Cost-effectiveness of optimizing prevention in patients with coronary heart disease: the EUROASPIRE III health economics project

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Aims
The EUROASPIRE III survey indicated that the guidelines on cardiovascular disease prevention are poorly implemented in patients with established coronary heart disease (CHD). The purpose of this health economic project was to assess the potential clinical effectiveness and cost-effectiveness of optimizing cardiovascular prevention in eight EUROASPIRE III countries (Belgium, Bulgaria, Croatia, Finland, France, Italy, Poland, and the UK).

Methods and results
The individual risk for subsequent cardiovascular events was estimated, based on published Framingham equations. Based on the EUROASPIRE III data, the type of suboptimal prevention, if any, was identified for each individual, and the effects of optimized tailored prevention (smoking cessation, diet and exercise, better management of elevated blood pressure and/or LDL-cholesterol) were estimated. Costs of prevention and savings of avoided events were based on country-specific data. A willingness to pay threshold of €30 000/quality-adjusted life year (QALY) was used. The robustness of the results was validated by sensitivity analyses. Overall, the cost-effectiveness analyses for the eight countries showed mainly favourable results with an average incremental cost-effectiveness ratio (ICER) of €12 484 per QALY. Only in the minority of patients at the lowest risk for recurrent events, intensifying preventive therapy seems not cost-effective. Also, the single impact of intensified cholesterol control seems less cost-effective, possibly because their initial 2-year risk was already fairly low, hence the room for improvement is rather limited.

Conclusion
These results underscore the societal value of optimizing prevention in most patients with established CHD, but also highlight the need for setting priorities towards patients more at risk and the need for more studies comparing intensified prevention with usual care in these patients.

Keywords
Cost-effectiveness • Secondary prevention • Coronary heart disease

Introduction
In 2008, >4.58 million people died in Europe due to cardiovascular diseases (CVD).1 CVD continues to be the main cause of morbidity and mortality, with >30% of life-years lost and nearly half of all deaths.2 Consequently, CVD adds significantly to the increasing healthcare costs. According to Leal et al, the economic burden of CVD in the EU amounts to €169 billion annually; 62% of these costs are healthcare-related. Per 1000 people, 2.4 working-years are lost due to mortality and 591 days are lost because of morbidity; representing a total EU cost (in 2003) of €24 384 million and €10 768 million, respectively. In addition, informal care of CVD patients was estimated to cost €29 050 million yearly.3

During the previous decades several guidelines on cardiovascular prevention have been published. The first Joint European...
guidelines on the prevention of CVD in clinical practice were published in 1994 with regular updates since.4–7

Within the European Society of Cardiology (ESC), secondary prevention was given the highest priority. Therefore, the ESC conducted three surveys (European Action on Secondary and Primary Prevention by Intervention to Reduce Events-EUROASPIRE) to ascertain whether the guidelines are being implemented in clinical practice.8–10 In the latest survey (EUROASPIRE III) many coronary patients still did not achieve the targets for CVD prevention, indicating that the integration of the guidelines in routine clinical care is still substandard. Hence there is considerable room for improvement to raise the standards of prevention in these patients through more effective lifestyle interventions, control of risk factors, and appropriate use of cardioprotective medication.8 Optimizing the management of these coronary heart disease (CHD) patients would decrease the occurrence of subsequent CVD events, hence increasing their quality of life and extend their survival. Many studies already reported on the cost-effectiveness of single prevention strategies.11–17 However, none conducted an integrated tailor-made cost-effectiveness analysis on secondary cardiovascular prevention targeting different intervention strategies simultaneously, adapted to the current prevention status of patients. This paper reports on the cost-effectiveness of such optimized prevention in cardiovascular patients in eight European countries, using the EUROASPIRE III data.

Methods

European cardiovascular disease prevention model

An individual-based state-transition model was designed to quantify the clinical and cost-effectiveness of optimizing secondary prevention. Opposed to common Markov models, based on a cohort with an average risk profile and average transition probabilities, the current model allows to simulate the health and economic outcomes of individual patients taking into account their individual characteristics and their prevention status. The model makes use of 6-month cycles and includes three disease states, two post-event states, and a death state, and was developed after exploring the literature (Figure 1).12,15 All EUROASPIRE III patients start in the initial state. The model predicts their likelihood to develop fatal and non-fatal CVD or to die from other causes. Every cycle, patients can suffer a coronary event, a stroke, or heart failure and move to the CHD state, CVD state, or congestive heart failure (CHF) state, respectively. Once in one of these subsequent event states, patients enter a post-event state after one cycle.

EUROASPIRE III survey

The design and the principal findings of the EUROASPIRE III survey have been reported extensively elsewhere.8 In brief, the study aimed to determine whether the joint European guidelines on CVD prevention are being implemented in CHD patients at that time.4 The survey was conducted in 22 European countries during 2006–07. Patients were aged 18–80 years and admitted to a hospital for an acute coronary event or a cardiac procedure [i.e. coronary artery bypass graft (CABG); percutaneous transluminal coronary angioplasty (PTCA), myocardial infarction (MI), or acute myocardial ischaemia]. EUROASPIRE patients from eight countries were included in our analysis (Bulgaria, Belgium, Croatia, Finland, France, Italy, Poland, and the UK). Depending on the country only 3–43% of patients are meeting all targets, i.e. achieving blood pressure (BP) target, cholesterol target, physical activity target, and smoking target. In total 2693 patients not on target on at least one of the risk factors were included in our study.

Base case risk and risk reductions

Performing a tailor-made analysis necessitates the calculation of individuals’ future cardiovascular risk. The Framingham risk prediction algorithms were used to calculate the different CVD outcomes since these allow risk estimation based on individual patient risk factors.18–20 However, evidence indicates that the Framingham risk calculators might overestimate CVD risk; in addition the Framingham population differs in characteristics from the EUROASPIRE population. Therefore, in order to use the Framingham risk calculators, calibration was applied based on mean CHD, stroke, and CHF risk figures available in the literature.21–24 If the figures in the literature differed from our calculated
risk, based on the mean of the individual patient calculations, then our individual patient calculations were multiplied with a correction factor in order to have the same overall risk figure as those reported in a typical European CHD population.

Optimizing prevention

Optimizing prevention was based on the 2003 joint European guidelines. In those patients not on target, several strategies were theoretically applied in order to improve their risk factors and consequently their cardiovascular risk. Hence their future risk was calculated assuming optimized risk target treatment.

About 17% of the patients included in our analyses were smokers. Optimal smoking cessation was installed through counselling and pharmacotherapy [varenicline or nicotine replacement therapy (NRT)].

Fifty-two per cent of the patients had a total cholesterol not on target. Simvastatin 20 mg per day was initiated in patients with an elevated total cholesterol of ≥4.5 mmol/L and not yet receiving cholesterol treatment. It was assumed that in those ≤6% above target it was an issue of improving compliance. In patients with a cholesterol level between 6 and 12% above target, the statin dose was doubled if possible and atorvastatine 40 mg/day was given if patients were already on the maximum dose of a weaker statin (type fluvastatin, lovastatin, pravastatin, or simvastatin). Ezetimibe was added in patients already on a maximum dose of a strong statin (type atorvastatin or rosuvastatin). This was based on the literature indicating a 6% additional fall in the risk factor level by doubling the dose.

An elevated BP was found in 60% of patients. Those with a raised BP (BP > 140/90 mmHg and BP > 130/80 mmHg for CHD patients without diabetes, and with diabetes, respectively) and not yet on treatment were placed on one inexpensive antihypertensive drug (e.g. beta-blocker or diuretic). For those with a slightly increased BP (BP > 140/90 and <150/95 mmHg for non-diabetics and BP > 130/80 and <140/90 mmHg for diabetics), but already on treatment, a compliance problem was assumed. When the BP exceeded 150/95 and 140/90 mmHg, respectively, in non-diabetics and diabetics already on treatment, a combination therapy was installed with a maximum of four different BP-lowering drugs.

Regarding physical activity a lifestyle intervention was implemented in 77% of patients because they were not regularly physically active.

Calculation of the risk reduction

Optimizing the preventive actions in coronary patients leads to a reduction in cardiovascular events. Relative risks (RRs) related with these preventive actions were gathered from meta-analyses or large clinical trials (Table 1). Note that the risk reduction associated with smoking cessation was based on the effect of the smoking cessation therapy, accounting for the willingness to quit and the yearly relapse rate.

These RRs indicate the effect of targeting one risk factor; however, in reality many patients have multiple risk factors not on target. Within our cohort, 41.3% of patients included in the analyses had two risk factors, 26.2% had three risk factors and 4.2% had all four risk factors not on target. Optimizing prevention implies addressing these risk factors simultaneously. Adding up the individual risk reduction would result in an overestimation of the total risk reduction, therefore, when multiple interventions are initiated a correction was made: 1 − (1 − RR1 × RR2) × 0.8. The equation was formulated by comparing the effect of controlling multiple risk factors simultaneously vs. controlling individual risk factors separately.

Country, age, and gender-specific general mortality probabilities were derived from WHO data. Cardiovascular mortality rates were based on data published by Vaartjes et al.

Cost of optimized prevention

Optimizing prevention involves additional country-specific treatment costs for the health-care sector (Table 2). For smoking cessation, the cost of a 12 week drug treatment was considered, supplemented with the cost of two cardiologist visits and three motivational support visits. Regarding cholesterol and BP treatment daily medication and two yearly cardiologist visits were accounted for. These visits were assumed to increase adherence with the treatment. The lifestyle intervention to increase physical activity included individual sessions, group sessions, and a fitness programme.

Cost of avoided events

Effective prevention should lead to a decrease in the number of cardiovascular events and therefore the health-care costs associated with these events will decrease. Country-specific data were gathered by the national coordinators to estimate these costs (Table 3).

Quality of life

The main outcome is expressed as quality-adjusted life years (QALYs). QALYs combine the quantity and quality of life, whereby the latter is represented by a utility value varying between 0 (death) and 1 (perfect health). To calculate the total QALYs associated with a given condition, the utility value is multiplied with the expected number of life years spent in that condition.

The EUROASPIRE III database contains utility values for each patient during his initial disease state. A subsequent coronary event was assigned a penalty value of 0.0578 for the remainder of the model.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Relative risks associated with different interventions to optimize prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>CHD</td>
</tr>
<tr>
<td>Smoking cessation</td>
<td>0.68 (0.57–0.82) 12</td>
</tr>
<tr>
<td>Cholesterol-lowering medication</td>
<td><strong>Standard vs. no therapy</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Intensive vs. no therapy</strong></td>
</tr>
<tr>
<td>Blood pressure-lowering medication</td>
<td><strong>Standard vs. no therapy</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Intensive vs. no therapy</strong></td>
</tr>
<tr>
<td>Physical activity</td>
<td>0.62 (0.44–0.87) 36</td>
</tr>
</tbody>
</table>
whereas stroke and CHF are appointed the penalty value 0.2743 and 0.1372, respectively.39,40

Cost-effectiveness

An incremental cost-effectiveness ratio (ICER) defined as the ratio between the net total costs and the net effects expressed in QALYs was calculated:

$$\frac{\text{Cost}_{\text{optimized prevention}} - \text{Cost}_{\text{current prevention}}}{\text{Effectiveness}_{\text{optimized prevention}} - \text{Effectiveness}_{\text{current prevention}}}.$$ 

Sensitivity analyses

Health economic modelling entails uncertainty around the input parameters, therefore sensitivity analyses were performed. Each input parameter is assumed to vary within a range of possible values defined by their probability distribution, based on standard error estimates from the literature (if not available a ±30% range was used). Moreover, different scenario’s were tested such as the use of NRT vs. varenicline, Framingham calibration vs. no calibration and applying an adjustment when combining the individual risk reduction vs. no adjustment. In addition, a cost-effectiveness acceptability curve estimating the probability that the results are cost-effective at different willingness to pay thresholds was calculated.

Results

Base case scenario

Assuming a 10-year time horizon, a time period often used in CVD prediction, analyses revealed a higher QALY increase of ~0.25 compared with the current situation; corresponding with three additional months in perfect health. Likewise optimizing prevention is associated with a mean cost increase of €2493 per patient, resulting in an overall cost-effectiveness ratio of ~12 484/E/QALY (Figure 2). These results differ between countries with lower ratios for Bulgaria (€7029/QALY), Poland (€7161/QALY), Croatia (€8406/QALY) and higher ratios for Finland (€11 660/QALY), Italy (€14 627/QALY), France (€16 939/QALY), Belgium (€19 862/QALY), and the UK (€23 491/QALY) (Table 4).
Result according to risk profile

As shown in Figure 3, a better cost-effectiveness is more likely to occur in patients with a higher cardiovascular risk. Patients with a 2-year risk estimation <5% have a mean ICER of €24,862/QALY, whereas the ICER of patients with a 2-year risk between 5 and 10% equals €12,630/QALY. Those with a 2-year risk exceeding 10% have a mean ICER of €7,844/QALY.

Several factors contribute to this relationship. The mean ICER improves with increasing age varying from €26,816/QALY for those <50 years old to €87,630/QALY for those >65 years of age. The ICER is the highest in those patients with a single cholesterol problem (ICER = 26,069€/QALY) and the lowest in those only in need for BP treatment (ICER = 9108€/QALY). Subanalyses reveal a low gain in QALY in smokers and high-cholesterol patients (0.024 and 0.071 QALY, respectively). On the contrary, the physical activity and BP-lowering interventions are associated with a high incremental effect (0.22 and 0.13 QALY, respectively). Similar but more moderate results were found for patients with more risk factors not on target (Table 5).

Sensitivity analyses

The results of the sensitivity analyses are presented in a Tornado diagram (Figure 4). The cost-effectiveness result was mainly sensitive to changes in the Framingham risk calibration, changes in the risk reduction following cholesterol-lowering therapy and changes in utility values. In addition, the methodology for calculating the total risk reduction, the costs related to cholesterol-lowering and BP-lowering treatment and the changes in the risk reduction following BP-lowering therapy and smoking cessation were of importance.

The cost-effectiveness acceptability curve clearly shows a higher cost-effectiveness probability at a lower threshold for Bulgaria, Croatia, and Poland, compared with the other countries (Figure 5). At a threshold of €30,000/QALY, optimizing prevention in the UK and Belgium have the lowest probability of being cost-effective (~80%).

Discussion

The EUROASPIRE III survey has shown a considerable potential to improve preventive strategies in order to achieve risk factor targets. The current study evaluates the cost-effectiveness of optimizing tailor-made cardiovascular prevention in coronary patients. Overall, we found that optimizing secondary prevention is cost-effective compared with the current degree of cardiovascular prevention with an ICER of 12,484€/QALY. A willingness to pay threshold of 30,000€/QALY is commonly used. For Poland, Bulgaria and Croatia a lower threshold should be applied based on their gross domestic product (GDP). Incremental cost-effectiveness ratios below the willingness to pay threshold are called cost-effective because the effectiveness of the intervention exceeds that of the current situation, however, at an additional cost.

Results differed considerably between countries ranging from €7,029/QALY to €23,491/QALY and were mainly driven by the
country-specific costs. These results are consistent with the GDP of the eight countries with Bulgaria, Poland, and Croatia having a GDP of €10 700, €15 300, and €14 800 per capita, respectively, whereas Belgium, Finland, France, Italy, and the UK have a GDP between €24 000 and €30 000 per capita. To our knowledge this is the first cost-effectiveness analysis on optimized, integrated, and tailor-made prevention. In the past, several studies have been published focusing on single (risk) factors and comparing prevention vs. no prevention. A recent study investigated the cost-effectiveness of a smoking cessation programme based on varenicline in smokers with CVD. Promising results were found with ICERs ranging between €5151 and €6120 per QALY gained. A recent paper, based on the treating to new targets study investigating the cost-effectiveness of 80 mg atorvastatin vs. 10 mg atorvastatin found ratios of €9500, €21 000, and €15 000 per QALY for UK, Spain, and Italy, respectively. Likewise, Soini et al. evaluated the cost-effectiveness of atorvastatin (20 mg), rosuvastatin (10 mg), simvastatin (40 mg) and the combination of simvastatin (40 mg) with ezetimibe (10 mg) as secondary prevention strategy, reporting analogous results. Lindgren et al. reported on the cost-effectiveness of high dose atorvastatin compared with regular dose simvastatin based on the results from the IDEAL trial. The predicted ICER ranged between €25 210 and €62 639. Regarding antiplatelet medication an ICER of $36 343/QALY was found for clopidogrel plus aspirin vs. aspirin alone. A comprehensive review by Heeg et al., including 21 studies, reported that aspirin dominates placebo in secondary prevention as it has both a greater effectiveness and a lower cost. A Canadian study examined the cost-effectiveness of exercise training for the secondary prevention of CVD and reported ICERs around $15 000 per life year saved. Subanalyses of our results revealed a better cost-effectiveness probability in higher risk patients, because of their larger room for improvement due to more potentially preventable events. Hence a greater absolute risk reduction can be established with similar intervention investments. Optimizing prevention seems particular cost-effective in elderly patients, and in those patients with a high BP or patients not physically active. Previous studies came to similar conclusions indicating the patients' level of risk being inversely correlated with the cost-effectiveness ratio.

Some assumptions and limitations of the study should be accounted for when interpreting the results. First, the Markov model includes only three CVD states whereby each subsequent event can only occur once per patient, potentially leading to an underestimation of the costs and an overestimation of QALY’s both for optimized and current prevention, therefore in reality, optimizing prevention might be associated with a greater health gain. Furthermore, potential savings not related to CVD events were not considered. Secondly, our study used Framingham risk equations to estimate the subsequent CHD risk, stroke risk, and heart failure risk. However, the Framingham population has other characteristics than the EUROASPIRE population.

Table 5 Results according to subgroup classification

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients &lt;50 years old</td>
<td>€26 816/QALY</td>
</tr>
<tr>
<td>Patients &lt;60 years old</td>
<td>€17 996/QALY</td>
</tr>
<tr>
<td>Patients &lt;65 years old</td>
<td>€15 692/QALY</td>
</tr>
<tr>
<td>Patients &gt;65 years old</td>
<td>€8 786/QALY</td>
</tr>
<tr>
<td>One risk factor not on target</td>
<td>€12 732/QALY</td>
</tr>
<tr>
<td>Two risk factors not on target</td>
<td>€11 856/QALY</td>
</tr>
<tr>
<td>Three risk factors not on target</td>
<td>€12 846/QALY</td>
</tr>
<tr>
<td>Four risk factors not on target</td>
<td>€14 616/QALY</td>
</tr>
<tr>
<td>Single risk factor: cholesterol elevated</td>
<td>€26 069/QALY</td>
</tr>
<tr>
<td>Single risk factor: smoking</td>
<td>€14 681/QALY</td>
</tr>
<tr>
<td>Single risk factor: blood pressure elevated</td>
<td>€9 108/QALY</td>
</tr>
<tr>
<td>Single risk factor: physical inactivity</td>
<td>€10 533/QALY</td>
</tr>
<tr>
<td>Multiple risk factors: cholesterol among others</td>
<td>€14 796/QALY</td>
</tr>
<tr>
<td>Multiple risk factors: smoking among others</td>
<td>€15 233/QALY</td>
</tr>
<tr>
<td>Multiple risk factors: blood pressure among others</td>
<td>€11 069/QALY</td>
</tr>
<tr>
<td>Multiple risk factors: physical inactivity among others</td>
<td>€11 743/QALY</td>
</tr>
</tbody>
</table>

Figure 3 Cost-effectiveness results in function of the risk status.
Furthermore, the data are from an era with little or no revascularization and with available medicines very different from nowadays. However, since no other equation exists to estimate CHD, stroke, and CHF risk, based on a similar population, and using the risk factors collected during the EUROASPIRE III survey, it was the only option. In order to account for the above-mentioned shortcomings, a calibration was applied. Furthermore, with the exception of ageing of patients, typical changes in individuals’ risk factors due to time progression were not accounted for. In addition, average European age-specific regional mortality figures where used, despite the differences in the cardiovascular death rate throughout Europe.45 Thirdly, assumptions were made with regard to optimizing treatment. For risk factors close to target a compliance problem was assumed which could be resolved by increasing the number of cardiologist visits. For risk factors with values further away from target, optimized prevention consisted of a dose increase or the addition of a supplementary drug. Fourthly, some assumptions were made regarding the risk reductions. For those strategies for which no RR was available an extrapolation was conducted. To estimate the risk reduction associated with a combination of preventive actions individual risk reduction cannot simply be added or multiplied, since this would induce an overestimation of the total health gain. Therefore a formula was calculated taking into account a correction factor which was estimated from existing literature.36,46,47 In addition, no age-related difference in the risk reductions was applied. It might be, however, that older patients, for example, benefit less from a physical activity intervention than younger patients.14 Furthermore, losses in the quality of life inherent to the intervention, for example the patients’ perspective of losing the quality of life due to the fact that he is not allowed to smoke anymore, or due to statin side effects, were not accounted for. Finally, cost data were provided by local coordinators, hence although several attempts made to minimize heterogeneity between data input, there is no complete certainty on consistency between countries.

![Figure 4](https://academic.oup.com/eurheartj/article-abstract/33/22/2865/531058) Tornado diagram based on uncertainty around input parameters.

![Figure 5](https://academic.oup.com/eurheartj/article-abstract/33/22/2865/531058) The cost-effectiveness acceptability curve for each individual country indicates the probability that the intervention is cost-effective given a range of willingness to pay thresholds.
In conclusion, this tailor-made model on integrated secondary prevention in Europe is to our knowledge the first attempt to assess the cost-effectiveness of optimized tailor made and integrated prevention. Overall, optimizing prevention is cost-effective based on the EUROASPIRE III data. The best results are found in elderly and in patients with a high BP or in patients not physically active. Introducing preventive treatment actions in CHD patients should be based on their individual risk level since this is a key driver for cost-effectiveness.

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References


