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Scientific Update™

Insights from the Results of the Incremental Decrease in Endpoint through Aggressive Lipid Lowering (IDEAL) Trial

Originally presented by: Terje Pedersen, MD

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By GORDON W. MOE, M.D.

Recent data suggest that lowering levels of low-density lipoprotein cholesterol (LDL-C) beyond those achieved in previous prevention trials may provide greater benefits in patients with coronary heart disease (CHD). The Incremental Decrease in Endpoint through Aggressive Lipid Lowering (IDEAL) trial was a multicentre prospective, randomized, open-label, blinded, endpoint classification study designed to determine whether additional clinical benefit is gained through a strategy that decreases levels of LDL to a greater extent than those currently achieved with established statin therapy in patients with CHD. This issue of *Cardiology Scientific Update* reviews the late-breaking results of the IDEAL study and their clinical implications.

Lipid-lowering has been proven to reduce cardiovascular (CV) events in a broad range of patient populations, including those who have survived ischemic events.[1-8] The Scandinavian Simvastatin Survival Study (4S) was one of the first studies to demonstrate that cholesterol lowering with simvastatin reduced mortality and morbidity in patients with CHD, as defined by the presence of angina or previous myocardial infarction (MI).[1] However, subsequent studies have suggested that greater percent decreases in LDL-C levels than those achieved in 4S may yield greater benefits in patients with CHD.

In the Heart Protection Study (HPS), for example, treatment with simvastatin 40 mg produced similar reductions in relative risk in patients whose LDL-C levels were below the then recommended target levels, as compared to the risk reductions observed in patients with higher LDL-C levels.[3] These benefits were attributed to a mean difference in LDL-C levels of about 1.0 mmol/L between the treated and control groups. This difference is considerably smaller in magnitude than the mean difference between the simvastatin- and placebo-treated subjects in 4S (ie, 1.7 mmol/L [from 4.9 mmol/L at baseline]).

The investigators of the IDEAL study, therefore, reasoned that an additional decrease in LDL cholesterol of 0.6 to 0.7 mmol/L, using 80 mg of atorvastatin (which was estimated to produce a mean 55% decrease in baseline LDL-C levels), would provide more clinical benefit than a more modest 35% decrease in baseline LDL-C levels.[9] The rationale behind choosing these agents and targeting the magnitude of LDL lowering was based on the beneficial effects on clinical endpoints observed with a 35% decrease in LDL cholesterol with atorvastatin 10 mg/day in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA).[10] In addition, the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction-22 (PROVE IT-TIMI 22) trial demonstrated that atorvastatin 80 mg provided greater protection than pravastatin 40 mg in patients with acute coronary syndrome.[4]

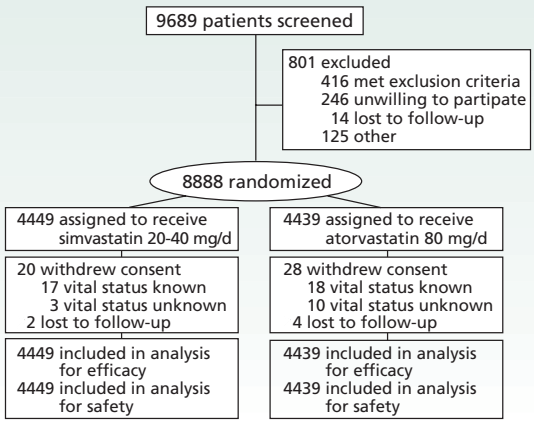
The IDEAL Study

Study design

The IDEAL study was a multicentre, prospective, randomized, open-label, blinded, endpoint (PROBE) classification study. Its primary aim was to investigate whether an incremental decrease in CHD risk could be achieved by a greater decrease in LDL-C (in patients using secondary prevention) than that attained with the then best treatment strategy established by the 4S study. The rationale and study design, as well as the baseline characteristics of IDEAL, have been previously published.[9] Briefly, men and women, aged ≤80 years, who had been hospitalized for, or had a history of a definite MI, and qualified for statin therapy according to guidelines at the time of recruitment, were considered eligible for study entry. Besides the standard exclusion criteria, patients with plasma triglycerides >6.8 mmol/L or those who were already titrated to a dose of statin more than the equivalent of simvastatin 20 mg daily or with previous adverse experience to statins were excluded. Eligible patients were randomized to either atorvastatin 80 mg/day or simvastatin 20 mg/day. Simvastatin therapy could be titrated to 40 mg/day if the patient's total cholesterol levels remained >4.9 mmol/L. There were no washouts from existing statin therapy.

St. Michael's Hospital, 30 Bond St., Suite 7049, Queen Wing, Toronto, Ontario M5B 1W8 Fax: (416) 864-5941

Figure 1: The IDEAL study – flow of subjects



The primary clinical outcome was the time to first occurrence of a major coronary event defined as:

- coronary death,
- hospitalization for nonfatal MI based on the Joint European Society of Cardiology/American College of Cardiology criteria,
- resuscitated cardiac arrest.

Secondary outcomes included:

- major CV event (any primary event plus stroke),
- any CHD event (any coronary revascularization procedures or hospitalization for unstable angina,
- any CV event [the above plus hospitalization with a primary diagnosis of heart failure and peripheral arterial disease (PAD), the latter defined as a new diagnosis of PAD or hospitalization for PAD]
- individual components of composite endpoints, and
- all-cause mortality.

In the sample size calculation, it was assumed that recurrent event rates would be 10% and 7.9% for simvastatin (20 to 40 mg/day) and atorvastatin (80 mg/day), respectively. It was subsequently calculated that 8,888 patients would be required to provide a 90% power to detect a 21% decrease in recurrent coronary events over 5 years between the 2 treatment groups (2-tailed $\alpha = 0.05$). Enrollment was carried out at 190 centres in Norway, Sweden, Finland, Denmark, Iceland, and the Netherlands. The first patient was recruited on March 31, 1999 and the final patient was randomized on March 29, 2001. Of the 9,689 patients screened, 8,888 were randomized to open-label prescription treatment with atorvastatin (80 mg/day) or simvastatin (20 mg/day). Median follow-up was for a period of 4.8 years.

Results of the IDEAL trial

The results of the IDEAL study were recently presented and published.[11] The study flow is summarized in Figure 1 and selected baseline characteristics are shown in Table 1. Follow-up was reasonably complete. The median time since the last MI was 22 and 21 months in the simvastatin and atorvastatin groups, respectively. Over 75% of the patients were on statins, including simvastatin, prior to randomization. At 24 weeks of follow-up, 900 patients (21%) in the simvastatin group had their dosage increased to 40 mg/d. At the end of the study, 1034 (23%) were prescribed simvastatin, 40 mg/d. Overall adherence was excellent, with 89% adherence in the atorvastatin group and 95% adherence in the simvastatin group.

Table 1: Baseline characteristics of the IDEAL study

Characteristics	Simvastatin (n = 4449)	Atorvastatin (n = 4439)
Age, mean (SD), y	61.6 (9.5)	61.8 (9.5)
Male sex	3597 (80.8)	3590 (80.9)
Blood pressure, mean (SD), mm Hg		
Systolic	137.0 (19.9)	136.7 (20.2)
Diastolic	80.6 (10.2)	80.1 (10.3)
Body mass index, mean (SD)†	27.0 (3.8)	27.3 (3.9)
Cardiovascular history		
>1 previous MIs	756 (17.0)	738 (16.6)
≤2 mo since last MI	506 (11.4)	493 (11.1)
Coronary angioplasty only	877 (19.7)	885 (19.9)
CABG surgery only	747 (16.8)	732 (16.5)
Both angioplasty and CABG	163 (3.7)	127 (2.9)
Cerebrovascular disease	376 (8.5)	353 (8.0)
Peripheral vascular disease	195 (4.4)	182 (4.1)
Congestive heart failure	244 (5.5)	293 (6.6)
Atrial fibrillation or flutter	336 (7.6)	347 (7.8)
Risk factors		
Current smoker	943 (21.2)	892 (20.1)
Former smoker	2614 (58.8)	2577 (58.1)
Systemic hypertension	1469 (33.0)	1461 (32.9)
History of diabetes mellitus	537 (12.2)	532 (12.0)
Prerandomization statin therapy		
Simvastatin	2230 (50.1)	2233 (50.3)
Atorvastatin	512 (11.5)	499 (11.2)
Pravastatin	431 (9.7)	419 (9.4)
Other statins	202 (4.5)	187 (4.2)
Concomitant therapy		
Aspirin	3536 (79.5)	3494 (78.7)
Warfarin or dicoumarol	559 (12.6)	558 (12.6)
ß-blockers	3281 (73.7)	3377 (76.1)
Calcium antagonists	840 (18.9)	882 (19.9)
ACE inhibitors	1367 (30.7)	1296 (29.2)
Angiotensin II blockers	270 (6.1)	263 (5.9)

CABG = coronary artery bypass graft

The effects on lipid parameters with the 2 drugs are shown in Table 2. Because a great majority of the patients were already on statins prior to randomization, baseline LDL-C levels were lower

Table 2: Changes in lipid parameters in IDEAL

	Concentrations (mmol/L)			
	Baseline	1 Year	2 Years	3 Years
	Number			
Simvastatin	4438	4290	4168	4033
Atorvastatin	4425	4200	4099	3984
LDL-C				
Simvastatin	3.14	2.64	2.68	2.76
Atorvastatin	3.15	2.05	2.13	2.22
Total cholesterol				
Simvastatin	5.07	4.56	4.58	4.67
Atorvastatin	5.10	3.82	3.89	4.00
HDL-C				
Simvastatin	1.19	1.22	1.22	1.23
Atorvastatin	1.19	1.18	1.19	1.20
Triglycerides				
Simvastatin	1.66	1.58	1.54	1.54
Atorvastatin	1.71	1.31	1.29	1.30

than those observed in earlier trials such as 4S. For the same reasons, the magnitude of treatment effect on lipid values was smaller as compared to 4S. Patients in the simvastatin group, who were not taking a statin at the time of randomization, had an average reduction in LDL-C of 33% after 12 weeks. On the other hand, in the group allocated to atorvastatin, statin-naïve patients had a mean reduction in LDL-C of 49%. During treatment in the randomized phase, mean LDL-C levels were 2.7 mmol/L in the simvastatin group and 2.1 mmol/L in the atorvastatin group. Total cholesterol and triglyceride levels were also lower in the atorvastatin group compared with the simvastatin group, whereas high-density lipoprotein cholesterol (HDL-C) levels were slightly higher in the simvastatin group.

The complete primary and secondary endpoint data are listed in Table 3. The primary endpoint of coronary death, acute MI, or cardiac arrest with resuscitation occurred in 10.4% and 9.3% of the simvastatin and atorvastatin groups, respectively. The relative risk reduction of 11% with atorvastatin did not reach statistical significance (P=.07). However, nonfatal MI, a component of the primary endpoint, was significantly reduced (P=.02), as was the composite secondary endpoint of a major CV event (major coronary event and stroke) (P=.02), any CHD event (P<.001), and any CV event (P<.001). In terms of absolute benefit, the number needed to treat for approximately 5 years to prevent one CHD event is about 30. Selected components of the secondary endpoint, including non-fatal MI, coronary revascularization, and peripheral arterial disease, were also significantly reduced (Figure 2). Mortality was not significantly reduced and, of note, mortality from cancer was similar in the 2 groups.

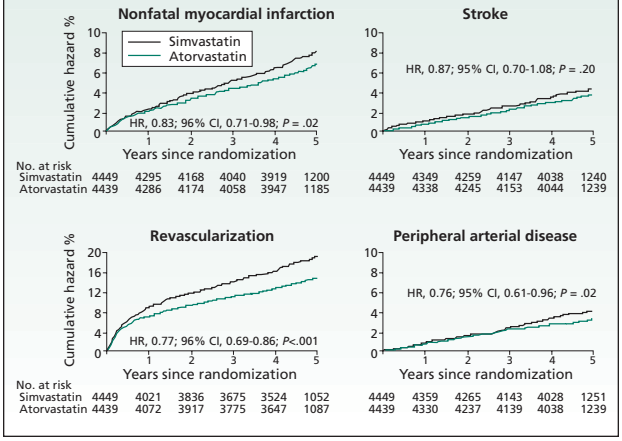
The frequency of serious adverse experiences was also similar in the 2 groups. There were, however, more patients in the atorvastatin group who discontinued the study medication because of investigator-reported adverse effects. Elevation of hepatic enzyme levels occurred more frequently in the atorvastatin group, but this was not considered clinically significant. Myalgias occurred more frequently in the atorvastatin group, but myopathy rates were low in both the atorvastatin and simvastatin groups.

Table 3: Primary and secondary endpoints in IDEAL

Outcome measures	Simvastatin, No. (%) (n = 4449)	Atorvastatin, No. (%) (n = 4439)	Hazard ratio (95% CI)	*P* value
Major coronary event (primary outcome)	463 (10.4)	411 (9.3)	0.89 (0.78-1.01)	.07
CHD death	178 (4.0)	175 (3.9)	0.99 (0.80-1.22)	.90
Nonfatal MI	321 (7.2)	267 (6.0)	0.83 (0.71-0.98)	.02
Cardiac arrest	7 (0.2)	10 (0.2)		
Any CHD event	1059 (23.8)	898 (20.2)	0.84 (0.76-0.91)	<.001
Coronary revascularization	743 (16.7)	579 (13.0)	0.77 (0.69-0.86)	<.001
Hospitalization for unstable angina	235 (5.3)	196 (4.4)	0.83 (0.69-1.01)	.06
Fatal or nonfatal stroke	174 (3.9)	151 (3.4)	0.87 (0.70-1.08)	.20
Major cardiovascular event	608 (13.7)	533 (12.0)	0.87 (0.78-0.98)	.02
Hospitalization for nonfatal HF	123 (2.8)	99 (2.2)	0.81 (0.62-1.05)	.11
Peripheral arterial disease	167 (3.8)	127 (2.9)	0.76 (0.61-0.96)	.02
Any cardiovascular event	1370 (30.8)	1176 (26.5)	0.84 (0.78-0.91)	<.001
All-cause mortality	374 (8.4)	366 (8.2)	0.98 (0.85-1.13)	.81
Cardiovascular	218 (4.9)	223 (5.0)	1.03 (0.85-1.24)	.78
Noncardiovascular	156 (3.5)	143 (3.2)	0.92 (0.73-1.15)	.47
Malignant disease	112 (2.5)	99 (2.2)	0.89 (0.68-1.16)	.38
Suicide/accidental death	9 (0.2)	5 (0.1)	–	–
Other	30 (0.7)	32 (0.7)	–	–
Unclassified	5 (0.1)	7 (0.2)	–	–

CHD = coronary heart disease; HF = heart failure; MI = myocardial infarction; CI = confidence interval.

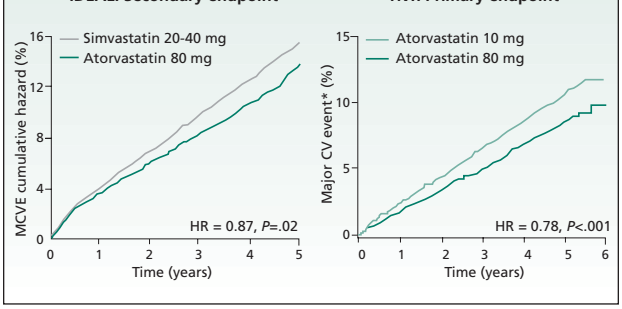
Figure 2: Components of secondary outcomes



Comments and clinical implications

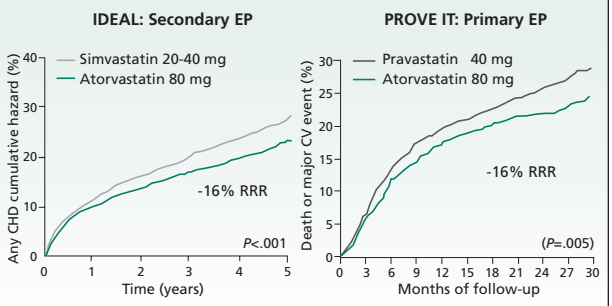
Observations from the IDEAL study constitute an important addition to the increasingly large pool of data,[4,12] including the recently reported Treatment to New Target (TNT) trial,[13] that demonstrate a convincing relationship between the magnitude of LDL-C lowering and the clinical benefits of reducing morbidity and mortality in patients with, or deemed at risk for, CV disease. In the IDEAL study, the use of atorvastatin, 80 mg/d, as compared with simvastatin 20 to 40 mg/d (which was the active treatment intervention in 4S), achieved a 0.6 mmol/L lower LDL-C level and led to an 11% trend in the reduction of the primary endpoint of CHD death, MI, or cardiac arrest with resuscitation (P=.07). Although the primary endpoint was not met, most of the secondary endpoints were, including a 17% reduction in nonfatal MI, a 13% reduction in major CV events (the pre-specified primary endpoint of the TNT trial), as well as a 16% reduction in any CHD events (the primary endpoint in the PROVE IT-TIMI 22 trial).

Figure 3: Major cardiovascular events: IDEAL versus TNT



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

Figure 4: Any coronary heart disease events: IDEAL versus PROVE IT-TIMI 22



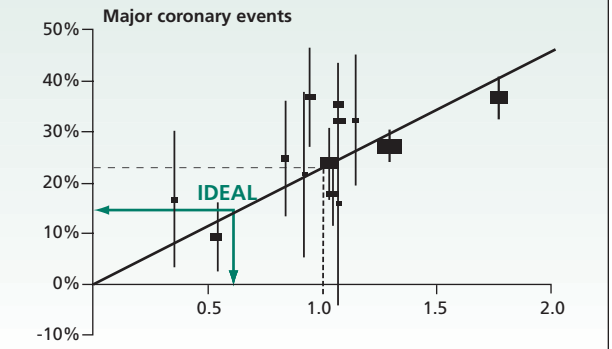
EP = endpoint

Indeed, the relative reductions of these common endpoints were remarkably similar between IDEAL and the previous trials (Figures 3 and 4).

A recently published prospective meta-analysis of data from 90,056 individuals in 14 randomized trials of statin therapy reported an overall reduction of about 20% in the 5-year incidence of major coronary events, coronary revascularization, and stroke per 1 mmol/L reduction in LDL-C, largely irrespective of the initial lipid profile.[14] The relationship between the proportional reduction in coronary events and the mean absolute reduction in LDL-C is shown in Figure 5. The benefit demonstrated in the IDEAL study is, therefore, consistent with the effect of LDL-C lowering as calculated from this and previous meta-analyses, as well as epidemiological studies.[14-16]

The lack of a benefit on mortality with more aggressive lipid-lowering in the IDEAL study is not unexpected, given that the trial was not powered to assess mortality. On the other hand, the observation of a nonsignificant higher incidence of non-CV death in the simvastatin group in IDEAL is particularly reassuring. This is because there were concerns regarding the safety of aggressive lipid-lowering raised in the TNT study, which reported a non-significant excess in non-CV death in the atorvastatin 80 mg over the atorvastatin 10 mg group.[13]

Figure 5: Proportional reduction in coronary event and absolute reduction of LDL-C in one year



The implication of the findings of IDEAL and other statin trials for clinicians who treat patients with CHD is that the greater the LDL-C reduction, the better the clinical outcome. This can be achieved by treating patients with a relatively high dose of a statin with reasonable safety. Nonpharmacologic measures such as diet and exercise continue to play an important role in conjunction with drug therapy.

Dr. Moe reports that he has no conflicts of interest to disclose.

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