Explaining the Decrease in Coronary Heart Disease Mortality in Italy Between 1980 and 2000

Luigi Palmieri, DrStat, Kathleen Bennett, PhD, Simona Giampaoli, MD, and Simon Capewell, MD

Objectives. We examined the extent to which the decrease in coronary heart disease (CHD) mortality rates in Italy could be explained by changes in cardiovascular risk factors versus the use of medical and surgical treatments.

Methods. We used a validated model to combine data on changes in risk factors and uptake and effectiveness of cardiac treatments among adult men and women in Italy between 1980 and 2000. Data sources included results of published trials, meta-analyses, official statistics, longitudinal studies, and national surveys. The difference between observed and expected CHD deaths in 2000 was partitioned among treatments and risk factors.

Results. From 1980 to 2000, the age-adjusted CHD mortality rate in Italy fell among persons aged 25 to 84 years, resulting in 42 930 fewer CHD deaths in 2000. Approximately 40% of this decrease was attributed to treatments and 55% to changes in risk factors.

Conclusions. Over half of the CHD mortality fall in Italy between 1980 and 2000 was attributable to reductions in major risk factors, mainly cholesterol and blood pressure, and less than half to evidence-based medical therapies. These results are becoming increasingly important, both for understanding past trends and for planning future prevention and treatment strategies. (*Am J Public Health.* 2010; 100:684–692. doi:10.2105/AJPH.2008.147173)

The favorable position of Italy in terms of coronary heart disease (CHD) and cardiovascular disease has been consistently documented by official mortality statistics and different epidemiological studies.[1–7] However, CHD still represents one of the main causes of death in Italy, accounting for 13% of general mortality and 32% of circulatory system deaths in the country.

Coronary heart disease (CHD) death rates in Italy have shown profound changes during the second half of the 20th century. After a steep increase in CHD death rates up until the first years of the 1970s,[8] a short plateau occurred during the late 1970s, when a slight decline began and has continued until recent years.[9–13] This has been observed in both men and women. This decline is not easy to explain, but some findings are suggestive.

First, population data collected between 1980 and 2000 in the age range of 35 to 64 years[5,14] suggest that a substantial decrease in certain cardiovascular risk factors has occurred: smoking prevalence has decreased in men and increased in women,[15] systolic blood pressure mean values fell and an improvement in treatment medications was registered, treatments for hypertension appeared effective in men and much more so in women,[15] and obesity increased slightly in men but decreased in women—although mean levels of body mass index remained in the overweight range in both genders.[15]

Second, recent decades have seen a revolution in treatments for established CHD in post–myocardial infarction prevention and in secondary prevention such as effective evidence-based therapies including the use of thrombolysis, coronary artery bypass graft (CABG) surgery, coronary angioplasty and stenting, angiotensin-converting enzyme inhibitors, and the use of statins.

Determining the respective contributions of prevention and therapy to falling CHD mortality rates is therefore becoming increasingly important, both for understanding past trends and for planning future strategies.

The previous application of the cell-based IMPACT model[16] in various industrialized countries helped to demonstrate that the proportion of the CHD mortality rate decrease attributable to reductions in major CHD risk factors between 1980 and 2000 ranged from 44% to 76%,[17–26] with a complementary contribution from cardiovascular treatments. However, no studies in Mediterranean countries have considered the large changes in mortality rates since 1980, nor have they attempted to quantify the relative contributions from specific therapies and risk factor trends. We therefore applied an epidemiological model that was successfully used in other countries to examine the decline in CHD mortality in Italy between 1980 and 2000.

METHODS

To examine the contributions of various factors to the changes in CHD mortality rates among Italian adults aged 25 to 84 years, we used an updated version of the IMPACT mortality model, which has been previously validated in Europe, New Zealand, the United States, and China.[16,22–27] This mortality model has been described in detail elsewhere.[16,22,23,27] The model is comprehensive, incorporating major population risk factors for CHD (smoking, blood pressure, total cholesterol, obesity, diabetes, and physical inactivity) and all usual medical and surgical treatments for CHD.

Wherever possible, data sources specific to the Italian population were used in constructing the Italian IMPACT model. When more than 1 data source was available, the "best" source was chosen on the basis of being judged the most representative, unbiased, and up-to-date. (Detailed information regarding data sources is available as supplement to the online version of this article at http://www.ajph.org).

Estimating the Number of Deaths Prevented or Postponed

Total population and age distribution data for Italy in 1980 and 2000 were obtained from the Italian National Institute of Statistics. Deaths by age and gender and CHD mortality

rates in 1980 and 2000 were obtained from the National Vital Statistics System of the Italian National Institute of Statistics. We calculated the number of CHD deaths expected in 2000 if the CHD mortality rates in 1980 had persisted by multiplying the age-specific mortality rates for 1980 by the population for each 10-year age stratum in the year 2000 (thus accounting for the aging of the population). Subtracting the number of deaths observed in 2000 then yielded the fall in the number of CHD deaths prevented or postponed in 2000 that the model needed to explain.

Mortality Benefits From Treatments

Figures for the prevalence of CHD by diagnosis, the estimated frequency of use of specific treatments, the case fatality rate by diagnosis, and the risk reduction because of treatment, all stratified by age and gender, were obtained from published sources. (The data are tabulated in tables available as supplements to the online version of this article at http://www.ajph.org.) The number of deaths prevented or postponed as a result of each intervention in each group of CHD patients in the year 2000 (Table 1) was then calculated by multiplying the number of people in each diagnostic group by the proportion of these patients receiving a particular treatment, by the case-fatality rate over 1 year, and by the relative reduction in 1-year case-fatality by the administered treatment.[23,24] For example, in Italy in 2000, approximately 10 045 men aged 55 to 64 years were hospitalized with acute myocardial infarction. Accordingly, 56%[28,29] were given aspirin, with an expected mortality reduction of 15%, as from a previous study.[30] The expected age-specific 1-year case-fatality rate was approximately 12%.[31] The number of deaths prevented or postponed for at least 1 year by the use of aspirin among men aged 55 to 64 years hospitalized with acute myocardial infarction was then calculated as $10\,045 \times 0.56 \times 0.15 \times 0.12 = 101$.

Several adjustments were made to this basic analysis. Although most of the therapeutic measures studied were not in use in 1980, in some cases such use was already significant (e.g., CABG surgery for stable angina pectoris). In such cases, the number of deaths prevented or postponed as a result of the therapy, as used in 1980, was calculated and subtracted from the figure for 2000 to calculate the net benefit. We assumed that compliance (the 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.[16,23,32,33]

To avoid the double counting of patients treated, we identified potential overlaps between different groups of patients and made appropriate adjustments (see Table 9 in the appendix, available as a supplement). For example, approximately one quarter of acute myocardial infarction survivors developed heart failure within 1 year, and approximately half the patients receiving CABG surgery have a previous myocardial infarction.[16,23] The potential interaction effects of medications and main risk factors on the change in CHD mortality were also addressed. For example, the number of deaths prevented or postponed by hypertension treatment were estimated and then subtracted from the total deaths prevented or postponed attributed to the declining trend (which has been lasting for centuries) in population blood pressure to assess the individual contributions of the two components (see table 9 in the appendix, available online).

To address the potential effect on relative reduction in the case-fatality rate for individual patients receiving multiple treatments, we used the Mant and Hicks cumulative relative benefit approach[34]:

(1) Relative benefit = 1 − [(1 − relative reduction in case-fatality rate for treatment A) × (1 − relative reduction in case-fatality rate for treatment B) × . . . × (1 − relative reduction in case-fatality rate for treatment N)].

Risk Factors and Mortality Benefits

Two approaches were used to calculate the numbers of deaths prevented or postponed as a result of changes in risk factors. We used the regression approach for systolic blood pressure, cholesterol, and body mass index (BMI; weight in kilograms divided by height in meters squared). The number of deaths prevented or postponed as a result of the change in the mean of each of these risk factors (Table 2) was estimated as the product of 3 variables: the number of CHD deaths observed in 1980 (the base year), the subsequent reduction in that risk factor (see table 2 in the appendix, available online), and the regression coefficient quantifying the change in CHD mortality per unit absolute change in the risk factor (see table 6 in the appendix, available online). For example, in 1980, there were 2403 CHD deaths among 2 992 174 women aged 55 to 64 years. Mean systolic blood pressure in this group decreased by 8.73 mm Hg between 1980 and 2000. The largest meta-analysis reports an estimated age- and gender-specific reduction in mortality of 2.5% for every 1 mm Hg reduction in systolic blood pressure and 50% for every 20 mm Hg reduction in systolic blood pressure, thereby generating a logarithmic coefficient of −0.035.[35]

The number of deaths prevented or postponed as a result of this change was then estimated as:

(2) $(1 - \mathrm{EXP}[\text{coefficient} \times \text{change}]) \times (\text{deaths in } 1980) = (1 - \mathrm{EXP}[-0.035 \times 8.73]) \times 2403 = 635$.

The population-attributable risk fraction approach[36] was used to determine the impact of the changing prevalence of smoking, diabetes, and physical inactivity. The population-attributable risk fraction is calculated as:

(3) $(P \times [RR - 1]) / (1 + P \times [RR - 1])$,

where P is the prevalence of the risk factor (see table 2 in the appendix, available online) and RR is the relative risk for CHD mortality associated with that risk factor (see table 7 in the appendix, available online). The number of deaths prevented or postponed was then estimated as the number of CHD deaths in 1980 multiplied by the difference between the population-attributable risk fraction of 1980 and that of 2000 (Table 2). For example, the prevalence of diabetes in men aged 65 to 74 years increased from 13.4% in 1980 to 16.3% in 2000. Given a relative risk of 1.93, the population-attributable risk fraction increased from 0.111 to 0.132. Additional deaths in 2000 attributable to increased diabetes prevalence were therefore as follows:

(4) CHD deaths in 1980 (18 447) × (0.132 − 0.111) = 384.[16,22,23,27]

Because independent regression coefficients and relative risks for each risk factor were

TABLE 1—Estimated Coronary Heart Disease Deaths Prevented or Postponed by Medical or Surgical Treatments: Italy, 2000

Patient Groups and Specific Treatments	Patients Eligible	Treatment Uptake, %	Relative Risk Reduction	1-Year Mean Case Fatality	Absolute Risk Reduction	Deaths Prevented or Postponed					
						No.	Minimum No.	Maximum No.	% of Total Decline	Minimum No.	Maximum No.
Acute myocardial infarction											
Total	53 430	. . .	. . .	0.051	. . .	2120	886	2595	4.9	2.1	6.0
Community resuscitation	2458	49	0.07	0.051	0.110	160	131	196	0.4	0.3	0.5
Hospital resuscitation	2137	99	0.21	0.051	0.212	429	180	769	1.0	0.4	1.8
Thrombolysis	53 430	39	0.21	0.051	0.039	798	190	1023	1.9	0.4	2.4
Aspirin	53 430	56	0.15	0.051	0.031	907	555	1514	2.1	1.3	3.5
β blocker	53 430	21	0.04	0.051	0.008	91	8	486	0.2	0.0	1.1
ACE inhibitor	53 430	22	0.07	0.051	0.009	166	21	373	0.4	0.0	0.9
Primary angioplasty	53 430	6	0.28	0.051	0.056	167	90	278	0.4	0.2	0.6
Minus AMI treatments in 1980[a]						−598	−290	−2045	−1.4	−0.7	−4.8
Unstable angina	19 961			0.069		439	243	838	1.0	0.6	2.0
Aspirin and heparin		60	0.33	0.069	0.027	305	194	512	0.7	0.5	1.2
Aspirin alone		30	0.15	0.069	0.013	69	38	154	0.2	0.1	0.4
GP IIB/IIIA antagonists and clopidogrel		50	0.09	0.069	0.007	65	11	172	0.2	0.0	0.4
Secondary prevention											
Post–myocardial infarction											
Total	162 613			0.051		2208	1763	2929	5.1	4.1	6.8
Aspirin		75	0.15	0.051	0.009	679	587	1045	1.6	1.4	2.4
β blocker		52	0.23	0.051	0.014	600	94	1157	1.4	0.2	2.7
ACE inhibitor		46	0.20	0.051	0.012	428	71	1469	1.0	0.2	3.4
Statin		44	0.22	0.051	0.014	296	87	380	0.7	0.2	0.9
Warfarin		4	0.22	0.051	0.014	65	9	119	0.2	0.0	0.3
Rehabilitation		17	0.26	0.051	0.016	173	29	332	0.4	0.1	0.8
Post–CABG/PTCA											
Total	165 122			0.02	0.028	411	269	2734	1.0	0.6	6.4
Aspirin		97	0.15	0.02	0.003	121	63	965	0.3	0.1	2.2
β blocker		70	0.23	0.02	0.005	93	42	515	0.2	0.1	1.2
ACE inhibitor		58	0.20	0.02	0.001	103	86	587	0.2	0.1	1.4
Statin		48	0.22	0.02	0.006	85	75	402	0.2	0.2	0.9
Warfarin		5	0.22	0.02	0.003	6	3	147	0.0	0.0	0.3
Rehabilitation		20	0.26	0.02	0.005	3	0	117	0.0	0.0	0.3
Minus secondary prevention treatments in 1980[b]						−30					
Chronic angina treatments	180 241					4212	1833	7674	9.8	4.3	17.9
CABG surgery 1990–2000 (minus 1980)	82 905	100	0.39	0.020	0.010	272	223	750	0.6	0.5	1.7
Angioplasty 1990–2000	97 336	100	0.13	0.016	0.002	223	173	343	0.5	0.4	0.8
Aspirin in the community	2 013 984	72	0.15	0.011	0.003	2770	1207	5233	6.5	2.8	12.2
Statins in the community	2 013 984	34	0.22	0.011	0.006	947	230	1349	2.2	0.5	3.1
Heart failure with hospital admission	44 789	35		0.246	0.126	1942	1001	3374	4.5	2.3	7.9
ACE inhibitor		47	0.20	0.246	0.061	731	213	1108	1.7	0.5	2.6
β blocker		28	0.35	0.246	0.140	787	639	1786	1.8	1.5	4.2
Spironolactone		5	0.30	0.246	0.120	250	21	257	0.6	0.0	0.6

Continued

TABLE 1—*Continued*

Aspirin		19	0.15	0.246	0.010	120	78	162	0.3	0.2	0.4
Statins		18	0.22	0.246	0.008	54	50	62	0.1	0.1	0.1
Heart failure in the community (minus 1980)	293 227			0.081		3929	1583	8998	9.2	3.7	21.0
ACE inhibitor		56	0.20	0.081	0.020	1488	609	3048	3.5	1.4	7.1
β blocker		22	0.35	0.081	0.023	964	451	1865	2.2	1.1	4.3
Spironolactone		7	0.31	0.081	0.021	274	88	1162	0.6	0.2	2.7
Aspirin		56	0.15	0.081	0.015	1117	396	2688	2.6	0.9	6.3
Statin		7	0.22	0.081	0.017	197	40	234	0.5	0.1	0.5
Minus heart failure treatment effect in 1980						–112					
Hypertension treatments	11 644 212	38	0.13	0.006	0.0005	644	328	1157	1.5	0.8	2.7
Statins and so on, for primary prevention lipid reduction	8 330 610	17	0.35	0.003	0.0011	1164	186	2701	2.7	0.4	6.3
Total treatments						17 068	8092	33 000	39.8	18.8	76.9

Note. ACE = angiotensin-converting enzyme; AMI = acute myocardial infarction; CABG = coronary artery bypass graft surgery; GP IIB/IIIA = glycoprotein IIB/IIIA inhibitors; PTCA = percutaneous transluminal coronary angioplasty. Numbers of eligible patients and category totals of deaths prevented or postponed were rounded to 0 or 5; therefore, totals may not sum exactly.
[a]To depurate the 20-year period overall effect from the effects caused by treatments in 1980.
[b]To depurate the 20-year period overall effect from the effects caused by secondary prevention treatments in 1980.

taken from published multivariate analyses including adjusting factors, we assumed that there was no further synergy between the treatment and risk factor sections of the model or between the major risk factors. The main sources of the models were the InterHeart Study[37] and the Prospective Studies Collaboration's meta-analyses of cholesterol and blood pressure.[35,38]

The number of deaths prevented or postponed as a result of risk factor changes were systematically quantified for each specific patient group to account for potential differences in effect. Lag times between risk factor rate change and event rate change were not modeled; it was assumed that these would be relatively unimportant over 2 decades.[24,27,38,39]

Comparison of Estimated and Observed Mortality Changes

The model estimates for the total number of deaths prevented or postponed by each treatment and for each risk factor change were rounded to the nearest 5 deaths (e.g., 696 became 695). All of these figures were then summed and compared with the observed changes in mortality for men and women in each specific age group. Any shortfall in the overall model estimate was then presumed to be attributable to other unmeasured risk factors.[16,23,24]

Sensitivity Analyses

All of the assumptions and variables listed previously were tested in a multiway sensitivity analysis using the analysis of extremes method.[16,23,24,40] For each model parameter, a lower and upper value was assigned using 95% confidence intervals where available, or, when any assumption was possible, a threshold of ±20% (for patient numbers, treatment uptake, and compliance) was chosen to estimate a range of potential variability. Multiplying all the lower-bound estimates simultaneously yielded the lower-bound estimate, and multiplying all the upper-bound estimates simultaneously yielded the upper bound estimate. For example, for aspirin treatment among men aged 55 to 64 years hospitalized with acute myocardial infarction, the best estimate was:

(5) Patient numbers×treatment uptake× relative mortality reduction×1-year case fatality= deaths prevented or postened,

or 10 045×0.56×0.15×0.12=101 deaths prevented or postponed. The minimum estimate from the multiway sensitivity analysis was 8036×0.448×0.12×0.096=41 deaths prevented or postponed, and the maximum estimate was 12 054×0.672×0.18×0.144= 210 deaths prevented or postponed.

(The data sources are detailed in the appendix, available online.)

RESULTS

From 1980 to 2000, the age-adjusted mortality rate of CHD fell from 267.1 to 141.3 per 100 000 population among men aged 25 to 84 years and from 161.3 to 78.8 per 100 000 population among women aged 25 to 84 years. In 1980, 65 640 deaths among people aged 25 to 84 years were recorded with a diagnosis of CHD (*International Classification of Diseases, Ninth Revision* [*ICD-9*],[41] codes 410–414). In 2000, 45 890 such deaths were recorded (*ICD-9* codes 410–414). However, had the age-specific death rates from 1980 persisted to 2000, an additional 42 930 deaths from CHD would have occurred in 2000 (58% among men and 42% among women).

The Italian IMPACT model explained approximately 40 730 (95%) of this 42 930 decrease in the number of CHD deaths. Under the assumptions of the sensitivity analysis, the extreme minimum and maximum numbers of CHD deaths explained were 28 350 (67%) and 61 455 (127%). The agreement between the

TABLE 2—Association of Coronary Heart Disease Deaths Prevented or Postponed With Population Risk Factor Changes: Italy, 1980–2000

	Absolute Level of Risk Factor[a]		Risk Factor Change		Men			Women			Deaths Prevented or Postponed					
	1980	2000	Absolute Change	Relative Change, %	Regression Coefficient,[b] B	Aged < 55 Years, RR	Aged ≥ 55 Years, RR	Regression Coefficient,[b] B	Aged < 65 Years, RR	Aged ≥ 65 Years, RR	Best Estimate, No.	Minimum, No.	Maximum, No.	% of Total Decline	Minimum %	Maximum %
Smoking prevalence	31.7%	27.8%	-3.9%	-12.5		3.33	2.52		4.49	2.14	1602	1203	2234	3.7	2.8	5.2
Systolic blood pressure[c]	136.5 mm Hg	131.8 mm Hg	-5.3 mm Hg	-3.4	-0.0329			-0.0401			10714	9684	12048	25.0	22.6	28.1
Total cholesterol[d]	5.62 mmol/L	5.27 mmol/L	-0.35 mmol/L	-6.2	-0.6668			-0.5705			10043	8923	13372	23.4	20.8	31.1
Physical inactivity	30.1%	20.0%	-10.1%	-32.7		1.30	1.27		1.35	1.33	2491	1395	3239	5.8	3.3	7.5
Body mass index	26.2 kg/m^2	26.5 kg/m^2	0.22 kg/m^2	0.8	0.0676			0.0646			-246	-138	-381	-0.6	-0.3	-0.9
Diabetes prevalence	6.1%	6.2%	0.1%	2.5		2.66	1.93		3.53	2.59	-945	-810	-2056	-2.2	-0.7	-4.8
Total risk factors											23660	20259	28455	55.1	48.4	66.3

Note. RR = risk ratio. Numbers of deaths prevented or postponed were rounded to 0 or 5; therefore, totals may not sum exactly. Total adult population in 1980 was 41 506 207.

[a]Data for 1980 was gathered from the RIFLE Project (Risk Factors and Life Expectancy), except for diabetes and physical inactivity, which were from the MATISS Project (Malattie Aterosclerotiche ISS). Data for 2000 was gathered from the OEC (Osservatorio Epidemiologico Cardiovascolare) survey.[14,45]

[b]Change in mortality rate per unit of risk factor.

[c]Excluding hypertension treatments.

[d]Excluding statins.

number of estimated deaths and the number of observed deaths was reasonably good for men across all groups and for women younger than 75 years (Figure 1). Changes in medical treatments accounted for approximately 40% and risk factor changes accounted for approximately 55% of the decrease in deaths (Tables 1 and 2).

Medical and Surgical Treatments

Approximately 17 070 (40%) of the CHD deaths prevented or postponed were attributable to medical therapies (minimum estimate, 8090; maximum estimate, 33 000; Table 1).

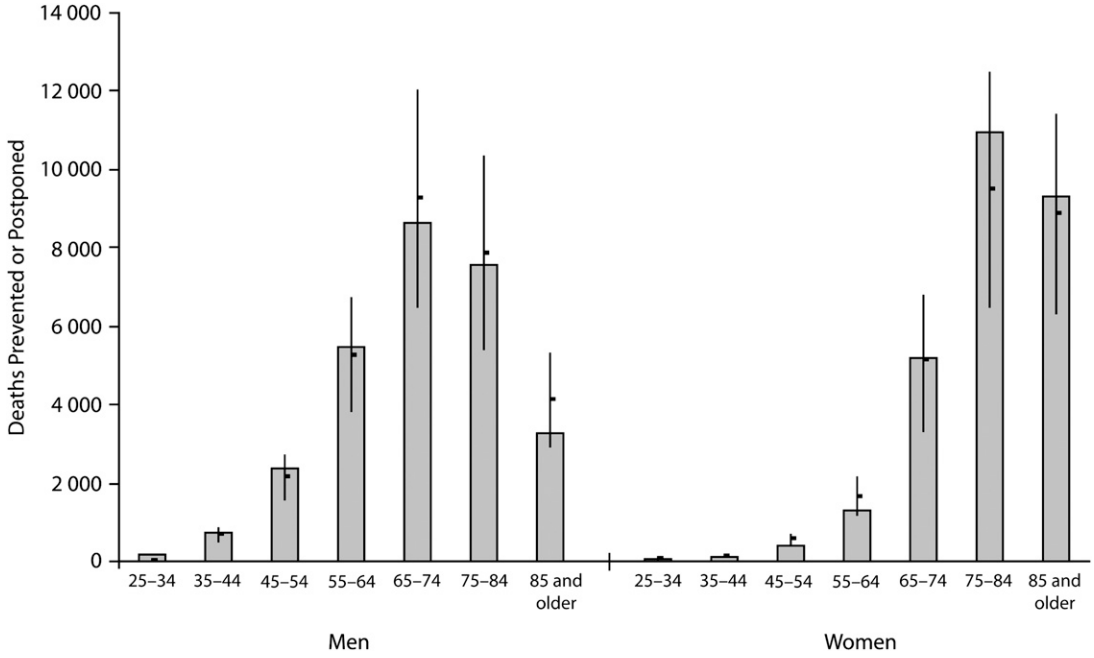
The largest reductions in deaths came from the use of treatments for heart failure (hospital and community, approximately 5870 deaths), treatments for chronic angina (approximately 3720 deaths), and secondary prevention medications or rehabilitation (after acute myocardial infarction or after revascularization, approximately 2620 deaths), followed by initial treatments for acute myocardial infarction or unstable angina (approximately 2560 deaths), treatments of hypertension, and statins for primary prevention. Of note, the use of revascularization for chronic angina resulted in a reduction of approximately 660 fewer deaths representing approximately 1.5% of the total decline.

Risk Factors

Approximately 23 660 (55%) fewer CHD deaths were attributable to changes in risk factors (minimum estimate, 20 260; maximum estimate, 28 455; Table 2). Decreases in systolic blood pressure (–5.3 mm Hg), total cholesterol concentration (–0.35 mmol/L), and smoking prevalence (–4.0%) were estimated to have prevented or postponed approximately 10 715 (25%), 10 045 (23%), and 1600 (4%) deaths, respectively. The (–10%) decrease in physical inactivity prevented or postponed approximately 2490 deaths. The 0.1% increase in diabetes prevalence resulted in approximately 945 additional deaths overall, whereas the small increase in BMI resulted in approximately 245 additional deaths (Table 2).

Proportional Contributions in the Sensitivity Analysis

The proportional contributions of specific treatments and risk factor changes to the overall fall in CHD deaths in 2000 remained



Note. Columns are the observed decrease in deaths in each age group, boxes are the best model estimate, and bars are the extreme minimum and maximum estimates from sensitivity analysis.

FIGURE 1—Model-estimated and observed reductions in deaths from coronary heart disease in Italy between 1980 and 2000, by age and gender.

relatively consistent in the sensitivity analyses (Tables 1 and 2). Thus, cholesterol level decrease accounted for approximately 10 045 fewer deaths, representing 23.4% of the total 42 930 decrease in deaths. The minimum estimated contribution was 8925 fewer deaths (20.8%), and the maximum was 13 370 (31.1%). The contribution of cholesterol therefore remained consistently greater than that of smoking, irrespective of whether best, minimum, or maximum estimates were compared (Table 2).

DISCUSSION

We examined CHD trends in Italy, where CHD mortality rates are far lower than in northern Europe and the United States. Mortality rates fell by over 40% between 1980 and 2000. Our analyses suggest that more than half the of the decrease (approximately 55%) was attributable to reductions in major risk factors, mainly systolic blood pressure and cholesterol among men and women and smoking among men, and less than half (approximately 40%) were attributable to evidence-based medical therapies. However, the rise in smoking rates among women generated additional deaths.

Even though CHD mortality rates fell by 41% between 1980 and 2000 in Italy, the burden of coronary heart disease in Italy remains an important public health issue. Coronary disease still accounts for 13% of all deaths and causes substantial loss of quality of life, disability, and long-term dependence on health services and medications; furthermore, coronary disease is an important factor related to stroke occurrence during older age. During the 2 decades of the study there has been rapid growth in costly medical technology and pharmaceutical treatments for CHD, as well as substantial public health efforts to reduce the levels of major cardiovascular risk factors. Establishing the relative contributions of these 2 approaches is therefore of considerable importance.

This is the first time the IMPACT model has been applied to a Mediterranean country such as Italy, which is characterized by lower CHD mortality rates compared with northern European countries[24,27] and the United States,[42] despite the latter populations having similar or lower levels of the main cardiovascular risk factors (the Mediterranean paradox).[24,27,43] We found that improvements in major risk factors accounted for approximately 55% of the recent decrease in CHD deaths, as in most other industrialized countries studied.[19–27]

In Italy, at the beginning of the 1980s, cardiovascular risk factors levels were lower than those of most industrialized countries.[43,44] Therefore the overall effect of risk factor improvements in Italy during the 20-year period of estimation contributed to a lower proportion of CHD deaths prevented or postponed compared with that estimated in other industrialized countries.[20–22,24–27,42]

Smoking prevalence in men fell from 47% to 32%,[15] continuing the slow decline from the early 1960s when more than 60% of middle-aged men smoked.[2] However, among women, a worrying adverse trend was registered, especially in the last 20 years, during which smoking prevalence among women increased from 18% to 24%,[15] resulting in additional coronary deaths.

The largest mortality benefit came from changes in systolic blood pressure (about 25% of deaths prevented or postponed) and total cholesterol (about 23% of deaths prevented or postponed). Cholesterol and blood pressure

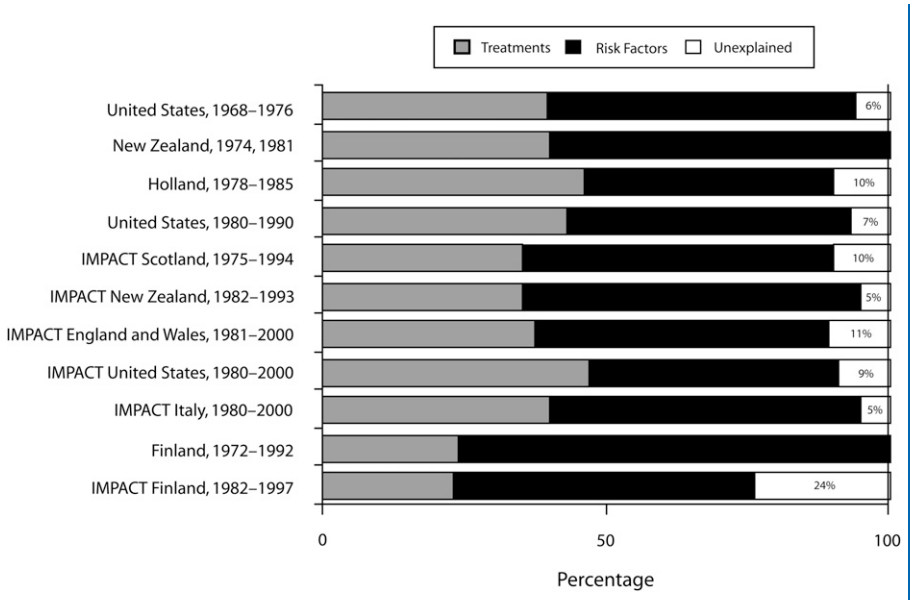
have more steadily decreased over the last 20 years.[15] The decline in systolic blood pressure was more evident among men than among women and in northwest and central Italy than in northeast and southern Italy; in the same period of time, the proportion of treated hypertensives rose to 50% among men and to 66% among women,[45] even though only half of them had hypertension that was adequately under control (28% of hypertensive men; and 39% of hypertensive women).[45–47]

The overall (0.35 mmol/L) decline in serum cholesterol level reflects a decline in north-central regions of the country, and some increase in the south and the islands. We have observed that in certain areas of Italy more people adopt a more healthful diet, choose leaner food, and avoid visible fats (i.e., fats that are easily detectable in foods and dishes) than in other regions.

Although most of the changes in risk factors between 1980 and 2000 led to reductions in CHD deaths, 2 major exceptions are noteworthy. Our analysis estimated that even though BMI has slightly decreased among women, it rose among men, resulting in about 245 additional deaths, and the increase in diabetes prevalence accounted for 945 additional deaths from coronary heart disease in 2000. These trends are reassuringly consistent with recent studies in other industrialized countries.[15] Efforts to address obesity and diabetes should therefore receive particular attention in future measures to improve the public health.[14,15]

Irrespective of whether best, minimum, or maximum assumptions were used, we found that the largest contributions from medical therapies consistently came from those treating heart failure, followed by treatments for chronic angina in the community, then secondary prevention. Revascularization by CABG surgery or coronary angioplasty for stable and unstable disease together accounted for approximately 1.5% of the overall fall in CHD deaths, even less than in previous studies elsewhere.[23–26,48,49]

A very small part of the CHD mortality decline was attributed to hypertension treatment of primary prevention (1.5% of deaths prevented or postponed). This implies that only high-risk individuals receive treatment and that, furthermore, during the 1980s, international guidelines used higher levels as the threshold for the commencement of treatment than are used today.[50] In the 1980s hypertensive medications were less targeted and less varied, and therapy was usually started at higher levels of blood pressure, when organ damage was already present. Consequently only a small proportion of the population was treated.



[a]Capewell et al.[23] focused on specific treatments and inferred contribution from risk factors.
[b]Vartiainen et al.[20] focused on risk factors and inferred contribution from treatments.

FIGURE 2—Comparison of percentage of decrease in coronary heart disease deaths attributed to treatments and to risk factor changes in other populations, by study.

Modeling studies have a number of potential strengths, including the ability to transparently integrate and simultaneously consider huge amounts of data from many sources and then test explicit assumptions by sensitivity analyses. Our analysis of extremes approach suggested that the proportional contributions to the overall reductions in deaths from specific treatments and risk factor changes remained reasonably consistent, irrespective of whether best, minimum, or maximum estimates were used (Tables 1 and 2). This was reassuring, as was the general consistency with most studies performed elsewhere (Figure 2).[20,21,23,24]

Limitations

All modeling analyses have limitations and should be interpreted with appropriate caution. All require the gathering of data from numerous sources, each with recognized shortcomings. Therefore, we sometimes had to use data from studies possibly constrained by geographic, ethnic, or selection bias or extrapolate to older age groups. For instance, results from 2 different studies were used to estimate cholesterol levels at the beginning and at the end of the study period,[5,14,15] and changes in laboratory methods, equipment, and reagents for cholesterol assay also occurred over the last 20 years. Variations from different study designs and study periods can potentially influence results. Even though unpublished original data were used together with published ones, publication bias exists. However, the results were reasonably consistent in a series of sensitivity analyses.

Advances in medications in CHD treatment and diagnosis during the study period were great. For example, during the 20-year study period, the blood pressure guidelines continually suggested lower thresholds for hypertension treatment initiation, and this was true for other risk factors (e.g., total cholesterol). In addition, more-targeted and more-sophisticated new medications (e.g., statins), surgical treatments (e.g., CABG and percutaneous transluminal coronary angioplasty), and the primary prevention of heart

failure were introduced. These advances in CHD prevention and treatment, combined with the earlier diagnoses of milder, nonfatal cases and earlier treatment both in primary and secondary prevention, almost certainly influenced trends in the incidence and prevalence of nonfatal events and in the apparent decline in CHD mortality. Survival bias, selection bias, and competitive risks effects might thus all influence the epidemiology of CHD mortality.

Any assumption that CHD epidemiology was exactly the same during all the study period would clearly be brave and problematic. Hence the crucial importance of rigorous sensitivity analyses, which were reassuring.

Risk estimates were not necessarily fully independent of each other. Furthermore, most interactions were averaged across broad groups. Basing the Italian treatment prevalence on data from the United Kingdom likely created an overestimation of benefit. This emphasizes the crucial need for local data in the future. The majority of treatment uptake and case fatality rates were based on UK and US data because little specific Italian data were available. However, these assumptions made only a small difference in the sensitivity analysis.

We make explicit assumptions regarding main cardiovascular diseases and risk factors in the community and surgical and medicine treatments compliance and efficacy, which are detailed in table 9 in the online appendix. Moreover, we only analyzed the estimated fall in CHD deaths, not life-years gained or quality of life.[51] These merit further work, as do economic analyses.

The risk factor estimates clearly remain imprecise. The use of the sensitivity analysis with more than 20% thresholds, only in the case of 95% confidence intervals not being available for each parameter, has the limitation of not permitting the estimation of something with a certain confidence, but it does give a realistic range into which the real value will occur. We also did not explicitly consider the effect of lag times; however, they may be relatively unimportant over the course of a 20-year analysis.[24,27,33,38,39] Although major efforts were made to address overlaps, residual double-counting of some individual patients remains possible. We also assumed that, after adjustments for lower dosing and imperfect compliance, the efficacy of treatments in randomized controlled trials could be generalized to population effectiveness in usual clinical practice.[52,53] Both assumptions may have led to the potential overestimation of the true treatment effect.

Conclusions

Our findings emphasize the importance of a comprehensive strategy that actively promotes primary prevention of CHD, particularly a healthful diet and tobacco control, and that maximizes population coverage of effective treatments. ■

About the Authors

Luigi Palmieri and Simona Giampaoli are with the National Centre of Epidemiology, Surveillance, and Promotion of Health, National Institutes of Health, Rome, Italy. Kathleen Bennett is with the Trinity Centre for Health Sciences, St James's Hospital, Dublin, Ireland. Simon Capewell is with the Department of Public Health, University of Liverpool, Liverpool, England.

Correspondence should be sent to Luigi Palmieri, National Centre of Epidemiology, Surveillance, and Promotion of Health, National Institutes of Health, Via Giano della Bella, 34, 00162 Rome, Italy (e-mail: luigi.palmieri@iss.it). Reprints can be ordered at http://www.ajph.org by clicking the "Reprints/Eprints" link.

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Contributors

L. Palmieri participated in the origination of the study; acquisition, analysis, and interpretation of data; and writing and critical revision of the article. K. Bennett participated in the analysis and interpretation of data and the writing and critical revision of the article. S. Giampaoli participated in the origination of the study, the acquisition of data, and the writing and critical revision of the article. S. Capewell participated in the origination of the study, the analysis and interpretation of data, and the compilation and critical revision of the article.

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Human Participant Protection

No human participants were involved in this study.

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