# The Influence of Statins on Glucose Tolerance and Incipient Diabetes

James H O'Keefe, MD,[1] James J DiNicolantonio, PharmD,[2] Carl J Lavie, MD[3] and David SH Bell, MD[4]

*1. Cardiologist, Saint Luke's Hospital, Mid America Heart Institute, Kansas City, Missouri, US; 2. Cardiovascular Research Scientist, Saint Luke's Hospital, Mid America Heart Institute, Kansas City, Missouri, US; 3. Professor of Medicine, Medical Director, and Cardiac Rehabilitation and Prevention Director, Stress Testing Laboratory, Heart and Vascular Institute, Ochsner Clinical School, The University of Queensland School of Medicine, New Orleans, and Department of Preventive Medicine, Pennington Biomedical Research Center, Baton Rouge, Louisiana, US; 4. Professor of Medicine (Retired), University of Alabama Medical School and Southside Endocrinology, Birmingham, Alabama, US*

## Abstract

The US Food and Drink Administration (FDA) recently published a warning that statin usage may increase the risk for type 2 diabetes. However, the incidence of new-onset diabetes varies substantially among clinical trials investigating the efficacy and safety of statins. Meta-analyses indicate that statin therapy is associated with an increased risk for diabetes of approximately 9 %. The risk for incident diabetes may be associated with higher doses and potencies of statins. Mechanisms explaining the potentially higher incidence of type 2 diabetes with statin therapy have not been fully elucidated, and statins differ considerably in terms of their effect on glucose metabolism and ultimately incident diabetes. It is widely accepted that the cardiovascular benefits associated with statin use greatly outweigh the risks for diabetes. However, the effect of different statins on glycemic parameters may influence the choice of statin in those with risk factors for diabetes. Unlike the other stains, pitavastatin raises adiponectin levels, which in turn lowers insulin resistance and improves insulin secretion. Furthermore, numerous studies have concluded that pitavastatin and pravastatin do not affect glycemic control and may be favorable treatment options in patients with, or at risk for, type 2 diabetes.

## Keywords

Type 2 diabetes, statins, pitavastatin, pravastatin, atorvastatin

**Disclosure**: James H O'Keefe, MD, and James J DiNicolantonio, PharmD, have no conflicts of interest to declare. Carl J Lavie, MD, has served as a consultant and/or speaker for Pfizer and Abbott. David SH Bell, MD, is a consultant and/or speaker for Novo Nordisk, Boehringer Ingelheim, Eli Lilly, Takeda, AstraZeneca, and Salix.
**Acknowledgments:** Editorial assistance was provided by Katrina Mountfort, PhD, at Touch Medical Media.
**Received**: March 5, 2014 **Accepted**: April 29, 2014 **Citation**: *US Endocrinology*, 2014;10(1):68–74 *DOI: 10.17925/USE.2014.10.01.68*
**Correspondence**: James H O'Keefe, MD, Saint Luke's Mid America Heart Institute, 4330 Wornall Rd, Ste 2000, Kansas City, MO 64111, US. E: jokeefe@saint-lukes.org

**Support**: The publication of this article was supported by Kowa Pharmaceuticals Inc. The views and opinions expressed are those of the authors and not necessarily those of Kowa Pharmaceuticals Inc.

Statins are the cornerstone of dyslipidemia management, lowering low-density lipoprotein (LDL) cholesterol levels and substantially reducing the risk for cardiovascular disease (CVD). However, many patients on statins have CVD despite reductions in LDL cholesterol.[1] Furthermore, the co-occurrence of dyslipidemia, type 2 diabetes, and hypertension is common.[2] A considerable body of evidence demonstrates substantial benefits of statins in terms of reduction of major cardiovascular (CV) events, stroke, and mortality in patients with or without diabetes.[3] Higher doses and more intensive (i.e. more potent at LDL reduction) statin therapy are more effective than lower doses in both improving lipid levels and reducing adverse CV events.[4] However, statin therapy has been demonstrated to increase the risk for incident type 2 diabetes,[5] more so at higher doses.[6,7] Type 2 diabetes and the metabolic syndrome are strong, independent risk factors for CVD.[8–10] As a result, the US Food and Drug Administration (FDA) has added an adverse warning to statin labels. Seven statins are approved by the FDA: simvastatin, lovastatin, fluvastatin, atorvastatin, rosuvastatin, pravastatin, and pitavastatin. This article aims to examine the differential metabolic effects among the various statins, the clinical evidence outlining the effect of statins on glucose tolerance, the results of recent meta-analyses on the risk for statins and incident diabetes and, finally, discuss how clinical data influences dyslipidemia management in patients with a high risk for type 2 diabetes.

## Statin Pharmacokinetics and Efficacy

The pharmacokinetics of individual statin drugs are influenced by their lipophilic or hydrophilic nature. Atorvastatin, lovastatin, simvastatin, and pitavastatin are lipophilic molecules; however, they are not all metabolized in the same way. Atorvastatin, lovastatin, and simvastatin undergo extensive metabolism via the cytochrome P450 isoenzyme CYP3A4. A study of >950,000 patient records from two US databases in 2005–6 showed that 83 % of patients with dyslipidemia used a CYP3A4-metabolized statin and that, of these, 25 to 30 % also received a CYP3A4 inhibitor,[11] suggesting that there is a need for physician education regarding the impact of these inhibitors on the metabolism of lovastatin, simvastatin, and atorvastatin. The

## Table 1: Randomized Trials Evaluating the Effect of Statin Use on Risk for Incident Type 2 Diabetes

| Study Name | Study Population | Median Follow-up | Intervention | Relative Risk of Developing Diabetes (95 % CI) |
|---|---|---|---|---|
| WOSCOPS[18] | Men aged 45–67 years (mean 55.2 years) with moderately elevated cholesterol | 4.9 years | Pravastatin 40 mg (n=2,999) versus placebo (n=2,975) | 0.69 (0.49–0.96) |
| HPS[56] | Adults (78 % men) aged 40–80 years with occlusive arterial disease (mean 62.1 years) 5,963 UK adults (aged 40–80 years) known to have diabetes, and an additional 14,573 with occlusive arterial disease (but no diagnosed diabetes) | 4.6 years | Simvastatin 40 mg (n=7,291) versus placebo (n=7,282) | 1.14 (0.98–1.33) |
| ASCOT-LLA[50] | Adults aged 40–79 years (mean 63.2 years) with hypertension and at high risk for CVD | 3.3 years | Atorvastatin 10 mg (n=3,910) versus placebo (n=3,863) | 1.14 (0.98–1.46) |
| LIPID[55] | Adults aged 31–75 years (mean 62 years) with CVD | 5 years | Pravastatin 40 mg (n=3,970) versus placebo (n=3,967) | 0.91 (0.71–1.17) |
| CORONA[53] | Elderly adults (mean age 73 years) with heart failure | 2.7 years | Rosuvastatin 10 mg (n=1,771) versus placebo (n=1,763) | 1.14 (0.84–1.55) |
| JUPITER[52] | Apparently healthy men and women (median age 66 years) with LDL cholesterol <130 mg/dl and hsCRP ≥2.0 mg/l | 1.9 years | Rosuvastatin, 20 mg (n=8,901) versus placebo (n=8,901) | 1.26 (1.04–1.51) |
| PROSPER[54] | Men and women aged 70–82 years with a history of, or risk factors for, vascular disease | 3.2 years | Pravastatin 40 mg (n=2,891) versus placebo (n=2,913) | 1.32 (1.03–1.69) |
| TNT[48] | Patients with clinically evident CHD and LDL cholesterol levels of less than 130 mg/dl | 4.9 years | Atorvastatin 10 mg or 80 mg (n=10,001) | 1.10 (0.94–1.29) |
| SEARCH[57] | Men and women aged 18-80 years with a history of MI | 6.7 years | Simvastatin 80 mg (n=6,031) versus simvastatin 20 mg (n=6,033) | 1.07 (0.95–1.19) |
| MEGA[74] | Adults with hypercholesterolemia and no history of CHD or stroke | Mean 5.3 years | Diet (n=3,966) or diet plus 10–20 mg pravastatin (n=3,866) | 1.07 (0.86–1.35) |
| SPARCL[75] | Adults who had had a stroke or TIA within 1 to 6 months | 4.9 years | Atorvastatin 80 mg/day versus placebo (n=4,731) | 1.37 (1.08–1.75) |

*CHD = coronary heart disease; CI = confidence interval; CVD = cardiovascular disease; hsCRP = high-sensitivity C-reactive protein; LDL = low density lipoprotein; MI = myocardial infarction; TIA = transient ischemic attack.*

most recently introduced statin, pitavastatin, has a characteristic structure consisting of a heptenoate basic structure with a quinoline ring, moieties of fluorophenyl, and a cyclopropyl side chain (see *Figure 1*), which provides optimal activity and enhanced drug absorption. Unlike other lipophilic statins, pitavastatin is predominantly metabolized via glucuronidation and only minimally by CYP450, marginally by CYP2C9 and to a lesser extent CYP2C8. Pravastatin, fluvastatin, and rosuvastatin are relatively hydrophilic. Rosuvastatin is minimally metabolized by CYP2C9; fluvastatin is metabolized via CYP2C9 and pravastatin is not metabolized via cytochrome pathways.

While no direct comparisons of the efficacy of all of the various statins exist, the following commonly prescribed dosage levels are considered to be therapeutically equivalent, with the ability to reduce LDL cholesterol (LDL-C) by 20–30 %: atorvastatin 10 mg, rosuvastatin 5 mg, fluvastatin 80 mg, lovastatin 40/80 mg pravastatin, and simvastatin 20 mg.[12,13] Pitavastatin 4 mg has been found to be significantly more effective than pravastatin 40 mg in terms of reduction of LDL-C (see *Figure 2*).[14–16] However, there is a lack of randomized controlled trial data regarding CV morbidity and mortality with pitavastatin.

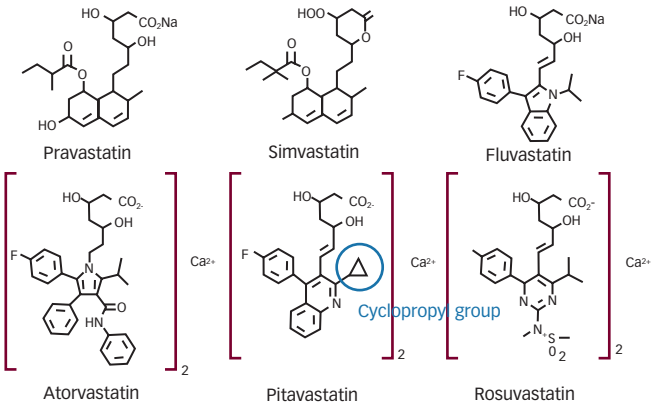
## Effect of Statins on Blood Glucose

On February 28, 2012, the FDA published a safety communication to alert the public and healthcare providers to changes in the prescribing information for statins.[17] The adverse event information has been updated to include the potential for increased blood sugar and glycated hemoglobin ($HbA_{1c}$). Clinical studies, however, have yielded inconclusive results on the association between statin usage and blood sugar. A large-scale study showed that pravastatin reduced the rate of new-onset diabetes by 30 %,[18] while, conversely, multiple studies have implicated atorvastatin, rosuvastatin, and simvastatin in increasing both $HbA_{1c}$ and fasting plasma glucose (FPG) levels.[19–22]

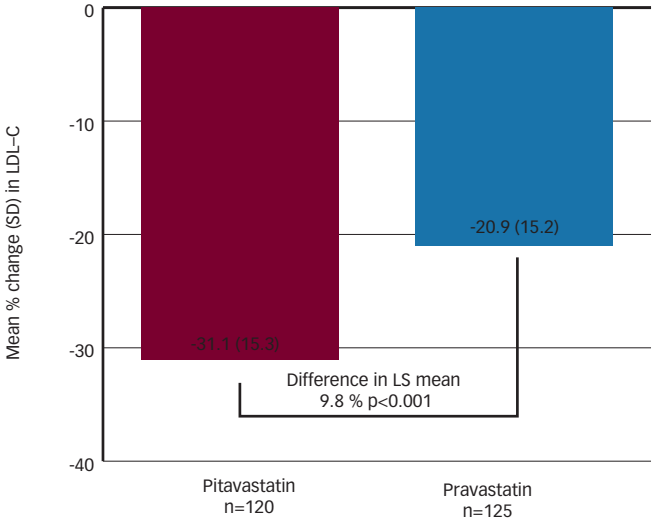
Several mechanisms have been proposed to explain the increased risk for diabetes in patients taking statins. The increased production of plasma-derived LDL cholesterol in response to the statin-induced inhibition of cholesterol synthesis might result in direct inflammation and oxidation within the β-cell, resulting in cellular apoptosis and impaired insulin secretion.[23] Other potential mechanisms include the effects of statins on hydroxymethylglutaryl-CoA reductase inhibition, isoprenoid synthesis, calcium ($Ca^{2+}$) release, glucose transport, $Ca^{2+}$-mediated pancreatic insulin secretion, decreasing various isoprenoids that enhance glucose uptake via glucose transporter 4 (Glut 4) in adipocytes, decrease in adiponectin, and/or insulin resistance.[23,24]

Preclinical and clinical data have demonstrated the effect of statins on various parameters of glycemic control. Atorvastatin attenuates adipocyte maturation and *SLC2A4* expression by inhibiting isoprenoid synthesis, and impairs glucose tolerance.[25] Simvastatin has been demonstrated to block L-type $Ca^{2+}$ channels resulting in decreased insulin secretion.[26] Lovastatin was shown to downregulate insulin-responsive Glut 4 and upregulate Glut 1 in 3T3-L1 adipocytes, leading to inhibition of insulin-stimulated glucose transport.[27] Atorvastatin has been demonstrated to reduce sensitivity to insulin in rats with streptozocin-induced diabetes.[28] A systematic literature review concluded that statins had no significant impact on insulin sensitivity compared with placebo

## Figure 1: Chemical Structure of Statins




## Figure 2: The INTREPID Phase IV Trial—Mean Percent Change in Low-density Lipoprotein Cholesterol from Baseline to Week 12




*Mean percent change from baseline to week 12 in low-density lipoprotein cholesterol (LDL-C). SD = standard deviation. LS= least squares. Source: Aberg et al. 2013.[14]*

(standardized mean difference [SMD] –0.084; 95 % confidence interval [CI] –0.210 to 0.042; p=0.19). Pravastatin was associated with improved insulin sensitivity (SMD 0.342, 95 % CI 0.03–0.621; p=0.03), whereas simvastatin significantly impaired insulin sensitivity (SMD –0.321; 95 % CI –0.526 to –0.117; p=0.03).[29]

It has been suggested that lipophilic and hydrophilic statins may have different effects on glycemic parameters.[19] Insulin secretion has been demonstrated to decrease in MIN6 β-cell lines treated with simvastatin and atorvastatin but not with hydrophilic pravastatin.[30] The Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE-IT TIMI 22) trial found that although 80 mg atorvastatin and 40 mg pravastatin were both associated with a small increase in $HbA_{1c}$ (atorvastatin 0.37 % and pravastatin 0.18 %), atorvastatin significantly increased the risk for developing $HbA_{1c}$ >6 % compared with pravastatin (relative risk [RR] 1.84; 95 % CI 1.52–2.22; p<0.0001).[31]

Statins decrease levels of ubiquinone ($CoQ_{10}$), especially at higher doses, which delays insulin release by decreasing levels of pancreatic β-cells.[7,32] It has been postulated that, as a result of decreased levels of $CoQ_{10}$, mitochondrial glycerol-3-phosphate dehydrogenase (G3PD) is underexpressed, and that correction of suboptimal $CoQ_{10}$ status, by supplementation, may improve the glucose-stimulated insulin secretion of β-cells and thereby decrease postprandial glucose.[33]

Studies of the effect of statins on insulin levels have noted the association between changes in adipocytokine levels, including leptin and adiponectin. Adiponectin is a hormone secreted by adipocytes that reduces insulin resistance and suppresses fatty acid-induced β-cells apoptosis.[34] A study found that other statins tend to decrease adiponectin levels, although this study reported no effect on insulin sensitivity.[35] Other studies have reported inconsistent effects of statins on adiponectin levels.[25,36–40] Unlike the other statins, pitavastatin consistently raises adiponectin levels, which in turn lowers insulin resistance and improves insulin secretion.[20,41–43] This might explain the observation that, to date, pitavastatin has not precipitated new-onset diabetes or decreased glycemic control.[44,45] Pitavastatin has also been shown to increase glucose uptake, improve insulin sensitivity, and the response to intraperitoneal insulin in $KKA^{y}$ mice.[46]

These data do not provide a clear explanation of the effects of statins on glycemic parameters. Evidence suggests that pravastatin and pitavastatin are the two statins least associated with worsening insulin sensitivity. However, a unifying mechanism to explain the association between statins and diabetes risk has not yet been identified.

## Clinical Studies of the Effect of Statins on Glucose Tolerance

Clinical studies have yielded conflicting results regarding glycemic control and the incidence of new-onset diabetes in patients taking statins, although taken as a whole, the data suggest an association between statin therapy and new-onset diabetes (see *Table 1*).[47] Nevertheless, caution should be used in interpreting these data. The studies were not designed to detect incident diabetes and therefore were not statistically powered to evaluate this outcome; the definition of diabetes varies across trials; and some studies did not rigorously screen for new-onset diabetes. Furthermore, baseline populations differed considerably between trials, and therefore have varying risk factors for diabetes.

### Atorvastatin

A significant positive relationship has been reported between the dose of atorvastatin (10, 20, 40, and 80 mg) with fasting plasma insulin and $HbA_{1c}$ levels, together with an inverse relationship with insulin sensitivity.[21,24] The Incremental Decrease in End Points through Aggressive Lipid Lowering (IDEAL) and Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm (ASCOT-LLA) studies have found nonsignificant increased relative risks for diabetes in patients taking atorvastatin.[48–50] High-dose atorvastatin treatment is also associated with a slightly increased risk for new-onset diabetes. A post-hoc analysis of clinical trials found that in the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial, incident diabetes was higher in patients randomized to atorvastatin 80 mg/day compared with placebo (RR 1.37; 95 % CI 1.08–1.75).[51] In the Treating to New Targets (TNT) study, a higher incidence of new-onset diabetes was also found in atorvastatin 80 mg/day compared with 10 mg/day, but this was not statistically significant.[51]

## Rosuvastatin

In the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial comparing 20 mg of rosuvastatin to placebo, a statistically significant increase in physician reported type 2 diabetes was noted (p=0.01).[52] The Controlled Rosuvastatin Multinational Study in Heart Failure (CORONA) study reported a nonsignificant risk for developing diabetes while taking rosuvastatin (RR 1.15; 95 % CI 0.91–1.44).[53]

## Pravastatin

The West of Scotland Coronary Prevention Study (WOSCOPS) trial identified pravastatin as a protective rather than deleterious factor in the development of diabetes (RR 0.70; 95 % CI 0.50–0.99), reducing the onset of diabetes by 30 %.[18] However, these analyses were based on a nonstandardized definition of diabetes (FPG >126 mg/dl plus a 36 mg/dl increase from baseline). When a subsequent meta-analysis reanalysed these data using a more standardized definition, a smaller effect was found.[5] Furthermore, the patient characteristics in the WOSCOPS study differed from other studies in that it did not enrol female participants, and the body mass index (BMI) among participants averaged 25.9 mg/m$^2$ whereas the mean BMI exceeded 27 kg/m$^2$ in other trials.[52,53] In the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) trial, there was a 32 % higher incidence of diabetes with pravastatin therapy (RR 1.32; 95 % CI 1.03–1.69), particularly in those with the metabolic syndrome.[54] The Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) trial reported no significant effect of pravastatin on the development of diabetes (RR 0.95; 95 % CI 0.77–1.16).[55]

## Simvastatin

The Heart Protection Study (HPS) of simvastatin 40 mg/day reported a nonsignificant trend towards an increased development of diabetes (RR 1.14; 95 % CI 0.98–1.33).[56] The Study of the Effectiveness of Additional Reductions in C, Homocysteine (SEARCH) trial found a small increased incidence of new-onset diabetes with high-dose (80 mg) compared with low-dose (20 mg) simvastatin (RR high dose versus low simvastatin, 1.07; 95 % CI 0.95–1.19).[57] A dose-dependent reduction in insulin sensitivity was reported in patients in treated with simvastatin (10, 20, 40, or 80 mg daily) versus placebo.[20]

## Pitavastatin

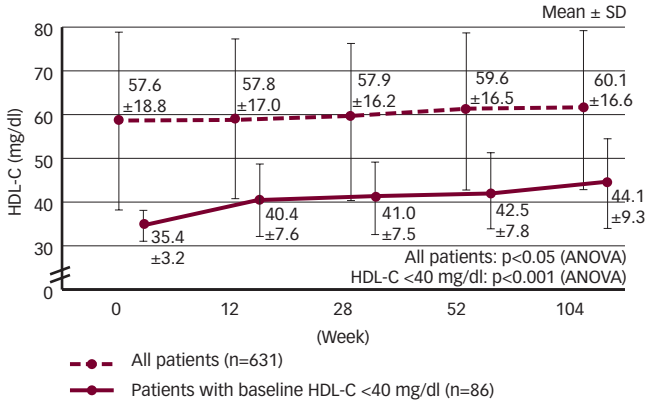
Numerous studies have concluded that pitavastatin has a neutral and possibly beneficial effect on glycemic control. A study comparing the long-term efficacy and tolerability of pitavastatin compared with atorvastatin in patients with type 2 diabetes found no significant differences in their effects on LDL-C; however, unlike atorvastatin, pitavastatin had no significant effect on FPG.[58] In a retrospective analysis that compared the effects of atorvastatin 10 mg/day, pravastatin 10 mg/day, and pitavastatin 2 mg/day on glycemic control in patients with type 2 diabetes during a 3-month treatment period, only atorvastatin significantly increased FPG and $HbA_{1c}$. Neither pravastatin nor pitavastatin had any significant influence on FPG and $HbA_{1c}$.[44]

In the extension study of the LIVALO Effectiveness and Safety (LIVES) postmarketing surveillance study, patients (n=6,580) with hypercholesterolemia were treated with pitavastatin 1, 2, or 4 mg/day over 5 years. Pitavastatin was demonstrated to significantly decrease $HbA_{1c}$ in patients with diabetes (see *Figure 3*).[59] In a recent study, patients aged ≥65 years with primary hyperlipidemia or mixed dyslipidemia were given pitavastatin (1 mg, 2 mg, and 4 mg) or pravastatin (10, 20, or 40 mg). There were no significant changes over 12 weeks in FPG within each treatment group.[60] Pitavastatin and pravastatin also had no effect on FPG over 6 months in patients with the metabolic syndrome who had multiple risk factors for diabetes.[61] In the HIV-infected Patients and Treatment with PItavastatin versus Pravastatin for Dyslipidemia (INTREPID) phase IV, multicenter, 12-week, randomized, double-blind study (n=252), neither pitavastatin 4 mg nor pravastatin 40 mg had any significant effect on FPG or $HbA_{1c}$ levels. However, pitavastatin 4 mg was superior to pravastatin 40 mg in terms of LDL-C reduction (see *Figure 2*).[14] Similar results were demonstrated prospectively in the Pitavastatin Compared with Pravastatin In Lowering LDL-C in the US (PREVAIL US) study comparing pitavastatin 4 mg with pravastatin 40 mg in patients with primary hyperlipidemia or mixed dyslipidemia, neither statin had clinically relevant effects on glucose metabolism.[15]

Post-hoc analyses of phase III noninferiority trials comparing pitavastatin with other statins have evaluated the effect of statins on FPG. In a post-hoc analysis of a 12-week randomized multicenter, double-blind trial of pitavastatin 4 mg versus atorvastatin 20 mg, no significant changes in FPG were noted with pitavastatin while atorvastatin significantly increased FPG in patients with type 2 diabetes and combined dyslipidemia.[62] In a post-hoc analysis of a 12-week, randomized, multicenter, double-blind trial of pitavastatin 4 mg versus simvastatin 40 mg, no significant changes in FPG were noted with pitavastatin. No significant changes in FPG from baseline were observed with pitavastatin at 12 weeks (mean change –0.03 mg/dl; p=0.963) or at 56 weeks (2.2 mg/dl; p=0.060). With simvastatin, FPG was unchanged at 12 weeks (–1.40 mg/dl; p=0.209), but was significantly increased (7.5 mg/dl; p=0.0001) at 56 weeks. Patients had primary hyperlipidemia or mixed lipidemia and ≥2 risk factors for coronary heart disease.[63]

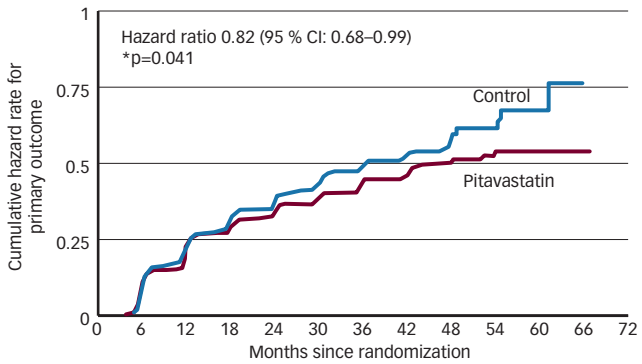
Much of the data in support of the beneficial effect of pitavastatin on glycemic parameters have been obtained from relatively small, retrospective, and/or single-center studies. In order to provide more

## Figure 3: The Time Course of High-density Lipoprotein Cholesterol for 104 weeks Before and After Administration of Pitavastatin 1–4 mg/day in the LIVES Study




*HDL-C = high-density lipoprotein cholesterol; SD = standard deviation. Source: Kawai et al. 2011.[76]*

## Figure 4: Effect of Pitavastatin on the Incidence of Diabetes—The J-PREDICT Study




Number at risk

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Control | 556 | 500 | 405 | 350 | 277 | 190 | 123 | 77 | 42 | 15 | 5 |
| Pitavastatin | 534 | 475 | 385 | 320 | 263 | 178 | 124 | 101 | 68 | 30 | 23 |

*p value was calculated using a log-rank test that was stratified according to the 5 assignment factors (sex, age, body mass index, 2-h plasma glucose, and presence of hypertension)

*Source: Odawara et al., 2013.*[64]

conclusive evidence, the Japan Prevention Trial of Diabetes by Pitavastatin in Patients with Impaired Glucose Tolerance (J-PREDICT) study is a prospective randomized, open-label controlled trial evaluating the effect of pitavastatin on the development of diabetes. Patients (n=1,269) with impaired glucose tolerance (IGT) were randomized to either pitavastatin (1–2 mg/day) plus lifestyle modification or the control group (lifestyle modification only). Preliminary data from this study showed that pitavastatin in combination with lifestyle modification was associated with a lower incidence of diabetes than was lifestyle modification alone in Japanese patients with IGT (see *Figure 4*).[64]

## Meta-analyses of the Effect of Statins on Glucose Tolerance

These meta-analyses involved trials with differences in treatment regimen, patient characteristics, and duration of follow-up. Such differences must be considered when interpreting results. A meta-analysis of five clinical trials, including 39,791 patients, did not identify a significantly increased risk for diabetes in the group receiving statins. However, when the WOSCOPS trial data were removed from the analysis the RR of diabetes increased to 1.14 (95 % CI 1.02–1.28).[65] A similar effect was noted in a meta-analysis of six clinical trials including 57,593 patients, which found a small increase in the risk for diabetes (RR 1.13; 95 % CI 1.03–1.23) if the WOSCOPS study was removed from the analysis. The RR was lower (1.06) and not statistically significant when WOSCOPS was included.[47] A larger meta-analysis of 13 major statin trials including 91,140 participants identified a 9 % increased risk for the development of diabetes in those taking statins (RR 1.09; 95 % CI 1.02–1.17).[5] Physician-reported diagnosis as opposed to standardized diagnostic criteria may overstate this effect. When FPG levels alone were used as the definition for diabetes, the risk was no longer statistically significant (RR 1.07; 95 % CI 0.97–1.17). This study did not find a clear difference between lipophilic statins (RR 1.10) and hydrophilic statins (RR 1.08). Nonsignificant trends were associated with atorvastatin (RR 1.14) and simvastatin (RR 1.11). For pravastatin the RR was 1.03; for lovastatin it was 0.98, which may suggest that the more potent statins have a stronger effect on diabetes risk.

A recent meta-analysis analyzed 17 randomized controlled trials reporting the incidence of new-onset diabetes during statin treatment between 1994 and October 2012, including a total of 113,394 patients. The study concluded that risk is both statin and dose dependent. Results demonstrated that pravastatin 40 mg/day was associated with the lowest risk for new-onset diabetes compared with placebo (RR 1.07, 95 % CI 0.86–1.30). Rosuvastatin 20 mg/day was associated with a 25 % increased risk for diabetes compared with placebo (RR 1.25; 95 % CI 0.82–1.90). Atorvastatin 80 mg/day had an intermediate risk for diabetes compared with placebo (RR 1.15; 95 % CI 0.90–1.50).[66]

## Effect of Dose Regimen and Risk Factors at Baseline

Intensive dose statin therapy has been associated with reduced CV risk compared with low or moderate doses, but some studies have suggested that high-dose regimes confer a greater risk for diabetes. Compared with lower-dose statin therapy, atorvastatin 80 mg/day did not increase the incidence of new-onset diabetes in patients with 0 to 1 diabetes risk factors but a 24 % increased incidence was found among patients with 2 to 4 diabetes risk factors. The number of CV events was significantly reduced with atorvastatin 80 mg in both risk groups.[67] This finding raises the possibility that statin therapy may increase the risk for diabetes only in those at higher baseline risk for developing the disease. In the JUPITER trial, 77 % of the patients in the rosuvastatin group who developed diabetes had impaired fasting glucose at baseline.[52] Furthermore, more than 40 % of the patients in JUPITER met the criteria for the metabolic syndrome. The PROSPER trial, which also reported a higher incidence of new-onset diabetes with statin use, recruited an elderly patient population, who were therefore more likely to have a higher risk for diabetes compared with the normal population.[5] However, further studies are required to confirm this hypothesis.

In 2011, a meta-analysis of 32,752 patients from five large-scale clinical trials examined the impact of the intensity of statin therapy on diabetes risk. There was a 12 % higher risk for developing new-onset diabetes in those treated with intensive dose statin therapy versus moderate dose statin therapy (RR 1.12; 95 % CI 1.04–1.22).[6] However, a review of 5-year data from the Enhanced Feedback for Effective Cardiac Treatment (EFFECT) study found no association between higher diabetes risk and more intensive statin therapy. The risk for diabetes was in fact lower in the high-dose groups.[68]

## Retrospective and Observational Studies

Observational studies have also failed to provide conclusive evidence regarding the association between statin use and diabetes incidence. A Women's Health Initiative observational study recruited 161,808 women aged 50–79 years from 1993 to 1998. Results showed found that statin use at baseline was associated with an almost 50 % increased risk for diabetes (RR 1.48; 95 % CI 1.38–1.59).[69] However, the study was limited by its observational nature, and the data set contained unequal representation of statins that may have influenced the outcomes. In addition, not all the currently available statins were in use during the study period, and women who took statins may have changed statin type prior to new onset.

In a Canadian population-based retrospective cohort study of more than 1.5 million people, compared with pravastatin (the reference drug in all analyses), there was an increased risk for incident diabetes with

atorvastatin (RR 1.22, 95 % CI 1.15–1.29), rosuvastatin (RR 1.18; 95 % CI 1.10–1.26), and simvastatin (RR 1.10, 95 % CI 1.04–1.17). There was no significantly increased risk among people who received fluvastatin (RR 0.95, 95 % CI 0.81–1.11) or lovastatin (RR 0.99, 95 % CI 0.86–1.14).[70] The risk for incident diabetes did not differ between patients with or without CVD. This study also found an association between development of diabetes and statin potency and dose.

## Recommendations for Dyslipidemia Treatment in Patients with a Risk for Diabetes

New-onset diabetes on statin therapy has not yet been associated with an increase in adverse CV events. In an analysis of trials of atorvastatin therapy, major CV events occurred in 11.3 % of patients with new-onset diabetes, 10.8 % without new-onset diabetes (hazard ratio [HR] 1.02; 95 % CI 0.77–1.35), and 17.5 % of patients who had diabetes at baseline.[67] However, the follow-ups of 5 years or less in these trials may be insufficient to evaluate the impact of new-onset diabetes on future CV events. In a recent clinical trial, the use of statins was associated with a 39 % reduction in the primary end point (myocardial infarction, stroke, admission to hospital for unstable angina, arterial revascularization, or CV death) in patients with ≥1 risk factors for diabetes, but in patients with no risk factors for diabetes, statins were associated with a 52 % reduction in the primary endpoint.[71]

Despite the risk for future adverse CV events, clinical data to date suggest that the benefit of statin usage far outweighs the risk for diabetes. In an analysis of the JUPITER data in patients with diabetes risk factors who did not have CVD at baseline, for every 54 new cases of diabetes at follow-up, 134 CV events or deaths were prevented. For patients with no diabetes risk factors at baseline, 86 CV events or deaths were prevented with no new cases of diabetes.[71] A meta-analysis estimated that treating 255 patients with standard-dose statin therapy for 4 years would avoid 9 vascular events while leading to one case of new-onset diabetes (9:1 benefit versus risk ratio).[5] A meta-analysis of intensive statin therapy found that for every case of diabetes caused, 3.2 CV events were prevented per year with intensive-dose statin therapy.[6] A literature review of reports of new-onset diabetes associated with statin use among women concluded that benefits outweighed risks though emphasized the paucity of long-term studies focusing on the risks and benefits of statins in women.[72] A recent study concluded that the risk:benefit ratio favoring statins is extremely strong, even in those who have an increase in blood glucose levels on statin therapy.[73] It is therefore recommended that statins should still be first-line therapy for the majority of patients with dyslipidemia and risk for CVD. However, it is advisable that patients treated with statins undergo regular blood glucose monitoring.

## Summary and Concluding Remarks

The incidence of new-onset diabetes varies substantially among clinical trials investigating the efficacy and safety of statins, with only JUPITER and PROSPER finding statistically significant increases in the risk for type 2 diabetes. However, as a whole, clinical data suggest that statin therapy is associated with an increased risk for diabetes of about 9 %. It appears that patients with a predisposition for diabetes may be at greatest risk for developing diabetes while on statin therapy. Some studies comparing high- with lower-dose statin regimes suggest that there may be a higher risk for incident diabetes at higher doses. Furthermore, more potent statins, such as atorvastatin and simvastatin, have been associated with a higher rate of diabetes compared with lower potency statins.

There is a need for continued efforts to understand the relationships between statin therapy and diabetes, both in future clinical trials and pre-clinical investigations. Many questions remain, such as: how does diabetes associated with statin treatment progress? How should it be treated? What mechanisms underlie the observed differences between statins on glycemic parameters? How should these findings affect statin usage? It is also important to examine how the increase in absolute risk for new-onset diabetes reported in meta-analyses compares with the benefits of statin treatment in terms of CV risk reduction.

Statins are now used with the understanding that a slightly increased risk for diabetes is outweighed by the CV benefits. However, the differential metabolic effects of the various statins should be taken into account when deciding treatment plans for patients with a high risk for developing diabetes. Based on meta-analyses, pravastatin is considered the statin with the least risk for incident diabetes; however, pitavastatin consistently shows neutral to beneficial effects on glycemic parameters similar to that of pravastatin, and has shown superior lipid-lowering ability compared with pravastatin. In comparative studies, pitavastatin has demonstrated a favorable effect on glycemic parameters compared with other statins. Further data are needed to confirm these findings and assess their relevance to clinical outcomes. ■


1. Sacks FM, Tonkin AM, Shepherd J, et al., Effect of pravastatin on coronary disease events in subgroups defined by coronary risk factors: the Prospective Pravastatin Pooling Project, *Circulation*, 2000;102:1893–900.
2. Selby JV, Peng T, Karter AJ, et al., High rates of co-occurrence of hypertension, elevated low-density lipoprotein cholesterol, and diabetes mellitus in a large managed care population, *Am J Manag Care,* 2004;10:163–70.
3. Cholesterol Treatment Trialists Collaboration, Kearney PM, Blackwell L, et al., Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis, *Lancet*, 2008;371:117–25.
4. Cholesterol Treatment Trialists Collaboration, Baigent C, Blackwell L, et al., Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials, *Lancet*, 2010;376:1670–81.
5. Sattar N, Preiss D, Murray HM, et al., Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials, *Lancet*, 2010;375:735–42.
6. Preiss D, Seshasai SR, Welsh P, et al., Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis, *JAMA*, 2011;305:2556–64.
7. Bell DS, Dinicolantonio JJ, O'Keefe JH, Is statin-induced diabetes clinically relevant? A comprehensive review of the literature, *Diabetes Obes Metab*, 2013;[Epub ahead of print].
8. Ray KK, Seshasai SR, Wijesuriya S, et al., Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials, *Lancet*, 2009;373:1765–72.
9. Emerging Risk Factors Collaboration, Sarwar N, Gao P, et al., Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies, *Lancet*, 2010;375:2215–22.
10. Galassi A, Reynolds K, He J, Metabolic syndrome and risk of cardiovascular disease: a meta-analysis, *Am J Med*, 2006;119:812–9.
11. Ming EE, Davidson MH, Gandhi SK, et al., Concomitant use of statins and CYP3A4 inhibitors in administrative claims and electronic medical records databases, *J Clin Lipidol*, 2008;2:453–63.
12. Ose L, Budinski D, Hounslow N, et al., Comparison of pitavastatin with simvastatin in primary hypercholesterolaemia or combined dyslipidaemia, *Curr Med Res Opin*, 2009;25:2755–64.
13. Weng TC, Yang YH, Lin SJ, et al., A systematic review and meta-analysis on the therapeutic equivalence of statins, *J Clin Pharm Ther,* 2010;35:139–51.
14. Aberg J, Sponseller C, Kryzhanovski VA, et al., Neutral effects of pitavastatin 4 mg and pravastatin 40 mg on blood glucose and HbA1c levels over 12 weeks: prespecified safety analysis from the INTREPID (HIV-infected patieNts and TREatment with Pitavastatin versus pravastatin for Dyslipidemia) Phase 4 Trial. Poster presented at the Endocrine Society Annnual Meeting, June 15–18, 2013; San Francisco, CA, US.
15. Kryzhanovski V, Morgan RE, Sponseller CA, et al., Pitavastatin 4 mg provides significantly greater reduction in LDL-C compared to pravastatin 40 mg with neutral effects on glucose metabolism: prespecified safety analysis from the short-term phase 4 PREVAIL US trial in patients with primary hyperlipidemia or mixed dyslipidemia, Poster presented at the American College of Cardiology Annual Scientific Sessions, March 24–27, 2012; Chicago, IL, US.
16. Stender S, Budinski D, Gosho M, et al., Pitavastatin shows greater lipid-lowering efficacy over 12 weeks than pravastatin in elderly patients with primary hypercholesterolaemia or combined (mixed) dyslipidaemia, *Eur J Prev Cardiol*, 2013;20:40–53.
17. FDA, Drug safety communication: important safety label changes to cholesterol-lowering statin drugs. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm293101.htm (accessed May 13, 2014).
18. Freeman DJ, Norrie J, Sattar N, et al., Pravastatin and the development of diabetes mellitus: evidence for a protective treatment effect in the West of Scotland Coronary Prevention Study, *Circulation*, 2001;103:357–62.

19. Ishikawa M, Namiki A, Kubota T, et al., Effect of pravastatin and atorvastatin on glucose metabolism in nondiabetic patients with hypercholesterolemia, *Intern Med*, 2006;45:51-5.
20. Koh KK, Quon MJ, Han SH, et al., Simvastatin improves flow-mediated dilation but reduces adiponectin levels and insulin sensitivity in hypercholesterolemic patients, *Diabetes Care*, 2008;31:776–82.
21. Koh KK, Quon MJ, Han SH, et al., Atorvastatin causes insulin resistance and increases ambient glycemia in hypercholesterolemic patients, *J Am Coll Cardiol*, 2010;55:1209–16.
22. Kostapanos MS, Milionis HJ, Agouridis AD, et al., Rosuvastatin treatment is associated with an increase in insulin resistance in hyperlipidaemic patients with impaired fasting glucose, *Int J Clin Pract*, 2009;63:1308–13.
23. Sampson UK, Linton MF, Fazio S, Are statins diabetogenic? *Curr Opin Cardiol*, 2011;26:342-7.
24. Koh KK, Sakuma I, Quon MJ, Differential metabolic effects of distinct statins, *Atherosclerosis*, 2011;215:1–8.
25. Nakata M, Nagasaka S, Kusaka I, et al., Effects of statins on the adipocyte maturation and expression of glucose transporter 4 (SLC2A4): implications in glycaemic control, *Diabetologia*, 2006;49:1881–92.
26. Yada T, Nakata M, Shiraishi T, et al., Inhibition by simvastatin, but not pravastatin, of glucose-induced cytosolic Ca2+ signalling and insulin secretion due to blockade of L-type Ca2+ channels in rat islet beta-cells, *Br J Pharmacol*, 1999;126:1205–13.
27. Chamberlain LH, Inhibition of isoprenoid biosynthesis causes insulin resistance in 3T3-L1 adipocytes, *FEBS Lett*, 2001;507:357–61.
28. Kanda M, Satoh K, Ichihara K, Effects of atorvastatin and pravastatin on glucose tolerance in diabetic rats mildly induced by streptozotocin, *Biol Pharm Bull*, 2003;26:1681–4.
29. Baker WL, Talati R, White CM, et al., Differing effect of statins on insulin sensitivity in non-diabetics: a systematic review and meta-analysis, *Diabetes Res Clin Pract*, 2010;87:98–107.
30. Ishikawa M, Okajima F, Inoue N, et al., Distinct effects of pravastatin, atorvastatin, and simvastatin on insulin secretion from a beta-cell line, MIN6 cells, *J Atheroscler Thromb*, 2006;13:329–35.
31. Sabatine MS, Wiviott SD, Morrow DA, et al., High-dose atorvastatin asssociated with worse glycemic control: A PROVE-IT TIMI 22 substudy (Abstract), *Circulation*, 2004;110:S834.
32. Ellis CJ, Scott R, Statins and coenzyme Q10, *Lancet*, 2003;361:1134–5.
33. McCarty MF, Can correction of sub-optimal coenzyme Q status improve beta-cell function in type II diabetics? *Med Hypotheses*, 1999;52:397–400.
34. Turer AT, Scherer PE, Adiponectin: mechanistic insights and clinical implications, *Diabetologia*, 2012;55:2319–26.
35. Ding YA, Hsu PF, Lu TM, Statin therapy on insulin resistance and plasma level of adiponectin in non-diabetic, hypercholesterolemic patients, *Acta Cardiol Sin*, 2009;25:183–9.
36. Forst T, Pfutzner A, Lubben G, et al., Effect of simvastatin and/or pioglitazone on insulin resistance, insulin secretion, adiponectin, and proinsulin levels in nondiabetic patients at cardiovascular risk--the PIOSTAT Study, *Metabolism*, 2007;56:491–6.
37. Chan KC, Chou HH, Huang CN, et al., Atorvastatin administration after percutaneous coronary intervention in patients with coronary artery disease and normal lipid profiles: impact on plasma adiponectin level, *Clin Cardiol*, 2008;31:253–8.
38. Sonmez A, Dogru T, Tasci I, et al., The effect of fluvastatin on plasma adiponectin levels in dyslipidaemia, *Clin Endocrinol (Oxf)*, 2006;64:567–72.
39. Kai T, Kanamasa K, Effects of increasing the dose of pravastatin on serum adiponectin level in Japanese mild hypercholesterolemic and hypertensive patients, *Arzneimittelforschung*, 2009;59:445–50.
40. Kai T, Arima S, Taniyama Y, et al., Comparison of the effect of lipophilic and hydrophilic statins on serum adiponectin levels in patients with mild hypertension and dyslipidemia: Kinki Adiponectin Interventional (KAI) Study, *Clin Exp Hypertens*, 2008;30:530–40.
41. Nomura S, Shouzu A, Omoto S, et al., Correlation between adiponectin and reduction of cell adhesion molecules after pitavastatin treatment in hyperlipidemic patients with type 2 diabetes mellitus, *Thromb Res*, 2008;122:39–45.
42. Inami N, Nomura S, Shouzu A, et al., Effects of pitavastatin on adiponectin in patients with hyperlipidemia, *Pathophysiol Haemost Thromb*, 2007;36:1–8.
43. Nomura S, Inami N, Shouzu A, et al., The effects of pitavastatin, eicosapentaenoic acid and combined therapy on platelet-derived microparticles and adiponectin in hyperlipidemic, diabetic patients, *Platelets*, 2009;20:16–22.
44. Yamakawa T, Takano T, Tanaka S, et al., Influence of pitavastatin on glucose tolerance in patients with type 2 diabetes mellitus, *J Atheroscler Thromb*, 2008;15:269–75.
45. Kryzhanovski V, Gumprecht J, Zhu B, et al., Atorvastatin but not pitavastatin significantly increase plasma glucose in patients with type 2 diabetes and combined dyslipidemia, *J Am Coll Cardiol*, 2011;57:E575.
46. Ishihara Y, Ohmori K, Mizukawa M, et al., Beneficial direct adipotropic actions of pitavastatin in vitro and their manifestations in obese mice, *Atherosclerosis*, 2010;212:131–8.
47. Rajpathak SN, Kumbhani DJ, Crandall J, et al., Statin therapy and risk of developing type 2 diabetes: a meta-analysis, *Diabetes Care*, 2009;32:1924–9.
48. LaRosa JC, Grundy SM, Waters DD, et al., Intensive lipid lowering with atorvastatin in patients with stable coronary disease, *N Engl J Med*, 2005;352:1425–35.
49. Pedersen TR, Faergeman O, Kastelein JJ, et al., High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial, *JAMA*, 2005;294:2437–45.
50. Sever PS, Dahlof B, Poulter NR, et al., Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial, *Lancet*, 2003;361:1149–58.
51. Waters DD, Ho JE, DeMicco DA, et al., Predictors of new-onset diabetes in patients treated with atorvastatin: results from 3 large randomized clinical trials, *J Am Coll Cardiol*, 2011;57:1535–45.
52. Ridker PM, Danielson E, Fonseca FA, et al., Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein, *N Engl J Med*, 2008;359:2195–207.
53. Kjekshus J, Apetrei E, Barrios V, et al., Rosuvastatin in older patients with systolic heart failure, *N Engl J Med*, 2007;357:2248–61.
54. Shepherd J, Blauw GJ, Murphy MB, et al., Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial, *Lancet*, 2002;360:1623–30.
55. Keech A, Colquhoun D, Best J, et al., Secondary prevention of cardiovascular events with long-term pravastatin in patients with diabetes or impaired fasting glucose: results from the LIPID trial, *Diabetes Care*, 2003;26:2713–21.
56. Collins R, Armitage J, Parish S, et al., MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial, *Lancet*, 2003;361:2005–16.
57. Study of the Effectiveness of Additional Reductions in C, Homocysteine Collaborative G, Armitage J, et al., Intensive lowering of LDL cholesterol with 80 mg versus 20 mg simvastatin daily in 12,064 survivors of myocardial infarction: a double-blind randomised trial, *Lancet*, 2010;376:1658–69.
58. Gumprecht J, Gosho M, Budinski D, et al., Comparative long-term efficacy and tolerability of pitavastatin 4 mg and atorvastatin 20-40 mg in patients with type 2 diabetes mellitus and combined (mixed) dyslipidaemia, *Diabetes Obes Metab*, 2011;13:1047–55.
59. Teramoto TU, Urashima M, Shimano H et al, A large-scale survey on cardio-cerebrovascular events during pitavastatin (LIVALO tablet) therapy in Japanese patients with hypercholesterolemia, *Jpn Pharmacol Ther*, 2011;39:789–803.
60. Sponseller C, Stemder S, Zhu B, et al., Neutral effects of pitavastatin and pravastatin on fasting plasma glucose over 12 weeks in elderly patients with primary hyperlipidemia or mixed dyslipidemia, Poster presented at the 7th World Congress on Prevention of Diabetes and its Complications (WCPD 2012), November 11-14, 2012; Madrid, Spain.
61. Hounslow N, Robillard P, Suzuki M, et al., Pitavastatin is without effect on glycaemic parameters in metabolic syndrome, presented at the 7th World Congress on Prevention of Diabetes and its Complications (WCPD 2012), November 11-14, 2012; Madrid, Spain. Abstract 7161542.
62. Sponseller C, Gumprecht J, Zhu B, et al., Atorvastatin, but not pitavastatin, significantly increases fasting plasma glucose in patients with type 2 diabetes and combined dyslipidemia, Poster presented at the American College of Cardiology 60th Annual Scientific Sessions, April 2-5, 2011; New Orleans, LA, US.
63. Kryzhanovski V, Eriksson M, Hounslow N, et al., Short-term and long-term effects of pitavastatin and simvastatin on fasting plasma glucose in patients with primary hyperlipidemia or mixed dyslipidemia and ≥2 risk factors for coronary heart disease, Poster presented at the American College of Cardiology Annual Scientific Sessions, March 24-27, 2012; Chicago, IL, US.
64. Odawara M, Yamazaki T, Kishimoto J, et al., Effect of pitavastatin on the incidence of diabetes in Japanese individuals with impaired glucose tolerance, presented at the 49th Annual European Association for the Study of Diabetes (EASD) Meeting, September 23-27, 2013; Barcelona, Spain. Presentation no 128.
65. Coleman CI Reinhart K, Kluger J, et al., The effect of statins on the development of new-onset type 2 diabetes: a meta-analysis of randomized controlled trials, *Curr Med Res Opin*, 2008;24:1359–62.
66. Navarese EP, Buffon A, Andreotti F, et al., Meta-analysis of impact of different types and doses of statins on new-onset diabetes mellitus, *Am J Cardiol*, 2013;111:1123–30.
67. Waters DD, Ho JE, Boekholdt SM, et al., Cardiovascular event reduction versus new-onset diabetes during atorvastatin therapy: effect of baseline risk factors for diabetes, *J Am Coll Cardiol*, 2013;61:148–52.
68. Yousef A, Tu JV, Wang J, et al., The association of intensive statin therapy on long-term risks of cardiovascular events and diabetes following acute myocardial infarction (abstract), *Circulation*, 2012;125:e859.
69. Culver AL, Ockene IS, Balasubramanian R, et al., Statin use and risk of diabetes mellitus in postmenopausal women in the Women's Health Initiative, *Arch Intern Med*, 2012;172:144–52.
70. Carter AA, Gomes T, Camacho X, et al., Risk of incident diabetes among patients treated with statins: population based study, *BMJ*, 2013;346:f2610.
71. Ridker PM, Pradhan A, MacFadyen JG, et al., Cardiovascular benefits and diabetes risks of statin therapy in primary prevention: an analysis from the JUPITER trial, *Lancet*, 2012;380:565–71.
72. Ma Y, Culver A, Rossouw J, et al., Statin therapy and the risk for diabetes among adult women: do the benefits outweigh the risk? *Ther Adv Cardiovasc Dis*, 2013;7:41–4.
73. Wang KL, Liu CJ, Chao TF, et al., Statins, risk of diabetes, and implications on outcomes in the general population, *J Am Coll Cardiol*, 2012;60:1231–8.
74. Nakamura H, Arakawa K, Itakura H, et al., Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA Study): a prospective randomised controlled trial, *Lancet*, 2006;368:1155–63.
75. Amarenco P, Bogousslavsky J, Callahan A, 3rd, et al., High-dose atorvastatin after stroke or transient ischemic attack, *N Engl J Med*, 2006;355:549–59.
76. Kawai Y, Sato-Ishida R, Motoyama A, et al., Place of pitavastatin in the statin armamentarium: promising evidence for a role in diabetes mellitus, *Drug Des Devel Ther*, 2011;5:283–97.