Original Article

Explaining the Decline in Coronary Heart Disease Mortality in Portugal Between 1995 and 2008

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Background—We aimed to quantify the contribution of treatments and risk factors to the decline in coronary heart disease (CHD) mortality in Portugal, 1995 to 2008.

Methods and Results—The IMPACT mortality model was used to integrate data on trends in uptake of treatments and exposure to risk factors to explain the CHD mortality variation. Between 1995 and 2008, CHD mortality rates in Portugal decreased by 29% in men and 21% in women aged 25 to 84 years, corresponding to 3760 fewer deaths in 2008 than expected if 1995 mortality rates had persisted. Approximately 92% of the estimated decrease in number of deaths could be explained by the model; the remaining 8% were attributed to changes in unmeasured factors. Approximately 50% of the decrease explained by the model was attributable to an increased uptake of treatments, mainly antihypertensive medication (12%) and initial treatments after an acute myocardial infarction (10%), and 42% to population risk factor reductions, mainly blood pressure (27% in men and 60% in women), total cholesterol (14% in men and 5% in women), and smoking (11% in men). However, these reductions were partially offset by adverse trends in diabetes mellitus (18% in men and 2% in women) and obesity (6% in men and 5% in women) and smoking (2% in women).

Conclusions—In this low CHD risk population, modern treatments explained approximately half of the overall decline in CHD deaths. The biggest contributions to the CHD mortality decline came from secular decreases in blood pressure and increases in hypertension treatment. **(*Circ Cardiovasc Qual Outcomes*. 2013;6:634-642.)**

Key Words: coronary artery disease ■ decision modeling ■ mortality ■ risk factors ■ therapeutics

The trends in coronary heart disease (CHD) mortality rates differ widely across countries.[1] In Europe, there is a northeast to southwest gradient in age-standardized CHD mortality,[2] and Portugal has been a low-risk country for decades.[3] Although the CHD mortality rates have been declining since the 1980s, more steeply after the mid-1990s, particularly among women,[1,3] CHD remains the second most common cause of death in Portugal.[4]

A high prevalence of hypertension and high stroke mortality are distinguishing features of the cardiovascular disease epidemiology in Portugal.[5] However, the risk factor distributions changed in the past several decades, with steep decreases in blood pressure levels since the 1970s,[6] a decrease in the prevalence of smoking among men but increase among women,[7] and an increase in the frequency of obesity in the younger age groups.[8] In addition, there were several improvements in the management of CHD, namely, in the availability of drug treatments, in the access to reperfusion and revascularization interventions, with the development of a hospital referral network for interventional cardiology, and the implementation of a coronary fast track system.[9]

It is important to assess the relative contribution of these underlying factors to the observed decline in CHD mortality in different settings, plan future health policy, and prioritize strategies for primary and secondary prevention. The IMPACT model, a cell-based policy model, uses epidemiological information to estimate the contributions of population-level risk factor changes (impacting mainly on incidence) and changes in the uptake of evidence-based treatments (impacting mainly on case fatality) on mortality decline between 2 points in time (the start year and the end year). In the present investigation, we aimed to model the decline in CHD mortality between 1995 and 2008 in Portugal, quantifying the contribution of changes in the use of evidence-based treatments and in the levels of major cardiovascular risk factors using IMPACT.

Methods

IMPACT CHD Mortality Model

We used an updated version of the IMPACT CHD mortality model to investigate how changes in risk factors and treatments have affected the substantially decreasing mortality rates in CHD among men and women 25 to 84 years of age in Portugal. The IMPACT model has

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WHAT IS KNOWN

- Trends in coronary heart disease mortality rates differ widely across countries; Portugal has been a low-risk country for decades.
- Coronary heart disease mortality rates in Portugal have been declining since the 1980s, more steeply after the mid-1990s, particularly among women.
- A relatively high prevalence of hypertension and high stroke mortality are distinguishing features of the cardiovascular disease epidemiology in Portugal.

WHAT THE STUDY ADDS

- Approximately half of the coronary heart disease deaths prevented or postponed between 1995 and 2008 were attributed to increasing use of evidence-based therapies.
- Approximately 42% of the decline was attributable to the trends in major risk factors, mainly systolic blood pressure, although the rise in the prevalence of diabetes mellitus and mean body mass index in both sexes and in smoking prevalence among women generated additional deaths.
- The proportional contribution of treatments and risk factors for coronary heart disease mortality trends in Portugal differs from other countries mainly because of a higher contribution of treatments.

been used previously in diverse populations, namely, in the United States,[10] New Zealand,[11] China,[12] and Europe,[13] including other Southern European populations, namely, Italy[14] and Spain.[15]

The IMPACT model incorporates data on trends in the distribution of the main cardiovascular risk factors: high systolic blood pressure (SBP), smoking, high total cholesterol, high body mass index (BMI), diabetes mellitus, and physical inactivity. It also includes ≈50 evidence-based treatments for all CHD patient groups: acute myocardial infarction (AMI), cardiac arrest, unstable and chronic angina, and mild and acute heart failure (Appendix in the online-only Data Supplement). The model compares data from a baseline year (1995) against data observed in a more recent year (2008). The main outcome of the model is the relative contributions of cardiovascular risk factors and treatment groups to CHD mortality decline, measured as deaths prevented or postponed (DPPs). The calculation of the relative contributions is based on the well-studied relationships between each risk factor change and the relative reduction in CHD mortality and between treatment uptake and reductions in case-fatality in patients with a specific form of CHD.

Number of DPPs

The starting point for the model is to calculate the target number of deaths the model needs to explain. Data on the total population and the number of CHD deaths for Portugal, according to the *International Classification of Diseases* (*ICD*), in 1995 and 2008, were obtained from the Portuguese official statistics, by 10-year age bands.[4]

We calculated the number of CHD deaths expected in 2008 if the CHD mortality rates in 1995 had persisted by multiplying the age-specific mortality rates for 1995 by the population for each 10-year age stratum in the year 2008 (ie, simple direct standardization). Subtracting the number of observed deaths in 2008 from the number of expected deaths generates the reduction in the number of CHD deaths in 2008, which the model aims to explain. We will refer to them as DPPs.

Identification and Assessment of Relevant Data

To build the Portuguese IMPACT model, we used specific data from the Portuguese population whenever possible. When >1 data source was available, we chose the most representative and least biased source. A detailed description of all the sources of data used is found in the Appendix in the online-only Data Supplement.

Data on number of patients admitted to a hospital with myocardial infarction, unstable angina, and heart failure were obtained from the National Hospital Discharge Registry, centrally held in the Central Administration of the Health System for Portugal.[16] The proportion of patients treated for myocardial infarction, unstable angina, or heart failure during hospitalization were obtained from clinical epidemiological studies on samples of patients consecutively admitted to Portuguese hospitals.[17,18] The number of patients in the community eligible for treatments for chronic angina and heart failure and for statin therapy to reduce cholesterol and antihypertensive medications to control blood pressure was obtained from epidemiological studies on representative samples of the general Portuguese population; the proportion of patients treated for those conditions were taken from the same studies.[19,20]

Data on the effectiveness of therapeutic interventions, on the association between cardiovascular risk factors and CHD mortality and case-fatality rates, were obtained from published meta-analyses, randomized controlled trials, and international cohort studies (see Appendix in the online-only Data Supplement).

In 1995, data on mean total cholesterol, mean SBP, mean BMI, and prevalence of diabetes mellitus were obtained from a systematic review that summarizes the evidence from studies providing data on the distribution of risk factors in Portuguese adults.[6,21,22] Data on the prevalence of smoking and physical inactivity were obtained from the National Health Survey conducted from 1995 to 1996.[23] Data of risk factors in 2008 were obtained from 2 cross-sectional studies in random samples of the general population.[20,24]

Mortality Reductions Attributable to Treatments

The analysis of the contribution of treatments is reported for men and women together after confirming that in this population, no important sex heterogeneity was found in these results. Therefore, the proportional contribution of each treatment presented in the Results section and Figure 2 was computed using all DPPs as the denominator.

The DPPs associated with a specific CHD treatment within a disease subgroup at a specific time point (in either 2008 or 1995 for treatments available at that time) was estimated by taking the product of the number of people in the subgroup by the proportion of those patients who received the particular treatment at that time, 1-year case-fatality rates, and the relative risk reduction attributed to that specific treatment based on the published literature (Table 1).

We assumed that the compliance (proportion of treated patients actually taking therapeutically effective levels of medication) was 100% among hospital patients, 70% among symptomatic community patients, and 50% among asymptomatic community patients.[25,26] To avoid double counting of patients treated, we identified potential overlaps between different groups of patients and made appropriate adjustments (Appendix in the online-only Data Supplement). To address the potential effect of multiple treatments in the same patient on the relative reduction in case-fatality rate, we used the Mant and Hicks cumulative relative benefit approach[27] (Appendix in the online-only Data Supplement).

The effect of the increase in the use of treatments from 1995 to 2008 was assessed by subtracting the DPPs attributable to each treatment in 1995 from those in 2008.

Mortality Reductions Attributable to Changes in Risk Factors

The time trends in risk factors followed different patterns in men and women, resulting in heterogeneous contribution to the CHD mortality decline. The results of the analysis of the contribution of risk factors are therefore presented by sex, and the proportional contribution

Table 1. Estimated CHD Deaths Prevented or Postponed by Treatments in Portugal, 1995 to 2008

	No. of Eligible Patients*		Treatment Uptake†				No. of Deaths Prevented or Postponed‡ Best Estimate* (Minimum Estimate; Maximum Estimate)		
	1995	2008	1995	2008	Relative Risk Reduction	Case-Fatality Rate	1995	2008	Increase in DPPs (DPPs in 2008 minus DPPs in 1995)
Acute phase disease management									
AMI									
Community CPR	0	1770	0.00	0.01	0.05	0.110	0 (0; 0)	0 (0; 0)	0 (0; 0)
Hospital CPR	255	510	0.03	0.05	0.31	0.101	0 (0; 5)	5 (5; 15)	5 (5; 10)
Thrombolysis	7050	11 800	0.04	0.07	0.23	0.101	5 (0; 10)	10 (5; 25)	5 (5; 15)
Aspirin	7050	11 800	0.70	0.78	0.15	0.110	70 (30; 145)	115 (45; 230)	45 (15; 85)
β-Blocker	7050	11 800	0.35	0.63	0.04	0.110	10 (5; 20)	25 (10; 50)	15 (5; 30)
ACE-inhibitor	7050	11 800	0.32	0.59	0.07	0.110	15 (5; 30)	40 (15; 85)	25 (10; 55)
PCI (STEMI)	7050	11 800	0.00	0.60	0.32	0.110	0 (0; 0)	170 (70; 355)	170 (70; 355)
PCI (NSTEMI)	7050	11 800	0.00	0.35	0.32	0.110	0 (0; 0)	95 (40; 190)	95 (40; 190)
CABG	7050	11 800	0.00	0.02	0.20	0.110	0 (0; 0)	5 (0; 10)	5 (0; 10)
Cardiac rehabilitation	7050	11 800	0.00	0.02	0.26	0.110	0 (0; 0)	0 (0; 5)	0 (0; 5)
Total AMI	…	…	…	…	…	…	100 (40; 205)	470 (195; 960)	370 (155; 760)
Unstable angina									
Aspirin and heparin	3310	2275	0.00	0.56	0.33	0.069	0 (0; 0)	20 (10; 45)	20 (10; 45)
Aspirin	3310	2275	0.70	0.79	0.15	0.069	20 (10; 45)	15 (5; 25)	−5 (−5; −20)
Platelet glycoprotein IIB/IIIA inhibitors	3310	2275	0.00	0.17	0.09	0.069	0 (0; 0)	0 (0; 5)	0 (0; 5)
CABG	3310	2275	0.00	0.01	0.43	0.069	0 (0; 0)	0 (0; 0)	0 (0; 0)
PCI	3310	2275	0.00	0.33	0.32	0.069	0 (0; 0)	10 (5; 23)	10 (5; 23)
Total unstable angina	…	…	…	…	…	…	20 (10; 45)	50 (20; 100)	30 (10; 55)
Total AMI+unstable angina	…	…	…	…	…	…	120 (50; 245)	530 (215; 1060)	410 (165; 815)
Secondary prevention									
Post-AMI									
Aspirin	27 555	52 840	0.179	0.355	0.150	0.070	20 (5; 55)	75 (25; 190)	55 (20; 135)
β-Blocker	27 555	52 840	0.157	0.310	0.230	0.070	30 (10; 70)	100 (35; 250)	70 (25; 180)
ACE-inhibitor	27 555	52 840	0.142	0.281	0.200	0.070	25 (5; 55)	80 (25; 205)	55 (20; 150)
Statin	27 555	52 840	0.181	0.360	0.220	0.070	30 (10; 65)	105 (35; 255)	75 (25; 190)
Warfarin	27 555	52 840	0.008	0.015	0.220	0.070	0 (0; 5)	5 (0; 15)	5 (0; 10)
Cardiac rehabilitation	27 555	52 840	0.008	0.015	0.260	0.070	0 (0; 5)	5 (0; 15)	5 (0; 15)
Total secondary prevention post-AMI	…	…	…	…	…	…	105 (25; 185)	375 (125; 930)	265 (100; 750)
Post-CABG/PCI									
Aspirin	0	26 440	0.422	0.849	0.150	0.018	0 (0; 0)	15 (10; 80)	15 (10; 80)
β-Blocker	0	26 440	0.360	0.710	0.230	0.018	0 (0; 0)	15 (15; 100)	15 (15; 100)
ACE-inhibitor	0	26 440	0.329	0.661	0.200	0.018	0 (0; 0)	15 (10; 85)	15 (10; 85)
Statin	0	26 440	0.000	0.781	0.220	0.018	0 (0; 0)	15 (15; 110)	15 (15; 110)
Warfarin	0	26 440	0.009	0.029	0.220	0.018	0 (0; 0)	0 (0; 5)	0 (0; 5)
Cardiac rehabilitation	0	26 440	0.025	0.041	0.260	0.018	0 (0; 0)	0 (0; 5)	0 (0; 5)
Total post-CABG/PCI	…	…	…	…	…	…	0 (0; 0)	60 (50; 385)	60 (50; 385)
Chronic angina									
Aspirin	57 590	115 180	0.35	0.41	0.15	0.07	105 (34; 260)	120 (80; 255)	

(*Continued*)

Table 1. Continued

	No. of Eligible Patients*		Treatment Uptake†				No. of Deaths Prevented or Postponed‡ Best Estimate* (Minimum Estimate; Maximum Estimate)		
	1995	2008	1995	2008	Relative Risk Reduction	Case-Fatality Rate	1995	2008	Increase in DPPs (DPPs in 2008 minus DPPs in 1995)
Statin	57 590	115 180	0.00	0.48	0.22	0.07	0 (0; 0)	155 (80; 390)	155 (80; 390)
Total chronic angina	…	…	…	…	…	…	105 (70; 260)	280 (185; 640)	175 (120; 380)
Heart failure with hospital admission									
ACE-inhibitor	575	675	0.26	0.530	0.200	0.225	0 (0; 5)	5 (0; 15)	5 (0; 10)
β-Blocker	575	675	0.00	0.602	0.350	0.225	0 (0; 0)	10 (0; 30)	10 (0; 30)
Spironolactone	575	675	0.00	0.231	0.300	0.225	0 (0; 0)	5 (0; 10)	5 (0; 10)
Aspirin	575	675	0.23	0.459	0.150	0.225	0 (0; 5)	5 (0; 10)	5 (0; 5)
Total heart failure with hospital admission	…	…	…	…	…	…	5 (0; 10)	20 (5; 60)	15 (5; 50)
Heart failure in the community									
ACE-inhibitor	30 575	40 765	0.10	0.479	0.200	0.081	15 (5; 50)	90 (25; 275)	75 (20; 225)
β-Blocker	30 575	40 765	0.00	0.320	0.350	0.081	0 (0; 0)	145 (45; 360)	145 (45; 360)
Spironolactone	30 575	40 765	0.00	0.040	0.310	0.081	0 (0; 0)	15 (5; 40)	15 (5; 40)
Aspirin	30 575	40 765	0.00	0.300	0.150	0.081	0 (0; 0)	60 (20; 145)	60 (20; 145)
Total heart failure in the community	…	…	…	…	…	…	15 (5; 45)	310 (95; 815)	295 (90; 775)
Primary prevention									
Statins for primary prevention	1 037 176	2 074 350	0.00	0.273	0.215	0.007	0 (0; 0)	215 (55; 645)	215 (55; 645)
Hypertension treatments	2 883 717	3 310 225	0.36	0.628	0.130	0.008	210 (55; 625)	675 (135; 1680)	465 (80; 1050)
Total primary prevention	…	…	…	…	…	…	210 (55; 625)	890 (170; 3825)	680 (115; 1735)
Total treatments	…	…	…	…	…	…	560 (125; 820)	2450 (865; 6220)	1890 (660; 4845)

ACE indicates angiotensin-converting enzyme; AMI, acute myocardial infarction; CABG, coronary artery bypass graft; CHD, coronary heart disease; CPR, cardiopulmonary resuscitations; DPPs, deaths prevented or postponed; NSTEMI, non–ST-segment–elevation myocardial infarction; PCI, percutaneous coronary intervention; and STEMI, ST-segment–elevation myocardial infarction.

*Numbers were rounded to nearest 5; totals may therefore not always be exact.

†Proportion of patients who received prescription for the treatment. These values were subsequently adjusted assuming that compliance was 100% among hospital patients, 70% among symptomatic community patients, and 50% in asymptomatic individuals taking statins or antihypertensives for primary prevention.

‡The numbers reported were obtained after adjustment for polypharmacy.

presented in the Results section and Figure 2 was computed using the DPPs in each sex as the denominator.

Two approaches were used to calculate the DPPs as a result of changes in risk factors. We used a regression approach for continuous variables, namely, for SBP, cholesterol, and BMI. The number of DPPs as a result of the change in the mean of value for each risk factor (Table 2) was estimated as the product of 3 variables: the number of CHD deaths observed in 1995 (the baseline year), the absolute reduction in that risk factor, and the regression coefficient quantifying the independent association between population change in a specific cardiovascular risk factor and the consequent change in mortality from CHD. For dichotomous variables, a population-attributable risk fraction approach was used to determine the impact of changing prevalence of smoking, diabetes mellitus, and physical inactivity. The population-attributable risk fraction was calculated conventionally as $(P\times(RR-1))/(1+P\times(RR-1))$, where P is the prevalence of the risk factor and RR is the relative risk for CHD mortality associated with that risk factor (Appendix in the online-only Data Supplement). The number of DPPs was then estimated as the number of deaths from CHD expected in 2008 if 1995 rates had persisted multiplied by the difference between the population-attributable risk fraction in 2008 and that in 1995 (Table 2).

To separate the DPPs explained by SBP and total cholesterol into those resulting from pharmacological treatment of hypertension and hyperlipidemia versus lifestyles changes, we subtracted the age- and sex-specific DPPs calculated in the treatment section (ie, statins for primary prevention and hypertension treatments) from the DPPs calculated in the risk factor section for the variation in mean total cholesterol and SBP.

Because independent regression coefficients and relative risks for each risk factor were taken from multivariable analyses, we assumed that there was no further confounding between the treatment and risk factor sections of the model or among the major risk factors.

The numbers of DPPs as a result of risk factor changes were quantified systematically for each specific age and sex group to account for potential differences in effect. Lag times between the change in the risk factor rate and event rate change were not modeled; we assumed that lag times were relatively unimportant during a period of 13 years; also, lag times are not expected to have changed significantly during the period of analysis.[28]

Table 2. Estimated CHD Deaths Prevented or Postponed as a Result of Population Risk Factor Changes in Portugal, 1995 to 2008

	Absolute Level of Risk Factor		Change in Risk Factor				Deaths Prevented or Postponed Best Estimate‡ (Minimum Estimate; Maximum Estimate)
	1995	2008	Absolute	Relative	Regression Coefficient*	Relative Risk†	
Mean systolic blood pressure, mm Hg§							
Men	137.5	131.0	6.5	0.047	–0.033	…	845 (560; 1165)
Women	139.0	126.3	12.4	0.093	–0.040	…	1165 (795; 1555)
Smoking prevalence, %							
Men	32.3	25.6	6.6	0.214	…	3.03	235 (150; 335)
Women	6.9	10.3	–3.4	–0.812	…	3.92	–35 (–25; –50)
Mean total cholesterol, mmol/L§							
Men	5.40	5.30	0.10	0.008	–0.604	…	390 (225; 490)
Women	5.26	5.22	0.05	0.002	–0.588	…	200 (115; 250)
Mean body mass index, kg/m^2							
Men	26.16	27.80	–1.64	–0.063	0.028	…	–135 (–80; –210)
Women	26.62	28.23	–1.61	–0.060	0.027	…	–85 (–45; –130)
Diabetes mellitus prevalence, %							
Men	5.3	10.2	–4.9	–0,654	…	2.39	–395 (–255; –570)
Women	6.2	6.3	–0.1	–0.022	…	3.30	–30 (–20; –40)
Physical inactivity prevalence, %							
Men	90.1	67.0	23.2	0.260	…	1.32	75 (45; 105)
Women	92.9	72.4	20.5	0.532	…	2.28	30 (20;40)
Total risk factors	…	…	…	…	…	…	2260 (1490; 2945)
Total risk factors minus statins and antihypertensive medication	…	…	…	…	…	…	1575 (1355; 1880)

CHD indicates coronary heart disease.

*Units are (log transformed) percent change in mortality rate per unit of risk factor.

†Relative risk estimates of CHD mortality for the presence versus absence of each risk factor.

‡Numbers of deaths prevented or postponed were rounded to nearest 5; totals may therefore not always be exact.

§Deaths prevented or postponed because of the reduction in the mean values of the risk factor, independently of the reasons for this decline (pharmacological treatment or lifestyles changes).

Comparison of Estimated With Observed Mortality Changes

The estimates from the model for the total number of DPPs explained by each treatment and each risk factor change were rounded to the nearest multiple of 5 deaths. Any shortfall in the overall model estimate was then presumed to be attributable to either inaccuracies in our model estimates or other unmeasured risk factors. Estimates were then summed and compared with the observed changes in mortality for men and women in each age group (Figure 1).

Sensitivity Analyses

Given the uncertainty surrounding many of the values input in the model, multiway sensitivity analyses were performed using the analysis of extremes method.[29] For each variable in the model, we

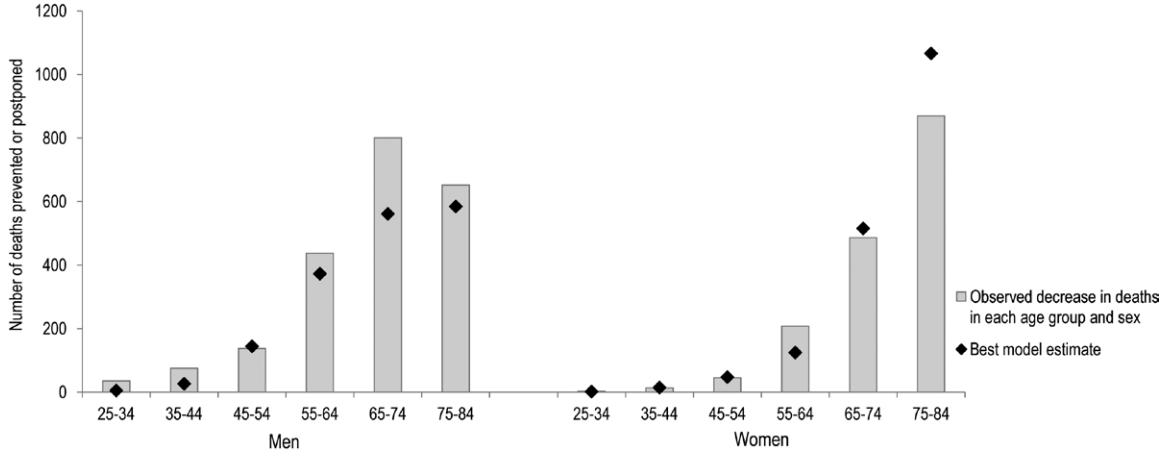

Figure 1. Comparison between model estimates and observed reductions in deaths from coronary heart disease in Portugal, 1995 to 2008.

assigned a lower value and an upper value, using 95% confidence intervals when available and otherwise using ±20% (for the number of patients, use of treatment, and compliance). For treatments assumed as 0, no uncertainty analysis was performed.

Detailed information on all methods is shown in the Appendix in the online-only Data Supplement.

Results

From 1995 to 2008, the age-adjusted mortality rate of CHD fell from 157.7 to 112.3 cases per 100 000 population among men aged 25 to 84 years and from 113.3 to 89.1 among women of the same age range. This resulted in 3760 fewer deaths in 2008, 2136 in men and 1624 in women, compared with the expected number if the rates in 1995 had persisted.

Approximately 3465 (92%) of the estimated decrease in number of deaths between 1995 and 2008 could be explained using the Portugal IMPACT model. The remaining 8% were attributed to changes in other unmeasured factors. Under the assumptions of the sensitivity analysis, the extreme minimum and the maximum number of deaths from CHD that were explained were 2015 (54%) and 6725 (180%). The agreement between the estimated and observed mortality decreases for men and women in each age group was generally good, except for men aged 65 to 74 years of age, where the model explained less than the observed DPPs, and women aged 75 to 84 years, where the model predicted more DPPs than observed (Figure 1).

Treatments

Treatments together prevented or postponed ≈1890 deaths (minimum estimate, 660; maximum estimate, 4845) related to CHD (Table 1). These treatment effects together explained ≈50% of the mortality reduction. The largest reductions came from the use of antihypertensive medication (12%) and initial treatments for AMI or unstable angina (11%). Within initial AMI treatments, the largest contributions came from percutaneous coronary intervention and aspirin.

The mortality decreases attributable to secondary prevention after AMI and heart failure treatments were 7% and 8%, respectively. Smaller proportions were explained by primary prevention using statins (6%) and treatment of chronic angina (5%). Secondary prevention after coronary artery bypass surgery and percutaneous coronary intervention accounted for <2% of deaths DPPs (Table 1).

Risk Factors

Changes in the major cardiovascular risk factors together accounted for ≈1575 fewer deaths (42%; minimum estimate: 1225; maximum: 2310; Table 2), 630 (29%) among men and 945 (58%) among women, after subtracting the effect of statins and antihypertensive treatment for primary prevention.

Decreases in mean population SBP, by 6.5 mm Hg in men and 12.4 mm Hg in women, were estimated to have contributed to 40% of the decrease in deaths in men and 72% in women. This difference was mainly attributable to lifestyle changes because the effect of antihypertensive treatment was smaller in men and women (13% and 12%, respectively). Mean population total cholesterol levels decreased by 0.10 mmol/L in men and 0.05 mmol/L in women, contributing to 18% of the estimated decrease in DPPs in men and 12% in women, approximately half attributable to lifestyle changes and half to the use of statins. Physical inactivity prevalence decreased by 23.2% in men and 20.5% in women, contributing to a decrease of 4% in DPPs in men and 2% in women (Table 2). Adverse trends were observed in diabetes mellitus and BMI, with the prevalence of diabetes mellitus increasing from 5.3% to 10.2% in men and 6.2% to 6.3% in women and mean BMI increasing from 26.2 to 27.8 kg/m^2 in men and 26.6 to 28.2 kg/m^2 in women between 1995 and 2008. These 2 risk factors together generated a 25% increase in DPPs in men and 7% in women. In men, the prevalence of smoking decreased, contributing to a 11% decrease in DPPs, whereas it increased in women, resulting in 2% extra deaths.

Sensitivity Analyses

The proportional contributions of specific treatments and risk factor changes to the overall decrease in CHD mortality in Portugal between 1995 and 2008 remained relatively consistent in the sensitivity analysis (Figure 2).

Discussion

We quantified the contribution of risk factors and treatments to the decline in CHD mortality in Portugal, a country in Southern Europe where the CHD mortality rates are much lower than in Northern Europe or the United States.[1,10] CHD mortality rates in Portugal fell by >25% between 1995 and 2008. The reductions attributable to evidence-based therapies accounted for approximately half of the DPPs. Approximately 42% of the fall was because of the trends in major risk factors, mainly SBP, although the rise in the prevalence of diabetes mellitus and mean BMI in both sexes and in smoking prevalence among women generated additional deaths.

The observed decrease in the mortality in the period considered was noteworthy,[1] despite the lower rates in the baseline year, even when compared with other Southern European countries with low baseline CHD mortality rates where this model was applied, namely, Spain (1988–2005)[15] and Italy (1980–2000).[14] The proportional contribution of treatments and risk factors for CHD mortality trends in Portugal is to some extent different from the aforementioned countries mainly because of a higher contribution of treatments. Most of the previous studies have consistently shown either a similar or slightly higher contribution of reduction in population risk factor levels compared with treatments,[10,14,15] but in the Icelandic population, the proportional contribution of risk factors was much higher than in Portugal.[30] However, comparisons with previous models must be interpreted with caution because of different time periods being assessed and the pace of evolution in treatments in the past 15 years.[31]

Advances in CHD diagnosis and treatment allowed the earlier identification of cases, the diagnoses of milder cases of disease, and consequently the decrease in the proportion of fatal acute events. The increasing number of centers with catheterization laboratory and the implementation of the coronary fast track system in the early 2000s in Portugal allowed for a more effective use of percutaneous coronary intervention and other invasive treatments.[9] Also, the period of analysis covers a time of steep changes in the availability and uptake

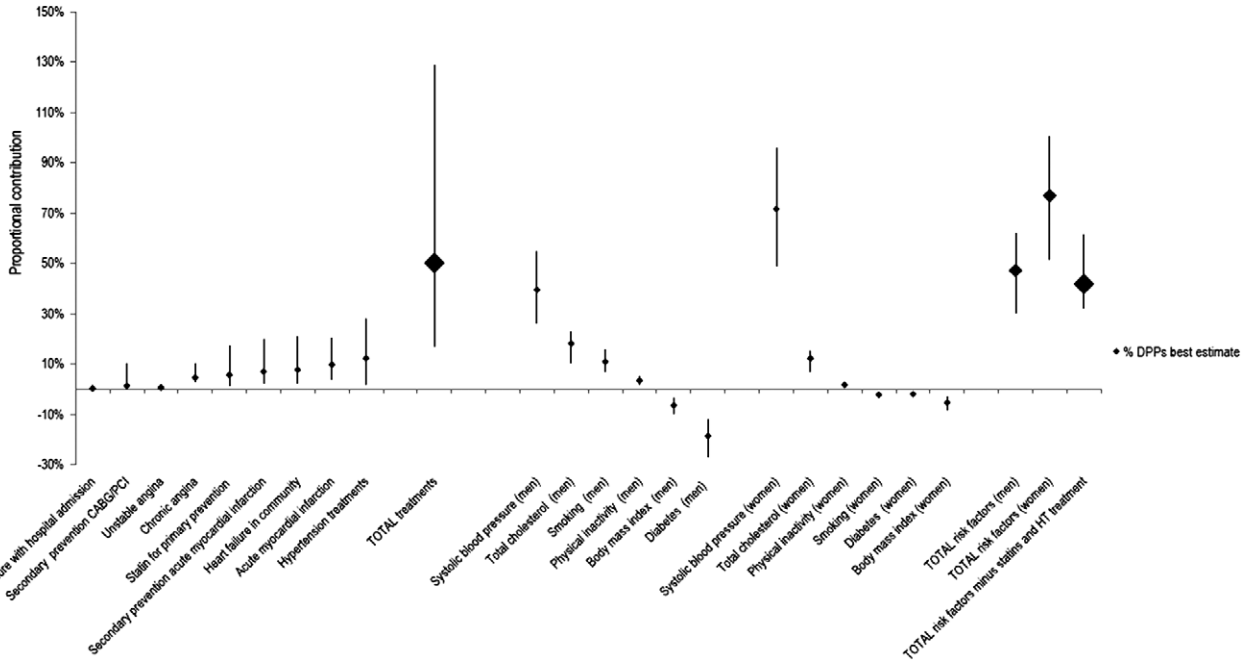

Figure 2. Proportion of all coronary heart disease deaths prevented or postponed explained by the model, which were attributed to the contribution of treatments and risk factors in Portugal, 1995 to 2008. The diamonds are the best model estimate and the vertical lines the extreme minimum and maximum estimates in sensitivity analysis. CABG indicates coronary artery bypass graft; DPPs, deaths prevented or postponed; HT, hypertension; and PCI, percutaneous coronary intervention.

of drugs for the initial treatments after an acute coronary syndrome and for secondary prevention after an AMI. The prescription of double antiplatelet therapy during hospitalization increased significantly over time, from 33% in 2002 to 95% in 2008. The same trend was observed in the prescription of β-blockers, angiotensin-converting enzyme inhibitors, and statins.[9] Also, recommended combined therapy for secondary prevention of events at hospital discharge (including the combination of double antiplatelets, angiotensin-converting enzyme inhibitors, β-blockers, and statins) increased from 14% in 2002 to 63% in 2008.[9] These important recent changes may explain the larger contribution of treatments, compared with risk factors, in our population.

Portugal has been described as one of the countries with the highest median blood pressure levels,[32,33] and in 2003, 3 million adults (42%) had hypertension.[34] However, from 1975 to 2005, mean SBP decreased remarkably in men after middle age and in women at all ages, adding up to a cumulative decrease of 22 and 32 mm Hg in SBP at an average age of 70 years, in men and women, respectively.[6] The proportion of hypertensives treated in Portugal increased in the past few decades, and in the beginning of the 2000s, almost half of hypertensives were treated.[19,34] The high prevalence of hypertension results in a large impact of any improvement in treatment rates because of the high number of people experiencing such benefit. Although the European guidelines in 1995 already recommended the prescription of pharmacological treatment aiming the target used today (SBP <140 mm Hg and diastolic <90 mm Hg),[35] pharmacological treatment for primary prevention in daily practice focused on high-risk individuals, and consequently only a relatively small proportion of the population was treated.

Total cholesterol has decreased slightly during the past years in Portugal,[20,22] as in most other European countries.[36] The overall decline in cholesterol level does not yet reflect the recent trends in the food intake in Portugal, where the consumption of fish and soup is decreasing and the consumption of fat-containing foods, such as meat and snacks, is increasing steeply.[37] However, other developed countries have shown even higher decreases in cholesterol levels despite the adverse trends in food intake.[14,15] When compared with other Mediterranean countries, we report a lower contribution of changes in the cholesterol after excluding the effect of pharmacological treatment (10% in Portugal versus 31% in Spain and 23% in Italy). The higher contribution of statins (6% in Portugal versus 1% in Spain and 3% in Italy) and the relatively faster trends in the diet transition toward a more unhealthy diet[38] suggest that in Portugal the reduction in total cholesterol was achieved mainly through the use of pharmacological treatment. In 1995, the use of statins was residual in Portugal (4.43 defined daily doses per 1000 inhabitants per day), but because of an average annual growth of 35%, in 2004, the number increased significantly (60.73 defined daily doses per 1000 inhabitants per day).[39]

The results of this study reflect the recent trends in smoking prevalence, which place Portuguese women in stage II of the smoking epidemic (characterized by a rapid increase of the prevalence of smoking along with few deaths attributable to smoking), whereas men are at a later stage, between stages III and IV (characterized by a decrease in the prevalence of smoking and a peak in smoking-attributable mortality).[7] As expected, we found differences in the trends in smoking prevalence trends according to sex. Although smoking prevalence in men decreased, it increased among women, resulting in 35 additional coronary deaths.

Apart from smoking among women, 2 other major risk factors led to increases in CHD deaths. The contribution of BMI to the increase in the total number of CHD deaths was important, as well as the dramatic increase in diabetes mellitus prevalence. These trends are consistent with recent studies in other industrialized countries.[14,15] Efforts to address obesity and diabetes mellitus should therefore receive particular attention in future policies to improve the public's health, especially because the prevalence of overweight/obesity in younger age groups of the Portuguese population is increasing.[8,21]

Modeling studies have several potential strengths, including the ability to transparently integrate and simultaneously consider huge amounts of data from many sources and testing the uncertainty inherent to such complexity by sensitivity analyses. However, models are highly dependent on the quality of data available. We made all the efforts to include in this model the most representative and unbiased data available in Portugal. We performed a systematic review that aimed to critically summarize the evidence from studies that quantified the distribution and frequency of all risk factors included in this model.[6,7,21,22] It was not possible to obtain representative data of treatment uptake in Portugal in 1995 because most of the existing studies reflected the usual care in higher quality specialized centers, which limits their generalizability. Therefore, we included estimates that represented a general consensus of a group of experts who critically evaluated the evidence available. The majority of the treatment data for 2008 were from EURHOBOP, a study that reported data from 3009 patients with acute coronary syndrome consecutively recruited in 10 Portuguese hospitals.[17] Even so, in some cases, the data used were obtained from studies possibly constrained by geographic or selection bias. In addition, because we used data from different studies for the first and last years, the variations in the study designs and study populations can potentially influence the results of the model. The majority of treatment uptake and case-fatality rates were based on data from the United Kingdom and the United States because little or no specific Portuguese data were available. Although major efforts were made to address overlaps, residual double counting of some individual patients remains possible. We also assumed that, after adjustments for imperfect compliance,[25] the efficacy of treatments in randomized controlled trials could be generalized to population effectiveness in usual clinical practice. All the assumptions that we made are presented in the Appendix in the online-only Data Supplement (Tables 1 and 2). Finally, we did not consider the direct effect of trends in socioeconomic status, compliance, or access to care. Although the trends in socioeconomic status and access to care are somehow indirectly measured because of their effect on the variation of risk factors and treatments, the variation in compliance was not assessed, and we do not have data in the Portuguese population to be able to estimate in which direction and to which extent this may have affected the results.

In conclusion, CHD mortality in Portugal decreased 25% between 1995 and 2008. Overall, treatments explained half of the overall decline in CHD deaths, and risk factor changes were more important among women than men. The decrease in mean SBP and increase in hypertension treatment contributed most to the CHD mortality decline. These results encourage the use of comprehensive efforts to actively promote primary prevention, particularly a healthy diet and tobacco control, as well as maximizing the population coverage of effective treatments.

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Disclosures

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References

1. Levi F, Chatenoud L, Bertuccio P, Lucchini F, Negri E, La Vecchia C. Mortality from cardiovascular and cerebrovascular diseases in Europe and other areas of the world: an update. *Eur J Cardiovasc Prev Rehabil*. 2009;16:333–350.
2. EUROCISS Working Group. Coronary and cerebrovascular population-based registers in Europe: are morbidity indicators comparable? Results from the EUROCISS Project. *Eur J Public Health*. 2003;13:55–60.
3. Levi F, Lucchini F, Negri E, La Vecchia C. Trends in mortality from cardiovascular and cerebrovascular diseases in Europe and other areas of the world. *Heart*. 2002;88:119–124.
4. Óbitos (N.º) por Sexo e Causa de morte. Anual [database on the Internet]. Instituto Nacional de Estatística. http://www.ine.pt/xportal/xmain?xpid=INE&xpgid=ine_main. 2010.
5. Nichols M, Townsend N, Luengo-Fernandez R, Leal J, Gray A, Scarborough P, Rayner M. *European Cardiovascular Disease Statistics 2012*. Brussels: European Society of Cardiology, Sophia Antipolis; 2012.
6. Pereira M, Carreira H, Vales C, Rocha V, Azevedo A, Lunet N. Trends in hypertension prevalence (1990-2005) and mean blood pressure (1975-2005) in Portugal: a systematic review. *Blood Press*. 2012;21:220–226.
7. Carreira H, Pereira M, Azevedo A, Lunet N. Trends in the prevalence of smoking in Portugal: a systematic review. *BMC Public Health*. 2012;12:958.
8. Ferreira RJ, Marques-Vidal PM. Prevalence and determinants of obesity in children in public schools of Sintra, Portugal. *Obesity (Silver Spring)*. 2008;16:497–500.
9. Santos JF, Aguiar C, Gavina C, Azevedo P, Morais J; Registo Nacional de Síndromes Coronárias Agudas da Sociedade Portuguesa de Cardiologia. Portuguese Registry of Acute Coronary Syndromes: seven years of activity. *Rev Port Cardiol*. 2009;28:1465–1500.
10. Ford ES, Ajani UA, Croft JB, Critchley JA, Labarthe DR, Kottke TE, Giles WH, Capewell S. Explaining the decrease in U.S. deaths from coronary disease, 1980-2000. *N Engl J Med*. 2007;356:2388–2398.
11. Capewell S, Beaglehole R, Seddon M, McMurray J. Explanation for the decline in coronary heart disease mortality rates in Auckland, New Zealand, between 1982 and 1993. *Circulation*. 2000;102:1511–1516.
12. Critchley J, Liu J, Zhao D, Wei W, Capewell S. Explaining the increase in coronary heart disease mortality in Beijing between 1984 and 1999. *Circulation*. 2004;110:1236–1244.
13. Unal B, Critchley JA, Capewell S. Explaining the decline in coronary heart disease mortality in England and Wales between 1981 and 2000. *Circulation*. 2004;109:1101–1107.

14. Palmieri L, Bennett K, Giampaoli S, Capewell S. Explaining the decrease in coronary heart disease mortality in Italy between 1980 and 2000. *Am J Public Health*. 2010;100:684–692.
15. Flores-Mateo G, Grau M, O'Flaherty M, Ramos R, Elosua R, Violan-Fors C, Quesada M, Martí R, Sala J, Marrugat J, Capewell S. Analyzing the coronary heart disease mortality decline in a Mediterranean population: Spain 1988-2005. *Rev Esp Cardiol*. 2011;64:988–996.
16. Correia R. *Geographic and Temporal Variation of the Procedures Used in Myocardial Infarction*. Porto: University of Porto, Medical School; 2011.
17. Kirchberger I, Azevedo A, Davoli M, Farmakis D, Ferrieres J, Garel P, Haekkinen U, Marrugat J, Torre M, Meisinger C. European Hospital Benchmarking in Acute Coronary Syndrome: the EURHOBOP project. *Congress of the European Society of Cardiology (ESC)*. 2012;22:297.
18. Almeida P, Rodrigues J, Lourenço P, Maciel MJ, Bettencourt P. Prognostic significance of applying the European Society of Cardiology consensus algorithm for heart failure with preserved systolic function diagnosis. *Clin Cardiol*. 2012;35:770–776.
19. Pereira M, Azevedo A, Barros H. Determinants of awareness, treatment and control of hypertension in a Portuguese population. *Rev Port Cardiol*. 2010;29:1779–1792.
20. Gray LJ, Barros H, Raposo L, Khunti K, Davies MJ, Santos AC. The development and validation of the Portuguese risk score for detecting type 2 diabetes and impaired fasting glucose. *Prim Care Diabetes*. 2013;7:11–18.
21. Carreira H, Pereira M, Azevedo A, Lunet N. Trends of BMI and prevalence of overweight and obesity in Portugal (1995-2005): a systematic review. *Public Health Nutr*. 2012;15:972–981.
22. Carreira H, Pereira M, Alves L, Lunet N, Azevedo A. Dyslipidaemia, and mean blood cholesterol and triglycerides levels in the Portuguese population: a systematic review. *Arq Med*. 2012;26:112–123.
23. Instituto Nacional de Estatística. *Inquérito Nacional de Saúde 1995–1996*. Lisbon: Instituto Nacional de Saúde Doutor Ricardo Jorge; 1997.
24. Gardete-Correia L, Boavida JM, Raposo JF, Mesquita AC, Fona C, Carvalho R, Massano-Cardoso S. First diabetes prevalence study in Portugal: PREVADIAB study. *Diabet Med*. 2010;27:879–881.
25. Nichol MB, Venturini F, Sung JC. A critical evaluation of the methodology of the literature on medication compliance. *Ann Pharmacother*. 1999;33:531–540.
26. Butler J, Arbogast PG, BeLue R, Daugherty J, Jain MK, Ray WA, Griffin MR. Outpatient adherence to beta-blocker therapy after acute myocardial infarction. *J Am Coll Cardiol*. 2002;40:1589–1595.
27. Mant J, Hicks N. Detecting differences in quality of care: the sensitivity of measures of process and outcome in treating acute myocardial infarction. *BMJ*. 1995;311:793–796.
28. McAlister FA. Commentary: relative treatment effects are consistent across the spectrum of underlying risks usually. *Int J Epidemiol*. 2002;31:76–77.
29. Briggs A, Sculpher M, Buxton M. Uncertainty in the economic evaluation of health care technologies: the role of sensitivity analysis. *Health Econ*. 1994;3:95–104.
30. Aspelund T, Gudnason V, Magnusdottir BT, Andersen K, Sigurdsson G, Thorsson B, Steingrimsdottir L, Critchley J, Bennett K, O'Flaherty M, Capewell S. Analysing the large decline in coronary heart disease mortality in the Icelandic population aged 25-74 between the years 1981 and 2006. *PLoS One*. 2010;5:e13957.
31. Nabel EG, Braunwald E. A tale of coronary artery disease and myocardial infarction. *N Engl J Med*. 2012;366:54–63.
32. Danaei G, Finucane MM, Lin JK, Singh GM, Paciorek CJ, Cowan MJ, Farzadfar F, Stevens GA, Lim SS, Riley LM, Ezzati M; Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group (Blood Pressure). National, regional, and global trends in systolic blood pressure since 1980: systematic analysis of health examination surveys and epidemiological studies with 786 country-years and 5·4 million participants. *Lancet*. 2011;377:568–577.
33. The INTERSALT Co-operative Research Group. Appendix tables. Centre-specific results by age and sex. *J Hum Hypertens*. 1989;3:331–407.
34. Macedo ME, Lima MJ, Silva AO, Alcantara P, Ramalhinho V, Carmona J. Prevalence, awareness, treatment and control of hypertension in Portugal: the PAP study. *J Hypertens*. 2005;23:1661–1666.
35. WHO. 1993 guidelines for the management of mild hypertension: memorandum from a WHO/ISH meeting. *Bull World Health Organ*. 1993;71:503–517.
36. Farzadfar F, Finucane MM, Danaei G, Pelizzari PM, Cowan MJ, Paciorek CJ, Singh GM, Lin JK, Stevens GA, Riley LM, Ezzati M; Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group (Cholesterol). National, regional, and global trends in serum total cholesterol since 1980: systematic analysis of health examination surveys and epidemiological studies with 321 country-years and 3·0 million participants. *Lancet*. 2011;377:578–586.
37. Marques-Vidal P, Ravasco P, Dias CM, Camilo ME. Trends of food intake in Portugal, 1987-1999: results from the National Health Surveys. *Eur J Clin Nutr*. 2006;60:1414–1422.
38. Chen Q, Marques-Vidal P. Trends in food availability in Portugal in 1966-2003: comparison with other Mediterranean countries. *Eur J Nutr*. 2007;46:418–427.
39. Teixeira IJ, Escoval A, Schiappa M. Lipid-lowering drugs: use and expenditure in Portugal (1995-2004). *Rev Port Cardiol*. 2007;26:475–493.