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A REPORT BY THE DIVISION OF CARDIOLOGY
ST. MICHAEL'S HOSPITAL, UNIVERSITY OF TORONTO, ONTARIO

Scientific Update™

Effect of Lowering LDL Cholesterol Substantially below Currently Recommended Levels in Patients with CHD: Results of the Treating to New Targets Study

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A Report on a Special Session at the Late-Breaking Clinical Trials Session of the American College of Cardiology Annual Scientific Session 2005

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The target for lipid-lowering treatment currently recommended for patients with coronary artery disease (CAD) or those at risk for events is a low-density lipoprotein cholesterol (LDL-C) level of 2.5 mmol/L. More recently, clinical benefit has been demonstrated at levels that are <2.5 mmol/L. More intensive lipid-lowering regimens have been associated with clinical benefits over moderate lipid-lowering regimens. However, to date, studies demonstrating the superior benefit of more aggressive lipid-lowering have compared different lipid-lowering regimens. Given the potential for different potencies and pleiotropic properties between lipid-lowering agents, the recommendations for lowering LDL-C targets require the support of trials comparing clinical outcomes from lipid-lowering to different targets using the same agent. The Treating to New Targets (TNT) trial was a parallel group study that randomized 10,003 patients from 14 countries to double-blind treatment with atorvastatin, 10 or 80 mg, to compare the effects on cardiovascular events. In this issue of *Cardiology Scientific Update*, the late-breaking results of the TNT trial and their clinical implications are reviewed.

Lipid-lowering has been proven to reduce cardiovascular (CV) events in a wide range of patient populations. Canadian and other international recommendations and practice guidelines have proposed that patients with established atherosclerosis or those deemed at high risk for CV events have appropriate therapy to lower LDL-C to 2.5 mmol/L (100 mg/dL).[1-4] However, results from more recent clinical trials have suggested that there are benefits in outcome with LDL-C levels below 2.5 mmol/L (100 mg/dL),[5-8] Indeed, this has prompted the coordinating committee of the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III to consider the therapeutic option of lowering LDL-C to <1.8 mmol/L (or to <70 mg/dL) for high risk patients.[9] Although more intensive lipid-lowering regimens have yielded clinical benefits over more moderate lipid-lowering regimens,[6,7] to date, studies demonstrating the superior benefit of more aggressive treatment have primarily involved the comparison of different lipid-lowering regimens.[6,7] Given the potential for differences in potency and pleiotropic properties between different lipid-lowering agents, making definite recommendations for lowering LDL-C targets to <2.5 mmol/L requires the support of trials that not only compare clinical outcomes from lipid-lowering to different targets, but also those comparing the effects of different doses of the same lipid-lowering agent.

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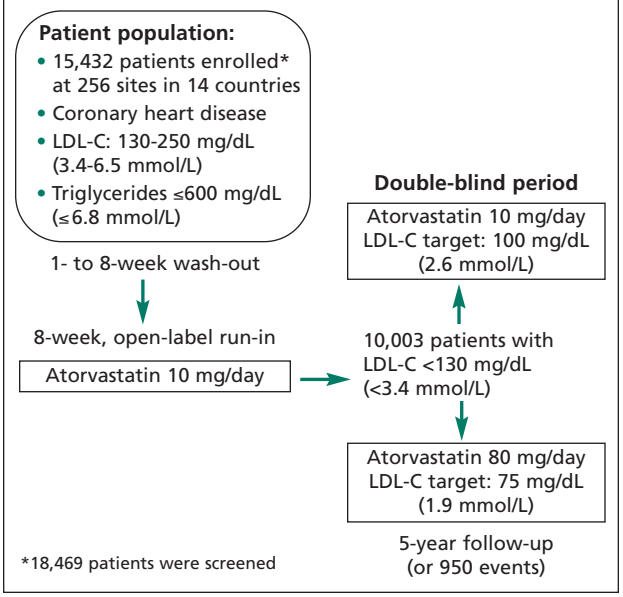
Figure 1: TNT study design and protocol



The Treating to New Targets (TNT) study

The Treating to New Targets (TNT) study was designed to test the primary hypothesis that incremental reductions in CV risk can be achieved by lowering LDL-C to levels beyond the currently recommended minimum targets. To test this hypothesis, 2 doses of atorvastatin (10 mg and 80 mg, once daily) were employed in a double-blind parallel group design. The occurrence of major CV endpoints was then compared in the 2 groups of patients: one achieving an average LDL-C of approximately 100 mg/dL (2.6 mmol/L) and the other achieving an average LDL-C of approximately 75 mg/dL (1.9 mmol/L).

TNT study design

The rationale and study design, as well as the baseline characteristics of TNT, have been reported previously.[10] The study design and protocol are depicted in Figure 1. In brief, men or women, aged 35 to 75 years, were eligible for the study if they fulfilled the following inclusion criteria:

- clinically evident coronary heart disease (CHD), defined as a previous myocardial infarction (MI), previous or present angina with objective evidence of atherosclerotic CHD, or having undergone a coronary revascularization procedure
- LDL-C 130-250 mg/dL (3.4-6.5 mmol/L) and triglycerides ≤ 600 mg/dL (≤ 6.8 mmol/L) at the beginning of the open-label run-in period
- LDL-C <130 mg/dL (<3.4 mmol/L) at the end of the open-label run-in period.

The principal exclusion criteria included hypersensitivity to statins, active liver disease or hepatic dysfunction (defined as alanine aminotransferase or aspartate aminotransferase >1.5 times the upper limit of normal), and an MI, coronary revascularization procedure, or severe/unstable angina within 1 month of screening. Patients received dietary information to comply with the NCEP Step I, Step II, or another equivalent diet. Previously prescribed lipid-regulating drugs were discontinued at screening and patients went through a washout period of 6 weeks. After discontinuation of previous lipid-lowering therapies, all patients were treated with atorvastatin 10 mg/day during an 8-week, open-label, run-in period. Lipid profiles were assessed after 4 and 6 weeks of open-label treatment (Figure 1). After 8 weeks of open-label treatment, patients with a mean LDL-C level of <130 mg/dL (<3.4 mmol/L) at weeks 4 and 6 of the run-in period were randomized to double-blind therapy with either atorvastatin 10 mg/day or 80 mg/day. Lipid levels at this time point represented the baseline values for the TNT study.

TNT study endpoints

The primary endpoint was the time to occurrence of a major CV event, defined as:

- CHD death
- nonfatal non-procedure-related MI
- resuscitated cardiac arrest
- fatal or nonfatal stroke.

Secondary study endpoints consisted of any of the following:

- major coronary event (CHD death, nonfatal non-procedure-related MI, or resuscitated cardiac arrest)
- any coronary event (major coronary event, revascularization procedure, procedure-related MI, or documented angina)
- cerebrovascular event (fatal or nonfatal stroke, transient ischemic attack)
- peripheral vascular disease
- hospitalization for congestive heart failure (CHF)
- any CV event
- all-cause mortality.

TNT results

Results of the TNT study were recently presented and published.[11] Patients (18,469) were screened at 256 sites in 14 countries including Canada, United States, Europe, South

Table 1: Baseline characteristics of patients in the TNT study

Characteristic	10 mg of atorvastatin (N = 5006)	80 mg of atorvastatin (N = 4995)
Age (years)	60.9±8.8	61.2±8.8
Male gender no. (%)	4045 (80.8)	4054 (81.2)
White race no. (%)	4711 (94.1)	4699 (94.1)
Systolic BP (mm Hg)	131±17	131±17
Diastolic BP(mm Hg)	78±10	78±10
Body mass index (mean ±SD)	28.6±4.7	28.4±4.5
CV history no. (%)		
Current smoker	672 (13.4)	669 (13.4)
Former smoker	3167 (63.3)	3155 (63.2)
Systemic hypertension	2721 (54.4)	2692 (53.9)
History of diabetes mellitus	753 (15.0)	748 (15.0)
Myocardial infarction	2888 (57.7)	2945 (59.0)
Angina	4067 (81.2)	4084 (81.8)
Cerebrovascular accident	263 (5.3)	255 (5.1)
Peripheral artery disease	570 (11.4)	603 (12.1)
Congestive heart failure	404 (8.1)	377 (7.6)
Arrhythmia	927 (18.5)	907 (18.2)
Coronary revascularization		
Angioplasty	2719 (54.3)	2688 (53.8)
Bypass surgery	2338 (46.7)	2317 (46.4)
Lipids mg/dL (mmol/L)		
LDL cholesterol (mean ±SD)	98±18 (2.5±0.5)	97±18 (2.5±0.5)
Total cholesterol	175±24 (4.5±0.6)	175±24 (4.5±0.6)
Triglycerides	151±72 (1.7±0.8)	151±70 (1.7±0.8)
HDL cholesterol	47±11(1.2±0.3)	47±11(1.2±0.3)

BP = blood pressure; CV = cardiovascular

Africa, and Australia. After screening and exclusions, a total of 10,003 patients were randomized to treatment in the TNT study between July 1998 and December 1999 (Figure 1). Patients were followed for a median of 4.9 years. Selected baseline characteristics are shown in Table 1. The two groups were well-matched at baseline and concomitant treatments were also similar.

During the open-label period, LDL-C levels were reduced from 3.9 mmol/L (152 mg/dL) to 2.6 mmol/L (98 mg/dL) (baseline values before randomization). The effect of randomized therapy on lipids is shown in Table 2. At the end of

Table 2: Lipid levels achieved at the end of the TNT study

	LDL-C	Total-C	Triglycerides	HDL-C
	mmol/L (mg/dL)			
Atorvastatin 10 mg	2.6 (101)	4.6 (178)	1.8 (156)	1.2 (47)
Atorvastatin 80 mg	2.0 (77)	3.9 (150)	1.5 (132)	1.2 (47)

C = cholesterol

the study, LDL-C, total cholesterol, and triglyceride levels were lower in the atorvastatin 80 mg group versus the 10 mg group, whereas high-density lipoprotein-cholesterol (HDL-C) levels were not different between the 2 groups.

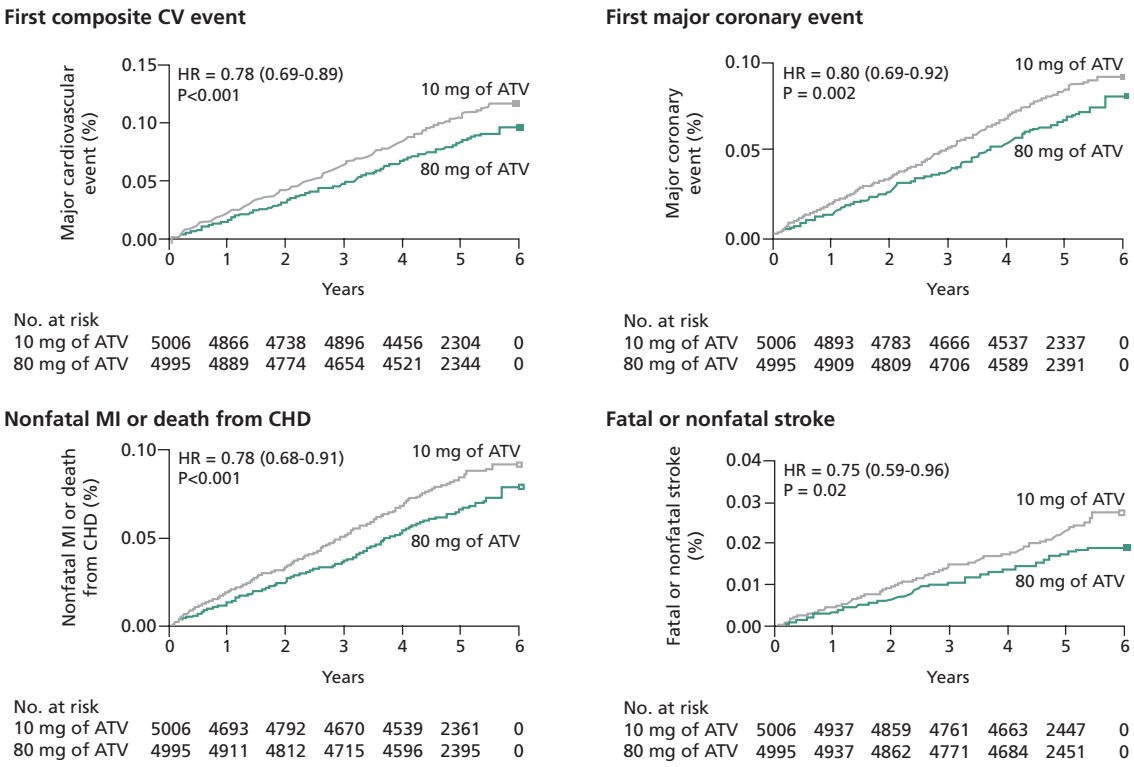
Data for the primary efficacy outcomes are shown in Figure 2. The primary endpoint, the time to the first composite CV event (defined as death from CHD, non-procedure-related MI, resuscitated cardiac arrest, and fatal or nonfatal stroke), is shown in the upper left panel. Compared to the atorvastatin 10 mg group, CV events in the 80 mg group were reduced by 22%, (548 versus 434 first events and 10.9% versus 8.7% for an absolute reduction of 2.2%). Selected components of the primary outcome are shown in the remainder of Figure 2. The time to a first major coronary event, nonfatal MI or death from CHD, as well as fatal and

Table 3: Hazard ratio for the components of the secondary outcomes

Outcome	10 mg of atorvastatin (N=5006)	80 mg of atorvastatin (N=4995)	Hazard ratio (95% CI)	P value
	Number with first event (%)			
Major coronary event	418 (8.3)	334 (6.7)	0.80 (0.69-0.92)	0.002
Cerebro-vascular event	250 (5.0)	196 (3.9)	0.77 (0.64-0.93)	0.007
Hospitali-zation CHF	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 CV 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

CHF = congestive heart failure; CV = cardiovascular

Figure 2: Primary and key secondary outcomes



ATV = atorvastatin; HR = hazard ratio

nonfatal stroke, were significantly reduced in the 80 mg group. In addition, death from CHD was reduced by 20% (127 versus 101 events, p=0.09) and nonfatal non-procedure-related MI was reduced by 22% (308 versus 243 events, p=0.004). However, resuscitation after cardiac arrest (26 versus 25 events) was not altered.

Data for the secondary outcomes are shown in Table 3. Among these secondary endpoints, major coronary events, cerebrovascular events, hospitalizations for heart failure, as well as any CV and coronary events, were significantly reduced with 80 mg versus 10 mg atorvastatin. The risk of death from any cause did not differ between the two groups. In addition:

- There were 155 deaths (3.1%) from CV causes in the 10 mg atorvastatin group and 126 (2.5%) in the 80 mg atorvastatin group [hazard ratio (HR), 0.80; 95% confidence interval (CI), 0.64 to 1.08; p=0.09].
- There were 127 deaths (2.5%) from non-CV causes in the 10 mg atorvastatin group and 158 (3.2%) in the 80 mg group (HR, 1.25; 95% CI, 0.99 to 1.57; p=0.07).
- Non-CV deaths accounted for half of all deaths.
- Among non-CV deaths, cancer accounted for half in both groups: 75 (1.5%) in the 10 mg group and 85 (1.7%) in the 80 mg group (HR, 1.13; 95% CI, 0.83 to 1.55; p=0.42).
- Death from hemorrhagic stroke or trauma (including accidental death and suicide) was infrequent and there was no difference between the 2 study groups.

Safety data are shown in Table 4. There was no difference between the 2 groups in terms of all adverse events considered related to treatment. There was no persistent increase in muscle enzymes. Rhabdomyolysis, as defined by the criteria of the American College of Cardiology, American Heart Association, and National Heart, Lung, and Blood Institute,[12] occurred in 5 cases, none of which were thought to be related to treatment.

Comments and clinical practice implications

Cumulative data from placebo-controlled trials involving >100,000 patients have clearly demonstrated a

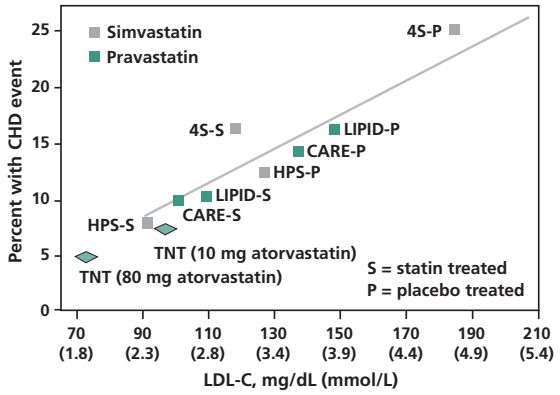
Table 4: Safety data

	10 mg atorvastatin	80 mg atorvastatin
	Number (%)	
Any adverse events related to treatment	289 (5.8)	406 (8.1)
Myalgia	234 (4.7)	241 (4.8)
Rhabdomyolysis	3 (0.06)	2 (0.04)
Persistent increase in liver enzymes	9 (0.2)	60 (1.2)

relationship between CV event reduction and LDL-C reduction.[5,13-18] The Canadian Working Group on Hypercholesterolemia and Other Dyslipidemias, the United States NCEP ATP III, as well as the most recent guidelines of the third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice recommend that patients with CHD or those at high risk for CHD be treated with appropriate measures to lower LDL-C levels to <2.5 mmol/L or 100 mg/dL.[2,3] However, the Heart Protection Study (HPS) and lipid-lowering arm of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) have demonstrated reductions in CV events in patients deemed at high risk for CV events, regardless of their baseline cholesterol levels.[5,8] Furthermore, the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL)[19] and the Atorvastatin vs. Simvastatin on Atherosclerosis Progression (ASAP)[20] studies have both demonstrated that more aggressive lowering of LDL-C using atorvastatin 80 mg is associated with greater attenuation of atherosclerosis progression in the coronary and carotid arteries, respectively, compared to the more modest reductions achieved with pravastatin and simvastatin.

More recently, the Prasvastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) trial, conducted in patients with acute coronary syndromes (ACS), demonstrated improved clinical CV outcomes with more intensive lipid-lowering using atorvastatin 80 mg.[6] On the basis of findings from HPS and PROVE-IT,[5,6] the NCEP, in conjunction with the American Heart Association and the American College of Cardiology, introduced a more aggressive, yet optional, LDL-C target of <70 mg/dL (1.8 mmol/L) in patients at high risk for CV events, such as those with ACS.[9] However, PROVE-IT was conducted in a very high-risk population,[6] whereas HPS and ASCOT involved comparisons with placebo.[5,8] Definite proof for benefit of lipid-lowering beyond 2.5 mmol/L

Figure 3: Effects of statins on CHD events in secondary prevention trials



CARE = Cholesterol and Current Events trial
HPS = Heart Protection Study
LIPID = Long-term Intervention with Pravastatin in Ischemic Disease Study
4S = Scandinavian Simvastatin Survival Study

(100 mg/dL) in patients with CHD requires a comparison of 2 lipid-lowering strategies, preferably using the same agent, one that lowers LDL-C to 2.6 mmol/L and one that lowers LDL-C further to 1.8 mmol/L (70 mg/dL).

The late-breaking results of TNT therefore represent a proof-of-concept that intensive lipid-lowering beyond the recommended target level of 2.5 mmol/L to 1.8 mmol/L derives incremental benefit in reducing CV outcome in a broad spectrum of patients with CHD. This incremental benefit can be achieved using atorvastatin 80 mg daily with little side effects. It is useful to put the results of TNT in the context of other outcomes trials examining the use of statins in secondary prevention (Figure 3). These data indicate that the relationship between reduced LCL-C levels and reduced CHD events demonstrated in prior trials of secondary prevention is observed even at very low levels of LDL-C. For clinicians, the absolute benefit of reducing LDL-C from 2.5 mmol/L to 2.0 mmol/L over a 5-year period translates into the prevention of 34 major CV events per 1000 treated CHD patients. The results of the TNT study will have an impact on clinical practice, as well as upcoming practice guidelines. Further support for this aggressive approach to lipid-lowering in high-risk patients is likely to be forthcoming and includes the ongoing Study of the Effectiveness of Additional Reductions of Cholesterol and Homocysteine (SEARCH) that

is comparing simvastatin 20 mg/day and 80 mg/day in 12,000 patients with a history of MI.

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