Patient Knowledge of Coronary Risk Profile Improves the Effectiveness of Dyslipidemia Therapy

The CHECK-UP Study: A Randomized Controlled Trial

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Background: Despite increasing evidence that treating dyslipidemia reduces cardiovascular events, many patients do not achieve recommended lipid targets.

Methods: To determine whether showing physicians and patients the patient's calculated coronary risk can improve the effectiveness of treating dyslipidemia in a primary care setting, patients were randomized to receive usual care or ongoing feedback regarding their calculated coronary risk and the change in this risk after lifestyle changes, pharmacotherapy, or both to treat dyslipidemia. Outcomes, based on intention-to-treat analysis, included changes in blood lipid levels, coronary risk, and the frequency of reaching lipid targets.

Results: Two hundred thirty primary care physicians enrolled 3053 patients. After 12 months of follow-up, 2687 patients (88.0%) remained in the study. After adjustment for baseline lipid values, significantly greater mean reductions in low-density lipoprotein cholesterol levels and the total cholesterol to high-density lipoprotein cholesterol ratio were observed in patients receiving risk profiles (51.2 mg/dL [to convert to millimoles per liter, multiply by 0.0259] and 1.5, respectively) vs usual care (48.0 mg/dL and 1.3, respectively), but the differences were small (–3.3 mg/dL; 95% confidence interval [CI], –5.4 to –1.1 mg/dL; and –0.1; 95% CI, –0.2 to –0.1, respectively). Patients in the risk profile group were also more likely to reach lipid targets (odds ratio, 1.26; 95% CI, 1.07 to 1.48). A significant dose-response effect was also noted when the impact of the risk profile was stronger in those with worse profiles.

Conclusions: Discussing coronary risk with the patient is associated with a small but measurable improvement in the efficacy of lipid therapy. The value of incorporating risk assessment in preventive care should be further evaluated.

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Group Information: The CHECK-UP Study Group members are listed on page 2301.

ALTHOUGH INCREASING evidence indicates that treating dyslipidemia can reduce cardiovascular disease (CVD) outcomes,[1-6] expert guidelines for treating dyslipidemia recognize that primary prevention will be most effective and cost-effective if high-risk individuals are targeted for therapy.[7-9] Accordingly, as recently discussed by Jackson et al,[9] one of the challenges facing health professionals is to identify such patients while reassuring those who are at low risk. Many treated patients do not achieve recommended lipid targets.[10-13] This is due, in part, to inadequate treatment by physicians and suboptimal patient adherence to prescribed therapy.[14-19] Therefore, once therapy is targeted to those at high risk, a second challenge is to maximize patient adherence to lifestyle modifications and medical treatment.

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Bodenheimer et al[20] and Holman[21] argued that patient self-management is inevitable in chronic illness. The active participation of asymptomatic patients in management of disease risk factors is no less essential. Simons et al[18] showed that approximately one-third of those who discontinue lipid medication remain unconvinced of the need for treatment. Benner

et al[15] suggested that better compliance might result from improving patients' understanding of their coronary risk and the potential benefits of therapy.

Improving communication through shared decision making and clinical decision aids has been advocated by many as one approach to optimizing patient care in the presence of clinical uncertainty.[22-24] Given that recent expert guidelines[7-9] recommend calculating the future risk of cardiovascular events to identify high-risk patients, we hypothesized that sharing this information with patients might enhance the effectiveness of treating dyslipidemia in a primary care setting. The Cardiovascular Health Evaluation to Improve Compliance and Knowledge Among Uninformed Patients (CHECK-UP) Study was a randomized clinical trial designed to test this hypothesis and demonstrate this proof of principle.

METHODS

STUDY DESIGN

Physicians were identified from multiple sources, including professional association databases. Interested investigators were invited to 1 of 4 regional investigator meetings, which consisted of a full-day educational session, including information on the national lipid guidelines, the study protocol, and how to interpret the risk profiles. Of 330 physicians who attended one of the investigator meetings, 230 participated in the study.

Using office medical record reviews or prebooked clinic appointments, patients were identified who were likely to have untreated hyperlipidemia, including those who had diabetes mellitus, established CVD, or multiple risk factors for CVD. Patient inclusion criteria were based on the 2000 Canadian Working Group on Hypercholesterolemia and Other Dyslipidemias lipid guidelines and included men and women aged 30 to 70 years with CVD or diabetes mellitus or men aged 45 to 70 years and women aged 55 to 70 years who had a calculated 10-year coronary risk of at least 10% based on Framingham equations.[25] At screening, patients provided written informed consent and had a complete medical evaluation, including a full lipid profile. The study protocol and informed consent were approved by local ethics review boards. Randomization was completed at a central coordinating center, where patients, not physicians, were randomized to receive risk profiles or usual care.

Patients were eligible for the study if (1) they had CVD or diabetes mellitus or a calculated 10-year coronary risk greater than 30%, with a low-density lipoprotein cholesterol (LDL-C) level of 97 mg/dL or greater (to convert to millimoles per liter, multiply by 0.0259) or a total cholesterol to high-density lipoprotein cholesterol (TC:HDL-C) ratio of 4 or greater; (2) the calculated 10-year risk was 20% to 30%, with an LDL-C level of 116 mg/dL or greater or a TC:HDL-C ratio of 5 or greater; or (3) the calculated 10-year risk was 10% to 20%, with an LDL-C level of 155 mg/dL or greater or a TC:HDL-C ratio of 6 or greater. Exclusion criteria included hypersensitivity to statins, risk of pregnancy, breastfeeding, active liver disease or elevated aspartate aminotransferase or alanine aminotransferase levels (≥3 times normal), elevated creatine kinase levels (≥5 times normal), elevated triglyceride levels (>939 mg/dL [to convert to millimoles per liter, multiply by 0.0113]), a history of pancreatitis, and significant renal insufficiency.

To replicate the usual barriers to adherence, all medications were purchased at a pharmacy chosen by the patient. Drug costs were borne by patients using private insurance, public drug plans, or out-of-pocket payment. A few weeks before each visit, patients completed a fasting lipid profile, and risk profiles were completed at the central coordinating center. At each visit, study physicians discussed the risk profile with patients randomly assigned to receive it. Profiles were withheld from patients in the usual care group, who received routine care as practiced by their physician. Routine care could include a calculation of coronary risk. However, physicians were unlikely to systematically estimate risk in their practice because lipid guidelines first recommended using risk tables in the year preceding the study.

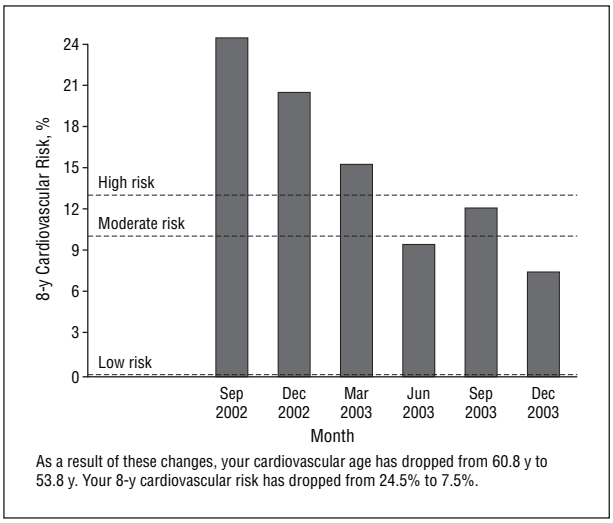

Figure 1. A coronary risk profile of a hypothetical patient demonstrating the reduction in risk after risk factor modification. The broken horizontal lines represent risk tertiles for Canadians of the same age and sex based on data from the Canadian Heart Health Surveys. The associated decrease in cardiovascular age represents the forecasted increased life expectancy associated with lifelong risk reduction. For an explanation of cardiovascular age, see the "Coronary Risk Profile" subsection below.

CORONARY RISK PROFILE

The coronary risk profile is a 1-page computer printout that displays a patient's probability of developing coronary disease (**Figure 1**). For individuals with previously diagnosed CVD, these estimates were calculated using the previously published and validated Cardiovascular Life Expectancy Model based on data from the Lipid Research Clinics Follow-up Cohort.[26] For individuals without CVD, these risk estimates were based on Framingham equations,[27] and life expectancy was calculated using the Cardiovascular Life Expectancy Model. For these primary prevention patients, the profile also included their "cardiovascular age," calculated as the patient's age minus the difference between his or her estimated remaining life expectancy (adjusted for coronary and stroke risk) and the average remaining life expectancy of Canadians of the same age and sex.[27,28] For example, a 50-year-old with a life expectancy of 25 more years (vs 30 more years for the average Canadian) would be assigned a cardiovascular age of 55 years. Once the study was completed, the risk profile became freely available at the McGill Cardiovascular Health Improvement Program Web site (http://www.chiprehab.com).

At entry into the study, patients randomized to the risk profile group were shown their coronary risk profile. The relative risk was graphically summarized by comparing this risk with a representative sample of Canadians of the same age and sex using data from the Canadian Heart Health Surveys.[29] Population risk tertiles were constructed for each profile based on these data so that each patient could see his or her absolute risk com-

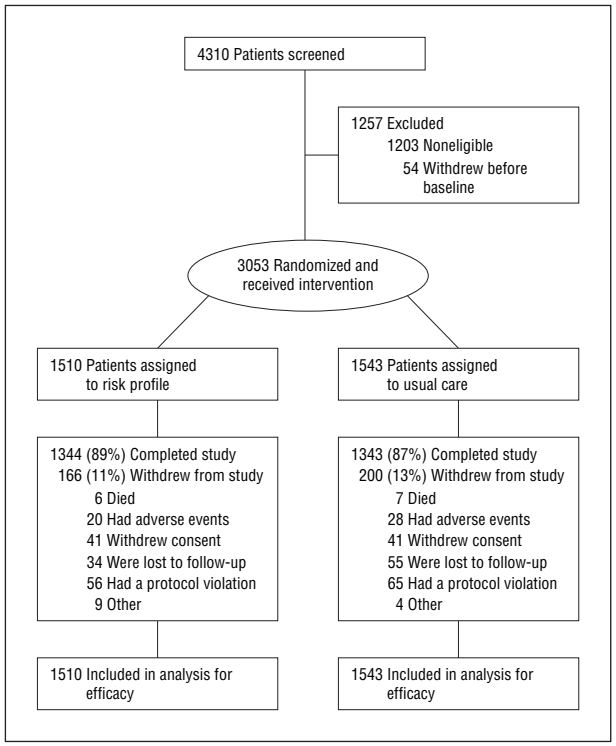

Figure 2. Flow of patients through the trial.

pared with that of peers. Finally, a copy of the profile was given to the patient to take home.

The second profile at the 3-month follow-up visit compared baseline risk with the risk after statin therapy or lifestyle modification. Each subsequent profile compared the patient's current global risk status with all profiles obtained at previous visits so that patients could follow their response to therapy (Figure 1).

STUDY VISITS

The baseline visit occurred 2 to 4 weeks after screening. Follow-up visits occurred at 3, 6, 9, and 12 months, with a reevaluation of lipids and safety variables 2 to 4 weeks before each visit. Patients receiving lifestyle modification who did not reach lipid targets at the 3-month follow-up visit were asked to start statin therapy as per the national guidelines. Those who reached lipid targets could continue lifestyle modification. When pharmacotherapy was initiated, the choice of statin and the starting dose were chosen by the physician, and at each visit, statin therapy could be modified based on physician and patient preferences. Although the primary objective was to treat patients to achieve recommended lipid levels, the study protocol did not force physicians to switch or titrate medication to achieve these targets.

SAMPLE SIZE CONSIDERATIONS

Sample size calculations were performed using classic and Bayesian approaches. It was assumed that each enrolled patient would provide a baseline and at least 1 follow-up assessment, with a 1:1 randomization between study arms.

The classic sample size calculation was performed to provide adequate power (90%) to detect anticipated changes in LDL-C levels when tested using a 2-sided *t* test ($\alpha = .05$). In a previous study,[30] risk assessment feedback resulted in an incremental reduction in LDL-C levels of 8.9% (95% confidence interval [CI], 1.9%-15.9%). Given the lower bound of 1.9%, 2282 patients would be required. Further adjusting for an anticipated 30% dropout rate required 3260 patients to be randomized.

Bayesian sample size calculations were based on ensuring sufficiently accurate interval estimation of the between-group difference in LDL-C reduction. A mixed Bayesian/likelihood average coverage criterion was used.[31] This criterion uses previous information to predict which data are likely to arise in the trial, but then it ensures accurate estimation assuming that standard CIs will be used for final inferences. A gamma density with settings of 23.08 and 2652.93 was used for the variance in each treatment group, which was derived assum-

Table 1. Baseline Characteristics of the 3053 Study Patients

Characteristic	Risk Profile Group (n = 1510)	Usual Care Group (n = 1543)
Age, mean (SD), y	56.4 (8.3)	56.3 (7.9)
Male sex, No. (%)	1010 (66.9)	1080 (70.0)
Cholesterol, mean (SD), mg/dL		
Total	237.8 (40.4)	234.9 (40.3)
HDL	44.6 (11.3)	44.6 (11.1)
LDL	152.8 (34.3)	150.5 (33.7)
Triglycerides	209.6 (115.5)	209.1 (115.9)
TC:HDL cholesterol ratio, mean (SD)	5.58 (1.44)	5.50 (1.36)
Treatment gap, mean (SD)[a]		
LDL, mg/dL	1.14 (0.86)	1.07 (0.83)
TC:HDL cholesterol ratio	1.13 (1.56)	1.03 (1.47)
BMI, mean (SD)	30.7 (5.6)	31.2 (5.8)
Systolic blood pressure, mean (SD), mm Hg	137 (17)	137 (16)
Diastolic blood pressure, mean (SD), mm Hg	82 (10)	83 (9)
Known CVD, No. (%)	347 (23.0)	350 (22.7)
Known diabetes mellitus, No. (%)	751 (49.7)	776 (50.3)
Family history of premature CVD, No. (%)	626 (41.5)	635 (41.2)
Current smokers, No. (%)	435 (28.8)	446 (28.9)
Hypertension medications, No. (%)		
ACE inhibitors	460 (30.5)	492 (31.9)
Angiotensin II antagonists	164 (10.9)	196 (12.7)
Anti-adrenergic agents	26 (1.7)	24 (1.6)
β-Blocking agents	226 (15.0)	225 (14.6)
Calcium channel blockers	196 (13.0)	246 (15.9)
Diuretics	209 (13.8)	260 (16.9)
Diabetes mellitus medications, No. (%)		
Insulins	89 (5.9)	64 (4.1)
Oral medications	459 (30.4)	479 (31.0)
Daily aspirin, No. (%)	394 (26.1)	411 (26.6)
10-y risk, mean (SD)		
Total coronary risk in those without CVD	17.9 (7.7)	17.7 (7.3)
Fatal coronary risk in those with CVD	17.1 (14.1)	17.7 (14.3)
Coronary heart disease risk for all	17.7 (9.6)	17.7 (9.3)
Cardiovascular age[b] for those without CVD	59.7 (7.7)	59.4 (7.5)

Abbreviations: ACE, angiotensin-converting enzyme; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CVD, cardiovascular disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol.

SI conversion factors: To convert total, HDL, and LDL cholesterol to millimoles per liter, multiply by 0.0259; triglycerides to millimoles per liter, multiply by 0.0113.

[a] Differences between baseline and target lipid levels before treatment.

[b] Cardiovascular age is calculated as the patient's age minus the difference between his or her estimated remaining life expectancy (adjusted for coronary risk) and the average remaining life expectancy of Canadians of the same age and sex.

Table 2. Outcomes After 12 Months[a]

	Risk Profile Group		Usual Care Group			
	Baseline	Absolute Change	Baseline	Absolute Change	Difference	*P* Value[b]
TC, mg/dL	237.8 (40.4)	−58.4 (34.1)	234.9 (40.3)	−54.5 (35.4)	−3.9	.02
LDL cholesterol, mg/dL	152.8 (34.3)	−51.2 (29.5)	150.5 (33.7)	−48.0 (29.7)	−3.3	.02
HDL cholesterol, mg/dL	44.6 (11.3)	1.0 (6.0)	44.6 (11.1)	0.8 (5.7)	0.2	.37
TC:HDL cholesterol ratio	5.6 (1.4)	−1.5 (1.1)	5.5 (1.4)	−1.3 (1.0)	−0.1	.002
Systolic blood pressure, mm Hg	136.9 (16.9)	−6.3 (13.5)	137.1 (15.9)	−5.3 (13.2)	−0.9	.005
Diastolic blood pressure, mm Hg	82.5 (9.6)	−3.8 (7.9)	83.1 (9.3)	−3.6 (7.7)	−0.2	.01
10-y risk of CVD (for patients without CVD)	17.9 (7.7)	−5.9 (4.5)	17.7 (7.3)	−5.3 (4.3)	−0.6	<.001

Abbreviations: CVD, cardiovascular disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol.
SI conversion factors: To convert total, HDL, and LDL cholesterol to millimoles per liter, multiply by 0.0259.
[a] Data are given as mean (SD) unless otherwise indicated.
[b] The *P* values are for the difference between the 2 groups adjusting for baseline values using analysis of covariance.

ing that standard deviations will be within 9% to 14%.[31] A sample size of 2200 patients provides an accuracy of ±1% in estimating LDL-C reduction differences, which is sufficiently accurate for clinical decision making. Further adjusting for the dropout rate of approximately 30% again means that approximately 3000 patients need to be randomized to retain the accuracy desired.

DATA ANALYSIS

All the end points were prespecified, and the data from all enrolled patients were analyzed on an intention-to-treat basis. The prespecified primary end points were the change in LDL-C levels, the TC:HDL-C ratio, and the percentage of patients who reached national lipid targets. Secondary end points included the change in nonlipid risk factors and global 10-year risk. We used the summary measures approach for continuous variables. Changes in continuous variables were analyzed using the difference between baseline and the mean of all follow-up measurements. Analysis of covariance was used to adjust for any differences at baseline. Differences in binary characteristics at the 12-month follow-up visit between the study arms were evaluated using the χ^2 test, and multiple logistic regression was used to adjust for any important differences in baseline values. When patients withdrew prematurely, the results from the last visit were carried forward.

In this study, the unit of analysis was the patient. However, the possibility remained that between-physician differences could have an effect on estimated treatment efficacy.[32] Accordingly, a mixed-effects model was also fitted to estimate the effect of the intervention compared with the control group after adjustment for between-physician variability.[33] To adjust for the effectiveness of different statins at various doses, we defined a standardized statin dose as atorvastatin calcium, 10 mg, equal to any of the following: simvastatin, 30 mg; pravastatin sodium, 60 mg; lovastatin, 60 mg; fluvastatin sodium, 90 mg; and rosuvastatin calcium, 5 mg.[34-36]

RESULTS

PARTICIPANT ENROLLMENT AND FOLLOW-UP

Physician participation (n=230) in each of the 10 provinces approximated the population distribution across Canada, including the Maritime provinces (8%), Quebec (26%), Ontario (43%), and the western provinces (23%). These community physicians screened 4310 patients, 3053 of whom were eligible for the study, were randomized, and completed the baseline visit (**Figure 2**). The study started May 10, 2001, and ended August 25, 2003, when all the patients had completed 12 months of follow-up or were withdrawn. Of the 366 patients who did not complete the study (166 in the risk profile group and 200 in the usual care group), 82 (22.4%) withdrew consent, 89 (24.3%) were lost to follow-up, 48 (13.1%) experienced an adverse event, and 13 (3.6%) died.

Baseline characteristics of all eligible patients are summarized in **Table 1**. Patients not completing the 12-month follow-up (n=366) were compared with those who did (n=2687) and were, on average, slightly older (mean±SD, 56.6±8.0 vs 54.6±8.8 years) and less likely to be smokers (27.9% vs 35.8%). There were no other important differences among early termination patients in the 2 treatment arms.

BLOOD LIPID CHANGES

Despite similar statin dosages, the mean change in LDL-C level from baseline for the risk profile group was −51.2 mg/dL (95% CI, −52.8 to −49.7 mg/dL) and for the usual care group was −48.0 mg/dL (95% CI, −49.5 to −46.4 mg/dL), with a significant mean difference of −3.3 mg/dL (95% CI, −5.4 to −1.1 mg/dL; *P*=.02) (**Table 2**). Between-group differences were also observed for TC level (−3.9 mg/dL; 95% CI, −6.4 to −1.4 mg/dL) and the TC:HDL-C ratio (−0.1; 95% CI, −0.2 to −0.1). Using a random-effects model to account for between-physician differences, these results between study arms remained essentially unchanged.

REACHING LIPID TARGETS

Overall, patients in the risk profile group were no more likely to reach lipid targets than those receiving usual care (55.2% vs 52.2%) (odds ratio [OR], 1.13; 95% CI, 0.98-1.30). However, at baseline, patients in the risk profile group had higher levels of TC and LDL-C and a higher TC:HDL-C ratio (Table 1). Accordingly, after adjusting for baseline differences in LDL-C levels and the TC:HDL-C ratio risk pro-

Table 3. Probability of Reaching Recommended Lipid Targets Stratified by Clinical Status

Study Participants	Patients Identified as High Risk, %[a]	Age, Mean, y			Patients Reaching Lipid Targets, %	OR (95% CI)[d]
		Cardiovascular[b]	Actual	Gap[c]		
With CVD						1.25 (0.89-1.75)
Risk profile	96	NA	NA	NA	50	
Usual care	95	NA	NA	NA	48	
Without CVD						
Overall						1.26 (1.04-1.53)
Risk profile	70	59.7	55.8	3.9	57	
Usual care	68	59.4	55.5	3.9	54	
Without diabetes mellitus						1.00 (0.72-1.39)
Risk profile	63	59.1	58.0	1.0	64	
Usual care	63	58.1	57.0	1.2	66	
With diabetes mellitus						1.42 (1.11-1.81)
Risk profile	74	60.1	54.1	6.0	52	
Usual care	71	60.3	54.4	5.9	45	

Abbreviations: CI, confidence interval; CVD, cardiovascular disease, NA, not applicable; OR, odds ratio.
[a]High risk is defined as the upper tertile for Canadians of the same age and sex.
[b]Cardiovascular age is calculated as the patient's age minus the difference between his or her estimated remaining life expectancy (adjusted for coronary risk) and the average remaining life expectancy of Canadians of the same age and sex.
[c]The age gap is defined as an individual's cardiovascular age minus his or her actual age.
[d]The ORs are adjusted for the difference between the baseline total cholesterol to high-density lipoprotein cholesterol ratio and target and the difference between baseline low-density lipoprotein cholesterol level and the target.

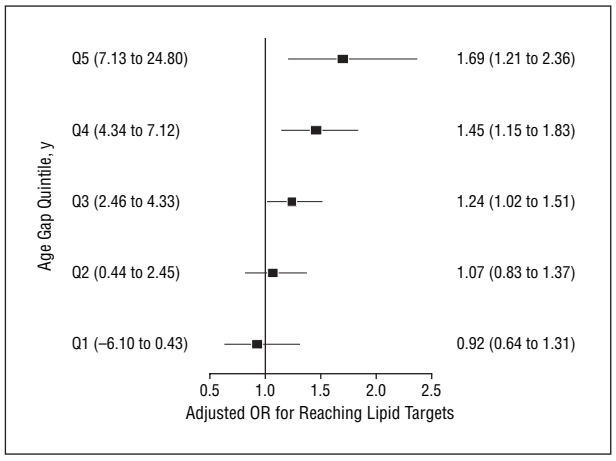

Figure 3. Mean adjusted odds ratios (ORs) for reaching lipid targets in individuals receiving a risk profile (vs usual care) are stratified by age gap quintiles (Qs). Using multiple logistic regression analysis, the impact of the risk profile is adjusted for the difference between baseline low-density lipoprotein cholesterol level and target, baseline total cholesterol to high-density lipoprotein cholesterol ratio and target, and statin dosage. Also included is the significant interaction (P=.04) between the risk profile and the age gap, indicating that the positive impact of the risk profile increases with an increasing age gap. For example, in individuals at relatively low risk for cardiovascular disease, the age gap is small or even negative (quintile 1: –6.10 to 0.43 years), indicating that the estimated life expectancy is greater than or equal to the average life expectancy for Canadians of the same age and sex. The corresponding adjusted OR for reaching lipid targets in individuals who are reassured that they are at low risk is 0.92. With an increasing age gap, the positive impact of the risk profile also increases so that the OR of reaching lipid targets is highest (OR, 1.69) for those in the highest age gap quintile. Horizontal bars represent 95% confidence intervals.

file, patients demonstrated a greater likelihood of reaching lipid targets (OR, 1.26; 95% CI, 1.07-1.48).

When the probability of reaching lipid targets was examined according to the patient's clinical status, the risk profile did not have a significant effect in individuals with preexisting CVD (OR, 1.25; 95% CI, 0.89-1.75) (**Table 3**). Cardiovascular age could not be calculated in this subgroup, but 95% to 96% of individuals with CVD were in the highest risk tertile for their age and sex. In the presence of symptomatic disease, it seems that a risk profile did not substantially improve the effectiveness of treatment. On the other hand, it was in individuals without CVD that a risk profile increased the likelihood of reaching targets (OR, 1.26; 95% CI, 1.04-1.53). This was primarily due to the impact on individuals with diabetes mellitus (OR, 1.42; 95% CI, 1.11-1.81).

The risk profile assigned each patient to a risk tertile compared with Canadians of the same age and sex. However, the baseline risk tertile did not seem to affect patient responses. Individuals without CVD were also given their cardiovascular age, their actual age, and the resulting "age gap" (cardiovascular age–actual age). This variable seemed to modify the degree to which patients responded to the risk profile. For example, among patients with diabetes mellitus who received a risk profile, the increased probability of reaching lipid targets may have been associated with the large age gap (cardiovascular age–actual age) of approximately 6 years. This hypothesis was further evaluated in all primary prevention patients. Patients in the risk profile group with a cardiovascular age greater than their chronologic age (age gap >0) demonstrated larger LDL-C reductions compared with patients receiving usual care. On the other hand, LDL-C reductions were smaller in patients in the risk profile group who were reassured that their risk was low because their age gap was less than 0 (**Figure 3**).

The interaction between the risk profile and an increased age gap in individuals without CVD was further examined by plotting the adjusted OR for reaching lipid

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targets against age gap quintiles (Figure 3). Multiple logistic regression analysis was used to adjust for the difference between baseline lipid levels and lipid targets (LDL-C and the TC:HDL-C ratio) and the statin dose. In individuals in the lowest age gap quintile (–6.10 to 0.43 years), the OR for reaching lipid targets using a risk profile (vs usual care) was 0.92. A dose-response effect was noted, with a significant interaction observed where the risk profile was more effective in individuals with larger age gaps (highest quintile: OR, 1.69; 95% CI, 1.21-2.36; $P = .04$).

COMMENT

These results demonstrate the proof of principle that statin therapy can be enhanced by informing patients of their calculated coronary risk. The reductions in the LDL-C level and the TC:HDL-C ratio were greater for patients receiving risk profiles. After adjustment for baseline differences in blood lipid levels, the risk profile group was also more likely to reach the recommended lipid targets. Finally, the significant interaction effect between the risk profile and the age gap (cardiovascular age – actual age) demonstrated that the higher a patient's risk, as evidenced by increased cardiovascular age, the greater the impact associated with the risk profile.

The strengths and weaknesses of this study must be recognized. Despite positive results for the prespecified outcomes, the clinical impact of risk profile feedback was small. This was due, in part, to a study protocol that may have minimized the impact of the intervention by encouraging physicians to treat patients in both treatment arms to achieve nationally recommended targets and minimized loss to follow-up even among those receiving usual care. The lipid changes required to reach treatment targets (see "Treatment gap" in Table 1) were also modest for LDL-C level and the TC:HDL-C ratio (–41 mg/dL and –1.03, respectively, for the control group); hence, there

was a high probability of success in both treatment arms. Also, the inclusion in the study of some relatively low-risk patients, whose small or negative age gap may have reassured them that their risk was low, may have reduced the overall perceived need for treatment in the risk profile group. Finally, this trial was not a cluster design based on physician randomization because an earlier study[30] demonstrated low retention rates for physicians in the control arm. Randomizing patients may have reduced the observed effectiveness of the intervention because physicians may have incorporated the knowledge gained from treating patients in the risk profile group when treating individuals in the control group. Given this possible contamination of the control group, these study results may underestimate the potential impact of the risk profile. It is possible that the impact of a profile would be even greater in patients still contemplating the pros and cons of therapy. Ideally, low-risk patients would be reassured, whereas higher-risk patients would be motivated to start and adhere to treatment.

Given that masking is impossible in a decision aid study, the Hawthorne effect (a change in behavior resulting from the knowledge that one is being studied) is always a concern. However, patients in both interventions signed informed consent documents and understood that they were participating in a study. Moreover, the profile was most helpful in those with the largest age gap, demonstrating a dose-response effect consistent with the underlying study hypothesis. Patient behavior seems to have been modified as the odds of reaching lipid targets increased approximately 25% after adjustment for statin dose and baseline lipid levels. This suggests greater adherence with statins or other lifestyle changes.

On the other hand, the strengths of the study include a cross-country randomized trial in a primary care setting. The choice of medication and the decision to switch or titrate this medication was left to the individual physician. The cost of medication and the effort to obtain it also reflected patient care as currently practiced under a national health care plan.

Given the enormous clinical and economic burden of CVD in our communities, primary prevention cannot be avoided. Communicating risk is consistent with many of the recommendations to improve adherence, including enhancing self-monitoring and using the support of family and friends.[7,8] Informing patients of their coronary risk may also increase the effectiveness of primary prevention by identifying individuals most likely to benefit from treatment while reassuring those at low risk. This information may also assist physicians in treatment selection while improving patient adherence.

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REFERENCES

1. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet.* 1994;344(8934):1383-1389.
2. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med.* 1996;335(14):1001-1009.
3. Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med.* 1998;339(19):1349-1357.
4. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: a randomised placebo-controlled trial. *Lancet.* 2002;360(9326):7-22.
5. Colhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet.* 2004;364(9435):685-696.
6. Sever PS, Dahlof B, Poulter NR, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA): a multicenter randomised controlled trial. *Lancet.* 2003;361(9364):1149-1158.
7. De Backer G, Ambrosioni E, Borch-Johnsen K, et al. European guidelines on cardiovascular disease prevention in clinical practice: Third Joint Task Force of European and other Societies on Cardiovascular Disease Prevention in Clinical Practice. *Eur Heart J.* 2003;24(17):1601-1610.
8. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP): Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA.* 2001; 285(19):2486-2497.
9. Jackson R, Lawes C, Bennet D, Milne R, Rodgers A. Treatment with drugs to lower blood pressure and blood cholesterol based on an individual's absolute cardiovascular risk. *Lancet.* 2005;365(9457):434-441.
10. Pearson TA, Laurora I, Chu H, Kafonek S. The Lipid Treatment Assessment Project (L-TAP): a multicenter survey to evaluate the percentages of dyslipidemic patients receiving lipid-lowering therapy and achieving low-density lipoprotein cholesterol goals. *Arch Intern Med.* 2000;160(4):459-467.

11. Schrott HG, Bittner V, Vittinghoff E, Herrington DM, Hulley S; HERS Research Group. Adherence to National Cholesterol Education Program treatment goals in postmenopausal women with heart disease: the Heart and Estrogen/Progestin Replacement Study (HERS). *JAMA*. 1997;277(16):1281-1286.
12. Schectman G, Hiatt J. Drug therapy for hypercholesterolemia in patients with cardiovascular disease: factors limiting achievement of lipid goals. *Am J Med*. 1996;100(2):197-204.
13. McBride P, Schrott HG, Plane MB, Underbakke G, Brown RL. Primary care practice adherence to national cholesterol education program guidelines for patients with coronary heart disease. *Arch Intern Med*. 1998;158(11):1238-1244.
14. Marcelino JJ, Feingold KR. Inadequate treatment with HMG-CoA reductase inhibitors by health care providers. *Am J Med*. 1996;100(6):605-610.
15. Benner JS, Glynn RJ, Mogun H, Neumann PJ, Weinstein MC, Avorn J. Long-term persistence in use of statin therapy in elderly patients. *JAMA*. 2002;288(4):455-461.
16. Jackevicius CA, Mamdani M, Tu JV. Adherence with statin therapy in elderly patients with and without acute coronary syndromes. *JAMA*. 2002;288(4):462-467.
17. Avorn J, Monette J, Lacour A, et al. Persistence of use of lipid-lowering medications: a cross-national study. *JAMA*. 1998;279(18):1458-1462.
18. Simons LA, Levis G, Simons J. Apparent discontinuation rates in patients prescribed lipid-lowering drugs. *Med J Aust*. 1996;164(4):208-211.
19. Andrade SE, Walker AM, Gottlieb LK, et al. Discontinuation of antihyperlipidemic drugs: do rates reported in clinical trials reflect rates in primary care settings? *N Engl J Med*. 1995;332(17):1125-1131.
20. Bodenheimer T, Lorig K, Holman H, Grumbach K. Patient self-management of chronic disease in primary care. *JAMA*. 2002;288(19):2469-2475.
21. Holman H. Chronic disease: the need for a new clinical education. *JAMA*. 2004;292(9):1057-1059.
22. Deber RB, Kraetchmer N, Irvine J. What role do patients wish to play in treatment decision making? *Arch Intern Med*. 1996;156(13):1414-1420.
23. Braddock CH, Edwards KA, Hassenberg NM, Laidley TL, Levinson W. Informed decision making in outpatient practice: time to get back to basics. *JAMA*. 1999;282(24):2313-2320.
24. Barry MJ. Involving patients in medical decisions: how can physicians do better? *JAMA*. 1999;282(24):2356-2357.
25. Fodor JG, Frohlich JJ, Genest JJ Jr, McPherson PR; Working Group on Hypercholesterolemia and Other Dyslipidemia. Recommendations for the management and treatment of dyslipidemia. *CMAJ*. 2000;162(10):1441-1447.
26. Grover SA, Paquet S, Levinton C, Coupal L, Zowall H. Estimating the benefits of modifying risk factors of cardiovascular disease: a comparison of primary vs secondary prevention. *Arch Intern Med*. 1998;158(6):655-662.
27. Grover SA, Abrahamowicz M, Joseph L, Brewer C, Coupal L, Suissa S. The benefits of treating hyperlipidemia to prevent coronary heart disease: estimating changes in life expectancy and morbidity. *JAMA*. 1992;267(6):816-822.
28. Grover SA, Lowensteyn I, Esrey K, Steinert Y, Joseph L, Abrahamowicz M. How accurately do Canadian physicians assess the coronary risk of their patients? the preliminary results of the Coronary Health Assessment Study (CHAS). *BMJ*. 1995;310(6985):975-978.
29. MacLean DR, Petrasovits A, Nargundkar M, et al; Canadian Heart Health Surveys Research Group. Canadian heart health surveys: a profile of cardiovascular risk: survey methods and data analysis. *CMAJ*. 1992;146(11):1969-1974.
30. Lowensteyn I, Joseph L, Levinton C, Abrahamowicz M, Steinert Y, Grover SA. Can computerized risk profiles help patients improve their coronary risk? the results of the Coronary Health Assessment Study (CHAS). *Prev Med*. 1998;27(5, pt 1):730-737.
31. Joseph L, du Berger R, Bélisle P. Bayesian and mixed Bayesian/likelihood criteria for sample size determination. *Stat Med*. 1997;16(7):769-781.
32. Lee KJ, Thompson SG. Clustering by health professional in individually randomised trials. *BMJ*. 2005;330(7483):142-144.
33. Sullivan LM, Dukes KA, Losina E. Tutorial in biostatistics: an introduction to hierarchical linear modelling. *Stat Med*. 1999;18(7):855-888.
34. Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. *BMJ*. 2003;326(7404):1423-1429.
35. Jones PH, Davidson MH, Stein EA, et al. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR* Trial). *Am J Cardiol*. 2003;92(2):152-160.
36. Jones P, Kafonek S, Laurora I, Hunninghake D. Comparative dose efficacy study of atorvastatin versus simvastatin, pravastatin, lovastatin and fluvastatin in patients with hypercholesterolemia (the CURVES study). *Am J Cardiol*. 1998;81(5):582-587.