Supplementary Online Content

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eAppendix. The Ontario IMPACT Model

We evaluated the Ontario population aged from 25 to 84 years using an updated version of the IMPACT model. This is a cell-based model, constructed using Microsoft Excel, which integrates available country-specific epidemiological data to explain an observed decrease in CHD mortality. The tables included in this supplementary appendix document provide details about these methods. This model has been validated in Europe, New Zealand, China and the United States.[1-6]

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

The data sources used are shown in eTable 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 eTable 1 for details.)

Expected and observed number of deaths from CHD

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 1994 mortality rates remained constant. The expected number of CHD deaths was calculated by multiplying age and gender specific mortality rates in 1994 by the population size for each 10-year age-gender stratum in 2005.

Patient Groups

The treatment arm of the Model includes the following groups:

- hospitalized patients with an acute myocardial infarction (AMI) within the last year,
- hospitalized patients with Acute Coronary Syndrome (ACS) within the last year,
- community-dwelling patients who have survived an AMI in the past 6 years,
- community-dwelling patients with chronic stable coronary artery who have undergone revascularisation procedure (Coronary Artery Bypass Grafting (CABG), or a Percutaneous Coronary Intervention(PCI), within the last year for chronic stable coronary artery disease.
- community-dwelling patients with chronic stable coronary artery disease (no revascularisation and/or previous MI)
- hospitalized patients with heart failure within the last year,
- community-dwelling patients with heart failure,
- hypertensive patients eligible for pharmacological therapy
- hypercholesterolemic patients eligible for cholesterol lowering therapy

The numbers of patients within each of these groups was estimated using administrative databases, as summarized in eTable 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.

Potential overlaps between patient groups:

There are potential overlaps between patient groups. 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 eTable 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 eTable 2.
The deaths prevented or postponed associated with a specific CHD treatment within a disease subgroup was estimated by taking the product of the number of people in the subgroup (eTable 1), the proportion of those patients who received a particular treatment (eTable 2), the 1 year mortality rate (eTable 3), Supplementary Appendix), and the relative risk reduction attributed to that specific treatment based on the published literature (eTable 4).
We assumed that compliance defined as the proportion of patients prescribed medications on therapeutic doses of medication, was 100% among hospital patients, 70% among symptomatic community patients and 50% in asymptomatic individuals taking statins or anti-hypertensives for primary prevention.[7-10]
All these assumptions were tested in subsequent sensitivity analyses.

EXAMPLE 1: estimation of DPPs from a specific treatment

In Ontario in 2005, 2791 men aged 55-64 were hospitalized with AMI. Utilization of aspirin was 94.3%.[11] Efficacy of aspirin is 15%.[12] 1-year case-fatality rate was 6.4%.[13]

The deaths prevented or postponed (DPPs) was calculated as:

Patient numbers x treatment uptake x relative mortality reduction x one-year case fatality
= 2791x 94.3% x 15% X 6.4% = 25deaths prevented or postponed.

Risk factors

The IMPACT model calculates the DPPs associated with changes in CHD risk factors, including smoking, total cholesterol, systolic blood pressure, body mass index, diabetes mellitus, and physical inactivity. Data sources are shown in eTable 1. 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 were used to calculate DPPs, the **regression approach** and the **population-attributable risk factor (PARF) approach**

The regression approach was used for continuous variables (systolic blood pressure, total cholesterol, and body mass index). The number of expected deaths from CHD occurring in 2005 (the end 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. Natural logarithms were used, assuming a 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

In 2005, there were 448 CHD expected deaths (had 1994 mortality rates remained constant) among 476,670 women aged 55-64 years. Mean systolic blood pressure decreased by 6.9 mmHg (from 139.3 in 1994 to 132.4 mmHg in 2005). For every 20 mmHg reduction in systolic blood pressure, we estimated an age- and sex-specific reduction in mortality of 50 percent. This generates a logarithmic coefficient of –0.035.[14]

The number of deaths prevented or postponed:

= (1-(EXP(coefficient*change))*expected deaths in 2005)
= (1-(EXP(-0.035*6.88))* 448)
= 96 DPPs

Data sources for the number of CHD deaths and risk factors are shown in eTable 1, and sources for the coefficients in eTable 5.

The PARF approach was used for categorical variables (smoking, diabetes, and physical inactivity). PARF was calculated 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 multiplied by the difference in the PARF for 1994 and 2005.

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

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,[15] 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

Data sources for the prevalence of risk factors and for the number of CHD deaths are shown in Table e1. The relative risks used in these PARF analyses were obtained from the INTERHEART study,[15] which provides independent RR values, adjusted for other major risk factors.

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

There is a paucity of data on the efficacy of treatment combinations. Simply assuming that the efficacy of multiple treatments was additive would over-estimate the treatment effect; we therefore we used the Mant and Hicks method to estimate case-fatality reduction by polypharmacy for all treatments evaluated.[16] This approach was subsequently endorsed by Yusuf[17] and Law and Wald.[18] This approach estimates a cumulative relative benefit 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).

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

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 the uncertainty surrounding many of the values, multi-way sensitivity analyses were performed.[19] For each model parameter, a maximum and minimum plausible 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. The maximum and minimum plausible values were fed in to the model generating maximum and minimum estimates for deaths prevented or postponed.

eTable 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,I22)	
ACS	CIHI DAD (ICD-9: 411, 413)	CIHI DAD (ICD-10: I20,I24)	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-MI	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 Chronic Stable Coronary Artery Disease	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 **Systolic Blood Pressure** **Total Serum Cholesterol** **Physical Inactivity** **Obesity (BMI)** **Diabetes**	National Population Health Survey (NPHS), Southwestern Ontario Database Canadian Heart Health Database	Canadian Community Health Survey (CCHS), Southwestern Ontario Database	

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

eTable 2. Treatment Utilization Data Sources

	1994	Source	2005	Source
		Myocardial Infarction		
Fibrinolysis	31.3	Tran et al.[20]	34.8	Canadian ACS Registry I[21], Canadian
Primary PCI	0		15.6	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[20]	54.6	Canadian ACS Registry I[21], Canadian
b-blocker	49.5		78.5	GRACE & GRACE 2[22]
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 proportion of	91.3	Canadian ACS Registry I[21], Canadian
Beta Blockers	51.4	2005 rates based on AMI	84.9	GRACE & GRACE 2[22]
ACE Inhibitors/ARB	24.6	subgroup	66.9	
Statins	9		88.3	
Warfarin	0		14.3	
Cardiac Rehabilitation	0		15	
		Chronic Stable Coronary Artery Disease		
Aspirin	63.7	calculated as same proportion of	78.3	GOALL and VP Registries (2004 available)[23]
Statins	7.9	2005 rates based on AMI	77.6	
ACE	19.6	subgroup	53.3	
		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[20].	46	Southwestern Ontario Database
		Hyperlipidemia Primary Prevention		
Treated (%)				Southwestern Ontario Database
statin	19.8	% of eligible patients in Tran et al[20].	45	
niacin	0		2	
gembrozil	0		6	

- Assumed to be similar to US rates

eTable 3. Age-Specific Case Fatality Rates for Each Patient Group

	AMI	Post AMI	CABG	PTCA	ACS	Hosp HF	Community HF	Chronic Stable Coronary Artery Disease	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

eTable 4. Clinical Efficacy of Interventions: Relative Risk Reductions Obtained From Meta-Analyses, and Randomized Controlled Trials

Treatments	Current Relative Risk Reduction
AMI	
Fibrinolysis[24;25]	31% (95% CI: 14, 45)
Aspirin [26]	15% (95% CI: 11, 19)
Primary PCI [27]	30% (95% CI: 15, 42)
Primary CABG surgery[28]	39% (95% CI: 23, 52)
Beta blockers[29]	4% (95% CI: -8, 15)
ACE inhibitors/ARB[30]	7% (95% CI: 2, 11)
Clopidogrel[31;32]	3% (95% CI: 1, 6)
Community CPR[33;34]	5%-15% (95% CI: 4, 15.3)
Hospital CPR[35]	33% (95% CI: 10, 36)
ACS	
Aspirin alone[26]	15% (95% CI: 11, 19)
Aspirin & Heparin[36]	33% (95% CI: -2,56)
Platelet glycoprotein IIB/IIIA inhibitors[37]	9% (95% CI: 2,16)
PCI [38]	32% (95% CI: 5-51)
CABG surgery[28]	43% (95% CI: 19,60)
Clopidogrel[39]	7% (95% CI: 2, 11)
2nd Prevention post AMI	
Aspirin[26]	15% (95% CI: 11, 19)
Beta blockers[29]	23% (95% CI: 15, 31)
ACE inhibitors/ARB[40]	23% (95% CI: 13, 26)
Statins[41;42]	22% (95% CI: 10, 26)
Warfarin[43;44]	22% (95% CI: 13, 31)
Rehabilitation[45]	27% (95% CI: 10, 39)
CHRONIC STABLE CORONARY ARTERY DISEASE	
CABG surgery [46]	21% (95% CI: 0.43 – 1.43)
Angioplasty [47]	13% (95% 0.65-1.16)
Aspirin[26]	15% (95% CI: 11, 19)
Statins[48]	22% (95% CI: 10-26)
ACE Inhibitors/ARB[49]	17% (6%-28%)
HOSPITAL HEART FAILURE	
ACE Inhibitors/ARB[40]	20% (95% CI: 13,26)
Beta blockers[50]	35% (95% CI:26,43)
Spironolactone[51]	31% (95% CI: 18, 42)
Aspirin[26]	15% (95% CI: 11, 19)
Statins[52;53]	NO EFFECT
COMMUNITY HEART FAILURE	
ACE Inhibitors/ARB[40]	20% (95% CI: 13,26)

Beta blockers[50]	35% (95% CI:26,43)
Spironolactone[51]	31% (95% CI: 18, 42)
Aspirin[26]	15% (95% CI: 11, 19)
Statins[52;53]	NO EFFECT
PRIMARY PREVENTION HYPERTENSION	
[54]	13% (95% CI: 6,19)
PRIMARY PREVENTION HYPERLIPEMIA	
Statins[55]	29%(95% CU:11,62)
Gemfibrozil[56]	7%(95% CI: -8, 19)
Niacin[56]	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.

eTable 5. Specific Beta Coefficients for Major Risk Factors

	Age groups (years)				
CHOLESTEROL	25-44	45-54	55-64	65-74	75-84
Men	**0.900**	**0.650**	**0.450**	**0.333**	**0.317**
Women	**0.734**	**0.530**	**0.367**	**0.272**	**0.258**

Source: Law & Wald meta-analysis, 1994[57]
UNITS: % mortality change per 1 mmol/l (39mg/dl) change in total cholesterol

	Age groups (years)			
BODY MASS INDEX (BMI)	<44	45-59	60-69	70-79
Men	**0.100**	**0.050**	**0.040**	**0.030**
Women	**0.100**	**0.050**	**0.040**	**0.030**

Source: Whitlock et al[58], James et al. 2004[59]
UNITS: % mortality change per 1 kg/m^2 change in BMI

	Age groups (years)				
BLOOD PRESSURE	25-44	45-54	55-64	65-74	75-84
Men	**0.49**	**0.49**	**0.52**	**0.58**	**0.65**
Women	**0.40**	**0.40**	**0.49**	**0.52**	**0.59**

Source: Lewington, Law et al[14,54]
UNITS: % mortality change per 20 mmHg change in systolic blood pressure.

Reference List

(1) Bennett K, Kabir Z, Unal B et al. Explaining the recent decrease in coronary heart disease mortality rates in Ireland, 1985-2000. J Epidemiol Community Health 2006;60:322-327.

(2) Bjorck L, Rosengren A, Bennett K, Lappas G, Capewell S. Modelling the decreasing coronary heart disease mortality in Sweden between 1986 and 2002. Eur Heart J 2009;30:1046-1056.

(3) 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.

(4) Capewell S, O'Flaherty M. What explains declining coronary mortality? Lessons and warnings. Heart 2008;94:1105-1108.

(5) 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.

(6) Ford ES, Ajani UA, Croft JB et al. Explaining the decrease in U.S. deaths from coronary disease, 1980-2000. N Engl J Med 2007;356:2388-2398.

(7) Capewell S, Beaglehole R, Seddon M, McMurray J. Explaining the decline in Coronary Heart Disease Mortality in Auckland, New Zealand between 1982 and 1993. Circulation 2000;102:1511-1516.

(8) Unal B CJCS. IMPACT, a validated, comprehensive coronary heart disease model. 2-2-2006.
: Internet Communication

(9) Butler J, Arbogast PG, BeLue R et al. Outpatient adherence to beta-blocker therapy after acute myocardial infarction. J Am Coll Cardiol 2002;40:1589-1595.

(10) Nichol MB, Venturini F, Sung JC. A critical evaluation of the methodology of the literature on medication compliance. Ann Pharmacother 1999;33:531-540.

(11) Rogers WJ, Canto JG, Lambrew CT et al. Temporal trends in the treatment of over 1.5 million patients with myocardial infarction in the US from 1990 through 1999: the National Registry of Myocardial Infarction 1, 2 and 3. J Am Coll Cardiol 2000;36:2056-2063.

(12) Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002;324:71-86.

(13) van Domburg RT, Miltenburg-van-Zijl AJ, Veerhoek RJ, Simoons ML. Unstable angina: good long-term outcome after a complicated early course. J Am Coll Cardiol 1998;31:1534-1539.

(14) Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002;360:1903-1913.

(15) Yusuf S, Hawken S, Ounpuu S et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet 2004;364:937-952.

(16) 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.

(17) Yusuf S. Two decades of progress in preventing vascular disease. Lancet 2002;360:2-3.

(18) Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. BMJ 2003;326:1419.

(19) Briggs A, Sculpher M, Buxton M. Uncertainty in the economic evaluation of health care technologies: the role of sensitivity analysis. Health Economics 1994;3:95-104.

(20) Tran CT, Laupacis A, Mamdani MM, Tu JV. Effect of age on the use of evidence-based therapies for acute myocardial infarction. Am Heart J 2004;148:834-841.

(21) Yan AT, Yan RT, Tan M et al. Optimal medical therapy at discharge in patients with acute coronary syndromes: temporal changes, characteristics, and 1-year outcome. Am Heart J 2007;154:1108-1115.

(22) Goodman SG, Huang W, Yan AT et al. The expanded Global Registry of Acute Coronary Events: baseline characteristics, management practices, and hospital outcomes of patients with acute coronary syndromes. Am Heart J 2009;158:193-201.

(23) Yan AT, Yan RT, Tan M et al. Contemporary management of dyslipidemia in high-risk patients: targets still not met. Am J Med 2006;119:676-683.

(24) Collins R, MacMahon S, Flather M et al. Clinical effects of anticoagulant therapy in suspected acute myocardial infarction: systematic overview of randomised trials. BMJ 1996;313:652-659.
(25) Estess JM, Topol EJ. Fibrinolytic treatment for elderly patients with acute myocardial infarction. Heart 2002;87:308-311.
(26) Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002;324:71-86.
(27) Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. Lancet 2003;361:13-20.
(28) Yusuf S, Zucker D, Peduzzi P et al. Effect of coronary artery bypass graft surgery on survival: overview of 10-year results from randomised trials by the Coronary Artery Bypass Graft Surgery Trialists Collaboration. Lancet 1994;344:563-570.
(29) Freemantle N, Cleland J, Young P, Mason J, Harrison J. beta Blockade after myocardial infarction: systematic review and meta regression analysis. BMJ 1999;318:1730-1737.
(30) Latini R, Maggioni AP, Flather M, Sleight P, Tognoni G. ACE inhibitor use in patients with myocardial infarction. Summary of evidence from clinical trials. Circulation 1995;92:3132-3137.
(31) Chen ZM, Jiang LX, Chen YP et al. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. Lancet 2005;366:1607-1621.
(32) Sabatine MS, Cannon CP, Gibson CM et al. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. N Engl J Med 2005;352:1179-1189.
(33) Nichol G, Stiell IG, Hebert P, Wells GA, Vandemheen K, Laupacis A. What is the quality of life for survivors of cardiac arrest? A prospective study. Acad Emerg Med 1999;6:95-102.
(34) Rea TD, Eisenberg MS, Culley LL, Becker L. Dispatcher-assisted cardiopulmonary resuscitation and survival in cardiac arrest. Circulation 2001;104:2513-2516.
(35) Tunstall-Pedoe H, Bailey L, Chamberlain DA, Marsden AK, Ward ME, Zideman DA. Survey of 3765 cardiopulmonary resuscitations in British hospitals (the BRESUS Study): methods and overall results. BMJ 1992;304:1347-1351.
(36) Oler A, Whooley MA, Oler J, Grady D. Adding heparin to aspirin reduces the incidence of myocardial infarction and death in patients with unstable angina. A meta-analysis. JAMA 1996;276:811-815.
(37) Boersma E, Harrington RA, Moliterno DJ et al. Platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: a meta-analysis of all major randomised clinical trials. Lancet 2002;359:189-198.
(38) Fox KA, Poole-Wilson P, Clayton TC et al. 5-year outcome of an interventional strategy in non-ST-elevation acute coronary syndrome: the British Heart Foundation RITA 3 randomised trial. Lancet 2005;366:914-920.
(39) Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001;345:494-502.
(40) Flather MD, Yusuf S, Kober L et al. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. ACE-Inhibitor Myocardial Infarction Collaborative Group. Lancet 2000;355:1575-1581.
(41) Baigent C, Blackwell L, Collins R et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet 2009;373:1849-1860.
(42) Wilt TJ, Bloomfield HE, MacDonald R et al. Effectiveness of statin therapy in adults with coronary heart disease. Arch Intern Med 2004;164:1427-1436.
(43) Anand SS, Yusuf S. Oral anticoagulant therapy in patients with coronary artery disease: a meta-analysis. JAMA 1999;282:2058-2067.
(44) Lau J, Antman EM, Jimenez-Silva J, Kupelnick B, Mosteller F, Chalmers TC. Cumulative meta-analysis of therapeutic trials for myocardial infarction. N Engl J Med 1992;327:248-254.
(45) Brown A, Taylor RS, Noorani H, Stone J, Skidmore B. A Systematic Clinical and Economic Review of Exercise-Based Cardiac Rehabilitation Programs for Coronary Artery Disease Ottawa, Canada. Canadian Coordinating Office for Health Technology Assessment.

(46) Hueb W, Lopes NH, Gersh BJ et al. Five-year follow-up of the Medicine, Angioplasty, or Surgery Study (MASS II): a randomized controlled clinical trial of 3 therapeutic strategies for multivessel coronary artery disease. Circulation 2007;115:1082-1089.

(47) Boden WE, O'Rourke RA, Teo KK et al. Optimal medical therapy with or without PCI for stable coronary disease. N Engl J Med 2007;356:1503-1516.

(48) Baigent C, Keech A, Kearney PM et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 2005;366:1267-1278.

(49) Al-Mallah MH, Tleyjeh IM, Abdel-Latif AA, Weaver WD. Angiotensin-converting enzyme inhibitors in coronary artery disease and preserved left ventricular systolic function: a systematic review and meta-analysis of randomized controlled trials. J Am Coll Cardiol 2006;47:1576-1583.

(50) Shibata MC, Flather MD, Wang D. Systematic review of the impact of beta blockers on mortality and hospital admissions in heart failure. Eur J Heart Fail 2001;3:351-357.

(51) Pitt B, Zannad F, Remme WJ et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med 1999;341:709-717.

(52) Kjekshus J, Apetrei E, Barrios V et al. Rosuvastatin in older patients with systolic heart failure. N Engl J Med 2007;357:2248-2261.

(53) Tavazzi L, Maggioni AP, Marchioli R et al. Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. Lancet 2008;372:1231-1239.

(54) Law M, Wald N, Morris J. Lowering blood pressure to prevent myocardial infarction and stroke: a new preventive strategy. Health Technol Assess 2003;7:1-94.

(55) Pignone M, Phillips C, Mulrow C. Use of lipid lowering drugs for primary prevention of coronary heart disease: meta-analysis of randomised trials. BMJ 2000;321:983-986.

(56) Studer M, Briel M, Leimenstoll B, Glass TR, Bucher HC. Effect of different antilipidemic agents and diets on mortality: a systematic review. Arch Intern Med 2005;165:725-730.

(57) Law MR, Wald NJ, Thompson SG. By how much and how quickly does reduction in serum cholesterol concentration lower risk of ischaemic heart disease? BMJ 1994;308:367-372.

(58) Whitlock G, Lewington S, Mhurchu CN. Coronary heart disease and body mass index: a systematic review of the evidence from larger prospective cohort studies. Semin Vasc Med 2002;2:369-381.

(59) James WPT, Jackson-Leach R, Mhurchu CN et al. Overweight and obesity (high body mass index). In: Ezzati M, Lopez AD, Rodgers A, Murray CJL, eds. Comparative quantification of risk. Global and regional burden of disease attributable to selected major risk factors. Volume 1. Geneva: World Health Organization; 2004;497-596.