American Diabetes Association Indications for Statins in Diabetes

Is there evidence?

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INTRODUCTION — The American Diabetes Association (ADA) standards of care for diabetes state that statin therapy should be initiated in individuals with diabetes and other cardiovascular risk factors with a target LDL cholesterol of <100 mg/dl. Furthermore, a possible target LDL of <70 mg/dl is stated in patients with diabetes and cardiovascular disease. In this mini-review, we examine the evidence that exists regarding LDL cholesterol–based treatment goals in individuals with diabetes. From our review of the current literature, it is evident that the majority of clinical trials were designed using a fixed dose of statins and not in an LDL cholesterol–based “treat-to-target” approach (thus differing from the common design of blood glucose control trials). This leads us to reassess the current guidelines with special emphasis on the very-low-risk and very-high-risk individuals with diabetes, where the evidence is less robust. We conclude that in this subset of individuals with diabetes, statin therapy should be based on the existing evidence and prescribed in a fixed-dose manner.

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ublished yearly, the ADA standards of clinical care portray the principle guidelines of diabetes care based on the constantly evolving body of evidence for the treatment of patients with diabetes. The 2008 standards of care state the following for statin use in diabetic individuals (1):

1) Statin therapy should be added to lifestyle therapy, regardless of baseline lipid levels, for diabetic patients a) with overt cardiovascular disease (CVD) (A; level of evidence as described in the ADA evidence-grading system [Table 1]); the primary goal is an LDL cholesterol <100 mg/dl (<2.6 mmol/l) (A); a lower LDL cholesterol goal of 70 mg/dl (1.8 mmol/l), using a high dose of a statin, is an option (E); and b) without CVD who are over the age of 40 years and have one or more other CVD risk factor. The primary goal is an LDL cholesterol <100 mg/dl (<2.6 mmol/l) (A).

2) For lower-risk patients than those specified above (e.g., without overt CVD and under the age of 40 years), statin therapy should be considered in addition to lifestyle therapy if LDL cholesterol remains >100 mg/dl or in individuals with multiple CVD risk factors (E).

3) If drug-treated patients do not reach the above targets on maximal tolerated statin therapy, a reduction in LDL cholesterol of >40% from baseline is an alternative therapeutic goal (A).

4) Combination therapy using statins and other lipid-lowering agents may be considered to achieve lipid targets but has not been evaluated in outcome studies for either CVD outcomes or safety (E).

5) Statin therapy is contraindicated in pregnancy (E).

These guidelines are based on numerous trials showing a benefit for statin therapy both as primary and secondary prevention of cardiovascular disease and mortality (2–7). Trials like the Collaborative Atorvastatin Diabetes Study (CARDS), proved beyond doubt that patients with type 2 diabetes and other risk factors for CVD should be treated with a statin, apparently disregarding their initial LDL cholesterol level (5). However, most of these trials did not set a goal LDL cholesterol level for treatment but examined the effect of a predetermined statin dose on the outcome (2–5). Extrapolated from these trials and from epidemiologic data (8–11), a goal LDL of 100 mg% seems adequate for the majority of patients. Yet because of the problematic interpretation of clinical trial data that was not inherent in its basic structure, alternative treatment goals have arisen, including a reduction of LDL by 40% (in patients where LDL reduction could not reach the 100 mg% goal) or a reduction below 70 mg% (in very-high-risk patients—those with prior cardiovascular disease or acute coronary syndromes).

Some questions are raised from these guidelines. First, the overall efficacy of statin use for primary prevention raises the question who should get a statin, i.e., what is the evidence for their use as primary prevention in diabetic individuals. Should a statin be given on an LDL-based treat-to-target goal (as stated in the guidelines, reduce the LDL below 100 mg%), existence of other vascular risk factors, age, or regardless of the measured cholesterol at predetermined doses (similar to current use of aspirin).

The second question is what is the evidence for the target LDL in secondary prevention in high-risk diabetic individuals—how aggressive should we be, and should we limit ourselves to an LDL-targeted therapy versus a comprehensive high-dose statin strategy. Again there is the question of the target LDL versus the “evidence-based” fixed dose?

These questions are further stressed by the relatively poor efficacy of other cholesterol-reducing treatments. In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, fenofibrate failed to reduce the primary
outcome of coronary events (coronary heart disease death or nonfatal myocardial infarction), although achieving a significant 12% reduction in LDL cholesterol levels (12). The recently published ENHANCE (Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression) trial failed to show additive value of ezetimibe therapy on carotid and femoral intima-media thickness in patients with familial hypercholesterolemia (although it showed a significant 16.5% reduction in LDL levels in the ezetimibe-treated cohort) (13). Furthermore, among the various lipid measurements, LDL is not the strongest predictor of cardiovascular disease (10,11), thus pointing to a possible beneficial effect of statins, regardless of their cholesterol-reducing properties.

These beneficial/pleiotropic effects of statins have been suggested in various disease processes: statins have been implicated in plaque stabilization (14), reduction of inflammation (as noted by a reduction in C-reactive protein [CRP] levels) (15), reversal of endothelial dysfunction (16), and decreased thrombogenicity (17). They are thought to result from a reduction in proinflammatory nonsteroidal isoprenoid compounds synthesis through the inhibition of mevalonic acid processing by 3-hydroxy-3-methyl-3-glutaryl CoA (HMG-CoA) reductase (18). Proof of the importance the pleotropic effect is suggested by the dissociation between the immediate beneficial effect of statins in acute inflammatory states such as acute coronary syndrome and their delayed LDL-reducing effect (19).

In this mini-review, we would like to examine the evidence that currently exists regarding the questions raised above, suggest a different interpretation of the existing clinical trial data, and offer our viewpoint as to the controversies that exist in the current ADA guidelines.

**PRIMARY PREVENTION: IS THERE A DIABETIC INDIVIDUAL WHO SHOULD NOT GET A STATIN?** — Diabetes is a significant cardiovascular risk factor (confering a three time absolute adjusted risk of CVD death). Furthermore, in individuals with diabetes, a log linear relationship exists between cholesterol levels and CVD regardless of the baseline LDL (20). Thus, it was assumed, that regardless of the baseline cholesterol level, reducing the LDL will reduce the occurrence of CVD. This led to a number of primary cardiovascular prevention trials using statin therapy as the principal intervention. It has been clearly shown (and thus clearly incorporated into the ADA guidelines) that diabetic individuals with other risk factors should indeed be treated with a statin (4,5).

Yet only a few studies have included diabetic individuals without other CVD risk factors (Table 2). In the Heart Protection Study (HPS), 5,963 individuals with diabetes were randomized to 40 mg simvastatin or placebo regardless of their baseline LDL or prior vascular disease status. A significant 22% reduction in the first event rate of major vascular outcomes (first major coronary event, stroke, or revascularization) was noted (2). Based on the HPS data, an evaluation of the cost-effectiveness of lifetime simvastatin treatment found it to be cost saving even in patients as young as 35 years or with a 5-year risk of major vascular events as low as 5% (considered moderate CVD risk) (21). These criteria include almost all of the diabetic individuals, including individuals with type 1 diabetes over the age of 30 years (22) and individuals with type 2 diabetes over the age of 32 years for men and 38 years for women (23).

On the contrary, the recent Atorvastatin Study for Prevention of Coronary Heart Disease End Points in non-insulin-dependent diabetes (ASPEN) failed to show a significant reduction in primary prevention of major vascular outcomes (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, revascularization, coronary artery bypass surgery, resuscitated cardiac arrest, and worsening or unstable angina requiring hospitalization) with 10 mg atorvastatin in patients with type 2 diabetes. This was partially explained by a short duration of diabetes in the study population, changing guidelines necessitating the addition of lipid-lowering therapy to 26.9% of the placebo group and a low overall event rate (3).

In the ADA standards of care, a scale of evidence grade is used (A–E) (Table 1), where grade “A” evidence refers to evidence from a meta-analysis that incorporated quality ratings in the analysis. Such a meta-analysis was recently published by the Cholesterol Treatment Trialists (CTT) Collaborators (24). In this work, the effect of statin treatment in 18,686 individuals with diabetes was evaluated from 14 randomized trials (inclusion criteria were unconfounded trials with lipid-lowering primary interventions that aimed to recruit at least 1,000 participants with treatment duration lasting at least 2 years). The mean duration of follow-up was 4.3 years. Participants with diabetes had a 9% reduction in all-cause mortality per millimole per liter LDL cholesterol reduction (relative risk 0.91, 99% CI 0.82–1.01; P = 0.02). The overall effect was a consistent reduction of 21% in major vascular effects.
| Intervention | n   | Primary outcome composition | Results |
|--------------|-----|-----------------------------|---------|
| Heart Protection Study (2) | Simvastatin 40 mg or placebo regardless of their baseline LDL or prior vascular disease status | 5,963 | First major coronary event, stroke, or revascularization | 22% (95% CI 13–30) reduction in the event rate (P < 0.0001). 33% reduction in event rate (95% CI 17–46, P = 0.0003) among the 2,912 diabetic without CVD at entry, and 27% reduction in first event rate (95% CI 13–40, P = 0.0007) among 2,426 diabetic participants whose pretreatment LDL cholesterol concentration was <3.0 mmol/l |
| Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in non-insulin-dependent diabetes mellitus (ASPEN) (3) | 10 mg of atorvastatin or placebo in a 4-year double-blind parallel-group study | 2,410 | Cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, re-canualization, coronary artery bypass surgery, resuscitated cardiac arrest, and worsening or unstable angina requiring hospitalization | Composite primary end point rates were 13.7 with atorvastatin vs. 15.0% in the placebo group (hazard ratio 0.90 [95% CI 0.73–1.12]). Among 1,905 subjects without prior myocardial infarction or interventional procedure, 10.4% of atorvastatin-treated and 10.8% of placebo-treated subjects experienced a primary end point (0.97 [0.74–1.28]) |
| Cholesterol Treatment Trialists (CTT) Collaborators meta-analysis (24) | Unconfounded trials with lipid-lowering primary interventions that aimed to recruit at least 1,000 participants with treatment duration lasting at least 2 years | 18,686 (14 randomized trials) | All-cause mortality and major vascular events (myocardial infarction or coronary death, stroke, or coronary revascularization) | 9% reduction in all-cause mortality per mmol/l LDL cholesterol reduction (RR 0.91, 99% CI 0.82–1.01; P = 0.02); 21% in major vascular events per millimole per liter LDL cholesterol reduction (0.79, 99% CI 0.72–0.86; P < 0.0001) |
| Stop Atherosclerosis in Native Diabetics Study (SANDS) (25) | Adults with type 2 diabetes treated to reach aggressive targets (LDL cholesterol of ≤7.0 mg/dl and systolic blood pressure of ≤115 mmHg) vs. standard targets (LDL cholesterol of ≤100 mg/dl and systolic blood pressure of ≤130 mmHg) | 499 | Progression of atherosclerosis measured by common carotid artery intimal medial thickness | Intimal medial thickness regressed in the aggressive group and progressed in the standard group (−0.012 vs. 0.038 mm; P < 0.001) |
events per millimole per liter LDL cholestero
terol reduction (defined as the composite out
come of myocardial infarction or coro
mary death, stroke, or coronary revascula
(0.79, 99% CI 0.72–0.86; P <
results did not change dra
ametrically after incorporation of the AS
PEN results; a 20% risk reduction was
culated). Subgroup analysis revealed this
vation was consistent irrespective of
whether patients had prior cardiovascu
, other CVD risk factors (hypertension, smokin
, BMI, renal function, HDL levels), or baseline LDL (up to an LDL
level of 2.6 mmol/l). Thus, even in diabetic
individuals without other cardiovascular
risk factors, a beneficial effect of statins
was noted. This outcome may be a result of
the pleotropic effect of statins, as a different
mechanism of CVD disease reduction, iso
lated from their LDL-lowering properties.

These studies lead us to reassess the
ADA guidelines for statin use in primary
prevention of CVD. It appears that based
on current available data, all individuals
with diabetes should be treated with a statin
unless they apply to very specific exclusion
criteria. These criteria include a patient
with type 2 diabetes under the age of 32 years
or 38 years in women), short duration of di
ase (<10 years), and no apparent CVD risk
factors (including a baseline LDL >100
mg%). In individuals with type 1 diabetes,
the age should be even lower, i.e., <30
years of age. To not be prescribed a statin,
a patient will have to have all these exclusion
criteria present (Table 4).

What would the target LDL be in an
individual without prior CVD or CVD
risk factors and a baseline LDL below 100
mg% is yet an unanswered question.
Some data exist as to a goal reduction of
LDL below 70 mg%, as was shown in the
recently published STOP Atherosclerosis
in Native Diabetics Study (SANDS) using
carotid intimal medial thickness as a sur
rogate marker for CVD progression (25).
Yet, until “hard” major vascular event data
are published, we feel that the initial statin
regimen for all diabetic patients
would support a fixed high-dose atorva
tin (20 mg) or high-dose atorvastatin (80
mg). Again, after a mean follow-up of 4.8
years, the treatment arm failed to show a
superior reduction in the occurrence of
major coronary events but did show a re
duction in nonfatal acute myocardial in
farction, coronary revascularization, and
peripheral vascular disease (29). These
were corroborated by several trials exam
ining surrogate cardiovascular disease
markers such as intimal media thickness
(as previously described) (25) and intra
vascular ultrasound to measure atheroma
volume progression (14).

None of the clinical outcome trials
were treat-to-target LDL trials. All were
based on a fixed-dose statin algorithm
disregarding the reduction in LDL
achieved. Thus, it would not be wholly
adequate to blame the mere reduction in
LDL for the beneficial effect noted. As
proven by the Pravastatin or Atorvastatin
Evaluation and Infection Therapy
(PROVE-IT TIMI22) trial and others,
at least part of the statin effect can be ana
lyzed through its reduction of other sur
rogate markers such as CRP (26,30,31). A
more prudent evidence-based approach
would support a fixed high-dose atorva
stin regimen for all diabetic patients
with proven coronary heart disease with
an exclusion criteria of initial LDL chole
sterol <70 mg% (due to lack of evi
dence) (Table 4).

Currently, trials that try to answer
some of the questions raised above are
under way. The IMPROVE-IT trial [Ex
amining Outcomes in Subjects With
Acute Coronary Syndrome: Vytorin
(Eezetimibe/Simvastatin) versus Simvasta
tin], programmed to end by 2011, will
assess the additive value of ezetimibe
therapy to statin therapy, in high-risk pa
tients presenting with acute coronary syn
drome (32). HPS2-THRIVE (Treatment of
LDL to Reduce the Incidence of Vascular
Events) and AIM-HIGH (Athero-thrombo
sis Intervention in Metabolic syndrome
with low HDL/High triglyceride and Im
pact on Global Health Outcomes study)
### Table 3—High-dose statin secondary prevention trials

| Intervention | n | Primary outcome composition | Results |
|--------------|---|----------------------------|---------|
| PROVE-IT TIMI22 (15) | 4,162 (18% suffered from diabetes) | Death from any cause, myocardial infarction, unstable angina requiring rehospitalization, revascularization, and stroke | A 16% reduction in the hazard ratio in favor of atorvastatin in the total cohort \((P = 0.005; 95\% \text{ CI } 5–26\%); \) a nonsignificant 5.8% reduction in the diabetic patient subgroup |
| Treating to New Targets (TNT) study (27) | 1,501 patients with diabetes | Time to first major cardiovascular event, defined as death from coronary heart disease, nonfatal non–procedure-related myocardial infarction, resuscitated cardiac arrest, or fatal or nonfatal stroke | 25% reduction in the rate of major cardiovascular events in the high-dose group \((\text{hazard ratio } 0.75, 95\% \text{ CI } 0.58–0.97, P = 0.026)\) |
| A to Z (28) | 4,497 | Cardiovascular death, nonfatal myocardial infarction, readmission for acute coronary syndrome, and stroke | 16.7% in the placebo plus simvastatin group vs. 14.4% in the simvastatin-only group experienced the primary end point \((\text{hazard ratio } 0.89, 95\% \text{ CI } 0.76–1.04, P = 0.14)\); from 4 months through the end of the study, the primary end point was significantly reduced in the simvastatin-only group \((\text{HR } 0.75, 95\% \text{ CI } 0.60–0.95, P = 0.02)\) |
| IDEAL trial (29) | 8,888 | Major coronary event, including coronary death, confirmed nonfatal acute myocardial infarction, or cardiac arrest with resuscitation | 10.4% major coronary events with simvastatin as opposed to 9.3% with atorvastatin \((\text{HR } 0.89, 95\% \text{ CI } 0.78–1.01, P = 0.07)\); nonfatal acute myocardial infarction occurred in 7.2 and 6.0% in the two groups \((\text{HR } 0.83, 95\% \text{ CI } 0.71–0.98, P = 0.02)\); major cardiovascular events occurred in 608 and 533 in the two groups, respectively \((\text{HR } 0.87, 95\% \text{ CI } 0.77–0.98, P = 0.02)\); occurrence of any coronary event was reported in 1,059 simvastatin and 898 atorvastatin patients \((\text{HR } 0.84, 95\% \text{ CI } 0.76–0.91, P < 0.001)\) |
both include high-risk patients (including patients with diabetes and documented vascular disease) and examine a possible additive effect of a new extended-release niacin formulation to statin therapy on “hard” cardiovascular outcomes (i.e., time to first major vascular event in HPS2-THRIVE and composite of cardiovascular death, nonfatal myocardial infarction, nonhemorrhagic stroke, and hospitalization for high-risk acute coronary syndrome with objective evidence of ischemia in AIM-HIGH), targeting not only a preliminary reduction in LDL but also further niacin-induced elevation of HDL (33,34). A fourth study is the lipid treatment arm of the ACCORD trial (Action to Control Cardiovascular Risk in Diabetes) examining whether a combined change in the atherogenic lipid profile (i.e., reducing LDL and triglycerides while elevating HDL) using a combination of statins and fibrates will reduce cardiovascular outcomes in individuals with type 2 diabetes and good glycemic control (33). The JUPITER trial (Justification for the Use of statins in Primary prevention: an Intervention Trial Evaluating Rosuvastatin) is a statin-based trial that targets individuals with high CRP levels and initial low LDL cholesterol levels (LDL cholesterol <130 mg/dl (<3.36 mmol/l) and high-sensitivity CRP >2 mg/l) in primary prevention of cardiovascular outcomes (35,36). The trial was recently stopped early, after a median follow-up of 1.9 years, due to a significant reduction in the primary end point (combined primary end point of myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina, or death from cardiovascular causes) (0.77 and 1.36 per 100 person-years of follow-up in the rosuvastatin and placebo groups, respectively; hazard ratio for rosuvastatin, 0.56; 95% CI 0.46–0.69; \(P < 0.00001\)) (31). Although these trials may shed light on the additive effects of other lipid-altering drugs and cardiovascular risk markers, only the AIM-HIGH is planned as a treat-to-target trial (using simvastatin and ezetimibe to reach an LDL cholesterol <80 mg%/yet this approach will be taken in both control and study groups) (37). Indeed, although common in trials examining glycemic control, no other treat-to-target statin trials are expected in the near future. Furthermore, because of the already-proven efficacy of statin therapy and the costliness of such trials, the chances of future trials planned in this manner are slim.

### Table 4—ADA standards of clinical care recommendations versus evidence-based suggestions for revised recommendations

| ADA standards of clinical care recommendations | Suggestion for revised recommendations |
|-----------------------------------------------|---------------------------------------|
| 1. Statin therapy should be added to lifestyle therapy, regardless of baseline lipid levels, for diabetic patients: All of the ADA recommendations and the following: | a. With overt CVD (A level of evidence as described in the ADA evidence-grading system; Table 1). The primary goal is an LDL cholesterol <100 mg/dl (<2.6 mmol/l) (A). A lower LDL cholesterol goal of 70 mg/dl (<1.8 mmol/l), using a high dose of a statin, is an option (E). |
| b. Without CVD who are over the age of 40 years and have one or more other CVD risk factors. The primary goal is an LDL cholesterol <100 mg/dl (<2.6 mmol/l) (A). Type 2 diabetes under the age of 32 years (or 38 years in women) or type 1 diabetes under the age of 30 years (E). | 2. For lower-risk patients than those specified above (e.g., without overt CVD and under the age of 40), statin therapy should be considered in addition to lifestyle therapy (E). |
| c. With overt CVD (A level of evidence as described in the ADA evidence-grading system; Table 1). The primary goal is an LDL cholesterol <100 mg/dl (<2.6 mmol/l) (A). A lower LDL cholesterol goal of 70 mg/dl (<1.8 mmol/l), using a high dose of a statin, is an option (E). | 3. If drug-treated patients do not reach the above targets on maximal tolerated statin therapy, a reduction in LDL cholesterol of >40% from baseline is an alternative therapeutic goal (A). |
| d. Statin therapy is contraindicated in pregnancy (E). | 4. Combination therapy using statins and other lipid-lowering agents may be considered to achieve lipid targets but has not been evaluated in outcome studies for either CVD outcomes or safety (E). |
| e. Secondary prevention Consider a fixed high-dose 80-mg atorvastatin regimen for all diabetic patients with proven CHD and LDL cholesterol >100 mg%/ (C). | 5. Statin therapy is contraindicated in pregnancy (E). |
| f. and no apparent CVD risk factors and short duration of disease (<10 years) Type 2 diabetes under the age of 32 years (or 38 years in women) or type 1 diabetes under the age of 30 years (C). | 6. All of the ADA recommendations and the following: |
| g. Consider statin therapy in all individuals with diabetes unless they have all of the following exclusion criteria (C): | |
| h. Consider statin therapy in all individuals with diabetes unless they have all of the following exclusion criteria (C): | |
| i. Consider statin therapy in all individuals with diabetes unless they have all of the following exclusion criteria (C): | |
| j. Consider statin therapy in all individuals with diabetes unless they have all of the following exclusion criteria (C): | |
CONCLUSIONS — Both in primary prevention and in the very-high-risk patients, it seems that statins reduce major cardiovascular events irrespective (at least in part) of the baseline and post-therapy LDL levels achieved. Should statins be generally prescribed in a fixed-dose manner? We would not go so far as to suggest that, but indeed, in the diabetic individual whose LDL cholesterol is seemingly within normal limits, this should be considered. The indication for statin therapy in diabetic individuals should not rely solely on LDL levels but on the inherent cardiovascular risk that accompanies this disease (even if goal LDL levels are met).

We believe that the standards of care for individuals with diabetes should mirror the evidence. Replacing a fixed-dose statin trial scheme with a treat-to-target LDL guideline is controversial. This inherent problem of the current guidelines should be amended. Evidence based on “hard” outcome trials of statin use should guide our treatment goals and considerations, not epidemiologic or extrapolated LDL-based data.

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