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**Coronary Prevention in Two European Areas with Different Risk Levels,  
Stockholm and Sicily: Doctors' Risk Judgments and Statin Utilization**

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Academic dissertation for Doctoral degree (Ph.D.) to be defended on Friday 23 May  
at 9.00, room 615, Alfred Nobels allé 12, Karolinska Institutet, Huddinge



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## Abstract

### *Introduction*

International guidelines on the primary prevention of cardiovascular disease recommend that preventive measures should be based on the doctors' quantitative total risk assessment of the patient. Treatment is recommended when the patient's risk is above a certain threshold. Risk scoring systems have been developed to assist clinicians with risk estimates. However, in clinical practice this estimation is usually made subjectively. This implies that factors unrelated to the true risk of the patients may influence the doctors' risk estimates and decisions about treatment.

### *Aim*

We aimed to study coronary preventive care in two areas with different coronary risk levels, with special reference to doctors' attitudes in investigating risk factors, and their risk assessments and decisions about treatment. In accordance with the different levels of cardiovascular risk in the areas studied, we also aimed to test the hypothesis that the same set of risk factors may be perceived as indicating higher risk in a high-risk country, than in a low-risk country.

### *Methods*

The studies were performed in two European areas, one with a high and the other with a low level of population cardiovascular risk, Stockholm county and Sicily, respectively. Questionnaires on doctors' clinical practice (Study I) and written patient cases (Studies II-IV) were presented to random samples of doctors in Stockholm and in Sicily. The cases were constructed according to the Framingham scoring system, ranging from very high- to very low-risk cases. Differences in the use of statins and coronary mortality in the populations (Study V) were studied by collecting official data from the health care systems in both areas.

### *Results and Discussion*

There were differences in the management of hyperlipidaemia (Study I). More doctors in Stockholm investigated lipids in patients with other cardiovascular risk factors. The cholesterol level at which doctors started lipid-lowering treatment was higher in Stockholm than in Sicily. In Study II, General Practitioners (GPs) were asked to evaluate nine written patient cases. Their coronary risk estimates showed large variability, especially in high-risk cases, and in general the risk was underestimated compared to the risk calculated according to the Framingham equations. Contrary to the hypothesis, GPs in Stockholm made lower estimates and less often decided to start lipid-lowering treatment than was the case in Sicily. A possible reason for this is that a high background risk level of the population tends to suppress the risk estimate of an individual with a certain set of risk factors, and vice versa if the population risk is low. Support to such line of thinking was found comparing risk estimates and decisions about treatment between doctors who usually deal with coronary preventive care: GPs, cardiologists and internists (Study III). Compared to the other specialists, cardiologists, who usually deal with high-risk patients, showed lower risk estimates when assessing the same set of patient cases. In study IV we found that the task of risk rating and the task of making decisions about treatment did not mutually influence each other. Female GPs and GPs with shorter clinical experience were more likely to make correct decisions.

The differences in coronary risk ratings and decisions about treatment observed in the two areas with different population coronary risk levels may be related to the use of statins in the whole population of the respective area. Study V investigated the time trends in the relations between population coronary risk levels, expressed as coronary mortality, and use of statins, in the period 2001-2011. In both areas there was a reduction in coronary mortality and an increase in statin utilization. A larger reduction in coronary mortality was observed in Stockholm compared to Sicily, whereas the statin utilization increased more in Sicily than in Stockholm. Thus, the changes over time in statin utilization seem inversely associated with the changes in coronary mortality. However, the influence of other variables that are independent of the population coronary risk, such as cost containment policies, socioeconomic gradients in the use of statins, and drug discontinuation rate, must be taken into account.

### *Conclusions*

There are several differences in primary coronary prevention between the two European areas with different population cardiovascular risk profiles. Doctors' quantitative risk estimates and decisions about treatment are influenced by factors not directly related to the actual risk of the patients, and seem tentatively to be inversely related to the background cardiovascular risk in the population. The differences in primary coronary prevention may contribute to an increase in statin utilization that is not justified by changes in population coronary risk. The results of the thesis may help in the development of decision tools and recommendations for primary coronary prevention.

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Stockholm 2014

Front cover illustration by Sergio

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Published by Karolinska Institutet.

Printed by Universitetsservice AB

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ISBN 978-91-7549-560-6

*Felix qui potuit rerum cognoscere causas*  
*(Fortunate who was able to know the causes of things)*

*Virgil, Georgics, II, 490*

*To Carla, Sergio, Edoardo and Riccardo*

## Abstract

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International guidelines on the primary prevention of cardiovascular disease recommend that preventive measures should be based on the doctors' quantitative total risk assessment of the patient. Treatment is recommended when the patient's risk is above a certain threshold. Risk scoring systems have been developed to assist clinicians with risk estimates. However, in clinical practice this estimation is usually made subjectively. This implies that factors unrelated to the true risk of the patients may influence the doctors' risk estimates and decisions about treatment.

### Aim

We aimed to study coronary preventive care in two areas with different coronary risk levels, with special reference to doctors' attitudes in investigating risk factors, and their risk assessments and decisions about treatment. In accordance with the different levels of cardiovascular risk in the areas studied, we also aimed to test the hypothesis that the same set of risk factors may be perceived as indicating higher risk in a high-risk country, than in a low-risk country.

### Methods

The studies were performed in two European areas, one with a high and the other with a low level of population cardiovascular risk, Stockholm county and Sicily, respectively. Questionnaires on doctors' clinical practice (Study I) and written patient cases (Studies II-IV) were presented to random samples of doctors in Stockholm and in Sicily. The cases were constructed according to the Framingham scoring system, ranging from very high- to very low-risk cases. Differences in the use of statins and coronary mortality in the populations (Study V) were studied by collecting official data from the health care systems in both areas.

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rating and the task of making decisions about treatment did not mutually influence each other. Female GPs and GPs with shorter clinical experience were more likely to make correct decisions.

The differences in coronary risk ratings and decisions about treatment observed in the two areas with different population coronary risk levels may be related to the use of statins in the whole population of the respective area. Study V investigated the time trends in the relations between population coronary risk levels, expressed as coronary mortality, and use of statins, in the period 2001-2011. In both areas there was a reduction in coronary mortality and an increase in statin utilization. A larger reduction in coronary mortality was observed in Stockholm compared to Sicily, whereas the statin utilization increased more in Sicily than in Stockholm. Thus, the changes over time in statin utilization seem inversely associated with the changes in coronary mortality. However, the influence of other variables that are independent of the population coronary risk, such as cost containment policies, socioeconomic gradients in the use of statins, and drug discontinuation rate, must be taken into account.

## Conclusions

There are several differences in primary coronary prevention between the two European areas with different population cardiovascular risk profiles. Doctors' quantitative risk estimates and decisions about treatment are influenced by factors not directly related to the actual risk of the patients, and seem tentatively to be inversely related to the background cardiovascular risk in the population. The differences in primary coronary prevention may contribute to an increase in statin utilization that is not justified by changes in population coronary risk. The results of the thesis may help in the development of decision tools and recommendations for primary coronary prevention.

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## List of Publications

This thesis is based on the following papers, which will be referred to by their Roman numerals.

- I. Danielsson B, Vancheri F, Åberg H, Strender L-E.  
Hyperlipidaemia: Differences in management practices and attitudes in two regions in Europe – Sicily and the Stockholm area  
European Journal of Epidemiology 1998; 14: 477-482
- II. Vancheri F, Strender L-E, Bring J, Montgomery J, Skånér Y, Backlund L.  
General practitioners' coronary risk assessment and lipid-lowering treatment decisions in primary prevention: comparison between two European areas with different cardiovascular risk levels.  
Primary Health Care Research & Development 2008; 9: 248-256
- III. Vancheri F, Strender L-E, Montgomery H, Skånér Y, Backlund LG.  
Coronary risk estimates and decisions on lipid-lowering treatment in primary prevention. Comparison between general practitioners, internists, and cardiologists  
European Journal of Internal Medicine 2009; 20: 601-606
- IV. Vancheri F, Strender L-E, Backlund LG.  
General practitioners' coronary risk estimates, decisions to start lipid-lowering treatment, gender and length of clinical experience: their interactions in primary prevention.  
Primary Health Care Research & Development 2013; 14: 394-402
- V. Vancheri F, Wettermark B, Strender L-E, Backlund LG.  
Trends in coronary heart disease mortality and statin utilization in two European areas with different population risk levels: Stockholm and Sicily.  
International Cardiovascular Forum 2014; issue 3: 140-146

## List of Abbreviations

CHD	Coronary heart disease
CVD	Cardiovascular disease
GP	General Practitioner
LDL	Low-density lipoproteins
HDL	High-density lipoproteins
VLDL	Very-low density lipoproteins
RR	Relative risk
RRR	Relative risk reduction
ARR	Absolute risk reduction
NNT	Number needed to treat
DDD/TID	Defined daily doses per 1000 inhabitants per day
ARB	Angiotensin receptor blockers
ACE	Angiotensin converting enzyme inhibitors
CCB	Calcium channel blockers
BB	Beta blockers
ICD	International Classification of Diseases

## Introduction

Coronary heart disease (CHD) refers to a heart disease due to the atherosclerotic process in the coronary arteries and the complications of this process. CHD includes myocardial infarction, angina pectoris, silent myocardial ischaemia, and sudden death. CHD is part of the more general term 'cardiovascular disease' (CVD), which also includes stroke, transient ischaemic attacks, and peripheral artery disease.

Primary prevention of CHD should be based on a doctor's identification of risk factors and quantitative estimate of the risk of developing coronary events, whereas patients with established coronary disease (secondary prevention, see below) are already at very high risk. Specific tools, such as charts or computer programs, have been developed and recommended in the quantification of CHD risk <sup>1,2</sup>. Clinical guidelines have been published to standardize and simplify clinical decision-making in reducing CHD risk <sup>3-5</sup>. Preventive treatment in primary coronary prevention should be considered if the patient's risk exceeds a certain cut-off level. Although there is wide knowledge about the management of coronary risk factors such as hypertension and elevated blood lipids, the quality of preventive care is inadequate, especially in high-risk subjects <sup>6-9</sup>. In clinical practice, about three-quarters of doctors rarely or never use risk prediction tools and are more likely to make assessments subjectively, combining measurable variables with qualitative knowledge of the patient's characteristics <sup>10-13</sup>. This may explain the observation that coronary risk is often underestimated when it is high <sup>14,15</sup> and overestimated when it is low <sup>16,17</sup>, which may contribute to inappropriate use of lipid-lowering treatments <sup>18-20</sup>.

Given the subjective component of the risk estimates, it might be expected that factors not directly related to the actual risk of the patient may influence the CHD risk management. Indeed, some studies have shown that women <sup>21</sup> older individuals <sup>22</sup> and patients with multiple chronic conditions <sup>23</sup> receive an unjustifiably low level of coronary preventive care. This bias may be the result of subconscious perceptions rather than a deliberate decision.

The topic of the present thesis is the CHD prevention management in two European areas with different coronary risk levels and mortality rates. The study was conducted in two areas. The first was Stockholm county, an area with relatively high risk and mortality levels for CHD <sup>24</sup>, although in recent years the risk of cardiovascular diseases has decreased to low-moderate levels <sup>25,26</sup>. The

second area was Sicily, which is part of Italy, a country with lower CHD risk and mortality levels<sup>24,27,28</sup>. The health systems in both countries have universal coverage and are predominantly based on direct taxation. There are demographic differences (Table 1). The gross domestic income per capita, which is an indicator of standard of living, and the proportion of people with higher education, are three times higher in Stockholm than in Sicily. The proportion of people engaged in agricultural work is much higher in Sicily. Both Stockholm and Sicily are only partially representative of the respective entire countries.

**Table 1**  
Demographics of the two studied areas

	Stockholm county	Sweden	Sicily	Italy
population (2011)	2.054.343	9.415.570	5.051.075	60.626442
women (%)	50.5	50.2	51.7	51.5
age up to 64 years (%)	85.0	81.5	81.5	79.7
Gross Domestic Product Euros per inhabitant (2010)	50.700	37.300	16.800	25.700
tertiary education (%)	44.4	35.7	12.8	15.7
economically active (%)	56.0	52.1	33.4	40.7
farm labour force (%)	0.2	1.5	8.5	5.6

Data from Eurostat<sup>29</sup>, referring to years 2010 or 2011

## Some Notes on Terminology

*Serum cholesterol* consists of sub-fractions. Two thirds are low-density lipoproteins (LDL cholesterol), one quarter is formed of high-density lipoproteins (HDL cholesterol), the remaining are very-low density lipoproteins (VLDL) and chylomicrons. The LDL fraction carries most of the atherogenic properties. However, many epidemiological studies and clinical trials have measured

only serum total cholesterol. As changes in total cholesterol are highly correlated with changes in LDL, the absolute reduction in total cholesterol induced by diet or drugs is close to the reduction in LDL<sup>30,31</sup>.

*Relative risk (RR)*. The probability of an event in a treatment group divided by the probability of the event in a control group.

*Relative risk reduction (RRR)*. The proportional reduction in rates of a certain outcome between treatment and control participants in a trial, calculated as (experimental event rate minus control event rate)/control event rate. It may also be calculated as  $1 - RR$ .

*Absolute risk reduction (ARR)*. The absolute arithmetic difference in the probability of an event between control and treatment groups, calculated as the control event rate minus the experimental event rate.

*Number needed to treat (NNT)*. A measure of clinical benefit that represents the number of individuals who would need to be treated to prevent one additional person from having the event. It is calculated as the inverse of the absolute risk reduction between two treatments ( $1/ARR$ ).

## The Concept of Coronary Risk Factor

Cardiovascular disease is the leading cause of death from non-communicable diseases worldwide<sup>32</sup>. In Europe, it accounts for over 4.3 million deaths each year and about 1.9 million are due to CHD<sup>33</sup>. Over one in five men and the same proportion of women die from these diseases each year. The ageing of populations will result in a significant increase in coronary deaths over the next 25 years<sup>34</sup>. CHD is related to interconnecting genetic, physiological, social, and environmental factors. Recent research indicates that influences during early life may contribute to the development of CHD in later life<sup>35</sup>. In the last century it became evident that certain factors actually cause atherosclerosis, and that their modification, such as smoking cessation and reduction of blood pressure and blood cholesterol, can reduce cardiovascular mortality.

### *Definition of Coronary Risk Factor*

In this context, a risk factor is defined as a characteristic of a person that is associated with an increased risk of developing atherosclerotic CHD<sup>36,37</sup>. To be clinically relevant an observed association between a risk factor and disease has to fulfil the criteria of causality, according to the strength of the association (high relative risk), the consistency or the observation in different persons, the temporal relationship of the association (the cause precedes the effect), the dose-response curve (the greater the exposure the higher the risk), and biological plausibility<sup>38</sup>. Several risk factors for CHD have been identified that meet the criteria of causation and are of major relevance from a public health perspective. They are usually categorized into 'not modifiable', such as increasing age, male gender, and family history of premature CVD, or 'modifiable' (also called "major" or "conventional") risk factors, such as hyperlipidaemia, hypertension, diabetes, cigarette smoking, overweight, inappropriate diet and physical inactivity<sup>39,40</sup>. It has been well established that high levels of major modifiable risk factors are associated with high rates of CHD, whereas low levels of risk factors are associated with low CHD rates<sup>41-46</sup>. The analysis of randomized clinical trials<sup>47</sup> and prospective cohort studies of fatal and non-fatal CHD<sup>48</sup> have shown that exposure to at least one major risk factor was present in more than 80% of patients<sup>49</sup>. Novel risk factors, such as markers of systemic inflammation or serum homocysteine levels, have been investigated, but none has demonstrated the same epidemiological relevance as the conventional risk factors<sup>50-52</sup>.

## Prevention of CHD

### *Primary and Secondary Prevention*

Primary prevention refers to interventions that aim to prevent cardiovascular events in individuals who show no clinical evidence of CVD. Secondary prevention aims to prevent recurrence of cardiovascular events in individuals who already have clinical evidence of CVD. However, the distinction between the two concepts is not always clear-cut. Since the atheromatous disease which leads to CVD is a progressive condition, some individuals may have asymptomatic (or subclinical) atherosclerotic diseases, and thus may be at equal or even higher risk than individuals with established CVD<sup>53</sup>. Moreover, about a fifth of acute myocardial infarctions are clinically silent<sup>54</sup>.

### *Population and High-Risk Approaches for Prevention*

People with high levels of risk factors have higher CHD risk than people with lower levels, but the population fraction with lower levels of risk is much greater. Thus, at population level, the majority of CHD cases do not occur among the small number of individuals at greatest risk, but among the

much larger number of individuals at lower levels of absolute risk<sup>55</sup>. As an example, in the MRFIT Study there were 846 CHD deaths among 72,476 people in the upper quintile of serum cholesterol ( $\geq 6.7$  mmol/L), whereas among 283,746 people in the lower quintiles of serum cholesterol the number of CHD deaths was almost double (1,412)<sup>43</sup>. In patients followed in routine primary care, about 60% of cardiovascular events occurred in those without prior CHD<sup>56</sup>. In CHD prevention, there are two general strategies: the high-risk approach, which is intended to identify and treat individuals at high risk, and the population approach, in which population-wide changes in risk factors shift the population distribution of risk factors to reduce the incidence of disease<sup>55</sup>. The high-risk strategy is the natural choice for medical practitioners as they are concerned about the cardiovascular risk of the individual patient who may benefit from treatment in the short term. On the other hand, population strategies bring much benefit to populations but offer little to each individual. Relatively small reductions in the population risk levels would lead to large reductions in major CVD events<sup>57</sup>. Studies in the US and Europe have shown that population-wide improvements in the major risk factors may reduce the rate of cardiovascular deaths by more than half<sup>58-61</sup>. A successful population strategy to reduce the levels of the main cardiovascular risk factors was developed in North Karelia, Finland, in 1972<sup>62</sup>. The interventions reduced serum cholesterol, blood pressure and smoking at the population level. Over the following twenty years the age-standardized CHD mortality decreased by 73%<sup>63</sup>. However, current risk scoring systems for the primary prevention of CVD have been formulated to detect individuals with absolute high risk rather than for population strategies. There is an inverse relation between the threshold for treatment of high risk individuals and the reduction in CVD events<sup>64</sup>. As the threshold for treatment is reduced, the estimated number of CVD events avoided increases as well as the proportion of people to treat. Therefore, the choice of a cut-off to define the high risk individuals and the need for treatment in most guidelines is a compromise between scientific evidence and funding resources, and population strategies are aimed at maximizing the reduction of the total burden of CHD.

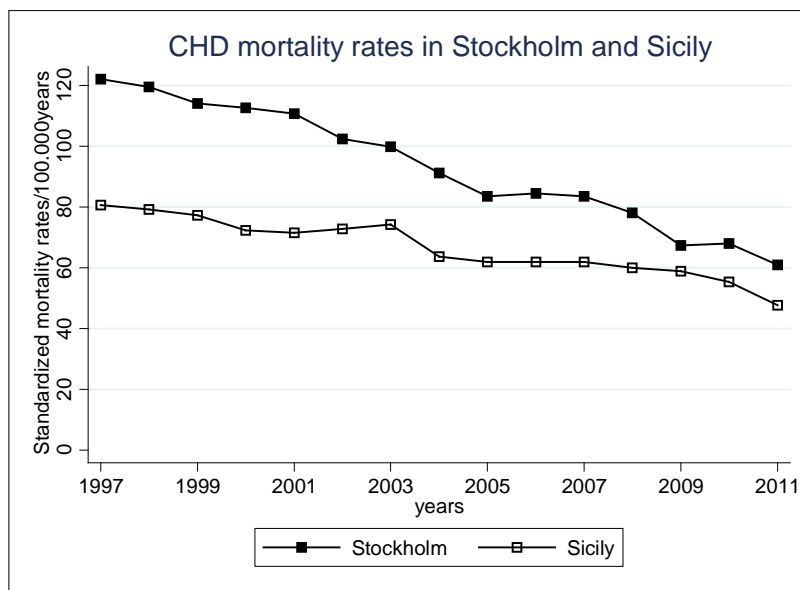
## CHD Across Europe

There are large differences in CHD mortality between countries in Europe, with a north-east to south-west gradient<sup>24</sup>. The highest mortality rates are observed in central and eastern countries, whereas the lowest rates are recorded in France, Portugal, Italy, and Spain. There is also a north to south gradient within countries. In the MONICA study, the coronary mortality in the two northernmost counties of Sweden was about 30% higher than in Göteborg, on the south-west coast, which was interpreted as due to higher population cholesterol levels<sup>65,66</sup>.



During the last four decades a substantial decrease in CHD mortality has been observed in Western European countries, whereas in eastern countries a decrease started more than twenty years later, thus explaining the differences between the two areas recorded in recent years<sup>67,68</sup>. Such variations in CHD mortality rates are accompanied by differences in populations' coronary risk levels assessed by cohort studies.

In Stockholm county the CHD mortality rates/100.000 (all ages, standardized according to the European population) decreased from 122.0 in 1997 to 60.8 in 2011 (-50.1%)<sup>69</sup>. In the same period in Sicily there was a reduction from 80.5 to 47.5 (-40.9%)<sup>70</sup>. Thus, the two curves have tended to become closer in recent years (Figure 1).



**Figure 1.** Trends in all ages mortality rates for ischaemic heart disease in Stockholm and Sicily. Age standardized according to the European population. ICD 10 codes I20-I25 (\*). Data from The National Board of Health and Welfare, Socialstyrelsen, Cause of Death Statistics<sup>69</sup>, and from Istituto Superiore di Sanità, La mortalità per causa in Italia<sup>70</sup>. Sicilian data for 2004-2005 and 2009-2011 which are not on the web site, were made available by Istituto Superiore di Sanità (Luigi Palmieri, personal communication), and by Regione Sicilia (Antonello Marras, personal communication). (\*) The causes of death in Stockholm were selected according to the international version of the disease classification (ICD-10), from I20 to I25 (ischaemic heart diseases), whereas in Sicily the ICD-9 codes 410-414 were used until 2005, and ICD-10 codes I20-I25 thereafter. There are slight differences in the disease inclusion criteria between the two codes. Specific studies have evaluated the changes from the old to the new system (bridge-coding studies) showing that

*3.18% more deaths have been classified according to ICD10 than ICD9<sup>71,72</sup>. Therefore, this percentage of deaths was added to the number of CHD deaths in Sicily, for each year from 1997 to 2005.*

### *Explaining the Reduction in CHD*

The largest contribution to the decrease of CHD mortality is attributable to the reduction of major risk factors, whereas only a minor proportion is due to the effects of better treatment of cardiac diseases. In the MONICA analysis of world populations with falling CHD mortality, about three quarters of the observed fall could be attributed to the decline in coronary event rates, which mainly reflects improvements in risk factors, while about one quarter could be attributed to a decrease in case fatality, which is related to medical treatment<sup>66</sup>. Great improvements in major CHD risk factors have been observed in Sweden since 1980<sup>73-77</sup>. The MONICA analysis also demonstrated an association between trends in coronary event rates and risk factors, which partly explained the population trends in CHD<sup>59</sup>. However, with this analysis it was not possible to quantify how much of the decrease in event rates could be attributed to changes in specific risk factors. Subsequent modelling analysis studies used the IMPACT model to estimate the proportion of the observed change in CHD mortality that can be attributed to risk factor changes or treatments<sup>78,79</sup>. This model employs regression coefficients derived from clinical trials. Each coefficient quantifies the change in mortality per unit of risk factor change. The number of CHD deaths prevented or postponed is calculated as a result of these factors. Evidences from several modelling studies suggests that more than half of the decrease in CHD mortality can be attributed to improvements in the major risk factors, mainly cholesterol, blood pressure and smoking (Table 2).

**Table 2**  
Relative decrease in CHD mortality attributed to risk factor changes or treatments in different population studies

	Decrease attributed to population risk factor improvement	Decrease attributed to treatment improvement
Sweden (1986-2002) <sup>80</sup>	55%	36%
Italy (1980-2000) <sup>81</sup>	55%	40%
England & Wales (1981-2000) <sup>79</sup>	58%	42%
Ireland (1985-2000) <sup>82</sup>	48%	43%
Poland (1991-2005) <sup>83</sup>	54%	37%
Finland (1982-1997) <sup>84</sup>	53%	23%
USA (1980-2000) <sup>61</sup>	44%	47%
Canada (1994-2005) <sup>85</sup>	48%	43%

All studies are based on IMPACT modelling analysis. The remaining percentage until 100% is the decrease in CHD mortality that is “unexplained” by risk factor or treatment changes. For clarity, values are rounded.

#### *Relationship Between Blood Lipids and CHD Events*

Although there has been some controversy concerning whether cholesterol is related to atherosclerosis <sup>86-88</sup>, prospective observational (cohort) studies have shown a strong and positive relationship between serum cholesterol concentrations and CHD deaths <sup>89-92</sup>. This association is constant in the total cholesterol range between about 4.0 mmol/L and 9.0 mmol/L, in which the lower limit is well below the values seen in high-income Western populations <sup>44,93-95</sup>. These studies also demonstrate that the relationship between serum cholesterol concentrations and CHD risk is graded and that the concept of “hyperlipidaemia” introduces an arbitrary dichotomy between normal and abnormal values.

The relationship between usual serum cholesterol, i.e. without pharmacological intervention, and CHD mortality shows that for 1 mmol/L reduction in mean population total cholesterol there is a relative reduction in the risk of CHD mortality of about 50% <sup>96</sup>.

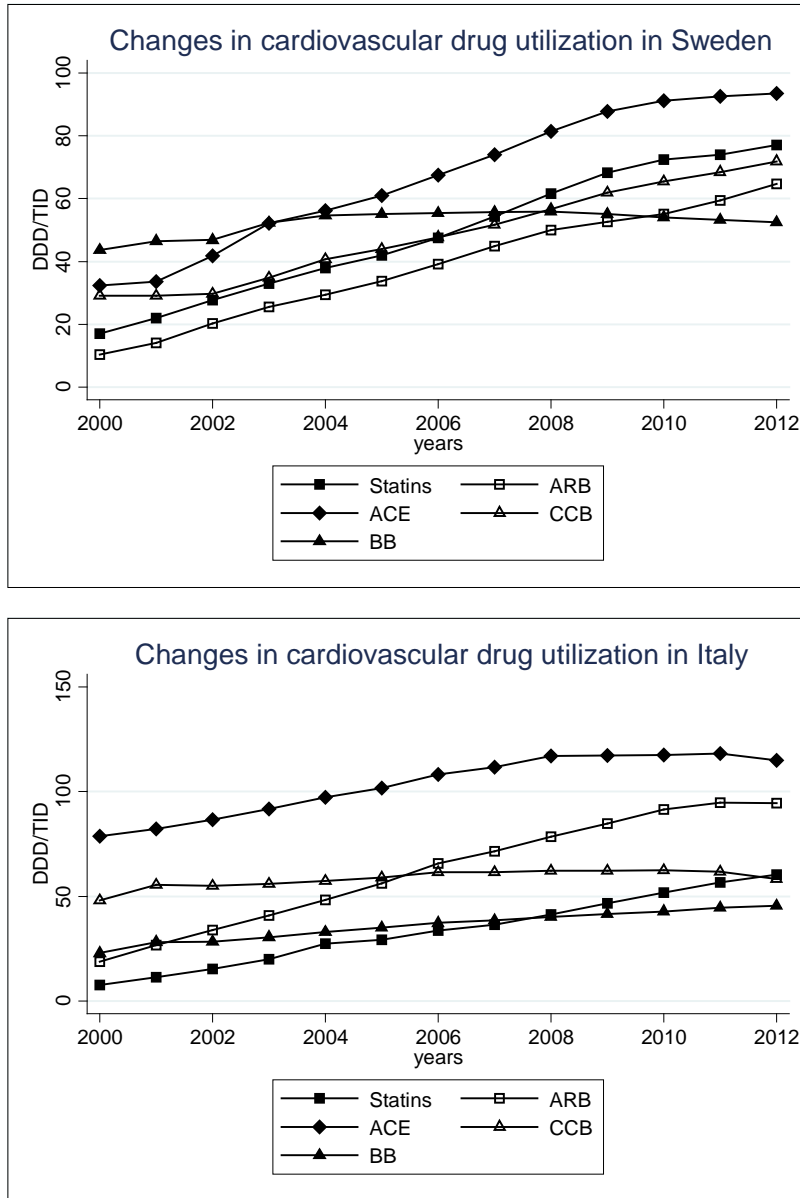
The decrease in mean population lipid levels, which induced the greatest reduction in CHD event rate and mortality observed in the last forty years, is largely attributable to dietary changes in the general population, consisting of reduced consumption of foods with a high content of saturated fats, whereas the contribution of lipid-lowering drugs has been limited <sup>97-100</sup>.

During these years, cholesterol levels in Sweden decreased from 6.1 mmol/L to 5.5 mmol/L <sup>80</sup>. The same trend has been observed in southern areas such as the Västra Götaland region, including Göteborg <sup>73,76,77,101</sup>. In Italy, in the same period, total cholesterol decreased from 5.6 mmol/L to 5.2 mmol/L <sup>81</sup>. However, in recent years both countries showed a tendency towards an increase in cholesterol levels. In Västerbotten County, Sweden, the downward trend observed since 1990 levelled out in 2002. Thereafter, cholesterol levels increased from 5.2 mmol/L in 2002 to 5.4 mmol/L in 2010, both in men and women <sup>102</sup>. In several areas of Italy, including Sicily, between 1998 and 2008, there was an increase from 5.3 mmol/L to 5.8 mmol/L in men, and from 5.4 to 6.0 in women <sup>103</sup>. Such unfavourable changes probably reflect the rapid increase in obesity in these populations and the rise of dietary fat intake.

#### *Role of Statins in CHD Prevention*

Statins are a class of drugs that inhibits 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which is involved in cholesterol synthesis, and they have been extensively investigated in the reduction of CHD events. Statins also have anti-inflammatory and antithrombotic effects, independent of their capacity to lower cholesterol <sup>104-106</sup>. The utilization of these drugs has been progressively increasing since their marketing began in the 1990s <sup>107,108</sup>. However, large decreases in population cholesterol levels had started before their introduction in clinical practice <sup>74,84,100,101,109</sup>. Moreover, CHD mortality started to reduce in the 1970s, several years before statin therapy became available <sup>33,110</sup>.

The increase in statin use in Sweden and Italy, in the period 2000 – 2012, compared to other cardiovascular drugs, is shown in Figure 2, and the percentages of increase are shown in Table 3.



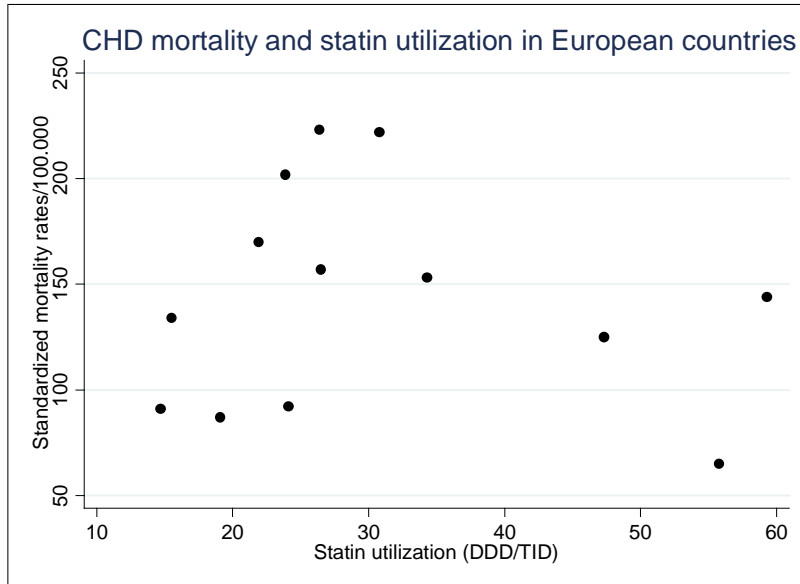
**Figure 2.** Changes in major cardiovascular drug utilization in Sweden and in Italy, in the period 2000-2012. ARB: angiotensin receptor blockers, ACE: angiotensin converting enzyme inhibitors, CCB: calcium channel blockers, BB: beta blockers. Swedish data from eHälsomyndigheten (Swedish eHealth Agency (Björn Wettermark, Desirée Loikas, personal communication). Italian data from Agenzia Italiana del Farmaco (AIFA), L'uso dei Farmaci in Italia, rapporto nazionale 2012, available at [www.agenziafarmaco.gov.it](http://www.agenziafarmaco.gov.it)

**Table 3**  
Percentage of increase in cardiovascular drug utilization in Sweden and Italy  
in the years 2000-2012

	Sweden	Italy
Statins	353	694
ARB including combination	521	400
ACE-inhibitors including combination	189	46
Calcium channel blockers	146	22
Beta blockers	202	98

ARB: angiotensin receptor blockers. ACE: angiotensin converting enzyme. Data as in Figure 2

Several factors, including an extensive marketing campaign by the pharmaceutical industries, may explain the more aggressive treatment guidelines that have increased the number of persons eligible for treatment <sup>5</sup>. Statin use has increased rapidly in all European countries <sup>111</sup>. In Stockholm county, the Defined Daily Doses/one Thousand Inhabitants/day (DDD/TID) rose from 20.3 in 2001 to 55.9 in 2011 <sup>112</sup>, and in Sicily from 10.5 to 61.3 <sup>113</sup>. The increase in statin utilization has shown wide variability across Europe but there seems to be no relation with CHD death rates in the different countries (Figure 3).



**Figure 3.** Relation between CHD mortality rates and statin utilization in Europe in the year 2000. Each dot indicates a country. Data from Müller-Nordhorn J<sup>24</sup> and Walley T<sup>111</sup>

It has also been observed that countries with similar mortality rates, such as Norway, Denmark and Sweden, have very different levels of statin utilization, and the country with the lowest CHD mortality, France, has the second highest level of statin utilization (Table 4).

**Table 4**  
CHD mortality rates and statin utilization in Europe in the year 2000

Country	SMR	Statin utilization
Ireland	223	26.4
Finland	222	30.8
UK	202	23.9
Austria	170	21.9
Germany	157	26.5
Sweden	153	34.3
Norway	144	59.3
Denmark	134	15.5
Netherlands	125	47.3
Spain	92	24.1
Italy	91	14.7
Portugal	87	19.1
France	65	55.8

SMR: standardized mortality rates. Statin utilization is expressed as DDD/TID (Defined Daily Doses/1000 inhabitants/day). Data from Müller-Nordhorn J<sup>24</sup> and Walley T<sup>111</sup>

The landmark study of the efficacy of statin treatment in patients with previous CHD (secondary prevention), the Scandinavian Simvastatin Survival Study (4S)<sup>107</sup>, showed that statin reduced LDL cholesterol and the risk of fatal and non-fatal coronary events (Table 5). Two subsequent secondary prevention studies in patients with average blood cholesterol levels (CARE, Cholesterol and Recurrent Events Trial Investigators)<sup>114</sup> and with a broad range of cholesterol levels (LIPID, the Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group)<sup>115</sup>, confirmed the previous results.

In individuals with no history of cardiovascular disease (primary prevention), a reduction in the incidence of coronary events associated with LDL cholesterol lowering during statin therapy has



been shown in several randomised clinical trials. The West of Scotland Coronary Prevention Study (WOSCOPS) <sup>108</sup>, including only men with hypercholesterolemia, and the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) <sup>116</sup>, which studied individuals with average total and LDL cholesterol levels, showed that reduction in LDL was associated with a decrease in the number of coronary events (Table 5). A further primary prevention trial, the JUPITER study <sup>117</sup>, was designed to investigate whether individuals with optimal LDL concentrations and elevations of high sensitive C-reactive protein, a biomarker of vascular inflammation related to atherosclerosis, might benefit from statin therapy. Although, the results of JUPITER have been criticised because of methodological problems <sup>118</sup>, it demonstrated that individuals with elevated levels of high sensitive C-reactive protein may be at increased CHD risk, despite low LDL cholesterol levels, and that statins are effective in reducing the risk.

Other prevention studies using statins represent a “mixed” primary and secondary prevention as they also include large proportions of patients with either existing vascular disease (coronary, cerebral or peripheral) or diabetes, which is known as a CHD equivalent <sup>119</sup>. The Heart Protection Study (HPS) <sup>120</sup>, the Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm (ASCOT-LLA) <sup>121</sup> and the Collaborative Atorvastatin Diabetes Study (CARDS) <sup>122</sup>, evaluated the effects of statins, compared with placebo, on vascular events in a wide range of high-risk patients. The Pravastatin in the Elderly at Risk (PROSPER) <sup>123</sup> studied the benefits of pravastatin therapy in an elderly cohort of individuals aged >70 years with CVD or at risk of developing CVD. The Anti-hypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial – Lipid Lowering Trial Component (ALLHAT-LLT) <sup>124</sup>, compared the effects of a statin with usual care in ambulatory persons. The risk reductions of acute CVD events were comparable to the secondary prevention studies, with the exception of the ALLHAT-LLT study. In this study the treatment produced only a modest reduction of lipids and no significant reduction of CHD mortality in comparison with patients allocated to usual care. The failure to reduce CHD events was attributed to the increased use of statins in patients given usual care.

The relative risk reductions of coronary events are similar in individuals with and without pre-existing CHD, but the absolute reductions of risk are greater in those at higher baseline risk due to previous disease (Table 5).

**Table 5**

Effects of statin treatment on LDL cholesterol and risk of major coronary events in randomized clinical trials

Study	LDL reduction (%)	Effect of treatment on major coronary events		
		RRR	ARR	NNT
Primary prevention				
WOSCOPS <sup>108</sup>	26	30	2.3	44
AFCAPS/TexCAPS <sup>116</sup>	25	37	2.0	49
JUPITER <sup>117</sup>	50	43	1.2	81
Secondary prevention				
4S <sup>107</sup>	35	31	8.6	12
CARE <sup>114</sup>	32	24	3.0	33
LIPID <sup>115</sup>	25	24	3.6	28
“Mixed”				
HPS <sup>120</sup>	29	26	3.1	32
ASCOT-LLA <sup>121</sup>	29	21	2.0	51
CARDS <sup>122</sup>	32	35	3.2	32
PROSPER <sup>125</sup>	34	19	2.1	47
ALLHAT-LLT <sup>124</sup>	14	9	0.8	129

RRR= relative risk reduction; ARR= absolute risk reduction; NNT= number needed to treat, calculated as the reciprocal of absolute risk reduction ( $NNT = 1 / ARR$ )

“Mixed”: primary prevention studies that include large proportions of patients with established CVD or diabetes

This means that patients with established CHD, as well as individuals with high overall coronary risk, are more likely to benefit from lipid-lowering treatment than individuals with low risk and no previous history of CHD. This is also expressed by the differences in the number needed to treat (NNT) in primary and secondary prevention trials. However, taking all the intervention trials together, the reduction in cardiovascular events produced by statins is not impressive. The reduction of total cholesterol or LDL cholesterol decreases the absolute risk of major coronary events by 1.0 – 3.1%, and the risk of all-cause mortality by 0.5% – 1.5% <sup>104,126,127</sup> (Table 6). In absolute terms, about 10 fewer major coronary events, or five fewer all-cause deaths will occur when 1000 individuals without established coronary heart disease are treated with statins for about five years. The corresponding preventive capacity for patients with previous coronary heart disease is about 30 and 15 out of 1000 treated patients, respectively. Moreover, the relation between statin treatment and cardiovascular risk reduction is not constant in all patient groups and may be modified by the

underlying clinical conditions. In patients at high cardiovascular risk due to heart failure or haemodialysis, the reduction in LDL cholesterol levels had no significant effect on cardiovascular events<sup>128,129</sup>.

**Table 6**  
Meta-analyses of studies on statins in primary and secondary prevention

	Primary prevention		ARR
	Statins	Placebo	
	Number of events/ total number of patients	Number of events/ total number of patients	
CHD events	1037/35470 (2.9%)	1392/35150 (3.9%)	1.0%
All-cause mortality	1369/34451 (3.9%)	1484/33884 (4.4%)	0.5%
Secondary prevention			
CHD events	1803/21193 (8.5%)	2462/21127 (11.6%)	3.1%
All-cause mortality	1736/23020 (7.5%)	2087/23093 (9.0%)	1.5%

CHD includes fatal and non-fatal events. ARR: absolute risk reduction. Data from Naci H<sup>127</sup>

## Risk Estimates

### *Total Cardiovascular Risk*

Total or “absolute” CVD risk is the individual’s overall risk (expressed as a percentage) of developing an event over a defined period of time, resulting from the multiplicative effect of all the factors that contribute to the risk<sup>130</sup>. Until recent years the management of CHD has been centred on the modification of single risk factors. However, there is epidemiological and clinical evidence that many risk factors tend to occur in clusters, thus confirming the multifactorial nature of CHD<sup>43,131,132</sup>. The likelihood of developing a coronary event does not depend on the presence of a specific risk factor but arises from the synergistic effects of multiple minor or moderate risk factors abnormalities<sup>133,134</sup>. Importantly, the increased risk resulting from multiple risk factors is not

simply additive, but multiplicative, amplifying the risk that depends on any single risk factor. Small increases of several different risk factors may lead to high risk of developing CHD. As a result, individuals with low blood cholesterol might have much higher absolute risk than others with high levels of this risk factor. On the other hand, a moderate increase in blood cholesterol or blood pressure, in the absence of other risk factors, may represent a negligible risk. These observations reduce some of the clinical relevance of the term “hypercholesterolaemia”. An important consequence of the multiplicative relation between risk factors is that interventions that affect one or two of them may greatly benefit overall risk.

### *Coronary and Cardiovascular Risk Scoring Systems*

The first step to achieving effective prevention is recognizing individuals who are at risk of coronary events. Patients with established CHD are at very high risk for recurrent CHD. However, there are also apparently healthy individuals who have slight abnormalities in multiple risk factors which may result in a much higher total risk than a single, more impressively elevated factor. Therefore, before making clinical management decisions, there is a need to evaluate the combined or total risk factor effects, rather than to identify individual risk factors.

Systems to estimate the individual’s total risk have been developed using data from cohort studies during follow-up intervals of several years. The cardiovascular risk factors are combined using weighted scores to calculate the likelihood that an individual will have an event over a given period of time. A prediction score is derived from the experience of a population cohort followed for some years in terms of their initial risk factor levels and subsequent cardiovascular morbidity and mortality. The data collected are then projected into a new disease-free population to predict future events.

The accuracy of a risk estimation system is assessed in terms of discrimination, which is the ability of a score to differentiate between people who will have an event from those who will not, and also in terms of calibration, which assesses how closely predicted estimates of absolute risk agree with actual outcomes <sup>135</sup>. There is a trade-off between these two measures and it is not possible to have a scoring system with both perfect calibration and discrimination <sup>136</sup>. The predictive abilities of the most widely used risk prediction models, in terms of discrimination and calibration, have been compared and no single score is most acceptable in all populations <sup>137</sup>. In general, they tend to perform better on the dataset from which they were developed. The predictive ability of the risk scoring systems may also change in relation to the baseline risk of the populations from which they

derive, and in relation to the secular trend of the population risk. Since baseline cardiovascular risk varies in different populations, a scoring system that is well calibrated in one geographic area may overestimate or underestimate the risk in another area <sup>138</sup>. Likewise, in the populations where the CHD incidence is decreasing, as in most areas of the developed world, the risk estimation systems will tend to overestimate the risk. Conversely, in populations where CHD rates are increasing, the risk estimation systems will underestimate the true risk.

The risk scores are usually designed as charts or electronic risk scores. Some are in use in several countries, in the original form or modified, for example the Framingham Heart Study <sup>139</sup>, the SCORE (Systematic COronary Risk Evaluation) <sup>28</sup>, the WHO/ISH (World Health Organization/International Society for Hypertension) <sup>140</sup>, and the Reynolds risk score <sup>141,142</sup>. Others are mainly applied in the same country where they were developed, such as CUORE <sup>143</sup>, PROCAM (Prospective Cardiovascular Münster) <sup>144</sup>, QRISK2 <sup>145</sup>, ASSIGN score (ASsessing cardiovascular risk using SIGN guidelines) from the Scottish Heart Health Extended Cohort <sup>146</sup>, and the Norwegian risk algorithm NORRISK <sup>147</sup>. Other risk score systems, such as the New Zealand <sup>148</sup> and Joint British Societies charts <sup>149</sup>, and the Sheffield table <sup>150</sup>, also derived from the Framingham, have been adopted as national references.

The Framingham system is the best known and most widely used. The study started in the 1950s, based on a sample from a white middle income North American community, and has been subjected to frequent developments. The Framingham equation takes into account the synergistic effect of age, gender, blood pressure, total and HDL cholesterol, smoking, diabetes and left ventricular hypertrophy on ECG <sup>42</sup>. Two further versions of this risk score have been developed <sup>139,151</sup>. Several guidelines for the prevention of cardiovascular disease are based on the Framingham risk functions, including the British <sup>149</sup> and the New Zealand <sup>152</sup> cardiovascular societies, the American Heart Association <sup>153</sup>, the National Cholesterol Education Program (NCEP-ATP III) <sup>5</sup> and the National Institute for Health and Clinical Excellence (NICE) Guidelines <sup>154</sup>. Comparison with different population cohorts showed that the Framingham risk scoring accuracy depends upon the background risk of the population to which it is applied <sup>155,156</sup>. This risk function makes accurate predictions of CHD risk in central and western European populations <sup>157</sup>, whereas it overestimates the risk in northern European countries, such as Scandinavia, and low-risk countries such as Italy and Spain <sup>158,159</sup>. The risk function has been re-calibrated so it can be used with European Mediterranean countries <sup>160,161</sup>.

A new risk algorithm, Pooled Cohort Equations, was developed in 2013 from multi-ethnic population-based cohort studies in North America, and the outcome is the first occurrence of fatal and non-fatal CHD or stroke <sup>162</sup>.

In Europe, to improve the applicability of the risk scoring systems to populations with different baseline CVD risk the SCORE system has been developed from 12 cohort studies <sup>28</sup>. The risk calculations are based on age, gender, total cholesterol and total cholesterol/HDL cholesterol ratio, systolic blood pressure and smoking. The outcome is a 10-year fatal cardiovascular event, rather than combined fatal and nonfatal events. CVD mortality was preferred as the end-point because non-fatal events are strictly dependent upon their definition and the methods used to collect them, whereas death is a clear end-point. The advantage of SCORE is that it is based on the national cardiovascular mortality data which are usually readily available. Thus, risk scores are calibrated to baseline risk within geographical regions, taking into account the differences between populations <sup>130</sup>. Different updated and re-calibrated charts are now available for high and low-risk countries <sup>1</sup>.

The CUORE risk prediction chart has been developed from 11 population cohorts from the north and centre-south of Italy <sup>163</sup>, deriving a function specific for the Italian population. The charts equations include the Framingham variables age, gender, total cholesterol, systolic blood pressure, and diabetes. In the individual electronic risk scores, two more risk factors, HDL cholesterol and hypertension drug treatment, have been added <sup>2</sup>. The CUORE scoring system is more accurate than Framingham in predicting coronary events when applied to a low-risk population <sup>143</sup>. It became available in 2004 and was recommended by the Italian Ministry of Health for cardiovascular risk assessment of the general adult Italian population, until 2013.

The essential feature of all risk estimation systems is their ability to categorize individuals to appropriate risk levels, because the decision on whether to start treatment depends on these classifications. However, studies assessing whether the use of risk estimation systems in daily practice improves risk factor control, have produced conflicting results <sup>164,165</sup>.

### *Guidelines on Lipid-Lowering Treatment*

According to the standard definition, guidelines are systematically developed statements to assist practitioners and patients when making decisions about appropriate health care for specific circumstances <sup>166</sup>. Guidelines on cardiovascular prevention are based on a systematic review of

clinical evidence, and aim to help physicians in their decision-making on primary and secondary cardiovascular prevention.

European guidelines were first published in 1994<sup>167</sup> and thereafter updated about every four years<sup>3,130,168,169</sup>. Their crucial element is the estimation of the total risk and definition of priorities to guide the preventive efforts. This strategy implies control of all components of the risk, such as smoking, blood lipids, blood pressure, and exercise. Pharmacological treatment of hyperlipidaemia is generally recommended following intensive lifestyle intervention for at least three months. A decision to treat blood lipids with drugs depends not only on the lipid levels but also on the absolute CVD risk. It is recognized that thresholds for starting treatment for CVD risk, as well as targets of treatment for individual risk factors, are arbitrary since cardiovascular risk is a continuum. The cut-off values for initiating lipid-lowering treatment as well as the treatment goals are 5 mmol/l (190 mg/dl) for total cholesterol and 3 mmol/L (115 mg/dl) for LDL cholesterol. In individuals at high cardiovascular risk and in patients with previous CHD, the treatment goals should be lower<sup>3</sup>. Until the publication of the Second Joint Task force in 1998, the suggested absolute risk estimates were based upon the Coronary Risk Chart derived from Framingham risk scoring equations. When the absolute risk of being affected by CHD within 10 years is  $\geq 20\%$  or will exceed 20% if projected to age 60 years (i.e. at least 20 of 100 individuals with the same risk profile are predicted to develop CHD within ten years), the risk is defined as high and drug treatment should be considered<sup>168</sup>. The subsequent revision, the Third Joint Task Force, made an important change, including in the treatment recommendations any form of cardiovascular disease, rather than just coronary disease<sup>169</sup>. Another change was the estimation of the absolute CHD risk using the SCORE model, in which the outcome is cardiovascular mortality, instead of fatal and non-fatal coronary events. Accordingly, the threshold to be considered at high risk is  $\geq 5\%$  instead of the previous  $\geq 20\%$ .

The American guidelines have focused on treating patients to reach a definite LDL cholesterol level target. According to the Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program (NCEP), the primary goal of treatment was to reduce LDL cholesterol levels<sup>5</sup>. This strategy has been criticised as clinical trials have shown the effects of fixed doses of statins on lowering lipid levels and cardiovascular events, but have never tested the benefits of treating patients according to LDL targets<sup>170,171</sup>. On the other hand, large reductions in LDL cholesterol with statin therapy in very high-risk patients, such as those with heart failure<sup>128</sup> or renal failure<sup>129</sup>, did not significantly reduce cardiovascular events. New guidelines, based on the Pooled Cohort Equations algorithm, switched the focus of prevention from LDL targets to the individuals' risk

levels<sup>172</sup>. Four groups of patients were identified for whom statin treatment should be started with appropriate intensity to reduce cardiovascular disease events. A predicted 10-year risk of greater than or equal to 7.5% is the threshold for starting statin therapy.

Swedish guidelines on cardiovascular prevention are in line with the recommendations of the European guidelines, adapted to the Second Joint Task Force of European guidelines until 2003 and to the Third Joint Task Force thereafter<sup>173</sup>. The Swedish adaptation to the European guidelines recognizes type 2 diabetes as a high coronary risk factor and suggests that these people should be given treatment as in the secondary prevention cases. The same is true for people at high risk due to familial hyperlipidaemia. In the remaining asymptomatic, apparently healthy individuals, the decision to recommend preventive drug treatment should be based upon the total cardiovascular risk estimated with the Framingham scoring system. For individuals whose total CHD risk is  $\geq 20\%$  over the next ten years, or will exceed 20% when the time span is projected to the age of 60, intensive risk factor modification, including pharmacological therapy, is recommended. When the recommendations of the Third Joint Task Force were introduced in 2003, The SCORE risk assessment system replaced Framingham, and the threshold for being at high risk was set at 5% instead of the previous 20%.

Italian guidelines refer to the 1998 Second Joint Task Force of European guidelines<sup>174</sup>, and the risk estimate was based on the Framingham scoring system until 2003 and on the CUORE system thereafter.

Although all guidelines agree on the use of absolute rather than relative risk and that a therapy should be started when a risk threshold is exceeded, their prediction of risk and their resulting recommendations about treatment vary widely<sup>175</sup>. It has been observed that when applied to the same group of patients, the prediction of CHD risk  $\geq 20\%$  over 10 years was 53% for NCEP-ATP III, 34% for Framingham and 26% for the European guidelines. Lipid-lowering treatment was considered in 52% of cases by NCEP-ATP III, 26% by European guidelines, and 35% by British guidelines<sup>176</sup>.



### *Physicians' Risk Assessments in Clinical Practice*

General practitioners (GPs) have the most important role in CVD prevention care. This role is shared with cardiologists and internists, both in Sweden and in Italy. According to the concept of total cardiovascular risk, the intensity of preventive efforts should match the individual's absolute risk. There is a widespread agreement that individuals with established CHD and apparently healthy individuals at high coronary risk should be offered lipid-lowering treatment to reduce cardiovascular morbidity and mortality, and that the absolute benefits of treatment are closely related to the baseline levels of CHD risk. Although most physicians agree with the content of clinical guidelines<sup>177</sup>, there are discrepancies between guideline recommendations and clinical practice. Recent evidence from large population surveys demonstrated that guidelines are only sporadically applied for patients with established CHD and that a substantial proportion of patients do not achieve the guidelines target<sup>7</sup>.

In primary prevention, the proportion of high-risk individuals with elevated blood lipids treated with lipid-lowering drugs varies widely between countries, from about half to three quarters<sup>8,20,178-181</sup>. However, less than half of the treated patients reach the total cholesterol reduction recommended by the guidelines<sup>182-184</sup>, 28% in Italy, and from 29% to 48% in Sweden<sup>8,185</sup>. Sub-optimal treatment is associated with less reduction of cardiac events<sup>186</sup>. An international European study showed that the incidence rate of cardiovascular events during three years of observation was more than double in individuals who did not reach the LDL cholesterol reduction target compared to those at target<sup>185</sup>. The presence of co-morbidities and also being female seem to reduce appropriate lipid-lowering treatment<sup>23,182</sup>. Conversely, an overuse of statins has been documented in low-risk individuals with low expected benefits<sup>19,20</sup>.

Accurate risk assessment is crucial for making rational treatment decisions. Despite the development of several risk scoring tools, more than half of physicians do not use them in daily practice<sup>177,187-190</sup>. Several barriers to implementing the risk assessment scores and guidelines in clinical practice have been identified<sup>187,191-193</sup>: difficulties in applying guidelines based on population studies to individual patients, disagreement about the oversimplification of risk assessment scores, lack of patient compliance, lack of motivation to change previous practice, time and financial constraints imposed by the national health systems. However, a trial of educational intervention aimed to improve GPs' recording and control of risk factors in secondary cardiovascular prevention, resulted in limited improvements in cholesterol reduction<sup>194</sup>. Moreover,

even within homogeneous groups of GPs, in the same countries, with uniform guidelines and risk assessment systems, there are large differences in knowledge, beliefs and practice patterns regarding primary prevention of CVD<sup>195,196</sup>. These observations indicate that barriers are important but do not fully explain the gap between guidelines and practice.

The risk estimates are usually made subjectively using physicians' own judgment and experience of CVD prevention. This practice has clinical relevance as different physicians may estimate risk differently and make different treatment decisions when assessing the same patients. Some studies on GPs, internists and cardiologists have been carried out to investigate the CVD risk assessments in simulated cases based on case vignettes, using the Framingham algorithm as a reference risk calculation. Overall, less than half of all physicians correctly categorized the case risk level and there were wide inter-individual differences in risk estimates. Physicians in Sweden and Norway underestimated the risk, especially in high-risk case histories<sup>14,134</sup>. North American studies have shown a tendency to overestimate the absolute baseline coronary risk<sup>16,17,197</sup>. GPs from outpatient clinics in Italy underestimated high-risk patients and overestimated those at low- and intermediate-risk.

Incorrect risk assessment may have consequences in medical practice, as underestimation of the true cardiovascular risk may result in high-risk people not reaching the treatment threshold, and thus not being given the appropriate drug treatment. On the other hand, overestimation of the risk may give a false perception of illness in healthy individuals, leading to their medicalization. Some conditions unrelated to the patients' risk, such as physicians' gender, length and content of clinical practice, psychological factors and how trial results are reported, may influence CHD risk estimates and treatment decisions. It has been shown that female physicians provide better lifestyle advice<sup>198</sup> but not better guidelines-based care compared to male physicians<sup>199</sup>. Studies on the relationship between years in clinical practice and quality of care have shown that physicians with longer practice are less likely to adhere to appropriate standards of care and have poorer patient outcomes<sup>6,200,201</sup>. The physicians' decisions about treatment may also be affected by how trial results are reported. Trial outcomes may be reported as relative risk reduction, absolute risk reduction and number needed to treat (Table 5). It has been observed that the presentation of the results in terms of relative risk reduction increases the physicians' perception of treatment benefits and willingness to prescribe much more than the presentation in terms of absolute risk reduction or number needed to treat<sup>202-205</sup>. This presentation of the results may be misleading as a large relative risk reduction may derive from small absolute risk changes when the patient's baseline risk is low. Such

observation is consistent with studies demonstrating that decisions are influenced not only by probabilities of possible outcomes, but also by the way these probabilities are presented. This shift in choices when the same options are presented in different ways has been termed the “framing effect”<sup>206-208</sup>.

## Aim

### General Aim

This research aimed to study how doctors in two different European areas with different cardiovascular risk levels, deal with cardiovascular risk and statin treatment. In particular, the focus is on factors not directly related to the actual coronary risk of the patients, such as doctors’ attitude in investigating risk factors, coronary risk level in the general population, and doctors’ speciality, clinical experience and gender. Increased knowledge in this area will enhance our information about the gap between evidence and practice in the prevention of CHD, and our options for improving clinical guidelines to manage CHD risk factors.

### Specific Aims

- to study the attitude of doctors towards the management of hyperlipidaemia, in two European areas with different population coronary risk profiles but similar national guidelines (study I);
- to test the hypothesis that the same set of risk factors is associated with higher risk estimates in a high-risk country than in a low-risk country, comparing the risk estimates and decisions to start lipid-lowering treatment in a high cardiovascular risk country in northern Europe and in a low risk country in southern Europe (study II).
- to study the differences in CHD risk estimates and willingness to start pharmacological treatment among different groups of specialists with a role in CHD prevention: GPs, cardiologists and internists (study III)
- to determine whether the GPs’ risk estimates and their decisions about starting lipid-lowering treatment may influence each other, and whether the gender of physicians and the length of their clinical practice may affect their risk ratings and treatment decisions (study IV)

-to study the relation between changes over time in population coronary risk levels and lipid-lowering drugs utilization, in order to assess whether different population risk profiles result in different use of statins (study V).

## Methods

### Setting

Studies I and II were performed in Stockholm county, which is in a high-moderate cardiovascular risk country (\*), and in the central area of Sicily which is a low-risk area. Studies III and IV were conducted in Sicily and in Stockholm, respectively. Study V was based on official data of coronary mortality and statin utilization in Stockholm County and Sicily.

(\*) At the time of these studies, Sweden was a high cardiovascular risk country, whereas now it is classified as a low-risk country

### Participants

In study I, a questionnaire was sent by mail to all 329 GPs of two medium-sized towns in central Sicily (districts of Caltanissetta and Enna), as well as to all 356 hospital internists in Sicily, to all 181 GPs in the south-western area of Stockholm county, and to 143 internists of six hospitals in Stockholm.

In study II, 90 GPs were randomly selected from the list of GPs in Stockholm, and the same number was randomly selected from the list of GPs in Sicily. The sample size was calculated to get a power of 80%. This required 30 doctors in each group. Assuming a response rate of 40%, a sample size of 90 gives 36 responses. Accordingly, this was the sample for each group of doctors.

Study III was performed in Sicily with three groups of specialists: first, the same random sample of Sicilian GPs as in study II; second, 90 internists randomly selected from a list of hospital specialists in internal medicine; third, the same number of cardiologists randomly selected from specialists in cardiology from the local hospitals.

Study IV involved three groups of 90 GPs in Stockholm, randomly drawn from the local database of specialists in family medicine, the same sample of Swedish GPs as in study II.

Study V refers to CHD mortality and statin utilization data in Stockholm county and Sicily populations in the years 2001-2011.

## Questionnaire and Patient Cases (Case Vignettes)

Study I was based on a questionnaire comprising 25 multiple-choice questions focusing on physicians' clinical practice in the management of hyperlipidaemia. The questionnaires were anonymous in order to increase the response rate, and were sent by mail, with subsequent written and telephone reminders. The questions were firstly formulated in Swedish, then translated into Italian, and re-translated into Swedish to make sure that each question had the same meaning in both languages.

In studies II to IV, written patient cases were used. Nine patient cases were constructed combining the variables included in the Framingham risk equation: age, sex, blood pressure, cholesterol level and smoking, without previous cardiovascular disease or diabetes (Table 7).

**Table 7**  
Summary of the nine cases

case number	1	2	3	4	5	6	7	8	9
age	53	39	68	41	70	59	60	52	51
sex	M	F	F	M	M	M	M	F	M
smoker	no	no	yes	no	yes	no	yes	yes	no
SBP	140	130	140	140	160	160	145	125	120
cholesterol									
mmol/L	7.0	6.4	8.0	6.1	7.8	8.0	7.2	7.2	7.9
Framingham									
risk level	17	3	28	8	45	27	33	16	15

The cases were constructed so that the resulting 10-year risk of a fatal or non-fatal coronary event, based on the Framingham equation <sup>42</sup>, represented a spectrum from high to low-risk patients. According to this equation, a 10-year absolute CHD risk of 20% is the threshold to start pharmacological treatment. Accordingly, 20% was the risk cut-off to define high-risk patients in our patient cases. We chose to construct the cases based on the Framingham algorithm because it is the best known and most widely used. More recently, the SCORE system has been adopted in most European countries. It calculates the 10-year risk of cardiovascular mortality, instead of the risk of

fatal and non-fatal events calculated by the Framingham, and the risk cut-off to start treatment is set at 5%<sup>28</sup>. Comparing the risk value of our patient cases based on the Framingham, with the risk calculated by the SCORE algorithm, we found a good correspondence between the two systems. Although the absolute values are different (as expected), the patients who need treatment according to Framingham (risk > 20%) are the same according to SCORE (risk > 5%) (Table 8).

**Table 8**  
Calculated CVD risk for the nine patient cases

	Framingham	SCORE Europe Low Risk	SCORE recalibrated for Sweden
Case #2	3%	1%	1%
Case #4	8%	1%	1%
Case #9	15%	1%	1%
Case #8	16%	1%	1%
Case #1	17%	2%	3%
Case #6	27%	6%	8%
Case #3	28%	6%	8%
Case #7	33%	8%	13%
Case #5	45%	17%	29%

Risk values are calculated with the Framingham algorithm and SCORE system for Europe low-risk countries and recalibrated for Sweden:  
<http://www.escardio.org/communities/EACPR/toolbox/health-professionals/Pages/SCORE-Risk-Charts.aspx>

The Framingham median risk score of our patient cases was 30.5 (range 27-45) for the four high-risk cases, 15.0 (range 3-17) for the five low-risk cases, and 17.0 (range 3-45) for all cases combined.

The cases were presented in a paper format and sent out as a postal questionnaire. To reduce the risk of an anchorage effect<sup>209</sup>, the first case presented in the questionnaire was a medium-risk case

while the others were randomly ordered. All participants received the same sequence of cases. The written instructions stated that all patients had tried lifestyle intervention for at least six months. The questionnaire asked for the physicians' age, gender and length of clinical experience, but was anonymous in order to increase the response rate. The participants were asked to make their judgments without using a risk table or any other decision support.

## Coronary Mortality and Statin Utilization Data

In study V, Stockholm mortality data were drawn from Socialstyrelsen <sup>69</sup>, whereas Sicilian data came from Istituto Superiore di Sanità <sup>70</sup> (years 2009-2011 were made available before publication on the web site). The causes of death in Stockholm were I20-I25 (ischaemic heart disease) according to the 10<sup>th</sup> revision of the International Classification of Disease. In Sicily, the 9<sup>th</sup> revision codes 410-414 were used until the year 2005, and the 10<sup>th</sup> revision codes I20-I25 thereafter. In order to make the two code systems comparable, a correction was made to Sicilian mortality data from 2001 to 2005. According to the bridge-coding studies <sup>71,72</sup>, the comparability ratio for ischaemic heart disease between the two systems is 1.0318. This means that 3.18% more deaths should be added to the data collected with the 9<sup>th</sup> revision codes. Accordingly, this percentage of deaths was added to the number of deaths in Sicily from 2001 to 2005. Mortality data in Stockholm and Sicily were standardized to the European population, to take into account the differences in classes of age composition.

Statin utilization data were collected from the Swedish Drug Registry <sup>112</sup> and from the Sicilian Regional Registry <sup>113</sup>. The Anatomical Therapeutic Chemical (ATC) classification codes were C10AA (statins) and C10AA01, 03, 04, 05 and 07 (simvastatin, pravastatin, fluvastatin, atorvastatin and rosuvastatin, respectively). To compare statin data between the two countries and in different years, the 2009 update of the Defined Daily Dose (DDD) per one Thousand Inhabitants per Day (DDD/TID) was used for all the time periods.

## Design, Procedure and Data Analyses

Studies I to IV were cross-sectional surveys. Study V was an ecological study.

### *Study I*

The study aimed to evaluate the differences in the management of hyperlipidaemia between doctors in the two regions, including the frequency of blood lipid measurement in individuals with cardiovascular risk, the frequency of cardiovascular investigations in individuals with hyperlipidaemia, the levels of cholesterol at which doctors started lipid-lowering drug treatment, type of drug used, and change of attitudes over time. Doctors were asked to fill in the questionnaire, marking one or more options for the multiple-choice questions, according to their clinical practice. The differences in the proportions of doctors' investigations in the management of hyperlipidaemia in Stockholm and Sicily were tested using the  $\chi^2$  test. The differences between means, such as mean levels of cholesterol to start treatment, were tested with the Student's t-test.

### *Study II*

This study aimed to investigate the differences in coronary risk estimates and decisions to start drug treatment between GPs in Stockholm and Sicily; the concordance between their risk estimates and the actual calculated Framingham risk of the patient cases; and the relation between GPs risk estimates and their decisions about treatment.

The task of the participating doctors was to rate the risk of CHD within 10 years for each case, marking a cross on a visual analogue scale (VAS) of 0%-100%, and to decide whether or not they would recommend starting a pharmacological lipid-lowering treatment for that patient.

The following is an example of a case description, with the response scale.



**Case 7.** The patient is a 60-year old man with no history of previous cardiovascular disease or diabetes. Smoker. Systolic blood pressure 145 mm Hg. Recent cholesterol value is 7,2 mmol/l.

Mark with a cross on the line your estimate of his risk to have coronary heart disease within 10 years.



Would you recommend a lipid-lowering drug in this case?

Yes      No

---

The distance of the marked cross in millimetres, divided by the actual length of the VAS scale, was converted into the percentage of risk.

Summary data of risk estimates for each GP across the nine cases were calculated. Decisions to start pharmacological treatment were expressed as proportions, calculated as the number of “yes” decisions divided by the total number of decisions for each doctor. The relation between ratings and decisions, within each group, was investigated as the proportion of GPs who decided to start treatment when their own risk estimates were above the cut-off limit of 20%. Data were expressed as medians or means depending on whether they were normally distributed. The resulting sets of medians or means were compared between the two groups of GPs in Stockholm and Sicily.

The statistical significance of the differences was tested with the two-sample t-test for independent data or Mann-Whitney rank sum test. The possible effect of GPs’ age and gender on estimates and decisions was investigated using a multiple linear regression analysis, with estimates and decisions as dependent variables, and age and gender as independent variables.

### *Study III*

The study was conducted in Sicily and aimed to investigate the differences in risk estimates and decisions to start treatment between three groups of specialists - GPs, internists and cardiologist - who have the main responsibility for cardiovascular prevention. The questionnaire and the task of the doctors were the same as in study II. Risk estimates and proportions of decisions to start treatment were calculated within each group of doctors. The differences in risk ratings and

willingness to start treatment between the three groups, the relation between estimates and decisions, as well as their relation with GPs' age and gender, were analysed with the same methods used in study II.

#### *Study IV*

The aim was to investigate whether there are mutual influences between GPs risk ratings and their decisions to start treatment, that is, whether the task of making estimates influences treatment decisions and whether the task of making decisions influences estimates. A second aim was to investigate whether GPs' gender and length of clinical experience influence the risk ratings and treatment decisions.

One group of GPs was asked to estimate the risk of CHD within 10 years on a VAS scale and make a decision about treatment, as in studies II and III (group R+D); a second group had the task of risk rating only on the same VAS scale (group R); a third group was asked only to make a decision about treatment, without rating the risk (group D).

In this study, the risk estimates were also calculated as the difference between the doctors' ratings and the calculated Framingham risk, of the clinical case (Framingham score). This means that when doctors overestimate the calculated risk, the Framingham score is positive, whereas when doctors underestimate the risk, the score is negative. The advantage of using the difference rather than the risk estimates is that the difference was approximately normally distributed, which was not the case for estimates. Proportions of decisions to start pharmacological treatment, as in study II, and proportions of correct decisions were calculated. Correct decisions were "no" decisions when the Framingham risk of the case was <20%, and "yes" decisions when the Framingham risk was >20%.

Since each doctor contributed nine times to the risk estimates and decisions (one for each patient case), the data generated were not independent but clustered. Such doctors' intra-correlation means that scores for the nine patients from an individual doctor were likely to be more similar to each other, than scores for the nine patients from different doctors. This may lead to incorrect interpretation of the associations between variables<sup>210</sup> and a significant result could be purely due to just one individual (outlying) doctor. To take this effect into account, a model was constructed with nine rows for each doctor for each case, thus adjusting for the clustering effect.

The effect of decisions on risk estimates was analysed with a linear regression model, including the actual Framingham risk for each case, the doctors' risk estimates in the two groups R+D and R, the gender and the years of clinical experience of the doctors as independent variables, and the difference between the doctors' risk estimates and Framingham risk (Framingham score) as a dependent variable.

The effect of risk ratings on treatment decisions was assessed with a logistic regression model, including Framingham scores of R+D and D groups, gender and clinical experience as independent variables, and proportion of correct decisions as a dependent variable.

The relative influence of gender and length of clinical experience was investigated including both terms as independent variables in the linear and logistic regressions.

All the analyses were adjusted for the repeated measures for each doctor using the cluster command in the STATA software package.

### *Study V*

The study investigated the relation between changes over time in population coronary risk and lipid-lowering drug utilization in two European areas with different population coronary risk levels. Population CHD mortality was used as a proxy of population coronary risk. Only statins were considered as lipid-lowering drugs since they account for almost the total amount of these drugs. Mortality and statin utilization data in Stockholm and Sicily were extracted from the official database and plotted against time, for the years 2001-2011. The mean annual change in CHD mortality and statin utilization were calculated for each year as the  $\beta$  coefficient of a linear regression in which mortality and statins were the outcomes and years the predictor.

## Results

### Study I

#### *Response rate and characteristics of doctors*

There was a lower response rate among GPs in Sicily (46%) than in Stockholm (66%), whereas about the same rate was observed among internists (59% and 56%, respectively). There was a statistically significant larger proportion of women doctors in Stockholm, and a longer clinical practice in Sicily, for both GPs and internists.

### *Differences in the management of hyperlipidaemia*

More than half of GPs (53%) and internists (67%) in Sicily checked lipids at the first visit of their patients, compared to 2% of GPs and 0% of internists in Stockholm. In both regions, the vast majority of doctors investigated lipids in patients presenting with diabetes, hypertension, cardiovascular disease, other cardiovascular risk factors or familial hyperlipidaemia. However, compared to Sicily, a larger proportion of GPs in Stockholm investigated lipids in patients with cardiovascular risk factors and familial hyperlipidaemia, and a larger proportion of internists investigated lipids in patients with cardiovascular disease and cardiovascular risk factors. There were also differences in the pattern of investigations in patients diagnosed with hyperlipidaemia. Body weight was measured more often by GPs in Stockholm (89% vs. 74%), whereas a larger proportion of internists in Sicily recorded an electrocardiogram (88% vs. 62%). The level of cholesterol at which doctors started lipid-lowering drug treatment was significantly lower in Sicily than in Stockholm.

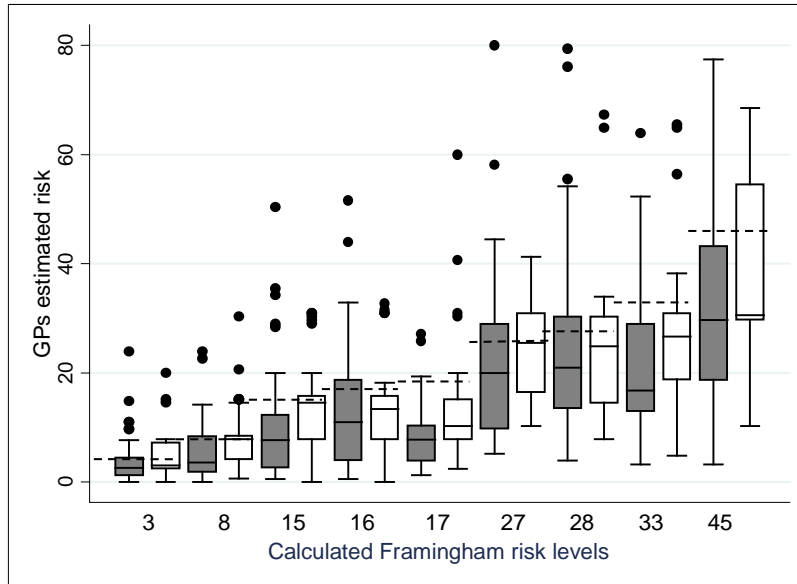
## Study II

### *Response rate*

The same number of doctors answered the questionnaire (38, response rate 42.2%) in both regions. There was a higher response rate among women doctors in Stockholm (60.5%) than in Sicily (23.7%).

### *Risk estimates*

Ratings were in general lower than the calculated Framingham risk and there were large differences within each group of doctors, especially in high-risk cases (Figure 4).



**Figure 4.** Boxplot of GPs' risk ratings in Stockholm (filled bars) and in Sicily (empty bars), along with the calculated Framingham risk level for each case (dashed lines). The continuous lines across the boxes are median values.

Compared to Sicilian doctors, Swedish doctors underestimated the risk, but the difference was statistically significant only when the cases were analysed separately, the four high-risk and the five low-risk cases.

The concordance between doctors' risk estimates and the Framingham risk of the cases was also calculated as the proportion of doctors' risk estimates above 20% when the Framingham risk was >20%, and doctors risk estimate below 20% when Framingham was <20%. GPs in Stockholm showed lower concordance than in Sicily, and the difference was statistically significant for all the cases (73% vs. 84%, respectively,  $p=0.006$ ) and for the high-risk cases subgroup (53% vs. 76% respectively,  $p=0.007$ ).

### Decisions

The proportions of decisions to start pharmacological treatment, divided by the total number of decisions, was lower in Stockholm than in Sicily, but statistically not significant. When GPs' willingness to start treatment was related to their own risk ratings, it was observed that Swedish GPs less often decided to start treatment even when their risk ratings were above 20%, whereas no

difference was found when the GPs' risk ratings were below 20%. Doctors' age or gender were not significantly related to risk estimates or treatment decision

## Study III

### *Response rate*

GPs, internists and cardiologists showed similar response rates (42.2%, 47.8% and 42.2%, respectively).

### *Risk estimates*

All groups rated the risk of the cases lower than the calculated Framingham, with large variability within each group, especially when estimating high-risk cases. In seven cases out of nine, the estimates of cardiologists were lower than the other groups, and the difference was statistically significant.

This group of specialists also showed the lowest concordance between their estimates and the Framingham risk of the cases, calculated as the proportion of estimates above 20% when Framingham was >20%, and estimates below 20% when Framingham was <20%. When estimating high-risk cases, only one third of their estimates were correctly rated >20%.

### *Decisions*

Internists were more prone to start pharmacological treatment than GPs and cardiologists (68%, 54% and 57%, respectively). More than 90% of doctors within each group of specialists decided to start pharmacological treatment when their risk estimates were above 20%, whereas less than half decided to treat when their estimates were below 20%. However, in the high-risk cases subgroup, more than three quarters of doctors, within each group of specialists, decided to start treatment even when their estimates were below 20%.

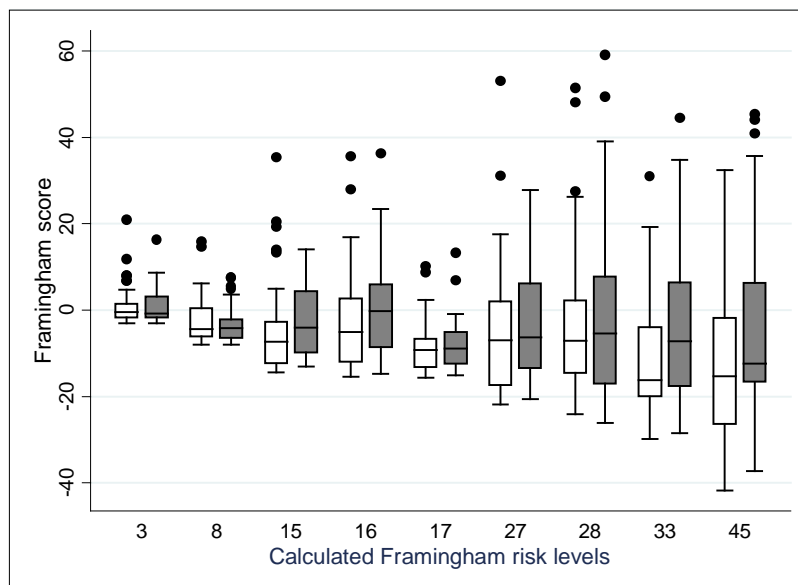
## Study IV

### *Response rate*

About an equal number of doctors from each group answered the questionnaire: 38 GPs (42.2%) in the group that made estimates and decisions (R+D), and 41 GPs (45.6%) both in the group that only estimated the risk (R) and in the group that only had to make a decision (D).

### *Risk estimates*

GPs' estimates varied widely, but in general all the groups underestimated the calculated Framingham risk, especially in high-risk cases. The difference between GPs' ratings and the calculated risk of the cases, expressed as doctors' risk estimates minus calculated Framingham risk (Framingham score), was greater in high-risk cases, thus indicating an underestimation of the risk, especially by GPs in the R+D group (Figure 5). However, the difference in the Framingham score between the R+D and R groups was not statistically significant, indicating that the task of making a decision does not have a significant effect on the task of estimating the risk. In both groups of GPs there was no significant relation between the Framingham score (difference between the doctors' ratings and the calculated Framingham risk of the clinical case) and GPs' gender or length of clinical experience.



**Figure 5.** Box plot of GPs' risk estimates in the R+D group (empty bars) and R group (filled bars) plotted against Framingham score (GPs' risk estimates minus calculated Framingham risk levels). Positive values indicate overestimation of the risk, whereas negative values indicate underestimation.

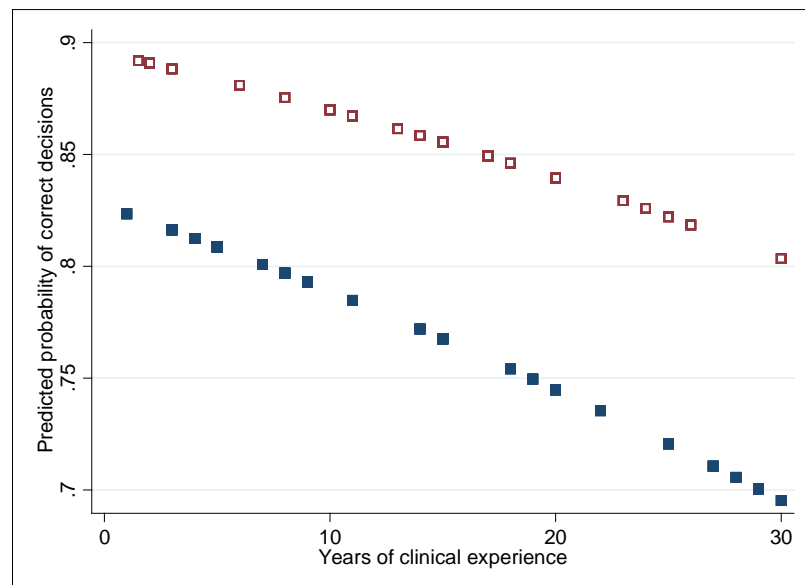
### *Decisions*

Overall, about half of the GPs decided to start pharmacological treatment. When the patient cases were analysed separately, it was observed that in the four high-risk cases there was no difference

between male and female GPs in the willingness to start treatment, whereas in the five low-risk cases more male GPs decided to start treatment compared to female GPs (24.4% vs.12.6%,  $p = 0.04$ ).

The proportion of correct decisions was significantly related to gender and length of clinical experience. Female GPs showed a higher rate of correct decisions (87.3% vs. 75.5%,  $p = 0.08$ ), and the years of experience were inversely related to the proportion of correct decisions, both in male and female GPs (Figure 6).

The task of making risk estimates showed no relevant effect on the task of making decisions. GPs in the R+D group were slightly more prone to start pharmacological treatment (48.3%) compared to GPs in the D group (44.4%), but the difference was not statistically significant.



**Figure 6.** Scatter plot of the results of a logistic regression with correct decision as the outcome and gender and experience as the dependent variables. Empty squares = females GPs, filled squares = males GPs. Each square represents one to six doctors with the same number of years of clinical experience and indicates the predicted proportion of correct decisions.



## Study V

### *CHD mortality*

Higher rates were observed in Stockholm. CHD mortality declined over the years in both areas, but the mean annual reduction was greater in Stockholm than in Sicily (standardized rates/100.000: -4.6 and -1.9, respectively). Accordingly, the two curves tend to become closer in recent years.

### *Statin utilization*

Rates were higher in Stockholm than in Sicily. A steady increase over the years was observed in both areas, but the mean annual increase was greater in Sicily than in Stockholm (5.1 vs. 3.7 DDD/TID, respectively). Thus, there was a “discordant” relation between CHD mortality and statin utilization. In other words, the largest increase in statin use occurred in the area with the slower reduction in CHD mortality.

## Discussion

The studies have shown that: a) there are differences in the management of coronary risk factors in two geographical areas with different population coronary risk profiles, b) the doctors' risk estimates and decisions about treatment with lipid-lowering drugs are subjective and influenced by factors unrelated to the actual risk of the patients, and c) there are different rates of increase in statin utilization in populations with different coronary risk levels.

## Methodological Considerations

Studies I to IV in this thesis are cross-sectional studies. Study V is an ecological study. The cross-sectional design has the advantage of being appropriate for comparative analyses<sup>211</sup> and relatively easy to perform. It has some limitations since the associations observed do not necessarily imply a causal relation and confounding factors may affect the relationship between the variables of interest.

In study I, the data were collected by using a questionnaire in which doctors were asked about their attitude when investigating patients with coronary risk factors. Studies II to IV were based on a questionnaire related to nine short clinical cases, to compare the clinical practice in different countries. Clinical vignettes or written case descriptions were used in different settings, from diagnostic testing to treatment decisions, as a convenient way of studying both the competence of

the clinicians and what clinicians actually do in clinical practice <sup>212-215</sup>. A large study comparing clinical vignettes with standardized patients and medical record abstraction has documented the validity of these vignettes as an accurate tool for measuring the quality of clinical practice <sup>216</sup>. When properly constructed, vignettes may concentrate the doctors' decision-making on specific factors of interest, avoiding influences from other factors in the environment. More importantly, they allow assessment of the differences between doctors when evaluating the same cases. However, doctors may answer in an ideal fashion that does not correspond to their clinical practice. Moreover, the structure of vignettes is limited to only a few variables which might not represent the complexity of real patients.

The response rates were 46% and 66% in study I, and between 42% and 47% in the other three studies. Although these rates are common in cross-sectional questionnaire studies <sup>217-219</sup>, the results of the studies cannot be generalised to all doctors.

In studies II to IV, the questionnaires were anonymous in order to increase the response rate. However, this made it impossible to trace non-responders and assess whether they were different from responders. Clinical cases were constructed using the variables and the risk categories of the Framingham scoring system. Although most European countries have adopted the SCORE system, the older Framingham system has been widely used for many years and is well known, both in Sweden and in Italy. However, its accuracy relates to the background risk of the population where it is used. In a high-risk population, the predicted risk of a patient, calculated according to Framingham, is lower than the observed risk, whereas in a low-risk population the predicted risk is higher than the observed <sup>138</sup>. This means that the actual risk of a patient in Stockholm is higher than the calculated Framingham risk, whereas in Sicily it is lower. In studies II to IV, the calculated Framingham risks of clinical cases were the same for all the doctors, without taking into account the background risk in the populations.

Study V was an ecological study in which the units of observation were groups of people, rather than individuals. The major limitation of this kind of study is that the associations observed at population level may not reflect association at individual level <sup>220</sup>. The study assumed that population coronary risk could be represented by CHD mortality, which has less diagnostic variance than measurement of risk factors. However, changes in risk factors account for about half of the changes in CHD mortality, whereas the other half are due to improvements in medical treatment, and unknown factors <sup>221</sup>.

## Management of Risk Factors (study I)

When the present study was started, the population mean cholesterol levels were substantially higher in Stockholm than in Sicily. Among doctors in Stockholm, checking for hyperlipidaemia on the patient's first visit was less frequent than in Sicily, whereas both groups had the same attitude towards making further investigations when hyperlipidaemia was found. Most importantly, the level of cholesterol at which doctors decided to start treatment with lipid-lowering drugs was significantly higher in Stockholm than in Sicily, in both primary and secondary prevention. This indicates poor compliance with Swedish national guidelines on treatment. Possible influences of the differences in populations' cardiovascular risk levels on the varying risk management approaches in Stockholm and Sicily, should be taken into consideration. Since the overall risk for individuals derives from the effects of multiple risk factors, the same cholesterol level may be associated with a greater risk of CHD events in high-risk populations compared to low-risk populations <sup>222</sup>. Therefore, doctors in Stockholm would be expected to start lipid-lowering treatment at lower cholesterol levels than in Sicily, which is at variance with our findings.

## Doctors' Risk Estimates and Decisions to Start Treatment (studies II to IV)

Within all groups of doctors there was a wide variability in risk ratings, and an underestimation of the coronary risk, compared to the calculated Framingham score. Both variability and underestimation were greater in high-risk cases. Such discrepancies may result in inadequate management of high-risk patients, who gain the greatest benefits from coronary prevention.

There were differences in risk ratings between doctors in the two areas studied. Compared to Sicilian doctors, Swedish GPs underestimated the risk when assessing the same set of clinical cases. The result was that a smaller number of GPs in Stockholm correctly categorized high-risk cases, compared to GPs in Sicily. The starting hypothesis was that doctors' risk estimates would be in agreement with the risk in the population. As a consequence, the same set of risk factors would be associated with higher risk estimates in a high-risk country than in a low-risk country. Our findings suggest a different pattern of risk estimation. In a high-risk population, an individual with a high level of risk would be perceived as having a lower risk, whereas the same risk pattern in a low-risk country would be considered as higher risk. The influence of the baseline coronary risk in the population on the doctors' perception of the risk is supported by the differences in risk assessment

among GPs, cardiologists and internists in Sicily. Cardiologists made significantly lower risk estimates when evaluating the same set of clinical cases. Since they usually manage high-risk patients, their background risk is high and their threshold for defining high-risk patients is higher than for GPs and internists. Within the group of cardiologists in Sicily, only one third correctly rated high-risk cases, compared to two thirds of GPs and internists. This underestimation of the individual risk has practical consequences as high-risk patients may be missed.

A simplified assumption is that a decision about treatment directly follows a risk estimate. The proportion of GPs who decided to start treatment was lower in Stockholm than in Sicily, even when the doctors' risk estimates were above 20%. The combination of underestimation of the risk and reluctance to treat may explain the observation that doctors in Stockholm tend to start lipid-lowering treatment at higher cholesterol levels than in Sicily (study I). On the other hand, doctors in Sicily were more prone to start treatment in high-risk cases, even when their own risk estimates were below 20%. In other words, decisions and risk estimates seem to be, at least in part, independent from each other.

The influence of GPs' risk estimates on their task of deciding whether or not to start a lipid-lowering treatment, and the influence of treatment decisions on the task of risk estimates, were evaluated in study IV. There was no evidence of a mutual influence between these two tasks.

Other factors than those related to the actual risk of the patients were found to influence the decisions about treatment. Within the group of GPs in Stockholm, the correctness of decisions (a 'yes' decision when the individual risk is above 20%; a 'no' decision when the risk is below) was influenced by the gender of the doctors and the length of their clinical experience. Female GPs and younger GPs were more likely to make correct decisions compared to male and more experienced GPs.

These data suggest that risk assessments and decisions about treatment are made based on doctors' knowledge, environmental conditions and cognitive processes such as risk perception, all factors that are not directly related to the actual risk of the patients. One way of analysing judgments and decisions within clinical medicine is to assume that doctors assign weights to clinical findings (cues) such as symptoms, signs, and laboratory tests, and their judgments are based on these <sup>223</sup>. In this model, termed Clinical Judgment Analysis, the relative importance of each clinical variable in determining the diagnostic judgment may be assessed statistically with regression analysis. The

probability that a doctor assigns to a disease is the dependent variable, whereas cues are the independent variables. This model has shown some inconsistencies in clinical reasoning. There are large variations in doctors' judgments when evaluating the same clinical cases, and the way doctors use clinical information to make judgments is different from how they think they do: even clinically relevant cues may not influence the decision-making, and most doctors use a very small number of cues, usually two or three<sup>18,224-226</sup>. This model can be incorporated in the more general dual-process theory of thinking<sup>227</sup>. There are two fundamental approaches to clinical judgment and decision-making: intuitive and analytical<sup>228-230</sup>. Neural correlates have been identified by neuroimaging techniques<sup>231,232</sup>. The intuitive approach, also termed System 1, is unconscious and "fast and frugal", fast because complex problems are best solved using simple rules, and frugal because a small amount of information is used in the decisions<sup>233-235</sup>. This model implies non-analytical reasoning, based on pattern recognition, which is the process of matching the presentation of symptoms and signs of a new patient with disease features of a previously encountered patient retrieved from memory<sup>236,237</sup>. It often leads to quick decisions and good judgments, but when the patient presentation is atypical, it may fail. Moreover, the system is highly influenced by the context, which includes patients' and physicians' non-medical factors, such as appearance, age, gender, and workload. In contrast, the analytical process, System 2, is based on conscious and rational reasoning. It is a step by step process where hypotheses are generated or discarded at each step, and hypothetic-deductive, as each hypothesis is used to predict which additional findings ought to be present if it is true. The analytical process is slow but effective when a patient presentation is not readily recognized and previous experience cannot inform judgments. The two components of the dual-process model are not independent but there is a continuum between them, with reciprocal influences. Doctors use the intuitive approach for common clinical problems, whereas complex and unusual problems are approached with the analytical process. There are also differences in the reasoning processes related to clinical experience. Expert doctors rely more often on pattern recognition, whereas less experienced doctors use more analytical strategies<sup>238-240</sup>.

## Population Coronary Risk Levels and Statin Utilization (study V)

The relationship between coronary prevention and population risk profile was approached from a different starting point in study V. Assuming CHD mortality as a proxy of population coronary risk, the statin utilization was higher in Stockholm, an area with higher CHD mortality rates, than in Sicily, an area with lower CHD mortality rates. However, it is not known whether the statin utilization in both areas was adequate for the population risk levels. It is not possible to exclude an

over- or under-utilization of statins compared to the actual CHD risk in the population. An important limitation of the studies that used a cross-sectional design is the uncertainty regarding whether statin use preceded the changes in population coronary risk or vice versa. More information may be drawn from the study of the changes over time in statin utilization compared to CHD mortality. If statins exert an effect on CHD mortality, the changes over time should be concordant, i.e. a greater increase in statin utilization associated with a faster reduction in CHD mortality. However, both Stockholm and Sicily showed a discordant pattern. Comparing the two areas, a smaller increase in statins was observed in Stockholm, an area with a faster reduction in CHD mortality, whereas a greater increase in statins was found in Sicily, an area with a slower reduction in CHD mortality. This suggests that statin utilization is not directly associated with changes in CHD mortality. Other factors unrelated to the actual coronary risk in the population, such as drug-cost containment policies, socioeconomic gradients, and discontinuation rate, may influence the changes in statin utilization. If we consider our other studies in this thesis (studies II-IV), the doctors' underestimation of the coronary risk in high-risk individuals may have contributed to a smaller increase in statin utilization in Stockholm over time, whereas the overestimation of low-risk individuals may be responsible for the greater increase in statin utilization in Sicily. The possibility of an effect of the population coronary risk level on statin utilization cannot be excluded. A faster reduction in CHD mortality in Stockholm, due to an improved population risk profile, may have reduced the need for statin treatment and limited the increase over time, whereas a slower reduction of CHD mortality in Sicily may have induced a greater increase in statins utilization.

## Conclusions

Cardiovascular prevention is based on two strategies: reduction of the cardiovascular risk in the whole population, and identification and treatment of high-risk individuals. The first implies public health interventions to reduce the level of cardiovascular risk factors in the population. The second requires doctors to make accurate assessments of patients' absolute risk, and decisions about appropriate treatment. International guidelines have proposed priorities for individuals at high risk of developing cardiovascular events. Although it is recognized that cardiovascular risk is a continuum, guidelines identify the risk factors to search for and the threshold values at which drug treatment is recommended. It is essential for clinicians to accurately assess individuals' global risk, to allow appropriate treatment decisions to be made.

The studies in this thesis suggest that the doctors' assessment of the coronary risk is largely based on subjective estimates. The use of questionnaires and clinical vignettes presented to doctors in

areas with different population risk profiles, allowed the investigation of the influence of factors not directly related to individuals' true coronary risk on the doctors' assessment of the risk and decisions about treatment. Compared with the predictions of the Framingham model, all groups of doctors underestimated the individuals' risk. Doctors in a high-risk area tend to start lipid-lowering treatment at higher cholesterol levels than doctors in a low-risk area. The doctors' risk estimates seem inversely related to the average coronary risk in the population. Female doctors and young doctors made more correct decisions about lipid-lowering treatment than did male and more experienced doctors.

The inverse relation between background coronary risk in the population and the doctors' risk judgment in the two areas studied, may result in unjustified differences in the use of statins in areas with different population risk profiles. The changes over time in statin utilization and CHD mortality in Stockholm and Sicily were studied to assess whether the use of statins is related to the coronary risk in the population. The relations between the reduction over the years in CHD mortality and the increase in statin utilization were different in the areas studied. A faster rise in statin utilization in the low-risk area was associated with a slower decrease in CHD mortality, whereas a slower increase in statin utilization in the high-risk area was associated with a greater reduction in CHD mortality. Although the coronary risk in the population seems to affect the relation between statin use and CHD mortality, changes in the prescription rules for statins may explain part of the findings.

The present research has shown that primary coronary prevention is not uniform in countries with different cardiovascular risk profiles, and doctors' preventive care is in general far from accurate as regards estimating and treating individual risk. Better understanding of subjective components of clinical judgment may reduce the gap between the true coronary risk of the patients and doctors' clinical interventions in primary prevention.

## Acknowledgments

I would like to express my deepest gratitude and appreciation to those who have supported and contributed to the research project which led to this thesis. In particular, I would like to acknowledge:

Lars Backlund, PhD, my main supervisor, for giving me the opportunity to do my PhD research, and to work on a fascinating project. He gave me guidance throughout the entire project, with valuable advice, remarks and thoughtful comments on my ideas, draft and manuscript. I wish to express my gratitude to him for sharing his experience and knowledge, and most importantly for giving me his friendship.

Professor emeritus Lars-Erik Strender, co-supervisor, for his central role in planning the research project, allowing me to become a PhD student and to introducing me to an exciting intellectual environment. I would like to acknowledge his brilliant and stimulating ideas, suggestions, and criticism, during the meetings in Huddinge, but also during unforgettable dinners at his home in Lidingö.

Simona Giampaoli, MD, Istituto Superiore di Sanità, Rome, my mentor, for introducing me to cardiovascular epidemiological studies and for generously sharing her profound knowledge of this field, and for her good advice and encouragement during the research.

Special thanks to Birgitta Danielsson, PhD, the first author of my first paper in 1998, and to Professor emeritus Hans Åberg, her supervisor at that time. Our collaboration started with a common interest in the doctors' attitude to the prevention of coronary heart disease, and evolved into a PhD research project that produced the present thesis.

Rosemary Tate, PhD, for answering my numerous questions on statistics and for her invaluable support in analysing research data using STATA.

My co-authors, for their invaluable contributions to the manuscripts:

Associate Professor Ylva Skånér, for sharing her knowledge in the field of decision-making in health care.

Professor Johan Bring, for giving the statistical background to the present research.

Professor Henry Montgomery, who contributed to the research with his outstanding knowledge of cognitive psychology.

Associate Professor Björn Wettermark, for generously sharing his deep expertise in pharmacoepidemiology, and for many fruitful discussions, and wise comments on the manuscript.

I would also like to thank Luigi Palmieri, Cinzia Lo Noce and Chiara Donfrancesco, from the Istituto Superiore di Sanità, in Rome, and Antonello Marras and Pasquale Cananzi, from the Assessorato Sanità, Regione Sicilia, for their generous support in giving me so much of epidemiological data and good advice on their interpretation.



All my colleagues at the Medical Unit, S.Elia Hospital: Maurizio, Antonio, Umberto, Bruno, Giovanni, Cettina, Gianfranco, Susanna and Christian, for allowing me the time to conduct research and for their support and encouragement throughout the years of this project. I am happy and proud to be part of this group.

I would like to thank all the doctors in Stockholm and Sicily who filled in the questionnaires and contributed to improving understanding of the management of preventive coronary care.

My gratitude goes to the Karolinska Library which allowed me access to many publications useful for my research.

Very special thanks to:

My parents, Sergio and Ada, for their love, advice and endless support.

My brother, who supported and encouraged me during all this work.

My wife Carla, for her warm support and patience during the years of this research.

My sons, Sergio, Edoardo and Riccardo, for being the most important part of my life and for being my future.

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# Sammanfattning på svenska

## Introduktion

Internationella riktlinjer för primärprevention av hjärt- och kärlsjukdomar rekommenderar att förebyggande åtgärder bör baseras på läkarnas totala riskbedömning av patienten. Behandling, t.ex. av förhöjda lipider (blodfetter), rekommenderas när patientens risk är över en viss tröskel. Riskbedömningssystem har utvecklats för att hjälpa kliniker med riskbedömning. Dock görs sådan bedömning oftast subjektivt i klinisk praxis. Detta innebär att faktorer som inte har något samband med patientens verkliga risk kan påverka läkarnas riskbedömning och beslut om behandling.

## Syfte

Vårt syfte var att studera förebyggande vård av kranskärslsjukdomar i två områden med olika risknivåer för kranskärslsjukdomar, med särskild hänsyn till läkarnas inställning till att undersöka riskfaktorer samt deras riskbedömning och beslut om behandling. I enlighet med de olika risknivåerna för hjärt- och kärlsjukdomar i de studerade områdena avsåg vi också att testa hypotesen att samma uppsättning riskfaktorer kan uppfattas som högre risk i ett högriskland än i ett lågriskland.

## Metod

Studierna utfördes i två europeiska områden, ett med hög och det andra med låg risk för hjärt- och kärlsjukdomar: Stockholm respektive Sicilien. Frågeformulär om läkarnas kliniska praxis (studie I) och skriftliga patientfall (studier II-IV) presenterades för ett slumpmässigt urval läkare i Stockholm och på Sicilien. Fallen var konstruerade enligt Framinghams riskbedömningssystem och sträckte sig från fall med mycket låg risk till fall med mycket hög risk. Skillnader i användning av statiner och kranskärslsjukdomars dödlighet bland befolkningen (studie V) studerades genom att samla in officiella data från sjukvårdssystemen i båda områden.

## Resultat och diskussion

Det fanns skillnader i hanteringen av förhöjda lipider (studie I). Fler läkare i Stockholm undersökte lipider hos patienter med andra riskfaktorer för hjärt- och kärlsjukdomar. Kolesterolnivåerna när läkarna påbörjade lipidsänkande behandling var högre i Stockholm än på Sicilien. I studie II ombads allmänläkare utvärdera nio skriftliga patientfall. Deras riskbedömning för kranskärslsjukdomar varierade mycket, särskilt i högriskfall, och riskerna underskattades i allmänhet jämfört med riskbedömningen enligt Framinghams ekvationer. Tvärt emot hypotesen bedömde allmänläkare i Stockholm riskerna lägre och beslutade om lipidsänkande behandling mer sällan än vad som var fallet på Sicilien. En möjlig anledning till detta är att en hög risknivå hos befolkningen tenderar att dämpa riskbedömningen för en individ med en viss uppsättning riskfaktorer, och vice versa om befolkningens risknivå är låg. Stöd för sådan tankegång hittades vid jämförelser av riskbedömningar och beslut om behandling mellan läkare som vanligtvis arbetar med förebyggande vård av kranskärslsjukdomar: allmänläkare, kardiologer och invärtesläkare (studie III). Jämfört med andra specialister gjorde kardiologer, som vanligtvis arbetar med högriskpatienter,

lägre riskbedömningar för samma uppsättning patientfall. I studie IV framkom att riskbedömning och beslut om behandling inte påverkade varandra ömsesidigt. Kvinnliga allmänläkare och allmänläkare med kortare klinisk erfarenhet var mer benägna att fatta rätt beslut.

Skillnaderna i riskbedömning av kranskärslssjukdomar och beslut om behandling som har studerats i de båda områdena med olika risknivåer för kranskärslssjukdomar för befolkningen kan vara relaterade till användningen av statiner av hela befolkningen i respektive område. Studie V undersökte tidstrenderna i befolkningens risknivåer för kranskärslssjukdom, definierat som mortalitet (dödlighet) i kranskärslssjukdom, och användningen av statiner under perioden 2001-2011. I båda områden fanns en minskning av mortalitet och en ökning av statinanvändning. Minskningen av mortalitet var större i Stockholm än på Sicilien medan statinanvändningen ökade mer på Sicilien än i Stockholm. Således verkar de långsiktiga förändringarna av statinanvändning vara omvänt associerad med förändringarna av kranskärslssjukdomars dödlighet. Dock måste man ta med i beräkningarna faktorer som är oberoende befolkningens risk för kranskärslssjukdomar, som t.ex. kostnadsbesparingar, socioekonomiska faktorer vid statinanvändning och nedtrappningshastighet av mediciner.

## Slutsatser

Det finns flera skillnader i primärprevention av kranskärslssjukdomar mellan de båda europeiska områdena med olika riskprofiler för hjärt- och kärlsjukdomar. Läkarnas kvantitativa riskbedömningar och beslut om behandling påverkas av faktorer som inte är direkt relaterade till patienternas faktiska risk, och verkar preliminärt vara omvänt relaterade till befolkningens risk för hjärt- och kärlsjukdomar. Olikheter i bedömningar och praxis vid primärprevention kan bidra till en ökning av statinanvändning som inte motiveras av förändringar av befolkningens risk för kranskärslssjukdomar. Avhandlingens resultat kan bidra till utvecklingen av beslutsverktyg och rekommendationer för primärprevention av kranskärslssjukdomar.

I



## Hyperlipidaemia: Differences in management practices and attitudes in two regions in Europe – Sicily and the Stockholm area

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Accepted in revised form 13 March 1998

**Abstract.** In order to compare attitudes and management concerning hyperlipidaemia and risk factors for coronary heart disease among doctors in northern and in southern Europe, a questionnaire study was undertaken among doctors in primary health care and departments of internal medicine in Sicily and Stockholm. The regions differed in culture and health-care structure. Guidelines were similar, but screening of healthy individuals was recommended in Sicily, and not in Sweden. One hundred and fifty-three general practitioners in Sicily and 120 in Stockholm, 211 internists in Sicily and 83 in Stockholm participated. Main outcome measures were management policies for investigation and treatment and also attitudes. Routine lipid checks at first visits were done by few doctors in Stockholm but by a majority in Sicily ( $p < 0.001$ ); in the presence of general cardiovascular risk factors (other

than heredity, diabetes, cardiovascular disease and hypertension), routine checks were carried out more often by both general practitioners ( $p < 0.001$ ) and internists ( $p < 0.005$ ) in Stockholm. Drug treatment was initiated at lower cholesterol levels for secondary and primary intervention, cardiovascular disease, cardiovascular risk factors and hereditary hyperlipidaemia by both groups in Sicily ( $p < 0.001$ ), as was dietary treatment. Secondary prevention was considered important by all groups, but primary prevention only by Sicilian doctors. We concluded that there were differences in views and management practice between doctors in Sicily and in Stockholm on the investigation and treatment of patients with hyperlipidaemia. Doctors tested lipids at first visits in Sicily but not in Stockholm. Treatment was initiated at lower levels of cholesterol in Sicily.

**Key words:** Cholesterol, Doctors, General practitioners, Hyperlipidaemia, Internists, Management

### Introduction

Treatment studies in the last few years have increased our knowledge of the effectiveness of cholesterol-lowering in preventing cardiovascular disease [1–4]. During this period, new guidelines have been issued [5–8], and changes in treatment practice have probably also taken place. National studies have shown differences in the management of hyperlipidaemic patients between groups of doctors as regards treatment practice and attitudes [1, 9–15], but few international studies have been performed [16, 17]. At the time of the study, guidelines in Stockholm and Sicily were similar in terms of investigation and treatment levels, with the difference that screening of all adults was recommended in Sicily [5, 18]. The aim of this study was to compare the attitudes and practices of doctors in regions where the guidelines were similar, but where the food habits, health-care structure and culture differed.

The study was focused on management routines for

patients with hyperlipidaemia and/or diabetes mellitus, hypertension, cardiovascular disease and other risk factors for cardiovascular disease, and on changes in attitudes towards hyperlipidaemia over the preceding five years.

### Materials and methods

This report is based on an earlier Stockholm questionnaire study [14]. The questions were translated into Italian and re-translated into Swedish for verification. At the time of this study, the 1988 National Board of Health and Welfare recommendations were still in use in Stockholm [18]. In Sicily, the recommendations were those of the European Atherosclerosis Society (EAS) of 1992 [5]. The guidelines were the same concerning investigation, with the exception for general screening of adults (EAS), and the same concerning levels of secondary and primary preventive treatment

of hyperlipidaemia. In the questionnaire, secondary prevention was defined as 'presence of cardiovascular disease, e.g. myocardial infarction', and primary prevention defined as 'no cardiovascular disease'.

The study was conducted in May 1995. A postal questionnaire was used, with two written reminders in Stockholm, and one telephone reminder in Sicily. All 329 family doctors (general practitioners) in the districts of Caltanissetta and Enna (both medium-sized towns in central Sicily), and all 181 family doctors (general practitioners) in the south-western region of Stockholm County were invited to participate, as well as all the 356 doctors in the 53 wards of internal medicine of 35 hospitals in Sicily, and all 143 doctors working at that time in the departments of internal medicine of six hospitals in Stockholm.

To analyse whether non-responders differed from responders with regard to their answers, 18% of all non-responders were randomly chosen and contacted by telephone.

#### Statistical analysis

Summary statistics were analysed by standard methods, using the Quest software programme [19]. Confidence intervals (95% CI) were used in comparing doctors in terms of testing practices.  $\chi^2$  tests were employed to test differences in management practice and views among the groups. Fisher's exact test was used to compare gender among responders and non-responders. Student's t-test was used to compare age and duration of work, and response rates, and to compare levels of intervention amongst the groups of doctors.

#### Results and comments

##### Response rates and characterisation of doctors

An overview of the participating doctors is shown in Table 1. The response rate among general practitioners was lower in Sicily than in Stockholm. We were,

however, able to compare the general practitioners in the town of Caltanissetta, where all the 43 general practitioners had answered the questionnaire, with the remaining general practitioners and found a statistically significant difference in only one question, concerning the level at which doctors initiated drug treatment in secondary prevention, which was  $6.0 \pm 0.7$  mmol T-Chol/l (Caltanissetta) vs.  $6.3 \pm 0.7$  mmol T-Chol/l (remaining doctors) ( $p = 0.03$ ). Gender differences were few in regard to responses, with no trends seen, but there was a statistically significant, larger proportion of women doctors in Stockholm. An inter-regional difference between years in practice was found. Sicilian doctors are authorized to practice after graduation, while Swedish doctors have two years of internship before authorization. The question was phrased 'after graduation' in Sicily, and 'after certification' in Stockholm. In addition, Swedish students are older when entering medical school.

In a follow-up survey polling 18% of the non-responders in both areas, no significant difference was found between responders and non-responders. Comparisons between age-groups among responders showed no significant age-differences in key questions.

##### Frequency of patients with hyperlipidaemia in doctors' practices

Both groups of doctors in Sicily were more apt to check lipids in their patients than their Stockholm counterparts. Checking lipids at first visits was done by 53% of general practitioners in Sicily and by 2% in Stockholm, by 67% of internists in Sicily and by 0% in Stockholm. About 50% of the Stockholm general practitioners had not seen any patients with lipid-lowering medication during the previous week, while this was true for only 1% among general practitioners in Sicily. Among the internists, about half of the doctors had seen between one and three patients using lipid lowering drugs the previous week in both Stockholm and Sicily (data not shown).

**Table 1.** Response rate, age (95% CI) duration of practice (95% CI) and proportion of men (95% CI). t-test comparing practice duration significantly different for general practitioners (GPs) and for internists ( $p < 0.001$ ).  $\chi^2$ -test for proportion of women significant for both general practitioners and internists ( $p < 0.001$ )

	GPs		Internists	
	Sicily	Stockholm	Sicily	Stockholm
N	153	120	211	83
Response rate	46%	66%	59%	56%
Mean age (95% CI)	44.9 (43.5–46.2)	45.7 (44.6–46.7)	43.3 (42.2–44.3)	43.9 (42.1–45.7)
Mean no of years in practice (95% CI)	18.1 (16.8–19.4)	13.0 (11.7–14.3)	17.8 (16.7–18.8)	12.8 (10.8–14.8)
Men (95% CI)	0.79 (0.73–0.86)	0.53 (0.44–0.61)	0.81 (0.76–0.86)	0.64 (0.54–0.74)



**Table 2.** Proportions of doctors (95% CI) who investigate lipids when patients present diabetes mellitus, hypertension, cardiovascular disease (CVD), cardiovascular risk factors (CRF), and heredity for hyperlipidaemia (Heredity), respectively.  $\chi^2$ -tests comparing general practitioner groups were significantly different for cardiovascular risk factors ( $p < 0.001$ ) and heredity for hyperlipidaemia ( $p < 0.001$ ), and for internists when comparing cardiovascular disease ( $p < 0.001$ ) and cardiovascular risk factors ( $p = 0.003$ )

	GPs		Internists	
	Sicily	Stockholm	Sicily	Stockholm
N	153 (95% CI)	120 (95% CI)	211 (95% CI)	79 (95% CI)
Diabetes mellitus	0.94 (0.90–0.98)	0.95 (0.91–0.99)	0.92 (0.88–0.96)	0.92 (0.87–0.98)
Hypertension	0.87 (0.82–0.92)	0.90 (0.84–0.95)	0.85 (0.80–0.90)	0.74 (0.65–0.84)
CVD	0.93 (0.90–0.97)	0.94 (0.90–0.98)	0.83 (0.78–0.88)	0.98 (0.94–1.01)
CRF	0.59 (0.51–0.67)	0.87 (0.81–0.93)	0.64 (0.57–0.70)	0.82 (0.73–0.90)
Heredity	0.85 (0.79–0.91)	0.97 (0.95–1.00)	0.84 (0.79–0.89)	0.92 (0.86–0.98)

#### *Assessment of lipids and investigations when hyperlipidaemia was found*

Patterns in the investigation of patients with chronic diseases and other cardiovascular risk factors are shown in Table 2. No definitions for 'other risk factors' were given in this question, although they were exemplified in later questions in the questionnaire. The difference common to both general practitioners and internists in the two regions was the testing pattern in the presence of risk factors other than those reported in the Table. In addition, Sicilian physicians were more active in investigating HDL and LDL in their patients, without prominent differences in triglycerides testing (data not shown).

When hyperlipidaemia was found, further investigations were carried out as shown in Table 3. All the groups tested blood pressure and blood glucose in their hyperlipidaemic patients. Comparisons showed

that electrocardiography was utilised more in Sicily by both groups.

#### *Intervention levels of cholesterol*

Dietary intervention was initiated at significantly lower ( $p < 0.001$ ) total cholesterol values in mmol/l (with 95% CI) in Sicily – GPs 6.35 (6.26–6.45), and internists 6.46 (6.38–6.54) – than in Stockholm – GPs 6.92 (6.79–7.04) and internists 6.81 (6.66–6.96). Both groups of Sicilian doctors started drug intervention at significantly lower levels of cholesterol than did the doctors in Stockholm, and no significant differences were found among the groups of Sicilian doctors (Table 4). In Stockholm, general practitioners started treatment at significantly higher levels than the internists in interventions for both secondary and primary prevention, and in patients with hereditary hyperlipidaemia.

**Table 3.** Proportions of doctors (95% CI) who in the presence of hyperlipidaemia investigate blood pressure (BP), weight, take an electrocardiogram (ECG), test B-glucose, S-uric acid (S-URAT), and S-gamma glutamyltransferase (S- $\gamma$ -GT), respectively.  $\chi^2$ -tests comparing general practitioner groups were significantly different for weight ( $p < 0.001$ ), ECG ( $p < 0.001$ ) and S- $\gamma$ -GT ( $p < 0.001$ ); and for internists ECG ( $p < 0.001$ ) and S-URAT ( $p < 0.001$ )

	GPs		Internists	
	Sicily	Stockholm	Sicily	Stockholm
N	152 (95% CI)	119 (95% CI)	211 (95% CI)	77 (95% CI)
BP	0.97 (0.95–1.00)	1	0.98 (0.96–1.00)	0.97 (0.94–1.01)
Weight	0.74 (0.67–0.81)	0.89 (0.83–0.95)	0.94 (0.91–0.97)	0.91 (0.84–0.97)
ECG	0.66 (0.58–0.73)	0.42 (0.33–0.51)	0.88 (0.83–0.92)	0.62 (0.52–0.73)
B-glucose	0.94 (0.90–0.98)	0.95 (0.91–0.99)	0.98 (0.96–1.00)	0.99 (0.96–1.01)
S-URAT	0.44 (0.36–0.52)	0.42 (0.33–0.51)	0.70 (0.64–0.76)	0.35 (0.24–0.46)
S- $\gamma$ -GT	0.39 (0.32–0.47)	0.61 (0.52–0.69)	0.41 (0.34–0.47)	0.36 (0.26–0.47)

**Table 4.** Mean value of 1-Cholesterol (95% CI) for drug intervention reported by doctors by group, by disease/ risk factor. Student's t-tests comparing general practitioners all significantly different ( $p < 0.001$ ). t-tests comparing internists for secondary intervention significantly different ( $p = 0.008$ ), all other comparisons ( $p < 0.001$ )

	GPs		Internists	
	Sicily	Stockholm	Sicily	Stockholm
Secondary intervention	6.25 (6.14–6.37)	7.01 (6.84–7.18)	6.38 (6.27–6.48)	6.66 (6.49–6.83)
Primary intervention	7.08 (6.98–7.18)	8.04 (7.91–8.17)	7.14 (7.06–7.22)	7.70 (7.54–7.87)
Cardiovascular risk factors	6.49 (6.38–6.60)	7.41 (7.25–7.57)	6.39 (6.28–6.49)	7.16 (6.98–7.33)
Hereditary				
Hyperlipidaemia	6.50 (6.39–6.61)	7.38 (7.25–7.52)	6.55 (6.45–6.65)	6.88 (6.71–7.04)

#### *Use of lipid-lowering drugs*

In their answers to questions on drug utilisation, 99.5% of the Sicilian doctors named at least one drug; in Stockholm the rate was lower (91% among general practitioners, and 90% among internists). The three most common types of drugs were resins, fibrates and statins. Resins were used by 4% of general practitioners in Sicily, as opposed to 43% in Stockholm. The corresponding numbers were 7% of internists in Sicily and 54% in Stockholm. Fibrates were used by 91% of general practitioners in Sicily and by 84% of general practitioners in Stockholm, and by 87% of internists in Sicily and 82% in Stockholm. Statins were used by 95% of general practitioners in Sicily and 85% among general practitioners in Stockholm ( $p = 0.009$ ), by 81% of internists in Sicily and by 89% of internists in Stockholm.

#### *Frequencies of patients' visits*

There was a marked difference between the frequencies of patients' visits to a doctor in Sicily and in Stockholm. In Sicily, 23% of the general practitioners and 28% of the internists saw their hyperlipidaemic patients once a month when on non-pharmacological treatment, and patients with drug treatment were seen once a month by 36% of the general practitioners and by 27% of the internists. In Stockholm, 98% of the doctors saw their patients either 2–3 times a year or once a year. None saw their patients once a month.

#### *Change of attitude over time*

The doctors were asked to state whether they thought that the prevention of cardiovascular disease was more important now than five years ago. Secondary prevention was considered more important now by majorities in all four groups, whereas primary prevention was seen as more important now only by the Sicilian doctors. These opinions were substantiated by the opinions expressed on screening for lipids, and testing patients for lipids as a routine at first visits. Sicilian doctors were positive to both screening and to

routine testing at first visits and the Stockholm doctors were not. A majority of doctors stated that they prescribed more drugs than five years ago, with the exception of the general practitioners in Sicily, of whom slightly less than half said so (data not shown).

#### **Discussion**

This study included all the doctors in defined areas in Sicily and in Stockholm. One central question is whether the results are skewed, owing to the large groups of non-responders. We cannot be sure, but there seems to be no reason to think that there is a systematic difference in non-responders between Sicily and Stockholm. The most important differences found between doctors in Sicily and in Stockholm are the lipid-testing patterns and the cholesterol levels at which the doctors intervened with diet and drugs. These results are supported by the findings of Shepherd and Pratt (analysing a market survey) [17]. Our findings that treatment was initiated only at high cholesterol levels by Swedish doctors was also found by Trocin et al. [16]. These differences in treatment levels do not reflect the respective guidelines used in Sicily and in Stockholm.

Identifying risk factors can be seen as the first step in the management of patients with cardiovascular disease. More Stockholm doctors seem to do more testing to find hypercholesterolaemia in patients with other diseases, thus adhering to Swedish guidelines, than their Sicilian counterparts. On the other hand, many Sicilian doctors had already used first visits to check lipids (adhering to EAS guidelines), and also sub-fractions HDL and LDL. The procedure of checking lipids at first visits was confirmed by their positive attitude to primary preventive screening – a view which was not shared by the Stockholm doctors.

Intervention was initiated at lower levels of cholesterol in Sicily than in Stockholm, and not all Stockholm doctors stated that they prescribe drugs. The

reason for the latter is unclear, but an increase has occurred from 60% in 1990 [14], to 91% in 1995. Shepherd and Pratt have found similar results and have shown that Stockholm doctors have poor compliance with national guidelines in terms of treatment [17]. The Stockholm doctors report changes in attitudes over the past five years, but the patients are still not treated according to the present guidelines, and the general practitioners are more conservative than the internists. This conservatism among Stockholm doctors does not seem to be due to 'poorer' investigation patterns in patients with related diseases and risk factors. One earlier Stockholm study has shown regional differences within Sweden [13], and another has pointed more to differences among doctors' specialties [14].

It is worthy of note that the Sicilian population has lower lipid levels than the Swedish population. Two Sicilian studies report a mean T-Chol of 4.63 [20] and 4.97 mmol/l [21], respectively, and two Swedish studies 5.93 [22] and 5.9 mmol/l [23]. In Sweden, the mortality rate reported for ischaemic heart disease was slightly more than three times higher among men, and slightly less than five times higher among women, in comparison to Sicily [24, 25]. The possible influence of this difference on the actions of the doctors has to be taken into consideration.

The frequent follow-up visits in Italy should be attributed to the Sicilian prescribing laws, which state that prescriptions have to be renewed every month. The Sicilian subsidies from the social-security system – lowering costs for the patient with higher levels of cholesterol – may be influential not only on prescribing, but also on the awareness of the problem of hyperlipidaemia. In Stockholm, drug-reduction rates were not related to the level of hyperlipidaemia.

In discussing the answers to a questionnaire, the study by Lomas et al. should be remembered, in which it is shown that it is not necessarily certain that the answers given by the doctors reflect their actual management [26]. This would not, however, account for the differences reported between the two populations. And there is the question whether the systematic testing of new patients alerts the doctors to the problem of hyperlipidaemia.

In order to manage patients with cardiovascular risks or disease, it is of importance that doctors should be in agreement, since this is the basis for making patients understand the treatment and comply with it. International comparisons may be useful as a starting-point also for national discussions about the management of these patients.

## Conclusions

There are differences in the views among the professional groups in Sicily and in Stockholm as to how patients should be investigated with regard to blood lipids. There are also differences in prescribing patterns between Sicilian and Stockholm doctors, in which the Sicilian doctors adhere more closely to the guidelines in terms of treatment than those in Stockholm. The main findings are that doctors in Sicily test lipids at first visits and start the treatment of hyperlipidaemia at lower cholesterol levels than the doctors in Stockholm.

## Acknowledgements

This study was supported by grants from the Karolinska Institute, Stockholm, the health authority of the county council of Stockholm, and the 'Förenade Liv' the Mutual Life Insurance Company funds.

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II



# General practitioners' coronary risk assessments and lipid-lowering treatment decisions in primary prevention: comparison between two European areas with different cardiovascular risk levels

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**Aim:** To investigate whether general practitioners (GPs) in countries with different levels of cardiovascular risk would make different risk estimates and choices about lipid-lowering treatment when assessing the same patients. **Background:** Primary prevention of coronary heart disease should be based on the quantitative assessment of an individual's absolute risk. Risk-scoring charts have been developed, but in clinical practice risk estimates are often made on a subjective basis. **Methods:** *Mail survey.* Nine written case simulations of four cases rated by the Framingham equations as high risk, and five rated as low-risk were mailed to 90 randomly selected GPs in Stockholm, as a high-risk area, and 90 in Sicily as a low-risk area. GPs were asked to estimate the 10-year coronary risk and to decide whether to start a lipid-lowering drug treatment. **Findings:** Overall risk estimate was lower in Stockholm than in Sicily for both high-risk cases (median 20.8; interquartile range (IQR) 13.5–30.0 versus 29.1; IQR 21.8–30.6;  $P = 0.033$ ) and low-risk cases (6.4; IQR 2.2–9.6 versus 8.5; IQR 6.0–14.5;  $P = 0.006$ ). Swedish GPs were less likely than Sicilian GPs to choose to treat when their estimate of risk was above the recommended cut-off limit for treatment, both for the entire group (means of GPs' decision proportions: 0.64 (0.45) and 0.92 (0.24), respectively,  $P = 0.001$ ) and for high-risk cases (0.65 (0.45) and 0.93 (0.23),  $P = 0.001$ ). **Conclusions:** The cardiovascular risk level in the general population influences GPs' evaluations of risk and subsequent decisions to start treatment. GPs' risk estimates seem to be inversely related to the general population risk level, and may lead to inappropriate over- or under-treatment of patients.

**Key words:** coronary risk assessment; general practitioners; lipid-lowering treatment; primary cardiovascular prevention

Received: 21 May 2008; accepted: 17 September 2008

## Introduction

Guidelines for the primary prevention of coronary heart disease (CHD) are based on the assessment

of an individual's absolute risk of developing CHD rather than the value of any single risk factor (Grundy *et al.*, 1999; Jackson, 2000). These guidelines encourage quantitative risk assessment and suggest that preventive treatment should be considered if the patient's absolute risk exceeds a certain cut-off point. Therefore, a crucial task for

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clinicians involved in cardiovascular prevention is combining quantitative risk assessment with decisions about whether or not to treat individual patients. The effectiveness of drug treatment recommendations depends on the accuracy with which the clinician can estimate CHD risk in individual patients.

The most widely used algorithms for the assessment of CHD risk are based on equations derived from the Framingham Heart Study (Anderson, 1991). However, questions have been raised about the usefulness of these equations as a practical clinical tool for primary prevention. Equations based on Framingham data tend to overestimate the true cardiovascular risk in low-risk populations and underestimate it in high-risk populations (Menotti *et al.*, 2000a; Empana *et al.*, 2003; Brindle *et al.*, 2006), which may lead to inappropriate treatment decisions. Therefore, a risk-scoring system based on a large pool of European data sets (SCORE), which includes separate equations for high- and low-risk regions, has been adopted in Sweden (Conroy *et al.*, 2003), and a system based on national data (CUORE) has been developed in Italy (Giampaoli *et al.*, 2004).

There is evidence that risk estimation tools, such as charts or computer programs, are used rarely in clinical practice (Frolkis *et al.*, 1998; Hickling *et al.*, 2005; Mosca *et al.*, 2005; Van Wyk *et al.*, 2005). Judgements tend to be intuitive or subjective. Doctors' intuitive risk estimates have been shown to deviate systematically from calculations derived from risk equations based on epidemiological data. Some studies using simulated patient cases show that general practitioners (GPs) overestimate the absolute risk when it is low (Grover *et al.*, 1995; Friedman *et al.*, 1996), while other studies show an underestimation of the risk, especially when it is high (Meland, 1994; Backlund *et al.*, 2004). This is consistent with the observation that in primary and secondary prevention lipid-lowering treatment is often inappropriate, leading to underuse or overuse of statins (McBride *et al.*, 1998; Abookire *et al.*, 2001; Tonstad *et al.*, 2004). Difficulties in assessing the risk may be behind the deviation from guidelines and may influence the physician's decision about treatment. Furthermore, some studies have shown that factors that are not directly related to the actual risk of the patient may influence risk management practices. For example, women (Kim *et al.*, 2003), older individuals (Ko

*et al.*, 2004), and patients with multiple chronic conditions (Redelmeier *et al.*, 1998) have been shown to receive suboptimal cardiovascular preventive care.

The possible influence of the average risk level in a particular population on the doctors' perceptions of CHD risk levels has not been directly investigated. Variations in mean levels of cardiovascular risk factors and cardiovascular disease mortality across European regions have been described (Murray and Lopez, 1997; Sans *et al.*, 1997; Menotti *et al.*, 2000a; 2000b; Houterman *et al.*, 2002; Levi *et al.*, 2002; Conroy *et al.*, 2003). In this study, we aimed to assess whether GPs in a high CHD risk country in northern Europe and in a low-risk country in southern Europe, give different estimations of cardiovascular risk and recommendations regarding lipid-lowering treatment for the same series of patient cases. Some evidence suggest that the decision to start cardiovascular therapies is dependent on patients' baseline cardiovascular risk (Backlund *et al.*, 2000; Alter *et al.*, 2004). If physicians are appropriately attuned to the risk profiles of their patients, it might be assumed that patients at highest baseline risk will be investigated and treated more aggressively. Our hypothesis was that the GPs' risk estimates would be attuned to the population risk level in a comparison between the high- and the low-risk country. As a consequence, the mean risk estimate would be higher in the high-risk country and at least as many cases would be selected for treatment in the high-risk country as in the low-risk country. The rationale for this should be a combination of clinical experience from the outcomes of patients with different patterns of risk factors, knowledge from the literature of the different risk levels in different countries, and also experience from using the recent and more correct risk-estimating tools. We also wished to investigate the correspondence between treatment decisions and the Framingham risk levels of the cases. The Framingham cut-off of the risk of developing CHD within 10 years is 20%, which is a cost-effective level for statin treatment and is currently recommended as a threshold for intensified risk factor intervention (Wood *et al.*, 1998). The study also aimed to estimate the extent to which a subjective risk estimate of 20% was actually used as the criterion to recommend drug treatment.



We therefore investigated (a) the risk estimates and treatment decisions of GPs in two countries with known high and low cardiovascular risk; (b) the correspondence between subjective risk estimates and treatment decisions on the one hand and Framingham-derived risk estimates and recommended decisions on the other; and (c) the correspondence between doctors' own risk estimates and treatment decisions.

## Methods

### Setting

The study was conducted in Stockholm, Sweden, which is part of northern Europe and represents a high cardiovascular risk area (Sans *et al.*, 1997; Conroy *et al.*, 2003), and in Sicily (the Caltanissetta, Enna, and Agrigento districts), which is part of southern Europe and represents a low cardiovascular risk area (Menotti *et al.*, 2000b; Levi *et al.*, 2002). The populations of the two areas are 1 212 000 and 870 000, respectively.

### Design

The study was a cross-sectional survey. A questionnaire relating to nine clinical cases was mailed to 180 GPs (90 in each area) in October 2005, with a written reminder sent within two weeks. All GPs received the same set of nine

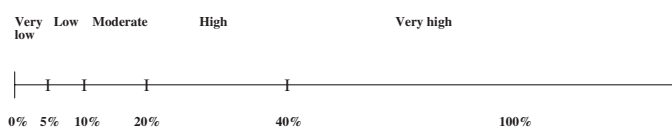
cases in the same order. Physicians were asked to estimate the risk of CHD within 10 years on a visual analogue scale (VAS) between 0% and 100% without using a risk table or any other decision support. The risk categories currently indicated in the Framingham-based tables (low <5%, mild 5–10%, moderate 10–20%, high 20–40%, and very high risk >40%) were provided as anchorage points within the scale. We chose the older Framingham risk equation because it is the most widely used method for the assessment of cardiovascular risk, on which most other risk prediction methods are based (Wood *et al.*, 1998; Jones *et al.*, 2001). Although recent risk equations have been published in Sweden and Italy, they differ regarding the risk events chosen as endpoints. Sweden has adopted the SCORE system (Conroy *et al.*, 2003), which estimates 10-year total cardiovascular risk, defined as fatal coronary and non-coronary cardiovascular events. Meanwhile, risk charts published in Italy take the first major fatal or non-fatal cardiovascular event as the endpoint (Giampaoli *et al.*, 2004). These two methods are neither comparable nor used for reference in both countries.

For each case, doctors were asked to specify whether they would recommend a pharmacological lipid-lowering treatment for the patient, assuming that lifestyle interventions had been tried for at least six months (Figure 1 provides an

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Case 1. The patient is a 53-year-old man with no history of previous cardiovascular disease or diabetes. Non-smoker. Systolic blood pressure 140 mmHg. Recent cholesterol value is 270 mg/dL (7 mmol/L).

Mark with a cross on the line your estimate of his risk to have coronary heart disease within 10 years.



Would you recommend a lipid-lowering drug in this case?

Yes ☐ No ☐

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**Figure 1** Example of a case description

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example of a case). The questionnaire asked for participants' age and sex, but were anonymous to increase the likelihood that answers would be given without the use of risk tables or other decision supports.

### Sample

A random sample of 90 GPs was drawn from each local database of healthcare professionals, which comprised 828 GPs in Stockholm and 732 GPs in the Sicilian study area. To enter the research study, physicians had to be Family Medicine specialists in Stockholm and board certified in Sicily.

### Clinical cases

Each GP was presented with nine patient cases with a combination of the variables included in the Framingham risk tables: age, sex, systolic blood pressure, cholesterol, and smoking. No patient had a history of cardiovascular disease or diabetes, as risk assessment is not relevant for patients with such conditions, and no patient had systolic blood pressure of above 160 mmHg, since higher values might have caused the doctors to consider the treatment of hypertension more relevant than the treatment of hypercholesterolemia. The cases were constructed so that the resulting 10-year risk of a fatal or non-fatal coronary event, based on the Framingham equation (Anderson, 1991), was composed of a spectrum of high- to low-risk patients. According to this equation, a 10-year absolute CHD risk of 20% or more is the threshold for pharmacological lipid-lowering treatment. Therefore, 20% was the cut-off level when defining high- and low-risk cases in the Results section. The calculated Framingham median score for all cases was 17.0 (range 3–45), for the four high-risk cases 30.5 (range 27–45), and for the five low-risk cases it was 15.0 (range 3–17).

To minimize the risk of an anchorage effect (Tversky and Kahneman, 1974), we opened the questionnaire with the medium-risk case; the following cases were randomly ordered.

A summary of the nine cases presented to the doctors is shown in Figure 2.

### Statistical analysis

Summary measures for normally distributed continuous variables are given as means (SD) and

for others as medians (interquartile range). Categorical variables are presented as percentages. The statistical significance of the differences between Stockholm and Sicily was tested with the independent two-sample *t*-test or Mann-Whitney rank sum test. Multiple linear regression analysis was used to identify independent predictors of risk estimate and decision to start treatment, with risk estimate and proportion of decisions to treat as dependent variables, and sex and age as independent variables.

We used Minitab (version 13) for statistical analysis.

## Results

### General data

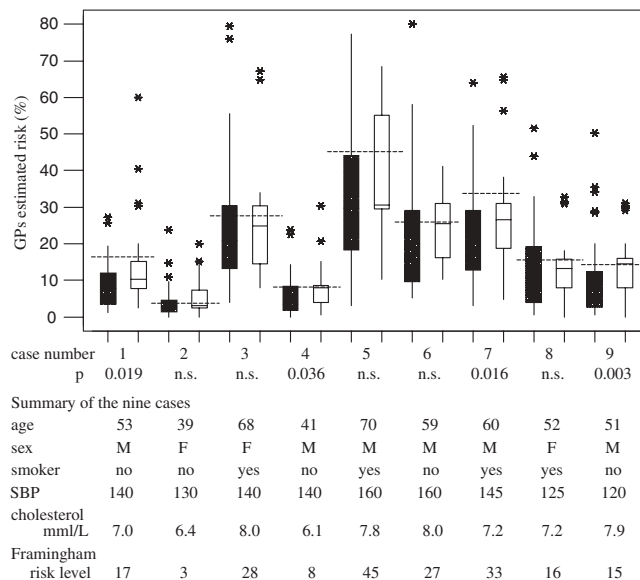
Thirty-eight doctors (42.2%) answered the questionnaire in Stockholm (median age 54 years, range 43–65) and the same number in Sicily (median age 51 years, range 42–70), respectively. There were more men among GPs in Sicily (76.3%) than in Stockholm (39.5%). Risk estimate and proportion of decisions to treat were not significantly related to the doctor's age or sex according to the regression analysis.

### Ratings

GPs' risk estimates for each case are shown in Figure 2 as box-plots. The inter-individual differences within each group in rating risk were large, and in both groups the ratings were in general lower than the Framingham-derived estimates. The risk estimates for each of the nine cases are shown in Table 1 as medians.

The median ratings, one for each GP across the nine cases, were calculated and compared between the two groups of doctors (Table 2). Overall risk estimates did not differ significantly. However, when the cases were divided according to their actual Framingham risk level into four high-risk cases and five low-risk cases and analysed separately, estimates from Stockholm were significantly lower for both high- and low-risk cases.

The concordance of GPs' risk estimates to the calculated Framingham risk, defined as the mean value of the proportions of each GP's risk estimates above 20% when the actual Framingham



**Figure 2** Boxplot of doctors' risk estimate in Stockholm (filled bars) and Sicily (empty bars) and summary of the nine cases in the order they were presented to the doctors, along with the calculated Framingham risk level for each case (dashed lines). The bottom of the boxes are at the first quartile, the top at the third quartile, and the continuous lines across the boxes are at the median value. The whiskers are drawn to the highest and lowest values that are not considered as outliers. Outliers, marked with asterisks, are estimates outside these limits

**Table 1** Risk estimates for each case

	Stockholm	Sicily	P
Case 1	7.7 (3.5–11.9)	10.3 (7.7–15.1)	0.019
Case 2	2.6 (1.3–4.6)	3.0 (2.4–7.2)	0.103
Case 3	20.9 (13.3–30.5)	24.8 (14.5–30.3)	0.592
Case 4	3.5 (1.7–8.4)	7.8 (3.9–8.6)	0.036
Case 5	29.6 (18.2–44.0)	30.6 (29.5–55.1)	0.093
Case 6	20.0 (9.7–29.2)	25.4 (16.2–30.9)	0.060
Case 7	16.7 (12.7–29.2)	26.7 (18.8–31.0)	0.016
Case 8	10.9 (3.9–19.2)	13.3 (7.9–15.7)	0.675
Case 9	7.7 (2.6–12.3)	14.5 (7.9–16.0)	0.003

Data are expressed as medians (interquartile range).

risk was above 20%, and each GP's risk estimates below 20% when the actual Framingham risk was below 20%, was significantly lower in Stockholm than in Sicily for both the entire group of cases (0.73 (0.17) and 0.84 (0.13), respectively,  $P = 0.006$ ) and the high-risk cases subgroup (0.53 (0.42) and 0.76 (0.27), respectively,  $P = 0.007$ ).

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The difference was not statistically significant for the low-risk group.

### Decisions

Table 3 shows the mean values of the proportions of GPs' decisions to start pharmacological treatment, calculated as the number of 'yes' decisions divided by the total number of decisions for each GP. These were higher in Sicily than in Sweden, but the difference was not statistically significant in the entire group or in the high- and low-risk subgroups.

### Relation between estimates and decisions

Compared to Sicilian GPs, Swedish GPs less often decided to start pharmacological treatment when their estimated risk was above the cut-off limit of 20% (Table 4). The difference was statistically significant for the entire group of cases and for high-risk cases, but there was no

**Table 2** Risk estimates for the entire group of cases, high- and low-risk cases

	Stockholm ( <i>n</i> = 38)	Sicily ( <i>n</i> = 38)	<i>P</i>
All cases	12.9 (5.8–18.7)	14.5 (10.3–16.3)	0.240
High-risk cases (>20%)	20.8 (13.5–30.0)	29.1 (21.8–30.6)	0.033
Low-risk cases (<20%)	6.4 (2.2–9.6)	8.5 (6.0–14.5)	0.006

Data are expressed as medians (interquartile range).

**Table 3** GPs' decisions to treat for the entire group of cases, high- and low-risk cases

	Stockholm ( <i>n</i> = 38)	Sicily ( <i>n</i> = 38)	<i>P</i>
All cases	0.46 (0.20)	0.54 (0.22)	0.106
High-risk cases (>20%)	0.82 (0.26)	0.88 (0.25)	0.271
Low-risk cases (<20%)	0.18 (0.23)	0.27 (0.29)	0.158

Data are expressed as means (SD) of GPs' proportions to treat.

**Table 4** Relation between GPs' risk estimate and decision to start treatment

	Stockholm ( <i>n</i> = 38)	Sicily ( <i>n</i> = 38)	<i>P</i>
All cases			
GPs estimate > 20%	0.64 (0.45)	0.92 (0.24)	0.001
GPs estimate < 20%	0.25 (0.23)	0.27 (0.28)	0.741
High-risk cases			
GPs estimate > 20%	0.65 (0.45)	0.93 (0.23)	0.001
GPs estimate < 20%	0.72 (0.32)	0.76 (0.42)	0.731
Low-risk cases			
GPs estimate > 20%	0.69 (0.46)	0.92 (0.23)	0.207
GPs estimate < 20%	0.10 (0.18)	0.20 (0.28)	0.087

Data are expressed as means (SD) of GPs' estimate proportions.

significant difference when the estimated risk was below 20%.

### Discussion

This study demonstrates that two groups of GPs from areas with different cardiovascular risk levels, Sweden and Sicily, make different cardiovascular risk estimates when assessing the same set of clinical cases.

We found that the GPs' estimates were lower in Stockholm than in Sicily, which was contrary to our hypothesis. Current guidelines recommend starting treatment on the basis of global risk rather than single risk factors, but the influence of the risk level in the overall population on a GP's risk estimate for a single patient has received little attention. It is generally assumed that GPs are attuned to the risk level in their country and

judge accordingly. Thus a patient with a certain pattern of risk factors should be correctly judged as having a higher risk by Swedish doctors than the corresponding patient in a Sicilian context. However, our findings support a different line of thinking in accordance with the demonstrated relativism of judgments in everyday life (Parducci, 1968). When the background risk of the population is high, a subject with a high absolute risk level is perceived as having a medium risk. Conversely, a subject with the same risk pattern in a low-risk population will be considered as very high risk. We suggest that the different background cardiovascular risk in the two populations leads to the underestimation of actual cardiovascular risk of a patient in Sweden and to the overestimation in Sicily. The differences in risk estimate reflect the differences in the population cardiovascular risk profile between the two countries.

Sicilian doctors estimate closer to Framingham values and they appear to use the 20% risk level as a criterion for treatment decision to a greater extent than Swedish doctors. This could be in part because they are more familiar with risk estimates; statins are free of charge in this region for patients with an absolute cardiovascular risk of above 20%, calculated with the national risk charts. A rule such as this may induce doctors to raise the risk estimate to the desired 20% level.

Our results are in line with a previous study that demonstrated that Swedish GPs underestimate the risk for high- and moderate-risk patients (Backlund *et al.*, 2004).

When we investigated the relation between subjective risk estimates and decisions to treat with respect to the cut-off level of 20%, we found that GPs in Stockholm were less likely than GPs in Sicily to start treatment when their risk estimate was above 20%. Therefore, Swedish GPs tend to under-treat both through underestimation of the risk and reluctance to treat even when their own risk estimate is above 20%.

In this latter situation, reluctance to treat may be due to the lack of awareness of 20% as a recommended cut-off point to start treatment. Also, there seems to be some perception of the risk level of a specific case compared to that of the population, which may influence the decision to treat, independent of the quantitative estimate. Due to the doctors' perception of the high background cardiovascular risk in the population, even a patient with a subjective risk estimate well above 20% may not be considered as a candidate for pharmacological treatment. This could have important implications in clinical practice. Subjects who are at high risk may not reach the threshold for treatment and thus lack appropriate drug therapy. This result is consistent with our previous finding that pharmacological intervention tends to be started at higher levels of cholesterol in Stockholm than in Sicily (Danielsson *et al.*, 1998). Finally, the reluctance to treat may reflect disagreement with the guidelines. Regardless of the reasons, the implication should be encouraging the use of objective risk estimation tools and to improve doctors' education to identify subjects for whom the benefits of lipid-lowering drugs are documented.

Our study has some limitations. Firstly, the GPs' estimates might have been influenced by the

structure of the clinical cases, which was limited to a few variables and might not reflect real-life practice. Because all doctors faced the same cases, however, valid comparisons can still be made. Furthermore, the use of clinical vignettes to measure the quality of physicians' practice has been shown to have a rather good validity (Kelly *et al.*, 2002; Peabody *et al.*, 2004). Nonetheless, physicians may respond to clinical vignettes in an ideal fashion that differs from their usual practice. Secondly, the moderate response rate we observed was a possible source of bias, although this rate is not unusual for a mail survey (Friedman *et al.*, 1996). Thirdly, we cannot exclude the possibility that some GPs used risk tables in their risk estimate and treatment decisions. However, a recent European survey showed that the proportion of doctors using risk calculator charts is only 13% (Hobbs and Erhardt, 2002). In Italy, the main use of risk charts is for economical reasons, as statins are free of charge when the calculated cardiovascular risk of the patient is above 20%.

In conclusion, we found that GPs' cardiovascular risk estimates and pharmacological lipid-lowering treatment recommendations in a high cardiovascular risk country in northern Europe differ from those made in a low-risk country in southern Europe, for the same series of patient cases.

Our results provide evidence that the average cardiovascular risk in the general population influences the GPs' perception of cardiovascular risk in a single patient. The GPs' risk estimates seem to be inversely related to the background risk of the population. This has practical implications. In high-risk populations, true cardiovascular risk is likely to be underestimated, and high-risk individuals may not receive appropriate drug treatment. Conversely, overestimation of true risk in low-risk populations may lead to drug treatment overuse.

These results are unexpected and contrary to our hypothesis that the GPs' risk estimates would be higher in the high-risk country.

Moreover, our results also give some information about the prescription attitude, which is not related to the actual risk of the patient, but may instead result from the doctors' perceived risk.

Further studies in more areas with different risk levels might be useful in testing our tentative hypothesis of an inverse relation between doctors'

risk judgements and the background risk in the population.

Knowledge of such differences may allow risk scores to be a more effective clinical tool.

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III





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European Journal of Internal Medicine

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Original article

## Coronary risk estimates and decisions on lipid-lowering treatment in primary prevention Comparison between general practitioners, internists, and cardiologists

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### article info

#### Article history:

Received 7 December 2008

Received in revised form 2 April 2009

Accepted 8 April 2009

Available online 21 May 2009

#### Keywords:

Primary cardiovascular prevention

Coronary risk assessment

Lipid-lowering treatment

### abstract

**Background:** Quantitative assessment of an individual's absolute cardiovascular risk is essential for primary prevention. Although risk-scoring tools have been developed for this task, risk estimates are usually made subjectively. We investigated whether general practitioners (GPs), internists and cardiologists differ in their quantitative estimates of cardiovascular risk and their recommendations about lipid-lowering treatment for the same set of patients.

**Methods:** Mail survey. Nine written clinical vignettes, four rated high-risk and five rated low-risk according to the Framingham equation, were mailed to 90 randomly selected GPs and to the same number of internists and cardiologists in Sicily. The doctors were then asked to estimate the 10-year coronary risk in each case and to decide whether they would recommend a lipid-lowering treatment.

**Results:** In the majority of the nine cases, the cardiologists' risk estimates were significantly lower than those of the other two groups. A higher proportion of internists (mean value 0.68) decided to start treatment than GPs (0.54) or cardiologists (0.57). In all three groups, the doctors' willingness to begin treatment was over 90% when their risk estimate was above 20%, and less than 50% when it fell below this level. Internists were more prone to treat than the other two groups even when their patients' estimated risk was below 20%. **Conclusion:** When presented with the same set of clinical cases, GPs, internists and cardiologists make different quantitative risk estimates and come to different conclusions about the need for lipid-lowering treatment. This may result in over- or under-prescription of lipid-lowering drugs and inconsistencies in the care provided by different categories of doctors.

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### 1. Introduction

The prevention of cardiovascular disease requires primary prevention strategies that address cardiovascular risk factors, while the treatment of people already suffering from cardiovascular disease requires secondary prevention strategies. Individuals most likely to benefit from the latter are easily identifiable due to their history of cardiovascular disease. However, identifying subjects in need of primary prevention is less straightforward. The assessment of an individual's cardiovascular risk is therefore critical for the appropriate lifestyle advice and prescription of pharmacological treatment.

Current guidelines for primary prevention of cardiovascular disease state that the decision to start long-term preventive drug therapy should be based on a quantitative assessment of an individual's global burden of risk rather than on any one specific

risk factor. However, despite the wide dissemination of knowledge about how to manage such factors, the quality of cardiovascular preventive care is suboptimal, especially in high-risk individuals [1,2]. Multivariate risk assessment functions have been devised and are recommended in the identification of high-risk subjects [3–5], but their use in clinical practice is limited and clinicians are more likely to make their own subjective assessment of risk [6–9].

In Italy, the responsibility for primary cardiovascular prevention care usually falls to three groups of clinicians: general practitioners (GPs), internists and cardiologists. Previous research suggests that cardiologists have better specialist knowledge and practice than GPs in areas such as coronary disease and heart failure [10,11]. It has also been reported that GPs tend to over- or underestimate the cardiovascular risk [13,12], and that the knowledge and attitudes of generalists like GPs and internists deviate systematically from the guidelines for managing cardiovascular risk [14].

However, most studies comparing generalist and specialist care for single discrete conditions suffer from methodological shortcomings, including a lack of case-mix adjustment for possible patient selection

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bias [15]. Moreover, little is known about the relative expertise of generalists and specialists in primary cardiovascular prevention.

In the present study, we investigated the quantitative perception of baseline cardiovascular risk for a series of patient cases and subsequent recommendations regarding lipid-lowering treatment in a sample of practicing family physicians, general internists and cardiologists.

We also aimed to assess how well treatment decisions corresponded with the Framingham risk levels of the individual cases. The threshold for intensified risk factor intervention, according to the Framingham algorithm, is a 20% risk of developing CHD within 10 years; this is regarded as a cost-effective level for statin treatment [16]. The study was also designed to estimate the extent to which a subjective risk estimate of 20% was in fact used as the criterion to recommend drug treatment.

We therefore investigated a) the quantitative risk estimates and lipid-lowering treatment decisions of the three groups of physicians; b) the concordance between subjective risk estimates and treatment decisions on the one hand and Framingham-derived risk estimates and recommended decisions on the other; and c) the correspondence between doctors' own risk estimates and their treatment decisions.

## 2. Methods

### 2.1. Setting

The study was conducted in the Caltanissetta, Enna and Agrigento districts of Sicily. The area's population is about 870,000.

### 2.2. Design

The study was a cross-sectional survey. We mailed a questionnaire relating to nine clinical cases to 90 GPs, 90 internists and 90 cardiologists working in the area hospitals; this was followed with a written reminder within two weeks. All physicians received the same set of nine cases in the same order and were asked to estimate the risk of CHD within 10 years on a visual analogue scale (VAS) between 0% and 100% without using a risk table or any other decision support. The risk categories currently indicated in the Framingham-based tables (low b5%, mild 5–10%, moderate 10–20%, high 20–40% and very high risk N40%) were provided as anchorage points within the scale. We chose the older Framingham risk equation because it is the most

widely used method for assessment of cardiovascular risk and is the basis for most other risk prediction methods [17]. Although newer risk equations have been published in Italy, their use is not widespread [5].

For each case, doctors were asked to specify whether they would recommend a pharmacological lipid-lowering treatment for the patient, assuming that lifestyle interventions had been tried for at least six months. Fig. 1 provides an example of a case.

The questionnaires asked for the physicians' age, sex and length of experience, but remained anonymous to increase the likelihood that answers would be given without the use of risk tables or other decision supports.

### 2.3. Sample

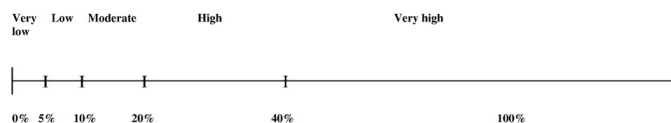
A random sample of 90 GPs was drawn from a local database of healthcare professionals, which comprised of 732 GPs in the study area. The 90 internists were randomly selected from 111 hospital specialists in Internal Medicine in the study area, and the same number of cardiologists were randomly selected from 116 specialists from the local hospitals. In order to enter the research study physicians had to be board certified.

### 2.4. Clinical cases

We presented each physician with nine patient cases that incorporated a combination of the variables from the Framingham risk tables: age, sex, systolic blood pressure, cholesterol level and smoking. The patients had no history of cardiovascular disease or diabetes, as risk assessment is not relevant for patients with such conditions, nor did they have systolic blood pressure levels of above 160 mm Hg, since higher values might have led the doctors to consider the treatment of hypertension more relevant than the treatment of hypercholesterolemia. The set of cases was constructed to represent a spectrum of patients with a 10-year-risk of a fatal or non-fatal coronary event ranging from high to low, based on the Framingham algorithm [3]. According to this equation, a 10-year absolute CHD risk of 20% or more is the threshold for pharmacological lipid-lowering treatment. Therefore, 20% was used as the cut-off point for defining high- and low-risk cases in the Results section. The calculated Framingham median score was 17.0 (range 3–45) for all cases, 30.5 (range 27–45) for the four high-risk cases and 15.0 (range 3–17) for the five low-risk cases.

Case 1. The patient is a 53-year old man with no history of previous cardiovascular disease or diabetes. Non-smoker. Systolic blood pressure 140 mm Hg. Recent cholesterol value is 270 mg/dl (7.0 mmol/l).

Mark with a cross on the line your estimate of his risk to have coronary heart disease within 10 years.



Would you recommend a lipid-lowering drug in this case?

Yes ☐ No ☐

Fig. 1. Example of a case description.

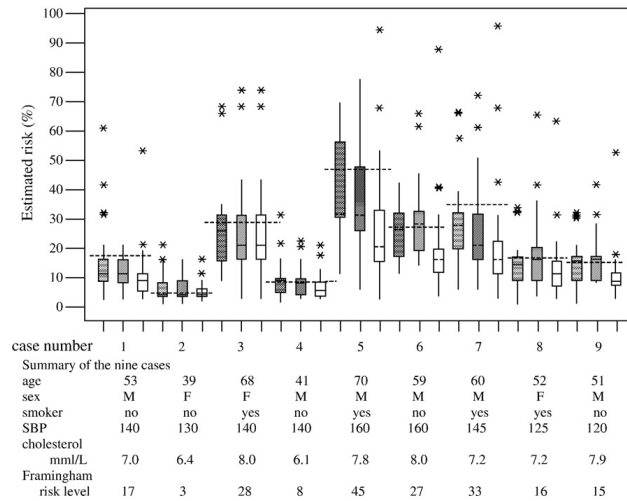


Fig. 2. Boxplot of the risk estimate of GPs (cross slant bars), internists (right slant bars), and cardiologists (empty bars), and summary of the nine cases in the order they were presented to the doctors, along with the calculated Framingham risk level for each case (dashed lines). The bottom of the boxes are at the first quartile, the top at the third quartile, and the continue lines across the boxes are at the median value. The whiskers are drawn to the highest and lowest values that are not considered as outliers. Outliers, marked with asterisks, are estimates outside these limits. SBP: systolic blood pressure.

To minimise the risk of an anchorage effect, we opened the questionnaire with a medium-risk case and ordered the rest at random.

A summary of the nine cases presented to the doctors is shown in Fig. 2.

### 2.5. Statistical analysis

We analysed the data in three ways: 1) risk estimates of each group of doctors for each case; 2) estimates and decisions of each group of doctors across all of the cases; 3) estimates and decisions between high- and low-risk subgroups.

Summary measures for normally distributed continuous variables are given as means (SD) and for others as medians (interquartile range). Categorical variables are presented as percentages. The statistical significance of the differences between the three groups of specialists was tested with the independent two-sample *t*-test or the Mann-Whitney rank sum test. Multiple linear regression analysis was used to identify independent predictors of risk estimate and decision to start treatment, with risk estimate and proportion of decisions-to-treat taken as dependent variables, and sex, age, and length of clinical experience as independent variables.

We used Minitab (version 13) for statistical analysis.

## 3. Results

### 3.1. General data

Thirty-eight GPs (42.2%), forty-three internists (47.8%) and thirty-eight cardiologists (42.2%) answered the questionnaire. Men represented a higher proportion of cardiologists (94.1%) than GPs (76.3%) and internists (71.0%). Internists were younger (median age 47 years) than GPs (51 years) and cardiologists (50 years) and their length of clinical experience was shorter (median 15 years) than physicians in the other groups (GPs 23 years; cardiologists 17.5 years). Risk estimate and the proportion of decision to start treatment were not

significantly related to the doctor's age, sex or length of clinical experience according to the regression analysis.

### 3.2. Ratings

Risk estimates within each group of doctors for each case are shown as box-plots in Fig. 2. The estimates were wide ranging, with more pronounced variation in the high-risk cases. In general, the median estimates of the three groups of doctors were lower than the calculated Framingham risks, with the greatest discrepancies seen in the high-risk cases. In the majority of cases, cardiologists made significantly lower estimates than the other two groups, whereas none of the differences between GPs and internists were significant (Table 1).

We defined the variability of risk estimates as the difference between the doctors' third and first quartile of estimates for each case. Large values indicate high disagreement in estimates among doctors and vice versa. No significant differences were seen between the three groups when the distributions of interquartile ranges across the nine cases were compared, but there were large inter-individual differences within each

Table 1  
Risk estimates for each case.

	GPs (n = 38)	Internists (n = 43)	Cardiologists (n = 38)	p <sup>1</sup>	p <sup>2</sup>	p <sup>3</sup>
case 1	10.3 (7.7–15.1)	10.3 (7.7–15.1)	7.9 (4.4–10.3)	0.636	0.011	0.034
case 2	3.0 (2.4–7.2)	3.0 (2.4–7.8)	3.0 (2.4–5.0)	0.843	0.614	0.519
case 3	24.8 (14.5–30.3)	20.0 (15.1–30.3)	14.5 (10.3–18.6)	0.911	0.005	0.001
case 4	7.9 (3.9–8.6)	7.2 (3.0–8.4)	4.5 (2.4–7.4)	0.573	0.010	0.041
case 5	30.6 (29.5–55.1)	30.3 (24.8–46.6)	19.4 (14.4–31.7)	0.204	0.0002	0.007
case 6	25.4 (16.2–30.1)	27.2 (18.1–31.5)	15.1 (10.7–18.6)	0.676	0.0001	0.0001
case 7	26.7 (18.8–31.1)	20.0 (15.0–30.4)	15.1 (10.3–21.3)	0.206	0.0003	0.022
case 8	13.3 (7.9–15.8)	15.1 (7.9–19.0)	10.3 (6.2–14.5)	0.210	0.181	0.009
case 9	14.5 (7.9–16.0)	15.1 (7.9–16.0)	7.6 (6.3–10.4)	0.821	0.0002	0.0001

Data are expressed as medians (interquartile range).  
p<sup>1</sup> GPs vs. Internists, p<sup>2</sup> GPs vs. Cardiologists, p<sup>3</sup> Internists vs. Cardiologists.  
Statistical test: Mann-Whitney.

Table 2  
Risk estimates for each group of doctors for the entire group of cases and the high- and low-risk subgroups.

	GPs (n = 38)	Internists (n = 43)	Cardiologists (n = 38)	p <sup>1</sup>	p <sup>2</sup>	p <sup>3</sup>
All cases	14.5 (10.3–16.3)	15.1 (9.7–20.0)	10.3 (7.9–13.9)	0.905	0.002	0.006
High-risk cases (≥20%)	29.1 (21.8–30.6)	22.7 (18.8–30.9)	15.3 (10.9–21.2)	0.280	0.0001	0.0002
Low-risk cases (<20%)	8.5 (6.0–14.5)	8.5 (7.2–14.5)	7.2 (3.6–8.6)	0.909	0.013	0.003

Data are expressed as medians (interquartile range).

p<sup>1</sup> GPs vs. Internists, p<sup>2</sup> GPs vs. Cardiologists, p<sup>3</sup> Internists vs. Cardiologists.

Statistical test: Mann-Whitney.

group, especially for high-risk cases. Cardiologists showed the lowest variability when compared to the other groups of specialists.

The median rating was calculated for each doctor across the nine cases and the resulting set of medians was compared between the groups of doctors (Table 2). The ratings were significantly lower for cardiologists than for internists and GPs, both across the entire set of nine cases and in the high- and low-risk subsets.

We tested the concordance of the doctors' risk estimates to the calculated Framingham risk as the sum of estimates that were above 20% when the Framingham risk was above 20% or below 20% when the Framingham risk was below 20%, divided by the total number of estimates. Across all nine cases, the concordance was lowest for cardiologists; only one third of their ratings for high-risk patients were above 20% (Table 3), a proportion that was less than half that of the other groups of doctors. There was no difference between GPs and internists.

In absolute numbers, only 9 (23.7%) GPs, 6 (13.9%) internists, and 4 (10.5%) cardiologists, correctly categorised the risk level of all the nine cases as per the Framingham cut-off of 20%. In high-risk cases the corresponding figures were 17 (44.7%) GPs, 17 (39.5%) internists, and 7 (18.4%) cardiologists. In low-risk cases they were 27 (71.0%) GPs, 30 (69.7%) internists and 35 (92.1%) cardiologists.

### 3.3. Decisions

The proportion of decisions to start pharmacological treatment was calculated as the number of "yes" decisions divided by the total number of decisions for each doctor.

Overall, more than 50% of the decisions made were in favour of treatment, regardless of the doctor group. Internists showed higher proportions of decisions to treat than the other two groups of specialists (Table 4). The differences were statistically significant in the entire set of cases, and in the high- and low-risk subsets.

Table 3  
Concordance of risk estimate to the calculated Framingham risk, defined as the sum of each doctor's risk estimate (across the nine cases) that was above 20% when the Framingham risk was above 20%, or was below 20% when the Framingham risk was below 20%, divided by the total number of estimates.

	GPs (n = 38)	Internists (n = 43)	Cardiologists (n = 38)	n <sup>1</sup>	n <sup>2</sup>	n <sup>3</sup>
All cases	0.82 (0.14)	0.79 (0.13)	0.67 (0.15)	0.306	0.0001	0.0001
High-risk cases (≥20%)	0.75 (0.29)	0.65 (0.34)	0.31 (0.39)	0.167	0.0001	0.0001
Low-risk cases (<20%)	0.89 (0.20)	0.90 (0.19)	0.96 (0.14)	0.993	0.116	0.091

p<sup>1</sup> GPs vs. Internists, p<sup>2</sup> GPs vs. Cardiologists, p<sup>3</sup> Internists vs. Cardiologists.

Statistical test: two-sample t-test.

Data are shown as means (SD) for the entire group of cases and the high- and low-risk cases.

### 3.4. Relationship between estimates and decisions

In general, the doctors decided to start pharmacological treatment in over 90% of the cases for which they had estimated the risk as at least 20% (Table 5). They decided to treat fewer than 50% of the cases that they had designated as below 20%, both for the entire group of cases and for the Framingham-defined low-risk cases. However, doctors made the decision to treat more than three quarters of all high-risk cases, even when their estimates of risk were below 20%. GPs were less inclined than the other groups to treat when their judgments were below 20%, while internists were most likely to decide to treat despite an estimated risk of below 20%.

## 4. Discussion

We found significant differences in the quantitative assessment of baseline cardiovascular risk made by the three sets of physicians evaluating the same set of clinical cases. All groups tended to underestimate the risk. This supports previous observations comparing the estimates of GPs and medical students in similar cases [18], and comparing GPs in two areas with different cardiovascular risk levels [13].

The risk assessment was not related to length of clinical experience. This result did not support a previously suggested relationship [19] between clinical experience and cardiovascular risk assessment.

There was a wide variability in the risk assessment within each group of specialists. This finding is consistent with the results of other studies that have assessed clinicians' perceptions of cardiovascular risk and the accuracy of their subjective estimates [12,20].

Cardiologists made lower risk estimates than GPs and internists on average. This result appears to be in accordance with one previous

Table 4  
Decision to start pharmacological treatment.

	GPs (n = 38)	Internists (n = 43)	Cardiologists (n = 38)	p <sup>1</sup>	p <sup>2</sup>	p <sup>3</sup>
All cases	0.54 (0.22)	0.68 (0.16)	0.57 (0.22)	0.003	0.642	0.012
High-risk cases (≥20%)	0.88 (0.25)	0.97 (0.07)	0.85 (0.23)	0.042	0.559	0.004
Low-risk cases (<20%)	0.27 (0.29)	0.45 (0.26)	0.33 (0.29)	0.005	0.340	0.068

Data are shown as means (SD).

p<sup>1</sup> GPs vs. Internists, p<sup>2</sup> GPs vs. Cardiologists, p<sup>3</sup> Internists vs. Cardiologists.

Statistical test: two-sample t-test.

Data are calculated as mean values of the proportions of "yes" decisions divided by the total number of decisions for each doctor across the nine cases.

Data for the entire group of cases and the high- and low-risk cases.

Table 5  
Relationship between doctors' risk estimate and decision to start pharmacological treatment.

	GPs (n = 38)	Internists (n = 43)	Cardiologists (n = 38)	n <sup>1</sup>	n <sup>2</sup>	n <sup>3</sup>
All cases						
estimate ≥20%	0.92 (0.24)	0.98 (0.08)	0.97 (0.07)	0.161	0.226	0.776
estimate <20%	0.27 (0.28)	0.47 (0.30)	0.46 (0.26)	0.004	0.004	0.921
High-risk cases						
estimate ≥20%	0.93 (0.23)	0.93 (0.25)	0.98 (0.07)	0.943	0.248	0.219
estimate <20%	0.76 (0.42)	0.91 (0.22)	0.79 (0.32)	0.137	0.793	0.101
Low-risk cases						
estimate ≥20%	0.92 (0.23)	0.88 (0.29)	0.93 (0.12)	0.722	0.901	0.620
estimate <20%	0.20 (0.28)	0.38 (0.29)	0.30 (0.29)	0.004	0.101	0.224

Data are expressed as means (SD).

p<sup>1</sup> GPs vs. Internists, p<sup>2</sup> GPs vs. Cardiologists, p<sup>3</sup> Internists vs. Cardiologists.

Statistical test: two-sample t-test.

Data are calculated as mean values of "yes" decisions among cases rated more than 20% and less than 20% respectively for each doctor across the nine cases.

Data for the entire group of cases and the high- and low-risk cases.

study which found that family physicians and internists overestimated baseline cardiovascular risk compared to cardiologists [12]. However, in the present study, cardiologists had lower concordance between their risk estimate and the corresponding Framingham risk than the other specialists did. Cardiologists in general underestimated the cardiovascular risk to a greater extent than internists and GPs; the estimates made by the latter groups were more accurate. This interpretation is supported by our previous research showing an inverse relationship between the background cardiovascular risk of the population and the physicians' risk estimate [13]. One possible hypothesis is that the higher cardiovascular risk of the patients that cardiologists usually deal with compared to GPs and internists influences their quantitative perception of cardiovascular risk, setting the threshold of "normal" values at higher levels and leading them to underestimate actual risk.

In this study, only a fourth of GPs and smaller percentages of the other specialists made a correct categorisation of the risk according to the calculated Framingham risk level as above or below 20% for all the nine cases. This finding suggests that in clinical practice, the majority of physicians dealing with primary cardiovascular prevention may misclassify their patient's risk levels, which can lead to inappropriate care.

Internists tended to be more prone to start pharmacological treatment than the two other groups of doctors. This finding is supported by studies that have shown internists order more diagnostic tests for hypercholesterolemia and prescribe more lipid-lowering drugs than GPs or cardiologists do [21,22]. However, the reasons for these differences are not fully understood. Our results suggest that they are not explained entirely by different risk levels among the patients. GPs tended to be more accurate as they showed a lower percentage of treatment decisions for low-risk patients than the other groups. All groups of doctors decided to treat the majority of high-risk patients.

When the decision to start pharmacological treatment was compared with the physician's own risk estimate, we found that around half of internists and the same percentage of cardiologists decided to start lipid-lowering treatment even when their own risk estimate was below the value of 20%, the threshold to recommend drug treatment. Only a small proportion of GPs started drugs when their risk assessment was below 20%. In other words, they seem to have used 20% as a cut-off point to a greater extent than the other two categories of doctors. In clinical practice the internists' and cardiologists' attitude may result in over-prescription of lipid-lowering drugs. This result would be compatible with previous research in primary prevention showing that physicians may overuse statins in low-risk subjects [23].

Within each of the three groups of physicians the relationship between risk estimate and treatment decision was different when high and low-risk cases were analysed separately. In low-risk cases (below 20% according to Framingham formula) the treatment decision was more likely to be yes than no only when the doctor's own estimate was above 20%. When the subjective estimate was below 20%, treatment decisions were mainly no. Conversely, in high-risk cases there was a high rate of decision to treat, regardless of a physician's risk estimate. Somewhat unexpectedly, there appears to be some perception of the actual risk level of a specific case that influences the decision to treat independently of the quantitative estimate. Thus, high-risk cases are perceived as "high" and induce a decision to start drugs even when the doctor's own quantitative estimate is below 20%. Further research is needed to investigate which component of the risk profile induces such perception.

Our study has some limitations. Firstly, the 42% response rate, although not unusual for a mail survey of physicians [19,24], makes it hazardous to generalise to all doctors. Secondly, case vignettes limited to a few variables may not reflect real-life practice. However, the use of case vignettes has been shown to be an effective method to measure the quality of physicians' practice [25,26]. Since all physicians faced

the same cases, a comparison was possible. Thirdly, we cannot exclude that physicians responded to the questionnaire in an ideal fashion that does not accurately reflect their practice. Finally, we cannot be sure that no doctors used risk calculators, even though they were instructed not to.

In conclusion, our results provide further evidence of how doctors' risk estimates and treatment decisions may be influenced by factors not related to an individual patient's risk. The level of risk estimates, willingness to recommend pharmacological treatment and use of the recommended cut-off point differed across all three groups of physicians. Cardiologists may underestimate the cardiovascular risk of high-risk patients who are referred to them, while conversely treatment may be overused in low-risk patients referred to internists. These findings may have practical implications in exploring the gap between evidence and practice in the prevention and management of cardiovascular disease and serve as a basis to implement educational support that encourages uniformity in doctors' risk assessment.

## 5. Learning points

- Cardiovascular risk estimates are usually made subjectively.
- When evaluating the same set of clinical cases, cardiologists make lower estimates than general practitioners and internists, whereas internists are more prone to start pharmacological treatment than the other two groups.
- There is evidence that the doctors' cardiovascular risk estimates and treatment decisions are influenced by factors not directly related to the individual patient's risk.

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IV



# General Practitioners' coronary risk estimates, decisions to start lipid-lowering treatment, gender and length of clinical experience: their interactions in primary prevention

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**Aim:** We investigated whether the risk estimates of General Practitioners (GPs) and their treatment decisions mutually influence each other and whether factors not related to the patient's risk, such as the gender and length in clinical practice, interact.

**Background:** The quantitative assessment of the absolute risk of developing coronary heart disease (CHD) and the decision to start treatment with lipid-lowering drugs are crucial tasks in the primary prevention of CHD. **Methods:** Nine clinical vignettes, four rated high-risk and five rated low-risk according to the Framingham equation, were mailed to three groups of 90 randomly selected GPs in Stockholm. One group (R) was asked to estimate the risk of CHD within 10 years on a visual analogue scale. A second group (R + D) was asked to estimate the risk and to specify whether they would recommend a pharmacological lipid-lowering treatment. A third group (D) only to indicate whether they would recommend treatment. **Results:** Response rate ranged from 42.2% to 45.6%. The median risk estimates were higher in the R group than in the R + D group (difference not statistically significant). R + D group showed higher proportions of correct decisions to start treatment compared with the R group (86.2% versus 77.5%,  $P = 0.19$ ). More correct decisions were made by female doctors (OR 1.77, 95% CI 1.19–2.61,  $P = 0.004$ ) and by less experienced doctors (OR 0.97, 95% CI 0.95–0.99,  $P = 0.016$ ). **Conclusions:** The task of making CHD risk estimates and the task of making decisions whether to start lipid-lowering treatment do not seem to influence each other. The gender of physicians and the length of clinical experience seem to affect treatment decisions. Female GPs and less experienced GPs are more likely to make correct decisions. However, the relatively low response rate to the questionnaires may limit the generalizability of these results.

**Key words:** coronary risk estimates; gender of physicians; general practitioners' length of experience; lipid-lowering treatment; primary cardiovascular prevention

Received 20 November 2011; accepted 4 October 2012; first published online 25 January 2013

## Introduction

The primary prevention of coronary heart disease (CHD) is based on the assessment of the

individual's absolute risk of developing CHD rather than on the value of any specific risk factor, and preventive treatment should be considered if the patient's absolute risk exceeds a certain cut-off point (Expert Panel, 2001). Therefore, the key factor in proper CHD prevention is combining quantitative risk assessments with decisions about whether or not to treat individual patients.

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Although there is extensive knowledge about how to manage cardiovascular risk, the quality of preventive care is suboptimal, especially in high-risk subjects (Durrington *et al.*, 1999; Grundy *et al.*, 1999; Ford *et al.*, 2003; Erhardt and Hobbs, 2007; Doroodchi *et al.*, 2008).

Risk assessment tools, such as charts or computer programs, have been developed and are recommended in the identification of high-risk subjects, but their use in clinical practice is limited, and clinicians are more likely to make their own assessment subjectively (Graham *et al.*, 2006; Eichler *et al.*, 2007).

We have previously observed that the decision to start pharmacological treatment with lipid-lowering drugs does not come in a straightforward way from the doctor's estimate of the patient's risk (Vancheri *et al.*, 2008). When the relationship between physicians' subjective risk estimates and decisions to treat with respect to a defined cut-off level was investigated using clinical vignettes, we found that in simulated cases with high actual risk level, there was a high rate of decision to treat even when the physicians' own quantitative estimate was below the risk rate defining the cut-off level to start pharmacological treatment. This observation may indicate that in high-risk cases the decision to start pharmacological treatment is to some degree independent from the physicians' own quantitative risk estimate. Therefore, risk estimates and treatment decisions may be partially independent. Other studies have documented a discordance between knowledge and action in medical decision making (Redelmeier and Shafir, 1995; Kaufman *et al.*, 1999). Within studies of physician's risk estimates and treatment decisions, it is not known whether the task of making a decision about treatment influences the quantitative risk estimate and vice versa.

Moreover, although the influences of the gender of physicians and their clinical experience on management of patients at risk for cardiovascular events have been investigated, there is limited information about their role in the area of risk estimates and treatment decisions in primary CHD prevention (Choudhry *et al.*, 2005; Christian *et al.*, 2006; Baguet *et al.*, 2007; Berthold *et al.*, 2008; Baumhäkel *et al.*, 2009; Tabenkin *et al.*, 2010; Southern *et al.*, 2011).

In the present study, we aimed to assess:

- 1) whether the risk estimates of General Practitioners (GPs) and their treatment decisions mutually influence each other, that is, whether decisions influence ratings and whether ratings influence decisions;
- 2) whether the gender of physicians and the number of years they have been in clinical practice influences risk estimates and treatment decisions.

The answers to the first question are of theoretical interest within the field of decision making in general and should be of importance in the interpretation of previous and future studies in the field of risk estimates and treatment decisions. The second question relates to individual differences in clinical decision making, especially the role of physicians' gender and the length of clinical experience, and may help explain variations in quality of care.

We investigated three groups of GPs confronted with the same series of simulated clinical case descriptions. Each group had one of the following tasks: risk rating only (R group), risk rating and decisions about pharmacological treatment (R + D group) and treatment decision only (D group). To answer the question about whether decisions influence ratings, risk assessments made by R and R + D groups were compared. To investigate whether ratings influence decisions, we compared decisions made by the R + D and D groups. All comparisons were analyzed in relation to gender and length of clinical experience.

## Methods

### Setting

This study was conducted in Stockholm, Sweden. The data were collected in 2006.

### Sample

A random sample of 270 GPs was drawn from the local database of healthcare professionals, which comprised 828 GPs. Only Family Medicine specialists were included in the study.

### Design

The study design was a cross-sectional survey. A questionnaire describing nine clinical cases was

mailed to three groups of 90 randomly selected GPs in Stockholm. All physicians received the same set of nine cases in the same order.

One group of GPs (R) was asked to estimate the risk of CHD within 10 years on a visual analogue scale (VAS), between 0% and 100%, without using a risk table or any other decision support. The risk categories currently indicated in the Framingham-based tables (low <5%, mild 5–10%, moderate 10–20%, high 20–40% and very high risk >40%) were provided as anchorage points within the scale. We chose the older Framingham risk equation because it is the most widely used method for assessment of cardiovascular risk and is the basis for most other risk prediction methods (Cooney *et al.*, 2009). The cardiovascular risk assessed using Framingham was compared with the SCORE algorithm, recently introduced in Europe (De Backer *et al.*, 2003), producing the same results regarding the relation to the respective cut-off values and almost identical ranking of the cases in terms of risk.

A second group of GPs (R + D) was asked to estimate the risk of CHD within 10 years on a VAS and to specify whether or not they would recommend a pharmacological lipid-lowering treatment for the patient, assuming that lifestyle interventions had been tried for at least six months. Figure 1 provides an example of a case as presented to the R + D group.

A third group (D) was asked only to indicate whether they would recommend a pharmacological lipid-lowering treatment for the patient.

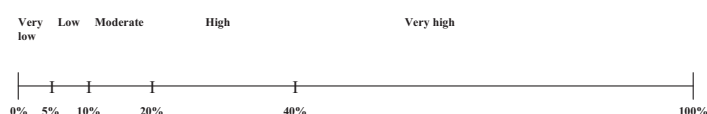
The questionnaires asked for the physicians' age, gender and length of experience, but remained anonymous to increase the likelihood that answers would be given without the use of risk tables or other decision supports (as the instruction to the doctors prescribed). Because the number of years GPs have been in clinical practice is closely related to their age, we included only the length of experience in the analyses.

### Clinical cases

We presented each physician with nine patient cases that incorporated a combination of the variables from the Framingham risk tables: age, sex, systolic blood pressure, cholesterol level and smoking. The patient cases were constructed by two of the authors (L.B., L.-E.S.) based on their own clinical experience. The patients had no history of cardiovascular disease or diabetes, as risk assessment for deciding about initiation of lipid-lowering treatment is not relevant for patients with such conditions; in addition, none had systolic blood pressure levels of above 160 mmHg, as higher values might have led the doctors to consider the treatment of hypertension more relevant than the treatment of hypercholesterolemia. The set of cases was constructed to represent a spectrum of patients with a 10-year risk of a fatal

Case 1. The patient is a 53-year old man with no history of previous cardiovascular disease or diabetes. Non-smoker. Systolic blood pressure 140 mm Hg. Recent cholesterol value is 7.0 mmol/l (270 mg/dl).

Mark with a cross on the line your estimate of his risk to have coronary heart disease within 10 years.



Would you recommend a lipid-lowering drug in this case?

Yes ☐ No ☐

**Figure 1** Example of a case description

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or non-fatal coronary event ranging from high to low, based on the Framingham algorithm (Wood *et al.*, 1998). According to this equation, a 10-year absolute CHD risk of 20% or more is the threshold for pharmacological lipid-lowering treatment. Therefore, 20% was used as the cut-off point for defining high- and low-risk cases in the Results section. The calculated Framingham median score was 17.0 (range 3–45) for all cases combined, 30.5 (range 27–45) for the four high-risk cases and 15.0 (range 3–17) for the five low-risk cases.

To minimize the risk of an anchorage effect, we opened the questionnaire with a medium-risk case and ordered the rest at random.

A summary of the nine cases presented to the doctors is shown in Figure 2, below the box plots.

The study was approved by the regional ethics committee in Stockholm (no. 2005/603–31).

### Statistical analysis

To account for the clustering effect of each doctor being represented nine times, we used generalized linear models (linear and logistic

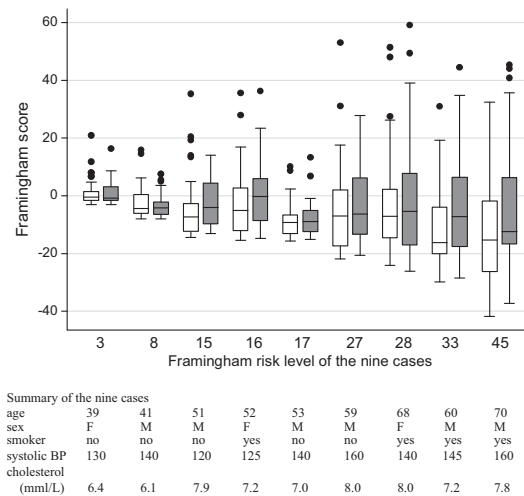
regression) with robust standard errors for all of the analyses, with nine rows for each doctor for each case. We used multivariable models to test for the effect of Framingham score, experience and gender.

### Investigation of risk estimate (R + D and R groups)

For the risk estimates, we used the difference between the doctors' estimates and the calculated Framingham risk (Framingham score) because it is approximately normally distributed. A multivariable linear regression model was constructed that included (as independent variables) the actual Framingham risk (in order to ascertain how this affected the score), the group (R and R + D), the gender of the doctor and the number of years of experience.

### Investigation of treatment decisions (R + D and D groups)

The effect of making a risk estimate on treatment decisions was first assessed by comparing



**Figure 2** Box plot of doctors' risk estimates in the R group (empty bars) and R + D group (filled bars) and summary of the nine cases along with the calculated Framingham risk level. Framingham score is GPs' risk estimates minus Framingham risk levels. The bottom of the boxes is at the first quartile, the top is at the third quartile and the continuous lines across the boxes are at the median value. The whiskers are drawn to the highest and lowest values that are not considered as outliers. Outliers, marked with dots, are estimates outside these limits. The first five cases are low-risk cases, according to Framingham. The others are high-risk cases, eligible for treatment.

the proportion of decisions made in the R + D and D groups, and the *P*-value for difference in the proportion of decisions was assessed using a logistic regression model that included both groups with decision as the outcome.

The effect of group experience, Framingham score, gender and experience on the proportion of correct decisions was investigated using multi-variable logistic regression with correct decisions as the outcome. 'No' decisions were considered correct if the Framingham risk for the case was <20%, and 'yes' decisions were considered correct if the risk was ≥20%.

We tested for interactions between the covariates in both models.

STATA (version 9.2) was used for statistical analysis.

## Results

### General data

Response rates to the questionnaire were as follows: 41 GPs (45.6%) from the R group (median age 55 years, range 38–69), 38 (42.2%) from the R + D group (median age 54 years, range 43–65) and 41 (45.6%) from the D group (median age 51 years, range 37–63). The percentage of male respondents in each group was 51.2, 41.7 and 50.0, respectively. The median length of clinical experience was similar in the three groups (15 years in the first, range 2–31; 15 years in the second, range 2–30 and 13.5 years in the third, range 1–30).

### Ratings

Risk estimates within the R + D group and the R group for each case are shown as a box plot in Figure 2 as differences between the Framingham scores and the GPs' risk estimates. There was a wide range of estimates, particularly for the high-risk cases. In general, the median estimates in the R group were higher than in the R + D group, especially for the high-risk cases, but the difference between the two groups was statistically significant in only one of the cases.

The median estimates of both groups were lower than the calculated Framingham risks for all nine cases, with the greatest discrepancies in the high-risk cases.

The difference between the doctors' risk estimates and the calculated Framingham risk

(doctors' risk estimates minus Framingham risk) was not related to group (*P* = 0.27), gender (*P* = 0.74) or length of experience (*P* = 0.57). However, it was significantly related to the calculated Framingham risk (*P* = 0.04), with the differences getting larger as the Framingham risk increases.

### Decisions

To investigate the effect of risk estimates on the task of making a decision, the proportion of decisions to start pharmacological treatment was calculated as the number of 'yes' decisions divided by the total number of decisions for each doctor. Overall, about half (48.3%) of the GPs' decisions in the R + D group were favourable to start a treatment, compared with 44.4% in the D group (*P* = 0.62). For the five low-risk cases, the female GPs were significantly less willing to treat compared with the male GPs (12.6% versus 24.4%, *P* = 0.04; Figure 3).

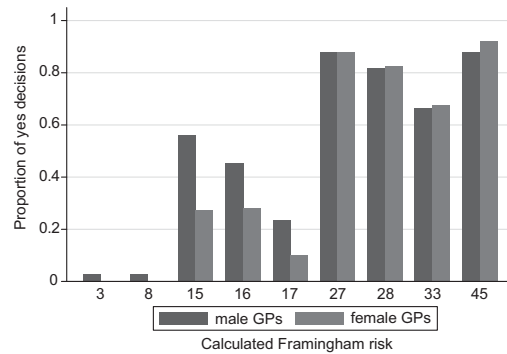
The proportions of correct decisions, based on the number of doctors to account for clustering, were higher in the R + D group for high-risk cases (86.2% and 77.5%, respectively), but this difference was not statistically significant (*P* = 0.19).

Correct decisions decreased with calculated Framingham score of the case, but this decrease was not significant (*P* = 0.12).

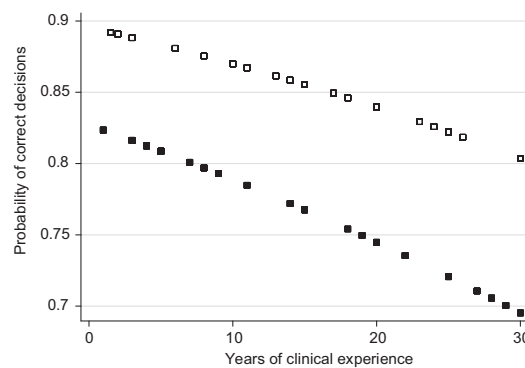
The effect of gender and length of clinical experience on correct decisions was investigated by including both variables as independent variables in the logistic regression model together with Framingham score. Correct decisions were significantly related to gender (being female; OR 1.77, 95% CI 1.19–2.61, *P* = 0.004) and negatively related to years of clinical experience (OR 0.97, 95% CI 0.95–0.99, *P* = 0.016). This indicates that correct decisions were more likely to be carried out by less experienced doctors. Figure 4 shows the predicted proportions of correct decisions as a function of clinical experience and gender. Female GPs made a higher rate of correct decisions (87.3% versus 75.5%, *P* = 0.08).

### Discussion

Our results suggest that the task of risk rating and the task of deciding whether or not to start a lipid-lowering treatment do not influence each other.



**Figure 3** Proportion of 'yes' decisions (R + D and D combined groups) by GPs' gender for each case according to the level of calculated Framingham risk.



**Figure 4** Plot of probability of correct decisions against the length of clinical experience by gender. The squares (empty = female doctors and filled = male doctors) represent the predicted proportions of correct decisions. Each square represents one to six doctors with the same number of years of clinical practice.

All groups of GPs tended to underestimate risk compared with the calculated Framingham risk, supporting previous observations comparing the estimates of GPs and medical students in similar cases (Backlund *et al.*, 2004) and comparing GPs in two European areas with different cardiovascular risk levels (Vancheri *et al.*, 2008).

There was wide variability in the risk assessments within each group of GPs. This finding is consistent with the results of other studies that have assessed clinicians' perceptions of cardiovascular risk and the accuracy of their

subjective estimates (Dolan *et al.*, 1986; Friedmann *et al.*, 1996).

Among all the groups of GPs, the largest discordance between the GPs' risk estimates and the calculated Framingham risk, as well as the lowest rate of correct decisions about treatment, were observed in the high-risk cases. This speaks to the uncertainties that doctors experience when estimating risk and deciding the treatment of high-risk patients, the patients for whom preventive efforts are most important. Preventive efforts in high-risk subjects are important, as the benefit of



treatment increases with increased absolute risk. This observation has practical consequences, as the effectiveness of drug treatment in CHD prevention depends on the accuracy with which the clinician estimates risk in individual patients (Durrington *et al.*, 1999; Grundy *et al.*, 1999). Once the risk for a given individual is accurately identified, appropriate interventions exist that substantially reduce cardiac events. This paradigm assumes that decisions about treatment are direct consequences of estimates. However, our results support the opinion that risk assessments and decisions about treatment are complex cognitive processes that involve interactions between doctors' knowledge, risk perception and the task of decision making (Reyna and Lloyd, 2006; Reyna, 2008).

In the present study, the gender of GPs and the length of their clinical experience were shown to influence their decisions about treatment. Female GPs performed better than male GPs and, in particular, were less prone to start treatment in low-risk cases.

Previous research has suggested that male and female physicians differ in the treatment of patients with heart failure (Baumhäkel *et al.*, 2009), in the control of some risk factors in patients with diabetes (Berthold *et al.*, 2008), and in providing preventive care (Henderson and Weisman, 2001). It has been proposed that perception and interpretation of clinical symptoms may be different because female physicians tend to have a more patient-centred communication style (Roter *et al.*, 2002) and to spend more time with the patient (Bertakis *et al.*, 1995). However, our study is based on paper-simulated cases, which eliminates gender differences due to the interaction between the physician and the patient. Therefore, we can speculate that the gender differences in treatment decisions observed in our sample may reflect true differences in the decision-making process that are independent of factors related to the physician–patient relationship.

We also found that the length of time in clinical practice seems to affect decisions. Shorter experience was associated with a higher number of correct decisions. These findings support previous reports of lower quality care with increasing years in practice (Choudhry *et al.*, 2005; Southern *et al.*, 2011).

There are some limitations to this study. First, the 42–45% response rate, although not unusual

for a mail survey of physicians (Castaldo *et al.*, 2005; Christian *et al.*, 2006; Erhardt and Hobbs, 2007), compromises generalizability of the study results to all doctors. In addition, the response rate produced relatively small groups for the statistical analyses. In this case, there may be the risk of a type II error, that is, failing to find a true association between the task of risk assessments and the task of treatment decisions because of the small sample size. Second, case vignettes limited to a few variables may not reflect real-life practice. However, the use of case vignettes has been shown to be an effective method to measure the quality of physicians' practice (Peabody *et al.*, 2004; Veloski *et al.*, 2005). Third, we cannot exclude the possibility that physicians responded to the questionnaire in a manner that does not accurately reflect their practice, and we cannot eliminate the possibility that some doctors may have used risk calculators, even though they were instructed not to. Finally, risk assessments and treatment decisions may be influenced by several other factors than what is included in the case vignettes or attributable to the individual doctors. Such environmental factors may be information campaign from health services, the media or by pharmaceutical industries. The possibility of these influences may further limit the generalizability of our results.

## Conclusions

GPs seem to underestimate CHD risk when compared with the calculated Framingham risk. Female GPs are more likely to make correct decisions, and GPs with more experience may paradoxically provide lower quality care. These findings may have practical consequences, as they indicate some level of inappropriate CHD primary prevention. Innovative educational approaches are needed to improve the quality of medical decision making.

## Acknowledgement

The authors express their appreciation to Rosemary Tate, PhD, for her contribution to the statistical analyses.

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## Errata

Paper IV. Figure 2. First line of the legend “Box plot of doctors’ risk estimates in the R group (empty bars) and R+D group (filled bars)” should be read “Box plot of doctors’ risk estimates in the R+D group (empty bars) and R group (filled bars)”.





# Trends in coronary heart disease mortality and statin utilization in two European areas with different population risk levels: Stockholm and Sicily

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## Abstract

**Background and Aim:** The reduction in coronary heart disease (CHD) mortality in Europe has been associated with a reduction in coronary risk factors, including dyslipidaemia. Statins reduce blood cholesterol levels and the risk of coronary events. Their utilization has substantially increased over the years. Although statins should be prescribed according to clinical guidelines, doctors' decisions about treatment are usually made subjectively and are influenced by the population risk level. The aim of this study was to investigate the relation between the time trend of population risk level and statin utilization in two areas with different levels of coronary risk in the population.

**Methods:** CHD mortality, as a proxy of population coronary risk level, and statin utilization trends in the period 2001-2011, were compared between a relatively high-risk CHD area, Stockholm county, and a low-risk area, Sicily.

**Results:** There was a reduction in CHD mortality and an increase in statin utilization in both areas. The mean annual reduction in CHD mortality rate/100,000 was greater in Stockholm than in Sicily (-4.6, 95% CI -5.3 -4.0, and -1.9 95% CI -2.6 -1.2, respectively). The mean annual increase in statin DDD/TID utilization was larger in Sicily than in Stockholm (5.1, 95% CI 4.8 - 5.3, and 3.7, 95% CI 3.2 - 4.1, respectively). In Stockholm the increase in statin use was mainly due to increased utilization of simvastatin, whereas it included a greater variety of statins in Sicily.

**Conclusion:** The relations between time trends of CHD mortality and statin utilization in Stockholm and in Sicily were different. A larger increase in statins was observed in the low-risk area, associated with a slower reduction in CHD mortality, whereas a smaller increase in statins was observed in the high-risk area, associated with a greater reduction in CHD mortality. Other factors apart from the actual risk of the patients may explain these observations, such as differences in socioeconomic factors, adherence to treatment, policies of drug cost-containment, and population CHD risk profiles.

**Key words:** coronary heart disease, statins, population coronary risk

## Introduction

During the last four decades, coronary heart disease (CHD) mortality has decreased substantially in Western European countries<sup>1, 2</sup>. The greatest contribution to the decrease comes from the reduction in major CHD risk factors including dyslipidaemia, one of the strongest predictors of the development of coronary disease<sup>3-5</sup>.

Statins, the most used lipid-lowering agents, are associated with a decrease in CHD events and mortality in both primary and secondary prevention<sup>7-11</sup>. The use of statins has increased in most European countries, though with wide variations<sup>12-14</sup>. This has raised some debate on the appropriateness of the prescribing pattern, especially for primary prevention in otherwise healthy individuals, i.e. the risk-benefit balance between lower mortality from aggressive lipid-lowering treatment and the adverse effects<sup>15-18</sup>.

According to current guidelines, the decision to start lipid-lowering treatment for CHD prevention should be based on the assessment of the individual's global risk of developing

CHD<sup>19, 20</sup>. This should be translated into more frequent use of statins in high-risk countries, compared to low-risk countries, partly due to higher levels of coronary risk factors in the former. Few studies have investigated the relation between coronary risk levels and utilization of statins in large populations<sup>21-24</sup>. Comparisons between CHD death rates in different countries<sup>25</sup> and statin utilization in the year 2000<sup>12</sup>, show wide variability in statin utilization, independent of CHD mortality rates. However, such studies have been cross-sectional, focusing on a single year without accounting for the appropriateness of the increase to the change in the population cardiovascular risk.

Doctors' subjective perception of risk may have an influence on the prescription of statins. We have previously observed that the doctors' estimate of the coronary risk in a single patient with a specified set of risk factors seems to be related to the coronary risk in the general population. In our study<sup>26</sup> the estimates were inversely related to the population risk level in the two areas studied. This unexpected result may be associated with inappropriate prescribing of lipid-lowering drugs.

**Table 1:** CHD mortality in Stockholm and Sicily

Year	Stockholm		Sicily		OR
	n° of deaths	mortality rates	n° of deaths	mortality rates	
2001	3111	110.6	5435	71.5	1.5
2002	2942	102.3	5660	72.7	1.4
2003	2940	99.7	5950	74.2	1.3
2004	2703	91.1	5131	63.6	1.4
2005	2522	83.5	5105	61.8	1.3
2006	2625	84.4	5383	61.8	1.2
2007	2644	83.4	5520	61.9	1.2
2008	2481	78.0	5541	59.9	1.1
2009	2173	67.3	5584	58.8	0.9
2010	2211	67.9	5399	55.2	1.0
2011	2026	60.8	4433	47.5	1.1
Mean annual reduction		-4.6 (-5.3, -4.0)			-1.9 (-2.6, -1.2)

Mortality rates are expressed as standardised rates/100.000 (95% CI). OR: odds ratio

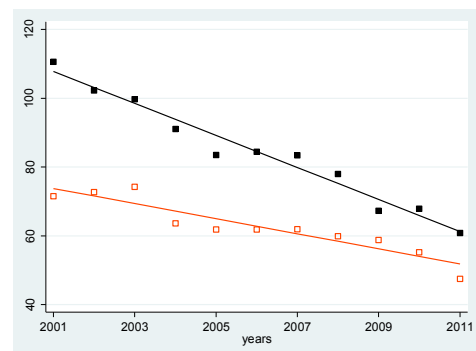
An analysis of the time trends in both coronary risk and statin utilization could increase our understanding of the relation between the two, especially if we compare patterns between areas with different coronary risk levels. This study aimed to assess the relation between the trends over time in statin utilization and the changes in the population coronary risk levels, expressed as CHD mortality, and to assess whether different levels of coronary risk in the population may be associated with differences in the utilization of statins. We also evaluated the variation over time in the choice of substances prescribed. Since different substances induce different degrees of cholesterol lowering<sup>27</sup>, a small increase in more potent statins would theoretically have the same cholesterol-lowering effect in the population as large increase in utilization of less potent drugs.

## Methods

This was an ecological study comparing trends in CHD mortality with statins utilization, in the period 2001-2011, in the regions of Stockholm county (2,054,343 inhabitants in 2011) in Sweden, and Sicily (5,051,075 inhabitants in 2011) in Italy. Stockholm is the capital of Sweden, a country with relatively high CHD mortality levels<sup>25</sup>, although in recent years the risk has decreased to low-moderate<sup>28</sup> and total cholesterol levels are now lower than in Italy<sup>29</sup>. Sicily is part of Italy, a country with lower CHD mortality<sup>30</sup>. Both countries have similar public health system with universal coverage, based on direct taxation of the inhabitants.

**CHD mortality.** This was used as expression of population coronary risk level since it has less diagnostic variance than measurement of risk factors. Several studies have consistently demonstrated that changes in CHD mortality are associated with changes in risk factors<sup>31-33</sup>.

We used data from The Swedish National Board of Health and Welfare (Socialstyrelsen)<sup>34</sup>, a government agency in Sweden under the Ministry of Health and Social Affairs, and from Istituto



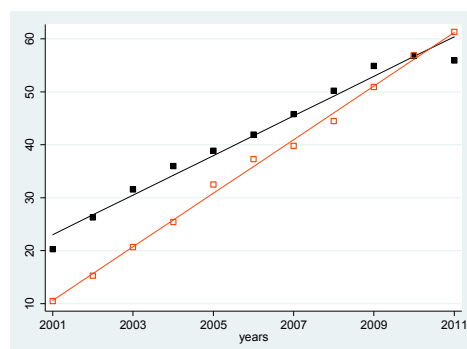
**Figure 1:** Changes in standardised CHD mortality rates/100.000 and estimated values from multiple regression model (lines) in Stockholm (black squares) and Sicily (empty squares).

Superiore di Sanità for CHD mortality in Sicily<sup>35</sup>. Sicilian data 2009-2011, which are not provided on the web-site, were made available by Istituto Superiore di Sanità before publication (Luigi Palmieri, personal communication). In Stockholm the causes of death were selected according to the international version of the disease classification (ICD-10), from codes I20 to I25 (ischaemic heart diseases), whereas in Sicily the ICD-9 codes 410-414 were used until 2005, and ICD-10 codes I20-I25 thereafter. Corrections were made to the Sicilian mortality data from 2001 to 2005, to account for the changes in the causes of death classification from ICD-9 to ICD-10. The changes from the old coding system to the new one have been assessed by bridge-coding studies. These have shown good comparability for CHD mortality between the two systems<sup>36,37</sup> with a comparability ratio for ischaemic heart disease of 1.0318. This means that 3.18% more deaths are classified to this group in ICD-10 compared to ICD-9. Accordingly, these percentages of deaths were added to the number of CHD deaths in Sicily, for each year from 2001 to 2005. All ages were included. To take into account the possible bias of different age classes in the two areas of the study, mortality data were age-standardised according to the population of Europe, and expressed as rates/100,000.

**Statin utilization.** Only the changes in the use of statins were analysed since these drugs account for more than 90% of lipid-lowering drugs prescribed in both countries.

The data were extracted from the Swedish Prescribed Drug Register of the National Board of Health and Welfare<sup>38,39</sup> and from the Sicilian Assessorato Regionale della Salute<sup>40</sup>. Both these databases have complete records of all drugs dispensed to the inhabitants in the regions. To enable international comparisons in different periods, we used the Anatomical Therapeutic Chemical (ATC) classification and the standard international method for estimating drug use across populations, the Defined Daily Dose (DDD) per one Thousand Inhabitants per Day (DDD/TID). DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults<sup>41,42</sup>. Analyses in this study were based on the 2009 DDDs update for all the time periods. The ATC codes were C10AA (statins) and C10AA01, 03, 04, 05 and 07 (simvastatin, pravastatin, fluvastatin, atorvastatin and rosuvastatin, respectively).





**Figure 2:** Changes in statin utilization, expressed as DDD/TID, and estimated values from multiple regression model (lines) in Stockholm (black squares) and Sicily (empty squares).

The time trend changes in the use of statins as a pharmacological group, as well as separate statins, were analysed.

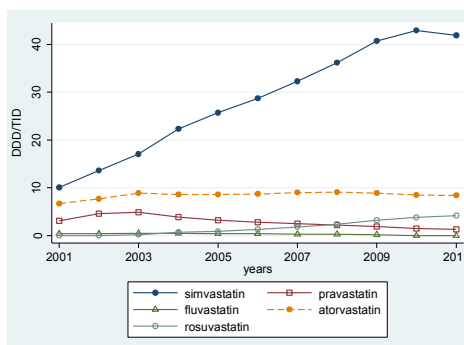
Statistical analysis. CHD mortality rates and volumes (DDD/TID) of dispensed statins in Stockholm and in Sicily between 2001-2011 were tabulated and mean values with 95% confidence intervals were calculated. The odds ratios of CHD mortality between Stockholm and Sicily were computed for each year. Multiple linear regression was used to investigate the trends and the overall differences in CHD mortality and statin utilization in the two areas. An interaction term between year and area was included in both models to ascertain whether the effect of time on the two outcomes, death rates and statin utilization, was different in the two areas. Statistical analyses were carried out using STATA 11. Analytic weights (Stata aweights) were used in the regression analysis to adjust for the different population sizes in the two regions.

## Results

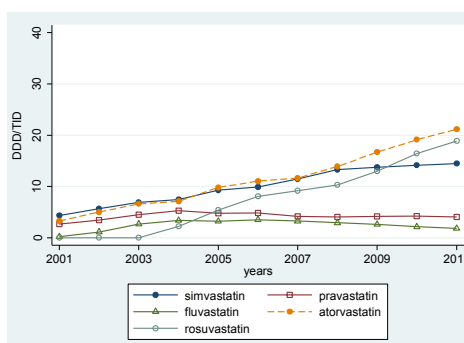
The overall CHD mortality rates were higher in Stockholm than in Sicily for each of the years studied (Table 1). A greater rate of reduction in CHD mortality ( $p < 0.001$ ) was observed in Stockholm compared to Sicily (Figure 1). Between 2001 and 2011, the odds ratio of CHD mortality in Stockholm compared to Sicily, decreased from 1.5 (95% CI 1.4-1.6) to 1.1 (95% CI 1.0-1.2).

The overall utilization of statins was higher in Stockholm, at least until 2009 (Table 2), and increased steadily over the years in both regions (Figure 2). The interaction between time and area in statin utilization was statistically significant ( $p < 0.001$ ) in the two areas, with Sicily having a steeper increase.

The analysis of the time trend of individual substances showed a marked increase of simvastatin in Stockholm (mean annual increase 3.4 DDD/TID) compared to the other statins (mean annual increase  $< 1$  DDD/TID) (Figure 3A). In Sicily there was a more homogeneous increase: atorvastatin showed the greatest increase rate over time, followed by rosuvastatin and simvastatin (mean annual increase 1.9, 1.7, 1.1 DDD/TID respectively) (Figure 3B).



**Figure 3A:** Changes in utilization of different statins in Stockholm, expressed as DDD/TID.



**Figure 3B:** Changes in utilization of different statins in Sicily, expressed as DDD/TID.

## Discussion

We found a higher overall CHD mortality and utilization of statins in Stockholm than in Sicily. If we accept CHD mortality as a marker for CHD risk level, the results are compatible with a hypothesis that high cardiovascular risk in general leads to a great need for risk-lowering actions, e.g. prescription of lipid-lowering drugs.

The mortality declined in both regions between 2001 and 2010 and the gap between the two areas decreased over time. During the same period, statin utilization increased in both areas, with a steeper increase in Sicily.

The relation between coronary risk and statin utilization may be considered from two angles: as an effect of statins on cardiovascular risk, or as changes in statin utilization following changes in risk levels. If we find a large increase in statins over time in an area with a rapid reduction in coronary disease, this may support the concept of statins as an important factor behind reduction in coronary disease. If the reverse is found, a larger increase in statin utilization in an area with slower reduction in coronary disease, we should consider other factors

**Table 2:** Utilization of statins in Stockholm and Sicily

Year	Stockholm	Sicily
2001	20.3	10.5
2002	26.3	15.3
2003	31.6	20.7
2004	36.0	25.4
2005	38.9	32.5
2006	41.9	37.3
2007	45.8	39.8
2008	50.2	44.5
2009	54.9	50.9
2010	56.8	56.9
2011	55.9	61.3
Mean annual increase DDD/TID (95%CI)	3.7 (3.2-4.1)	5.1 (4.8-5.3)

behind changes in statin utilization, e.g. attitudes among doctors, and other factors within society and the medical community<sup>26</sup>. The increase in statin utilization we observed in both areas, with a corresponding decrease in mortality, may suggest that statins exert a powerful effect on CHD mortality. In this case, changes in statin utilization and mortality should be “concordant”, i.e. a larger increase in statins should accompany a faster reduction in mortality. However, we found a “discordant” relation, i.e. larger increase in statins accompanied a slower reduction in mortality, which supported the idea that there are other factors than risk levels behind the rise in statin utilization. Although it is widely recognised that a decrease in population total cholesterol makes a large contribution to CHD mortality reduction<sup>43</sup>, the trend we observed cannot be entirely attributed to statins since mortality rates in these countries started to reduce in the '70s, several years before statin therapy became available<sup>44, 45</sup>. Moreover, both in Sweden and Italy, more than half of the decrease in CHD mortality between 1980 and 2000 is attributable to a reduction in major risk factors, mainly cholesterol, blood pressure and smoking prevalence<sup>46, 47</sup>.

Moreover, statins cannot fully explain the reduction in CHD deaths observed in more recent years<sup>48</sup>. Clinical trials show that their contribution to absolute reduction of CHD mortality ranges from <1% to 3.5% in both primary and secondary prevention<sup>19</sup>. A comparison of CHD age-standardised mortality rates in two neighbouring Nordic countries, Denmark and Norway, shows no difference despite a fourfold wider use of statins in Norway<sup>12, 25</sup>. Studies in Sweden and England demonstrated that a large increase in statin prescriptions was associated with no effect or only a modest reduction in admission rates for myocardial infarction<sup>21, 50</sup>. In the present study, it seems unlikely that the statins made a large contribution to CHD mortality reduction at a population level since the large increase in statins in Sicily was associated with a smaller reduction in mortality, compared to Stockholm.

Observational studies have documented a large discrepancy between guideline recommendations and clinical practice, and a substantial proportion of patients do not achieve the guidelines target<sup>51-53</sup>. This may be partly explained by poor patient adherence to treatment. Discontinuation of statins is linked to increased risk of CHD events<sup>54, 55</sup>, whereas higher adherence is associated with lower CHD mortality<sup>56-58</sup>. The rate

of statins discontinuation is probably lower in Sweden than in Italy.

Previous studies have shown discontinuation rates of about 20% and 50% respectively, during the first year of treatment<sup>59-61</sup>. Moreover, It has been observed that poor adherence is associated with lower income status<sup>62, 63</sup>. Since the gross domestic product per capita in Sicily is about one third that of Stockholm (14,100 Euros per inhabitant in 2001 and 16,800 in 2010, compared to 38,800 in 2001 and 50,700 in 2010)<sup>64</sup>, this may have contributed to the slower decrease in CHD mortality observed in Sicily compared to Stockholm.

The variation between the two regions in total statin use might in part be explained by the rise in relative use of more potent statins in Sicily. DDDs of statins are not equipotent and the lipid-lowering effect per unit varies for different statins<sup>65</sup>. At a dose equivalent to one DDD there is a gradient in lowering LDL cholesterol. Clinical trials have shown that reductions of LDL cholesterol for rosuvastatin, atorvastatin, simvastatin, pravastatin and fluvastatin, are about 46%, 43%, 39%, 30%, 23%, respectively<sup>66, 67</sup>. Consequently, the use of more potent statins could result in a larger reduction in LDL cholesterol with a smaller increase in DDDs. Our results contrast with this possibility since more potent statins accounted for a larger proportional increase in DDD/TID in Sicily compared to Stockholm.

However, if there is a trend favouring the use of a high dosage of a statin whose DDD is set at a low dose, there will be a disproportionate number of DDDs of that substance. Consequently, the volume of that statin will increase much more than the number of patients. This may be the case with atorvastatin in Sicily. Without information on prescribed daily doses we cannot exclude this possibility to explain the rapid rise of statin prescriptions in Sicily.

Restrictive regulations about reimbursement of statins were introduced in Sweden in 2009 as cost-containment measures<sup>60</sup>. Reimbursement was excluded completely for atorvastatin 10 mg and rosuvastatin 5mg as well as for branded simvastatin, whereas reimbursement for the higher strengths of atorvastatin and rosuvastatin was restricted to patients not reaching goals with generic simvastatin. The new scheme resulted in decreasing utilization of low-doses atorvastatin and rosuvastatin, switching to higher doses of generic simvastatin and an increase in discontinuation of treatment. However, such changes occurred quite late in this study period. In Italy there was full reimbursement of statins for patient with 10-year cardiovascular risk  $\geq 20\%$ , according to the European guidelines<sup>68</sup>, until 2003<sup>69</sup>. Reimbursement criteria were revised in 2004. The main change was the introduction of a new national scoring system<sup>70</sup>. This produced a slight decrease in statin use, since the absolute risk in the Italian population is lower than in the European population<sup>71</sup>. However, it is important to recognize that the country difference in the choice of statins may be attributable to other differences in pharmaceutical policies between the countries. In Sweden, generic substitution was introduced in 2002, whereas in Italy the patent for simvastatin expired in 2007<sup>13, 14</sup>. This resulted in very low prices for generic simvastatin in Sweden, leading to substantially larger price differences between the different statins than in Italy<sup>72</sup>.

The lack of correspondence between the rate of reduction in coronary mortality and the rate of increase in statins use could be related to differences in the doctors' risk judgement in the two areas studied. Although treatment decisions should be

based on global assessment of the patients' risk, changes over time in single risk factors may influence the decision about treatment. Observational studies in the northern Swedish population in the last 20 years, have shown a reduction in blood pressure, total cholesterol and smoking, a slight increase in body weight, and a stable incidence of diabetes<sup>73,74</sup>. On the other hand, in the same period, observations in different areas of Italy, including Sicily, have documented an increase in cholesterol and body weight<sup>75</sup>. These trends in single risk factors may have influenced the use of statins independently from the global risk of the patients.

It has previously been observed that statins are overused in individuals with low cardiovascular risk, whereas are underused in those at high risk<sup>76,77</sup>. The decision about treatment should follow the estimate of cardiovascular risk, so risk estimation is a crucial task for physicians. Despite the development of specific tools for risk assessment, their use in clinical practice is limited and the risk estimate for a single patient is usually made subjectively<sup>78</sup>. In our previous study of risk estimates made by primary care doctors from Stockholm and Sicily we found that the risk estimates tended to be inversely related to the average cardiovascular risk in the population<sup>26</sup>, and that Swedish doctor tended to underestimate high-risk patients<sup>79</sup>. Moreover, doctors in Stockholm were less likely to start lipid-lowering treatment even when their estimate of the risk was above the threshold at which guidelines recommend that pharmacological treatment should start<sup>26</sup>. In a separate study we found that treatment of hyperlipidaemia in Stockholm was initiated at higher levels of cholesterol than in Sicily<sup>80</sup>. These observations may have clinical implications, as patients at high coronary risk may be undertreated and at risk of cardiovascular morbidity, whereas low-risk patients may be unnecessarily treated, generating adverse effects and increasing costs. However, the linkage between the time trends in the present study and differences in doctors' risk estimates and willingness to prescribe statins is not wholly clear as we have no data on time trends in doctors' judgments.

There are some limitations to our study. Data on prescriptions of statin according to age, gender and socioeconomic status was not available for either region. Moreover, there are demographic differences between Stockholm, which is a large city, and Sicily, more rural. The farm labour force in Stockholm is 0.2% of population, compared to 8.5% in Sicily<sup>81</sup>. The corresponding values for Sweden and Italy (1.5% and 5.6%, respectively) indicate that both Stockholm and Sicily are only partially representative of the entire country. Some studies have shown higher prescription rates of statins in the elderly<sup>24</sup> and for women<sup>82</sup>. A socioeconomic gradient in the utilization of statins has also been observed<sup>22,23,83</sup>. Patients with higher income and educational level are more prone to start statin treatment compared to patients with lower income, especially in secondary prevention. A different distribution of these patients in the two regions we studied, might have affected the statins prescribing pattern.

Another possible weakness was the limited information on statin prescription according to indication, whether primary or secondary prevention, and on the level of cardiovascular risk in the areas of the study. Some national data show that in Italy the prevalence of statin utilization in primary prevention is double that of secondary prevention<sup>71</sup>, whereas in Sweden it is equally distributed<sup>84</sup>. A Danish study showed an increasing use of statin in asymptomatic individuals, and in patients with diabetes or peripheral atherosclerosis<sup>85</sup>. The relative contribution of the growth of treatment of these latter types of atherosclerotic

patients to the rise in statin prescribing in Stockholm and Sicily is not known.

## Conclusions

In the period 2001 to 2011, CHD mortality in Stockholm decreased more than in Sicily, whereas the rise in statin utilization was greater in Sicily. The greatest contribution to the statins increase was from simvastatin in Stockholm, whereas in Sicily more statins contributed. The inverse relation between CHD mortality which reflects the cardiovascular risk in the population, and statin utilization pattern in the two areas, may be partly explained by factors outside the global risk level of the patients, such as differences in adherence to treatment, the socioeconomic gradient between Stockholm and Sicily, different trends in single risk factors, and differences in doctors' coronary risk management in geographical areas with different population risk profiles.

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