APPENDIX 1 (as supplied by the authors): detailed methodology

METHODS

Health gains and costs associated with new cardiovascular disease (CVD) treatments

Estimate number of individuals receiving cardiovascular treatments

To estimate the number of unique users for different interventions to treat or prevent cardiovascular heart disease from 1994 to 2005 in Canada, we made use of the Ontario IMPACT model (1). Our approach can be described in five steps:

a) Identify interventions and patient groups
b) Estimate the numbers of patients in each patient group
c) Estimate the uptake of each intervention by each patient group
d) Compute the number of users of each intervention in each patient group (by multiplying the values obtained in steps b) and c)
e) Compute the number of unique users for each intervention in each patient group

We identified interventions and patient groups through the Ontario IMPACT model (1). In particular, we examined nine mutually exclusive groups eligible for cardiovascular treatment - acute myocardial infarction (AMI), acute coronary syndrome; post-AMI survivors; chronic angina and cardiovascular heart disease; hospital heart failure; community heart failure; hypertension; hyperlipidemia and heart transplant – as well as smoking cessation. Within each of these groups, a total of 47 medical and surgical therapies were assessed (Table B). We scaled up the numbers of patients in each patient group using accurate population data obtained from Statistics Canada (3) by population weights. High quality data were only available for six time points (1994, 1995, 1996,

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2004, 2005, and 2006). Linear interpolation technique was used to estimate data for missing time points.

To estimate the number of unique users for each intervention in each patient group, we made use of Buxton et al.'s work (2). In their analysis, the authors computed the number of unique users in each year by subtracting the number of users in each year from the number of users in the previous year, while accounting for the number of deaths from all causes among users in the previous year. This approach assumed that patients in each patient group would remain in the same patient group for their life year. We relaxed this assumption and employed three different methods to estimate the number of unique users for each intervention in each patient group.

1. For medications that were likely to be used on a long-term basis (for example aspirin, ACE-inhibitors and β-blockers), we developed a new method to estimate accurately the number of unique users per year.

   First, we estimated the total number of users for each intervention across all patient groups for each year based on the result from step d). For example, in 1995, there were 1,784,031 patients across the disease states, with 628,955 (35.3%) on aspirin (ASA) (35,561 in AMI; 31,764 in ACS; etc).

   Next, we estimated the number of new users per year for each intervention for all patient groups. To do so, we calculated the difference in users for each year compared to the previous year, while accounting for users who died. For example, of the patients on ASA in 1995 (628,955), 0.3% died. Therefore, 627,068 patients on aspirin survived until 1996. We assumed they remained on aspirin.

Lastly, surviving patients on a particular therapy, such as aspirin, were distributed across the different disease states: some in the AMI group, others in ACS and others in HF. We distributed the surviving users from a previous year into the appropriate patient groups in the current year, using the same distribution of patients as in the current year. For example, in 1996, of the total 631,399 patients on ASA, 5.0% were in AMI, 3.2% were in ACS. We assigned the surviving ASA users from 1995 to the 1996 groups in a similar fashion. Therefore, 216[1] unique ASA users were counted in the 1996 AMI disease category. This process was applied to all chronic treatments, such as aspirin, β-blockers, angiotensin-converting enzyme inhibitors, statins and warfarin. This method allowed for patients to transition between patient groups.

2. For acute in-hospital therapies (PCI, coronary artery bypass grafting (CABG), fibrinolysis, CPR, heparin, GP IIb/IIa, clopidogrel, and angioplasty), we assumed that the number of total users was equal to the number of unique users.
3. For hypertension and hyperlipidemia treatments, we used the Buxton et al. (2) approach to calculate the number of unique users. We computed the number of unique users in each year by subtracting the number of users in each year from the number of users in the previous year, while accounting for the number of deaths from all causes among users in the previous year.

Table B summarizes our results.

Next, we examined two channels through which medical and CVD research reduced smoking: (i) encouraging smokers to quit; and (ii) discouraging young people from

[1] (Total ASA 1996 – Total Survive ASA 1995) * ASA in AMI ratio = (631399 – 627068)* 0.05 = 216

starting smoking. To estimate the number of individuals for each category, first we calculated the number of quitters and non-smokers and then estimated the proportion of these numbers that could be attributed to the influence of medical/CVD research. To calculate the number of quitters and non-smokers, we used data from the National Population Health Survey (1995-1998) (4) and the Canadian Community Health Survey (2000-2005) (5). To estimate the proportion of quitters and non-smokers due to the influence of medical/CVD research, we made use of the Canadian Tobacco Use Monitoring Survey (CTUMS) (6). The CTUMS asked former smokers why they quit smoking; about 30% stated they the main reason they quit was because they were worried about the future (6). We assumed 70% of smokers' concern about future health was informed by medical/CVD research. The proportion of individuals who quit smoking due to medical/CVD research was thus estimated to be 21% (0.3 * 0.7). For non-starters, we assumed that medical/CVD research accounted for 20% of non-starting decisions among young people.

Determine magnitude of health gains associated with each new treatment, expressed in QALYs

A systematic review of the economic literature was performed to obtain estimates of the QALYs gained for each intervention over a lifetime horizon (7-43). Studies were obtained through Pubmed[2]. In addition, the references of papers that were retrieved were searched. We first searched for papers that most accurately reflected the specific intervention considered and the specific patient group to whom the intervention was

[2] http://www.ncbi.nlm.nih.gov/pubmed/

offered in Canada. Whenever possible we used Canadian studies to reflect Canadian practice patterns and costs. Studies that compared the intervention to placebo or standard of care were preferred. When an economic evaluation was not available for a particular patient group or intervention, estimates of a patient group that was most closely related to the patient group of interest was used. If a QALY estimate was not available for a particular intervention, we calculated the QALY gain using the incremental life expectancy gain and the utility estimate for the most relevant health state. Articles that incorporated a lifetime time horizon were preferred. There was no single discount rate used by all studies and we did not adjust for the differences in discount rates of each of the studies.

The marginal lifetime cost for each health care intervention was also collected from the same systematic search. When possible, cost estimates were obtained from the same paper; Canadian costs were preferred. When these were not available, we used non-Canadian studies and converted the costs to Canadian dollars using the Purchasing PowerParity[3]. All costs were inflated to 2005 Canadian dollars using the Consumer Price Index from Statistics Canada. The estimates for QALY gains and the incremental costs can be found in Table B.

To estimate QALY gains and costs associated with each smoking quitter, we relied on a study by Wang et al. (43). This study undertook a systematic review of the effectiveness of nicotine replacement therapies in smoking cessation and estimated their cost-effectiveness. Wang et al. reported QALY gains for quitters at different ages; we used

[3] http://www.oecd.org/department/0,3355,en_2649_34357_1_1_1_1_1,00.html

the value of 0.99 QALYs gained for the age group 55-64 from their study. This study did not include an estimate of the QALY gains associated with smoking deterrence but the authors reported a gain of 2.22 QALYs from quitting smoking for the under-35 age group. We used this value as the QALY gain estimate for a nonstarter. In terms of the costs of quitting, we used the cost estimate provided by Wang et al., $119 CAD per smoker. For nonstarters, we assumed that there was no cost involved. These costs are likely an overestimate, as they do not include cost savings from reduced health care use associated with successful quitting or deterrence.

"Monetize" health gains

Having obtained the QALY gains for CVD interventions as well as for quitting smoking and smoking deterrence, we then converted these QALY gains into monetary values by multiplying the QALY gains by the monetary value of a QALY. We assumed that one QALY was worth $50,000[4] in our baseline estimate. In our optimistic scenario calculation, we assumed that one QALY's value was $60,000, and in the pessimistic scenario, $40,000. With the monetized QALY gains and net health care costs, we then calculated the net monetary benefit for each CVD interventions by deducting the net health care costs from the monetized QALY gains. Thus, this net monetary benefit metric attached a monetary value to net health benefit of CVD interventions.

[4] This is comparable with the QALY value in Buxton et al (3) (£25,000.

Spillovers

Beyond the health gains discussed beforehand, medical research can produce economic gains. In this last step, we estimated the magnitude of economic gains (social return) that are generated by public/charitable sector sponsorship of cardiovascular medical research in Canada. In other words, we sought to estimate the additional national income that was generated from publicly/charitably funded medical research in Canada. To quantify the non-health gains obtained from research, we estimated the spillover that occurred from undertaking research, i.e., the "benefit" or return that a given firm/organization obtains because of research and development (R&D) undertaken by other firms/organizations. We employed two approaches to estimate this return using values from the existing literature. In the first approach, the 2-stage approach, first we estimated the private R&D stimulated by public/charitable research, and second we estimated the social rate of return to private R&D stimulated by public/charitable R&D. In the second approach, the 1-stage approach, we estimated directly the social rate of return on public/charitable research generated by all transmission mechanisms. See Buxton et al (2) for a detailed description of each approach.

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Table A. Nine Patient Groups Definition

Patient Groups	**Patient Groups Definition**
AMI	hospitalized patients with an acute myocardial infarction (AMI) within the last year
ACS	hospitalized patients with Acute Coronary Syndrome (ACS) within the last year
Post AMI	community-dwelling patients who have survived an AMI in the past 6 years
Chronic Angina and CHD	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; and community-dwelling patients with chronic stable coronary artery disease (no revascularisation and/or previous AMI)
Hospital Heart Failure	hospitalized patients with heart failure within the last year
Community Heart Failure	community-dwelling patients with heart failure
Hypertension Treatment	hypertensive patients eligible for pharmacological therapy
Hyperlipidemia Treatment	hypercholesterolemic patients eligible for cholesterol lowering therapy
Heart Transplant	Patient who have undergone heart transplant procedure

Abbreviations:
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 B. Treatments considered in the model for the nine patient groups

Patient Groups	Treatments considered in the model
AMI	Fibrinolysis (1, 2), Aspirin (3), Beta blocker (4), ACE inhibitor/ARB(5), Clopidogrel (6, 7), Primary PCI (8), Primary CABG (9), Statin (10, 11), Community CPR (12, 12), Hospital CPR (14)
ACS	Aspirin and Heparin (15), Aspirin alone (3), Gp IIB/IIA (16), ACE Inhibitor/ARB (5). Beta blocker (4), Clopidogrel (17), CABG surgery for ACS (9), PCI for ACS (18), Statin (10, 11)
Post AMI	Aspirin (3), Beta blocker (4), ACE inhibitor (19), Statin(10, 11), Warfarin (20, 21), Rehabilitation (22)
Chronic Angina and CHD	Aspirin in community(3), Statins in community (23, 24), ACE inhibitor (25), CABG surgery (26), Angioplasty (27)
Hospital Heart Failure	ACE inhibitor (19), Beta blocker (28), Spironolactone (29), Aspirin (3), Statin (23, 24)
Community Heart Failure	ACE inhibitor/ARB (19), Beta blocker (28), Spironolactone (29), Aspirin (3), Statin (23, 24)
Hypertension Treatment	all hypertension (30)
Hyperlipidemia Treatment	Statins 1' prevention (31), Gemfibrozil 1' prevention (32), Niacin 1' prevention (32)
Heart Transplant	Heart Transplant (33)

Abbreviations:
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

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