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Cardiovascular drugs that increase the risk of new-onset diabetes

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The prevalence of type 2 diabetes is increasing worldwide, and diabetes is a strong adverse prognostic factor among patients with cardiovascular (CV) disease. Four classes of drugs that are commonly used for CV risk reduction, statins, niacin, thiazide diuretics, and β -blockers, have been shown to increase the risk of new-onset diabetes (NOD) by 9% to 43% in meta-analyses or large-scale clinical trials. Clinical predictors for drug-related NOD appear to be similar to the predictors that have been described for NOD unrelated to drugs: fasting blood glucose >100 mg/dL and features of the metabolic syndrome such as body mass index >30 kg/m², serum triglycerides >150 mg/dL, and elevated blood pressure, among others. The mechanisms whereby these drugs increase the risk of NOD are incompletely understood, although different hypotheses have been suggested. Lifestyle intervention consisting of diet and exercise has been shown in multiple studies to reduce the risk of NOD by approximately 50%, with persistent benefit during long-term follow-up. In patients at high risk for NOD, niacin should be avoided, and for hypertension, an angiotensin-converting enzyme inhibitor or even a β_1 -selective blocker might be a better choice than a standard β -blocker. For thiazide diuretics and particularly statins, benefit in terms of CV event reduction outweighs the risk of NOD. (Am Heart J 2014;167:421-8.)

Worldwide, the prevalence of type 2 diabetes continues to increase rapidly, with more than 371 million cases in the year 2012.¹ Diabetes is thus becoming a more prevalent risk factor for cardiovascular (CV) disease, and a higher proportion of patients with CV disease have diabetes. Among patients with CV disease, diabetes is a strong adverse prognostic factor. Controlling for blood pressure, low-density lipoprotein cholesterol, and glycosylated hemoglobin (HbA_{1c}) levels reduces CV risk in patients with diabetes; however, only a minority of them successfully attains these multiple goals,² despite recent increasing use of drug treatment.³

Within this context, it is troublesome that some of the drugs used to reduce CV risk have been shown either to increase the risk of new-onset diabetes (NOD) or to interfere with glucose control in patients with established diabetes. The purpose of this article is to review clinical

trial data for 4 commonly used classes of drugs, statins, niacin, thiazide diuretics, and β -blockers. For each drug class, an attempt will be made to quantify the benefit of treatment and potential harm based on clinical trial results and meta-analyses of trials. The data from these sources documenting the increased risk of NOD with these drugs are summarized in Figure 1.

Predictors of NOD

Studies in different populations have consistently identified the same cluster of risk factors for NOD. *Impaired fasting glucose* (IFG; defined as a fasting blood sugar from 100 to 125 mg/dL), a family history of diabetes, and features of the metabolic syndrome are associated with an increased risk of NOD.⁴ Lifestyle factors, low body mass index (BMI), diet, nonsmoking, moderate alcohol consumption, and regular physical activity were all associated with a reduced risk of NOD in a large cohort study, with BMI being the most important of these factors.⁵

Algorithms that predict the risk of NOD have been developed.⁶ These scores can be used to assess the risk of NOD using self-reported or routinely available clinical data, reserving laboratory testing for subjects at higher risk. Parental diabetes, obesity, and metabolic syndrome traits effectively predicted NOD in the Framingham Offspring Study cohort.⁷ The addition of variables that are more difficult to obtain, including a 2-hour post-oral glucose tolerance test glucose level, levels of fasting

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Figure 1

Meta-analyses and clinical trials of CV drugs that increase the risk of NOD. Included are a meta-analysis of statin vs placebo trials, a meta-analysis of intensive vs moderate statin treatment trials, 2 studies of niacin vs placebo, a meta-analysis of thiazide diuretics vs placebo, and a meta-analysis of β-blocker vs other blood pressure drugs.

insulin, and CRP levels, did not improve the discrimination of the clinical model.

Statins and NOD

In a meta-analysis of 13 large randomized placebo-controlled statin trials with 91,140 participants, of whom 4,278 developed diabetes during a mean follow-up of 4 years,⁸ statin treatment was associated with a 9% increased risk of diabetes (odds ratio [OR] 1.09, 95% CI 1.02-1.17). It was concluded from this meta-analysis that treatment for 225 patients with a statin for 4 years would result in one extra case of diabetes. The risk appeared to be similar for lipophilic and hydrophilic statins. Pravastatin or lovastatin was used in 7 of the 13 trials in this meta-analysis, and the results may thus underestimate the risk of NOD with higher doses of more potent statins.

The results of the Stroke Reduction by Aggressive Reduction in Cholesterol Levels (SPARCL) trial were not available for this meta-analysis. In that trial, placebo was compared with atorvastatin 80 mg/d in 4,731 patients over a median follow-up of 4.9 years.⁹ The risk of NOD was increased in the atorvastatin group (OR 1.34, 95% CI 1.05-1.71). Adding this trial to the previous meta-analysis increases the risk of NOD from 1.09 to 1.12 (95% CI 1.05-1.18).

A subsequent meta-analysis compared the risk of NOD between intensive and moderate-dose statin treatment across 5 trials involving 32,752 participants, of whom 2,749 developed NOD.¹⁰ Compared with moderate-dose therapy, intensive treatment was associated with a 12% increase in the risk of NOD (OR 1.12, 95% CI 1.04-1.22), but a 16% decrease (OR 0.84, 95% CI 0.75-0.94) in the risk of a first major CV event. The risk of NOD was similar for

simvastatin 80 mg and atorvastatin 80 mg compared with moderate treatment; however, high-dose atorvastatin significantly reduced CV events (OR 0.78, 95% CI 0.73-0.85) compared with moderate treatment, whereas high-dose simvastatin did not (OR 0.95, 95% CI 0.88-1.03). The authors calculated that one extra case of diabetes per year would occur for every 498 patients treated with an intensive vs a moderate dose, but that one fewer patients would experience a major CV event for every 155 patients treated per year.

In 3 large trials where atorvastatin 80 mg was compared with atorvastatin 10 mg (Treating to New Targets; TNT), simvastatin 10 to 20 mg (Incremental Decrease in Endpoints Through Aggressive Lipid Lowering; IDEAL), or placebo (Stroke Reduction by Aggressive Reduction in Cholesterol Levels; SPARCL), the same 4 clinical factors independently predicted NOD: fasting blood glucose (FBG) >100 mg/dL, triglycerides >150 mg/dL, BMI >30 kg/m², and a history of hypertension.⁹ These factors are similar to those that predict NOD in people not being treated with a statin, as discussed in the previous section. The risk of developing NOD for 5 years was <2% in each trial for patients with none of the 4 NOD risk factors, but increased to 25% or greater when all 4 were present.

In a subsequent report involving 15,056 participants from 2 of these trials (TNT and IDEAL), the risk of NOD was compared with CV event reduction according to the number of NOD risk factors at baseline.¹¹ Among 8,825 patients who had 0 or 1 NOD risk factor at baseline, NOD developed during 5 years of follow-up in 3.22% of those randomized to atorvastatin 80 mg and to 3.35% of those randomized to lower dose statin treatment. Among these patients at low risk for NOD, high-dose atorvastatin treatment was associated with a significant reduction in

Figure 2

Risk of NOD (top) and CV events (bottom) according to the number of NOD risk factors. The NOD risk factors are FBG >100 mg/dL, fasting triglycerides >150 mg/dL, BMI >30 kg/m², and history of hypertension. Atorva, atorvastatin; Simva, simvastatin. From Waters et al,¹¹ with permission.

major CV events (8.51% vs 9.80%, hazard ratio [HR] 0.87, 95% CI 0.775-0.995). Among 6,231 patients with 2 to 4 NOD risk factors, NOD developed in 14.32% of those in the high-dose atorvastatin group and in 11.86% of those in the low-dose groups (HR 1.24, 95% CI 1.08-1.42). Among these patients at high risk for NOD, the CV event rate was higher than that in those with none or 1 NOD risk factor, but was reduced 18% by high-dose atorvastatin compared with low-dose statin (10.07% vs 12.02%, HR 0.82, 95% CI 0.71-0.96). These relationships are depicted in Figure 2.

Similar results have been reported from the Justification for Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial,¹² using slightly different risk factors for NOD: metabolic syndrome, IFG, BMI >30 kg/m², and HbA_{1c} >6%. Study participants with 1 or more of these risk factors had a 28% increase in NOD compared with the placebo group (HR 1.28, 95% CI 1.07-1.54) during the mean follow-up period of 1.9 years, but they experienced a 39% decrease in the primary end point (HR 0.61, 95% CI 0.47-0.79). For patients without NOD risk factors, no increase in NOD was seen with rosuvastatin, but the primary end point was reduced by 52%.

In short-term studies in relatively small numbers of patients, statins have been shown to increase HbA_{1c} and insulin levels both in patients without and with diabetes. For example in a 2-month study, doses of atorvastatin

from 10 to 80 mg increased bA_{1c} by 0.2% to 0.3%, with no changes in FBG.¹³ In a randomized study of patients with established diabetes, HbA_{1c} increased by 0.3% with atorvastatin 20 mg for 4 months.¹⁴

In long-term placebo-controlled trials, the changes in HbA_{1c} levels have been smaller than the changes reported in short-term studies. In the Collaborative Atorvastatin Diabetes Study (CARDS), where 2,838 patients with type 2 diabetes were randomized to atorvastatin 10 mg/d or placebo and followed up for a median of 3.9 years,¹⁵ the adjusted mean difference in HbA_{1c} between the treatment groups at the end of the study was only 0.105% (*P* = .03). In the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-insulin-dependent Diabetes (ASPEN), where 2,410 patients with type 2 diabetes were randomized to atorvastatin 10 mg/d or placebo and followed up for 4 years, the changes in HbA_{1c} were identical, 0.2%, in the 2 treatment groups.¹⁶ A random sample of 1,087 participants with diabetes in the Heart Protection Study had HbA_{1c} measurements at baseline and after an average of 4.6 years of follow-up. The increase in HbA_{1c} was slightly but not statistically significantly higher in the simvastatin 40 mg group compared with placebo.¹⁷

Statins have been clearly shown to reduce CV events in patients with established diabetes.¹⁷⁻²⁰ The CARDS study was stopped early because of a 37% reduction in CV

events among patients with diabetes randomized to low-dose atorvastatin compared with placebo.¹⁸ A meta-analysis of 18,686 patients with diabetes from 14 trials concluded that the relative reduction in CV risk was similar in patients with and without diabetes.¹⁹ A subgroup analysis of the 1,501 patients in the TNT trial with diabetes at baseline showed a statistically significant reduction in CV events, with 80 mg compared with 10 mg of atorvastatin.²⁰

The mechanism whereby statins increase the risk of NOD is uncertain; however, several different possibilities have been advanced, as discussed in more detail elsewhere.²¹ Statins have been shown to decrease β -cell secretion of insulin in animal models.²² Statins may decrease insulin sensitivity by decreasing isoprenoids, which up-regulate glucose uptake.²³ Insulin-like growth factor proteins have been shown to decrease in a dose-dependent fashion after atorvastatin therapy, providing another potential mechanism whereby statins could worsen glucose tolerance.²⁴ Finally, in an animal model, statin-induced myopathy is associated with an increase in insulin resistance in muscle.²⁵

Niacin and NOD

The Coronary Drug Project was completed in 1975, but the results with respect to NOD were not published until 2013.²⁶ During a mean follow-up of 6.2 years, the incidence of NOD was 11.4% in niacin-treated patients and 8.62% in the placebo group (HR 1.37, 95% CI 1.12-1.68, $P = .012$). Randomization to niacin treatment was associated with an increase in NOD both in those with a normal FBG at baseline (6.8% vs 4.9%, HR 1.41, 95% CI 0.97-2.05, $P = .07$) and in those with IFG (19.8% vs 15.2%, HR 1.34, 95% CI 1.00-1.80, $P = .05$). Niacin also increased FBG in patients with type 2 diabetes at baseline. The dose of niacin in this trial was 3 g/d.

In the Heart Protection 2-Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) trial, 25,673 patients with established CV disease were randomized to placebo or to 2 g of extended-release niacin plus 40 mg/d of laropiprant, a prostaglandin inhibitor. The trial was stopped after a median follow-up of 3.9 years because of a lack of efficacy and an excess of serious adverse events.²⁷ New-onset diabetes developed in 9.1% of niacin/laropiprant patients without diabetes at baseline, compared with 7.3% in the placebo group (HR 1.27, 95% CI 1.14-1.41, $P < .0001$). Among the 8,299 patients with type 2 diabetes at randomization, 11.1% in the active treatment group and 7.5% in the placebo group (HR 1.55, 95% CI 1.34-1.78, $P < .0001$) developed a diabetic complication, the most common of which was hyperglycemia.

In the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) trial, 3,414 patients

with established CV disease were randomized to placebo or extended-release niacin 1.5 to 2.0 g/d and followed up for a mean of 3 years.²⁸ The trial was stopped because of a lack of efficacy. The incidence of NOD was not reported; however, 29 niacin-treated patients and 14 placebo-treated patients discontinued treatment because of an increased glucose level (1.7% vs 0.8%, HR 2.06, 95% CI 1.09-3.92, $P = .027$).

Niacin is known to increase insulin resistance, but the molecular mechanism has not been defined. In any case, the failure of niacin to reduce events in the AIM-HIGH and HPS2-THRIVE trials, along with high rates of drug intolerance and adverse effects, including NOD, should push niacin toward obsolescence.

Thiazide diuretics and NOD

Shortly after the introduction of thiazide diuretics in the 1950s, it became apparent that they could worsen the control of established type 2 diabetes²⁹ and increase the incidence of NOD.³⁰ Despite this, thiazide diuretics continue to be recommended as first-line therapy for hypertension,³¹ although at lower doses than those used in the early trials. Calibrating the risk of NOD from clinical trials of antihypertensive drugs is complicated because the comparator drug is rarely placebo and may itself have a beneficial or detrimental effect on NOD. Many trials evaluate combination therapy, for example, a thiazide plus a β -blocker. Hypertension is already a risk factor for NOD, and other features of the study population may make patients more or less susceptible to NOD, complicating comparisons across studies.

However, data from large antihypertensive drug trials indicate clearly that thiazide diuretics increase the incidence of NOD and that the risk is shared among chlorthalidone, hydrochlorthiazide, and bendroflumethiazide.³² The Antihypertensive and Lipid Lowering treatment to prevent Heart Attack Trial (ALLHAT) is typical of these trials;³³ patients were randomized to chlorthalidone, amlodipine, or lisinopril, and after 4 years of follow-up, the rates of NOD in the 3 treatment groups were 11.6%, 9.8%, and 8.1%, respectively. A network meta-analysis of 48 randomized groups from 22 clinical trials with 143,153 participants without diabetes at baseline stratifies the risk of NOD among the classes of antihypertensive drugs, as shown in Table.³⁴ Rates of NOD are lower for all classes of antihypertensive drugs compared with diuretics, with the exception of β -blockers.

Whether diuretic-associated NOD increases CV event rates is controversial. Despite an increased incidence of NOD in the diuretic arm of ALLHAT compared with the amlodipine and lisinopril arms, CV event rates did not differ among the 3 treatments.³³ No association was seen between diuretic-related changes in FBG or NOD at 2 years and CV or renal disease risk over the subsequent 2.9

Table. Effect of different classes of antihypertensive drugs on the incidence of NOD

Class	OR (95% CI)	P
Diuretic	1.00 (referent)	–
β-Blocker	0.90 (0.75-1.09)	.300
Placebo	0.77 (0.63-0.94)	.009
Calcium-channel blocker	0.75 (0.62-0.90)	.002
ACEI	0.67 (0.56-0.80)	<.0001
ARB	0.57 (0.46-0.72)	<.0001

P values are in comparison with diuretic.
Data adapted from Elliott and Meyer.³⁴

years.³⁵ With 4 additional years of follow-up, the ALLHAT investigators reported that thiazide-related NOD carried a lower risk for CV events than NOD developing in patients receiving either of the other 2 treatments.³⁶

In the Systolic Hypertension in the Elderly Program (SHEP), 4,732 patients who had been randomized to chlorthalidone or placebo were followed up for a mean of 14.3 years.³⁷ Chlorthalidone lowered CV mortality (19% vs 22%, HR 0.85, 95% CI 0.75-0.97). Diabetes at baseline and NOD developing in the placebo group were associated with an increased CV risk and an increased total mortality; however, NOD developing in the chlorthalidone group was not. Chlorthalidone reduced CV risk among patients with diabetes at baseline. These data from ALLHAT and SHEP suggest that the beneficial effects of thiazide diuretics in hypertension outweigh any harmful consequences of NOD.

On the other hand, studies with very long follow-up, 18 and 25 years, demonstrate that NOD exerts a negative impact in patients with hypertension.^{38,39} Furthermore, in an observational study of Swedish men, those with hypertension and those with an FBG increase between ages 50 and 60 years were more likely to develop myocardial infarction during 17 years of follow-up.⁴⁰ Among those treated for hypertension, mainly with thiazide diuretics and β-blockers, an increase in FBG was independently predictive of myocardial infarction.

The mechanism whereby thiazide diuretics increase the risk of NOD appears most likely to be related to hypokalemia.^{41,42} In an analysis of 59 clinical trials with 83 thiazide diuretic study arms,⁴¹ diuretic-associated change in blood potassium was inversely correlated with change in blood glucose ($r = -0.54$, $P < .01$). In SHEP, the risk of NOD during the first year of follow-up in chlorthalidone-treated patients was approximately double the risk in the placebo group,⁴² but statistical adjustment for change in serum potassium reduced the excess risk by 41%. Each 0.5-mEq/L decrease in serum potassium level was independently associated with a 45% increase in the risk of NOD. The authors suggested that the thiazide-induced change in serum potassium levels might prevent the closure of potassium channels on the pancreatic β-cell surface, leading to a decrease in insulin

secretion. On the other hand, in a small study where subjects with newly diagnosed hypertension were treated with hydrochlorothiazide for 9 weeks, there was no significant correlation between changes in FBG levels and changes in serum potassium levels.⁴³

Because hyperkalemia increases insulin secretion, diuretic-associated hypokalemia may inhibit insulin secretion, leading to hyperglycemia.⁴⁴ Moreover, hypokalemia could also stimulate insulin resistance, independent of its effect on insulin secretion.⁴⁴ Diuretics can also stimulate sympathetic nervous and renin-angiotensin systems, leading to insulin resistance and hyperglycemia.⁴⁴ In a recent cross-sectional study, lower serum potassium level was independently associated with prediabetes and with newly diagnosed diabetes in hypertensive subjects, but not in normotensive subjects: the association in hypertensive subjects was independent of the use of diuretics.⁴⁵

Unlike thiazide diuretics, potassium-sparing diuretics such as amiloride do not have adverse effect on blood glucose.⁴⁶ Importantly, lower doses of thiazide diuretics are recommended in clinical practice because they produce similar blood pressure-lowering effects but with smaller changes in potassium and glucose levels.⁴⁷

β-Blockers and NOD

β-Blockers were recommended as first-line therapy for hypertensive patients with ischemic heart disease, according to the seventh Joint National Committee guidelines published in 2003.³¹ However, in the United Kingdom, β-blockers have not been first- or second-line treatment since 2006.⁴⁸ Recent meta-analyses suggest that for uncomplicated hypertension, compared with other antihypertensive drugs, β-blockers are associated with an increased risk of stroke, especially in the elderly, with no benefit for other end points.⁴⁹ β-Blockers are, however, effective treatment of heart failure and for patients with previous myocardial infarction.

In a meta-analysis of 12 studies involving 94,492 patients, β-blocker use was associated with a 22% increase in NOD (relative risk 1.22, 95% CI 1.12-1.33) compared with nondiuretic antihypertensive agents.⁵⁰ Both FBG and BMI were among the predictors of NOD. The risk of NOD was greater with atenolol, in the elderly, and in studies where β-blockers were less efficacious antihypertensive agents. The risk of NOD increased exponentially with duration of treatment. This is different from the pattern with thiazide diuretics, where NOD occurs mainly in the first year,⁴² or with statins, where the increased risk of NOD appears to be constant over time.⁹

In the network meta-analysis of antihypertensive drugs,³⁴ the risk of NOD with β-blockers was not significantly different from the risk of NOD with thiazide diuretics, as shown in Table. The risk of NOD associated

with β -blockers can be mitigated with concomitant angiotensin-converting enzyme inhibitor (ACEI) treatment; in a trial of patients with stable coronary disease,⁵¹ β -blockers increased the incidence of NOD (HR 1.63, 95% CI 1.29-2.05), but patients receiving combined β -blocker/ACEI therapy had a much lower risk (HR 1.11, 95% CI 0.87-1.42).

In patients with established diabetes, older β -blockers worsen glucose control, but newer β_1 -selective blockers appear to have little or no effect, at least in short-term studies. In one randomized comparison of atenolol and captopril in 1,148 hypertensive patients with diabetes,⁵² HbA_{1C} averaged 7.5% for 4 years in the atenolol group and 7.0% in the captopril group ($P = .0044$), and at 4 years, more atenolol-treated patients required an additional drug for diabetes control (66% vs 53%, $P = .0015$). In another study of 1,235 patients with 35 weeks of follow-up, HbA_{1C} increased by 0.15% with metoprolol and 0.02% with carvedilol ($P = .004$), with the same blood pressure lowering.⁵³

β -Blockers increase the risk of NOD both by inhibiting insulin secretion and by inducing insulin resistance.⁵⁴ Because the pancreatic β -adrenoreceptor is the β_2 type, nonselective β -blockers such as propranolol, but not β_1 -selective blockers such as nebivolol, exhibit a hyperglycemic effect.^{46,55} In fact, high doses of old β_1 -selective β -blockers such as atenolol can adversely affect blood glucose as well because they are not completely selective and partially block the β_2 -adrenoreceptor.⁵⁴ Other possible mechanisms involved in β -blocker-associated NOD include reduced muscle lipoprotein lipase, body weight gain, reduced insulin clearance, reduced peripheral blood flow, and increased total peripheral vascular resistance.^{56,57}

Prevention of drug-related NOD

Irrespective of whether or not drug-related NOD affects long-term CV risk, its prevention is important. New-onset diabetes increases the health care burden at both a population level and an individual level. The patient with NOD will likely require more medications, more medical visits, more laboratory tests, and glucose monitoring. In some health care systems, such a patient may have to pay more for health insurance. The cumulative effect of these changes is likely to worsen quality of life, to some degree.

As previously discussed, the risk of NOD can be accurately assessed by the presence of simple clinical risk factors, including an FBG >100 mg/dL, and other features of the metabolic syndrome. There is no evidence that these risk factors differ for drug-related NOD. The risk of NOD should be assessed in patients beginning these drugs. Although physicians should strive to prevent diabetes in all patients at higher risk, initiation of a drug associated with NOD presents a special opportunity to focus on diabetes prevention. Patients starting on one of

these drugs should be targeted with advice about diabetes prevention.

Lifestyle intervention focusing on diet and exercise has been shown in multiple studies to reduce the risk of NOD.⁵⁸⁻⁶⁰ The reduction in risk approximates 50% and was shown in the extended follow-up of one study to persist at 43% at 7 years.⁶¹ Furthermore, even small reductions in body weight, particularly if maintained, reduce the risk of NOD. For example, in the TNT trial, we noted that the increase in body weight during the first year after randomization was greater in patients with subsequent NOD than in those without NOD (1.6 kg vs 0.9 kg, $P < .001$), and this association of change in body weight with subsequent NOD remained significant after adjustment for other predictors of NOD (unpublished observations). Because smoking is a risk factor for NOD,⁵ smoking cessation should be stressed for smokers. The lifestyle interventions that reduce the risk of NOD also reduce the risk of CV events.⁶²

Niacin should be avoided, particularly because it did not reduce CV events in 2 recent large trials.^{27,28} For patients with hypertension at high risk for NOD, an ACEI or an angiotensin receptor blocker (ARB) is preferable to a β -blocker.^{63,64} In fact, an ACEI or an ARB will reduce the risk of NOD.^{65,66} If multiple drugs are needed to control blood pressure, a newer vasodilating β -blocker such as carvedilol and nebivolol would be a better choice than an old β -blocker such as atenolol and metoprolol in terms of diabetes prevention. Although thiazide diuretics increase the risk of NOD, the long-term follow-up data from ALLHAT and SHEP^{36,37} suggest that the risk of CV events is not increased with thiazide-related NOD. Lower doses of thiazides reduce the risk of NOD. For statins, benefit in terms of CV event reduction outweighs any risk of NOD¹⁰⁻¹²; in fact, patients with the metabolic syndrome⁶⁷ or diabetes¹⁷⁻²⁰ derive particular benefit from statins.

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