

Should every patient with diabetes receive a statin?

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Patients with diabetes mellitus have an increased risk of developing cardiovascular disease (CVD) [1,2]. It is well established that aggressive risk factor modification results in improved CVD outcomes in the diabetic population. One example of risk factor modification is lipid lowering therapy with statins, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors. This therapy has demonstrated significant cardiovascular (CV) event reduction [3]. Yet despite the widespread use of statin therapy in patients with diabetes, routine statin treatment in every diabetic patient, including those without history of CVD or with starting lipid profiles already at treatment goals, remains controversial.

There is a well-recognized linear relation between low-density lipoproteins cholesterol (LDL-C) levels and the event rates in all the major statin prevention trials. However, in the diabetic subgroups, the event rates in the statin-treated patients exceed those of the placebo-treated patients without diabetes. The justification for more aggressive LDL-C targets in patients with CVD is based on three large statin outcome trials: the Heart Protection Study (HPS) [4], the Treating to New Targets (TNT) study [5], and the Incremental Decrease in Endpoints Through Aggressive Lipid Lowering (IDEAL) study [6], which demonstrated conclusively the "lower is better" hypothesis but also identified the diabetic subgroup as a cohort of patients with high residual risk even on statin therapy. Overall, the diabetic population taking statins has a higher event rate than patients without diabetes taking placebo [7].

Relative risk reduction is the most frequent measure of the benefits of lipid lowering therapy in statin trials. A 1% decrease in LDL-C is generally associated with a 1% relative risk reduction in CV events [4-7]. In the subgroup of patients with type 2 diabetes, the relative risk reduction is similar to that in the non-diabetic population, but there is generally a greater absolute risk reduction, especially in patients with documented CVD, because of the much higher baseline risk of CV events [7]. Therefore, in patients with type 2 diabetes, absolute risk reduction, which determines the number

needed to treat to reduce events and thereby drives the cost and benefits of therapy, represents the better term to evaluate the overall benefits of treatment. In general, relative risk reduction is driven by the percent reduction in LDL-C whereas absolute risk reduction is determined by the baseline risk for CV events. Since patients with type 2 diabetes have a much higher baseline risk for CV events, the residual risk remains elevated despite statin therapy (Figure) [4-8].

Based on the concept of treating the patients with the greatest absolute risk most aggressively, the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) identified treatment goals for patients at high risk for CV events: including those with CVD, diabetes mellitus, or a 10-year coronary heart disease (CHD) risk of >20%. The recommendations established an LDL-C goal <70 mg/dl and non-high-density lipoprotein cholesterol (non-HDL-C) goal of <100 mg/dl for those patients at the highest risk of CHD [4,9,10].

Several trials have confirmed the goals of the NCEP ATP III, demonstrating that treatment to more aggressive LDL-C results in additional risk reduction. The TNT trial [11] showed that lowering LDL-C to mean levels of 77 mg/dl with atorvastatin 80 mg/24 h reduced the rate of major CV events by 22% compared with atorvastatin 10 mg/24 h ($p = 0.026$) over a median follow up of 5 years. These results are similar to those seen in the HPS trial which found a 22% reduction in the risk of CV events in patients with CHD or diabetes and a baseline LDL-C of <100 mg/dl, when treated with 40 mg simvastatin daily. In HPS there was a similar risk reduction in patients regardless of baseline LDL-C levels [4]. The most recent clinical trial of aggressive cholesterol-lowering treatment using high-dose statin, the IDEAL study, compared 20–40 mg simvastatin daily with 80 mg atorvastatin in patients with CHD. The study demonstrated a 22% reduction in LDL-C levels and a 13% reduction in the primary endpoint of major coronary events in patients. Although this reduction did not achieve statistical significance, the trend is similar to previously reported trials [6].

In the Collaborative Atorvastatin Diabetes Study (CARDS) trial [12], statins for primary prevention of CVD were investigated in patients with type 2 diabetes without high LDL-C. Atorvastatin, 10 mg daily, was safe and efficacious in reducing the risk of first CV events. During a follow-up of 3.9 years, a significant reduction of 37% of major CV events was found. Even in diabetic patients with a baseline LDL-C of <100 mg/dl, the treatment with atorvastatin, 10 mg once daily,

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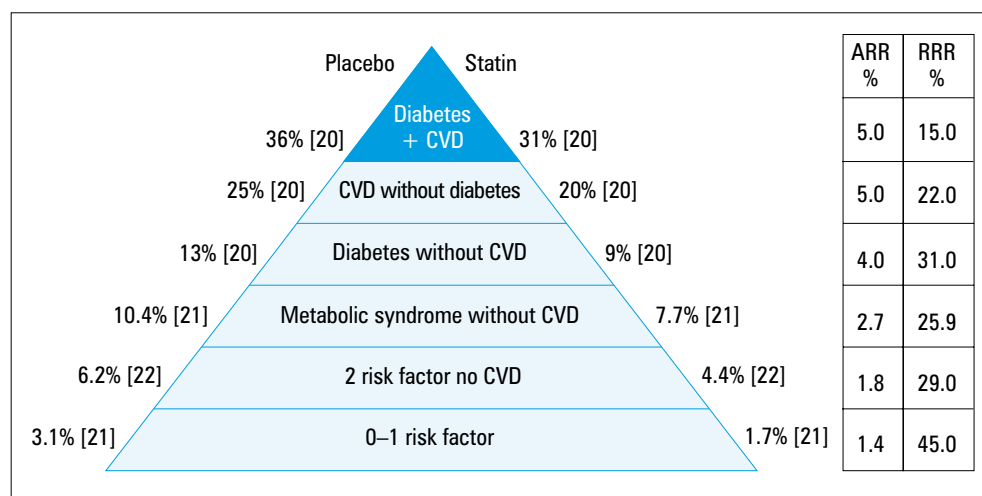
Received: May 6, 2008. Accepted: June 9, 2008.

Conflict of interest: none declared.

Pol Arch Med Wewn. 2008; 118 (7-8): 398-401

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Fig. Five-year absolute risk of future cardiovascular disease events. CVD – cardiovascular disease



led to a relative 37% risk reduction in the first occurrence of acute CHD events, coronary revascularization, or stroke. The American Diabetes Association (ADA) 2008 Standards of Medical Care in Diabetes recommends that statin therapy be added to lifestyle therapy, regardless of baseline lipid levels, for all diabetic patients with overt CVD or those without CVD who are over the age of 40 and have CVD risk factors [13].

But despite aggressive LDL-C lowering therapy, there remains a significant residual risk of morbidity and mortality in patients with diabetes. In fact, the event rates in subgroups of high risk patients, such as those with diabetes, are often found to be higher in the statin treatment group than the placebo group [4,14–16]. Recognizing this observation there is an emerging need to identify new treatment targets, in addition to lowering LDL-C, in this high risk group.

In patients with diabetes, there is a high prevalence of elevated triglycerides (TG), low HDL-C, and an increase in the number of small, dense LDL particles. This clustering of lipid abnormalities has been given multiple names, including, recently, the atherogenic index of plasma, defined as $\log(TG/HDL-C)$, with a ratio of ≥ 3.5 reflective of a high prevalence of insulin resistance [17]. An elevated TG/HDL-C ratio has been demonstrated to be a good indication of outcome benefits with fibrates and therefore may help guide the choice for lipid-altering therapy in addition to statin treatment. In addition, pioglitazone has been shown to significantly reduce the atherogenic index of plasma in patients with type 2 diabetes [18]. Alternatively, more precise measurements of LDL particle size are available to access increased residual risk in patients with type 2 diabetes.

Apolipoprotein B (apo B) levels have been advocated as a better measure of CVD risk than either LDL-C or non-HDL-C and have the advantage of providing a target for a single parameter as opposed to multiple targets of LDL-C and non-HDL-C, if TG exceed 200 mg/dl [19]. Apo B reflects all the atherogenic lipoproteins and has con-

sistently been demonstrated to predict CVD risk better than LDL-C in outcome trials [20]. An apo B level <90 mg/dl has been proposed as an alternative to the NCEP ATP III goal of LDL-C <100 mg/dl and non-HDL-C <130 mg/dl [17]. On the basis of an evaluation of $>22,000$ patients receiving statin therapy in clinical trials, if apo B was <90 mg/dl, almost all the patients were at the dual goal of LDL-C <100 and non-HDL-C <130 mg/dl [19]. Alternatively, many high-risk patients at the NCEP ATP III LDL-C and non-HDL-C goals had apo B levels >90 mg/dl. A recent ADA/ACC Consensus statement recommends an apo B <80 mg/dl for high risk patients with type 2 diabetes mellitus [21].

The apo B/apo A1 ratio has been shown to have the greatest predictive value in epidemiologic and outcome trials, and a goal of <0.7 has been proposed for high-risk patients [20].

High sensitivity C-reactive protein (hs-CRP) has been shown in multiple trials to enhance risk prediction independently and additively to LDL-C [22]. In both the PROVE-IT and A to Z trials with acute coronary syndromes, the dual goal of LDL-C <70 mg/dl and hs-CRP <20 mg/l was associated with the lowest risk for recurrent CV events [23]. Because hs-CRP is reflective of an increased risk factor milieu, this inflammatory marker, if elevated, may help guide the intensification of risk factor modification. In the PROVE-IT trial, in the cohort of patients with all the major risk factors corrected, the hs-CRP was low, and the event rates were also concurrently reduced. The JUPITER trial [24] was designed to determine whether treatment with rosuvastatin 20 mg daily can prevent CVD among a cohort of patients with an LDL-C <130 mg/dl but hs-CRP >2.0 mg/l. The study has been stopped early because of a reported unequivocal reduction in CV morbidity and mortality amongst patients who received rosuvastatin when compared to placebo. The results of this study have not yet been published.

Yet achieving lipid-lowering treatment goals in the diabetic population continues to be a clinical challenge. Notably, less than one-half of patients in the atorvastatin 80 mg arm

of TNT achieved an LDL-C goal of <70 mg/dl. This suggests that statin therapy alone is often not sufficient in achieving target goals in the patients with diabetes. The NEPTUNE II survey demonstrated this difficulty [25]. 75% of the CVD population surveyed were classified as high risk and therefore eligible for LDL-C goals of <70 mg/dl. However of this group, only 18% of patients achieved this LDL-C goal.

Aggressive statin therapy should still be considered the cornerstone of initial therapy in patients with diabetes. Clinical trial evidence in statin trials have demonstrated both safety and event reduction of higher statin doses. Although statins have a 40% higher rate of adverse effects than placebo, the rates of significant musculoskeletal and hepatic toxicity are very low in high dose statin therapy [26]. This increased risk of liver enzyme elevations or myopathy does not correlate with level of LDL-C reduction. Rather, plots of LDL-C reduction by dose of statin indicate that the toxicity rate increases once a specific dose threshold is exceeded [27]. In general, statin doses are very safe until the 40 mg dose, and the titration from 40 to 80 mg is associated with a 3-fold increase in liver toxicity or myopathy [7]. This suggests that combination therapy for patients on a 40 mg dose, rather than an increase in that statin dose, may be more effective in achieving LDL-C goals while remaining at an acceptable safety profile.

Ezetimibe, a cholesterol absorption inhibitor, added to statin therapy results in an additional 15% to 20% reduction in LDL-C [28]. This addition does not increase the risk of myopathy or liver toxicity beyond that of statin therapy alone. Furthermore the addition of ezetimibe to statin therapy has been shown to be significantly more effective in lowering LDL-C and achieving LDL-C target goals than doubling the statin monotherapy dose.

In patients with a mixed hyperlipidemia, levels of LDL-C alone do not adequately represent the risk associated with atherogenic lipoproteins. The NCEP ATP III guidelines have recommended a non-HDL-C goal of <100 mg/dl in addition to an LDL-C goal of <70 mg/dl as a secondary target of therapy in patients with serum TG levels >200 mg/dl. Statin treatment alone is often insufficient to achieve the non-HDL-C targets. In patients with persistent hypertriglyceridemia while on statin therapy, the addition of a TG-lowering agent, such as a fibrate, is recommended as a therapeutic option to reduce levels of non-HDL-C.

Historically, however, fibrate and statin combination therapy has been a source of safety concerns. The major reason combination therapy with fibrates is seldom clinically used is the perception of adverse safety associated with combining a statin and fibrate. Although there is an increase in reports of rhabdomyolysis with statin and fibrate combined therapy, this risk appears to be about fifteen times higher with gemfibrozil than for fenofibrate when used with statins [7]. Data from the FIELD trial suggests that combining fenofibrate with statins does not significantly increase the risk of myopathy in a cohort of patients with diabetes [29].

In summary, there is sufficient evidence of an effective reduction of CV events by secondary and primary prevention with statins in the high-risk group of diabetic patients regardless of baseline LDL-C levels. Treatment goals to reduce this risk include lowering the LDL-C to <70 mg/dl and non-HDL-C to <100 mg/dl. In addition new clinical markers are emerging as additional treatment targets, such as hs-CRP and apo B. Aggressive high-dose statins should remain the initial therapy for all patients with diabetes. However, statin treatment alone is often insufficient to achieve treatment goals highlighting the importance of combination therapy to further lower the risk of CV events in patients with diabetes.

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