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.

Published 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 *not* 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

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Table 1—*ADA evidence grading system for clinical practice recommendations*

A	Clear evidence from well-conducted generalizable randomized controlled trials that are adequately powered, including: • Evidence from a well-conducted multicenter trial • Evidence from a meta-analysis that incorporated quality ratings in the analysis Compelling nonexperimental evidence, i.e., "all or none" rule developed by the Centre for Evidence-Based Medicine at Oxford Supportive evidence from well-conducted randomized controlled trials that are adequately powered, including: • Evidence from a well-conducted trial at one or more institutions • Evidence from a meta-analysis that incorporated quality ratings in the analysis
B	Supportive evidence from well-conducted cohort studies, including: • Evidence from a well-conducted prospective cohort study or registry • Evidence from a well-conducted meta-analysis of cohort studies Supportive evidence from a well-conducted case-control study
C	Supportive evidence from poorly controlled or uncontrolled studies, including: • Evidence from randomized clinical trials with one or more major or three or more minor methodological flaws that could invalidate the results • Evidence from observational studies with high potential for bias (such as case series with comparison with historical controls) • Evidence from case series or case reports
D	Conflicting evidence with the weight of evidence supporting the recommendation
E	Expert consensus or clinical experience

Adapted from the American Diabetes Association (1).

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 (conferring 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, recanalization, 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

Table 2—*Primary prevention trials and meta-analysis of statin use in diabetic individuals with no other CVD risk factors*

	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-canalization, 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 ≤70 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 cholesterol reduction (defined as the composite outcome of myocardial infarction or coronary death, stroke, or coronary revascularization) (0.79, 99% CI 0.72–0.86; $P < 0.0001$) (these results did not change dramatically after incorporation of the ASPEN results; a 20% risk reduction was calculated). Subgroup analysis revealed this reduction was consistent irrespective of whether patients had prior cardiovascular disease, other CVD risk factors (hypertension, smoking, 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, isolated 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 disease (<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 surrogate marker for CVD progression (25). Yet, until "hard" major vascular event data are published, we feel that the initial statin dose should be fixed and based on published clinical trial data (i.e., 10 mg atorvastatin or 40 mg simvastatin), thus changing the current concept of treat-to-target LDL with statins in this subset of patients.

SECONDARY PREVENTION: HOW LOW SHOULD WE GO?

— In patients with overt CVD, the guidelines state an optional goal LDL of 70 mg%. This recommendation is based on several recently published trials that examined the effect of aggressive LDL lowering therapy (i.e., high dose statin therapy) in high risk populations of patients (Table 3). In the PROVE-IT TIMI 22 trial, 4,162 patients 10 days after an acute coronary syndrome (acute ST-segment elevation myocardial infarction [STEMI], non–ST-segment elevation myocardial infarction [NSTEMI], or high-risk unstable angina) were randomized to standard 40 mg pravastatin treatment or high dose/aggressive 80 mg atorvastatin treatment (15). Patients were followed for 18 to 36 months and achieved an average LDL cholesterol level of 62 mg% in the atorvastatin group and 95 mg% in the pravastatin group. In the aggressive therapy group versus the control group, a significant 16% reduction in the primary end point (a composite of death from any cause, myocardial infarction, unstable angina requiring re-hospitalization, revascularization and stroke) was noted. 18% of the ~1,600 patients in each treatment arm suffered from diabetes and showed similar risk reduction to that of the general cohort. A post hoc analysis of the PROVE-IT TIMI 22 trial data revealed a reduction not only in LDL cholesterol but also in CRP levels. This reduction in CRP was significantly associated with a reduction in cardiovascular events irrespective of the associated LDL reduction (26).

Another important trial was the Treating to New Targets (TNT) study (27). In one arm of this study, a total of 1,501 patients with diabetes, stable coronary heart disease, and LDL levels <130 mg% were randomized to receive low-dose (10 mg) or high-dose (80 mg) atorvastatin and followed for 4.9 years. At the end of the study, LDL levels in the low-dose group were 98 versus 77 mg% in the high-dose group. This was associated with a significant 25% reduction in the rate of major cardiovascular events (defined as death from coronary heart disease, nonfatal non–procedure-related myocardial infarction, resuscitated cardiac arrest, or fatal or nonfatal stroke) in the high-dose versus the low-dose group.

Similar interventions were done in the A to Z trial and the IDEAL trial. In the A to Z trial, a little over 2,200 patients with acute coronary syndrome were randomized to placebo for 4 months and then 20 mg simvastatin (standard therapy) or aggressively with 40 mg simvastatin for 1 month starting immediately after enrollment and then increased to 80 mg. Follow-up was for at least 6 months and up to 24 months. LDL in the standard treatment group was reduced to 77 versus 63 mg% in the intensive therapy after 8 months of treatment. Although not statistically significant, a trend toward a reduction in the primary outcome (comprising a composite of cardiovascular death, nonfatal myocardial infarction, readmission for acute coronary syndrome, and stroke) was observed in the intensive treatment arm (28). In the IDEAL trial, 8,888 patients after myocardial infarction were randomized to receive low-dose simvastatin (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 reduction in nonfatal acute myocardial infarction, coronary revascularization, and peripheral vascular disease (29). These were corroborated by several trials examining surrogate cardiovascular disease markers such as intimal media thickness (as previously described) (25) and intravascular 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 analyzed through its reduction of other surrogate markers such as CRP (26,30,31). A more prudent evidence-based approach would support a fixed high-dose atorvastatin regimen for all diabetic patients with proven coronary heart disease with an exclusion criteria of an initial LDL cholesterol <70 mg% (due to lack of evidence) (Table 4).

Currently, trials that try to answer some of the questions raised above are under way. The IMPROVE-IT trial [Examining Outcomes in Subjects With Acute Coronary Syndrome:Vytorin (Ezetimibe/Simvastatin) versus Simvastatin], programmed to end by 2011, will assess the additive value of ezetimibe therapy to statin therapy, in high-risk patients presenting with acute coronary syndrome (32). HPS2-THRIVE (Treatment of HDL to Reduce the Incidence of Vascular Events) and AIM-HIGH (Athero-thrombosis Intervention in Metabolic syndrome with low HDL/High triglyceride and Impact on Global Health Outcomes study)

Table 3—*High-dose statin secondary prevention trials*

	Intervention	*n*	Primary outcome composition	Results
PROVE-IT TIMI22 (15)	10 days after an acute coronary syndrome (acute STEMI, NSTEMI, or high-risk unstable angina) randomized to 40 mg pravastatin or 80 mg atorvastatin	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% CI 5–26%); a nonsignificant 5.8% reduction in the diabetic patient subgroup
Treating to New Targets (TNT) study (27)	Patients with diabetes, stable coronary heart disease, and LDL levels <130 mg% randomized to 10 or 80 mg atorvastatin and followed for 4.9 years	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 (hazard ratio 0.75 [95% CI 0.58–0.97], $P = 0.026$)
A to Z trial (28)	Patients with acute coronary syndrome randomized to 40 mg/day simvastatin for 1 month followed by 80 mg/day thereafter, or placebo for 4 months followed by 20 mg/day simvastatin	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 (hazard ratio [HR] 0.89; 95% 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 (HR 0.75; 95% CI 0.60–0.95; $P = 0.02$)
IDEAL trial (29)	Patients with a history of acute myocardial infarction, randomized to atorvastatin 80 mg or simvastatin 20 mg	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 (HR 0.89; 95% CI 0.78–1.01; $P = 0.07$); nonfatal acute myocardial infarction occurred in 7.2 and 6.0% in the two groups (HR 0.83; 95% CI 0.71–0.98; $P = 0.02$); major cardiovascular events occurred in 608 and 533 in the two groups, respectively (HR 0.87; 95% CI 0.77–0.98; $P = 0.02$); occurrence of any coronary event was reported in 1,059 simvastatin and 898 atorvastatin patients (HR 0.84; 95% 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 suggestion 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: 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).	All of the ADA recommendations and the following:	
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).	Primary prevention	Consider statin therapy in all individuals with diabetes unless they have **all** of the following exclusion criteria (C):
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 if LDL cholesterol remains >100 mg/dl or in those with multiple CVD risk factors (E).		Type 2 diabetes under the age of 32 years (or 38 years in women) or type 1 diabetes under the age of 30 years
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).		**and** short duration of disease (<10 years)
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).	Secondary prevention	**and** no apparent CVD risk factors 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).		

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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References

1. American Diabetes Association. Standards of medical care in diabetes: 2008. Diabetes Care 2008;31(Suppl. 1):S12–S54
2. Collins R, Armitage J, Parish S, Sleigh P, Peto R. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. Lancet 2003; 361:2005–2016
3. Knopp RH, d'Emden M, Smilde JG, Pocock SJ. Efficacy and safety of atorvastatin in the prevention of cardiovascular end points in subjects with type 2 diabetes: the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in non-insulin-dependent diabetes mellitus (ASPEN). Diabetes Care 2006;29:1478–1485
4. Sever PS, Poulter NR, Dahlof B, Wedel H, Collins R, Beevers G, Caulfield M, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Ostergren J. Reduction in cardiovascular events with atorvastatin in 2,532 patients with type 2 diabetes: Anglo-Scandinavian Cardiac Outcomes Trial–lipid-lowering arm (ASCOT-LLA). Diabetes Care 2005;28: 1151–1157
5. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ, Thomason MJ, Mackness MI, Charlton-Menys V, Fuller JH. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet 2004;364:685–696
6. Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med 1998;339:229–234
7. Deeg MA, Buse JB, Goldberg RB, Kendall DM, Zagar AJ, Jacober SJ, Khan MA, Perez AT, Tan MH. Pioglitazone and rosiglitazone have different effects on serum lipoprotein particle concentrations and sizes in patients with type 2 diabetes and dyslipidemia. Diabetes Care 2007;30: 2458–2464
8. Stamler J, Wentworth D, Neaton JD. Is relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356,222 primary screenees of the Multiple Risk Factor Intervention Trial (MRFIT). JAMA 1986;256:2823–2828
9. Cohen JC, Boerwinkle E, Mosley TH Jr, Hobbs HH. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. N Engl J Med 2006;354:1264–1272
10. Simons LA, Simons J, Friedlander Y, McCallum J. Cholesterol and other lipids predict coronary heart disease and ischaemic stroke in the elderly, but only in those below 70 years. Atherosclerosis 2001;159:201–208
11. Ingelsson E, Schaefer EJ, Contois JH, McNamara JR, Sullivan L, Keyes MJ, Pencina MJ, Schoonmaker C, Wilson PW, D'Agostino RB, Vasan RS. Clinical utility of different lipid measures for prediction of coronary heart disease in men and women. JAMA 2007;298:776–785
12. Keech A, Simes RJ, Barter P, Best J, Scott R, Taskinen MR, Forder P, Pillai A, Davis T, Glasziou P, Drury P, Kesaniemi YA, Sullivan D, Hunt D, Colman P, d'Emden M, Whiting M, Ehnholm C, Laakso M. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. Lancet 2005;366:1849–1861
13. Kastelein JJ, Akdim F, Stroes ES, Zwinderman AH, Bots ML, Stalenhoef AF, Visseren FL, Sijbrands EJ, Trip MD, Stein EA, Gaudet D, Duivenvoorden R, Veltri EP, Marais AD, de Groot E. Simvastatin with or without ezetimibe in familial hypercholesterolemia. N Engl J Med 2008;358: 1431–1443
14. Nissen SE, Tuzcu EM, Schoenhagen P, Brown BG, Ganz P, Vogel RA, Crowe T, Howard G, Cooper CJ, Brodie B, Grines CL, DeMaria AN. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. JAMA 2004;291:1071–1080
15. Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, Joyal SV, Hill KA, Pfeffer MA, Skene AM. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med 2004;350:1495–1504
16. Treasure CB, Klein JL, Weintraub WS, Talley JD, Stillabower ME, Kosinski AS, Zhang J, Boccuzzi SJ, Cedarholm JC, Alexander RW. Beneficial effects of cholesterol-lowering therapy on the coronary endothelium in patients with coronary artery disease. N Engl J Med 1995;332:481–487
17. Rosenson RS, Tangney CC. Antiatherothrombotic properties of statins: implications for cardiovascular event reduction. JAMA 1998;279:1643–1650
18. Corsini A, Ferri N, Cortellaro M. Are pleiotropic effects of statins real? Vasc Health Risk Manag 2007;3:611–613
19. Patti G, Pasceri V, Colonna G, Miglionico M, Fischetti D, Sardella G, Montinaro A, Di Sciascio G. Atorvastatin pretreatment improves outcomes in patients with acute coronary syndromes undergoing early percutaneous coronary intervention: results of the ARMYDA-ACS randomized trial. J Am Coll Cardiol 2007;49:1272–1278
20. Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. Diabetes Care 1993;16: 434–444
21. Mihaylova B, Briggs A, Armitage J, Parish S, Gray A, Collins R. Lifetime cost effectiveness of simvastatin in a range of risk groups and age groups derived from a randomised trial of 20,536 people. BMJ 2006;333:1145
22. Krolewski AS, Kosinski EJ, Warram JH, Leland OS, Busick EJ, Asmal AC, Rand LI, Christlieb AR, Bradley RF, Kahn CR. Magnitude and determinants of coronary artery disease in juvenile-onset, insulin-dependent diabetes mellitus. Am J Cardiol 1987;59:750–755
23. Booth GL, Kapral MK, Fung K, Tu JV. Relation between age and cardiovascular disease in men and women with diabetes compared with non-diabetic people: a population-based retrospective cohort study. Lancet 2006;368:29–36
24. Kearney PM, Blackwell L, Collins R, Keech A, Simes J, Peto R, Armitage J, Baigent C. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. Lancet 2008;371:117–125
25. Skyler JS, Bergenstal R, Bonow RO, Buse J, Deedwania P, Gale EA, Howard BV, Kirk-

man MS, Kosiborod M, Reaven P, Sherwin RS. Intensive glycemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA diabetes trials: a position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology Foundation and the American Heart Association. Diabetes Care 2009;32:187–192
26. Ridker PM, Cannon CP, Morrow D, Rifai N, Rose LM, McCabe CH, Pfeffer MA, Braunwald E. C-reactive protein levels and outcomes after statin therapy. N Engl J Med 2005;352:20–28
27. Shepherd J, Barter P, Carmena R, Deedwania P, Fruchart JC, Haffner S, Hsia J, Breazna A, LaRosa J, Grundy S, Waters D. Effect of lowering LDL cholesterol substantially below currently recommended levels in patients with coronary heart disease and diabetes: the Treating to New Targets (TNT) study. Diabetes Care 2006; 29:1220–1226
28. de Lemos JA, Blazing MA, Wiviott SD, Lewis EF, Fox KA, White HD, Rouleau JL, Pedersen TR, Gardner LH, Mukherjee R, Ramsey KE, Palmisano J, Bilheimer DW, Pfeffer MA, Califf RM, Braunwald E. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. JAMA 2004;292:1307–1316
29. Gaede P, Lund-Andersen H, Parving HH, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. N Engl J Med 2008;358:580–591
30. Nissen SE, Tuzcu EM, Schoenhagen P, Crowe T, Sasiela WJ, Tsai J, Orazem J, Magorien RD, O'Shaughnessy C, Ganz P. Statin therapy, LDL cholesterol, C-reactive protein, and coronary artery disease. N Engl J Med 2005;352:29–38
31. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, Koenig W, Libby P, Lorenzatti AJ, MacFadyen JG, Nordestgaard BG, Shepherd J, Willerson JT, Glynn RJ. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008;359:2195–2207
32. Drazen JM, Morrissey S, Curfman GD. Rosiglitazone: continued uncertainty about safety. N Engl J Med 2007;357:63–64
33. Mitka M. Therapies aim to boost "good" cholesterol. JAMA 2008;299:509–510
34. Windler E, Schoffauer M, Zyriax BC. The significance of low HDL-cholesterol levels in an ageing society at increased risk for cardiovascular disease. Diab Vasc Dis Res 2007;4:136–142
35. Ridker PM, Fonseca FA, Genest J, Gotto AM, Kastelein JJ, Khurmi NS, Koenig W, Libby P, Lorenzatti AJ, Nordestgaard BG, Shepherd J, Willerson JT, Glynn RJ. Baseline characteristics of participants in the JUPITER trial, a randomized placebo-controlled primary prevention trial of statin therapy among individuals with low low-density lipoprotein cholesterol and elevated high-sensitivity C-reactive protein. Am J Cardiol 2007;100:1659–1664
36. Davignon J, Leiter LA. Ongoing clinical trials of the pleiotropic effects of statins. Vasc Health Risk Manag 2005;1:29–40
37. Psaty BM, Furberg CD. Rosiglitazone and cardiovascular risk. N Engl J Med 2007; 356:2522–2524