Controversy

The 2003 Canadian recommendations for dyslipidemia management: Revisions are needed

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The recommendations of the 2003 Canadian guidelines for the management and treatment of dyslipidemia, if applied in clinical practice, will result in more people being screened and prescribed statin therapy.[1,2] When compared with the 2000 guidelines, the 2003 guidelines recommend screening more people with fewer risk factors for coronary artery disease (CAD) and lower lipid level targets for people in all risk groups (Table 1). We are concerned that these changes will result in hundreds of thousands more people receiving treatment and a marked increase in costs to the Canadian health care system, with small overall improvements to CAD outcomes. Simple revisions to the new guidelines could reduce the number of people receiving treatment

Table 1: Comparison of the recommendations of the 2000 and 2003 Canadian guidelines for the management and treatment of dyslipidemia

Point of comparison	2000 guidelines	2003 guidelines
Event used to predict baseline risk	10-year risk of CAD-related death or nonfatal myocardial infarction, unstable angina	10-year risk of CAD-related death or nonfatal myocardial infarction
Data used for risk model	Framingham	Revised Framingham
Risk factors considered for risk nomogram	Total cholesterol level, HDL-C level, systolic blood pressure, age, smoking status	Total cholesterol level, HDL-C level, systolic blood pressure (considered along with hypertension treatment status), age, smoking status
Who is recommended for risk assessment?	Men > 40 yr old; women > 50 yr old; adults with ≥ 2 risk factors for CAD; patients with clinical evidence of CAD, peripheral vascular disease or carotid atherosclerosis; patients with diabetes; patients with xanthomata or other stigmata of dyslipidemia; and patients with a family history of dyslipidemia or CAD	Men > 40 yr old; women > 50 yr old or postmenopausal; all patients with diabetes; patients with risk factors such as hypertension, smoking or abdominal obesity; patients with a strong family history of premature cardiovascular disease; patients with manifestations of hyperlipidemia or evidence of symptomatic or asymptomatic atherosclerosis
Definition of risk groups and target lipid levels	**Very high risk** (10-year risk of CAD > 30%, or history of CVD or diabetes): LDL-C level < 2.5 mmol/L or total cholesterol:HDL-C ratio < 4.0 or TG level < 2 mmol/L	
	High risk (10-year risk of CAD 20%–30%): LDL-C level < 3.0 mmol/L or total cholesterol:HDL-C ratio < 5 or TG level < 2 mmol/L	**High risk** (10-year risk of CAD ≥ 20%, or history of diabetes or any atherosclerotic disease): LDL-C level < 2.5 mmol/L and total cholesterol:HDL-C ratio < 4
	Moderate risk (10-year risk of CAD 10%–20%): LDL-C level < 4.0 mmol/L or total cholesterol:HDL-C ratio < 6 or TG level < 2.0 mmol/L	**Moderate risk** (10-year risk of CAD 11%–19%): LDL-C level < 3.5 mmol/L and total cholesterol:HDL-C ratio < 5
	Low risk (10-year risk of CAD < 10%): LDL-C level < 5.0 mmol/L or total cholesterol:HDL-C ratio < 7 or TG level < 3.0 mmol/L	**Low risk** (10-year risk of CAD ≤ 10%): LDL-C level < 4.5 mmol/L and total cholesterol:HDL-C ratio < 6

Note: CAD = coronary artery disease, CVD = cardiovascular disease, LDL-C = low-density lipoprotein cholesterol, HDL-C = high-density lipoprotein cholesterol, TG = triglyceride.

and at the same time prevent more CAD-related deaths.

There is no doubt that statins are efficacious. They reduce CAD-related mortality by 15% to 30%.[3,4] However, the absolute benefit provided by statins (and the number needed to treat to achieve that benefit) varies enormously, depending on whether patients are at high, medium or low risk of CAD (Table 2).[5] Under the 2003 recommendations, low-risk patients will be given statin therapy for many years with only a very small reduction in the number of CAD events.

Table 2: Benefit of statin therapy in preventing CAD-related events and deaths by risk group as defined by the 2003 guidelines for the management and treatment of dyslipidemia

Risk group with patient example	"Hard" CAD-related event*		CAD-related death	
	10-year risk, %	NNT to prevent 1 event with 10 yr of statin treatment	5-year risk, %	NNT to prevent 1 death with 5 yr of statin treatment
Low (10-yr risk of CAD ≤ 10%): 42-yr-old man with total cholesterol level of 6.5 mmol/L	2	210	0.05	9 100
Medium (10-yr risk of CAD 11%–19%): 64-yr-old female smoker with total cholesterol level of 6.5 mmol/L, HDL-C level of 0.9 mmol/L and untreated systolic blood pressure of 160 mm Hg	14	30	2.9	150
High (10-yr risk of CAD ≥ 20% or history of diabetes mellitus or any atherosclerotic disease): 70-yr-old man with history of heart disease	37	11	11	36

Note: NNT = number needed to treat.
*A "hard" CAD event is CAD-related death or nonfatal myocardial infarction.

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

Analysis	Low risk	Moderate risk	High risk	Very high risk	Total	Very high risk + high risk‡	Very-high-risk subgroups		
							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

*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 Table 1 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[7] given a 24% relative efficacy of statins.[8]
¶Calculated using risk scoring from the 2003 recommendations given the same 24% relative efficacy of statins.[8]

We used the approach of MacLean and colleagues[6] and data from the Canadian Heart Health Survey (CHHS) to estimate how the 2003 guideline revisions would affect the Canadian population in terms of the number of people who would be screened and the people for whom treatment with statins would be recommended. Details about the methods are available at www.cmaj.ca/cgi/content/full/172/8/1027/DC1. In brief, we used CHHS data to identify the proportion of respondents aged 18–74 years who were eligible for screening according to both the 2000 and 2003 guidelines (e.g., respondents who had diabetes, CAD or 1 or more risk factors for CAD, men older than 40 years, women older than 50 years). Data on the lipid level profile, smoking status and blood pressure of CHHS respondents were also available. Using this information, we determined whether the CHHS respondents were at low, medium or high risk of experiencing a "hard" CAD event (i.e., CAD-related death or nonfatal myocardial infarction) in the next 10 years as determined by the Framingham-based risk point scoring system used in the respective guidelines. Since the Framingham scoring system applies only to people without known cardiovascular disease, we estimated the probability of CHHS respondents with existing cardiovascular disease experiencing a "hard" CAD event using the age-specific 10-year "hard" CAD event rates experienced by an Ontario cohort of patients aged 18–74 who were previously admitted to hospital because of cardiovascular disease between 1988 and 1992. CHHS sampling weights were applied to generate estimates for all Canadians 18–74 years of age.

We then evaluated the health impact of the 2000 and 2003 guidelines on the Canadian population in terms of the number of CAD events potentially prevented and the number needed to treat to prevent a CAD event with statin therapy. The number needed to treat to prevent 1 event was calculated as 1 over the absolute baseline risk of people receiving treatment in each guideline risk group multiplied by the relative effectiveness of statins (assumed to be a constant 24%[3] for all risk groups and outcomes). The number needed to treat for some people in the low-risk groups was very large because their baseline risk was extremely low. The guidelines defined the low-risk group as anyone with a 10-year baseline risk of a "hard" CAD event less than 10% in 2000 and 10% or less in 2003. The number of deaths potentially prevented in each risk group was calculated by dividing the total number of people in a risk group by the number needed to treat in that group.

Using the Canadian population aged 18–74 years in 1992 as the reference population, the number of people for whom statin therapy is recommended increased by 27%, from 2 million using the 2000 guidelines to 2.53 million using the 2003 guidelines (Table 3 and Table 4). Almost all

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 Table 1 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[7] given a 24% relative efficacy of statins.[8]
¶Calculated using risk scoring from the 2003 recommendations given the same 24% relative efficacy of statins.[8]

of the increase consisted of patients in the low-risk category. The number of low-risk people for whom statins are recommended if lifestyle modification fails to achieve target lipid levels increased 10-fold, from 61 000 to 595 000. Yet, the relative benefit of statin therapy for many people in the low-risk group is incredibly small. By our estimates, among the 149 000 Canadians who fall within the highest-risk quartile in this group, the number needed to treat with 5 years of statin therapy to prevent 1 CAD-related death would be 19 600. The number needed to treat to prevent 1 CAD-related death in the low-risk group recommended for statin therapy (n = 595 000) would be 1550.

Conversely, according to CHHS data, about 12.5% (193 000/1 543 000) (Table 4) of high-risk people have low-density lipoprotein cholesterol levels below the recommended target. According to the 2003 guidelines, these people would not be recommended for statin treatment. However, the Heart Protection Study[4] is widely cited as providing evidence for the benefit of statin therapy for most of these people. The 2003 guidelines acknowledge the evidence of this and other studies. In our estimate, the number needed to treat for 5 years to prevent 1 death is 10 times more favourable for high-risk people currently not recommended therapy than for low-risk people who are recommended therapy (141 v. 1550).

By these calculations, if the 2003 guidelines were modi-fied to recommend statins for all high-risk people and no low-risk people, 1010 more deaths over 5 years might be prevented and 398 000 fewer people (2.5% of the total population) given treatment. Although the guidelines recommend screening the entire adult population, in practice not everyone will be screened or offered treatment or will persist on statin therapy. Thus, the actual impact in terms of the potential number of deaths prevented or people treated would be considerably lower.[9–13]

In Canada, statin prescriptions increased over 3-fold between 1996 and 2000 to 11 million prescriptions at a cost of $1.1 billion annually.[11] The further 27% increase incurred if the revised recommendations are followed would contribute an additional $250 million in drug costs each year. On the other hand, recommending statins for all high-risk people and no low-risk people, using the 2003 definitions for the risk groups, would reduce the number of people recommended statins by 16% and avoid more deaths (Fig. 1). The New Zealand approach of recommending treatment for all people with a history of CAD or a 10-year risk of CAD-related death greater than 15%[14] is even more efficient. Applying the New Zealand guidelines in Canada would result in the prevention of slightly more CAD-related deaths, treatment of 37% fewer people and savings of $100 million compared with using the revised 2003 guidelines (Fig. 1).[14]
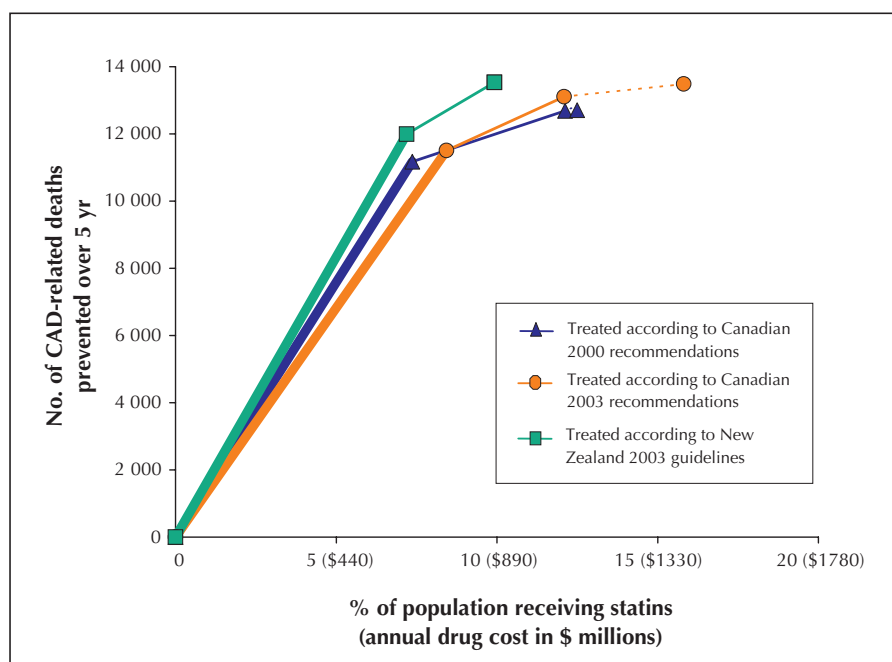
Fig. 1: No. of deaths from coronary artery disease (CAD) prevented over 5 years among people aged 18–74 years receiving statin therapy according to the 2000 and 2003 Canadian recommendations and the 2003 New Zealand guidelines. This assumes that all eligible people were screened and were compliant with the statin therapy recommended and that the drug cost was $1.52 per day. Thick solid rules represent people at high risk for CAD, thinner solid rules represent people at moderate risk, and dotted rules represent people at low risk; for the 2000 Canadian recommendations, the categories of high and very high risk have been combined.

These calculations have implications for patients, clinicians, funding agencies and those interested in population health. Fully informed patients are often less aggressive about therapy than their clinicians.[15] As well, low-risk patients will paradoxically sometimes receive more aggressive treatment than high-risk patients.[13,16] The very small absolute benefits associated with statin therapy in low-risk patients highlights the importance of informing these patients about the absolute benefits and risks of statins. Our analysis reinforces the importance of ensuring that clinicians offer statin therapy to high-risk patients, since they are the patients with the most to gain. Even high-risk patients whose low-density lipoprotein cholesterol levels are below the target given in the 2003 guidelines should be considered for statin therapy.

It is important to remember that a drug that is efficacious in high-risk patients is also typically efficacious in very-low-risk patients, but the absolute benefits and cost-effectiveness are almost always lower. Costs for the individual (including costs related to the drug, testing, doctor and clinic visits, being labeled as "sick" or carrying a risk factor) and for society (drug and treatment costs) suggest that the funds spent on statins for low-risk patients may be better used elsewhere. Including information on the absolute benefits and cost-effectiveness of statin therapy in dyslipidemia guidelines — as New Zealand and European guidelines do[14,17] — allows for more meaningful discussions about who should receive the therapy. Our analysis demonstrates that estimating absolute benefit can improve guidelines by more clearly identifying who will benefit most from statins. Since there is no clear threshold of benefit or cost-effectiveness of statins, societal views should be elicited before expanding recommendations to a large number of low-risk people. The editors and reviewers of *CMAJ* should call on guideline authors to include measures of absolute benefit and to address resource implications of recommendations that are published in the journal.[18] We urge the authors of the Canadian dyslipidemia guidelines to consider our analysis and revise their recommendations.

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