>8</sup> Since then, many other cohort studies have developed their own equations such as PROCAM,<sup>9</sup> SCORE<sup>10</sup> and QRISK.<sup>11</sup> These cohort studies differ significantly in terms of study population characteristics, risk predictors and outcomes.<sup>12</sup>

Cardiovascular risk scores measure baseline risk factors to predict future cardiovascular morbidity



This paper is freely available online under the BMJ Journals unlocked scheme, see <http://heart.bmj.com/site/about/unlocked.xhtml>

## Systematic review

and mortality, but most do not account for changes in treatment during the years of follow-up. Failure to adjust for such treatment effects will cause cardiovascular risk scores to systematically underestimate predicted risk. This problem is greater for more recent studies with the progressive increase in the use of effective medication for blood pressure and lipids over the past 20–30 years.<sup>13 14</sup>

We aimed to review the strengths and limitations of current cardiovascular risk scores, to assess how these may impact on the classification of patients' risk of cardiovascular disease, and to identify the scores that may be most appropriate for use in clinical care.

### METHODS OF REVIEW

#### Objectives

The objective of this review is to assess the strengths and limitations of cardiovascular risk scores available to clinicians for the assessment of global or absolute risk of cardiovascular disease. A particular focus was on how the risk scores dealt with the effects of treatment during follow-up.

#### Search methods for identification of studies

We searched Medline (1966 to May 2009) using a mixture of MeSH terms and free text for the keywords 'cardiovascular', 'risk prediction' and 'cohort studies'. To identify other studies that answered our question, we also used our own literature files, previous reviews of cardiovascular scores, and citation tracking.

A study was eligible if it fulfilled the following criteria: (1) it was a cohort study of adults in the general population with no prior history of cardiovascular disease and not restricted by a disease condition; (2) the primary objective was the development of a cardiovascular risk score/equation that predicted an individual's absolute cardiovascular risk in 5–10 years; and (3) the score could be used by a clinician to calculate the risk for an individual patient.

#### Identifying studies

We screened the titles and abstracts of all retrieved records to identify exclusions. Full copies or reprints of records not excluded were then assessed to determine if they met with the inclusion criteria for the review. Any disagreements were resolved through discussion.

#### Data extraction

Two reviewers, LSM and JD, appraised and selected the studies, then extracted information from each study for analysis. Information extracted included study demographics, outcomes, predictors and treatment effect.

#### Analytical methods

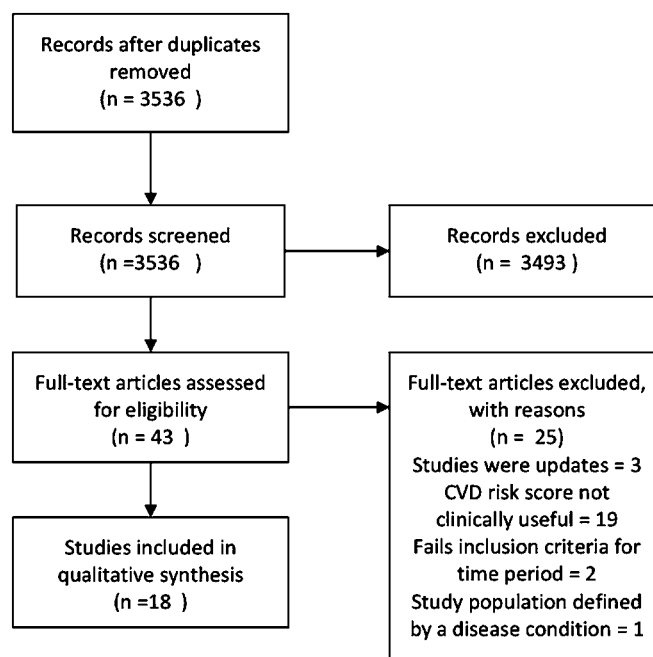
Study methods were assessed using criteria adapted from Wasson *et al*<sup>15</sup> and Royston *et al*,<sup>16</sup> including sampling, predictors, follow-up, outcomes, data quality and performance of the rule.

### RESULTS

A total of 3536 papers were retrieved after removal of duplicates from records identified through the Medline search and other sources. Figure 1 shows the PRISMA flow diagram. The PRISMA statement and review protocol are available online as supplemental material.

#### Description of studies

We identified 21 risk scores eligible for the review (table 1) from 18 papers. Five were from Framingham,<sup>8 17–19</sup> three from the



**Figure 1** PRISMA flow diagram.

Munster group (PROCAM)<sup>9 20</sup> and ARIC (Atherosclerosis Risk in Communities),<sup>21 22</sup> two each from QRISK<sup>11 23</sup> and Reynolds,<sup>24 25</sup> and one each from the Scottish Heart Health Extended Cohort,<sup>26</sup> Strong Heart Study,<sup>27</sup> USA-PRC (People's Republic of China Collaborative Study of Cardiovascular Epidemiology)<sup>28</sup> and NHEFS (National Health and Nutrition Examination Survey NHANES 1 Epidemiologic Follow-up Study).<sup>29</sup> Some risk scores used multiple cohorts: SCORE<sup>10</sup> was derived from a pool of 12 European cohorts, and Progetto CUORE<sup>30</sup> from a pool of Italian cohorts. Twelve are from North America, eight are European, and one from China.

Figure 2 shows a timeline chart of the reviewed cohort studies and the introduction of several drugs.<sup>13 14</sup>

#### Analytical methods

Table 2 compares the analytical methods of the reviewed risk scores.

The areas in which most of the risk equations did poorly were: (1) reporting loss to follow-up; (2) percentage of missing values; and (3) blind assessment of outcomes.

#### Risk predictors and their definitions

The final number of risk predictors ranged from five (PROCAM stroke) to 15 in QRISK 2 (table 3). Selection of predictors was mostly by significance testing (table 2). All scores included age, gender, blood pressure and smoking, and most included lipids and diabetes. Lipid levels were not used in the non-laboratory model of the 2008 Framingham risk score, the PROCAM 2007 risk equation for stroke, or the NHEFS risk score. Diabetes, glucose intolerance or HbA1c level was a predictor for all except the European SCORE. Other risk predictors included by some scores were left ventricular hypertrophy, antihypertensive medication use, body mass index, ethnicity, family history, socioeconomic status, medical diseases, biomarkers (hsCRP and albuminuria) and physical activity.

Definitions for risk predictors differed from score to score. In the original Framingham cohort, diabetes was defined as a random blood glucose measurement  $\geq 150$  mg/dl (8.3 mmol/l) or treatment with insulin or oral hypoglycaemics. In the

**Table 1** Description of the studies

Study	Country	Population	Sample size	Age	% Female	Recruitment period
Framingham 1976	USA	Population cohort	5209	35–64	55	1948–1952
Framingham 1991	USA	Population cohort (original + offspring)	5573	30–74	54	1968–1971; 1971–1975
Framingham 1998	USA	Population cohort (original + offspring)	5345	30–74	53	1968–1971; 1971–1975
Framingham 2008	USA	Population cohort (original + offspring)	8491	30–74	53	1968–1971; 1971–1975; 1984–1987
PROCAM 2002	Germany	Occupational cohort	5389	35–65	0	1979–1985
PROCAM 2007	Germany	Occupational cohort	26 975	20–75	32	1978–1995
CHD	Germany	Occupational cohort	8130	35–65	27	1978–1995
SCORE 2003	Europe	Pooled dataset of cohort studies	205 178	45–64	43	1967–1991
ARIC 2003	USA	Population cohort	14 054	45–64	57	1987–1989
Progetto CUORE 2004	Italy	Pooled dataset of cohort studies	20 647	35–69	64	1983–1997
Strong Heart Study 2006	USA	Population cohort - American Indian	4372	45–74	61	1989–1991
USA-PRC 2006	China	Population cohort	9903	39–59	51	1983–1984
ASSIGN 2007	UK	Population cohort	13 297	30–74	51	1984–1995
Reynolds women 2007	USA	Women's Health Study trial subjects	16 400	45+	100	1992–1995
Reynolds men 2008	USA	Physician Health Study trial subjects	10 724	50–80	0	1995–1997
Personal Heart 2007	USA	Population cohort	14 343	45–64	57	1987–1989
QRISK 2007	UK	Electronic medical database	1 283 174	35–74	50	1995–2007
QRISK2 2008	UK	Electronic medical database	1 535 583	35–74	50	1993–2008
NHEFS 2008	USA	Population cohort	6186	25–74	54	1971–1975

Framingham Offspring cohort, this definition was broadened to a fasting plasma glucose level  $\geq 140$  mg/dl (7.7 mmol/l) or treatment requirement.<sup>13</sup> This in turn differs from the current definition used by the World Health Organization (WHO) of

fasting plasma glucose  $\geq 126$  mg/dl (7.0 mmol/l).<sup>31</sup> Hence, patients with fasting plasma glucose between 126 and 150 mg/dl (7–8.3 mmol/l) would be classed as non-diabetics by the first Framingham score. Systolic blood pressure measurement

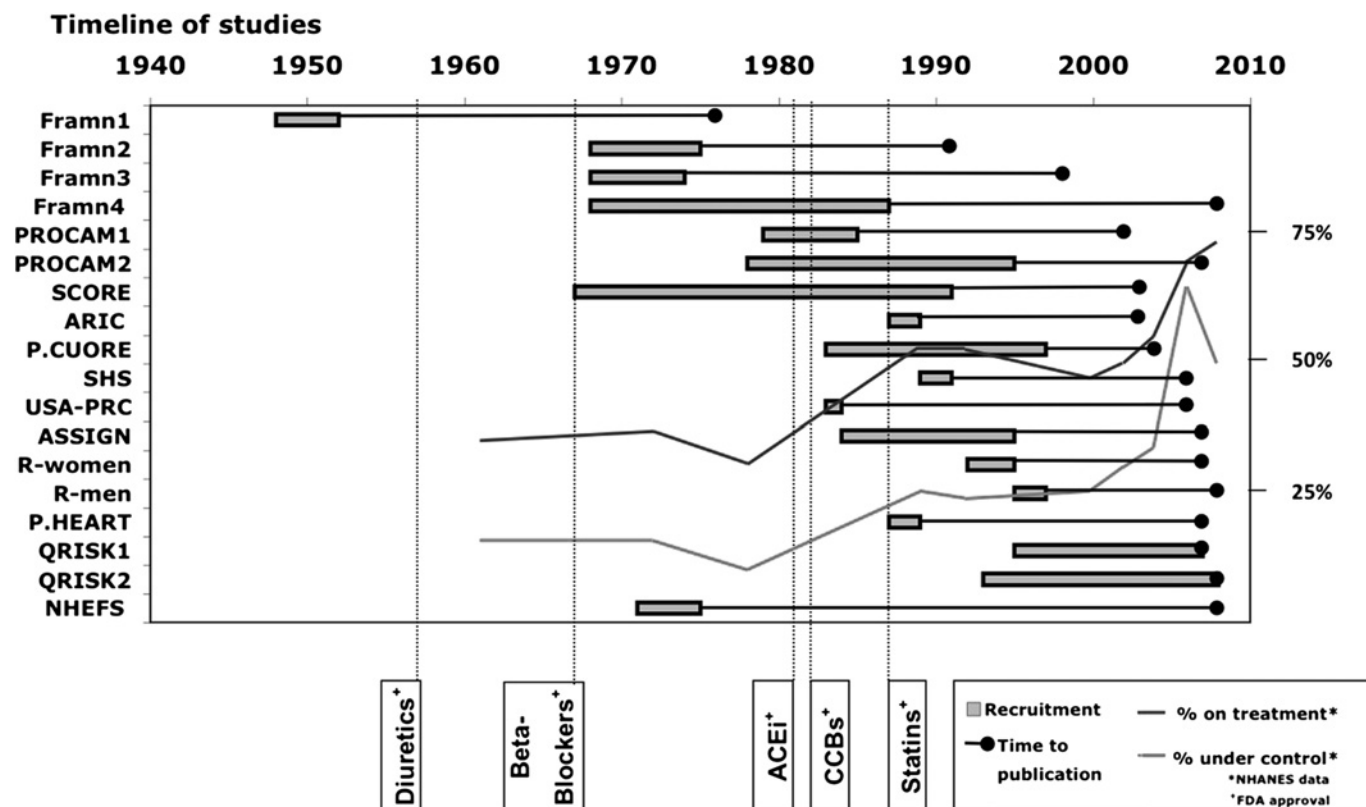
**Figure 2** Timeline of studies.

Table 2 Analytical methods

Study	Prospective	Predictors defined	Predictor selection	Follow-up loss	Missing values	Outcomes defined	Objective outcomes	Blinded assessment of outcomes	Model used	Results of rule
Framingham 1976	Yes	EGC-LVH	NR	NR	Complete data - IC	Yes	Includes angina	NR	Logistic regression	NR
Framingham 1991	Yes	EGC-LVH	Significance testing	NR	Complete data - IC	Yes	Includes angina	NR	Weibull model	c statistic
Framingham 1998	Yes	Yes	Significance testing	NR	Complete data - IC	Yes	Includes angina	NR	Cox model	c statistic
Framingham 2008	Yes	Yes	Significance testing	NR	Complete data - IC	Yes	Includes angina	Adjudication committee	Cox model	c statistic and calibration
PROCAM 2002	Yes	Yes	Significance testing	Yes	NR	Yes	Yes	NR	Cox model	ROC + calibration
PROCAM 2007										
CHD	Yes	Yes	Significance testing	NR	NR	Yes	Yes	NR	Weibull model	ROC
Stroke	Yes	Yes	Significance testing	NR	NR	Yes	Yes	Yes	Cox model	ROC
SCORE 2003	Pooled prospective cohorts	Pooled cohorts	A priori	NR	No HDL in some cohorts	Yes	Yes	Used diagnostic codes	Weibull model	ROC
ARIC 2003	Yes	Yes	Significance testing	Yes	Complete data - IC	Yes	Includes revascularisation	NR	Cox model	ROC
Progetto CUORE 2004	Pooled prospective cohorts	Yes	Significance testing	NR	NR	Yes	Includes revascularisation	Used diagnostic codes	Cox model	ROC
Strong Heart Study 2006	Yes	Yes	Significance testing	Yes	Yes	Yes	Includes angina and revascularisation	NR	Cox model	ROC + calibration
USA-PRC 2006	Yes	Yes	A priori	Yes	Complete data - IC	Yes	Yes	Adjudication committee	Cox model	ROC + calibration
ASSIGN 2007	Yes	Yes	Significance testing	NR	NR	Yes	Includes angina and revascularisation	Used diagnostic codes	Cox model	ROC
Reynolds women 2007	Yes	Trial data	Model testing - BIC	NR	NR	Yes	Includes revascularisation	NR	Cox model	ROC + calibration
Reynolds men 2008	Yes	Trial data	Model testing - BIC	NR	Complete data - IC	Yes	Includes revascularisation	Adjudication committee	Not specified	ROC + calibration
Personal Heart 2007	Yes	Self report	Significance testing	NR	NR	Yes	Includes revascularisation	NR	Cox model	c statistic
ORISK 2007	No	Retrospective GP record	Model testing - BIC	NR	Significant missing data	Diagnosis from GP records or death certificate	Includes angina	Used diagnostic codes	Cox model	ROC + calibration
ORISK 2 2008	No	Retrospective GP record	Model testing - BIC	NR	Significant missing data	Diagnosis from GP records or death certificate	Includes angina	Used diagnostic codes	Cox model	ROC + calibration
NHEFS 2008	Yes	Yes	A priori	NR	Complete data - IC	Yes	Includes revascularisation	Used diagnostic codes	Cox model	ROC + calibration

EGC-LVH, left ventricular hypertrophy on electrocardiogram; NR, not reported; IC, inclusion criteria; ROC, receiver operating characteristic; CHD, coronary heart disease; HDL, high density lipoprotein cholesterol; BIC, Bayes Information Criteria; GP, general practice.

**Table 3** Predictors

		Age	Sex	Smoking	SBP	DBP	Sr. Chol	HDL	Tg	Diabetes	LVH	Antihpt med.	BMI	Ethnicity	Family hx	SCE status	Rh arthritis	Chronic renal ds	Atrial fib.	Bio-markers	Physical activity	No of predictors/ no of candidate predictors
Framingham 1976		Years	M/F	Y/N	average of 2 readings		TC			RBS ≥ 8.3 / urine +	ECG-LVH											7/19+
Framingham 1991		Years	M/F	Y/N	average of 2 readings	SBP alternative	TC			Original RBS ≥8.3; Offspring FBS ≥7.7	ECG-LVH											8/19+
Framingham 1998		Years	M/F	Y/N	average of 2 readings	SBP alternative	TC or LDL															7/19+
Framingham 2008	General	Years	M/F	Y/N	average of 2 readings		TC			Original FBS ≥7.7; Offspring FBS ≥6.9		Y/N										8/19+
	Non-Lab	Years	M/F	Y/N	average of 2 readings							Y/N	3 groups									7/19+
PROCAM 2002		Years	NA	Y/N	2 readings - 2nd taken		LDL			FBS ≥ 6.6					Y/N							8/57
PROCAM 2007	CHD	Years	M/F	Y/N	2 readings - 2nd taken		LDL			FBS ≥ 6.6					Y/N							9/57
	Stroke	Years	M/F	Y/N	2 readings - 2nd taken					FBS ≥ 6.6												5/57
SCORE 2003		Years	M/F	Y/N	Not stated		TC or ratio															5/5
ARIC 2003		Years	M/F	Y/N	average of last 2 of 3 readings		TC			FBS ≥ 7.0		Y/N		2 groups								9/27
Progetto CUORE 2004		Years	M/F	Y/N	average of 2 readings		TC			FBS ≥ 7.0		Y/N										8/19
SHS 2006		Years	M/F	Y/N	average of last 2 of 3 readings		TC or LDL			FBS ≥ 7.0		Y/N								albuminuria		9/14
USA-PRC 2006		Years	M/F	Y/N	average of 3 readings		TC			FBS ≥ 7.0			2 groups									7/7
ASSIGN 2007		Years	M/F	Y/N plus cigs/day	average of 2 readings		TC			Not stated				Y/N	SIMD							9/11+
Reynolds women 2007		Years	NA	Y/N	self reported		TC			HbA1c if diabetic				Y/N						hsCRP		8/35
Reynolds men 2008		Years	NA	Y/N	self reported		TC			excluded at baseline				Y/N						hsCRP		8/8
Personal Heart 2007	men	Years	NA	Y/N/ Former	previous diagnosis of hypertension		previous diagnosis of hypercholesterolaemia			previous diagnosis of diabetes				Y/N							often/ sometimes/ never	7/10
	women	Years	NA	Y/N/ Former	previous diagnosis of hypertension		previous diagnosis of hypercholesterolaemia			previous diagnosis of diabetes			2 groups									6/10
QRISK 2007		Years	M/F	Y/N	GP record		TC/HDL ratio			excluded at baseline		Y/N	recorded value		Y/N	Townsend						9/11
QRISK 2 2008		Years	M/F	Y/N	GP record		TC/HDL ratio			recorded diagnosis		Y/N	recorded value	9 groups	Y/N	Townsend	recorded diagnosis	recorded diagnosis	recorded diagnosis			14/14
NHEFS 2008		Years	M/F	Y/N	average of last 2 of 3 readings					previous diagnosis of diabetes			4 groups									6/6

Shaded areas, Predictors not included in risk score; SBP, systolic blood pressure; DBP, diastolic blood pressure; Sr. Chol, serum cholesterol; HDL, high density lipoprotein cholesterol; Tg, triglycerides; LVH, left ventricular hypertrophy; Antihpt med, antihypertensive medication; BMI, body mass index; Family hx, family history; SCE, socioeconomic; Rh arthritis, rheumatoid arthritis; Atrial fib, atrial fibrillation; No, number; M, male; F, female; Y, yes; N, no; TC, total cholesterol; RBS, random blood sugar; FBS, fasting blood sugar; LDL, low density lipoprotein cholesterol; Non-lab, non-laboratory; NA, not applicable; Cigs, cigarettes; SIMD, Scottish Index of Multiple Deprivation; HbA1c, haemoglobin A1c; hsCRP, high sensitivity c-reactive protein; GP, general practice.

methods included averages taken from two readings (Framingham, Progetto CUORE, ASSIGN), average of last two of three readings (ARIC, SHS, NHEFS), average of three readings (USA-PRC) and second reading taken from two readings (PROCAM). For some scores, the measurement method was ill defined: self-report (Reynolds Study), general practitioner record (QRISK studies) or a previous diagnosis of hypertension (Personal HEART), to not being stated (SCORE).

### Outcomes predicted

The outcomes predicted differ widely between the risk scores (table 4), ranging from general cardiovascular risk to specific disease outcomes. Almost all scores predict myocardial infarction and death from coronary heart disease. Only 12 of the 21 scores included cerebrovascular events. SCORE only predicts fatal cardiovascular events.

Methods to assess outcome events also differed. The SCORE and ASSIGN scores used hard outcomes with diagnostic codes such as ICD 9/10 codes. 'Hard outcomes' can be defined as irrevocable events<sup>32</sup> that have permanent consequences, such as myocardial infarction and death, as opposed to 'soft events', such as hospitalisation for angina. The Framingham studies included a broader composite of hard and soft end points. Diagnostic criteria for outcomes in Progetto CUORE and the USA-PRC cohorts followed the WHO-MONICA Study (WHO—MONItoring trends and determinants in Cardiovas-

cular disease project).<sup>28 30</sup> Expert panels reviewed medical records and hospital notes in the Framingham studies, PROCAM scores, ARIC, SHS, Reynolds studies and the NHEFS. QRISK1 and 2 used general practice electronic recorded diagnosis or death certificates linked to the computer system.

### Adjustment for treatment effects

Methods used to adjust for the effect of medication were absent or weak (table 5). The effect of treatment is not fully assessed or adjusted for by any of the reviewed risk scores. Treatment effect includes (1) that which occurs by risk factor modification (eg, blood pressure-lowering medication), (2) that which works independently of risk factors (eg, platelet inhibitors such as aspirin), and (3) that which works by both means (eg, statins). Twelve of the cardiovascular risk score studies (Framingham 1998, Framingham 2008, ARIC, Progetto CUORE, SHS, USA-PRC, Reynolds 2007, Reynolds 2008, Personal Heart, QRISK1, QRISK2, and NHEFS) reported data on prior treatment, but this was mainly limited to antihypertensive treatment. Only seven (Framingham 2008, ARIC, Progetto CUORE, SHS, QRISK1, QRISK2 and NHEFS) included the use of antihypertensive drugs as a risk predictor. The Reynolds studies were the only ones to report prior use of lipid-lowering agents. None of the studies reported on the prior use of platelet inhibitors.

Two treatment effects need to be considered: (1) prior treatment (started before enrolment in the study) and (2) subsequent

## Systematic review

Table 4 Outcomes

	Outcomes	Death from CHD	MI	Ischaemic stroke	Haemorrhagic stroke	TIA	Angina pectoris	Revascularisation interventions	PAD	Hypertensive CCF
Framingham 1976	General CVD events	I								
Framingham 1991	CHD									
Framingham 1998	CHD									
Framingham 2008	General CVD events	I								
PROCAM 2002	CHD									
PROCAM 2007	CHD									
	Cerebral ischaemic events									
SCORE 2003	Fatal CVD events	I	F	F					F	F
ARIC 2003	CHD									
Progetto CUORE 2004	CVD events	I								
SHS 2006	CHD									
USA-PRC 2006	CVD events	I								
ASSIGN 2007	CVD	I	A	A	A	A	A			
Reynolds women 2007	CVD events	I								
Reynolds men 2008	CVD events	I								
Personal Heart 2007	CHD									
QRISK 2007	CVD events	I								
QRISK 2 2008	CVD events	I								
NHEFS 2008	CVD events	I								

Shaded areas, outcomes not included in risk score; I, includes other fatal CVD; F, only if fatal; A, only if admitted; CHD, coronary heart disease; MI, myocardial infarct; TIA, transient ischaemic attack; PAD, peripheral artery disease; CCF, congestive cardiac failure; CVD, cardiovascular disease.

treatment started during study follow-up (treatment drop-ins). None of the risk scores addressed the effect of treatment drop-ins. For early studies, such as the older Framingham Study, this may be minimal. Recent cohorts such as QRISK may have had more than half of their study population receiving treatment with their blood pressure under control (see NHANES data<sup>33–37</sup> in figure 2).

## DISCUSSION

For users of cardiovascular risk scores, this review has two main findings: that cardiovascular risk scores differ considerably in terms of population, predictors and outcomes, which may not match those used by clinicians, and that treatment 'drop-in' is poorly accounted for by most rules.

Whichever risk equation they choose, clinicians should know which outcomes are predicted. As the outcomes predicted differ significantly, the risk scores are not interchangeable. For example, the Framingham risk scores predict a broad range of cardiovascular events (including cerebrovascular events), whereas SCORE only predicts fatal cardiovascular events. The Framingham Study risk scores have been criticised for the inclusion of 'soft'

(subjective) outcomes such as angina,<sup>10</sup> although the Framingham investigators argue that such outcomes estimate the total cardiovascular disease burden<sup>19</sup> and are clinically important to both patient and doctor. Revascularisation interventions may also be criticised as being subjective.

Time is a major obstacle to the use of risk scores by physicians<sup>4</sup>; obtaining more information from a patient will further decrease the use of risk calculators. Of the risk scores, QRISK2 had the most predictors, which included disease conditions such as atrial fibrillation and chronic renal disease. QRISK2 score is designed to use data in the patient's electronic health record, with imputed values for missing data. However, the proportion with missing data for these factors in the derivation cohorts was substantial (>70% for ethnicity; >60% for cholesterol).<sup>23</sup>

The second limitation is that the effect of treatment has not been considered fully by any of the reviewed risk scores. Treatment decreases the true effect of risk factors on outcomes,<sup>38,39</sup> as illustrated by figure 3. The combined effects of risk reduction due to treatment can be as much as 50%.<sup>40</sup> If 25% of the population started treatment during follow-up, it would mean

**Table 5** Treatment effect

	Risk Predictors	Follow-up	Prior Treatment			Treatment during the study	
	Measurement		Treatment exclusions	Treatment assessed	Adjustment methods	Trial medication	Treatment drop ins
Framingham 1976	Single	2 yearly exams					
Framingham 1991	Single	2-4 yearly exams					
Framingham 1998	Single	2-4 yearly exams		Antihpt			
Framingham 2008	Single	2-4 yearly exams		Antihpt	SBP if treated and SBP if not treated included as predictor		
PROCAM 2002	Single	2 yearly questionnaire					
PROCAM 2007	Single	2 yearly questionnaire					
SCORE 2003	Single	Varies between cohorts					
ARIC 2003	Single	3 yearly exams. Outcomes from yearly interviews		Antihpt	Included as predictor		
Progetto CUORE 2004	Single	Varies between cohorts		Antihpt	Included as predictor		
SHS 2006	Single	3-4 yearly exams. Outcomes from yearly interviews and records		Antihpt	Included as predictor		
USA-PRC 2006	Single	2-4 yearly exams		Antihpt and OCP			*
ASSIGN 2007	Single	None for pred. Outcomes from record linkage					
Reynolds women 2007	Single	None for pred. Outcomes from 6-12 monthly questionnaire	Several	Antihpt, lipid lowering, hormone therapy, vitamins		Aspirin, vitamin E	
Reynolds men 2008	Single	None for pred. Outcomes from annual questionnaire	Vitamins	Antihpt, lipid lowering		Beta carotene, vitamin C, vitamin E, multivitamins	
Personal HEART 2007	Single	3 yearly exams. Outcomes from yearly interviews		Antihpt			
QRISK 2007	Single	None for pred. Outcomes from record linkage		Antihpt	Included as predictor		
QRISK 2 2008	Single	None for pred. Outcomes from record linkage	Those on statins	Antihpt	Included as predictor		
NHEFS 2008	Single	None for pred. Outcomes from 5 to >10 yearly survey interviews		Antihpt	Included as predictor in model but not risk chart		

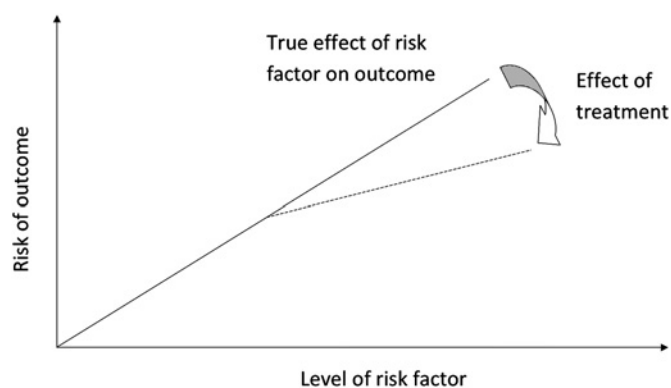
Shaded areas, information not reported; Antihpt, antihypertensive medication; SBP, systolic blood pressure; pred, predictors.

\*Corrected for change in risk factors by factoring in changes at midpoint of follow-up—that is, 1993/1994.

a population risk reduction of 12.5%. But this would be greater in the high-risk groups, who are more likely to be treated. These differences are similar to those found between QRISK 2 and Framingham (11.6%), which was obtained in a recent validation study of QRISK 2.<sup>41</sup>

Ideally, a cardiovascular risk score to determine the risk of a cardiovascular event and to stratify patients for risk factor modification should be derived in a population receiving no treatment at the start of and during the study. Such an ideal study is not tenable or ethical. We know of three possible





**Figure 3** True effect of risk factor on outcome.

solutions. First, we could favour the use of older studies, when less aggressive treatment occurred. Second, treatment uptake could be monitored and appropriate adjustments such as the application of a penalised Cox model made to account for the effect of treatment.<sup>42</sup> Until such studies have been performed, study cohorts where there is minimal treatment drop-in during follow-up should be preferred. Alternatively, to minimise treatment drop-in, we could study cohorts with much larger numbers over much shorter periods (Rod Jackson, personal communication).

We have not addressed how risk scores may change over time. However, a common misconception is that the strength of the risk scores change with population health status. Changes in the prevalence of a risk factor should not change the underlying relationship of a risk predictor to a disease outcome. For example, lower rates of smoking will not change the RR reduction due to smoking. Study participants may have changed their risk behaviour—for example, stopped smoking during the study. However, that is another treatment effect and should ideally be measured.

The lack of accounting for treatment makes the use of most cardiovascular risk scores for treatment decisions problematic. We need to examine how doctors use cardiovascular risk scores in clinical practice. If the aim is to discuss with patients the risk of remaining untreated, then the use of the majority of these risk scores would be incorrect.

### Strengths and weaknesses of the study

The review was limited to studies in which participants had no previous history of cardiovascular disease and excluded those who were restricted to a disease condition. A prior diagnosis of cardiovascular disease or a disease such as diabetes raises the patient into the high-risk category, removing the need for risk scoring. This has also been advocated by the NICE guidelines, which states that risk equations should not be used for those with a previous history of cardiovascular disease or other high-risk diseases such as diabetes.<sup>1</sup> Furthermore, the majority of these patients would have received treatment, potentially altering study outcomes.

This is a detailed review with a clear and focused question and explicit methodology. The review is particularly relevant to the recent modification of the NICE guidelines and offers the most up-to-date comparison of available cardiovascular risk scores. It has also identified a major gap in risk assessment studies, namely, the effect of treatment.

### Strengths and weaknesses in relation to other studies, discussing particularly any differences in results

The 2005 review by Beswick *et al*<sup>43</sup> included in the appendix of the NICE guidelines identified 110 studies, with 70 meant

specifically for application in primary prevention. The difference in the number of studies identified is due to their wider inclusion criteria, which included studies restricted to a disease condition, studies that had participants with prior cardiovascular disease, studies that were recalibrations or modifications of the original cohort study, studies that did not use absolute risk scoring, and studies where the duration of prediction was not specified. More recent studies such as QRISK and Reynolds scores are not included, as their search concluded in April 2005.

### Meaning of the study: possible mechanisms and implications for clinicians or policymakers

The recent change in the NICE guidelines has major implications for clinical practice. Selecting an appropriate risk score is likely to be difficult because of the wide variation in available risk scores. This review has attempted to address the problem by comparing features of all the cardiovascular risk scores.

### Unanswered questions and future research

This review did not address the effectiveness or accuracy of the cardiovascular risk scores, which would require a review of validation studies instead of the original cohort studies. The reviews by Beswick *et al* and Brindle *et al*<sup>44</sup> have tried to assess this, but do not include the more recent studies. However, it should be pointed out that any validation study of risk scores might also suffer the same problem of treatment drop-in, which would attenuate the true cardiovascular risk. Researchers should also attempt to address the effect of treatment in future studies in this field by collecting data on treatment at the start and during the course of cohort studies, as this will impact on the final outcomes.

### Authors' conclusions

#### Implications

These results show that there are substantial differences in the available cardiovascular risk scores in terms of study characteristics, predictors and outcomes. The effect of treatment on the study population has not been taken into account by these cohort studies. Further study is required for the translation of such research into clinical practice.

**Funding** This study was funded in part by the NHMRC Project Grant 511217 and Prof Glasziou's NIHR Fellowship.

**Competing interests** None.

**Contributors** SM, JD and PG are responsible for the study concept and design. SM and JD extracted data. SM and PG undertook analysis and interpretation of the data. SM drafted the manuscript, and JD and PG undertook critical revisions of the manuscript. All three authors read and approved the final manuscript and as such act as guarantors for the study.

**Provenance and peer review** Not commissioned; internally peer reviewed.

### REFERENCES

1. Cooper A, Nherera L, Calvert N, *et al*. *Clinical Guidelines and Evidence Review for Lipid Modification: cardiovascular risk assessment and the primary and secondary prevention of cardiovascular disease*. London, National Collaborating Centre for Primary Care and Royal College of General Practitioners, 2008.
2. British Cardiac Society, British Hypertension Society, Diabetes UK, HEART UK, Primary Care Cardiovascular Society, Stroke Association. JBS 2: Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice. *Heart* 2005;**91**(Suppl 5):v1–52.
3. Sposito AC, Ramires JAF, Jukema JW, *et al*. Physicians' attitudes and adherence to use of risk scores for primary prevention of cardiovascular disease: cross-sectional survey in three world regions. *Curr Med Res Opin* 2009;**25**:1171–8.
4. Graham IM, Stewart M, Hertog MG. Cardiovascular Round Table Task Force. Factors impeding the implementation of cardiovascular prevention guidelines: findings from a survey conducted by the European Society of Cardiology. *Eur J Cardiovasc Prev Rehabil* 2006;**13**:839–45.

5. **Montgomery AA**, Fahey T, MacKintosh C, *et al.* Estimation of cardiovascular risk in hypertensive patients in primary care. *Br J Gen Pract* 2000;**50**:127–8.
6. **Imms A**, Quinn S, Nelson M. General practitioners' use of cardiovascular risk calculators. *Aust Fam Physician* 2010;**39**:57.
7. **Eichler K**, Zoller M, Tschudi P, *et al.* Barriers to apply cardiovascular prediction rules in primary care: a postal survey. *BMC Fam Pract* 2007;**8**:1.
8. **Kannel WB**, McGee D, Gordon T. A general cardiovascular risk profile: the Framingham Study. *Am J Cardiol* 1976;**38**:46–51.
9. **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**:310–15.
10. **Conroy RM**, Pyorala K, Fitzgerald AP, *et al.* Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. *Eur Heart J* 2003;**24**:987–1003.
11. **Hippisley-Cox J**, Coupland C, Vinogradova Y, *et al.* Derivation and validation of QRISK, a new cardiovascular disease risk score for the United Kingdom: prospective open cohort study. *BMJ* 2007;**335**:136.
12. **Ferket BS**, Colkesen EB, Visser JJ, *et al.* Systematic review of guidelines on cardiovascular risk assessment: which recommendations should clinicians follow for a cardiovascular health check? *Arch Intern Med* 2010;**170**:27–40.
13. **Piepho RW**, Beal J. An overview of antihypertensive therapy in the 20th century. *J Clin Pharmacol* 2000;**40**:967–77.
14. **Endo A**. The discovery and development of HMG-CoA reductase inhibitors. *J Lipid Res* 1992;**33**:1569–82.
15. **Wasson JH**, Sox HC, Neff RK, *et al.* Clinical prediction rules. applications and methodological standards. *N Engl J Med* 1985;**313**:793–9.
16. **Royston P**, Moons KG, Altman DG, *et al.* Prognosis and prognostic research: Developing a prognostic model. *BMJ* 2009;**338**:b604.
17. **Anderson KM**, Wilson PW, Odell PM, *et al.* An updated coronary risk profile. A statement for health professionals. *Circulation* 1991;**83**:356–62.
18. **Wilson PW**, D'Agostino RB, Levy D, *et al.* Prediction of coronary heart disease using risk factor categories. *Circulation* 1998;**97**:1837–47.
19. **D'Agostino RB Sr**, Vasan RS, Pencina MJ, *et al.* General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation* 2008;**117**:743–53.
20. **Assmann G**, Schulte H, Cullen P, *et al.* Assessing risk of myocardial infarction and stroke: new data from the Prospective Cardiovascular Munster (PROCAM) study. *Eur J Clin Invest* 2007;**37**:925–32.
21. **Chambless LE**, Folsom AR, Sharrett AR, *et al.* Coronary heart disease risk prediction in the Atherosclerosis Risk in Communities (ARIC) study. *J Clin Epidemiol* 2003;**56**:880–90.
22. **Mainous AG 3rd**, Koopman RJ, Diaz VA, *et al.* A coronary heart disease risk score based on patient-reported information. *Am J Cardiol*. 2007;**99**:1236–41.
23. **Hippisley-Cox J**, Coupland C, Vinogradova Y, *et al.* Predicting cardiovascular risk in England and Wales: prospective derivation and validation of QRISK2. *BMJ* 2008;**336**:1475–82.
24. **Ridker PM**, Buring JE, Rifai N, *et al.* Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: the Reynolds Risk Score. *JAMA* 2007;**297**:611–19.
25. **Ridker PM**, Paynter NP, Rifai N, *et al.* C-reactive protein and parental history improve global cardiovascular risk prediction: the Reynolds Risk Score for men. *Circulation* 2008;**118**:2243–51, 4p following 2251.
26. **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.
27. **Lee ET**, Howard BV, Wang W, *et al.* Prediction of coronary heart disease in a population with high prevalence of diabetes and albuminuria: the Strong Heart Study. *Circulation* 2006;**113**:2897–905.
28. **Wu Y**, Liu X, Li X, *et al.* Estimation of 10-Year Risk of Fatal and Nonfatal Ischemic Cardiovascular Diseases in Chinese Adults. *Circulation* 2006;**114**:2217–25.
29. **Gaziano TA**, Young CR, Fitzmaurice G, *et al.* Laboratory-based versus non-laboratory-based method for assessment of cardiovascular disease risk: the NHANES I Follow-up Study cohort. *Lancet* 2008;**371**:923–31.
30. **Palmieri L**, Panico S, Vanuzzo D, *et al.* Evaluation of the global cardiovascular absolute risk: the Progetto CUORE individual score. *Ann Ist Super Sanita* 2004;**40**:393–9.
31. **2006 World Health organization - International Diabetes Federation.** *Definition and Diagnosis of Diabetes Mellitus and Intermediate Hyperglycemia: Report of a WHO/IDF Consultation.* Switzerland: WHO Press, World Health Organization, 2006.
32. **Nissen SE.** Cardiovascular outcomes in randomized trials: should time to first event for "hard" end points remain the standard approach? *J Am Coll Cardiol* 2009;**54**:2363–5.
33. **Burt VL**, Cutler JA, Higgins M, *et al.* Trends in the prevalence, awareness, treatment, and control of hypertension in the adult US population. Data from the health examination surveys, 1960 to 1991. *Hypertension* 1995;**26**:60–9.
34. **Hajjar I**, Kotchen TA. Trends in prevalence, awareness, treatment, and control of hypertension in the United States, 1988–2000. *JAMA* 2003;**290**:199–206.
35. **Ong KL**, Cheung BM, Man YB, *et al.* Prevalence, awareness, treatment, and control of hypertension among United States adults 1999–2004. *Hypertension* 2007;**49**:69–75.
36. **Ostchega Y**, Yoon SS, Hughes J, *et al.* Hypertension awareness, treatment, and control—continued disparities in adults: United States, 2005–2006. *NCHS Data Brief* 2008;**(3)**:1–8.
37. **Egan BM**, Zhao Y, Axon RN. US trends in prevalence, awareness, treatment, and control of hypertension, 1988–2008. *JAMA* 2010;**303**:2043–50.
38. **Wilson PW**, Anderson KM, Castelli WP. Twelve-year incidence of coronary heart disease in middle-aged adults during the era of hypertensive therapy: the Framingham offspring study. *Am J Med* 1991;**90**:11–16.
39. **Brown BG**, Zhao X. Nicotinic acid, alone and in combinations, for reduction of cardiovascular risk. *Am J Cardiol* 2008;**101**:58B–62.
40. **Messerli FH**, Bakris GL, Ferrera RD, *et al.* on behalf of the AVALON Investigators. Efficacy and safety of coadministered amlodipine and atorvastatin in patients with hypertension and dyslipidemia: results of the AVALON trial. *J Clin Hypertens (Greenwich)* 2006;**8**:571–83.
41. **Collins GS**, Altman DG. An independent and external validation of QRISK2 cardiovascular disease risk score: a prospective open cohort study. *BMJ* 2010;**340**:c2442.
42. **Simes J**, Voysey M, O'Connell R, *et al.* FIELD Study Investigators. A novel method to adjust efficacy estimates for uptake of other active treatments in long-term clinical trials. *PLoS One* 2010;**5**:e8580.
43. **Beswick AD**, Brindle P, Fahey T, *et al.* A systematic review of risk scoring methods and clinical decision aids used in the primary prevention of coronary heart disease. Appendix K. Clinical Guidelines and Evidence Review for Lipid Modification. Cardiovascular Risk Assessment and the Primary and Secondary Prevention of Cardiovascular Disease, 2007; CG67. London: National Collaborating Centre for Primary Care and Royal College of General Practitioners. <http://www.nice.org.uk/nicemedia/live/11982/40758/40758.pdf> (accessed 16 Mar 2011).
44. **Brindle P**, Beswick A, Fahey T, *et al.* Accuracy and impact of risk assessment in the primary prevention of cardiovascular disease: a systematic review. *Heart* 2006;**92**:1752–9.



## Cardiovascular risk scores do not account for the effect of treatment: a review

S M Liew, J Doust and P Glasziou

*Heart* 2011 97: 689-697

doi: 10.1136/hrt.2010.220442

---

Updated information and services can be found at:

<http://heart.bmj.com/content/97/9/689.full.html>

---

*These include:*

- |                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|-------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>References</b>             | This article cites 41 articles, 23 of which can be accessed free at:<br><a href="http://heart.bmj.com/content/97/9/689.full.html#ref-list-1">http://heart.bmj.com/content/97/9/689.full.html#ref-list-1</a>                                                                                                                                                                                                                                                                                                                                                                 |
| <b>Open Access</b>            | This is an open-access article distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license. See:<br><a href="http://creativecommons.org/licenses/by-nc/2.0/">http://creativecommons.org/licenses/by-nc/2.0/</a> and<br><a href="http://creativecommons.org/licenses/by-nc/2.0/legalcode">http://creativecommons.org/licenses/by-nc/2.0/legalcode</a> . |
| <b>Email alerting service</b> | Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.                                                                                                                                                                                                                                                                                                                                                                                                                                            |
- 

### Topic Collections

Articles on similar topics can be found in the following collections

[Unlocked](#) (764 articles)  
[Drugs: cardiovascular system](#) (24141 articles)  
[Epidemiology](#) (5420 articles)

---

### Notes

---

To request permissions go to:

<http://group.bmj.com/group/rights-licensing/permissions>

To order reprints go to:

<http://journals.bmj.com/cgi/reprintform>

To subscribe to BMJ go to:

<http://group.bmj.com/subscribe/>