e-Appendix: Detailed description of methods

Data sources

Data from the Canadian Heart Health Survey (CHHS) were used to estimate the number of people eligible for statin therapy according to the 2000 and 2003 recommendations of the Canadian Working Group on Hypercholesterolemia and Other Dyslipidemias.[1–3] The CHHS contains data from 10 provincial heart health surveys conducted between 1988 and 1992. The CHHS was conducted before the widespread adoption of statin therapy for the management of coronary artery disease (CAD). The data can be used to evaluate current guidelines because the risk of CAD among Canadians has probably remained the same (or slightly decreased) over the last decade,[4] given that the incidence of the disease is stable and, except for smoking, risk factors are unchanged or have shown only small prevalence increases.[5] The target population of the CHHS was men and women between 18 and 74 years of age. The survey was a stratified, 2-stage probability sample and consisted of a home interview followed by a clinic visit, where physical measurements, such as height, weight and fasting blood samples, were taken. All blood lipid level analyses were done at the Lipid Research Laboratory of the University of Toronto and have been discussed in detail elsewhere.[6] The response rate for the home interview was 78% (N = 23 129), and 64% (18 688) of all respondents provided a fasting blood sample during the clinic interview.

Estimates of the baseline risks of CAD-related death and of "hard" CAD events (defined as death from CAD, nonfatal myocardial infarction or, in the 2000 guidelines, unstable angina) are necessary to estimate the number needed to treat. Framingham risk models are used in the Canadian guidelines and in this study; however, they apply only to people without known cardiovascular disease (CVD). For people with CVD, the baseline risk of a "hard" CAD event was estimated using a population-based prevalence cohort of CVD patients from the Canadian Institutes for Health Information (CIHI) hospital discharge abstract database. These data have been used previously to examine CVD incidence and survival.[7,8] We identified all people 18–74 years of age in Ontario who were discharged from hospital between 1988 and 1992 with ischemic heart disease (International Classification of Diseases, ninth revision [ICD-9] codes 410-414), cerebrovascular disease (ICD-9 codes 433-436) or peripheral arterial disease (ICD-9 codes 440 and 444) for any reason (most responsible diagnosis, diagnosis contributing to hospital stay or pre-existing condition). Their age-specific 5-year risk of CAD-related death and their 10-year risk of a "hard" CAD event from 1992 were calculated (Table 1) and applied to CHHS respondents with CVD.

Estimating the rates of CAD-related death and of "hard" CAD events on the basis of patients who were discharged within the 4 years before the observation period will overrepresent the number of patients who had a recent CVD event. This may lead to the overestimation of CAD-related event rates of CHHS respondents with prevalent CVD. The extent of this potential bias on mortality was examined using alternative approaches for creating a CVD prevalence cohort. Using CIHI hospitalization data in Ontario that extend back to 1988, a longer "wash-in" of incident cases was applied to create a 1997 prevalence cohort for CVD. Increasing the wash-in period from 4 years (1992–1997) to 9 years (1988–1997) resulted in a small increase in the 5-year risk of CAD-related death, from 15.5% to 16.2%. We further validated the baseline risk of our cohort by comparing all-cause risk of death in the control group of the LIPID statin effectiveness study involving high-risk CAD patients,[9] held from 1990 to 1997, with the Ontario population during the same period. This comparison showed that the baseline risk of the LIPID trial cohort

e-Table 1: Risk of CAD-related events among Ontario patients discharged between 1988 and 1992 from acute care hospitals after a stay because of ischemic heart disease, cerebrovascular disease or peripheral arterial disease

Patient characteristic	5-yr risk of CAD-related death (1992–1997), %	10-yr risk of "hard" CAD event* (1992–2002), %
Sex		
Female	6.6	24.1
Male	7.2	29.4
Age group, yr		
Women		
18–44	2.0	7.7
45–54	3.1	15.1
55–59	4.1	16.9
60–64	5.2	21.0
65–69	6.7	24.8
69–74	9.2	31.2
Men		
18–44	2.6	17.6
45–54	3.0	22.3
55–59	4.2	24.0
60–64	5.9	26.0
65–69	8.0	31.2
69–74	11.4	37.4
All		
18–44	2.4	14.3
45–54	3.0	20.5
55–59	4.2	22.0
60–64	5.7	24.5
65–69	7.6	29.2
70–74	10.6	35.1
Overall	7.1	27.7

Note: CAD = coronary artery disease.
*A "hard" CAD event refers to death from CAD or nonfatal myocardial infarction.

e-Table 2: Screening criteria, classification of risk groups and therapy targets as defined in the 2000 and 2003 recommendations for the management of dyslipidemia and applied to the population in the Canadian Heart Health Survey (CHHS)

Guideline recommendations		CHHS
Screening criteria according to the 2000 recommendations		
Age	• Men > 40 yr; women > 50 yr	• Men > 40 yr; women > 50 yr
Risk factors	• ≥ 2 of the risk factors for CAD	• ≥ 2 of the following risk factors: obesity (BMI ≥ 30 kg/m^2), hypertension (blood pressure over 140/90 mm Hg), self-reported smoking and sedentary lifestyle
Family history	• Family history of dyslipidemia or CAD	• Not included
Disease state	• Presence of diabetes	• Self-reported diabetes
	• Presence of xanthomata or other stigmata of dyslipidemia	• Previous myocardial infarction or angina
	• Clinical evidence of CAD, peripheral vascular disease or carotid atherosclerosis	
Screening criteria according to the 2003 recommendations		
Age	• Men > 40 yr; women > 50 yr or postmenopausal	• Men > 40 yr; women > 50 yr
Risk factors	• Presence of 1 risk factor for CVD	• 1 of the following risk factors: obesity (BMI ≥ 30 kg/m^2), hypertension (blood pressure over 140/90 mm Hg), self-reported smoking or sedentary lifestyle
Family history	• Strong family history of premature CVD	• Not included
Disease state	• Presence of diabetes or manifestations of hyperlipidemia	• Self-reported diabetes
	• Evidence of atherosclerosis	• Previous myocardial infarction or angina
Risk group definitions according to the 2000 recommendations		
Very high	10-yr risk of "hard" CAD event (CAD-related death, nonfatal myocardial infarction or unstable angina) ≥ 30%, or history of diabetes or CVD	10-yr risk of "hard" CAD event (CAD-related death, nonfatal myocardial infarction or unstable angina) ≥ 30%, or self-reported diabetes or self-reported past myocardial infarction or angina
High	10-yr risk of "hard" CAD event 20%–30%	10-yr risk of "hard" CAD event 20%–30%
Moderate	10-yr risk of "hard" CAD event 10%–20%	10-yr risk of "hard" CAD event 10%–20%
Low	10-yr risk of "hard" CAD event < 10%	10-yr risk of "hard" CAD event < 10%
Risk group definitions according to the 2003 recommendations		
High	10-yr risk of "hard" CAD event (CAD-related death or nonfatal myocardial infarction) ≥ 20%, or history of diabetes or any atherosclerotic disease	10-yr risk of "hard" CAD event (CAD-related death or nonfatal myocardial infarction) ≥ 20%, or self-reported diabetes or self-reported past myocardial infarction or angina
Moderate	10-yr risk of "hard" CAD event 11%–19%	10-yr risk of "hard" CAD event 11%–19%
Low	10-yr risk of "hard" CAD event ≤ 10%	10-yr risk of "hard" CAD event ≤ 10%
Therapy targets according to the 2000 recommendations		
Very high	LDL-C level < 2.5 mmol/L or total cholesterol:HDL-C ratio < 4.0 or triglyceride level < 2.0 mmol/L	LDL-C level < 2.5 mmol/L
High	LDL-C level < 3.0 mmol/L or total cholesterol:HDL-C ratio < 5.0 or triglyceride level < 2.0 mmol/L	LDL-C level < 3.0 mmol/L
Moderate	LDL-C level < 4.0 mmol/L or total cholesterol:HDL-C ratio < 6.0 or triglyceride level < 2.0 mmol/L	LDL-C level < 4.0 mmol/L
Low	LDL-C level < 5.0 mmol/L or total cholesterol:HDL-C ratio < 7.0 or triglyceride level < 3.0 mmol/L	LDL-C level < 5.0 mmol/L
Therapy targets according to the 2003 recommendations		
High	LDL-C level < 2.5 mmol/L and total cholesterol:HDL-C ratio < 4.0	LDL-C level < 2.5 mmol/L
Moderate	LDL-C level < 3.5 mmol/L and total cholesterol:HDL-C ratio < 5.0	LDL-C level < 3.5 mmol/L
Low	LDL-C level < 4.5 mmol/L and total cholesterol:HDL-C ratio < 6.0	LDL-C level < 4.5 mmol/L

Note: BMI = body mass index, CVD = cardiovascular disease, LDL-C = low-density lipoprotein cholesterol, HDL-C = high-density lipoprotein cholesterol.

was similar to that of the Ontario population (risk of death 14.1% v. 16.9% over 6.1 years respectively) when the same inclusion and exclusion criteria were used (analyses not shown). The higher baseline risk in the Ontario population was a consequence of LIPID study criteria that included people with a recent hospital admission because of acute myocardial infarction or unstable angina.

The risk of CAD-related death among CHHS respondents with CVD was estimated using a proportion of all-cause risk of death (as obtained from the CIHI), since cause of death for patients admitted to hospital in Ontario is not recorded in the CIHI database. The proportion of all deaths among people with CVD that were attributed to CAD has been examined in clinical trials for statins.[9–12] The estimate we used (47% of all deaths due to CAD) most closely reflected a population-based CVD prevalence cohort.[12] The proportion of deaths attributed to CAD from 4 studies examined ranged from 47% to 74%.[9–12]

Analysis

Step 1: Identifying people eligible for lipid screening

Table 2 highlights the screening criteria of the 2000 and 2003 recommendations and those applied to the CHHS respondents. Changes in the 2003 guidelines include recommended screening of patients with at least 1, and not 2, risk factors for CAD and the screening of postmenopausal women. Although recommended in the 2000 and 2003 guidelines, family history of CAD was not used as a screening criterion for CHHS respondents, since only a subset was asked the pertinent questions. There were only small differences in the study outcomes when analysis was performed using the subset of the CHHS with a family history of CAD. Menopausal status was not ascertained in the CHHS and was also not used as a screening criterion.

Step 2: Identifying people eligible for statin therapy

The 2000 and 2003 recommendations classify diabetic patients over the age of 30 and people with pre-existing CVD as being at high risk for experiencing a "hard" CAD event (Table 2). In this study, diabetes and CVD status were determined using self-reported disease status in the CHHS. Using self-reported diabetes and CVD likely underrepresents physician-diagnosed disease status[1,13] and therefore may underestimate the prevalence and population health benefit of statin therapy in the high-risk population. However, estimates of CVD prevalence in the CHHS are similar to other estimates of CVD, and therefore potential

e-Table 3: Analysis of Canadian population in 1992 by risk group using 2000 recommendations for the management of dyslipidemia*†

							Very-high-risk subgroups		
Analysis	Low risk	Moderate risk	High risk	Very high risk	Total	Very high risk + high risk‡	History of CVD	History of diabetes and age > 30 yr	10-yr risk of CAD > 30%
Estimated no. (%) of people	12 500 000 (78.2)	2 110 000 (13.2)	211 000 (1.3)	1 160 000 (7.3)	16 000 000	1 380 000 (8.6)	499 000 (3.1)	491 000 (3.1)	174 000 (1.1)
% recommended for lipid testing	38	99	100	100	52	100	100	100	100
No. recommended for statin therapy	61 000	758 000	191 000	986 000	2 000 000	1 180 000	404 000	409 000	173 000
% recommended for testing who are subsequently recommended for treatment	1.3	36.1	90.2	84.7	24.2	85.6	81.1	83.2	99.4
NNT to prevent 1 CAD-related death with 5 yr of statin therapy (25th–75th percentile)§	2 880 (2330–13 500)	502 (391–1070)	142 (119–163)	100 (70–282)	157 (102–836)	105 (76–240)	64 (52–99)	253 (169–2 250)	93 (81–122)
CAD-related deaths prevented over 5 yr§	21	1 510	1 340	9 840	12 700	11 200	6 360	1 620	1 850
Mean probability of CAD-related death over 5 yr, %§	0.1	0.8	2.9	4.2	2.7	4.0	6.6	1.6	4.5
NNT to prevent 1 "hard" CAD event with 10 yr of statin therapy (25th–75th percentile)¶	81 (69–139)	38 (30–69)	21 (19–25)	23 (17–54)	28 (20–54)	23 (17–42)	16 (13–20)	49 (35–208)	19 (17–21)
"Hard" CAD events prevented over 10 yr¶	754	20 100	9 200	42 200	72 300	51 400	24 900	8 290	9 060
Mean probability of "hard" CAD event over 10 yr, %¶	5.2	11.1	20.0	17.9	15.1	18.2	25.7	8.4	21.8

Note: NNT = number needed to treat.
*The reference population is Canadians in 1992 aged 18–74 years. Data from the Canadian Heart Health Survey were used to identify the risk categories of respondents.
†See e-Table 2 for risk group definitions.
‡The very-high- and high-risk categories of the 2000 recommendations were combined for comparison with the high-risk category of the 2003 recommendations.
§Calculated using Framingham study equations[15] given a 24% relative efficacy of statins.[9]
¶Calculated using risk scoring from the 2003 recommendations given the same 24% relative efficacy of statins.[9]

e-Table 4: Analysis of Canadian population in 1992 by risk group using 2003 recommendations for the management of dyslipidemia*†

Analysis	Low risk	Moderate risk	High risk‡	Total	High-risk subgroups		
					History of CVD	History of diabetes and age > 30 yr	10-yr risk of CAD > 30%
Estimated no. (%) of people	13 400 000 (83.8)	1 040 000 (6.5)	1 543 000 (9.7)	16 000 000	499 000 (3.1)	491 000 (3.5)	553 000 (3.5)
% recommended for lipid testing	72	100	100	76	100	100	100
No. recommended for statin therapy	595 000	585 000	1 350 000	2 530 000	404 000	409 000	534 000
% recommended for testing who are subsequently recommended for treatment	6.2	56.2	87.3	20.7	81.1	83.2	96.5
NNT to prevent 1 CAD-related death over 5 yr of statin therapy (25th–75th percentile)§	1 550 (1 031–19 600)	366 (270–975)	117 (80–394)	187 (130–1 805)	64 (52–99)	253 (169–2 250)	151 (116–333)
CAD-related deaths prevented over 5 yr§	384	1 600	11 500	13 500	6 360	1 620	3 520
Mean probability of CAD-related death over 5 yr, %§	0.3	1.1	3.6	2.2	6.6	1.6	2.8
NNT to prevent 1 "hard" CAD event over 10 yr of statin therapy (25th–75th percentile)¶	91 (69–208)	31 (26–35)	22 (17–30)	29 (21–69)	16 (13–20)	49 (35–208)	18 (17–21)
"Hard" CAD events prevented over 10 yr¶	6 550	19 100	62 400	88 100	24 900	8 360	29 200
Mean probability of "hard" CAD event over 10 yr, %¶	4.6	13.6	19.3	14.5	25.7	8.5	22.8

*The reference population is Canadians in 1992 aged 18–74 years. Data from the Canadian Heart Health Survey were used to identify the risk categories of respondents.
†See e-Table 2 for risk group definitions.
‡The very-high- and high-risk categories of the 2000 recommendations were combined for comparison with the high-risk category of the 2003 recommendations.
§Calculated using Framingham study equations[15] given a 24% relative efficacy of statins.[9]
¶Calculated using risk scoring from the 2003 recommendations given the same 24% relative efficacy of statins.[9]

e-Table 5: Number of people in 1992 no longer recommended and newly recommended for statin therapy by risk group according to the 2003 recommendations for the management of dyslipidemia compared with the 2000 recommendations*

Analysis	Risk group†					
	Low risk	Moderate risk	High risk	Very high risk	Combined	Very high risk + high risk‡
No. of people for whom statin therapy is recommended	61 000	758 000	191 000	986 000	2 000 000	1 180 000
No. (%) of people for whom statin therapy is no longer recommended	0 (0)	170 000 (92.9)	10 100 (5.5)	2 140 (1.2)	183 000	12 000 (6.6)
No. (%) of people for whom statin therapy is newly recommended	422 000 (59.2)	283 000 (39.7)	8 140 (1.1)	0 (0)	713 000	8 140 (1.1)
NNT to prevent 1 CAD-related death with 5 yr of statin therapy§						
People for whom statin therapy is no longer recommended	NA	779	195	129	636	179
People for whom statin therapy is newly recommended¶	5 180	473	NA	NA	668	296
NNT to prevent 1 "hard" CAD event with 10 yr of statin therapy**						
People for whom statin therapy is no longer recommended	NA	66	34	26	62	33
People for whom statin therapy is newly recommended¶	135	31	NA	NA	40	19

Note: NA = not available.
*The reference population is Canadians in 1992 aged 18–74 years. Data from the Canadian Heart Health Survey were used to identify the risk categories of respondents.
†Risk groups are defined according to the 2000 recommendations. See e-Table 2 for risk group definitions.
‡The very-high- and high-risk categories of the 2000 recommendations were combined for comparison with the high-risk category of the 2003 recommendations.
§Calculated using Framingham study equations[15] given a 24% relative efficacy of statins.[9]
¶For the calculation of the NNT for patients newly recommended for statin therapy, respondents were placed in the risk categories described in the 2003 guidelines.
**Calculated using risk scoring from the 2003 recommendations given the same 24% relative efficacy of statins.[9]

error is likely small. The prevalence of diabetes is low (4.5% in 1998 in Ontario,[1] compared with 3.1% in the CHHS study population), and the coefficients for diabetes status in the Framingham equations used to predict CAD risk are relatively small.

Other respondents were allocated to risk groups on the basis of their 10-year probability of a "hard" CAD event as determined by the Framingham-based risk point scoring system in the respective guidelines.[14,15] The risk scoring in both guidelines considered total cholesterol levels, high-density lipoprotein levels, systolic blood pressure and self-reported age, sex and smoking status, and the 2003 recommendations also considered interactions of age with total cholesterol levels and smoking status and of hypertension treatment with systolic blood pressure.

In accordance with the 2000 recommendations, respondents were considered eligible for statin therapy if their low-density lipoprotein level exceeded the target level set for their particular risk category (Table 2). Also in accordance with the recommendations, it was assumed that people whose low-density lipoprotein level was below the recommended target but whose total cholesterol:high-density lipoprotein ratio was above the target were not to be given statins. The survey sampling weights were applied to generate estimates for all Canadians 18–74 years of age.

Step 3: Estimating the number needed to treat

The calculation of the number needed to treat with statins for 5 or 10 years to prevent 1 CAD-related death or "hard" event requires an estimate of baseline risk for these outcomes. For people without pre-existing CVD, the risk of CAD-related death was estimated using the Framingham risk equations created and extensively validated and applied for the purpose.[15,16] The risk of a "hard" CAD event was estimated using the Framingham-based risk point scoring system outlined in the 2003 guidelines.[1] The estimation of baseline risks for people with CVD has been described in the earlier section. The relative effectiveness of statins in preventing a "hard" CAD event was assumed to be 24%, as used in the LIPID study.[9] The number of "hard" CAD events prevented among patients for whom treatment is recommended was calculated by summing the products of the baseline risk estimates and the relative effectiveness of statins. The number needed to treat to prevent 1 "hard" CAD event was estimated as the sum of the number of people treated divided by the sum of the number of "hard" CAD events prevented.

The detailed results of the analyses for the 2000 and 2003 recommendations are shown in Tables 3 and 4. The results for people newly recommended and people no longer recommended for treatment according to the 2003 recommendations (when compared with the 2000 recommendations) are presented in Table 5.

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