Should you put all diabetic patients on statins?

Aggressive statin therapy achieves greater cardiovascular benefit, regardless of baseline LDL, than just "treating to goal"

LAWRENCE A. LEITER, MD, FRCPC, FACP

Division of Endocrinology and Metabolism, St Michael's Hospital; Department of Medicine and Nutritional Sciences, University of Toronto leiterl@smh.toronto.on.ca

In this article

- Cardiovascular outcomes data for drugs other than statins.
- Reduction of cardiovascular risk for diabetes patients in statin trials. ❑

Practice recommendations

- Statins are the therapy of choice for lowering LDL cholesterol in patients with diabetes (**A**).
- All diabetes patients over the age of 40 should receive statin therapy, regardless of baseline LDL cholesterol (**A**).
- Diabetes patients experience greater cardiovascular benefit from aggressive lipid-lowering therapy than from more moderate lipid-lowering therapy (**B**). ❑

Strength of recommendation (SOR)

A. Good quality patient-oriented evidence.
B. Inconsistent or limited-quality patient-oriented evidence.
C. Consensus, usual practice, opinion, disease-oriented evidence, case series. ❑

Dyslipidemia in patients with diabetes is underdiagnosed and undertreated, and diabetes patients not receiving statin therapy are at high risk for cardiovascular disease. Clinical trial data show that we should consider statins for all adults with diabetes, irrespective of cardiovascular disease status or baseline low-density lipoprotein (LDL) cholesterol levels. Furthermore, aggressive statin therapy is more beneficial than moderate treatment. Patients with diabetes typically have elevated triglycerides and low high-density lipoprotein (HDL) cholesterol levels, but their LDL cholesterol levels are similar to those in the general population. (1) Nevertheless, emerging evidence shows that patients with diabetes may benefit from statins even in the absence of elevated LDL. (2-4) Though various agents can reduce LDL cholesterol, the most impressive cardiovascular outcomes are associated with statins. (4-10) ❑

We're undertreating

Despite overwhelming evidence supporting use of statins for lipid-lowering, management of cholesterol levels is inadequate in clinical practice. (11,12) Furthermore, data from US medical records suggest that lipid management in diabetes patients is particularly poor. (13) In the decade between National Health and Nutrition Examination Surveys I and II, coronary heart disease (CHD) mortality declined significantly among patients without diabetes (44% in men, 30% in women) but far less so among patients with diabetes. (14) International treatment guidelines such as those of the American Diabetes Association (ADA), (15) National Cholesterol Education Program Third Adult Treatment Panel (NCEP ATP III), (16,17) and the Joint European Societies (18) classify diabetes as a CHD risk equivalent and, accordingly, have established stringent lipid goals for diabetes patients. ❑

Stringent lipid goals

The first priority is to reduce LDL cholesterol to <100 mg/dL (2.6 mmol/L), as advocated by all 3 guidelines.

– For patients with diabetes and established cardiovascular disease, the recent ATP III guideline update and the ADA recommendations suggest the option of lowering LDL cholesterol even further, to <70 mg/dL (1.8 mmol/L). (17)
– Immediate initiation of statin therapy, in addition to dietary and lifestyle changes, is also generally recommended regardless of baseline LDL cholesterol levels in all patients with diabetes and established cardiovascular disease. (15,17)
– It is also recommended for most diabetes patients without clinically evident cardiovascular disease (15) or LDL cholesterol=130 mg/dL (2.6 mmol/L). (17)

Undertreatment of hypercholesterolemia may be more widespread in patients with diabetes than in those without diabetes (Figure). (19-21) Outpatient medical data from 47,813 patients with coronary heart disease revealed that patients with diabetes were: 26% less likely to have their lipid profile assessed than patients without diabetes, and 17% less likely to receive a lipid-lowering medication. (13) The AUDIT survey (Analysis and Understanding of Diabetes and Dyslipidemia: Improving Treatment) (22) of physicians who specialized in the management of diabetes revealed that:

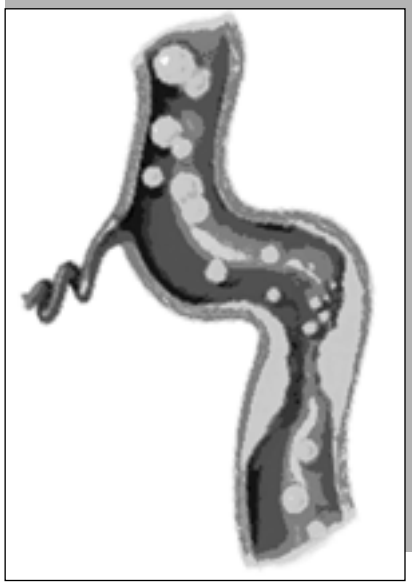

Figure. In diabetes, LDL is more atherogenic

– Most (=90%) routinely assess total cholesterol, LDL and HDL cholesterol, or triglycerides.
– Only 20% believe that at least 80% of patients achieve LDL cholesterol goals.
– They were more likely to set less stringent LDL goals for diabetes patients without cardiovascular disease than for those with cardiovascular disease.

LDL particles in patients with diabetes tend to be small and dense, and more atherogenic and liable to oxidation than larger LDL particles. (19) A meta-analysis of large, randomized, controlled trials revealed a 25% reduction in cardiac events with lipid-lowering therapy in patients with diabetes, but no significant reduction with glucose lowerers. (20)

In the UK Prospective Diabetes Study (UKPDS), initial dietary therapy did not eliminate excess cardiovascular risk in patients with diabetes. (21) Consequently, treatment of hypercholesterolemia in patients with diabetes needs to be a healthcare priority. ❑

LIPID-LOWERING TREATMENTS

Statins are the therapy of choice for lowering LDL cholesterol levels (including small, dense LDL), (15,17,18) and they also reduce triglycerides and modestly elevate HDL cholesterol. Statins generally are well tolerated with few side effects. (23,24) Myopathy is the most serious adverse event, but it occurs only rarely. Unlike other lipid-lowering therapies, statins boast a wealth of data from large, randomized, placebo-controlled trials conclusively demonstrating significant reduction in both primary and secondary cardiovascular risk. (5-10,25-28) Because of efficacy and safety, they are the first-line option.

Other pharmacologic options include bile acid sequestrants, ezetimibe, fibrates, and niacin (Table 1). (29-32)

Bile acid sequestrants modestly reduce LDL and slightly increase HDL cholesterol, and have no effect or even mildly increase triglycerides, which are often elevated in patients with diabetes. Side effects (constipation, gastrointestinal distress) have limited their use.

Ezetimibe belongs to a new class of lipid-lowering agents that inhibit cholesterol transport. It reduces LDL cholesterol by around 18%, increases HDL cholesterol slightly, and modestly reduces triglycerides. However, no outcomes data have ascertained an effect on cardiovascular morbidity or mortality. It has been associated with increases in liver enzymes when administered with statin therapy.

Fibrates are most effective for patients with very high triglycerides levels. They increase HDL cholesterol levels and generally produce modest reductions in LDL cholesterol. Though contraindicated for patients with severe renal or hepatic disease, they are generally well tolerated, with the most common adverse events being dyspepsia and gallstones.

Table 1

Major cardiovascular outcomes data in primary prevention, placebo-controlled trials for drugs other than statins STUDY (N)	LDL-C TREATMENT	REDUCTION	RELATIVE (ABSOLUTE) REDUCTION VS PLACEBO	ENDPOINT	P
LRC-CPPT (29) (3806)	Cholestyramine	11%	19% (1.6%)	CHD death and nonfatal MI	.006
VAHIT (30) (2531)	Fenofibrate	0%	22% (4.4%)	CHD death and nonfatal MI	NA
HHS (31) (4081)	Gemfibrozil	10%	34% (NA)	Fatal and nonfatal MI, sudden cardiac death, and unwitnessed death	<.02
FIELD (32) (9795)*	Fenofibrate	12%	11% (0.7%)	CHD death and nonfatal MI	.16

LDL-C, low-density lipoprotein cholesterol; CHD, coronary heart disease; MI, myocardial infarction; NA, not available.

* Recruited patients with type 2 diabetes

Niacin is the most effective agent for increasing HDL cholesterol; it also lowers triglyceride levels, but reduces levels of LDL cholesterol only modestly. Its use has been limited because of adverse events such as flushing, gout, and hepatoxicity. (33) Initial data suggest cardiovascular benefits with niacin (34) or a combination of niacin and simvastatin. (35) ❑

FAST TRACK

Cardiovascular benefits were seen in diabetes patients whose LDL levels would not conventionally require lowering.

STATIN TRIALS

Although early statin trials found reductions in cardiovascular events in diabetes patients, (36,37) recent prospective analyses found this benefit even in those whose baseline LDL level would not conventionally require lowering (Table 2).

The *Cholesterol and Recurrent Events (CARE) trial* (37) included 586 patients with diabetes, a history of myocardial infarction, and average cholesterol levels. In a post-hoc analysis, diabetes patients randomized to receive pravastatin 40 mg/d had a 25% relative reduction in risk (absolute risk reduction [ARR]=8.0%) for fatal coronary events or myocardial infarction (MI) compared with placebo (*P*=.05) after 5 years.

Post-hoc analysis of 1077 diabetes patients with CHD recruited in the *Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) trial* (36) also showed a reduction in the relative risk of a major CHD event (RR=19%; ARR=4.0%) after a mean of 6.1 years among patients who received pravastatin compared with those who received placebo; the relative risk of any cardiovascular event was reduced by 21% (*P*=.008). Subsequent trials specified analyses beforehand to assess cardiovascular risk reductions.

The lipid-lowering arm of the *Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT-LLA)* (3) included patients with diabetes, hypertension, and at least 3 additional cardiovascular risk factors, and normal or slightly elevated LDL cholesterol. In the diabetes subgroup (N=2532), a 16% relative risk reduction (ARR=0.8%) in nonfatal MI and CHD death was observed in atorvastatin (Lipitor)-treated patients compared with placebo. Because the lipid-lowering arm closed early after a median follow-up of 3.3 years due to a highly significant cardiovascular benefit observed with atorvastatin vs placebo, nonfatal MI and CHD deaths were infrequent (N=84) and the risk reduction in diabetes patients was not significant. A larger composite endpoint–major cardiovascular events and procedures–showed a significant 23% relative risk reduction (ARR=2.7%) vs placebo (116 vs 151; *P*=.036) in the diabetes subgroup. (3)

The *Heart Protection Study (HPS)* (26) included 5963 patients with diabetes (of whom 10% had type 1), with or without occlusive arterial disease,

Table 2

Reduction of cardiovascular risk for diabetes patients in large statin trials STUDY (N) AND CONCLUSION	TREATMENT	TYPE OF ANALYSIS	MEAN BASELINE LDL CHOLESTEROL	RELATIVE (ABSOLUTE) % RISK REDUCTION*	ENDPOINT
Collaborative Atorvastatin Diabetes Study (CARDS)[4] (2838)	Atorvastatin 10 mg	Prospective randomized trial in diabetes patients	117 mg/dL (3.0 mmol/L)	37% (3.2%)	Major CV events
Atorvastatin 10 mg daily is safe and eff icacious in reducing the risk of first CV events, including stroke, in patients with type 2 diabetes without high LDL cholesterol. No justification is available for having a particular threshold level of LDL as the sole arbiter of which patients with type 2 diabetes should receive statins.					
Atorvastatin Study for Prevention of CHD Endpoints in Non-insulin-dependent diabetes mellitus (ASPEN) (38) (2410)	Atorvastatin 10 mg	Prospective randomized trial in diabetes patients	114 mg/dL (2.9 mmol/L)	10% (1.3%)	Composite†
The results from this trial do not confirm the benefit of therapy but do not detract from the imperative that the majority of diabetes patients deserve LDL cholesterol lowering to the currently recommended targets.					
Heart Protection Study (HPS) (2) (5963)	Simvastatin 40 mg	Predefined subanalysis	124 mg/dL (3.2 mmol/L)	27% (3.2%)	Nonfatal MI and CHD death
Allocation to 40 mg simvastatin daily reduced the rate of first major vascular events by about a quarter in a wide range of diabetes patients studied. After making allowance for noncompliance, actual use of this regimen should reduce these rates by about a third. Statin therapy should be considered routinely for all diabetes patients at sufficiently high risk of major vascular events, irrespective of their initial cholesterol concentrations.					
Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT-LLA) (3) (2532)	Atorvastatin 10 mg	Predefined subanalysis	128 mg/dL (3.3 mmol/L)	16% (0.8%)	Nonfatal MI and CHD death
Atorvastatin significantly reduced the risk of major cardiovascular events and procedures among diabetes patients with well -controlled hypertension and without a history of CHD or markedly elevated cholesterol concentrations. The proportional reduction in risk was similar to that among partici pants who did not have diagnosed diabetes (NNT for 1 year=111).					
Treating to New Targets (TNT) (39) (1501)	Atorvastatin 80 mg	Post-hoc subanalysis	<130 mg/dL (3.4 mmol/L)	25%‡ (4.1%)	Major CV events
Patients who received atorvastatin 80 mg also experienced 25% fewer major cardiovascular events (CHD death, nonfatal heart attacks, resuscitated cardiac arrest, and fatal or non-fatal strokes).					
Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) (36) (1077)	Pravastatin 40 mg	Post-hoc subanalysis	43 mg/dL (3.7 mmol/L)	19% (4.0%)	Nonfatal MI and CHD death
Pravastatin therap y prevents cardiovascular events, including stroke, in patients with diabetes or impaired fasting glucose and established CHD.					
Cholesterol and Recurrent Events (CARE) (37) (586)	Pravastatin 40 mg	Post-hoc subanalysis	136 mg/dL (3.5 mmol/L)	25% (8.0%)	Nonfatal MI, CABG PTCA, CHD death
Diabetes patients and patients with IFG are at high risk of recurrent coronary events that can be substantially reduced by pravastatin treatment.					
CABG, coronary artery bypass graft; CHD, coronary heart disease; CV, cardiovascular; LDL, low -density lipoprotein cholesterol; MI, myocardial infarction; NNT, number needed to treat; PTCA, percutaneous transluminal coronary angioplasty.					

* Compared with placebo in diabetes patients
† Composite of cardiovascular death, nonfatal MI, nonfatal stroke, recanalization, CABG, resuscitated cardiac arrest, and worsening or unstable angina requiring hospitalization
‡ Compared with atorvastatin 10 mg.

who were randomized to receive simvastatin 40 mg/d or placebo. After a mean of 5 years, significant relative risk reductions in major coronary events (27%), stroke (25%), revascularizations (24%), and major vascular events (24%) (all $P<.0001$) were achieved with simvastatin compared with placebo. (2) Significant risk reductions vs placebo were also observed among patients with diabetes but no known cardiovascular disease.

More recent trials were specifically designed to assess effects in diabetes patients.

The *Collaborative Atorvastatin Diabetes Study (CARDS)* (4) was the first prospective statin cardiovascular prevention trial conducted solely for patients with type 2 diabetes without CHD (N=2838). (6) Patients were randomized to atorvastatin 10 mg/d or placebo. The trial was stopped 2 years earlier than expected, because the early stopping rule for efficacy had been met. After 4 years, the mean LDL cholesterol level in the atorvastatin group was 82 mg/dL (2.1 mmol/L), substantially lower than recommended goals. A significant 37% reduction in major cardiovascular events and a 48% reduction in stroke were observed in the atorvastatin group compared with placebo (ARR=1.3%).

In the *Atorvastatin Study for Prevention of CHD Endpoints in Non-insulin-dependent diabetes mellitus (ASPEN),* (38) atorvastatin 10 mg reduced the primary endpoint by 10% compared with placebo. The difference did not reach significance, perhaps due to the study design, the patient population recruited, the nature of the primary endpoint, and protocol changes needed during the trial due to revised treatment guidelines; the lack of significance does not detract from the known benefits of statin therapy in diabetes patients. ❑

IMPORTANCE OF TREATING BEYOND GOAL

By current guidelines, final mean LDL cholesterol levels in the CARE and LIPID studies would have been at or above goal (CARE=98 mg/dL [2.5 mmol/L], LIPID=~104 mg/dL [2.7 mmol/L]). However, in the later studies, greater LDL cholesterol reduction was achieved and further reduced cardiovascular risk.

In the HPS diabetes population, LDL cholesterol levels were reduced from 124 mg/dL (3.2 mmol/L) at baseline to 89 mg/dL (2.3 mmol/L), and a highly significant reduction in major vascular events in favor of simvastatin was observed for patients with baseline LDL cholesterol levels <116 mg/dL (3.0 mmol/L; $P=.0007$).

Likewise in CARDS, patients with baseline LDL cholesterol <116 mg/dL (3.0 mmol/L) randomized to receive atorvastatin experienced significant relative risk reductions in major cardiovascular events compared with placebo ($P=.025$); 743 patients with baseline LDL cholesterol <100 mg/dL (2.6 mmol/L) exhibited a nonsignificant 26% relative reduction in major cardiovascular events. Results for diabetes patients without overt CHD or elevated LDL led the authors to question whether CHD risk can be low enough in any diabetes patient to justify withholding statin therapy. ❑

FAST TRACK

For patients with CHD, aggressive therapy reduced cardiovascular morbidity and mortality more than moderate therapy.

THE CASE FOR AGGRESSIVE THERAPY

Recent trials have shown that, for patients with CHD, aggressive statin therapy reduced cardiovascular morbidity and mortality to a greater extent than moderate therapy. Patients receiving aggressive therapy had their lipids reduced to levels below the goals recommended by national and international guidelines.

The Aggressive *Lipid-Lowering Initiation Abates New Cardiac Events (ALLIANCE)* (38) randomized 2442 CHD patients with hypercholesterolemia to atorvastatin 10 to 80mg/d or usual care. After about 1 year, LDL levels had been reduced to 95 mg/dL (2.5 mmol/L) in the atorvastatin group and 111 mg/dL (2.9 mmol/L) in the usual-care group, with a 17% reduction in the cardiovascular event rate vs usual care ($P=.02$).

In the *PROVE IT–TIMI 22 trial* (8) 2099 patients randomized to aggressive therapy with atorvastatin 80 mg/d after hospitalization for acute coronary syndrome achieved LDL levels of 62 mg/dL (1.6 mmol/L), compared with 95 mg/dL (2.5 mmol/L) for 2063 patients randomized to more moderate therapy, pravastatin, 40 mg/d. After 2 years, the atorvastatin group had a 16% relative risk reduction (ARR=3.9%) in primary cardiovascular events compared with the pravastatin group. Event reduction in diabetes patients was similar to that in the overall population.

FAST TRACK

More recent trials were specifically designed to assess effects in diabetes patients.

The *Treating to New Targets (TNT) study* (39) prospectively assessed the efficacy of lowering LDL

cholesterol to <100 mg/dL (2.6 mmol/L) among 10,001 patients with stable CHD and LDL cholesterol <130 mg/dL (3.4 mmol/L). After almost 5 years of follow-up, atorvastatin 80 mg/d conferred significant benefits across a range of cardiovascular end points compared with atorvastatin 10 mg/d. A post-hoc analysis of 1501 patients with diabetes from the TNT study showed similar benefits of atorvastatin 80 mg/d. (39) About 15% of the subjects had diabetes at baseline, and these patients randomized to atorvastatin 80 mg/d achieved LDL cholesterol levels of 77 mg/dL (2.0 mmol/L) at the end of the study compared with 99 mg/dL (2.6 mmol/L) for patients who received atorvastatin 10 mg/d. This reduction in LDL over that achieved with atorvastatin 10 mg/d translated into a 25% relative reduction (ARR=4.1%) in major cardiovascular events (*P*=.026) and a 31% reduction (ARR=3.0%) in cerebrovascular events (*P*=.037). (37)

In the *Steno-2 study,* (40) 160 patients with diabetes and microalbuminuria were randomized to intensive or conventional multiple risk factor intervention. The risk factors targeted in both groups included blood pressure, cholesterol, triglycerides, and glycosylated hemoglobin levels, but goals for the intensive intervention group were more stringent. The difference in the percentage of patients who achieved goal in the intensive intervention group vs the conventional intervention group was greater for cholesterol goals than for any other risk factor. There was a significant reduction in incidence of cardiovascular and microvascular events by approximately 50% in the intensive-therapy relative to the conventional-therapy group. ❑

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