Title: The Impact of Treatment and Time on Cardiovascular Risk Scores

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Abstract

Cardiovascular risk scores predict an individual's risk of developing cardiovascular disease. Many were developed and validated in study cohorts on risk-factor lowering treatment – a cause of inaccuracy. In addition, risk scores are criticised as being biased towards the elderly due to the prominence of age as a risk predictor. Although present guidelines advocate the use of short-term (5-10 year) absolute risk scores, other approaches to redress this perceived imbalance such as lifetime risk scores are being considered.

The overall objective of this thesis is to identify the most appropriate cardiovascular risk score for use in general practice, taking account of the impact of treatment and time on assessed risk.

This objective was met by three different methods. First, a systematic review of cardiovascular risk scores was conducted. This explored the derivation of each score, including the extent of treatment. Next, doctors were interviewed in depth to understand their perception and use of risk scores. Finally, mathematical models were devised to determine whether a true difference in life expectancy exists at different ages but the same short-term cardiovascular risk. The models incorporated age-specific case fatality rates, competing risks and time preference to estimate the potential years of life lost due

to a five-year treatment delay in different age groups with the same short-term coronary heart disease risk.

The findings demonstrate that cardiovascular risk scores do not take account of treatment effects. This significantly affects their application in clinical practice. In addition, there is little difference in potential life years lost between ages at the same risk level because of higher case-fatalities in older people. When time preference is considered, any residual case for treating the same level of short-term risk differently at different ages is abolished.

The overall conclusion is that the five to ten-year absolute cardiovascular risk score is the most appropriate approach to primary cardiovascular disease prevention. By overestimating risk in the young, other approaches benefit the few at the expense of the many.

Preface

The hardest question to answer in the past three years was the one asked right at the beginning by my then 6-year old daughter. She asked me why I wanted to go to Oxford (leaving my husband and her in Malaysia); was it because I wanted to be the best scientist in the world? This made me think. I was afraid that the wrong answer would make her feel that I had chosen my career over her. Finally, I replied that not going would have meant spending the rest of my life wondering what it would have been like and regretting not giving it a try.

Looking back now, I am convinced that it was the right answer. Doing my DPhil in Oxford has been a wonderful and enriching experience. I have learnt so much and enjoyed the process immensely. The separation from my family was the most difficult thing I have ever done but it has changed the way I think and work. My time here has brought me many good friends and experiences. Oxford will always be dear to me.

I want to thank my supervisors, Paul Glasziou and David Mant, who guided me skilfully through the process. They answered every query, listened patiently to my woes and dispensed advice and wisdom with patience, kindness and good humour. Many others also contributed significantly to my work with their kind assistance but I would like to single out the following: Chia Yook Chin, Khoo Ee Ming, Ng Chirk Jenn, Carl Heneghan and Rod Jackson helped with their suggestions and comments; Jenny Doust acted as the second reviewer; Nia Roberts gave assistance with understanding literature search, Claire Blacklock acted as the second coder, Michael Goldacre helped provide data on disease rates, Richard Stevens assisted my understanding of models; and Jenny Hislop helped to guide the qualitative work.

I am also very grateful to the AsiaLink project, Ministry of Higher Education Malaysia, University of Malaya and the Department of Primary Health Care, Oxford University who made it possible for me to study in Oxford. I would also like to thank the GPs who contributed time and effort to participate in the study. I am also very grateful to all my friends who helped to support me along the way.

My parents, Liew Yoon Loy and Anne Teoh Ah Nya were a major source of encouragement and support as they have always been throughout my life. Not only did they help care for Elena, they did so willingly and with great love.

I could not and would not have been able to do my DPhil without the support and love provided by my husband, Saini Jeffery. He has unreservedly encouraged me through it all and is simply the most wonderful and caring person I know.

To my daughter, Elena May, thank you for understanding when Mummy missed your first day in school, three birthdays, numerous performances and parties. It has been hard to rationalise being away from you and Daddy but you made it easier with your love and cheerfulness. I am coming home.

Abbreviations

AHA	American Heart Association
ARIC	Atherosclerosis Risk in Communities Study
ASSIGN	ASSessing cardiovascular risk, using Scottish Intercollegiate Guidelines Network
ATP III	Adult Treatment Panel III
BHS-IV	British Heart Society -IV
BUPA	British United Provident Association
CFR	Case Fatality Rates
CHD	Coronary Heart Disease
CHEP	Canadian Hypertension Education Program
CKS	Clinical Knowledge Summaries
CVD	Cardiovascular disease
DALY	Disability Adjusted Life Years
DBP	Diastolic Blood Pressure
ESC	European Society of Cardiology
EURIKA	European Study on Cardiovascular Risk Prevention and Management in Usual Daily Practice
GP	General Practice/Practitioner
HbA1c	Haemoglobin A1c or glycated haemoglobin
hsCRP	High sensitivity C-reactive protein
ICD	International Classification of Disease
ISH	International Society of Hypertension
JBS	Joint British Societies
JNC	Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure

LDL	Low Density Lipoprotein
LE	Life Expectancy
LY	Life Years
MeSH	Medical Subject Headings
MI	Myocardial Infarction
NHF	National Heart Foundation
NHEFS	NHANES I Epidemiologic Follow-up Study
NHANES	National Health and Nutrition Examination Survey
NICE	National Institutes of Clinical Excellence
NNT	Numbers Needed to Treat
NVDPA	National Vascular Disease Prevention Alliance
OSOP	One Sheet of Paper
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROCAM	Prospective Cardiovascular Munster Heart Study
PYLL	Potential Years of Life Lost
QALY	Quality-Adjusted Life Year
REACT	Reassessing European Attitudes about Cardiovascular Treatment
SCORE	Systematic COronary Risk Evaluation
SHS	Strong Heart Study
UKPDS	United Kingdom Prospective Diabetes Study
USA-PRC	United States of America – Peoples' Republic of China
USPTF	United States Preventive Services Task Force
WHO	World Health Organisation

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Chapter 1. Introduction

Cardiovascular disease remains the leading cause of death globally. (1) Despite treatment advances, improvements in public health and the decline in myocardial infarction rates, the lifetime risk of developing cardiovascular disease is 52% for men and 39% for women at 50 years of age. (2) This is greater than the lifetime risks of developing all cancers combined. (2, 3) In order to address this, the high-risk approach (focusing treatment on those at highest risk of cardiovascular disease) has been identified as one of five interventions that are feasible, cost effective and capable of averting millions of death worldwide. (4) This approach involves the use of cardiovascular risk scores to identify those who are at high risk.

1.1 Definition of cardiovascular risk scores

Cardiovascular risk scores are risk assessment tools that predict the risk of developing a cardiovascular event in a specified time period from risk factors determined by history, physical examination or investigations. These tools are developed from cohort studies where multiple potential risk factors are measured at baseline and the study population subsequently followed-up over time to identify those who develop the outcome of interest. Mathematical models are then used to determine which of the risk factors significantly and independently predict the risk of having a cardiovascular event and these are combined in multivariable formulations to determine an individual's global cardiovascular risk. (5)

1.2 History

The Framingham study was the first cohort study to develop cardiovascular risk scores. The study was started in 1949 with the objective of finding a single main cause of cardiovascular disease. It became clear from the study that there was no single cause but multiple factors that synergistically contributed to the pathogenesis of the disease. (5) In the beginning, these risk factors were combined into risk profiles by logistic regression. Later risk scores used improved statistical methods such as Cox regression and Weibull models.

The initial Framingham risk profile predicted the risk of developing cardiovascular disease in general, combining both coronary heart disease and cerebrovascular disease outcomes. (6) Subsequent Framingham risk scores predicted disease specific outcomes. (7-10) In 2008, a new Framingham risk score was published which once again predicted the risk of developing any major atherosclerotic cardiovascular outcome but with several improvements to the 1976 equation. (11)

Although there was progress in statistical techniques used and the development of new Framingham models, the equations produced were still not practical for use in clinical practice. (7-10) In 1981, Rod Jackson, a cardiovascular epidemiologist in New Zealand, was studying the levels of cardiovascular risk factors in an Auckland population. On reviewing the medical literature, he found that there were different definitions for hypertension. Application of the different definitions to his population data resulted in a range in the number of those diagnosed with hypertension from 5 to 50%. (Rod Jackson; oral communication) This finding combined with insights from two landmark papers changed his approach from targeting hypertension and hyperlipidaemia to global cardiovascular risk prevention.

The first landmark paper was by Geoffrey Rose, the eminent British epidemiologist who recognised high blood pressure as a risk factor and not a disease. (12) He used life insurance data to show that there was no blood pressure threshold – no plateau after which morbidity and mortality increases suddenly. The definition of hypertension is therefore an arbitrary one and creates difficulty in its use as a target for preventive strategies.

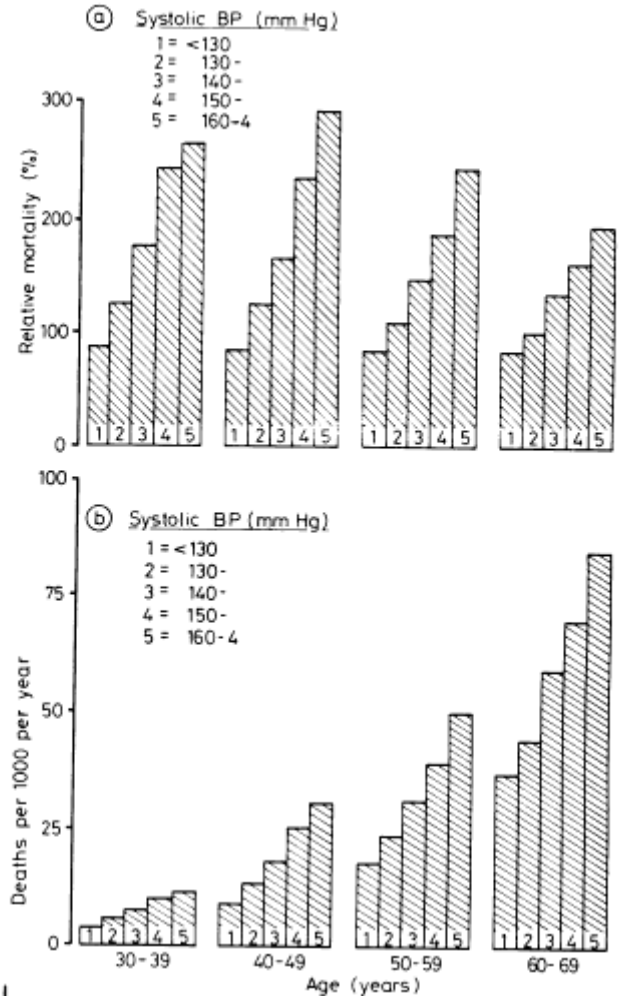


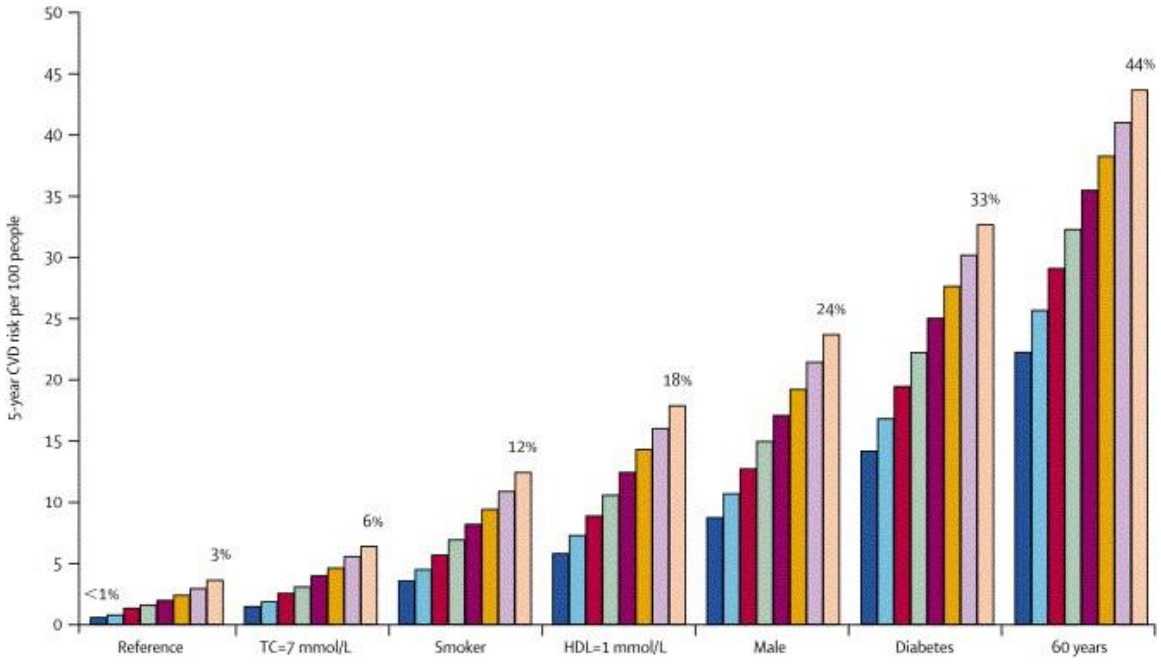
Figure 1: (a) Relative risk and (b) absolute risk of mortality in men according to blood pressure and age (12)

Graph b of Figure 1 shows the actual numbers of deaths instead of relative mortality (as seen in graph a). The slope of graph b is much steeper than for relative risk in those above 50. Although high blood pressure is associated with similar relative mortality across the age groups, the absolute excess risk is greater in older age groups. Rose also showed that treatment was most effective in those with the highest baseline risk but this could only be seen with the use of absolute numbers rather than relative risk reduction. (Table 1)

Table 1: Relative and absolute benefits from the treatment of hypertension, according to age and the presence of cardiovascular-renal abnormality (12)

Age (yr)	Cardiovascular renal abnormality	Treatment effectiveness (%)	Lives saved per 100 treated
< 50	–	59	6
	+	62	14
> 50	–	50	15
	+	60	29

The other landmark paper was on risk profiles in the Framingham study and showed that risk factors worked synergistically to increase risk. (Figure 2) (7,13) Age and blood pressure were only 2 out of the multiple factors that lead to cardiovascular disease. There was no single cause of cardiovascular disease – "*only guilt by association*". (5)



Reference category is a non-diabetic, non-smoker female aged 50 years with total cholesterol of 4·0 mmol/L and HDL of 1·6 mmol/L. Risks are given for systolic blood pressure levels of 110, 120, 130, 140, 150, 160, 170, and 180 mm Hg. In the other categories additional risk factors are added consecutively, for example, the diabetes category is a diabetic 50-year-old male cigarette smoker, with a total cholesterol of 7 mmol/L and HDL of 1 mmol/L. TC=total cholesterol.

Figure 2: Absolute five-year cardiovascular risk by systolic blood pressure and other risk factors (14)

In 1993, Rod Jackson et al published a paper recommending that decisions to treat blood pressure should be based on estimated cardiovascular risk and not blood pressure levels. (13) A chart was included in the report that estimated absolute cardiovascular risk according to the number of risk factors present, age and blood pressure. (Figure 3)

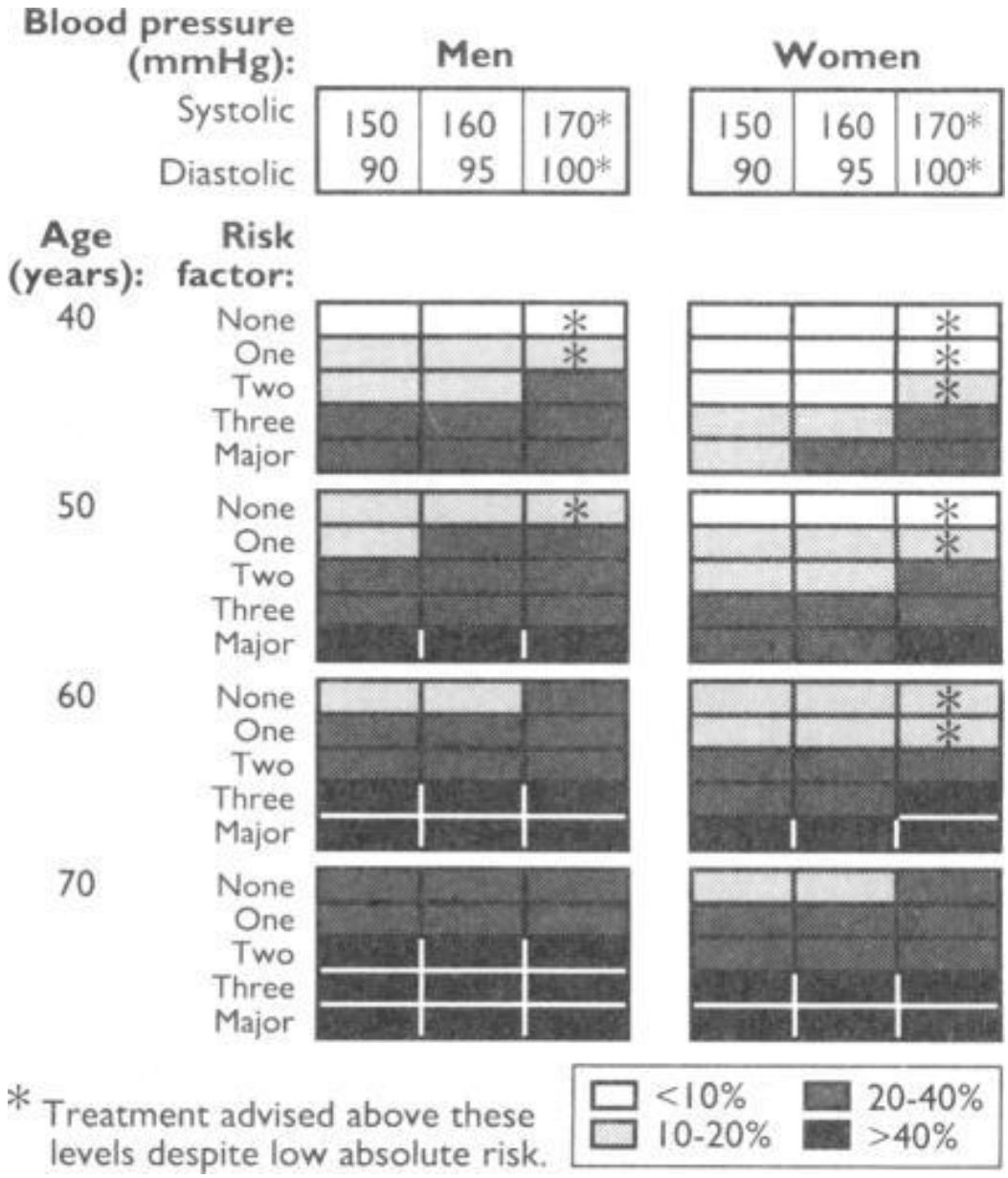


Figure 3: Absolute ten-year cardiovascular risk chart (Jackson et al BMJ 1993 (13))

This approach was adopted by the European Society of Cardiology in their 1994 guidelines. (15) Their guideline advised a change from uni-factorial management of individual risk factors such as hypertension or hyperlipidaemia to a multi-factorial assessment of cardiovascular risk. A chart was also included, which allowed a simplified

estimation of cardiovascular risk from 5 factors – age, gender, smoking status, blood pressure and cholesterol level.

In the United Kingdom, the Joint British Society (JBS) comprising the British Cardiac Society, British Hypertension Society, British Hyperlipidaemia Association and British Diabetes Association first published their charts, based on Framingham data, in *Heart* in 1998. (16) Following this, the National Service Framework for Coronary Heart Disease, (17) published in March 2000, recommended the use of various cardiovascular risk assessment tools for use in clinical practice that were based on Framingham data. These included the Sheffield tables, the European Coronary Risk chart and the New Zealand risk assessment tool. The Joint British Societies 2 guidelines (18) were published in 2005. Unlike the earlier guidelines, JBS 2 advocated prevention of all atherosclerotic cardiovascular disease, not just coronary heart disease.

Several cohort studies other than the Framingham study have also developed cardiovascular disease risk scores. A systematic review of cardiovascular disease risk scores by Beswick et al in 2005 identified 110 risk score methods with 70 scores meant specifically for application in primary prevention. (19) Examples of risk scores from the United Kingdom included in the review were the Dundee risk score (20), which used relative risk to rank individuals in their specific age group, and the UKPDS risk engine for diabetics. (21) In Europe, there have been the PROCAM risk scores from Germany (22, 23) and SCORE from a pooled dataset of cohort studies from different countries. (24) More recent scores such as the Reynolds scores for men (25) and women (26) from the United States and QRISK from United Kingdom (27, 28) are not included in the Beswick review.

1.3 Literature review

1.3.1 Guidelines

Most national cardiovascular guidelines recommend the use of risk scores to predict global risk rather than focusing on single risk factor modification. The majority advocate the use of Framingham risk scores or scores that have been calibrated from Framingham data. (Table 2)

In the United Kingdom, guidelines had also advocated the use of Framingham risk scores or JBS charts which used Framingham data until a recent update by the National Institute for Clinical Excellence (NICE). (29) This update stated that NICE would withdraw the recommendation that the Framingham risk equation should be the equation of choice for assessment of CVD risk, but agreed that it should be considered as one of the possible equations to use.

Other exceptions include the European guidelines that advocate the use of SCORE, (30, 31) the World Health Organisation guidelines that recommend the use of its own charts (32) derived by modelling, and the Canadian guidelines for dyslipidaemia (33) which recommend the use of the Reynolds score along with the latest Framingham risk score.

Reasons given for selection of the Framingham risk score were its wide usage, familiarity, continuity, ease of use, and that it had been validated for the population in question. These reasons are all linked to Framingham being the oldest study of its kind. SCORE had been validated for the European populations and the WHO/ISH charts used ten-year sub-regional data. Several guidelines included cautions on the use of the risk scores in specific populations such as women, the young and the elderly, and those from ethnic minorities.

In terms of threshold levels for treatment initiation, time periods ranged from 5-year to 10-year predictions and outcomes considered from coronary heart disease to total cardiovascular disease. Different threshold levels were considered such as 10-year risk of fatal CVD >5%, 5-year risk of CVD >15% and 10-year risk of CVD ≥20%.

A number of the guidelines also specifically recommended the use of the UK Prospective Diabetes Study risk score (21) for diabetics.

Table 2: Risk scores, thresholds and statements on cardiovascular risk assessment in national guidelines

Guideline	Statement	Risk Score	Stated strengths	Stated limitations	Threshold level
UK					
2004 BHS-IV (34)	The assessment of total risk is increasingly endorsed and encouraged as a guide to clinical practice, and strategies which do not incorporate such an approach are likely to be less cost-effective.	JBS charts (based on Framingham 1991) UKPDS for diabetics	Validated and user friendly.	Inaccurate for certain populations.	10-year risk of CVD ≥20%
2005 JBS 2 (18)	All adults from 40 years onwards, who have no history of CVD or diabetes, and who are not already on treatment for blood pressure or lipids, should be considered for an opportunistic comprehensive CVD risk assessment in primary care.	JBS charts (based on Framingham 1991)	Charts have been widely adopted and are familiar to physicians. Current alternatives do not offer sufficient advantage over Framingham.	2 studies showed inaccuracies in predictions for British population.	10-year risk of CVD ≥20%
2006 NICE guidelines for hypertension (35)	If raised blood pressure persists and the patient does not have established cardiovascular disease, ask to formally assess the patient's cardiovascular risk.	JBS charts (based on Framingham 1991)	Best current assessment of CVD risk over 10 years.	Poor validation in UK ethnic minorities and younger population.	10-year risk of CVD ≥20%
2008 NICE guidelines for lipid modification (36)	People should be offered information about their absolute risk of CVD and about the absolute benefits and harms of an intervention over a 10-year period.	Framingham 1991 equations Update in Feb 2010: No longer recommend a single risk score.	Most widely used and understood.	Inaccurate for certain populations. Several risk factors are not included.	10-year risk of CVD ≥20%

Guideline	Statement	Risk Score	Stated strengths	Stated limitations	Threshold level
2008 CKS library (37)	Assessment of cardiovascular risk is central to prevention strategies for individuals and is an important component of population-based strategies to reduce the burden of cardiovascular disease.	Joint British Societies cardiac risk assessor (based on Framingham 1991) UKPDS for diabetics	Recommended by NICE guidelines.	Inaccurate for certain populations. Several risk factors are not included.	10-year risk of CVD ≥20%
US and Canada					
2002 ATP III (38)	Short-term risk reduction depends almost exclusively on absolute-risk assessment for its selection of persons for intense clinical intervention.	Risk factor counting for initial assessment with Framingham risk scoring (Wilson 1998)	Continuity with previous guidelines. Addition of Framingham risk scoring gives a more quantitative absolute risk prediction.	May not be practical in clinical setting or apply to all populations. Do not account for variability of risk factor levels over time and requires extra steps in risk assessment.	If 2 or more risk factors found and 10 yr risk of CHD >20%, this is considered a CHD equivalent
2002 AHA (39)	All adults ≥40 y of age should know their absolute risk of developing CHD. Goal: As low risk as possible.	Framingham (no specific version)	Widely used.	May not apply to all sex, race, and ethnic groups.	10-year risk of CHD >20%
2003 JNC 7 (40)	The presence of each additional risk factor compounds the risk from hypertension. The easy and rapid calculation of a Framingham CHD risk score using published tables may assist the clinician and patient in demonstrating the benefits of treatment.	Framingham (ATP III)	Easy and rapid to use.	None given.	None given
USPSTF 2004 (41)	Asymptomatic adults clearly benefit from risk factor modification proportional to their degree of CHD risk (i.e., more intensive risk factor modification for people at higher risk).	No specific risk score selected (ATP III and Wilson 1998, given as examples)	More accurate than simply risk factor counting.	None given.	10-year risk of CHD >15%

Guideline	Statement	Risk Score	Stated strengths	Stated limitations	Threshold level
2007 AHA women (42)	The panel believed that a Framingham global risk score of >20% could be used to identify a woman at high risk but that a lower score is not sufficient to ensure that an individual woman is at low risk.	AHA women clinical classification which includes Framingham (ATP III)	Framingham score of >20% can identify high-risk women.	Not good at determining low risk, inaccurate in certain populations and narrow focus on short-term risk.	10-year risk of CHD >20%
2009 Canadian guidelines for dyslipidaemia (33)	It is important to keep in mind that none of the traditional CVD risk factors or biomarkers reflects the actual presence or absence of atherosclerosis. They help to establish CVD event risk rather than the risk or presence of CVD itself.	Framingham (D'Agostino 2008) or Reynolds Risk Score (RRS)	Framingham validated in Canada; shown to increase adherence to treatment. RRS validated in American population and includes additional variables.	Framingham underestimated risk in youth, women and possibly in those with metabolic syndrome. RRS has not been validated in Canada.	10-year risk of CVD ≥20%
2009 CHEP (43)	Global cardiovascular risk should be assessed. Multifactorial risk assessment models can be used to predict an individual's global cardiovascular risk more accurately and to use antihypertensive therapy more efficiently.	No specific risk score given but states that use of absolute levels of risk should be avoided because of absence of Canadian data	Not applicable.	Not applicable.	Statins should be considered in nondyslipidaemic hypertensive patients with 3 or more RF
Australia and New Zealand					
2003 New Zealand guidelines on cardiovascular risk (44)	Assessment of absolute cardiovascular risk is the starting point for all discussions with people who have cardiovascular risk factors measured. Reduction in cardiovascular risk is the goal of treatment.	NZ charts (based on Framingham 1991) UKPDS for diabetics	Validated in New Zealand. More accurate than using levels of individual risk factors.	Inaccurate for certain populations and those < 35.	5-year risk of CVD >15%

Guideline	Statement	Risk Score	Stated strengths	Stated limitations	Threshold level
2005 NHF and Cardiac Society of Australia and New Zealand on lipid management (45)	In order to initiate the most cost-effective cardiovascular disease (CVD) risk factor management strategies, it is necessary to identify those individuals at higher absolute risk of a CVD event, and who therefore have the most to benefit.	NZ charts (based on Framingham 1991)	Validated in NZ and suitable for Australian population.	Inaccurate for certain populations.	5-year risk of CVD >15%
2008 NHF guidelines on management of hypertension (46)	Numerical absolute cardiovascular risk assessment is now recommended for all Australians aged 45–74 (Aboriginal and Torres Strait Islander adults aged 35 and older) who are not already known to be at high risk, whether or not they have hypertension.	Australian cardiovascular risk charts adapted from NZ guidelines group (based on Framingham 1991)	Developed for Australian population.	May underestimate CVD risk in specific groups.	5-year risk of CVD >15%
2009 NVDPA (47)	It is reasonable to expect that a CVD preventive strategy based on estimated absolute risk will be more effective and enable more efficient use of resources, than the traditional clinical management approach based on identifying and correcting individual risk factors through the application of several separate guidelines.	Framingham risk equation (version not specified)	Predictive ability equal or superior to other methods of calculating absolute CVD risk.	Inaccurate for certain populations.	5-year risk of CVD >15%

Guideline	Statement	Risk Score	Stated strengths	Stated limitations	Threshold level
International					
2007 WHO guidelines on CVD prevention (32)	The total risk of developing cardiovascular disease is determined by the combined effect of cardio-vascular risk factors, which commonly coexist and act multiplicatively. An individual with several mildly raised risk factors may be at a higher total risk of CVD than someone with just one elevated risk factor.	WHO/ISH risk prediction charts derived from modelling using mean of risk factors and average ten-year rates from countries of the specific sub region	Particularly useful in populations where cohort data and resources are not readily available. Not validated for individual populations at national and local levels.	May underestimate in certain populations.	10-year risk of CVD >20% but level can be adapted according to availability of resources
2007 ESC guidelines on management of hypertension (31)	In order to maximize cost-efficacy of the management of hypertension the intensity of the therapeutic approach should be graded as a function of total cardiovascular risk.	SCORE	Estimate risk of dying from all cardiovascular (not just coronary) disease and allow calibration for individual countries.	CVD risk models do not consider duration of exposure to a risk factor. Strong effect of age may bias against young individuals.	10-year risk of fatal CVD >5%
2007 ESC guidelines on CVD prevention (30)	The encouragement of total risk estimation as a crucial tool to guide patient management has been a cornerstone of the Guidelines since the first edition. This is because clinicians treat whole people (and not individual risk factors), whose cardiovascular risk usually reflects the combined effects of several risk factors that may interact, sometimes multiplicatively.	SCORE	Estimate risk of dying from all cardiovascular (not just coronary) disease. Outcome is objective and allows recalibration for individual countries and changes in CVD mortality with time.	Age has such a strong effect that there is a possibility of excessive use of drugs in the elderly and concealed risk in young. May underestimate in certain populations.	10-year risk of fatal CVD >5%

1.3.2 Absolute Risk versus Relative Risk

The cardiovascular risk scores predict the risk of a cardiovascular outcome in a specified time period. This risk can be expressed as absolute risk or relative risk. Absolute risk is simply the incidence of the event in a group of people. Thus if a person's 10-year absolute cardiovascular risk is 20%, it means that in a group of 100 persons with the same risk profile, 20 would develop a major cardiovascular outcome such as a myocardial infarction or stroke in 10 years. Relative risk is the ratio of two absolute risks. For example, the relative cardiovascular risk for a smoker is 1.6 times that of a non-smoker and is obtained by dividing the absolute cardiovascular risk of a group of smokers by the absolute cardiovascular risk of a group of non-smokers. (48)

For the purposes of medical decision-making, absolute risk has been the preferred method of representation of risk. In 1993, Rod Jackson et al recommended the use of absolute cardiovascular risk in treatment decisions for blood pressure as opposed to blood pressure levels alone. As relative risk reduction remained constant whatever the background absolute risk of the disease, those with high initial absolute risk benefited most from treatment. In those with low initial absolute risk, the possibility of side effects or harms may outweigh the benefits of treatment. (13)

Sommers and Zeckhauser in their paper 'Probabilities and preferences: What economics can teach doctors and patients making difficult treatment decision', (49) described absolute risk as a risk statistic that 'tells the whole story' unlike relative risk. Relative risk simply describes the relationship between two different risks and does not differentiate whether the risks are small or big. A ratio of 6:7 is the same as that for 60:70. Relative risk is useful for statistical purposes. Geoffrey Rose, the epidemiologist, stated "All policy decisions should be based on absolute measures of risk; relative risk is strictly for researchers only." (50) In an editorial, Gigerenzer et al also criticised the nature of

relative risk which does not provide information about baseline risk and that therefore tends to mislead people into over- or under-estimating actual risk. (51)

There have been supporters of relative risk who argue that it is useful in the young and the old. A young individual would have a low absolute risk because age is such a powerful risk predictor. However, a young person with higher risk factor levels can be identified by using the individual's relative risk, which would be greater than that of others in the same age group. Similarly, an elderly person would have a high absolute risk but it may be comparable to others at the same age. (52, 53)

In a recent editorial, Tunstall-Pedoe highlighted the problem of a threshold level based on absolute risk that would essentially limit treatment only to those above a certain age group. (54) Tunstall-Pedoe was the developer of the Dundee Risk Disc in 1991 which incorporated three modifiable risk factors i.e. high blood pressure, high cholesterol levels and smoking, and expressed coronary risk as a relative risk. The intention was to motivate patient and health care practitioners to improve modifiable risk. Tunstall-Pedoe was of the opinion that the use of absolute risk was unnecessary and the inclusion of non-modifiable risk factors in absolute risk scores complicated the calculation and interpretation of risk. (20)

Others are of the opinion that both risk statistics should be presented together. (55) For example, the 1998 Framingham risk score by Wilson et al estimates both the absolute and relative risk for the individual. (56)

Studies on patients' preferences indicate that relative risk is preferred to absolute risk. (57-59) The authors of two of the studies (57, 58) caution that it is unknown whether this is related to truly informed decision-making. It is likely that patients respond similarly to doctors in preferring the greater reduction in relative risk than absolute risk in drug trials.

(60, 61) For patients to understand better, the authors of both studies suggested that risk should be presented in both ways. A systematic review found that natural frequencies were better understood than probabilities, relative risk reduction was more persuasive for treatment prescription or acceptance than absolute risk reduction and numbers needed to treat, and there were no differences between health professionals and patients in the results. (62)

1.3.3 Usage of the risk scores

Despite there being widespread recommendation by guidelines on the use of cardiovascular risk scores in clinical practice, the use of the risk score is surprisingly limited. The majority of the studies that have investigated the usage of the risk scores have been large-scale surveys, appropriately so when the main objective is to determine the percentage of health care practitioners using the risk scores in clinical practice.

The REACT study (63) was conducted in 5 European countries to assess the acceptance and implementation of cholesterol and coronary heart disease guidelines. Although the study methods were by semi-structured 15 minutes telephone interviews comprising both quantitative and qualitative questions, the results were mainly quantitative in nature. Rates of refusal to participate in the study were very high ranging from 47 to 83%. Only 56% of study participants reported that they sometimes or always used risk calculators, with usage ranging from 45% in France and 90% in Italy. Barriers to the implementation of guidelines identified by the study were lack of time, prescription cost, lack of patient compliance, too many guidelines around and lack of awareness of guidelines.

A survey conducted by the European Society of Cardiology on cardiologists and general practitioners in six countries had similar findings with 48% of respondents stating that

they used specific guidelines or risk calculators. (64) Barriers to guideline implementation were identified as lack of patient compliance, lack of time, guidelines were too theoretical, financial constraints and guidelines were too complex.

A questionnaire survey in 10 countries on cardiologists, general practitioners and endocrinologists (65) found that 48% (37-54%) of respondents were regular users of cardiovascular risk scores. Reasons given for lack of use were that the risk scores takes up too much time, the respondent did not believe that the risk score added value to the clinical evaluation and lack of awareness.

The European Study on Cardiovascular Risk Prevention and Management in Usual Daily Practice (EURIKA) was a questionnaire study assessing physician use of risk scores and guidelines in 12 European countries. 68.5% of all respondents reported use of cardiovascular risk scores. (66) Reasons given for non-use were time constraints, lack of conviction on their usefulness, and lack of awareness.

Findings from the above studies indicate that the usage of the risk scores ranged from 48-68.5%. More than a third of doctors did not use the cardiovascular risk scores to assess risk in clinical practice. The studies above were carried out in Europe with the exception of the survey by Sposito et al, which also included North, Central and South American countries. The usage of the risk scores is other regions is not known.

1.3.4 Accuracy of the risk scores

1.3.4.1 In comparison to clinicians' estimates of risk

As noted in the section above, many clinicians rely on subjective estimates of cardiovascular risk. This has been shown to be inaccurate. A study by Friedmann et al found that doctors overestimated baseline risk as well the risk reduction by treatment. (60) Participants were told to give their best estimates and not to consult the literature. It

is not stated if they were allowed to use risk scores. Montgomery et al found that general practitioners and nurses only correctly estimated cardiovascular risk in 21% of their patients; in the majority, 63%, risk was underestimated. (67) Pignone et al reported a similar level of accuracy (24%) but in contrast, found that doctors tended to overestimate risk. (68) Grover et al also found that doctors overestimated risk. (69) The studies by Friedmann, Pignone and Grover used scenarios in contrast to the study by Montgomery, which used real patients. Another difference was that the patients in the study by Montgomery et al were at higher risk.

1.3.4.2 In terms of studies looking at the performance of the risk scores

The accuracy of cardiovascular risk scores is important. Hense (70) noted that, as the risk scores are used to identify high-risk individuals for treatment, inaccuracy of the risk scores would mean that a part of the population would be inappropriately elected for or withheld from treatment.

The performance of a risk score is usually expressed in terms of its ability to discriminate and calibrate. Discrimination describes the ability of the risk score to separate those who develop the outcome from those who do not. It is typically measured by the area under the receiver operating curve (AUROC), which expresses the maximum achievable sensitivity or specificity. Calibration is the predicted probability. It is a measure of how closely the predicted outcome agrees with the observed outcome. For example, does 10% of the population develop the outcome if a risk score predicts the risk to be 10%? It is usually measured by goodness of fit or predicted-to-observed ratios. (71) A score can have good discrimination but poor calibration, in that, it separates high- and low-risk folk well, but assigns the wrong risk number. Cooney estimated that the discrimination abilities of most risk scores were similar but that calibration was dependent on how similar the population was to that of the study population. A new measure, the net

reclassification index, has recently been developed which describes the percentage that is reclassified correctly by a new risk score to a more appropriate risk category. (71)

Hense pointed out that the area under the receiver operating curve is most useful for determining threshold levels. As threshold levels are already set in guidelines and risk score studies, the use of the AUROC may not be as appropriate for clinical practice as other measures such as sensitivity, specificity and predictive values. (70)

The sensitivity and specificity of the risk scores are surprisingly low. Milne et al showed that at a 5-year cardiovascular risk threshold level of 15%, the Framingham risk equation had a specificity of more than 90% but a sensitivity of less than 20%. Specificity was very poor below 10% risk and sensitivity became very poor above 15% risk. (72)

Similarly in a population of British men, Brindle et al found a sensitivity of 16% and specificity of 94% with a 10-year cardiovascular risk threshold of 30%. The sensitivity increased to 75% but specificity dropped to 55% when the threshold was changed to 15%. (73)

A systematic review by Brindle et al found that the predicted to observed ratio ranged from an under-prediction of 0.43 (95% CI 0.27 to 0.67) in a high-risk population to an over-prediction of 2.87 (95% CI 1.91 to 4.31) in a lower-risk population. (74) They concluded that the accuracy of the Framingham risk score was dependent on the baseline risk of the population. (Figure 4)

Data obtained from a validation study by Collins and Altman in 2010 (75) showed that the sensitivity and specificity of QRISK was 40% and 88% respectively whereas for the NICE Framingham equation, sensitivity was 54% and specificity 79%.

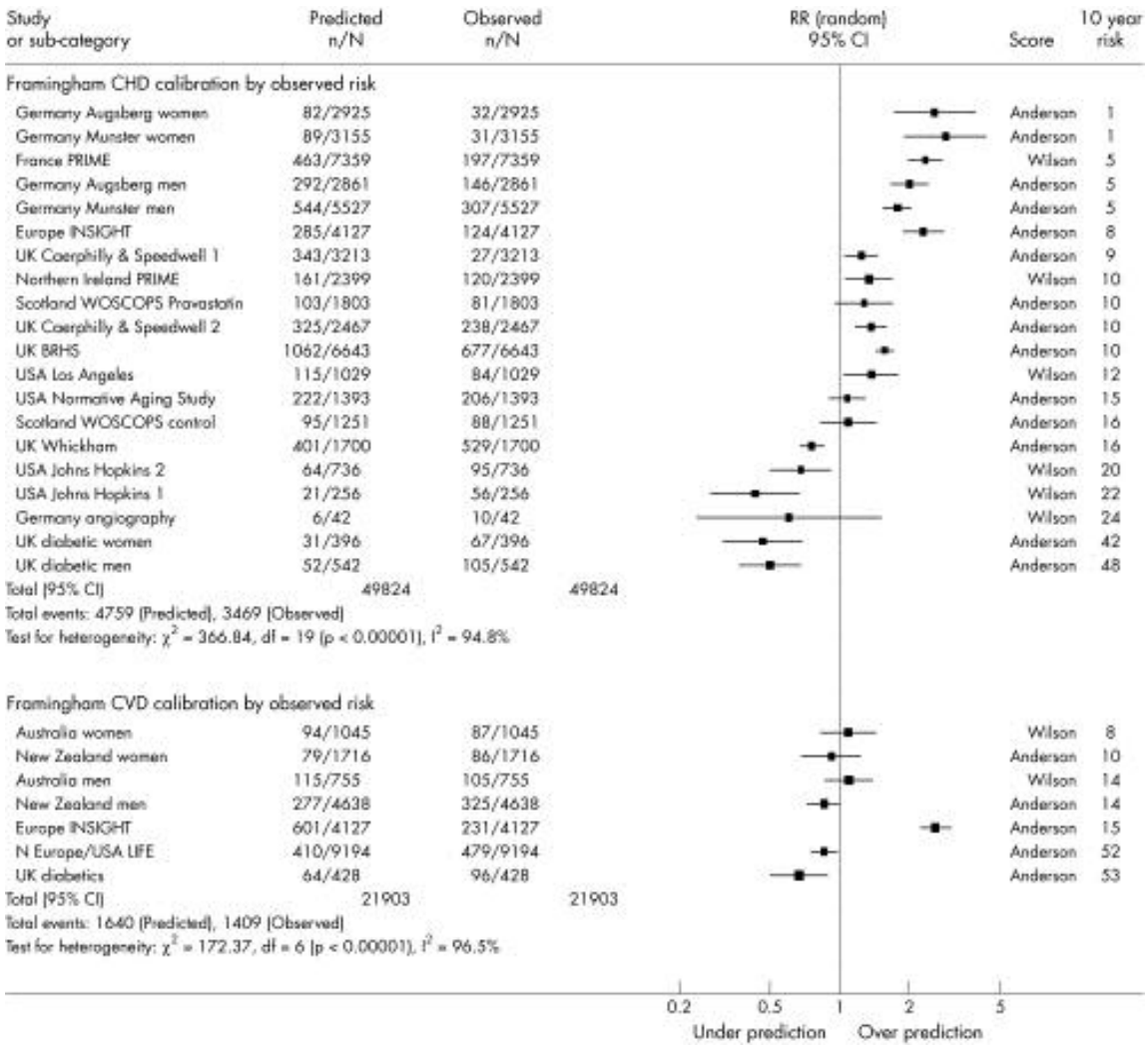


Figure 4: External validity of Framingham risk score by Brindle et al (74)

1.3.4.3 The effect of treatment affecting accuracy

Effective treatment for cardiovascular risk reduction has been available for the past 20 to 30 years. (76, 77) Data from the United States show that the rates of those on hypertension treatment increased to 73% and those on treatment and controlled was 69% in 2007-2008. (78) In risk score studies, the relationship between baseline risk factor levels and cardiovascular outcomes is examined in large cohort study populations. The potential for bias is great as those who are found to have high risk factor levels are likely to be started on treatment.

In an editorial (79), Hennekens and D'Agostino pointed out the increasing difficulty in developing new risk scores in a time where treatment is widely available. The use of medications such as statins, aspirin and blood pressure lowering agents would modify the risk estimates. Milne pointed out in a rapid response to the publication of QRISK (80) that "the paper implicitly assumes either that there was no prophylactic use of preventive measures between 1995 and 2007 (which we know to be untrue) or, paradoxically, that prophylactic use of interventions makes no difference to outcome (which would render detection redundant)." One method of partially correcting for the effect of treatment would be the inclusion of risk predictors such as antihypertension medication usage in the risk prediction methods. (70)

The problem of interventions affecting outcomes also occurs in validation studies. This was highlighted by Hense who stated that clinical end-points were biased in validation studies that do not take into account the amount of intervention in the study population. (70) This bias would make predictions by the risk scores appear worse.

1.3.4.4 Population versus individual

It should be understood that cardiovascular risk scores are derived and validated in population studies and that the accuracy of the risk score may be different when applied to an individual rather than a population. Hense noted that the use of a threshold of 20% in ten years meant that in a population of 100 individuals with the same risk profile, 20 would experience a cardiovascular outcome but *80 would not.* Also for those with a cardiovascular risk below 20%, up to 19 in 100 individuals with similar risk factor levels are likely to experience a cardiovascular event in the next ten years. (70)

1.3.5 Age as a risk predictor

We are as old as our arteries.

William Osler

Age is the most important risk predictor in determining cardiovascular risk. (14, 53) Tunstall-Pedoe pointed out that the use of absolute risk for treatment decisions would mean that treatment would essentially be limited to those above a certain age. (54) This can clearly be demonstrated by the JBS 2 charts (Figure 5) which have no green areas (low ten-year cardiovascular risk of < 10%) for any man aged 50 and above and are almost completely red (high ten-year cardiovascular risk of >20%) for any man aged 60 and above.

As discussed above in the section on 'Absolute risk versus Relative risk', the issue of age has divided opinions in the medical fraternity. Absolute risk models tend towards treatment in the older age group whereas relative risk models tend towards treatment in younger individuals. (81) The difficulty for those in the younger age group to reach risk factor levels high enough for treatment initiation is the reason for the adoption of different approaches such as the use of relative risk and lifetime risk scores and the extrapolation to 60 years by the European guidelines. (71) There have also been suggestions for the use of relative risk, specific biomarkers or risk scores specifically for the old to ensure that there is no overestimation of risk due to the dominance of age as a risk predictor.

The long latency in atherosclerotic pathology creates an impression that the early treatment would prevent cardiovascular disease. (82) Two recent meta-analyses have challenged this notion. (83, 84) The Cochrane review found limited evidence for the use of statins for primary prevention in people at low absolute cardiovascular risk. The meta-analysis by Ray et al found that in those at high risk but with no previous history of

cardiovascular disease, there was no significant reduction in all-cause mortality with the use of statins.

The notion that treating those in the younger age group would be beneficial also arises from the longer life expectancies of the young. This approach led to the development of the lifetime risk scores.

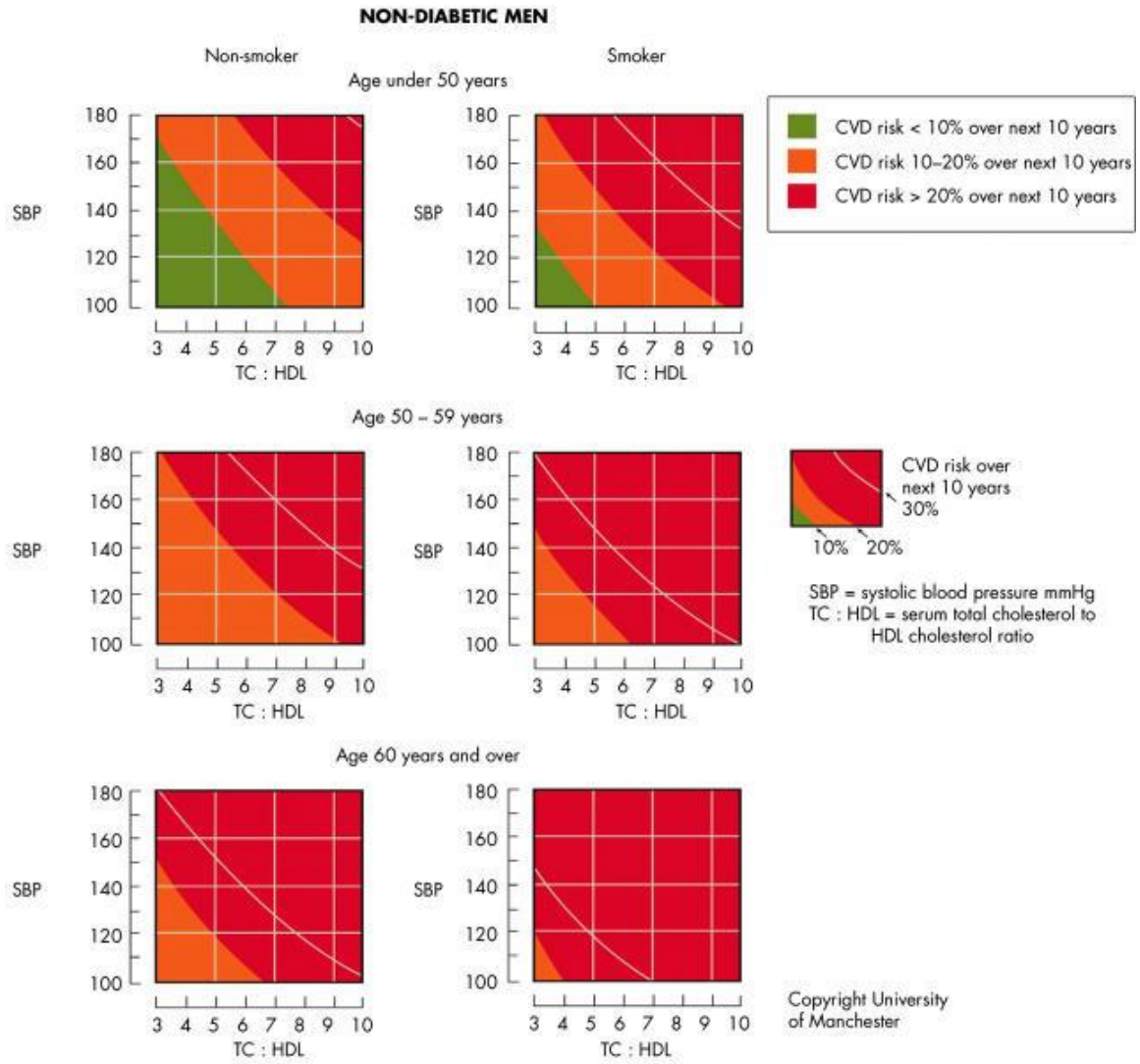


Figure 5: Joint British Societies' cardiovascular disease risk prediction chart

1.3.6 Lifetime risk scores

Lifetime risk is the risk that a person has of developing a cardiovascular outcome over his or her lifetime. Lifetime risk scores would give higher risk to those who are young because their longer life expectancy would increase the chances of developing cardiovascular outcomes. (85) This has been shown in the lifetime model developed by the QRISK group where a greater proportion of men at a younger age were identified compared with a 10-year QRISK model. There has been controversy over the use of lifetime risk for individual risk assessment.

Advocates of lifetime risk scores are mainly concerned with the identification of young individuals with high risk factor levels who are at greater risk compared to their peers. Grundy et al expressed concern over the "*misconception that most of the excess risk accumulated over many years can be erased by aggressive short-term prevention introduced later in life."* (52) Pencina et al showed that an adverse risk profile at young age resulted in long-term high risk that is missed with the use of a ten-year risk score. The study also showed that projections of ten-year risks in different combinations to predict long-term risk were inaccurate. (86) Sniderman and Furberg were also worried that the short window of opportunity to arrest disease progress would be missed if treatment was delayed to later in life. (87) Berger et al pointed out the importance of lifetime risk for strategising health policies, improving public awareness and for research but concluded that short-term risk was more useful for treatment decisions. (88)

Jackson has opposed the use of lifetime cardiovascular risk scores, which are high for almost everybody in the economically developed world and therefore not useful for differentiating those at high risk. (89) He noted that almost 97% of the men in the Framingham study had a lifetime risk ranging from 37% to 69% at 50 years of age. (2) A lifetime probability of between one in two and one in three did not offer the range of

variability provided by the shorter-term risk scores. Jackson concurred with Berger on the importance of lifetime risk scores for informing health policy and planning but criticised its use in individual risk prediction. (90)

Also there is indication that the greater part of the risk is reversed within five years. (91) Randomised controlled trials on cardiovascular risk interventions mostly follow-up participants for 6 years, so further benefit after this time is unknown. (89) Furthermore, early initiation of treatment may not bring the desired reduction in events (see the section above regarding the Cochrane review and meta-analysis on the use of statins in low risk) and may increase the likelihood of harms from side-effects.

1.3.7 Effectiveness of the risk scores

The absolute risk approach is a difference in philosophy - it is considered more efficient for a population as fewer individuals require treatment to achieve the same event reduction; for an individual, it can be used to weigh absolute benefit to harm of treatment. To assess the effectiveness of the risk score, the following sections discuss its use as a screening tool and in the modification of clinical outcomes.

1.3.7.1 As a screening tool

Cardiovascular risk scores are used to identify individuals in the high-risk category in order to target them for treatment. A history of cardiovascular disease confers a 20% increase in 5-year absolute risk compared to patients without a previous history of cardiovascular disease. (92) Management of patients with prior cardiovascular disease should therefore be prioritised and these patients do not require further estimation of risk for treatment considerations. (18, 30)

When an individual risk factor level is very high, this in itself would categorise the patient as high-risk. Similarly if all risk factors are very low, the patient would fall into the low-risk

category without the need for classification. The cardiovascular risk scores are especially useful in identifying those who fall in the intermediate group where the risk factors, though minimally elevated, combine synergistically to increase the patient's risk to a level requiring treatment. (93)

There has been debate in the medical literature as to the most effective method to prevent cardiovascular disease. Critics of the absolute risk approach frequently cite the mass population strategy by Geoffrey Rose who showed that small shifts in the distribution curve of a single risk factor over the whole population were more effective in reducing death than treating only those with high levels of the risk factor. (94, 95) Rose listed the disadvantages of the high-risk approach, which were: difficulties and costs of screening; palliative and temporary—not radical; limited potential for (a) individual (b) population; behaviourally inappropriate. He also argued that the use of the high-risk approach to prevention was limited because "*a large number of people at a small risk may give rise to more cases of disease than the small number who are at a high risk."*

However, a modelling study comparing the likely effectiveness in practice of population wide and high-risk interventions to prevent cardiovascular disease showed that the high-risk approach was cost-effective and likely to avert more disability adjusted life years (DALYs) than population strategies. (96) The absolute risk approach was also more effective in averting DALYs and costs than approaches based on single risk factor intervention. The authors concluded that the best approach would be a combination of both population wide and high-risk interventions.

Table 3 shows the number needed to treat (NNT) for different levels of risk. The NNT rises with the decrease in baseline risk.

Table 3: Numbers needed to treat at different cardiovascular risk levels (44)

Risk level: 5-year CV risk (fatal and non-fatal)	Benefits: NNT for 5 years to prevent one event (CVD events prevented per 100 people treated for 5 years)		
	1 intervention (25% risk reduction)	2 interventions (45% risk reduction)	3 interventions (55% risk reduction)
30%	13 (7.5 per 100)	7 (14 per 100)	6 (16 per 100)
20%	20 (5 per 100)	11 (9 per 100)	9 (11 per 100)
15%	27 (4 per 100)	15 (7 per 100)	12 (8 per 100)
10%	40 (2.5 per 100)	22 (4.5 per 100)	18 (5.5 per 100)
5%	80 (1.25 per 100)	44 (2.25 per 100)	36 (3 per 100)

Based on the conservative estimate that each intervention: aspirin, blood pressure treatment (lowering systolic blood pressure by 10 mm Hg) or lipid modification (lowering LDL-C by 20%) reduces CV risk by about 25% over 5 years.

Jackson has also pointed out that the high predicted total cardiovascular risk approach is different from the high risk factor approach and was not assessed in Rose's analysis. (97) An analysis comparing three different approaches (a population health strategy to lower cholesterol uniformly in the population; single raised risk factor strategy where those with high cholesterol are treated; high baseline risk strategy where those with increased cardiovascular risk are treated) found that the number of deaths avoided was greatest with the high baseline risk approach. (98) However, the authors cautioned against over-interpretation of this finding, as the analysis was dependent on the cholesterol level targets and population characteristics. Indeed, a study by Cooney et al which used a 10% reduction in population risk factors levels (as opposed to Manuel's study which used a 2% drop in population cholesterol level) found that the population wide strategy saved more lives than the high-risk strategy. (99) The authors of both

studies again advocate that a combination of population and baseline risk strategies should be employed.

1.3.7.2 In modification of clinical outcomes

A systematic review by Brindle et al in 2006 concluded that there was no clear evidence that risk assessment improved clinical outcomes. (74) The review included four randomised controlled trials; three were on patients with hypertension and the other on patients with diabetes. In the study by Hall et al, (100) it was found that the intervention group were more likely to be prescribed risk factor lowering medications. In the trial by Montgomery et al, (101) there were three arms; a computerised clinical decision support system with risk chart, risk chart alone and usual care. The chart only group had significantly lower blood pressure and were more likely to be prescribed cardiovascular drugs. The other two trials found no differences in outcomes between the intervention and control groups.

A more recent review by Sheridan et al (102) published in 2008 found 11 studies; six addressed clinical benefits and 5 studied harms. The studies by Hall et al and Montgomery were also included in this review, where it was noted that there was an increase in cardiovascular drug prescription in high-risk patients. Two other studies found no difference in prescribing. The review found that physician's knowledge of global cardiovascular risk scores modestly increased prescribing of cardiovascular drugs. There were also modest short-term reductions in CHD risk factors without clinical harm

The conclusions of the above reviews appear to show limited benefit in using cardiovascular risk scores in clinical practice. However, interpretation of this requires caution. None of the individual trials addressed cardiovascular event rates. Some of the trials simply used prescription changes as the main outcome. Study durations were short

with none of the trials exceeding a year. There was poor uptake of the risk scores by doctors even in the intervention groups. As pointed out by Sheridan, the trials did not assess the intermediary steps required from doctors' knowledge to patient understanding and finally to improved clinical outcome.

In a follow-up to this, Sheridan et al conducted a systematic review (103) to determine the effect of giving global coronary heart disease risk information to patients. None of the included studies measured the effect of global risk information on aspirin use or actual cardiovascular event rates. Their review found that provision of information on coronary heart disease risk improved accuracy of risk perception among adults at moderate to high risk. Repeated risk communication and counselling also significantly reduced predicted coronary heart disease risk.

Krones et al conducted a trial on a decision aid based on calculating absolute cardiovascular risk and found that patients in the intervention group were significantly more satisfied with the process and result compared to those in the control group. Decisional regret was also lower in the intervention group. Cardiovascular risk at 6 months follow-up was lowered in both groups but was not significantly different. (104)

Rather than disputing the potential advantages of cardiovascular risk scores, the reviews highlighted problems in the utilisation of the risk scores. The individual trials reviewed showed poor uptake of the risk scores by doctors even in the intervention groups, and lack of translation of knowledge to management.

1.4 Summary of main points in the literature

Cardiovascular risk scores predict the risk of developing cardiovascular outcomes from risk factor profiles. They are developed from mathematical models based on data derived from large cohort studies. The first such study was the Framingham heart study and many other cardiovascular risk scores have been developed by other studies. Most guidelines advocate the use of the Framingham risk score.

Absolute risk is the form of risk statistic generated by most cardiovascular risk scores. Use of the risk scores by clinicians is not universal, ranging from 48-68% of survey responders. Clinicians' estimates of risk have been shown to be inaccurate. However, validation studies have also found the accuracy of the risk scores to be quite low. Most scores have been derived on treated populations, contributing to the inaccuracy.

Age is the most powerful risk predictor in the cardiovascular risk scores. This may cause treatment of the young with relatively high risk factors levels to be delayed. Approaches such as lifetime risk scores have been developed to address this issue. The usefulness of lifetime risk in individual risk prediction is still under debate.

Cardiovascular risk scores are used for global high-risk screening. The combination of this approach with population wide strategies is considered to be the most potentially effective strategy for cardiovascular prevention in the population. However, there is limited evidence of improvement in clinical outcomes from randomised clinical trials of programmes promoting cardiovascular risk scores. These trials show poor implementation – in practice, the risk scores were not being used consistently by doctors to make treatment decisions. This must, in part, reflect lack of trust in the scores because of the continuing debate in the medical literature about their accuracy.

1.5 The evidence gap

Substantial amounts of time, effort and money have been used to create, refine and examine cardiovascular risk scores to ensure better accuracy. One indication of the amount of money involved in cardiovascular risk prediction is the prohibitive licensing cost of £10000 for QRISK. (105) Changes to national policies regarding cardiovascular risk prevention are costly and should go through extensive systematic evaluation prior to implementation.

In March 2010, NICE changed its guidance on cardiovascular risk scores with the stated intention of improving accuracy. It advised the consideration of scores other than Framingham. (29) In the press statement, it is stated that the reason for the change was new evidence that QRISK performed better than other risk scores. This evidence is likely to have been the validation study by Collins and Altman, which found that, although QRISK underestimated 10-year cardiovascular disease risk, the magnitude of under-prediction was less than the over-prediction with Framingham. (106) We postulate that a likely reason for both effects was treatment of the validation population in that study. (107)

Moreover, as was made clear earlier in the chapter, treatment of study populations is also likely to be a source of great inaccuracy in the derivation of the risk scores. It has been estimated that 50% (108) to 80% (109) of cardiovascular disease can be reduced by combination treatment of risk factors. It is unlikely and unethical for anyone found to have high risk factors to remain untreated and thus a significant proportion of participants in the cohort studies would have been on risk factor treatment. The extent to which treatment is adequately adjusted for in the risk assessment scores derived post-Framingham appears not to have been adequately explored or reported.

Finally, although NICE did not justify its decision to promote other scores on the basis of the preferability of lifetime risk scores, there are indications that such a recommendation may soon be adopted. (110) The academic controversy is outlined in section 1.3.6. Proponents believe that the short-term scores over-medicalise the elderly and ignore the risk in the young. Opponents believe in the opposite view; that lifetime risk scores over-medicalise the young and ignore the risk in the old. Perhaps more importantly, what is not known is whether there truly exists a difference in life expectancy between the old and young at the same short-term risk.

Chapter 2. Aims, objectives and overview

2.1 Overall aim

To identify the most appropriate cardiovascular risk score for use in general practice, taking account of the impact of treatment and time on assessed risk.

2.2 Objectives

1. To identify all the cardiovascular risk scores that have been developed and are available for general practitioners to use.
2. To determine whether (and how) these scores take into account the effect of treatment.
3. To explore how UK general practitioners use risk scores in their everyday clinical practice.
4. To determine if there exists a true difference in the impact to life expectancy between those at different ages but the same short-term risk.
5. To make recommendations about the most appropriate risk score for use in general practice in the light of the findings in relation to objectives 1-4.

2.3 Overview of subsequent chapters

Chapter 3 presents a systematic review, which compares the available cardiovascular risk scores. The focus is on the extent of treatment in the study populations and methods used to adjust for this.

Chapter 4 reports a qualitative study of general practitioners' views and usage of the cardiovascular risk score. This again focuses on the aspect of treatment in the perception of risk and use of the assessment tools in clinical practice.

Chapter 5 reports the results obtained from modelling the effect of a five-year treatment delay on potential life years lost for different ages at the same short-term cardiovascular risk. It addresses both age-specific case fatality rates and competing risks.

Chapter 6 explores and justifies the use of time preference as an additional factor in the mathematical models.

Chapter 7 discusses the contribution of this research to our knowledge in cardiovascular risk assessment. The implications for clinical practice are addressed.

Chapter 8 reports on the progression of work since original analysis. It includes published and pre-publication papers accompanied with commentaries on how the original analysis evolved into the final manuscript.

Chapter 9 addresses the implications for future research and includes a detailed explanation on the methodology of the proposed research.

Chapter 3. Systematic review of the cardiovascular risk scores

3.1 Introduction

For many years, the Framingham cardiovascular risk equation has been the preferred method of cardiovascular risk assessment. However, in February 2010, the National Institute for Health and Clinical Excellence (NICE) announced that the Framingham risk equation should be considered as just one of several acceptable methods. (29, 36)

In the appendix accompanying the guidelines is a review by Beswick et al (19) that identified over 100 different cardiovascular risk score methods. Clinicians are expected to select from these cardiovascular risk scores, one that is appropriate for their patients. How should they decide which one is most appropriate?

Cardiovascular risk scores measure baseline risk factors to predict future cardiovascular morbidity and mortality, but most do not account for changes in treatment during the years of follow-up. Failure to adjust for such treatment effects will cause cardiovascular risk scores to systematically underestimate predicted risk. This problem is potentially greater for more recent studies with the progressive increase in the use of effective medication for blood pressure and lipids over the past 20-30 years. (76, 77)

There is indirect evidence in the medical literature to support this theory. If risk scores derived from treated populations underestimate risk then, conversely, when risk scores derived from untreated populations are validated in treated populations, the risks should appear to be overestimated. The review by Beswick et al did indeed find that the more recent the validation study, the greater the over-estimation by the Framingham risk score. Further analysis also showed that the over-estimation was greater in effectively treated populations. (19)

3.2 Methods of review

3.2.1 Objectives

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

3.2.2 Search methods for identification of studies

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

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

3.2.3 Identifying studies

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

3.2.4 Data extraction

I appraised and selected the studies, then extracted information from each study for analysis in collaboration with a second reviewer. Information extracted included study demographics, outcomes, predictors and treatment effect.

3.2.5 Analytical methods

Study methods were assessed using criteria adapted from Wasson et al (111) and Royston et al, (112) including sampling, predictors, follow-up, outcomes, data quality and performance of the rule.

3.3 Results

A total of 3536 papers were retrieved after removal of duplicates from records identified through the Medline search and other sources. Figure 6 shows the PRISMA flow diagram. The PRISMA statement and review protocol are available in Appendix A and B respectively.

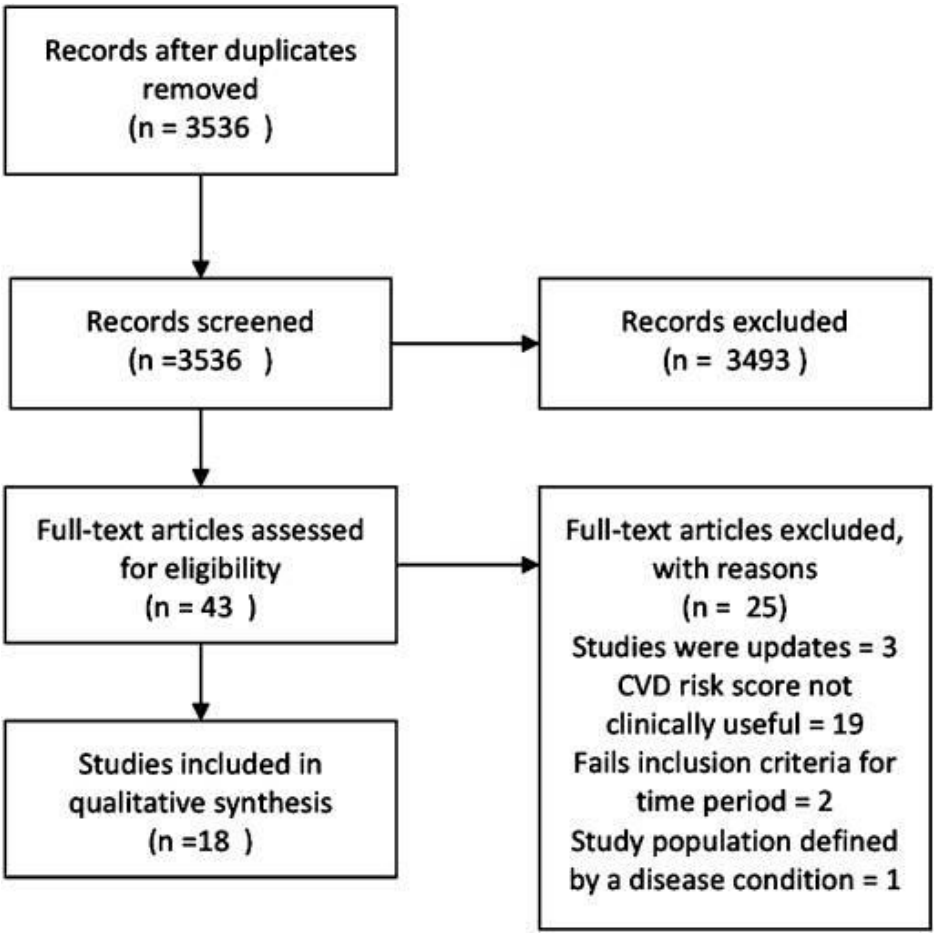


Figure 6: PRISMA flow diagram for systematic review

3.3.1 Description of studies

I identified 21 risk scores eligible for the review (Table 4) from 18 papers. Five were from Framingham (6, 7, 11, 56), three from the Munster group (PROCAM) (22, 23) and ARIC (Atherosclerosis Risk in Communities) (113, 114), two each from QRISK (27, 28) and Reynolds (25, 26) and one each from the Scottish Heart Health Extended Cohort (115), Strong Heart Study (116), USA-PRC (People's Republic of China Collaborative Study of Cardiovascular Epidemiology) (117) and NHEFS (National Health and Nutrition Examination Survey NHANES 1 Epidemiologic Follow-up Study) (118). Some risk scores used multiple cohorts: SCORE (24) was derived from a pool of 12 European

cohorts, Progetto CUORE (119) from a pool of Italian cohorts. Twelve are from North America, eight are European and one from China.

Figure 7 shows a timeline chart of the reviewed cohort studies and the introduction of several medications. (76, 77)

Table 4: Description of included studies

	Country		Population	Sample size	Age	% Female	Recruitment period
Framingham 1976	USA		Population cohort	5209	35-64	55	1948-1952
Framingham 1991	USA		Population cohort (Original + Offspring)	5573	30-74	54	1968-1971; 1971-1975
Framingham 1998	USA		Population cohort (Original + Offspring)	5345	30-74	53	1968-1971; 1971-1975
Framingham 2008	USA		Population cohort (Original + Offspring)	8491	30-74	53	1968-1971; 1971-1975; 1984-1987
PROCAM 2002	Germany		Occupational cohort	5389	35-65	0	1979-1985
PROCAM 2007	Germany	CHD	Occupational cohort	26975	20-75	32	1978-1995
		Stroke	Occupational cohort	8130	35-65	27	1978-1995
SCORE 2003	Europe		Pooled dataset of cohort studies	205178	45-64	43	1967-1991*
ARIC 2003	USA		Population cohort	14054	45-64	57	1987-1989
Progetto CUORE 2004	Italy		Pooled dataset of cohort studies	20647	35-69	64	1983-1997
Strong Heart Study 2006	USA		Population cohort - American Indian	4372	45-74	61	1989-1991
USA-PRC 2006	China		Population cohort	9903	39-59	51	1983-1984
ASSIGN 2007	UK		Population cohort	13297	30-74	51	1984-1995
Reynolds women 2007	USA		Women's Health Study trial subjects	16400	45+	100	1992-1995
Reynolds men 2008	USA		Physician Health Study trial subjects	10724	50-80	0	1995-1997
Personal Heart 2007	USA		Population cohort	14343	45-64	57	1987-1989
QRISK 2007	UK		Electronic medical database	1283174	35-74	50	1995-2007
QRISK 2 2008	UK		Electronic medical database	1535583	35-74	50	1993-2008
NHEFS 2008	USA		Population cohort	6186	25-74	54	1971-1975

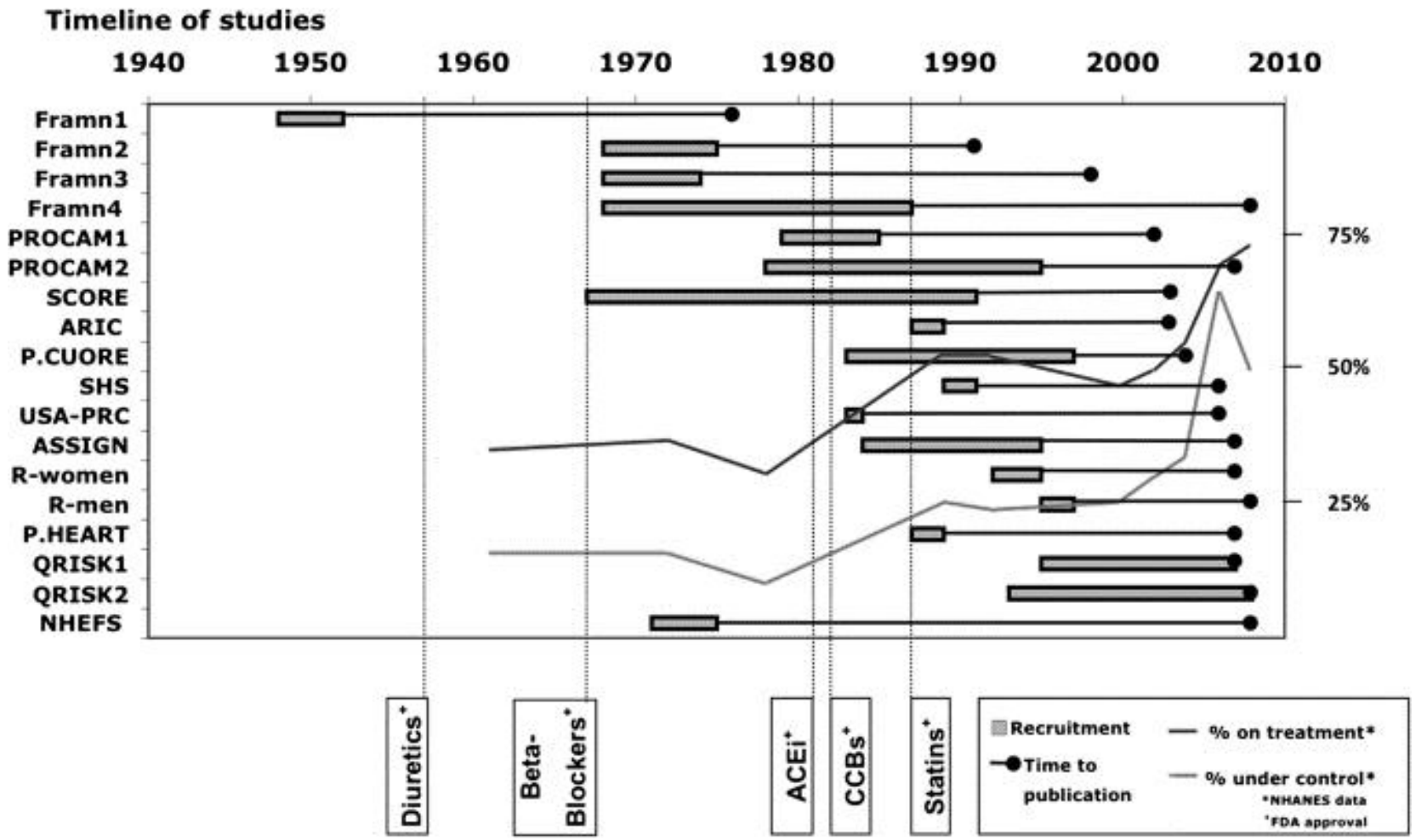


Figure 7: Timeline chart of included studies and the introduction of risk factor-lowering medications

3.3.2 Analytical methods

Table 5 compares the analytical methods of the reviewed risk scores.

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

3.3.3 Risk predictors and their definitions

The final number of risk predictors ranged from five (PROCAM stroke) to fifteen in QRISK 2 (Table 6). Selection of predictors was mostly by significance testing (Table 5). All scores included age, gender, blood pressure, and smoking, and most included lipids and diabetes. Lipid levels were not used in the non-laboratory model of the 2008 Framingham risk score, the PROCAM 2007 risk equation for stroke, or the NHEFS risk score. Diabetes, glucose intolerance or HbA1c level was a predictor for all except the European SCORE. Other risk predictors included by some scores were left ventricular hypertrophy, antihypertensive medication use, body mass index, ethnicity, family history, socioeconomic status, medical diseases, biomarkers (hsCRP and albuminuria) and physical activity.

Definitions for risk predictors differed from score to score. In the original Framingham cohort, diabetes was defined as a random blood glucose measurement ≥ 150 mg/dL (8.3 mmol/L) or treatment with insulin or oral hypoglycaemics. In the Framingham Offspring cohort, this definition was broadened to a fasting plasma glucose level ≥140 mg/dL (7.7 mmol/L) or treatment requirement. (56) This in turn differs from the current definition used by the World Health Organisation of fasting plasma glucose ≥ 126 mg/dL (7.0 mmol/L). (120) Hence, patients with fasting plasma glucose between 126 and 150 mg/dL (7 – 8.3 mmol/L) would be classed as non-diabetics by the first Framingham score. Systolic blood pressure measurement methods included averages taken from two

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

3.3.4 Outcomes predicted

The outcomes predicted differ widely between the risk scores (Table 7), ranging from general cardiovascular risk to specific disease outcomes. Almost all scores predict myocardial infarction and death from coronary heart disease. Only 12 of the 21 scores included cerebrovascular events. SCORE only predicts fatal cardiovascular events.

Methods to assess outcome events also differed. The SCORE and ASSIGN scores used hard outcomes with diagnostic codes such as ICD 9/10 codes. ‘Hard outcomes’ can be defined as irrevocable events (121) that have permanent consequences, such as myocardial infarction and death, as opposed to ‘soft events’, such as hospitalisation for angina. The Framingham studies included a broader composite of hard and soft end points. Diagnostic criteria for outcomes in Progetto CUORE and the USA-PRC cohorts followed the WHO-MONICA study (World Health Organisation – MONItoring trends and determinants in CArdiovascular disease project). (117, 119) Expert panels reviewed medical records and hospital notes in the Framingham studies, PROCAM scores, ARIC, SHS, Reynolds studies and the NHEFS. QRISK1 and 2 used general practice electronic recorded diagnosis or death certificates linked to the computer system.

3.3.5 Treatment effect

Methods used to adjust for the effect of medication were absent or weak (Table 8). The effect of treatment is not fully assessed or adjusted for by any of the reviewed risk scores. Treatment effect includes (1) that which occurs by risk factor modification (e.g. blood pressure lowering medication), (2) that which works independently of risk factors (e.g. platelet inhibitors such as aspirin), and (3) that which works by both means (e.g. statins). Twelve of the cardiovascular risk score studies (Framingham 1998, Framingham 2008, ARIC, Progetto CUORE, SHS, USA-PRC, Personal HEART, QRISK1, QRISK2, Reynolds 2007, Reynolds 2008 and NHEFS) reported data on prior treatment, but this was mainly limited to antihypertensive treatment. Only seven (Framingham 2008, ARIC, Progetto CUORE, SHS, QRISK1, QRISK2 and NHEFS) include the use of antihypertensive medications as a risk predictor. The Reynolds studies were the only ones to report prior use of lipid lowering agents. None of the studies reported on the prior use of platelet inhibitors.

Two treatment effects need to be considered: (1) prior treatment (started before enrolment in the study) and (2) subsequent treatment started during study follow-up (treatment drop-ins). None of the risk scores addressed the effect of treatment drop-ins. For early studies, such as the older Framingham Study, this may be minimal. Recent cohorts such as QRISK may have had more than half of their study population receiving treatment with their blood pressure under control. (See NHANES data (78, 122-125) in figure 7)

Table 5: Analytical methods of included studies

		Prospective	Predictors defined	Predictor selection	Follow-up loss	Missing values	Outcomes defined	Objective outcomes	Blinded assessment of outcomes	Model used	Results of rule
Framingham 1976		Yes	ECG-LVH	NR	NR	Complete data - IC	Yes	Includes angina	NR	Logistic regression	NR
Framingham 1991		Yes	ECG-LVH	Significance testing	NR	Complete data - IC	Yes	Includes angina	NR	Weibull model	c statistic
Framingham 1998		Yes	Yes	Significance testing	NR	Complete data - IC	Yes	Includes angina	NR	Cox model	c statistic
Framingham 2008		Yes	Yes	Significance testing	NR	Complete data - IC	Yes	Includes angina	Adjudication committee	Cox model	c statistic and calibration
PROCAM 2002		Yes	Yes	Significance testing	Yes	NR	Yes	Yes	NR	Cox model	ROC + calibration
PROCAM 2007	CHD	Yes	Yes	Significance testing	NR	NR	Yes	Yes	NR	Weibull model	ROC
	Stroke	Yes	Yes	Significance testing	NR	NR	Yes	Yes	Yes	Cox model	ROC
SCORE 2003		Pooled prospective cohorts	Pooled cohorts	A priori	NR	No HDL in some cohorts	Yes	Yes	Used diagnostic codes	Weibull model	ROC
ARIC 2003		Yes	Yes	Significance testing	Yes	Complete data - IC	Yes	Includes revascularisation	NR	Cox model	ROC
Progetto CUORE 2004		Pooled prospective cohorts	Yes	Significance testing	NR	NR	Yes	Includes revascularisation	Used diagnostic codes	Cox model	ROC

	Prospective	Predictors defined	Predictor selection	Follow-up loss	Missing values	Outcomes defined	Objective outcomes	Blinded assessment of outcomes	Model used	Results of rule
Strong Heart Study 2006	Yes	Yes	Significance testing	Yes	Yes	Yes	Includes angina and revascularisation	NR	Cox model	ROC + calibration
USA-PRC 2006	Yes	Yes	A priori	Yes	Complete data - IC	Yes	Yes	Adjudication committee	Cox model	ROC + calibration
ASSIGN 2007	Yes	Yes	Significance testing	NR	NR	Yes	Includes angina and revascularisation	Used diagnostic codes	Cox model	ROC
Reynolds women 2007	Yes	Trial data	Model testing - BIC	NR	NR	Yes	Includes revascularisation	NR	Cox model	ROC + calibration
Reynolds men 2008	Yes	Trial data	Model testing - BIC	NR	Complete data - IC	Yes	Includes revascularisation	Adjudication committee	Not specified	ROC + calibration
Personal Heart 2007	Yes	Self-report	Significance testing	NR	NR	Yes	Includes revascularisation	NR	Cox model	c statistic
QRISK 2007	No	Retrospective GP record	Model testing - BIC	NR	Significant missing data	Diagnosis from GP records or death certificate	Includes angina	Used diagnostic codes	Cox model	ROC + calibration
QRISK 2 2008	No	Retrospective GP record	Model testing - BIC	NR	Significant missing data	Diagnosis from GP records or death certificate	Includes angina	Used diagnostic codes	Cox model	ROC + calibration
NHEFS 2008	Yes	Yes	A priori	NR	Complete data - IC	Yes	Includes revascularisation	Used diagnostic codes	Cox model	ROC + calibration

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

Table 6: Predictors used in included studies

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

Table 7: Outcomes used in included studies

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

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

Table 8: Adjustment for treatment effect in included studies

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

Shaded areas, information not reported; Antihpt, antihypertensive medication; SBP, systolic blood pressure; pred, predictors; $, corrected for change in risk factors by factoring in changes at mid point of follow-up I.e. 1993/1994

3.4 Discussion

3.4.1 Statement of principal findings

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

Whichever risk equation they choose, clinicians should know which outcomes are predicted. As the outcomes predicted differ significantly, the risk scores are not interchangeable. For example, the Framingham risk scores predict a broad range of cardiovascular events (including cerebrovascular events), whereas SCORE only predicts fatal cardiovascular events. The Framingham study risk scores have been criticised for the inclusion of 'soft' (subjective) outcomes such as angina, (24) although the Framingham investigators argue that such outcomes estimate the total cardiovascular disease burden (11) and are clinically important to both patient and doctor. Revascularisation interventions may also be criticised as being subjective.

Time is a major obstacle to the use of risk scores by physicians (64); obtaining more information from a patient will further decrease the use of risk calculators. Of the risk scores, QRISK2 had the most predictors, which included disease conditions such as atrial fibrillation and chronic renal disease. QRISK2 score is designed to use data in the patient's electronic health record, with imputed values for missing data. However, the proportion with missing data for these factors in the derivation cohorts was substantial (>70% for ethnicity; >60% for cholesterol). (28)

The second limitation is that the effect of treatment has not been considered fully by any of the reviewed risk scores. Treatment decreases the true effect of risk factors on outcomes, (126,127) as illustrated by Figure 8. The combined effects of risk reduction due to treatment can be as much as 50%. (108) If 25% of the population started treatment during follow-up, it would mean a population risk reduction of 12.5%. But this would be greater in the high-risk groups, who are more likely to be treated. These differences are similar to those found between QRISK2 and Framingham (11.6%), which was obtained in a recent validation study of QRISK2. (75)

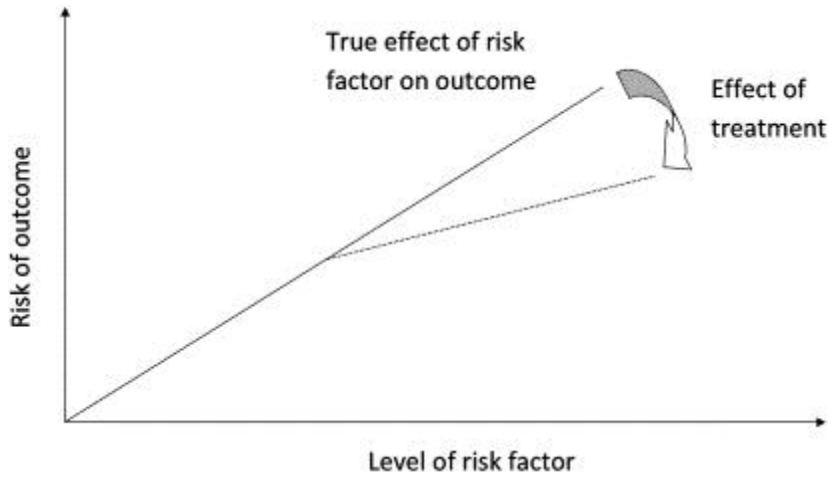


Figure 8: Treatment changes the effect of risk factors on outcome

Ideally, a cardiovascular risk score to determine the risk of a cardiovascular event and to stratify patients for risk factor modification should be derived in a population receiving no treatment at the start of and during the study. Such an ideal study is not tenable or ethical. There are three possible solutions. First is the use of older studies, when less aggressive treatment occurred. Second, treatment uptake could be monitored and appropriate adjustments such as the application of a penalised Cox model made to account for the effect of treatment. (128) Until such studies have been performed, study cohorts where there is minimal treatment drop-in during follow-up should be preferred.

Alternatively, to minimize treatment drop-in, we could study cohorts with much larger numbers over much shorter periods. (Rod Jackson, personal communication)

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

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

3.4.2 Strengths and weaknesses of the study

The review was limited to studies in which participants had no previous history of cardiovascular disease and excluded those who were restricted to a disease condition. A prior diagnosis of cardiovascular disease or a disease such as diabetes raises the patient into the high-risk category, removing the need for risk estimation. This has also been advocated by the NICE guideline, which states that risk equations should not be used for those with a previous history of cardiovascular disease or other high-risk diseases such as diabetes. (36) Furthermore, the majority of these patients would have received treatment, potentially altering study outcomes.

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

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

The 2005 review by Beswick et al (19) included in the appendix of the NICE guidelines identified 110 risk score methods, with 70 meant specifically for application in primary prevention. The difference in the number of studies identified is due to their wide inclusion criteria, which included studies restricted to a disease condition, studies that had participants with prior cardiovascular disease, studies that were recalibrations or modifications of the original cohort study, studies that did not use absolute risk scores, and studies where the duration of prediction was not specified. More recent studies such as QRISK and Reynolds scores were not included, as their search concluded in April 2005.

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

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

3.4.5 Unanswered questions and future research

This review did not address the effectiveness or accuracy of the cardiovascular risk scores, which would require a review of validation studies instead of the original cohort studies. The reviews by Beswick et al (19) and Brindle et al (74) have tried to assess this, but do not include the more recent studies. However, it should be pointed out that any validation study of risk scores is likely to also suffer the same problem of treatment drop-in, which would attenuate the true cardiovascular risk. Researchers should also attempt to address the effect of treatment in future studies in this field by collecting data on treatment at the start and during the course of cohort studies, as this will impact on the final outcomes.

3.5 Conclusions

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

Chapter 4. Doctors' views and usage of the risk scores

4.1 Introduction

The systematic review (Chapter 3) found that all existing cardiovascular risk scores for primary prevention do not take the effect of treatment into account. (129) It was postulated that this would result in inaccuracy in risk prediction if doctors use the predicted risk to inform patients of the risk of remaining untreated or for decisions on treatment initiation. The resulting inaccuracy is worse in the recent risk scores such as QRISK because of the greater availability and use of medications in their study populations.

Many doctors believe that the latest risk scores are more accurate simply because they are derived from contemporary study populations. This opinion is reinforced by validation studies which appear to show greater accuracy of the newer risk scores e.g. QRISK. (106) It is important to note that any validation studies conducted in recent times would also have an actively treated population. Therefore, it would have outcomes that more closely resemble QRISK than Framingham. As Hense pointed out, the problem of interventions affecting outcomes also occurs in validation studies. (70)

Recent risk scores such as QRISK are accurate at predicting the risk of an actively managed individual or population. However, they underestimate the true cardiovascular risk of an individual *if left untreated*. (107) Older risk scores are accurate in predicting cardiovascular risk for a patient if left untreated. Their cohorts were not 'exposed' to medication (i.e. treatment naïve). The predicted risk of an actively managed population is useful for public health planning but not for assessing individual risk in clinical practice. The complexity of the statistics used by the risk score research studies obscures this aspect from general practitioners.

The key finding is that the recent risk scores are better at predicting risk in those who are actively managed but not as good in predicting the risk of an individual if left untreated. It is not known whether this has affected the use of risk scores in clinical practice.

The main objective in conducting the qualitative interviews was to understand the views of GPs on the use of cardiovascular risk scores in clinical practice, especially with regards to the issue of treatment. What did they mean when they communicate risk to a patient? Is it the 'treated risk' or the 'untreated risk'? 'Treated risk' is the risk that the patient would have at the end of an actively managed length of time. 'Untreated risk' is the risk that the patient would have if he remained untreated. This question is important because it affects selection of the risk score.

In the next section, I describe the methods used for this study and why this study design was selected. This is followed by the results, which are grouped according to the 3 main themes that developed from this study. The chapter concludes with a discussion on the findings in relation to previous existing literature.

4.2 Methodology

A qualitative method was specifically chosen because it allows greater exploration of the topic than a closed-question survey. Qualitative interviewing allowed the participants to articulate their understanding and experiences in their own words instead of having to choose between different definitions of risk as defined by the researcher. (130) Some structure was necessary in the form of a list of broad themes. This helped to guide the interview and ensure coverage of important topics especially as interview time was limited by clinic work. However, the semi-structured design was flexible enough to allow the investigation of issues or themes that were unexpected.

4.2.1 Objective

The study aimed to investigate the views of general practitioners (GPs) on the use of cardiovascular risk scores in clinical practice, especially with regards to the issue of treatment.

4.2.2 Study design

A qualitative study design was used with one-to-one semi-structured interviews of general practitioners working in Oxfordshire. Ethics approval was obtained from the Oxfordshire REC B Research Ethics Committee (REC reference: 10/H0605/42).

4.2.3 Sample and setting

A list of practices and the names of general practitioners working at those practices was obtained from the Thames Valley Primary Care Agency and practice websites. Purposive sampling was used as the intention was not to draw a statistical inference from the results of this study but to obtain an in-depth exploration of the use of cardiovascular risk scores from 'information-rich' general practitioners. (131) These were likely to be doctors with an interest in cardiovascular disease prevention. Postal invitations were sent out to 222 general practitioners. 10 participants were recruited solely by this method. No incentives were offered to the participants, a possible reason for the low numbers recruited by post. In order to increase the sample size, invitations were also sent out by electronic mail from suggestions given by participants who had been interviewed, a method known as 'snowballing'. Recruitment continued until data saturation, a theoretical point achieved when no additional data is being found. (132) This was achieved after 20 interviews. (See table 14 in Appendix C for participant demographics)

4.2.4 Methods

All the interviews were carried out at the participant's workplace or home depending on his or her preference. The interviews lasted between 30 minutes to an hour. Interviews were audio-recorded and transcribed verbatim by a transcriber using study codes to keep the identities anonymous (e.g. R1, R2 etc). Permission to tape record conversation was obtained and recorded on a signed consent form prior to the interview. An interview guide was used with a list of open-ended questions covering broad themes (See Appendix D). Participants were allowed to diverge into new directions with interesting diversions followed up by further exploration from the interviewer. In keeping with the principles of qualitative research, an iterative approach was used whereby later questioning was informed by the use of answers from earlier interviews.

All participants were asked whether they perceived the calculated absolute risk to be the risk that the patient had if he or she remained untreated. This was done to understand whether doctors used the risk scores to estimate untreated (or unmodified) risk for use in clinical practice. This question was generated by the findings of the systematic review. However as the question was open to interpretation, it required the interviewer to explain the findings of the systematic review, namely that the risk scores were derived from cohort studies where treatment of the population during the study was mostly ignored. The derivation of the score was based solely on the relationship of risk factors measured at the start of the study and outcomes at the end of the study. This explanation was necessary to ensure that the participants' answers were based on proper understanding of the question being asked.

4.2.5 Coding and analysis

The transcripts were checked for accuracy. After repeated reading of the transcripts, the text was coded independently under different headings by two coders, using a thematic

approach to analysis. The few discrepancies in coding were resolved by discussion. Once coding was finished, a written and graphical summary of the issues was created for each code using the OSOP (one sheet of paper) method where every section of data relevant to that code from all the different interviews is noted. (133) Themes are patterns found in the retrieved qualitative information and thematic analysis allows the researcher to use the data in an organised and systematic manner to enable interpretation and understanding of the qualitative data. (134) The software package NVivo9 facilitated the analysis of themes and systematic comparison across transcripts.

4.3 Results

The GPs' responses could be categorised around three main themes:

- Treated versus untreated risk
- The use of the cardiovascular risk scores in patients already on treatment
- Manipulation of risk factor levels in communicating risk

4.3.1 Treated versus untreated risk

In the interviews, all the participants were asked the same question - did they consider the calculated risk to be the risk of the patient remaining untreated? There was a mixed response to this question. Some understood the question immediately whereas others required further explanation. The basis of the question was explained to all whether or not they required further elaboration. (See Methodology section)

4.3.1.1 Immediate response

The replies of those who answered immediately without need of further elaboration show that they agreed that it was the risk of the patient remaining untreated.

> R7: (This is the risk) over the next ten years (if he remains) as he is, that's what I've taken it to be. If he stays as he is. And if we can change some of those things, we can reduce that risk for him.

> R10: I suppose I would see it as the risk if no intervention was made, if there was, you know, assuming these parameters, this blood pressure, and this lipid profile, if that is unmodified, this is your risk over the following ten years.

> I: And this is the risk that she would have if she remained untreated, is that right?
> R11: Yes if she doesn't change, if she doesn't do anything, her risk. If there are a hundred women in the room like her, twenty will have an episode.

> R13: I would say, this is the risk you'd have without doing anything and obviously if you do these things, if we can get your blood pressure down a bit by you taking more exercise, cutting down salt, may be cutting down on alcohol…then your risk will come down. So that would be what I would say.

Some doctors made a distinction about the timing of the treatment. They did not consider treatment to preclude the need for risk assessment in the patient. They considered the calculated risk to be the current risk, given the most recent risk factor levels whether lowered by treatment or not, but before the next intervention.

> R17: The way I interpret it is they give you a snapshot of that particular time given the most recent blood pressure and cholesterol levels and smoking habits. That is what the risk from that day is for the next ten years.

> R19: What I'm communicating is what their current risk is. So using QRISK in treated hypertension; that obviously means as things are at the moment, with them currently being treated for their hypertensions but before the next intervention.

Doctors were divided into two groups, those who believed that the risk scores should be used only in patients who had not been started on any risk factor lowering treatment previously (untreated risk) and those who believed that risk scores can be used in patients who are already on treatment (current risk). This will be discussed in detail in section 4.3.2. Relevant to this section, is that both groups agreed that the risk was that *if no further intervention* was made after baseline.

4.3.1.2 Response to findings of the review

This drew different responses. Some of the participants were of the opinion that their use of the risk score did not require such detailed examination.

> R15: So they didn't allow for whether they'd had treatment or not? I probably do it at an even more basic level than that…I kind of use it really as a very simple decision making tool at that kind of level, rather than trying to go into as much detail as you're sort of implying.

> R19: My understanding is much more simplistic. It is what their current level of risk is at this precise moment.

To the others, it was an important and surprising issue that the risk scores did not take treatment during the study into account. They had not reflected on this previously or had simply assumed that the methodology of the studies would be able to adjust for treatment effects.

R13: I didn't actually realise that. I thought this was the untreated risk.

R17: I wasn't aware of that. I kind of assumed that, maybe naively, that the data is updated…It would seem to me that taking the original Framingham data is unpolluted by any subsequent intervention. So one assumes that that in some ways is probably cleaner for whatever it means or interpreted. I wouldn't pretend to understand… I think intuitively it makes sense that the older data is probably going to be more useful but I don't know.

A number of doctors pointed out that by ignoring treatment in their populations, the studies were compromising accuracy.

R8: So you take your population at year zero, you follow them all through but you don't actually know who's been treated. Oh gosh, yes, so that actually brings huge inaccuracy into the risk scores then.

R6: Yes it does, of course it does, because the people being treated while they're being observed – even just lifestyle treatment can make a huge difference. And we're all far more health conscious than we were fifty years ago. So yes, I think that is a strong case in favour of the older (risk scores).

The fact that the studies ignored treatment was going against a core belief. Doctors treat patients to reduce outcome rates. By not taking treatment of the study population into account, studies were implying that treatment of risk factors had no effect on outcomes.

R3: I hadn't thought of that...It's obvious when you think about it, that there's an issue about how treatment is going to change outcomes. And that'll interfere with prediction.

> R14: But that's what you have to do, isn't it? Because somebody's ten-year risk is what is was before they went on treatment is nonsense if you then treat them. And risk scores are partly about being able to assess the effect of treatment. If your treatment isn't going to lower the risk, then what's the good of treating in the first place?

One of the doctors pointed out the difficulties faced by researchers in countering the effect of treatment in modern study populations. He noted the impossibility of having *the perfect risk score in unadjusted patients who are naïve to all treatment*, calling it a Utopia. He also felt that adjustments for this in research would be very difficult.

> R18: Do you attenuate the risk? If someone's on blood pressure treatment, do you take the baseline risk or the attenuated current risk or do you say that treatment of blood pressure reduces it by two thirds and therefore you need to modify for the third as not being attenuated? It's all very, very grey, isn't it?

The results showed that the study participants perceived the calculated risk to be the patient's risk at that point in time prior to modification by lifestyle or treatment. Most were surprised that the treatment of study populations were ignored. This appeared to contradict their core belief that treatment would reduce cardiovascular outcomes. Some of the doctors questioned the accuracy of the risk score. One doctor considered the inclusion of treatment effect to be difficult for researchers to achieve in risk score derivation studies. Others felt that this level of examination of the risk scores was unnecessary for their usage in clinical practice.

4.3.2 The use of the cardiovascular risk scores in treated patients

The doctors in the study had conflicting views on whether the risk scores could be used on those who were already on risk factor lowering treatments. As shown in the section

above, those who used the risk scores on treated patients were of the opinion that the risk was estimated using the latest risk factor levels and therefore reflected the current state of the patient.

> R13: Obviously it gets quite complicated when you talk about, you know, is the risk the same if you're on treatment. But I tend to look at it that this is the risk that depends on your cholesterol level, your blood pressure whatever, whether or not you're on treatment.

Other participants appeared to have an understanding that the risk scores were not to be used in those who were already on treatment. They felt that the risk scores were not designed for this use and therefore not valid.

> R7: We're doing the fire and forget. You know, we're just treating, we're not testing again, because I have to get them out of an expectation that I'm going to then check their cholesterol and put it in and tell them how much better it is. So I wouldn't. I do it with blood pressure and I do with smoking and things like that, and I usually do it at the beginning but I don't tend then. Once they're on it, I ignore, I don't do it. Well, it doesn't work afterwards anyway. Once you're on treatment, it's no longer valid, is it?

Doctor R6 said that there was no longer any point in doing it after treatment was started.

> I: That's interesting. Does that mean that you do it once and then you don't do it again?
>
> R6: No, it's more the fact that all my overweight patients with high blood pressure have had their risk done and they're already on statins, so I've done it…
>
> I: Okay

R6: So there's no point in then redoing it.

I: So you don't do it once they have started treatment?

R6: No, once they've done it, I say, "This is your risk. Government says a 20% is threshold on it, you know, give or take. Let's lower your blood pressure, let's lower your cholesterol and see how you go." End of story is carry on with the treatment.

Doctor R6 defined the risk score as "a piece of paper in my drawer that I look at when I think that somebody might be in need of various treatments." So it was clear that he used the risk score mainly for treatment initiation which would make it unnecessary for someone who is already being treated. Doctor R2 also did not see the point in repeating the risk calculation after treatment. He felt that in doing so, "you're just patting yourself on the back for having lowered their blood pressure but it's not actually changing your management of them."

The high prevalence rates of hypertension and hyperlipidaemia does mean that a substantial number of patients would already be on treatment. So this further complicated the issue. One doctor, R10, who also worked with BUPA (a private healthcare company) alongside his GP work, mentioned that BUPA specifically instructed its doctors not to use the risk scores in patients who were already on treatment. However, he did still use the risk scores in his own general practice on patients who were on treatment to help them understand cardiovascular risk. He then added "Where's the science when the evidence behind that is less clear, isn't it?" indicating doubts as to whether this was the right approach.

There was obvious uncertainty over this issue. Doctor R4 for example stated that the risk score was "more useful in determining whether you start somebody on treatment, not to

monitor. Once you've got somebody on treatment, you can't really use it to work out their risk." However, Doctor R4 had also stated earlier that for a treated hypertensive, one should take their risk on their untreated blood pressure and not their treated blood pressure. The contradicting statements made by the same participant were a reflection of the confusion that the doctors have on this issue.

4.3.2.1 Framingham versus QRISK in patients already on treatment

Two further issues came up in those who were using the risk scores on treated patients. The first one was that some of the doctors believed that Framingham could only be used on those who were treatment naïve whereas QRISK could or should be used in those who were already on treatment.

> R1: Well, I know the Framingham is supposed to be a pre-treatment risk. I think QRISK is different in that it gives you the risk on that specific day treated.
>
> R19: And also importantly, it (QRISK) also includes patients that have got treated hypertension and in practice, a big prescribing decision obviously is when patients are already on hypertensive treatment, about making the decision about whether they should go on and have statins etc. And again the problem with the Framingham risk score is not being able to do that, whereas with QRISK obviously, that takes that into account.

Doctor R19 went on to ask whether his belief that Framingham was not supposed to be applied to treated patients was correct. Again, there is uncertainty over the use of the risk scores.

4.3.2.2 Risk factor levels to be applied in patients already on treatment

The second problem that arose when using the risk scores in treated patients was whether or not pre-treatment values should be used. The participants in the study talked about the difficulty they had in using pre-treated values.

> R3: That's something I've never clarified. Do you use their pre-treatment blood pressure or their treated blood pressure and once they're on treatment, is their treated blood pressure all you need to know, or should you also put in they're hypertensive and that? Well, you do put that in. I don't know.

> R11: So what number should you put in? Should you put their pre-treatment cholesterol in? If a fit young bloke goes on a statin aged 20 because he's got familial hypercholesterolaemia, what does that do to his risk? Do you put his pre-treatment in or do you put his treatment in?

Doctor R4 believed that the worst blood pressure and cholesterol reading should be used to work out the risk. Doctor R1 would "do a sort of rough adjustment when that situation arises." It was clear that the doctors were uncertain over the appropriate risk factor readings to use.

Another participant felt that using pre-treatment values was unfair because treatment decreases risk with time even though he recognized that the true risk may be higher due to a history of exposure to higher levels of risk factor.

> R14: I know some people advocate using baseline, you know, pre-treatment values to calculate it. I think that's slightly unfair because I think your risk does fall with… the whole reason we treat is your risk does fall with time if you're established on treatment and I don't think I have the time or energy to say "Well, this person has been on treatment for six years but that person's only been on

treatment for two weeks." So I mean, it's a murky compromise using actual readings but that's what we do.

Doctor R18 felt that this issue regarding pre-treatment levels needed to be resolved urgently and that it was more important than all the other problems around the use of the risk scores.

R18: Obviously the bigger issue for me, is not so much which score, but the fact that you have somebody who is hypertensive who comes to see you, talking about their cardiovascular risk and whether they should be on statin, well, how do you calculate that person's risk? Because of course they're no longer a naïve patient. They've already had modification of their risk, which has been partially attenuated but not completely. So we have to use pre-morbid scores and you have to be very careful if you use the computer which just sucks out current data and doesn't actually realize that it's using attenuated data because of the fact that they've already been on hypertensive treatment.

There was a lot of uncertainty among those using the risk scores with regards to patients who were already on treatment. Some have resolved this by using Framingham for those who were not treated and QRISK for those on treatment. Others simply did not assess risk in those who were already on treatment. Furthermore in those who used it on treated patients, there was further doubt about whether to use current or pre-treatment values.

4.3.3 Manipulation of risk factor levels in communicating risk

A number of the GPs changed the levels of the risk factors to predict the effect of intervention especially during risk communication with their patients. This was easily done with the paper-based charts where the doctor switched values to show the effect of

treatment. It was slightly more difficult with the online/electronic calculators especially with electronic records systems that automatically updated calculators with the latest values but still possible. The doctors used it to change modifiable risk factors such as blood pressure, cholesterol and smoking to illustrate the effect of medication and lifestyle changes on the patient's cardiovascular risk.

> R4: And that's when I can change the numbers on the Framingham thing that's on our computer, to say if we got your blood pressure down to this, we got your cholesterol down to this, then we could reduce your risk down to this much.

> R6: And I find it quite useful, I suppose, in showing people that if they weren't a smoker, how it would put them into a different bracket, if their blood pressure was lower, put them into a different bracket and how if their cholesterol was better, it possibly could reduce their risk.

This method of risk communication was particularly favoured for showing the effect of smoking cessation. One of the participants, R16, demonstrated how effortless and quick it was to do this as it just required the doctor to unclick the box on the online calculator to show a reduction in the cardiovascular risk score. It was even easier with the paper charts as doctors could just move from the smoking chart to the non-smoking charts to show the reduction in risk. Doctor R6 would tell his patient "look there's no red, for instance, there's orange on this one and there's only red on the smoking side." Other than the simplicity, the method was also favoured for smoking cessation because it showed a greater risk reduction than for the other risk factors.

> R18: (demonstrating online calculator) We can say to the patient for example, if you stop smoking, this is what happens, you know, as opposed to I got your blood pressure, say from 150 down to say 140, what could happen. You see that

> doesn't make much difference compared to the fairly dramatic effect of you stopping smoking. So we will do it by talking.

This simple and quick approach is likely to have been used because it is linked to the uses of the cardiovascular risk score by the doctors, in assisting decision making about treatment, informing patients and motivating behavioural modifications such as smoking cessation. Some of the participants discussed the usefulness of the method to show risk reduction to patients. One doctor, R18, mentioned that it made it less "boring for the patient." The word powerful was used by two different doctors who described it as a very effective way of motivating patients to modify behaviour.

> R7: What it gives me is a display, so I could say to a patient, for instance, let's say their cardiovascular risk was 20% but they smoked 20 a day, I could then change that figure and say, look, we stop you smoking and your risk drops to 14%. What a powerful tool to help change people's behaviour.

> R11: …I bet I'm not the only person that uses them in the way that I've described. ..Because it's a really powerful thing.

When asked what encouraged use of the risk score, Doctor R15, describes how he enjoyed using the Joint British Societies (JBS) charts because it was so easy and helpful in allowing data change to show people the risk reduction. So this approach not only helped educate patients, it also motivated doctors to use risk scores more often.

When asked about their views regarding the accuracy of changing risk factor levels to show risk reduction, some of the participants did state that it was not entirely accurate due to the previously high risk factors. One participant, R18, described it as "a little crude." In order to communicate the risk more accurately, some participants tell patients

that it takes time for the risk to fall. Doctor R14 also carefully selected his words to ensure that he was as accurate as possible by discussing the possibility of residual risk.

> R14: That's why I say… I choose my words carefully. In smoking as an example because obviously smoking is a modifiable risk factor, modifying it changes your risk. It has to. But it's not fair to say that if you stop smoking, your risk will fall to what a non-smoker would have. But I do say to smokers, you know, you're a smoker, here's your risk. If you're a non smoker, that's what your risk would be which is perfectly true, and if they then say "ah yes, doctor but I stop smoking now, what will the actual effect be?" And then I say, "well, you know, you've got to be a non-smoker for five years before, you know, your risk starts to approximate to that of a life-long non-smoker. And you have a certain number of years of smoking that are always going to affect you. But nonetheless, the sooner you stop the better.

> R11: What I have been doing is fundamentally, well, it's not dishonest, it is…, I am providing people with inaccurate information. But it happens to fit the information I want them to have, so I give them that information. So what I need to do, all I need to do, is modify, what I say.

A reason for the popularity of this method may be the difficulty that doctors find in estimating the risk reduction that will be achieved after treatment or lifestyle change. It is made more difficult because of the complex interaction of risk factors and combined therapy.

> R19: What I'm not good at and what I should perhaps be better at is taking that to the next step which is to help patients deciding to go on statins. I'm quite good at saying that you've got a 20% risk and so therefore, if you could go on statin, you

could reduce that risk. What I'm not good at is taking that to the next step which is giving the patient more of a quantitative estimate of what their absolute risk reduction would be if they went on to their statin.

However, manipulation of the risk factors is dependent on the type of risk score used. One of the participants noted that:

R15: I used to do that (manipulating the risk factors) with the JBS 2 because it was easy to do it on that. I don't really on the QRISK. I haven't been doing that on the QRISK. But you know, it's a thought but the QRISK is less good for that because the figures are lower. They're smaller figures. So it's a less dramatic demonstration than the JBS, you know.

As the more recent scores such as QRISK would give a lower calculated risk estimate and the older scores a higher risk estimate, the reduction in risk showed by manipulating the risk factor levels would be lower for QRISK than Framingham.

Manipulation of risk factor levels to demonstrate the effect of treatment or lifestyle changes was a popular use of the risk score by the doctors in this study. The sheer simplicity of the method gave doctors a quick and easy way to estimate the effect of treatment on reducing global risk and an effective means to demonstrate this to patients.

4.4 Discussion

4.4.1 Statement of principal findings

4.4.1.1 Treated versus untreated risk

The main finding of this study is that the risk calculated by the cardiovascular risk scores is perceived by doctors to be the patient's risk at that point in time prior to modification by lifestyle or treatment. Doctors were surprised to learn that the treatment of study

populations was ignored in the derivation cohort studies as this contradicted a core belief – that treatment of risk factors would reduce cardiovascular events. The use of risk scores to determine the need for treatment and the way that treatment was disregarded in derivation studies were incongruous. This contradiction in research and practice has been highlighted previously by Milne (80) and Hense. (70)

As Milne pointed out, QRISK assumes that a partially treated risk is the same as an untreated one by ignoring the effect of treatment in the derivation and validation population. This, in effect, creates under-recognition of high-risk patients in clinical practice. The finding that doctors use unmodified risk in communication and decision making supports the belief that for individual risk prediction, the older risk scores should be preferred; the recent risk scores are inaccurate for such use and future risk scores should adjust for the effect of treatment in their study populations.

4.4.1.2 The use of the cardiovascular risk scores in treated patients

Another significant finding of this study was the uncertainty that doctors had regarding the use of the risk scores in treated patients. They were unsure as to whether the risk scores could be used in patients who were already on risk factor treatment. Some believed that the QRISK score was specifically designed for those on treatment and that Framingham should be used in those who were treatment-naïve. There was also doubt about whether to use current or pre-treatment values. (Figure 9)

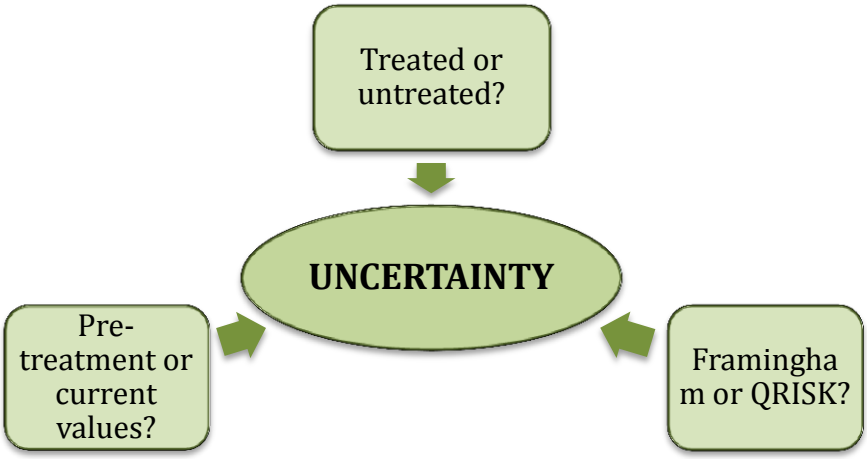


Figure 9: Issues causing uncertainty in the use of cardiovascular risk scores

The uncertainty is probably due to conflicting advice regarding the use of these risk scores in treated patients. In 1998, JBS 1 stated that values for blood pressure and cholesterol before treatment "*should be entered instead of the current value(s) on treatment*". (16) However, later publications of the same guidelines (135,136) specifically excluded those who were already on treatment - "*The chart should not be used to estimate risk after treatment of hyperlipidaemia or blood pressure has been initiated*."

The ambiguity of the guidelines did not improve but persisted with subsequent updates. JBS 2 stated: (18)

> *"Using an 'on-treatment' value for, say, blood pressure will underestimate true CVD risk… Therefore, it is important to try and estimate CVD risk retrospectively, by using the pre-treatment value of a risk factor, whenever this can be found in the person's medical record. If there is no record of the pretreatment value then as a rule of thumb assume for blood pressure that it was at least 160 mm Hg, and for the total cholesterol to HDL cholesterol ratio assume that it was at least 6.*

These values will give a pragmatic but conservative retrospective estimate of CVD risk".

The September 2010 British National Formulary (BNF) had a slightly different version where it stated that the JBS 2 charts could only be a guide for those already receiving therapy unless pre-treatment risk factor values are available. (137) These conflicting statements did not help to answer the questions that general practitioners had about the risk scores but created further confusion.

The use of pre-treatment values proved to be difficult for doctors. The risk estimation in using the pre-treated value would likely cause over-estimation of risk if the patient's risk factor had been controlled over a long period of time whereas the treated value would cause under-estimation if the patient had only recently been started on treatment.

Table 9: Estimated and actual cardiovascular risk in treated and non-treated patients

	Risk factor control	Entered values	Estimated risk
Treatment Naive		Current	Close to actual risk
Treated	Long term	Current	Close to actual risk
	Long term	Pre-treatment	Overestimation of actual risk
	Short term	Current	Underestimation of actual risk
	Short term	Pre-treatment	Close to actual risk
Risk scores with large % of population on treatment			Underestimation of actual risk

The uncertainty over the use of specific risk scores in treated patients came about when QRISK was first published. QRISK1 incorporated antihypertensive use as a risk predictor and Framingham was criticised for not doing the same. (27) In actual fact, the latest Framingham score does incorporate antihypertensive use as a predictor. (11) However, the addition of this risk predictor only partly addresses the problem as only antihypertensive treatment is accounted for. It also does not address the problem of inaccuracy in estimating risk, as treatment started after baseline measurements were taken was not considered.

4.4.1.3 Manipulation of risk factor levels in communicating risk

Another major finding of this study was that doctors changed the levels of the patient's risk factor values to show the effect of treatment. For predicting the effect of treatment on global cardiovascular risk by manipulating the risk factors in the risk score to be accurate, two questions need to be answered:

1. Is the effect of risk factors on cardiovascular outcomes totally reversible?

2. How long does recovery of risk level take?

Studies have attempted to answer the above two questions by comparing the results of observational studies and randomised control studies of treatment on individual risk factors. (91,138-143)

In their meta-analysis of trials, MacMahon and Collins found that for a diastolic blood pressure (DBP) difference of 5-6 mm Hg, the risk of stroke by reduced by 42% (95% CI: 33-50), an effect similar to that predicted by observational studies. (91,138) For coronary heart disease, the same DBP reduction with treatment in the trials only partially reduced the risk predicted by observational study (14% versus 20-25%). In contrast, a more recent and larger meta-analysis by Law et al found that the reduction in risk for coronary

heart disease was similar in both trial and observational studies (22% versus 25%). (142)

For cholesterol, Law et al in 1994 found that the reduction in coronary heart disease by a 0.6 mmol/L decrease in cholesterol was less in trials compared to observational studies. In the trials there was a decrease of 22% at 2.1 to 5 years and 25% after 5 years compared to 27% predicted by the observational studies. (143) A more recent systematic review by Law et al showed that the reduction in coronary heart disease risk in those without previous disease due to LDL cholesterol reduction in clinical trials was similar though still less than that expected from observational cohort studies. (141) However, for stroke, the results from both trials and that predicted by the cohort studies were similar.

Lightwood noted that a small amount of excess long-term risk for cardiovascular disease remained after smoking cessation ($RR_{\infty}=1.17$). (140) This was probably due to chronic disease changes such as atherosclerotic plaques or a side effect of treatment that limited the CHD reduction.

In summary, the more recent evidence appears to show that there is minimal difference in the reduction in cardiovascular risk between short-term trials and long-term observational studies. The full expected decrease in stroke events with reduction in blood pressure and cholesterol is achieved within the short time frame of a clinical trial. For coronary heart disease, the full prediction reduction is almost but not completely achieved with reduction in blood pressure and cholesterol within the duration of the clinical trials.

What is not certain is whether the above evidence can be extrapolated to the calculation of risk reduction with treatment by the manipulation of risk factor levels entered into the

cardiovascular risk score. Tom Marshall commented that the risk scores were devised for the estimation of risk and not for the effectiveness of treatment. (144) Prolonged exposure to previous high levels and the presence of established chronic changes would mean that the expected maximal reduction may take longer than 5 years and may not reach the level of a treatment naïve patient. Gueyffier and Boissel were also doubtful about the use of the risk scores in this manner. Instead, they suggested the application of relative risk reduction estimates obtained from systematic reviews of clinical trials to determine the effect of treatment on cardiovascular risk. (145)

4.4.2 Strengths and weaknesses of the study

Studies looking into cardiovascular risk score use have mainly been large quantitative surveys of physicians. This study used a qualitative approach to examine the use of risk scores by general practitioners. This allowed an in-depth investigation into the effect of treatment in the use of cardiovascular risk scores, a previously unexplored area. The use of a qualitative design in this study allowed enough flexibility to enable us to unearth interesting themes such as the difficulties that doctors had with pre-treated patients and the manipulation of risk factor levels in the risk scores to demonstrate the benefits of treatment. It is unlikely that the same results would have been found if a quantitative approach such as a survey was used.

Despite the purposive sampling, there was difficulty obtaining maximum diversity in the demographic characteristics of the study population. Only 4 (20%) of the participants were women which is significantly different from that of statistics for England where 40% of GPs in 2004 were women. (146) They were also all of Caucasian origin. However, there was diversity in terms of roles, age and practice size. (Appendix C)

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

This is the first study that specifically looked at the issue of treatment in cardiovascular risk assessment. There are two qualitative studies which mentioned that the manipulation of modifiable risk factors was useful for showing how risk can be lowered. One was a mixed methods study looking at the impact of JBS on clinical practice in the United Kingdom (147) and the other was a focus group study looking at the views of 36 GPs in Australia on cardiovascular risk tools. (148) The study by Torley et al did have a quote by a participant GP who noted that risk factor manipulation of the risk scores was a “powerful tool” to show how risk changed with risk factor reduction. (148)

Studies in this area have mainly concentrated on determining the percentage of doctors who use the risk scores and have therefore been mostly large surveys of doctors. (63-66) There have been a few qualitative studies on cardiovascular risk score use but these concentrated on looking at barriers to the use. A common barrier was the difficulty for both doctors and patients to understand the concept of risk and in interpreting the numerical information such as relative and absolute risk. (147-149) GPs in a mixed methods study with survey and focus groups in Berlin challenged the accuracy of risk scores developed in population studies in predicting individual risk and this was a barrier to use. (150) This did imply that doctors felt that it was very important for risk scores to be accurate for individual risk prediction.

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

The findings of this study indicate that the older risk scores such as Framingham (6, 7) are more appropriate for clinical practice because doctors are using them to inform patients about their risk if left untreated (or on the same treatment from that point

onwards). Doctors say they want to know the untreated risk to guide treatment decisions and to educate and assist patients about risk.

The findings also suggest that GPs will continue to manipulate risk factor levels to show the effect of treatment because the estimation of risk reduction after treatment is complex and not intuitive and this approach offers a simple and fast way to demonstrate risk reduction to patients. The GP should accompany risk communication with the added caution that the true risk is likely to be higher, will only fall to the predicted risk after prolonged treatment to maintain risk factor reduction, and may never reach the predicted risk level of those with similar levels but who are treatment naïve because of irreversible chronic disease changes.

The doctors in the study had many unanswered questions regarding the use of cardiovascular risk scores. Yet, doctors continue to use the cardiovascular risk scores in clinical practice despite uncertainty. In fact, some of the doctors were indifferent to the need to better understand the cardiovascular risk scores. They were content to use the risk scores in clinical practice in the manner advocated by the guidelines that they had read.

Guideline changes seem to have made a complex subject even more confusing for doctors especially with regards to treated patients and risk factor levels to enter into the risk calculation. The ambiguity and conflicting advice from past and present guidelines simply creates confusion and, this research suggests, should be replaced by clear succinct statements. The simplification of guidelines was also recommended by Hobbs (63) and Graham (64).

4.4.5 Unanswered questions and future research

The findings of this study and the review indicate that there is considerable gap between research and practice. The simplification of guidelines using clear and concise directions with input from both researchers and users of the risk scores seems to be the likely answer to this problem. However, research is needed to confirm this theory.

Researchers should also consider incorporating a more accurate way of showing risk reduction after treatment into new risk scores by using the data from randomised controlled trials of treatments that reduce risk factor levels. This method was used by QIntervention (website for QRISK scores) to demonstrate the risk reduction with statins but not for other risk factors.

4.5 Conclusion

There remains a gap between research and clinical use of the risk scores. This has resulted in incorrect usage of the risk scores and uncertainty. There needs to be a revision of practice guidelines to ensure that the development and application of risk scores are in concordance.

Chapter 5. Mathematical models

5.1 Should identical 10-year CVD risks in young and old patients be managed identically?

A common criticism of using short-term (e.g. five or ten-year) CVD risk calculators is that they strongly favour treating older individuals who generally have high short-term risk but lower life expectancy. (52, 53, 151) Intuitively, a young person at the same short-term CVD risk as an old person would appear to lose more in terms of life years simply because of their longer life expectancy. The dilemma is brought into sharpest focus when we consider folk at the same short-term risk but of different ages. Given a predicted cardiovascular disease (CVD) risk, of say 20% in ten years, who stands to gain more from treatment: the young or the old patient?

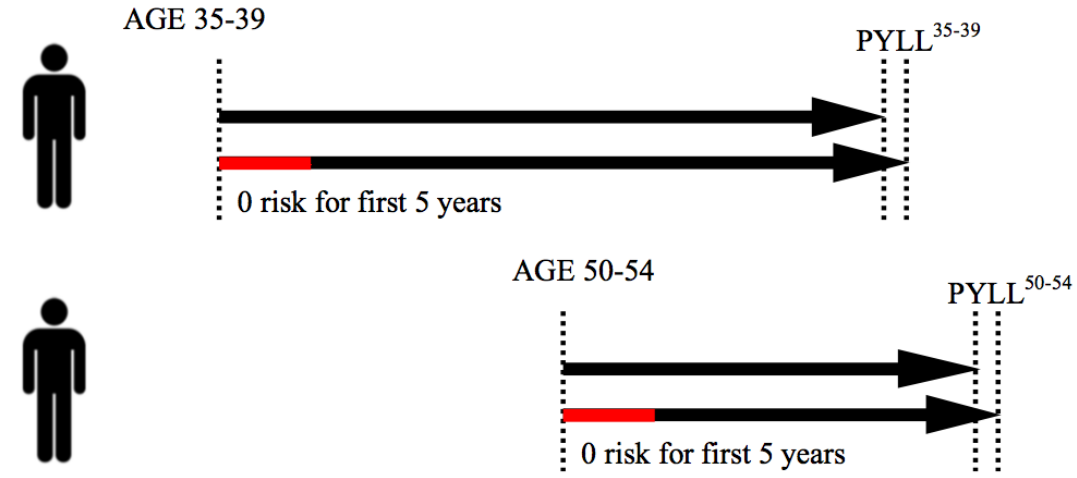
This apparent limitation of short-term CVD risk prediction may explain the increasing interest in models that attempt to redress the perceived imbalance towards age such as lifetime CVD risk prediction models. (2, 151) These models are promoted as being better at identifying individuals who do not reach the recommended treatment threshold using standard five or ten-year risk calculators (152) but have an increased relative risk of CVD compared to their peers: mainly young males with multiple but modestly increased risk factors. (151) It has been proposed that these individuals, who are at low ten-year risk but high lifetime risk, should be started on treatment.

Experts, however, have questioned the use of such approaches in clinical practice. (14, 110, 144) It is true that the elderly have a shorter life expectancy than the young but they also have higher case fatality rates after a cardiovascular event. The case fatality rates from other competing risks i.e. non-cardiovascular diseases are also higher with age.

My study answers the fundamental question: does a true difference in life years lost exist between different ages at the same short-term cardiovascular risk? If there is no difference, then attempts to correct the perceived imbalance are unnecessary and have unintended harmful consequences. In this chapter, mathematical models were used to quantify the size and direction of any differences in losses of young and old patients at identical short-term risks of cardiovascular disease. These models incorporate the factors of age-specific case fatality rates and competing risks.

5.2 Methods

In order to answer the question of whether the young and old should be treated differently, a comparison of potential life years lost for a five-year treatment delay versus no delay is obtained at different ages at the same short-term coronary heart disease (CHD) risk. This simulates a scenario where two patients - one young and the other old, presents at the exact same absolute short-term CHD risk; does one patient suffer greater potential life year loss from a five-year treatment delay than the other?



PYLL – Potential years of life lost at a 5-year coronary heart disease risk level

Arrows indicate life expectancies in those treated immediately for 5 years and those not treated. Red bar indicates treatment period.

Figure 10: Method used to estimate Potential Years of Life Lost for a five-year treatment delay

Figure 10 illustrates the method. First, the life expectancy of a person in the age group 35-39 at a specified short-term CHD risk e.g. 10% who remains untreated is calculated. Next, the life expectancy of a person of identical age and risk is estimated but with the CHD risk for the first 5 years reduced to zero (the hypothetical treatment is assumed to be 100% effective). The difference in life expectancy from the results of both arms gives the potential years of life lost (PYLL) due to a treatment delay of five years for that age and short-term CHD risk.

The figure shows how the same process is used to determine the PYLL due to a treatment delay for a person in the age group 50-54 at the same short-term CHD risk. The $PYLL^{35-39}$ can then be compared with the $PYLL^{50-54}$ to compare the life years lost with treatment delay at different ages but at the same absolute risk level.

The process is repeated for different age groups from age 35 to 85. This allows the graphical comparison and detection of trends of losses due to treatment delay at different ages but at the same specified short-term risk level.

Treatment is assumed to be 100% effective. While this will exaggerate the absolute effect of treatment, it provides a valid relative comparison of the PYLL for a treatment delay of five years at different ages and at different risk levels. The difference of 100% effectiveness applies to ALL strategies, so it "overestimates" equally for all; it would give the same relative results if a 30% or 50% reduction was used.

Two different modelling approaches (age-based residual life expectancy models and Markov simulation cohort models) are used to determine the potential years of life lost by not initiating treatment earlier in patients with the same 5-year coronary heart disease (CHD) risk but at different ages. 5-year risk levels of 5% and 10% were selected as they are approximately equivalent to 10-year risks of 10% and 20% - the key thresholds in UK and European guidelines. (30,36)

5.2.1 Age-based residual life expectancy model

In this model, the hypothetical treated cohort has a zero risk of CHD death during the 5-year treatment period, returns to the average risk of the general population at 5 years, and then uses the average further life expectancy (beyond the 5 years) for the population to calculate the PYLL.

The potential years of life lost due to being exposed to a set short-term CHD risk level at different ages was then calculated using the following formula:

Potential life years lost at age A = CHD risk X CFR_A X LE

where CHD is coronary heart disease, CFR_A is the age-specific case fatality rate and LE_r is the life expectancy. Estimated life expectancy by age and sex was obtained from interim life tables for the years 2005-2007 from the Office of National Statistics, United Kingdom. (153) Case fatality rates by age and sex for 1994-1998 were obtained from a 2001 report to the UK Department of Health on data from the Oxford record linkage study. (154) (Appendix E)

5.2.2 Markov simulation cohort model

As with the first (i.e. age-based residual life expectancy model, the hypothetical treated cohort in the Markov model has a zero CHD mortality risk during the 5-year treatment period. However in contrast to the first model, the Markov model subsequently differentiates between the ongoing competing risks of death, CHD and non-CHD, of both the treated and untreated hypothetical cohorts.

The Markov model calculates the life expectancy of simulated cohorts with 100 hypothetical people for 5-year age groups starting from 35 (i.e. 35-39, 40-44 etc). The cohorts were modelled with a base CHD risk of 5% in 5 years and the process was repeated using a base CHD risk of 10% in 5 years. (Appendix F) All the cohort members start in the 'well state.' The length of each cycle is set at 5 years. In every cycle, the numbers who die due to CHD (starting with the base CHD risk specified and age-specific MI case fatality rates (154)) and those due to non-CHD using non-CHD case fatality rates are estimated. (155, 156) Non-CHD rates were derived from the Office of National Statistics on UK death registrations by age, sex and underlying cause and population estimates for 2007. (155, 156) The relative risk of CHD per year of increasing age was used (RR =1.05 for men and RR=1.04 for women) as given by the Framingham study (56) to calculate the increase in coronary heart disease risk in each cycle. The process

is repeated, moving more and more members into the ‘dead state’, until the cycle sum falls below 1 person-cycle where every member is dead. (157) The life expectancy of the cohort is obtained by adding up the number of person life-years in the ‘well’ column. For the same age band, the process is repeated using the same rates except that for the first cycle, the CHD risk is reduced to 0. The potential life years lost for one person is then calculated by the following formula:

PYLL at age A = ($LE^{\text{COHORT WITH BASE RISK}} - LE^{\text{COHORT INITIAL RISK 0}}$)/100 X 5

where LE is the life expectancy of the cohort which is divided by 100 (the number of people in the cohort) and multiplied by 5 (the length of a cycle) to obtain the potential years of life lost for one individual in the age group.

This, in effect, allows the results of the simulation to be comparable to the first method.

5.3 Results

Figure 11 shows the results obtained from both models. The dotted lines represent the age-based residual life expectancy models and the solid lines represent the Markov models. The square symbols indicate the results for five-year risks of 10% and the triangles for five-year risks of 5%.

The results show that for a treatment delay of five-years, the PYLL over a lifetime for a 35-39 year old person at 10% five-year CHD risk is slightly greater than 1 year in the age-based residual life expectancy (age-based residual LE) model and 0.75 year in the Markov model. The results for different ages for both the 5% and 10% five-year CHD risk levels can be read from the graph.

The PYLL is higher for all models at 10% risk compared to that for 5% risk. The gap between the graphs for the age-based residual life expectancy models narrows at the

higher age groups because of the difference in short-term risk level which changes the gradient of the slope. However, the gradient of the graph for both the 10% and the 5% risk is almost flattened by the Markov models which incorporate the increase in case fatality rates from both CHD and non-CHD causes with increasing age.

For the age-based residual life expectancy models, the PYLL is greater in the younger age groups compared to the older age groups as can be seen by the downward slope of the dotted line graphs. This indicates that the younger age groups had more losses caused by treatment delay compared to the older age groups at the same absolute risk. Although this looks to be quite steep, the actual difference is only a maximum of about 0.70 year (8.5 months) in the 10% risk model. The Markov model reduces the maximal difference further to about 0.20 year (2.5 months).

To put this in perspective, figure 12 juxtaposes the graph for estimated life expectancy with the PYLL estimates from the models. Despite the substantial difference in life expectancy between ages as shown by the steep gradient of the graph, there is very little difference in the PYLL between age groups.

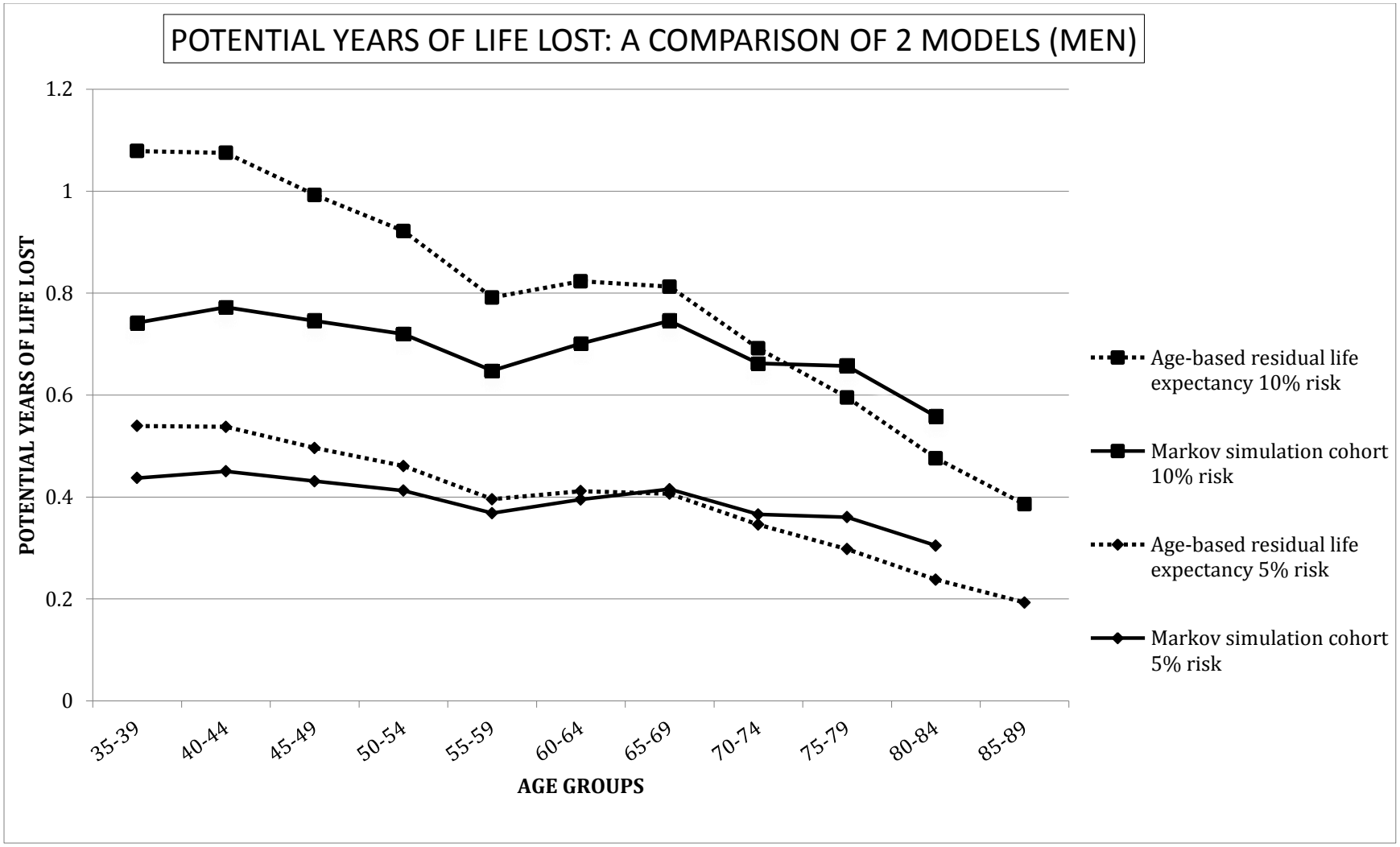


Figure 11: Potential Years of Life Lost by delayed treatment for men at different ages but same five-year risk – 5% and 10%

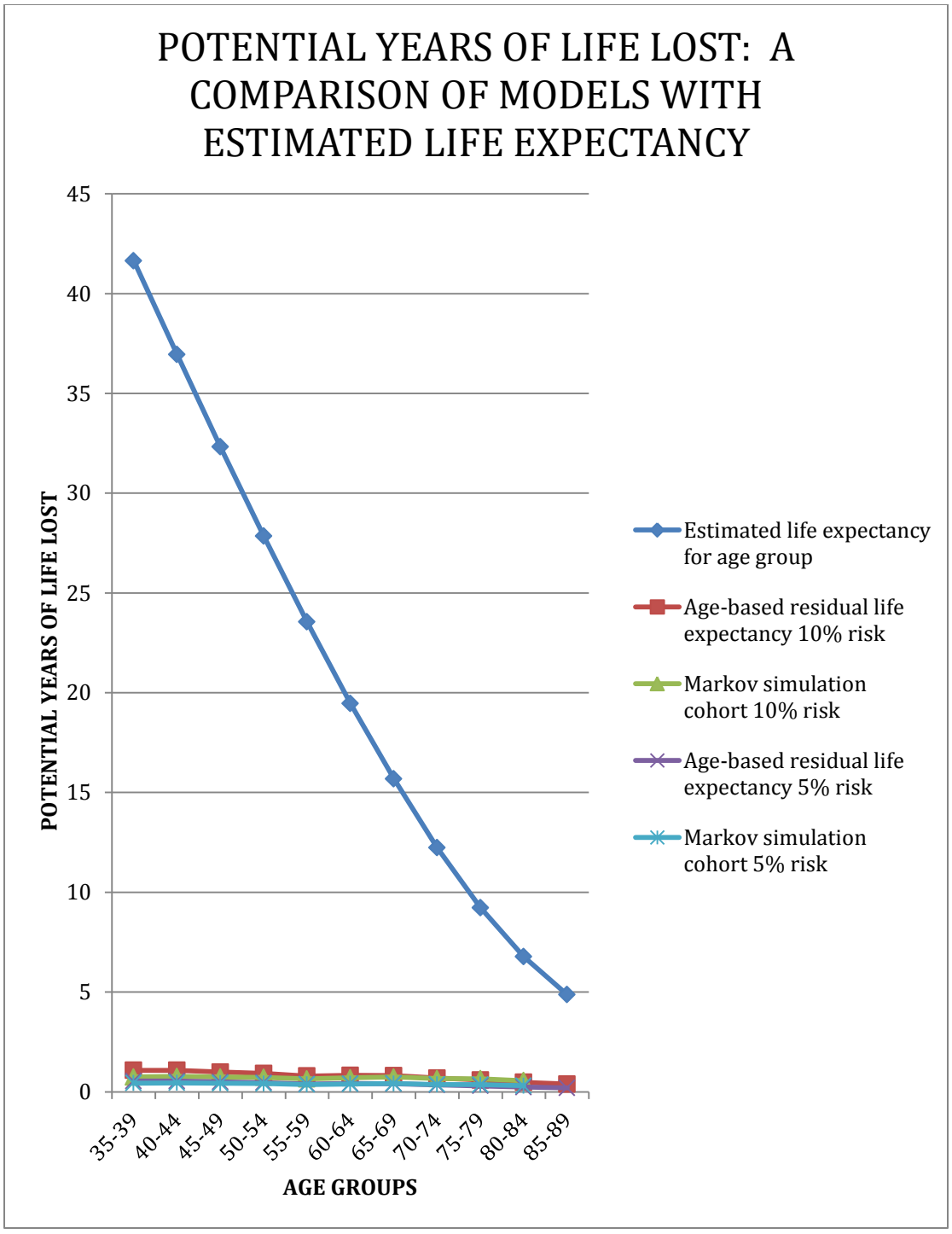


Figure 12: A comparison of estimated life expectancy and potential years of life lost by delayed treatment at different ages but same five-year risk – 5% and 10%

5.4 Discussion

5.4.1 Statement of principal findings

Clinicians are increasingly being advised to use short-term CVD risk prediction tools to help determine the effects of multiple risk factors on their patients' risks of developing CVD and to help weigh the benefits and costs of starting treatment in individual patients. Intuitively, short-term risk prediction does not appear to consider that younger people with a longer life expectancy would lose more years of life following a CVD event than older people with a shorter life expectancy but the same short-term CVD risk. However further analysis suggests that the additional benefit to life expectancy by preventive therapy in younger compared to older patients is smaller than that predicted as seen by Figure 12. The modest difference in PYLL between the very young and the very old can be explained by a number of factors.

Firstly, younger patients have lower case fatality rates. That is, in younger individuals facing the same short-term risk of a CHD event, fewer will die from the event and only those few who do die will lose more life years than older individuals.

Secondly, older individuals also face higher combined competing risks, both CHD and non-CHD deaths as accounted for by the Markov simulation cohort method.
The inclusions of both these factors flatten the slope of the graph and diminish the difference in potential years of life lost between the old and the young. There remains a small downward trend, indicating that the young are still likely to lose more life years than the old for a treatment delay of five years at the same short-term cardiovascular risk level. However, the maximum difference is only about 2.5 months for a five-year 10% coronary heart disease risk.

5.4.2 Strengths and weaknesses of the study

A potential limitation of this study is that both methods only took into account life years lost through death and not quality of life lost from non-fatal events. However the severity of non-fatal events is also likely to increase with age, so it is unlikely that including non-fatal events in the models would change the direction of the findings. Moreover there is no robust evidence on the impact of CHD events on the quality of life at different ages and therefore it is unlikely that the added number of assumptions required and increased complexity of analyses would generate more meaningful conclusions.

The complexity of the models could have been increased with the use of multiple states. For example, 'post CHD' could have been another state other than the ones used which were 'Well', 'CHD death', and 'non-CHD death'. Those who survive an event would have a higher than normal risk of CHD and death. Other states were also options; for example, the model could have incorporated states of post double or triple CHD events, different types of events such as heart failure and so on. However, all models are approximations and the models used here allow a satisfactory differentiation between the young and old with minimal bias. The addition of other states would necessitate greater assumptions, which would increase complexity but not accuracy as bias is also increased.

Indeed, as more of the young would have survived events, there would be greater numbers of them in the post CHD event state. This means that the absolute gain for the young would have been smaller than that estimated; the results likely overestimated the life expectancy for the young more than that for the old.

Also, the models did not take account of case fatality rates from cerebrovascular disease i.e. strokes (only CHD case fatality was used) as there were no published case fatality rates for total cardiovascular disease for the UK population data used by these models.

However, a study in New Zealand (158) and another from Sweden (159) showed that the five-year case fatality by age is similar for definite MI, other CHD and stroke. (Figure 13) Hence the addition of cerebrovascular disease is unlikely to cause a significant change in the results.

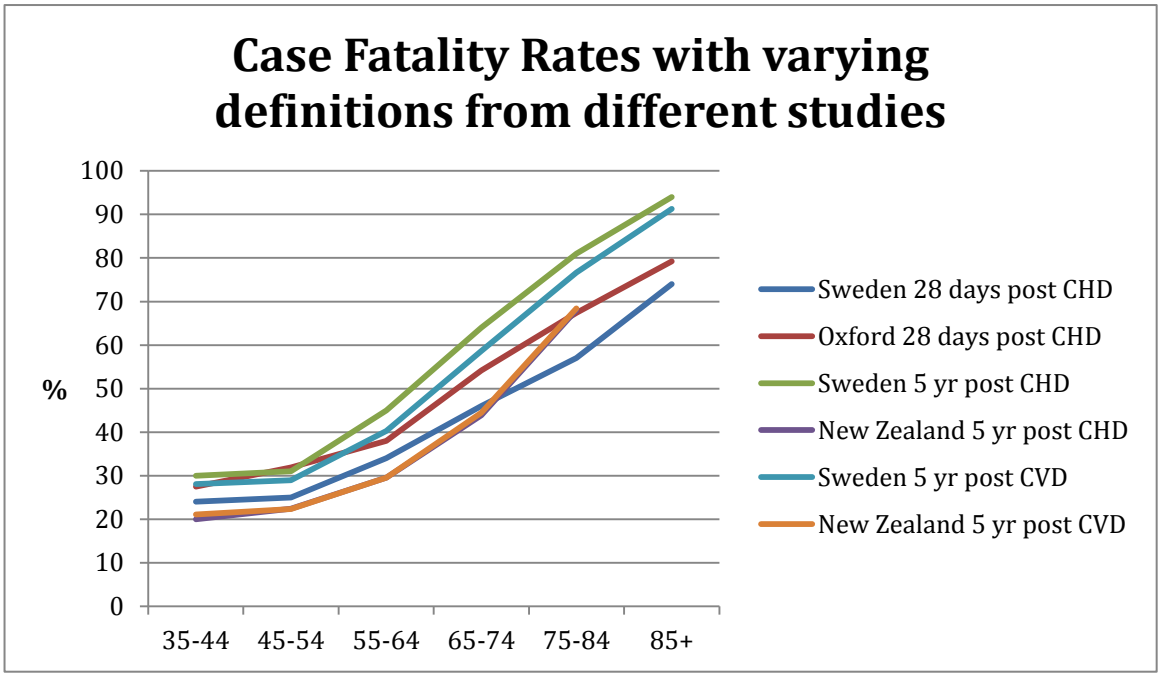


Figure 13: Case fatality rates at different ages for coronary heart disease alone compared with case fatality rates for total cardiovascular disease (154, 158, 159)

When data of total cardiovascular CVD five-year case fatality rates from the New Zealand study (158) are used in the models, there is little difference in the graphs for coronary heart disease (UK data) and cardiovascular disease (NZ data). Therefore, the overall conclusion remains the same. It is interesting that the addition of stroke to the data shifts the trend of the graph for PYLL upwards with increasing age. (Figure 14)

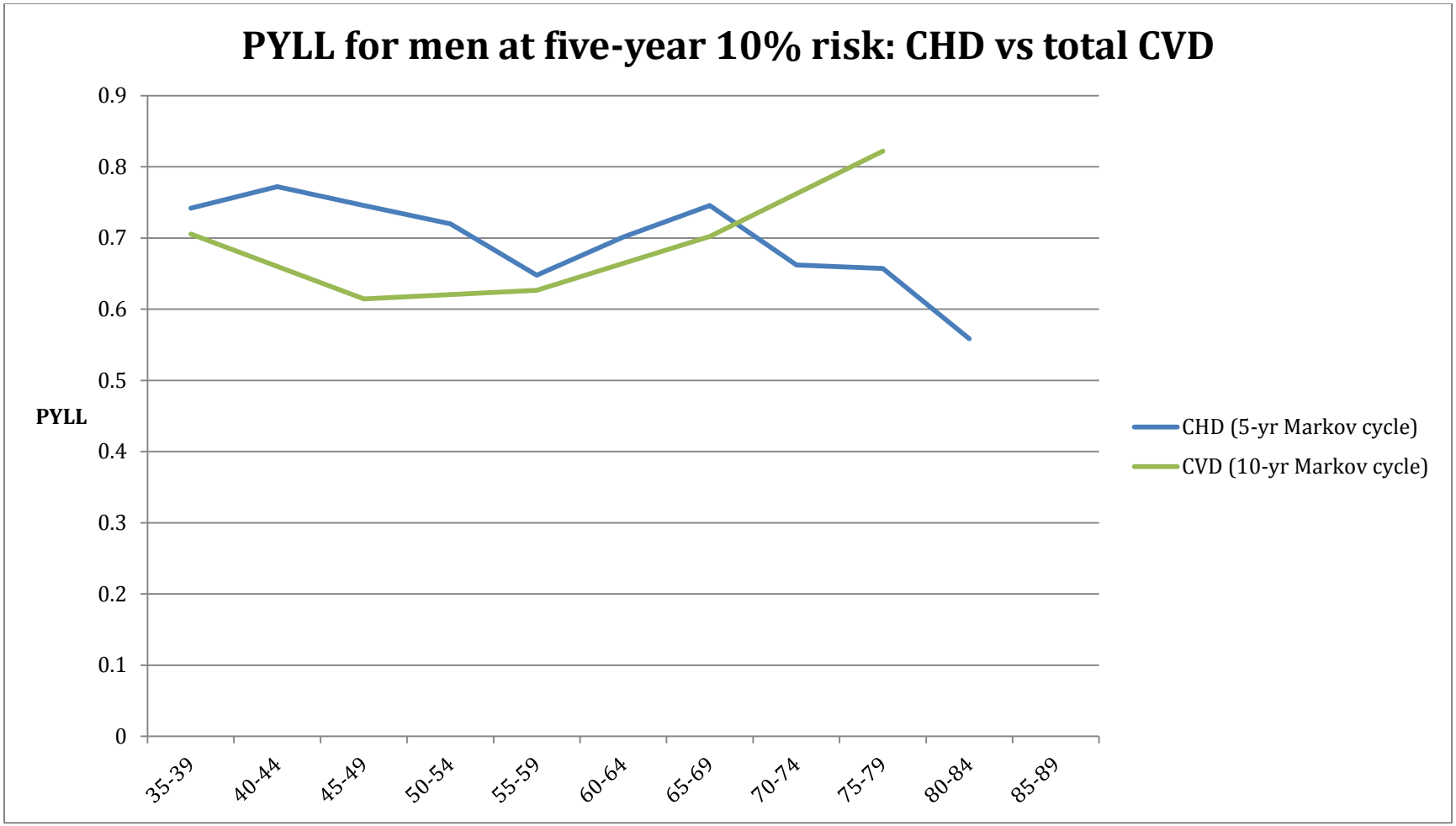


Figure 14: Potential Years of Life Lost for men at five-year 10% coronary heart disease risk versus five-year 10% total cardiovascular disease risk using the Markov model

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

5.4.3.1 Model used by Ulrich et al

In a BMJ paper in 2000, Ulrich et al suggested the use of mathematical models to calculate the so-called ‘optimum age' of starting treatment for younger individuals who are below the absolute risk threshold. (81) Their model showed the number of event free life years obtained per year of treatment at different ages, individualised to the patient’s risk profile. This allowed the prediction of an ‘optimum age’ for which the ratio is greatest.

The Ulrich model took into account competing risks in the form of age-specific death rates for deaths not due to coronary heart disease. However, there were 3 major flaws in their model – the exclusion of age-specific case fatality rates as discussed in the earlier sections of this chapter, the use of event free life years and life years gained per year of treatment as the main outcomes.

5.4.3.1.1 Event free life years

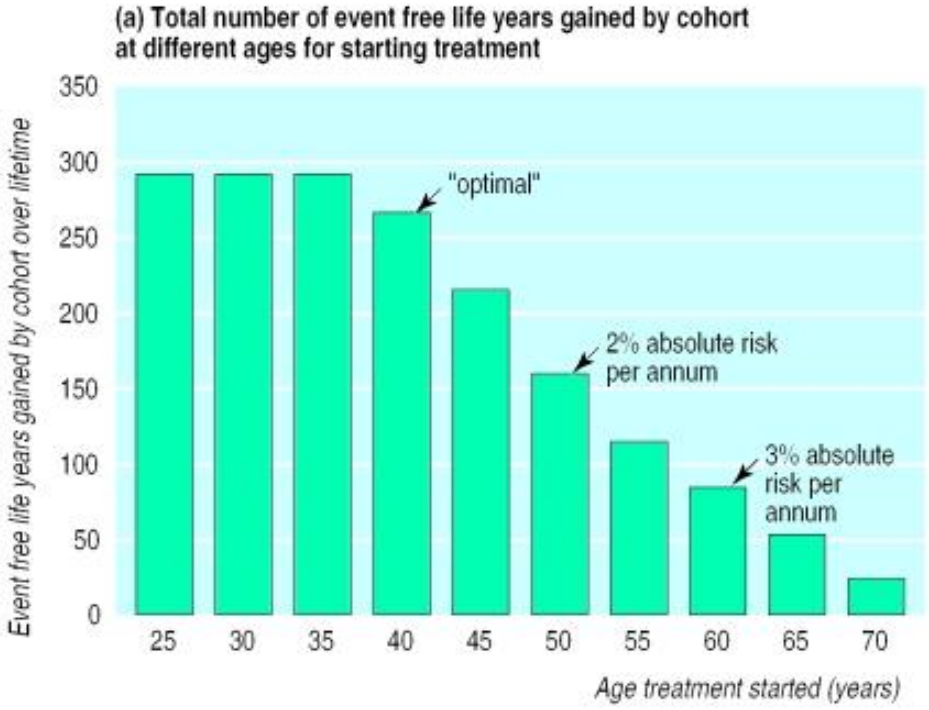


Figure 15: Event free life years as an outcome in model by Ulrich et al (81)

The use of event free life years as the main outcome indicates that the value of life after a coronary heart disease event is considered as equivalent to being dead. In a study of 978 Australians with diabetes, measurements of quality of life in those who have had a myocardial infarction were close to that of those who have not. (160) (Figure 16)

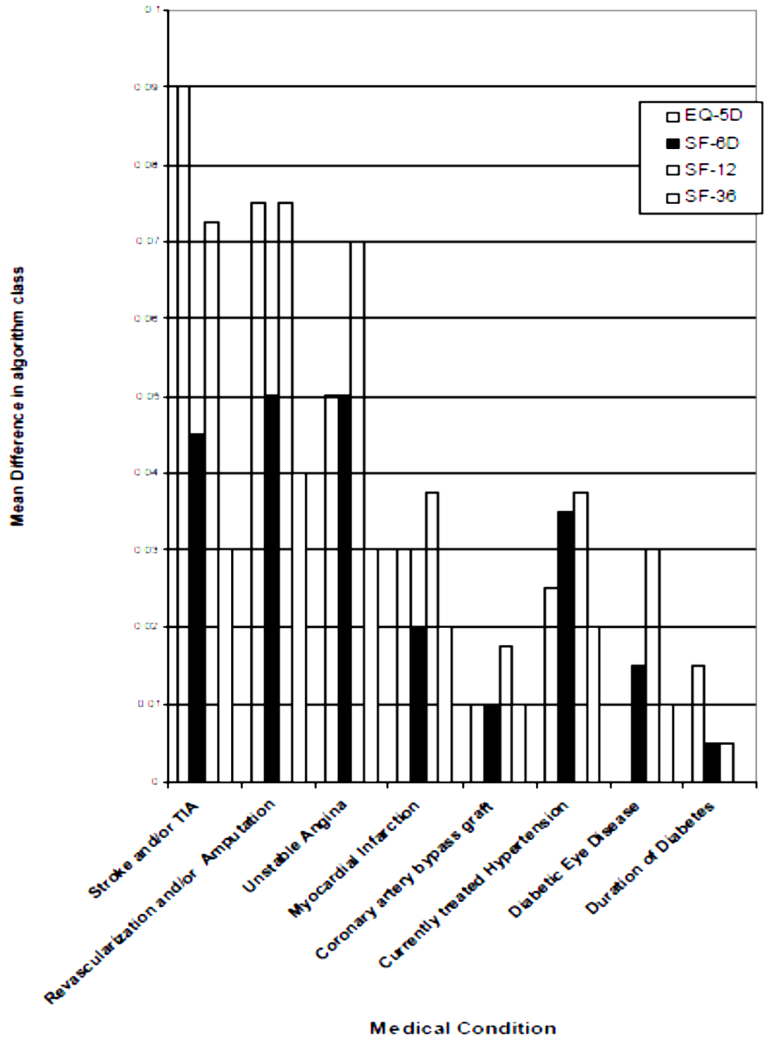


Figure 16: Mean difference in quality of life scores between those with and without the medical condition (160)

In those with a coronary heart bypass graft, quality of life was equivalent to those without a similar history. (160) The differential score for quality of life was greatest for stroke or transient ischaemic attacks as can be expected. However, Ulrich's model only included coronary heart disease and not total cardiovascular disease.

Figure 17 also illustrates that quality of life in those who have had a myocardial infarction is close to that for those who have not had a myocardial infarction.

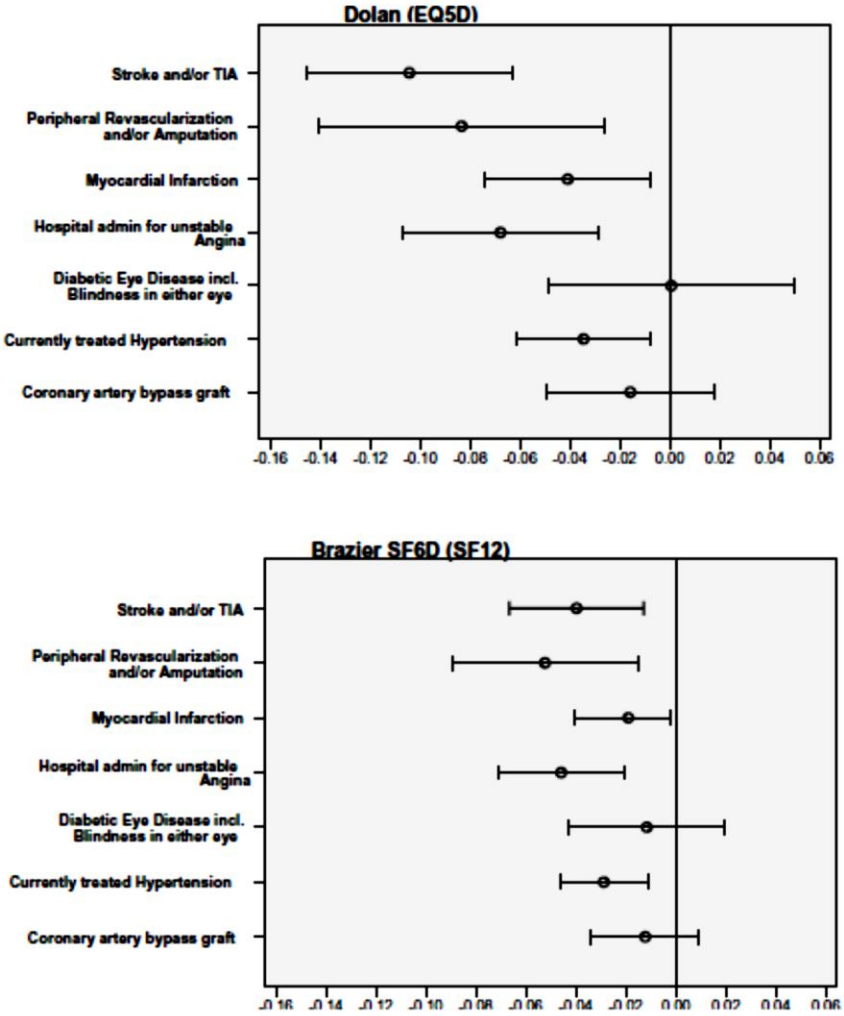


Figure 17: Mean differences and 95% CI in quality of life score between those with and those without the medical condition (160)

5.4.3.1.2 Life years gained per year of treatment

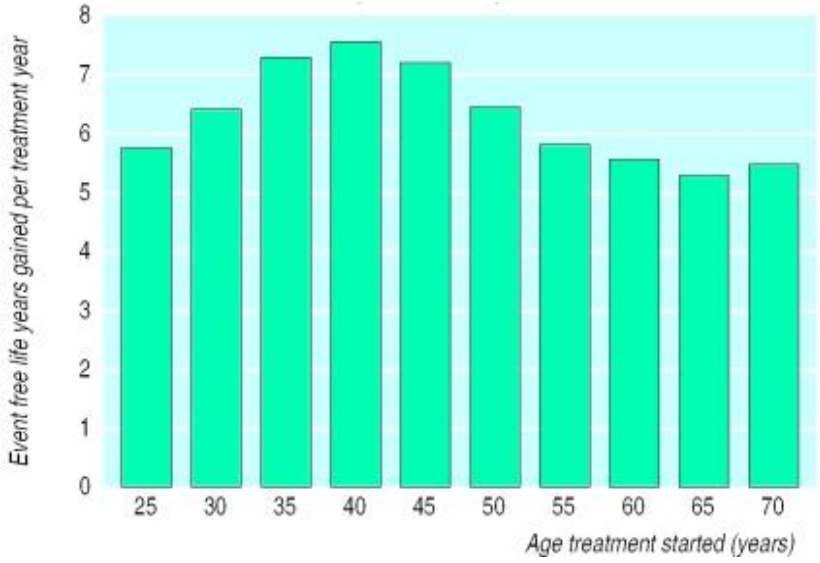


Figure 18: Life years gained per year of treatment in model by Ulrich et al (81)

The Ulrich model also used life years gained per year of treatment as an outcome. In a letter responding to the paper by Ulrich, Marshall (144) showed that when case fatality rates were taken into account, there was little difference in the life years gained per year of treatment. The life years gained per year of treatment (last column of Table 10 and obtained by dividing the life years gained by treatment with the life expectancy for that age) actually increased in the older age groups because of their higher case fatality rates.

Table 10: Correction of life years gained per year of treatment by Marshall (144)

Age	Event free life years expected	Life expectancy (years)	Case fatality rate* (%)	Life years lost after cardiovascular event	Life years gained by treatment†	Life years gained per year of treatment
20	38.4	55.5	23	12.8	3.8	0.06
30	28.7	45.9	23	10.6	3.2	0.06
40	19.5	36.5	23	8.4	2.5	0.06
50	11.6	27.1	29	7.9	2.4	0.08
60	5.5	18.7	46	8.6	2.6	0.12
70	1.8	11.7	56	6.6	2.0	0.14
80	0.3	6.7	56	3.8	1.1	0.14

*Mortality after myocardial infarction is used as a proxy for mortality after a cardiovascular event.
†Relative risk reduction adjusted to 30% at all ages.

Exclusion of age-specific case fatality rates is not the only flaw in this model. Life years gained per year of treatment is a form of cost-effectiveness ratio. However, it is the wrong ratio to use as it is an average ratio and not an incremental ratio. (161) In the models used by Ulrich and Marshall, it compares the life years gained when treatment is started at an 'optimum' age as opposed to no treatment at all. Instead an incremental ratio should be used where this method is compared to a model where treatment is started at an age prescribed by the current screening method.

Rather, the correct formula should be:

$$\text{LY gained per yr of treatment} = \frac{\textbf{LY gained using optimum age} - \textbf{LY gained using conventional start age}}{\textbf{life expectancy}}$$

This value should then be divided by the number of extra years of treatment needed to obtain the correct ratio i.e. extra life years gained per extra year of treatment. The incremental ratio would give a much smaller benefit than that obtained by either Ulrich or Marshall.

5.4.3.2 Model used by Montgomery et al

Montgomery et al used simulation models to estimate the effectiveness and cost-effectiveness of blood pressure-lowering treatment over a lifetime. (162) One of their objectives was to compare the increase in life expectancy from treatment at different ages. This appears to be similar to my objective – they measured gains from treatment while I studied losses from treatment delay. However, their model evaluated lifetime treatment versus lifetime non-treatment. My models sought to answer the impact of only a five-year delay. This is a crucial difference. The young person who presents at one point in time with a cardiovascular risk score that is higher than average for his age group will be monitored and assessed again at a future point in time. This will mean that he is likely to receive treatment as he ages. To compare treatment and no treatment for a lifetime is not a fair comparison.

The 'low' and 'high' risk profiles used in the Montgomery model is also based on age-specific mean values for systolic blood pressure and centile values for other risk factors. As the values used are age-specific, it is likely that the absolute risk category for the young and old are different i.e. the low risk elderly is likely to have overlapping absolute risk with the high risk young in the model. The differentiation of absolute risk by this method would be smaller in the older age groups and bigger in the younger age groups resulting in a reduction of gains in life expectancy with treatment as age increases. This would account for the greater gains in life expectancy seen in the young compared to the old in their paper. (162) (Figure 19)

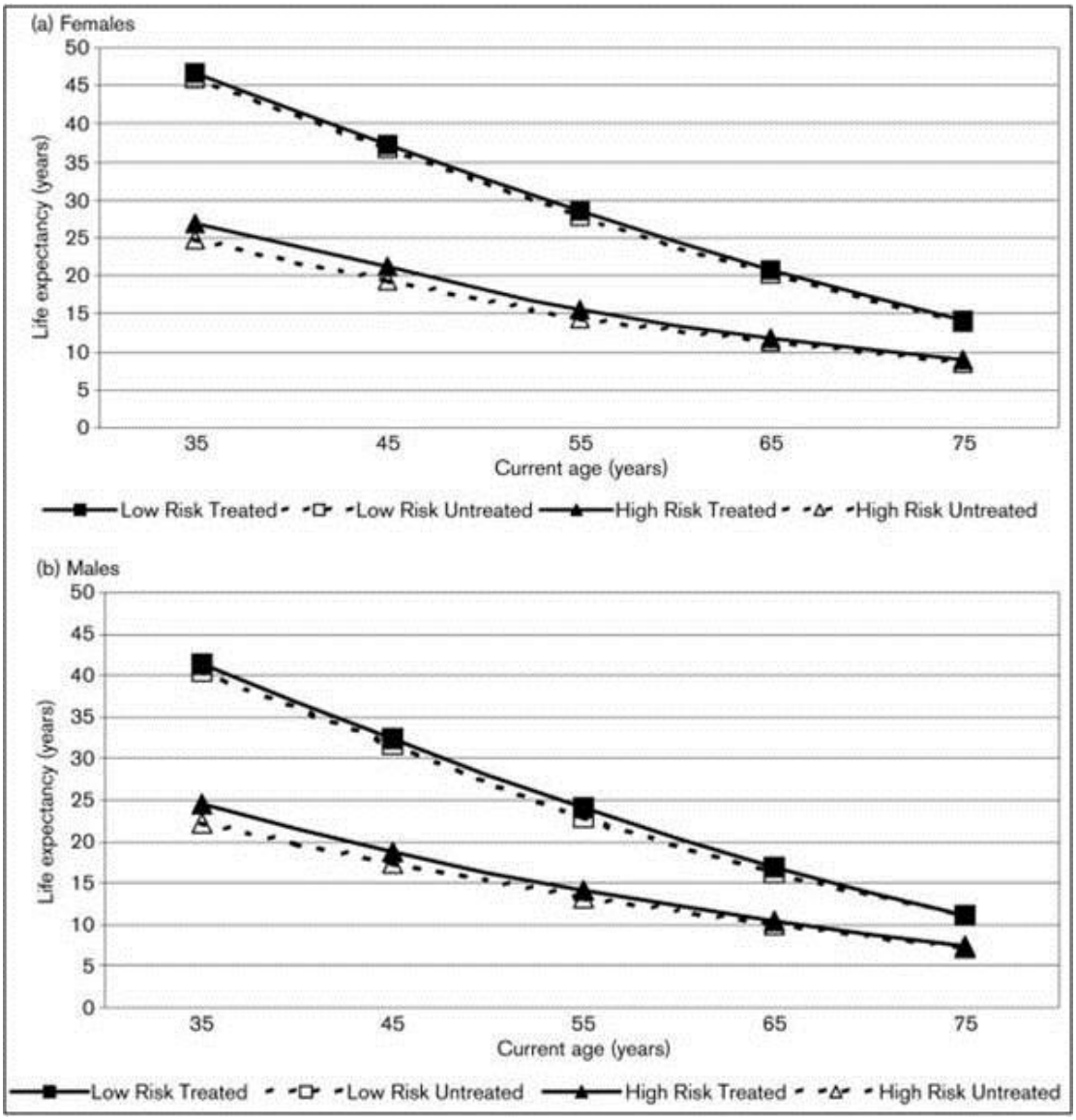


Figure 19: Results from Montgomery et al (162) showing increase in life expectancy with lifetime blood pressure treatment versus lifetime no treatment

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

The high case fatality rates for both CHD and non-CHD diseases in the elderly reduce but do not negate the greater loss of potential life years in the young. The maximum difference between the old and the young is 8.5 months when only age-specific case fatality rates are considered and 2.5 months when the impact of competing causes of death are also included.

5.5 Conclusion

The higher case fatality rates for competing risks in the elderly reduce but do not completely remove the difference in life expectancy between age groups at the same short-term risk with the young experiencing a slightly greater loss of potential life years with a five-year treatment delay.

Chapter 6. Models with time preference

6.1 Predicting the future

In Chapter 5, the results showed that the although case fatality rates and competing risks reduced the difference in loss of potential life years between the old and young, those who were younger would still have to withstand greater losses with treatment delays.

One crucial factor has been ignored despite these refinements to the models. **All years are not created equal.** The models in Chapter 5 still do not take into consideration that a gain of year 1 to year 2 is not the same as the gain from year 21 to year 22. Despite the fact that the gain in both is essentially the same i.e. 1 year, the addition of a year to the first instance is not equal to the addition of a year to the second instance. This is not simply due to the doubling of time – other factors such as uncertainty, individual preference etc also account for differences in the two examples. Time preference is the concept that is employed to account for these differences with time. When considering future events, the impact of time must be taken into account.

Risk scores are used to predict the likelihood of an individual developing a disease event in a period of time, which can range from the immediate future (diagnostic scores) to an entire lifetime (lifetime risk scores). When the scores are used for diagnosis of the immediate future such as for the prediction of an ankle fracture, then the impact of time is lessened. However, the cardiovascular risk scores are used to predict events that occur in a substantial period of time, ranging from years to a lifetime.

I have incorporated the effect of time into the model with the use of time preference.

6.2 Theories underlying the use of time preference

Time preference is a concept that values the near-future over the distant future. Individuals give greater worth to an object such as money or life years in the present than in the future. (163)

Goodin outlined four reasons for this. The first two points, pure time preference and uncertainty of the future, are of greater relevance to healthcare. Economists also talk about the other 2 underlying theories i.e. diminishing value and opportunity costs. These may have correlates in terms of health, for example quality of life. However, it is not necessary to accept the relevance of these 2 points – they are not the main focus for the models as the first two are overriding reasons.

6.2.1 Pure time preference

This is where a benefit is devalued simply because it is distant in time. Individuals prefer to have immediate or near-future gratification to waiting. This would mean that they would consider a smaller amount in the present to be equal to that of a larger amount in the future. (164)

The concept of individual time preference is accepted even by those who fundamentally disagree with the use of the approach in creating public policies. (163) Time preference has been considered unethical and even a human psychological frailty by earlier thinkers. (163) Komlos et al called it a reflection of individual impatience. (165) However, current thought emphasises the importance of individual preferences in decisions affecting society. (164) This has been strengthened by current beliefs of patient autonomy in medical decision-making. Time preference has been applied to the field of health care especially in the evaluation of preventive programs.

Individual propensity for time preference has been found to dictate behaviour e.g. research has shown that a higher time preference (with greater devaluing of health benefits with temporal distance) is related to poor preventative health behaviour such as alcohol intake, obesity and smoking. (165) Chapman et al conducted a study to determine if time preference affected adherence to medication and found weak or no relationship between scenario measures of time preference and preventive heath behaviours. (166) The paper describes three separate studies in different settings that examined individual time preference rates with health behaviour. Results found that there was some correlation between time preference rates determined by scenarios and health behaviours, namely adherence as determined by pill counting and flu vaccination, but the authors felt that these correlations were small. This implied that responses to hypothetical scenarios were not good indicators of real world behaviours. However, another study by Bradford (167) noted that time preference did have an effect on the use of mammography, Pap smears, prostate examinations, dental visits, cholesterol testing, access of flu shots, exercise, cigarette abstinence and an aggregate measure of all health behaviours. This study was conducted on of 987 participants aged 50 years and above who were asked a set of questions on time preference. This was used to estimate their individual time preference rate, which was then correlated to health behaviours measured in another section of the survey. Results showed that those with high time preference rates had significantly lower rates of health behaviours. (167) If individual time preference is ignored, actions to implement prevention would not be effective.

Time preference also has implications for freedom of choice in health decision-making. Young individuals that are put on medication face immediate side effects with distant health benefits. Individual time preference would suggest that for decision-making

regarding treatment initiation, the person would need to devalue the life years in the future in order to properly weigh the harms and benefits of the decision.

6.2.2 Uncertainty about the future

Another reason for devaluing the future is uncertainty, which increase with temporal distance. Potential risk is increased with delay. For instance, one might have an accident causing premature death. Other uncertainties can also affect the future such as significant improvements in treatment. This would make preventive efforts less worthwhile or even unnecessary.

An example of this is cardiovascular disease. The mortality rates from coronary heart disease have been declining in the United Kingdom. (168) (Figure 20) It is estimated that over 40% of the decrease is due to modern effective treatment of heart disease and 58% due to population risk factor reductions. A new medication or intervention that significantly improves revascularisation would further decrease morbidity and mortality and reduce the need for extensive preventive efforts; similar to the end of vaccination programs for smallpox after the disease was eradicated.

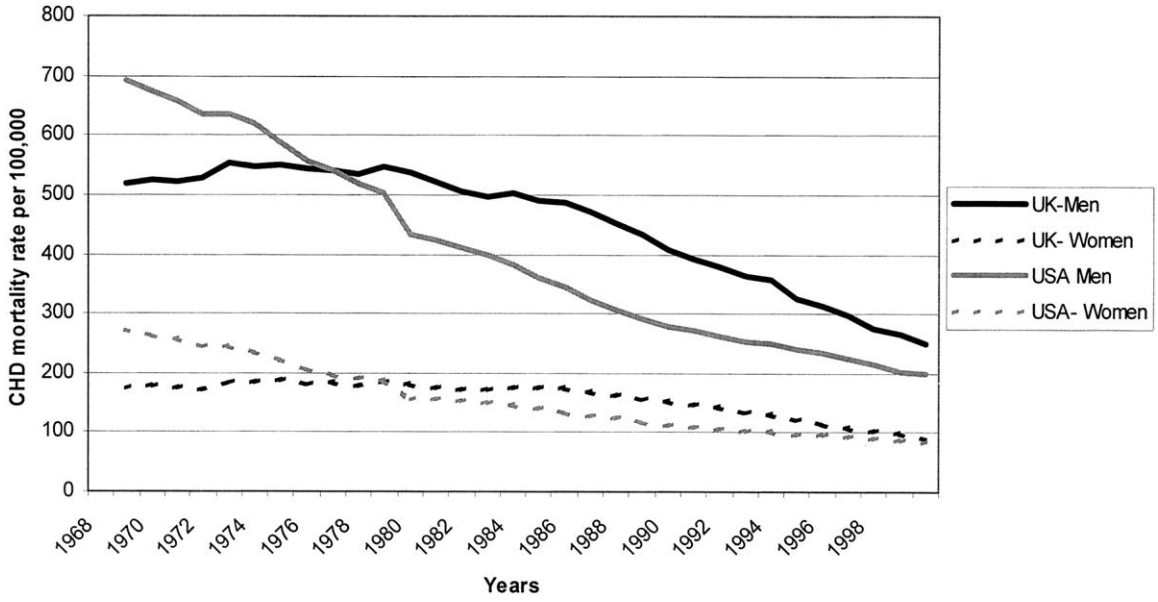


Figure 20: Age-standardized death rates from coronary heart disease for men and women in United Kingdom and United States between 1968 and 2000 (168)

6.2.3 Diminishing value

The future is valued less because of diminishing marginal utility. This occurs because the value of a good (e.g. ten pounds) is worth more now when wealth is less, than in the future when wealth is likely to be increased.

This reasoning is compatible with studies on Quality of Life (QoL). The English Longitudinal Study of Ageing showed that quality of life as measured by CASP-19, an index with 19 Likert-scaled items, declines over time in older aged people. Age and initial quality of life were the strongest predictor of change in quality of life over time. (169)

Another paper using data from the same study showed that quality of life at baseline was poorer among older adults and declined more rapidly over time. The authors used age-vector graphs to show baseline values, the direction and extent of decline of quality of life with increasing age. (170) (Figure 21)

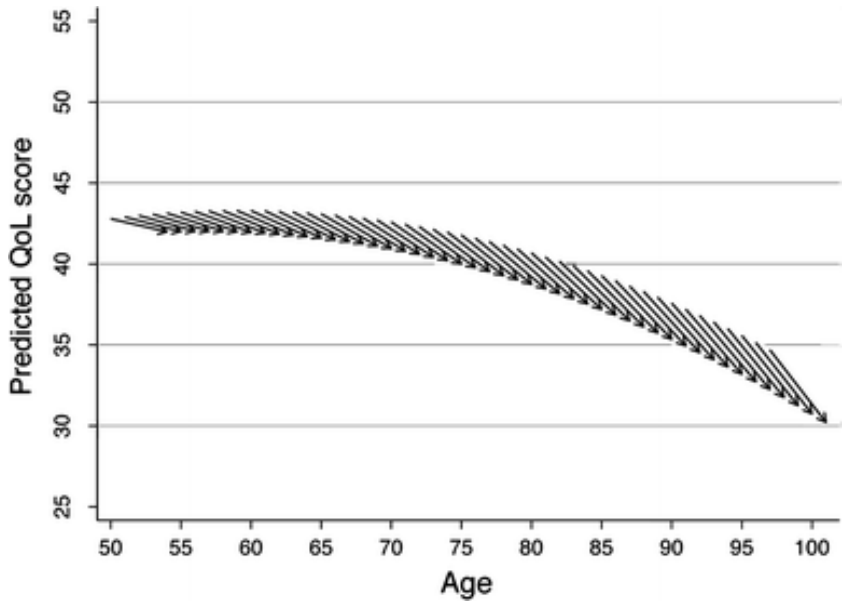


Figure 21: Four-year age vector graph showing decline in quality of life (170)

6.2.4 Opportunity costs

Opportunity costs are based on the valuation of life years on monetary terms. It is used in health care planning. It is based on the idea that resources are scarce and that the best value should be made of any resource. For example, money spent on a health program can be invested in another program that may yield higher returns. The opportunity costs of a health program are the expected return from the next best use of the money invested in the program. Money or goods in the present time can be utilised to create more goods in the future. So a pound that is invested can create more money in the future.

6.3 Time preference rates

In order to calculate the effect of time, the value of future goods is reduced by factoring in the time preference rate and the number of years it is in the future, with the present value.

For example, if the value of a life year is 1 in the present, then a life year 10 years from now would be calculated as $1/(1+r)^{10}$, where r is the time preference rate. If r is 5%, then a year of life saved next year is worth 95% of a year of life saved this year. A year of life saved 2 years from now is worth 90.7% and 10 years from now, 61% of a year of life saved this year. The graph below shows how the value of a life year declines at a steeper slope with increasing time preference rates.

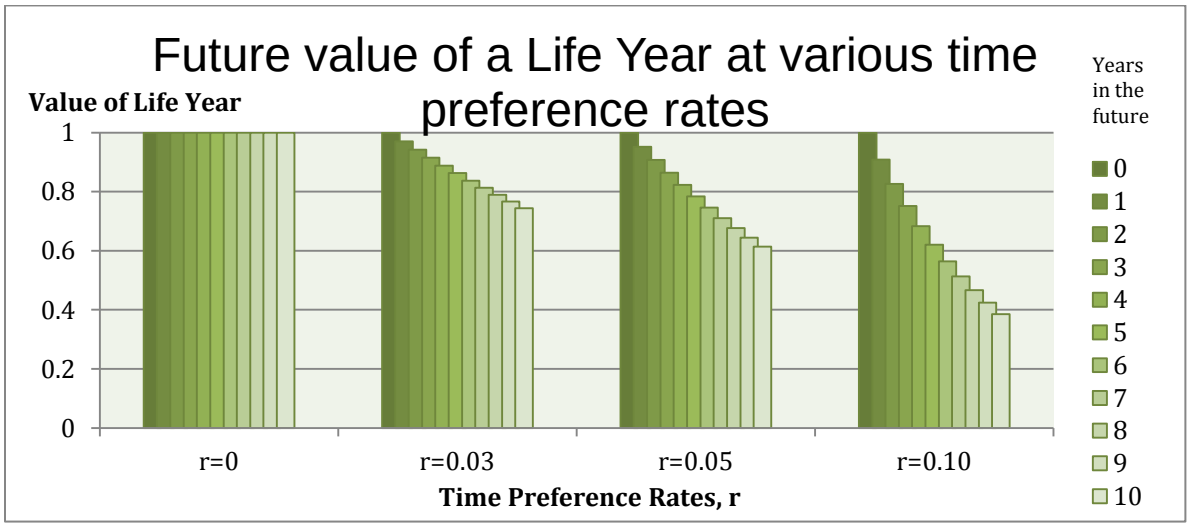


Figure 22: Future value of a life year using different time preference rates

What value should we choose as the time preference rate? Research using scenarios in questionnaires have obtained rates that differ between individuals and populations. Individual time preference rates have been reported to range from 0.4 to 17.3%. (171) Olsen found in a study that participants had high time preference rates (17.3% for life saving and 22.9% for health improvement) for health care resource allocation. This was contrary to the very low time preference rates of near zero that some felt should be applied to health care planning. He postulated that this was due to obligations that the participants felt towards those who were sick and needed health care urgently as opposed to spending money on preventive care for the future for those were healthy

now. Indeed, he felt that it was worse to discount the health of those in poorer countries of the same generation (evidenced by the national retainment of a country's health care resources) than to discount the health of future generations in one country.

Theorists have argued that the time preference rate for devaluing health benefits such as life years should be the same as the standard rate used to discount costs. Weinstein and Stason stated that this was necessary for consistency. (172) The Keeler and Cretin paradox states that if health benefits are not discounted, causing a discrepancy between the costs and benefits – this would create a paradox whereby it would always be more cost effective to delay the implementation of a health program. (173) If such a discrepancy existed, it would always be better to invest the money and buy even more health in a few years time.

In order to evaluate the benefits of a public health program, countries use a social rate of time preference. This differs between countries, ranging from 3% in Germany to 15% in Philippines. (174) In the United Kingdom, the rate has dropped from 10% in 1969 to 3.5% in 2003. The Green Book of the HM Treasury uses lower time preference rates for projects over 30 years. For example, the rate is 3% for projects estimated to take 31-75 years. (175)

6.4 Time preference rate for model

Pure time preference was the main theoretical basis for the incorporation of time preference into the model. Although cardiovascular scores are derived from *population* studies, their main role is in *individual* decision-making. Individual or pure time preference rates should therefore play an important role in the use of these scores in predicting risk for the future.

The time preference rate of an individual is difficult to determine but for health care, appear to be higher than societal rates that are usually used. (171) I used three time preference rates (0, 3 and 5%) in both models. A time preference rate of 0 means that every year is considered to be equal in value i.e. a life year that occurs ten years in the future is equal to a life year that occurs in the present time. A 3% rate is a conservative time preference rate and recommended by the Green Book for projects estimated to take 31-75 years. (175) As the age group in the models start at 35, this time span covers a life span. A 5% rate is the conventional rate chosen in the medical literature. (164) As Krahn and Gafni pointed out in their paper, most health analyses simply pull their "rates either out of the air or off the shelf, and the lucky number is most often 5%." The selection of three different time preference rates allowed me to evaluate the effect of systematically changing the rate. This coupled with the use of two different models formed the sensitivity analysis for the models. The increase in r changes the slope of the graph and this trend allows us to predict the results of further increases of the time preference rate.

An additional point made by Krahn and Gafni was about the problem of double discounting. (164) Measures such as quality-adjusted life years (QALY) incorporate elements of time preference as their methods use techniques such as time trade-off. Therefore using time preference with QALY would mean 'double discounting' leading to a systematic undervaluation of future health benefits. No such measures are used in the two models.

6.5 Methods

The same 2 models (age-based residual life expectancy models and Markov simulation cohort models) were used. Sensitivity analysis was conducted by the use of two different models and various time preference rates.

6.5.1 Age-based residual life expectancy model with time preference

The calculation was repeated with a time preference rate to account for the increasingly lower value patients currently give to life years further out into the future. (Appendix G)

The formula for life expectancy with time preference is: (176)

$$Life\ expectancy\ with\ time\ preference\ r\ = \frac{1}{r}.\left[1 - \frac{1}{(1+r)^{LE}}\right]$$

where r is the time preference rate and LE is the national life expectancy estimates. A minimal time preference rate of 0.03 was used, which values the next year as worth 97% of the previous year. This preference rate is applied throughout the remaining estimated years of life of the cohort.

The potential years of life lost due to being exposed to a set CHD risk level at different ages was then calculated using the following formula:

Potential life years lost at age A = CHD risk X CFR_A X LE_r

where CHD is coronary heart disease, CFR_A is the age-specific case fatality rate and LE_r is the life expectancy with time preference. The data used in the calculation is otherwise the same as that used in the models without time preference in Chapter 5.

6.5.2 Markov simulation cohort model with time preference

A time preference rate is applied to the Markov simulation cohort model described in Chapter 5. (Appendix F) This is done in rows where the time preference rate is applied to the total person cycles in the well column at the beginning of each cycle with the following formula:

$$Total\ person\ life\ years\ in\ row\ = \frac{Number\ of\ people\ alive\ at\ cycle\ start}{(1+r)^n}$$

where r is the time preference rate and n is the number of years away from the cycle start.

As with the models described in Chapter 5, the life expectancy of the cohort is obtained by adding up the number of person life-years in the column. For the same age band, the process is repeated using the same rates except that for the first cycle, the CHD risk is reduced to 0. The potential life years lost for one person is then calculated by the following formula:

PYLL at age A = ($LE^{\text{COHORT WITH BASE RISK}}$ – $LE^{\text{COHORT INITIAL RISK 0}}$)/100 X 5

where LE is the life expectancy of the cohort which is divided by 100 (the number of people in the cohort) and multiplied by 5 (the length of a cycle) to obtain the potential years of life lost for one individual in the age group.

The Markov simulation cohort assumes that transition from one state to another occurs between cycles and that the number of participants in each state remains stable during the cycle. If membership of the cohort is counted at the beginning of the cycle, this leads to overestimation of the life expectancy of the cohort. If counted at the end of the cycle, there is underestimation of the life expectancy of the cohort. To correct this, a half cycle

correction is employed whereby transition is assumed to occur halfway through the cycle. (157) (Appendix H)

6.6 Results

Using a time preference rate of 0.03, the life expectancies for different age groups were obtained as shown in Table 11.

Table 11: Estimates of life expectancy, United Kingdom; without time preference (r=0) and with a time preference rate (r=0.03)

Age group	Age-specific CHD case fatality rates (%)	5-year CHD death rate (%) for 5%; 10% 5-year CHD risk	Life expectancy (yrs) – national estimates without time preference	Life expectancy with time preference rate of 0.03
35-39	25.9	1.3; 2.6	41.65	23.6
40-44	29.1	1.5; 2.9	36.95	22.15
45-49	30.7	1.5; 3.1	32.33	20.51
50-54	33.1	1.7; 3.3	27.85	18.7
55-59	33.6	1.7; 3.4	23.55	16.72
60-64	42.3	2.1; 4.2	19.46	14.58
65-69	51.8	2.6; 5.2	15.69	12.37
70-74	56.5	2.8; 5.7	12.24	10.12
75-79	64.5	3.2; 6.5	9.23	7.96
80-84	70.3	3.5; 7.0	6.77	6.05
85+	79.2	4.0; 7.9	4.87	4.47

As shown in Chapter 5, the PYLL in the model without time preference has a downward trend. But this trend almost disappears in the age range from 35-9 to about 70-4 years with the application of a minimal (3%) time preference rate. In the older age groups (over about 75 years), the time preference adjustment has a minimal effect. (Figure 23 and 24)

The slope of the reducing PYLL trend with increasing age in the Markov models, already flattened by the incorporation of competing risks from non-CHD death, is leveled further by the inclusion of time preference. This indicates that there are negligible differences in the potential life years lost at different ages.

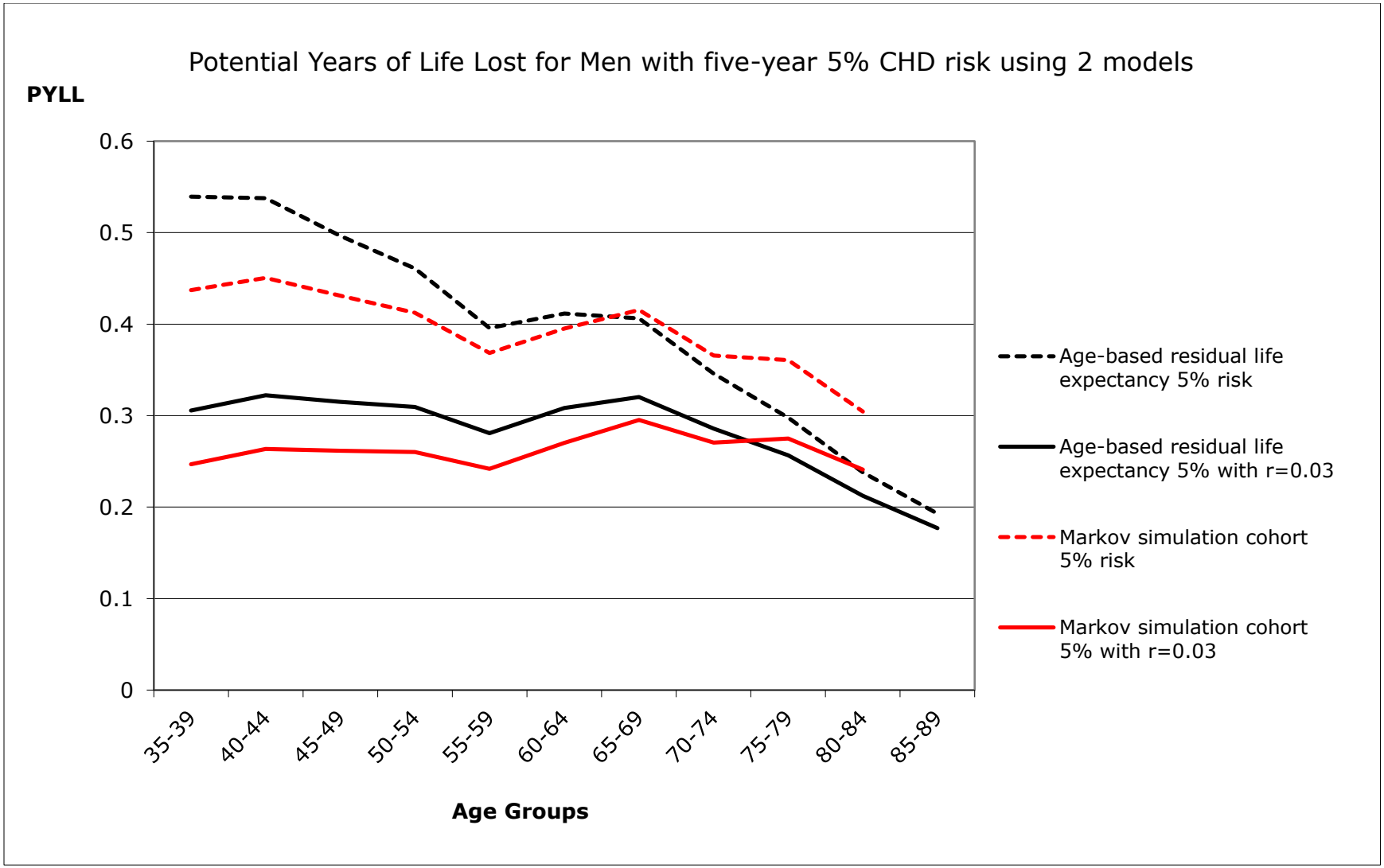


Figure 23: Potential Years of Life Lost for men at five-year 5% coronary heart disease risk; with and without time preference

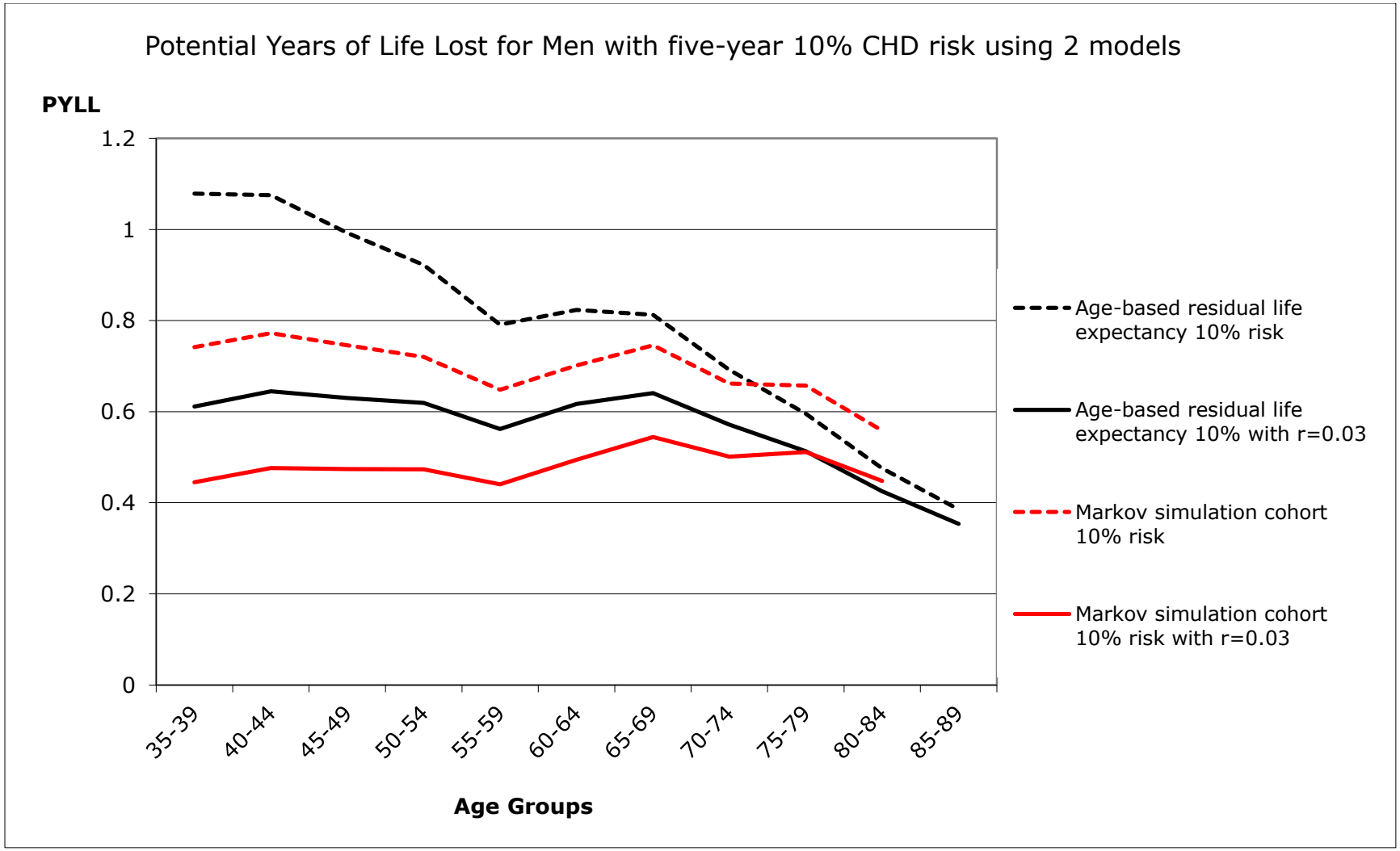


Figure 24: Potential Years of Life Lost for men at five-year 10% coronary heart disease risk; with and without time preference

Indeed, when time preference is incorporated into the Markov model, there is some indication of an upward trend in PYLL with increasing age from the age group 35-39 to 65-69. This suggests that when increasing case fatality with age, time preference and competing risks are considered, there is no difference in PYLL from delaying treatment for 5 years, for men at different ages with the same CHD risk.

The analysis was sensitive to the time preference rate used, though for typical rates the PYLL was similar at different ages. The sensitivity analysis also showed that an increase in time preference rate would actually increase the PYLL at older age groups. (Figure 25)

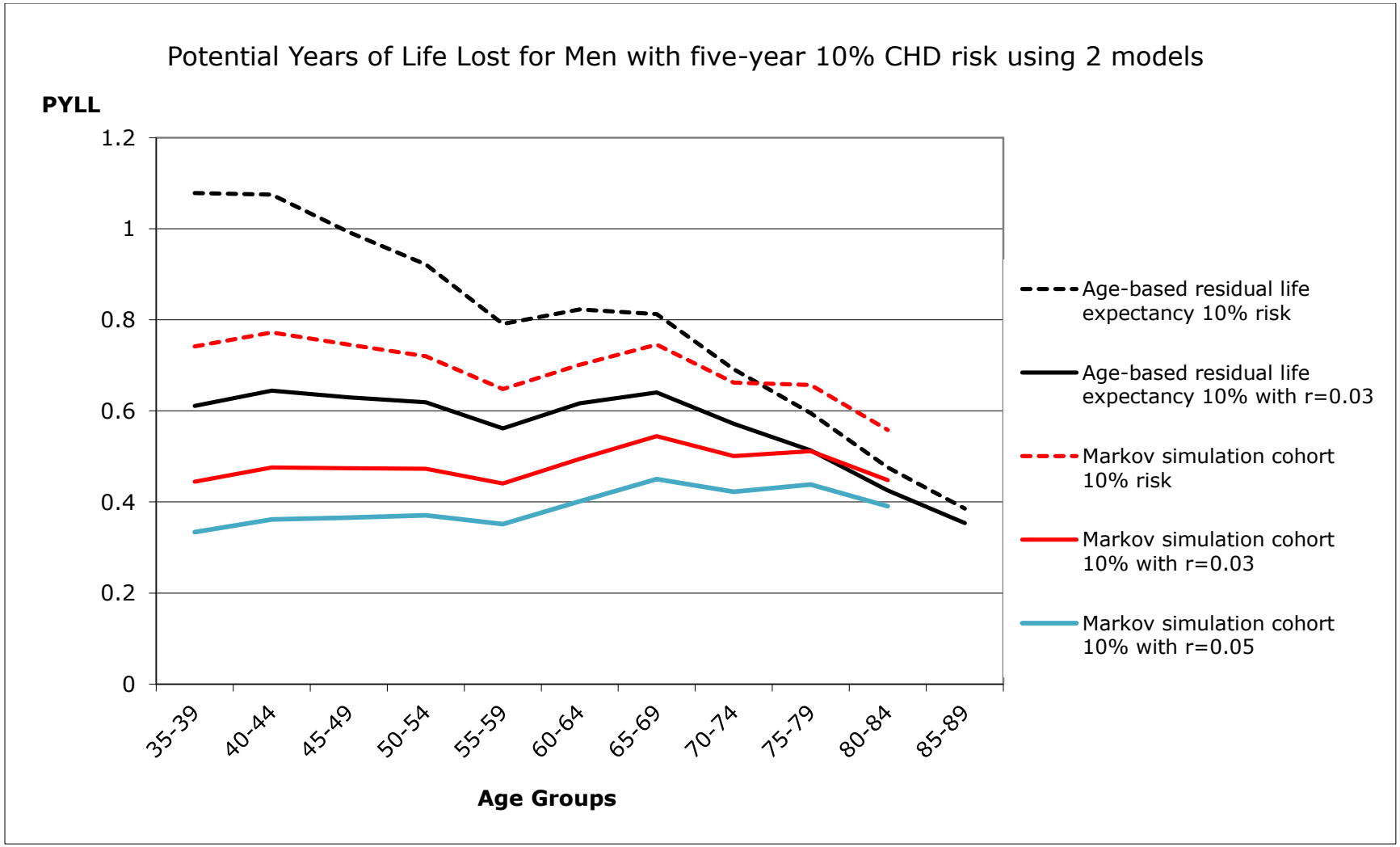


Figure 25: Potential Years of Life Lost for men at five-year 10% coronary heart disease risk using different time preference rates

6.7 Discussion

6.7.1 Statement of principal findings

Critics of time preference say that it is unfair to assign lower values to health gains that occur in the future. (177) However, each of the “potential life years lost” is not considered as equal by patients. A life year in the far off future is unlikely to be valued as much as one in a near future, especially when there exist the possibility of harm and other immediate costs due to the intervention. Balanced treatment decisions should therefore account for how people value future events. This has been done by modelling a time preference rate. In the age-based residual life expectancy model, a time preference rate of only 3% is used and even this minimal rate had a major effect on the potential life years lost: for the same cardiovascular risk, there is little difference in potential life years lost at different ages.

The results are corroborated by the Markov simulation cohort method, which also takes in the third factor - the competing risks of both future CHD and non-CHD deaths. When all three factors (i.e. case fatality rates, time preference and competing risks) are taken into account, the PYLL curve is flattened with even a hint of an upward trend from 35-39 to 65-69 years suggesting that, for this age range, the older age groups lose more potential life years compared to the younger age groups at the same estimated 5-year CHD risk. Indeed, when the conventional time preference rate of 5% is used, the PYLL was greater with age.

These findings suggest that models that do not take time preference into account will overestimate the benefits of treatment in younger patients and may possibly underestimate the benefits in older people.

6.7.2 Strengths and weaknesses of the study

This study suggests that there is little difference in the life years lost caused by having the same cardiovascular risk at different ages. Two different methods were used and the results corroborate, which strengthens the argument for the use of time preference. Neither method relies on the use of a particular risk score, meaning that the findings are applicable across a wide range of risk scores.

The weaknesses of the study are similar to those of the models without time preference and have been described in Chapter 5.

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

The QRISK group in the UK has recently developed a lifetime cardiovascular risk calculator. Using a threshold of > 50% lifetime risk of cardiovascular disease, over half of men identified as being at high risk were in the youngest age group (30-44 years of age). In women, over one third were in this age group. (151) The authors presented several case studies that raised concerns about the clinical usefulness of lifetime risk and stated that they were uncertain whether using such an approach was appropriate for treatment decisions. Yet recent media articles have suggested new national UK guidelines will change from advocating the use of ten-year risk to lifetime risk calculators in clinical practice. (110)

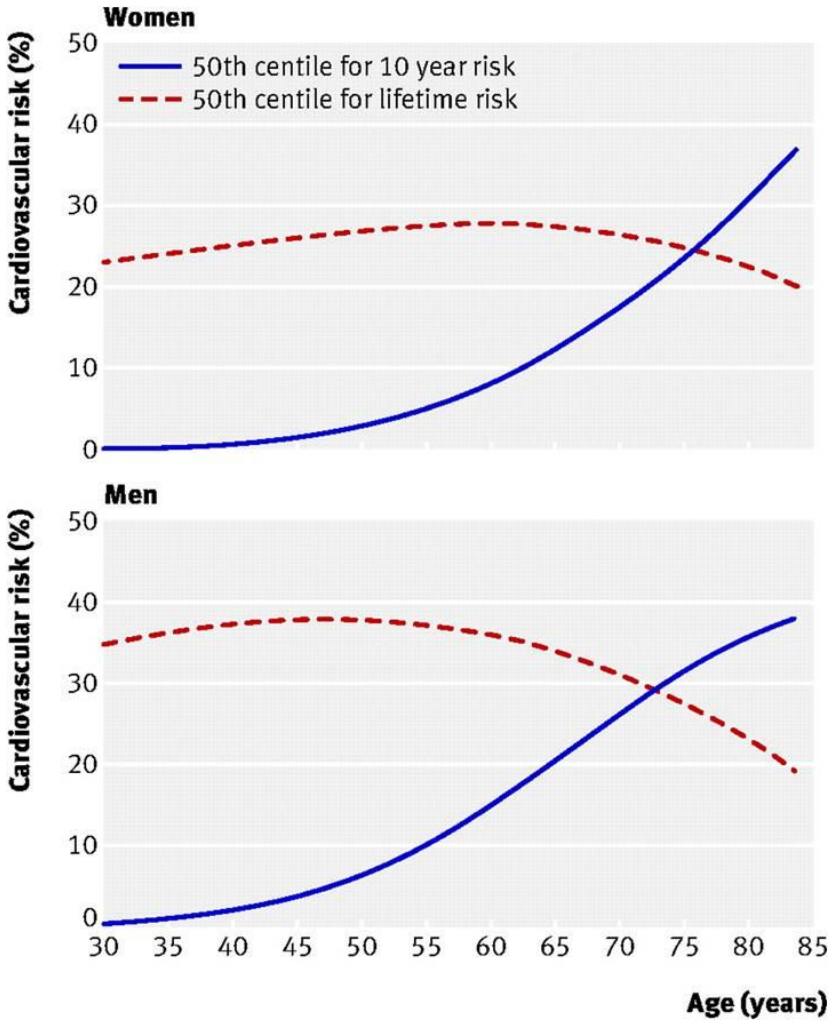
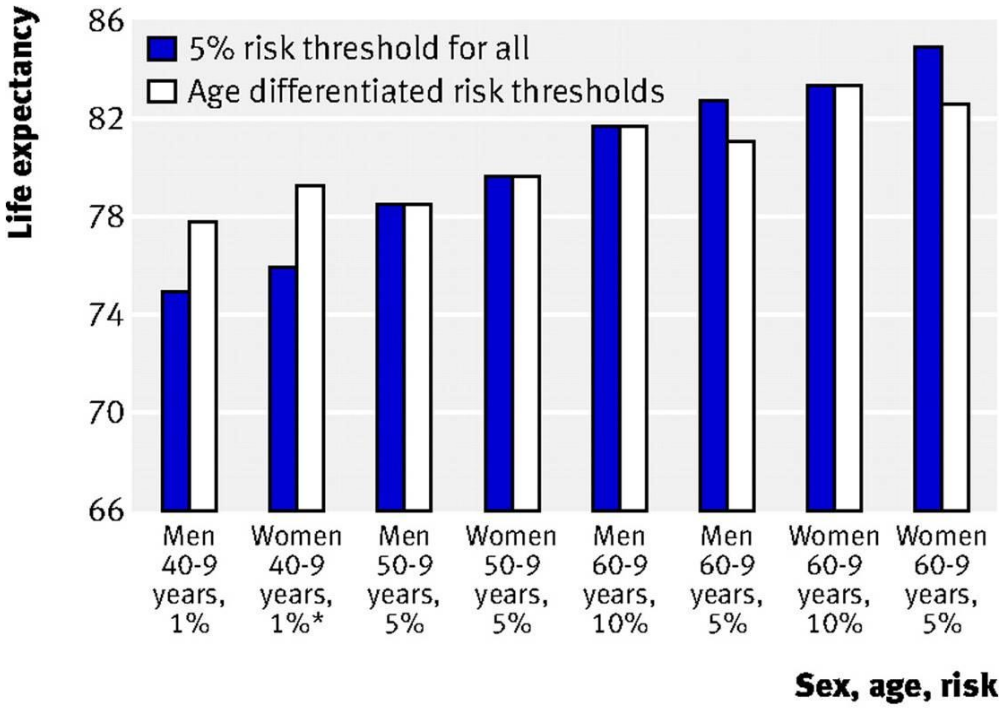


Figure 26: 50th centile of cardiovascular disease risk by age and sex: lifetime risk versus 10-year risk using QRISK2 (151)

In Norway, a different approach has been adopted where thresholds for treatment are different for different ages. For those aged 40-49, the threshold is set at a 10-year risk of cardiovascular death of 1% whereas for those aged 60-69, it is set at 10%. The new recommendations are based on a Markov model, which showed that more life years were gained using age differentiated thresholds. As the Norwegian risk score (based on SCORE) predicts only fatal outcomes, the increase in case fatality rates with age is accounted for in their model but not time preference or competing risks. (177)



* According to the epidemiological study from Norway, there are no women (or very few) in this risk group

Figure 27: Life expectancy by sex, age, and ten-year risk of cardiovascular death; 5% risk threshold versus age-differentiated risk thresholds (177)

To make the results comparable between their model and mine, I have extracted data from Table 1 of their paper. (Table 12)

Norheim et al estimated the undiscounted life years gained per individual from treatment with a statin and two antihypertensives using a Markov model. (177) Although not stated, the duration of treatment is probably lifetime. Their results also found little difference in life years gained at different ages. There was more life years gained by treatment of younger age groups with the use of the old thresholds but the difference is small (even with lifetime therapy) and would certainly even out with the use of time preference.

Table 12: Undiscounted life years gained per individual from treatment: old versus new Norwegian thresholds

	Old threshold of 5% for all ages	New age differentiated thresholds
	Men	Men
40-49	? not given but would probably be around 5 or 6	2.9
50-59	3.0	3.0
60-69	1.7	2.3

A greater cause of concern is that their result showed that the use of the new age-differentiated risk thresholds would not increase the life years gained for their population but decrease the number of those who would be recommended treatment. Application of the guidelines in a population in Tromso would mean that 78000 men and women aged 60-69 (17% of women; 22% of men in age group) would be denied treatment while 29000 men aged 40-49 (8.4% of age group) would be recommended treatment under the new thresholds. This implies removing treatment from many to increase potential life years in a few.

The results of both the QRISK lifetime and Norwegian models show that the adoption of a lifetime risk approach or age differentiated thresholds will overestimate CVD in younger people and lead to a substantial (and unnecessary) increase in the number of young people on medication.

Unlike these models, the models in this study analysed the combined effect of all three relevant factors. This was also done in 5-year increments – an appropriate period of

time for reviewing decisions on treatment initiation in an individual patient. It has been noted that patients find it difficult to fully comprehend long risk time periods. (178)

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

These findings show that there is no difference in losses to life expectancy due to a five-year treatment delay in those at different ages but the same short-term risk. A move towards the use of approaches that attempt to redress the issue of age would not add usefully to individual risk prediction but would mean that greater numbers of low-risk individuals would be exposed to long-term medication with questionable benefits.

6.7.5 Unanswered questions and future research

In examining the use of CVD risk for young versus old patients, only the issues of age-specific case fatality rates, competing risks and time preference have been addressed. However, there are other factors that clinicians and patients may consider when making treatment decisions based on CVD risk. Both the frequency and impact of adverse effects may differ between young and old. The elderly may also have a different attitude to mortality, and may consider the mode of death as well as the timing of death. Further research is needed to address the impact of these issues on the use of CVD risk in cardiovascular risk management.

6.8 Conclusion

When case fatality rates, competing risks and time preference are taken into account, there is minimal difference in the potential life years lost from experiencing a CVD event for different age groups at the same short-term cardiovascular risk. Time preference and case fatality need to be considered when assessing the impact of an event that occurs in the far off future. Models that do not account for the effect of time preference or

differentiate between the impacts of fatal versus non-fatal events would therefore overestimate the benefits of treating those with longer life expectancies.

6.9 Summary points

- Current UK guidance base clinical treatment decisions on estimates of short-term (5-10 year) cardiovascular risk without taking account of age. In Norway, recommended thresholds for treating cardiovascular risk are different at different ages. Recent media articles have suggested that new national UK guidelines will advocate making treatment decisions on the lifetime risk estimated by QRISK.

- Potential years of life lost from cardiovascular disease (PYLL) at different ages were estimated using two different modelling approaches: an age-based residual life expectancy model and Markov simulation cohort. Age-specific case fatality rates and time preferences were applied to both models. In addition, competing mortality risks were incorporated into the Markov model.

- Both models gave similar results. Younger age groups have more potential life years to lose if their risk is untreated, but the maximum difference between age 35 and age 85 is less than 1 year with increasing case fatality rate and competing mortality risks with age. Moreover, when account is taken of time preference, the maximum difference falls to about 1 month and with more PYLL in people aged about 60-80 years than in younger people.

- There is no reason to change existing national guidance. Treatment decisions should be based on estimation of short-term cardiovascular risk irrespective of age. Other approaches may over-estimate the benefit of treating young people.

Chapter 7. Conclusions

7.1 Summary of main findings

- Cardiovascular risk scores, particularly the most recently derived scores, underestimate risk because they do not take adequate account of the effect of treatment.
- General practitioners are uncertain about the correct use of the risk scores, reflecting inconsistency in national clinical guidelines.
- When account is taken of differential case fatality and the fact that people value avoidance of near-events more than distant events, there is no case for treating the same level of risk differently at different ages.

7.1.1 Cardiovascular risk scores do not account for treatment

A major finding of the systematic review is that cardiovascular risk scores do not take account of treatment. Risk prediction that ignores treatment effects may mislead clinicians and patients by underestimating the untreated risk of events. After a systematic review of risk scores carried out in 2005 (19) noted that the risk of cardiovascular disease varied over time, consistent with increasing levels of treatment in the cohorts used to derive the scores, the NICE lipid guidelines (36) recommended that risk prediction studies should consider the impact of treatment. Yet, this recommendation has not been followed by any of the risk scores following on from the guidance.

Ignoring the effect of treatment goes against two key pieces of evidence. First, that treatment of risk factors is effective in reducing cardiovascular events; second, that the relationship between risk factor and disease outcome does not depend on the prevalence of the risk factor.

The Framingham risk score is frequently cited as irrelevant because the study population was from a small town in America at a time when myocardial event rates were at a peak; it has therefore been argued that it over-predicts risk. However, it is the only score derived from a largely untreated population. The results from the systematic review highlights treatment as a major confounding factor that has been ignored and that can account for the differences in predicted and observed results from derivation and validation studies conducted in more recent times.

Some cardiovascular risk scores have recently attempted to adjust for treatment by: (a) excluding those on treatment from the study e.g. QRISK2 excludes those on statins (28), (b) incorporating the use of antihypertensives as a risk predictor e.g. ARIC (113), QRISK (27, 28), and (c) adjusting for the impact of antihypertensive treatment on systolic blood pressure in the model e.g. Framingham 2008 (11). However, these adjustments have focused on antihypertensive treatment only at baseline. No CVD risk scores have considered the effects of other treatments such as platelet inhibitors or statin or, more importantly, treatment started after baseline examination. Hence CVD risk scores will tend to underestimate CVD risk, and this underestimation is greater in more recent cohorts (and more recent tools) because of the increasing use of risk modifying treatments.

7.1.2 General practitioners are uncertain about the correct use of risk scores

General practitioners perceive risk scores as providing an assessment of current risk to guide treatment decisions. However, they remain uncertain about the application of the scores to patients who have already been treated or modified their lifestyle on medical advice. Paradoxically, they also report using the scores to show the effect of treatment and lifestyle modification, showing patients their estimated risk with different levels of

risk-factors (i.e. smoking or non-smoking; high or low blood pressure; high or low cholesterol).

Although during consultations doctors find it useful to show patients how risk falls by changing risk factor values, this is misleading because of the mismatch between the risk estimates of observational studies and randomised controlled trials. For example, if blood pressure is lowered by 10 mmHg, does the risk score accurately predict the risk reduction with the treatment? Risk prediction studies do not usually report or account for the extent of missing data regarding number of patients on treatment, type of treatment and extent of control of risk factors. The effects of treatment on the absolute risk are best derived from results of randomised clinical trials.

In addition, the guidelines are unclear about the use of the cardiovascular risk scores in previously treated patients, leading to considerable uncertainty. There was uncertainty over basic issues such as whether the risk scores should even be used in patients already on treatment, selection of the appropriate risk score, re-estimation of risk during follow-up to more complex issues such as whether global risk reduction matches the risk factor reduction with treatment. Only two scores are well known in the United Kingdom, i.e. the Framingham risk score and the QRISK scores. The Joint British Societies guidelines were effective in disseminating and streamlining information about the use of the Framingham-derived risk score. An important factor in this is the easy to use and well-distributed JBS risk charts. However, uncertainty arose because of the contradictory and limited information about the use of the score in treated populations. Presently, the updated NICE guidance states that a doctor can choose any of a number of risk scores. Inadequate guidance is given on the issues, which might guide choice, and this will give rise to further uncertainty. Instead, guidelines should give clear, concise and firm recommendations to resolve uncertainties. As was pointed out by participants in the

interviews, not every doctor is interested in the details of risk prediction and nor is it necessary. Guideline committees need better input from researchers, policy makers and clinicians who have expertise in this area.

7.1.3 There is no case for treating risk differently at different ages.

The mathematical models in Chapter 5 show that the difference in potential life years lost between the old and the young at the same level of event risk is minimal because higher case fatality rates in the elderly balance the greater life expectancy of the young.

When time preference is added to the analysis in Chapter 6, the maximum difference falls further and with more life-years lost in people aged about 60-80 years than in younger people.

7.2 Reliability of findings

7.2.1 Systematic review

The systematic review may have missed some published papers. Compared to randomised controlled trials, prognostic studies are more difficult to identify with electronic searches. (179) As the objective was to identify studies that combined multiple risk predictors into scores/equations, we had to filter out prognostic studies that were simply researching associations between risk predictors and outcomes but did not combine them into a clinically usable method that would predict absolute risk of an individual developing a cardiovascular outcome. Some studies may have been missed if details had been left out of the abstract. In order to lower the chances of missing eligible studies, the search was conducted in Medline, two reviewers appraised and selected the studies, and we also searched alternative sources such as literature files, previous reviews of cardiovascular scores and citation tracking.

Unlike systematic reviews for interventions, this review did not attempt to do a meta-analysis of an effect measure and therefore publication bias was not as important. It was important to obtain and review studies of important risk scores used in clinical practice. Missing risk scores not used in clinical practice would not affect the findings of the review.

7.2.2 Qualitative interviews

The qualitative interviews offer an in-depth understanding of the way that general practitioners use the cardiovascular risk scores but only represent the views of the 20 doctors who were interviewed. Although the study aimed to obtain maximum diversity of users, the demographic characteristics of the participants question whether this was achieved. Again, although I believe I reached data saturation, it remains possible that interviewing more GPs would have revealed other important themes.

7.2.3 Models

The argument against the use of the risk scores has mainly been on the powerful effect of age on absolute risk. The results show that at the same absolute event risk, there is no difference in the PYLL at different ages. Factoring in age-specific case fatality rates and competing risks removes almost all the difference between age groups. The use of a conservative 3% time preference rate obliterates any difference and shows a slight increase in years of life lost at older age groups. As the use of time preference remains controversial, the models in Chapter 5 only factor in the other two factors and the results are already strikingly different from the intuitive approach, which considers only life expectancy. The models in Chapter 6 add another dimension, namely time, to the analysis. As the risk scores predict the future, it is important that the factor of time be incorporated into the models. All years are not created equal.

Another possible limitation of the risk scores is the assumption that relative risk remains the same with age. There has been evidence that relative risk of certain risk predictors is attenuated in the older age groups. An example is lipids. The attenuation of risk has been shown by observational trial. (180) (Figure 28) Reduction in risk by statins remains similar for in all age groups. Although the models in this study use only population data, this issue does have an indirect effect on my results as I compare the effect of cardiovascular risk at different ages.

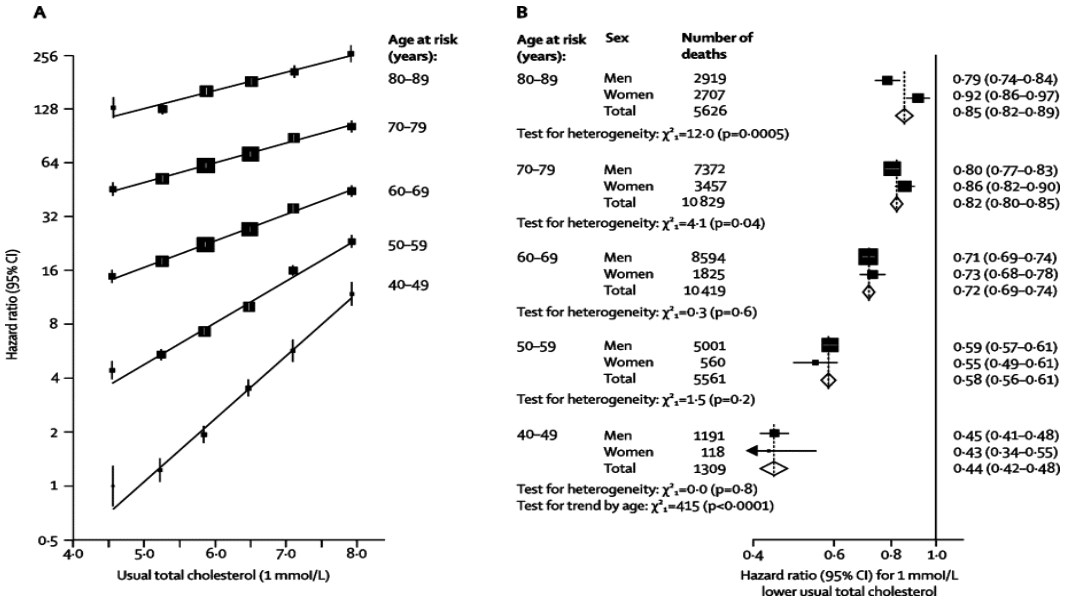


Figure 28: Relationship between total cholesterol and coronary heart disease mortality in different age groups (180)

7.3 Implications for reducing cardiovascular risk in general practice

My findings have implications for re-evaluating the three main approaches to the reduction of cardiovascular morbidity and mortality in general practice:

1. Population wide approach without individual risk assessment
2. Targeting those at highest cardiovascular event risk
3. Targeting those at greatest risk of lost life years

7.3.1 Population wide approach

One possible response to the inadequacy of current risk scores and confusion about their use would be to avoid assessing individual risk at all. This population-wide approach is exemplified by the “polypill” – offered to everyone above a certain age. Age is the main selection criterion as it is the strongest marker of population risk but there is no attempt to identify individual risk. Wald envisioned a polypill made up of four components (three blood-pressure lowering medications and one statin) and the target population to be healthy individuals above the age of 55. (The original version included folate too but this has been discredited) The medication would be provided after screening with a few questions (age, use of existing medication and medical history) by pharmacist prescribers. (181)

The population strategy, as exemplified by the polypill approach, is not vastly different from the present method which uses absolute risk scores. A significant proportion over the age of 55 will fall into the high-risk group as calculated by present risk calculators. (Table 13 and Figure 29) Only those who fall into a select group (those with excellent risk profiles) will not be classified as high-risk. Thus, the absolute risk calculators do not greatly affect the profile of those receiving treatment – it simply screens out the few who remain at very low risk. However, there is a cost to screening which is not necessary in the population wide approach.

Table 13: Distribution of population at high cardiovascular disease risk in Norway (177) and the United Kingdom (28)

	Tromso[a]	Qresearch database[b]	
		QRISK2	Framingham
40-49	0	1	5
50-59	23.4	8	27
60-69	58.7	46	63

[a] % of Tromso population with 10 year estimated fatal CVD risk of >5% by Norwegian risk score [b] % of patients in QRESEARCH validation cohort with 10 year estimated fatal and non-fatal CVD risk of >20% by QRISK2 and Framingham risk scores

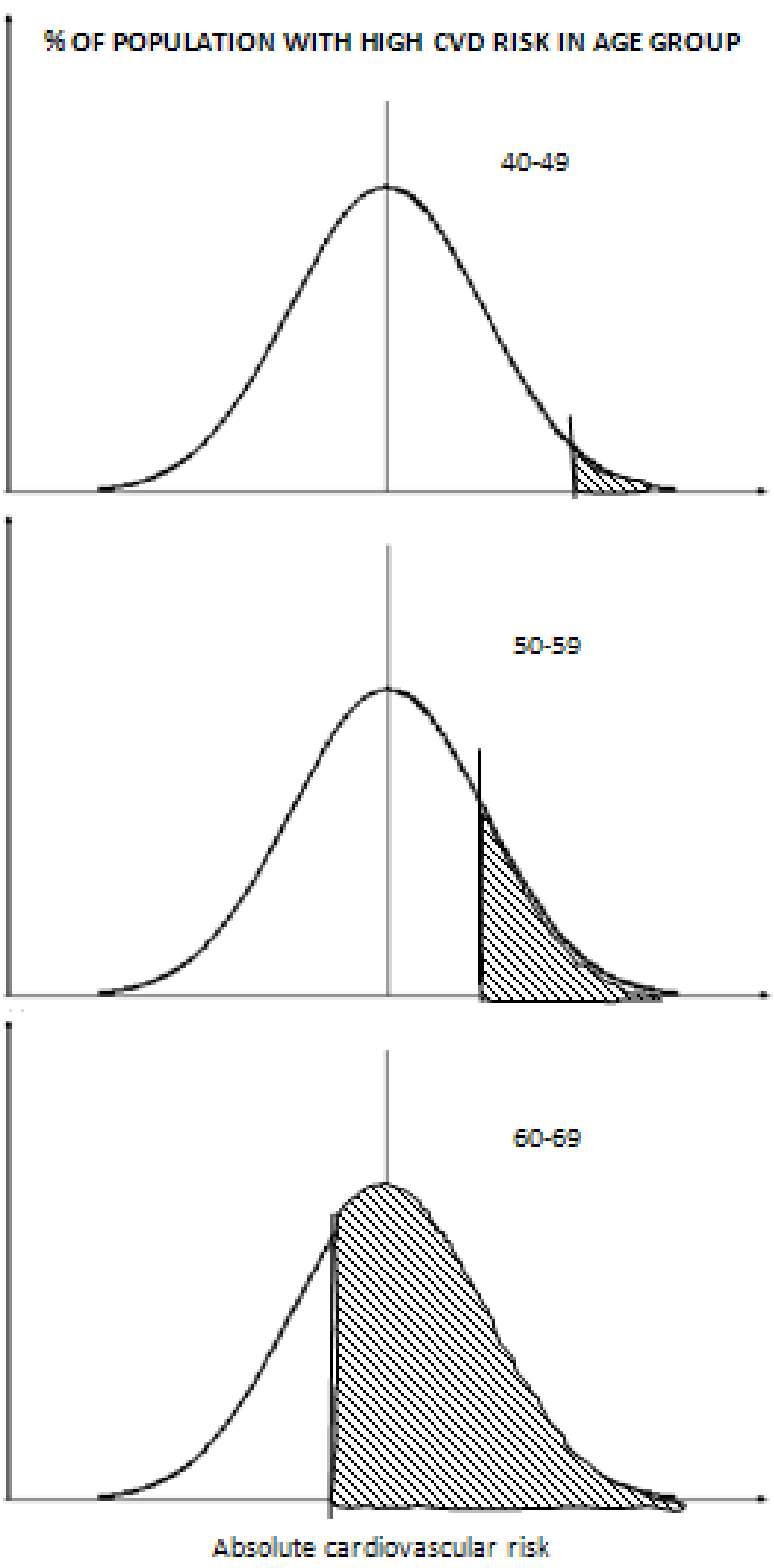


Figure 29: Distribution of population at high cardiovascular disease risk according to age groups

For the polypill concept to work, the entire population will have to take medication when they reach an agreed age. (181) This would require a radical change in medical thinking and practice. We would have to change the way that we think about blood pressure lowering or lipid lowering medications – no longer as therapeutic drugs but as preventative measures for cardiovascular disease. A comparison would be fluoridation of water to prevent tooth decay. (182) Fluoridation of water has been extensively researched and has been shown to effectively reduce decay with dental fluorosis as the only adverse effect. (183) Yet, there is still controversy in the addition of fluorides into water despite this having been done in the United States for over 60 years. (184) Medicine has evolved towards the primacy of individual autonomy. One major contentious point of the fluoride and polypill debate is the ethics of mass medication where many of those receiving treatment would be healthy. As pointed out by Charlton, such an approach would be contrary to ethical clinical practice, which is based on the voluntary treatment of an autonomously consenting patient who is asking for help. (182) Of course, fluoridation of public drinking water would mean that individuals would have no choice in the matter. The key issue for the polypill would be population compliance with such a policy. Compliance was 65-70% and loss to follow-up 27% in a randomised controlled trial of a polypill that followed participants for a year. (185) Another trial found side-effects in 1 in 6 people taking the polypill for 3 months. (186)

7.3.2 Targeting those at highest cardiovascular event risk

The second approach, advocated by many current guidelines, is the use of 5-10 year absolute cardiovascular risk scores to target treatment. This targets those who are at highest-risk of a cardiovascular event such as a heart attack or stroke. As absolute risk is greatly influenced by age, this approach means that almost everyone above the age of 60 is classified as at high risk.

The current cardiovascular risk scores approach reflects evidence that those who benefit most from treatment are those at higher baseline risk. The time period over which risk is assessed needs to be of the appropriate length – not too long for patients to comprehend or for treatment review. The main criticisms of these risk scores are the perceived greater cost-efficiency of population wide strategies such as the polypill (because they avoid the cost of screening) and that the scores as biased towards the elderly unlike models that account for life expectancy.

7.3.3 Targeting those at greatest risk of loss

The third approach targets those who are at greater risk of loss or have more to lose. This is often construed as those who are young with high risk factors as they have greater life expectancy and therefore stand to lose more by having their lives cut short by cardiovascular disease. Life expectancy models, lifetime risk scores and age-differentiated risk thresholds represent strategies which are based on the third approach.

This approach is based on the concept that treatment should be directed to those at greatest risk of losing potential life years. These models are therefore biased towards the young as they have greater life expectancy. However, my results show that there is minimal difference in potential life years lost when important and objective factors such as case fatality rates and competing risks are considered. When time preference is added, this difference is largely abolished. The time preference rate used in the model is a conservative rate and the results show that there is slightly greater loss of potential life years in the older age groups. This trend increases with higher time preference rates.

The application of lifetime risk models predisposes to increased prescribing of medication in young asymptomatic men and decreased prescribing in both men and women in older age groups. As noted in Chapter 5 and 6, this would require many young

adult men to take medication for years with the immediate risk of adverse effects. Similarly to the polypill approach, the key issue would likely be compliance to medication. Poor adherence to treatment occurs even in those with a prior history of cardiovascular events. Non-compliance is likely to be an even bigger problem in asymptomatic individuals with no prior history of cardiovascular disease. Just a month after suffering a myocardial infarction, more than 1 in 5 patients discontinue treatment with aspirin, beta-blockers or statins and 1 in 8 discontinue use of all three medications. (187)

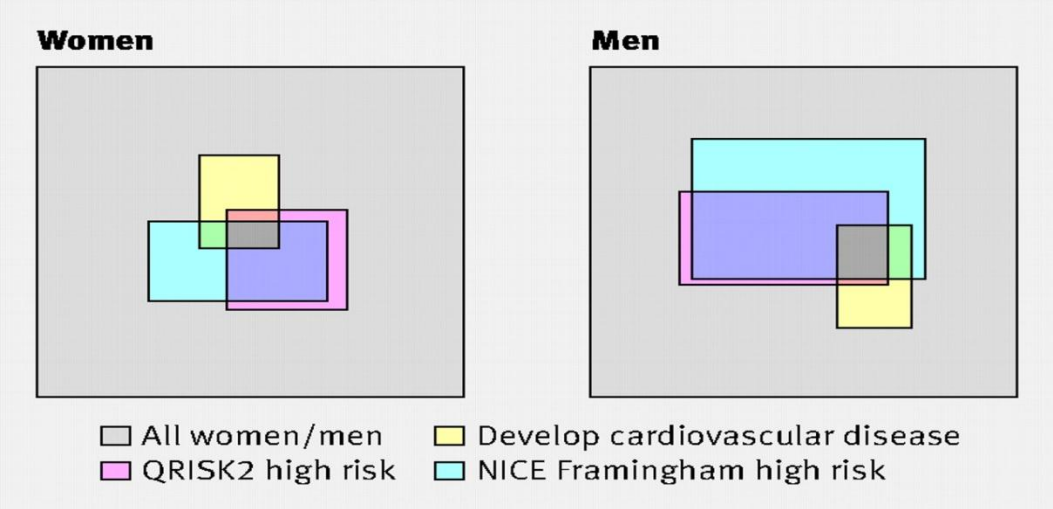


Figure 30: Validation study of QRISK2 and Framingham in THIN database (75)

The use of models which preferentially treat the young would mean that a number of people in older age groups would not be offered preventive treatment and would therefore go on to develop cardiovascular disease. Figure 30 was taken from a validation study of the QRISK2 and Framingham risk score in the United Kingdom. (75) The results show a substantial number of false positives and false negatives for both risk scores. If the effects of treatment had been taken into account, there would have been greater overlap of the areas in the scaled rectangular diagrams in the validation study.

Some of those cases considered to be ‘false positives’ would have gone on to develop cardiovascular disease but were prevented by treatment during the study.

The models in this study show that the approaches of targeting those at high short-term risk and those with greatest lifetime risk make little difference to who is identified and treated in clinical practice. Potential life years lost is higher with increasing absolute risk levels but do not differ according to age. Therefore, those who are more likely to lose more life years are those at high five-year risk.

7.4 Implications for treating individual patients in practice

Accepting that individual assessment of short-term cardiovascular risk remains the optimal clinical strategy, my results also have three important implications for using risk scores and treating individual patients in everyday clinical practice:

Firstly, clinicians should continue to use risk scores or charts derived from the Framingham study as this was based on a treatment naïve cohort. Doubts about the exclusion of certain risk predictors, geographical distance, time of the study and the decline in prevalence of outcomes affecting risk prediction might be dispelled with proper provision of information to physicians on the reason for preferring a score based on a historical treatment naïve cohort in the absence of a good alternative. Use of the risk scores derived from treated populations is inconsistent with the way doctors perceive and use the scores. The prognosis or risk in a treated individual is only of value when used in comparison to untreated baseline risk. When used in this manner, it is highly effective for showing patients that their risk of having a major cardiovascular event can be decreased with risk factor lowering. But by itself, treated absolute risk has no application in clinical practice except when used to predict population data for health care planning. It is of no clinical value in individual risk prediction when used alone.

Secondly, clear and concise guidance should be provided to clinicians regarding the use of risk scores, especially in patients who are already on treatment. Specifically, doctors should be told that risk scores can be used on treated patients (with the caveat that the actual risk may be higher than estimated depending on the duration and efficacy of treatment).

Thirdly, absolute 5 to 10-year cardiovascular risk calculators should be preferred to approaches that attempt to improve risk prediction by 'correcting' a perceived imbalance towards treatment in the elderly. Treatment guidance should continue to prescribe short-term risk calculators and not change to other models which will overestimate risk in young men and underestimate risk in older men and women.

7.5 Conclusion

This thesis has shown that the use of the 5-10 year absolute cardiovascular risk score is still the most appropriate and useful approach to primary cardiovascular disease prevention in individuals. Models such as lifetime risk and age-differentiated risk thresholds overestimate risk in the young at the expense of the old. Older risk scores are to be preferred as they provide the most accurate representation of risk appropriate for individual decision-making. The health care professional relies on guidance on this complex topic and should be provided with clear and concise instructions on the appropriate method to use.

Chapter 8. Progression of work

This chapter discusses progression of work that has occurred since original analysis. It includes published or pre-publication papers accompanied with a commentary on how the original analysis evolved into the final manuscript.

8.1 Published letter in response to validation study

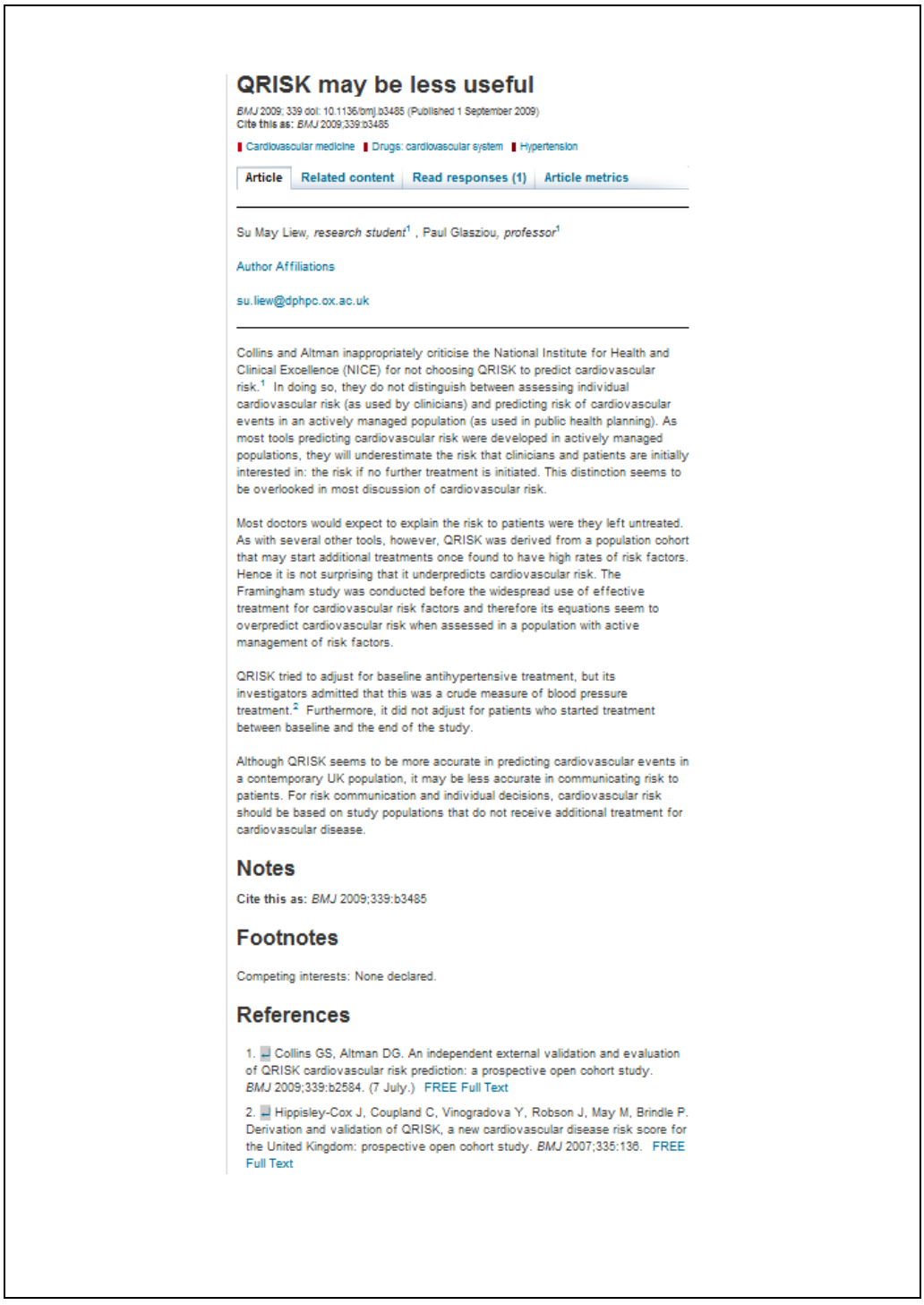
In July 2009, the British Medical Journal published an independent validation study (106) comparing the performance of QRISK with two Framingham risk scores on an external UK general practice database; THIN (THE Health Improvement Network). Although Collins and Altman found that QRISK underestimated ten-year CVD risk, the magnitude of under-prediction was smaller than the over-prediction by Framingham.

Submitted as a Rapid Response, this letter was written to highlight the difference between predicting individual risk for treatment decisions and population risk projections for health planning. (107)

The authors' response was to state that it was practically and ethically impossible to obtain a treatment naïve cohort at the present time. They were also unsure as to whether prognosis was best assessed from an untreated population. (188)

This is incorrect. The risk score derived from an actively managed population will underestimate true CVD risk. This was foreseen by Hense (70) and shown in the review by Beswick (19), which found the Framingham risk score to over-estimate in treated, and more recent study populations. Doctors also use the risk score in clinical practice to derive untreated individual risk as shown by the qualitative interviews in Chapter 4.

Collins and Altman published another validation study, this time on QRISK2 in May 2010. Although our concerns were noted, there continued to be no adjustments for treatment. (75)



QRISK may be less useful

BMJ 2009; 339 doi: 10.1136/bmj.b3485 (Published 1 September 2009)
Cite this as: *BMJ* 2009;339:b3485

Cardiovascular medicine | Drugs: cardiovascular system | Hypertension

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Collins and Altman inappropriately criticise the National Institute for Health and Clinical Excellence (NICE) for not choosing QRISK to predict cardiovascular risk.[1] In doing so, they do not distinguish between assessing individual cardiovascular risk (as used by clinicians) and predicting risk of cardiovascular events in an actively managed population (as used in public health planning). As most tools predicting cardiovascular risk were developed in actively managed populations, they will underestimate the risk that clinicians and patients are initially interested in: the risk if no further treatment is initiated. This distinction seems to be overlooked in most discussion of cardiovascular risk.

Most doctors would expect to explain the risk to patients were they left untreated. As with several other tools, however, QRISK was derived from a population cohort that may start additional treatments once found to have high rates of risk factors. Hence it is not surprising that it underpredicts cardiovascular risk. The Framingham study was conducted before the widespread use of effective treatment for cardiovascular risk factors and therefore its equations seem to overpredict cardiovascular risk when assessed in a population with active management of risk factors.

QRISK tried to adjust for baseline antihypertensive treatment, but its investigators admitted that this was a crude measure of blood pressure treatment.[2] Furthermore, it did not adjust for patients who started treatment between baseline and the end of the study.

Although QRISK seems to be more accurate in predicting cardiovascular events in a contemporary UK population, it may be less accurate in communicating risk to patients. For risk communication and individual decisions, cardiovascular risk should be based on study populations that do not receive additional treatment for cardiovascular disease.

Notes

Cite this as: *BMJ* 2009;339:b3485

Footnotes

Competing interests: None declared.

References

1. Collins GS, Altman DG. An independent external validation and evaluation of QRISK cardiovascular risk prediction: a prospective open cohort study. *BMJ* 2009;339:b2584. (7 July.) FREE Full Text

2. Hippisley-Cox J, Coupland C, Vinogradova Y, Robson J, May M, Brindle P. Derivation and validation of QRISK, a new cardiovascular disease risk score for the United Kingdom: prospective open cohort study. *BMJ* 2007;335:136. FREE Full Text

8.2 Systematic review of cardiovascular risk scores

In 2010, the review paper was submitted and subsequently accepted for publication after revision of the following issues. (129)

8.2.1 Quality score of reviewed studies

The quality of the reviewed studies was initially assessed using a method described by Sheridan et al (102), whereby quality ratings for each element were converted into numerical values (0=poor, 1=fair, 2=good), giving each item equal weight. The average composite rating for each study was obtained by dividing the total with the number of elements. The quality grades were based on the following scale: a mean score ≥ 1.5 was considered good quality; a mean score of 1.0 to 1.49 was considered fair quality; and a mean score < 1.0 suggested the study had significant methodological limitations. Elements used in the assessment were study descriptions of outcomes, predictors, sampling, follow-up, data quality, treatment effects, and performance of the rule based on criteria adapted from Wasson (111) and Royston et al (112).

It was agreed that the use of a single quantitative score did not contribute to the review and that a table presenting the important methodological aspects of each study would be more informative to the reader. Table 2 was modified accordingly.

8.2.2 Solutions on how to account or adjust for treatment effect in studies

In the initial submission, no solution was offered on how this issue should be handled. A paragraph was added to the revised paper describing 3 possible approaches to the problem.

i. Favouring the use of older risk scores in the meantime

ii. The use of a penalised Cox model to account for the effect of treatment

iii. The use of large cohorts studied over short periods

The methodologies for the last two approaches are described in Chapter 9.

8.2.3 Multiple imputations versus complete case ascertainment

In the quality rating score used for the initial submission, the QRISK scores were penalised more for significant missing values compared to those using complete case data as an inclusion criteria. This was a flaw of the quality score as the use of complete case data may lead to loss of information and study power, and more importantly, may cause bias if the excluded sample is systematically different from the included cases. The qualitative score was removed from the final publication and replaced with a table presenting the different methods with no penalisation as discussed above.

Imputation offers a method of replacing the missing information by using the observed data of other subjects to estimate the distribution of the missing data in the source population. (189) This may use univariable (e.g. mean values) or multivariable (regression model) approaches. The multivariable approach will give an estimated distribution from which the imputed value may be randomly drawn to replace the missing value for the subject in the study.

Single imputation procedure is the term when the imputation is done only once. A more sophisticated technique is multiple imputations where different imputations are made based on a random draw from different estimated underlying distributions. This creates multiple data sets, each which is then analysed as in a complete case dataset. The results are then combined to produce a summary estimate of the association. The technique incorporates uncertainty of the missing data not accounted for by single imputation procedures. (190)

Marshall et al stated that “no definitive guidelines appear to exist on the allowable proportion of missing data to validly apply MI techniques.”(190) Barzi and Woodward found that when missing data was less than 10%, complete case analysis gave similar

results to imputation techniques. (191) With more than 60% missing data, the extreme uncertainty of the imputed values resulted in very high standard deviations and problems in reaching convergence in the distribution of the missing data.

In their study looking at missing data in multiple covariates, Marshall et al found that a 25% missing data affected the significance of covariates in the model analysed by complete case analysis. (190) Multiple imputations produced biased estimates when there were 50% or more missing data when the data was missing at random. However, when the mechanism of missing data was not by random (where the probability of missingness is associated with the unobserved values), multiple imputations produced biased results with more than 10% incomplete cases.

Therefore, complete case analysis is acceptable in studies where the level of missing data is small. Multiple imputations technique is preferable in studies with sizable missing data. With very high levels of missing data (50% for covariate studies and 60% for univariate studies) or when the mechanism of missing data is not at random, the use of multiple imputations is unable to satisfactorily replace the missing information.

In the QRISK studies, there were substantial missing data with more than 70% for ethnicity and more than 60% for cholesterol. (28) Although better than complete case analysis and described as a strength of their study, the use of multiple imputations in the QRISK cohort must be viewed with suspicion with the very high levels of missing data for the risk predictors used in the model.

8.2.4 Performance of different risk scores in the same population

The systematic review highlighted the substantial differences between the existing risk scores in terms of population, predictors and outcomes. It is thus not surprising that the performance of risk scores vary in comparison studies.

As noted in Section 2.3.4.2, the discrimination (ability of the risk score to separate those who develop the outcome from those who do not) of most of the risk scores were similar but calibration was not. (71) Essentially, this means that the ability of the risk scores to rank individuals in a population according to risk is similar but calibration, the translation of ranking into actual absolute risk, differs.

The reason why discrimination is similar is because “biological risk factors behave similarly in diverse populations”. (54) The different risk scores use similar predictors and this similarity allows for acceptable ranking of individuals. But the weight given to each risk predictor is different for each score and thus, the calibration is different. For good calibration, the test population should be similar to that of the derivation population of the risk score. This ensures that the background risks as well as levels of as yet unidentified risk factors for cardiovascular disease in both populations are the same. (70) As noted by Tunstall-Pedoe, if cardiovascular disease was determined exclusively by the classical risk factors, we would have been able to predict the incidence rates of the disease accurately. (54)

Our review has demonstrated that a major factor accounting for differences in calibration is the level of treatment in the study population. This explains why more recent risk scores perform better in validation studies with contemporary populations – the validation population have the similar levels of treatment as the derivation population. Older risk scores would perform badly in comparison. An example is the use of aspirin, which is more widely used in recent times. Increased usage of aspirin in more contemporary populations would decrease the background risk of the population and therefore affect calibration of the older risk scores.

However, the aim of risk prediction in clinical practice is to discuss the patient's risk of having a cardiovascular event if he were to forego treatment. The use of the older risk scores, where the population was largely treatment naïve, is therefore more appropriate for this purpose.

More worryingly, the findings of a recent review by Siontis et al suggest that validation studies on risk scores were open to biases. (192) Their review found 56 pairwise comparisons of 8 risk scores. Of these, only 10 comparisons (18%) found the relative difference in the area under the receiver operating characteristic curve to exceed 5%. In the 38 comparisons that reported calibration, observed versus predicted ratio estimates were inconsistent. The reviewers found significant biases such as outcome selection biases (performance was superior in models where the outcome was the same as that used to derive the model but not its comparator) and optimism biases (authors always claimed superiority of models that they have developed versus comparators). This highlights the need for standardised reporting of such studies by wholly independent researchers.

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

S M Liew,[1,2] J Doust,[3] P Glasziou[2,3]

ABSTRACT

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

Design Review of cardiovascular risk scores.

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

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

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

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

What is already known on this subject

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

What this study adds

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

INTRODUCTION

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

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

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

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

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

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

METHODS OF REVIEW

Objectives

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

Search methods for identification of studies

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

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

Identifying studies

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

Data extraction

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

Analytical methods

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

RESULTS

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

Description of studies

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

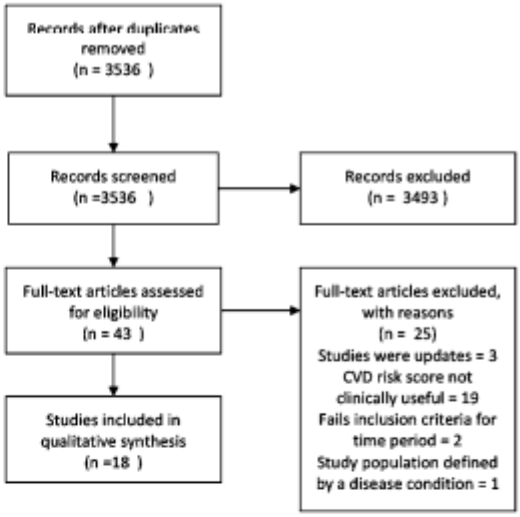


Figure 1 PRISMA flow diagram.

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

Figure 2 shows a timeline chart of the reviewed cohort studies and the introduction of several drugs.[13 14]

Analytical methods

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

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

Risk predictors and their definitions

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

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

Table 1 Description of the studies

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

Framingham Offspring cohort, this definition was broadened to a fasting plasma glucose level ≥140 mg/dl (7.7 mmol/l) or treatment requirement.[18] This in turn differs from the current definition used by the World Health Organization (WHO) of fasting plasma glucose ≥126 mg/dl (7.0 mmol/l).[31] Hence, patients with fasting plasma glucose between 126 and 150 mg/dl (7–8.3 mmol/l) would be classed as non-diabetics by the first Framingham score. Systolic blood pressure measurement

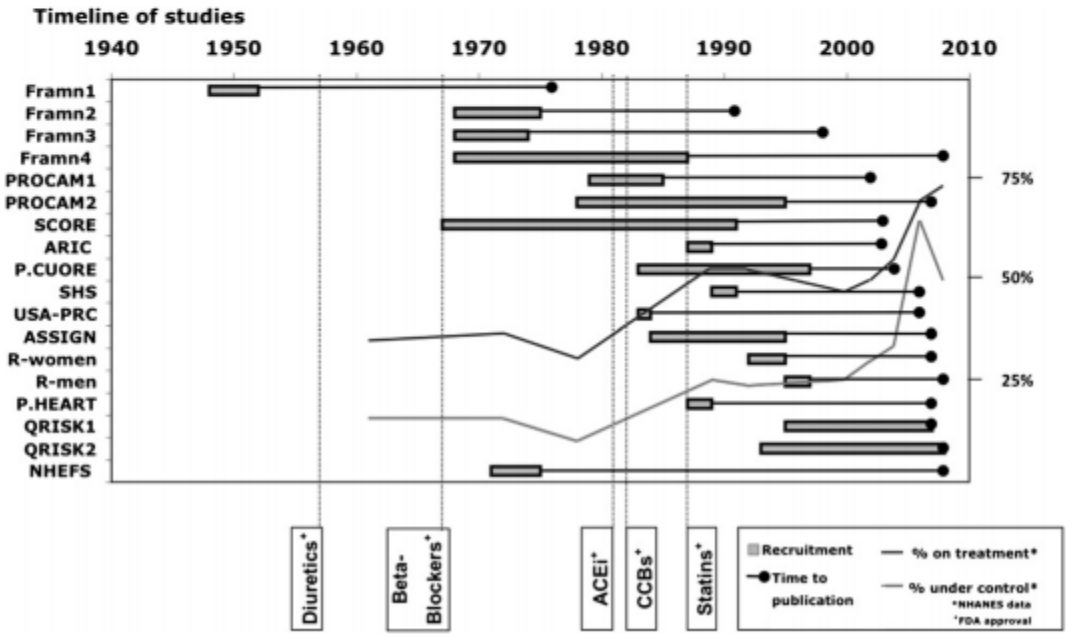


Figure 2 Timeline of studies.

Table 2 Analytical methods

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

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

Table 3 Predictors

		Age	Sex	Smoking	SBP	DBP	Sr. Chol	HDL	Tg	Diabetes	LVH	Antihyp med.	BMI	Ethnicity	Family hx	SCE status	Rh. arthritis	Chronic renal dx	Atrial fib.	Bio-markers	Physical activity	No of predictors/ no of candidate predictors
Framingham 1976		Years	M/F	Y/N	average of 2 readings		TC			FBS≥ 6.3 / urine +	ECG-LVH											7/19+
Framingham 1991		Years	M/F	Y/N	average of 2 readings	SBP alternative	TC			Original: FBS≥6.3; Offspring: FBS≥7.7	ECG-LVH											8/19+
Framingham 1998		Years	M/F	Y/N	average of 2 readings	SBP alternative	TC or LDL															7/19+
Framingham 2008	General	Years	M/F	Y/N	average of 2 readings		TC			Original: FBS≥7.7); Offspring: FBS≥6.9		Y/N										8/19+
	Rare Lab	Years	M/F	Y/N	average of 2 readings							Y/N	3 groups									7/19+
PROCAM 2002		Years	NA	Y/N	2 readings+ 2nd taken		LDL			FBS ≥ 6.6					Y/N							8/87
PROCAM 2007	CHD	Years	M/F	Y/N	2 readings+ 2nd taken		LDL			FBS ≥ 6.6					Y/N							8/87
	Stroke	Years	M/F	Y/N	2 readings+ 2nd taken					FBS ≥ 6.6												8/87
SCORE 2003		Years	M/F	Y/N	Not stated		TC or ratio															9/9
ARIC 2003		Years	M/F	Y/N	average of last 2 of 3 readings		TC			FBS≥ 7.0		Y/N		2 groups								9/27
Progetto CUORE 2004		Years	M/F	Y/N	average of 2 readings		TC			FBS ≥ 7.0		Y/N										8/19
SHS 2006		Years	M/F	Y/N	average of last 2 of 3 readings		TC or LDL			FBS≥ 7.0		Y/N								albuminuria		9/14
USA-PRC 2008		Years	M/F	Y/N	average of 3 readings		TC			FBS≥ 7.0			2 groups									7/7
ASSIGN 2007		Years	M/F	Y/N plus eligibility	average of 2 readings		TC			Not stated HbA1c if diabetic					Y/N	BMD						9/11+
Reynolds women 2007		Years	NA	Y/N	self reported		TC								Y/N					hsCRP		8/28
Reynolds men 2008		Years	NA	Y/N	self reported		TC			excluded at baseline					Y/N					hsCRP		8/8
Personal Heart 2007	men	Years	NA	Y/M Partner	previous diagnosis of hypertension		previous diagnosis of hypercholesterolemia			previous diagnosis of diabetes					Y/N							7/13
	women	Years	NA	Y/M Partner	previous diagnosis of hypertension		previous diagnosis of hypercholesterolemia			previous diagnosis of diabetes			2 groups									6/13
QRISK 2007		Years	M/F	Y/N	GP record		TC/HDL ratio			excluded at baseline		Y/N	recorded value		Y/N	Townsend						9/11
QRISK 2 2008		Years	M/F	Y/N	GP record		TC/HDL ratio			recorded diagnosis		Y/N	recorded value	9 groups	Y/N	Townsend	recorded diagnosis	recorded diagnosis	recorded diagnosis			14/14
NHEFS 2008		Years	M/F	Y/N	average of last 2 of 3 readings					previous diagnosis of diabetes			4 groups									8/8

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

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

Outcomes predicted

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

Methods to assess outcome events also differed. The SCORE and ASSIGN scores used hard outcomes with diagnostic codes such as ICD 9/10 codes. 'Hard outcomes' can be defined as irrevocable events[32] that have permanent consequences, such as myocardial infarction and death, as opposed to 'soft events', such as hospitalisation for angina. The Framingham studies included a broader composite of hard and soft end points. Diagnostic criteria for outcomes in Progetto CUORE and the USA-PRC cohorts followed the WHO-MONICA Study (WHO—MONItoring trends and determinants in CArdiovascular disease project).[28 30] Expert panels reviewed medical records and hospital notes in the Framingham studies, PROCAM scores, ARIC, SHS, Reynolds studies and the NHEFS. QRISK1 and 2 used general practice electronic recorded diagnosis or death certificates linked to the computer system.

Adjustment for treatment effects

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

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

Table 4 Outcomes

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

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

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

DISCUSSION

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

Whichever risk equation they choose, clinicians should know which outcomes are predicted. As the outcomes predicted differ significantly, the risk scores are not interchangeable. For example, the Framingham risk scores predict a broad range of cardiovascular events (including cerebrovascular events), whereas SCORE only predicts fatal cardiovascular events. The Framingham Study risk scores have been criticised for the inclusion of 'soft' (subjective) outcomes such as angina,[10] although the Framingham investigators argue that such outcomes estimate the total cardiovascular disease burden[19] and are clinically important to both patient and doctor. Revascularisation interventions may also be criticised as being subjective.

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

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

Table 5 Treatment effect

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

Shaded areas, information not reported; Antihpt, antihypertensive medication; SBP, systolic blood pressure; pred, predictors.
*Corrected for change in risk factors by factoring in changes at midpoint of follow-up—that is, 1993/1994.

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

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

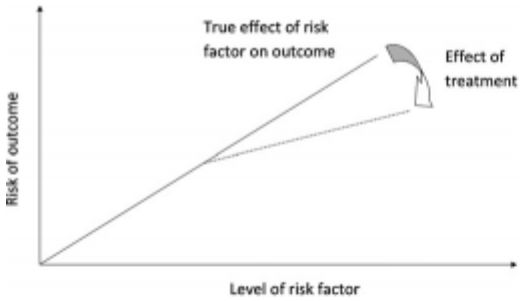


Figure 3 True effect of risk factor on outcome.

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

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

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

Strengths and weaknesses of the study

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

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

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

The 2005 review by Beswick *et al*[43] included in the appendix of the NICE guidelines identified 110 studies, with 70 meant specifically for application in primary prevention. The difference in the number of studies identified is due to their wider inclusion criteria, which included studies restricted to a disease condition, studies that had participants with prior cardiovascular disease, studies that were recalibrations or modifications of the original cohort study, studies that did not use absolute risk scoring, and studies where the duration of prediction was not specified. More recent studies such as QRISK and Reynolds scores are not included, as their search concluded in April 2005.

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

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

Unanswered questions and future research

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

Authors' conclusions

Implications

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

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Competing interests None.

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8.3 Manuscript for qualitative study

A manuscript of qualitative study has been prepared for submission for publication. The article was shortened for succinctness with the main issues prioritised in each section for the intended audience, that is, general practitioners in the United Kingdom. This was to ensure that the paper was clear and readable yet novel enough for publication without subversion of the original data or analysis.

How this study fits in:

All general practitioners in the UK are now required to use risk scores in their clinical practice but informal discussion suggested variability in how they are interpreted and used. Only one previous qualitative study outside the UK has explored this issue and our findings suggest considerable confusion in understanding and variability in practice. National guidance does not appear to be fit for purpose as it has become increasingly complex while failing to reflect how practitioners are actually using the scores and the advice that they need. Patients would be better served by simple advice to practitioners to use a Framingham score and exercise more clinical judgement, explaining to patients the necessary imprecision of any individual estimate of risk.

Abstract

Background

NICE guidelines and the Quality Outcomes Framework require practitioners to use risk scores in the primary prevention of cardiovascular disease

Aim

To explore general practitioners understanding and use of cardiovascular risk scores

Design

Qualitative study with purposive maximum variation sampling

Participants and setting

Twenty general practitioners working in Oxfordshire, UK

Method

Thematic analysis of transcriptions of face-to-face interviews with participants undertaken by two individuals (one clinical, one non-clinical).

Results

General practitioners use cardiovascular risk scores primarily to guide treatment decisions by estimating the risk of a vascular event if the patient remains untreated. They expressed considerable uncertainty about how and whether to take account of existing treatment or other form of prior risk modification. They were also unclear about the choice between the older scores based on the Framingham study and newer scores such as QRISK. There was substantial variation in opinion about whether scores could legitimately be used to show patients the effect of treatment. The overall impression was of considerable confusion.

Conclusion

National guidance needs to be simplified and to reflect better the ways in which cardiovascular risk scores are used in general practice to be fit for purpose. Patients would be better served by simple advice to use a Framingham score and exercise more clinical judgement, explaining to patients the necessary imprecision of any individual estimate of risk. The drive to estimate risk more precisely by qualifying guidance and promoting new scores based on partially-treated populations appears to have created unnecessary confusion for little obvious benefit.

Introduction

It would not be surprising if general practitioners in the UK were confused. They are incentivised by the Quality and Outcomes Framework to use an “agreed risk score” in all patients to inform their decision to prescribe medication for the primary prevention of stroke or heart attack [1]. However, it is no longer clear what risk score is “agreed”. The clarity of the early guidance on what risk scoring system to choose and how to apply it in practice has been lost - for example, in 2010 NICE withdrew their firm recommendation to use a Framingham-derived score [2]. Moreover, both the scientific literature and coffee-table professional newspapers have been questioning the usefulness of the 10-year risk scores in common use. Again for example, the BMJ has devoted substantial space to QRISK and in August 2011 the newspaper *Pulse* reported that a score based on lifetime risk was now favoured by both NICE and the responsible expert committee [3-6].

Informal discussion with general practitioner colleagues produced a broad consensus that a score based on a study done fifty years ago in another country must be out-of-date. There was also a broadly expressed view, supported by a previous study reported in this journal [7], that any risk score based purely on physiological measurements and reported smoking habit would underestimate the real cardiovascular risk in areas of social deprivation. However, these informal views did not appear to be based on a very clear understanding of the difference between the risk scores or how they had been derived. They also revealed a substantial variation in the way that colleagues actually used the risk scores in everyday practice. We report here a formal qualitative study to explore and expose this important issue.

Method

Setting and participants

This study involved one-to-one, semi-structured interviews of general practitioners working in Oxfordshire, United Kingdom. Postal invitations were initially sent out to 222 practitioners from a list compiled from the Thames Valley Primary Care Agency and practice websites; those who volunteered to be interviewed were also asked to suggest potentially interested colleagues to whom a further invitation was sent by e-mail. Recruitment continued until data saturation which was achieved after 20 interviews. Participants were between 32 and 61 years; four were women. Most participants were profit-sharing partners in the practice, three were salaried partners and one was a registrar. All participants used on-desk computers for record keeping in the consultation and so had access to electronic versions of the risk scores.

Data collection

Interviews were conducted at the participant's workplace or home depending on his or her preference. The interviews lasted between 30 to 60 minutes, were audio-recorded and transcribed verbatim using study codes to keep the identities anonymous. An interview guide was used with a list of open-ended questions covering broad themes (see appendix). Participants were allowed to diverge into new directions with interesting diversions followed up by further exploration from the interviewer. An iterative approach was used whereby later questioning was informed by the use of answers from earlier interviews.

Data analysis

The transcripts were checked for accuracy. After repeated reading of the transcripts, the text was coded independently under different headings by two coders, using a

thematic approach to analysis. The few discrepancies in coding were resolved by discussion. Once coding was finished, a written and graphical summary of the issues was created for each code using the OSOP (one sheet of paper) method where every section of data relevant to that code from all the different interviews is noted. The software package NVivo9 facilitated the analysis of themes and systematic comparison across transcripts [8]. Given the volume of data and the main objective of this study, detailed analysis focused on the use of cardiovascular risk scores to inform treatment decisions.

Results

What do practitioners say the risk scores predict?

All the participants said initially that they perceived the calculated risk to be the patient's risk prior to any modification by treatment or lifestyle change and this is what they communicate to patients.

GP7: (This is the risk) over the next ten years (if he remains) as he is, that's what I've taken it to be. If he stays as he is. And if we can change some of those things, we can reduce that risk for him.

GP10: I suppose I would see it as the risk if no intervention was made, if there was, you know, assuming these parameters, this blood pressure, and this lipid profile, if that is unmodified, this is your risk over the following ten years.

However, when encouraged to reflect on whether scores did in fact assess this unmodified risk, when many had been derived from populations whose identified risk had been treated, considerable uncertainty was expressed.

GP3: It's obvious when you think about it, that there's an issue about how treatment is going to change outcomes. And that'll interfere with prediction.

GP6: People being treated while they're being observed – even just lifestyle

treatment can make a huge difference. And we're all far more health conscious than we were fifty years ago. So yes, I think that is a strong case in favour of the older (risk scores).

GP8: So you take your population at year zero, you follow them all through but you don't actually know who's been treated. Oh gosh, yes, so that actually brings huge inaccuracy into the risk scores then.

Two of the participants explicitly reflected on the difficulties faced by those constructing risk scores in allowing for the effect of treatment in modern study populations. One of them noted the impossibility of having the perfect risk score, calling it a "Utopia".

GP17: I kind of assumed that, maybe naively, that the data is updated…. I wouldn't pretend to understand… I think intuitively it makes sense that the older data is probably going to be more useful but I don't know.

GP18: If someone's on blood pressure treatment, do you say that treatment of blood pressure reduces (the assessed risk) by two thirds and therefore you need to modify for the third as not being attenuated? It's all very, very grey, isn't it?

Do practitioners use risk scores in patients already on treatment?

The participants expressed conflicting views on whether the risk scores could be used in patients who had already received risk factor lowering treatment or lifestyle advice. Some felt that the risk scores were not designed for this use and therefore not valid. One doctor, who also worked with BUPA alongside his GP work, mentioned that BUPA specifically instructed its doctors not to use the risk scores in patients who were already on treatment.

GP6: No… I say, "This is your risk…..Let's lower your blood pressure, let's lower your cholesterol and see how you go." End of story is carry on with the treatment.

GP7: Once they're on it, I ignore, I don't do it. Well, it doesn't work afterwards anyway. Once you're on treatment, it's no longer valid, is it?

However in the past general practitioners have used cardiovascular risk charts to show how changing risk factors might influence risk (e.g. using the charts in the back of the British National Formulary to show how they would be in the green rather than red zone if they were a non-smoker rather than smoker) and one participant said explicitly that he used the risk scores to help patients on treatment to "understand" cardiovascular risk, although he added that "the evidence behind that is less clear, isn't it?"

Participants also seemed to discriminate between assessing initial risk in patients who might have received prior treatment or lifestyle advice, when a number felt that the risk score could be used, and using risk scores to monitor the effect of treatment on risk, which was seen as invalid.

GP4 (Risk scores are) more useful in determining whether you start somebody on treatment, not to monitor. Once you've got somebody on treatment, you can't really use it to work out their risk.

GP13: Obviously it gets quite complicated when you talk about, you know, is the risk the same if you're on treatment. But I tend to look at it that this is the risk that depends on your cholesterol level, your blood pressure whatever, whether or not you're on treatment.

How do practitioners take account of treatment?

A number of participants felt that when they used the risk scores in patients who had already received treatment they should make some adjustment to the assessed risk.

GP1: I do a sort of rough adjustment when that situation arises.

GP3: That's something I've never clarified. Do you use their pre-treatment blood

pressure or their treated blood pressure and once they're on treatment, is their treated blood pressure all you need to know, or should you also put in they're hypertensive and that? Well, you do put that in. I don't know.

GP11: So what number should you put in? Should you put their pre-treatment cholesterol in?

Participant GP4 believed that the worst blood pressure and cholesterol reading should be used to work out the risk. Another participant felt that using pre-treatment values was unfair because treatment decreases risk with time even though he recognized that the true risk may be higher due to a history of exposure to higher levels of risk factor.

GP14: I know some people advocate using baseline, you know, pre-treatment values to calculate it. I think that's slightly unfair because I think your risk does fall with… the whole reason we treat is your risk does fall with time if you're established on treatment and I don't think I have the time or energy to say "Well, this person has been on treatment for six years but that person's only been on treatment for two weeks." So I mean, it's a murky compromise using actual readings but that's what we do.

How do practitioners choose which score to use?

A number of participants said that they used a Framingham-derived score for patients who were not treated and QRISK for those on treatment. Some participants believed that Framingham could only be used on those who were treatment naïve whereas QRISK could or should be used in those who were already on treatment.

GP1: Well, I know the Framingham is supposed to be a pre-treatment risk. I think QRISK is different in that it gives you the risk on that specific day treated.

GP19: And also importantly, it (QRISK) also includes patients that have got treated

hypertension and in practice, a big prescribing decision obviously is when patients are already on hypertensive treatment, about making the decision about whether they should go on and have statins etc. And again the problem with the Framingham risk score is not being able to do that, whereas with QRISK obviously, that takes that into account.

However, most participants expressed uncertainty about which risk score to use. Participant GP19 quoted immediately above went on to ask whether his belief that Framingham was not supposed to be applied to treated patients was correct.

Do practitioners think score accuracy matters?

Although a number of participants were very concerned about what they perceived to be a lack of clarity in the application of risk scores, others took a contrary view. They saw a risk score as something simple to use pragmatically and expressed little interest in taking account of treatment or any other perceived complexity in its application.

GP15: I probably do it at an even more basic level than that [taking account of treatment].....I kind of use it really as a very simple decision making tool at that kind of level, rather than trying to go into as much detail as you're sort of implying.

GP 19: My understanding is much more simplistic. It is what their current level of risk is at this precise moment.

This emphasis on pragmatic simplicity rather than accuracy may seem surprising as the risk is communicated to patients who take it at face value. However, it may reflect practitioners' understanding of the limited power of any risk score to make an individual prediction of risk highlighted in some guidelines. For example, the Scottish SIGN guidance states explicitly that "risk scores cannot predict absolute risk", rather stressing their utility in "prioritising treatment on an equitable basis" [9].

Discussion

Summary of main findings

The main finding of the study is to highlight variation, and considerable confusion, among practitioners in how they use cardiovascular risk assessment scores. The current guidance does not appear to address very effectively the difficulties experienced by practitioners in using the scores in everyday practice. General practitioners use them primarily to estimate (and communicate to their patients) their risk of a vascular event if they remained untreated. They therefore want the best possible estimate of pre-treatment risk and need simple guidance on how to adjust this estimate for any existing drug treatment or other prior modification of risk.

The current situation, where NICE has withdrawn its guidance to use a Framingham-derived score to allow practitioners to make their own decision, is challenged by our findings. The simplicity of a national recommendation to use a score derived from an untreated population to estimate and communicate untreated risk has been lost. Our participants were very unclear about the differences between scores and the benefits and drawbacks of more recent scores derived in partially treated populations. They also exhibited substantial variation in opinion about whether they could legitimately use any score to show patients the effect of treatment and, if so, how best to do that. The recommendation of new scores predicting lifetime rather than 10-year risk seems likely to further complicate what is already a poorly understood choice.

The specific uncertainty expressed about the use of risk scores in patients who have already received some drug treatment probably reflects in part changes in advice over time. The guidance on use of the Joint British Societies' risk charts first published in the BMJ in 2000 stated simply that they "should not be used to estimate risk after treatment of hyperlipidaemia or blood pressure has been initiated" [9].

However, the two-page “How to use the risk prediction charts” section in the British National Formulary reflects the 2005 Joint British Societies guidance to estimate CVD risk retrospectively, stating that “unless recent pre-treatment risk factors are available it is generally safest to assume that CVD risk is higher than predicted” [10]. Criticism about the potential inaccuracy of estimated risk has also led to an increasing number of qualifications in guidance about the use of risk scores in different sub-groups which may have exceeded the attention span of many users.

Strengths and weaknesses

Most previous studies in this area have been quantitative surveys to determine the percentage of doctors who use risk scores [11-14]. The few qualitative studies have focused on barriers to use and the difficulty experienced by doctors and patients in interpreting numerical information such as relative and absolute risk [15-17]. Only one previous study from Berlin has used qualitative methodology to explore in-depth general practitioners’ understanding and use of risk scores [18]. This placed more emphasis than expressed by our participants on the importance of accuracy in individual risk prediction.

The use of a qualitative approach in our study allowed practitioners to express the issues that were important to them, flagging up in particular their uncertainty about how to use risk scores when patients had already modified their risk to some extent through lifestyle modification or treatment. It also allowed exploration of the thorny issue of choice between risk scores and whether doctors’ believed they were communicating to patients the risk before or after risk modification. It is unlikely that the same issues would have been highlighted if a quantitative approach had been used.

The weakness of the study is that all participants were from practices in Oxfordshire

(where general practice is well staffed), came from a restricted demographic group (mainly white male Caucasians), and probably agreed to participate because they found the issue of interest. So despite the intention to purposively sample to obtain a maximum diversity sample, this was achieved only in terms of age, employment status and practice size. It seems likely that participants would have been more enthusiastic and knowledgeable about cardiovascular risk scores than the average general practitioner in the UK or elsewhere. A true maximum variability sample is likely to have discovered less enthusiasm for risk scores and more misunderstanding.

Implications for clinical practice and research

Maybe cardiovascular risk scores have gone beyond their sell-by date. Some would argue that individual risk prediction is both illogical and cost-inefficient and should now be superseded by a polypill approach to cardiovascular disease prevention, offering primary preventive treatment to all over a certain age on a "fire and forget" basis [19]. However, we should not forget that when risk scores were introduced they were welcomed for three reasons: 1) they showed very effectively the interaction between risk factors and support holistic decisions based on assessment of cumulative risk; 2) they allowed practitioners to demonstrate to patients the potential benefits of risk modification; 3) they were simple. The older authors practising at the time certainly saw them as a heuristic aid to prescribing and communication rather than a mechanism for accurately predicting individual risk. They were particularly liked by health policy makers concerned with directing scarce resources to those most likely to benefit and the accuracy of individual risk prediction was unimportant for this purpose.

Our findings certainly suggest that pursuing the holy grail of a perfect cardiovascular

risk prediction score is helping neither doctors nor patients. The participating general practitioners were clear that they wanted to know the untreated risk, both to guide treatment decisions and to educate and assist patients about risk. NICE should therefore reinstate its firm recommendation to use a Framingham derived score and simplify its message. No risk score has the potential to estimate accurately individual risk but demonstrating the impact and interaction of untreated risk to an individual patient is a simple and worthwhile activity in general practice which is in danger of being lost.

Others have already called for a simplification of guidelines [11, 12]. This is not simply a call to address the likelihood that 2-pages of introductory qualifications and refining algorithms are unlikely to be read and implemented in practice. It is also a call for communicating clarity of purpose. Risk scores were being used by our participants, with varying appropriateness, to assess and communicate four different things: 1) unmodified risk; 2) risk after partial treatment; 3) the potential benefit of treatment; 4) the effect of treatment. No single score or guidance to modify a risk estimate will be optimal for all four tasks.

Conclusion

General practitioners use risk scores mainly to communicate untreated risk. To do that simply and effectively they need simpler guidance and advice on how to use a Framingham-derived score. The knowledge that the estimates are based on an archaic population is probably helpful in reminding practitioners and patients that the score provides only a very approximate estimate of individual risk which, as everyone agrees, is no substitute for a holistic clinical judgement taking full account of non-cardiovascular co-morbidity and the wishes of the patient.

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8.4 Modelling study published in BMJ Open

In 2011, the modelling study was submitted and subsequently accepted for publication after revision of the following issues. (193)

8.4.1 Research question

The research question was not clearly described in the initial submission and was misinterpreted to be about the advantages of starting treatment 5 years earlier. This differs from the actual research question, which was whether the young and the elderly should be treated differently, that is “does a true difference in impact on life years lost in those at different ages but the same cardiovascular risk?”

In the revision, a paragraph was added to the introduction to ensure that the research question was clear.

8.4.2 Markov modelling

Another issue was on whether patient preferences and costs were necessary components of Markov modelling. Markov analysis is used to answer many different types of questions and does not need to include patient preferences and costs. (157) The two factors were not included because they were irrelevant to the research question.

8.4.3 The use of fatal versus non-fatal events in the model

The selection of only fatal events in the model was for the following reasons:

1. The main argument for differential treatment of the same level of risk at different ages is that the young live longer and risk greater loss of life years than the old.

In order to counter this, our model focused on the estimation of life year lost due to fatal events. Studies researching the cost effectiveness of cardiovascular risk factor treatments have found that the loss of quality of life after a myocardial event is minimal. (160, 194)

2. As in quality-adjusted life years, time preference incorporates the use of techniques such as time trade-off. The use of both QALYs and time preference in the same model leads to ‘double discounting’, as noted in section 7.4.
3. There is a substantial heterogeneity in utility estimates for cardiovascular health states reported in the literature. A recent systematic review found the EQ-5D, a health-related quality of life measure, to range from 0.24 (SD 0.39) to 0.90 (SD 0.16) for patients with cardiovascular diseases. (195) The wide variation occurred due to differences in disease stage, treatment and patient characteristics.
4. The addition of non-fatal events would necessitate greater assumptions. For example, in the decision analysis model created by Montgomery, every second cardiovascular event was fatal and the same probabilities were used for all ages, sex and risk strata for cardiovascular event recurrence rates because of the lack of age- and sex-specific data. (162)

Although the use of non-fatal events was considered, the final decision was to use only fatal events because adjusting for quality of life would have not contributed significantly to the results but would have increased uncertainty and necessitated greater assumptions.

Should identical CVD risks in young and old patients be managed identically? Results from two models

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ABSTRACT

Objectives: To assess whether delaying risk reduction treatment has a different impact on potential life years lost in younger compared with older patients at the same baseline short-term cardiovascular risk.

Design: Modelling based on population data.

Methods: Potential years of life lost from a 5-year treatment delay were estimated for patients of different ages but with the same cardiovascular risk (either 5% or 10% 5-year risk). Two models were used: an age-based residual life expectancy model and a Markov simulation model. Age-specific case fatality rates and time preferences were applied to both models, and competing mortality risks were incorporated into the Markov model.

Results: Younger patients had more potential life years to lose if untreated, but the maximum difference between 35 and 85 years was <1 year, when models were unadjusted for time preferences or competing risk. When these adjusters were included, the maximum difference fell to about 1 month, although the direction was reversed with older people having more to lose.

Conclusions: Surprisingly, age at onset of treatment has little impact on the likely benefits of interventions that reduce cardiovascular risk because of the opposing effects of life expectancy, case fatality, time preferences and competing risks. These findings challenge the appropriateness of recommendations to use lower risk-based treatment thresholds in younger patients.

ARTICLE SUMMARY

Article focus

- Short-term cardiovascular risk scores have been criticised as being biased towards treatment of older patients and for leading to delayed treatment in younger patients.
- The fundamental question remains as to whether there is a true difference in potential life years lost for patients of different ages but with the same short-term cardiovascular risk.
- We used mathematical models to compare the potential life years lost for a 5-year treatment delay versus no delay obtained for patients at different ages but at the same short-term coronary heart disease (CHD) risk. These models incorporate age-specific case fatality rates, competing risks and time preference.

Key messages

- Patient age at onset of treatment will have little impact on the likely benefits of interventions that reduce cardiovascular risk.
- This is because of the opposing effects of life expectancy, case fatality, time preferences and competing risks.
- These findings challenge the appropriateness of recommendations to use lower risk-based treatment thresholds in younger patients.

Strengths and limitations of this study

- Two different models were used and the results corroborate. Neither relies on the use of a particular risk score.
- The models only accounted for life years lost due through death and not quality of life lost due to non-fatal events. As the severity of non-fatal events also increases with age, the direction of the findings would likely be similar if these events were included.
- Only case fatality rates for CHD were used in the models as relevant data for total cardiovascular disease were not available. The results are unlikely to change with the addition of cerebrovascular disease as 5-year case fatality rates by age are similar for CHD and stroke.

INTRODUCTION

A common criticism of using short-term (eg, 5- or 10-year) cardiovascular disease (CVD) risk calculators is that they strongly favour treating older individuals who generally have high short-term risk but lower life expectancy.[1–3] Intuitively, a young person at the same short-term CVD risk as an old person would appear to lose more in terms of life years simply because of their longer life expectancy. The dilemma is brought into sharpest focus when we consider patients at the same short-term risk but of different ages. Given a predicted CVD risk, of say 20% in 10 years, who stands to gain more from treatment: the young or the old patient?

This apparent limitation of short-term CVD risk prediction may explain the increasing interest in models that attempt to redress the perceived imbalance towards treating older people, such as lifetime CVD risk prediction models.[3 4] These models are promoted as being better at identifying individuals who do not reach the recommended treatment threshold using standard 5- or 10-year risk calculators[5] but have an increased relative risk (RR) of CVD compared with their peers: mainly young men with multiple but modestly increased risk factors.[3] It has been proposed that these individuals, who are at low 10-year risk but high lifetime risk, should be started on treatment.

Experts, however, have questioned the use of such approaches in clinical practice.[6 7] It is true that older people have a shorter life expectancy than the young but they also have higher case fatality rates after a cardiovascular event.[8] The case fatality rates from other competing risks, that is, non-CVDs, are also higher with increasing age. The consequences of using lifetime risk assessment would mean that larger numbers of young asymptomatic individuals would be expected to take drugs every day for many years, potentially causing short-term harm, in order to prevent or delay an event occurring in the far-off future. Indeed, the lifetime risk approach may not accurately represent the decisional issues as it ignores three important factors: age-specific case fatality rates, competing risks and 'time preferences' that value the near future over the distant future.

This study addresses the fundamental question: is there a true difference in potential life years lost for patients of different ages but with the same short-term cardiovascular risk? If there is no difference, then attempts to correct the perceived imbalance are unnecessary and will have unintended harmful consequences. In this paper, mathematical models were used to quantify the size and direction of any differences in losses of young and old patients at identical short-term risks of CVD. These models incorporate the factors of age-specific case fatality rates, competing risks and time preference.

METHODS

In order to answer the question of whether the young and old should be treated differently, a comparison of potential life years lost for a 5-year treatment delay versus no delay is obtained for patients at different ages but at the same short-term coronary heart disease (CHD) risk. This simulates a scenario where two patients—one young and the other old—present with identical absolute CHD risks; does one patient suffer greater potential life year loss from a 5-year treatment delay than the other?

Figure 1 illustrates the method used to address the study question. First, the life expectancy is calculated for a person in the age group 35–39 at a specified 5-year CHD risk (for example, 10%) who remains untreated (top arrow). Next, the life expectancy of a person of identical age and risk is estimated but with the CHD risk for the first 5 years reduced to zero (the hypothetical treatment is assumed to be 100% effective—second arrow). The difference in life expectancy from the results of both arms gives the potential years of life lost (PYLL) due to a treatment delay of 5 years for that age and CHD risk.

Figure 1 also shows how the same process is used to determine the PYLL due to a treatment delay for a person in the age group 50–54 at the same CHD risk as the younger person. The $PYLL^{35-39}$ can then be compared with the $PYLL^{50-54}$ to compare the life years lost with treatment delay at different ages but at the same absolute risk level.

The process was repeated for different age groups from age 35 to 85. This allows the graphical comparison and detection of trends of losses due to treatment delay at different ages but at the same specified absolute risk level.

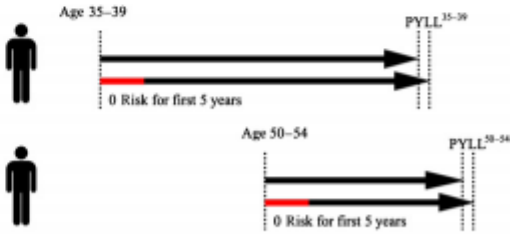
Treatment is assumed to be 100% effective. While this will exaggerate the absolute effect of treatment, it provides a valid relative comparison of the PYLL for a treatment delay of 5 years at different ages and at different risk levels. The difference of 100% effectiveness applies to all strategies, so it 'overestimates' equally for all; it would give the same relative results if a 30% or 50% reduction was used.

Two different modelling approaches (age-based residual life expectancy models and Markov simulation cohort models) are used to determine the PYLL by not initiating treatment earlier in patients with the same 5-year CHD risk but at different ages. Five-year risk levels of 5% and 10% were selected, as they are approximately equivalent to 10-year risks of 10% and 20%—the key thresholds in UK and European guidelines.[9 10]

Sensitivity analysis was conducted by the use of two different models and various time preference rates.

Age-based residual life expectancy model

In this model, the hypothetical treated cohort has a zero risk of CHD death during the 5-year treatment period,



PYLL = Potential years of life lost at a 5-year coronary heart disease risk level

Figure 1 Method used to estimate the potential years of life lost for a 5-year treatment delay in older and younger patients with the same 5-year cardiovascular disease risk. Arrows indicate life expectancies in those treated from baseline for 5 years (red part of lower arrow for each patient) and those not treated.

returns to the average risk of the general population at 5 years and then uses the average further life expectancy (beyond the 5 years) for the population to calculate the PYLL. The calculation was done with and without a time preference rate to account for the increasingly lower value that patients currently give to life years further out into the future. The preference rate accounts for both the uncertainty surrounding future events ('risk aversion') and the natural preference for present gratification as compared with future benefit (time preference). A positive time preference rate is placed on later years, meaning that the further it is in the future, the smaller the value of that life year.[11 12]

The formula for life expectancy with time preference is[13]

$$\text{Life expectancy with time preference } r = \frac{1}{r}\cdot\left[1-\frac{1}{(1+r)^{LE}}\right],$$

where r is the time preference rate and LE is the national life expectancy estimates. A minimal time preference rate of 0.03 was used, which values the next year as worth 97% of the previous year. This preference rate is applied throughout the remaining estimated years of life of the cohort.

The PYLL due to being exposed to a set CHD risk level at different ages was then calculated using the following formula:

$$\text{Potential life years lost at age A} = \text{CHD risk} \times \text{CFR}_A \times \text{LEr},$$

where CHD is coronary heart disease, CFR is the age-specific case fatality rate and LE_r is the life expectancy with time preference. Estimated life expectancy by age and sex was obtained from interim life tables for the years 2005–2007 from the Office of National Statistics, UK.[14] Case fatality rates by age and sex for 1994–1998 were obtained from a 2001 report to the UK Department of Health on data from the Oxford record linkage study.[15]

Markov simulation cohort

As with the first (age-based residual life expectancy) model, the hypothetical treated cohort in the Markov model has a zero CHD mortality risk during the 5-year treatment period. However, in contrast to the first model, the Markov model subsequently differentiates between the ongoing competing risks of death, CHD and non-CHD, of both the treated and untreated hypothetical cohorts.

The Markov model calculates the life expectancy of simulated cohorts with 100 hypothetical people for 5-year age groups starting from 35 (ie, 35–39, 40–44, etc). The cohorts were modelled with a base CHD risk of 5% in 5 years, and the process was repeated using a base CHD risk of 10% in 5 years. All the cohort members start in the 'well state'. The length of each cycle is set at 5 years. In every cycle, we calculate the numbers who die due to CHD (starting with the base CHD risk specified and age-specific myocardial infarction (MI) case fatality rates[15]) and those due to non-CHD using non-CHD case fatality rates.[16 17] Non-CHD rates were derived from the Office of National Statistics on UK death registrations by age, sex and underlying cause and population estimates for 2007.[16 17] We used the RR of CHD per year of increasing age (RR=1.05 for men and RR=1.04 for women) as given by the Framingham study[18] to calculate the increase in CHD risk in each cycle. The process is repeated, moving more and more members into the 'dead state', until the cycle sum falls below 1 person-cycle where every member is dead.[19] The life expectancy of the cohort is obtained by adding up the number of person life years in the 'well' column. For the same age band, we repeat the process using the same rates except that for the first cycle, the CHD risk is reduced to 0. The potential life years lost for one person is then calculated by the following formula:

$$\text{PYLL at age A} = \left(LE^{\text{COHORT WITH BASE RISK}} - LE^{\text{COHORT INITIAL RISK 0}}\right)/100\times 5.$$

This, in effect, allows the results of the simulation to be comparable to the first method.

We then applied a time preference rate with half cycle correction to the Markov simulation cohort model. The Markov simulation cohort assumes that transition from one state to another occurs between cycles and that the number of participants in each state remains stable during the cycle. If membership of the cohort is counted at the beginning of the cycle, this leads to overestimation of the life expectancy of the cohort. If counted at the end of the cycle, there is underestimation of the life expectancy of the cohort. To correct this, a half cycle correction is employed whereby transition is assumed to occur halfway through the cycle.[19]

RESULTS

Using a time preference rate of 0.03, the life expectancies for different age groups were obtained as shown in table 1. Figure 2 shows the PYLL with and without using the time preference rate of 0.03.

Figures 2 and 3 show the results obtained from both models. The black lines represent the age-based residual life expectancy models and the red lines represent the Markov models. The dotted lines indicate the results of the models without time preference and the solid lines for those with time preference.

The PYLL from delaying treatment by 5 years for different ages for both the 5% and 10% 5-year CHD risk levels can be read from the graphs. For example, the results show that for a treatment delay of 5 years, the PYLL over a lifetime for a 35–39-year-old person at 10% 5-year CHD risk is slightly >1 year in the age-based residual life expectancy model and 0.75 year in the

Table 1 Estimates of life expectancy, UK; without time preference (r=0) and with a time preference rate (r=0.03)

Age group	Age-specific CHD case fatality rates (%)	5-year CHD death rate (%) for 5%; 10% 5-year CHD risk	Life expectancy (yrs)—national estimates without a time preference	Life expectancy with time preference rate of 0.03
35–39	25.9	1.3; 2.6	41.65	23.6
40–44	29.1	1.5; 2.9	36.95	22.15
45–49	30.7	1.5; 3.1	32.33	20.51
50–54	33.1	1.7; 3.3	27.85	18.7
55–59	33.6	1.7; 3.4	23.55	16.72
60–64	42.3	2.1; 4.2	19.46	14.58
65–69	51.8	2.6; 5.2	15.69	12.37
70–74	56.5	2.8; 5.7	12.24	10.12
75–79	64.5	3.2; 6.5	9.23	7.96
80–84	70.3	3.5; 7.0	6.77	6.05
85+	79.2	4.0; 7.9	4.87	4.47

CHD, coronary heart disease.

Markov model when time preference is not taken into account.

As expected, the PYLL is higher for all models at 10% risk compared with that for 5% risk.

The estimated PYLL in the age-based residual life expectancy model without time preference for the cohorts with both 5% and 10% 5-year CHD risk has a downward slope with increasing age, indicating that younger age groups have more potential life years to lose than older age groups at the same CHD risk level. Although this appears quite steep, the actual difference is only a maximum of about 0.70 years (8.5 months) in the 10% risk model. Moreover, in the Markov model, which accounts for competing causes of death in addition to the age-specific case fatality rates, the maximum difference in PYLL between the youngest and oldest age categories reduces to about 0.20 years (2.5 months).

With the application of a minimal (3%) time preference rate, the difference in PYLL almost disappears for the age-based residual life expectancy model in the age range from 35–39 to about 70–74 years. In the older age groups (over about 75 years), the time preference adjustment has a minimal effect.

When time preference is incorporated into the Markov model, there is some indication of an upward trend in PYLL with increasing age from the age groups 35–39 to

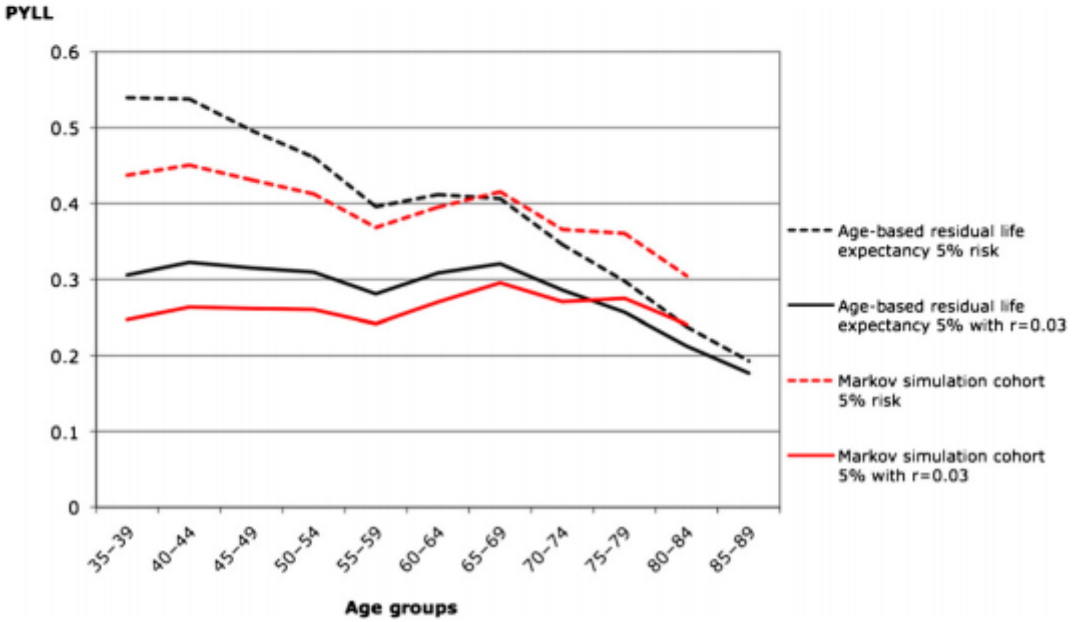


Figure 2 Potential years of life lost (PYLL) for men at 5-year 5% coronary heart disease risk—with and without time preference.

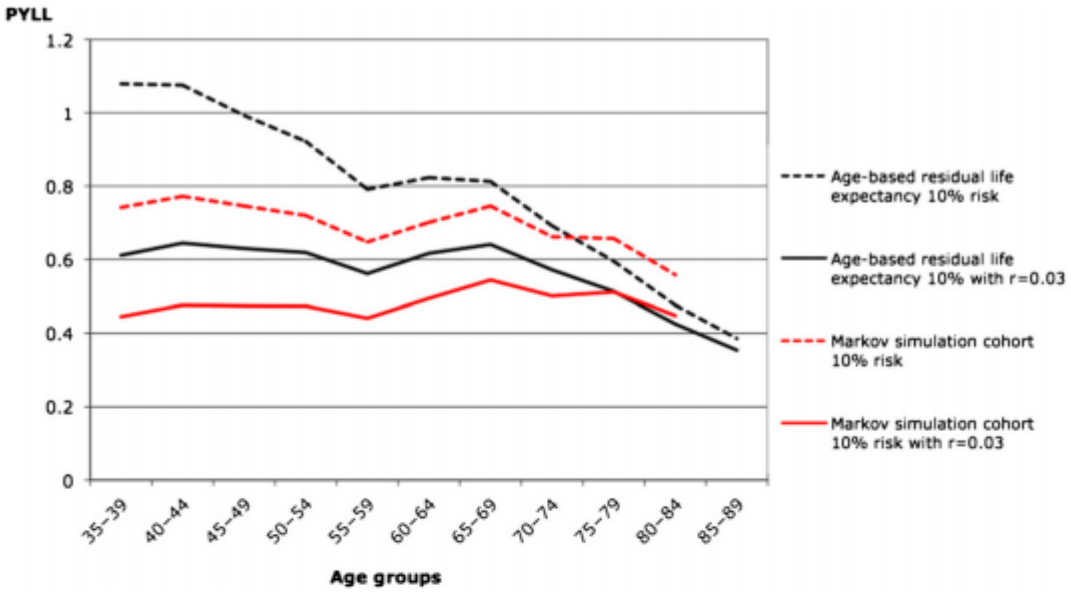


Figure 3 Potential years of life lost (PYLL) for men at 5-year 10% coronary heart disease risk—with and without time preference.

65–69. This suggests that when increasing case fatality with age, time preference and competing risks are considered, there is no difference in PYLL from delaying treatment for 5 years, for men at different ages with the same CHD risk.

The analysis was sensitive to the time preference rate used, though for typical rates the PYLL was similar at different ages. The sensitivity analysis also showed that an increase in time preference rate would actually increase the PYLL at older age groups.

DISCUSSION

Statement of principal findings

Clinicians are increasingly being advised to use short-term CVD risk prediction tools to help determine the effects of multiple risk factors on their patients' risks of developing CVD and to help weigh the benefits and costs of starting treatment in individual patients. Intuitively, short-term risk prediction does not appear to acknowledge that younger people have a longer life expectancy and would lose more years of life following a CVD event than older people who have a shorter life expectancy. However, our findings suggest that the additional benefit to life expectancy by preventive therapy in younger compared with older patients is counterbalanced by a number of opposing factors.

First, younger patients have lower case fatality rates. That is, in younger individuals with the same short-term CVD risk as older individuals, fewer will die from the event and only those few who do die will lose any life years.

Second, older individuals also face increasing risks of other causes of death that 'compete' with their CVD risk. In other words, for a given estimated 5-year CVD mortality risk, older people are more likely to die of another cause than younger people. This effect is illustrated by the difference between the results of the age-based residual life expectancy model, which does not account for competing risk, and the Markov simulation cohort method, which does.

Finally, each of the 'potential life years lost' is not considered as equal by patients. A life year in the far-off future is unlikely to be valued as much as one in a near future, especially when there exist the possibility of harm and other immediate costs due to the intervention. Balanced treatment decisions should therefore account for how people value future events. We have done this by modelling a time preference rate. We used a time preference rate of only 3% and even this minimal rate had a major effect on the potential life years lost; for the same cardiovascular risk, there is little difference in potential life years lost at different ages.

These findings suggest that models that do not take the factors of case fatality rates, time preference and competing risks into account will overestimate the benefits of treatment in younger patients and may possibly underestimate the benefits in older people.

Strengths and weaknesses of the study

This study suggests that there is little difference in the potential life years lost by delaying treatment in younger compared with older patients who have the same estimated short-term cardiovascular risk. Two different methods were used and the results corroborate. Neither

method relies on the use of a particular risk score, meaning that the findings are applicable across a wide range of risk.

A potential limitation of this study is that both methods only took into account life years lost through death and not quality of life lost as a result of non-fatal events. However, the severity of non-fatal events is also likely to increase with age, so it is unlikely that including non-fatal events in the models would change the direction of the findings. Moreover, there is no robust evidence on the impact of CVD events on the quality of life at different ages and therefore we considered it unlikely that the added number of assumptions required and increased complexity of analyses would generate more meaningful conclusions.

The complexity of the models could have been increased by including multiple disease states. For example, a 'post-CHD' state could have been added to the three states included (ie, 'well', 'CHD death' and 'non-CHD death') as those who survived an event would have a higher than normal risk of CHD and death. Other states were also options; for example, the model could have incorporated states of post double or triple CHD events, different types of events such as heart failure and so on. However, all models are approximations and the models used here allow a satisfactory differentiation between the young and old with minimal bias. The addition of other states would necessitate greater assumptions, which would increase complexity but not necessarily the accuracy as additional bias and uncertainty is also increased.

Also, the models did not take account of case fatality rates from cerebrovascular disease (only CHD case fatality was used) as we were unable to find case fatality rates for total CVD for the UK population data used by our models. However, a study in New Zealand[20] and another from Sweden[21] showed that the 5-year case fatality by age is similar for definite MI, other CHD and stroke. Hence, the addition of cerebrovascular disease, that is, stroke, is unlikely to cause a significant change in our results.

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

The QRISK group in the UK has recently developed a lifetime CVD risk calculator. Using a threshold of >50% lifetime risk of CVD disease, over half of men identified as being at high risk were in the youngest age group (30–44 years of age). In women, over one-third were in this age group.[3] The authors presented several case studies that raised concerns about the clinical usefulness of lifetime risk and stated that they were uncertain whether using such an approach was appropriate for treatment decisions. Yet recent media articles have suggested new national UK guidelines will change from advocating the use of 10-year risk to lifetime risk calculators in clinical practice.[7]

In Norway, a different approach has been adopted where thresholds for treatment are different for different ages. For those aged 40–49 years, the threshold is set at a 10-year risk of CVD death of 1%, whereas for those aged 60–69 years, it is set at 10%. The new recommendations are based on a Markov model, which showed that more life years were gained using age-differentiated thresholds. Their model adjusted for the increase in case fatality rates with age but did not account for time preference or competing risks.[22]

This is a cause for concern given that our study demonstrates that the adoption of approaches such as these that seek to redress the issue of age in short-term risk scores overestimate the CVD in younger people and lead to a substantial (and unnecessary) increase in the number of young people on medication.

Montgomery *et al*[23] used simulation models to estimate the effectiveness and cost-effectiveness of blood pressure-lowering treatment over a lifetime. One of their objectives was to compare the increase in life expectancy from treatment at different ages. This appears to be similar to our objective—they measured gains from treatment, while we examined losses from treatment delay. However, their model evaluated lifetime treatment versus lifetime non-treatment. Our models sought to answer the impact of only a 5-year delay. This is a crucial difference. The young person who presents at one point in time with a cardiovascular risk score that is higher than average for his age group will be monitored and assessed again at a future point in time. This will mean that he is likely to receive treatment as he ages. Therefore, to compare treatment and no treatment for a lifetime is not a clinically relevant comparison.

The 'low-' and 'high-risk' profiles used in the Montgomery model are also based on age-specific mean values for systolic blood pressure and centile values for other risk factors. As the values used are age specific, it is likely that the absolute risk category for the young and old are different, that is, the low-risk elderly is likely to have overlapping absolute risk with the high-risk young in the model. The differentiation of absolute risk by this method would be smaller in the older age groups and bigger in the younger age groups resulting in a reduction of gains in life expectancy with treatment as age increases. This would account for the greater gains in life expectancy seen in the young compared with the old in their paper.

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

Our findings show that there is minimal difference in potential life years lost from delaying treatment for 5 years in younger and older patients when important and objective factors such as case fatality rates and competing risks are considered. When a time preference adjuster is also added, the difference is largely abolished. This suggests that the use of models that preferentially treat younger over older patients would mean that a number of low-risk individuals would be exposed to long-term medication with questionable benefits and an even greater number of those in older age groups would

not be offered preventive treatment and could go on to develop preventable CVD.

Unanswered questions and future research

In examining the use of CVD risk for young versus old patients, we have only addressed the issues of age-specific case fatality rates, competing risks and time preference. However, there are other factors that clinicians and patients may consider when making treatment decisions based on CVD risk. Both the frequency and impact of adverse effects may differ between young and old. The older people may also have a different attitude to mortality and may consider the mode of death as well as the timing of death. Further research is needed to address the impact of these issues on the use of CVD risk in cardiovascular risk management.

CONCLUSIONS

When case fatality rates, competing risks and time preference are taken into account, there appears to be minimal differences in the potential life years lost from experiencing a CVD event among patients of different ages but the same short-term cardiovascular risk. These factors need to be considered when assessing the potential impact of future CVD events in patients of different ages.

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8.5 Conclusion

The process required for the publication of research findings from this thesis into the medical literature has been demanding. However, the reviews and comments have helped in the development of the research contained in this thesis.

Chapter 9. Implications for future research

It is impossible to complete a thesis without wanting to undertake further research to address the uncertainties identified. Such further research is needed in four areas in particular:

9.1 Adjustment for the effects of treatment in cardiovascular risk scores

Current cardiovascular risk scores have not properly accounted for patients commencing treatment during the cohort studies. Hence research is needed that aims to develop a cardiovascular risk score where the effect of treatment is adjusted for by methods such as a penalised Cox model. (128)

The most appropriate study design would be a cohort study in a population free from cardiovascular disease and not restricted by a disease condition. Risk predictors (and method of measurement) and outcomes will be clearly defined from the start of the study. As in the other risk score cohort studies, all risk predictors are measured at baseline and outcomes determined throughout the study period. However, to account for treatment, history and/or medical records would be checked to determine the usage of any risk factor treatment including blood pressure lowering medication, statin or aspirin. Risk factor lowering treatments would be determined not only at baseline but also throughout the study to account for drop-in treatment. In order to adjust for the effect of treatment, risk predictor levels and adherence to medications would also be measured during the study. This would be done in specific time intervals of two to four-yearly examinations.

Estimates of the effect of risk factor lowering treatment would be determined from published systematic reviews of randomized trials of these therapies. (128) The

estimates can then be used to adjust the hazard ratio for the specific risk predictors. This would modify the value of the coefficients in the risk equation. The absolute risk obtained by this method would then be a more accurate representation of the individual untreated risk.

This may also be more easily conducted using existing datasets which may already have recording of treatment at baseline and throughout the study such as in cohorts that used electronic medical records or trial populations e.g. Reynolds. (25, 26)

Differences in coefficients and the final risk score would allow an estimation of the effect of treatment on the study population.

Alternatively, research should be undertaken on the use of large databases to develop risk scores. The increasing use of electronic medical record keeping will be useful for such research. The large numbers would enable the detection of outcomes over short periods of time, for example, a year instead of the conventional five to ten-year periods. This would minimise treatment drop-in during the period of follow-up. However, the use of such databases for research is not straightforward. An example is the collection of data on risk predictors such as ethnicity and social deprivation where definitions are blurred. (28) The requirements as listed for the cohort study above should also be applied to this alternative method.

9.2 Questionnaire survey of general practitioners

The results from the qualitative study in Chapter 4 cannot be generalised to the larger population. Hence, quantitative research methods would be useful for external validation. The conclusion would be strengthened by convergence and corroboration of findings from both the qualitative and quantitative research.

Findings from the interviews will be used to design and adapt a questionnaire to be distributed to a larger physician population. The survey will be carried out by means of an electronic questionnaire survey that assesses the GPs' use of cardiovascular risk scores using topics developed and refined through the interviews. The survey will aim to quantify the prevalence, magnitude and order of importance of the issues raised by the interview study and allows examination of relationships between socio-demographic factors and outcomes such as usage of the risk scores. Targeting for at least 400 participants, 800 general practitioners will be invited (using a response rate of 50% as obtained by a study with similar methodology (196)). Questionnaires will be sent to these 800 GPs through a link on an online network bulletin. The questionnaire will allow the respondent to fill answers online. The returned electronic questionnaires will be stored in a secure password protected computer with identifiers removed. Each questionnaire should take about 30 minutes to complete. Data will be analysed using the appropriate statistical software. Fisher's Exact test will be used to test for associations between individual characteristics and clinical behaviour.

9.3 Risk scores for other conditions

It is unknown whether the effect of treatment similarly affects risk scores predicting other diseases. Cardiovascular risk scores are a form of clinical prediction rule. Many risk scores exist for other conditions. A Google search for the term 'clinical prediction rule' obtained nearly 7 million hits. The same search in PubMed obtained over 700 hits. It is likely that similar issues can be found for scores that estimate risk for other conditions especially those that predict long-term outcomes and where treatment exists for risk predictors used in the score.

The most appropriate study design would be a systematic review of risk scores similar to that in Chapter 3.

9.4 Effectiveness of different approaches to cardiovascular risk reduction

Finally, there is a lack of evidence on the clinical effectiveness of the different approaches towards cardiovascular morbidity and mortality reduction as outlined in Chapter 7.

The appropriate study design would be a randomised controlled trial with three arms: 1. the absolute cardiovascular risk calculated and presented to the health care practitioner during the clinical consultation, 2. the polypill approach without screening, and 3. a control arm in the form of usual care. Follow-up will have to be of sufficient length to capture outcomes. The trial will have to be conducted in a health care system where the use of cardiovascular risk scores is still limited.

Acknowledgments

Prior to doing a doctoral degree, I was working as an academic GP lecturer at the University Malaya Medical Centre. A substantial proportion of my working timetable was spent in clinic, seeing patients and overseeing the Masters of Family Medicine students' clinic consultations. The top reason for consultation in our clinics was chronic disease management especially cardiovascular disease prevention and diabetes care.

In Malaysia, cardiovascular disease is on the rise. Ischaemic heart disease and cerebrovascular disease were the top two leading causes of death in Malaysia in the year 2000. (197) Coronary heart disease has increased three-fold in the past 40 years and appears to be increasing. (198) The National Health and Morbidity Survey conducted in 1996 showed that 61% of Malaysians had one or two atherosclerotic risk factors. (199) The same survey also showed that 33% of Malaysian adults aged 30 or older had hypertension. (200) The prevalence of diabetes mellitus is also of growing concern. In 1986, the prevalence of diabetes was estimated to be 6.3%. However, in 1996, the Second National Health and Morbidity survey showed that the national prevalence of diabetes and impaired glucose tolerance in Malaysia was 8.3% and 4.8% respectively. (201)

In my practice, I mainly assessed and treated patients for hypertension, hyperlipidaemia and other risk factors without using a formal global risk assessment. On occasion, I used the ATP III guidelines (Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults in the United States (202)) which employ risk factor counting (and the Framingham risk score) for statin treatment decisions. I did not routinely use risk scores in consultations. This was despite guidelines advocating the use of formal risk calculators. The hesitation to use the risk scores was not unlike that

felt with the adoption of any other new medications or technology in clinical practice. I felt uncertain and unwilling to use these tools until I understood their method of use and efficacy.

I wanted to assess the applicability of the cardiovascular risk scores to the Malaysian population. This formed the basis of the first draft of my research proposal – to determine the validity of the Framingham risk score in the Malaysian population, to see if other risk factors not included in the risk score were of more importance locally and to estimate the effect of treatment on cardiovascular outcomes in a group of patients that had been actively managed.

In discussion with Paul Glasziou, we decided that I should examine the effect of treatment in the derivation of risk scores. This topic developed from a question that had been niggling at me – on finding out that I intended to do research on the cardiovascular risk scores, a colleague had asked me how the derivation studies adjusted for treatment in the study population. If treatment was not adjusted for, this was likely to be a source of inaccuracy in cardiovascular risk assessment.

From this initial question, the idea and proposal for the doctoral research grew. I was to examine how the risk scores were derived, focusing on the methods used to adjust for treatment effects in the study population. This led naturally to the need to determine how doctors used the risk scores. I also had a meeting with my other supervisor, David Mant, and the epidemiologist, Rod Jackson, to discuss other areas to cover. At that meeting, the issue of age in cardiovascular risk assessment was discussed. Doctors appeared to be treating patients at different age groups differently despite them having the same absolute cardiovascular risk. Was this the right thing to do?

Essentially my research aimed to select the most appropriate risk assessment tool to use in clinical practice. To discover this, I had to understand how the risk scores were derived, then how they were used, and compare discrepancies in derivation and usage. The impact of absolute risk had to be examined in detail especially with the consideration of age as a factor.

After the research objectives were determined, the subsequent steps to take followed accordingly. Methods that were appropriate to answer the questions were selected and outlined in the proposal. The research question was refined, modulated and changed with time and greater understanding. The ideas evolved to form the research project that is described in this thesis.

Appendices

Appendix A: PRISMA statement and electronic search for systematic review

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page 1: Title
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 1: Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 1-2: Introduction
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 2: Objectives
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Protocol available online
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 2: Search methods
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 2: Search methods

Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Page 2: Search methods and below
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 2: Identifying studies and PRISMA flowchart
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 2: Data extraction
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 2: Data extraction
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 2: Analytical methods
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Not relevant: Review of clinical prediction rules without meta-analysis
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Not relevant: Review of clinical prediction rules without meta-analysis
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Page 2: Analytical methods
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Not relevant: Review of clinical prediction rules without meta-analysis
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	PRISMA flow diagram
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Page 2-3: Description of studies and Table 1

Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Page 2: Analytical methods and Table 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Not relevant: Review of clinical prediction rules without meta-analysis
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Page 2-6: Results and Tables 1-5
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Page 2: Analytical methods and Table 2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Not relevant: Review of clinical prediction rules without meta-analysis
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page 6-8: Statement of principal findings
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Page 8: Strengths and Weaknesses
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 8: Authors' conclusions
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page 8: Funding

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Electronic search

#43 128989

("cardiovascular system"[MeSH Terms] OR ("cardiovascular"[All Fields] AND "system"[All Fields]) OR "cardiovascular system"[All Fields] OR "cardiovascular"[All Fields]) AND ("risk"[MeSH Terms] OR "risk"[All Fields])

#51 #43 + #51=13716

("risk"[MeSH Terms] OR "risk"[All Fields]) AND ("prediction"[All Fields] OR "engine"[All Fields] OR "score"[All Fields] OR "categories"[All Fields] OR "profile"[All Fields])

#34 #45 + #51 +#34=4404

("Cohort Studies"[Mesh] OR "Algorithms"[Mesh]) OR ("Proportional Hazards Models"[Mesh] OR "Models, Statistical"[Mesh])

#59

"Review "[Publication Type] OR "Randomized Controlled Trial "[Publication Type] AND ("humans"[MeSH Terms] AND ("adult"[MeSH Terms:noexp] OR "middle aged"[MeSH Terms] OR ("middle aged"[MeSH Terms] OR "aged"[MeSH Terms]) OR "aged"[MeSH Terms] OR "aged, 80 and over"[MeSH Terms]))

(#43 AND #51 AND #34) NOT #59 =3511

Appendix B: Protocol for systematic review

Review protocol: Cardiovascular Risk Scores

Background

The World Health Organization has predicted that cardiovascular disease will be the leading cause of death in the world in 2030. (203) It will surpass communicable disease as a cause of death.

Cardiovascular disease is caused by many factors and the effect of these risk factors are additive; intervention is most effective amongst those with the highest baseline risk. (204) Several prognostic cohort studies have analysed the effects of these risk factors, which are taken from history, physical examination and laboratory investigations and derived mathematical models allowing a quantification of the absolute risk. This may be in the form of a risk calculator, table, charts etc.

A risk score is important as it allows the identification of high-risk patients. This identification spurs the patient and the doctor to intervene and change the risk profile. It also helps to determine indication for pharmaceutical treatment in the primary prevention of coronary heart disease. (67, 205, 206)

A review of 12 cardiovascular risk assessment tools showed that the majority were based on the Framingham study data. (207) Other assessment tools such as the PROCAM score, (22) the UKPDS risk engine (21) and the SCORE risk charts (24) were derived from their own data sources. However, their use is limited by their populations' characteristics. For example, the initial PROCAM score included no minorities, women or men over the age of 65. The UKPDS Risk Engine is specific for individuals with a diagnosis of diabetes and SCORE is derived from a pool of 12 European cohort studies.

The Framingham risk scores have been found to overestimate coronary heart disease in many populations. (73, 208-210) A possible cause of this overestimation is that the Framingham risk score was derived from data obtained prior to the development and widespread use of newer and more effective treatments for cardiovascular risk factors such as angiotensin converting enzyme inhibitors for hypertension and statins for hyperlipidaemia. The effect of treatment on risk factors does not appear to be addressed in the development of cardiovascular risk scores.

A review of the various cardiovascular risk calculators would be useful for the following reasons:

- To appraise the quality of the studies
- To compare the risk scores in terms of population characteristics, predictors and outcomes
- To analyse the methods used by the studies to address the effect of treatment

Objectives:

- To review and assess in terms of quality, primary studies which use risk factors obtained by history, clinical examination and investigations, to develop a cardiovascular risk prediction too/score/equation that predicts the absolute risk of an adult, without prior history of cardiovascular disease, of developing an acute cardiovascular event in 5-10 years.
- To evaluate the methods used to address the effect of treatment by the cohort studies.

Criteria for considering studies for this review

Types of studies:

- Cohort studies

Exclusion criteria:

- Studies of risk prediction tools that use derived data such as Sheffield risk table and other charts that use Framingham data
- Studies that are specifically looking at a population with a particular disease e.g. diabetes, rheumatoid arthritis

Types of participants:

- Adults in the general population without history of prior cardiovascular disease

Types of intervention/exposure:

- Risk factors/predictors of future cardiovascular event from history, physical examination or laboratory investigations

Outcomes:

- Major cardiovascular event such as myocardial infarction, stroke or death in 5-10 years

Sources for the review:

- Medline

Search strategy for identification of studies

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

Methods of the review

Selection of trials

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

Assessment of methodological quality

Quality will be assessed by using criteria for clinical prediction rules as laid out by Wasson (111) and Royston. (112) This will be laid out in the form of a table.

Data management and extraction

After reaching consensus on the studies to be included, LSM will extract information from each study for analysis. Data will be extracted on study quality, population characteristic, predictors, outcomes as well as the method used to take into account the effect of treatment.

Data synthesis

We will combine the studies by using tables looking at the following:

1. Study population characteristics
2. Methodological quality
3. Predictors
4. Outcomes
5. Treatment effect

Changes in Protocol

Date	Change	Reason
November 2008	Exclusion of risk prediction tools that use derived data.	This review is only for the primary studies.
November 2008	Exclusions of studies that are specifically looking at a population with a particular disease and those with a previous history of cardiovascular disease.	The review will look at adults in the general population without a previous history of cardiovascular disease as diseases such as diabetes and rheumatoid arthritis or a previous history of cardiovascular disease substantially increases CVD risk and NICE advises that risk scoring should not be done in these populations.
December 2008	Re-clarification of inclusion/exclusion criteria specifically: 1. Only absolute risk 2. 5-10 years	The inclusion of all types of risk and time periods would make the type of studies to be included too heterogeneous to compare.
June 2009	Exclusions of studies that did not have the method/equation/chart for the clinician to calculate the	A study which does not offer the clinician a way to calculate the absolute risk would not be included in this review as it would

	absolute risk in the paper or in a place accessible to the clinician e.g. online website.	be of limited use in clinical practice.
June 2009	Methodological quality was assessed by incorporating elements suggested by Royston. (112)	The paper by Royston added more elements to assessing the methodological quality of prognostic research.

Appendix C: Tables from qualitative interviews

Table 14: Demographic variables of participants in the qualitative study

	Gender	Age	Year qualified	Role in the practice	Electronic record keeping	Practice Size	Number of GPs in practice
R1	M	47	2003	PARTNER	Y	8 000	5
R2	M	34	2002	REGISTRAR	Y	7 000	5
R3	M	58	1975	PARTNER	Y	2 000	2
R4	F	36	1998	PARTNER	Y	17 000	9
R5	M	43	1992	PARTNER	Y	6 000	6
R6	M	44	1991	PARTNER	Y	10 000	9
R7	F	53	1981	PARTNER	Y	11 000	5
R8	F	60	1975	PARTNER	Y	4 000	4
R9	F	46	1991	PARTNER	Y	6 000	4
R10	M	61	1972	SALARIED	Y	8 000	7
R11	M	53	1981	PARTNER	Y	16 000	9
R12	M	46	1989	PARTNER	Y	13 000	9
R13	M	37	1998	SALARIED	Y	1 000	2
R14	M	55	1978	PARTNER	Y	18 000	8
R15	M	59	1975	PARTNER	Y	13 000	8
R16	M	53	1985	PARTNER	Y	11 000	7
R17	M	49	1986	PARTNER	Y	8 000	6
R18	M	43	1991	PARTNER	Y	12 000	9
R19	M	46	1988	PARTNER	Y	13 000	8
R20	M	32	2003	SALARIED	Y	4 000	6

Risk scores	Currently used	Previously used	Heard of but never used
R1	Framingham	QRISK	
R2	QRISK	JBS	
R3	QRISK	Framingham/Dundee	
R4	Framingham/QRIS		
R5	QRISK	JBS/Sheffield tables	
R6	QRISK	JBS	
R7	JBS		QRISK
R8	Framingham/JBS		QRISK
R9	Framingham/JBS	QRISK	
R10	Framingham		QRISK
R11	Framingham		QRISK/ASSIGN
R12	QRISK	NPC	
R13	Framingham/JBS		QRISK
R14	Framingham		QRISK
R15	QRISK	Framingham/JBS	
R16	JBS	Framingham	
R17	Framingham/QRIS		ASSIGN
R18	Framingham		QRISK/ASSIGN
R19	QRISK	Framingham	NZ /Sheffield tables
R20	Framingham (Univ. of Edinburgh risk tool)/QRISK		UKPDS

Table 15: Risk scores used by participants in the qualitative study

*the JBS, NZ and Sheffield tables are derived from Framingham data; Dundee from the Heart Disease Prevention Project; UKPDS from the UK Prospective Diabetes Study. Framingham and QRISK scores were derived from data from their own study cohorts.

Appendix D: Qualitative interviews topic guide

Cardiovascular Risk Scores Interview Guide – Healthcare Professionals

Study Title: Cardiovascular Risk Scores
Protocol Ref: PIS Qualitative Interviews HCP
Date and Version: 23072010 Version 002
Oxfordshire REC B : 10/H0605/42

Part 1 – Participant

1. Can you please tell me about your background in general practice?

Part 2 – Cardiovascular (CVD) risk scores

2. What do you understand by the term 'cardiovascular risk scores'?
3. We are interested in your experience in using CVD risk scores. Have you used the risk scores in practice? (If yes) When was the last time you used a CVD risk score with a patient? Can you describe the experience to me?
4. What role does CVD risk play in the decision making process?
5. In your opinion, what are the advantages of using CVD risk scores?
6. What are the disadvantages of using CVD risk scores?
7. What has influenced your opinions or shaped your beliefs about CVD risk scores?
8. What are the factors that lead or would lead to your successful adoption of CVD risk scores?
9. What would be barriers that you face or might face in using CVD risk scores?
10. What would help to overcome these barriers?
11. Have you heard of recommendations or guidelines about CVD risk scores use in clinical practice? What do you think about these?
12. How would you communicate risk to a patient? (Ask participant for a real example or use given scenario if participant is unable to give an example)
13. In your opinion, should the risk communicated be the risk that the patient faces if he is left untreated or if he is treated? Or do you think that it does not matter?
14. Which group of patients would you use the CVD risk score on? Why?
15. Anything else that you would like to tell me or think that I should have asked?
16. We are trying to get a wide variety of opinions and views about CVD risk score use by GPs. Is there a GP that you think I should interview?

Oxfordshire REC B 10/H0605/42
Cardiovascular Risk Scores Interview Guide – Healthcare Professionals

Appendix E: Excel chart of age-based residual life expectancy model

Table 16: Potential Years of Life Lost using the age-based residual life expectancy model for a five-year coronary heart disease risk of 10% without time preference

Age group	Mid point age	5 year risk	Age spp CFR	IHD mortality risk	LE	Potential Years of Life Lost
35-39	37	10	25.9	2.59	41.65	1.078735
40-44	42	10	29.1	2.91	36.95	1.075245
45-49	47	10	30.7	3.07	32.33	0.992531
50-54	52	10	33.1	3.31	27.85	0.921835
55-59	57	10	33.6	3.36	23.55	0.79128
60-64	62	10	42.3	4.23	19.46	0.823158
65-69	67	10	51.8	5.18	15.69	0.812742
70-74	72	10	56.5	5.65	12.24	0.69156
75-79	77	10	64.5	6.45	9.23	0.595335
80-84	82	10	70.3	7.03	6.77	0.475931
85+	87	10	79.2	7.92	4.87	0.385704

Appendix F: Excel chart of Markov simulation cohort model

Age Group	People alive at cycle start	CVD event rate	Age Specific CFR	Age Specific CFR	IHD mortality rate for 5 years	non-IHD rate for 1 year	non-IHD rate for 1 year	non-IHD rate for 5 years	Total mortality	Number dead in cycle	Years in the future n	(1+r) to the power of n	LY with r=0.03
35-39	100	0.1	25.9	0.259	0.0259	0.138	0.00138	0.006881	0.032781	3.278098	0	1	100
40-44	96.7219	0.127628	29.1	0.291	0.03714	0.138	0.00138	0.006881	0.044021	4.257773	5	1.159274	83.43316
45-49	92.46413	0.162889	30.7	0.307	0.050007	0.277	0.00277	0.013773	0.063781	5.897413	10	1.343916	68.802
50-54	86.56672	0.207893	33.1	0.331	0.068813	0.277	0.00277	0.013773	0.082586	7.149199	15	1.557967	55.56388
55-59	79.41752	0.26533	33.6	0.336	0.089151	0.692	0.00692	0.034124	0.123275	9.790214	20	1.806111	43.97155
60-64	69.6273	0.338635	42.3	0.423	0.143243	0.692	0.00692	0.034124	0.177367	12.3496	25	2.093778	33.25439
65-69	57.2777	0.432194	51.8	0.518	0.223877	1.79	0.0179	0.086353	0.310229	17.76922	30	2.427262	23.59765
70-74	39.50848	0.551602	56.5	0.565	0.311655	1.79	0.0179	0.086353	0.398008	15.72467	35	2.813862	14.04066
75-79	23.7838	0.703999	64.5	0.645	0.454079	5.029	0.05029	0.227399	0.681479	16.20815	40	3.262038	7.291087
80-84	7.575649	0.898501	70.3	0.703	0.631646	5.029	0.05029	0.227399	0.859045	6.507826	45	3.781596	2.003294
	1.067822	1.14674	79.2	0.792	0.908218	13.285	0.13285	0.50969	1.417908	1.514073	50	4.383906	0.243578

Base Risk	0.1									r	0.03		
Sum of cohort LY	654.011											Sum of cohort LY with r=0.03	432.2012
LY per person	32.70055											LY with r=0.03 per person	21.61006

Age Group	People alive at cycle start	CVD event rate	Age Specific CFR	Age Specific CFR	IHD mortality rate for 5 years	non-IHD rate for 1 year	non-IHD rate for 1 year	non-IHD rate for 5 years	Total mortality	Number dead in cycle	Years in the future n	(1+r) to the power of n	LY with r=0.03
35-39	100	0	25.9	0.259	0	0.138	0.00138	0.006881	0.006881	0.688098	0	1	100
40-44	99.3119	0.127628	29.1	0.291	0.03714	0.138	0.00138	0.006881	0.044021	4.371787	5	1.159274	85.66732
45-49	94.94011	0.162889	30.7	0.307	0.050007	0.277	0.00277	0.013773	0.063781	6.055333	10	1.343916	70.64436
50-54	88.88478	0.207893	33.1	0.331	0.068813	0.277	0.00277	0.013773	0.082586	7.340639	15	1.557967	57.05176
55-59	81.54414	0.26533	33.6	0.336	0.089151	0.692	0.00692	0.034124	0.123275	10.05237	20	1.806111	45.14901
60-64	71.49177	0.338635	42.3	0.423	0.143243	0.692	0.00692	0.034124	0.177367	12.6803	25	2.093778	34.14487
65-69	58.81147	0.432194	51.8	0.518	0.223877	1.79	0.0179	0.086353	0.310229	18.24504	30	2.427262	24.22955
70-74	40.56643	0.551602	56.5	0.565	0.311655	1.79	0.0179	0.086353	0.398008	16.14575	35	2.813862	14.41663
75-79	24.42068	0.703999	64.5	0.645	0.454079	5.029	0.05029	0.227399	0.681479	16.64217	40	3.262038	7.486326
80-84	7.778508	0.898501	70.3	0.703	0.631646	5.029	0.05029	0.227399	0.859045	6.682092	45	3.781596	2.056938
	1.096416	1.14674	79.2	0.792	0.908218	13.285	0.13285	0.50969	1.417908	1.554617	50	4.383906	0.2501

Base Risk	0.1										r =0.03		
Sum of cohort LY	668.8462											Sum of cohort LY with r=0.03	441.0969
LY per person	33.44231	0.74176										LY with r=0.03 per person	22.05484

LY per person with r of 0 = 0.74176. LY per person with r of 0.03 = 22.05484– 21.61006= 0.44478

Table 17: Potential Years of Life Lost for a man, age group 35-39, with a five-year coronary heart disease risk of 10% using the Markov model

Appendix G: Excel chart of age-based residual life expectancy model with time preference

Table 18: Potential Years of Life Lost using the age-based residual life expectancy model for a five-year coronary heart disease risk of 10% and time preference rate of 3%

Age group	Mid point age	5 year risk	Age spp CFR	IHD mortality risk	LE	1+r	(1+r) to the power of LE	1/left cell	1-left cell	dLE	Potential Years of Life Lost
35-39	37	10	25.9	2.59	41.65	1.03	3.43	0.291964	0.708036	23.60119	0.611271
40-44	42	10	29.1	2.91	36.95	1.03	2.98	0.335478	0.664522	22.15072	0.644586
45-49	47	10	30.7	3.07	32.33	1.03	2.60	0.384567	0.615433	20.51442	0.629793
50-54	52	10	33.1	3.31	27.85	1.03	2.28	0.439019	0.560981	18.69937	0.618949
55-59	57	10	33.6	3.36	23.55	1.03	2.01	0.498521	0.501479	16.71597	0.561657
60-64	62	10	42.3	4.23	19.46	1.03	1.78	0.562584	0.437416	14.58052	0.616756
65-69	67	10	51.8	5.18	15.69	1.03	1.59	0.628903	0.371097	12.36989	0.64076
70-74	72	10	56.5	5.65	12.24	1.03	1.44	0.696422	0.303578	10.11927	0.571739
75-79	77	10	64.5	6.45	9.23	1.03	1.31	0.761224	0.238776	7.959203	0.513369
80-84	82	10	70.3	7.03	6.77	1.03	1.22	0.818638	0.181362	6.045394	0.424991
85+	87	10	79.2	7.92	4.87	1.03	1.15	0.86593	0.13407	4.469005	0.353945

Appendix H: Excel chart of Markov simulation cohort model with time preference

Age Group	People alive at cycle start	CVD event rate	Age Specific CFR	Age Specific CFR	IHD mortality rate for 5 years	non-IHD rate for 1 year	non-IHD rate for 1 year	non-IHD rate for 5 years	Total mortality	Number dead in cycle	Years in the future n	(1+r) to the power of n	LY with r=0.03
35-39	100	0.1	25.9	0.259	0.0259	0.138	0.00138	0.006881	0.032781	3.278098	0	1	91.71658
40-44	96.7219	0.127628	29.1	0.291	0.03714	0.138	0.00138	0.006881	0.044021	4.257773	5	0.862609	76.11758
45-49	92.46413	0.162889	30.7	0.307	0.050007	0.277	0.00277	0.013773	0.063781	5.897413	10	0.744094	62.18294
50-54	86.56672	0.207893	33.1	0.331	0.068813	0.277	0.00277	0.013773	0.082586	7.149199	15	0.641862	49.76772
55-59	79.41752	0.26533	33.6	0.336	0.089151	0.692	0.00692	0.034124	0.123275	9.790214	20	0.553676	38.61297
60-64	69.6273	0.338635	42.3	0.423	0.143243	0.692	0.00692	0.034124	0.177367	12.3496	25	0.477606	28.42602
65-69	57.2777	0.432194	51.8	0.518	0.223877	1.79	0.0179	0.086353	0.310229	17.76922	30	0.411987	18.81916
70-74	39.50848	0.551602	56.5	0.565	0.311655	1.79	0.0179	0.086353	0.398008	15.72467	35	0.355383	10.66587
75-79	23.7838	0.703999	64.5	0.645	0.454079	5.029	0.05029	0.227399	0.681479	16.20815	40	0.306557	4.647191
80-84	7.575649	0.898501	70.3	0.703	0.631646	5.029	0.05029	0.227399	0.859045	6.507826	45	0.264439	1.123436
	1.067822	1.14674	79.2	0.792	0.908218	13.285	0.13285	0.50969	1.417908	1.514073	50	0.228107	0.121789

Base Risk	0.1									r	0.03		
Sum of cohort LY	654.011											Sum of cohort LY with r=0.03	382.2012
LY per person	32.70055											LY with r=0.03 per person	19.11006

Age Group	People alive at cycle start	CVD event rate	Age Specific CFR	Age Specific CFR	IHD mortality rate for 5 years	non-IHD rate for 1 year	non-IHD rate for 1 year	non-IHD rate for 5 years	Total mortality	Number dead in cycle	Years in the future n	(1+r) to the power of n	LY with r=0.03
35-39	100	0	25.9	0.259	0	0.138	0.00138	0.006881	0.006881	0.688098	0	1	92.83366
40-44	99.3119	0.127628	29.1	0.291	0.03714	0.138	0.00138	0.006881	0.044021	4.371787	5	0.862609	78.15584
45-49	94.94011	0.162889	30.7	0.307	0.050007	0.277	0.00277	0.013773	0.063781	6.055333	10	0.744094	63.84806
50-54	88.88478	0.207893	33.1	0.331	0.068813	0.277	0.00277	0.013773	0.082586	7.340639	15	0.641862	51.10039
55-59	81.54414	0.26533	33.6	0.336	0.089151	0.692	0.00692	0.034124	0.123275	10.05237	20	0.553676	39.64694
60-64	71.49177	0.338635	42.3	0.423	0.143243	0.692	0.00692	0.034124	0.177367	12.6803	25	0.477606	29.18721
65-69	58.81147	0.432194	51.8	0.518	0.223877	1.79	0.0179	0.086353	0.310229	18.24504	30	0.411987	19.32309
70-74	40.56643	0.551602	56.5	0.565	0.311655	1.79	0.0179	0.086353	0.398008	16.14575	35	0.355383	10.95148
75-79	24.42068	0.703999	64.5	0.645	0.454079	5.029	0.05029	0.227399	0.681479	16.64217	40	0.306557	4.771632
80-84	7.778508	0.898501	70.3	0.703	0.631646	5.029	0.05029	0.227399	0.859045	6.682092	45	0.264439	1.153519
	1.096416	1.14674	79.2	0.792	0.908218	13.285	0.13285	0.50969	1.417908	1.554617	50	0.228107	0.12505

Base Risk	0.1										r =0.03		
Sum of cohort LY	668.8462											Sum of cohort LY with r=0.03	391.0969
LY per person	33.44231	0.74176										LY with r=0.03 per person	19.55484

LY per person with r of 0 = 0.74176. LY per person with r of 0.03 = 19.55484 – 19.11006 = 0.44478

Table 19: Potential Years of Life Lost for a man, age group 35-39, with a five-year coronary heart disease risk of 10% using the Markov model with time preference and a half cycle correction

Appendix I: Table of other materials

Table 20: List of other materials available on request

Systematic review	Identification of studies	List of titles of studies retrieved by search
		List of abstracts of studies retrieved by search
		List of full-text articles assessed for eligibility
	Data extraction	Data extraction sheets
Qualitative interviews	Ethics approval	NHS REC form
		Amended invitation letters
		Amended consent forms
		Amended participant information sheets
		Ethics approval letter
	Funding from the National Schools of Primary Care Research	Clinical research protocol
		Funding approval letter
	Coding and thematic analysis	Coding and thematic analysis of transcripts
Mathematical models	Models	Excel tables with models with data analysis and results

Administrative papers	Transfer to DPhil status	Transfer report
		Transfer approval letter
	Confirmation of status	Application form
		Confirmation letter

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