Estimation of lifetime benefits from the optimisation of secondary prevention in patients with established atherosclerotic cardiovascular disease

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Abstract:

Cardiovascular disease causes almost four million deaths in Europe, costing the EU €282billion/annum. Future mortality rate improvements will be gained through improving secondary prevention of atherosclerotic cardiovascular disease (ASCVD) events. Wide gaps exist between ASCVD prevention/treatment guidelines and their implementation across Europe. We aim to estimate lifetime benefits available via optimised secondary prevention in patients with ASCVD in Denmark, France, Germany, Italy, Poland, Spain and the UK.

A literature review identified ASCVD risk factor prevalence in ASCVD populations in seven countries. The simulation used an analytical framework and the SMART-REACH survival model to derive event probabilities over 1-year, associated with being 'at-risk' and 'risk free'. The effect of modifying four risk-factors in the SMART-REACH model - hypertension, hypercholesterolaemia, diabetes and tobacco smoking - was examined. The impact of improving treatment coverage and smoking cessation from (estimated) 43% to 70% (i.e. 70% of patients reach treatment targets/cease smoking) was analysed.

Over 94,359 cardiovascular-event-free life years could be gained/year across seven countries by improving secondary ASCVD prevention: 25,333 years in Germany, 21,144 in Italy, 14,584 in France, 13,324 in the UK, 9,393 in Spain, 9,369 in Poland and 1,212 in Denmark.

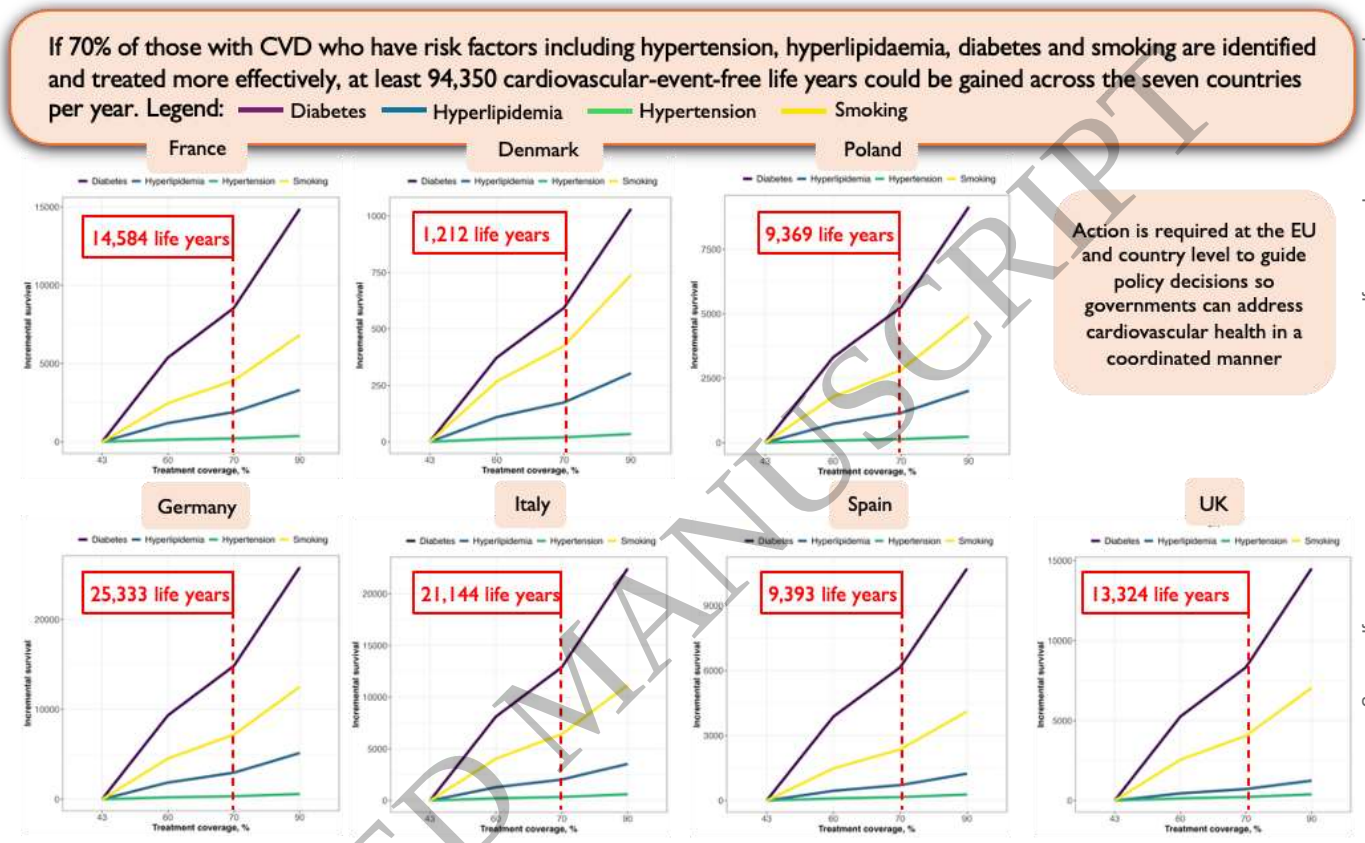
This is a step in better quantifying the impact of improved secondary ASCVD prevention, giving an indication of the potential of EU and national Cardiovascular Health Plans in cardiovascular survival gains. Countries should incentivise proactive identification of patients at risk and ensure subsequent, timely treatment according to guidelines. Future work should utilise updated data and modelling integrating additional cardiometabolic risk factors.

Abstract Word Count - 250

Key words:

Cardiovascular Disease; Cardiovascular Risk Estimation; Secondary Prevention; Lifetime Benefits; SMART-REACH; Cardiovascular Health Policy.

Graphical Abstract



Lay Summary

This study estimates the potential health benefits of improving treatment for people with atherosclerotic cardiovascular disease (ASCVD) in seven European countries.

- Improving treatment for hypertension, hypercholesterolemia, diabetes mellitus and smoking cessation rates to 70% could save over 94,000 cardiovascular-event-free life years annually across Denmark, France, Germany, Italy, Poland, Spain, and the UK.
- The findings highlight the importance of closing the gap between clinical guidelines and real-world care to reduce deaths and improve cardiovascular health outcomes.

Introduction

Cardiovascular disease is responsible for almost four million deaths in Europe each year (1) and a fifth of disability-adjusted life years (DALYs) in the EU (2). The annual direct and indirect costs to the EU economy amount to €282 billion (3). Recent plateauing in mortality rates in those with atherosclerotic cardiovascular disease (ASCVD) (4) suggests acute care gains are "maximised" and future improvements will require optimized prevention of subsequent events, such as myocardial infarction (MI) and ischaemic stroke. The causal relationships between ASCVD risk factors like hypercholesterolaemia, hypertension, diabetes, obesity, physical inactivity and smoking and subsequent cardiovascular events underscore the opportunity for enhanced secondary prevention strategies. The European Action on Secondary and Primary Prevention by Intervention to Reduce Events (EUROASPIRE) revealed a wide implementation gap with poor lifestyle management and inadequate control of risk factors in patients with coronary heart disease (CHD) (5).

Individuals with established ASCVD are at very high risk of recurrent events if risk factors are not effectively treated. Determining this risk, in the form of average lifetime benefit as a result of risk reduction, may improve the communication of anticipated benefits in a shared decision-making process with patients. Risk can be determined using stratification tools for secondary prevention, including the Secondary Manifestations of Arterial Disease (SMART) risk score (6) and the EUROASPIRE risk model (7).

Whilst this approach has benefits at the individual level, determining the impact of risk reduction at the population level could generate valuable evidence that enables decision-makers to effectively implement interventions for improved secondary ASCVD prevention. Relevant examples include joint diabetes and heart health checks and national cardiovascular health (CVH) plans to reduce inequalities seen across the EU.

We aimed to estimate the lifetime benefits, in terms of life year gains free of recurrent cardiovascular events, from the optimized control of four key risk factors in patients with established ASCVD in Denmark, France, Germany, Italy, Poland, Spain and the UK, chosen as they represent a cross section of European countries with variation in health systems and ASCVD impact.

Methods

Determining the modelling approach

A targeted literature review determined methods previously used to estimate population life years gained in secondary ASCVD cohorts. Studies that investigated treatment effects based on individual and population life years were sought. We searched Pubmed/MEDLINE, Embase and Google Scholar for studies published in English in the last twenty years. Search terms included ("ASCVD" OR "atherosclerotic cardiovascular disease" OR "cardiovascular disease") AND ("secondary prevention") AND ("life years" OR "life expectancy" OR "years of life lost" OR "years of life gained") AND ("treatment effect" OR "benefit estimation" OR "risk models"). We included studies that provided sufficient explanation on applied estimation methods and excluded studies limited to primary prevention cohorts. Literature screening was performed by two independent reviewers and shortlisted papers were reviewed in full to evaluate alignment with inclusion criteria. Two peer-reviewed articles were identified, each for their exclusive population-level and individual-level features.

Farley et al. (2010), a population-level study conducted in the United States of America (USA) (looking at the impact of treating 70% of people with hypertension, and 72% of people with hypercholesterolaemia), provides an analytic framework for estimating life year gains from reducing mortality and extending 'treatment coverage' in the ASCVD cohort (8). Risk reductions to mortality for specific ASCVD risk factors were determined from existing literature and translated into mortality benefits for hypothetical US patients receiving treatment. These mortality benefits were applied to an increasing proportion of patients in the ASCVD cohort and translated into life year gains. We adopted the same analytical approach using data sources specific to European populations.

Kaasenbrood et al. (2018) provided the individual-level, SMART-REACH model to estimate the probability of a recurrent ASCVD event in 1-year for a single patient, based on the presence of relevant risk factors and their severity denoted on a clinical scale. The authors developed the model using the REACH Western Europe sample (N=14,259) and provided external validation utilizing the REACH North America

(N=19,170) and SMART Netherlands (N=6,959) cohorts, which provided real-world clinical representation. All patients had clinically apparent ASCVD, including coronary, cerebrovascular and/or peripheral arterial disease, including abdominal aortic aneurysm. They utilized a composite endpoint, so that a given probability of a ASCVD event that is derived using the SMART-REACH model is a probability of either non-fatal MI, non-fatal stroke and cardiovascular death. Importantly, the model includes age and gender as predictors of survival, which can be used to determine survival probabilities for specific sub-groups of the ASCVD cohort (9). Farley et al. defined age-groups based on 5-year age categories, which is the approach we follow when estimating survival probabilities using the Kaasenbrood et al. approach. To facilitate convenient use of the survival models computed by the authors, we transformed the regression inputs into coefficients, as described below.

Modelling Process

To estimate the survival benefits from increasing treatment coverage of ASCVD risk factors, we adopted and modified the Farley framework. The analysis determines the impact of increasing 'treatment coverage' to 70% (and latterly 90%), whereby 70% of the population reaches treatment targets. Whilst we chose an arbitrary 70% coverage, this figure was based on work showing the benefit of increasing treatment coverage of secondary preventive medication (10). Whilst the work of Mennini et al focused specifically on the impact of improving adherence, it is important to note that the definition of 'coverage' here is specific to this analysis, whereby we explored the impact of improving the probability of survival by better controlling risk factors for a larger proportion of the ASCVD population. We made no assertions about how the risk factors may be modified, although one can speculate about improved testing, better adherence to treatment and combinations of these (11).

To determine the impact of improved treatment coverage, we estimated survival probabilities of three subpopulations within the ASCVD population, using the modified Farley framework: 1) people with ASCVD risk factors not receiving preventative treatment; 2) people with ASCVD risk factors receiving preventative treatment; and 3) people without ASCVD risk factors. Apart from age-group and gender, control (or lack

thereof) of risk factors determined the number of subpopulations from which modelled estimates of cardiac event-free survival (CEFS) were derived. As outlined below, the number of subpopulations that comprise the total population is limited by the availability of data on the prevalence of any given subpopulation, for each country.

The total survival for a country was estimated as the sum of survival for these three subpopulations (Formula 1, in Table 1 in Supplementary Material). Outcomes were expressed as the incremental survival achieved by increasing the proportion of patients receiving optimal secondary prevention compared to current coverage, estimated to be 43% (12). Data from the Antiplatelet Treatment Observational Registry (APTOR) showed that only 43% of patients experiencing an acute coronary syndrome (ACS) event received optimal secondary prevention across 14 European countries (12). Outcomes were expressed for men, women and jointly for the total population of the country.

Model parameters

Estimation of survival rates

Survival was estimated by multiplying the estimated survival probability specific to each of the three subpopulations by the number of people in these populations. To estimate these survival probabilities, we used the SMART-REACH model, which estimates life expectancy without recurrent cardiovascular events for individuals with coronary, cerebrovascular, and/or peripheral artery disease.

SMART-REACH was developed using data from patient cohorts in Western Europe and North America, where participants were followed up for the occurrence of cardiovascular events and mortality. The cumulative incidence of recurrent cardiovascular events for these cohorts were used to estimate baseline age-specific, event free survival rates, from ages 45 to 84. SMART-REACH fitted a competing risk model (a survival analysis technique used to account for events (competing risks) influencing the primary event under consideration) to estimate the cumulative incidence of recurrent cardiovascular events (Formula 2, Table 1).

The regression coefficients of this model (Table 2, Supplementary Material) quantify the relationship between the predictors and recurrent cardiovascular events. A coefficient in this risk model gives the change in probability (derived as log hazards) for a one-unit increase in the corresponding predictor variable, assuming all other predictors stay constant. A positive coefficient indicates that an increase in that predictor is associated with a higher hazard of a recurrent cardiovascular event. A negative coefficient means an increase in that predictor is associated with a lower hazard. This model also included quadratic terms for SBP and total cholesterol, to account for a U-shaped (quadratic) relationship. The modelling to estimate absolute population-level impact from modifying these probabilities therefore inherits these relationships.

This risk model was used to estimate the additive and independent effect of these predictors on the age-specific baseline survival probabilities (i.e., holding other risk factors at their baseline values), based on the cumulative incidence for recurrent cardiovascular events for the ASCVD population. This was calculated using Formula 3 on Table 1.

Continuous variables were set to derive 'at-risk' and 'risk-free' probabilities associated with their optimisation; for SBP, these were 150mmHg and 140mmHg, and for cholesterol these were 6.8mmol/L and 4.0mmol/L, respectively. We did not examine the effect of changing/optimising creatinine due to data limitations. It was set at 93 μmol/L (9) in both the 'at-risk' and 'risk-free' models.

If the baseline probability of CEFS for a 46-year-old female is 0.8539, then smoking (ignoring the presence of other predictors) will reduce the probability of CEFS to:

$$0.8539^{\exp(0.4309)} = 0.7842$$

Then, as described in Formula 1, this estimate of CEFS is multiplied by the prevalence of smokers amongst 46-year-old females with ASCVD not receiving preventative treatment, such as smoking cessation programmes and nicotine replacement therapy. For instance, for an assumed treatment coverage of 43%, the number of people smoking and not receiving preventive 'treatment' is derived as follows: 1) estimation of the number of people receiving preventive treatment for smoking as 43% of the prevalence of smokers with ASCVD; and 2) subtraction of (1) from the prevalence of ASCVD smokers.

This was repeated for other female age-groups. The sum of these estimates was the total CEFS for smoking women with ASCVD not receiving preventative treatment for smoking. These steps were repeated for men who smoke and do not receive preventative treatment. The sum value for men and women is the estimated CEFS for the ASCVD smoking subpopulation not receiving preventative treatment for smoking, i.e., $survival_u$*$population_u$ in Formula 1.

To estimate survival for the second subpopulation, i.e., smokers with ASCVD receiving preventative treatment ($survival_i$*$population_i$ in Formula 1), we multiplied the prevalence of smokers receiving preventative treatment based on the assumed treatment coverage by the probability of CEFS for non-smokers. For example, for an assumed 'treatment coverage' of 43%, $population_i$ would be 43% of the prevalence of smokers with ASCVD. Like the first subpopulation, these were calculated by age-group for men and women, and then summed to estimate survival. For the third subpopulation, survival in people without the risk factor ($survival_n$*$population_n$), we multiplied the baseline probability of CEFS by the prevalence of the non-smoking population with ASCVD. The ASCVD non-smoking population is estimated as the prevalence of ASCVD minus the prevalence of smokers in the ASCVD population to give $population_n$. These steps were followed to estimate survival in these three subpopulations.

Survival probabilities are augmented by the presence or absence of a diabetes diagnosis, represented as a binary variable in the Kaasenbrood et al. model. Survival is adjusted for the presence of diabetes (or not), therefore the relationship between diabetes severity and survival cannot be estimated using this equation. We, therefore, estimated the effect of expanding treatment coverage to 70% for populations with and without diabetes (see summary of scenarios, below).

The sum of survival for the three subpopulations provides estimates of total survival, i.e., $survival_t$*$population_t$, for an assumed level of treatment coverage for one year. To estimate the total survival for a different level of treatment coverage, the steps outlined in equation 1 were followed, adjusting $population_u$, $population_i$ and $population_n$ based on the hypothetical scenario for treatment coverage i.e., 70%. Thus, incremental survival from increasing treatment coverage is calculated using Formula 4 (Table 1, Supplementary Material).

In summary, four main scenarios were estimated:

Scenario 1a) current annual life years in the ASCVD population without diabetes, assuming 43% of patients are in a state of control for the risk factors we could examine;

Scenario 1b) as for scenario 1a., assuming the ASCVD population also has a diabetes diagnosis.

Scenario 2a) hypothetical annual life years in the ASCVD population without diabetes, assuming 70% of patients are in a state of control for the risk factors we could examine;

Scenario 2b) as for scenario 2a., assuming the ASCVD population also has a diabetes diagnosis.

Using this method we analysed the impact, in terms of life years gained, of better controlling four risk factors: hypertension (defined here as systolic blood pressure above 140/90 mmHg) hypercholesterolaemia (total cholesterol of more than 5 mmol/L), diabetes (having a diagnosis of diabetes) and smoking (utilising tobacco cigarettes). We also looked at the impact of increasing treatment coverage to 90%. Whilst unlikely to meet the threshold of clinical plausibility, it is informative for gauging the upper boundary of observed effects.

Country selection and estimation of prevalence and mean risk factor levels

The countries under scope – Denmark, France, Germany, Italy, Poland, Spain and the UK – were chosen due to the existence of population-based data from large observational studies in ASCVD populations. They also represent a cross-section of European countries with representation from Northern, Western and Central/Eastern Europe, along with a non-EU comparator with variation evident in health systems and ASCVD impact.

A further literature review was conducted in peer-reviewed and grey literature to gather data by age-group and gender, prevalence of ASCVD by age-group and prevalence of risk factors among the ASCVD population in the seven countries of interest. As individual-level datasets were not available, we utilised large scale, observational studies in ASCVD populations which use standardized protocols, are geographically diverse and include comprehensive patient histories and clinical examination, representative of ASCVD population characteristics. The primary sources include the following: REACH (13) and EUROASPIRE (5) registries, the Survey of Risk Factors (SURF) clinical audit (14), the Dyslipidemia International Study (DYSIS) (15), the

Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy (STABILITY) trial (16), and the LIPIDOGRAM2015 study (17).

Results

Country-specific prevalence rates of risk factors in ASCVD population are shown on Table 1.

Table 1 here

Table 2 outlines the number of cardiovascular-event-free life years gained by increasing treatment coverage from 43% to 70% for four risk factors in seven countries. In total, 94,356 cardiovascular-event-free life years could be gained across the seven countries per year by improving secondary ASCVD prevention via the increased treatment coverage of the four risk factors. The greatest impact was seen in Germany (25,333 years), followed by Italy (21,144 years), France (14,584 years), the UK (13,324 years), Spain (9,393 years), Poland (9,369 years) and finally, Denmark (1,212) cardiovascular-event-free life years gained.

Table 2 here

Looking at the impact of secondary prevention per million population in each country (Table 2), in Denmark, France, Spain and the UK roughly 200 cardiovascular-event-free life years will be gained per million population (209, 215,198 and 198 years respectively). In Germany, Italy and Poland these values are higher at 293, 358 and 247 years, respectively.

In Denmark, France, Germany and Spain the impact of increased treatment coverage was greater for men than women for each of the risk factors. In Italy and the UK, this was the case for hypertension only, whilst in Poland increasing treatment coverage had a greater impact in women than in men for all risk factors analysed. Across all countries, improved hypertension management contributed to about 1.5% of the life year gains (ranging from 1.3% in Germany to 1.7% in Spain), improved hypercholesterolaemia management contributed to 10% of the life year gains (ranging from 5% in the UK to 14% in Denmark), increasing smoking cessation rates contributed to 28% of the life year gains (ranging from 25% in Spain to 35% in Denmark) and improved diabetes management contributed to 60% of the life years gains (ranging from 48% in Denmark to 65% in Spain).

Comparing the number of life years gained per country with that of the number of deaths due to MI and ischaemic stroke events (Table 3) highlights that Germany has the highest number of deaths due to MIs and strokes at 309,642 (per year) as well as the highest potential cardiovascular-event-free life years gained. Denmark has the lowest number of deaths due to MIs and strokes (13,030 per year) as well as potential cardiovascular-event-free life years gained. In most cases, the potential cardiovascular-event-free life years gained are around a tenth of the ASCVD deaths due to MI and stroke. Poland is a slight outlier with almost 15,000 deaths due to MI and stroke but only 9369 cardiovascular-event-free life years gained. This could suggest an underestimation of the impact of improved secondary ASCVD prevention in Poland.

Table 3 here

Finally, alongside the impact of improved treatment coverage to 70%, we briefly looked at the impact of improving coverage to 90%. Whilst this is unlikely to reflect actual clinical practice, it gives insight into the potential of further improving secondary ASCVD prevention. In total, increasing treatment coverage to 90% could lead to 164,247 cardiovascular-event-free life years gained per year across the seven countries.

Discussion

Improving secondary prevention by achieving higher treatment coverage of four ASCVD risk factors – hypertension, hypercholesterolaemia, diabetes and higher smoking cessation rates – from a predicted baseline of 43% to 70%, could lead to over 94,000 cardiovascular-event-free life years gained per annum across seven countries. Across 25 years this equates to the avoidance of 2.35 million cardiovascular events. These improvements are not surprising given quantifiable links between reductions in risk factor values and ASCVD events. For example, a meta-analysis performed by the Cholesterol Treatment Trialists' Collaboration showed that, for each 1 mmol/L reduction in LDL-C, the annual rate of MI, revascularisation and ischaemic stroke is reduced by over a fifth alongside a reduction in all-cause mortality of 10% (24). Similarly, a 5mmHg reduction of systolic BP reduces the risk of major cardiovascular events by around 10% (25), whilst a

10mmHg reduction in systolic BP significantly reduces the risk of major ASCVD events, coronary heart disease, stroke, heart failure, and all-cause mortality by 20%, 17%, 27%, 28%, and 13%, respectively (26).

Our work complements an increasing body of high-quality research using SMART-REACH and other predictive models to estimate the potential benefits of improved secondary prevention. Previous studies have quantified treatment-specific benefits and estimated life years gained under target attainment scenarios (27-29). Holtrop et al. (2024) and Kaasenbrood et al. (2016) have also provided valuable insight into regional differences in 10-year risk and anticipated benefit under alternative scenarios (30, 31). This study estimated aggregate cardiovascular-event-free life years gained at the country-population level under estimated current versus optimized treatment coverage scenarios, focusing on system-level implementation gaps rather than individual treatment effects. Under our definition of optimized treatment coverage, we derive best case estimates in a comparative framework for European populations. Benefits of risk factor modification for different risk profiles within these populations requires causal modelling and prevalence rates specific to each of these profiles, the latter of which is a major constraint on the scope of the analysis performed.

There is limited published evidence of estimates of the population-wide benefits, in terms of life-year gains, from extending coverage as defined here, therefore a direct comparison of the findings reported here with prior work is unfeasible. Work by Maciosek et al. estimated the quality-adjusted life-years (QALY) gained by increasing the utilization of preventive services including **aspirin chemoprophylaxis,** hypertension screening, cholesterol screening and diabetes screening among others (32). Increasing these services to 90% from current utilisation levels suggested large potential gains from smoking cessation counselling. Smaller gains were seen for cholesterol and hypertension screening - levels were reported close to 90% for those (32). It is important to point out, however, that in certain groups with genetic conditions, like familiar hypercholesterolaemia, fewer than 10% have actually been diagnosed (33). This potentially suggests greater population benefits related to improved management of hypertension and high cholesterol via improving treatment and adherence, rather than enhanced screening for these conditions in isolation. Kontis et al. estimated that increasing the treatment of hypertension to 70% as well as reducing sodium intake by just

under a third and eliminating artificial trans-fat intake could delay 94 million deaths globally during a period of 25 years (34).

Farley et al. estimated the number of preventable deaths from incremental improvements in LDL-C reduction, hypertension status, aspirin prophylaxis, and smoking cessation (8). Their US-based analysis found that, in an all-cause model, every 10% increase in hypertension treatment prevented 14,000 deaths whilst every 10% increase in treatment of LDL-C or aspirin prophylaxis prevented 8000 deaths in those aged <80 years (8). In the recent Global Cardiovascular Risk Consortium study, hypertension was identified as having the greatest potential for prevention, followed by non-HDL cholesterol, Body Mass Index (BMI), diabetes and smoking (35). In the present study, diabetes had the greatest potential for prevention, followed by smoking, hypercholesterolaemia and hypertension. At a minimum, these differences are likely due to differences in data input and methodologies. Furthermore, both Farley et al. and The Global Cardiovascular Risk Consortium looked at cardiovascular prevention in general, whilst the current study focused on the impact of secondary ASCVD prevention which may have impacted observed results.

The SMART-REACH model, built on a large, geographically and clinically diverse dataset of over 40,000 patients with established ASCVD, provided robust estimates for lifetime risk and quantified the relative contribution of each risk factor to the annual survival of ASCVD patients. The benefits from reducing blood pressure and the relationship between blood pressure and survival are derived from thousands of observations in the SMART dataset. Clinically, the relationship between blood pressure reduction and ASCVD risk improvement is clear (25,26); however, the relative contribution of blood pressure control to the probability of survival, when compared to improvements in cholesterol (LDL-C) and smoking status, is not yet fully elucidated, with little evidence for comparison at the population-level. Importantly, the analysis used here assumes all risk factors operate independently of each other; therefore, the dynamics of the relationships between treating one risk factor and the production of potential benefits to other risk factors cannot currently be addressed mathematically. This mirrors current clinical evidence, since the interactions between patient phenotypes and treatment combinations and their precise effects on survival are poorly understood.

Limitations

Our approach took advantage of a robust clinical risk model for ASCVD populations; however, it was constrained by the modelling parameters utilised in the SMART-REACH study. It reflects a pragmatic approach, constrained by available data, limiting our ability to implement a full causal modelling framework or to incorporate external treatment effects as in prior studies (27, 36). As such, our findings do not represent the causal effects of risk factor modification, rather a best case from maximising the improvement of risk factors.

The utilised method is a necessary iteration leveraging existing high-quality studies. The lack of large individual-level datasets constrained the model inputs and modelling approach; therefore, we employed an age-based cohort methodology to calculate incremental survival, operating under the assumption that the existence and severity of risk factors were uniformly distributed across all patients in each of the three subpopulations. These subpopulations represented the risk of an average individual within their respective groups. We posited that the survival benefits derived from improved management of ASCVD risk factors would be uniformly distributed, contingent upon the baseline age-based survival probability.

In terms of inputs, our model was subject to the following constraints: First, the baseline systolic blood pressure utilised was 140 mmHg. We were unable to model the effect of further blood pressure reductions due to the functional relationship between systolic BP and risk status that is encoded by the SMART-REACH dataset and the risk model derived from it. Given recent evidence describing this relationship, (without interdependencies to other risk factors), further risk reductions and life year / ASCVD event gains / reductions might be expected. This assumption might deviate from prevailing national clinical guidelines; however, addressing it requires significant further investigation.

Second, whilst accepted as rigorous, the large-scale observational studies did not capture data at a granularity level necessary for more nuanced analyses. Data gaps were managed in a systematic manner utilising average risk factor values across countries. The number of locations of ASCVD and histories of atrial fibrillation/congestive heart failure could not be accounted for in the model, due to limited reporting of

prevalence rates. These inputs were treated as dummy variables in the model with an assumed value of '0'. A baseline level of 93 mmol/L creatinine was utilised based on research by Kaasenbrood et al (9). Furthermore, confidence intervals for prevalence estimates were not consistently reported in the original survey publications and could not be computed from available aggregate data, which may limit interpretation of precision. Constraints on our modelling approach reflect the novelty of analysis performed; however, they also reflect limited data availability for population-level research on this topic. While epidemiological data are relatively more available in the general population, obtaining homogeneous, guideline-adherent data for patients with established ASCVD across countries remains limited, reflecting variability in national surveillance systems, different collection methodologies and the frequent omission of sex-stratified figures in publicly available datasets.

Third, the SMART-REACH model incorporated cholesterol as total cholesterol, despite lack of a specific clinical guideline threshold for total cholesterol levels. This is the product of historical data cohort studies, and the extensive research work conducted to derive risk models using these existing datasets. Despite these deviations from normal clinical practice, the SMART-REACH score has been clinically validated over several years and has shown excellent predictive performance. Additionally, total cholesterol has demonstrated acceptable predictive utility in established cardiovascular risk models (e.g., Framingham, SCORE2 (37,38)), reflecting a pragmatic alternative for population-level estimation in the absence of more granular data. For these reasons, this analysis represents an important advancement in the use of the SMART-REACH model and existing epidemiological data on ASCVD prevalence (by risk factor and age-group) in Europe.

Fourth, obesity was not represented in the model, despite known links with ASCVD risk. Numerous studies have shown that weight loss results in significant improvements in cardiometabolic risk factors and can lead to clinically relevant reductions in blood pressure and glucose regulation, particularly in those at highest risk (39). Any future studies on the benefits of secondary ASCVD prevention should factor in the impact of reducing obesity.

Fifth, the definition of 'treatment coverage' used here should be considered specific to this analysis; the applied model explored the impact of improving the probability of survival by controlling risk factors, and, in effect, applying these benefits to a larger proportion of the ASCVD population. No assertions were made related to how the risk factor is modified. Adherence is not considered explicitly in the model, rather it is implicit, and assumptions inherited such that treatment coverage is a product of adherence to medication as well as all other factors that contribute to improvements in risk factor levels. Whilst evidence is relatively clear about the relationship between adherence to medication, efficacy, effectiveness and, in turn, cardiovascular risk (40), we cannot speculate about the effect of adherence on the model outcome. Moreover, our approach did not explicitly incorporate transitions between health states over time and could not address uncertainties regarding treatment dynamics or recurrence of events. Utilization of granular patient-level longitudinal data would be a valuable extension for future work. Whilst extending coverage to achieve reductions in ASCVD risk factors might be achieved through improved adherence, this analysis also captured key drivers of risk factor control in ASCVD patients. These risk factor control drivers may inform policy makers to determine methods of improving secondary prevention.

Sixth, diabetes was represented in the model in a binary manner such that analysis was limited to assessing differences in survival between those living with diabetes and those living without diabetes. Again, this might deviate from clinical reality but is a core input of the SMART-REACH mathematical model, which is the outcome of large cohort studies and validated modelling work carried out using ASCVD epidemiological datasets.

Seventh, whilst a specific cost-benefit analysis of secondary ASCVD prevention was out of the scope of this manuscript, there is evidence that secondary prevention of ASCVD is cost effective (41) with a societal return of $10 for every $1 invested (42). However, it is possible that improving prevention coverage to 70% may increase marginal costs significantly due to the need to include and improve management of underrepresented populations. Additional research regarding the specific cost implications is needed.

Finally, using data collected through cardiovascular large-scale, cross-sectional surveys may have introduced positive selection bias (volunteer bias), due to overrepresentation of a more adherent or

accessible population segment. Those volunteering for such surveys tend to have better baseline health and lifestyle (43), which means that our findings may underestimate the true picture in terms of secondary prevention potential.

Conclusion

Our approach is a step in better quantifying the impact of improved secondary prevention of ASCVD. We have determined that improving secondary prevention and ensuring that 70% of those with ASCVD who have risk factors including hypertension, hypercholesterolaemia, diabetes and smoking are identified and treated more effectively, could lead to at least 94,350 cardiovascular-event-free life years gained across the seven countries each year. This provides evidence that targeted action is required at national and EU level to address residual cardiovascular health risk. According to the ambitious vision of the European Alliance for Cardiovascular Health (EACH), an EU Cardiovascular Health Plan should incorporate interventions aimed at better managing risk factors in Europe, improving primary and secondary prevention of ASCVD by incentivising both the proactive identification of patients at risk as well as subsequent, timely initiation of guideline-based treatment. This study points towards the importance of improving the availability of consistent, accessible data across Europe, for example in the form of the European Health Data Space (44), to allow for better determination of lives saved and cost-benefit analysis of secondary prevention interventions. Future research would require updated data and modelling approaches, while also integrating additional cardiometabolic risk factors such as obesity and alcohol intake.

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Data Availability Statement:

The data underlying this article are available in the article and in its online supplementary material.

Author Contribution:

PGK, AWC, EAA and SAJ contributed to the conception or design of the work. AWC, EAA, SAJ, JLG, AM and KP contributed to the acquisition, analysis, or interpretation of data for the work. JLG, AM and KP drafted the manuscript. PGK, EAA and AWC critically revised the manuscript. All gave final approval and agree to be accountable for all aspect of work ensuring integrity and accuracy.

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Tables

Table 1: Country-specific risk-factor prevalence rates

		Hypertension (%) (defined as >140/90mmHG)	*Elevated total cholesterol (%) (total chol >5mmol/L)*	*Smoking (%) (current, daily smoker)*	*Diabetes (%)*
Denmark	Men	63	70.5	24	23
	Women	63	70.5	24	23
France	Men	45.1	74.2	14.3	30.8

	Women	47.5	74.2	14.3	30.8
Germany	Men	46.9	73.3	16.7	34
	Women	45.7	73.3	16.7	34
Italy	Men	54.8	54.9	16.2	30.7
	Women	50.2	54.9	16.2	30.7
Poland	Men	57.6	39.4	13	30.7
	Women	52.4	39.4	13	30.7
Spain	Men	59.5	41.3	12.8	32.9
	Women	43.7	41.3	12.8	32.9
UK	Men	56.8	30.5	16.1	32.7
	Women	49.1	30.5	16.1	32.7

Sources:

Denmark: (14) (SURF study, data collected 2012-2013). Prevalence only available across sex; France: Smoking, diabetes prevalence and hypercholesterolaemia prevalence (18) (REACH Registry, data published 2008), hypertension prevalence (19) (EUROASPIRE IV, data collected 2012-2013); Germany: Smoking, diabetes and hypercholesterolaemia prevalence (20) (REACH Registry, data published 2008), hypertension prevalence (19) (EUROASPIRE IV, data collected 2012-2013); Italy: The average values from the 6 other countries were used; Poland: Smoking and diabetes prevalence (17) (LIPIDOGRAM, data collected 2015-2016), hypercholesterolaemia and hypertension prevalence (19) (EUROASPIRE IV, data collected 2012-2013); Spain: Smoking and hypercholesterolaemia prevalence (21) (REACH Registry, data published 2009), diabetes prevalence (5) (EUROASPIRE IV, data collected 2012-2013), and hypertension prevalence (19) (EUROASPIRE

IV, data collected 2012-2013); UK: Smoking, diabetes prevalence (5) (EUROASPIRE IV, data collected 2012-2013), hypercholesterolaemia and hypertension prevalence (19) (EUROASPIRE IV, data collected 2012-2013).

Table 2: Incremental survival by increasing treatment coverage from 43% to 70%

	Cardiovascular-event-free life years gained (per year)		
	Men	*Women*	*Total*
Denmark			
Hypertension	10.9	9.4	20.3
Hyperlipidaemia	91.2	83.2	174.4
Diabetes	309.6	283.2	592.9
Tobacco Smoking	221.8	202.8	424.6
Total (Denmark)	633.5	578.6	**1212.2**
Cardiovascular-event-free life years gained per million population (Denmark)	-	-	**209**
France			
Hypertension	108.1	107.1	215.2
Hyperlipidaemia	980.6	920.8	1901.4
Diabetes	4409.2	4141.2	8550.5

Tobacco Smoking	2019.7	1896.9	3916.7
Total (France)	7517.6	7066	**14583.8**
Cardiovascular-event-free life years gained per million population (France)	-	-	**215.1**
Germany			
Hypertension	177.9	160.9	338.9
Hyperlipidaemia	1532.9	1422.5	2955.4
Diabetes	7699.5	7145.3	14844.8
Tobacco Smoking	3731.2	3462.6	7193.7
Total (Germany)	13141.5	12191.3	**25332.8**
Cardiovascular-event-free life years gained per million population (Germany)	-	-	**293.2**
Italy			
Hypertension	177.5	175.2	352.7
Hyperlipidaemia	979.8	1056	2035.8
Diabetes	5936.4	6398	12334.4

Tobacco Smoking	3090.4	3330.9	6421.3
Total (Italy)	10184.1	10960.1	**21144.2**
Cardiovascular-event-free life years gained per million population (Italy)	-	-	**358.4**
Poland			
Hypertension	59.7	72.8	132.6
Hyperlipidaemia	514.5	643.2	1157.7
Diabetes	2336.9	2919.9	5256.8
Tobacco Smoking	1254.2	1567.2	2821.4
Total (Poland)	4165.3	5203.1	**9368.5**
Cardiovascular-event-free life years gained per million population (Poland)	-	-	**247.9**
Spain			
Hypertension	93.4	68.3	161.7
Hyperlipidaemia	357.5	355.9	713.4
Diabetes	3083.4	3071.5	6154.9

Tobacco Smoking	1183.5	1179.1	2362.6
Total (Spain)	4717.8	4674.8	**9392.6**
Cardiovascular-event-free life years gained per million population (Spain)	-	-	**198.2**
UK			
Hypertension	119	106.6	225.6
Hyperlipidaemia	352.2	365.2	717.4
Diabetes	4090.6	4242.6	8333.3
Tobacco Smoking	1987.4	2060.7	4048.1
Total (UK)	6549.2	6775.1	**13324.4**
Cardiovascular-event-free life years gained per million population (UK)	-	-	**198**
Total for all countries	46909	47449.3	**94358.5**

Notes: A treatment coverage level of 70% equates to 70% of the ASCVD population in each country received optimal secondary prevention and achieving targets. These targets were limited by the baseline values used by Kaasenbrood et al (9). For hypertension the target blood pressure was 140mmHG, baseline target

cholesterol was considered to be 5.0 mmol/L total cholesterol. Smoking and diabetes were binary variables in the model.

Table 3: Comparison of life years gained and number of ASCVD deaths due to myocardial infarction and ischaemic stroke.

	Total cardiovascular-event-free life years gained (per year)	Number of cardiovascular deaths (per year)[1]	Number of deaths due to myocardial infarction and ischaemic stroke (per year)[2]
Denmark	1212.0	15330.2	13030.7
France	14584.0	166496.0	141521.6
Germany	25333.0	364284.7	309642.0
Italy	21144.0	236507.1	201031.1
Poland	9369.0	174736.3	148525.9
Spain	9393.0	131492.8	111768.9
UK	13324.0	188113.0	159896.0

Notes:

1. This is the number of deaths across both sexes and all age groups in 2019 (22).

2. This value was calculated using the number of ASCVD-related deaths and the fact that roughly 85% of cardiovascular deaths due to ASCVD are the result of fatal myocardial infarctions and ischaemic strokes (23).

Graphical Abstract: Cardiovascular-event-free life years that could be gained across seven European countries.