Lower is better: Implications of the Treating to New Targets (TNT) study for Canadian patients

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Recent clinical trials have indicated that lowering low-density lipoprotein cholesterol (LDL-C) levels below currently recommended targets results in favourable surrogate and clinical end points. The Treating to New Targets (TNT) study now confirms that aggressive cholesterol lowering to a mean LDL-C of 2.0 mmol/L with atorvastatin 80 mg daily, compared with the previous target of 2.5 mmol/L with atorvastatin 10 mg daily, results in improved clinical outcomes in high-risk patients with coronary artery disease. A lower LDL-C target of less than 2.0 mmol/L will present therapeutic challenges, because approximately only one-half of high-risk patients will achieve this target using monotherapy with the newer and more powerful statins. Furthermore, registry data show that one-half of these patients are not even achieving the current LDL-C target of 2.5 mmol/L. Causes of the care gap are discussed and possible remedies to achieve the new lower targets are suggested.

Key Words: Cholesterol; Coronary disease; Lipids

Recent clinical trials have suggested that lowering cholesterol below currently recommended targets results in improved outcomes. Epidemiological studies have demonstrated the relationship between cholesterol levels and the development of coronary artery disease (CAD) (1-3). Furthermore, lower cholesterol levels, even in ethnic groups with lower average levels, are associated with fewer cardiovascular (CV) events.

Analyses of multiple large, randomized controlled trials of more than 100,000 patients have confirmed that the reduction of CV events is proportional to both the overall reduction of low-density lipoprotein cholesterol (LDL-C) and the level achieved during treatment (4-9) (Figure 1). The Cholesterol Treatment Trialists' (CTT) Collaboration (10) analyzed cholesterol-lowering trials of more than 1000 patients treated for over two years and demonstrated that mortality is reduced 12% for every 1 mmol/L of LDL-C reduction; this benefit is largely driven by a 17% reduction of CV mortality. The benefits of lowering LDL-C levels are seen in a wide range of individuals with and without known CAD, in older and diabetic patients, following myocardial infarction (MI) and among different racial groups. The Scandinavian Simvastatin Survival Study (4S) (4,11) showed that patients within the lowest tertile of LDL-C levels, between 1.5 mmol/L and 2.7 mmol/L, had

Moins, c'est mieux : Les répercussions de l'étude *Treating to New Targets* (TNT) sur les patients canadiens

Selon de récents essais cliniques, la diminution du cholestérol à lipoprotéines de basse densité (C-LDL) sous les cibles actuellement recommandées assure des valeurs substitués et cliniques favorables. L'étude *Treating to New Targets* (TNT) confirme qu'une diminution énergique du cholestérol à un C-LDL moyen de 2,0 mmol/L à l'aide de 80 mg d'atorvastatine par jour, par rapport à la cible antérieure de 2,5 mmol/L à l'aide de 10 mg d'atorvastatine par jour, améliore l'issue clinique des patients très vulnérables atteints d'une coronaropathie. Une cible de C-LDL inférieure à 2,0 mmol/L posera des défis thérapeutiques, car seulement la moitié environ des patients très vulnérables atteindront cette cible à l'aide d'une monothérapie aux nouvelles statines, plus puissantes. De plus, les données du registre démontrent que la moitié de ces patients n'atteignent même pas la cible de C-LDL actuelle de 2,5 mmol/L. Les causes de ces écarts dans les soins sont abordées, et des possibilités pour atteindre les nouvelles cibles plus basses sont proposées.

the lowest coronary event rates. Analysis of the Heart Protection Study (HPS) (6) showed that the reduction in CV end points achieved with simvastatin 40 mg daily in patients with a baseline LDL-C of less than 2.6 mmol/L was similar to that in patients with higher LDL-C levels. The CTT meta-analysis (10) demonstrated a 21% to 26% reduction of major CV events in patients with baseline total cholesterol over a range of less than 3 mmol/L to greater than 4.5 mmol/L.

Current guidelines for the management of dyslipidemia from the Adult Treatment Panel III of the National Cholesterol Education Program (NCEP ATP III [12]) in the United States and the Lipid Working Group in Canada (13) recommend that the optimal treatment target is an LDL-C level of less than 2.5 mmol/L for patients at high risk for CV events, such as those with established CV disease or diabetes mellitus. Recent studies (REVERSAL of Atherosclerosis with Lipitor [REVERSAL] [14], Atorvastatin versus Simvastatin on Atherosclerosis Progression [ASAP] [15], A Study to Evaluate the Effect of Rosuvastatin On Intravascular ultrasound-Derived coronary atheroma burden [ASTEROID] [16]) using surrogate end points of disease progression, as well as the Pravastatin or Atorvastatin Evaluation and Infection Therapy – Thrombolysis in Myocardial Infarction 22 Investigators (PROVE-IT TIMI-22 [17]) that involved patients with acute

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Figure 1) Event rates related to low-density lipoprotein cholesterol levels during statin therapy in secondary prevention studies (adapted from reference 18 with permission). Event rates for the Heart Protection Study (HPS [6]), Cholesterol and Recurrent Events (CARE [7,8]) trial and the Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID [8]) study are for death from coronary artery disease and non-fatal myocardial infarction. Event rates for the Scandinavian Simvastatin Survival Study Group (4S [4]) and the Treating to New Targets (TNT [18]) study also include resuscitation after cardiac arrest

coronary syndromes suggest that there may be additional benefit when LDL-C levels are reduced below the target of the current Canadian guidelines. The Treating to New Targets (TNT [18]) study showed, for the first time, that in patients with stable CAD, a more aggressive lipid-lowering strategy to lower LDL-C targets results in the reduction of adverse CV events.

TNT STUDY

The TNT study (18) was designed to assess the efficacy and safety of lowering LDL-C levels to well below the current NCEP ATP III treatment goal of 2.6 mmol/L for patients with stable CAD and an LDL-C of 3.4 mmol/L to 6.5 mmol/L. During the eight-week run-in period, all potential candidates received atorvastatin 10 mg daily and needed to reach LDL-C levels less than 3.4 mmol/L to be randomly assigned one of two doses of atorvastatin (10 mg or 80 mg daily). Mean LDL-C levels during treatment were 2.0 mmol/L with atorvastatin 80 mg daily and 2.6 mmol/L with atorvastatin 10 mg daily.

The primary combined end point of CAD death, nonfatal nonprocedure-related MI, resuscitated cardiac arrest and fatal or nonfatal stroke was reduced by 22% during a treatment period of up to six years among patients receiving atorvastatin 80 mg compared with that of those receiving a 10 mg dose (Table 1). Although MI and stroke rates were significantly reduced by the higher dose of atorvastatin, the study was underpowered to show a significant reduction in CAD mortality. Hospitalization for heart failure, any CV event and any coronary event were also significantly reduced. Death from any cause and peripheral artery disease were not significantly reduced by the higher dose of atorvastatin.

The 1500 diabetic patients with established CAD in the TNT study (19) had 25% more CV events and 50% more coronary events than the nondiabetic patients. In the Canadian Vascular Protection (VP) registry (20), event rates were also significantly higher in the diabetic patients with CAD than in the nondiabetic patients with CAD. Stroke and MI rates in the diabetic patients with CAD were more than

50% greater than in nondiabetic patients with CAD. Aggressive cholesterol lowering with atorvastatin 80 mg in the very high-risk patients with both diabetes and CAD in the TNT study resulted in a 25% risk reduction of the primary combined end point, compared with that of 22% in the nondiabetic subjects. Consequently, lowering LDL-C levels to 2.0 mmol/L in this very high-risk group resulted in a large reduction of vascular complications.

The TNT study showed that the more intensive regimen of atorvastatin 80 mg daily lowered LDL-C to 2.0 mmol/L and resulted in an important clinical benefit compared with a less intensive regimen of 10 mg daily. The use of atorvastatin 80 mg daily compared with that of 10 mg daily in 1000 patients for a period of five years would prevent 34 major CV events. Approximately 30 patients need to be treated more aggressively to prevent one major CV event. The higher dose of atorvastatin was safe and well tolerated. Although there was a modest increase (1.2% versus 0.2%) in abnormal liver function tests, all of which resolved on discontinuation of the drug, there was no increase in serious adverse reactions (eg, rhabdomyolysis). The TNT study confirmed the hypothesis that the linear and quantitative relationship between a reduced LDL-C level and CAD risk holds even at very low levels of LDL-C (Figure 1).

INCREMENTAL DECREASE IN END POINTS THROUGH AGGRESSIVE LIPID LOWERING (IDEAL) STUDY

The Incremental Decrease in End points through Aggressive Lipid lowering (IDEAL) study (21) compared the outcomes of treatment of atorvastatin 80 mg with simvastatin 20 mg to 40 mg (the same dose as used in the 4S study [11]) among 8888 patients with a history of MI. The primary combined end point of coronary death, nonfatal MI and survival from cardiac arrest was reduced 11% in the atorvastatin group compared with that of the simvastatin group; however, the difference for this combined end point did not achieve statistical significance ($P=0.07$). However, when the same combined end point of the TNT study (18) (coronary death, nonfatal MI, survival from cardiac arrest and stroke) was used, events were reduced by 13% ($P=0.02$). A 16% reduction of events ($P<0.001$) was observed when the combined end points (which included coronary revascularization) of the PROVE-IT TIMI-22 trial (17) were applied. In the IDEAL study, 68 CV events were prevented among 1000 patients managed with atorvastatin 80 mg compared with those receiving simvastatin 40 mg daily. The mean LDL-C level in patients receiving simvastatin 40 mg was 2.7 mmol/L compared with that of 2.1 mmol/L in those receiving atorvastatin 80 mg. Using the results of the CTT meta-analysis, the difference of LDL-C of 0.6 mmol/L would be expected to result in a 13.8% reduction of major coronary events. Thus, the results of the IDEAL study are consistent with the hypothesis that additional benefit can be achieved by more intensive LDL-C lowering.

SHOULD WE LOWER OUR CURRENT LDL-C TARGET TO LESS THAN 2.0 MMOL/L?

The HPS (6) was the first large clinical trial to suggest that 'lower is better': patients who entered the trial with relatively low LDL-C levels received similar clinical benefit as those who entered the trial with higher LDL-C levels. In patients with recent acute coronary syndromes, the PROVE-IT TIMI-22

TABLE 1
Results of the Treating to New Targets (TNT) study

Outcome	Atorvastatin 10 mg (n=5006)	Atorvastatin 80 mg (n=4995)	Hazard ratio (95% CI)	P
Primary outcome, n (%)				
Total major cardiovascular events	548 (10.9)	434 (8.7)	0.78 (0.69–0.89)	<0.001
Death from coronary artery disease	127 (2.5)	101 (2.0)	0.80 (0.61–1.03)	0.09
Nonfatal, nonprocedure-related myocardial infarction	308 (6.2)	243 (4.9)	0.78 (0.66–0.93)	0.004
Resuscitation after cardiac arrest	26 (0.5)	25 (0.5)	0.96 (0.56–1.67)	0.89
Fatal or nonfatal stroke	155 (3.1)	117 (2.3)	0.75 (0.59–0.96)	0.02
Secondary outcomes, n (%)				
Major coronary event	418 (8.3)	334 (6.7)	0.80 (0.69–0.92)	0.002
Cerebrovascular event	250 (5.0)	196 (3.9)	0.77 (0.64–0.93)	0.007
Hospitalization for congestive heart failure	164 (3.3)	122 (2.4)	0.74 (0.59–0.94)	0.01
Peripheral artery disease	282 (5.6)	275 (5.5)	0.97 (0.83–1.15)	0.76
Death from any cause	282 (5.6)	284 (5.7)	1.01 (0.85–1.19)	0.92
Any cardiovascular event	1677 (33.5)	1405 (28.1)	0.81 (0.75–0.87)	<0.001
Any coronary event	1326 (26.5)	1078 (21.6)	0.79 (0.73–0.86)	<0.001

Adapted from reference 18 with permission

study (17) demonstrated that a more aggressive cholesterol-lowering strategy with atorvastatin 80 mg daily resulted in more improved clinical outcomes than a less effective cholesterol-lowering treatment with pravastatin 40 mg daily. Now, the TNT (18) and IDEAL (21) studies confirm that a more aggressive treatment strategy to reduce LDL-C levels to a mean of 2.0 mmol/L reduces the incidence of MI and stroke than has been shown in patients treated with the less aggressive strategy to achieve the current Canadian and NCEP ATP III target LDL-C of 2.5 mmol/L. Although the higher dose of atorvastatin (or the other statins used) may have resulted in greater pleiotropic effects independent of cholesterol lowering, the totality of the evidence supports the hypothesis that the benefits are the result of greater cholesterol lowering.

The use of lipid-lowering agents other than statins has not been shown to consistently reduce CV events. The recently reported Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial (22) comprising almost 10,000 type 2 diabetic patients with total cholesterol of less than 6.5 mmol/L resulted in a modest 12% reduction of LDL-C. After a follow-up period of five years, there was a nonsignificant 11% reduction in the primary end points of CAD death and nonfatal MI among those patients receiving fenofibrate compared with the placebo-treated group. The FIELD study shows that fenofibrate alone does not produce the benefits observed in the multiple statin trials with diabetic patients. Consequently, fibrates cannot be recommended as first-line treatment for most diabetic patients.

Following the publication of the PROVE-IT TIMI-22 trial (17), an update of the NCEP ATP III (23) suggested that for very high-risk patients (such as those with diabetes in addition to CAD or an acute coronary syndrome) an optional therapeutic LDL-C treatment target should be less than 1.8 mmol/L. In an earlier review (24), we had suggested that the application of the optional treatment target was premature and should await the publication of studies, such as TNT and IDEAL. In both studies, the mean LDL-C levels achieved with an aggressive lipid lowering strategy were 2.0 mmol/L and 2.1 mmol/L,

respectively, with one-half of patients in both studies not reaching the target LDL-C level of 2.0 mmol/L. Hence, it is likely that the benefit from aggressive lipid lowering is under-represented. To generalize the observations of both clinical trials to clinical practice, it is necessary to apply an LDL-C target of 2 mmol/L, which was the LDL-C target identified a priori in the study protocols.

WHAT IS THE BENEFIT OF LOWER LDL-C TARGETS IN CANADA?

Patients with established CV disease or with diabetes and more than two additional risk factors for CV disease are at high risk and have an annual CV event rate (death, MI or stroke) of 3% to 6% (25,26). The TNT (18) study demonstrated that CV event rates can be reduced a further 22% by more aggressively reducing LDL-C. In this high-risk population, atorvastatin 80 mg daily compared with treatment of a 10 mg dose would result in between 30 to 70 fewer major CV events for every 1000 patients treated for five years. Similar additional benefits were observed in the IDEAL study (21) when atorvastatin 80 mg daily was compared with simvastatin 40 mg daily. Approximately two million Canadians have CV disease; an aggressive cholesterol treatment strategy in these individuals could result in 12,000 to 28,000 fewer CV events each year.

CHALLENGES TO ACHIEVING LOWER LDL-C TARGETS

A major challenge in lipid management is achieving the currently recommended LDL-C treatment goal of less than 2.5 mmol/L. There is a large care gap in patient management that results in only one-half of high-risk patients achieving the current NCEP ATP III LDL-C goal of less than 2.5 mmol/L. An analysis of 8182 patients from two prospective Canadian registries (VP and the Guideline Orientated Approach to Lipid Lowering [GOALL] [27]) shows that 78% of high-risk patients, with either established CV disease or diabetes, were

receiving a lipid-lowering agent. However, only 51.2% of these patients had achieved the currently recommended LDL-C target of less than 2.5 mmol/L. Among patients with diabetes without CV disease, the target was achieved in only 44.7%. Patients with both vascular disease and diabetes are at the highest CV risk, but only 59% of individuals in this group had LDL-C levels at or below the NCEP ATP III threshold of 2.5 mmol/L, and only 11.7% achieved the optional NCEP ATP III LDL-C target of less than 1.8 mmol/L.

Neither a lack of awareness of treatment guidelines nor a knowledge gap appears to be the most important factor in the suboptimal management of lipids in these high-risk patients (those with both vascular disease and diabetes). In the GOALL registry, 96% of physicians were aware of the current NCEP ATP III LDL-C target level of less than 2.5 mmol/L. Causes for the action gap responsible for the failed implementation of the current lipid guidelines are unclear, but may include patient noncompliance, drug intolerance, inappropriate drug selection, limited drug efficacy or a failure to titrate therapy. Because only 10% of those patients who failed to achieve LDL-C targets were on high-dose statins, it appears that inadequate titration of already initiated therapy is all too common.

Achieving an LDL-C target of less than 2.0 mmol/L consistently will require a more stringent treatment strategy than the one used in routine care of patients in the VP and GOALL registries. However, this lower target is likely achievable in many patients with adequate doses of more effective cholesterol-lowering statins (such as atorvastatin or rosuvastatin), or by using combinations of statins with cholesterol absorption inhibitors (such as ezetimibe) or with niacin.

Atorvastatin 80 mg daily in the TNT study achieved an average LDL-C of 2.0 mmol/L in a group of patients selected by their response to atorvastatin 10 mg. In the IDEAL study (21), atorvastatin 80 mg in an unselected group of patients lowered LDL-C levels to a mean of 2.1 mmol/L. Among patients in the PROVE-IT TIMI-22 study (17), atorvastatin 80 mg resulted in LDL-C levels of 1.6 mmol/L (interquartile range 1.29 mmol/L to 2.04 mmol/L). In the REVERSAL study (14), atorvastatin 80 mg daily reduced LDL-C to 2.05 ± 0.76 mmol/L from a baseline LDL-C level of 3.24 mmol/L to 5.44 mmol/L. The Achieve Cholesterol Targets Fast with Atorvastatin Stratified Titration (ACTFAST) study (28) assigned patients a starting dose of atorvastatin according to the baseline LDL-C and status of statin usage. A further up-titration was made six weeks later if the LDL-C target had not been reached. Among patients not previously receiving a statin, 80% achieved an LDL-C level of 2.5 mmol/L. Of patients previously receiving a statin, 59% reached the desired goal. Of patients previously receiving a statin and requiring atorvastatin 80 mg, only 50% achieved the LDL-C goal. Thus, some patients will require multiple agents to achieve current goals and certainly to achieve the lower targets suggested beneficial by the TNT study.

It is therefore possible that the proposed LDL-C target of 2.0 mmol/L is achievable in approximately 50% to 80% of patients with moderately elevated LDL-C levels by using atorvastatin 80 mg daily. The combination of a statin and ezetimibe or niacin may permit achievement of LDL-C goals in patients failing to attain the desired target. However, the safety of the combination therapy and high-dose statin therapy in this context remains to be determined, especially in the older patients.

IS THERE A COST TO AGGRESSIVE REDUCTION OF LDL-C?

Achievement of lower levels of LDL-C as recommended by the TNT study may not be attainable for many patients, even with the use of multiple medications. For the older population with a high prevalence of renal dysfunction and risk of multiple drug interactions, such stringent targets could result in an unacceptably high incidence of adverse reactions.

In the TNT study, overall mortality was not altered by the use of atorvastatin 80 mg daily compared with the 10 mg dose. It should be noted that the study was not powered to demonstrate a reduction in mortality. Furthermore, the annual mortality rate, even in the atorvastatin 10 mg group, was lower than that observed in the active treatment group of any of the previous landmark statin trials. A low CV mortality rate was also observed in the IDEAL study (21). Although there were trends toward a reduction of CV mortality in the TNT study (2.0% versus 2.5%, hazard ratio 0.80 [95% CI 0.61 to 1.03]) and an increase in death from non-CV causes (3.2% versus 2.5%, hazard ratio 1.25 [95% CI 0.99 to 1.57]; $P=0.06$) in patients receiving atorvastatin 80 mg daily, one must be cautious in over-interpreting statistically nonsignificant differences. Because no such increase in non-CV death was observed in the atorvastatin-treated patients in the IDEAL study (21), it is likely that the observation in the TNT study was a chance finding.

CONCLUSIONS

With the observed care gap in the management of patients with CAD, a treatment strategy based on the TNT and IDEAL studies with atorvastatin 80 mg daily could result in 12,000 to 28,000 fewer CV events in Canada alone. Patients with diabetes and CAD have a 25% to 50% greater CV event rate than nondiabetic subjects, and thus have an enhanced absolute benefit from the more aggressive lipid lowering than the overall group of patients. High-risk patients with coronary, cerebrovascular and peripheral artery disease and those with diabetes have benefited from lipid lowering with statins. However, recent surveys show that approximately one-half of these high-risk patients fail to achieve the recommended target levels. Achieving the lower LDL-C target of 2.0 mmol/L indicated by the TNT study will be a challenge for most patients and physicians. It is estimated that approximately 50% to 75% of patients will achieve this new target with high doses of the newer statins such as atorvastatin or rosuvastatin alone. Other patients will require statin and cholesterol absorption inhibitor combinations.

CONFLICTS OF INTEREST: Dr D Fitchett has participated in continuing medical education on behalf of, and has acted as a consultant to, AstraZeneca, Merck Frosst/Schering Pharmaceuticals, Fournier, Bristol-Myers Squibb, Sanofi-Aventis and Pfizer. Dr L Leiter has received research funding from, has done continuing medical education on behalf of, and has acted as a consultant to, AstraZeneca, Merck Frosst/Schering Pharmaceuticals and Pfizer. Dr S Goodman has received research grant support, and speaker and consulting honoraria from AstraZeneca, Bristol-Myers Squibb, Merck Frosst, Pfizer and Schering-Plough. Dr A Langer has received research funding from, participated in continuing medical education on behalf of, or has acted as a consultant to, AstraZeneca, Bristol-Myers Squibb, Fournier, Merck Frosst/Schering Pharmaceuticals, Oryx, Sanofi-Aventis and Pfizer.

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