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Clinical Research

Use of a Treatment Optimization Algorithm Involving Statin-Ezetimibe Combination Aids in Achievement of Guideline-Based Low-Density Lipoprotein Targets in Patients With Dyslipidemia at High Vascular Risk Guideline-Based Undertaking to Improve Dyslipidemia Management in Canada (GUIDANC)

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ABSTRACT

Background: Despite the well-established benefits of strategies to reduce low-density lipoprotein cholesterol (LDL-C), many patients fail to achieve the guideline recommended targets. The objective of this study was to evaluate the impact of an enhanced 26-week algorithm-based treatment optimization strategy, involving titration of statin monotherapy and/or combination therapy with statin and ezetimibe, on achievement of guideline-based LDL-C targets in patients at high risk for atherosclerotic disease.

Methods and Results: In this national (172-physician) quality enhancement research initiative involving 2334 Canadian men and women (median age, 65 years) at high vascular risk who were not at the guideline-recommended LDL-C target despite statin therapy, 36.6% and 45.5% of patients achieved an LDL-C <2.0 mmol/L at visit 2 and visit 3, respectively, using the treatment optimization algorithm.

RÉSUMÉ

Introduction : En dépit des bénéfices bien établis des stratégies pour réduire le cholestérol à lipoprotéines de faible densité (LDL), plusieurs patients ne parviennent pas aux objectifs des recommandations. Le but de cette étude était l'évaluation de l'impact d'une stratégie d'un algorithme d'optimisation de traitement de 26 semaines impliquant le titrage d'une statine en monothérapie, et/ou traitement associant la statine à l'ézétimibe, selon l'atteinte des objectifs des recommandations de base en matière de LDL chez les patients à risque élevé de maladie athérosclérotique.

Méthodes et résultats : Dans cette initiative nationale (172 médecins) de l'amélioration de la qualité de la recherche impliquant 2 334 hommes et femmes canadiens (âge moyen de 65 ans) à risque vasculaire élevé, ne respectant pas les objectifs des recommandations en matière de cholestérol LDL malgré un traitement aux statines, 36,6 % et 45,5 % des pa-

Low-density lipoprotein cholesterol (LDL-C) is a well-established risk factor for cardiovascular disease, and there is considerable evidence that lowering LDL-C reduces the risk of both cardiovascular events and mortality in patients with, or at high risk for, vascular disease.[1] Nonetheless, strategies for lowering LDL-C are poorly adopted in clinical practice, and many patients fail to reach the guideline-recommended targets.[2-10] Thus, these patients may not receive the same benefits in cardiovascular risk reduction observed in clinical trials.

Although statins remain the mainstay of dyslipidemia management, attainment of the recommended LDL-C targets can be difficult without use of combination therapy.[11] While clinical outcome data have yet to be established except for patients with renal disease,[12,13] prior clinical experience has demonstrated that the addition of the cholesterol absorption inhibitor

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The percentage of patients achieving the 2009 Canadian Cardiovascular Society (CCS)-recommended target of either LDL-C <2.0 mmol/L or a 50% or greater reduction from baseline increased from 6.8% at visit 1 to 43.3% at visit 2 and to 52.1% at visit 3. Attainment of LDL-C targets increased significantly with consecutive visits ($P < .001$). Use of ezetimibe in combination with statin therapy was associated with greater target achievement.

Conclusions: Use of a structured treatment optimization algorithm, based on titration of statin dosages and incorporation of ezetimibe therapy when required, enabled the majority of high-risk patients to achieve guideline-recommended targets, thereby narrowing the care gap that exists in dyslipidemia management.

tients ont atteint un taux de cholestérol LDL < 2,0 mmol/l à la 2e visite et à la 3e visite, respectivement, d'après l'algorithme d'optimisation du traitement. Le pourcentage de patients ayant atteint les objectifs recommandés par la Société canadienne de cardiologie (SCC) 2009, soit un LDL < 2,0 mmol/l ou une réduction minimale de 50 % par rapport à la situation initiale augmentait de 6,8 % à la 1re visite, à 43,3 % à la 2e visite et à 52 % à la 3e visite. L'obtention des objectifs de cholestérol LDL augmentait significativement lors des visites consécutives ($P <$ 0,001). L'utilisation de l'ézétémibe combinée au traitement aux statines était associée à une atteinte plus grande des objectifs.

Conclusions : L'utilisation structurée d'un algorithme d'optimisation de traitement, basé sur le titrage de la dose des statines et l'introduction d'un traitement à l'ézétimibe, lorsque nécessaire, permettait à la majorité des patients à risque élevé d'atteindre les objectifs des recommandations, réduisant ainsi l'écart actuel dans la gestion des soins de la dyslipidémie.

(CAI) ezetimibe is safe and provides further LDL-C lowering compared with statin monotherapy.[14-24]

We have previously established, in patients at high vascular risk, the utility of an algorithm-based treatment regimen in reducing the care gap in dyslipidemia management.[23] The 26-week program, involving uptitration of statin dosages, and/or combination therapy with statin and ezetimibe, resulted in 71% of subjects not previously at target successfully achieving an LDL-C level <2.5 mmol/L and 41% achieving a level <2.0 mmol/L at final visit. Consequently, we hypothesized that modifying the treatment algorithm to incorporate more specific instructions could further improve achievement of LDL-C targets.

The purpose of this observational study was to evaluate the impact of an enhanced 26-week algorithm-based treatment optimization strategy, involving uptitration of statin monotherapy and/or combination therapy with statin and ezetimibe, on the achievement of the 2006 Canadian Cardiovascular Society (CCS) guideline-recommended LDL-C targets for patients at high risk for atherosclerotic disease.

Methods

This study was a multicentre, observational, management-oriented, quality-enhancement research initiative. Between January 2007 and August 2008, 172 physicians across 10 provinces in Canada, of whom 159 (92%) were general practitioners or family doctors, participated (see Appendix). Guideline-based treatment strategies were provided to physicians caring for patients with hypercholesterolemia at high vascular risk with LDL-C that was not yet at the recommended target of <2.0 mmol/L despite statin therapy. All treatment decisions, including the decision to follow these recommendations, were left to the physician's discretion; there was no formal intervention or mandated treatment in this study.

The study was supported by an unrestricted grant from Merck & Co., Kirkland, Québec, Canada. However, the sponsor played no role in the study design, the development of the paper, or the decision to publish. Approval for the study protocol was received from an independent central ethics review board (Optimum Clinical Research, Inc, Ethics Review Board, Oshawa, Ontario, Canada) and the Research Ethics Review Committee of the College of Physicians and Surgeons of Alberta. Physician-participants were recruited by direct mail or fax campaigns, continuing medical education events, and from participation in previous or ongoing registries with the coordinating centre, the Canadian Heart Research Centre (Toronto, Ontario, Canada). Participating physicians were instructed to consecutively enroll patients who met all the inclusion criteria but no exclusion criteria. Participation was voluntary, and written consent was obtained from all study subjects.

Eligible subjects were male and female adults (18 years or older) with a diagnosis of primary hypercholesterolemia, defined as being "high risk" according to the 2006 Canadian Cardiovascular Society Working Group on Dyslipidemia[25] (calculated 10-year risk of coronary artery disease ≥ 20% based on the Framingham model, history of diabetes mellitus, cardiovascular disease, or any combination) who had not achieved the recommended LDL-C target (<2.0 mmol/L) while on statin therapy and were not already on a CAI. Cardiovascular disease included coronary artery disease, evidence of peripheral vascular disease or a history of cerebrovascular disease. Coronary artery disease was defined as at least one of the following: previous myocardial infarction, coronary artery bypass grafting (CABG), unstable angina, percutaneous coronary intervention (balloon angioplasty, stent) or stable angina with angiogram ≥ 50% stenosis in ≥ 1 major artery or a positive stress test. Evidence of peripheral vascular disease was confirmed by a history of intermittent claudication, documented decrease in pulses or bruits supported by an ankle-brachial index of <0.9, duplex ultrasound diagnosis of >50% stenosis in >1 major artery or prior revascularization procedure. Criteria for cerebrovascular disease included prior stroke, transient ischemic attack or revascularization procedure. Diabetes mellitus was defined as the presence of at least one of the following: symptoms of diabetes (including fatigue, polyuria, polydipsia, and unexplained weight loss) plus a random plasma glucose value >11.1 mmol/L, fasting plasma glucose >7.0 mmol/L, a 2-hour plasma glucose value >11.1 mmol/L following oral glucose tolerance test, or current treatment with an oral antihyperglycemic agent, insulin, or both.

Individuals were excluded from participation if they had received treatment with any investigational drug within 30 days of screening or had clinically significant concomitant illnesses of liver, muscle, or kidney; secondary causes of hypercholesterolemia (eg, hypothyroidism, nephrotic syndrome); or poor mental function or drug or substance abuse that in the

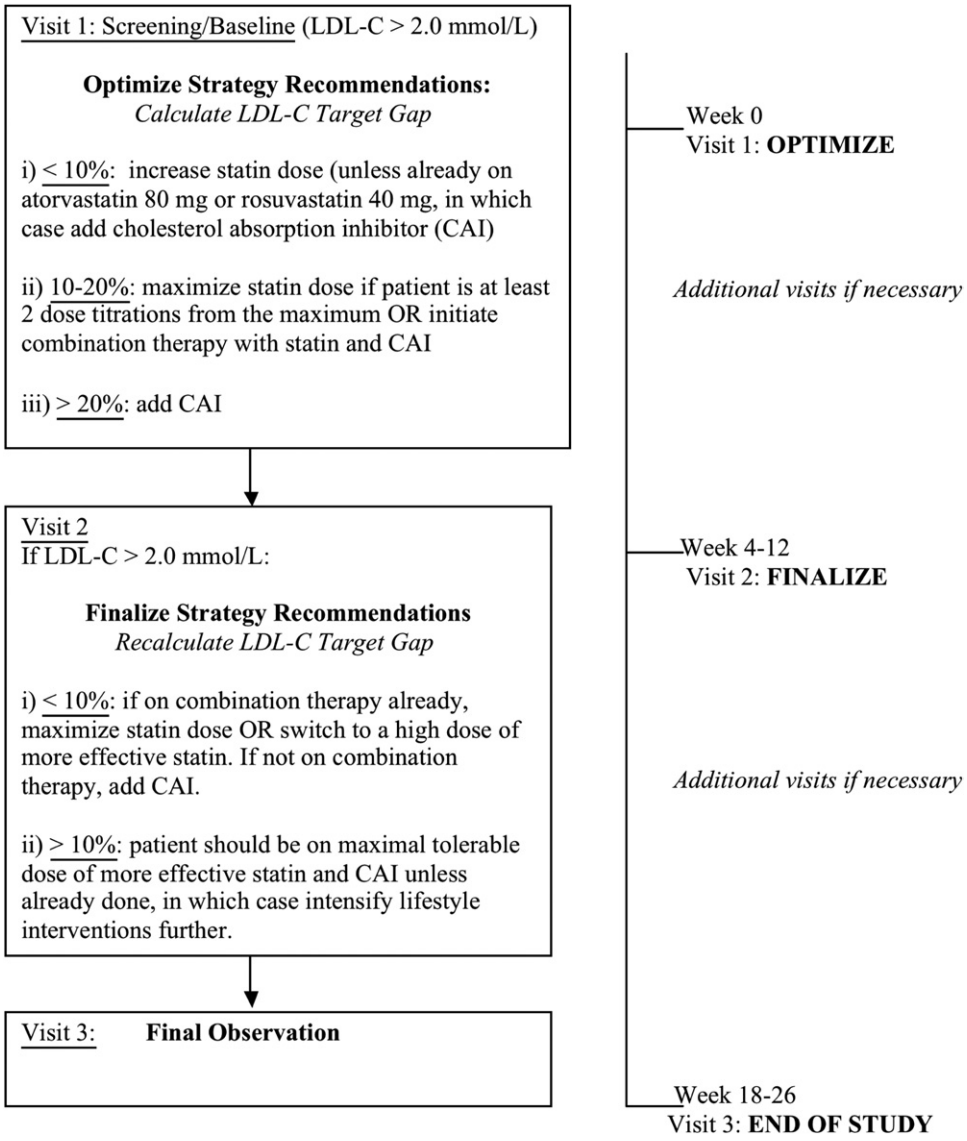

Figure 1. Study schematic for the Guideline-Based Undertaking to Improve Dyslipidemia Management in Canada (GUIDANC). LDL-C, low-density lipoprotein cholesterol.

opinion of the investigator might interfere with optimal participation in the study.

Figure 1 illustrates the study schematic consisting of 3 potential visits over 26 weeks. Physicians were encouraged to schedule additional visits as often as required to achieve therapeutic targets and optimize management of overall cardiovascular risk and other comorbid conditions. At visit 1 (screening/baseline, week 0), inclusion and exclusion criteria were assessed, and informed consent was obtained. Patients underwent a medical history; review of prior/concomitant medication use; and physical examination, including vital signs and anthropometric measurements. A fasting lipid profile and routine blood tests were obtained. The primary care physician (or his or her designate) recorded all information on standard case-report forms. In addition to the current lipid profile, investigators were asked to record historical lipid profiles collected prior to and after statin initiation.

Completed case-report forms were collated and scanned using TELEform 7 (Cardiff Software, Inc., San Diego, California), and data were stored in an electronic database at the Canadian Health Research Centre.

The optimization of lipid-lowering strategy began at visit 1. Specific treatment recommendations were based on the calculated "LDL-C target gap," which is the percentage of LDL-C lowering needed to achieve an LDL-C $<$2.0 mmol/L (LDL-C target gap = current LDL-C $-$ 2.0/current LDL-C $\times$ 100). If the LDL-C target gap was $<$10%, physicians were encouraged to change to a more effective statin or increase the dose of statin, unless the patient was already on atorvastatin 80 mg or rosuvastatin 40 mg, in which case addition of the CAI ezetimibe was recommended. If the LDL-C target gap was 10%-20% and the patient was at least 2 dose titrations from the maximum, suggestions included either maximizing the statin dose or adding a CAI. If the LDL-C target gap was $>$20%, addition of a CAI was recommended. Throughout

the study, selection and dosing of therapy remained at the discretion of the treating physicians and were not mandated by the study protocol.

During each subsequent visit, investigators were asked to review the patients' medication profile and any side effects. Vital signs and anthropometric measurements were obtained, and a lipid profile was performed, along with other necessary laboratory investigations. Investigators were encouraged to document any counseling efforts, such as advice regarding smoking cessation, promotion of regular physical activity, or discussion of healthy eating habits.

Throughout the study period, as part of routine clinical care, plasma lipid measurements were performed in local laboratories used by the participating physicians. A complete lipid profile, consisting of fasting total cholesterol, calculated LDL-C (using the Friedewald formula), high-density lipoprotein cholesterol (HDL-C), and triglyceride levels, was determined. When high plasma triglyceride levels precluded calculation of LDL-C, the patient's lipid data were not included for that visit.

The treatment strategy was finalized at visit 2 (weeks 4-12). If the LDL-C target was achieved, physicians were encouraged to continue the patient's current therapy. For those subjects not yet at target, the LDL-C target gap was recalculated. If the treatment gap was <10% and the patient was not on combination therapy, addition of CAI was recommended. However, if the patient was already on combination therapy, suggested approaches included either maximizing the statin dose or switching to a high dose of a more effective statin. If the LDL-C target gap was >10%, the suggested approach was to place the patient on the maximum tolerable dose of a more effective statin and CAI, unless already done, in which case further intensification of lifestyle interventions was recommended. Visit 3 (weeks 18-26) marked completion of the study period.

Primary measurements of efficacy in this study were the percentage of patients achieving LDL-C target <2.0 mmol/L and the mean change in plasma LDL-C between baseline visit and final study assessment. The LDL-C target of <2.0 mmol/L was chosen on the basis of the 2006 CCS Recommendations for Dyslipidemia Management in patients at high vascular risk. In 2009, after study completion, the CCS Guidelines were revised such that the primary target for high-risk patients is LDL-C <2.0 mmol/L or a reduction of 50% or greater from baseline LDL-C.[26]

We therefore also conducted a post hoc analysis to determine the number of patients who would have been considered at target based on these new criteria. The most recent lipid profile was used as the baseline measurement to determine the percentage LDL-C reduction that occurred as a result of therapy at each visit. Additional secondary measurements of efficacy included the proportion of patients achieving LDL-C target after 12 weeks of appropriate treatment optimization (visit 2), combination therapy impact on proportion of patients achieving LDL-C target at visits 2 and 3, and changes in lipid profile parameters other than LDL-C (total cholesterol, triglycerides, HDL-C, total cholesterol-to-HDL-C ratio).

Descriptive analysis was performed for demographic variables, physical examination, medical history, and lipid profile parameters. Frequency tables of the categorical variables and the means, standard deviations, and quartiles of the quantitative variables are presented. Factors thought to be related to achievement of LDL-C target levels were explored using logistic regression, while factors possibly related to changes in lipid profile were studied using repeated measures ANOVA.

Results

Of the 2344 patients assessed, 2334 fulfilled all necessary enrollment criteria without protocol violation and were included in the analysis population; flow through the study registry is outlined in Figure 2. Baseline demographics and clinical characteristics of the final cohort are presented in Table 1.

Table 2 shows the mean fasting lipid profiles at each visit. The mean percentage and absolute reduction in LDL-C from visit 1 (screening/baseline) was 31.7% (0.52 mmol/L) at visit 2 and 38.5% (0.63 mmol/L) at visit 3. Repeated measures ANOVA on LDL-C at each visit demonstrated a significant ($P < .001$) linear decrease in LDL-C levels across visits. HDL-C and triglyceride levels also differed significantly from visit 1 to visits 2 and 3 ($P < .003$ and $P < .0001$, respectively). When a historical LDL-C measurement prior to initiation of statin therapy was available (n = 1526), the mean percentage reduction in LDL-C was 42.4% at the first study visit, 83.0% at visit 2, and 87.7% at visit 3. Of those patients who had not achieved the LDL-C target at visit 3 (n = 969), the mean LDL-C treatment gap at that point, based on the 2006 CCS guidelines, was 29.2%, or 0.57 mmol/L (SD = 0.705).

Overall, 2006 target levels were successfully reached by 36.3% and 45.5% of total participants at visit 2 and visit 3, respectively (Fig. 3). The increase in target attainment observed from visit 1 to visit 2 and from visit 2 to visit 3 was significant ($P < .001$). The percentage of patients achieving the 2009 guideline-recommended LDL-C targets (either an LDL-C <2.0 mmol/L or a 50% or greater reduction from baseline LDL-C) increased from 6.8% at visit 1 to 43.3% at visit 2 and 52.1% at visit 3 (both $P < .001$ compared with visit 1). The increase in 2009 target attainment observed with consecutive visits was also significant ($P < .001$).

The addition of ezetimibe resulted in an additional 0.61 mmol/L reduction in mean LDL-C between visit 2 and visit 3 (95% CI, 0.51-0.71). An additional 0.29 mmol/L (95% CI, 0.21-0.37) reduction in mean LDL-C was observed with further increase in statin dosage, and an additional 0.28 mmol/L (95% CI, 0.11-0.44) with change in statin therapy compared with an increase of 0.02 mmol/L (95% CI, −0.06 to −0.02) with no change in active management.

At each study visit, atorvastatin and rosuvastatin were the most prescribed statins, followed by simvastatin and pravastatin. Including visit 3, 41.9% of patients received prescriptions for atorvastatin and 30.8% were prescribed rosuvastatin during the study period. Ezetimibe was started or continued in 26.7%, 33.7%, and 37.7% of patients at visits 1, 2, and 3, respectively.

Gender, diabetes status, baseline body mass index, smoking status, and ezetimibe prescription at visit 1 were entered as covariates in a logistical regression model predicting target achievement at visit 2 and visit 3. Ezetimibe prescription at visit 1 was a significant predictor of LDL-C target achievement at visit 2, odds ratio (OR) 2.61 (95% CI, 1.88-3.62, $P < .001$) and visit 3, OR 1.77 (95% CI, 1.27-2.44, $P = .001$). Similarly, ezetimibe prescription at visit 2 predicted target achievement at visit 3, OR 1.86 (95% CI, 1.38-2.51, $P < .001$). Thus, prescription of ezetimibe was associated with a higher probability of target achievement in all 3 regression analyses.

Of those patients who were not at target at visit 3 but were not prescribed ezetimibe (n = 560), the most common

Figure 2. Flow of patients through the Guideline-Based Undertaking to Improve Dyslipidemia Management in Canada registry (GUIDANC). In cases of high plasma total cholesterol (>9.4 mmol/L) or triglyceride (>4.5 mmol/L) levels, or both, precluding accurate determination of circulating low-density lipoprotein cholesterol (LDL-C) with the Friedewald formula, patient data were not included in the final analysis.

reasons cited by the treating physician were plan to optimize statin further (39.1%), current level "good enough" for patient (18.4%), and noncompliance (22.9%). Cost was a limiting concern for 63 patients (11.3%). Of the patients who were judged by their physician to be close enough to target without further therapy, 69.9% had an LDL-C between 2.00 and 2.29 and 18.4% were between 2.30 and 2.59, with only 11.7% having LDL-C levels of 2.60 or above.

Counseling efforts were frequently noted on the case report forms. Dietary advice and recommendations about exercise were recorded during the study period for 97.3% and 95.6% of patients, respectively. Smoking cessation counseling was documented in 85.8% of those who smoked. Patients with diabetes were more likely to receive dietary counseling ($P = .004$) but were no more likely than other participants to be advised regarding exercise or smoking at any of the 3 visits. Patients with diabetes were also more likely to reach LDL-C targets than were their counterparts without diabetes (visit 2: 39.1% vs 31.9%, $P < .002$; visit 3: 47.4% vs 42.6% ($P < .05$)].

Discussion

In this national observational cohort of 2334 high–cardiovascular-risk patients with persistent hypercholesterolemia despite statin monotherapy, 45.5% successfully achieved the guideline-recommended LDL-C target of <2.0 mmol/L during the study period. These findings are comparable to our previously published study, in which 41% of patients reached an LDL-C <2.0 mmol/L using a treatment optimization algorithm.[23] Importantly, however, guidelines at that time had advocated a less stringent LDL-C target of <2.5 mmol/L.[27]

The present study has a number of important strengths. Our cohort of 2334 patients is likely diverse and representative as it was derived from the practices of 172 physicians from across Canada, who were instructed to enroll consecutive patients. Provision of advice regarding healthy diet or exercise was documented in more than 95% of subjects, which may be evidence of the comprehensive nature of care provided by participating physicians. Compared with the previous study, improvements in the current study design include fewer follow-up visits and the incorporation of more specific treatment recommendations into the therapeutic

Table 1. Baseline characteristics of final study cohort (N = 2334)

Age (years)	64.9 (57, 73)
Male	1236 (52.9)
White	1816 (77.8)
Blood pressure (mm Hg)	
Systolic	130 (120, 140)
Diastolic	76 (70, 80)
Body mass index (kg/m^2)	30.2 (25.8, 33.1)
Waist circumference (cm)	102.1 (92, 110)
Coronary artery disease	850 (36.4)
Myocardial infarction	441 (18.9)
Coronary artery bypass grafting	186 (8.0)
Percutaneous coronary intervention	215 (9.2)
Unstable angina pectoris	174 (7.5)
Stable angina pectoris	193 (8.3)
Peripheral vascular disease	202 (8.7)
Cerebrovascular disease	267 (11.4)
Stroke	122 (5.2)
Transient ischemic attack	144 (6.2)
Diabetes mellitus	1428 (61.2)
10-year Framingham risk >20%	519 (22.2)
Hypertension	1684 (72.2)
Current smoker	385 (16.5)

Values are means (25th, 75th percentiles) or numbers of patients (percentages). Where data are missing, valid percentage is reported.

algorithm. The LDL-C target gap was used to facilitate treatment decisions. It is a simple calculation that physicians can readily adopt into clinical practice.

It is also important to consider several limitations of the study design. By including only patients who were not at target despite statin therapy, a bias may have been introduced for those less responsive or less adherent to therapy, resulting in an underestimation of treatment success. This is in contrast to the previous study, in which not all participants were receiving statin therapy at enrollment.[23] On the other hand, patient adherence to medications was not formally monitored during the study and therefore may have been overestimated. This was an observational study; therefore, while physicians were provided with treatment recommendations, their implementation was at the physicians' discretion. Thus, our results are not necessarily generalizable to other physician populations. As well, a proportion of patients (approximately 20%) did not return for follow-up at visit 3 or did not have LDL-C levels available. Some of these patients may have had tolerance or compliance issues that limited their response to therapy. Their inclusion, therefore, could have lowered the percentage of patients achieving target.

Table 2. Mean fasting lipid profile according to study visit

	Historical; Prior to Statin Initiation	Visit 1 (Baseline) N = 2334	Visit 2 N = 1958	Visit 3 N = 1891
Total cholesterol	5.99	4.81	4.22	4.10
Low-density lipoprotein cholesterol	3.77	2.79	2.27	2.15
High-density lipoprotein cholesterol	1.26	1.25	1.24	1.24
Ratio, total cholesterol to high-density lipoprotein cholesterol	4.96	4.04	3.60	3.49
Triglycerides	2.18	1.70	1.56	1.55

All values are in mmol/L.

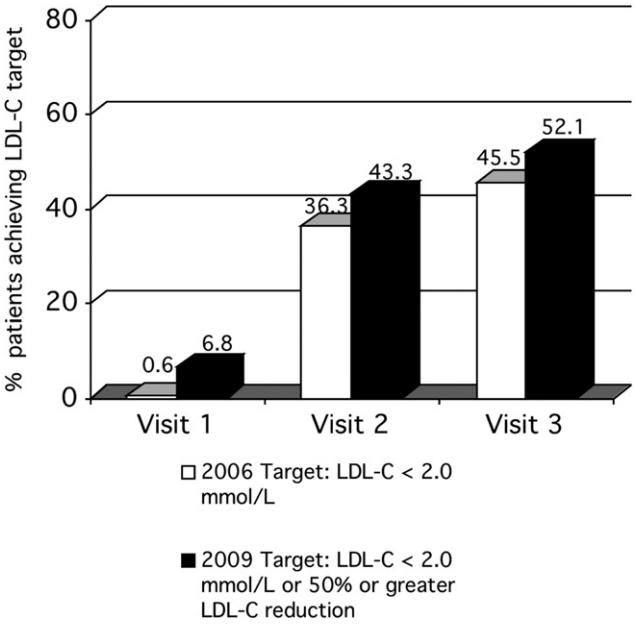

Figure 3. Temporal trend in the percentage of study subjects achieving low-density lipoprotein cholesterol (LDL-C) target at each visit according to Canadian Cardiovascular Society Guidelines. In white is the 2006 target for high–vascular-risk patients: LDL-C <2.0 mmol/L. In black is the 2009 target for high–vascular-risk patients (published after completion of study): LDL-C <2.0 mmol/L or a 50% or greater reduction in LDL-C from baseline.

At visit 1, those patients who had an available historical lipid profile had already experienced a mean reduction in LDL-C of 42.4%, consistent with the expected response to therapy but also suggesting limited room for further reduction with additional titration of statin dosage alone. Ezetimibe was included in the treatment algorithm in this study because of its additional LDL-C–lowering effect, which is on the order of 15% to 20%. Indeed, use of ezetimibe was associated with greater target achievement in this study. However, despite greater LDL-C target achievement, the impact of ezetimibe therapy on clinical outcomes has yet to be established for any but patients with renal disease.[12-13] The results of the Study of Heart and Renal Protection demonstrate that the use of ezetimibe in addition to simvastatin was safe and effective in lowering atherosclerotic events in patients with chronic kidney disease. Although this benefit was obtained in comparison with a placebo, prior experience with atorvastatin and rosuvastatin in a similar group of patients without a significant benefit suggests that the combination therapy using a less effective statin may be of importance.[28-29] This concept thus highlights the potential benefit of combining an agent that inhibits cholesterol synthesis with an agent that inhibits a rebound in cholesterol absorption, resulting in a more effective lowering of the cholesterol than could be achieved with a higher dose of a more effective statin.

According to the 2009 CCS Guidelines, over half of patients (52.1%) would have been considered at target at the final study visit. Furthermore, 14% of patients at visit 3 were judged by their physician to have satisfactory LDL-C levels despite not being at target. Of those patients, the vast majority, approximately 70%, were near target, with an LDL-C level between 2.0 and 2.3 mmol/L. High-quality evidence exists to support the cardiovascular benefits of intensively lowering LDL-C to 2.0 mmol/L from

2.6 mmol/L using statin monotherapy in patients with stable coronary artery disease.[30] However, at present similar evidence is not available to compare LDL-Cs of 2.0 mmol/L vs 2.3 mmol/L, although all current evidence suggests that the lower LDL-C would be associated with better outcomes. In clinical practice, physicians are often divided regarding how to manage patients in this "grey zone," particularly if the patients are already receiving aggressive therapy. In fact, the absolute reduction in LDL-C achieved may be more important than the realization of a particular LDL-C target level. The Cholesterol Treatment Trialists' Collaboration meta-analysis of statin trials in persons with diabetes previously calculated a significant 21% proportional reduction in major vascular events for every 1-mmol/L decrease in LDL-C levels.[1] The 0.63-mmol/L reduction in mean LDL-C observed during the study period could therefore be expected to translate into a 13.2% additional reduction in events, although this expectation has yet to proven in a clinical trial. Taken together, these results support the use of an algorithm-based approach in the treatment of patients with hypercholesterolemia at high vascular risk.

Conclusion

As evidence-based guidelines continue to advocate progressively lower LDL-C levels, new strategies are necessary to help physicians aid their patients in achieving these targets. Use of a treatment optimization algorithm involving uptitration of statin dosages and combination therapy with ezetimibe when required facilitates target achievement and can narrow the care gap in dyslipidemia management.

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Disclosures

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Appendix

The following investigators and coordinators participated in GUIDANC (by province, in order of enrollment): **Ontario:** Richard Y. Y. Chen, Mississauga; Selwyn X. De Souza, Ottawa; Eleanor De Souza, Nepean ; Zsuzsanna Gabor, Scarborough; Talaat Lotfallah, Kingston; Kinga Koprowicz, Kirkfield; Louis S. Zavodni, Hamilton; Wendy Rosenthall, Mississauga; Alan Faiers, Toronto; Joseph C. Berlingieri, Burlington; Paul DeYoung, Cornwall; Ian K. Shiozaki, Newboro; Gao-Nan Chang, Toronto; Arif R. Chaudri, Toronto; Pooi-Lin Tham, London; Howard Rudner, Toronto; Osborne Isaac Noronha, Belleville; Ming-Jarm Lau, North York; Bharat B. Kalra, Scarborough; Cathy V. Andrew, Toronto; Claudius Che, Fort Erie; Doris S. Lee, Etobicoke; Daniel Yim, North York; Robert G. Luton, London; Shajahan Deen, Kitchener; Clement Lam, Etobicoke; Joseph Kozak, Toronto; William L. Cunningham, Belleville; F. B. T. Forbes, Bramalea; Max Leung Sui Fung, Oshawa; Roger C. Bunn, Brampton; Galina Gotesman, Toronto; Ralph Epstein, Hamilton; Earl Schwartz, Toronto; Tommy Hong, Mississauga; Gerald L. Rockman, Scarborough; David Y. K. Chan, Toronto; Thangamani Subramanian, Hamilton; James Ying, Georgetown; James R. Conway, Smiths Falls; Harry Jim, Keswick; Andrew Kuchtaruk, Sudbury; Ragbir S. Kumar, Cambridge; Bill York Ball Lim, Toronto; Gino Pannozzo, Waterloo; Shiraz B. K. Shariff, Brampton; Yaw Twum-Barima, Oakville; Henry J. Vlaar, Ayr; Ashwani Choudhry, Mississauga; Ken H. M. Ng, Markham; Patrick K. K. Pang, Niagara Falls; Yeun Ming Lam, Dashwood; Allan Studniberg, Scarborough; Gloria S. Meneses, Scarborough; John Axler, Toronto; Eitel E. R. Beduhn, Sault Ste Marie; Chi-Tak Leung, Toronto; Kenneth J. Greenwald, Toronto; Laurence H. S. Gibbs, Thedford; S. John Spiers, Milverton; Natan Khotianov, Toronto; Marshall C. Foo, Toronto; William R. Awrey, Hamilton; Swaran Syan, Sudbury; Ronald J. Bornstein, Thornhill; Mohamed D. Mohamed, Toronto; Upender K. Mehan, Cambridge; David W. Burt, Ottawa; David Henry, St. Catharines; Michael T. W. Cheng, Richmond Hill; Rod Shemilt, North Bay; M. Farook Dawood, Kitchener; Blake Bowler, London; Edgard A. Arcia-Bravo, London; Brenda B. Loewith, Ancaster; Martin L. Kates, Etobicoke; Donald P. Carom, Windsor; Navraj Dhiraj, Milton; Michael W. J. Zajner, Windsor. **Québec:** Samuel Serfaty, Montreal; Lucien Paul Fruchtermann, Montreal; Ginette Barriere, Sainte-Catherine; Sabine Tjia, Lasalle; Simon Plourde, Rouyn Noranda; Jacques Desroches, Saint-Pie; Michel Lynch, Lachute; Mario Labbe, Clermont; Gilles Brouillette, Lasalle; Lyne Theriault, Princeville; Robert Gagnon, Clermont; Maria B. Berjat, Ville St-Laurent; Ngoc Vinh Hoang, Anjou; Normand Lavoie, Rosemère; Gordon Yee, Lasalle; Andre Poisson, Dolbeau-Mistassini; Benoit Castonguay, Rimouski; Jacques Chabonneau, Ste-Julie; Domenico Ciricillo, Saint-Léonard; Mario Lebel, Saint-Pascal; Raja Chehayeb, Greenfield Park; Pierre Dauth, Cowansville; Bernard Doyon, Beloeil; Danielle Houde, Courcelette; France Simard, Laval; Hany Keryakes, Rivière Rouge; Jean Bouthiellier, Gatineau; Jean-Baptiste Girard, Hebertville; André Jolicoeur, Saint-Georges; Mario Boucher, Laval; Hélène Laporte, St-Charles-Borromée; Richard Veilleux, Thetford Mines; Gilles Gaudreau, Sorel-Tracy; Pierre Payer, L'Ile-Perrot; Nader H. Habib, Chomedy Laval; Christian Guité, Québec; Meenalosany Rajakesari, Montreal; Esmeralda Lopez, Princeville; Benoit Loranger, Saint-Eustache. **British Columbia:** Shahin Jaffer, Delta; Marianne P. K. Ho-Asjoe, Vancouver; Cristina Kiai, North Vancouver; Richard H. Horner, Vancouver; Bing Quon Gore, Vancouver; Maura Cormack, North Vancouver; Daniel Ezekiel, Vancouver; Ronnald Schriemer, Kelowna; Wilfred T. Wong, Coquitlam; Danny Wong, Richmond; Mandy Karim, Vancouver; Alex She, Vancouver; Kenneth Cho, Vancouver; Parmjit S Sohal, Surrey; Niloofer Baria, Vancouver; A Parikh, Surrey; Julia C. Reynolds, New Westminster; Boon Lit Wong, Richmond; Betty Lin, Burnaby; Karime Mitha, Burnaby; Kin V. Phord-Toy, Vancouver; Gordon N Hoag, Victoria; Shelley Ross, Burnaby; Jessica Chan, Vancouver; Raymond Simkus, Langley. **Alberta:** Richard A. Ward, Calgary; Philippa Keegan, Calgary; Bruce H. Wheeler, Calgary; Sandeep Agarwal, Calgary; Patrick Ma, Calgary. **Manitoba:** Terry Babick, Winnipeg; Rajendranath Ramgoolam, Winnipeg; Stanley Szajkowski, Winnipeg; David Haligowski, Winnipeg. **New Brunswick:** Daniel G. Scott, Grand Bay-Westfield. **Newfoundland:** Lydia Hatcher, Mount Pearl; Karl Bruff, Stephenville; Paul E. Walsh, Holyrood; Deborah Callahan-Dyer, St. John's; Noel John Browne, St. John's. **Prince Edward Island:** Harold W. Molyneaux, Summerside; Paul Phelan, Kensington.