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[1, 2]. 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[3-6].

Statins, the most used lipid-lowering agents, are associated with a decrease in CHD events and mortality in both primary and secondary prevention[7-11]. The use of statins has increased in most European countries, though with wide variations[12-14]. 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[15-18].

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[19, 20]. 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[21-24]. Comparisons between CHD death rates in different countries[25] and statin utilization in the year 2000[12], 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[26] 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

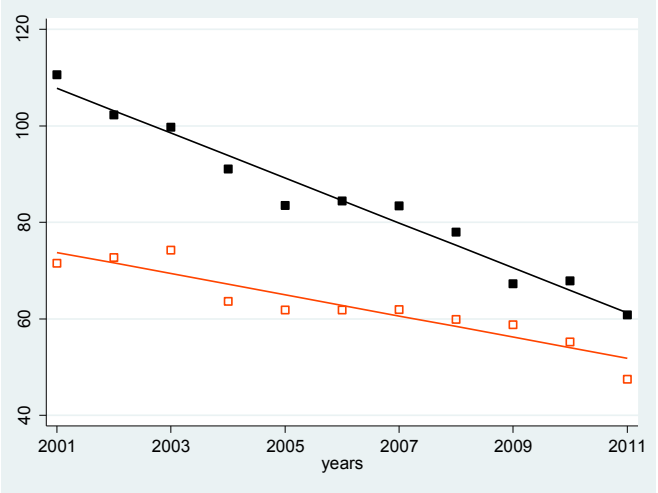

Figure 1: Changes in standardised CHD mortality rates/100.000 and estimated values from multiple regression model (lines) in Stockholm (black squares) and Sicily (empty squares).

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[27], 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[25], although in recent years the risk has decreased to low-moderate[28] and total cholesterol levels are now lower than in Italy[29]. Sicily is part of Italy, a country with lower CHD mortality[30]. 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[31-33].

We used data from The Swedish National Board of Health and Welfare (Socialstyrelsen)[34], a government agency in Sweden under the Ministry of Health and Social Affairs, and from Istituto Superiore di Sanità for CHD mortality in Sicily[35]. 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[36, 37] 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[38,39] and from the Sicilian Assessorato Regionale della Salute[40]. 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[41, 42]. 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).

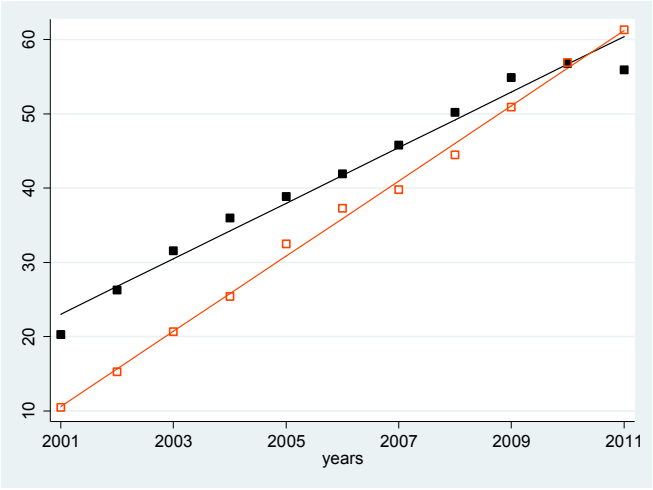

Figure 2: Changes in statin utilization, expressed as DDD/TID, and estimated values from multiple regression model (lines) in Stockholm (black squares) and Sicily (empty squares).

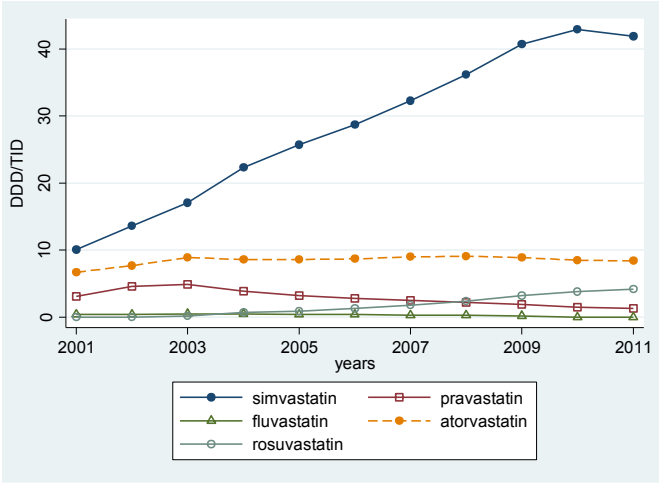

Figure 3A: Changes in utilization of different statins in Stockholm, expressed as DDD/TID.

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).

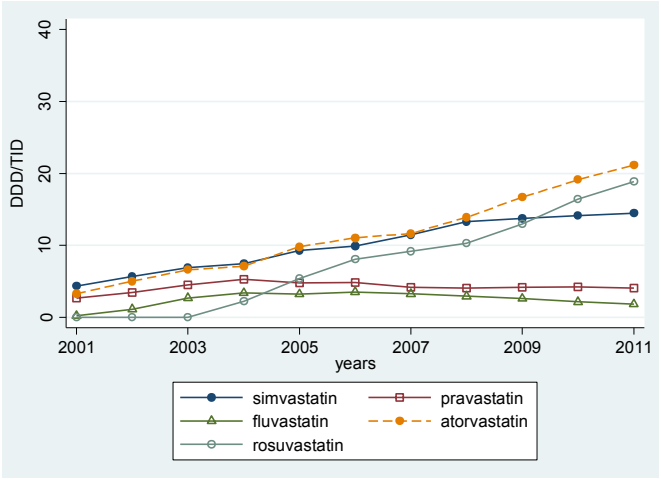

Figure 3B: Changes in utilization of different statins in Sicily, expressed as DDD/TID.

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[26]. 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[43], 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[44, 45]. 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[46, 47].

Moreover, statins cannot fully explain the reduction in CHD deaths observed in more recent years[48]. Clinical trials show that their contribution to absolute reduction of CHD mortality ranges from <1% to 3.5% in both primary and secondary prevention[49]. 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[12, 25]. 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[21, 50]. 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[51-53]. This may be partly explained by poor patient adherence to treatment. Discontinuation of statins is linked to increased risk of CHD events[54, 55], whereas higher adherence is associated with lower CHD mortality[56-58]. 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[58-61]. Moreover, It has been observed that poor adherence is associated with lower income status[62, 63]. 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)[64], 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[65]. 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[66, 67]. 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[60]. 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 ≥20%, according to the European guidelines[68], until 2003[69]. Reimbursement criteria were revised in 2004. The main change was the introduction of a new national scoring system[70]. This produced a slight decrease in statin use, since the absolute risk in the Italian population is lower than in the European population[71]. 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[13, 14]. This resulted in very low prices for generic simvastatin in Sweden, leading to substantially larger price differences between the different statins than in Italy[72].

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[73, 74]. 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[75]. 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[76, 77]. 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[78]. 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[26], and that Swedish doctor tended to underestimate high-risk patients[79]. 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[26]. In a separate study we found that treatment of hyperlipidaemia in Stockholm was initiated at higher levels of cholesterol than in Sicily[80]. 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[81]. 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[24] and for women[82]. A socioeconomic gradient in the utilization of statins has also been observed[22, 23, 83]. 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[71], whereas in Sweden it is equally distributed[84]. A Danish study showed an increasing use of statin in asymptomatic individuals, and in patients with diabetes or peripheral atherosclerosis[85]. 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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