

Effect of Community Pharmacist Intervention on Cholesterol Levels in Patients at High Risk of Cardiovascular Events: The Second Study of Cardiovascular Risk Intervention by Pharmacists (SCRIP-*plus*)

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Despite strong evidence and wide dissemination of practice guidelines, a large proportion of patients with dyslipidemia are not diagnosed or started on appropriate therapy to lower cholesterol levels (1–10). Multidisciplinary care may help to improve the management of dyslipidemia (11). The purpose of this study was to assess the effect of a community pharmacist-initiated management program on cholesterol levels in patients at high risk of cardiovascular events.

METHODS

Study Design

The study, which utilized a before-after design, involved the participation of 42 Pharmasave community pharmacies in six provinces in Canada (Appendix). Approval was obtained from the Research Ethics Board of the University of Alberta. Trial management, data quality assurance, and analysis were conducted by the Epidemiology Coordinating and Research (EPICORE) Centre, University of Alberta.

We enrolled patients who were at “very high” risk of cardiovascular events, defined as a history of coronary artery disease, coronary revascularization procedures, peripheral vascular disease, or cerebrovascular disease; presence of diabetes (>30 years of age); or a 10-year Framingham risk score >30% (12). Exclusion criteria included a low-density lipoprotein (LDL) cholesterol level ≤ 2.5 mmol/L (≤ 97 mg/dL), which is the recommended

target level for very high-risk patients; enrollment in another lipid-lowering study; being followed in a specialty risk reduction clinic; dosage changes or use of a new lipid-lowering medication within the previous 6 weeks; or myocardial infarction within the previous 3 months.

The pharmacist training program consisted of a Web-based educational module and a workshop (13). Pharmacists approached potential subjects based on known history of cardiovascular disease or use of marker medications (e.g., nitroglycerin products, oral hypoglycemic agents/insulin) (14,15). Subjects were then invited to attend a baseline (screening) visit held at the pharmacy, during which the pharmacist performed two fasting cholesterol measurements 5 to 10 minutes apart using the point-of-care device, Cholestech LDX (Cholestech Corporation, Hayward, California). Patients had been instructed to fast for 8 to 12 hours before the test.

Only patients with an LDL cholesterol level > 2.5 mmol/L (> 97 mg/dL) were enrolled in the study and followed for 6 months. Pharmacists completed intervention forms detailing the results of the lipid measurements, risk factors assessed, and recommendations for therapeutic interventions (including lifestyle changes), and faxed these forms to the patients’ physician.

The pharmacist contacted the patients by telephone at weeks 2 and 4 after enrollment, and at the 3- and 6-month (in-person) follow-up visits. Follow-up visits assessed progress with the intervention(s) recommended at the baseline visit, medication adherence, adverse effects or drug interactions, and patient education.

Outcome Measures

The primary endpoint of the study was the change in LDL cholesterol level between baseline and 6 months of follow-up. Secondary outcomes were the proportion of patients reaching target LDL cholesterol levels as defined by the Canadian Dyslipidemia (12) and National Cholesterol Education Program (NCEP) III (16) guidelines, or the proportion of patients with dosage changes to their lipid-lowering medication, who began lipid-lowering treatment, or who adhered to lipid-lowering medication. Adherence was calculated with the following formula: number of units dispensed between first and last prescription/number of days between first and last prescription \times number of units taken per day.

Sample Size

Based on an estimated average LDL cholesterol level of 3.2 mmol/L (124 mg/dL) for very high-risk patients, a detectable change of 10%, and a two-sided α of 0.01, a sample size of 235 patients was required for 99% power. In order to have power to evaluate secondary endpoints, a sample size of 400 was chosen.

Table 1. Characteristics of the 419 Patients

Characteristic	Number (%) or Mean \pm SD
Age (years)	63.5 \pm 10.8
Female sex	161 (38)
Baseline LDL cholesterol* (mmol/L)	3.5 \pm 0.7
Indicators of very high risk of a cardiovascular event [†]	
Myocardial infarction	108 (26)
Unstable angina	39 (9)
Stable angina	114 (27)
Coronary revascularization	57 (14)
Cerebrovascular disease	43 (10)
Peripheral vascular disease	27 (6)
Diabetes (age >30 years)	274 (65)
Framingham risk >30%	5 (1)
Cardiovascular risk factors [†]	
Age \geq 45 years (men) or \geq 55 years (women)	370 (88)
Positive family history	212 (51)
Smoking	68 (16)
Hypertension (blood pressure >140/90 mm Hg)	274 (65)
Obesity (body mass index >25 kg/m ²)	328 (78)
Sedentary	196 (47)
Baseline medications	
ACE inhibitor	178 (42)
Angiotensin II blocker	37 (9)
Aspirin	170 (41)
Beta-blocker	125 (30)
Calcium channel blocker	112 (27)
Loop diuretic	35 (8)
Long-acting nitrate	61 (15)
Lipid-lowering medication	169 (40)

* Average of two fasting measurements. To convert to mg/dL, divide by 0.02586.

[†] Items not mutually exclusive.

ACE = angiotensin-converting enzyme; LDL = low-density lipoprotein.

Statistical Analysis

A paired *t* test was used to assess the primary endpoint. The proportion of patients who met the target LDL cholesterol levels after the study was assessed using a 95% confidence interval. Descriptive statistics were used for other endpoints where appropriate. All analyses were by intention-to-treat principles, using the last value carried forward for patients without 6-month data. Analyses were performed using SAS (Cary, North Carolina).

RESULTS

Of the 970 patients screened, 211 patients were excluded because they did not meet the inclusion criteria or refused to participate in the study. Of the 759 patients who were invited to the baseline screening visit, 340 patients were

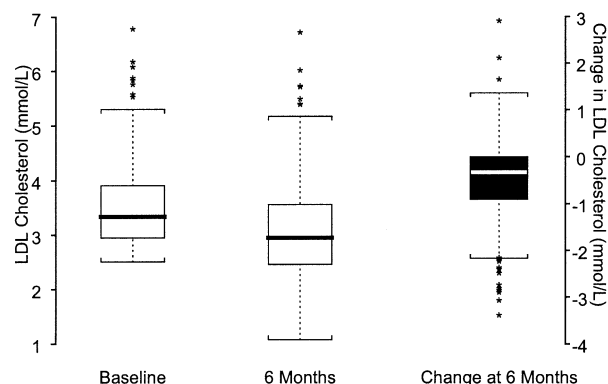


Figure. Effect of pharmacist intervention on low-density lipoprotein cholesterol levels in patients at high risk of cardiovascular events. Last value carried forward method was used in cases of missing data at 6 months. Error bars represent $1.5 \pm$ interquartile range (25th to 75th percentile); asterisks (*) indicate outliers that fall outside of this range. To convert low-density lipoprotein (LDL) cholesterol values to mg/dL, divide by 0.02586.

excluded because of failure to show up ($n = 55$), a Framingham risk score \leq 30% ($n = 59$), uninterpretable LDL cholesterol results ($n = 54$), and LDL cholesterol levels \leq 2.5 mmol/L (24%, $n = 172$). In the 419 enrolled patients (Table 1), the mean (\pm SD) age was 63.5 ± 10.8 years, and 161 patients (38%) were female. The mean LDL cholesterol level at baseline was 3.5 ± 0.7 mmol/L.

Complete follow-up data were not available in 60 patients (14%) because of withdrawal of consent or loss to follow-up. The primary endpoint of mean change in LDL cholesterol level from baseline to 6-month follow-up was -0.5 mmol/L (95% confidence interval [CI]: -0.4 to -0.6), a relative reduction of 13.4% (from 3.5 ± 0.7 mmol/L at baseline to 3.0 ± 0.9 mmol/L at 6 months, $P < 0.0001$; Figure).

At 6 months, 27% (95% CI: 23% to 32%) of patients achieved the target LDL cholesterol level (Table 2); a similar proportion of patients met the NCEP III target level. A total of 16% of patients started a new lipid-lowering medication, 1% had another agent added to their existing regimen, 5% changed medications, and 9% had a dosage increase. Adherence in those receiving lipid-lowering medications was 84%.

DISCUSSION

In this era of health care reform, there is a need to develop and rigorously evaluate novel approaches to the delivery of care. Pharmacists are highly accessible, community-based primary care providers who are underutilized. In this study, we found that enhanced pharmacist care reduced LDL cholesterol levels by about 0.5 mmol/L (18 mg/dL) during a 6-month period.

Table 2. Secondary Outcomes among the 419 Patients

Outcome	Number (%) or Mean \pm SD
Achieved LDL cholesterol target level \leq 2.5 mmol/L	114 (27)
Achieved NCEP III target level \leq 2.6 mmol/L*	124 (31)
New lipid-lowering medication added (not previously treated)	69 (16)
Added medication to existing regimen	6 (1)
Changed existing lipid-lowering medication	23 (5)
Dosage increase of lipid-lowering medication	36 (9)
Adherence with lipid-lowering medication [†]	84% \pm 17%

* Of the 402 patients with cholesterol levels above NCEP III goals at baseline.

[†] Based on the 205 patients prescribed a lipid-lowering medication during the 6-month observation period, and calculated from dispensing records.

To convert to mg/dL, divide by 0.02586.

LDL = low-density lipoprotein; NCEP = National Cholesterol Education Program.

The baseline characteristics of the study sample provide insight into the management of cardiovascular risk in the community. Only 24% of screened patients met the target LDL cholesterol level, consistent with published reports (10). By design, the patients studied were at high risk of cardiovascular events, and many had cardiovascular disease, diabetes, or both. The baseline LDL cholesterol level was 3.5 mmol/L (135 mg/dL), which is about 30% above target levels. Despite this, only 40% of patients were receiving lipid-lowering therapy at baseline. Consistent with previous reports of underuse of preventive therapies (17,18), only 42% of these high-risk patients were receiving angiotensin-converting enzyme inhibitors, 41% were taking aspirin, and 30% were taking beta-blockers.

Although the reduction in LDL cholesterol level was statistically significant, a larger effect size might have been expected. Statin use increased from 40% at baseline to only 59% at 6 months, and only about 10% had a dosage increase. Feedback from the pharmacists suggested that physician resistance and a relatively short follow-up period may be factors.

Twenty-seven percent of patients attained the target LDL cholesterol levels by the end of the study. Although the goal would be to eventually get all patients to meet the target lipid levels, this rate is indeed an improvement, considering that no patients met target levels at baseline. The rate of medication adherence was quite high at 84%, which may be a beneficial effect of the program. Alternatively, the high adherence rate may have been due to volunteer bias, since those most interested in managing their dyslipidemia would have consented to participating, or to the short follow-up, since 6 months constitutes only two refill cycles for many patients. As pointed out by Gordis, there are many challenges in adherence measurement (19).

Community pharmacists are well placed to make a major contribution to primary health care in areas such as dyslipidemia (11,20,21). The forerunner to the present study, the Study of Cardiovascular Risk Intervention by Pharmacists (SCRIP), was a 54-center trial in which 675 patients at high risk of cardiovascular events were ran-

domly assigned to enhanced pharmacist care or usual care (11). SCRIP was terminated early due to the large benefit observed with enhanced care: process-based outcomes of cholesterol measurement and treatment were achieved in 57% of patients in the pharmacist care group versus 31% in the usual care group ($P < 0.001$). Due to the design of SCRIP, however, the effect of enhanced pharmacist care on LDL cholesterol levels could not be assessed properly, which led to the design of the present study. Taken together, these studies provide strong evidence of the benefit of pharmacist involvement in the management of patients with dyslipidemia.

The main limitation of this study is the before-after design, which provides a lower level of causal inference. However, due to the early termination of SCRIP, randomization to "usual care" was deemed unethical. However, the present study employed a multicenter design and broad entry criteria, which provided high external validity. We utilized the Cholestech LDX analyzer to measure cholesterol, which has good accuracy (22,23). We also performed duplicate measurements of cholesterol to enhance precision and reduce regression to the mean.

In conclusion, our study demonstrated that an enhanced pharmacist care program was associated with a reduction in LDL cholesterol levels. In the context of primary health care reform, programs such as this should be strongly considered, as they are community based, accessible, multidisciplinary, and effective. It is hoped that health policymakers and payers will recognize the benefits of such programs, and encourage their use on a more widespread basis.

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APPENDIX

Participating Investigators

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Saskatchewan: Allan Appenheimer (Fort Qu'Appelle), Tony Chow (Regina), Sandra Cyr (Prince Albert), Patrick Edmunds (Tisdale), Christine Gee (Moose Jaw), Lena Hartman (Moose Jaw), Jahnaya Mann (Swift Current).

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New Brunswick: Stanley Knowles (Miramichi).

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