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Toronto Health Economics and Technology Assessment Collaborative

Ontario IMPACT Model

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Contents

Executive Summary

Objective
Coronary heart disease (CHD) mortality has declined substantially in Canada over recent decades. Our objective was to determine what proportion of this decline was associated with temporal trends in CHD risk factors and advancements in medical treatments.

Methods
The validated IMPACT model was used for all analyses, integrating data on population size, CHD mortality, in addition to risk factor and treatment uptake changes in adults 25 years and older between 1994 and 2005 in Ontario. Relative risks and regression coefficients from the published literature quantified the relationship between CHD mortality and a) evidence-based therapies in 8 distinct CHD sub-populations (acute myocardial infarction (AMI), acute coronary syndromes, secondary prevention post-AMI, chronic angina/CHD, in-hospital, heart failure, community heart failure, and 1° prevention for hyperlipidemia or hypertension) and b) population trends in 6 risk factors (smoking, diabetes mellitus, systolic blood pressure, plasma cholesterol, exercise, and obesity). The outcome of interest was the number of deaths prevented or postponed.

Results
From 1994-2005, the age-adjusted CHD mortality rate in Ontario fell 35% from 190.9 to 124.8 deaths per 100,000 inhabitants, translating to an estimated 7585 fewer CHD deaths in 2005. Improvements in medical treatments accounted for approximately 43% of the total mortality decrease, most notably in AMI (8%), chronic angina (17%) and community heart failure (10%). Trends in risk factors explained approximately 48% of the total mortality decrease, specifically reductions in plasma cholesterol (23%), and systolic blood pressure (20%). Increasing diabetes prevalence and body mass index had a negative impact, increasing CHD mortality by approximately 6% and 2%, respectively.

Conclusion
Our results suggest that future CHD strategies should maximise evidence-based therapies and support more aggressive policies to promote healthy lifestyles.

Background

Coronary heart disease (CHD) remains the most common cause of death worldwide, and generates a large economic burden.[1;2] Reassuringly, CHD mortality rates have been decreasing substantially over the last three decades.[3] Understanding the underlying factors associated with this decline in CHD mortality is critical for planning future health policy, and in particular prioritizing strategies for primary and secondary prevention.[4]

Previous studies have shown that the largest portion of this reduction in CHD burden can be attributed to improvements in modifiable lifestyle and dietary risk factors.[4-10] For example, from a population perspective, a 1 mmol/L reduction in mean plasma cholesterol levels is associated with a 40% reduction in CHD mortality.[11;12] Treatment strategies have also played a pivotal role, with an estimated 25% to 55% of the international CHD mortality decreases being attributed to improved uptake of evidence-based pharmacological and interventional therapies.[10] The relative importance of risk factor modification and treatment uptake may vary substantially depending on the country and the time period studied.[4;6-8;10;13;14]

The underlying factors associated with trends in CHD mortality in Canada have not been evaluated. Accordingly, our objective was to model CHD deaths between 1994 and 2005 in the province of Ontario with the goal of better understanding the contribution of prevention and treatment strategies to the Canadian decline in CHD mortality.

Methods

Epidemiological model and data sources

We evaluated the Ontario population aged from 25 to 84 years (estimated total population of 8.5 million) using an updated version of the IMPACT model. This is a cell-based model, constructed in Microsoft Excel, which integrates local epidemiological data on major population risk factors including smoking, diabetes, systolic blood pressure, total cholesterol, exercise, and obesity, in addition to the uptake of evidence-based medical and surgical treatments for CHD at two cross-sectional time points. It estimates the relative reduction in CHD mortality associated with temporal trends in each risk factor and treatment. The IMPACT model has been previously validated in the United States, New Zealand, China and Europe.[6-9;13;14]

Whenever possible, we aimed to use data sources specific to the Ontario population. The two time points used in the Ontario model were 1994 and 2005, based on the availability of high quality data for these two periods. The data used to construct the Ontario IMPACT model are described in detail in the Supplementary appendix (see Table 1 of Supplementary appendix). Briefly, data on the Ontario population and age distribution and specific CHD death counts based on *International Classification of Disease (ICD) 9th and 10th edition*, were obtained from Statistics Canada, while that for major risk factors came from Ontario-specific self-reported population health surveys.[15] To determine the number of eligible patients for specific medical and surgical treatments and their associated 1-year mortality, we used linked administrative databases at the Institute for Clinical Evaluative Sciences (ICES), which allowed us to accurately account for potential overlaps between patient groups. This data was supplemented with utilization data from Ontario-specific clinical registries (see Table 1, Supplementary Appendix).

Deaths prevented or postponed

The primary output of the IMPACT model was the number of deaths prevented or postponed in 2005 due to the reduction in CHD mortality rates. This was calculated as the difference between the observed 2005 CHD deaths and the expected CHD deaths in 2005 had the 1994 mortality rates remained constant. Change in population size and age was considered using indirect standardisation. The expected number of CHD deaths was calculated by multiplying the age and gender specific mortality rates for 1994 by the population size for each 10-year age-gender stratum in 2005. Having calculated the total number of deaths prevented or postponed in 2005, we then determined the proportion that were associated with either trends in risk factors or treatment uptakes between 1994 and 2005.

Treatments and mortality reductions

The treatment arm of the model consisted of 8 mutually exclusive disease subgroups (see Table 1, Supplementary Appendix). These included patients hospitalized with an acute myocardial infarction (AMI), an acute coronary syndrome (ACS), or heart failure due to ischemic cardiomyopathy within the last year. In addition, the model evaluated community-dwelling patients who were post-AMI survivors, patients with stable angina (with and without percutaneous/surgical revascularization), and patients with heart failure. Finally, hypertensive and hypercholesterolemic individuals eligible

for primary prevention with pharmacological therapy were examined.

The deaths prevented or postponed attributable to a specific CHD treatment within a disease subgroup was estimated by taking the product of the number of people in the subgroup (Table 1, Supplementary Appendix), the proportion of those patients who received a particular treatment (Table 3, Supplementary Appendix), the 1 year mortality rate (Table 4, Supplementary Appendix), and the relative risk reduction attributed to that specific treatment based on the published literature (Table 2, Supplementary Appendix). For example, in Ontario in 2005, about 2790 men aged 55-64 were hospitalized with AMI of whom approximately 94% were given aspirin. Aspirin reduces the case-fatality rate by approximately 15%.[16] The underlying 1-year case-fatality rate in these men was approximately 6.4%. The number of deaths prevented or postponed attributable to aspirin use in AMI was therefore calculated as:

Patient numbers x treatment uptake x relative mortality reduction x one-year case fatality = 2790 * 91.3% * 15% * 6.4% = 24 deaths prevented or postponed, approximately (1)

There is a paucity of data on the efficacy of treatment combinations. Assuming that the efficacy of multiple treatments would be additive would lead to an over-estimation of treatment effect; therefore, we used the Mant and Hicks method to estimate case-fatality reduction by polypharmacy (see Supplementary Appendix for details).[17] Although many therapeutic interventions studied, such as clopidogrel or primary angioplasty for AMI were not available in 1994, other interventions such as aspirin for AMI, were widely used in 1994. In these cases, we calculated the net benefit of the intervention by subtracting the expected number of deaths prevented or postponed had the 1994 utilization rates remained constant from the observed deaths prevented as calculated in the example above. We assumed that compliance (adherence), the proportion of treated patients actually taking therapeutically effective levels of medication, was 100% among hospital patients, and 70% among symptomatic community patients and 50% among asymptomatic patients[4;8;18].

Risk factors and mortality reductions

The risk factors of interest included diabetes mellitus, total plasma cholesterol, systolic blood pressure, body mass index, smoking, and physical inactivity (Table 1, Supplementary Appendix). Two approaches were used to estimate the number of deaths prevented or postponed as a consequence of changes in CHD risk factors. The *regression coefficient approach* was used for risk factors expressed in continuous data: systolic blood pressure, total cholesterol, and body mass index. Three variables were used in this approach: the number of deaths from CHD occurring in 1994 (the base year) was multiplied by the absolute change in risk factor prevalence, and by a regression coefficient quantifying the change in CHD mortality that would result from the change in risk factor level (Table 5, Supplementary Appendix). For example, in 1994, there were 448 CHD deaths among 476,670 women aged 55-64 years. Mean systolic blood pressure in this group then decreased by 6.9mmHg (from 139.3 in 1994 to 132.4 mmHg in 2005). The largest meta-analysis evaluating the effect of blood pressure treatment on mortality reports an estimated age- and sex-specific reduction in mortality of 50 percent for every 20 mmHg reduction in systolic blood pressure, generating a logarithmic coefficient of –0.035.[19] The number of

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

*(1-(EXP(coefficient*change))*deaths in 1994)* = (1-(EXP(-0.035*6.88))* 1383) = 96 deaths prevented or postponed, approximately (2)

The second approach used was *the population-attributable risk fraction (PARF).* This approach was used to determine the mortality benefit due to changes in the prevalence of dichotomous risk factors: smoking, diabetes, and physical inactivity. PARF was calculated conventionally as:

(P(RR-1)) / (1 + P*(RR-1))*
(3)

where P is the prevalence of the risk factor and RR is the relative risk for CHD mortality associated with the presence of that risk factor. Deaths prevented or postponed were then estimated as the CHD deaths in 1994 (i.e. the base year) multiplied by the difference in the PARF between 1994 and 2005. For example, the prevalence of diabetes among men aged 65-74 years was 13.5% in 1994 rising to 18.3% in 2005. Assuming a Relative Risk of 1.93,[20] the PARF was calculated as 0.112 in 1994 and 0.145 in 2005. The number of deaths attributable to the increase in diabetes prevalence from 1994 to 2005 was therefore:

Deaths in 1994 x (PARF in 2005 – PARF in 1994) **=** (3196) * (0.145 - 0.112) = 105 additional deaths, approximately
(4)

Sensitivity Analyses

Because of uncertainty surrounding many of the values, multi-way sensitivity analyses were performed.[4] For each model parameter, a maximum and minimum feasible value was assigned using the 95% confidence intervals from the source documentation; if this was unavailable, we defined these limits as 20% above and below the best estimate.[4] The maximum and minimum feasible values were introduced into the model, generating the maximum and minimum estimates for deaths prevented or postponed.

Results

Overall mortality change from 1994 and 2005

From 1994 to 2005, the age-adjusted CHD mortality rate in Ontario fell 35% from 190.9 to 124.8 deaths per 100,000 inhabitants. Of the 8.4 million Ontario residents between the ages of 25 and 84 years in 2005, there were 10,060 CHD deaths. In contrast, in 1994 despite an overall population of only 7 million between the ages 25 to 84 years, there were 13,010 CHD deaths. After indirect age-standardization, the IMPACT model estimated that there were approximately 7585 deaths prevented or postponed in 2005 given the observed mortality rates, compared to the deaths expected had the 1994 CHD mortality rates remained constant.

The number of deaths prevented or postponed in 2005 based on age-gender strata is summarized in Figure 1. The decrease in observed CHD deaths were concentrated in older patients between 75-84 years, with 2148 fewer deaths in men and 1643 fewer deaths in women of this age group. Risk factor changes accounted for approximately 48% of the total mortality decrease, whereas new medical and surgical treatments accounted for approximately 43% of the decrease in CHD deaths. Overall, the Ontario IMPACT model was able to explain 91% of the observed decrease in CHD deaths, leaving 9% unexplained.

Treatment uptakes

Approximately 3280 of the total deaths prevented or postponed (43% of total; minimum estimate 11% - maximum estimate 121%) were associated with improvements in medical and surgical treatments between 1994 and 2005, as summarized in Table 1. The most substantial contributions came from treating patients with chronic angina, (1305 fewer deaths, representing approximately 17% of the overall reduction). Within this subgroup, statin medications had the greatest impact. In 1994, approximately 8% of patients with chronic angina were on statins, compared to 78% in 2005. This improvement in utilization rates was associated with 725 deaths prevented or postponed (9% of total). In contrast, percutaneous and surgical revascularizations were associated with relatively modest reductions in mortality, explaining only 1% of the overall deaths prevented or postponed.

Improvements in the treatment of patients with heart failure in the community accounted for approximately 750 fewer deaths (10% of total). This was primarily due to the increased use of ß-blocker medications, from 29% in 1994 to 67% in 2005. Interestingly, angiotension converting enzyme (ACE)-inhibitor/angiotensin receptor blocker (ARB) use actually decreased, from 89% in 1994 to only 69% in 2005. However, this was outweighed by the improved uptake of other medications including ß-blockers, and aldactone.

The deaths prevented or postponed from treatments for the acute hospital-based subgroups were relatively modest (Table 1). Although improvements in the treatment of AMI patients represented 8% of the overall deaths prevented and postponed, new acute treatment modalities such as primary angioplasty prevented or postponed only 105 deaths. Even with this subgroup of patients, improved secondary prevention with statin therapy represented the most important advance in treatment over the time horizon of the model, contributing to approximately 320 deaths prevented or postponed.

Risk factor changes

Overall, risk factor changes accounted for approximately 3660 fewer CHD deaths prevented or postponed (48% of total; minimum estimate 28% - maximum estimate 63%). Over the 11 year time horizon of the model from 1994-2005, there was an absolute 0.05 mmol/L reduction in the mean total plasma cholesterol levels in the Ontario population. (Table 2) After accounting for increased utilization of lipid-lowering pharmacologic treatments, we estimated that approximately 1730 CHD deaths were prevented or postponed due to reductions in cholesterol from life-style and dietary changes from 1994 to 2005, representing 23% of the overall reduction in CHD mortality. There was also a 1.4 mmHg absolute decrease in mean systolic blood pressure from 1994-2005. This was associated with 1545 fewer deaths (20% of total) after subtracting any deaths prevented due to advances in pharmacologic therapies (Table 2).

Reductions in smoking (6% absolute and 20 % relative), and physical inactivity (11% absolute and 17% relative) also led to 725 and 310 fewer CHD deaths, respectively. However, there was an increase in both diabetes prevalence (1% absolute and 24% relative) and in body mass index (0.37 kg/m^2 absolute), both increasing mortality by approximately 470 (6% of total) and 180 (2% of total) more CHD deaths, respectively.

Sensitivity analyses suggested substantial uncertainty in our estimates, as seen in Table 1 and 2. This was most pronounced in the treatment arm of the model. In comparison to the best estimate that 43% of the total deaths prevented or postponed was attributed to improvements in treatment uptake, the estimates ranged from a minimum of 11% to a maximum of 121%. In contrast, the uncertainty surrounding the risk factor estimates was less, with a range from 28% to 63% (best estimate of 48%).

Discussion

Using Ontario-specific epidemiologic data, we observed a reduction in the burden of CHD similar to that observed in other Western countries. From 1994 to 2005, this 35% decrease in CHD mortality translated into 7585 deaths prevented or postponed. The bulk of this mortality reduction was attributed to improvements in traditional CHD risk factors, particularly improvements in population plasma cholesterol levels and systolic blood pressure. These positive trends were offset by adverse trends in prevalence of obesity and diabetes. The reduction in CHD mortality associated with advances in surgical and medical treatments occurred principally in community dwelling patients with chronic stable angina and heart failure.

Understanding the underlying mechanisms for past trends in CHD mortality is critical for the planning and prioritization of future health policy strategies. The IMPACT model has been applied in a wide range of population and has consistently explained approximately 80-99% of the CHD mortality decline, with 50% or more being consistently attributed to temporal trends in CHD risk factors.[4;6-9;13] Despite our analysis being restricted to a more contemporary time horizon of 1994 to 2005, we observed similar mortality reductions associated with improvements in risk factors, particularly total cholesterol and systolic blood pressure. These population improvements in selected risk factors may reflect the general improvement in the population socioeconomic status, in turn supporting healthier foods and life styles. However, this may also lead to overconsumption, which may partially explain the recent epidemic of obesity and diabetes mellitus. Our results suggest that we have not reached the nadir of population cholesterol or blood pressure levels. Strategies to improve these areas will continue to be of importance. However, policies to address the increasing prevalence of obesity and diabetes mellitus will also be crucial if the gains realized over the last decade are not to be lost.

The Ontario IMPACT model found that less than half of the reduction in CHD mortality was associated with improvements in medical and surgical treatments. This is despite the fact that expenditures on medical technologies and drugs have increased exponentially over this period. We believe several factors are important in understanding these results. First, the baseline year of our analysis was 1994 so that many of the treatment strategies evaluated were already in use (unlike some previous IMPACT analyses). Any effect on CHD mortality would thus be due to the incremental increase in utilizations. Although utilization rates have improved for most treatments, these improvements have been modest. Second, the majority of new treatments developed over the last decade, such as primary angioplasty for AMI, Glycoprotein IIb/IIIa receptor inhibitors and clopidogrel for ACS or automated internal cardiac defibrillators for severe cardiomyopathy only affected a relatively small proportion of the patients with CHD. Patients with chronic stable angina continue to represent the largest burden of CHD disease. Improvements in their treatment have been limited to the increased utilization of statin and ACE inhibitor medications. Furthermore, invasive therapy such as angioplasty is no longer thought to reduce mortality when compared with optimal medical therapy.

The Ontario IMPACT model only explained approximately 91% of the CHD mortality decline, less than some studies. The unexplained portion may reflect imprecision around the major risk factors, or failure to quantify other important determinants such as the consumption of fruits and vegetables, psychosocial stress,

and abdominal obesity, all of which are not specifically captured in the current analysis.[5] The INTERHEART study investigators examined the relationship of these factors with the risk of AMI and found a population attributable risk that ranged from 10-25%.[5] This emphasises the importance of collecting population level data on these and other novel risk factors and incorporating them into future studies. Our results must be interpreted within the context of several limitations, most importantly, the use of multiple data sources for populating the mathematical model. However, we were able to use linked administrative databases for the majority of our estimates, which would mitigate this issue. Nonetheless, residual double counting of some patients may have occurred despite our best efforts. In addition, the generalizability of efficacy data derived from clinical trials when applied to clinical practice is potentially problematic, and may overestimate the clinical effectiveness. Finally, our risk factor reduction estimates were not necessarily fully independent, potentially overestimating the total effects.

In conclusion, our results suggest that approximately half the CHD mortality in Ontario between 1994 and 2005 was associated to improvements in major risk factors and approximately 43% advances in treatments. Worryingly, however, obesity and diabetes mellitus both increased substantially. This emphasises the need for aggressive health policies to ensure that the CHD mortality gains during the previous decade are not lost in the next decade.

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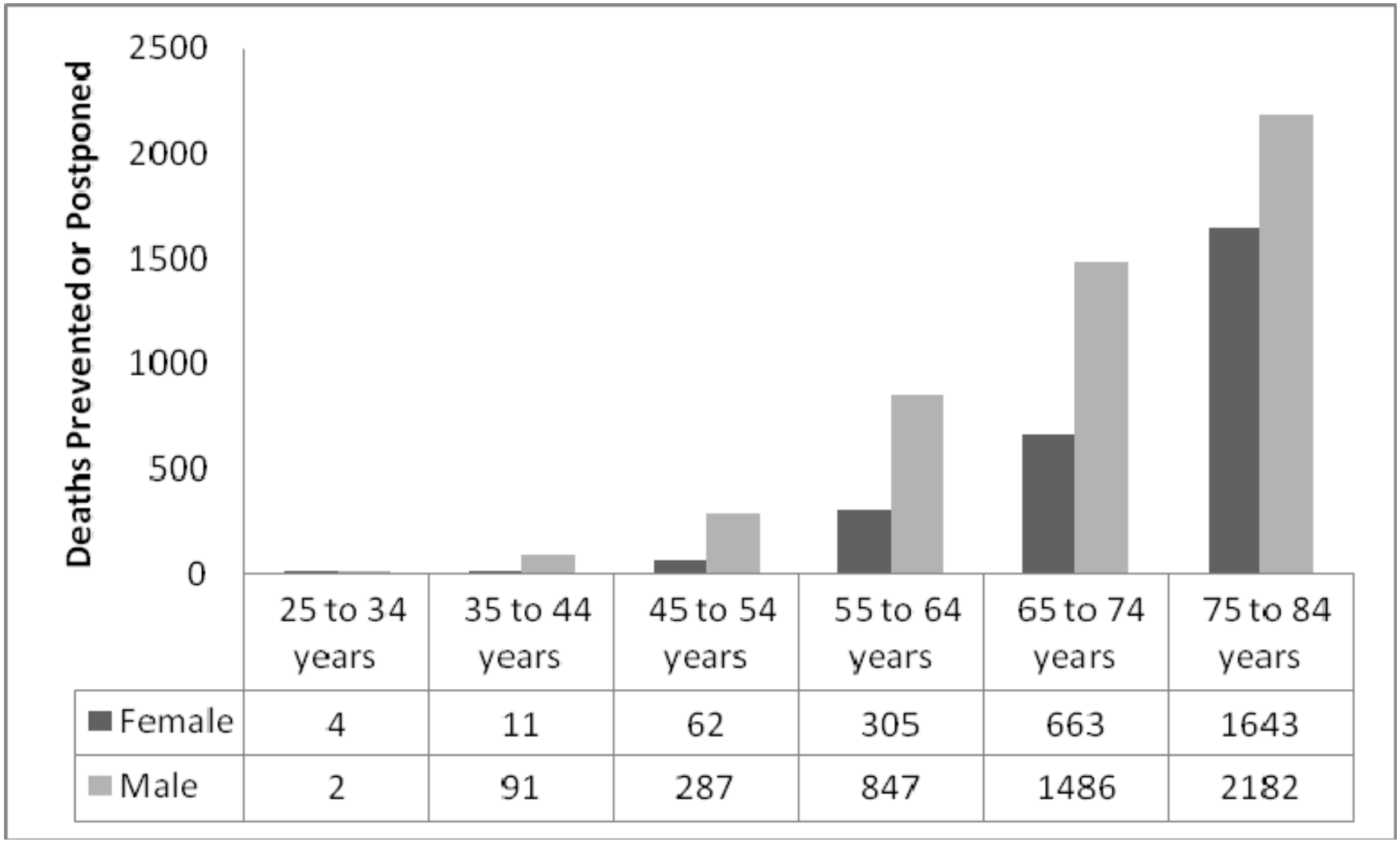
Disclosures

None of the authors have any conflicts of interest to declare.

Figures and Tables

Figure 1: Deaths Prevented or Postponed in 2005 stratified by age and sex



	25 to 34 years	35 to 44 years	45 to 54 years	55 to 64 years	65 to 74 years	75 to 84 years
Female	4	11	62	305	663	1643
Male	2	91	287	847	1486	2182

Table 1: Deaths prevented or postponed as a result of treatmentsfor CHD patients in the Ontario population from 1994 to 2005

						Deaths prevented or postponed			
	Patients Eligible	**Treatment Uptake in 2005**	**Treatment Uptake in 1994**	**Relative Risk Reduction**	**1-year Case Fatality**	**Mean**	**% overall**	**Min %**	**Max %**
AMI	**16640**				**0.164**	**630**	**8.3%**	**-5.1%**	**39.9%**
Fibrinolysis		35%	31%	24%		20	0.2%	0.1%	0.4%
Aspirin		94%	78%	15%		70	0.9%	0.5%	7.4%
Beta blocker		82%	40%	31%		25	1.4%	-0.4%	1.7%
ACE inhibitor/ARB		63%	23%	4%		50	0.3%	0.1%	1.5%
Clopidogrel		60%	0%	4%		35	0.5%	-0.6%	2.3%
Primary PCI		16%	0%	7%		105	0.7%	0.3%	1.0%
Primary CABG		0%	0%	39%		5	0.0%	0.0%	0.0%
Statin		88%	9%	22%		320	4.2%	-5.6%	23.8%
Community CPR		2.5%	1%	5%		10	0.1%	0.0%	0.0%
Hospital CPR		2%	2%	33%		0	0.0%	0.0%	0.0%
ACS	**10180**				**0.054**	**150**	**2.0%**	**0.7%**	**2.4%**
Aspirin and Heparin		80%	72%	33%		15	0.1%	0.0%	0.1%
Aspirin alone		11%	9%	15%		5	0.0%	0.0%	0.0%
Gp IIB/IIA		7%	0%	9%		0	0.0%	0.0%	0.0%
ACE Inhibitor/ARB		55%	23%	7%		10	0.1%	0.0%	0.1%
Beta blocker		79%	50%	0%		10	0.0%	0.0%	0.0%
Clopidogrel		51%	0%	7%		15	0.1%	0.0%	0.1%
CABG surgery for ACS		3%	0%	43%		10	0.0%	0.0%	0.0%
PCI for ACS		18%	0%	32%		30	0.1%	0.0%	0.2%
Statin		78%	8%	22%		60	0.8%	0.6%	1.9%
2' Prev Post AMI	**37500**				**0.026**	**170**	**2.3%**	**2.0%**	**10.0%**
Aspirin		91%	74%	15%		10	0.2%	0.1%	0.7%
Beta blocker		85%	51%	23%		35	0.4%	0.4%	2.0%

ACE inhibitor		67%	25%	20%		40	0.5%	0.5%	2.6%
Statin		88%	9%	22%		55	0.8%	0.6%	3.3%
Warfarin		14%	0%	22%		15	0.2%	0.2%	1.-%
Rehabilitation		15%	0%	26%		15	0.2%	0.0%	0.1%
Chronic Angina and CHD	**292210**					**1305**	**17.2%**	**7.0%**	**35.4%**
Aspirin in community		78%	64%	15%	0.030	130	1.7%	0.7%	3.6%
Statins in community		78%	8%	23%	0.030	725	7.7%	3.9%	19.8%
ACE inhibitor		53%	20%	17%	0.030	375	5.0%	2.0%	10.3%
CABG surgery		5880*	3470*	21%	0.048	60	0.8%	0.3%	1.4%
Angioplasty		5260*	1440*	13%	0.023	15	0.2%	0.0%	0.3%
Hospital Heart Failure	**3365**				**0.356**	**80**	**1.0%**	**0.4%**	**2.2%**
ACE inhibitor		62%	89%	20%		-45	-0.6%	-0.2%	-1.2%
Beta blocker		55%	29%	35%		70	0.9%	0.4%	1.9%
Spironolactone		21%	3%	30%		40	0.5%	0.2%	1.1%
Aspirin		52%	42%	15%		10	0.1%	0.1%	0.3%
Community Heart Failure	**50440**				**0.112**	**750**	**9.9%**	**6.1%**	**31.1%**
ACE inhibitor/ARB		70%	89%	20%		-125	-1.7%	-1.1%	-5.5%
Beta blocker		67%	29%	35%		760	10.0%	6.5%	32.8%
Spironolactone		5%	3%	30%		35	0.4%	0.3%	1.5%
Aspirin		52%	42%	15%		85	1.1%	0.4%	2.3%
Hypertension Treatment	**459900**	**46%**	**28%**	**13%**	**0.005**	**50**	**0.7%**	**-0.2%**	**0.9%**
Hyperlipidemia Treatment	**565295**				**0.004**	**90**	**1.2%**	**0.4%**	**2.6%**
Statins 1' prevention		45%	20%	35%		85	1.1%	0.5%	2.3%
Gemfibrozil 1' prevention		6%	0%	7%		5	0.1%	0.0%	0.3%
Niacin 1' prevention		2%	0%	5%		0	0.0%	0.0%	0.0%
Total Treatment						**3280**	**42.6%**	**11.2%**	**123.6%**

AMI = Acute myocardial infarction; ACE = Angiotensin-converting enzyme; ARB = angiotensin converting enzyme blocker; CABG = Coronary-artery bypass grafting; PCI = Percutaneous coronary intervention (with or without stenting); CPR: cardiopulmonary resuscitation; ACS=acute coronary syndrome; GpIIb/IIIa: glycoprotein IIb/IIIa receptor blocker; CHD= coronary heart disease;. *for PCI and CABG, actual number of PCI and CABG patients determined from administrative database

Table 2: Deaths prevented or postponed as a result of population risk factor changes in the Ontario population from 1994 to 2005

	Changes in risk factors		Changing factor	Deaths prevented or postponed			
Risk factors	**Absolute***	**Relative***		**Mean**	**% overall†**	**Min %**	**Max %**
			RR				
Smoking prevalence (%)	-6%	-20%		725	9.5%	7.6%	11.4%
Male			2.52				
Female			2.14				
Diabetes prevalence (%)	1%	24%		-470	-6.2%	-4.1%	-7.8%
Male			1.93				
Female			2.59				
Physical inactivity (%)	-11%	-17%		310	4.1%	3.3%	4.9%
Male			1.27				
Female			1.33				
			β				
Systolic blood pressure (mmHg)	-1.39	-1%		1545	20.4%	12.7%	26.0%
Male			-0.033				
Female			-0.041				
Total plasma cholesterol (mmol/L)	-0.05	-1%		1730	22.8%	9.8%	32.6%
Male			-0.922				
Female			-0.901				
BMI (kg/m2)	0.37	1%		-180	-2.3%	-1.3%	-3.6%
Male			0.029				
Female			0.028				
Total risk factors				**3660**	**48.3%**	**28.1%**	**63.5%**

BMI = Body mass index; kg/m2 = Kilograms per squared meters; mmHg = Millimetres of mercury; mmol/L = Millimoles per liter.
* Percentages may not sum to 100 because of rounding.

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Appendix

THE Ontario IMPACT MODEL: INTRODUCTION and DETAILED METHODOLOGY

The tables included in this supplementary appendix document provide details about the methods that were used in creating the Ontario IMPACT model. This model examines the effects of changes in treatments and risk factors trends on changes in mortality from coronary heart disease (CHD) among Ontario adults aged 25-84 years. Earlier versions of the IMPACT mortality model have been previously applied to data from Europe, New Zealand, China and the United States.[1-6] This cell-based mortality model, developed in Microsoft Excel, has been described in detail online and elsewhere.[1-6]

Changes in mortality rates from CHD in Ontario from 1994 to 2005

The data sources used in examining the changes in cardiovascular mortality rates from 1994 to 2005 among Ontario residents aged 25-84 years are shown in Table 1. Mortality rates from CHD were calculated using the underlying cause of death: International Classification of Diseases (ICD)-9 codes 410-414, 428, 429.2 and ICD-10 codes I20-I25, I50. As we were only interested in deaths from coronary artery disease we only included heart failure deaths that were a result of ischemic cardiomyopathy. (See below and Table 1 for details.)

Expected and observed number of deaths from CHD

The data sources needed to estimate the expected and observed numbers of deaths from CHD for 2005 are shown in Table 1. The expected number of deaths from CHD in 2005 was calculated by multiplying the age-specific mortality rates from CHD in 1994 by the population counts for 2005 in that age-stratum. Summing over all age strata then yielded the *expected* numbers of deaths from CHD. The difference between the numbers of *expected* and *observed* number of deaths from CHD represents the total number of *deaths prevented or postponed* (**DPPs**).

Patient Groups

The treatment arm of the Model includes the following populations of patients:

- those hospitalized with an acute myocardial infarction (AMI) within the last year,
- patients hospitalized with Acute Coronary Syndrome (ACS) within the last year,
- community-dwelling patients who have survived an AMI in the past 6 years,
- patients who have undergone revascularisation procedure (Coronary Artery Bypass Grafting (CABG), or a Percutaneous Coronary Intervention(PCI), within the last year for stable angina pectoris.
- community-dwelling patients with angina pectoris (no revascularisation and/or previous MI)
- patients admitted to hospital with heart failure within the last year,
- community-dwelling patients with heart failure (no hospital admission).
- Hypertensive individuals eligible for therapy
- Hypercholesterolemic subjects eligible for cholesterol lowering therapy

The numbers of patients within each of these groups was estimated using

administrative databases, as summarized in Table 1. We restricted our cohort to Ontario residents with valid health card numbers above the age of 25 years. For patients with multiple admissions per year with the same diagnosis, we used the first admission of a particular fiscal year as the index event.

Age-specific case-fatality rates for each patient group are obtained by linking the administrative databases summarized in Table 1 to the Registered Person Database (RPDB) abstracts 0-365 days after index event. Mortality rates for patients with stable coronary artery disease were assumed to be 50% of those who had had a previous MI, consistent with previous IMPACT models.

Potential overlaps between patient groups: avoiding double counting

There are potential overlaps between patient groups. For example, many of the patients having CABG surgery have had a previous AMI,[1-6] some of the AMI survivors develop heart failure within 12 months[7], and many CHD patients have a history of hypertension.[8] As we used administrative databases to define our patient groups, all individual patients are identified by a unique, encrypted identifier, thereby allowing linkage between all databases. This data-linkage allows one to account for patients who may be part of multiple groups in a particular fiscal year. In an exploratory analysis we identified all such patients who had any overlap across the 8 disease states. We developed a hierarchy of allocation based on one-year case fatality. Therefore for an individual patient who is in multiple patient groups, they would be assigned to just one patient group, that with the highest case fatality.

Heart Failure Group/Deaths

Within the hospitalized and community heart failure group, the use of ICD 9/10 codes would include both patients with ischemic cardiomyopathy and non-ischemic cardiomyopathy. As the purpose of the IMPACT model was to assess the impact of risk factors and treatments on coronary disease, we restricted this cohort to patients with ischemic disease. Using population-based administrative databases, for each individual patient identified as having heart failure (ICD 9:428 or ICD 10: I50), we performed a retrospective look-back over 10 years, examining patient specific administrative records to determine if that particular patient had had any records suggesting underlying coronary artery disease. The codes of interest used in the look back are specified in Table 1.

To ensure that population cardiac specific mortality included only the ischemic cardiomyopathy deaths, we determined the proportion of hospitalized heart failure patients for that year that were ischemic and adjusted the total number of heart failure deaths for the population accordingly.

Treatments

For each of the groups, we estimated the number of DPPs that were attributable to various treatments. All treatments of interest are listed in Table 2.

The general approach to calculating the number of DPPs from an intervention among a particular patient group was first to stratify by age and sex, then to multiply the estimated number of patients in the year 2005 by the proportion of these patients receiving a particular treatment, by the 1-year case-fatality rate, and by the relative reduction in the case-fatality rate

due to the administered treatment. Sources for estimates of efficacy (relative risk reductions) are shown in Table 2. Sources for treatment uptakes are shown in Table 3.

We assumed that compliance (concordance), the proportion of treated patients actually taking therapeutically effective levels of medication, was 100% among hospital patients, 70% among symptomatic community patients and 50% in asymptomatic individuals taking statins or anti-hypertensives for primary oprevention.[9-12]

All these assumptions were tested in subsequent sensitivity analyses.

Example 1: estimation of DPPs from a specific treatment

For example, in Ontario in 2005, about 2791 men aged 55-64 were hospitalized with AMI in 2005 of whom approximately 91.3% were given aspirin.[13] Aspirin use reduces case-fatality rate by approximately 15%.[14] The underlying 1-year case-fatality rate in these men was approximately 6.4%.[15]

the deaths prevented or postponed (DPPs) for at least a year were therefore calculated as

Patient numbers x treatment uptake x relative mortality reduction x one-year case fatality
= 2791x 91.3% x 15% X 6.4% = 24 deaths prevented or postponed.

This calculation was then repeated
a) for men and women in each age group, and
b) incorporating a Mant and Hicks adjustment for multiple medications
c) using maximum and minimum values for each parameter in each group, to generate a sensitivity analysis (see below).

Risk factors

The second part of the IMPACT model involves estimating the number of coronary heart disease DPPs related to changes in cardiovascular risk factor levels in the population. The Ontario IMPACT model includes smoking, total cholesterol, systolic blood pressure, body mass index, diabetes mellitus, and physical inactivity. Data sources used to calculate the trends in the prevalence (or mean values) of the specific risk factors are shown in Table 2.

Data sources were not available for total cholesterol or systolic blood pressure for 1994. Therefore, for systolic blood pressure, we used data from the Canadian Heart Health Survey, which was an Ontario representative database of patients from 1986 to 1992. For total cholesterol, we used 1999 values from the Southwestern Ontario database. To assess the validity of these assumptions, we compared the reductions in systolic blood pressure and total cholesterol over the time horizon of the Ontario IMPACT model to those observed in previous IMPACT models.

Two approaches to calculating DPPs from changes in risk factors were used.

In the **regression approach**—used for systolic blood pressure, total cholesterol, and body mass index—(all continuous variables), the number of deaths from CHD occurring in 1994 (the base year) were multiplied by the absolute change in risk factor prevalence, and by a regression coefficient quantifying the change in CHD mortality that would result from the change in risk factor level. Natural logarithms were used, as is conventional, in order to best describe the log-linear

relationship between changes in risk factor levels and mortality.

Example 2: estimation of DPPs from risk factor change using regression method

Mortality fall due to reduction in systolic blood pressure in women aged 55-64

For example, in 1994, there were 448 CHD deaths among 476,670 women aged 55-64 years. Mean systolic blood pressure in this group then decreased by 6.9 mmHg (from 139.3 in 1994 to 132.4 mmHg in 2005). The largest meta-analysis reports an estimated age- and sex-specific reduction in mortality of 50 percent for every 20 mmHg reduction in systolic blood pressure, generating a logarithmic coefficient of -0.035.[16]

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

= (1-(EXP(coefficient*change))*deaths in 1994)

= (1-(EXP(-0.035*6.88))* 1383)

= 96 DPPs

This calculation was then repeated

a) for men and women in each age group, and

b) using maximum and minimum values in each group, to generate a sensitivity analysis.

Data sources for the number of CHD deaths are shown in Table 2, sources for the population means of risk factors are shown in Table 2, and sources for the coefficients used in these analyses are listed in Table 6.

Example 3: estimation of DPPs from risk factor change using PARF method

The **population-attributable risk factor (PARF) approach** was used for smoking, diabetes, and physical activity, being categorical variables. PARF was calculated conventionally as: **(P x (RR-1)) / (P x (RR-1)) +1**

where P is the prevalence of the risk factor and RR is the relative risk for CHD mortality associated with that risk factor. DPPs were then estimated as the expected CHD deaths in 2005 (i.e. if the base year mortality persisted) multiplied by the difference in the PARF for 1994 and 2005.

For example, the prevalence of diabetes among men aged 65-74 years was 13.5% in 1994 and 18.3% in 2005. Assuming a Relative Risk of 1.93,[17] the PARF was 0.112 in 1994 and 0.145 in 2005. The number of deaths attributable to the increase in diabetes prevalence from 1994 to 2005 was therefore:

(3196) * (0.145 - 0.112) = 105 DPPs

This calculation was then repeated

a) for men and women in each age group,

b) for physical inactivity and smoking

c) using maximum and minimum values in each group, to generate a sensitivity analysis

Data sources for the prevalence of risk factors and for the number of CHD deaths are shown in Table 2. Sources for the relative risks used in these PARF analyses are listed in Table 7. All come from the INTERHEART study,[17] the largest international study to provide *independent* RR values, adjusted for other major risk factors.

The rationale for choosing the regression or PARF approaches for specific risk factors in the Ontario IMPACT Model is detailed in Table 8.

Other Methodological Considerations:

a. Systolic BP and Hyperlipidemia

In order to separate the DPPs from pharmacological versus non-pharmacological primary prevention of hypertension and hyperlipidemia, we subtracted the age-gender specific DPP's calculated in the treatment section (i.e. for primary hyperlipidemia and hypertension patient groups), from the DPP's calculated in the risk factor section.

b. Polypharmacy Issues

Individual CHD patients may take a number of different medications. However, data from randomized clinical trials on efficacy of treatment combinations are sparse. Mant and Hicks suggested a method to estimate case-fatality reduction by polypharmacy.[18] This approach was subsequently endorsed by Yusuf[19] and Law and Wald.[20]

Example 4: estimation of reduced benefit if patient taking multiple medications (Mant and Hicks approach)

If we take the example **of secondary prevention following acute myocardial infarction,** good evidence (Table 2) suggests that, for each intervention, the relative reduction in case fatality is approximately: aspirin 15%, beta-blockers 23%, ACE inhibitors 20%, statins 22% and rehabilitation 26%. The Mant and Hicks approach suggests that in individual patients receiving all these interventions, case-fatality reduction is very unlikely to be simply additive, i.e. not **106%** (15% + 23%+ 20% + 22% + 26%). Instead, having considered the 15% case fatality reduction achieved by aspirin, the next medication, in this case a beta-blocker, can only reduce the **residual** case fatality (1-15%). Likewise, the subsequent addition of an ACE inhibitor can then only decrease the **remaining** case fatality, which will be 1 - [(1- 0.15) X (1-0.23)].

The Mant and Hicks approach therefore suggests that a **cumulative relative benefit** can be estimated as follows:
Relative Benefit = 1 - ((1-relative reduction in case-fatality rate for treatment A) X (1-relative reduction in case-fatality rate for treatment B) X ...X (1- relative reduction in case-fatality rate for treatment N).

In considering appropriate treatments for AMI survivors, applying relative risk reductions (RRR) for aspirin, beta-blockers ACE inhibitors statins and rehabilitation then gives:

Relative Benefit = 1 - [(1 –aspirin RRR) X (1 - beta-blockers RRR) X (1 - ACE inhibitors RRR) X (1- statins RRR) X (1- rehabilitation RRR)]
= 1 - [(1- 0.15) X (1-0.23) X (1-0.20) X (1-0.22) X (1- 0.26)]
= 1 - [(0.85) X (0.77) X (0.80) X (0.78) X (0.74)]
= 0.70 i.e. a 70% lower case fatality

c. Sensitivity Analyses

Because of uncertainties surrounding many of the values, a multi-way sensitivity analysis was performed using the analysis of extremes method.[21] For each model parameter, a lower and upper value was assigned using either 95% confidence intervals where available (for instance therapeutic effectiveness quantified as a relative risk reduction in the relevant meta-analyses), or otherwise plus or minus 20%.
The maximum and minimum feasible values were fed in to the model. By multiplying through, the resulting product then generated maximum and minimum estimates for deaths prevented or postponed.

Table 1. Main Data Sources Populating the Ontario IMPACT Model

	1994	2005	Comments
Population Statistics	Statistics Canada	Statistics Canada	
Deaths by Age and Sex	Statistics Canada (ICD-9: 410-414, 428*, 429.2)	Statistics Canada (ICD-10: I20-I25, I50*)	Proportion of total Heart failure deaths ICD9 428 and ICD 10 I50 were multiplied by proportion of HF admissions for that year that were ischemic, based on look-back.
Number of Patients Admitted Yearly			
AMI	CIHI DAD (ICD-9: 410)	CIHI DAD (ICD-10: I21,I21)	
ACS	CIHI DAD (ICD-9: 411, 413)	CIHI DAD (ICD-10: I20,I23.82,24)	In other to exclude patients who were admitted to hospital with stable coronary artery disease for elective PCI, we excluded if primary diagnosis is ICD9: 413 and any of CCP code: 48.1, 48.02, 48.03, 48.09 (PCI) and ICD10: I20.1, I20.8 and I20.9 and any of CCI code 1.IJ.76, 1IJ50,1IJ57GQ.1IJ54GQAZ (PCI)
Heart Failure	CIHI DAD (ICD-9: 428)	CIHI DAD (ICD-10: I50)	In order to restrict to patients with ischemic cardiomyopathy, we restrict to patients with any of the following co-morbidity codes on index admission and in look-back window o f 10 years before index event: - CIHI DAD ICD9 410-414 ICD10 I20-25 or - OHIP diagnostic code: 410,412,413 or -CABG, PTCA codes:CCP: 48.1, 48.02, 48.03, 48.09 CCI:1IJ76, 1IJ50, 1IJ57GQ, 1IJ54GQAZ
Number of Patients Treated Yearly with			
CABG	CIHI DAD (CCP: 48.1X)	CIHI DAD (CCI 1.IJ.76)	exclude patients with following codes in index admission as most-responsible:

			ICD 9 410,411, 428 or ICD10 I20.0, I21-24, I50
PCI	CIHI DAD (CCP: 48.02,48.03,48.09)	CIHI DAD (CCI: 1.IJ.50, 1.IJ.57.GQxx,1.IJ.54.GQ-AZ)	exclude patients with following codes in index admission as most-responsible: ICD 9 410,411, 428 or ICD10 I20.0, I21-24, I50
		Number of patients in community	
Post-AMI	OHIP diagnostic code: 410,413,412	OHIP diagnostic code: 410,413,412	Exclude if patient is included in any of prior patient groups Restrict to patients with ICD9 code 410 or ICD 10 code I21, I22 in 6 year look back window in CIHI DAD
Community Stable Angina	OHIP diagnostic code: 410,413,412	OHIP diagnostic code: 410,413,412	Exclude if patient is included in any of prior patient groups, including Post-MI
Community Heart Failure	OHIP diagnostic code: 428	OHIP diagnostic code: 428	Exclude if patient is included in any of prior patient groups restrict to patients with any of the following co-morbidity codes on index admission and in look-back window—(10 years before index event): - CIHI DAD ICD9 410-414 or ICD10 I20-25 or -CABG, PTCA codes: CCP: 48.1, 48.02, 48.03, 48.09 CCI:1IJ76, 1IJ50, 1IJ57GQ, 1IJ54GQAZ
Hypertension (primary prevention)	Southwestern Ontario Database	Southwestern Ontario Database	number of patients with HTN (>140/90) - number of patients with established CAD or CHF
Hyperlipidemia (primary prevention)	Southwestern Ontario Database	Southwestern Ontario Database	number of patients with hyperlipidemia (based on Canadian Working Group definition) - number of patients with established HTN or CAD or CHF

Population Risk Factor Prevalence		
Current Smoking	National Population	Canadian Community
Systolic Blood	Health Survey (NPHS),	Health Survey (CCHS),
Pressure	Southwestern Ontario	Southwestern Ontario
Total Serum	Database	Database
Cholesterol	Canadian Heart Health	
Physical Inactivity	Database	
Obesity (BMI)		
Diabetes		

AMI = Acute myocardial infarction; CABG = Coronary-artery bypass grafting; PCI = Percutaneous coronary intervention (with or without stenting); ACS=acute coronary syndrome;

Table 2: Clinical efficacy of interventions: relative risk reductions obtained from meta-analyses, and randomised controlled trials

Treatments	Current Relative Risk Reduction
AMI	
Fibrinolysis[22;23]	31% (95% CI: 14, 45)
Aspirin [24]	15% (95% CI: 11, 19)
Primary PCI[25]	41% (95% CI: 5, 50)
Primary CABG surgery[26]	39% (95% CI: 23, 52)
Beta blockers[27]	4% (95% CI: -8, 15)
ACE inhibitors/ARB[28]	7% (95% CI: 2, 11)
Clopidegrol[29;30]	3% (95% CI: 1, 6)
Community CPR[31;32]	5%-15% (95% CI: 4, 15.3)
Hospital CPR[33]	33% (95% CI: 10, 36)
ACS	
Aspirin alone[24]	15% (95% CI: 11, 19)
Aspirin & Heparin[34]	33% (95% CI: -2,56)
Platelet glycoprotein IIB/IIIA inhibitors[35]	9% (95% CI: 2,16)
PCI Non-STEMI[36]	32% (95% CI: 5-51)
CABG surgery[26]	43% (95% CI: 19,60)
Clopidegrol[37]	7% (95% CI: 2, 11)
2nd Prevention post AMI	
Aspirin[24]	15% (95% CI: 11, 19)
Beta blockers[27]	23% (95% CI: 15, 31)
ACE inhibitors/ARB[38]	23% (95% CI: 13, 26)
Statins[39;40]	22% (95% CI: 10, 26)
Warfarin[41;42]	22% (95% CI: 13, 31)
Rehabilitation[43]	27% (95% CI: 10, 39)
CHRONIC CHD	
CABG surgery [44]	21% (95% CI: 0.43 – 1.43)
Angioplasty in Chronic angina,with stents[45]	13% (95% 0.65-1.16)
Aspirin[24]	15% (95% CI: 11, 19)
Statins[46]	22% (95% CI: 10-26)
ACE Inhibitors/ARB[47]	17% (6%-28%)
HOSPITAL HEART FAILURE	
ACE Inhibitors/ARB[38]	20% (95% CI: 13,26)
Beta blockers[48]	35% (95% CI:26,43)
Spironolactone[49]	31% (95% CI: 18, 42)
Aspirin[24]	15% (95% CI: 11, 19)
Statins[50;51]	NO EFFECT

COMMUNITY HEART FAILURE	
ACE Inhibitors/ARB[38]	20% (95% CI: 13,26)
Beta blockers[48]	35% (95% CI:26,43)
Spironolactone[49]	31% (95% CI: 18, 42)
Aspirin[24]	15% (95% CI: 11, 19)
Statins[50;51]	NO EFFECT
PRIMARY PREVENTION HYPERTENSION [52]	13% (95% CI: 6,19)
PRIMARY PREVENTION HYPERLIPEMIA	
Statins[53]	29%(95% CU:11,62)
Gemfibrozil[54]	7%(95% CI: -8, 19)
Niacin[54]	5% (95% CI: -10, 18)

AMI = Acute myocardial infarction; ACE = Angiotensin-converting enzyme; ARB = angiotensin converting enzyme blocker; CABG = Coronary-artery bypass grafting; PCI = Percutaneous coronary intervention (with or without stenting); CPR: cardiopulmonary resuscitation; ACS=acute coronary syndrome; GpIIb/IIIa: glycoprotein IIb/IIIa receptor blocker; CHD= coronary heart disease.

Table 3: Treatment Utilization Data Sources

	1994	Source	2005	Source
		Myocardial Infarction		
Fibrinolysis	31.3	Tran et al.[55]	34.8	Canadian ACS Registry I[56],
Primary PCI	0		15.6	Canadian GRACE & GRACE 2
Aspirin	76.7		94.3	EFFECT 2 (2004)
Beta Blockers	49.5		81.7	
ACE Inhibitors/ARB	23.1		62.8	
Primary CABG	0.3*		0.3	
Clopidogrel	0		60.4	
Community CPR	1*		2.5	
Hospital CPR	2*		2	
Statin	9.0		88.3	
		Acute Coronary Syndrome		
ACE inhibitor/ARB	23.1	Tran et al[55]	54.6	Canadian ACS Registry I[56],
b-blocker	49.5		78.5	Canadian GRACE & GRACE 2[57]
Clopidogrel	0		60	
Platelet IIB/IIIA Inhibitors	0		6.7	
Aspirin	76.7		85.5	
Aspirin and Heparin	71.7		79.9	
CABG	0		3.3	
PCI (within 5 days)	0		17.9	
Statin	8.0		78.3	
		Secondary Prevention Following Myocardial Infarction		
Aspirin	74.3	calculated as same	91.3	Canadian ACS Registry I[56],
Beta Blockers	51.4	proportion of 2005	84.9	Canadian GRACE & GRACE 2[57]
ACE Inhibitors/ARB	24.6	rates based on AMI	66.9	
Statins	9	subgroup	88.3	
Warfarin	0		14.3	
Cardiac Rehabilitation	0		15	

		Community Angina Treatment for Chronic Angina		
Aspirin	63.7	calculated as same	78.3	GOALL and VP Registries
Statins	7.9	proportion of 2005	77.6	(2004 available)[58]
ACE	19.6	rates based on AMI	53.3	
		subgroup		
		Hospitalized Heart Failure		
ACE Inhibitors/ARB	89.3	Assumed to be same as	61.5	EFFECT 2 (2004)
Beta Blockers	28.6	community	55.3	
Spironolactone	2.6		20.5	
Aspirin	42.2		51.9	
Statins	16.5		41.8	
		Community Heart Failure		
ACE Inhibitors/ARB	89.3	OHIP (>65 years)	69.5	OHIP (> 65 years)
Beta Blockers	28.6		66.9	
Spironolactone	2.6		4.5	
Aspirin	42.2		51.9	
Statins	16.5		60.7	
		Hypertension		
Treated (%)	27.9	% of b-blocker patients in Tran et al[55].	46	Southwestern Database
		Hyperlipidemia Primary Prevention		
Treated (%)				Southwestern Database
statin	19.8	% of eligible patients in Tran et al[55].	45	
niacin	0		2	
gembrozil	0		6	

- Assumed to be similar to US rates

Table 4: Age-specific case fatality rates for each patient group

	AMI	Post AMI	CABG	PTCA	ACS	Hosp HF	Community HF	Community Angina	Hypertension	Hypercholesterolemia
					MEN					
25-34	0.03	0.009	0.250	0.000	0.01	0.14	0.04	0.006	0.000	0.000
35-44	0.02	0.006	0.050	0.011	0.01	0.14	0.04	0.009	0.001	0.001
45-54	0.03	0.006	0.020	0.009	0.02	0.13	0.06	0.012	0.002	0.002
55-64	0.06	0.013	0.030	0.012	0.03	0.22	0.08	0.016	0.006	0.006
65-74	0.16	0.027	0.045	0.027	0.05	0.34	0.13	0.029	0.014	0.014
75-84	0.34	0.067	0.078	0.055	0.11	0.44	0.20	0.065	0.035	0.035
85+	*0.51*	*0.189*	0.194	0.118	0.26	*0.61*	0.32	0.163	0.094	0.094
					WOMEN					
25-34	0.03	0.008	0.000	0.000	0.01	0.50	0.05	0.007	0.000	0.000
35-44	0.05	0.008	0.000	0.000	0.01	0.17	0.05	0.007	0.001	0.001
45-54	0.06	0.011	0.033	0.016	0.02	0.06	0.05	0.010	0.002	0.002
55-64	0.11	0.014	0.044	0.025	0.02	0.24	0.08	0.014	0.004	0.004
65-74	0.18	0.028	0.064	0.021	0.05	0.31	0.12	0.025	0.014	0.014
75-84	0.30	0.052	0.084	0.044	0.10	0.39	0.17	0.054	0.035	0.035
85+	*0.49*	*0.177*	0.083	0.265	0.19	*0.37*	0.30	0.155	0.094	0.094

Table 5: Specific Beta Coefficients For Major Risk Factors: Data sources, values and comments

Estimated β coefficients from multiple regression analyses for the relationship between absolute changes in population mean risk factors and % changes in coronary heart disease mortality for men and women, stratified by age.

	Age groups (years)					
CHOLESTEROL	25-44	45-54	55-64	65-74	75-84	85+
Men	**0.900**	**0.650**	**0.450**	**0.333**	**0.317**	**0.211**
Women	**0.734**	**0.530**	**0.367**	**0.272**	**0.258**	**0.172**
Men Lower 95% CI	0.782	0.564	0.391	0.289	0.275	0.172
Men Upper 95% CI	0.995	0.718	0.497	0.368	0.350	0.219
Women Lower 95% CI	0.474	0.342	0.237	0.175	0.167	0.104
Women Upper 95% CI	0.947	0.684	0.474	0.351	0.333	0.208

Source: Law & Wald meta-analysis[56]
*UNITS: % mortality change per 1 mmol/l (39mg/dl) change in total cholesterol
Strengths: includes US data, includes randomized clinical trials (consistent with observational data), adjusted for regression dilution bias, results stratified by sex and age, with 95% CIs
Limitations: some publication bias still possible

	Age groups (years)				
BODY MASS INDEX (BMI)	<44	45-59	60-69	70-79	80+
Men*	**0.100**	**0.050**	**0.040**	**0.030**	**0.02**
Women*	**0.100**	**0.050**	**0.040**	**0.030**	**0.02**
Lower limits	0.08	.04	.03	.02	.015
Maximum values	1.110	1.090	1.050	1.040	1.03

Source: Whitlock et al[57], James et al. 2004[58]
*UNITS: % mortality change per 1 kg/m^2 change in BMI
Strengths: Mainly US cohorts, stratified by age, adjusted for regression dilution bias, consistent with James et al.,[58] 95% CIs available.
Limitations: may over-estimate, because not adjusted for cholesterol, blood pressure, activity, or diabetes; observational data

	Age groups (years)					
Blood Pressure	25-44	45-54	55-64	65-74	75-84	84+
Men	**0.020**	**0.020**	**0.020**	**0.020**	**0.015**	**0.010**
Women	**0.020**	**0.020**	**0.020**	**0.020**	**0.015**	**0.010**
Min	0.002	0.002	0.002	0.002	0.034	0.034
Max	0.044	0.044	0.044	0.044	0.044	0.060

Source: Law & Wald meta-analysis 2003,[59] plus Collins et al. meta-analysis 1990[60]
*UNITS: % mortality change per 1 mmHg diastolic blood pressure.
Strengths: includes US data, includes randomized clinical trials (consistent with observational data), cohorts adjusted for regression dilution bias, with 95% CIs.
Limitations: limited information on stratification by age and sex.

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