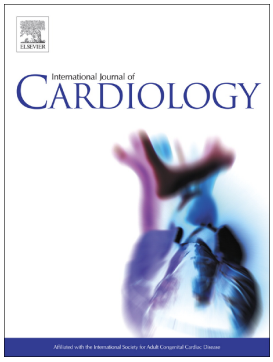
Cost-effectiveness of optimized adherence to prevention guidelines in European patients with coronary heart disease: Results from the EUROASPIRE IV survey



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TITLE PAGE

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Conflict of interest

Delphine De Smedt, Lieven Annemans, Guy De Backer, David Wood, Jan Bruthans, Renata Cifkova, Johan De Sutter, Marina Dolzhenko, Andrejs Erglis, Nina Gotcheva, Aleksandras Laucevicius, Dragan Lovic, Rafael Oganov, Nana Pogosova, Žjelko Reiner, Martin Stagmo, Dirk De Bacquer have nothing to declare

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Keywords

Secondary prevention; guidelines; cost-effectiveness; coronary heart disease; EUROASPIRE

ABSTRACT

Background: This study aims to assess the cost-effectiveness of optimized guideline adherence in patients with a history of coronary heart disease.

Methods: An individual-based decision tree model was developed using the SMART risk score tool which estimates the 10-year risk for recurrent vascular events in patients with manifest CVD. Analyses were based on the EUROASPIRE IV survey. Outcomes were expressed as an incremental cost-effectiveness ratio (ICER).

Results: Data from 4,663 patients from 13 European countries were included in the analyses. The mean estimated 10-year risk for a recurrent vascular event decreased from 20.13% to 18.61% after optimized guideline adherence. Overall, an ICER of 52,968€/QALY was calculated. The ICER lowered to 29,093€/QALY when only considering high-risk patients (≥20%) with decreasing ICERs in higher risk patients. Also, a dose-response relationship was seen with lower ICERs in older patients and in those patients with higher risk reductions. A less stringent LDL target (<2.5mmol/L vs. <1.8mmol/L) lowered the ICER to 32,591€/QALY and intensifying cholesterol treatment in high-risk patients (≥20%) instead of high-cholesterol patients lowered the ICER to 28,064€/QALY. An alternative method, applying risk reductions to the CVD events instead of applying risk reductions to the risk factors lowered the ICER to 31,509€/QALY.

Conclusion: Depending on the method used better or worse ICERs were found. In addition, optimized guidelines adherence is more cost-effective in older patients, in higher risk patients, in patients with higher risk reductions and when using a less conservative LDL-C target. Current analyses advice to maximize guidelines adherence in particular patient subgroups.

INTRODUCTION

The WHO health assembly adopted a resolution with a focus on active ageing, by encouraging active participation in the society, by increasing healthy ageing and by promoting high standards of health and well-being [1]. Despite declines in CVD mortality rates since the 1980's, CVD remains the most important cause of death globally as well as across Europe, with 40% of men and 49% of women dying from the illness. Overall, about 44% of the CVD deaths is due to coronary heart disease (CHD) with substantial differences between different European countries. Although CVD is more frequent in older persons, premature CVD mortality is a major problem, responsible for a third of deaths before the age of 65. The risk is especially high in patients with a history of CVD [2]. In Europe, about a quarter of all disability adjusted life years (DALYs) are caused by CVD [3].

Based on the most recent available scientific evidence, the European Society of Cardiology (ESC) regularly updates the European guidelines on cardiovascular disease prevention in clinical practice [4]. By setting risk factor goals and target levels, as well as proposing the appropriate treatment options, physicians are guided in patient treatment. In order to assess whether these guidelines are being implemented, the EUROASPIRE (European Action on Secondary Prevention through Intervention to Reduce Events) surveys were initiated in very high risk patients, with a history of CHD. Results from these cross-sectional surveys reveal a high prevalence of risk factors and inadequate risk factor control with a substantial room for improvement in CHD patients [5]. Although blood pressure and cholesterol levels decreased over time, the obesity and central obesity prevalence and the number of patients with diabetes increased [6]. There remains thus a considerable potential throughout Europe for secondary cardiovascular disease prevention.

In order for policy makers to make adequate and transparent decisions on their policy goals and whether or not to invest, they should rely on the best available evidence. In addition to the effectiveness of interventions, cost-effectiveness results are considered in their decision making process.

The aim of this study was to assess the cost-effectiveness of optimized adherence to the guidelines on CVD prevention in patients with a history of CHD. Optimized guideline adherence in order to prevent or delay cardiovascular disease is compared with the actual observed risk factor management based on individual patient data.

METHODS

Optimized adherence to the guidelines is defined as a combined strategy of tackling all uncontrolled modifiable risk factors at once, with the ultimate goal to approach the risk factor targets as defined in the guidelines. Data from the latest available EUROASPIRE IV survey were used as basis for current care.

Two strategies were explored. First the cost-effectiveness of optimized (achievable by treatment intensification) adherence to the guidelines was assessed. Within this analysis, optimized adherence to the guidelines (intervention group) was compared with current care (control group). Results are calculated as an incremental cost-effectiveness ratio (ICER), representing the differences in costs between the intervention and control group divided by the differences in health effects between both groups. Health effects are expressed as quality adjusted life years (QALY), combining both the quality of life (expressed as utility values between 0 and 1) and quantity of life. Whether or not optimized adherence will be considered cost-effective, depends on the willingness of a society to pay for one additional QALY, and varies across geographical areas. The WHO promotes the use of the per capita gross domestic product to define the ICER threshold [7]. An intervention that costs less than three times the national annual GDP per capita per QALY is considered cost–effective, whereas an intervention with an incremental cost less than once the national annual GDP per capita per QALY is considered highly

cost–effective. However, recently, the WHO nuanced this approach and indicated that other factors such as budget impact also play a role in societal willingness to pay for health interventions [8]. In reality different thresholds are used depending on the particular health care system. Some countries do not apply a strict threshold, others use a flexible threshold depending on the health loss, the number of affected persons and the available resources [8].

$$ICER = \frac{cost\ I - cost\ C}{QALY\ I - QALY\ C}$$

I= intervention group

C= control group

Secondly, a theoretical approach is applied taking a reverse point of view by answering the question: *"What may ideal prevention cost in order to be cost-effective?"*. The model used is identical to the model in the first scenario. However instead of implementing additional interventions in order to achieve the targets, accounting for the uncertainty of success associated with treatment (e.g. smoking cessation therapy effect), all risk factors 'above target' were changed to be 'on target'. This results in a decrease in fatal and non-fatal CVD events which leads to an increase in QALYs. Consequently, the maximum allowed intervention cost can be calculated based on the above formula taking into account a flexible willingness to pay threshold.

Model

An individual-based decision tree model was developed in order to model the cardiovascular events of individual patients, as well as the associated health-related quality of life and the associated costs. A 10-year time horizon is applied. The decision tree comprises four outcomes: no additional CVD event, or an additional CVD event divided in non-fatal myocardial infarction, non-fatal stroke or a fatal CVD event (see figure 1).

Risk calculator

The individual risk for a subsequent vascular event, is derived from the SMART (Secondary Manifestations of ARTerial disease) risk calculator. SMART was developed using a database from the University Medical Centre Utrecht in the Netherlands, including 5788 patients (mean age 60 years old) referred with various clinical manifestations of arterial disease between January 1996 and February 2010. About 788 recurrent vascular events were observed [9]. The tool was validated in three external populations (9447 patients with coronary artery disease From the TNT and IDEAL trials; 2366 patients with cardiovascular disease from the SPARCL trial and 6623 patients with peripheral artery disease from the CAPRIE trial) [10]. The SMART risk calculator includes the following predictors: age, gender, current smoking, systolic blood pressure, diabetes, history of coronary artery disease (CAD), history of cerebrovascular disease (CVD), history of abdominal aortic aneurysm (AAA), history of peripheral artery disease (PAD), years since first diagnosis of vascular disease, HDL cholesterol, total cholesterol, eGRF, hsCRP. For those variables that were not collected during EUROASPIRE, SMART values were used. The mean EUROASPIRE value was imputed for those patients with missing values.

$$\textit{SMART risk score} = 10 - year\ cardiovascular\ disease\ risk\ (\%) = \left(1 - 0.81066^{\exp[A+2.099]}\right) * 100\%$$

$$\begin{aligned} A = {} & -0.0850 * age + 0.00105 * age^2 + 0.156\,[if\ male] + 0.262[if\ current\ smoker] + 0.00429 \\ & * SBP + 0.223\,[if\ diabetic] + 0.140[if\ CAD] + 0.406\,[if\ CVD] + 0.558[if\ AAA] \\ & + 0.283[if\ PAD] + 0.0229 * years\ since\ first\ diagnosis\ of\ vascular\ disease \\ & - 0.426 * HDLcholesterol + 0.0959 * total\ cholesterol - 0.0532 * eGFR \\ & + 0.000306 * eGFR^2 + 0.139 * \log hsCRP \end{aligned}$$

SMART provides a 10-year risk for CVD, combining fatal as well as non-fatal events. Vascular disease as predicted by the SMART tool was divided over non-fatal myocardial infarction (40%), non-fatal stroke (31.6%) and fatal cardiovascular event (28.4%) using the short term follow up of the EUROASPIRE IV population.

EUROASPIRE sample

The patient information from the EUROASPIRE IV sample serves as input for the model. EUROASPIRE IV is a cross-sectional study undertaken at 78 centres across 24 European countries. A total of 7,998 patients (≤80 years), hospitalised for a coronary artery bypass graft, percutaneous coronary intervention or an acute coronary syndrome were examined and interviewed about their risk factor behaviour between 6 months and 3 years after their hospitalisation. Information on smoking status, physical activity, waist, blood pressure, cholesterol, diabetes, medication intake, and self-reported health status is collected. Cost data was provided by 13 countries (Belgium, Bulgaria, Croatia, Czech Republic, France, Latvia, Lithuania, Poland, Russia, Serbia, Sweden, Ukraine and United Kingdom with risk factor information on 4,663 patients). Table 1 provides an overview of the mean patient characteristics from the individuals included in the analyses.

Cost data

In order to calculate costs, both the cost of events as well as the cost of guideline implementation were accounted for. Country specific cost data were provided by the national coordinators. The cost of CVD events and preventive treatment was based on the available information in each country and was applied both to the intervention group and the current care group. An overview of country-specific costs is given in appendix 1.

HRQL data

Patient-specific utility data obtained from EQ-5D measurements was available in the EUROASPIRE IV survey. Suffering from an additional coronary or cerebrovascular event was associated with a further loss in HRQL, represented by a utility penalty (CHD-state: - 0.0578; Stroke-state: -0.2743) [11].

Risk factor targets & preventive strategies

The recently published 2016 European guidelines on cardiovascular disease prevention are used to set the targets [4]. The current study focuses on blood pressure, cholesterol and smoking status. In a base case scenario, the best available treatment strategy is simulated in those patients not on target on one or more risk factors.

Effect

The effect of the incorporated strategies on patients' individual risk factor values was gathered from the available scientific literature. A smoking cessation effect of 13% was assumed, accounting for the intention to quit smoking [12, 13]. Depending on the initial blood pressure level an absolute systolic blood pressure reduction between 8.7 and 29.0 mmHg and an absolute diastolic blood pressure reduction between 5.3 and 17.1 mmHg was modelled (see appendix 2) [14]. Likewise, a relative reduction between 4% and 43% for LDL-cholesterol was modelled depending on the initial level and the additional drug therapy offered (see appendix 2) [15]. Each doubling of the dose was associated with approximately 6% additional reduction in LDL cholesterol [16]. Adding ezetimibe to the treatment scheme was associated with an additional 24% reduction in LDL cholesterol [17].

Sensitivity & scenario analyses

In addition to a base case scenario, sensitivity analyses were performed to assess the robustness of the results. Deterministic one way sensitivity analyses were used to model the impact of varying one parameter within its range of uncertainty (+/- 30% range was assumed). Likewise, scenario analyses were

performed, in order to determine the outcome in certain subgroups, using different targets, or other treatment options.

The following scenarios were defined:

- Stratification by baseline CVD risk (10-year SMART score ≥10%, ≥20%, ≥30%, ≥40%)
- Stratification according to age class (<50 years, 50-59 years, 60-69 years, ≥70 years)
- Inclusion of patient in the analyses according to achieved risk reduction (risk reduction ≥0.5%, ≥1%, ≥2%, ≥3%, ≥4%)
- Using a less stringent LDL target (LDL target <2.5 mmol/ and <2 mmol/L versus <1.8 mmol/L)
- Intensifying statin therapy in high risk patients rather than in patients with high cholesterol levels (10-year SMART score ≥10%, ≥20%, ≥30%, ≥40%) [16]
- Adapting the high cholesterol treatment strategy according to the treatment stratification logic by Cannon et al (2017) [18]. If not on target and not on a statin, atorvastatin 20 mg/day was given. If already on a low intensity statin and not on target, statin therapy was up-titrated to atorvastatin 80mg/day. If already on a high intensity statin and not on target, ezetimibe was added to the treatment scheme
- Remove the ezetimibe option from the intensified treatment scheme
- Including compliance rates in medication intake (compliance of 79% for BP lowering medication and compliance of 93% for statins [19])
- SMART reducible risk estimation method applying relative risk reductions to the risk factors rather than recalculating the SMART risk with new risk factor values [10]
- Country in-country out analyses, where each country is excluded from the overall results one by one to assess the impact

RESULTS

Data from 4,663 EUROASPIRE IV patients were included. The mean estimated 10 year risk for a recurrent vascular event was 20.13% (risk distribution see appendix 3). Initiating optimized guideline adherence results in a mean ten year risk of 18.61%. The average baseline risk increased with age (<50 years: 10.11%; 50-59 years: 11.96%; 60-69 years: 17.88%; >70 years: 31.92%). Overall, for 554 patients no additional health gain was demonstrated according to the SMART calculator. For the others a 10-year absolute risk reduction of 1.73% was calculated, ranging between 0.001% to 17.03%.

Base case ICER

Assuming a 10-year time horizon, optimized adherence to the guidelines could result in an average QALY gain of 0.043. The additional cost associated with optimized adherences amounts to 2,269€ (an increase of 2,390€ due to intervention cost and decrease of 121€ due to avoided disease), resulting in an overall ICER of 52,968€/QALY. These results differ between countries and are shown in appendix 4b-6.

In a minority of patients (274 patients) a decrease in costs (average Δ cost= -233€) and an increase in QALYs (average Δ QALY= 0.053) was seen, resulting in a dominant outcome. Their mean 10-year risk reduction amounted to 1.88%. Likewise, 881 patients had an ICER<10,000€/QALY and an average 10-year risk reduction of 2.47%; 1331 patients had an ICER<20,000€/QALY and an average 10-year risk reduction of 2.37%; 1645 patients had an ICER <30,000€/QALY and an average 10-year risk reduction of 2.34%; 1883 patients had and ICER <40,000€/QALY and an average 10-year risk reduction of 2.32%; 2091 patients had an ICER <50,000€/QALY and an average 10-year risk reduction of 2.28%; 2268 patients had an ICER <60,000€/QALY and an average 10-year risk reduction of 2.25%; 2433 patients had an ICER <70,000€/QALY and an average 10-year risk reduction of 2.21%; 2559 patients had an ICER <80,000€/QALY and an average 10-year risk reduction of 2.19%; 2675 patients had an ICER <70,000€/QALY and an average 10-year risk reduction of 2.16%, and 2780 patients had an ICER

<100,000€/QALY and an average 10-year risk reduction of 2.14%. Finally, 1329 patients had an ICER ≥ 100,000€/QALY and a 10 year risk reduction of 0.88% (see appendix 4a).

Scenario analyses

In addition to the base case scenario, scenario analyses were performed (table 3).

One-way sensitivity analyses

In order to assess the robustness of the model one way sensitivity analyses were performed. Results show the effect of varying the disease and medication costs, as well as the utility-penalties and the risk reduction associated with treatment (appendix 7). In addition, country-in/country-out analyses (appendix 8) were performed to assess the impact of country-specific data in the overall outcome.

Maximal achievable gain

Applying the model from a theoretical point of view, gives an answer on the maximal achievable health gain and the maximum allowed intervention cost in order to be cost-effective. Having all the risk factors on target (risk factors included in the SMART risk calculator) in those patients not yet on target, results in a mean 10-year risk of 17.85%. Hence the theoretical absolute risk reduction amounts to 2.28%. In theory, bringing everyone on target can result in a potential QALY gain of 0.0640 QALY per patient over a 10-year period. Assuming a maximum willingness to pay threshold of 40,000€/QALY and taking into account the decreased disease costs, the average intervention cost per person may be as high as 2,742€ per patient over a 10-year period.

Cost-effectiveness acceptability curve

The cost-effectiveness acceptability curve (appendix 9) showS the probability that guidelines adherence is cost-effective given different willingness to pay thresholds.

DISCUSSION

According to the EUROASPIRE IV survey, one in six stable CHD patients were smokers, three out of five patients were not adequately active, one in four had diabetes, two out of five had an elevated blood pressure and four out of five had an elevated LDL-cholesterol. Hence, there remains a substantial room for improvement. Initiating optimized adherence to the guidelines on cardiovascular prevention results in an average absolute risk reduction for a new CVD event of 1.14% per patient over a 10-year period. Overall, the mean base case ICER amounted to 52,968€/QALY.

Subgroup analyses revealed better outcomes in particular patients groups. To start, the baseline CVD risk (baseline risk ≥20%), as well as the achievable risk reduction (risk reduction ≥1%) are good indicators of cost-effectiveness. Also, older age seems to be associated with better ICERs because of the larger risk reduction that can be achieved. Important to note however, is that this result is subject to the time horizon and hard endpoints included. A wider time horizon, and the inclusion of non CVD related endpoints are likely to favour the younger patients. Furthermore, the use of a less stringent LDL target had a favourable impact on the ICER. Since the aim was to assess the impact of optimized prevention according to the guidelines the 1.8 mmol/L target was used in the base case analyses. However in order to account for the discussion on the preferred LDL target in CHD patients we performed sensitivity analyses with <2 mmol/L and <2.5 mmol/L as target [20-22]. Whereas the meta-analysis of Silverman et al. (2016) concluded that lower LDL values are associated with lower coronary event rates, according to Leibowitz et al (2016) and Hagiwara et al (2017) no additional health benefit was gained by lowering the LDL target <1.8 mmol/L [20-22].

Likewise, statin treatment according to baseline CVD risk instead of treating all patients not on cholesterol target as well as omitting the (at the time of study analysis) rather expensive Ezetimibe (cost will decrease due to off-patent) from the treatment scheme had also a positive impact on the ICER.

Furthermore, although the recalculation method (recalculating the SMART score with new risk factor values) was used to calculate the base case ICER, one could discuss to apply relative risk reduction, drawn from clinical trials and meta-analyses instead. Based on the latter the average risk reduction further increased to 2.48%, resulting in an ICER of 31,509€/QALY. This partly explains the difference observed with our previous cost-effectiveness study based on EUROASPIRE III data (12,484€/QALY) [23]. Applying the EUROASPIRE III model strategy (similar risk factor targets) to the EUROASPIRE IV dataset results in an ICER of 19,660€/QALY. This is in line with the results from the EUROASPIRE III health economic analyses [23]. The residual difference can be explained by the use of a different risk calculator and the difference in included health states.

The current study is unique since it estimates the potential effect of a holistic treatment following the guidelines. Until recently, most studies had a focus on a single intervention. More recently several cost-effectiveness studies included a more holistic approach of cardiovascular prevention. Chew et al (2010) investigated the cost-effectiveness of a secondary prevention program, including optimisation of pharmacotherapy and lifestyle modification, assuming a 15% reduction in deaths and disability and a 40% program uptake, which resulted in an ICER of $8,081 per DALY prevented [24]. An Indian study by Megiddo et al (2014) focussed on expanding the use of aspirin, injection streptokinase, beta-blockers, angiotensin-converting enzyme inhibitors, and statins for the treatment and secondary prevention of AMI [25]. With 54% of CHD occurring before the age of 70, there is a huge room for improvement in India. An ICER of $6,450/QALY (ranging between $3,420 and $18,900 per QALY) is calculated.

Strengths and limitations

As discussed by Dorresteyn et al (2013), the most commonly known risk models suffer from different flaws [9]. Some are developed in 'healthy' populations and not validated in coronary patients, other do not include all relevant risk factors or are based on old and therefore not up to date medical data. The

SMART tool, incorporates a wide range of risk factors allowing to recalculate the individual risk after optimal prevention. Furthermore, SMART was validated in several large recent international cohorts i.e. the control arms of the TNT and IDEAL trials, the placebo arms of the SPARCL trial and both arms of the CAPRIE trial (14). The drawback however, of using the SMART score are the limited health outcomes. The risk for heart failure, as well as other non CVD diseases like, obesity, diabetes, kidney disease and others are not included. Hence a greater health gain, and hence a more cost-effective result can be assumed.

Furthermore, cost data, both disease costs as well as treatment costs were supplied by the national coordinators of the EUROASPIRE IV survey. Since most countries do not have readily available or published cost data, data is estimated based on the best available evidence (national or regional data). Due to the uncertainty associated with these costs, caution is needed when comparing the ICERs across countries. The one country in - one country out analyses however, where the overall ICER is considered for 12 countries (each country is omitted from the analyses once) showed no major differences. Also, the effect of physical activity programmes healthy lifestyle was not incorporated, because of the diversity in programmes and associated effects as well as the difficulty to have valid country specific costs. Likewise, the cost of side effects such as those related to statins are not explicitly included in the analyses, however we can assume that the average disease related cost covers the costs of potential side effects.

Finally, one should keep in mind that the current analysis is based on a modelling study with estimated effects drawn from the literature. Depending on the method used (recalculation of risk score, or risk reductions from clinical trials and meta-analyses) other cost-effectiveness results are seen. This is in line with the findings from Kempen et al (2012) which reported on three different methods to model the effect of statins based on the Rotterdam Study, the probability of the strategy to be cost-effective

ranged from 40% to 90% depending on the modelling method [26]. Longitudinal observational studies with treatment to the targets information would result in more valid results.

In conclusion, current analyses advice to optimize guidelines adherence in particular patient subgroups. Especially in elderly patients, higher risk patients and in patients with a higher room for improvement, additional investment in improved guidelines adherence seems worthwhile. Additional patient treatment, however with inclusion of a less conservative LDL-C target gives more favourable cost-effectiveness outcomes compared to a strict LDLD-target of 1.8 mmol/L.

In the end, health economic models remain estimates, based on the available evidence supplemented with several assumptions, therefore caution is needed when interpreting the results especially when they are used during the health care policy decision making process. In addition, they do not inform us about the budget impact and affordability for the health care system [8].

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APPENDIX

Appendix 1a: Estimation of Country specific cost of disease

	Fatal MI	Non-fatal MI - First year	Fatal stroke	Non-fatal Stroke - First year	Non-fatal stroke follow up/year
Belgium	9284€	13058€	7091€	13261€	4366€
Bulgaria	3495€	3171€	2110€	8501€	542€
Croatia	5000€	11450€	3150€	5300€	2800€
Czech Rep.	4885€	8553€	2415€	5765€	2867€
France	6007€	10109€	6254€	11418€	6051€
Latvia	3717€	9077€	888€	2888€	2000€
Lithuania	3429€	4443€	612€	3674€	2414€
Poland	2580€	3737€	1643€	7888€	2442€
Russia	376€	5880€	4804€	7245€	359€
Serbia	2665€	3310€	3075€	5598€	2764€
Sweden	1766€	9617€	4500€	32830€	23660€
Ukraine	98€	966€	116€	2884€	2560€
UK	1366€	4186€	2488€	5160€	2672€

Appendix 1b: Estimation of country specific treatment costs (€)

	Belgium	**Bulgaria**	**Croatia**	**Czech rep.**	**France**	**Latvia**	**Lithuania**	**Poland**	**Russia**	**Serbia**	**Sweden**	**Ukraine**	**UK**
Smoking cessation	145	29	69	45	155	64	60	98	126	148	72	85	81
Atorvastatin	0.13-0.24	0.07-0.42	0.12-0.17	0.06-0.30	0.25-0.61	0.15-0.93	0.08-0.61	0.10-0.36	0.47-1.10	0.26-0.62	0.08-0.24	0.23-0.35	0.05-0.13
Fluvastatin	0.14-0.28	0.14	0.10-0.20	0.09-0.19	0.11-0.41	0.41-0.82	0.16-0.32	0.07-0.40	0.45-1.96	0.20-0.25	NA	0.12-0.23	0.06-0.28
Lovastatin	NA	NA	NA	0.04-0.29	NA	NA	NA	0.07-0.52	0.18-0.66	NA	NA	0.11-0.88	NA
Pravastatin	0.09-0.32	0.07-0.12	0.16-0.17	NA	0.22-0.44	NA	NA	0.07-0.19	NA	0.06-0.29	0.05-0.14	0.21-0.33	0.05-0.09
Rosuvastatin	0.69-1.62	0.16-0.32	0.12-0.16	0.13-0.30	0.85-2.24	0.73-1.86	0.17-0.70	0.14-0.39	1.43-3.11	0.37-0.72	0.86-1.53	0.10-0.17	0.83-1.37
Simvastatin	0.08-0.40	0.07-0.34	0.17-0.32	0.04-0.29	0.13-0.78	0.11-0.40	0.13-0.92	0.06-0.48	0.54-2.86	0.11-0.46	0.06-0.24	0.21-0.42	0.04-0.09
Ezetimibe per day	1.40	0.13	0.85	1.32	1.34	0.72	0.91	1.18	1.40	0.75	1.17	0.19	1.21
β-blockers per day	0.20	0.07	0.04	0.08	0.25	0.09	0.12	0.09	0.10	0.48	0.08	0.07	0.04
Diuretics per day	0.15	0.03	0.08	0.09	0.22	0.20	0.06	0.19	0.05	0.33	0.14	0.08	0.06
Calcium CB per day	0.32	0.10	0.07	0.07	0.30	0.15	0.07	0.09	0.33	0.24	0.10	0.05	0.04
ACE inhibitors per day	0.20	0.14	0.04	0.08	0.27	0.15	0.31	0.13	0.10	0.22	0.08	0.05	0.05
ARBs per day	024	0.21	0.06	0.13	0.41	0.40	0.35	0.16	0.14	0.34	0.07	0.11	0.06

Appendix 2a: Effect of intensified blood pressure treatment

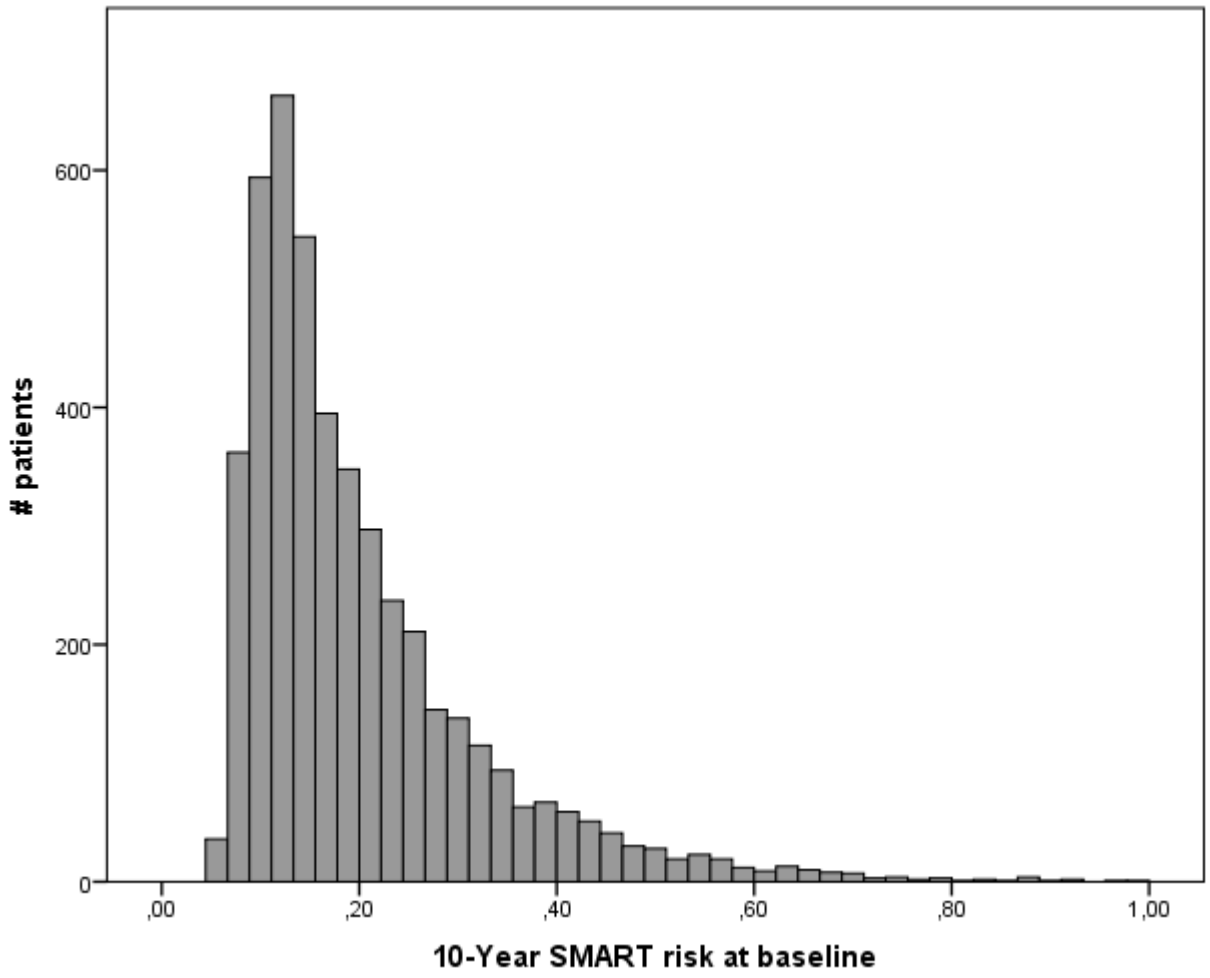
SBP 150 1drug	8,7 mmHg
DBP 95 1 drug	5,3 mmHg
SBP 160 2drug	18,4 mmHg
DBP 100 2 drug	11 mmHg
SBP 170 3drug	29 mmHg
DBP 105 3 drug	17,1 mmHg
SBP 170 (>60 years) 2drug	20,3 mmHg
DBP 105 (>60 years) 2 drug	12,1 mmHg

Appendix 2b: Effect of intensified statin treatment

Dose doubled		***Dose doubled twice***		***Dose doubled 3 times***		***Stratification logic (Cannon et al. 2017)***	
no treatment→S10	***27%***	no treatment→S20	***32%***	no treatment→S40	***37%***	no treatment→A20	***43%***
A10→A20	***6%***	A10→A40	***12%***	A10→A80	***18%***	A10→A10+ezetimibe	***24%***
A20→A40	***6%***	A20→A80	***12%***	A20→A80+ezetimibe	***36%***	A20→A20+ezetimibe	***24%***
A40→A80	***6%***	A40→A80+ezetimibe	***30%***	A40→A80+ezetimibe	***30%***	A40→A40+ezetimibe	***24%***
A80→A80+ezetimibe	***24%***	A80→A80+ezetimibe	***24%***	A80→A80+ezetimibe	***24%***	A80→A80+ezetimibe	***24%***
F10→F20	***6%***	F10→F40	***12%***	F10→F80	***18%***	F10→A80	***40%***
F20→F40	***6%***	F20→F80	***12%***	F20→A10	***16%***	F20→A80	***34%***
F40→F80	***6%***	F40→A10	***10%***	F40→A20	***16%***	F40→A80	***28%***
F80→A10	***4%***	F80→A20	***10%***	F80→A40	***16%***	F80→A80	***22%***
L10→L20	***8%***	L10→L40	***16%***	L10→L80	***24%***	L10→A80	***34%***
L20→L40	***8%***	L20→L80	***16%***	L20→A40	***20%***	L20→A80	***26%***
L40→L80	***8%***	L40→A40	***12%***	L40→A80	***18%***	L40→A80	***18%***
L80→A40	***4%***	L80→A80	***10%***	L80→A80+ezetimibe	***34%***	L80→A80	***10%***
P10→P20	***4%***	P10→P40	***9%***	P10→A10	***17%***	P10→A80	***35%***
P20→P40	***5%***	P20→A10	***13%***	P20→A20	***19%***	P20→A80	***31%***

P40→A10	***8%***	P40→A20	***14%***	P40→A40	***20%***	P40→A80	***26%***
R10→R20	***5%***	R10→R40	***10%***	R10→R40+ezetimibe	***34%***	R10→R10+ezetimibe	***24%***
R20→R40	***5%***	R20→R40+ezetimibe	***29%***	R20→R40+ezetimibe	***29%***	R20→R20+ezetimibe	***24%***
R40→R40+ezetimibe	***24%***	R40→R40+ezetimibe	***24%***	R40→R40+ezetimibe	***24%***	R40→R40+ezetimibe	***24%***
S10→S20	***5%***	S10→S40	***10%***	S10→S80	***15%***	S10→A80	***28%***
S20→S40	***5%***	S20→S80	***10%***	S20→A40	***17%***	S20→A80	***23%***
S40→S80	***5%***	S40→A40	***12%***	S40→A80	***18%***	S40→A80	***18%***
S80→A40	***7%***	S80→A80	***13%***	S80→A80+ezetimibe	***19%***	S80→A80	***13%***

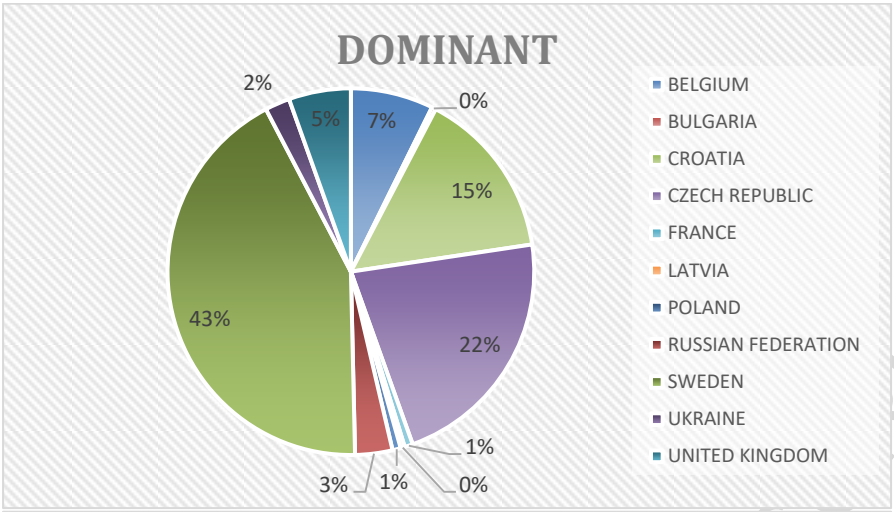
Appendix 3: 10-year SMART risk distribution

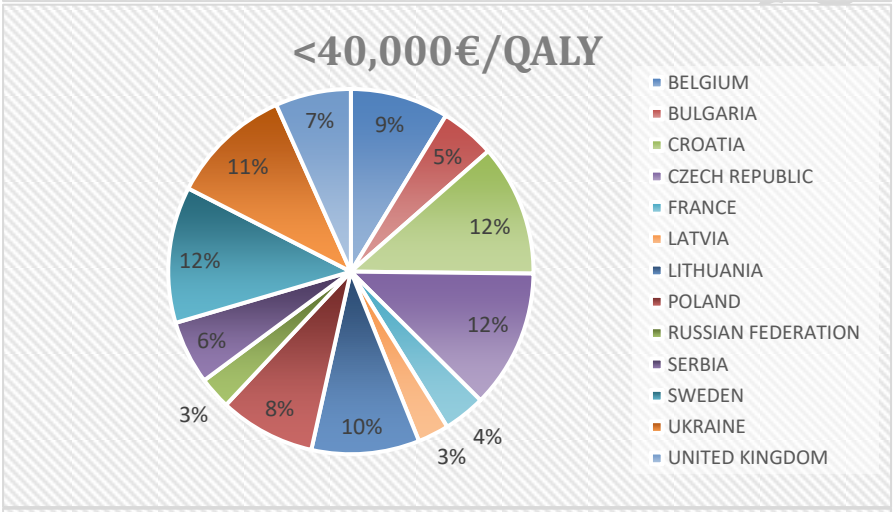


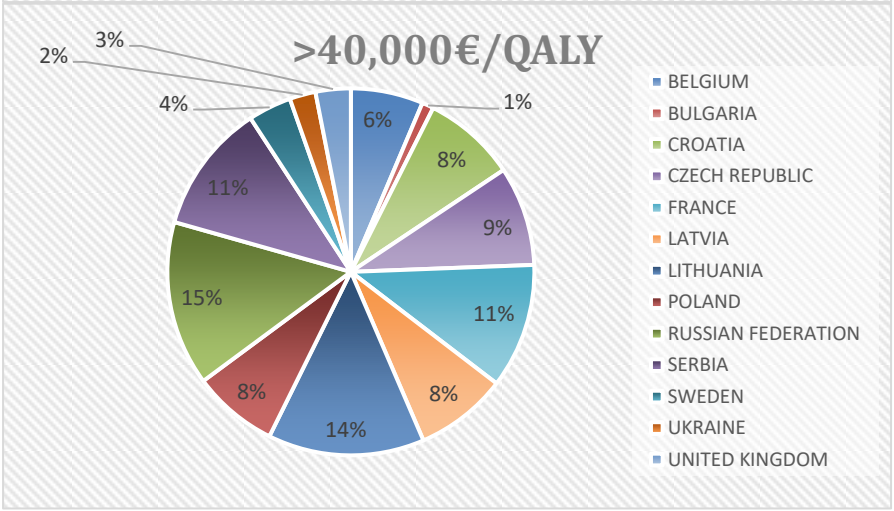
Appendix 4a: risk profile according to outcome (Mean (SD) or %)

	#	Age	diabetes	smoking	male	SBP	DBP	LDL	HDL	TC	10-year risk
Dominant	274	68.68 (8.5)	31,39%	23,72%	77,01%	132.22 (15.9)	76.16 (9.7)	2.59 (0.8)	1.2 (0.3)	4.5 (1)	26.39%
<10,000€/QALY	881	68.25 (8.6)	33,48%	19,18%	75,03%	138.52 (20)	79.47 (11.4)	2.77 (1)	1.18 (0.3)	4.7 (1.2)	27.13%
<20,000€/QALY	1331	67.14 (8.9)	33,73%	18,56%	74,91%	138.81 (20.4)	80.26 (11.6)	2.76 (1)	1.17 (0.3)	4.69 (1.2)	25.38%
<30,000€/QALY	1645	66.66 (9)	34,59%	18,05%	74,04%	139.14 (20.6)	80.62 (11.7)	2.77 (1)	1.17 (0.3)	4.7 (1.2)	24.72%
<40,000€/QALY	1883	66.48 (9.1)	34,04%	18,06%	72,92%	139.4 (20.7)	80.87 (11.7)	2.78 (1)	1.17 (0.3)	4.72 (1.3)	24.53%
<50,000€/QALY	2091	66.12 (9.2)	34%	18,7%	72,93%	139.28 (20.5)	81.05 (11.7)	2.78 (1)	1.17 (0.3)	4.73 (1.3)	24.1%
<60,000€/QALY	2268	65.93 (9.3)	33,33%	18,69%	72,66%	139.25 (20.5)	81.12 (11.7)	2.79 (1)	1.17 (0.3)	4.73 (1.3)	23.81%
<70,000€/QALY	2433	65.91 (9.3)	33,37%	18,66%	73,08%	139.09 (20.4)	81.07 (11.7)	2.79 (1)	1.16 (0.3)	4.74 (1.2)	23.76%
<80,000€/QALY	2559	65.87 (9.3)	32,63%	18,64%	73,19%	138.97 (20.4)	81.04 (11.6)	2.8 (1)	1.16 (0.3)	4.74 (1.2)	23.6%
<90,000€/QALY	2675	65.77 (9.3)	32,3%	18,69%	73,2%	138.9 (20.4)	81.13 (11.6)	2.79 (1)	1.16 (0.3)	4.74 (1.2)	23.44%
<100,000€/QALY	2780	65.79 (9.3)	31,87%	18,42%	73,09%	138.84 (20.3)	81.09 (11.6)	2.79 (1)	1.16 (0.3)	4.73 (1.2)	23.38%
≥100,000€/QALY	1329	60.05 (8.9)	14,37%	17,83%	74,34%	129.6 (14.8)	78.58 (9.7)	2.59 (0.6)	1.19 (0.3)	4.51 (0.8)	14.01%

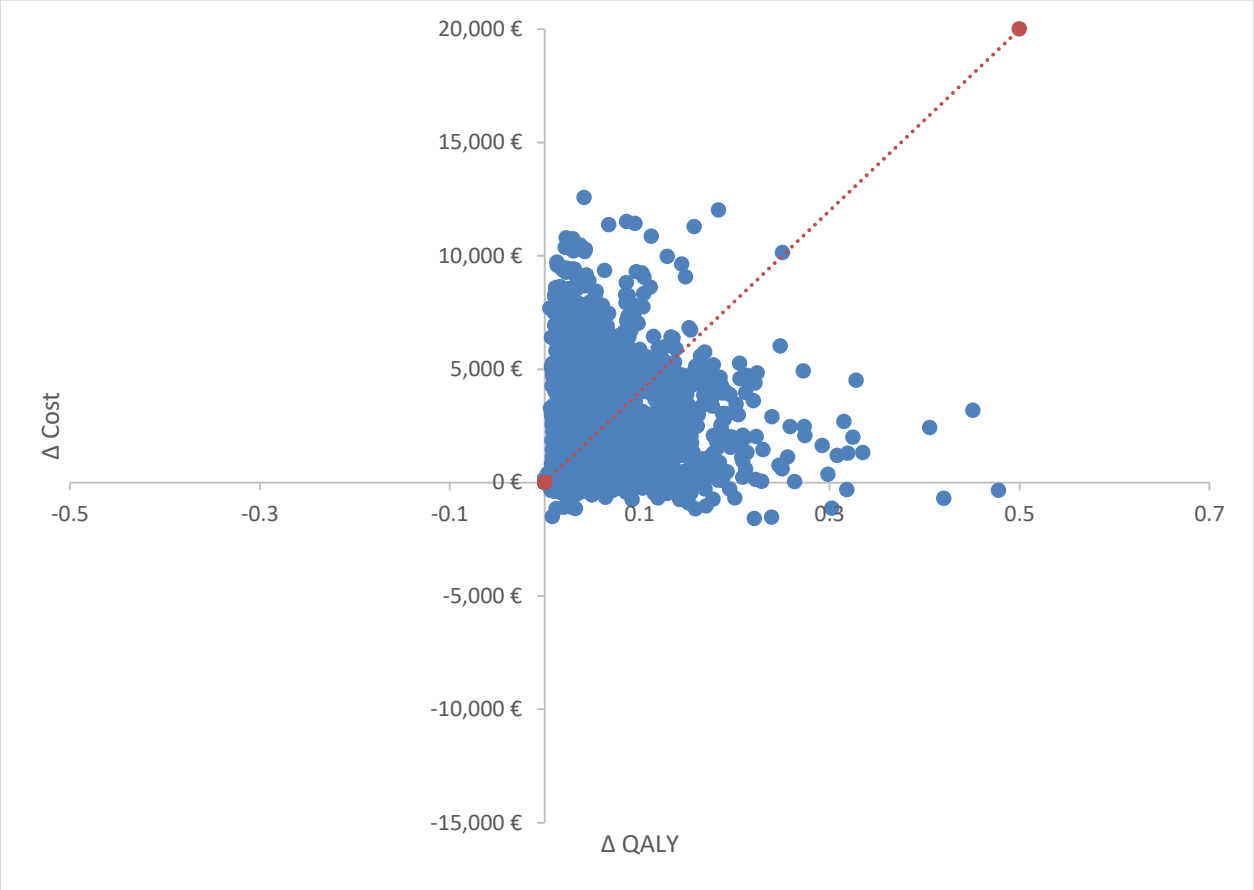
Appendix 4b: country according to outcome







Appendix 4c: Cost –effectiveness plane based on individual patient outcomes (Base case)



Appendix 5: Scenario analyses with basecase risk reduction method (recalculation of SMART risk score)

SMART SCORE	# patients	Age (years)	Smoking	Diabetes	SBP(mm/Hg)	DBP (mm/Hg)	LDL (mmol/L)	HDL(mmol/L)	TC(mmol/L)	ΔCOST	ΔQALY	ICER
<10%	681	52.14 (6.3)	8.4%	4.4%	124.30 (14.1)	78.37 (10.0)	2.38 (0.7)	1.24 (0.3)	4.25 (0.9)	2,446 €	0.01	164,644€/QALY
≥10% - <20%	2261	61.32 (7.0)	22.5%	22.9%	144.93 (17.3)	80.50 (10.7)	2.60 (0.9)	1.16 (0.3)	4.53 (1.1)	2,451 €	0.03	75,188€/QALY
≥20% - <30%	962	70.57 (5.5)	15.8%	36.4%	138.62 (19.2)	79.50 (11.2)	2.59 (1.0)	1.16 (0.3)	4.49 (1.2)	2,068 €	0.05	40,036€/QALY
≥30% - <40%	405	74.19 (5.0)	11.6%	37.5%	140.44 (22.1)	78.55 (11.9)	2.63 (1.0)	1.14 (0.3)	4.52 (1.3)	1,920 €	0.07	26,355€/QALY
≥40%	354	75.39 (4.6)	13.3%	52%	143.11 (22.0)	78.36 (12.0)	2.78 (1.1)	1.06 (0.3)	4.77 (1.6)	1,713 €	0.10	16,501€/QALY

SMART RISK REDUCTION	# patients	Age (years)	Smoking	Diabetes	SBP(mm/Hg)	DBP (mm/Hg)	LDL (mmol/L)	HDL(mmol/L)	TC(mmol/L)	ΔCOST	ΔQALY	ICER
≥0.5%	3671	64.98 (9.2)	19.18%	28.14%	137.36 (19.3)	80.76 (11.2)	2.79 (0.9)	1.17 (0.3)	64.98 (9.2)	2,624€	0.053	49,419€/QALY
≥1%	2443	66.64 (9.1)	19.65%	34.22%	141.61 (20.5)	82.25 (12.1)	2.96 (1)	1.16 (0.3)	66.64 (9.1)	2,588€	0.069	37,271€/QALY
≥2%	1140	67.87 (8.7)	23.95%	41.93%	148.94 (21.9)	84.62 (12.8)	3.22 (1.1)	1.15 (0.3)	67.87 (8.7)	2,550€	0.103	24,645€/QALY
≥3%	642	69.18 (8.3)	27.73%	47.04%	152.11 (22.2)	85.05 (12.8)	3.33 (1.2)	1.15 (0.2)	69.18 (8.3)	2,476€	0.131	18,966€/QALY
≥4%	359	70.8 (7.6)	28.97%	49.3%	154.63 (22.9)	85.19 (13.5)	3.48 (1.3)	1.15 (0.3)	70.8 (7.6)	2,288€	0.158	14,485€/QALY
≥5%	181	71.43 (7.4)	32.6%	52.49%	157.46 (23.5)	85.59 (13.4)	3.77 (1.4)	1.15 (0.3)	71.43 (7.4)	2,319€	0.191	12,160€/QALY

AGE CLASS	# patients	Age (years)	Smoking	Diabetes	SBP(mm/Hg)	DBP (mm/Hg)	LDL (mmol/L)	HDL(mmol/L)	TC(mmol/L)	ΔCOST	ΔQALY	ICER
<50 years	391	44.99 (4.4)	34.3%	15.9%	127.91 (14.8)	80.55 (10.2)	2.70 (0.9)	1.09 (0.3)	4.63 (1.1)	2,747€	0.027	102,006€/QALY
50-59 years	1115	55.74 (2.8)	28%	20.6%	131.61 (17.4)	81.19 (10.7)	2.62 (0.9)	1.13 (0.3)	4.58 (1.2)	2,737€	0.032	86,027€/QALY
60-69 years	1723	64.94 (2.8)	16.3%	29.7%	135.61 (18.9)	80.07 (11.1)	2.56 (0.9)	1.17 (0.3)	4.47 (1.1)	2,186€	0.039	55,863€/QALY
≥70 years	1434	74.72 (3.0)	6%	30%	137.87 (20.0)	77.70 (10.9)	2.55 (1.0)	1.20 (0.3)	4.43 (1.1)	1,873€	0.060	31,133€/QALY

COUNTRY	# patients	Age (years)	Smoking	Diabetes	SBP(mm/Hg)	DBP (mm/Hg)	LDL (mmol/L)	HDL(mmol/L)	TC(mmol/L)	ΔCOST	ΔQALY	ICER	
Belgium	343	66.15 (9.5)	8.2%	22.4%	133.13 (18.3)	78.18 (10.7)	2.38 (0.7)	1.24 (0.3)	4.27 (0.9)	2,405€	0,0350	68,757€/QALY	38,313€
Bulgaria	120	64.07 (9.9)	19.2%	30.8%	132.43 (16.4)	77.58 (10.2)	2.81 (0.8)	1.14 (0.2)	4.76 (1)	814€	0,0517	15,735€/QALY	6,958€
Croatia	467	63.58 (9.3)	17.6%	26.3%	136.29 (19.5)	82.64 (11.5)	2.49 (0.9)	1.12 (0.3)	4.34 (1.1)	1,387€	0,0436	31,837€/QALY	11,528€
Czech Rep.	490	65.84 (9)	17.6%	36.1%	136.55 (18.9)	82.25 (10.7)	2.39 (0.8)	1.17 (0.3)	4.37 (1)	2,137€	0,0448	47,668€/QALY	17,864€
France	377	60.18 (10.8)	25.2%	32.1%	137.14 (18)	76.27 (10.7)	2.29 (0.7)	1.13 (0.3)	4.17 (0.9)	3,557€	0,0355	100,296€/QALY	35,110€
Latvia	294	66.17 (9.4)	12.2%	20.4%	132.43 (13.7)	81.56 (6.7)	2.4 (1)	1.19 (0.3)	4.28 (1.1)	2,557€	0,0316	80,881€/QALY	13,463€
Lithuania	499	63.97 (9.9)	18%	18.6%	142.32 (21.1)	83.41 (11.3)	3.06 (1.1)	1.2 (0.3)	5.01 (1.3)	3,063€	0,0625	48,983€/QALY	14,206€
Poland	377	63.77 (8.6)	20.4%	31%	138.03 (21.3)	80.9 (11.8)	2.52 (1)	1.16 (0.3)	4.45 (1.3)	2,333€	0,0438	53,288€/QALY	11,896€
Russia	424	63.45 (9)	22.6%	20%	127.61 (17.9)	76.54 (11.7)	2.87 (1)	1.15 (0.3)	4.9 (1.4)	4,105€	0,0462	88,843€/QALY	9,211€
Serbia	391	62.87 (8.6)	18.2%	26.1%	129.8 (16.5)	79.69 (9.3)	2.71 (0.9)	1.07 (0.2)	4.53 (1.1)	2,180€	0,0392	55,558€/QALY	5,266€
Sweden	359	66.34 (8.5)	13.9%	27.9%	133.07 (17.4)	76.26 (9.5)	2.44 (0.8)	1.21 (0.3)	4.33 (1)	980€	0,0356	27,523€/QALY	47,109€
Ukraine	274	61.83 (9.5)	13.9%	22.6%	131.27 (15.5)	81.27 (9)	2.88 (1)	1.16 (0.3)	4.79 (1.1)	688€	0,0393	17,485€/QALY	2,139€
UK	248	64.92 (10.9)	16.1%	32.3%	136 (20)	73.69 (11.5)	2.3 (0.8)	1.2 (0.3)	4.2 (1)	1,327€	0,0418	31,711€/QALY	33,109€

Appendix 6: Scenario analyses with risk estimation method based on risk reduction in risk factors

SMART SCORE	# patients	Age (years)	Smoking	Diabetes	SBP(mm/Hg)	DBP (mm/Hg)	LDL (mmol/L)	HDL(mmol/L)	TC(mmol/L)	ΔCOST	ΔQALY	ICER
<10%	681	52.14 (6.3)	8.4%	4.4%	124.30 (14.1)	78.37 (10.0)	2.38 (0.7)	1.24 (0.3)	4.25 (0.9)	2,431 €	0,021	116,322€/QALY
≥10% - <20%	2261	61.32 (7.0)	22.5%	22.9%	144.93 (17.3)	80.50 (10.7)	2.60 (0.9)	1.16 (0.3)	4.53 (1.1)	2,405 €	0,049	49,057€/QALY

≥20% - <30%	962	70.57 (5.5)	15.8%	36.4%	138.62 (19.2)	79.50 (11.2)	2.59 (1.0)	1.16 (0.3)	4.49 (1.2)	1,970 €	0,086	22,999€/QALY
≥30% - <40%	405	74.19 (5.0)	11.6%	37.5%	140.44 (22.1)	78.55 (11.9)	2.63 (1.0)	1.14 (0.3)	4.52 (1.3)	1,755 €	0,126	13,971€/QALY
≥40%	354	75.39 (4.6)	13.3%	52%	143.11 (22.0)	78.36 (12.0)	2.78 (1.1)	1.06 (0.3)	4.77 (1.6)	1,462 €	0,186	7,855€/QALY

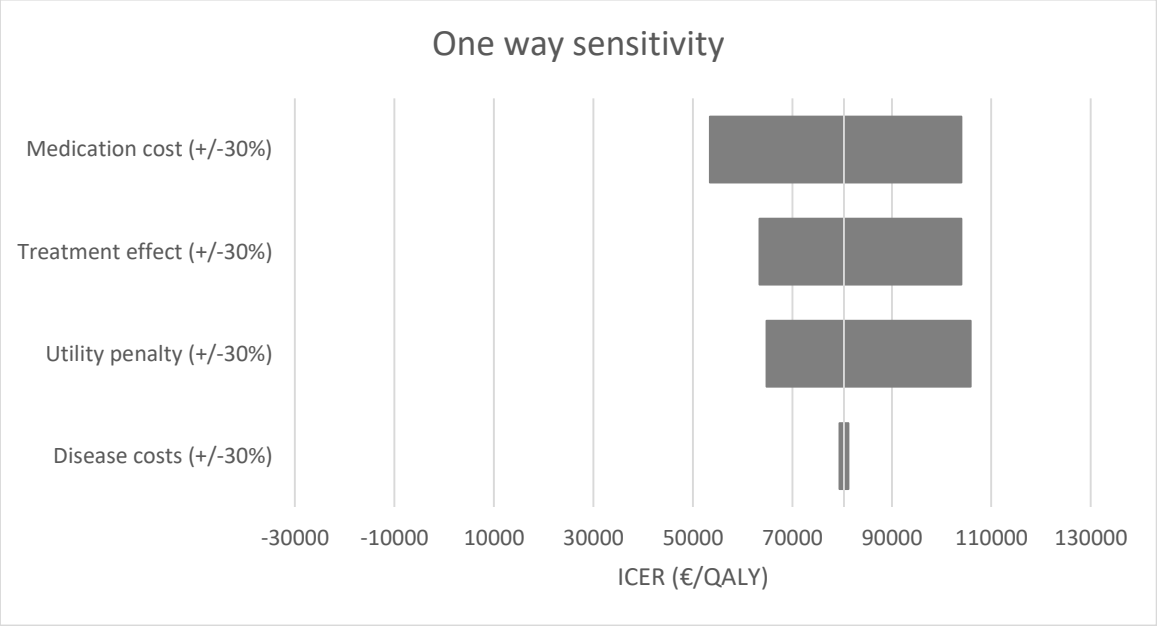
AGE CLASS	**# patients**	**Age (years)**	**Smoking**	**Diabetes**	**SBP(mm/Hg)**	**DBP (mm/Hg)**	**LDL (mmol/L)**	**HDL(mmol/L)**	**TC(mmol/L)**	**ΔCOST**	**ΔQALY**	**ICER**
<50 years	391	44.99 (4.4)	34.3%	15.9%	127.91 (14.8)	80.55 (10.2)	2.70 (0.9)	1.09 (0.3)	4.63 (1.1)	2,717€	0,038	71,222€/QALY
50-59 years	1115	55.74 (2.8)	28.0%	20.6%	131.61 (17.4)	81.19 (10.7)	2.62 (0.9)	1.13 (0.3)	4.58 (1.2)	2,686€	0,052	51,785€/QALY
60-69 years	1723	64.94 (2.8)	16.3%	29.7%	135.61 (18.9)	80.07 (11.1)	2.56 (0.9)	1.17 (0.3)	4.47 (1.1)	2,119€	0,062	34,100€/QALY
≥70 years	1434	74.72 (3.0)	6.0%	30%	137.87 (20.0)	77.70 (10.9)	2.55 (1.0)	1.20 (0.3)	4.43 (1.1)	1,747€	0,101	17,356€/QALY

SMART RISK REDUCTION	**# patients**	**Age (years)**	**Smoking**	**Diabetes**	**SBP(mm/Hg)**	**DBP (mm/Hg)**	**LDL (mmol/L)**	**HDL(mmol/L)**	**TC(mmol/L)**	**ΔCOST**	**ΔQALY**	**ICER**
≥0.5%	3769	64.77 (9.3)	19.0%	28.0%	137.17 (19.2)	80.74 (11.2)	2.78 (0.9)	1.17 (0.3)	64.77 (9.3)	2,515 €	0.085	29,590€/QALY
≥1%	2687	66.04 (9.3)	19.2%	34.2%	141.15 (20)	82.24 (11.9)	2.89 (1)	1.16 (0.3)	66.04 (9.3)	2,429 €	0.111	21,898€/QALY
≥2%	1625	65.82 (9.1)	20.4%	42.8%	148.46 (19.9)	85.42 (12.2)	2.97 (1.1)	1.15 (0.3)	65.82 (9.1)	2,371 €	0.157	15,077€/QALY
≥3%	1177	66.69 (8.7)	17.9%	49.1%	154.01 (19)	87.36 (12.5)	2.95 (1.2)	1.15 (0.3)	66.69 (8.7)	2,297 €	0.191	12,012€/QALY
≥4%	915	67.48 (8.3)	17.7%	51.9%	158.01 (18)	88.43 (12.7)	2.94 (1.2)	1.14 (0.3)	67.48 (8.3)	2,267 €	0.218	10,391€/QALY
≥5%	700	68.71 (7.8)	17.0%	56.4%	161.35 (16.9)	88.98 (12.6)	2.94 (1.2)	1.14 (0.3)	68.71 (7.8)	2,246 €	0.246	9,117€/QALY

COUNTRY	**# patients**	**Age (years)**	**Smoking**	**Diabetes**	**SBP(mm/Hg)**	**DBP (mm/Hg)**	**LDL (mmol/L)**	**HDL(mmol/L)**	**TC(mmol/L)**	**ΔCOST**	**ΔQALY**	**ICER**	
Belgium	343	66.15 (9.5)	8.2%	22.4%	133.13 (18.3)	78.18 (10.7)	2.38 (0.7)	1.24 (0.3)	4.27 (0.9)	2,292 €	0.0585	39,205	38,313€

Bulgaria	120	64.07 (9.9)	19.2%	30.8%	132.43 (16.4)	77.58 (10.2)	2.81 (0.8)	1.14 (0.2)	4.76 (1)	764 €	0.0799	9,562	6,958€
Croatia	467	63.58 (9.3)	17.6%	26.3%	136.29 (19.5)	82.64 (11.5)	2.49 (0.9)	1.12 (0.3)	4.34 (1.1)	1.294 €	0.0747	17,332	11,528€
Czech Rep.	490	65.84 (9)	17.6%	36.1%	136.55 (18.9)	82.25 (10.7)	2.39 (0.8)	1.17 (0.3)	4.37 (1)	2.051 €	0.0780	26,290	17,864€
France	377	60.18 (10.8)	25.2%	32.1%	137.14 (18)	76.27 (10.7)	2.29 (0.7)	1.13 (0.3)	4.17 (0.9)	3.441 €	0.0633	54,344	35,110€
Latvia	294	66.17 (9.4)	12.2%	20.4%	132.43 (13.7)	81.56 (6.7)	2.4 (1)	1.19 (0.3)	4.28 (1.1)	2.523 €	0.0476	52,980	13,463€
Lithuania	499	63.97 (9.9)	18%	18.6%	142.32 (21.1)	83.41 (11.3)	3.06 (1.1)	1.2 (0.3)	5.01 (1.3)	2.993 €	0.1041	28,763	14,206€
Poland	377	63.77 (8.6)	20.4%	31%	138.03 (21.3)	80.9 (11.8)	2.52 (1)	1.16 (0.3)	4.45 (1.3)	2.260 €	0.0800	28,254	11,896€
Russia	424	63.45 (9)	22.6%	20%	127.61 (17.9)	76.54 (11.7)	2.87 (1)	1.15 (0.3)	4.9 (1.4)	4.079 €	0.0600	67,951	9,211€
Serbia	391	62.87 (8.6)	18.2%	26.1%	129.8 (16.5)	79.69 (9.3)	2.71 (0.9)	1.07 (0.2)	4.53 (1.1)	2.147 €	0.0573	37,499	5,266€
Sweden	359	66.34 (8.5)	13.9%	27.9%	133.07 (17.4)	76.26 (9.5)	2.44 (0.8)	1.21 (0.3)	4.33 (1)	765 €	0.0577	13,247	47,109€
Ukraine	274	61.83 (9.5)	13.9%	22.6%	131.27 (15.5)	81.27 (9)	2.88 (1)	1.16 (0.3)	4.79 (1.1)	673 €	0.0553	12,166	2,139€
UK	248	64.92 (10.9)	16.1%	32.3%	136 (20)	73.69 (11.5)	2.3 (0.8)	1.2 (0.3)	4.2 (1)	1.276 €	0.0719	17,761	33,109€

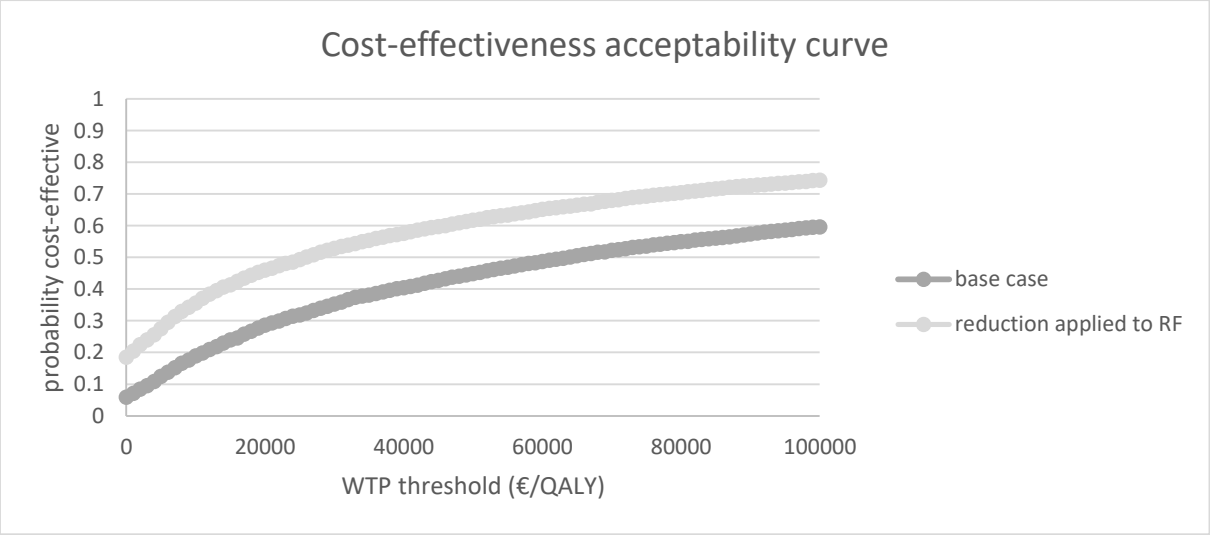
Appendix 7: One-way sensitivity analysis



Appendix 8: Country in-country out sensitivity analyses

	ΔCOST	ΔQALY	ICER
All countries (Except Belgium)	2.258 €	0.0435	51.959€/QALY
All countries (Except Bulgaria)	2.307 €	0.0426	54.161€/QALY
All countries (Except Croatia)	2.367 €	0.0428	55.363€/QALY
All countries (Except Czech rep.)	2.285 €	0.0426	53.622€/QALY
All countries (Except France)	2.156 €	0.0435	49.572€/QALY
All countries (Except Latvia)	2.250 €	0.0436	51.605€/QALY
All countries (Except Lithuania)	2.174 €	0.0405	53.705€/QALY
All countries (Except Poland)	2.263 €	0.0428	52.939€/QALY
All countries (Except Russia)	2.085 €	0.0425	49.066€/QALY
All countries (Except Serbia)	2.277 €	0.0432	52.752€/QALY
All countries (Except Sweden)	2.377 €	0.0434	54.706€/QALY
All countries (Except Ukraine)	2.368 €	0.0431	54.990€/QALY
All countries (Except UK)	2.322 €	0.0429	54.132€/QALY

Appendix 9: Cost-effectiveness acceptability curve



WTP: willingness to pay; RF: risk factors

Table 1: Patient characteristics (Mean (SD) or %)

Age (mean (SD))	64.07 (9.56)
Male (%)	74.4% (3469/4663)
Education	
Low	15.1% (697/4622)
Intermediate	59.6% (2754/4622)
High	25.3% (1171/4622)
CVD history (%)	24.1% (308/1278)
PAD history (%)	7.9% (207/2618)
EQ-5D (mean)	0.76 (0.20)
Smoking	17.4% (812/4663)
Physically active	39.9% (1712/4290)
Waist (males)	102.2 (12.0)
Waist (females)	95.8 (13.4)
Diabetes	26.6% (1234/4641)
SBP	134.50 (18.88)
DBP	79.45 (10.97)
LDL-C	2.58 (0.96)
HDL-C	1.16 (0.29)
HbA1C*	7.2 (1.4)
BP lowering medication	95.6% (4425/4631)
Cholesterol lowering medication	86.0% (3982/4631)

* if self-reported diabetes

SBP: systolic blood pressure; DBP: systolic blood pressure; LDL-C: LDL-cholesterol; HDL-C: HDL-cholesterol;

Table 2: Risk factor goals and preventive strategies

Target	**Preventive strategy**
Non-smoking	→ *smoking cessation medication*
BP <140/90 mmHg (140/85 mmHg if diabetes); BP between 140-150/90 mmHg if patient > 60 years old and SBP ≥160	If <150/95 → *one (additional) inexpensive antihypertensive drug (type beta blocker or diuretic)* If <150/95 and already on two inexpensive drug regimens → *additional expensive antihypertensive drug (type ACE inhibitor, angiotensin II receptor blocker or calcium channel blocker)* If between 150/95 and 160/100 → *two inexpensive hypertensive drugs were added* If between 150/95 and 160/100 and already on one or two inexpensive antihypertensive drugs respectively → *one cheap and one expensive, or two expensive antihypertensive drugs* If >160/100 → *two inexpensive and one expensive antihypertensive drugs,* If >160/100 and already on one or two inexpensive antihypertensive drugs respectively → *one inexpensive and two expensive antihypertensive drugs, or three expensive hypertensive drugs*
LDL-C <1.8 mmol/L (<70 mg/dL), or a reduction of at least 50% if the baseline is between 1.8 and 3.5	If ≤6% above target and not yet on statin → *low dose statin (Simvastatin 10mg/d)* If ≤6% above target and already on statin

mmol/L (70 and 135 mg/dL)	→ *the statin dose was doubled*
	If ≤6% above target and already on max dose
	→ *stronger statin (Atorvastatin)*
	If ≤6% above target and already on max dose of a strong statin
	→ *ezetimibe*
	If between 6% and 12% above target and not yet on statin
	→ *medium dose statin (Simvastatin 20mg/d)*
	If between 6% and 12% above target and already taking statins
	→ *the statin dose was doubled twice*
	If between 6% and 12% above target and already on maximum statin dose
	→ *stronger statin (such as Atorvastatin)*
	If between 6% and 12% above target and already on maximum dose of a strong statin
	→ *ezetimibe*
	If >12% above target not yet on medication
	→ *high dose statin (Simvastatin 40mg/d)*
	If >12% above target and already taking statins
	→ *statin dose was doubled three times*
	If >12% above target and already on maximum statin dose
	→ *a stronger statin (such as Atorvastatin)*
	If >12% above target and already on maximum dose of a strong statin
	→ *ezetimibe*

* In agreement with the guidelines this tree structure was adapted for >60 old patients and for patients with diabetes.

Table 3: Scenario analyses

SCENARIO	COST EFFECTIVENES
Stratification according to baseline CVD risk (appendix 5)	
Low 10-year risk (<10%)	132,255€/QALY
Moderate 10-year risk (10% to <20%)	64,386€/QALY
High 10-year risk (20% to <30%)	32,550€/QALY
Very high 10-year risk (30% to <40%)	26,594€/QALY
Extremely high 10-year risk (≥40%)	17,623€/QALY
≥10%	40,409€/QALY
≥20%	26,379€/QALY
≥30%	21,775€/QALY
≥40%	17,623€/QALY
Stratification according to age class (appendix 5)	
<50 years	102,006€/QALY
50-59 years	86,027€/QALY
60-69 years	55,863€/QALY
≥70 years	31,133€/QALY
≥50 years	50,238€/QALY
≥60 years	41,978€/QALY
≥70 years	31,133€/QALY

Inclusion according to risk reduction (appendix 5)	
≥0.5%	49,419€/QALY
≥1%	37,271€/QALY
≥2%	24,645€/QALY
≥3%	18,966€/QALY
≥4%	14,485€/QALY
≥5%	12,160€/QALY
≥10%	3,692€/QALY
Less conservative LDL target	
LDL-C < 2 mmol/L	47,495€/QALY
LDL-C < 2.5 mmol/L	32,591€/QALY
Intensifying statin therapy in high risk patients versus high cholesterol patients	
≥10%	46,990€/QALY
≥20%	28,064€/QALY
≥30%	20,233€/QALY
≥40%	17,035€/QALY
Treatment stratification logic	49,841€/QALY
Remove the ezetimibe option	21,033€/QALY
Including compliance rates	59,554€/QALY
SMART Reducible risk estimation method with risk reduction in risk factors (appendix 6)	37,763€/QALY
SMART Reducible risk estimation method +LDL-C<2.5mmol/L	19,660€/QALY

Highlights

- Guidelines adherence is more cost-effective in higher risk patients
- The room for improvement is a key driver of the ICER
- Depending on the method used better or worse outcomes were found

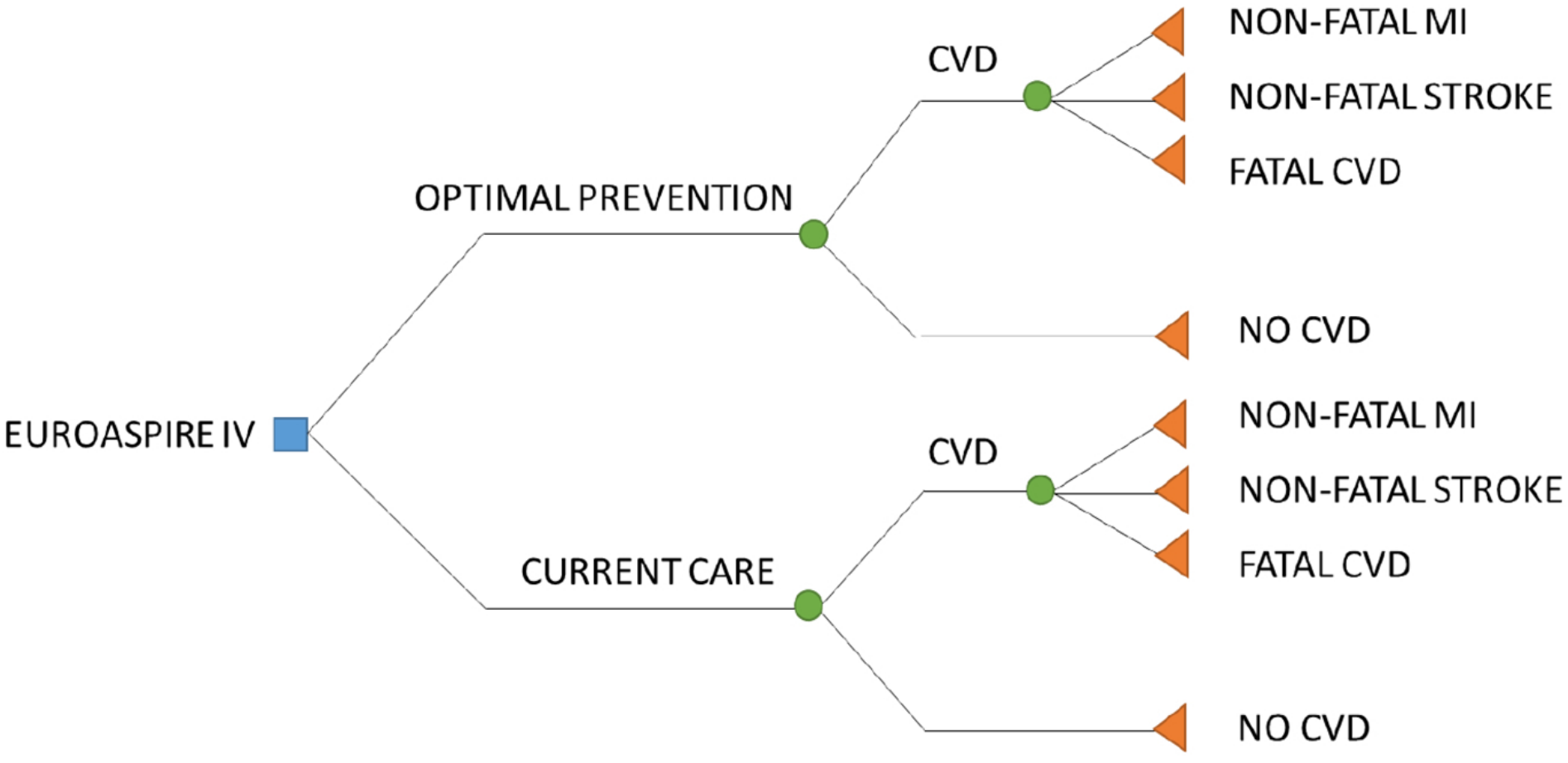

EUROASPIRE IV
OPTIMAL PREVENTION
CURRENT CARE
CVD
CVD
NON-FATAL MI
NON-FATAL STROKE
FATAL CVD
NO CVD
NON-FATAL MI
NON-FATAL STROKE
FATAL CVD
NO CVD

Figure 1