

# The Natural History of LDL Control in Type 2 Diabetes

A prospective study of adherence to lipid guidelines

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Despite randomized trials repeatedly showing the benefits of lowering LDL cholesterol with hydroxymethylglutaryl (HMG)-CoA reductase inhibitors (statins) (1–3), these medications are suboptimally used in type 2 diabetes (4–10). Although this care gap in type 2 diabetes has been frequently described in cross-sectional studies (6–11), it may be as informative to understand LDL control over time. In particular, there is growing recognition of care gaps in diabetes when comparing urban and academic settings with rural settings (11,12). Therefore, we examined changes over an 18-month period for adherence to guideline-recommended LDL cholesterol targets in a rural cohort with type 2 diabetes and determined the rates and correlates of 1) losing control of LDL cholesterol in those who were initially at target and 2) achieving control of LDL cholesterol in those who were not initially at target.

## RESEARCH DESIGN AND METHODS

— The Diabetes Outreach Van Enhancement (DOVE) study was a controlled trial of a multifaceted intervention directed at health care providers to improve the quality of care for rural patients with type 2 diabetes in northern Alberta, Canada. The intervention consisted of an educational outreach (“academic detailing”) service, whereby specialist phy-

sicians promoted aggressive cardiovascular risk reduction for diabetes to primary care physicians. The study rationale, design, and outcomes have been previously published (12–16). All subjects provided written consent, and the study was approved by the University of Alberta.

All patients had universal health care coverage and fee-for-service primary care physicians, with the nearest specialists being ~6 h away by vehicle. Patients were eligible if they were aged  $\geq 20$  years, had type 2 diabetes, and understood English. They were excluded for shortened life expectancy or inability to consent. Data were collected from 2000 through 2001, and patients were assessed at baseline and 18 months. Clinical data were collected by in-person interviews and physical assessments, while laboratory measurements were drawn locally and analyzed in one central laboratory.

Primary outcomes were defined according to LDL cholesterol levels  $< 2.5$  mmol/l, which was the target recommended during the study (12–14,17). To explore independent correlates of guideline adherence, three multivariable logistic regression analyses were built using Stata (version 8.2; StataCorp, College Station, TX). The first model represented LDL guideline adherence at baseline; the second, loss of LDL control among those well controlled at baseline; and the third,

new achievement of LDL guideline adherence over 18 months among those not controlled at baseline. The educational intervention had no effect on lipid levels or lipid-lowering medications (14–16), but we adjusted for it in all analyses. Otherwise, candidate variables had to have a univariate significance of at least  $P < 0.1$  and a multivariate significance of  $P < 0.05$ .

**RESULTS** — Overall, 393 patients with type 2 diabetes were enrolled, and 346 (88%) had complete data for these analyses. Patient-level characteristics, according to LDL target status over time, are displayed in Table 1. At baseline, 216 patients (62%) were not at LDL targets. In a cross-sectional multivariable model, independent correlates of LDL  $> 2.5$  mmol/l were older age ( $P = 0.014$ ) and not using lipid-lowering medications (adjusted odds ratio 2.1 [95% CI 1.2–3.6],  $P = 0.013$ ).

After 18 months, 80% ( $n = 278$ ) of the study population was not at recommended LDL targets. Of the 130 patients who had met targets at baseline, 83 (64%) lost control of LDL cholesterol over 18 months (Table 1). The variables independently associated with loss of LDL control were younger age ( $P = 0.026$ ) and better education ( $P = 0.041$ ) (Table 1).

Of the 216 patients not at LDL targets at study entry, 195 (90%) never achieved recommended LDL levels over 18 months (Table 1). In multivariable analyses, the only independent correlate of achieving LDL  $< 2.5$  mmol/l was starting lipid-lowering medication (adjusted odds ratio 9.2 [95% CI 3.5–24.2],  $P < 0.0001$ ).

**CONCLUSIONS** — Nearly two-thirds of rural patients with a median duration of type 2 diabetes of 5 years were not at guideline-recommended targets for LDL cholesterol at the start of our study, and 18 months later, nonadherence with LDL targets had actually risen to 80%. This occurred in the context of their health care providers being exposed to an educational intervention during this period that was intended to help improve cardiovascular risk management.

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**Abbreviations:** HMG, hydroxymethylglutaryl.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Table 1—Characteristics of 346 patients with type 2 diabetes according to achievement of LDL cholesterol target <2.5 mmol/L, at baseline and over 18 months of follow-up

Characteristics	Baseline (cross-sectional data)			Over 18 months of follow-up					
	Not at target (n = 216)	Already at target (n = 130)	Adjusted odds ratio (95% CI)*	Never at target (n = 195)	Achieved target (n = 21)	Adjusted odds ratio (95% CI)*	Maintains target (n = 47)	Lost target (n = 83)	Adjusted odds ratio (95% CI)*
Age >60 years	62	50	1.8 (1.1-2.8)	62	62	—	66	41	0.6 (0.4-0.9)
Female	60	52	—	62	38	—	43	59	—
High school or more	28	39	—	22	40	—	23	48	2.4 (1.0-5.5)
Income >\$40,000/year	24	27	—	22	40	—	17	33	—
Aboriginal	26	24	—	24	19	—	28	26	—
Current smoker	16	21	—	30	10	—	20	22	—
Median duration of diabetes (years)	5	5	—	5	7	—	5	5	—
HbA <sub>1c</sub> (%)	7.1 ± 1.4	7.4 ± 1.7	—	7.1 ± 1.4	7.4 ± 1.2	—	7.3 ± 1.7	7.4 ± 1.7	—
BMI >27 kg/m <sup>2</sup>	77	84	—	79	57	—	77	88	—
Systolic blood pressure (mmHg)	132 ± 19	129 ± 17	—	131 ± 19	134 ± 20	—	129 ± 16	130 ± 17	—
Total cholesterol (mmol/L)	5.4 ± 0.8	4.1 ± 1.0	—	5.4 ± 0.8	3.6 ± 0.3	—	3.5 ± 0.4	4.8 ± 0.5	—
LDL cholesterol (mmol/L)	3.3 ± 0.6	2.0 ± 1.4	—	3.4 ± 0.5	2.3 ± 0.2	—	2.2 ± 0.3	3.0 ± 0.3	—
Lipid-lowering therapy									
Taking	14	24	2.1 (1.2-3.6)	23	71	—	30	18	—
Started	NA	NA	NA	13	57	9.2 (3.5-24.0)	9	5	—
Stopped	NA	NA	NA	2	0	—	4	4	—

Data are means ± SD or percent unless otherwise indicated. \*All odds ratios adjusted for intervention status (P > 0.5, all analyses, see text) and those variables presented in the table that were significant at P < 0.05 in the relevant multivariable model. NA, not applicable; —, not included in multivariable analyses.

To our knowledge, the only comparable study examining temporal trends in hyperlipidemia management in type 2 diabetes was conducted by Mehler et al. (18), who demonstrated a stable nonadherence rate to lipid guidelines of ~50% over 5 years; specific losses or gains of adherence were not reported. Similar to our baseline findings, other cross-sectional studies have shown nonadherence to LDL guidelines ranging from 50 to 80% in Canadian (6), Australian (7), and U.S. (8-11) populations. Our results suggest that cross-sectional studies likely overestimate quality of care.

Recently, it has been suggested that it may be more useful to promote absolute reductions in LDL cholesterol rather than unattainable LDL targets, given that there is a 20% reduction in major coronary events for every 1-mmol reduction in LDL irrespective of initial LDL levels (2). Using this approach, only 12% of our population achieved a 1-mmol LDL reduction over 18 months, suggesting even modest improvements are not being achieved. This could be explained by physician chart audits, which suggest that 4% of dyslipidemic patients are treated with maximal doses of statins and even fewer are treated with combination regimens (19). Conversely, physicians themselves cite patient adherence as the most common barrier to attaining LDL targets (20). Clearly, this example of clinical inertia is a systems problem, with barriers (and potential solutions) at multiple levels (21).

This study had several limitations. First, we did not have information regarding doses of, or adherence to, lipid-lowering medications. Second, we did not collect data about changes in diet and lifestyle. Third, since patients were volunteers, our results may overestimate rates of achieving LDL targets and underestimate losses of LDL control. Fourth, given how few patients' LDL levels changed (for better or worse) over time, we were underpowered to determine all factors potentially associated with guideline adherence. Last, we examined rural patients in one Canadian province, and our results may not be generalizable to urban populations or to other nations.

In summary, we found that target LDL cholesterol levels are rarely attained and, even when achieved, are all too easily lost in patients with type 2 diabetes. Much remains to be done to learn how to translate evidence into everyday clinical practice (21).

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