

Absolute cardiovascular disease risk

Technical report: review of the evidence and evidence-based recommendations for practice

Based on evidence published up to 13 April 2006

An initiative of the National Vascular Disease Prevention Alliance



The NVDPA is a group of four leading and well-known Australian charities: Kidney Health Australia, Diabetes Australia, the National Heart Foundation of Australia and the National Stroke Foundation. It was established in 2000 and aims to reduce cardiovascular disease in Australia. Links to the full guidelines can be found on NVDPA member websites: www.strokefoundation.com.au, www.kidney.org.au, www.diabetesaustralia.com.au and www.heartfoundation.org.au.

The NVDPA would like to acknowledge Monash Institute of Health Services Research for their work in developing this report.

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ISBN: 978-1-921226-41-0

PRO-075

Suggested citation: National Vascular Disease Prevention Alliance. Technical report: review of the evidence and evidence-based recommendations for practice. 2009.

The full guidelines, quick reference guide, consumer booklet and consumer summary sheet are also available at www.strokefoundation.com.au, www.kidney.org.au, www.diabetesaustralia.com.au and www.heartfoundation.org.au.

Abbreviations

AP	Angina pectoris	MONICA	Multinational Monitoring of Trends and Determinants in Cardiovascular Disease
ARIC	Atherosclerosis Risk in Communities study	MS	Metabolic syndrome
AUC	Area under the ROC curve	NACCHO	National Aboriginal Community Controlled Health Organisation
BIRNH	Belgian Inter-university Research on Nutrition and Health	NCEP I	First National Cholesterol Education Program
BMI	Body mass index	NCEP II	Second National Cholesterol Education Program
BP	Blood pressure	NHANES I	First National Health & Nutrition Examination Survey
BPFS	Belgian Physical Fitness Study	NHANES II	Second National Health & Nutrition Examination Survey
CABG	Coronary artery bypass grafting	NPHS-II	The Second Northwick Park Heart Study
CCCC	Canadian Consensus Conference on Cholesterol	NVDPA	National Vascular Disease Prevention Alliance
CD	Coronary death	NZRC	New Zealand risk charts
CHD	Coronary heart disease	PHS	Physicians' Health Study
CHF	Congestive heart failure	PRHHP	Puerto Rico Heart Health Program
CHS	Cardiovascular Health Study	PRIME	Prospective Epidemiological Study of Myocardial Infarction
CKD	Chronic kidney disease	PROCAM	Prospective Cardiovascular Münster Study
CRM	Computer risk model	PTCA	Percutaneous transluminal coronary angioplasty
CUORE	Italian Heart Project	PVD	Peripheral vascular disease
CVD	Cardiovascular disease	RACGP	Royal Australian College of General Practitioners
DALY	Disability-adjusted life year	RF	Risk factor
DBP	Diastolic blood pressure	ROC	Receiver operating characteristic
ECG	Echocardiogram	SBP	Systolic blood pressure
ERICA	European Risk and Incidence; a Co-ordinated Analysis	SD	Sudden death
ESCRPM	European Society of Cardiology Risk Prediction Model	SHS	Strong Heart Study
FEV ₁	Forced expiratory volume in 1 second	TC	Total cholesterol
FRE	Framingham risk equation	UKPDS	United Kingdom Prospective Diabetes Study risk score
GCRS	Global Coronary Risk Score	WBC	White blood cell
GFR	Glomerular filtration rate	WC	Waist circumference
GP	General practitioner	WHO	World Health Organization
HDL	High-density lipoprotein	WHR	Waist-to-hip ratio
HHP	Honolulu Heart Program	WOSCOPS	West of Scotland Coronary Prevention Study
IC	Intermittent claudication		
IHD	Ischaemic heart disease		
IMT	Intima-media thickness		
ISH	International Society of Hypertension		
LDL	Low-density lipoprotein		
LRC	Lipid Research Clinic		
LVH	Left ventricular hypertrophy		
MI	Myocardial infarction		
MIHSR	Monash Institute of Health Services Research		

1 Introduction

1.1 Purpose of the technical report

The Monash Institute of Health Services Research was commissioned by the National Vascular Disease Prevention Alliance to produce a technical report that identifies, appraises and summarises the best available evidence and presents recommendations to guide clinical practice and inform policy for the assessment of absolute cardiovascular disease (CVD) risk in Australia. This report does not provide recommendations for management of CVD.

1.2 Scope of the technical report

1.2.1 Condition

The term CVD is used throughout this technical report to refer to coronary heart disease (CHD) and stroke collectively. It is acknowledged that heart, stroke and vascular diseases have unique attributes and although the term 'CVD' is often employed in the literature, it is important to identify the separate clinical endpoints which include CVD events and mortality. However, as these diseases share many common risk factors, particularly related to atherosclerosis, for these guidelines 'CVD' will be employed as a summary term. Specific endpoints in the evidence presented in these guidelines include: admission to hospital, angina pectoris (AP), cardiac procedures, cerebrovascular disease, congestive heart failure (CHF), coronary death (non-sudden, sudden), coronary events (non-fatal, fatal), CHD (non-fatal, fatal, acute), CVD, death (CHD, CVD, cerebrovascular, stroke), heart attack, heart failure (non-fatal, fatal), intermittent claudication (IC), ischaemic heart disease (IHD), morbidity and mortality, myocardial infarction (MI; non-fatal, fatal, acute, silent, hospitalised), new major Q wave on the ECG, peripheral vascular disease (PVD), revascularisation, stroke (non-fatal, fatal), subarachnoid haemorrhage, sudden death (SD), surgery for AP, transient ischaemic attack.

1.2.2 Population

This technical report covers the assessment of absolute CVD risk in adults over the age of 18 years who are not known to have CVD, classified into the following categories:

- a) a mixed population not known to have CVD or diabetes (diagnosed using WHO criteria, 2006 [1])
- b) a mixed population not known to have CVD and who have diabetes (diagnosed using WHO criteria, 2006 [1])
- c) a mixed population not known to have CVD and who are overweight (defined as BMI within the range 25.0–29.9 kg/m²[2]) or obese (BMI ≥30 kg/m² [2])
- d) a mixed population not known to have CVD and who have chronic kidney disease (GFR <60 mL/min)
- e) Aboriginal and Torres Strait Islander peoples not known to have CVD.

Methods used to assess CVD risk assume that a person's CVD risk is unknown. This is not the case for people with established CVD, therefore CVD risk assessment scores do not apply in people with established CVD and this population is excluded from this technical report.

1.2.3 Target audience

This technical report has been developed for use by general practitioners (GPs), Aboriginal health workers and other health professionals assessing CVD risk in primary care. It is also intended to provide health system policy makers with the best available evidence on CVD risk assessment, as a basis for population health policy.

2 Predictive ability of absolute CVD risk assessment methods in adults without known CVD or diabetes

Chapter overview

Search results:

- Ten high-quality studies compared the predictive ability of different absolute risk assessment methods [6Š15].
- Three studies of varying quality compared the ability of absolute risk assessment methods to classify into risk categories [16Š18].
- Fifteen studies of varying quality reported the predictive ability of individual absolute risk assessment methods [19Š33].
- All of the eight studies that compared the Framingham risk equation to other methods found it has a higher or equivalent predictive ability [6Š13].

Recommendation:

B

In adults not known to have CVD or diabetes use the Framingham risk equation to predict absolute cardiovascular risk over 5 or 10 years.

2.1 Background

CVD is one of the leading health problems for Australians. These conditions collectively were responsible for about 36% of all deaths in 2004 [3]. The prevalence of CVD has increased by almost 20% over the last decade, with the total burden expected to increase in the future due to the growing number of elderly Australians, among whom these diseases are most common. The increasing prevalence of CVD relates strongly to modifiable physiological and lifestyle risk factors [4]. Modifications to these risk factors have been clearly shown to reduce mortality and morbidity [5].

2.2 Comparison of different absolute risk assessment methods

Our search identified 10 studies, all of high quality with very low risk of bias, comparing the predictive ability of different absolute risk assessment methods in adults not known to have CVD or diabetes. A summary of these studies is provided in table 2.2.1. Detailed descriptions of the evidence are provided in **section 2.2.1**.

Table 2.2.1 Summary of studies comparing the predictive ability of different absolute risk assessment methods in adults not known to have CVD or diabetes

Study	Level of evidence	Quality	AUC data	Location
Cooper 2005 Section 2.2.1.2	II	High	FRE=0.6184 (M) [95%CI, 0.58–0.66] PROCAM=0.6295 (M) [95%CI, 0.59–0.67]	UK
Empana 2003 Section 2.2.1.2	II	High	FRE=0.66 (high-risk group, M) PROCAM=0.61 (high-risk group, M) FRE=0.68 (low-risk group, M) PROCAM=0.64 (low-risk group, M)	France, Ireland
Ferrario 2005 Section 2.2.1.2	II	High	FRE=0.723 (M) [95% CI, 0.67–0.78] PROCAM=0.735 (M) [95% CI, 0.68–0.79] CUORE=0.742 (M) [95% CI, 0.68–0.80]	Italy
Folsom 2003 Section 2.2.1.7	II	High	Basic RFs=0.680 (M) Basic RFs+=0.716 (M) Basic RFs=0.779 (F) Basic RFs+=0.792 (F)	USA
Grover 1995 Section 2.2.1.6	II	High	CRM=0.85 ± 0.02 (M&F) CCCC=0.70 ± 0.03 (M&F) NCEPI=0.72 ± 0.03 (M&F) NCEPII=0.74 ± 0.03 (M&F)	USA
McNeill 2005 Section 2.2.1.4	II	High	FRE=0.634 (M) FRE & MS=0.631 (M) FRE=0.731 (F) FRE & MS=0.729 (F)	USA
Milne 2003 Section 2.2.1.1	II	High	FRE=0.74 (M) [95%CI, 0.73–0.75] NZRC=0.73 (M) [95%CI, 0.72–0.74] FRE=0.77 (F) [95%CI, 0.74–0.80] NZRC=0.78 (F) [95%CI, 0.75–0.81]	New Zealand
Orford 2002 Section 2.2.1.3	II	High	FRE 5 risk categories=0.60 (M) FRE 20 risk categories=0.63 (M) ESCRPM 5 risk categories=0.58 (M)	USA
Stern 2004 Section 2.2.1.4	II	High	FRE=0.816 (M&F) FRE & MS=0.811 (M&F)	USA
Wannamethee 2005 Section 2.2.1.4 and section 2.2.1.5	II	High	FRE 10 years=0.73 (M) [95% CI, 0.71–0.75] MS 10 years=0.63 (M) [95% CI, 0.61–0.65] p<0.001 FRE 20 years=0.68 (M) [95% CI, 0.66–0.70] MS 20 years=0.59 (M) [95% CI, 0.57–0.61] p<0.001	UK

(M) Males, (F) Females. Where AUCs are not reported, refer to original data in **appendix I**.

FRE, Framingham risk equation; NZRC, New Zealand risk chart; PROCAM, Prospective Cardiovascular Münster Heart Study; CUORE, Italian Heart Project; ESCRPM, European Society of Cardiology Risk Prediction Model; MS, metabolic syndrome; CRM, Computer Risk Model; CCCC, Canadian Consensus Conference on Cholesterol; NCEPI, first National Cholesterol Education Program; NCEPII, second National Cholesterol Education Program; RF, risk factor.

2.2.1 Results

2.2.1.1 Framingham risk equation versus New Zealand risk chart

A follow-up study (*Milne 2003*) [6] was conducted in New Zealand. The study comprised 6354 participants of both genders, aged 35–74 years, recruited from 1992 to 1993. CVD outcomes included admission to NZ hospital and subsequent diagnosis with IHD, cerebrovascular disease, CHF, PVD, IC or SD, cause unknown and/or if they died in NZ during the 5 year period and recorded causes of death had an ICD-9 code in these ranges. The quality of the study was high with very low risk of bias. The study found no statistically significant difference between the AUCs for the FRE and New Zealand risk chart derived from the FRE in prediction of 5 year CVD risk in males (0.74 [95%CI, 0.73–0.75] versus 0.73 [95%CI, 0.72–0.74]) and females (0.77 [95%CI, 0.74–0.80] versus 0.78 [95%CI, 0.75–0.81]).

This evidence suggests that in a New Zealand population the FRE and the New Zealand risk chart which is derived from the FRE have similar 5 year predictive ability.

2.2.1.2 Framingham risk equation versus PROCAM risk score versus CUORE risk score

Three studies compared the FRE with the Prospective Cardiovascular Münster Study (PROCAM) risk score. All three studies are of high quality with very low risk of bias.

The first study was a follow-up study (*Empana 2003*) [7] conducted in France and Ireland which included 9758 male participants aged 50–59 years. CVD outcomes included first observed coronary event of AP, MI and CD. The second study (*Cooper 2005*) [8] was the UK-based Second Northwick Park Heart Study, a follow-up study which included 2732 male participants aged 50–64 years. CVD outcomes included acute CHD events, sudden coronary death (CD), fatal acute MI, non-fatal acute MI, new major Q wave on the ECG (after 5 years follow-up), surgery for AP with CHD angiographically demonstrated. Neither study found a statistically significant difference between the AUCs of the Framingham and PROCAM risk scores in their ability to predict 5 year CVD risk (Belfast 0.66 versus 0.61; France 0.68 versus 0.64) and 10 year CVD risk (0.62 [95% CI, 0.58–0.66] versus 0.63 [95% CI, 0.59–0.67]). However both studies found that CVD risk was overestimated by both scores. The ratio of predicted over observed events for the FRE was 2.35 and 1.34 for France and Ireland respectively. The ratio of predicted over observed events for PROCAM was 2.76 and 1.78 for France and Ireland respectively.

The third study (*Ferrario 2005*) [9], based in Italy, included 6865 male participants aged 35–69 years. CVD outcomes included first fatal and non-fatal major coronary events. This study compared the FRE and the PROCAM risk score with each other and with the CUORE (Italian Heart Project) risk equation and found no statistically significant differences between AUCs of the three methods to predict 10 year CVD risk (0.72 [95% CI, 0.670–0.779] versus 0.74 [95% CI, 0.678–0.790] versus 0.74 [95% CI, 0.684–0.796]). However, when predicted and observed events were shown graphically, both scores overestimated CVD risk.

This evidence suggests that in these populations the FRE and PROCAM risk score have similar 5 and 10 year predictive ability; and that the FRE, PROCAM and CUORE risk score have similar 10 year predictive ability. However, the FRE and PROCAM risk score overestimate CVD risk in these populations.

2.2.1.3 Framingham risk equation versus European Study of Cardiology risk score

The Normative Ageing Study (Orford 2002) [10] was a population-based follow-up study comprising 1393 predominantly white, community-dwelling male participants aged 30–74 years in the greater Boston area in the US. CVD outcomes included acute MI, old MI, AP and CHD death. This high-quality study with very low risk of bias compared different numbers of risk categories (5 and 20) of the Framingham and the European Study of Cardiology 5 risk categories scores. The 5 risk categories were low (<5%), mild (5–10%), moderate (10–20%), high (20–40%) and very high (>40%). The 20 risk categories were not defined. There were no statistically significant differences found between the AUCs of each of the methods to predict 10 year CVD risk (0.60 versus 0.63 versus 0.58). The authors also report a range of predicted and observed event rates for both scores in each of the risk categories. The authors concluded that both reliably stratify risk in the population; however, the FRE underestimated events in the low-risk group but overestimated events in the very high risk group, while the European Study of Cardiology 5 risk categories score overestimated events in the high-risk group.

This evidence suggests that in this population the FRE and the European Study of Cardiology risk score have similar 10 year predictive ability. While both risk scores reliably stratify risk in most of the risk categories, the FRE underestimated events in the low risk group but overestimated events in the very high risk group; and the European Study of Cardiology 5 risk categories score overestimated events in the high risk group.

2.2.1.4 Framingham risk equation alone versus Framingham risk equation plus presence of metabolic syndrome as an indicator of risk or presence of metabolic syndrome as an indicator of risk alone

A UK-based follow-up study (Wannamethee 2005) [11] compared the predictive accuracies of the FRE and the presence of metabolic syndrome as an indicator of risk. CVD outcomes included non-fatal MI, stroke and death. Comprising 5128 male participants aged 40–59 years, the quality of the study was high with very low risk of bias. This study found that the FRE had a higher AUC than the metabolic syndrome when predicting CVD risk over 10 years (0.73 [95% CI, 0.71–0.75] versus 0.63 [95% CI, 0.61–0.65], $p < 0.001$) and 20 years (0.68 [95% CI, 0.66–0.70] versus 0.59 [95% CI, 0.57–0.61], $p < 0.001$).

In the same study, sensitivity and specificity analyses were performed. At 10 year CVD risk, the FRE and the metabolic syndrome have lower sensitivity (56.5% and 39.5%) at a higher specificity cut-off point (75.0% and 75.0%). Similarly, at 20 year CVD risk, the FRE and the metabolic syndrome have lower sensitivity (47.2% and 35.5%) at a higher specificity cut-off point (75.7% and 75.7%).

Two high-quality studies with very low risk of bias investigated the effect of the addition of the metabolic syndrome to the FRE. The way in which risk factors of the metabolic

syndrome were combined to obtain a score is not described and neither is the way in which metabolic syndrome was combined with the FRE to obtain a score.

The San Antonio Heart Study (*Stern 2004*) [12], a follow-up study covering low, middle and high-income suburbs in San Antonio, Texas in the USA, comprised 2570 male and female participants aged 25–64 years. CVD outcomes included self-reported physician diagnosis of heart attack, revascularisation procedure, stroke or CVD death. When the FRE alone was compared with the FRE plus the metabolic syndrome, no statistically significant difference was found in the AUCs when predicting 7–8 year CVD risk (0.82 versus 0.81).

In the same study, sensitivity and specificity analyses were performed. At 7–8 year CVD risk, the FRE and the combination of the FRE and metabolic syndrome have higher sensitivity (81.4% and 81.4%) at a lower specificity cut-off point (34.2% and 34.2%).

Similar results were found in a sample from the Atherosclerosis Risk in Communities (ARIC) study (*McNeill 2005*) [13] covering North Carolina, Mississippi, Minnesota and Maryland in the USA. CVD outcomes included incident CHD and ischaemic stroke events. In the 12,089 participants aged 45–64 years of both genders, no statistically significant difference was found between the AUCs of the FRE alone and the FRE plus the metabolic syndrome when predicting 11 year CVD risk (females 0.73 versus 0.73; males 0.63 versus 0.63).

Predicted and observed event rates were not reported in any of these studies, hence no comment about under- or overestimation of risk can be made.

This evidence suggests that the FRE is a more accurate predictor of CVD risk than metabolic syndrome and that the addition of metabolic syndrome to the FRE does not improve 7–8, 10–11 or 20 year predictive ability over the FRE alone.

2.2.1.5 10 year Framingham risk equation versus 20 year Framingham risk equation

A UK-based follow-up study (*Wannamethee 2005*) [11] compared the ability of the FRE for predicting 10 year and 20 year risk. CVD outcomes included non-fatal MI, stroke and death. Comprising 5128 male participants aged 40–59 years, the quality of the study is high with very low risk of bias. This study found that the FRE had a higher AUC when 10 year CVD risk was calculated than when 20 year CVD risk was calculated (0.73 versus 0.68, p value not reported).

In the same study, sensitivity and specificity analyses were performed. The FRE has a higher sensitivity (56.5%) when used for 10 year risk than when used for 20 year risk (47.2%) at specificity cut-off points of 75.0% and 75.7% respectively. Predicted and observed event rates were not reported in this study, hence no comment about under- or overestimation of risk can be made.

This evidence suggests that the FRE has higher predictive ability when predicting 10 year rather than 20 year CVD risk.

2.2.1.6 *Computer Risk Model (based on the Framingham risk equation) versus Canadian Consensus Conference on Cholesterol risk score versus First National Cholesterol Education Program risk score versus Second National Cholesterol Education Program risk score*

Grover et al (Grover 1995) [14] conducted a follow-up study using the US-based Lipid Research Clinic Prevalence and Follow-up study cohort. This cohort comprised 3678 males and females aged 35–74 years. The CVD outcome was CHD death. This high-quality study with very low risk of bias compared the predictive ability of four CVD risk assessment methods: the Computer Risk Model (based on the FRE), Canadian Consensus Conference on Cholesterol risk score, and the first and second National Cholesterol Education Program risk scores. Over 12.2 years follow-up, the Computer Risk Model had a higher AUC (0.85 ± 0.02) than any of the other methods ($p < 0.03$). The Canadian Consensus Conference on Cholesterol risk score had an AUC of 0.70 ± 0.03 . The first and second National Cholesterol Education Program risk scores had AUCs of 0.72 ± 0.03 and 0.74 ± 0.03 respectively, where the second risk score was higher ($p < 0.03$). Predicted and observed event rates were not reported in any of these studies, hence no comment about under- or overestimation of risk can be made.

This evidence suggests that the Computer Risk Model based on the FRE has higher predictive ability than the Canadian Consensus Conference on Cholesterol risk score, and the first and second National Cholesterol Education Program risk scores.

2.2.1.7 *Traditional CVD risk factors versus non-traditional CVD risk factors*

A follow-up study (Folsom 2003) [15] was conducted in a cohort of 10,885 participants of both genders aged 45–64 years sampled from the ARIC study covering North Carolina, Mississippi, Minnesota and Maryland in the US. CVD outcomes included a validated definite or probable hospitalised MI, a definite CHD death, an unrecognised MI defined by ARIC ECG readings, or coronary revascularisation. This high quality study with very low risk of bias compared the predictive ability of basic traditional CVD risk factors (for example, age, race, TC, HDL, SBP, etc) with that of a combination of basic traditional CVD risk factors and non-traditional CVD risk factors (BMI, WHR, lipoprotein(a), albumin, creatinine, WBC count, fibrinogen, factor VIII, sport activity index, Keys score, LVH, IMT – continuous). The way in which these risk factors were combined to obtain a score was not described; we have contacted the authors for further details. This study found that there was no statistical difference between the AUCs of the two methods (females 0.78 versus 0.79; males 0.68 versus 0.72) to predict 10 year CVD risk. Predicted and observed event rates were not reported in this study, hence no comment about under- or overestimation of risk can be made.

This evidence suggests that the addition of non-traditional risk factors to traditional risk factors does not improve 10 year predictive ability in this population.

In summary, the most thoroughly tested absolute risk assessment method in adults not known to have either diabetes or CVD is the FRE. All of the identified studies that have directly compared the FRE to other absolute risk assessment methods (8 studies) report that it has equivalent or higher predictive ability than other methods for 5, 7–8, 10, 12 and 20 year CVD risk prediction.

2.3 Use of risk assessment to divide into categories of risk

Our search identified three studies of varying quality that compared the ability of absolute CVD risk assessment methods to classify populations into risk categories. A summary of these studies is provided in table 2.3.1. Detailed descriptions of the evidence are provided in **section 2.3.1**.

Table 2.3.1 Summary of studies that compare the ability of absolute CVD risk assessment methods to classify populations into risk categories in adults not known to have CVD or diabetes

Study	Level of evidence	Quality	AUC data	Location
Kornitzer 2000	II	High	AUCs not reported	Belgium
Leaverton 1987	II	High	AUCs not reported	USA
Persson 2003	III-2	Low	AUCs not reported	Sweden

(M) Males, (F) Females. Where AUCs are not reported, refer to original data in **appendix I**.

2.3.1 Results

A study was conducted by Leaverton et al (*Leaverton 1987*) [16] to assess the ability of two different US-derived absolute risk assessment methods over 10 years: the FRE was assessed in the First National Health and Nutrition Examination Survey (NHANES I) cohort, and the risk score derived from the NHANES I cohort was assessed in the Framingham cohort. CVD outcomes included CVD or death, non-fatal CHD or stroke. Comprising 8026 male and female participants aged 40–74 years, this high-quality study with very low risk of bias presented numbers of observed events for each risk quintile and the number of events expected was not reported. The data were presented graphically.

When applied to males and females in the NHANES I cohort, the FRE had appropriate discriminatory ability and higher event rates were reported in the high-risk categories with a steady decrease in rates, and remaining events appropriately distributed, in the lower risk categories. When applied to males and females in the Framingham cohort, NHANES I had similar discriminatory ability and higher event rates were reported in the high-risk categories with a steady decrease in rates and remaining events appropriately distributed in the lower risk categories. Observed rates were appropriately distributed between quintiles of risk.

This evidence suggests that the FRE and the NHANES I risk score have similar 10 year predictive ability in this population.

Kornitzer et al (*Kornitzer 2000*) [17] assessed the ability of two different absolute risk assessment methods over 10 years: the FRE was assessed in the Belgian Inter-university Research on Nutrition and Health (BIRNH) cohort, comprising 4310 males and females; and the Belgian Physical Fitness Study (BPFS) cohort, comprising 2186 males; and the Global Coronary Risk Score was assessed in the BPFS cohort only. The CVD outcome was CHD death. The participants in this high-quality study with very low risk of bias were aged 40–55 years. Numbers of observed events are presented for each risk quartile; however the number of events expected is not reported.

In males in all age groups in the BIRHN cohort, FRE had similar discriminatory ability and higher event rates were reported in the high-risk categories with a steady decrease in rates, and remaining events appropriately distributed in the lower risk categories. In females aged 50–74 years, FRE did not accurately discriminate between the two lowest risk quartiles. In males aged 40–55 years in the BPFs cohort, FRE had similar discriminatory ability and higher event rates were reported in the high-risk categories with a steady decrease in rates and remaining events appropriately distributed in the lower risk categories.

In males aged 40–55 years in the BPFs cohort, the Global Coronary Risk Score had similar discriminatory ability and higher event rates were reported in the high-risk categories with a steady decrease in rates, and remaining events appropriately distributed in the lower risk categories.

This evidence suggests that the FRE and the Global Coronary Risk Score have similar 10 year predictive ability in this population.

In a low-quality study with a high risk of bias, Persson et al (*Persson 2003*) [18] assessed the ability and distribution of cardiovascular risk in a cohort of people with hypertension, using different risk assessment methods: the FRE, the Northern Sweden (MONICA) risk equation and risk stratification by 1999 WHO Hypertension guidelines (WHO/ISH). The cohort of 5997 participants were pooled from the MONICA study and a new random sample, aged 30–74 years, and were followed for 1–14 years. CVD outcomes included acute MI or stroke. Results were presented graphically. The authors found agreement between the methods when the values obtained from each risk equation were averaged for each risk group, but when risk was predicted for each individual, the agreement was poor for the medium and high-risk groups.

This evidence suggests that the FRE, the MONICA risk equation and the WHO/ISH risk score have similar predictive ability in this population.

In summary, the most thoroughly tested absolute risk assessment method in adults not known to have either diabetes or CVD is the FRE. All of the identified studies that have compared the ability of absolute CVD risk assessment methods to classify populations into risk categories (3 studies) report that it has equivalent predictive ability to other tested methods for CVD risk prediction.

2.4 Assessment of predictive ability of absolute risk assessment methods in different regional populations

Our search identified 15 studies assessing the predictive ability of absolute risk assessment methods in different geographical populations of adults not known to have CVD or diabetes. Fourteen studies, of varying quality, examined the FRE and one high-quality study examined the Oriental risk score. A summary of these studies is provided in table 2.4.1. Detailed descriptions of the evidence are provided in **section 2.4.1**.

Table 2.4.1 Summary of studies assessing the predictive ability of absolute risk assessment methods in different geographical populations of adults not known to have CVD or diabetes

Study	Level of evidence	Quality	AUC data	Location
Assmann 2002 <i>Section 2.4.1.2</i>	II	High	FRE=0.78 (M)	Germany
Bastuji-Garin 2002 <i>Section 2.4.1.1</i>	III-2	Low	AUCs not reported	Europe, Israel
Brindle 2003 <i>Section 2.4.1.2</i>	II	High	AUCs not reported	UK
Brindle 2005 <i>Section 2.4.1.2</i>	II	High	FRE=0.73 [95% CI, 0.72–0.75] (All M&F) FRE=0.74 [95% CI, 0.71–0.78] (Non-manual social class M&F) FRE=0.72 [95% CI, 0.70–0.74] (Manual social class M&F)	Scotland
D'Agostino 2001 <i>Section 2.4.1.1</i>	II	High	FRE=0.75 ARIC (white M) FRE=0.67 ARIC (black M) FRE=0.63 PHS (white M) FRE=0.72 HHP (M) FRE=0.69 PRHHP (M) FRE=0.69 SHS (M) FRE=0.63 CHS (white M) FRE=0.83 ARIC (white F) FRE=0.79 ARIC (black F) FRE=0.75 SHS (F) FRE=0.66 CHS (white F)	USA
DPCG <i>Section 2.4.1.1</i>	II	High	FRE=0.73 NHANES I (M) FRE=0.77 NHANES II (M) FRE=0.81 Tecumseh (M) FRE=0.78 HHP (M) FRE=0.75 PRHHP (Urban) (M) FRE=0.77 PRHHP (Rural) (M) FRE=0.82 YU (M) FRE=0.76 YR (M) FRE=0.73 SCS (M) FRE=0.68 Renfrew (M) FRE=0.79 Israel IHD (M) FRE=0.77 GPS (M) FRE=0.72 NCS (M) FRE=0.75 RIS (M) FRE=0.81 LRC Random (M) FRE=0.77 LRC Hyperlip (M) FRE=0.72 HDFP RC (M) FRE=0.65 Mrfit UC (M) FRE=0.82 NHANES I (F) FRE=0.78 NHANES II (F) FRE=0.88 Tecumseh (F) FRE=0.74 Renfrew (F) FRE=0.82 NCS (F) FRE=0.80 Iceland (F) FRE=0.77 HDFP RC (F)	USA, Middle East, Europe, Asia and the Caribbean
Hense 2003 <i>Section 2.4.1.2</i>	III-2	Low	FRE=0.78 [95% CI 0.73, 0.84] (M MONICA cohort) FRE=0.73 [95% CI 0.70, 0.75] (M PROCAM cohort)	Germany

			FRE=0.88 [95% CI 0.80, 0.96] (F MONICA cohort) FRE=0.77 [95% CI 0.69, 0.85] (F PROCAM cohort)	
Liao 1999 <i>Section 2.4.1.2</i>	III–2	Low	FRE=0.71 (M NI cohort) FRE=0.74 (M NII cohort) FRE=0.80 (F NI cohort) FRE=0.76 (F NII cohort)	USA
Liu 2004 <i>Section 2.4.1.2</i>	II	High	FRE=0.705 [95%CI 0.665, 0.746] (M) FRE=0.742 [95%CI 0.686, 0.798] (F)	China
Milne 2003 <i>Section 2.4.1.1</i>	II	High	AUCs not reported	New Zealand
Simons 2003 <i>Section 2.4.1.2</i>	II	High	AUCs not reported	Australia
Suka 2001 <i>Section 2.4.1.1</i>	III–2	Low	(1) FRE=0.62 (M) (2) FRE=0.71 (M)	Japan
WOSCOPS 1998 <i>Section 2.4.1.1</i>	II	High	AUCs not reported	Scotland
Zanchetti 2001 <i>Section 2.4.1.1</i>	III–2	Low	AUCs not reported	Europe, USA, Canada, Latin America and Asia
Zhang 2005 <i>Section 2.4.1.2</i>	II	High	Oriental RS=0.76 (CHD) Oriental RS=0.78 (ischaemic stroke) Oriental RS=0.82 (haemorrhagic stroke)	China

(M) Males, (F) Females. Where AUCs are not reported, refer to original data in **appendix I**.

FRE, Framingham risk equation; ARIC, Atherosclerosis Risk in Communities Study; PHS, Physicians' Health Study; HHP, Honolulu Heart Program; PRHHP, Puerto Rico Heart Health Program; SHS, Strong Heart Study; CHS, Cardiovascular Health Study; NHANES I, First National Health & Nutrition Examination Survey; NHANES II, Second National Health & Nutrition Examination Survey; Tecumseh, Tecumseh Community Health Study; PRHHP Urban, Puerto Rico Heart Health Program; PRHHP Rural, Puerto Rico Heart Health Program; YU, Yugoslavia Cardiovascular Disease Study (Urban); YR, Yugoslavia Cardiovascular Disease Study (Rural); SCS, Scottish Collaborative Study; Renfrew, Renfrew and Paisley Study; Israel IHD, Israeli Ischemic Heart Disease Study; GPS, Glostrup Population Study; NCS, Norwegian Counties Study; RIS, Reykjavik Iceland Study; LRC Random, Lipid Research Clinics Prevalence Study; LRC Hyperlip, Lipid Research Clinics Prevalence Study; HDFP RC, Hypertension Detection and Follow-up Program (control group); Mrfit UC, Multiple Risk Factor Intervention Trial (control group); PROCAM, Prospective Cardiovascular Münster Study; MONICA, Multinational Monitoring of Trends and Determinants in Cardiovascular Disease; Oriental RS, Oriental risk score.

2.4.1 Results

2.4.1.1 4–8 year Framingham risk equation

A high-quality study with very low risk of bias (*D'Agostino 2001*) [19] was conducted in a large cohort comprising 32,886 male and female participants with an overall age range of 30–88 years. This study assessed the ability of the FRE to predict CVD risk in six ethnically diverse populations: 1) ARIC – Atherosclerosis Risk in Communities Study in black and white populations; 2) PHS – Physicians' Health Study in males with higher than average socioeconomic status; 3) HHP – Honolulu Heart Program in Japanese American males; 4) PRHHP – Puerto Rico Heart Health Program in Hispanic males; 5) SHS – Strong Heart Study in Native Americans; 6) CHS – Cardiovascular Health Study in older adults. CVD outcomes included MI (including silent), cardiac procedures, CHD events, morbidity and mortality.

II

The authors reported FRE AUCs separately for each population. In ARIC the AUCs were 0.75 and 0.83 for white males and females, respectively, and 0.67 and 0.79 for black males and females respectively for prediction of risk over 7.2 years. In PHS males with higher than average socioeconomic status, the AUC was 0.63 for prediction of risk over 5 years. In HHP Japanese American males, the AUC was 0.72 for prediction of risk over 5 years. In PRHHP Hispanic males, the AUC was 0.69 for prediction of risk over 5 years. In SHS Native American males and females, the AUCs were 0.69 and 0.75 respectively for prediction of risk over 5 years. In CHS older males and females, the AUCs were 0.63 and 0.66 for prediction of risk over 5 years. Confidence intervals were not provided. Observed and predicted rates were presented graphically.

The authors concluded that there was considerable variation in the age ranges for individual studies that may have affected the resulting AUCs.

This evidence suggests that in white and black males and females, predicted events using the FRE and observed event rates were similar for 5 year CVD risk; however, among Japanese American and Hispanic males, and Native American females, the FRE overestimates 5 year CVD risk.

A high-quality study with very low risk of bias (*DPCG 2002*) [20] was conducted in 161,955 male and female participants from 18 cohorts of different ethnicities with an overall age range of 35–74 years. This study assessed the ability of the FRE to predict CVD risk over 8 years in 18 populations of different ethnicities: 1) NHANES I – First National Health & Nutrition Examination Survey; 2) NHANES II – Second National Health & Nutrition Examination Survey; 3) Tecumseh Community Health Study; 4) HHP – Honolulu Heart Program; 5) PRHHP Urban – Puerto Rico Heart Health Program; 6) PRHHP Rural – Puerto Rico Heart Health Program; 7) YU – Yugoslavia Cardiovascular Disease Study (Urban); 8) YR – Yugoslavia Cardiovascular Disease Study (Rural); 9) SCS – Scottish Collaborative Study; 10) Renfrew – Renfrew and Paisley Study; 11) Israel IHD – Israeli Ischemic Heart Disease Study; 12) GPS – Glostrup Population Study; 13) NCS – Norwegian Counties Study; 14) RIS – Reykjavik Iceland Study; 15) LRC Random – Lipid Research Clinics Prevalence Study; 16) LRC Hyperlip – Lipid Research Clinics Prevalence Study; 17) HDFP RC – Hypertension Detection and Follow-up Program (control group); 18) Mrfit UC – Multiple Risk Factor Intervention Trial (control group). The CVD outcome was CHD death.

The authors reported FRE AUCs separately for each population. In the NHANES I cohort, the AUCs were 0.73 and 0.82 for males and females respectively, and 0.77 and 0.78 for males and females respectively in the NHANES II cohort. In Tecumseh the AUCs were 0.81 and 0.88, in Renfrew the AUCs were 0.68 and 0.74, in NCS the AUCs were 0.72 and 0.82, in RIS the AUCs were 0.75 and 0.80, and in HDFP RC the AUCs were 0.72 and 0.77 for males and females respectively. In HHP males, the AUC was 0.78, in PRHHP Urban males, the AUC was 0.75, while in PRHHP Rural males the AUC was 0.77. In YU males, the AUC was 0.82 while in YU males, the AUC was 0.76. In SCS males the AUC was 0.73, in Israeli IHD males the AUC was 0.79, in GPS males the AUC was 0.76, and in Mrfit UC males the AUC was 0.65. In LRC Random males the AUC was 0.81, whereas in LRC Hyperlip males the AUC was 0.77. Confidence intervals were not provided. Observed and predicted rates were presented graphically.

The authors concluded that in males, FRE tended to overestimate absolute risk in populations with a low observed CHD mortality and to underestimate risk in populations

with a high CHD mortality. In females, FRE underestimated 8 year CHD mortality in five cohorts.



This evidence suggests that in males, the FRE overestimates 8 year CVD risk in populations with a low observed CHD mortality and underestimates risk in populations with a high CHD mortality; whereas in females, the FRE underestimates 8 year CVD risk in five cohorts.

The West of Scotland Coronary Prevention Study (*WOSCOPS 1998*) [21], comprised 3293 male participants aged 45–64 years and is of high quality with very low risk of bias. CVD outcomes included non-fatal MI or CHD death plus revascularisation (PTCA or CABG). It should be noted that participants with cancer were excluded from this study. To assess the ability of the FRE to predict 4.4 year risk, participants were divided into two groups: in group A, participants were included according to strict plasma lipid restrictions matching those of the FRE; in group B, these strict restrictions on plasma lipids were removed. When the FRE was applied to group A, the predicted risk and observed event rates (per 100 participants) for a CVD outcome were 7.6 and 7.0 respectively. In group B, the predicted event rate per 100 participants was 8.5 and the observed event rate per 100 participants was 8.3.



This evidence suggests that predicted events using the FRE and observed event rates are similar for 4.4 year CVD risk in this population.

A New Zealand-based follow-up study (*Milne 2003*) [22] was conducted in a cohort of 6354 male and female participants aged 35–74 years to assess the ability of the FRE to predict 5 year risk. CVD outcomes included IHD, cerebrovascular disease, CHF, PVD or IC. Further information about this study and data are reported at 2.2.1.1 *FRE versus New Zealand risk chart*. The data were presented graphically. When using FRE in males and females, the number of observed events were very close to the predicted number of events in all age groups except females aged 70–74 years. Similar findings were reported when male and female data were combined.



This evidence suggests that predicted events using the FRE and observed event rates are similar for 5 year CVD risk in this population.

Bastuji-Garin et al (*Bastuji-Garin 2002*) [23] conducted a study in a cohort covering eight countries in Western Europe and Israel. CVD outcomes included fatal and non-fatal MI, cardiovascular death, AP, fatal and non-fatal stroke, transient ischaemic attack, subarachnoid haemorrhage, fatal and non-fatal heart failure and cerebrovascular death. This low-quality study with a high risk of bias comprised 4147 male and female participants, less than 75 years of age (mean age 64.1 ± 1.6 years) with hypertension. It is important to note that in this study, the follow-up period of 3.7 years is below the lower limit of the FRE validation of 4 years. The results showed that the FRE overestimated the risk in these populations. The number of predicted CHD events was approximately double the number of observed events for all countries with the exception of France, where events were



overpredicted by a factor of 4.0. The FRE did not overestimate the risk of stroke. No statistically significant differences between countries were established.

This evidence suggests that the FRE overestimates CVD risk in all countries in this study with the exception of France, where the FRE underestimates CVD risk. The short follow-up time of 3.7 years and the extremely low event rates within this study make interpretation of the results difficult and raise doubt over the study conclusions and generalisability.

A follow-up study (*Suka 2001*) [24] assessed the ability of the FRE in a Japanese population. The study was conducted in a cohort of 5611 males aged 30–59 years. This study was of low quality with a high risk of bias. The study did not include female participants and lacked sufficient description of the methodology to critique the recommended quality criteria. Furthermore, the FRE was used to predict 10 year risk, but follow-up continued for only 5–7 years. This is likely to result in an underestimate of the ability of the FRE. Two studies report analyses of data from this cohort. The first study [24] defined CVD outcomes as CHD, MI or AP. The AUC for the FRE in this study was 0.62. At 15% cut-off the sensitivity was 0.57 and the specificity was 0.72. Observed and predicted rates were presented graphically and FRE appears to overestimate risk. The second study [24] widened the definition of CVD outcomes to include coronary insufficiency. The AUC for the FRE in this study was 0.71. At 15% cut-off the sensitivity was 0.59 and the specificity was 0.74.

III–2

While this evidence suggests that the FRE may overestimate CVD risk in this population, these results should be interpreted with caution because follow-up was not continued for the appropriate length of time.

A study (*Zanchetti 2001*) [25] of low quality with a high risk of bias was conducted in a large cohort comprising 14,995 male and female hypertensive participants, aged over 55 years, from Europe, USA, Canada, Latin America and Asia. CVD outcomes included fatal and non-fatal MI, all fatal and non-fatal stroke and any other CVD death. Participants, who were on blood pressure lowering therapy, were divided into risk category groups and followed for a total of 71,051 patient-years, equivalent to a mean follow-up of 3.78 years per participant, which is below the lower limit of the FRE validation of 4 years. Participants allocated to the medium and high-risk groups had no prior CVD history and therefore are included in this analysis. In these groups, the authors assessed the ability of the FRE and the WHO/ISH guidelines risk score; however, the predictive ability of these two methods cannot be compared to each other because the reference standard for each was different. Both methods overestimated the risk in this study.

III–2

When the FRE was applied in the medium-risk group, the predicted risk and observed rates (per 1000 patient-years) of myocardial infarction and stroke were 16 and 5 respectively, while in the high-risk group, the predicted risk and observed rates (per 1000 patient-years) of MI and stroke were 18 and 6.6.

When the WHO/ISH guidelines risk score was applied in the medium-risk group, the predicted risk and observed rates (per 1000 patient-years) of all major cardiovascular events were 15–20 and 6.4 respectively, while in the high-risk group, the predicted risk and

observed rates (per 1000 patient-years) of all major cardiovascular events were 20–30 and 9.1.

This evidence suggests that both the FRE and the WHO/ISH risk score overestimate CVD risk in the medium and high-risk groups. It is unclear if overestimation results from inaccuracy of the absolute risk assessment methods or effect of treatment.

2.4.1.2 10–15 year Framingham risk equation

Simons et al (*Simons 2003*) [26] conducted a high-quality cohort study with very low risk of bias comprising 1800 elderly (60–79 years of age) male and female Australian participants residing in the semi-urban town of Dubbo, NSW. CVD outcomes included MI, CD or stroke. To assess the ability of the FRE to predict 10 year risk in this cohort, participants were divided into groups by gender and age: 60–64, 65–69, 70–74 and 75–79.

In males aged 60–64 years, the predicted and observed CVD incidence rates per 100 subjects were 11.9 and 10.3 respectively, while in males aged 65–69 years, the predicted and observed CVD incidence rates per 100 subjects were 16.5 and 13.6 respectively. In males aged 70–74 years, the predicted and observed CVD incidence rates per 100 subjects were 16.5 and 16.8 respectively, and in males aged 75–79 years, the predicted and observed CVD incidence rates per 100 subjects were 22.1 and 23.3 respectively.

Similar results were observed in females, where at 60–64 years, the predicted and observed CVD incidence rates per 100 subjects were 4.6 and 4.9 respectively; at 65–69 years, the predicted and observed CVD incidence rates per 100 subjects were 9.0 and 7.6 respectively; at 70–74 years, the predicted and observed CVD incidence rates per 100 subjects were 10.7 and 11.1 respectively; and at 75–79 years, the predicted and observed CVD incidence rates per 100 subjects were 18.2 and 14.6 respectively. The authors conclude that FRE accurately predicts 10 year incidence of CVD in males and females aged 60–79 years who are free of CVD and diabetes.

This evidence suggests that predicted events using the FRE and observed event rates are similar for 10 year CVD risk in this population.

In a follow-up study by Assmann (*Assmann 2002*) and colleagues [27], the ability of the FRE to predict 10 year risk was assessed in the Prospective Cardiovascular Münster (PROCAM) study cohort. This German cohort comprised 5389 males, aged 35–65 years. CVD outcomes included sudden CD or a definite fatal or non-fatal MI on the basis of ECG and/or cardiac enzyme changes. High in quality with a very low risk of bias, this study found that the FRE significantly overestimated 10 year risk in this cohort and has an AUC of 0.78.

This evidence suggests that the FRE overestimates 10 year CVD risk in this population.

In a high-quality follow-up study with very low risk of bias, Brindle et al (*Brindle 2003*) [28] assessed the ability of the FRE in the British Regional Heart Study cohort in the UK. The cohort comprised 6643 males aged 40–59 years. CVD outcomes included CHD death, MI or angina. Sensitivity and specificity analyses were performed at particular cut-off points. At 30% 10 year CHD event risk, the FRE has low sensitivity (16%) but high specificity (94%). At 15% 10 year CHD event risk, the FRE has a sensitivity and specificity of 75% and 55% respectively. Similar estimates were reported for risk of CHD death.

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In the same study, predicted and observed CHD event and CHD death rates were reported. In the whole study population, 270 CHD deaths were predicted, but only 183 were observed, an overprediction of 47% ($p < 0.0001$); 1062 CHD events were predicted, but only 677 were observed, an overprediction of 57% ($p < 0.0001$).

This evidence suggests that the FRE overestimates 10 year CVD risk in this population.

In a separate study, Brindle et al (*Brindle 2005*) [29] assessed the ability of the FRE to predict 10 year risk when applied to individuals of different area deprivation and social class in the west of Scotland. CVD outcomes included CVD and CHD deaths. This high-quality study with very low risk of bias comprised 12,304 participants of both genders, aged 45–64 years. These results were independent of gender. The overall AUC was 0.73 [95%CI, 0.72–0.75], while the AUC for the non-manual and manual employment sub-cohorts were 0.74 [95%CI, 0.71–0.78] and 0.72 [95%CI, 0.70–0.74] respectively. When the FRE was applied to the overall cohort, the predicted and observed event rates were 3.3 and 5.9. When applied to the non-manual cohort, the predicted and observed event rates were 2.9 and 4.2, and the manual cohort predicted and observed event rates 3.6 and 7.0. The study found that the FRE significantly underestimated the risk in all participants, and particularly socioeconomically deprived individuals. The authors also report a range of sensitivities and specificities; these can be found in **appendix I**.

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This evidence suggests that the FRE underestimates 10 year CVD risk in this population, and more so in socioeconomically deprived individuals.

A large follow-up study (*Liu 2004*) [30] assessed the ability of the FRE to predict 10 year CVD risk in a Chinese population. CVD outcomes included CD and MI. This high-quality study with very low risk of bias was conducted in a cohort of 30,121 males and females aged 35–64 years from a Chinese multi-provincial adult population. Closure of some of the study centres midway through the study led to the loss of 11,451 participants, allowing follow-up of only 63% of the original cohort. The AUC for the FRE was 0.71 [95%CI 0.67, 0.75] for males, and 0.74 [95%CI 0.69, 0.80] for females. Observed and predicted rates were presented graphically. The FRE substantially overestimated CVD risk in all deciles of risk within the Chinese Multi-Provincial Cohort Study.

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This evidence suggests that the FRE overestimates 10 year CVD risk in this population.

A study (*Hense 2003*) [31] of low quality and high risk of bias assessed the ability of the FRE in two German cohorts: Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA), comprising 5786 males and females aged 35–64 years (the first cohort was recruited in 1984, the second in 1989); and the Prospective Cardiovascular Münster Study (PROCAM), comprising 8682 males and females aged 16–65 years. CVD outcomes included non-fatal MI and fatal coronary events. In the MONICA cohort, the AUCs for the FRE to predict over a median follow-up time of 7.8–13.2 year risk were 0.78 and 0.88 for males and females respectively. In the PROCAM cohort, the AUCs for the FRE to predict 11 year risk were 0.73 for males and 0.77 for females. The authors also reported a range of predicted and observed event rates; these can be found in **appendix I**.

This evidence suggests that the FRE overestimates 11 year CVD risk in both the MONICA and PROCAM cohorts.

A study (*Liao 1999*) [32] of low quality and high risk of bias assessed the ability of the FRE to predict 15 year risk in two US cohorts: the first and second National Health and Nutrition Examination Survey (NHANES I and NHANES II). NHANES I comprised 6611 males and females aged 35–69 years; NHANES II included 5705 males and females, aged 35–69 years. The CVD outcome was CHD death. In the NHANES I cohort, the AUCs for the FRE were 0.71 and 0.80 for males and females respectively. In the NHANES II cohort, the AUCs for the FRE were 0.74 for males and 0.76 for females.

In the same study, sensitivity and specificity analyses were performed. In the NHANES I cohort, the FRE had higher sensitivity in males and females (67% and 83%) at a lower specificity cut-off point of 33%. Similarly, in the NHANES II cohort, the FRE had higher sensitivity in males and females (71% and 77%) at a lower specificity cut-off point of 33%. In the NHANES I cohort, the predicted and observed event rates were 11.6 and 10.4 respectively; in the NHANES II cohort the predicted and observed event rates were 11.4 and 7.4 respectively.

This evidence suggests that the FRE overestimates 15 year CVD risk in both the NHANES I and NHANES II cohorts.

2.4.1.3 *Oriental specific decision rule*

A follow-up study (*Zhang 2005*) [33] was conducted in a cohort of 4400 male participants over 35 years of age sampled from the Beijing Iron and Steel Complex, China. CVD outcomes included fatal and non-fatal CHD and fatal and non-fatal stroke. The authors caution that this small cohort may not be representative of the Chinese population. This high-quality study with very low risk of bias assessed the predictive ability of the European Task Force Recommendations risk score in the entire cohort and the Oriental specific decision rule in 1400 participants within the cohort. Since the two methods are not assessed in the same participants, we are unable to compare the two methods. This study

found that the Oriental specific decision rule had an AUC of 0.76 and the European Task Force Recommendations risk score had an AUC of 0.71 when used to predict 13.5 and 10 year CHD risk respectively. Using the Oriental specific decision rule, the AUCs for 13.5 year risk of ischaemic stroke and haemorrhagic stroke were 0.78 and 0.82 respectively. There were no statistically significant differences between predicted and observed event rates when the Oriental specific decision rule was used to predict 13.5 year risk. However, the European Task Force Recommendations risk score overestimated 10 year risk.

This evidence suggests that predicted events using the Oriental specific decision rule and observed event rates are similar for 13.5 year CVD risk in this population. However, the European Task Force Recommendations risk score overestimates 10 year risk in this population.

In summary, the most thoroughly tested absolute risk assessment method in adults not known to have either diabetes or CVD is the FRE. The identified studies that have assessed the predictive ability of absolute risk assessment methods in different geographical populations (14 studies) report different CVD risk prediction abilities.

2.5 Recommendations

The most thoroughly tested absolute risk assessment method in adults not known to have either diabetes or CVD is the FRE. All of the identified studies that have directly compared the FRE to other absolute risk assessment methods (8 studies) report that it has equivalent or higher predictive ability than other methods for 5, 7–8, 10, 12 and 20 year CVD risk prediction.

One study compared the predictive ability of the FRE over 10 or 20 years and showed that risk prediction was more accurate when the FRE was used to predict risk over 10 years rather than 20 years. No studies were identified which compared the predictive ability of the FRE over 5 years with risk prediction over other time periods. Given that 10 year risk prediction has been shown to be more accurate than 20 year risk prediction, 10 year risk prediction should be used in preference to 20 year risk prediction; however, in the absence of comparative evidence of the predictive ability of the FRE over 5 and 10 years, either time period may be used.

Given the limited testing of other absolute risk assessment methods in adults not known to have either diabetes or CVD, and in light of the fact that FRE is as accurate or more accurate than all methods with which it has been compared in this population, and in the interest of providing a single, clear recommendation, it was agreed that:

B In adults not known to have CVD or diabetes use the FRE to predict absolute cardiovascular risk over 5 or 10 years.

The FRE has been validated in populations including people aged from 25 to 88 years old [12, 19].

3 Predictive ability of absolute CVD risk assessment methods in Aboriginal and Torres Strait Islander adults without known CVD

Chapter overview

Search results:

- One high-quality study in a population of Aboriginal and Torres Strait Islander people examined the predictive ability of absolute risk assessment methods [38].
- The Framingham risk equation substantially underestimated absolute CVD risk.

Recommendation:

No evidence-based recommendation made.

3.1 Background

This section has been informed by the National Aboriginal Community Controlled Health Organisation (NACCHO) National guide to a preventive health assessment in Aboriginal and Torres Strait Islanders [34], published and endorsed by the Royal Australian College of General Practitioners (RACGP), and a related background document [35].

Aboriginal and Torres Strait Islander peoples have a high prevalence of risk factors for heart, stroke and vascular disease. They also have an exceedingly high age-standardised mortality that has not shown the downward trend seen in the rest of the Australian community over the past 40 years. In 2001–2002 death rates from heart, stroke and vascular disease for all Indigenous populations were 2.6 times higher compared to other Australians. Aboriginal and Torres Strait Islander people experience excess morbidity and mortality at a younger age compared to the wider Australian population. A total of 62% of heart, stroke and vascular deaths occur before age 65 years in Indigenous Australians, while only 10% occur by this age in the wider Australian population [36]. This contributes to the much shorter expected life span of Aboriginal and Torres Strait Islanders compared to other Australians. Male Aboriginal and Torres Strait Islanders born between 1998 and 2003 can expect to live an average of 56 years, which is 21 years less than other Australians, while females of this generation have a life expectation of 62.7 years – 19 years less than that of other Australian women [37].

3.2 Results

Our search identified one high-quality study with very low risk of bias examining the predictive ability of an absolute risk method in adult Aboriginal and Torres Strait Islander people not known to have CVD.

Wang et al (*Wang 2005*) [38] conducted a study to assess the ability of the FRE to predict risk over individualised follow-up times in an Australian Aboriginal community in the Northern Territory. CVD outcomes included MI, AP and other IHD. The study was of high quality with very low risk of bias and included a cohort comprising 687 Australian Aboriginal



males and females aged 20–74 years. The authors note that the population had a very high incidence of chronic renal disease. Inadequate data were reported with respect to sensitivity and specificity. The observed incidence rate for the whole study sample was 11.0 (95% CI 8.7, 13.9) per 1000 person-years and was 2.5 times the predicted rate of 4.4 (no CI given) per 1000 person-years. The authors concluded that the FRE underestimated CVD risk in this population.

3.3 Recommendations

Given that there is only one study assessing the predictive ability of an absolute CVD risk assessment method in this population, that the sample size in this study is small and that the FRE underestimates risk in this population, we are unable to make an evidence-based recommendation about the most appropriate risk assessment method for Aboriginal and Torres Strait Islander people.

Caution needs to be exercised in applying general absolute risk assessment methods to Aboriginal and Torres Strait Islander clients because these are likely to significantly underestimate risk in these people.

The FREs were derived from observations in the largely Caucasian population of Framingham, Massachusetts, USA. Initiatives to validate these equations in Australia have relied on the use of cohorts (Busselton) which included few, if any, Aboriginal or Torres Strait Islander people.

Given that age is the major driver of the FRE for estimating absolute coronary and cardiovascular risk, the different age-distribution of CVD events and the lowered life expectancy of Aboriginal and Torres Strait Islander people is likely to affect the applicability of Framingham-derived risk estimates to these populations.

There are factors that contribute significantly to CVD risk that are not included in the Framingham score. Many of these factors are more prevalent in Australian Aboriginal and Torres Strait Islander populations than in Framingham-like populations, such as obesity (BMI > 30 kg/m²) and/or high-risk waist circumference, insulin resistance (impaired fasting glucose, impaired glucose tolerance) and/or kidney impairment (proteinuria, chronic kidney disease).

In considering this issue, NACCHO's National Guide to a preventive health assessment in Aboriginal and Torres Strait Islanders [39] endorsed by the RACGP recommends that:

“If conventional CVD risk assessment tables (e.g. the FRE) are used to ascertain an individual's CVD risk score in Aboriginal and Torres Strait Islander clients, the following corrections should be considered:

- tables can be used from age 35 years
- tables for females may not apply to Aboriginal women

adjust the CVD risk upwards, clinical judgment is required to estimate the incremental CVD risk incurred.”

4 Predictive ability of absolute CVD risk assessment methods in adults with diabetes but without known CVD

Chapter overview

Search results:

- Two high-quality studies in populations with type 2 diabetes compared the predictive ability of different absolute risk assessment methods [15, 44].
- The Framingham risk equation and United Kingdom Prospective Diabetes Study risk score have similar 10 year predictive ability in mixed gender populations with type 2 diabetes, however both scores underestimate risk [44].
- The addition of non-traditional risk factors to absolute risk assessment may improve predictive ability, however the methods are not yet available [15].

Recommendation:

C

In adults with type 2 diabetes not known to have cardiovascular disease, use the Framingham risk equation to predict absolute cardiovascular risk over 5 or 10 years, with an awareness that it is likely to underestimate risk.

4.1 Background

Extensive evidence indicates that people with diabetes are at high risk for CVD, particularly in the arteries of the coronary, cerebrovascular and peripheral circulations. While sharing some of the same risk factors for their development (particularly hypertension), macrovascular complications occur more frequently than microvascular complications in type 2 diabetes [40]. In addition, both macrovascular and microvascular diseases often occur together in the same person. Indeed, the presence of microvascular disease increases the likelihood of macrovascular disease in type 2 diabetes [41]. In people with diabetes, macrovascular diseases account for about 75% of deaths.

Population strategies to reduce CVD risk factors in the general community, particularly lifestyle and nutritional approaches, may reduce the incidence of both type 2 diabetes and CVD. There is, however, increasing evidence that interventions focused on those at highest risk of CVD are particularly effective in reducing CVD mortality across the population. People with diabetes are at increased risk not only because of the risk inherently associated with diabetes [42] but also because the other risk factors for CVD are commonly found in people with diabetes [42].

Community trends in the burden associated with atherosclerosis in people with diabetes differ from those in people without diabetes. In an 8 year observational follow-up of the first NHANES study cohort, there was a 36.4% decline in age-adjusted CHD mortality in non-diabetic men and only a 13.1% decline in men with diabetes. For women, the situation was even worse, with a decline of 27% in non-diabetic

women, but an increase of 23% in diabetic women [43]. This may mean that the most appropriate method of CVD risk assessment for people with diabetes is different from that recommended for the general population.

4.2 Comparison of different absolute risk assessment methods

Our search identified two relevant studies, both of high quality with low risk of bias, comparing the predictive ability of different absolute CVD risk assessment methods in people with diabetes not known to have CVD. A summary of these studies is provided in table 4.2.1. Detailed descriptions of the evidence are provided in **section 4.2.1**.

Table 4.2.1 Summary of studies comparing the predictive ability of absolute risk assessment methods in different geographical populations of adults with diabetes not known to have CVD

Study	Level of evidence	Quality	AUC data	Location
Folsom 2003 <i>Section 4.2.1.2</i>	II	High	Basic RFs=0.682 (M) Basic RFs+=0.763 (M) Basic RFs=0.709 (F) Basic RFs+=0.776 (F)	USA
Guzder 2005 <i>Section 4.2.1.1</i>	II	High	FRE=0.657 [95% CI, 0.581–0.732] (M&F) UKPDS=0.670 [95% CI, 0.598–0.742] (M&F) FRE=0.726 [95% CI, 0.643–0.810] (M) UKPDS=0.673 [95% CI, 0.585–0.761] (M) FRE=0.697 [95% CI, 0.635–0.760] (F) UKPDS=0.618 [95% CI, 0.491–0.746] (F)	UK

(M) Males, (F) Females. Where AUCs are not reported, refer to original data in **appendix I**.
FRE, Framingham risk equation; UKPDS, United Kingdom Prospective Diabetes Study risk score; RF, risk factor.

4.2.1 Results

4.2.1.1 Framingham risk equation versus UKPDS risk score

A follow-up study (Guzder 2005) [44] of 428 participants of both genders aged 30–64 years with diabetes was conducted within the Poole Type 2 Diabetes Study, covering 24 general practices in the Poole Hospital catchment area of the UK. CVD outcomes included cerebrovascular disease, heart failure and PVD. This high-quality study with very low risk of bias, although a relatively small sample size, found that when the entire cohort was considered, there was no statistically significant difference between the AUCs of the FRE and the United Kingdom Prospective Diabetes Study (UKPDS) risk score (0.66 [95% CI, 0.58–0.73] versus 0.67 [95% CI, 0.60–0.74]). However when genders are considered separately, the FRE had a higher AUC than the UKPDS risk score for predicting 10 year CHD risk in type 2 diabetic participants of both genders (females 0.70 [95% CI, 0.64–0.76] versus 0.62 [95% CI, 0.49–0.75]; males 0.73 [95% CI, 0.64–0.81] versus 0.67 [95% CI, 0.59–0.76], statistical significance not examined due to small sample size). CHD events were underestimated by both methods (FRE 32%, UKPDS 13%, no statistical difference).

In the same study, sensitivity and specificity analyses were performed at particular cut-off points. At 30% 10 year CHD risk and TC >5 mmol/L, the Framingham and UKPDS risk scores have low sensitivity (29.6 [95% CI, 22.2–37.2] and 50.0 [95% CI, 39.7–60.3]), but the FRE has higher specificity (88.5 [95% CI, 86.3–90.7] versus 69.1 [95% CI, 63.8–74.0]).

At 15% 10 year CHD risk and TC >5 mmol/L, both the Framingham and UKPDS risk scores have higher sensitivity (72.4 [95% CI, 63.5–80.2] and 76.5 [95% CI, 66.9–84.5]) and lower specificity (45.2 [95% CI, 42.5–47.5] and 46.4 [95% CI, 40.9–51.9]). At 15% 10 year CHD risk without TC >5 mmol/L, both the Framingham and UKPDS risk score have higher sensitivity (85.7 [95% CI, 77.8–91.5] and 89.8 [95% CI, 82.0–95.0]) and lower specificity (33.0 [95% CI, 30.7–34.7] and 30.3 [95% CI, 25.4–35.6]). Statistical significance of these comparisons was not reported.

It is difficult to interpret this evidence given conflicting results between gender sub-group and whole group analysis. Further research into the nature of this difference is required.

This evidence suggests that the FRE and the UKPDS risk score have similar 10 year predictive ability when applied to mixed-gender populations. However, both methods underestimate 10 year CVD risk in people with diabetes.

4.2.1.2 Traditional versus non-traditional risk factors

A follow-up study (*Folsom 2003*) [15] was conducted in a cohort of 1237 participants of both genders with diabetes aged 45–64 years sampled from the Atherosclerosis Risk in Communities (ARIC) study covering North Carolina, Mississippi, Minnesota and Maryland in the US. CVD outcomes included a validated definite or probable hospitalised MI, a definite CHD death, an unrecognised MI defined by ARIC ECG readings, or coronary revascularisation. This high-quality study with very low risk of bias compared basic traditional CVD risk factors (for example, age, race, TC, HDL, SBP etc) with a combination of basic traditional CVD risk factors and non-traditional CVD risk factors such as BMI, WHR, lipoprotein(a), albumin, creatinine, WBC count, fibrinogen, factor VIII, sport activity index, Keys score, LVH and IMT (continuous). The way in which these risk factors were combined to obtain a score was not described; we have contacted the authors for further details. This study found that the combination of basic traditional CVD risk factors and non-traditional CVD risk factors had a higher AUC than basic traditional CVD risk factors when used to predict 10 year CVD risk (females 0.78 versus 0.71; males 0.76 versus 0.68, $p < 0.05$) in patients with diabetes. Predicted and observed event rates were not reported in this study.

This evidence suggests that assessment of non-traditional risk factors in combination with traditional risk factors is more accurate than traditional risk factors alone in people with diabetes.

4.3 Recommendations

There is very limited evidence on which to make a recommendation about absolute risk assessment in adults who have diabetes. One study has shown that FRE is as accurate as the UKPDS risk score, the only method with which it has been compared in this population; however, both methods underestimate CVD risk. The addition of non-traditional risk factors to traditional risk factors has been shown to be more accurate than assessment based on traditional risk factors alone, however the methods of combining the risk factors to develop a score are not currently available.

In light of this and in the interest of providing a single, clear recommendation in line with recommendations for the population not known to have diabetes, it was agreed that:

C In adults with type 2 diabetes not known to have CVD, use the FRE to predict absolute cardiovascular risk over 5 or 10 years, with an awareness that it is likely to underestimate risk.

However, caution should be exercised in applying the FRE to people with diabetes since the applicability of the FRE to predict CVD in people with diabetes has been questioned because of the low prevalence of diabetes in the Framingham study and other data [45].

5 Predictive ability of absolute CVD risk assessment methods in adults who are overweight or obese but without known CVD

Chapter overview

Search results:

No studies identified.

Recommendation:

No evidence-based recommendation made.

5.1 Background

Australian data on the relationship between overweight and obesity and heart, stroke and vascular diseases are limited. However, the results of a cross-sectional cohort study were published, linking data obtained from over 9000 Australian adults in the National Heart Foundation of Australia 1989 Australian Risk Factor Prevalence Study with the National Death Index to determine causes of death of the 473 survey subjects who had died before the end of 2000. This multivariate analysis concluded that obesity (in this study best measured by waist-to-hip ratio) is a dominant and independent predictive variable for CVD events and CVD deaths in Australian men and women [46]. The relationship between overweight or obesity and stroke (both ischaemic and haemorrhagic) is less clear. As indicated by the results of the review, the relationships are complex and several points of caution need to be made. These relate to the variability of associations, a relative lack of outcome data, limited Australian data, and chronic under-representation of certain groups in the relevant research, in particular 'at risk' populations.

Despite these uncertainties, the attributable burdens of obesity and overweight in relation to disability-adjusted life years (DALYs) for IHD, ischaemic stroke, hypertension and diabetes have been estimated for Australia. Around 4.3% of DALYs (from any cause) were attributed to overweight and obesity [47].

The rate of overweight and obesity is increasing in prevalence throughout all segments of the population. Since 1980, the rate of obesity has doubled [48]. The 1999–2000 Australian Diabetes, Obesity and Lifestyle Study [49] estimated that 2.6 million Australians aged 25 years and over were obese (21% of the population) and 7.5 million Australians aged 25 years and over were overweight (60% of the population) [49].

5.2 Results and recommendations

As our search did not identify any studies examining the predictive ability of an absolute risk method in people who are overweight or obese and not known to have CVD, we are unable to make an evidence-based recommendation about the most appropriate risk assessment method for this population.

6 Predictive ability of absolute CVD risk assessment methods in adults with chronic kidney disease but without known CVD

Chapter overview

Search results:

- Given that there is only one low-quality study assessing the predictive ability of an absolute CVD risk assessment method in this population, that the sample size in this study is small and that the Framingham risk equation is a poor predictor in this population, we are unable to make an evidence-based recommendation about the most appropriate risk assessment method for people with chronic kidney disease [52].

Recommendation:

No evidence-based recommendation made.

6.1 Background

Chronic kidney disease (CKD) is marked by long term and usually irreversible loss of kidney function. CKD is indicated by the presence of albumin protein in the urine, termed albuminuria, or by glomerular filtration rate (GFR), where $GFR < 60 \text{ mL/min/1.73 m}^2$ indicates CKD (see table 6.1.1) [50]. For people who develop CKD, treatment is expensive and requires intensive health services [50]. Cardiovascular disease is a major cause of morbidity and mortality in patients with end-stage kidney disease [51] [52], and the disease burden is significant in even the more moderate degrees of CKD [53] [54]. There is no information on the prevalence of different causes of CKD in general in Australia; however there are data on the prevalence of impaired kidney function. In Australia, it is estimated that the prevalence of impaired kidney function in the adult population is 11% [55] and among adults with impaired kidney function, 29.4% have CVD. Hypertension and type 2 diabetes are three times more frequent while hyperlipidaemia is nearly twice as frequent in people with impaired kidney function [56]. Kidney disease is particularly prevalent in Indigenous Australians – the average current incidence of treated end-stage kidney disease exceeds 1500 per million, and the age-adjusted rate is more than 20 times that of non-Aboriginal Australians [57] [58].

Table 6.1.1 Definitions of CKD stages

Stage 1: Kidney damage with GFR at least 90 mL/min/1.73 m²
People with stage 1 CKD have evidence of kidney damage (structural or functional abnormalities of the kidney), but without decreased GFR. There are usually no symptoms.
Stage 2: Kidney damage with GFR 60–89 mL/min/1.73 m²
People with stage 2 CKD have evidence of kidney damage with some reduction in GFR. Most patients at this stage have no symptoms. They usually have high blood pressure and may have laboratory abnormalities indicating dysfunction in other organs.
Stage 3: GFR 30–59 mL/min/1.73 m²*
People with stage 3 CKD have a significant reduction in GFR. They may or may not show other signs of kidney damage. Blood tests will show increased levels of urea and creatinine, and often there will be indications of dysfunction in other organs. Although patients may have symptoms, they often remain

asymptomatic even though their kidney function may be reduced by as much as 70%.
Stage 4: GFR 15–29 mL/min/1.73 m²*
People with stage 4 CKD have severely reduced kidney function. Blood levels of urea and creatinine increase, and there is greater evidence of dysfunction in other organs. Patients usually have only mild symptoms.
Stage 5: GFR less than 15 mL/min/1.73 m²*
In most cases, stage 5 CKD is marked by a range of symptoms and laboratory abnormalities in several organ systems, which are collectively referred to as uraemia. Patients at this stage may need to be prepared for kidney replacement therapy (dialysis or transplant), which will be required when kidney function is no longer sufficient to sustain life.

* with or without evidence of kidney damage

Source: Adapted from Obrador & Pereira 2002 in [50].

6.2 Results

Our search identified one low-quality study with a high risk of bias examining the predictive ability of an absolute risk method in adults with CKD, not known to have CVD.

A study of low quality and high risk of bias was conducted by Massy et al (*Massy 2005*) [52] to assess the ability of the FRE to predict risk over individualised follow-up times in a cohort of older adults with CKD stage 2–4. Mean duration of follow-up was 7.4 years. Participants were defined as having CKD by a creatinine clearance of 20–70 mL/min. The average age of this small cohort of 96 males and females was 65.3 years. CVD outcomes included fatal or non-fatal MI with or without revascularisation. Sensitivity and specificity analyses were performed at a risk cut-off point of 20%. At this cut-off the FRE had low sensitivity (24%) but high specificity (89%). In the same study, the participant’s data were divided into two groups: those that had an observed event and those that did not have an observed event over the duration of follow-up. The predicted median risks for these groups were 10.3% and 7.1% respectively. The authors concluded that the FRE was a poor predictor of CHD risk in people with CKD stage 2–4.



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6.3 Recommendations

Given that there is only one low-quality study assessing the predictive ability of an absolute CVD risk assessment method in this population, that the sample size in this study is small and that the FRE is a poor predictor in this population, we are unable to make an evidence-based recommendation about the most appropriate risk assessment method for people with CKD.

7 Effectiveness, cost effectiveness and economic implications of absolute CVD risk assessment

Chapter overview

Search results:

- There is no direct evidence to assess whether absolute CVD risk assessment leads to improved CVD outcomes or which risk assessment method is most effective in leading to improved CVD outcomes.
- Three papers comparing alternative methods of risk assessment for CVD were reviewed for the cost effectiveness section of the guideline [44, 62, 63].

Recommendation:

As there is limited evidence with respect to cost effectiveness no conclusion can be made as to the cost effectiveness of one tool for absolute CVD risk assessment over another in any of the identified populations.

The economic implications of implementing absolute CVD risk assessment depend on a range of factors which need to be decided at a policy level, including the risk threshold at which treatment should be undertaken, and also clinical decisions about risk management approaches which are beyond the scope of these guidelines.

7.1 Effectiveness of absolute CVD risk assessment

Our search did not identify any evidence to make recommendations about whether absolute CVD risk assessment leads to improved CVD outcomes or which risk assessment method is most effective in leading to improved CVD outcomes.

Several studies have reported changes in treatment, risk or risk factor levels as a result of risk assessment; however, none of these trials measure or report changes in CVD outcomes [18, 59–61].

7.2 Cost effectiveness of absolute CVD risk assessment

The method for the review of the literature with respect to cost effectiveness of alternative tools for absolute CVD risk assessment is outlined in **section 9** of these guidelines. **Section 9.9** shows the search strategy for the literature review undertaken for the economic component of these guidelines.

7.2.1 Abstract review

From 20,991 citations screened by title and abstract, five studies were identified that included 'economic evaluation', 'cost effectiveness', or 'cost' in the abstract review. These abstracts were separately reviewed by a health economist. Two studies were eliminated following this review as they were both comparisons of different imaging methods used to diagnose cardiac disease. The remaining three studies were reviewed by a health economist.

7.2.2 Results

None of the three papers reviewed met the inclusion criteria for a cost effectiveness analysis (refer to **section 9.9.2**).

Two of the three studies reviewed are comment or opinion with respect to cost effectiveness in absolute CVD risk factor assessment, but provide no actual evidence regarding cost effectiveness [44] [62]. The third paper is a literature review comparing the cost effectiveness of office-based methods of risk factor assessment with diagnostic imaging in CVD [63]. Table 7.2.2.1 below provides a summary of each of the papers reviewed.

Table 7.2.2.1. *Brief summary of papers reviewed on the cost effectiveness of assessment of absolute CVD risk*

Author	Reference	Brief summary
Guzder et al	[44]	<p>A comparison of the FRE with the UKPDS risk score for the detection of CVD in people with newly diagnosed diabetes. Predictive ability data for each method is reported (see appendix I), however the direct costs of each method are not reported, nor are a comparison of the direct costs of subsequent health care utilisation provided.</p> <p>Although they provide no evidence of cost effectiveness, the authors suggest that targeted treatment strategies based on risk assessment are likely to maximise cost effectiveness compared to single risk factor management such as achieving a cholesterol target. The authors further suggest that “an accurate measure of absolute risk may help inform the aggressiveness of therapy aimed at lowering risk in an individual”, further contributing to cost effective disease management.</p>
Rogowski et al	[62]	<p>This paper contains opinion only. The authors comment that the addition of the BMI to the Framingham CHD risk score might improve the cost effectiveness of this model in people with obesity.</p> <p>No supporting evidence is provided, and there are no cost data cited in the study.</p>
Shaw et al	[63]	<p>A review of the evidence available with respect to the cost effectiveness of office-based risk factor assessment versus cardiovascular imaging. The authors comment that much of the evidence of cost effectiveness cited in the articles reviewed was based on decision models or simulations rather than well-controlled clinical trials or large cohort studies.</p>

7.2.3 Conclusion

There is no evidence in the scientific literature of the cost effectiveness of one method or tool for absolute risk assessment in the prediction of future CVD events over another in any of the described populations (no CVD or diabetes; no CVD with diabetes; no CVD with overweight/obesity; Aboriginal/Torres Strait Islander people with no CVD; or CKD with no CVD).

7.3 Economic implications of using the Framingham risk equation to assess absolute CVD risk

This section outlines the likely economic implications associated with the implementation of national evidence-based practices guideline using a tool such as the FRE to assess absolute CVD risk in the Australian population. These guidelines are about screening for absolute risk of CVD; the evidence around treatment options once absolute risk has been established have not been reviewed in the scope of these guidelines. From an economic perspective, both screening and subsequent treatment will have implications with respect to both costs and benefits.

The following discussion considers the economic implications of implementing the guidelines; that is, those factors that would require further evidence in an economic analysis to assess the cost effectiveness of the implementation of these guidelines. These include:

- a description of the intervention and its comparator
- frequency of assessment for absolute CVD risk
- target population
- definition of the 'at risk' threshold.

7.3.1 A description of the intervention and its comparator

To undertake an economic evaluation, a full description of resources needed to implement the absolute CVD risk assessment program would be required. These will include the format of the absolute risk assessment (for example risk chart, formula or computer-based clinical decision support system), the change in impact on GP attendances (opportunistic screening or specific appointment), training requirements and any change in service use such as practice nurses, patient education or laboratory investigations. Where the assessment requires additional resources compared to 'current practice' – for example, requires specific training of health professionals – the costs of implementing absolute risk assessment for CVD will increase. Alternatively where a less formal or more ad hoc approach is taken to implementing these guidelines then poor uptake by practitioners may contribute to reduced effectiveness (where effectiveness is defined in intermediate outcomes as "the number of 'at risk' cases detected").

The comparator or control intervention for a cost effectiveness analysis would be 'current practice' rather than 'do nothing' or 'no risk factor management' in the general practice context. A 'do nothing' comparator assumes that GPs are not currently undertaking any risk factor assessment, including assessment and management of single risk factors for CVD. As this is unlikely to be the case, a comparison against 'do nothing' would overestimate the benefits of assessment of absolute CVD risk and underestimate the costs in the control group compared to a 'current practice' comparator.

7.3.2 Frequency of assessment for absolute CVD risk

The frequency of absolute risk factor assessment or time interval between assessments will impact on the cost effectiveness of assessment for absolute CVD risk. Increasing the frequency of screening – i.e. reducing the time interval between the assessment of individuals for absolute CVD risk – will obviously increase program costs. The size of the increase will depend on the actual intervention. On the effect side it is difficult to predict the impact on program outcomes; that is, the additional number of 'at risk' cases detected as a result of the increased screening interval.

7.3.3 Target population

The cost effectiveness of screening generally improves when higher ‘at risk’ sub-groups can be identified within the target population; this reduces the cost per case detected. With increasing proportions of the population undergoing absolute risk assessment, the economic impact will affect both cost and benefits. There will be an exponential increase in total cost as the program is rolled out to less accessible areas, thus the marginal cost of assessing the absolute CVD risk of each additional proportion of the population will increase. In addition, as those least at risk of CVD are assessed, the marginal benefit of the program will decline; the combination of increasing marginal cost and diminishing marginal benefit will have an impact on the cost effectiveness ratio. The magnitude of the impact on both cost and benefit will also be influenced by how the intervention is implemented – for example, opportunistic screening by GPs will target regular users of GP services, but may result in a proportion of the target population not assessed for absolute risk. Distributional and socioeconomic implications are further discussed in **section 8**.

7.3.4 Definition of the ‘at risk’ threshold

The economic impact of defining an ‘at risk’ threshold is also difficult to predict. The effect could be in either direction depending on whether it is the costs of screening that are driving the cost effectiveness ratio or the subsequent treatment costs. For example, a threshold set at 15% means a smaller proportion of the population will need to be screened to detect one ‘at risk’ case compared to a threshold set at 40%. However a threshold set at 15% means that for every 6.7 people detected as having a 15% risk of developing CVD, one person will actually get the disease; or 6.7 people will have to be treated to successfully prevent 1 case of CVD. A 40% risk of disease means that 2.5 people with this level of risk will have to be treated to prevent one case of CVD.¹

The direction of the economic impact is thus dependent on the threshold level of risk, which is influenced by a trade-off between screening and treatment. A low risk threshold implies that the cost effectiveness ratio for screening (the cost per detecting one ‘at risk’ case of CVD) will be low compared to the higher risk threshold group. However the cost effectiveness ratio of treatment (the cost per preventing one case of CVD) for the lower risk threshold will be higher compared to the high-risk threshold, as more people will require treatment. An economic evaluation comparing different levels of the ‘at risk’ threshold would calculate total costs as the sum of screening and treatment costs, with the cost effectiveness ratio expressed as the cost per case of CVD prevented.

The above discussion relates to the economic implications of implementing guidelines around the assessment of absolute risk for CVD. Other factors to consider that will also have an economic impact, but are directly associated with these guidelines, include:

- the relationship between screening and the cost effectiveness of subsequent treatment
- how the population currently being treated on the basis of a single risk factor for CVD, but who are not considered to meet the threshold level of absolute risk, are managed
- the translation of intermediate outcomes to final outcomes to model the cost effectiveness of these guidelines over time.

¹ The assumptions underlying this include that the assessment of risk is 100% accurate, that the treatment success rate associated with the given level of risk is 100% effective; and that the rate of compliance with therapy is 100%.

7.3.5 Relationship between screening and cost effectiveness of subsequent treatment

The above discussion concerning the definition of an ‘at risk’ threshold demonstrated that the cost effectiveness of screening guidelines will ultimately depend on the cost effectiveness of available treatment options or pathways.

Absolute risk assessment for CVD using the FRE requires a combination of single risk factors to be assessed. Ideally, cost effectiveness analyses or a modelling exercise would be undertaken to evaluate the impact of each treatment option associated with each level of risk and each combination of risk factors against the chosen comparator (current practice). This exercise would require evidence on the outcomes, costs and probability of adverse events for each treatment option, to populate the pathways in the model. As there are multiple combinations and pathways it is difficult to predict the magnitude and direction of the economic impact.

7.3.6 Management of the population with a CVD risk factor but without established CVD

The management of the population currently being treated for a CVD risk factor but without established CVD will also have implications in an economic analysis. If this population continues their current treatment, then the size of the target population will be reduced, thus impacting on the cost effectiveness of identifying new individuals with absolute CVD risk (marginal costs increase as the size of the population screened falls).² The total costs of treatment are also likely to be higher as the costs of treating new individuals will not be offset against the savings associated with discontinuing the treatment of currently managed individuals who do not reach the threshold level of absolute risk.

7.3.7 Translation of intermediate outcomes to final outcomes

Clinical or intermediate measures are the most common outcome measures for a screening intervention. When screening for absolute CVD risk, the intermediate outcome measures include “the number of ‘at risk’ cases of CVD detected” and “the number of cases of CVD prevented”. Intermediate measures have the advantage that they are clinically meaningful to the question asked; however, they are only relevant to the program or intervention being evaluated.

Outcome measures against which to evaluate the health care program or activity can also be defined broadly so they are relevant to, and can be compared across, a range of health care interventions. These include the number of lives saved, the number of life years saved, disability-adjusted life years saved (DALYs), and quality-adjusted life years saved (QALYs). To extrapolate intermediate or clinical measures to these more generalisable outcomes, evidence is required from previously published sources and/or sufficient follow-up of study participants in a randomised controlled trial or cohort study.

² This effect will reduce over time as the guideline is implemented and the ratio of new untreated individuals to previously treated individuals changes.

8 Review of existing evidence-based guidelines

Below is a table outlining existing evidence-based guidelines for assessment and management of CVD risk in people not known to have CVD. Each guideline has been appraised using the AGREE instrument [2], and their recommendations are summarised. The absolute CVD risk assessment methods recommended in these guidelines are based on the Framingham model.

	Risk Estimation and the Prevention of Cardiovascular Disease (SIGN 97) [64]	The Assessment & Management of Cardiovascular Risk (NZGG) [65]	Joint British Societies' Guidelines on Prevention of Cardiovascular Disease in Clinical Practice [66]	Lipids and the Primary Prevention of Coronary Heart Disease (SIGN40) [67]	Hypertension in Older People (SIGN49) [68]
Domain 1 (out of 12) Scope and Purpose (Domain 1) is concerned with the overall aim of the guideline, the specific clinical questions and the target patient population.	11	12	11	11	11
Domain 2 (out of 16) Stakeholder Involvement (Domain 2) focuses on the extent to which the guideline represents the views of its intended users.	13 [@]	13 [*]	8 [^]	14 ⁺	12 [#]
Domain 3 (out of 35) Rigour of Development (Domain 3) relates to the process used to gather and synthesise the evidence, the methods to formulate the recommendations and to update them.	26	22 ^{**}	17 ^{^^}	26 ⁺⁺	25
Domain 4 (out of 16) Clarity of Presentation (Domain 4) deals with the	15	16	15	16	16

language and format of the guideline.					
Domain 5 (out of 15) Applicability (Domain 5) pertains to the likely organisational, behavioural and cost implications of applying the guideline.	15	12	9^{^^^}	12	11^{##}
Domain 6 (out of 8) Editorial Independence (Domain 6) is concerned with the independence of the recommendations and acknowledgement of possible conflict of interest from the guideline development group.	7	8	3^{^^^^}	7	7
Notes	@SIGN50 [69] states that patient involvement and open meetings are appropriate, but there is no statement in the guideline to indicate this was done.	*Peer review and external endorsement are indicated, but no statement about piloting. **No statement demonstrating continued updates reflecting the current literature in the guideline or supporting documentation.	^Patient's views have not been sought; document has not been piloted amongst target users. ^^Inclusion/exclusion criteria not listed; methods of consensus recommendations not described; recommendations not referenced, levels of evidence not found; funding not described. ^^^Cost-effectiveness not reported. ^^^^Funding information not provided; conflicts of interest not provided.	+SIGN50 [69] states that patient involvement and open meetings are appropriate, but there is no statement in the guideline to indicate this was done. ++SIGN50 [69] outlines the correct criteria for selecting the evidence and methods to be used for formulating the recommendations, but there is no statement to indicate this process was undertaken.	#SIGN50 [69] states that patient involvement and open meetings are appropriate, but there is no statement in the guideline to indicate this was done. ##SIGN50 [69] acknowledges resource implications are important but not stated in guideline; no statement about lack of evidence; cost-effectiveness is listed in recommendations for further research.
Scope of guideline	This guideline predominantly covers prevention of CVD.	This guideline predominantly covers management of CVD.	This guideline predominantly covers management of CVD.	This guideline predominantly covers management of CVD.	This guideline predominantly covers management of CVD.

	<p>With respect to risk assessment in people not known to have CVD, these guidelines recommend the use of the Joint British chart and recommendations are made about:</p> <ul style="list-style-type: none"> • who should be assessed • frequency of CVD risk assessment • clinical measurements to be included the assessment;. 	<p>With respect to risk assessment in people not known to have CVD, these guidelines provide an absolute risk assessment method specific for the New Zealand population and recommendations are made about:</p> <ul style="list-style-type: none"> • who should be assessed • who should do the assessment • frequency of CVD risk assessment. 	<p>With respect to risk assessment in people not known to have CVD, these guidelines provide the Joint British chart and recommendations are made about:</p> <ul style="list-style-type: none"> • who to assess for CVD risk • how to assess for total CVD risk • which risk factors to measure • how to calculate total CVD risk from the CVD risk prediction charts • other CVD risk factors not included in the CVD risk prediction charts • which people should <i>not</i> have CVD risk calculated • calculating CVD risk in ethnic groups other than white Caucasians. 	<p>With respect to risk assessment in people not known to have CVD, the following recommendations are made:</p> <ul style="list-style-type: none"> • absolute rather than relative risk reduction gives a better estimate of the benefits of lipid lowering drug treatment • current assessment methods may underestimate risk in type 1 diabetics and type 2 diabetics with nephropathy. 	<p>With respect to risk assessment in people not known to have CVD, the following recommendations are made:</p> <ul style="list-style-type: none"> • a full assessment of cardiovascular risk should be carried out for all hypertensive patients • for risk assessment in primary prevention of CVD, use the Joint British chart. Note that the charts are only valid for patients aged 32–74 years and with no pre-existing atherosclerotic disease.
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SIGN 97, Scottish Intercollegiate Guidelines Network Risk Estimation and the Prevention of Cardiovascular Disease, A National Clinical Guideline [64]; NZGG, New Zealand Guidelines Group Best Practice Evidence-based Guideline for the Assessment and Management of Cardiovascular Risk [65]; SIGN 40, Scottish Intercollegiate Guidelines Network Lipids and the Primary Prevention of Coronary Heart Disease, A National Clinical Guideline [1]; SIGN 49, Scottish Intercollegiate Guidelines Network Hypertension in Older People, A National Clinical Guideline [68].

9 Methods

9.1 How the guidelines came about

Refer to Part B: Working group membership and terms of reference.

9.2 Guidelines development group

Refer to Part B: Working group membership and terms of reference.

9.3 Declaration of potential competing interests

Refer to Part B: Working group membership and terms of reference.

9.4 Funding

Development of these guidelines has been approved and funded by the National Board of the National Heart Foundation of Australia and endorsed by the National Vascular Disease Prevention Alliance (NVDPA).

9.5 Question development

The clinical questions on which these guidelines are based were originally set by the NVDPA based upon input from clinicians and consumers and further developed through consultation between the guideline developers in the Monash Institute of Health Services Research (MIHSR) team and the NVDPA team.

The clinical questions for these guidelines are:

1. Which absolute risk assessment method is most predictive of future CVD events in a mixed adult (aged >18) population not known to have CVD or diabetes [1]?
2. Which absolute risk assessment method is most predictive of future CVD events in a mixed adult (aged >18) population not known to have CVD and who have diabetes [1]?
3. Which absolute risk assessment method is most predictive of future CVD events in a mixed adult (aged >18) population not known to have CVD and who are overweight (defined as BMI within the range 25.0–29.9 kg/m² [2]) or obese (BMI ≥30 kg/m² [2])?
4. Which absolute risk assessment method is most predictive of future CVD events in adult (aged >18) Aboriginal and Torres Strait Islander peoples not known to have CVD?
5. Which absolute risk assessment method is most predictive of future CVD events in adult (aged >18) people with chronic kidney disease (GFR <60 mL/min) not known to have CVD?

9.6 Inclusion and exclusion criteria

The inclusion and exclusion criteria were determined from the clinical questions on which these guidelines are based. The first step in determining these criteria is to identify the participants (P), intervention (I), comparison (C) and the outcome (O) in each question, as below:

	Participants (P)	Intervention (I)	Comparison (C)	Outcome (O)
Inclusion criteria	Adults not known to have CVD	Predicted CVD risk using any absolute CVD risk assessment method – assessing 2 or more standard accepted biomedical risk factors (age; sex; blood pressure; smoking; lipids including triglycerides, TC, HDL, LDL and associated ratios; atrial fibrillation; weight, waist circumference; BMI; HbA _{1c} ; blood sugar; WHR; CKD socioeconomic status; GFR; microalbuminuria; serum creatinine; physical activity status; fruit and vegetable intake)	Observed CVD risk	AUC data Sensitivity/ specificity data
Exclusion criteria	Adults with CVD or following a CVD event	Predicted CVD risk using any risk assessment method – assessing only one of the standard accepted biomedical risk factors Predicted CVD risk using coronary calcium scores, C-reactive protein or any other anti-inflammatory marker		

*Studies that use previously collected data to develop new absolute risk assessment methods (modelling) were excluded.

9.7 Search methods

9.7.1 Databases searched

The following electronic databases were used to identify relevant literature:

- Australasian Medical Index
- CINAHL
- The Cochrane Library
 - Cochrane Database of Systematic Reviews (Cochrane Reviews)
 - Database of Abstracts of Reviews of Effects (Other Reviews)

- Cochrane Central Register of Controlled Trials (Clinical Trials)
- Cochrane Database of Methodology Reviews (Methods Reviews)
- The Cochrane Methodology Register (Methods Studies)
- Health Technology Assessment Database (Technology Assessments)
- NHS Economic Evaluation Database (Economic Evaluations)
- EMBASE
- EBM Reviews (OVID)
- Medline
- Medline in-process and other non-indexed citations.

We also searched the bibliographies of relevant studies identified by the search strategy and relevant reviews/meta-analysis for identification of additional studies. Relevant guideline and peak body websites were also searched.

9.7.2 Search strategy

A broad-ranging systematic search was developed through consultation between the MIHSR and a specialist search strategist. The search strategy was limited to English language articles and there were no limits on year of publication. A total of 20,991 records were retrieved on 13 April 2006 (**see appendix V**).

1. exp Coronary Disease/
2. exp Cerebrovascular Accident/
3. heart attack\$.tw.
4. stroke\$.tw.
5. myocardial infarction.tw.
6. (coronary adj (event\$ or disease or heart disease or mortality)).mp.
7. (cardiovascular adj (event\$ or mortality)).mp.
8. or/1-7
9. exp risk assessment/
10. exp risk/
11. risk.tw.
12. chance.tw.
13. likelihood.tw.
14. potential.tw.
15. probability.tw.
16. possib\$.tw.
17. prognosis.tw.
18. inciden\$.tw.
19. or/10-17
20. (decision aid\$ or decision support).tw.
21. tool\$.tw.
22. rule\$.tw.
23. model.tw.
24. assess\$.tw.
25. predict\$.tw.
26. calculat\$.tw.
27. (estimate\$ or estimation\$).tw.
28. equation\$.tw.
29. (score\$ or scoring).tw.
30. algorithm\$.tw.

31. chart\$.tw.
32. table\$.tw.
33. (framingham or procam).tw.
34. screen\$.tw.
35. or/20-34
36. 19 and 35
37. 9 or 36
38. 8 and 37
39. limit 38 to (humans and english language)
40. [Clinical Query: Medline: Therapy - Optimised]
41. randomized controlled trial.pt. or random\$.mp. or placebo.mp.
42. 39 and 41
43. [Clinical Query: Medline: Diagnosis - Optimized]
44. (sensitiv: or predictive value:).mp. or accurac:.tw.
45. 39 and 44

9.8 Review of evidence

9.8.1 Inclusion of studies

To determine the literature to be assessed further and on which to base these guidelines, a reviewer scanned the titles, abstracts and keywords of every record retrieved by the search strategy. Full articles were retrieved for further assessment if the information given suggested that the study met the inclusion criteria as described in **section 9.6**. Two independent reviewers decided on inclusion/exclusion of retrieved articles.

Where there was doubt regarding these criteria from the information given in the title and abstract, the full article was retrieved for clarification.

We included studies which compared the predictive ability of different methods of absolute risk assessment and recommendations were made on the basis of the results of these studies. We also reported the results of studies which investigated the predictive ability of individual absolute risk assessment methods to provide further information for the reader.

A table of excluded studies can be found in **appendix VI**.

9.8.2 Assessment and classification of evidence

Studies identified from the literature for inclusion in the review and development of these guidelines were initially classified according to the NHMRC levels of evidence (table 9.8.2.1).

9.8.2.1 Evidence hierarchy

Table 9.8.2.1 Designations of levels of evidence* according to type of research question

Level	Intervention ^s	Diagnosis ^{**}	Prognosis	Screening
I [*]	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A study of test accuracy with an independent, blinded	A prospective	A randomised controlled trial

		comparison with a valid reference standard, ^{§§} among consecutive patients with a defined clinical presentation. ^{††} This study has a very low risk of bias	cohort study ^{***}	
III-1	A pseudo-randomised controlled trial (i.e. alternate allocation or some other method)	A study of test accuracy with an independent, blinded comparison with a valid reference standard, ^{§§} among non-consecutive patients with a defined clinical presentation. ^{††} This study has a low risk of bias	All or none ^{§§§}	A pseudo-randomised controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: <ul style="list-style-type: none"> • non-randomised, experimental trial[†] • cohort study • case-control study • interrupted time series with a control group 	A comparison with reference standard that does not meet the criteria required for level II and III-1 evidence. This study has a high risk of bias	Analysis of prognostic factors amongst untreated control patients in a randomised controlled trial	A comparative study with concurrent controls: <ul style="list-style-type: none"> • non-randomised, experimental trial • cohort study • case-control study
III-3	A comparative study without concurrent controls: <ul style="list-style-type: none"> • historical control study • two or more single arm study[‡] • interrupted time series without a parallel control group 	Diagnostic case-control study. ^{††} This study has a high risk of bias	A retrospective cohort study	A comparative study without concurrent controls: <ul style="list-style-type: none"> • historical control study • two or more single arm study
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard). ^{‡‡} This study has a high risk of bias	Case series, or cohort study of patients at different stages of disease	Case series

Table notes

* A systematic review will only be assigned a level of evidence as high as the studies it contains, excepting where those studies are of level II evidence.

§ Definitions of these study designs are provided on pages 7–8 of *How to use the evidence: assessment and application of scientific evidence* (NHMRC 2000b).

† This also includes controlled before-and-after (pre-test/post-test) studies, as well as indirect comparisons (i.e. utilise A vs B and B vs C, to determine A vs C).

‡ Comparing single arm studies i.e. case series from two studies.

** The dimensions of evidence apply only to studies of diagnostic accuracy. To assess the effectiveness of a diagnostic test there also needs to be a consideration of the impact of the test on patient management and health outcomes. See *MSAC (2004) Guidelines for the assessment of diagnostic technologies*, available at www.msac.gov.au

§§ The validity of the reference standard should be determined in the context of the disease under review. Criteria for determining the validity of the reference standard should be pre-specified. This can include the choice of the reference standard(s) and its timing in relation to the index test. The validity of the reference standard can be determined through quality appraisal of the study. See Whiting P, Rutjes AWS, Reitsma JB, et al. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. *BMC Medical Research Methodology* 2003; 3: 25.

†† Well-designed population-based case-control studies (e.g. population-based screening studies where test accuracy is assessed on all cases, with a random sample of controls) do capture a population with a representative spectrum of disease and thus fulfill the requirements for a valid assembly of patients. However, in some cases the population assembled is not representative of the use of the test in practice. In diagnostic case-control studies a selected sample of patients already known to have the disease are compared with a separate group of normal/healthy people known to be free of the disease. In this situation patients with borderline or mild expressions of the disease, and conditions mimicking the disease, are excluded, which can lead to exaggeration of both sensitivity and specificity. This is called spectrum bias because the spectrum of study participants will not be representative of patients seen in practice.

‡‡ Studies of diagnostic yield provide the yield of diagnosed patients, as determined by an index test, without confirmation of the accuracy of this diagnosis by a reference standard. These may be the only alternative when there is no reliable reference standard.

*** At study inception the cohort is either non-diseased or all at the same stage of the disease.

§§§ All or none of the people with the risk factor(s) experience the outcome. For example, no smallpox develops in the absence of the specific virus; and clear proof of the causal link has come from the disappearance of small pox after large-scale vaccination.

††† If it is possible and/or ethical to determine a causal relationship using experimental evidence, then the 'Intervention' hierarchy of evidence should be utilised. If it is only possible and/or ethical to determine a causal relationship using observational evidence (i.e. cannot allocate groups to a potential harmful exposure, such as nuclear radiation), then the 'Aetiology' hierarchy of evidence should be utilised.

Note 1: Assessment of comparative harms/safety should occur according to the hierarchy presented for each of the research questions, with the proviso that this assessment occurs within the context of the topic being assessed. Some harms are rare and cannot feasibly be captured within randomised controlled trials; physical harms and psychological harms may need to be addressed by different study designs; harms from diagnostic testing include the likelihood of false positive and false negative results; harms from screening include the likelihood of false alarm and false reassurance results.

Note 2: When a level of evidence is attributed in the text of a document, it should also be framed according to its corresponding research question e.g. level II intervention evidence; level IV diagnostic evidence; level III–2 prognostic evidence.

Hierarchies adapted and modified from NHMRC 1999; Bandolier 1999; Lijmer et al 1999; Phillips et al 2001.

Source: Adapted from NHMRC additional levels of evidence and grades for recommendations for developers of guidelines PILOT PROGRAM 2005–2007.

9.8.3 Assessment of methodological quality

Methodological quality of the included studies was assessed.

9.8.3.1 Ability of the predictive method

The most rigorous study design for assessing predictive ability is considered to be a prospectively designed longitudinal cohort study that independently compares the absolute risk assessment method with an appropriate reference standard in consecutively selected patients from a relevant clinical population [70]. Based on these criteria, the validity of the methodology of included articles was assessed against the following checklist:

- a) specified inclusion/exclusion criteria
- b) explicit description of participants
- c) appropriate spectrum of consecutively selected participants
- d) prospective selection of participants
- e) absolute risk assessment method is compared with an appropriate reference (gold) standard – observed CVD event
- f) absolute risk assessment method is compared with the reference standard in all participants
- g) blinded assessment of absolute risk assessment method and reference standard results
- h) absolute risk assessment method and reference standard undertaken prior to any interventions.

Each criterion was graded as met, unmet or unclear, and a brief description provided in the Evidence Table of study performance against each criteria. Any disagreement was resolved by discussion to reach a consensus.

Studies were required to meet criteria e) and f) to be included. Studies which met all or the great majority of the quality criteria were considered to be at lower risk of bias/high quality (more likely to reflect the truth) than those that met few or none of the criteria, which were considered to have higher risk of bias/low quality. While no formal weighting was applied, the impact of each quality criterion on the potential for introduction of bias into the study was used to assess the overall quality.

9.8.4 Data extraction

Data, according to the inclusion criteria, were extracted from included studies using an evidence table. Information was collected on general details (title, authors, reference/source, country, year of publication, setting), participants (age, sex, inclusion/exclusion criteria, withdrawals/losses to follow-up, sub-groups), results (point estimates and measures of variability, frequency counts for dichotomous variables, number of participants) and validity results. The second reviewer performed double-data extraction on a subset of studies to ensure accuracy of results. Missing data were obtained from the authors wherever possible. Any disagreement was resolved by discussion and mediation with a third party to reach a consensus.

Where reported, data (including confidence intervals where available) on AUC, sensitivity and specificity, and under- or overestimation of risk were extracted.

Evidence tables can be found in **appendix I** and are summarised in **sections 2–7**.

9.8.4.1 Area under the receiver operator curve

Predictive ability is a two-edged sword: ‘successful’ prediction arises not only from correctly identifying true cases (‘sensitivity’), but also from correctly predicting non-cases (‘specificity’). These measures of success compete against each other – as a test’s sensitivity increases (as it gets better at predicting true cases), its specificity must get worse (its prediction of non-cases deteriorates).

The tension between sensitivity and specificity of test prediction is most apparent when choosing cut-off points based on a continuous absolute risk score. A low cut-off will have high sensitivity – because almost all true cases will be classed as ‘positive’ – but low specificity. Conversely, a high cut-off will correctly call most true non-cases ‘negative’ (high specificity), but miss relatively more true cases (low sensitivity).

A graph of the relation between sensitivity and specificity as the cut-off for any particular risk score is a good way to visualise the risk score’s performance. A good risk score will show a graph which gets close to ‘perfect’ sensitivity and specificity; a poorly performing risk score will have a graph which never gets close to these optimal characteristics.

The accompanying figure shows a typical graph of sensitivity against specificity for a typical risk score. For every possible value x of the risk score, we can calculate the proportion of CVD cases with risk score greater than x (the sensitivity, or probability of a true positive) and the proportion of those without CVD, the non-cases, with risk scores greater than x (the probability of a false positive, or $1 - \text{specificity}$). These two values, each between 0 and 1, are graphed against each other for all possible values of x . In the graph, a typical point is shown and labelled $P(x)$.

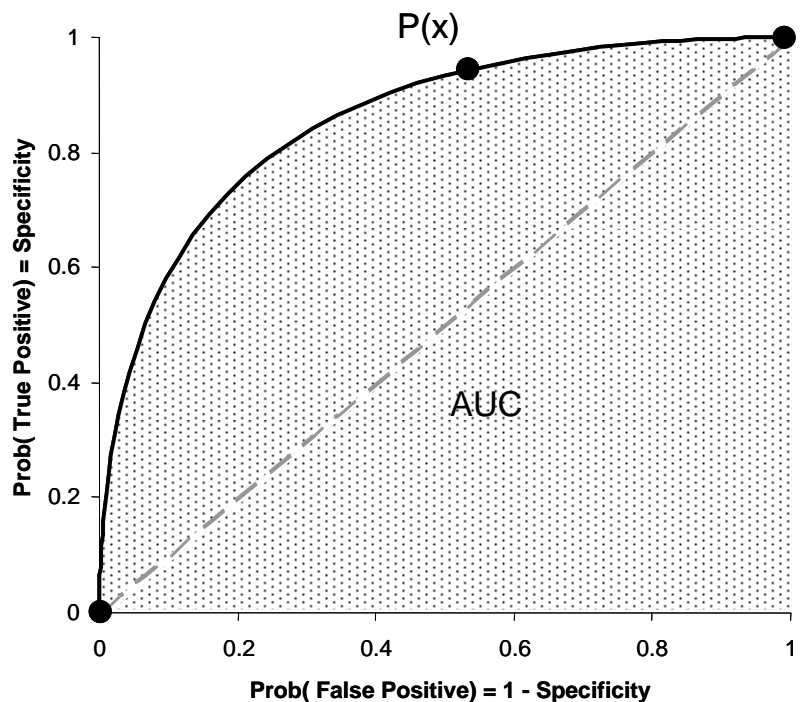
When these points are connected, they form a convex curve which stretches from the lower left to the upper right of the square. The area under the curve, or AUC, is shown as a stippled area in the graph.

When explained like this, the AUC seems to be little more than a mathematical construct. However, there is a practical interpretation of AUC which makes it more relevant to the epidemiological objective of predicting the future incidence of CVD.

Suppose from a large cohort study followed up for CVD, all eventual cases of CVD are listed, and from this list one is selected at random. At the same time, one person is selected randomly from all those who remain free from CVD.

Hanley and McNeil [71] have

demonstrated elegantly that AUC is equal to the probability that the baseline risk score of the case is greater than that of the non-case. In other words, AUC represents the chance that the risk score will correctly identify the case from the randomly selected pair of subjects.



Two special cases merit immediate attention. First, a perfect risk score is one which perfectly distinguishes CVD cases from non-cases; that is, for all points $P(x)$ in the figure, the sensitivity=1 and specificity=1, which effectively stretches the curve up into the top left corner of the square. In this case, AUC=1.0 (the stippling extends across the whole square), and, using Hanley and McNeil's interpretation [71], it means that every CVD case has a higher baseline risk score than every non-case.

On the other hand, a useless risk score is one which fails to distinguish eventual cases at all from eventual non-cases. This will happen if the chance is 50% that a case's risk score is greater than a non-case's; in other words, if AUC=0.5. From the graph, this will happen if the curve of $P(x)$ points lies along the dashed diagonal line, the area under which is 0.5. In this situation, the probability of a true positive (sensitivity) is equal to the probability of a false positive ($1 - \text{specificity}$) for all risk score cut-offs.

All practical risk scores, of course, have diagnostic characteristics which lie between these two extremes, with curves which look, theoretically at least, like the dark solid $P(x)$ curve in the figure above. Each risk score will have its own curve, and thus its own AUC value, the closeness of which to the ideal AUC=1.0 indicates the utility of the risk score in distinguishing cases from non-cases.

Some authors have assigned qualitative descriptors to values of AUC. Swets [72] has prompted the following classification:

Qualitative descriptor	Range of AUC values
Excellent	0.91 to 1.0
Good	0.81 to 0.90
Fair	0.71 to 0.80
Poor	0.61 to 0.70
Failed	0.51 to 0.60

There is no empirical justification of these labels used to qualify AUC values: these descriptors are based on subjective value judgements of Swets and other authors [72].

When data are collected from cohort studies, such as those documented in these guidelines, the curves are never as smooth as the theoretical version in the figure; they often look like flights of stairs, with variable stepsizes, but all extending from the lower left corner to the upper right. Authors can calculate an AUC value based on their sample cohort, and the better studies will also report the 95% confidence interval, which proscribes the limits between which the 'true', or theoretical AUC for this cohort, is likely to fall. The precision, usually reflecting the sample size, of any one study is evident from the width of the confidence interval reported.

One of the specific applications of the AUC statistic is to compare diagnostic utility between different risk factor scoring systems: generally, the risk score with higher AUC can be regarded as the better predictor of CVD risk. This provides a very useful objective method to compare and to distinguish between two or more diagnostic tests, and it is the method we have used in many comparisons within these guidelines.

Two caveats are necessary, however, when using AUC to compare risk scores. First, not only should the AUC values themselves be contrasted, but also their confidence intervals, if reported; the decision of superiority is unequivocal only if the confidence intervals are non-overlapping. Second, care should be taken in cases when the two AUC values, and their confidence intervals, have been computed based on the same individuals from the same cohort; in this case, the AUC statistics are not independent of each

other, and a simple comparison of the two confidence intervals is unwise, since it assumes independence. A reviewer must rely on authors to report appropriate comparisons, accounting for dependence, in cases in which risk score measures have been calculated from a single cohort.

For more information and demonstrations of AUC, visit the website:
www.anaesthetist.com/mnm/stats/roc/Findex.htm

9.9 Review of the economic literature

9.9.1 Search strategy

The main search strategy was considered broad enough to include articles related to economic evaluation and/or cost effectiveness.

9.9.2 Inclusion criteria for economic analysis

- i. A comparison of two different methods for absolute CVD risk assessment
- ii. Effectiveness data described as an intermediate clinical measure or longer-term health outcome
- iii. Inclusion of resource or cost impacts of each intervention, including the direct costs of each intervention and subsequent health system resource impacts.

9.9.3 Exclusion criteria for economic analysis

There was no additional exclusion criteria for the economic analysis to those described in **section 9.6**.

9.10 Formulation of recommendations

Where evidence exists to answer the clinical questions, evidence-based recommendations were made, with the level of the recommendation reflecting the volume, quality, clinical impact, applicability and generalisability of the evidence available to answer the question. The recommendations were graded and summarised in table form.

We included studies which compared the predictive ability of different methods of absolute risk assessment and recommendations were made on the basis of the results of these studies. We also reported the results of studies which investigated the predictive ability of individual absolute risk assessment methods to provide further information for the reader.

Where there was no, or very low quality, evidence to answer a clinical question, a statement has been included that highlights the lack of evidence and no recommendations were made. Implications for future research are presented in **chapter 9**.

Recommendations were not separated based on gender.

9.10.1 Recommendation grading system

The application of a grade to a recommendation is based on an assessment of all the included studies for that recommendation (the 'body of evidence').

Table 9.10.1 *Body of evidence assessment matrix*

Component	A	B	C	D
	Excellent	Good	Satisfactory	Poor
Volume of evidence	Several level I or II studies with low risk of bias	One or two level II studies with low risk of bias or a SR/multiple level III studies with low risk of bias	Level III studies with low risk of bias, or level I or II studies with moderate risk of bias	Level IV studies, or level I to III studies with high risk of bias
Consistency	All studies consistent	Most studies consistent and inconsistency may be explained	Some inconsistency reflecting genuine uncertainty around clinical question	Evidence is inconsistent
Clinical impact	Very large	Substantial	Moderate	Slight or restricted
Generalisability	Population/s studied in body of evidence are the same as the target population for these guidelines	Population/s studied in the body of evidence are similar to the target population for these guidelines	Population/s studied in body of evidence are different to the target population for these guidelines, but it is clinically sensible to apply this evidence to the target population	Population/s studied in body of evidence are different to the target population and it is hard to judge whether it is sensible to generalise to the target population
Applicability	Directly applicable to the Australian healthcare context	Applicable to the Australian healthcare context, with few caveats	Probably applicable to the Australian healthcare context, with some caveats	Not applicable to the Australian healthcare context

Source: NHMRC additional levels of evidence and grades for recommendations for developers of guidelines PILOT PROGRAM 2005 – 2007.

Table 9.10.2 Overall grade of recommendation

Grade of recommendation	Description
A	Body of evidence can be trusted to guide practice
B	Body of evidence can be trusted to guide practice in most situations
C	Body of evidence provides some support for recommendation(s) but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution

Source: NHMRC additional levels of evidence and grades for recommendations for developers of guidelines PILOT PROGRAM 2005 – 2007.

Body of evidence tables for grading of recommendations can be found in **appendix II**.

9.11 Stakeholder, GP and consumer consultation

Refer to Part B: Working group membership and terms of reference.

Appendix I: Evidence tables

NHMRC level of evidence for diagnosis studies key	51
Population: adults (aged >18) without known CVD or diabetes (WHO criteria, 1999)	52
Articles that compare different absolute CVD risk assessment methods	52
Milne 2003	52
Empana 2003	54
Cooper 2005	54
Ferrario 2005	57
Orford 2002	59
Wannamethee 2005	61
Stern 2004	62
McNeill 2005	64
Grover 1995	65
Folsom 2003	66
Articles that use risk assessment methods to divide populations into categories of risk	68
Leaverton 1987	68
Kornitzer 2000	70
Persson 2003	72
Articles that assess predictive ability of an absolute CVD risk assessment method	74
D'Agostino 2001	74
DPCG 2002	76
WOSCOPS 1998	79
Milne 2003	80
Bastuji-Garin 2002	81
Suka 2001	83
Zanchetti 2001	84
Simons 2003	85
Assmann 2002	88
Brindle 2003	89
Brindle 2005	91
Liu 2004	93
Hense 2003	94
Liao 1999	96
Zhang 2005	97
Population: adult (aged >18) Aboriginal and Torres Strait Islander peoples without known CVD	100
Articles that assess predictive ability of an absolute CVD risk assessment method	100
Wang 2005	100
Population: adults (aged >18) with diabetes (WHO criteria, 1999) but without known CVD	101
Articles that compare different absolute CVD risk assessment methods	101
Guzder 2005	101
Folsom 2003	66
Population: adults (aged >18) who are overweight or obese but without known CVD	103
No studies were identified	
Population: adults (aged >18) with chronic kidney disease (GFR <60 mL/min) but without known CVD	104
Articles that assess predictive ability of an absolute CVD risk assessment method	104
Massey 2005	104

The following evidence tables are separated into population categories and comprise extracted data and quality information from articles that:

- compare different absolute CVD risk assessment methods
- assess predictive ability of an absolute CVD risk assessment method
- use risk assessment methods to divide populations into categories of risk.

NHMRC level of evidence for diagnosis studies key:

Level I	A systematic review of level II studies.
Level II	A study of test accuracy with an independent, blinded comparison with a valid reference standard, among consecutive patients with a defined clinical presentation. This study has a very low risk of bias.
Level III–1	A study of test accuracy with an independent, blinded comparison with a valid reference standard, among non-consecutive patients with a defined clinical presentation. This study has a low risk of bias.
Level III–2	A comparison with reference standard that does not meet the criteria required for level II and III–1 evidence. This study has a high risk of bias.
Level III–3	Diagnostic case-control study. This study has a high risk of bias.
Level IV	Case series with either post-test or pre-test/post-test outcomes. This study has a high risk of bias.

Population: adults (aged >18) without known CVD or diabetes (WHO criteria, 1999)

Articles that compare different absolute CVD risk assessment methods

Evidence table: Comparison of different absolute CVD risk assessment methods			
Characteristics of study:			
Study citation	Milne R, et al. Discriminative ability of a risk-prediction tool derived from the Framingham Heart Study compared with single risk factors. N Z Med J 2003; 116 (1185): U663.		
Study ID	Milne 2003 [6]	Study design	Follow-up study
Setting	Participants were recruited in 1992–93 from the workforce of a nationwide multi-industry corporation (Fletcher Challenge Ltd 72% – 4577p) and the general electoral rolls of the Auckland metropolitan region (28% – 1777p), New Zealand (NZ).		
Participants	Total 6354, aged 35 to 74 years 4638 (73%) male – workforce = 3762, electoral = 876 1716 (27%) female – workforce = 815, electoral = 901		
Intervention	FRE		
Comparison	NZ risk charts (NZRC), Age, TC/HDL, SBP (p value data only compared back to FRE, not with each other, nor between males and females).		
Outcomes	Prediction of CVD, compared to observed data, measured by AUC.		
Quality of study:			
Quality criteria:	Met?	Comments	
Specified inclusion/exclusion criteria	Yes	Included if free of prior CVD, with risk factor data and available outcome data over 5 years. Further info described elsewhere (Milne 2003 N Z Med J).	
Explicit description of participants	Yes	Further info described elsewhere (Milne 2003 N Z Med J).	
Appropriate spectrum of consecutively selected participants	Yes	Age appropriate, but uneven male:female ratio.	
Prospective selection of participants	Yes	Not clear in this paper, may be described elsewhere (Milne 2003 NZ Med J), but likely given the design of the study.	
Test is compared with an appropriate reference (gold) standard	Yes	Reference standard is observed CVD outcome (defined as admission to NZ hospital and subsequently diagnosed with IHD, cerebrovascular disease, CHF, PVD or IC or SD, cause unknown and/or if they died in NZ during the 5 year period and recorded causes of death had an ICD-9 code in these ranges) over 5 years follow-up.	
Test is compared with the reference standard in all participants	Yes	Not described. Only participants with outcome data were reported in this paper, might be described elsewhere (Milne 2003 N Z Med J).	
Blinded assessment of test and reference standard results	Yes	Not described, might be described elsewhere (Milne 2003 N Z Med J), but given that risk is assessed at baseline, assessors are blind to the observed outcomes, which is the reference standard.	

Test and reference standard undertaken prior to any interventions	Some	Treatment for hypertension and/or diabetes was used for risk factor info.	
Level of evidence	II	Risk of bias	Very low
Results of study:			
FRE	AUC = 0.74 (male) [95%CI, 0.73-0.75] AUC = 0.77 (female) [95%CI, 0.74-0.80]		
NZRC	AUC = 0.73 (male) [95%CI, 0.72-0.74] AUC = 0.78 (female) [95%CI, 0.75-0.81]		
Other results of interest	No statistical difference between the two methods in males or females.		

Evidence table: Comparison of different absolute CVD risk assessment methods			
Characteristics of study:			
Study citation	Empana JP, et al. Are the Framingham and PROCAM coronary heart disease risk functions applicable to different European populations? The PRIME Study. [see comment]. Eur Heart J 2003; 24(21): 1903-11.		
Study ID	Empana 2003 [7]	Study design	Follow-up cohort study
		N (total)	9758
Setting	Prospective Epidemiological Study of Myocardial Infarction (PRIME) cohort – Lille, Strasbourg and Toulouse, France and Belfast, Ireland between 1991 and 1993. Consisted of workers in industry of various employment groups, GP's patients (Belfast), and volunteers attending health-screening centres.		
Participants	Total 9758 males aged 50–59; 2399 in Belfast, 7359 in France See table 1 for characteristics of participants in the two cohorts		
Intervention	FRE		
Comparison	PROCAM		
Outcomes	Prediction of CVD, compared to observed data, measured by AUC (defined as c-statistic in this paper).		
Quality of study:			
Quality criteria:	Met?	Comments	
Specified inclusion/exclusion criteria	Yes	Included if free of CVD. Described elsewhere (refs 15–17).	
Explicit description of participants	Yes	See table 1 for characteristics of participants in the two cohorts.	
Appropriate spectrum of consecutively selected participants	Yes	Gender and age restrictions.	
Prospective selection of participants	Unclear	Described elsewhere (refs 15–17), and likely given the design of the study.	
Test is compared with an appropriate reference (gold) standard	Yes	Reference standard is the first observed coronary event of AP, MI and CD for total endpoints and among MI and CD for hard endpoints over 5 years follow-up.	
Test is compared with the reference standard in all participants	Yes	Loss to follow-up not described	
Blinded assessment of test and reference standard results	Yes	Not described, may be described elsewhere (refs 15–17), but given that risk is assessed at baseline, assessors are blind to the observed outcomes, which is the reference standard.	
Test and reference standard undertaken prior to any interventions	Some	Diabetes was defined by oral hypoglycaemic or insulin intake in baseline measurements.	
Level of evidence	II	Risk of bias	Very low
Results of study:			
FRE	AUC = 0.66 (Belfast – high-risk group) AUC = 0.68 (France – low-risk group) Ratio of predicted over observed CHD events: Belfast=1.34, France=2.35		
PROCAM	AUC = 0.61 (Belfast – high-risk group) AUC = 0.64 (France – low-risk group) Ratio of predicted over observed CHD events: Belfast=1.78, France=2.76		
Other results of interest	Statistical difference between the two methods not reported. FRE and PROCAM overestimated risk in both cohorts.		

Evidence table: Comparison of different absolute CVD risk assessment methods			
Characteristics of study:			
Study citation	Cooper JA, et al. A comparison of the PROCAM and Framingham point-scoring systems for estimation of individual risk of coronary heart disease in the Second Northwick Park Heart Study. <i>Atherosclerosis</i> 2005; 181(1): 93-100.		
Study ID	Cooper 2005 [8]	Study design	Follow-up study
Setting	The Second Northwick Park Heart Study (NPHS-II), Britain.		
Patients	2732 healthy middle-aged Caucasian men, 50–64 years, recruited from nine UK general practices.		
Intervention	FRE		
Comparison	PROCAM scoring system		
Outcomes	Prediction of CVD, compared to observed data, measured by AUC.		
Quality of study:			
Quality criteria:	Met?	Comments	
Specified inclusion/exclusion criteria	Yes	Men with CVD and women were excluded. No other exclusion criteria described.	
Explicit description of participants	Yes	As above and characteristics/risk factors listed in table. Further information in refs 3–5.	
Appropriate spectrum of consecutively selected participants	Yes	Participants recruited from nine UK general practices.	
Prospective selection of participants	Yes	No further information regarding method of selection in this paper (refer to refs 3–5), but likely given the design of the study.	
Test is compared with an appropriate reference (gold) standard	Yes	Reference standard is observed CVD outcome (defined as acute CHD events, sudden CD, fatal acute MI, non-fatal acute MI, new major Q wave on the ECG after 5 years follow-up, surgery for AP with CHD angiographically demonstrated) over a median of 10.8 years follow-up.	
Test is compared with the reference standard in all participants	Unclear	Not described	
Blinded assessment of test and reference standard results	Unclear	Not described, but given that risk is assessed at baseline, assessors are blind to the observed outcomes, which is the reference standard.	
Test and reference standard undertaken prior to any interventions	Unclear	Not described	
Level of evidence	II	Risk of bias	Very low
Results of study:			
FRE	AUC = 0.6184 [95%CI, 0.58–0.66]		
PROCAM	AUC = 0.6295 [95%CI, 0.59–0.67]		
Other results of interest	No difference in predictive ability of the two methods (p=0.46). When observed is plotted against predicted, for both scores, all points lie below the line of identity, suggesting that both scores are overestimating risk (p<0.0001). The ratio of observed to predicted rates were 0.47 for Framingham and 0.46 for PROCAM.		

Evidence table: Comparison of different absolute CVD risk assessment methods			
Characteristics of study:			
Study citation	Ferrario M, et al. Prediction of coronary events in a low incidence population. Assessing accuracy of the CUORE Cohort Study prediction equation. <i>Int J Epidemiol</i> 2005; 34(2): 413-21.		
Study ID	Ferrario 2005 [9]	Study design	Fixed-cohort follow-up study
		N (total)	6865
Setting	Eleven cohorts in north and centre-south of Italy investigated between 1982 and 1996. Seven were randomly selected 25–64 years old residents of two WHO MONICA Italian populations (Brianza and Friuli). PAMELA study recruited a random sample of 25–74 year old residents in the town of Monza in 1990–93. Emostatico study random sample of 45–64 year old residents of Friuli. The MATISS study surveyed independent random samples of 20–69 year old residents of four small towns in Latina province (south of Rome) in different time periods between 1983 and 1995.		
Participants	6865 males 35–69 years of age		
Intervention	CUORE equation		
Comparison 1	FRE		
Comparison 2	PROCAM		
Outcomes	Prediction of CVD, compared to observed data, measured by AUC.		
Quality of study:			
Quality criteria:	Met?	Comments	
Specified inclusion/exclusion criteria	Yes	Exclusion of cohorts described. Included if free of CVD and with complete risk factor data.	
Explicit description of participants	Yes	As described in 'setting' above.	
Appropriate spectrum of consecutively selected participants	Yes	As described in 'setting' above. Restricted to males, but age is varied.	
Prospective selection of participants	Yes	As described in 'setting' above.	
Test is compared with an appropriate reference (gold) standard	Yes	Reference standard is observed CVD outcome (defined as first fatal and non-fatal major coronary events) over 10 years follow-up.	
Test is compared with the reference standard in all participants	Yes	Loss to follow-up not described.	
Blinded assessment of test and reference standard results	Yes	Not described, but given that risk is assessed at baseline, assessors are blind to the observed outcomes, which is the reference standard.	
Test and reference standard undertaken prior to any interventions	Unclear	Complete risk factor data (inclusion criteria) included use of antihypertensive medication and oral hypoglycaemic and insulin treatment.	
Level of evidence	II	Risk of bias	Very low
Results of study:			
CUORE equation	AUC = 0.742 [95% CI, 0.684–0.796]		

FRE	AUC = 0.723 [95% CI, 0.670–0.779]
PROCAM	AUC = 0.735 [95% CI, 0.678–0.790]
Other results of interest	No statistical differences between methods (reported but not shown). Predicted and observed risks were shown graphically. FRE and PROCAM overestimate risk in this population.

Evidence table: Comparison of different absolute CVD risk assessment methods			
Characteristics of study:			
Study citation	Orford JL, et al. A comparison of the Framingham and European Society of Cardiology coronary heart disease risk prediction models in the Normative Aging Study. <i>Am Heart J</i> 2002; 144(1): 95-100.		
Study ID	Orford 2002 [10]	Study design	Follow-up study
		N (total)	1393
Setting	Normative Aging Study, a population-based cohort. Participants recruited from the greater Boston area, USA.		
Participants	1393 community-dwelling males aged 30–74 years, predominantly white.		
Intervention/ Comparison	FRE 5 risk categories, FRE 20 risk categories, ESC risk prediction model (ESCRPM) 5 risk categories (compared with each other).		
Outcomes	Prediction of CVD, compared to observed data, measured by AUC (defined as c-statistic).		
Quality of study:			
Quality criteria:	Met?	Comments	
Specified inclusion/exclusion criteria	Yes	Described in 'participants'. Hypertension and diabetes excluded but not serum lipid abnormalities.	
Explicit description of participants	Yes	Described in 'participants' and table 1. Characteristics of participants.	
Appropriate spectrum of consecutively selected participants	Yes	Restricted to males.	
Prospective selection of participants	Yes	Not described, may be described elsewhere (ref 14), but likely given the design of the study.	
Test is compared with an appropriate reference (gold) standard	Yes	Reference standard is observed CVD outcome (defined as acute MI, old MI, AP and CHD death) over 10 years follow-up.	
Test is compared with the reference standard in all participants	Yes	Attrition rate of approximately 1% per year over the life of the study (established 1961, final year might be in ref 14, >6000 males) – not helpful for us.	
Blinded assessment of test and reference standard results	Yes	Not described, may be described elsewhere (ref 14), but given that risk is assessed at baseline, assessors are blind to the observed outcomes, which is the reference standard.	
Test and reference standard undertaken prior to any interventions	Unclear	Not described, may be described elsewhere (ref 14).	
Level of evidence	II	Risk of bias	Very low
Results of study:			
FRE 5 risk categories	AUC = 0.60		
FRE 20 risk categories	AUC = 0.63		
Other results of interest	Statistical difference between FRE 5 and FRE 20 for prediction of 10 year CVD risk not reported.		
ESCRPM 5 risk categories	AUC = 0.58		

Other results of interest	Statistical difference between FRE 5 and ESCRPM 5 for prediction of 10 year CVD risk not reported. Statistical difference between FRE 20 and ESCRPM 5 for prediction of 10 year CVD risk not reported.
FRE n (%)	Low risk (n=97): predicted=0–5 (0–5), observed=6 (6) Mild risk (n=399): predicted=20–40 (5–10), observed=38 (10) Moderate risk (n=611): predicted=61–122 (10–20), observed=99 (16) High (n=259): predicted=52–104 (20–40), observed=57 (22) Very high risk (n=27): predicted=>11 (>40), observed=6 (22)
ESCRPM n (%)	Low risk (n=6): predicted= (0–5), observed=0 (0) **n too low Mild risk (n=233): predicted=12–23 (0–5), observed=17 (7) Moderate risk (n=775): predicted=78–155 (10–20), observed=115 (15) High (n=378): predicted=75–151 (20–40), observed=74 (20) Very high risk (n=1): predicted=(>40), observed=0 (0) **n too low
Other results of interest	Authors conclude that both reliably stratify risk in the population; however, FRE underestimated CHD events in the low-risk group but overestimated CHD events in the very high risk group. ESCRPM overestimated CHD events in the high-risk group.

Evidence table: Comparison of different absolute CVD risk assessment methods				
Characteristics of study:				
Study citation	Wannamethee SG, et al. Metabolic syndrome vs Framingham Risk Score for prediction of coronary heart disease, stroke, and type 2 diabetes mellitus. Arch Intern Med 2005; 165(22): 2644-50.			
Study ID	Wannamethee 2005 [11]	Study design	Follow-up study	N (total) 5128
Setting	The British Regional Heart Study, participants 'drawn' from general practices in each of 24 towns in England, Wales & Scotland, UK.			
Participants	5128 males 40–59 years			
Intervention	FRE			
Comparison	MS (defined as in included study – Stern 2004)			
Outcomes	Prediction of CVD, compared to observed data, measured by AUC.			
Quality of study:				
Quality criteria:	Met?	Comments		
Specified inclusion/exclusion criteria	Yes	Males with prior CHD, stroke, known diabetes and asymptomatic hyperglycaemia were excluded. Males included if MS data available. Further info in ref 26.		
Explicit description of participants	Yes	As above in 'participants', table 1 and further info in ref 26.		
Appropriate spectrum of consecutively selected participants	Yes	Males only, age appropriate.		
Prospective selection of participants	Yes	Not described, may be described in ref 26, but likely given the design of the study.		
Test is compared with an appropriate reference (gold) standard	Yes	Reference standard is observed CVD outcome (defined as non-fatal MI, stroke and death) over 10 and 20 years follow-up.		
Test is compared with the reference standard in all participants	Yes	Loss to follow-up not described.		
Blinded assessment of test and reference standard results	Yes	Not described, may be described in ref 26, but given that risk is assessed at baseline, assessors are blind to the observed outcomes, which is the reference standard.		
Test and reference standard undertaken prior to any interventions	Some	Antihypertensive treatment is criteria for defining MS.		
Level of evidence	II	Risk of bias	Very low	
Results of study:				
FRE 10 years	AUC = 0.73 [95% CI, 0.71–0.75] Sensitivity = 56.5% Specificity = fixed at 75.0%			
MS 10 years	AUC = 0.63 [95% CI, 0.61–0.65] Sensitivity = 39.5% Specificity = fixed at 75.0%			
Other results of interest	FRE is more effective at predicting 10 risk of CVD than MS (p<0.001).			
FRE 20 years	AUC = 0.68 [95% CI, 0.66–0.70] Sensitivity = 47.2% Specificity = fixed at 75.7%			
MS 20 years	AUC = 0.59 [95% CI, 0.57–0.61] Sensitivity = 35.5% Specificity = fixed at 75.7%			
Other results of interest	FRE is more effective at predicting 20 year risk of CVD than MS (p<0.001).			

Evidence table: Comparison of different absolute CVD risk assessment methods			
Characteristics of study:			
Study citation	Stern MP, et al. (). Does the metabolic syndrome improve identification of individuals at risk of type 2 diabetes and/or cardiovascular disease? <i>Diabetes Care</i> 2004; 27(11): 2676-81.		
Study	Stern 2004 [12]	Study design	Population-based follow-up study
Setting	San Antonio Heart Study (USA) patients randomly selected from low-income, middle-income and high-income suburbs.		
Participants	Cohort of Mexican Americans, non-Hispanic whites, males and females, 25–64 years of age at baseline; 2758 at baseline and 2570 at 7–8 years after baseline exam.		
Intervention	FRE		
Comparison	FRE and MS; MS defined as meeting at least three of the National Cholesterol Education Program Adult Treatment Panel III [NCEP ATP-III] criteria: WC >102 cm (>40 in) in men and >88 cm (>35 in) in women, triglyceride concentration ≥ 1.70 mmol/L (150 mg/dL), HDL cholesterol <1.03 mmol/L (<40 mg/dL) in men and <1.29 mmol/L (<50 mg/dL) in women, BP $\geq 130/\geq 85$ mmHg or on hypertensive medication, and fasting glucose ≥ 6.1 mmol/L (≥ 110 mg/dL).		
Outcomes	Prediction of CVD, compared to observed data, measured by AUC.		
Quality of study:			
Quality criteria:	Met?	Comments	
Specified inclusion/exclusion criteria	Yes	At baseline, patients were required to be free of CVD and have the variables required to define MS or the FRE. Also, because one of the variables for defining MS is blood pressure $\geq 130/\geq 85$ mmHg or on antihypertensive medication, hypertensive individuals have been excluded.	
Explicit description of participants	No	No information provided on participant characteristics.	
Appropriate spectrum of consecutively selected participants	Some	Patients randomly selected from low-income, middle-income and high-income suburbs. Age group appropriate. No further information regarding method of selection.	
Prospective selection of participants	Unclear	As above.	
Test is compared with an appropriate reference (gold) standard	Yes	Reference standard is observed CVD outcome (defined as self-reported physician diagnosis of heart attack, revascularisation procedure, stroke or CVD death) over 7-8 years follow-up.	
Test is compared with the reference standard in all participants	Yes	188 patients were lost to follow-up.	
Blinded assessment of test and reference standard results	Unclear	Not described.	
Test and reference standard undertaken prior to any interventions	Some	One of the variables for defining MS is blood pressure $\geq 130/\geq 85$ mmHg or on antihypertensive medication.	
Level of evidence	II	Risk of bias	Very low
Results of study:			
FRE	AUC = 0.816 Sensitivity = 81.4% Specificity = fixed at 34.2%		

FRE & MS	AUC = 0.811 Sensitivity = 81.4% Specificity = fixed at 34.2%
Other results of interest	The difference in predictive ability of the two methods is not significant (p=0.10).

Evidence table: Comparison of different absolute CVD risk assessment methods			
Characteristics of study:			
Study citation	McNeill AM, et al. The metabolic syndrome and 11-year risk of incident cardiovascular disease in the Atherosclerosis Risk in Communities study. <i>Diabetes Care</i> 2005; 28(2): 385-90.		
Study ID	McNeill 2005 [13]	Study design	Follow-up study
		N (total)	12,089
Setting	ARIC study between 1987 and 1989 in 4 US communities in North Carolina, Mississippi, Minnesota and Maryland.		
Participants	12,089 black (1764 females, 1084 males) and white (5132 females, 4124 males) middle-aged (45–64 year old) individuals.		
Intervention	FRE		
Comparison	FRE and MS (MS defined as in included study – Stern 2004).		
Outcomes	Prediction of CVD, compared to observed data, measured by AUC.		
Quality of study:			
Quality criteria:	Met?	Comments	
Specified inclusion/exclusion criteria	Yes	Exclusions described in detail in 'research design and methods'. Excluded if prior CVD, race other than black or white, black participants residing in Minnesota or Maryland, missing data on MS, with prevalent diabetes.	
Explicit description of participants	Yes	As above in 'participants' and in table 1, baseline characteristics.	
Appropriate spectrum of consecutively selected participants	Yes	Large number of participants and age appropriate, but race exclusion and sample area may be restrictive.	
Prospective selection of participants	Yes	Not described. Population-based sample information may be described elsewhere (ref 15), but likely given the design of the study.	
Test is compared with an appropriate reference (gold) standard	Yes	Reference standard is observed CVD outcome (defined as incident CHD and ischaemic stroke events) over 11 years follow-up.	
Test is compared with the reference standard in all participants	Yes	No loss to follow-up.	
Blinded assessment of test and reference standard results	Yes	Not described, may be described elsewhere (ref 15), but given that risk is assessed at baseline, assessors are blind to the observed outcomes, which is the reference standard.	
Test and reference standard undertaken prior to any interventions	Unclear	Use of antihypertensive medication a requirement to calculate MS.	
Level of evidence	II	Risk of bias	Very low
Results of study:			
FRE	AUC = 0.731 (females) AUC = 0.634 (males)		
FRE & MS	AUC = 0.729 (females) AUC = 0.631 (males)		
Other results of interest	Statistical difference between the two methods not reported in either gender.		

Evidence table: Comparison of different absolute CVD risk assessment methods			
Characteristics of study:			
Study citation	Grover SA, et al. Identifying adults at increased risk of coronary disease: how well do the current cholesterol guidelines work? JAMA 1995; 274 (10): 801-806.		
Study	Grover 1995 [14]	Study design	Follow-up study
Setting	The Lipid Research Clinic Prevalence and Follow-up study was conducted from 1972 to 1987 in 10 North American clinics, USA.		
Participants	3678 males and females aged 35–74 years.		
Intervention	The Computer Risk Model (CHD Prevention Model), based on FRE.		
Comparison	Canadian Consensus Conference on Cholesterol (CCCC), first (NCEP I) and second (NCEP II) National Cholesterol Education Programs		
Outcomes	Prediction of CVD, compared to observed data in the form of AUCs.		
Quality of study:			
Quality criteria:	Met?	Comments	
Specified inclusion/exclusion criteria	Yes	Excluded if participants have history of CVD.	
Explicit description of participants	Yes	In text, as above and more detail may be in original refs.	
Appropriate spectrum of consecutively selected participants	Yes	Appropriate age group, not sure how many males: females, data not separated by gender.	
Prospective selection of participants	Yes	Not described, but likely given the design of the study.	
Test is compared with an appropriate reference (gold) standard	Yes	Reference standard is observed CVD outcome (defined as CHD mortality/deaths) over 12.2 years follow-up.	
Test is compared with the reference standard in all participants	Unclear	Vital status of 99% of the participants was established at least once during the follow-up period.	
Blinded assessment of test and reference standard results	Yes	Not described, but given that risk is assessed at baseline, assessors are blind to the observed outcomes, which is the reference standard.	
Test and reference standard undertaken prior to any interventions	Unclear	Participants were excluded if they were taking lipid-altering medication.	
Level of evidence	II	Risk of bias	Very low
Results of study:			
CHD Prevention Model	AUC = 0.85 ± 0.02		
CCCC	AUC = 0.70 ± 0.03		
NCEPI	AUC = 0.72 ± 0.03		
NCEPII	AUC = 0.74 ± 0.03		
Notes	NCEP II better than NCEP I p<0.03; CHD Prevention Model better than all others p<0.03.		

Evidence table: Comparison of different absolute CVD risk assessment methods			
Characteristics of study:			
Study citation	Folsom AR, et al. Prediction of coronary heart disease in middle-aged adults with diabetes. Diabetes Care 2003; 26(10): 2777-84.		
Study ID	Folsom 2003 [15]	Study design	Follow-up study
Setting	Sample from four US communities in the Atherosclerosis Risk in Communities (ARIC) study.		
Participants	45–64 years of age; 12,554 without diabetes (10,885 after loss to follow-up), 1500 with diabetes (1237 after loss to follow-up)		
Intervention	Basic (age, race, TC, HDL cholesterol, systolic BP, use of antihypertensive medication and smoking status)		
Comparison	Basic + non-traditional RFs + subclinical disease markers – BMI, WHR, lipoprotein(a), albumin, creatinine, WBC count, fibrinogen, factor VIII, sport activity index, Keys score, LVH, IMT (continuous).		
Outcomes	Prediction of CVD, compared to observed data, measured by AUC.		
Quality of study:			
Quality criteria:	Met?	Comments	
Specified inclusion/exclusion criteria	Yes	At baseline, patients were required to be free of CVD and have RF or BMI data available. Individuals who were not black or white and not those who were black in two centres (due to small numbers) were excluded.	
Explicit description of participants	Yes	Table 1 – lipid and BP profiles.	
Appropriate spectrum of consecutively selected participants	Yes	Age appropriate, not sure about exclusions.	
Prospective selection of participants	Yes	Not described, but likely given the design of the study.	
Test is compared with an appropriate reference (gold) standard	Yes	Reference standard is observed CVD outcome (a CHD event, defined as a validated definite or probable hospitalised MI, a definite CHD death, an unrecognised MI defined by ARIC ECG readings, or coronary revascularisation) over 10 years follow-up.	
Test is compared with the reference standard in all participants	Yes	Total 1932 lost to follow-up – 1669 without diabetes lost to follow-up, and 263 with diabetes lost to follow-up	
Blinded assessment of test and reference standard results	Yes	Not described, but given that risk is assessed at baseline, assessors are blind to the observed outcomes, which is the reference standard.	
Test and reference standard undertaken prior to any interventions	Some	One of the required RFs in the comparison group is use of antihypertensive medication.	
Level of evidence	II	Risk of bias	Very low
Results of study:			

Basic	AUC = 0.709 (females with diabetes) AUC = 0.779 (females without diabetes) AUC = 0.682 (males with diabetes) AUC = 0.680 (males without diabetes)
Basic + non-traditional RFs + subclinical disease markers	AUC = 0.776 (females with diabetes) AUC = 0.792 (females without diabetes) AUC = 0.763 (males with diabetes) AUC = 0.716 (males without diabetes)
Other results of interest	Significant differences between comparisons were $p < 0.05$. Basic was also compared with basic with other RFs either added or removed one at a time from this model (BMI, WHR, lipoprotein(a), albumin, creatinine, WBC count, fibrinogen, factor VIII, sport activity index, residual FEV ₁ , Keys score, pack-years smoking); however there were no significant differences between models.

Articles that use risk assessment methods to divide populations into categories of risk

Evidence table: Use of risk assessment to divide into categories of risk			
Characteristics of study:			
Study citation	Leaverton PE, et al. Representativeness of the Framingham risk model for coronary heart disease mortality: a comparison with a national cohort study. J Chronic Dis 1987; 40: 775-84		
Study	Leaverton 1987 [16]	Study design	Follow-up study
Setting	Two cohorts of (whites): Framingham, Massachusetts; First National Health and Nutrition Examination Survey (NHANES I), conducted in a probability sample of the civilian non-institutionalised population of the US, 1971–1993.		
Participants	FRE cohort: 1778 males and 2235 females aged 41–74 years. NHANES I cohort: 1902 males and 2111 females aged 40–74 years.		
Intervention	FRE and NHANES I scores applied to the cohorts in which they were not derived.		
Comparison	Observed data over 10 years.		
Outcomes	Prediction of CVD, compared to observed data in the form of percent of observed cases divided by quintiles of risk.		
Quality of study:			
Quality criteria:	Met?	Comments	
Specified inclusion/exclusion criteria	Yes	Excluded if participant has prior CVD history.	
Explicit description of participants	Yes	Methods study population and table 1.	
Appropriate spectrum of consecutively selected participants	Yes	Good age range, whites only.	
Prospective selection of participants	Yes		
Test is compared with an appropriate reference (gold) standard	Yes	Reference standard is observed CVD outcome (defined as CVD or death, non-fatal CHD or stroke) over 10 years follow-up.	
Test is compared with the reference standard in all participants	Some	In the NHANES I cohort of 4013 participants, 4% were lost to follow-up and 3% died of unknown causes. In the Framingham cohort, of the 4013 participants, fewer than 2% were lost to follow-up.	
Blinded assessment of test and reference standard results	Yes	Not described, but given that risk is assessed at baseline, assessors are blind to the observed outcomes, which is the reference standard.	
Test and reference standard undertaken prior to any interventions	Unclear	Not described.	
Level of evidence	II	Risk of bias	Very low
Results of study:			
FRE	Numbers of observed events are presented for each risk quintile; however the number of events expected is not reported. When applied to males and females in the NHANES I cohort, FRE has similar discriminatory ability and higher event rates were reported in the high-risk categories with a steady decrease in rates, and remaining events were appropriately distributed over lower risk categories. These data were presented graphically.		

NHANES I	Numbers of observed events are presented for each risk quintile; however the number of events expected is not reported. When applied to males and females in the Framingham cohort, NHANES I has similar discriminatory ability and higher event rates were reported in the high-risk categories with a steady decrease in rates, and remaining events were appropriately distributed over lower risk categories. These data were presented graphically.
Notes	Observed rates were appropriately distributed between quintiles of risk.

Evidence table: Use of risk assessment to divide into categories of risk			
Characteristics of study:			
Study citation	Kornitzer M, Koyunco R. Multifactorial approach to the prevention of coronary heart disease: from computer to paper and pencil? J Cardiovasc Risk 2000; 7: 201-207.		
Study	Kornitzer 2000 [17]	Study design	Follow-up study
Setting	Two cohorts: 1) Belgian Inter-university Research on Nutrition and Health (BIRNH), Belgian population from 42 Belgian districts, 3 communes were randomly chosen from census lists; 2) Belgian Physical Fitness Study (BPFS) (ref 18).		
Participants	BIRNH, 4310 males and females aged 30–74 years; BPFS, 2186 males aged 40–55 years.		
Intervention	FRE and Global Coronary Risk Score (GCRS).		
Comparison	Observed data over 10 years.		
Outcomes	Prediction of CVD, compared to observed data in the form of percentage of observed cases divided by quartiles of risk.		
Quality of study:			
Quality criteria:	Met?	Comments	
Specified inclusion/exclusion criteria	Yes	Excluded if participant has prior CVD history.	
Explicit description of participants	Yes	Described in detail in the methods section.	
Appropriate spectrum of consecutively selected participants	Unclear	Low (38%) participation rate in BIRNH.	
Prospective selection of participants	Yes		
Test is compared with an appropriate reference (gold) standard	Yes	Reference standard is observed CVD outcome (defined as CHD death) over 10 years follow-up.	
Test is compared with the reference standard in all participants	Some	Vital status was known for 99% of the sample. Cause-specific mortality known for 90% of deaths.	
Blinded assessment of test and reference standard results	Yes	Not described, but given that risk is assessed at baseline, assessors are blind to the observed outcomes, which is the reference standard.	
Test and reference standard undertaken prior to any interventions	Unclear	Not described.	
Level of evidence	II	Risk of bias	Very low
Results of study: (over page)			

FRE in BIRNH and BPFS	<p>Numbers of observed events are presented for each risk quartile, however the number of events expected is not reported.</p> <p>In males in all age groups in the BIRHN cohort, FRE has similar discriminatory ability and higher event rates were reported in the high-risk categories with a steady decrease in rates, and remaining events were appropriately distributed over lower risk categories. In females aged 50–74 years, FRE did not accurately discriminate between the two lowest quartiles.</p> <p>In males aged 40–55 years in the BPFS cohort, FRE has similar discriminatory ability and higher event rates were reported in the high-risk categories with a steady decrease in rates, and remaining events were appropriately distributed over lower risk categories.</p>
GCRS in BPFS	<p>Numbers of observed events are presented for each risk quartile, however the number of events expected is not reported. In males aged 40–55 years in the BPFS cohort, GCRS has similar discriminatory ability and higher event rates were reported in the high-risk categories with a steady decrease in rates, and remaining events were appropriately distributed over lower risk categories.</p>
Notes	<p>Observed rates were appropriately distributed between quintiles of risk.</p>

Evidence table: Use of risk assessment to divide into categories of risk				
Characteristics of study:				
Study citation	Persson M, et al. Risk stratification by guidelines compared with risk assessment by risk equations applied to a MONICA sample. <i>J Hypertens</i> 2003, 21: 1089-1095.			
Study	Persson 2003 [18]	Study design	Follow-up study	N (total) 5997
Setting	Northern Sweden Hypertensive Population.			
Participants	5997 participants with hypertension from Northern Sweden, aged 30–74 years, taken from the NSW MONICA study, the 1986 cohort (n = 1320), 1990 cohort (n = 1266), 1994 cohort (n = 1591) and new random sample in 1999 (n = 1826). Follow-up was until 31 Dec 2000.			
Intervention	<ol style="list-style-type: none"> 1. FRE. 2. Northern Sweden MONICA risk equation. 3. Risk stratification by 1999 WHO Hypertension guidelines. 			
Comparison	Observed CVD endpoints followed up for between 1 and 14 years.			
Outcomes	The investigators aimed to compare the predictive ability and distribution of cardiovascular risk in people with hypertension with different risk assessment methods when applied to the same set of individuals.			
Quality of study:				
Quality criteria:	Met?	Comments		
Specified inclusion/exclusion criteria	Yes	Excluded if participant has prior CVD history.		
Explicit description of participants	No	No explicit description given including sex distribution.		
Appropriate spectrum of consecutively selected participants	Yes	5997 participants with hypertension from Northern Sweden, age range appropriate, gender distribution not given.		
Prospective selection of participants	Yes			
Test is compared with an appropriate reference (gold) standard	No	Reference standard is observed CVD outcome (defined as acute MI or stroke). Duration of follow-up is poorly described and varies between 1 and 14 years. All subarachnoid haemorrhage or transitory ischaemic attacks were excluded.		
Test is compared with the reference standard in all participants	Yes	Out of 8359 invited, 6000 accepted (72%), and 5997 with recorded blood pressure values.		
Blinded assessment of test and reference standard results	Yes	Not described, but given that risk is assessed at baseline, assessors are blind to the observed outcomes, which is the reference standard.		
Test and reference standard undertaken prior to any interventions	No	Implied that participants were being treated for hypertension.		
Level of evidence	III–2	Risk of bias	High	
Results of study (over page):				

Results of interest	<p>The agreement between the methods was good when the values obtained from the risk equation were averaged for each risk group.</p> <p>With predicted risk for each individual, the agreement was poor for the medium and high-risk groups.</p> <p>Risk classification by the 1999 WHO/ISH hypertension guidelines is not accurate and detailed enough for medium and high-risk patients, which could be of clinical importance in the medium-risk group.</p>
Notes:	<p>Adjustments were made for the lack of data on HDL. The value 1.0 was used for all subjects in the equation.</p> <p>The FRE for 10-year risk of MI or stroke was used, yet the participants were followed up for a variable amount of time from between 20 years, and for the year 1999 cohort, only approximately 12 months. Data are only presented graphically.</p> <p>Since the HDL value was not included as a risk factor and data on HDL were not available for the MONICA sample, the value 1.0 was used for all subjects in the equation. Information on LVH was not available in the NSW MONICA population, and this value was therefore set to negative for all subjects.</p>

Articles that assess predictive ability of an absolute CVD risk assessment method

Evidence table: Assessment of predictive ability of an absolute CVD risk assessment method			
Characteristics of study:			
Study citation	D'Agostino RB, et al. Validation of the Framingham Coronary Heart Disease Prediction Scores. JAMA 2001; 286; 2.		
Study	D'Agostino 2001 [19]	Study design	Follow-up study
Setting	Six ethnically diverse cohorts.		
Participants	<p>32,886 participants (20,985 males and 11,901 females) from six ethnically diverse cohorts with an overall age range 30 to 88 years:</p> <p>1) ARIC – Atherosclerosis Risk in Communities study (1987–1999); male and female, white and black, aged 45–64 with 7.2 years follow-up; outcomes include MI (including silent), fatal CHD, cardiac procedures</p> <p>2) PHS – Physicians' Health Study (1982); males with higher than average socioeconomic status, aged 40–84 with 5 years follow-up; outcomes include MI</p> <p>3) HHP – Honolulu Heart Program (1980–1982); Japanese American males, aged 45–64 with 5 years follow-up; outcomes including CHD incidence</p> <p>4) PRHHP – Puerto Rico Heart Health Program (1965–1968); Hispanic males, aged 35–74 with 5 years follow-up; outcomes including hard CHD events</p> <p>5) SHS – Strong Heart Study (1989–1991); Native American males and females, aged 35–74 with 5 years follow-up; outcomes including CHD morbidity and mortality</p> <p>6) CHS – Cardiovascular Health Study (1989–1990); older adult males and females, aged 65–74 with 5 years follow-up; outcomes including CHD morbidity and mortality.</p>		
Intervention	FRE		
Comparison	CHD endpoints of coronary death and MI followed up over 5 years.		
Outcomes	Prediction of CVD, compared to observed data in the form of AUCs.		
Quality of study:			
Quality criteria:	Met?	Comments	
Specified inclusion/exclusion criteria	Yes	Not explicitly stated. Study refers to 'similar' criteria as Framingham population. When original references are sourced, all studies have excluded people with prior CVD.	
Explicit description of participants	Yes	Appropriate descriptions given in tables within the article.	
Appropriate spectrum of consecutively selected participants	Yes		
Prospective selection of participants	Yes		
Test is compared with an appropriate reference (gold) standard	Yes	Reference standard is observed CVD outcome (defined above) over 5 years follow-up. It is not stated how these endpoints were assessed.	
Test is compared with the reference standard in all participants	Yes	Implied minimal loss of participants.	

Blinded assessment of test and reference standard results	Yes	Not described, but given that risk is assessed at baseline, assessors are blind to the observed outcomes, which is the reference standard.	
Test and reference standard undertaken prior to any interventions	Unclear	Not described.	
Level of evidence	II	Risk of bias	Very low
Results of study:			
FRE	AUC = 0.75		
Men in ARIC (white)	AUC = 0.67		
in ARIC (black)	AUC = 0.63		
in PHS (white)	AUC = 0.72		
in HHP (Japanese American)	AUC = 0.69		
in PR (Hispanic)	AUC = 0.69		
in SHS (Native American)	AUC = 0.63		
in CHS (white)	AUC = 0.83		
Women in ARIC (white)	AUC = 0.79		
in ARIC (black)	AUC = 0.75		
in SHS (Native American)	AUC = 0.66		
in CHS (white)			
Other results of interest	Predicted and observed rates were presented graphically. In white and black males and females, predicted events using the FRE and observed event rates were similar for 5 year CVD risk. However among Japanese American and Hispanic males, and Native American females, the FRE overestimated 5 year CVD risk.		

Evidence table: Assessment of predictive ability of an absolute CVD risk assessment method				
Characteristics of study:				
Study citation	Diverse Populations Collaborative Group. Prediction of mortality from coronary heart disease among diverse populations: is there a common predictive function? Heart 2002; 88(3): 222-28.			
Study	DPCG 2002 [20]	Study design	Follow-up study	N (total) 161,955
Setting	18 ethnically diverse cohorts.			
Participants	<p>161,955 participants (105,420 males and 56,535 females) from 18 cohorts with an overall age range of 35–74 years:</p> <ol style="list-style-type: none"> 1) NHANES I – First National Health & Nutrition Examination Survey, 3856 males and females aged 35–74 2) NHANES II – Second National Health & Nutrition Examination Survey, 3354 males and females aged 35–74 3) Tecumseh Community Health Study, 1257 males and females aged 35–74 4) HHP – Honolulu Heart Program, 7625 males aged 45–68 5) PRHHP Urban – Puerto Rico Heart Health Program, 6612 males aged 35–74 6) PRHHP Rural – Puerto Rico Heart Health Program, 2879 males aged 35–74 7) YU – Yugoslavia Cardiovascular Disease Study (Urban), 3472 males aged 35–64 8) YR – Yugoslavia Cardiovascular Disease Study (Rural), 2868 males aged 35–62 9) SCS – Scottish Collaborative Study, 5734 males aged 35–74 10) Renfrew – Renfrew and Paisley Study, 6999 males and females aged 45–64 11) Israel IHD – Israeli Ischemic Heart Disease Study, 9712 males aged 40–73 12) GPS – Glostrup Population Study, 3844 males aged 39–71 13) NCS – Norwegian Counties Study, 24,204 males and females aged 35–49 14) RIS – Reykjavik Iceland Study, 8151 males and females aged 36–74 15) LRC Random – Lipid Research Clinics Prevalence Study, 1992 males aged 35–74 16) LRC Hyperlip – Lipid Research Clinics Prevalence Study, 1628 males aged 35–74 17) HDFP RC – Hypertension Detection and Follow-up Program (control group), 2531 males and females aged 35–69 18) Mrfit UC – Multiple Risk Factor Intervention Trial (control group), 6428 males aged 35–58. 			
Intervention	FRE			
Comparison	Observed CVD outcome is CHD death over 8 years follow-up.			
Outcomes	Prediction of CHD death, compared to observed data in the form of AUCs.			
Quality of study:				
Quality criteria:	Met?	Comments		
Specified inclusion/exclusion criteria	Yes	All participants free of CVD at baseline.		

Explicit description of participants	Yes	Appropriate descriptions given in tables within the article.	
Appropriate spectrum of consecutively selected participants	Yes		
Prospective selection of participants	Yes		
Test is compared with an appropriate reference (gold) standard	Yes	Reference standard is observed CVD outcome (CHD death) over 8 years follow-up.	
Test is compared with the reference standard in all participants	Unclear	Loss to follow-up not described.	
Blinded assessment of test and reference standard results	Yes	Not described, but given that risk is assessed at baseline, assessors are blind to the observed outcomes, which is the reference standard.	
Test and reference standard undertaken prior to any interventions	Unclear	Not described.	
Level of evidence	II	Risk of bias	Very low
Results of study:			
FRE Males:	AUC = 0.73		
NHANES I	AUC = 0.77		
NHANES II	AUC = 0.81		
Tecumseh	AUC = 0.78		
HHP	AUC = 0.75		
PRHHP (Urban)	AUC = 0.77		
PRHHP (Rural)	AUC = 0.82		
YU	AUC = 0.76		
YR	AUC = 0.73		
SC	AUC = 0.68		
Renfrew	AUC = 0.79		
Israel IHD	AUC = 0.77		
GPS	AUC = 0.72		
NCS	AUC = 0.75		
RIS	AUC = 0.81		
LRC Random	AUC = 0.77		
LRC Hyperlip	AUC = 0.72		
HDFP RC	AUC = 0.65		
Mrfit UC			

FRE Women:	
NHANES I	AUC = 0.82
NHANES II	AUC = 0.78
Tecumseh	AUC = 0.88
Renfrew	AUC = 0.74
NCS	AUC = 0.82
RIS	AUC = 0.80
HDFP RC	AUC = 0.77
Other results of interest	Predicted and observed rates were presented graphically. In males, FRE tended to overpredict absolute risk in populations with a low observed CHD mortality and to underpredict risk in populations with a high CHD mortality. In females, FRE underpredicted 8 year CHD mortality for five cohorts.

Evidence table: Assessment of predictive ability of an absolute CVD risk assessment method				
Characteristics of study:				
Study citation	West of Scotland Coronary Prevention Study Group. Influence of pravastatin and plasma lipids on clinical events in the West of Scotland Coronary Prevention Study (WOSCOPS). <i>Circulation</i> 1998; 97(15): 1440-1445.			
Study	WOSCOPS 1998 [21]	Study design	Cohort study (RCT for drug-related)	N (total) 3293
Setting	West of Scotland Coronary Prevention Study.			
Participants	A total of 3293 males, 45–64 years of age, with no history of CVD (Group B = 2042); 1251 of these were included based on strict criteria matched to Framingham (Group A; restrictions on plasma lipids: cholesterol 4.13–7.23 mmol/L; DBP 70–105 mmHg; SDP 110–170 mmHg).			
Intervention	FRE			
Comparison	Observed data over 4.4 years.			
Outcomes	Prediction of CVD, compared to observed data in the form of event rate per 100 participants over 4.4 years.			
Quality of study:				
Quality criteria:	Met?	Comments		
Specified inclusion/exclusion criteria	Yes	Excluded if prior history of CVD.		
Explicit description of participants	Yes	In text and described in further detail in refs 4 and 12.		
Appropriate spectrum of consecutively selected participants	Some	Study is in males only.		
Prospective selection of participants	Yes	Not described, but likely given the design of the study.		
Test is compared with an appropriate reference (gold) standard	Yes	Reference standard is observed CVD outcome, defined as non-fatal MI or CHD death plus revascularisation (PTCA or CABG), over 4.4 years follow-up.		
Test is compared with the reference standard in all participants	Unclear	Loss to follow-up not described.		
Blinded assessment of test and reference standard results	Yes	Not described, but given that risk is assessed at baseline, assessors are blind to the observed outcomes, which is the reference standard.		
Test and reference standard undertaken prior to any interventions	Unclear			
Level of evidence	II	Risk of bias	Very low	
Results of study:				
FRE (event rate per 100 participants)	Group A: predicted = 7.6, observed = 7.0 (p=0.58) Group B: predicted = 8.5, observed = 8.3 (p=0.86)			
Notes	Participants with cancer have been excluded.			

Evidence table: Assessment of predictive ability of an absolute CVD risk assessment method			
Characteristics of study:			
Study citation	Milne R, et al. Framingham Heart Study risk equation predicts first cardiovascular event rates in New Zealanders at the population level. N Z Med J 2003; 116 (1185): U662.		
Study	Milne 2003 [22]	Study design	Follow-up study
Setting	The Fletcher Challenge-University of Auckland Heart and Health Study, New Zealand, consisting of two sources: the workforce of a nationwide multi-industry corporation (Fletcher Challenge Ltd) and the general electoral rolls of the Auckland metropolitan region.		
Participants	4638 males (73%) and 1716 females (27%) aged 35–74 years. 10% of participants were Maori, 5% were Pacific people and 85% were European or other ethnicity.		
Intervention	FRE		
Comparison	Observed data over 5 years.		
Outcomes	Prediction of CVD, compared to observed data in the form of observed incident events per 1000 persons over 5 years.		
Quality of study:			
Quality criteria:	Met?	Comments	
Specified inclusion/exclusion criteria	Yes	Excluded if participant has prior CVD history.	
Explicit description of participants	Yes	Methods study population, table 1, more detail may be found in refs 6 and 7.	
Appropriate spectrum of consecutively selected participants	Yes	Although not even contribution of males:females, good age range, small contribution of non-European people.	
Prospective selection of participants	Yes	Not described, but likely given the design of the study. More detail may be found in refs 6 and 7.	
Test is compared with an appropriate reference (gold) standard	Yes	Reference standard is observed CVD outcome (defined as IHD, cerebrovascular disease, CHF, PVD or IC) over 5 years follow-up.	
Test is compared with the reference standard in all participants	Unclear	The authors report that 84 males and 33 females (1.8% of the total) had missing values of one or more risk factors and thus risk estimates for these people could not be made. The authors also report that four of the males but none of these women experienced a first-ever CVD event. It is not clear if these people are accounted for in the above N.	
Blinded assessment of test and reference standard results	Yes	Not described, but given that risk is assessed at baseline, assessors are blind to the observed outcomes, which is the reference standard.	
Test and reference standard undertaken prior to any interventions	No	Some diabetic participants were taking diabetic medication.	
Level of evidence	II	Risk of bias	Very low
Results of study:			
FRE	When using FRE in males and females, the number of observed events were very close to the predicted number of events in all age groups except females aged 70–74 years. Similar findings were reported when male and female data were combined. These data were presented graphically.		

Evidence table: Assessment of predictive ability of an absolute CVD risk assessment method				
Characteristics of study:				
Study citation	Bastuji-Garin S, et al. The Framingham prediction rule is not valid in a European population of treated hypertensive patients. J Hypertens 2002, 20: 1973-1980.			
Study	Bastuji-Garin 2002 [23]	Study design	Follow-up study	N (total) 4147
Setting	Eight countries of Western Europe and Israel.			
Participants	4147 hypertensive participants from eight countries of Western Europe and Israel, aged less than 75 years (mean age 64.1 ± 1.6 years); 2436 females and 1971 males.			
Intervention	FRE			
Comparison	Observed CHD endpoints with follow-up median of 3.7 years.			
Outcomes	Prediction of CVD, compared to observed data.			
Quality of study:				
Quality criteria:	Met?	Comments		
Specified inclusion/exclusion criteria	Yes	Excluded if participant has prior CVD history.		
Explicit description of participants	Yes	Detailed description presented within study and tables.		
Appropriate spectrum of consecutively selected participants	Yes	Mean age 64.1 ± 1.6 years; 2436 females and 1971 males. Participants were originally recruited as part of the International Nifedipine GITS Study; 'Intervention as a Goal in Hypertension Treatment' (INSIGHT). Patients from the two INSIGHT study groups were included because the two antihypertensive drugs were shown to be equally effective.		
Prospective selection of participants	Yes	Not described, but likely given the design of the study.		
Test is compared with an appropriate reference (gold) standard	No	FRE prediction is considered valid for 4–12 years; however this study only has 3.7 years follow-up, therefore a valid reference standard has not been used. Observed CHD outcomes included fatal and non-fatal MI, cardiovascular death and AP, fatal and non-fatal stroke, transient ischaemic attack and subarachnoid haemorrhage (for stroke equation). Fatal and non-fatal heart failure and cerebrovascular death of other origin.		
Test is compared with the reference standard in all participants	Yes			
Blinded assessment of test and reference standard results	Yes	Not explicitly stated but implied by study design.		
Test and reference standard undertaken prior to any interventions	No	Population were treated hypertensive patients.		
Level of evidence	III–2	Risk of bias	High	
Results of study:				

FRE	CVD: predicted/observed = 13% / 5% = 2.6 CHD: predicted/observed = 7% / 3% = 2.3 Stroke: predicted/observed = 2% / 2% = 1.0
Notes	FRE overpredicted in this population.

Evidence table: Assessment of predictive ability of an absolute CVD risk assessment method				
Characteristics of study:				
Study citation	(1) Suka M, et al. Validity of the Framingham Risk Model Applied to Japanese Men. <i>Methods Inf Med</i> 2001; 41: 213-215. [24] A second analysis of this cohort was conducted: (2) Suka M, et al. Application of the updated Framingham risk score to Japanese men. <i>Hypertens Res</i> 2001; 24(6): 685-9. [24]			
Study	Suka 2001 [24] [24]	Study design	Follow-up study	N (total) 5611
Setting	Longitudinal large cohort from an employee health management centre in a Japanese company.			
Participants	5611 males, aged 30–59 years.			
Intervention	FRE predicted for 10 years.			
Comparison	Observed CHD events.			
Outcomes	Prediction of CVD, compared to observed data in the form of AUCs.			
Quality of study:				
Quality criteria:	Met?	Comments		
Specified inclusion/exclusion criteria	Yes	Excluded if participant has existing CVD.		
Explicit description of participants	No	No table or detailed description of baseline characteristics of participants given.		
Appropriate spectrum of consecutively selected participants	Unclear	Males only, from a single company, age appropriate.		
Prospective selection of participants	Yes			
Test is compared with an appropriate reference (gold) standard	No	Reference standard is observed CVD outcome, defined as (1) CHD, MI or AP, (2) CHD, MI, AP or coronary insufficiency. Although FRE 10 year risk was predicted, follow-up was only for 5–7 years.		
Test is compared with the reference standard in all participants	Yes			
Blinded assessment of test and reference standard results	Unclear	Method of data collection leaves open the possibility of bias with no explicit description of steps taken to ensuring effective blinding.		
Test and reference standard undertaken prior to any interventions	Unclear	Not explicitly stated		
Level of evidence	III–2	Risk of bias	High	
Results of study:				
FRE (1)	AUC = 0.62 At 15% cut-off, sensitivity = 0.57 specificity = 0.72 Predicted and observed rates were presented graphically and FRE appeared to overestimated risk.			
FRE (2)	AUC = 0.71 At 15% cut-off, sensitivity = 0.59 specificity = 0.74			

Evidence table: Assessment of predictive ability of an absolute CVD risk assessment method			
Characteristics of study:			
Study citation	Zanchetti A, et al. Risk assessment and treatment benefit in intensively treated hypertensive patients of the Hypertension Optimal Treatment (HOT) study. J Hypertens 2001; 19: 819-825.		
Study	Zanchetti 2001 [25]	Study design	Follow-up study
Setting	The HOT study included and followed up participants from Europe (14,594), USA and Canada (3484), Latin America (96) and Asia (616). Total = 18,790 for a total of 71,051 patient-years.		
Participants	18,790 hypertensive participants with a baseline DBP between 100 and 115 mmHg. There were 9400 (50% of ,) medium-risk participants (47% males and 53% females, average age 80.2 ± 7) and 5595 (20.2% of 18,790) high-risk participants (62% males and 38% females, average age 80.6 ± 7.2). Inclusion for WHO/ISH guidelines is males >55 years and females >65 years.		
Intervention	FRE and WHO/ISH		
Comparison	Observed data		
Outcomes	Prediction of CVD, compared to observed data in the form of observed event per 1000 patient-years.		
Quality of study:			
Quality criteria:	Met?	Comments	
Specified inclusion/exclusion criteria	Yes	Participants were separated into low, medium, high risk, very high risk groups by WHO/ISH criteria. There were no data from the low-risk group. The very high risk group included participants with prior CVD history so data from this group have been excluded.	
Explicit description of participants	Yes	In text and see table 1.	
Appropriate spectrum of consecutively selected participants	Some	Large sample, even contribution of males: females, but not sure of the age range.	
Prospective selection of participants	Yes	Not described, but likely given the design of the study.	
Test is compared with an appropriate reference (gold) standard	No	Reference standard is observed CVD outcome (all major cardiovascular events was defined as the sum of all fatal and non-fatal MI, all fatal and non-fatal stroke and any other CVD death; all MI, all stroke, cardiovascular mortality and total mortality were considered separately) over a total of 71,051 patient-years follow-up, which is 3.78 years per participant on average, below the lower limit of FRE validation of 4 years.	
Test is compared with the reference standard in all participants	Unclear	Loss to follow-up not described.	
Blinded assessment of test and reference standard results	Yes	Not described, but given that risk is assessed at baseline, assessors are blind to the observed outcomes, which is the reference standard.	
Test and reference standard undertaken prior to any interventions	No	Hypertensive treatment was the subject of investigation in this study, so all participants were on blood pressure lowering therapy.	
Level of evidence	III-2	Risk of bias	High
Results of study:			

FRE (event per 1000 patient-years)	Medium risk: MI + stroke expected = 16, observed = 5 High risk: MI + stroke expected = 18, observed = 6.6
WHO/ISH guidelines (event per 1000 patient-years)	Medium risk: all major cardiovascular events expected = 15–20, observed = 6.4 High risk: all major cardiovascular events expected = 20–30, observed = 9.1

Evidence table: Assessment of predictive ability of an absolute CVD risk assessment method			
Characteristics of study:			
Study citation	Simons LA, et al. Risk functions for prediction of cardiovascular disease in elderly Australians: the Dubbo study. MJA 2003; 178: 113-116.		
Study	Simons 2003 [26]	Study design	Cohort study
Setting	The Dubbo study is an ongoing prospective study in an elderly Australian cohort started in 1988. All non-institutionalised residents of the semi-urban town of Dubbo, NSW (population 34,000), born before 1930 were eligible and the participation rate was 73%.		
Participants	1800 males (755) and females (1045), aged 60–79 years, free of CVD or diabetes. 60–64 years: 696 (M=310 F=386) 65–69 years: 504 (M=214 F=290) 70–74 years: 374 (M=149 F=225) 75–79 years: 226 (M=82 F=144)		
Intervention	FRE		
Comparison	Observed data over 10 years.		
Outcomes	Prediction of CVD, compared to observed data in the form of observed and predicted CHD incidence rates/100 subjects.		
Quality of study:			
Quality criteria:	Met?	Comments	
Specified inclusion/exclusion criteria	Yes	Excluded if prior history of CVD or diabetes.	
Explicit description of participants	Yes	In text, more info in ref 12.	
Appropriate spectrum of consecutively selected participants	Yes	Of the population of Dubbo, participation rate was 73% before exclusion of prior CVD and diabetes. Data separated by age groups and gender.	
Prospective selection of participants	Yes		
Test is compared with an appropriate reference (gold) standard	Yes	Reference standard is observed CVD outcome (CHD, defined as MI, CD or stroke) over 10 years follow-up.	
Test is compared with the reference standard in all participants	Mostly	At 10 years more than 95% follow-up.	
Blinded assessment of test and reference standard results	Yes	Not described, but given that risk is assessed at baseline, assessors are blind to the observed outcomes, which is the reference standard.	
Test and reference standard undertaken prior to any interventions	No	BP treatment status is a factor in the FRE calculation.	
Level of evidence	II	Risk of bias	Very low
Results of study (over page):			

FRE (incidence rates/100 participants)	<p>Males:</p> <p>60–64 years – observed = 10.3, predicted = 11.9 65–69 years – observed = 13.6, predicted = 16.5 70–74 years – observed = 16.8, predicted = 16.5 75–79 years – observed = 23.3, predicted = 22.1</p> <p>Females:</p> <p>60–64 years – observed = 4.9, predicted = 4.6 65–69 years – observed = 7.6, predicted = 9.0 70–74 years – observed = 11.1, predicted = 10.7 75–79 years – observed = 14.6, predicted = 18.2</p>
Notes	<p>X² tests showed no significant differences between observed and predicted rates for each age group.</p>

Evidence table: Assessment of predictive ability of an absolute CVD risk assessment method				
Characteristics of study:				
Study citation	Assmann G, et al. Simple scoring scheme for calculating the risk of acute coronary events based on the 10-year follow-up of the Prospective Cardiovascular Münster (PROCAM) Study. <i>Circulation</i> 2002; 105: 310-315.			
Study	Assmann 2002 [27]	Study design	Follow-up study	N (total) 5389
Setting	The Prospective Cardiovascular Münster (PROCAM) Study, sampled from 20,060 employees of 52 companies and local government authorities within a radius of approximately 100 km around the city of Münster in the northwest of Germany from 1979 to 1985.			
Participants	5389 males 35–65 years of age.			
Intervention	FRE predicted 10 year risk.			
Comparison	Observed data over 10 years.			
Outcomes	Prediction of CVD, compared to observed data in the form of AUCs.			
Quality of study:				
Quality criteria:	Met?	Comments		
Specified inclusion/exclusion criteria	Yes	Participants with prior CVD were excluded at recruitment.		
Explicit description of participants	Yes	In text and table 2.		
Appropriate spectrum of consecutively selected participants	Some	Large sample of appropriate age, but only males assessed in this study.		
Prospective selection of participants	Yes	Not described, but likely given the design of the study.		
Test is compared with an appropriate reference (gold) standard	Yes	Reference standard is observed CVD outcome (defined as the occurrence of sudden CD or a definite fatal or non-fatal MI on the basis of ECG and/or cardiac enzyme changes) over 10 years follow-up.		
Test is compared with the reference standard in all participants	Unclear	218 died from other causes – it is unclear whether the analysis excludes these participants.		
Blinded assessment of test and reference standard results	Yes	Not described, but given that risk is assessed at baseline, assessors are blind to the observed outcomes, which is the reference standard.		
Test and reference standard undertaken prior to any interventions	Unclear	Not described.		
Level of evidence	II	Risk of bias	Very low	
Results of study:				
FRE	AUC = 0.78			
Notes	The authors conclude that FRE overestimated risk in the PROCAM cohort. This article also discusses derivation of the PROCAM risk score but these data are not included here.			

Evidence table: Assessment of predictive ability of an absolute CVD risk assessment method			
Characteristics of study:			
Study citation	Brindle P, et al. Predictive accuracy of the Framingham coronary risk score in British men: prospective cohort study. BMJ 2003; 327: 1267.		
Study	Brindle 2003 [28]	Study design	Follow-up study
Setting	The British Regional Heart Study, where participants were randomly selected (1978–80) from the age and sex registers of one general practice in each of 24 towns in the UK. Data from four regions have been separated in this study: South of England (2086), Midlands and Wales (942), North of England (2783), Scotland (832).		
Participants	6643 (95.7% of population of British Regional Heart Study) males aged 40–59 years.		
Intervention	FRE predicted 10 year risk.		
Comparison	Observed data over 10 years.		
Outcomes	Prediction of CVD, compared to observed data in the form of sensitivity and specificity data, predicted observed event rate and % predicted and observed rates specific to 4 towns.		
Quality of study:			
Quality criteria:	Met?	Comments	
Specified inclusion/exclusion criteria	Yes	Participants with prior CVD history were excluded.	
Explicit description of participants	Yes	In text and table 2.	
Appropriate spectrum of consecutively selected participants	Some	Although the sample is large, only males are included in this study.	
Prospective selection of participants	Yes		
Test is compared with an appropriate reference (gold) standard	Yes	Reference standard is observed CVD outcome (CHD death and CHD events defined as CHD death, MI or angina) over 10 years follow-up.	
Test is compared with the reference standard in all participants	Unclear	The response rate was 78% for the total population from which participants were recruited; fewer than 1% of participants in the British Regional Heart Study were lost to follow-up.	
Blinded assessment of test and reference standard results	Yes	Not described, but given that risk is assessed at baseline, assessors are blind to the observed outcomes, which is the reference standard.	
Test and reference standard undertaken prior to any interventions	Unclear	Not described.	
Level of evidence	II	Risk of bias	Very low
Results of study (over page):			

FRE (sensitivity and specificity)	<p>≥30% likelihood of events: 16% sensitivity, 94% specificity ≥15% likelihood of events: 75% sensitivity, 55% specificity</p> <p>Similar estimates were obtained when using these thresholds to identify individuals at high risk of CHD death within 10 years.</p>
FRE (event rates)	<p>deaths: predicted=270 (4.1%), observed=183 (2.8%); overpredicted by 47% (p<0.0001) events: predicted=1062 (16%), observed=677 (10.2%); overpredicted by 57% (p<0.0001)</p>
FRE (% event rates, South of England)	<p>deaths: predicted=3.8, observed=2.3 events: predicted=15.4, observed=9.0</p>
FRE (% event rates, Midlands and Wales)	<p>deaths: predicted=3.8, observed=1.9 events: predicted=15.6, observed=9.1</p>
FRE (% event rates, North of England)	<p>deaths: predicted=4.2, observed=3.3 events: predicted=16.3, observed=10.6</p>
FRE (% event rates, Scotland)	<p>deaths: predicted=4.5, observed=3.0 events: predicted=16.8, observed=13.1</p>
Notes	<p>FRE overpredicted in this population.</p> <p>Use of a predicted ≥30% CHD 10 year event rate threshold to identify patients at high risk can fail to identify most who will go on to have a CHD event over the following 10 years.</p>

Evidence table: Assessment of predictive ability of an absolute CVD risk assessment method				
Characteristics of study:				
Study citation	Brindle PM, et al. The accuracy of the Framingham risk-score in different socioeconomic groups: a prospective study. Br J Gen Pract 2005; 55: 838-845.			
Study	Brindle 2005 [29]	Study design	Follow-up study	N (total) 12,304
Setting	General population of Renfrew and Paisley, west of Scotland.			
Participants	12,304 participants: 5626 males, 6678 females, aged 45–64, stratified for socioeconomic status.			
Intervention	FRE stratified for social class.			
Comparison	Observed CVD endpoints over 10 years.			
Outcomes	Prediction of CVD, compared to observed data in the form of AUCs.			
Quality of study:				
Quality criteria:	Met?	Comments		
Specified inclusion/exclusion criteria	Yes	Excluded if prior history of CVD.		
Explicit description of participants	Yes	As supplied in table 2. Baseline characteristics.		
Appropriate spectrum of consecutively selected participants	Yes	78% response rate from recruiting process; age 45–64 years – 5626 men and 6678 women.		
Prospective selection of participants	Yes			
Test is compared with an appropriate reference (gold) standard	Yes	Reference standard is observed CVD outcome (defined as CVD and CHD deaths) over 10 years follow-up.		
Test is compared with the reference standard in all participants	Yes	Study reports no loss to follow-up and all 'original' participants are accounted for.		
Blinded assessment of test and reference standard results	Yes	Not described, but given that risk is assessed at baseline, assessors are blind to the observed outcomes, which is the reference standard.		
Test and reference standard undertaken prior to any interventions	Unclear	Implied but not explicitly stated.		
Level of evidence	II	Risk of bias	Very low	
Results of study:				
for All	AUC = 0.73 [95% CI, 0.72–0.75] 40% threshold: sensitivity = 18.8 specificity = 96.1 30% threshold: sensitivity = 41.6 specificity = 85.4 20–30% threshold: sensitivity = 74.3 specificity = 59.5 10–30% threshold: sensitivity = 97.6 specificity = 18.7 Mortality rates (%): predicted = 3.3 observed = 5.9			

for Non-manual (social class)	AUC = 0.74 [95% CI, 0.71–0.78] 40% threshold: sensitivity = 16.9 specificity = 97.2 30% threshold: sensitivity = 38.5 specificity = 88.6 20–30% threshold: sensitivity = 70.4 specificity = 65.1 10–30% threshold: sensitivity = 96.9 specificity = 23.5 Mortality rates (%): predicted = 2.9 observed = 4.2
for Manual (social class)	AUC = 0.72 [95% CI, 0.70–0.74] 40% threshold: sensitivity = 19.5 specificity = 95.4 30% threshold: sensitivity = 42.8 specificity = 83.4 20–30% threshold: sensitivity = 75.7 specificity = 55.8 10–30% threshold: sensitivity = 97.9 specificity = 15.6 Mortality rates (%): predicted = 3.6 observed = 7.0
Notes	These results were independent of the gender of the participants. HDL cholesterol was not measured in the Renfrew and Paisley study. Default measures were used to represent the average HDL levels of the participants. In recording social class, housewives were categorised according to the occupation of their husbands.

Evidence table: Assessment of predictive ability of an absolute CVD risk assessment method				
Characteristics of study:				
Study citation	Liu J, et al. Predictive value for the Chinese population of the Framingham CHD risk assessment tool compared with the Chinese Multi-provincial Cohort Study. JAMA 2004; 291(21): 2591-2599.			
Study	Liu 2004 [30]	Study design	Follow-up study	N (total) 30,121
Setting	Multi-provincial Chinese Population.			
Participants	30,121 multi-provincial Chinese adults, aged 35–64 years; 16,065 males and 14,056 females.			
Intervention	FRE applied to the Chinese multi-provincial cohort.			
Comparison	Observed CHD endpoints (coronary death and MI) over 10 years of follow-up between 1992 and 2002.			
Outcomes	Prediction of CVD, compared to observed data in the form of AUCs.			
Quality of study:				
Quality criteria:	Met?	Comments		
Specified inclusion/exclusion criteria	Yes	Excluded if participant has history of CVD.		
Explicit description of participants	Yes	Described in detail in table 1 and 2.		
Appropriate spectrum of consecutively selected participants	Yes	30,121 multi-provincial Chinese adults, aged 35–64 years, comprising 16,065 men and 14,056 women; 27,003 were recruited between 1992 and 1993, with a further 3118 participants recruited in 1996 and 1999. The overall participation rate was 82%.		
Prospective selection of participants	Yes			
Test is compared with an appropriate reference (gold) standard	Yes	Observed CHD endpoints (CD and MI) over 10 years of follow-up between 1992 and 2002.		
Test is compared with the reference standard in all participants	Yes	Of the 27,003 participants recruited in 1992–93, the follow-up rate was 94%. The loss of six centres in 1995 led to the loss of 11,451 participants. The remaining 16,552 participants had a follow-up rate of 86% (63% of the original cohort).		
Blinded assessment of test and reference standard results	Yes	Not described, but given that risk is assessed at baseline, assessors are blind to the observed outcomes, which is the reference standard.		
Test and reference standard undertaken prior to any interventions	Unclear	Not described.		
Level of evidence	II	Risk of bias	Very low	
Results of study:				
FRE	AUC = 0.705 [95%CI 0.665, 0.746] for males AUC = 0.742 [95%CI 0.686, 0.798] for females			
Notes	Predicted and observed event rates were presented graphically. FRE overestimated risk in this population.			

Evidence table: Assessment of predictive ability of an absolute CVD risk assessment method				
Characteristics of study:				
Study citation	Hense H, et al. Framingham risk function overestimates risk of coronary heart disease in men and women from Germany – results from the MONICA Augsburg and PROCAM cohorts. Eur Heart J 2003; 24: 937-945.			
Study	Hense 2003 [31]	Study design	Cohort study	N (total) 14,468
Setting	Two cohorts: MONICA – city of Augsburg and the two counties of Augsburg and Aichach-Friedberg, Germany, covering a population of over 500,000 inhabitants from 1984 to 1997 PROCAM – sampled from 20,060 employees of 52 companies and local government authorities within a radius of approximately 100 km around the city of Münster in northwest Germany from 1979 to 1985.			
Participants	MONICA – males (2861) and females (2925) aged 35–64 years. PROCAM – males (5527) and females (3155) aged 16–65 years.			
Intervention	FRE			
Comparison	Observed data for MONICA over a median follow-up time of 7.8 to 13.2 years and ~11 years for PROCAM.			
Outcomes	Prediction of CVD, over individualised follow-up times compared to observed data in the form of AUCs.			
Quality of study:				
Quality criteria:	Met?	Comments		
Specified inclusion/exclusion criteria	Yes	Further details can be found in original cohort studies – participants with prior CVD were excluded at recruitment.		
Explicit description of participants	Yes	Further details can be found in original cohort studies; under 5% of participants had diabetes.		
Appropriate spectrum of consecutively selected participants	Yes	Large number of participants, fairly even contribution of males and females.		
Prospective selection of participants	Some	Although this article reports a retrospective study, the original recruitment was prospective, some selection used.		
Test is compared with an appropriate reference (gold) standard	Some	Reference standard is observed CVD outcome (non-fatal MI and fatal coronary events).		
Test is compared with the reference standard in all participants	Unclear	Loss to follow-up not described, probably because this study is retrospective and only includes subjects for which both baseline and follow-up data are available.		
Blinded assessment of test and reference standard results	Unclear	Not described and given that this study is retrospective and only includes subjects for whom both baseline and follow-up data are available, those who selected the study participants may not be blind to the baseline assessment and observed outcomes. Furthermore, follow-up data is adjusted so there is further potential for bias.		
Test and reference standard undertaken prior to any interventions	Unclear	Not described		
Level of evidence	III–2	Risk of bias	High	

Results of study:	
FRE	<p>MONICA cohort Males AUC = 0.78 [95% CI 0.73, 0.84] Risk (per 1000) 35–44 years: predicted=45.4, observed=21.0 [16.2; 25.8] 45–54 years: predicted=100.2, observed=47.3 [40.6; 54.0] 55–64 years: predicted=158.3, observed=84.0 [75.0; 93.0]</p> <p>Females AUC = 0.88 [95% CI 0.80, 0.96] Risk (per 1000) 35–44 years: predicted=5.7, observed=0 [–] 45–54 years: predicted=24.5, observed=8.9 [5.9; 11.9] 55–64 years: predicted=54.9, observed=23.2 [18.3; 28.1]</p> <p>PROCAM cohort Males AUC = 0.73 [95% CI 0.70, 0.75] Risk (per 1000) 35–44 years: predicted=52.9, observed=21.4 [18.3; 24.3] 45–54 years: predicted=114.3, observed=69.0 [63.5; 74.5] 55–64 years: predicted=174.6, observed=109.2 [99.4; 119.0]</p> <p>Females AUC = 0.77 [95% CI 0.69, 0.85] 35–44 years: predicted=9.4, observed=3.8 [1.9; 5.7] 45–54 years: predicted=31.8, observed=10.1 [7.3; 12.9] 55–64 years: predicted=65.5, observed=23.7 [17.2; 30.2]</p>
Notes	The authors suggest that FRE overestimates absolute risk by a factor of between 2 and 3 across all age groups.

Evidence table: Assessment of predictive ability of an absolute CVD risk assessment method				
Characteristics of study:				
Study citation	Liao Y, et al. How generalisable are coronary risk prediction models? Comparison of Framingham and two national cohorts. Am Heart J 1999; 137: 837-845.			
Study	Liao 1999 [32]	Study design	Cohort study	N (total) 16,485
Setting	Two retrospective cohorts: First and Second National Health and Nutrition Examination Survey (NHANES I and NHANES II), conducted in a probability sample of the civilian non-institutionalised population of the United States. NHANES I: 1971–1993, NHANES II: 1976–1992.			
Participants	NHANES I – 6611: 2753 males, 3858 females, 35–69 years of age. NHANES II – 5705: 2655 males, 3050 females, 35–69 years of age.			
Intervention	FRE prediction of 15 year risk.			
Comparison	Observed data over 15 years.			
Outcomes	Prediction of CVD, compared to observed data in the form of AUC.			
Quality of study:				
Quality criteria:	Met?	Comments		
Specified inclusion/exclusion criteria	Yes	Excluded if participant has history of CVD.		
Explicit description of participants	Yes	See table 1. Further detail may be found in refs 14 and 17. (Males and females in the FRE cohort were on average younger than these two cohorts.)		
Appropriate spectrum of consecutively selected participants	Yes	Age appropriate, male: female ratio fairly even but have deliberately selected only 'white' participants.		
Prospective selection of participants	No	Retrospective study, authors have selected participants who fit into the above age groups to be comparable to FRE.		
Test is compared with an appropriate reference (gold) standard	Yes	Reference standard is observed CVD outcome (defined as CHD death) over 15 years follow-up.		
Test is compared with the reference standard in all participants	Yes	This study is retrospective and only includes subjects for whom both baseline and follow-up data are available.		
Blinded assessment of test and reference standard results	Unclear	Not described; this study is retrospective and only includes subjects for whom both baseline and follow-up data are available. However the participant selectors were different people to those responsible for baseline and outcome assessment.		
Test and reference standard undertaken prior to any interventions	Unclear	Not described.		
Level of evidence	III–2	Risk of bias	High	
Results of study (over page):				

FRE	NHANES I: male AUC = 0.71 sensitivity=67% fixed specificity=33%; predicted=11.6, observed=10.4 NHANES I: female AUC = 0.80 sensitivity=83% fixed specificity=33% NHANES II: male AUC = 0.74 sensitivity=71% fixed specificity=33%; predicted=11.4, observed=7.4 NHANES II: female AUC = 0.76 sensitivity=77% fixed specificity=33%
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Evidence table: Assessment of predictive ability of an absolute CVD risk assessment method			
Characteristics of study:			
Study citation	Zhang XF, et al. A risk score predicted coronary heart disease and stroke in a Chinese cohort. J Clin Epidemiol 2005; 58: 951-958.		
Study	Zhang 2005 [33]	Study design	Cohort study
Setting	Male steelworkers from the Beijing Iron and Steel Complex, China, recruited from 1974 to 1980 in three waves. Study ended in 1993.		
Participants	European Task Force Recommendations risk score 4400 participants, Oriental specific decision rule 1400 participants, over 35 years of age.		
Intervention	Oriental specific decision rule prediction and European decision rule.		
Comparison	Observed data.		
Outcomes	Prediction of CVD, compared to observed data in the form of AUCs.		
Quality of study:			
Quality criteria:	Met?	Comments	
Specified inclusion/exclusion criteria	Yes	Excluded if participant has prior CVD history.	
Explicit description of participants	Yes	In text (results 3.1) and table 1.	
Appropriate spectrum of consecutively selected participants	Some	The authors are trying to determine the effect of a Caucasian risk assessment method in a Chinese population; however the sample is restricted to a small section/group in China. The authors conclude in their limitations that their occupational cohort may not be representative of all Orientals.	
Prospective selection of participants	Yes	Not described, but likely given the design of the study.	
Test is compared with an appropriate reference (gold) standard	Yes	Reference standard is observed CVD outcome (defined as fatal and non-fatal events of CHD, fatal and non-fatal stroke) over 10 years follow-up for the European rule and 13.5 years follow-up for the Oriental specific decision rule.	
Test is compared with the reference standard in all participants	Unclear	Loss to follow-up not described.	
Blinded assessment of test and reference standard results	Yes	Not described, but given that risk is assessed at baseline, assessors are blind to the observed outcomes, which is the reference standard.	
Test and reference standard undertaken prior to any interventions	Unclear	Not addressed.	
Level of evidence	II	Risk of bias	Very low
Results of study (over page):			

Oriental specific decision rule	<p>AUC = 0.76 for CHD AUC = 0.78 for ischaemic stroke AUC = 0.82 for haemorrhagic stroke</p> <p>The authors report that there are no statistically significant differences between predicted and observed events for all three outcomes.</p>
European risk score	<p>AUC = 0.71 for CHD</p> <p>10 year risk level for CHD: Low risk: predicted = <5%, observed = 0.4% Mild risk: predicted = 5–10%, observed = 1.5% Moderate risk: predicted = 10–20%, observed = 4.0% High risk: predicted = 20–40%, observed = 11.3% Very high risk: predicted = <40%, observed = –</p> <p>European risk score overestimated risk, particularly in lower risk groups.</p>
Notes	<p>Significance between rules not reported.</p>

Population: adult (aged >18) Aboriginal and Torres Strait Islander peoples without known CVD

Articles that assess predictive ability of an absolute CVD risk assessment method

Evidence table: Assessment of predictive ability of an absolute CVD risk assessment method				
Characteristics of study:				
Study citation	Wang Z, Hoy, W. Is the Framingham coronary heart disease absolute risk function applicable to Aboriginal people? MJA 2005; 182: 66-69.			
Study ID	Wang 2005 [37]	Study design	Follow-up study	N (total) 687
Setting	Cohort study in an Australian Aboriginal community in the Northern Territory.			
Participants	687 Australian Aboriginal people aged 20–74 years – 331 females, 356 males.			
Intervention	FRE. ECG-LVH was unavailable with the study results being divided into two categories, firstly assuming the ECG-LVH in the study sample was the same in the Framingham population, and secondly, assuming the prevalence of the ECG-LVH was 10 times that of the Framingham population.			
Comparison	Observed CHD endpoints, followed up from a baseline examination in 1992–1995 through to 31 December 2003.			
Outcomes	Prediction of CVD over individualised follow-up times measured by AUC.			
Quality of study:				
Quality criteria:	Met?	Comments		
Specified inclusion/exclusion criteria	Yes	Excluded if participant has prior CVD history and without full baseline data.		
Explicit description of participants	Yes	Characteristics of participants described in table 2, including presence of traditional risk factors.		
Appropriate spectrum of consecutively selected participants	Yes	Included 80% of Aboriginal community before exclusion criteria.		
Prospective selection of participants	Yes			
Test is compared with an appropriate reference (gold) standard	Yes	Reference standard is observed CVD outcome (defined as MI, AP and other IHD) from a baseline examination in 1992–1995 through to 31 December 2003. Follow-up times were individualised.		
Test is compared with the reference standard in all participants	Yes	All 687 selected participants were followed up without loss.		
Blinded assessment of test and reference standard results	Yes	Implied blinding by study method and participant selection and length of follow-up.		
Test and reference standard undertaken prior to any interventions	Unclear	Not explicitly stated.		
Level of evidence	II	Risk of bias	Very low	
Results of study (over page):				

FRE	Inadequate data were given to report upon test sensitivity and specificity. The observed incidence rate for the whole study sample (11.0 [95% CI 8.7, 13.9] per 1000 person-years) was 2.5 times the predicted rate of 4.4 (no CI given) per 1000 person-years.
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Population: adults (aged >18) with diabetes (WHO criteria, 1999) but without known CVD

Articles that compare different absolute CVD risk assessment methods

Evidence table: Comparison of different absolute CVD risk assessment methods			
Characteristics of study:			
Study citation	Guzder RN, et al. Prognostic value of the Framingham cardiovascular risk equation and the UKPDS risk engine for coronary heart disease in newly diagnosed type 2 diabetes: results from a United Kingdom study. <i>Diabet Med</i> 2005; 22(5): 554-62.		
Study ID	Guzder 2005 [44]	Study design	Community-based follow-up study
Setting	The Poole Type 2 Diabetes Study; 24 GP practices whose registered patients live in the Poole Hospital catchment area (78%), 1996–1998.		
Participants	455 total – 259 males, 196 females, aged 30–64 years.		
Intervention	FRE		
Comparison	UKPDS		
Outcomes	Prediction of CVD, compared to observed data, measured by AUC and sensitivity/specificity (%).		
Quality of study:			
Quality criteria:	Met?	Comments	
Specified inclusion/exclusion criteria	Yes	Included if newly diagnosed type 2 diabetes, excluded if prior CVD, as above and fig 1.	
Explicit description of participants	Yes	As above and fig 1 and table 2.	
Appropriate spectrum of consecutively selected participants	Yes	Age range appropriate, small sample number?	
Prospective selection of participants	Yes	Not described, may be described elsewhere (ref 14), but likely given the design of the study.	
Test is compared with an appropriate reference (gold) standard	Yes	Reference standard is observed CVD outcome (defined as CHD, cerebrovascular disease, heart failure, PVD) over 10 years follow-up.	
Test is compared with the reference standard in all participants	Yes	Loss to follow-up not described.	
Blinded assessment of test and reference standard results	Yes	Not described, may be described elsewhere (ref 14), but given that risk is assessed at baseline, assessors are blind to the observed outcomes, which is the reference standard.	
Test and reference standard undertaken prior to any interventions	Some	Some participants were on antihypertensive, lipid lowering or anti-platelet therapy.	
Level of evidence	II	Risk of bias	Very low
Results of study:			
FRE (CHD)	All cohort: AUC = 0.657 [95% CI, 0.581–0.732] Males: AUC = 0.726 [95% CI, 0.643–0.810] Females: AUC = 0.697 [95% CI, 0.635–0.760]		

UKPDS (CHD)	All cohort: AUC = 0.670 [95% CI, 0.598–0.742] Males: AUC = 0.673 [95% CI, 0.585–0.761] Females: AUC = 0.618 [95% CI, 0.491–0.746]
Other results of interest	Statistical significance not reported.
FRE	Sensitivity = 29.6 [95% CI, 22.2–37.2] Specificity = 88.5 [95% CI, 86.3–90.7] (30% 10 year CHD risk and TC >5 mmol/L) Sensitivity = 72.4 [95% CI, 63.5–80.2] Specificity = 45.2 [95% CI, 42.5–47.5] (15% 10 year CHD risk and TC >5 mmol/L) Sensitivity = 85.7 [95% CI, 77.8–91.5] Specificity = 33.0 [95% CI, 30.7–34.7] (15% 10 year CHD risk only)
UKPDS	Sensitivity = 50.0 [95% CI, 39.7–60.3] Specificity = 69.1 [95% CI, 63.8–74.0] (30% 10 year CHD risk and TC >5 mmol/L) Sensitivity = 76.5 [95% CI, 66.9–84.5] Specificity = 46.4 [95% CI, 40.9–51.9] (15% 10 year CHD risk and TC >5 mmol/L) Sensitivity = 89.8 [95% CI, 82.0–95.0] Specificity = 30.3 [95% CI, 25.4–35.6] (15% 10 year CHD risk only)
Other results of interest	Statistical significance not reported. FRE and UKPDS underestimate risk by 32% and 13% respectively.

See *Folsom 2003* [15] above.

Population: adults (aged >18) who are overweight or obese (BMI \geq 30kg/m² or waist circumference >102 cm for males and >88 cm for females) but without known CVD

No studies were identified.

Population: adults (aged >18) with chronic kidney disease (GFR <60 mL/min) but without known CVD

Articles that assess predictive ability of an absolute CVD risk assessment method

Evidence table: Assessment of predictive ability of an absolute CVD risk assessment method				
Characteristics of study:				
Study citation	Massy ZA, et al. [Prediction model of coronary heart disease in patients with chronic kidney disease: role of plasma fibrinogen as a new prognostic variable.] <i>Makedonska Akademija na Naukite i Umetnostite Oddelenie Za Bioloshki i Meditsinski Nauki Prilozi</i> 2005; 26: 63-77.			
Study	Massy 2005 [52]	Study design	Follow-up study	N (total) 96
Setting	1985–1997, Nephrology division, Necker Hospital, Paris, France.			
Participants	96 males (66%) and females, average age 65.3 years, with stage 2–4 CKD. Participants were divided into two groups: those with an event and those without an event. Defined as having CKD by a creatinine clearance of 20–70 mL/min/1.73 m ² .			
Intervention	FRE			
Comparison	Observed events over an average of 7.4 ± 2.2 years (range 4–12 years).			
Outcomes	Prediction of CVD, over individualised follow-up times compared to observed data in the form of sensitivity and specificity and predicted medians.			
Quality of study:				
Quality criteria:	Met?	Comments		
Specified inclusion/exclusion criteria	Yes	Excluded if participant has prior history of CVD and if taking lipid lowering therapy.		
Explicit description of participants	Yes	In 'patients and methods' and in table 1.		
Appropriate spectrum of consecutively selected participants	Yes	Males and females, small sample size, appropriate average age.		
Prospective selection of participants	Some	Selected prospectively initially.		
Test is compared with an appropriate reference (gold) standard	Yes	Reference standard is observed CVD outcome (defined as fatal or non-fatal MI with or without revascularisation) over an average of 7.4 ± 2.2 years follow-up. It is important to note that the probability of presenting CHD was calculated for each participant according to his/her own follow-up duration.		
Test is compared with the reference standard in all participants	Unclear	Participants who did not have follow-up of between 4–12 years were excluded; it is not clear how many participants were excluded on this basis.		
Blinded assessment of test and reference standard results	Unclear	The authors call this a prospective study but predict risk over the period of each individual's follow-up, which by nature is retrospective.		
Test and reference standard undertaken prior to any interventions	No	86% of patients were receiving antihypertensive therapies, and 24% were receiving ACE inhibitors.		
Level of evidence	III–2	Risk of bias	High	

Results of study:	
FRE (at 20%)	Sensitivity = 24% Specificity = 89% Predicted median risk of event for those without an event = 7.1% Predicted median risk of event for those with an event = 10.3%
Notes	The authors conclude that FRE is a poor predictor of CHD risk in people with CKD stage 2–4.


Appendix II: Body of evidence tables

The following tables are based on the NHMRC additional levels of evidence and grades for recommendations for developers of guidelines PILOT PROGRAM 2005–2007 and outline the criteria from which recommendations have been graded.

Key question: <i>Ability of absolute CVD risk assessment in adults not known to have CVD or diabetes</i>		
1. Volume of evidence (quantity, level, methodological quality and relevance to patients of the body of evidence for this question, based on critical appraisal of each individual study according to Minimum Requirements)		
<i>Nineteen level II studies and six level II–2 studies</i>	A	Excellent (several level I or II studies with low risk of bias)
	B	Good (one or two level II studies with low risk of bias or SR/multiple level III studies with low risk of bias)
	C	Satisfactory (level III studies with low risk of bias or level I or II studies with moderate risk of bias)
	D	Poor (level IV studies or level I to III studies with high risk of bias)
2. Consistency (the degree of consistency demonstrated by the available evidence. Where there are conflicting results, indicate how the group formed a judgement as to the overall direction of the evidence)		
<i>All of the studies that compare FRE to another absolute risk assessment method found that FRE was equivalent or better than the studies that it was compared to</i>	A	Excellent (all studies consistent)
	B	Good (most studies consistent and inconsistency can be explained)
	C	Satisfactory (some inconsistency, reflecting genuine uncertainty around question)
	D	Poor (evidence is inconsistent)
3. Clinical impact (the potential impact of the recommendation i.e. size of patient population, relevance of outcomes to the question, balance of risks and benefits, relative benefit over other management options, resource and organisational implications)		
<i>Recommendation applies to a large patient population, is associated with potential benefits via changed treatment, but no harms and has significant resource and organisational implications</i>	A	Excellent (very large clinical impact)
	B	Good (substantial clinical impact)
	C	Satisfactory (moderate clinical impact)
	D	Poor (slight or restricted clinical impact)
4. Generalisability (how reasonable is it to generalise from the results of the studies used as evidence to the target population for this guideline?)		
<i>May be generalisable and applicable to Caucasian populations</i>	A	Excellent (directly generalisable to target population)
	B	Good (directly generalisable to the target population with some caveats)
	C	Satisfactory (not directly generalisable to the target population but could be sensibly applied)
	D	Poor (not directly generalisable to target population and hard to judge whether it is sensible to apply)
5. Applicability (the extent to which the body of evidence is directly applicable to the Australian health care context)		
<i>Only one study in the Australian population; may be applicable to Caucasian population but no evidence for Indigenous populations</i>	A	Excellent (directly applicable to the Australian health care context)
	B	Good (applicable to the Australian health care context with few caveats)
	C	Satisfactory (probably applicable to the Australian health care context with some caveats)
	D	Poor (not applicable to the Australian healthcare context)

6. Other factors			
Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade the recommendation).			
NA			
EVIDENCE STATEMENT			
Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account. Please indicate any dissenting opinions.			
	Component	Descriptor	Grade
<i>Nine high-quality studies compared the predictive ability of absolute CVD risk assessment methods. Three studies of varying quality compared the ability of absolute CVD risk assessment methods to classify into risk categories. Fourteen studies of varying quality reported predictive ability of individual absolute CVD risk assessment methods. All of the studies that compared FRE to other methods found that it has a higher or equivalent predictive ability.</i>	Volume of evidence	<i>Excellent</i>	<i>A</i>
	Consistency	<i>Good</i>	<i>B</i>
	Clinical impact	<i>Excellent</i>	<i>A</i>
	Generalisability	<i>Good</i>	<i>B</i>
	Applicability	<i>Satisfactory</i>	<i>C</i>
RECOMMENDATION			↓
What recommendation (s) does the guidelines development group draw from this evidence?			
<i>In adults not known to have CVD or diabetes, use the FRE to predict absolute cardiovascular risk over 5 or 10 years.</i>	The overall grade is the summation of the grades for individual components. A recommendation cannot be graded A or B unless the volume and consistency of evidence are both A or B.		
	GRADES OF RECOMMENDATION		B

Key question: Ability of absolute CVD risk assessment in adults not known to have CVD and who have diabetes		
1. Volume of evidence (quantity, level, methodological quality and relevance to patients of the body of evidence for this question, based on critical appraisal of each individual study according to Minimum Requirements)		
Two level II studies	A	Excellent (several level I or II studies with low risk of bias)
	B	Good (one or two level II studies with low risk of bias or SR/multiple level III studies with low risk of bias)
	C	Satisfactory (level III studies with low risk of bias or level I or II studies with moderate risk of bias)
	D	Poor (level IV studies or level I to III studies with high risk of bias)
2. Consistency (the degree of consistency demonstrated by the available evidence. Where there are conflicting results, indicate how the group formed a judgement as to the overall direction of the evidence)		
One study compares FRE v UKPDS and the other study compares two different methods	A	Excellent (all studies consistent)
	B	Good (most studies consistent and inconsistency can be explained)
	C	Satisfactory (some inconsistency, reflecting genuine uncertainty around question)
	D	Poor (evidence is inconsistent)
3. Clinical impact (the potential impact of the recommendation i.e. size of patient population, relevance of outcomes to the question, balance of risks and benefits, relative benefit over other management options, resource and organisational implications)		
Recommendation applies to a large patient population, is associated with potential benefits via changed treatment, but no harms and has significant resource and organisational implications	A	Excellent (very large clinical impact)
	B	Good (substantial clinical impact)
	C	Satisfactory (moderate clinical impact)
	D	Poor (slight or restricted clinical impact)
4. Generalisability (how reasonable is it to generalise from the results of the studies used as evidence to the target population for these guidelines?)		
Age groups – yes The studies are in populations from the UK and US so may be generalisable and applicable to Caucasian populations	A	Excellent (directly generalisable to target population)
	B	Good (directly generalisable to the target population with some caveats)
	C	Satisfactory (not directly generalisable to the target population but could be sensibly applied)
	D	Poor (not directly generalisable to target population and hard to judge whether it is sensible to apply)
5. Applicability (the extent to which the body of evidence is directly applicable to the Australian health care context)		
May not be for Indigenous populations	A	Excellent (directly applicable to the Australian health care context)
	B	Good (applicable to the Australian health care context with few caveats)
	C	Satisfactory (probably applicable to the Australian health care context with some caveats)
	D	Poor (not applicable to the Australian health care context)

6. Other factors			
Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade the recommendation).			
NA			
EVIDENCE STATEMENT			
Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account. Please indicate any dissenting opinions.			
Two high-quality studies in populations with type 2 diabetes compared the predictive ability of absolute risk assessment methods. FRE and UKPDS RS have similar 10 year predictive ability in mixed gender populations. The addition of non-traditional risk factors to absolute risk assessment may improve predictive ability, however the methods are not yet available.	Component	Descriptor	Grade
	Volume of evidence	<i>Good</i>	<i>B</i>
	Consistency	<i>Satisfactory</i>	<i>C</i>
	Clinical impact	<i>Good</i>	<i>B</i>
	Generalisability	<i>Satisfactory</i>	<i>C</i>
	Applicability	<i>Satisfactory</i>	<i>C</i>
RECOMMENDATION			
What recommendation (s) does the guidelines development group draw from this evidence?			
<i>In adults with type 2 diabetes not known to have CVD, use the FRE to predict absolute cardiovascular risk over 5 or 10 years, with an awareness that it is likely to underestimate risk.</i>	The overall grade is the summation of the grades for individual components. A recommendation cannot be graded A or B unless the volume and consistency of evidence are both A or B.		
	GRADES OF RECOMMENDATION		C

Appendix III: Economic evaluation

Brief overview of economic evaluation

Economic evaluation is a method for assessing the efficiency of changes in health-related programs and is used to assist in decision-making between alternative interventions. Two key features characterise an economic evaluation regardless of the activities to which it is applied:

- economic evaluation is an analysis of both the costs and the consequences of programs
- economic evaluation provides a comparison of costs and benefits between alternative courses of action.

Economic evaluation relies on good-quality effectiveness data, the principles of which are the same as for the general approach to evidence-based clinical practice. That is, if the evidence base of effectiveness data is poor, there is no gain in taking the next step to an economic evaluation. A clinical trial may provide evidence of the efficacy of an intervention under ideal experimental conditions, however might provide misleading evidence of its effectiveness in the 'real world' conditions of program implementation. Factors such as take-up rates for screening or skill levels of practitioners may drive a wedge between efficacy and effectiveness. At best the economic evaluator would like information on the effectiveness of a program in practice, rather than its efficacy under trial conditions. Often, however, only the latter is available and it may be necessary to make reasonable assumptions about the effectiveness of a program based on the best available evidence. The important issue is that an economic evaluation relies on good underlying data on the effectiveness of the intervention in question.

Costing data for an economic evaluation can be obtained from large well-controlled clinical trials, including economic analysis alongside a clinical trial, systematic literature reviews and/or meta-analyses. In addition, if the intervention is well described, costs can be modelled retrospectively against effectiveness data. This approach might be possible for the comparison of one cardiovascular risk factor assessment method where both the method itself and the population to be screened are well defined. To complete an economic evaluation, the effectiveness data are combined with costing data so that the marginal cost and marginal benefits of the intervention can be compared.

The cost–benefit approach to evaluation stresses the importance of such comparisons at the margin. It suggests that we should treat up to a point where the extra cost per unit of health outcome, such as lives saved, is equal to some acceptable level. The relevant question to pose is 'What are the extra consequences and extra costs of one strategy when compared with another?' Marginal analysis is important, as with any intervention there will be diminishing marginal utility. For example a screening program will detect the most positive cases when the most 'at risk' population is screened. As the proportion of the population screened increases, the screening of each additional cohort will result in fewer cases detected.

Cost effectiveness analysis is the most common economic appraisal tool used in the health sector at present. It can answer the question: which of two alternative programs is the best means of achieving a particular end? The end can be defined as maximising the number of life-years in the community. It can also be a more intermediate or clinical outcome, such as the cost per case detected in a population-based risk assessment strategy for CVD. Cost effectiveness analysis adopts the objective of maximising the specified dimension of health outcome from the resources available to health care. Cost-utility analysis is a particular form of cost effectiveness analysis in that outcomes are measured in terms of health-related 'utility' (satisfaction or well-being). It thus goes a step further than cost effectiveness analysis by measuring not just clinical outcomes (lives saved, for example) but the quality of life of those who experience the outcomes.

Role of economic evaluation in the development of evidence-based practice guidelines

Evidence-based medicine has provided a framework for decision-making in health care; however, prioritising the use of limited health care resources across a variety of clinical programs and interventions has resulted in a more recent emphasis on incorporating evidence of cost effectiveness into these decisions. The NHMRC has recommended that evidence of cost effectiveness of health care programs be incorporated into the development of clinical practice guidelines, both as an indication of the costs and effectiveness of the intervention, and as to whether the proposed guidelines are cost effective.

Since 1993 the Pharmaceutical Benefit Advisory Committee has required evidence of cost effectiveness to be submitted by pharmaceutical companies as part of the decision process for the listing of new drugs onto the Pharmaceutical Benefits Schedule. In addition the likely impact of the new listing on total pharmaceutical expenditure is also evaluated. In 1997 the Medical Services Advisory Committee was established to advise the Minister for Health and Ageing on evidence relating to the cost effectiveness of new medical technologies and procedures prior to listing on the Medicare Benefits Schedule. In the UK, explicit efforts to apply evidence-based methods to both cost and effectiveness data have occurred through the National Institute for Clinical Effectiveness (NICE).

Often economic evaluation conducted alongside a clinical trial provides short-term effectiveness data on clinical or intermediate health outcomes. Economic models can then be developed to extrapolate data beyond the endpoints of the clinical trial. Such models incorporate data on the outcomes of the intervention often based on effectiveness data from the randomised controlled trial or from a systematic review of the literature; probability estimates for progressing between health states; and the costs and utilities associated with each stage of the disease. Each of these estimates is ideally based on a systematic review of the literature or other quality evidence and the source of the estimates should be transparent [73]. Population estimates on disease are obtained from epidemiological data such as observational studies, and estimates on the population accessing the intervention might be taken from secondary administrative data sources, for example Medicare statistics. Where uncertainty exists or a range of assumptions can be made, the probability, population estimates and economic assumptions – for example the discount rate – can be varied using sensitivity analyses.

Appendix IV: Absolute CVD risk assessment methods

The following are descriptions of each of the absolute CVD risk assessment methods that have been addressed in these guidelines.

Framingham risk equation [74]

Derived from a cohort of 5573 people in Framingham, Massachusetts, in 1968–1975.

Step 1

For CVD calculate*

$$\mu = 18.8144 - 1.2146 \times \text{female} - 1.8443 \times \log(\text{age}) + 0.3668 \times \log(\text{age}) \times \text{female} - 1.4032 \times \log(\text{SBP}) - 0.3899 \times \text{cigarettes} - 0.5390 \times \log(\text{total-C} / \text{HDL-C}) - 0.3036 \times \text{diabetes} - 0.1697 \times \text{diabetes} \times \text{female} - 0.3362 \times \text{ECG-LVH}$$

To compute probability of time until event (being less than arbitrary time t) for values of μ (location parameter) and σ (scale parameter):

$$\bar{\sigma} = \exp(0.6536 + (-0.2402 \times \mu))$$

Step 2

If $t = 5$ years, we have:

$$u = \log(5) - u / \sigma$$

Step 3

The 5 year predicted probability for CVD is then given by:

$$1 - \exp(-\exp(u)) =$$

*Risk factors are denoted as follows:

Age—age in years

Sex—1 if female, 0 if male

SBP—average of two office measurements of SBP in mm Hg

Total cholesterol—total serum cholesterol in mg/dl

HDL—HDL in mg/dl

Cigarettes—1 if cigarette smoker (or quit within last year), 0 otherwise

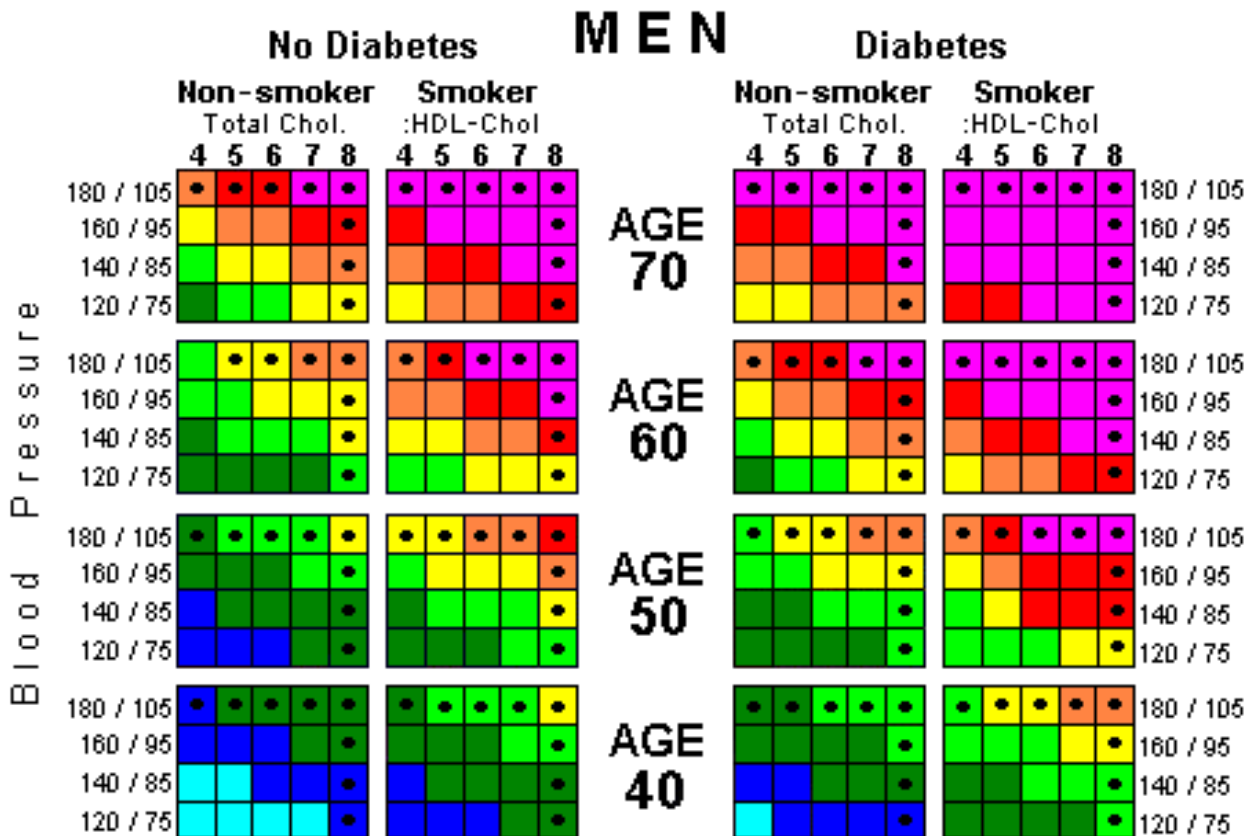
Diabetes—1 if diabetes, 0 otherwise

ECG-LVH—1 if definite ECG-LVH, 0 otherwise.

New Zealand risk equations [65]

Derived from a cohort of 6354 participants in Auckland, New Zealand, in 1992–93.

CVD risk chart for men:

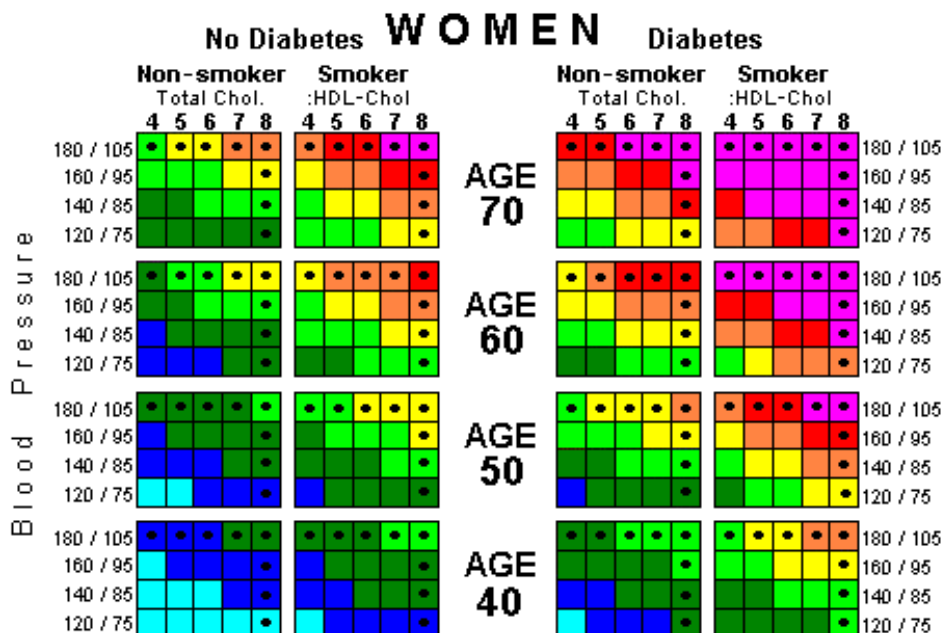


Key to Risk Tables				
Prognosis: 5 year CVD risk (non-fatal & fatal)		Benefit 1: CVD events prevented per 100 treated for 5 years *	Benefit 2: NNT for 5 years *	
> 30%	■	> 10 per 100	< 10	Suggested starting point for discussion with patient about drug treatment.
25-30%	■	9 per 100	11	
20-25%	■	7.5 per 100	13	
15-20%	■	6 per 100	16	
10-15%	■	4 per 100	25	
5-10%	■	2.5 per 100	40	
2.5-5%	■	1.25 per 100	80	
< 2.5%	■	< 0.8 per 100	> 120	

• Cells with this marker indicate that in patients with very high levels of cholesterol (> about 8.5-9 mmol/L) or blood pressure (> about 170 / 100 mmHg), the risk equations may underestimate the true risk. **Therefore it is recommended that treatment be considered at lower absolute CVD risks than in other patients.**

* Assumes BP reduction of about 12 / 6 mmHg in patients with BP > 140-150 / 90, or cholesterol reduction of about 20% in patients with total cholesterol > 5.0-5.5 mmol/L, produces an approximate 30% reduction in CVD risk, whatever the pre-treatment absolute risk.

CVD risk chart for women:



Key to Risk Tables		
Prognosis: 5 year CVD risk (non-fatal & fatal)	Benefit 1: CVD events prevented per 100 treated for 5 years *	Benefit 2: NNT for 5 years *
> 30%	> 10 per 100	< 10
25-30%	9 per 100	11
20-25%	7.5 per 100	13
15-20%	6 per 100	16
10-15%	4 per 100	25
5-10%	2.5 per 100	40
2.5-5%	1.25 per 100	80
< 2.5%	< 0.8 per 100	> 120

• Cells with this marker indicate that in patients with very high levels of cholesterol (\geq about 8.5-9 mmol/L) or blood pressure (\geq about 170 / 100 mmHg), the risk equations may underestimate the true risk. **Therefore it is recommended that treatment be considered at lower absolute CVD risks than in other patients.**

* Assumes BP reduction of about 12 / 6 mmHg in patients with BP \geq 140-150 / 90, or cholesterol reduction of about 20% in patients with total cholesterol \geq 5.0-5.5 mmol/L, produces an approximate 30% reduction in CVD risk, whatever the pre-treatment absolute risk.

How to use these colour charts

To estimate a person's absolute 5 year risk of a cardiovascular event (new angina, MI, CHD death, stroke or transient ischaemic stroke), find the colour block which best describes the patient's:

- gender
- age
- smoking
- diabetes status (on insulin, oral hypoglycaemics, or fasting blood glucose > 8.0 mmol/L Reflotron or laboratory measurement)
- BP (mean of two readings on each of two occasions sufficient for assessing risk but not for establishing pre-treatment baseline)
- total cholesterol/HDL ratio (mean of two non-fasting Reflotron measurements or one laboratory measurement sufficient for assessing risk but not for establishing pre-treatment baseline).

Patients with a strong family history of CVD (first-degree relatives: male with CVD before 55 years, female before 65 years) or obesity (BMI of about 30 kg/m² or more) are likely to be at greater risk than

the tables indicate – consider increasing one colour category. Read off 5 year risk from colour code in key to table.

PROCAM risk equation for men and women without diabetes [27, 75]

Derived from a cohort of 5389 men in Münster, Germany, in 1985.

PROCAM risk equation for men:

$$P = 100 \times (1 - 0.9369^a) \text{ for } a = \exp(y)$$

y risk factors in	mmol/L	(input range)	mg/dL	(input range)
y = - 8.9769				
+	0.103 x age	(35–65 years)		
+	0.010 x SBP	(100–225 mmHg)		
+	0.5026 x LDL cholesterol	(1.94–6.48 mmol/L)	0.013 x LDL C	(75–250 mg/dL)
-	1.2372 x HDL cholesterol	(0.65–1.94 mmol/L)	0.032 x HDL C	(25–75 mg/dL)
+	0.317 x log(TGL x 88.57)	(0.57–4.56 mmol/L)	0.317 x log(TGL)	(50–400 mg/dL)
+	0.658 x cigarette smoking	x (0=no,1=yes)	cigarette during	the past 12 months
+	0.399 x diabetes mellitus	x (0=no,1=yes)	known DM	or fasting blood glucose levels \geq 6.66 mmol/L (120 mg/dL)
+	0.382 x MI in family history	x (0=no,1=yes)	in 1st degree relative	before the age of 60 years

SBP = systolic blood pressure, LDL = low-density lipoprotein, HDL = high-density lipoprotein, TGL = triglycerides, DM = diabetes mellitus

For women without diabetes:

$$P = 100 \times (1 - 0.9369^a) \text{ for } a = \exp(y)$$

$$P \times 0.25$$

CUORE risk equation [76] [9]

Derived from a cohort of 6865 men in Rome, Italy.

Literature on the CUORE equation yields several different equations, with different ranges for cholesterol measurements and different co-efficients. Ferrario et al [9] do not provide an equation, but report the following CUORE prediction equation co-efficients when comparing equation co-efficients to Framingham:

Table 3 Comparison of proportional hazard predictive coefficients in the FHS and those calculated in the CUORE dataset

	FHS		CUORE		
	<i>b</i>	SE	<i>b</i>	SE	Z
Age (years)	0.049	0.005	0.071	0.007	2.56*
Blood pressure					
Normal including optimal (S < 130, D < 85)	Reference		Reference		
High normal (S < 140, D < 90)	0.270	0.151	0.308	0.195	0.15
Stage I hypertension (S < 160, D < 100)	0.513	0.136	0.141	0.176	-1.67
Stage II-IV hypertension (S ≥ 160, D ≥ 100)	0.610	0.154	0.515	0.175	-0.41
Current smoking (%)	0.519	0.104	0.534	0.114	0.10
Diabetes (%)	0.405	0.179	0.495	0.193	0.34
Total cholesterol (mg/dl)					
<200	Reference		Reference		
200-240	0.270	0.127	0.653	0.182	1.73
≥240	0.642	0.134	1.110	0.174	2.13*
HDL-cholesterol (mg/dl)					
<35	0.385	0.120	-0.011	0.195	-1.73
35-60	Reference		Reference		
≥60	-0.580	0.201	-0.525	0.156	0.22

* 0.01 < P < 0.05.

And different co-efficients when compared to PROCAM:

Table 4 Comparison of proportional hazard predictive coefficients in the PROCAM study and those calculated in the CUORE dataset

	PROCAM		CUORE		
	<i>b</i>	SE	<i>b</i>	SE	Z
Age (years)	0.103	0.008	0.062	0.008	-3.62*
LDL-cholesterol (mg/dl)	0.013	0.001	0.012	0.001	-0.71
HDL-cholesterol (mg/dl)	-0.032	0.006	-0.011	0.005	2.69**
ln Triglycerides (mg/dl)	0.317	0.134	-0.089	0.154	-1.99***
Systolic blood pressure (mm Hg)	0.010	0.003	0.012	0.003	0.47
Current smoking (%)	0.658	0.113	0.543	0.124	-0.69
Family history of MI (%)	0.382	0.135	0.290	0.142	-0.47
Diabetes (%)	0.399	0.158	0.280	0.217	-0.44

* P < 0.001, ** 0.001 < P < 0.01, *** 0.01 < P < 0.05.

And different co-efficients when tabulating the best prediction equation co-efficients for 35–69 year old Italian men:

Table 5 The best CUORE prediction equation for 35–69 years old Italian men

	Mean or proportion (SD)	β -Coefficient	P	Hazard ratio	95% CI
Age (years)	50.8 (9.2)	0.06318	<0.0001	1.065	1.050–1.081
Systolic blood pressure (10 mm Hg)	138.5 (20.5)	0.08800	0.0014	1.092	1.086–1.098
Current cigarette smoking (yes/no)	0.39 (0.49)	0.62903	<0.0001	1.876	1.495–2.353
Total cholesterol (10 mg/dl)	224.7 (43.7)	0.08900	<0.0001	1.093	1.091–1.096
HDL-cholesterol (10 mg/dl)	50.2 (13.9)	-0.12340	0.0044	0.884	0.876–0.891
Diabetes (yes/no)	0.05 (0.22)	0.41956	0.0331	1.521	1.034–2.238
Hypertension medications (yes/no)	0.10 (0.30)	0.60611	<0.0001	1.833	1.354–2.483
Family history of CHD (yes/no)	0.17 (0.37)	0.32015	0.0169	1.377	1.059–1.791
Baseline 10-year event-free survival ^a		0.96586			

^a 10-year survival at the mean of the risk factors.

Giampaoli et al [76] (not included in these guidelines) give the following equation to estimate the probability of a cardiovascular event:

$$1 - [S(t)]^{\{ \text{EXP} [\beta_1 * \text{age} + 0.0 \text{ (if SBP } \leq 129) + \beta_2 \text{ (if } 130 \leq \text{SBP} \leq 149) + \beta_3 \text{ (if } 150 \leq \text{SBP} \leq 169) + \beta_4 \text{ (if SBP } \geq 170) + 0.0 \text{ (if CHOL } \leq 173) + \beta_5 \text{ (if } 174 \leq \text{CHOL} \leq 212) + \beta_6 \text{ (if } 213 \leq \text{CHOL} \leq 251) + \beta_7 \text{ (if } 252 \leq \text{CHOL} \leq 290) + \beta_8 \text{ (if CHOL } \geq 291) + \beta_9 \text{ (if diabetic)} + \beta_{10} \text{ (if smoker)} - G(u)] \}}$$

where CHOL = cholesterolaemia, SBP = systolic blood pressure, S(t) = 10-year survival evaluated at mean value of risk factors; β_i correspond to risk factor coefficients; and G(u) is the linear combination of the risk factor averages or of the prevalence in each category for the corresponding β_i coefficients.

Giampaoli et al [76] give the following table for the co-efficients in the above equation:

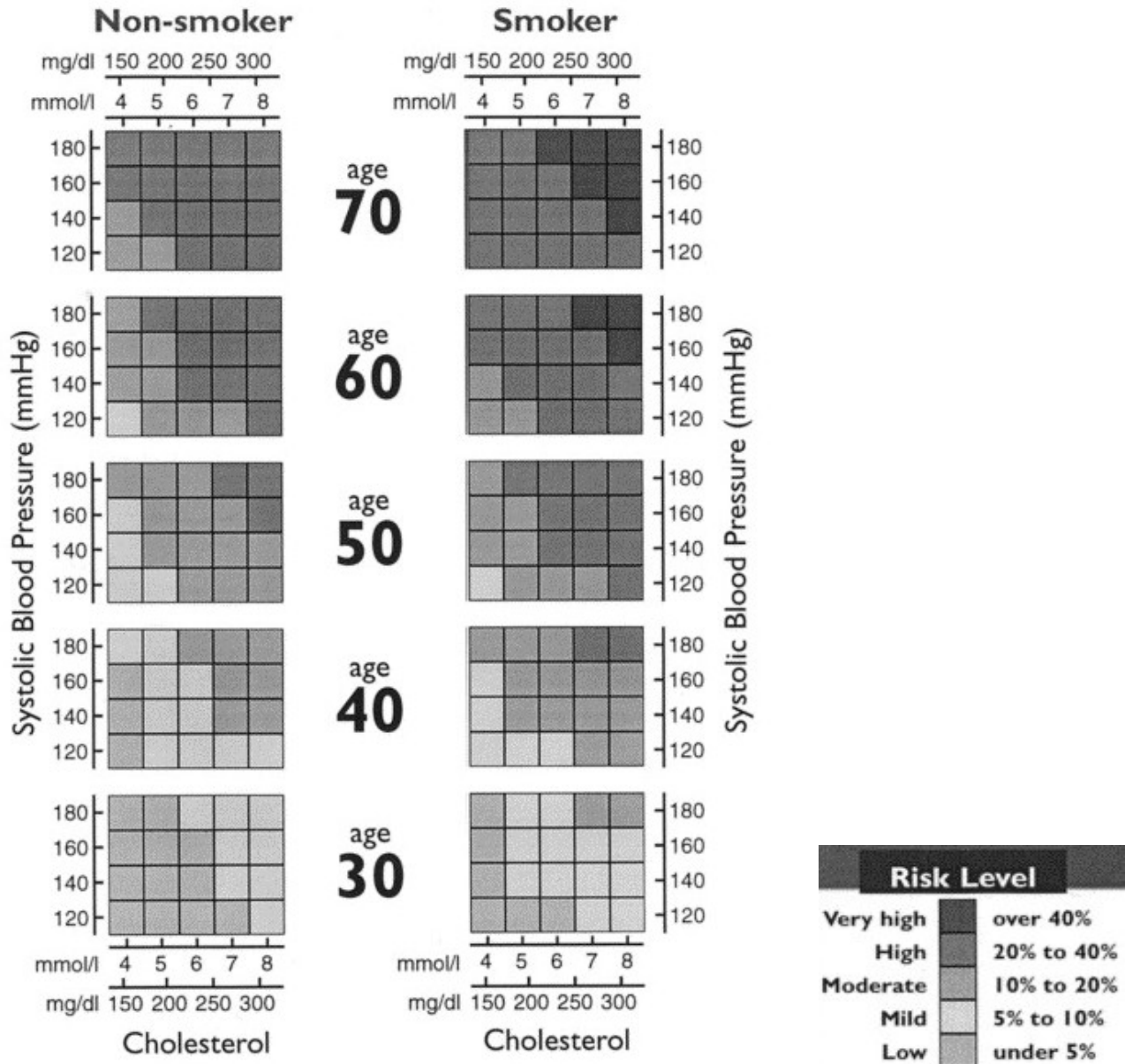
Table. β -coefficients and standard errors (SE) for risk factor categories, gender and main parameters for the 10-year risk chart (age 40-69 years).

		Uomini Men (n=6050)		Donne Women (n=11 185)	
		β	ES SE	β	ES SE
Eventi cardiovascolari incidenti <i>Incident cardiovascular events</i>		568		292	
Età (anni) <i>Age (years)</i>	β_1	0.083	0.006	0.088	0.009
Pressione arteriosa sistolica (mmHg) <i>Systolic blood pressure (mmHg)</i>					
≤ 129		Riferimento <i>Reference</i>		Riferimento <i>Reference</i>	
130-149	β_2	0.313	0.129	0.212	0.194
150-169	β_3	0.650	0.137	0.614	0.192
≥ 170	β_4	0.952	0.147	1.073	0.195
Colesterolo totale (mg/dl) <i>Total cholesterol (mg/dl)</i>					
≤ 173		Riferimento <i>Reference</i>		Riferimento <i>Reference</i>	
174-212	β_5	0.062	0.177	0.025	0.296
213-251	β_6	0.233	0.169	0.147	0.288
252-290	β_7	0.411	0.178	0.163	0.296
≥ 291	β_8	0.869	0.194	0.437	0.313
Diabete <i>Diabetes</i>	β_9	0.566	0.133	0.499	0.189
Fumo di sigaretta <i>Cigarette smoking</i>	β_{10}	0.489	0.086	0.715	0.154
$G(\mu)$		5.024		4.978	
$G'(t)$		0.942		0.986	
Sopravvivenza alla linea base, $S(t)$ <i>Survival at baseline, $S(t)$</i>		0.004		0.002	

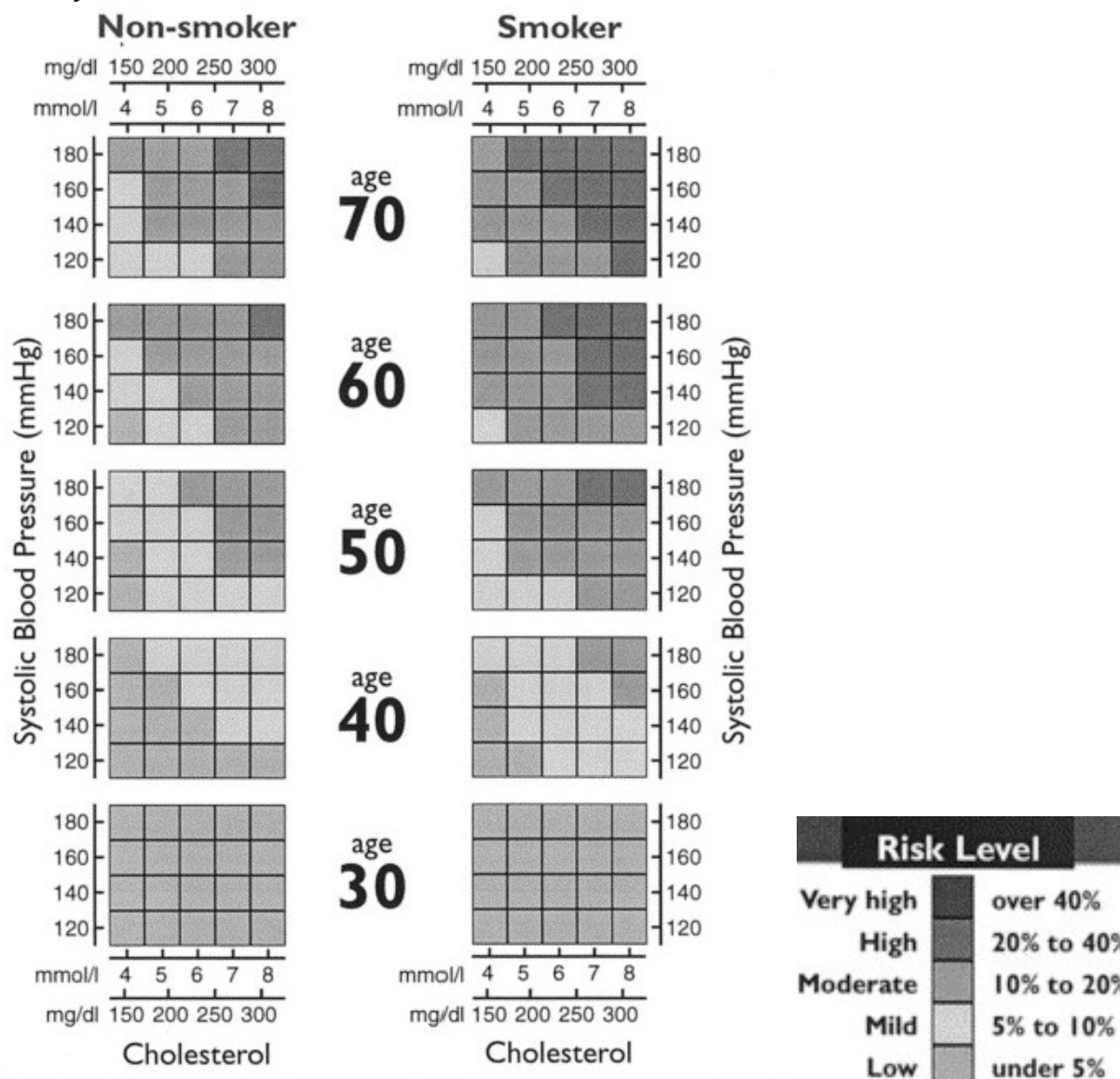
European Study of Cardiology risk chart [77]

Based on the Task Force of the European Society of Cardiology, European Atherosclerosis Society and European Society of Hypertension Joint Recommendations on the Prevention of CHD in Clinical Practice, 1994. No information is available for the cohort from which these risk charts are derived.

Coronary risk chart for men:



Coronary risk chart for women:



To estimate an individual's 10 year absolute risk of a CVD event, find the table for their gender, smoking status and age. Within the table, find the cell nearest to their systolic BP (mmHg) and total cholesterol (mmol/L or mg/dL).

CVD risk is higher than indicated in the chart for those with:

- familial hypercholesterolaemia
- diabetes: risk is approximately doubled in men and more than doubled in women
- those with a family history of premature CVD
- those with low HDL cholesterol; these tables assume HDL cholesterol to be 1.0 mmol/L (39 mg/dL) in men and 1.1 mmol/L (43 mg/dL) in women
- those with raised triglyceride levels – >2.0 mmol/L (>180 mg/dL)
- as the person approaches the next age category.

Metabolic syndrome as a risk score [11] [12] [13] [78]

Three studies compared Framingham alone with metabolic syndrome plus Framingham or metabolic syndrome alone.

Wannamethee et al (2005) [11] compared the Framingham equation with the number of metabolic abnormalities from the metabolic syndrome criteria, modified from the NCEP criteria [78]:

- fasting plasma glucose of at least 110 mg/dL (6.1 mmol/L)
- non-fasting serum triglyceride level of at least 200 mg/dL (2.28 mmol/L)
- serum HDL cholesterol level lower than 40 mg/dL (1.04 mmol/L)
- BP of at least 130/85 mmHg or controlled with antihypertensive treatment
- BMI of more than 28.9.

Stern et al (2004) [12] combined metabolic syndrome as a binary variable in the Framingham equation and performed logistic regression on this equation. The details of this logistic regression are not given. Participants were assumed to have metabolic syndrome if they met at least three of the NCEP criteria [78]:

- fasting plasma glucose of at least 111 mg/dL (6.1 mmol/L)
- fasting serum triglyceride level of at least 150 mg/dL (1.7 mmol/L)
- serum HDL cholesterol level lower than 40 mg/dL (1.04 mmol/L) or 50 mg/dL (1.29 mmol/L) in women
- BP of at least 130/85 mmHg or controlled with antihypertensive treatment
- waist circumference of more than 102 cm in men and 88 cm in women.

McNeill et al (2005) [13] used Cox proportional hazards regression to model the relationship between the metabolic syndrome and time to incident CHD or ischaemic stroke. Participants were assumed to have metabolic syndrome if they met three or more NCEP criteria [78]:

- fasting plasma glucose of at least 111 mg/dL (6.1 mmol/L)
- fasting serum triglyceride level of at least 150 mg/dL (1.7 mmol/L)
- serum HDL cholesterol level lower than 40 mg/dL (1.04 mmol/L) or 50 mg/dL (1.29 mmol/L) in women
- BP of at least 130/85 mmHg or controlled with antihypertensive treatment
- waist circumference of more than 102 cm in men and 88 cm in women.

Sex-specific logistic regression models were then generated (details are not given by the author) to include Framingham and Framingham plus metabolic syndrome.

NCEP criteria are described in the Executive Summary of the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). [78] No information is available for the cohort from which these risk charts are derived.

Computer Risk Model/Coronary Heart Model [14]

Derived from the cohorts of the Framingham Heart Study, Canadian Life Tables, and Canada Health Survey Data.

The annual probability of all CHD events is calculated as:

$$(1/8) \times \{[\exp(\text{RISK})]/[1+\exp(\text{RISK})]\} \times (\text{HDL}_{\text{MOD}}),$$

where $\text{HDL}_{\text{MOD}} = \exp(1.80 - 0.040 \times \text{HDL})$ for men, and
 $= \exp(2.42 - 0.044 \times \text{HDL})$ for women,

where $\text{RISK} = (0.29 \times \text{AGE}) - (0.0015 \times \text{AGE}^2) + (0.02 \times \text{CHL}) + (0.02 \times \text{DBP}) + (0.44 \times \text{CIG}) + (0.062 \times \text{LVH}) + (0.28 \times \text{GLU}) - (0.00027 \times \text{CHL} \times \text{AGE}) - 17.01$

where CHL = total serum cholesterol level

DBP = diastolic blood pressure

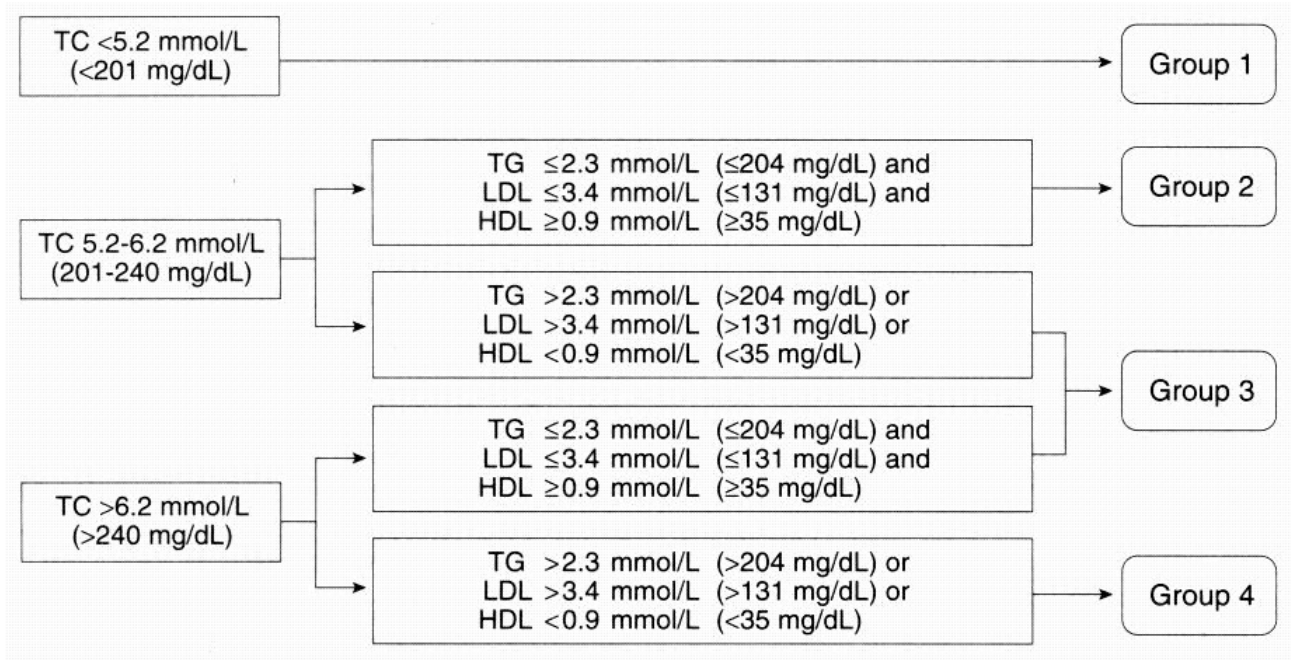
CIG = cigarette smoking as defined by Framingham Heart Study

LVH = left ventricular hypertrophy

GLU = glucose intolerance

Canadian Consensus Conference on Cholesterol risk score [14]

Based on the Canadian Consensus Conference on Cholesterol held in Ottawa, Canada in 1988. No clear information is available for the cohort from which these risk charts are derived.

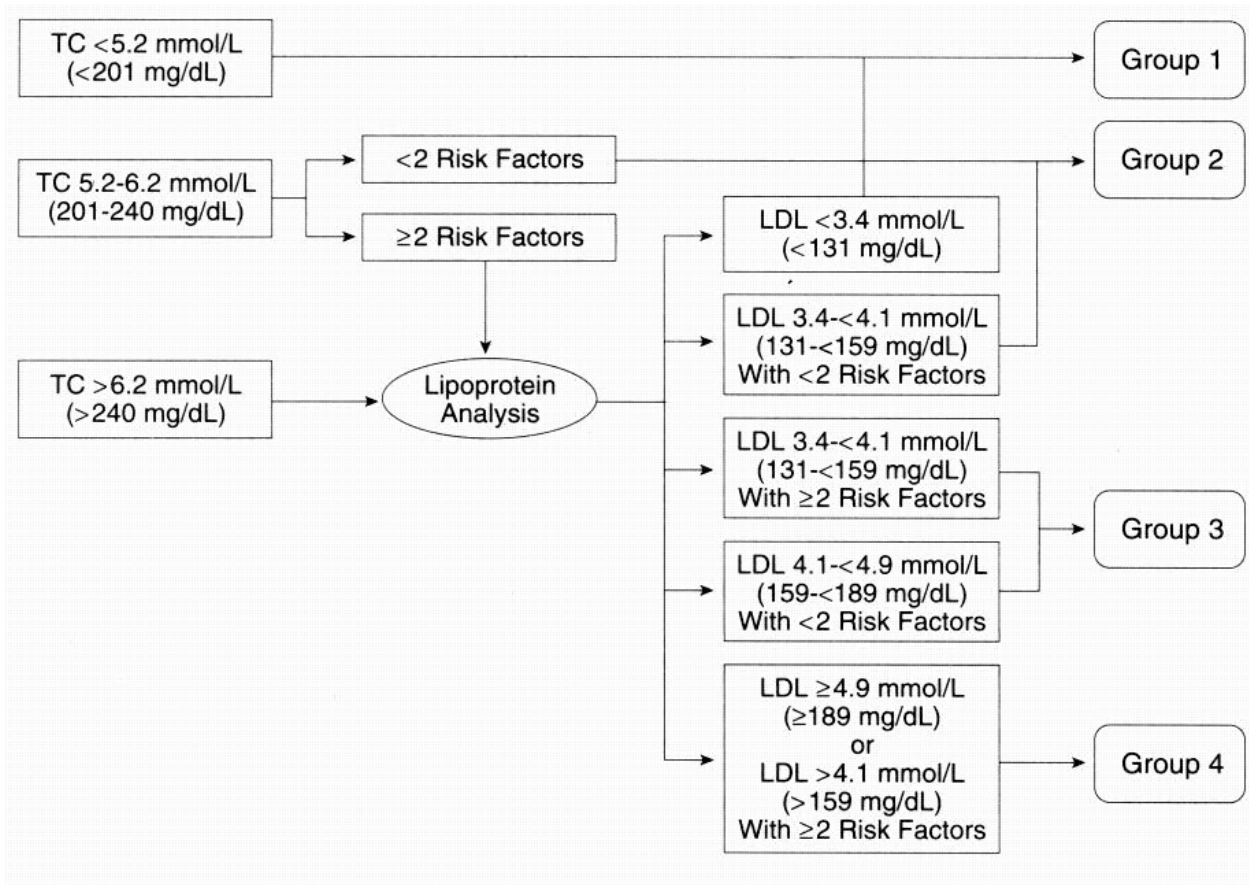


The Canadian Consensus Conference Guidelines allocated adults (aged greater than or equal to 30 years) to three coronary risk strata based on lipid measurements. Grover et al created a fourth, very high-risk group to allow comparison with the four strata of the National Cholesterol Education Program.

TC = total plasma cholesterol, HDL = high-density lipoprotein, LDL = low-density lipoprotein, TG = triglycerides

First National Cholesterol Education Program risk score [14]

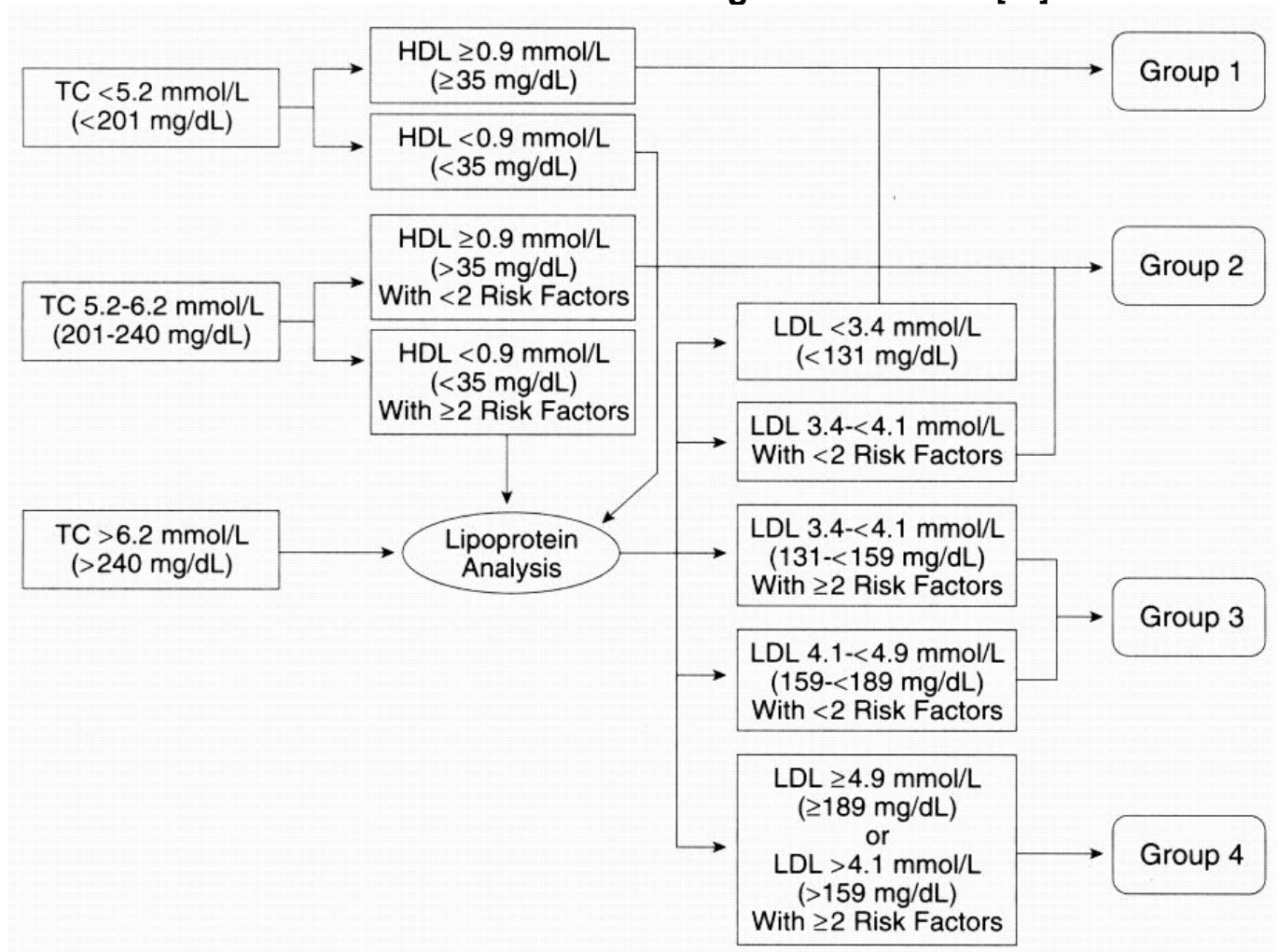
Based on the First National Cholesterol Education Program created in 1985. No clear information is available for the cohort from which these risk charts are derived.



The National Cholesterol Education Program Guidelines allocated adults to four coronary risk strata based on lipid measurements and the presence of non-lipid risk factors such as male age of 45 years or more, female age of 55 years or more or premature menopause without oestrogen replacement therapy, a family history of premature CHD, current cigarette smoking, hypertension or use of antihypertensive medication, a low HDL level, and diabetes mellitus.

TC = total plasma cholesterol, LDL = low-density lipoprotein

Second National Cholesterol Education Program risk score [14]



The Second National Cholesterol Education Program Risk Score differs from the First National Cholesterol Education Program Risk Score in the inclusion of HDL analysis as a further stratification into groups.

TC = total plasma cholesterol, HDL = high-density lipoprotein, LDL = low-density lipoprotein

Traditional/Non-traditional risk factors [15]

Derived from a cohort of 14,054 participants from the Atherosclerosis Risk in Communities study.

Folsom et al (2003) compared risk factors in a basic model with various other non-traditional risk factors in different combinations:

Basic model (age, race, total cholesterol, HDL cholesterol, systolic BP, use of antihypertensive medication, smoking status)

- Basic model – systolic BP and antihypertensive medication
- Basic model – cholesterol
- Basic model – HDL cholesterol
- Basic model – smoking status
- Basic model + BMI
- Basic model + waist-to-hip ratio
- Basic model + heart rate
- Basic model + sport activity
- Basic model + residual FEV₁
- Basic model + Keys score
- Basic model + cigarette pack-years
- Basic model + creatinine
- Basic model + lipoprotein(a)
- Basic model + alipoproteinA1
- Basic model + alipoproteinB
- Basic model + albumin
- Basic model + fibrinogen
- Basic model + factor VII
- Basic model + WBC count
- Basic model + factor VIII
- Basic model + von Willebrand factor
- Basic model + multiple risk factors (BMI, waist-to-hip ratio, lipoprotein(a), albumin, creatinine, WBC count, fibrinogen, factor VIII, sport activity, residual FEV₁, Keys score, pack-years smoking).

Folsom et al also compared a basic model with a full model in diabetic participants. The risk score XBETA for an individual is the sum of the products of the beta co-efficients for a factor as indicated in the table below.

Risk variable	Basic model		Full model	
	Women	Men	Women	Men
S _m	0.97507	0.93299	0.98353	0.95280
XBETA _{med}	0.99852	7.75110	2014640	17.9811
Age (years)	-0.03301	0.22777	0.02914	0.42128
Age ² (years)	0.000041	-0.00175	-0.00028	-0.00372
Race (white=1/black=0)	0.37361	0.49310	0.65568	0.52539
Total cholesterol (mg/dL)				
200–279	0.72618	0.46038	0.72122	0.38255
>280	1.10225	0.90874	0.85815	0.96119
HDL cholesterol (mg/dL)				
<45	0.45810	0.80719	0.39395	0.79065
45–49	0.55162	-0.25732	0.45172	-0.29731
Systolic BP (mmHg)	0.01314	0.00437	0.00549	0.00309
Hypertension medication (yes=1/no=0)	0.48246	-0.05461	0.43010	-0.16935
Current smoking (yes=1/no=0)	0.78920	0.15208	0.45265	-0.05033
BMI (kg/m ²)	-	-	-0.05122	-0.05070
Waist-to-hip ratio (1 unit)	-	-	3.29970	3.54309
Sport activity (1 unit)	-	-	-0.329970	-0.05680
Keys score (1 unit)	-	-	-0.32062	0.03085
Serum creatinine (mg/dL)	-	-	0.01014	1.09697
Serum albumin (g/dL)	-	-	0.06090	-0.02500
WBC (thousands/mm ³)	-	-	-0.78332	0.02362
Factor VIII (%)	-	-	0.00637	0.00619
LVH (yes=1/no=0)	-	-	0.51805	-0.87211
IMT (mm)	-	-	1.54553	0.81442

BMI = body mass index, WBC = white blood cell count, LVH = left ventricular hypertrophy, IMT = intima-media thickness

These risk scores can be converted by the following formula to probabilities of onset of CHD within 10 years:

$$P = 1 - S_M^{\exp(XBETA - XBETA_{med})}$$

where S_M is 1 minus the probability of a CHD event within 10 years for a person with 0 levels of the categorical variables in the risk score and with the median values of the continuous risk factors, and XBETA_{med} is the risk score calculated for such a person.

To apply this risk score to a new population, even though the score may properly rank individuals in the population for CHD risk, one would need to calibrate P to the overall 1 year risk level in the new population. An approximate way to do this is to replace XBETA_{med} with a corresponding value calculated still at zero values of categorical variables but at the new population's medians for the continuous variables, and to replace S_M with

$$\exp(-rt\{\exp(XBETA_{med} - \text{mean } XBETA)\})$$

where $X_{BETA_{med}}$ is for the new population, r is the average annual event rate for the new population, t is the years at which the risk probability is to be calculated, and $mean(X_{BETA})$ is the mean risk score for the new population. The latter is estimated from summing the β co-efficients multiplied times the estimated means of the associated risk factors in the new population.

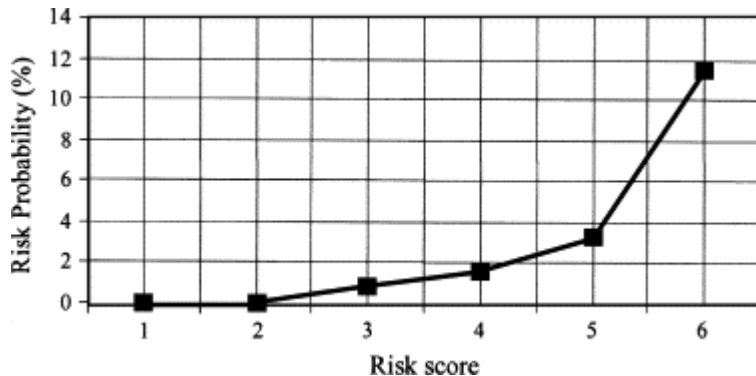
Oriental specific risk score [33]

Derived from a cohort of 5092 steel workers in Beijing, China, in 1993.

For CVD the following formula is used:

$$=(0.040 \times \text{age})+(0.023 \times \text{SBP})+(0.011 \times \text{total cholesterol})+(0.127 \times \text{BMI})+(0.843 \text{ if a smoker or } 0 \text{ if not a smoker}) - 7$$

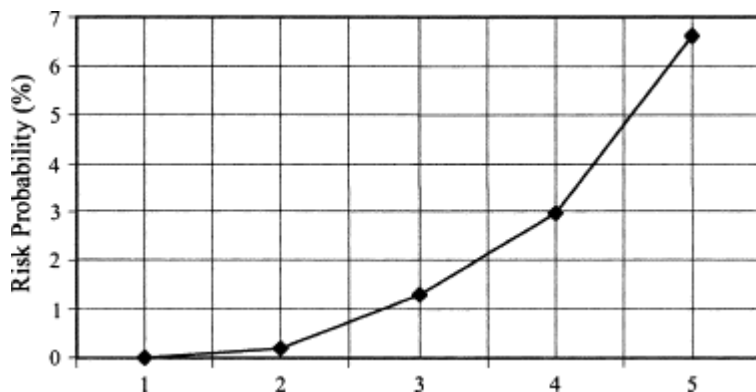
To calculate a risk probability for CVD the following graph is used:



For ischaemic stroke the following formula is used:

$$=(0.02305 \times \text{age})+(0.02812 \times \text{SBP})+(0.00326 \times \text{total cholesterol})+(0.69557 \text{ if a smoker or } 0 \text{ if not a smoker}) - 3$$

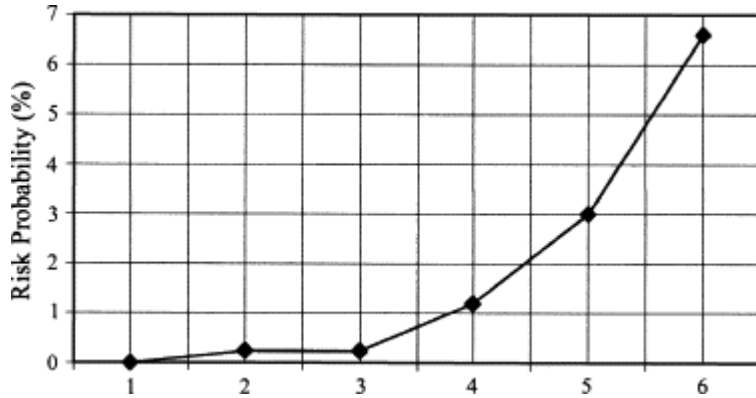
To calculate a risk probability for ischaemic stroke the following graph is used:



For haemorrhagic stroke the following formula is used:

$$=(0.06383 \times \text{age})+(0.02019 \times \text{SBP})+(0.03997 \times \text{DBP})+(0.00841 \times \text{total cholesterol}) - 4$$

To calculate a risk probability for haemorrhagic stroke the following graph is used:



UKPDS risk engine [79]

Derived from a cohort of 4549 newly diagnosed diabetic patients in the UK, between 1977 and 1991.

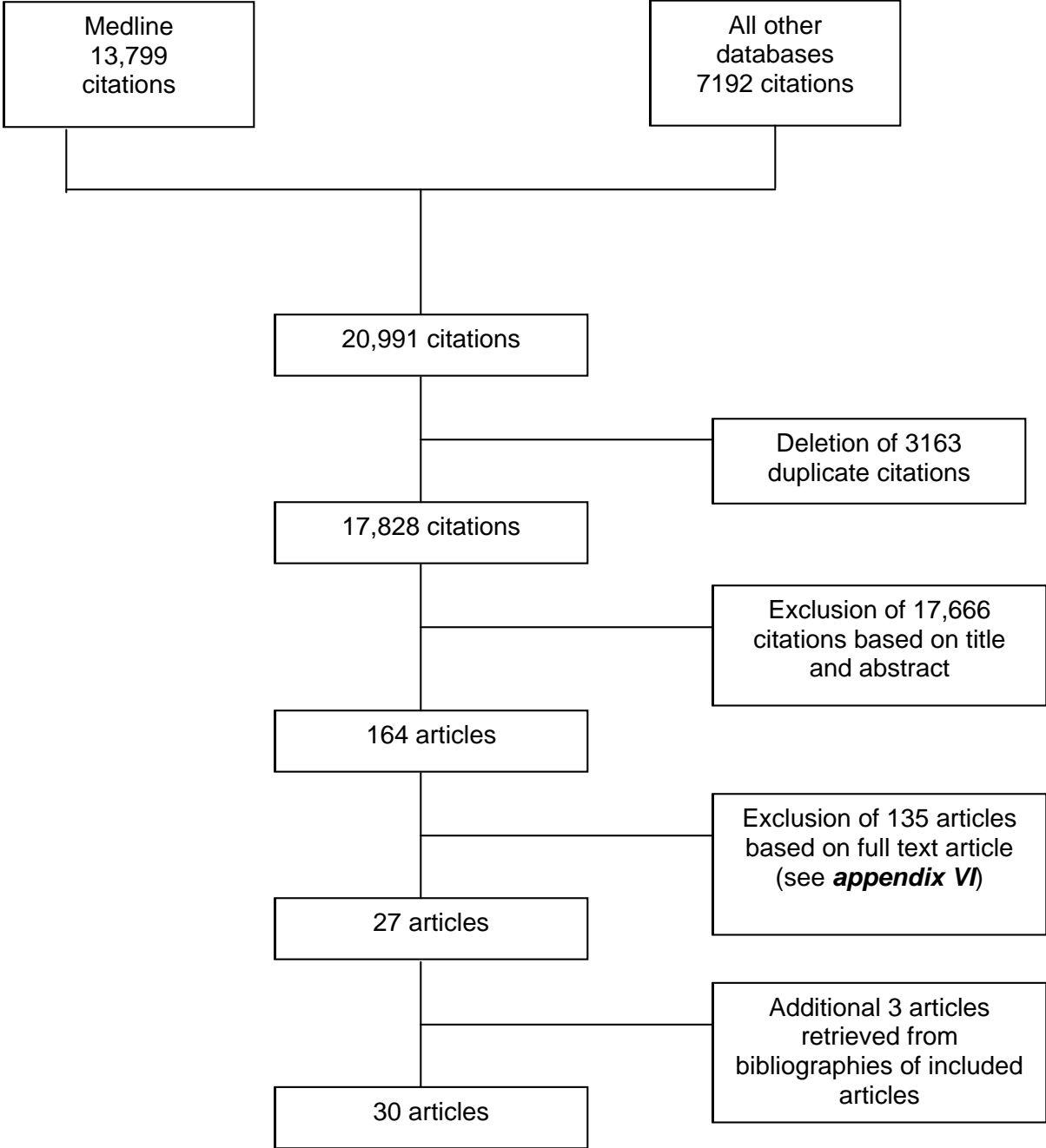
The probability of CVD can be calculated according to the following formula:

$$=1-\exp(-qd^{t-1})$$

Where $q = 0.0112 \times 1.059^{\text{AGE}-55} \times 0.525^{\text{FEMALE SEX}} \times 0.390^{\text{AFRO-CARRIBEAN ETHNICITY}} \times 1.350^{\text{SMOKING}} \times 1.183^{1\% \text{ increase in HbA1c}} \times 1.088^{(10\text{mmHg increase in SBP}-135.7)/10} \times 3.845^{\ln(\text{LIPID RATIO})-1.59}$

and $d=1.078$, defined as risk ratio for each year increase in duration of diagnosed diabetes

Appendix V: Search results



Appendix VI: Table of excluded articles

Citation	Comment
Aktas MK, Ozduran V, Pothier CE, Lang R, Lauer MS. Global risk scores and exercise testing for predicting all-cause mortality in a preventive medicine program. <i>JAMA</i> 2004; 292: 1462-1468	We are looking at CVD events, not all-cause mortality
Albert MA, Glynn RJ, Ridker PM. Plasma concentration of C-reactive protein and the calculated Framingham Coronary Heart Disease Risk Score. <i>Circulation</i> 2003; 108: 161-165	Correlates C-reactive protein with FRE
Anonymous. Relationship between baseline risk factors and coronary heart disease and total mortality in the Multiple Risk Factor Intervention Trial. Multiple Risk Factor Intervention Trial Research Group. <i>Prev Med</i> 1986; 15: 254-273	Not predictive ability
Anthony D. Diagnosis and screening of coronary artery disease. <i>Primary Care; Clinics in Office Practice</i> 2005; 32: 931-946	Narrative review
Assmann G, Schulte H. Modelling the Helsinki Heart Study by means of risk equations obtained from the PROCAM Study and the Framingham Heart Study. <i>Drugs</i> 1990; 40 (Suppl 1): 13-18	Not predictive ability
Assmann G, Schulte H, Cullen P. New and classical risk factors – the Münster heart study (PROCAM). <i>Eur J Med Res</i> 1997; 2(6): 237-42.	This article only includes modelling data
Armstrong KA, Rakhit DJ, Case C, Johnson DW, Isbel NM, Marwick TH. Derivation and validation of a disease-specific risk score for cardiac risk stratification in chronic kidney disease. <i>Nephrol Dialysis Transplant</i> 2005; 20: 2097-2104	Cohort has prior CVD history
Asselbergs FW, Hillege HL, Van Gilst WH. Framingham score and microalbuminuria: combined future targets for primary prevention? <i>Kidney Internat</i> 2004; Suppl 66: S111-S114	All-cause mortality outcome
Bainton D, Miller NE, Bolton CH, Yarnell JW, Sweetnam PM, Baker IA, Lewis B, Elwood PC. Plasma triglyceride and high density lipoprotein cholesterol as predictors of ischaemic heart disease in British men. The Caerphilly and Speedwell Collaborative Heart Disease Studies. <i>Br Heart J</i> 1992; 68: 60-66	Not predictive ability, single risk factors
Bairey Merz N. Assessment of patients at intermediate cardiac risk. <i>Am J Cardiol</i> 2005; 96: 2J-10J	Guide to management of risk categories; does follow up case studies though
Balady GJ, Larson MG, Vasan RS, Leip EP, O'Donnell CJ, Levy D. Usefulness of exercise testing in the prediction of coronary disease risk among asymptomatic persons as a function of the Framingham risk score. <i>Circulation</i> 2004; 110: 1920-1925	Compares a single variable (exclusion criteria) of exercise capacity to Framingham score
Bayly G. HDL-cholesterol and cardiac disease: which table to use? <i>Ann Clin Biochem</i> 2002; 39: 12-21	Narrative review
Bayly GR, Bartlett WA, Davies PH, Husband D, Haddon A, Game FL, Jones AF. Laboratory-based calculation of coronary heart disease risk in a hospital diabetic clinic. <i>Diabet Med</i> 1999; 16: 697-701	No follow-up
Becker DM, Blumenthal RS, Yanek LR, Moy TF, Becker LC. Markedly higher incidence of coronary disease events than predicted by Framingham Risk equation in the John Hopkins Sibling study <i>Circulation</i> 2001; 104(17): 3733	Study in people with CVD
Benfante R, Reed D, Frank J. Do coronary heart disease risk factors measured in the elderly have the same predictive roles as in the middle aged. Comparisons of relative and attributable	Not predictive ability

risks. <i>Ann Epidemiol</i> 1992; 2: 273-282	
Bernard S, Serusclat A, et al. Incremental predictive value of carotid ultrasonography in the assessment of coronary risk in a cohort of asymptomatic type 2 diabetic subjects. <i>Diabetes Care</i> 2005; 28(5): 1158-62.	Single risk factor comparison
Bruno G, Merletti F, Biggeri A, Barger G, Ferrero S, Runzo C, Prina Cerai S, Pagano G, Cavallo-Perin P, Casale Monferrato S. Metabolic syndrome as a predictor of all-cause and cardiovascular mortality in type 2 diabetes: the Casale Monferrato Study. <i>Diabetes Care</i> 2004; 27: 2689-2694	Not predictive ability
Brindle PM, Beswick AD, Fahey T, Ebrahim SB. The accuracy and impact of risk assessment in the primary prevention of cardiovascular disease: A systematic review. <i>Heart</i> 2006; 92(12): 1752-1759	That which is relevant has already been included and the others don't meet the inclusion criteria
Callaghan K. Civil Aviation Authority of New Zealand and cardiovascular risk assessment. <i>AVMEDIA: J Austr N Z Aviation Med Soc</i> 1999; 23: 8-12	Not predictive ability
Campbell CY, Nasir K, Blumenthal RS. Metabolic syndrome, subclinical coronary atherosclerosis, and cardiovascular risk. <i>Am Heart Hospital J</i> 2005; 3: 105-110	Narrative review
Cappuccio FP, Oakeshott P, Strazzullo P, Kerry SM. Application of Framingham risk estimates to ethnic minorities in the United Kingdom and implications for primary prevention of heart disease in general practice: cross sectional population based study. <i>BMJ</i> 2002; 325: 1271-1274	No follow-up
Catalan Agency for Health Technology Assessment and Research. Estimation of cardiovascular risk in primary care. CAHTA's Newsletter 2005;35:10. Available at: http://www.gencat.cat/salut/depsan/units/aatrm/pdf/but35en.pdf	Full text article only in Spanish or Catalan
Chambless LE, Folsom AR, Sharrett AR, Sorlie P, Couper D, Szklo M, Nieto FJ. Coronary heart disease risk prediction in the Atherosclerosis Risk in Communities (ARIC) study. <i>J Clin Epidemiol</i> 2003; 56: 880-890	Modelling
Chan AKL, Wun YT, Lam WK, Tsang LCY. An appraisal of the calibrated Framingham equation for Chinese – A tool to use in Hong Kong? – Part I. <i>Hong Kong Practitioner</i> 2004; 26: 477-483	Narrative review
Chowdhury T, Lasker SS. Predicting CHD risk in patients with diabetes. <i>Diabet Med</i> 2002; 19: 83-84	Comment paper/letter; discusses Framingham limitations
Conroy RM, Pyorala K, Fitzgerald AP, Sans S, Menotti A, De Backer G, De Bacquer D, Ducimetiere P, Jousilahti P, Keil U, Njolstad I, Oganov RG, Thomsen T, Tunstall-Pedoe H, 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. <i>Eur Heart J</i> 2003; 24: 987-1003	Modelling
Coppola WG, Whincup PH, Papacosta O, Walker M, Ebrahim S. Scoring system to identify men at high risk of stroke: a strategy for general practice. <i>Br J Gen Pract</i> 1995; 45: 185-189	Modelling
Criqui MH. Obesity, risk factors, and predicting cardiovascular events. <i>Circulation</i> 2005; 111: 1869-1870	Editorial
De Henauw S, De Bacquer D, de Smet P, Kornitzer M, De Backer G. Trends and regional differences in coronary risk factors in two areas in Belgium: final results from the MONICA Ghent-Charleroi Study. <i>J Cardiovasc Risk</i> 2000; 7: 347-357	No follow-up data
de Visser CL, Bilo HJ, Thomsen TF, Groenier KH, Meyboom-de Jong B. Prediction of	No observed follow-up

coronary heart disease: a comparison between the Copenhagen risk score and the Framingham risk score applied to a Dutch population. J Intern Med 2003; 253: 553-562	
Delaveyne R, Colombet I. Methods for assessing global cardiovascular risk (CVR): use of risk models. Paris: L'Agence Nationale d'Accreditation d'Evaluation en Sante (ANAES) 2004.	Commentary
Ducloux D, Kazory A, Chalopin JM. Predicting coronary heart disease in renal transplant recipients: a prospective study. Kidney Internat 2004; 66: 441-447	Renal transplant recipients
Everett CJ, Mainous AG, 3rd, Koopman RJ, Diaz VA. Predicting coronary heart disease risk using multiple lipid measures. Am J Cardiol 2005; 95: 986-988	Modelling
Girman CJ, Dekker JM, Rhodes T, Nijpels G, Stehouwer CD, Bouter LM, Heine RJ. An exploratory analysis of criteria for the metabolic syndrome and its prediction of long-term cardiovascular outcomes: the Hoorn study. Am J Epidemiol 2005; 162: 438-447	Modelling
Gliksman MD, Lazarus R, Wilson A, Leeder SR, Koutts J. The Western Sydney Stroke Risk in the Elderly Study. A 5-year prospective study. Ann Epidemiol 1994; 4: 59-66	No follow-up data
Gordon T, Kannel WB. Multiple risk functions for predicting coronary heart disease: the concept, accuracy, and application. Am Heart J 1982; 103: 1031-1039	Narrative review
Grundy SM. The changing face of cardiovascular risk. J Am Coll Cardiol 2005; 46: 173-175	Comment
Haq IU, Ramsay LE, Jackson PR, Wallis EJ. Prediction of coronary risk for primary prevention of coronary heart disease: a comparison of methods. QJM 1999; 92: 379-385	No observed outcome
Haq IU, Ramsay LE, Yeo WW, Jackson PR, Wallis EJ. Is the Framingham risk function valid for northern European populations? A comparison of methods for estimating absolute coronary risk in high risk men. Heart 1999; 81: 40-46	No follow-up
Hayashino Y, Nagata-Kobayashi S, Morimoto T, Maeda K, Shimbo T, Fukui T. Cost-effectiveness of screening for coronary artery disease in asymptomatic patients with Type 2 diabetes and additional atherogenic risk factors. J Gen Intern Med 2004; 19: 1181-1191	Modelling
Hollis JF, Connett JE, Stevens VJ, Greenlick MR. Stressful life events, Type A behavior, and the prediction of cardiovascular and total mortality over six years. MRFIT Group. J Behav Med 1990; 13: 263-280	Single risk factor
Isles CG, Ritchie LD, Murchie P, Norrie J. Risk assessment in primary prevention of coronary heart disease: randomised comparison of three scoring methods. BMJ 2000; 320: 690-691	No follow-up
Jousilahti P, Vartiainen E, Tuomilehto J, Puska P. Sex, age, cardiovascular risk factors, and coronary heart disease: a prospective follow-up study of 14 786 middle-aged men and women in Finland. Circulation 1999; 99: 1165-1172	Not predictive ability
Kannel WB. Framingham study insights into hypertensive risk of cardiovascular disease. Hypertens Res 1995; 18: 181-196	Discussion
Kannel WB, McGee DL. Composite scoring – methods and predictive validity: insights from the Framingham Study. Health Services Res 1987; 1995; 22: 499-535	Narrative review
Kannel WB, Vasan RS. Assessment of cardiovascular risk and choice of antihypertensive therapy. Curr Hypertens Reports 2004; 6: 346-351	Narrative review
Keil JE, Sutherland SE, Knapp RG, Tyroler HA. Does equal socioeconomic status in Black and White men mean equal risk of mortality? Am J Public Health 1992; 82: 1133-1136	Not prediction
Kent D, Griffith J. The Framingham scores overestimated the risk for coronary heart disease in	Commentary

Japanese, Hispanic, and Native American cohorts. ACP Journal Club 2002; 136: 36	
Kimata S, Hosoda S, Yokoyama I, Yamada N. An index predicting coronary heart disease: LDL/HDL x 5. Jap Heart J 1997; 38:1-9	Single risk factor
Knuiman MW, Vu HT. Prediction of coronary heart disease mortality in Busselton, Western Australia: an evaluation of the Framingham, national health epidemiologic follow up study, and WHO ERICA risk scores. J Epidemiol Community Health 1997; 51(5): 515-9.	Participants had prior CVD
Koenig W, Lowel H, Baumert J, Meisinger C. C-reactive protein modulates risk prediction based on the Framingham Score: implications for future risk assessment: results from a large cohort study in southern Germany. Circulation 2004; 109: 1349-1353	C-reactive proteins vs. Framingham
Kramer BK, Boger C, Kruger B, Marienhagen J, Pietrzyk M, Obed A, Paczek L, Mack M, Banas B. Cardiovascular risk estimates and risk factors in renal transplant recipients. Transplantation Proceedings 2005; 37: 1868-1870	Transplant recipients
Lakkireddy DR, Bhakkad J, Korlakunta HL, Ryschon K, Shen X, Mooss AN, Mohiuddin SM. Prognostic value of the Duke Treadmill Score in diabetic patients. Am Heart J 2005; 150: 516-521	Approval from NVDPA that angina is a pre-existing EC not absolute method
Lambert AP, Hunt MA, Day AP, Bayly GR, Dayan CM. Reproducibility of individualized coronary heart disease risk calculations in patients with diabetes mellitus. Diabet Med 2002; 19: 514-517	No observed follow-up
Liao Y, McGee DL, Cooper RS. Prediction of coronary heart disease mortality in blacks and whites: Pooled data from two national cohorts. Am J Cardiol 1999; 84: 31-36	Modelling
Lindenstrom E, Boysen G, Nyboe J. Influence of total cholesterol, high density lipoprotein cholesterol, and triglycerides on risk of cerebrovascular disease: the Copenhagen City Heart Study. BMJ 1994; 309: 11-15 [see comment; erratum appears in BMJ 1994; 309(6969): 1619].	Single risk factors
Lindquist P, Bengtsson C, Lissner L, Bjorkelund C. Cholesterol and triglyceride concentration as risk factors for myocardial infarction and death in women, with special reference to influence of age. J Intern Med 2002; 251: 484-489	Not predictive ability
Liu J, Hong YL, D'Agostino RB, et al. Recalibration of the Framingham functions to the Chinese population improved coronary heart disease risk estimates. ACP Journal Club 2004; 141(3); 81	Commentary of paper 'Predictive value for the Chinese population of the Framingham CHD risk assessment tool compared with the Chinese multi-provincial cohort study' which is already included
L'Ltalien G, Ford I, Norrie J, LaPuerta P, Ehreth J, Jackson J, Shepherd J. The cardiovascular event reduction tool (CERT) – a simplified cardiac risk prediction model developed from the West of Scotland Coronary Prevention Study (WOSCOPS). Am J Cardiol 2000; 85: 720-724	Modelling
Lopez-Alvarenga JC, Triana-Carmona LY, Gonzalez-Barranco J. Reliability and accuracy of a cardiovascular risk questionnaire and body shape figures for body size in Mexican obese subjects. Revista de Investigacion Clinica 2003; 55: 511-518	Full text in Spanish
Lowe LP, Greenland P, Ruth KJ, Dyer AR, Stamler R, Stamler J. Impact of major cardiovascular disease risk factors, particularly in combination, on 22-year mortality in women and men. Arch Intern Med 1998; 158: 2007-2014	Relationship of risk factors with CVD, not predictive ability
Luc G, Bard JM, Ferrieres J, Evans A, Amouyel P, Arveiler D, Fruchart JC, Ducimetiere P. Value of HDL cholesterol, apolipoprotein A-I, lipoprotein A-I, and lipoprotein A-I/A-II in prediction of coronary heart disease: the PRIME Study. Prospective Epidemiological Study of Myocardial Infarction. Arterioscler Thromb Vasc Biol 2002; 22: 1155-1161	Not predictive ability

Lumley T, Kronmal RA, et al. A stroke prediction score in the elderly: validation and Web-based application. <i>J Clin Epidemiol</i> 2002; 55(2): 129-136.	Participants had prior CVD history
Marrugat J, D'Agostino R, Sullivan L, Elosua R, Wilson P, Ordovas J, Solanas P, Cordon F, Ramos R, Sala J, Masia R, Kannel WB. An adaptation of the Framingham coronary heart disease risk function to European Mediterranean areas. <i>J Epidemiol Community Health</i> 2003; 57: 634-638	No extractable data, flagged for discussion
Matthews KA, Gump BB. Chronic work stress and marital dissolution increase risk of posttrial mortality in men from the Multiple Risk Factor Intervention Trial. <i>Arch Intern Med</i> 2002; 162: 309-315	Not assessing predictive ability
McCallum J, Simons LA, Simons J, Friedlander Y. The Dubbo study: preliminary factors for four-year survival. <i>Proceedings of the Annual Conference of the Australian Association of Gerontology</i> 1993; 28: 34-36	Relationship between RFs and CVD, no predictive ability data
McEwan P, Williams JE, Griffiths JD, Bagust A, Peters JR, Hopkinson P, Currie CJ. Evaluating the performance of the Framingham risk equations in a population with diabetes. <i>Diabet Med</i> 2004; 21: 318-323	No exclusion criteria applied
McNutt RA, Selker HP. How did the acute ischemic heart disease predictive instrument reduce unnecessary coronary care unit admissions? <i>Medical Decision Making</i> 1988; 8: 90-94	Assessing use of method not predictive ability of method
Menotti A, Keys A, Kromhout D, Nissinen A, Blackburn H, Fidanza F, Giampaoli S, Karvonen MJ, Pekkanen J, Punsar S, et al. Twenty-five-year mortality from coronary heart disease and its prediction in five cohorts of middle-aged men in Finland, The Netherlands, and Italy. <i>Prev Med</i> 1990; 19: 270-278	Modelling
Menotti A, Lanti M, Puddu PE, Carratelli L, Mancini M, Motolese M, Prati P, Zanchetti A. The risk functions incorporated in Riscard 2002: a software for the prediction of cardiovascular risk in the general population based on Italian data. <i>Italian Heart Journal: Official Journal of the Italian Federation of Cardiology</i> 2002; 3: 114-121	Modelling
Menotti A, Puddu PE, Lanti M. Comparison of the Framingham risk function-based coronary chart with risk function from an Italian population study. <i>Eur Heart J</i> 2000; 21: 365-370	No extractable data, flag for discussion
Michaelides AP, Triposkiadis FK, Boudoulas H, Spanos AM, Papadopoulos PD, Kourouklis KV, Toutouzas PK. New coronary artery disease index based on exercise-induced QRS changes. <i>Am Heart J</i> 1990; 120: 292-302	Previous MI not an exclusion criteria. Only assessing one risk/intervention
Mitrabasu PP, Shahapurkar JS, Sreekumar TP, Vyawahare MK, Sarma CG. Absolute coronary risk analyser-a tool for managing coronary heart disease risk. <i>Indian J Med Sci</i> 2003; 57: 238-243	No observed follow-up
Mora S, Yanek LR, Moy TF, Fallin MD, Becker LC, Becker DM. Interaction of body mass index and Framingham risk score in predicting incident coronary disease in families. <i>Circulation</i> 2005; 111: 1871-1876	Not predictive ability
Morrow DA, Antman EM, Murphy SA, Assmann SF, Giugliano RP, Cannon CP, Michael Gibson C, McCabe CH, Barron HV, Van De Werf F, Braunwald E. The Risk Score Profile: a novel approach to characterising the risk of populations enrolled in clinical studies. <i>Eur Heart J</i> 2004; 25: 1139-1145	Previous MI
Mosca L. Absolute risk assessment in the clinical setting. <i>Am J Med</i> 1999; 107: 7S-9S	Discussion on relevance of absolute risk to clinical practice

Nakanishi N, Takatorige T, Fukuda H, Shirai K, Li W, Okamoto M, Yoshida H, Matsuo Y, Suzuki K, Tatara K. Components of the metabolic syndrome as predictors of cardiovascular disease and type 2 diabetes in middle-aged Japanese men. <i>Diabet Res Clin Pract</i> 2004; 64: 59-70	Not predictive ability
Nakatou T, Nakata K, Nakamura A, Itoshima T. Carotid haemodynamic parameters as risk factors for cerebral infarction in type 2 diabetic patients. <i>Diabet Med</i> 2004; 21: 223-229	Single risk factors, previous stroke
Nawrot TS, Staessen JA, Thijs L, Fagard RH, Tikhonoff V, Wang JG, Franklin SS. Should pulse pressure become part of the Framingham risk score? <i>J Hum Hypertens</i> 2004; 18: 279-286	Not predictive ability
Pearson TA. New tools for coronary risk assessment: what are their advantages and limitations? <i>Circulation</i> 2002; 105: 886-892	Discussion of advantages and limitations of methods
Pekkanen J, Tervahauta M, Nissinen A, Karvonen MJ. Does the predictive value of baseline coronary risk factors change over a 30-year follow-up? <i>Cardiology</i> 1993; 82: 181-190	Single risk factors
Persson M, Carlberg B, Tavelin B, Lindholm LH. Doctors' estimation of cardiovascular risk and willingness to give drug treatment in hypertension: fair risk assessment but defensive treatment policy. <i>J Hypertens</i> 2004; 22: 65-71	Factors 'influencing' risk estimation – i.e. GP's perception and treatment
Pirie PL, Luepker RV, Jacobs DR Jr, Brown JW, Hall N. Development and validation of a self-scoring test for coronary heart disease risk. <i>J Community Health</i> 1983; 9: 65-79	Comparing self-assessed risk score to Framingham, but no observed follow-up event
Pocock SJ, McCormack V, Gueyffier F, Boutitie F, Fagard RH, Boissel JP. A score for predicting risk of death from cardiovascular disease in adults with raised blood pressure, based on individual patient data from randomised controlled trials. <i>BMJ</i> 2001; 323: 75-81	Modelling
Rabindranath KS, Anderson NR, Gama R, Holland MR. Comparative evaluation of the new Sheffield table and the modified joint British societies coronary risk prediction chart against a laboratory based risk score calculation. <i>Postgrad Med J</i> 2002; 78: 269-272	No observed outcome
Raikou M, McGuire A. The economics of screening and treatment in type 2 diabetes mellitus. <i>Pharmacoeconomics</i> 2003; 21: 543-564	Not predictive ability
Ramachandran S, French JM, Vanderpump MP, Croft P, Neary RH. Using the Framingham model to predict heart disease in the United Kingdom: retrospective study. <i>BMJ</i> 2000; 320: 676-677	No extractable data, flag for discussion
Reissigova J, Tomeckova M. State of the art coronary heart disease risk estimations based on the Framingham heart study. <i>Central Eur J Public Health</i> 2005; 13: 180-186	Narrative review
Reynolds TM, Twomey P, Wierzbicki AS. Accuracy of cardiovascular risk estimation for primary prevention in patients without diabetes. <i>J Cardiovasc Risk</i> 2002; 9: 183-190	Modelling
Richie RC. Non-invasive assessment of the risk of coronary heart disease. <i>J Insurance Med (Seattle)</i> 2002; 34: 31-42	Focus is assessments, not standard risk factors. Review
Ridker PM, Wilson PW, Grundy SM. Should C-reactive protein be added to metabolic syndrome and to assessment of global cardiovascular risk? <i>Circulation</i> 2004; 109: 2818-2825	Narrative review
Rimm EB, Stampfer MJ, Giovannucci E, Ascherio A, Spiegelman D, Colditz GA, Willett WC. Body size and fat distribution as predictors of coronary heart disease among middle-aged and older US men. <i>Am J Epidemiol</i> 1995; 141: 1117-1127	Single risk factors
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Sheu WH, Jeng CY, Young MS, Le WJ, Chen YT. Coronary artery disease risk predicted by insulin resistance, plasma lipids, and hypertension in people without diabetes. Am J Med Sci 2000; 319: 84-88	Prevalent CHD
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Wang TJ, Massaro JM, Levy D, Vasan RS, Wolf PA, D'Agostino RB, Larson MG, Kannel WB, Benjamin EJ. A risk score for predicting stroke or death in individuals with new-onset atrial fibrillation in the community: the Framingham Heart Study. <i>JAMA</i> 2003; 290: 1049-1056	Modelling
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Winocour PH, Fisher M. Prediction of cardiovascular risk in people with diabetes. <i>Diabet Med</i>	Narrative review

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Yikona JIN, Wallis EJ, Ramsay LE, Jackson PR. Coronary and cardiovascular risk estimation in uncomplicated mild hypertension. A comparison of risk assessment methods. <i>J Hypertens</i> 2002; 20: 2173-2182	No prospective follow-up
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Zarich SW. Cardiovascular risk factors in the metabolic syndrome: Impact of insulin resistance on lipids, hypertension, and the development of diabetes and cardiac events. <i>Rev Cardiovasc Med</i> 2005; 6: 194-205	Narrative review
Zoccali C, Tripepi G, Mallamaci F. Predictors of cardiovascular death in ESRD. <i>Semin Nephrol</i> 2005; 25: 358-362	Dialysis population
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Zodpey SP, Tiwari RR. A risk scoring system for prediction of haemorrhagic stroke. <i>Indian J Public Health</i> 2005; 49: 218-222	Modelling

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An initiative of the National Vascular Disease Prevention Alliance



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