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JOURNAL WATCH

High-Intensity Statin Therapy Alters the Natural History of Diabetic Coronary Atherosclerosis: Insights From SATURN

EDITOR'S VIEW

These findings of the study are in favor of the use of high-intensity statin in diabetic patients with atherosclerotic disease. However, further research is required to elucidate if specific low-density lipoprotein cholesterol (LDL-C) targets are required to achieve plaque regression and lower clinical event rates in these high-risk diabetic patients with and without clinical atherosclerotic disease. It should further be kept in mind that rosuvastatin is also more likely to aggravate the diabetic state than other statins. It is advisable to await further, more dependable long-term trials for final opinion.

Conventionally, statins can induce coronary atheroma regression. But this benefit needs to be established in diabetic individuals. Stegman *et al*. tested the hypothesis that high-intensity statin therapy may promote coronary atheroma regression in patients with diabetes.

The Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin Versus Atorvastatin (SATURN) used serial intravascular ultrasound measures of coronary atheroma volume in patients treated with rosuvastatin 40 mg or atorvastatin 80 mg for 24 months. This analysis compared changes in biochemistry and coronary percent atheroma volume (PAV) in patients with (n = 159) and without (n = 880) diabetes.

At baseline, patients with diabetes had lower low-density cholesterol (LDL-C) and high-density cholesterol (HDL-C) levels, but higher triglyceride and C-reactive protein (CRP) levels compared with patients without diabetes. At follow up, diabetic patients had lower levels of LDL-C (61.0 ± 20.5 vs. 66.4 ± 22.9 mg/dL, P = 0.01) and HDL-C (46.3 ± 10.6 vs. 49.9 ± 12.0 mg/dL, P < 0.001) but higher levels of triglycerides (127.6 [98.8, 163.0] vs. 113.0 mg/dL [87.6, 151.9], P = 0.001) and CRP (1.4 [0.7, 3.3] vs. 1.0 [0.5, 2.1] mg/L, P = 0.001). Both patients with and without diabetes demonstrated regression of coronary atheroma as measured by change in PAV (-0.83 ± 0.13 vs. -1.15 ± 0.13%, P = 0.08). PAV regression was less in diabetic compared with nondiabetic patients when on-treatment LDL-C levels were >70 mg/dL (-0.31 ± 0.23 vs. -1.01 ± 0.21%, P = 0.03) but similar when LDL-C levels were ≤70 mg/dL (-1.09 ± 0.16 vs. -1.24 ± 0.16%, P = 0.50).

The conclusion of the study is that high-intensity statin therapy is associated with coronary atheroma regression in both diabetic and nondiabetic patients, thus altering the progressive nature of diabetic atherosclerosis. This regression in diabetic individuals appears optimized when achieved LDL-C levels are below 70 mg/dL.

(Stegman B, Puri R, Cho L, *et al*. *Diabetes Care*. Published online September 4, 2014.)

The Effects of Dipeptidyl Peptidase-4 Inhibition on Microvascular Diabetes Complications

EDITOR'S VIEW

After several years of clinical use, it is clear as per preliminary data that glucagon-like peptide-1 (GLP-1) receptor agonists have stronger efficacy in terms of correction of the major risk factors for cardiovascular disease (CVD) (including blood pressure and lipids). The SAVOR, EXAMINE, and other smaller studies did not show any significant effect on both blood pressure and lipids. If these protective effects of DPP4-I on microvascular complications can lead to better outcomes in people with diabetes, they should be verified by several ongoing clinical trials.

However, one must be cautious when trying to translate findings obtained in animal models and small clinical studies to the heterogeneous population of diabetic patients. Rather we should wait until results from specifically designed randomized controlled trials are available. In addition to the aforementioned aspects, the effect of peptidase-4 inhibitors (DPP4-I) on bone marrow stem cells is also promising to achieve microvascular protection at distant sites. Ultimately, reducing the burden of microangiopathy may translate into improved cardiovascular, renal, and retinal outcomes in diabetes.

Avogaro and Fadini reviewed the literature to determine whether the dipeptidyl peptidase-4 inhibitors (DPP4-Is) may directly and positively influence diabetic microvascular complications both from the experimental and clinical evidences published between 1980 and 2014 in English-language peer-reviewed journals. Experimentally, DPP4-I appears to improve inflammation, endothelial function, blood pressure, lipid metabolism, and bone marrow function. Several experimental studies report direct potentially beneficial effects of DPP4-I on all microvascular diabetes-related complications. These drugs have the ability to act either directly or indirectly via improved glucose control, glucagon-like peptide-1 (GLP-1) bioavailability, and modifying nonincretin substrates. Although preliminary clinical data support that DPP4-I therapy can protect from microangiopathy, evidence is insufficient to conclude that this class of drugs directly prevents or decreases microangiopathy in humans independently from improved glucose control.

Experimental findings and preliminary clinical data suggest that DPP4-I, in addition to improving metabolic control, have the potential to interfere with the onset and progression of diabetic microangiopathy. Further evidence is needed to confirm these effects in patients with diabetes.

The current standards of care significantly reduce but unfortunately do not eliminate the risk of diabetic microangiopathy. This has important implications because, although microangiopathy is rarely the cause of death in diabetic patients, it is one of the most important risk factors for CVD. Furthermore, this implies that in the past years, the most commonly used glucose-lowering drugs were unable to effectively decrease plasma glucose in order to avoid the onset and the progression of microvascular disease. Another relevant issue is that many glucose-lowering agents need to be dose-adjusted or should not be used in the setting of stage III–IV chronic kidney disease (CKD) or in those receiving dialysis.

Indeed, the safety of DPP4-I has been demonstrated in several trials in patients with different degrees of renal impairment. Extensive experimental data and preliminary clinical studies indicate that DPP4-I may improve microvascular structure and function. Whether the effects of DPP4-I are mediated by improved glucose control or by pleiotropic off-target actions of DPP4-I on nonincretin substrates remains unclear. A few hints can help answer this question with available data.

Preclinical findings obtained *in vitro* and using animal models of T1D (e.g., STZ-induced diabetes) suggest that favorable effects of DPP4-I are conveyed independently of glycemic effects. Moreover, short-term studies in T2D patients, showing raised EPCs after just 4 weeks of sitagliptin treatment, are likely exploring pleiotropic rather than glycemic effects.

Finally, while lowering HbA_{1C} significantly prevents microangiopathy, the reduced development and progression of microalbuminuria in the SAVOR trial is unlikely to be fully explained by the marginal 0.2–0.3% reduction in HbA_{1C} obtained with saxagliptin compared with placebo throughout the trial.

(Avogaro A, Fadini GP. *Diabetes Care*. 2014;37:2884–94.)

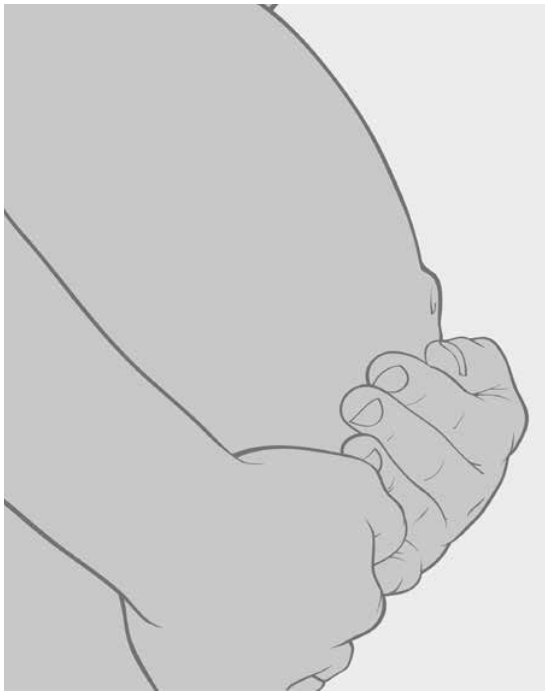
An Early-Pregnancy HbA_{1C} >5.9% (41 mmol/mol) Is Optimal for Detecting Diabetes and Identifies Women at Increased Risk of Adverse Pregnancy Outcomes

EDITOR'S VIEW

This study has shown the importance of measuring HbA_{1C} during early pregnancy. An HbA_{1C} measurement before 20 weeks of 5.9–6.4% (41–46 mmol/mol) in this study was associated with an increased risk of adverse pregnancy outcomes, including major congenital anomaly, preeclampsia, shoulder dystocia, and perinatal death. But, till date, because of some fallacies HbA_{1C} alone is not accepted as diagnostic marker of gestational diabetes mellitus (GDM) and the value of gold standard of blood glucose estimation still remains.

Pregnant women with undiagnosed diabetes are a high-risk group that may benefit from early intervention. Extrapolating from nonpregnancy data, HbA_{1C}> 6.5% (48 mmol/mol) is recommended to define diabetes in pregnancy. The aims of the study were to determine the optimal HbA_{1C} threshold for detecting diabetes in early pregnancy as defined by an early oral glucose tolerance test (OGTT) at <20 weeks' gestation and to examine pregnancy outcomes relating to this threshold.

During 2008–2010 in Christchurch, New Zealand, women were offered an HbA_{1C} measurement with their first antenatal bloods. Pregnancy outcome data were collected. A subset completed an early OGTT, and HbA_{1C} performance was assessed using World Health Organization (WHO) criteria.



HbA_{1C} was measured at a median 47 days' gestation in 16,122 women. Of those invited, 974/4,201 (23%) undertook an early OGTT. In this subset, HbA_{1C} >5.9% (41 mmol/mol) captured all 15 cases of diabetes, 7 with HbA_{1C} <6.5% (<48 mmol/mol).

This HbA_{1C} threshold was also 98.4% (95% CI 97–99.9%) specific for gestational diabetes mellitus (GDM) before 20 weeks (positive predictive value = 52.9%). A threshold >6.5% (48 mmol/mol) would have missed almost half of these women and is therefore too high for screening purposes. In this subgroup, 74% of women with an early pregnancy HbA_{1C} >5.9% (41 mmol/mol) had an abnormal OGTT at some stage in their pregnancy, with over two-thirds of these being identified before 20 weeks' gestation. An early pregnancy HbA_{1C} measurement of 5.9–6.4% (41–46 mmol/mol) was associated with an increased risk of adverse pregnancy outcomes, including major congenital anomaly, preeclampsia, shoulder dystocia, and perinatal death. In the total cohort, excluding women referred for GDM management, women with HbA_{1C} of 5.9–6.4% (41–46 mmol/mol; *n* = 200) had poorer pregnancy outcomes than those with HbA_{1C} <5.9% (<41 mmol/mol; *n* = 8,174); relative risk (95% CI) of major congenital anomaly was 2.67 (1.28–5.53), preeclampsia was 2.42 (1.34–4.38), shoulder dystocia was 2.47 (1.05–5.85), and perinatal death was 3.96 (1.54–10.16).

Measurements of HbA_{1C} were readily performed in contrast to the low uptake of early OGTTs. HbA_{1C} >5.9% (>41 mmol/mol) identified all women with diabetes and a group at significantly increased risk of adverse pregnancy outcomes.

(Hughes RCE, Moore MP, Gullam JE, *et al*. Diabetes Care. Published online September 4, 2014.)

Serious Harm from Inpatient Hypoglycemia: A Survey of Hospitals in the UK

EDITOR'S VIEW

Researchers asked the diabetes teams at each of the 142 acute National Health Service (NHS) trusts to recall and report any serious adverse events from inpatient hypoglycemia in the previous year. Only 68.3% of trusts that returned surveys were confident that they employed robust methods to ensure all such events were reported.

There were 12 serious adverse events reported from 9 trusts, including 3 deaths. Insulin therapy was implicated in 10 events, 3 of which involved the use of insulin/dextrose therapy to correct hyperkalemia.

As there may be possible under-reporting in this study, the authors conclude that an alarming number of serious adverse events due to hypoglycemia occur. They suggest that more robust reporting mechanisms are needed to determine the full extent of the problem.

In this study, Rajendran *et al*. estimated the incidence of serious harm to inpatients with diabetes from hypoglycemia. An anonymized questionnaire was emailed to lead organizers at the 142 acute NHS Trusts that contributed to the National Diabetes Inpatient Audit 2012. Each diabetes team was asked collectively to recall and report any serious adverse events from inpatient hypoglycemia in the previous year. A total of 83 trusts agreed to participate. Serious harm was defined as death, a cardiac or cerebral event, or a fall resulting in permanent physical injury or fracture.

A total of 41 trusts returned the survey. Of these, only 28 (68.3%) were confident that robust methods existed in their trust to ensure that all such events were reported, and only 23 (56.1%) were confident that all such events were reported to the diabetes team. Despite these reporting concerns, the retrospective nature of the survey and the reliance on recall, 12 serious adverse events were reported from 9 trusts: three deaths; two cases of permanent cerebral damage; two successfully resuscitated cardiac arrests; three seizures; and two undefined events. Insulin therapy was implicated in 10 events. Importantly, three events with two deaths occurred in patients who had received insulin/dextrose to correct hyperkalemia, only one of whom had diabetes.

An alarming number of serious adverse events was reported: 12 serious adverse events with 3 deaths over a 1-year period in 41 trusts. This may be the tip of the iceberg, considering the potential under-reporting. Robust reporting mechanisms are required to determine the full extent of this serious preventable harm.

(Rajendran R, Rayman G. *Diabet Med*. 2014;31(10)1218–21.)

Efficacy and Safety of the Once-Weekly GLP-1 Receptor Agonist Albiglutide versus Sitagliptin in Patients with Type 2 Diabetes and Renal Impairment: A Randomized Phase III Study

EDITOR'S VIEW

This phase III, randomized, double-blind, multicenter, 52-week study in patients with type 2 diabetes mellitus (T2DM) with inadequate glucose control and renal impairment has compared the efficacy of albiglutide with sitagliptin. The HbA_{1C} change from baseline at week 26 was significantly greater with albiglutide than sitagliptin (−0.83% vs. −0.52%; $P = 0.0003$), and the decrease in HbA_{1C} was seen through week 52. Most adverse events were mild or moderate. The incidence rates of overall gastrointestinal adverse effects were higher (31.7%) with albiglutide than with sitagliptin (25.2%). But the advantage of once-weekly administration of albiglutide than daily intake of sitagliptin is definite present.

Renally impaired patients with T2DM showed statistically superior glycemic improvement with once-weekly albiglutide therapy compared with daily sitagliptin therapy. Both drugs were similarly tolerated.

This study evaluated the weekly subcutaneous albiglutide versus daily sitagliptin in renally impaired patients with type 2 diabetes mellitus (T2DM) and inadequately controlled glycemia on a regimen of diet and exercise and/or oral antihyperglycemic medications.

In this phase III, randomized, double-blind, multicenter, 52-week study, the primary study end point was HbA_{1C} change from baseline at week 26 in patients with renal impairment, as assessed with estimated glomerular filtration rate (GFR) and categorized as mild, moderate, or severe (≥60 to ≤89,

≥30 to ≤59, and ≥15 to ≤29 mL/min/1.73 m^2, respectively). Secondary end points included fasting plasma glucose (FPG), weight, achievement of treatment targets, hyperglycemic rescue, and safety.

Baseline demographics were similar across treatment and renal impairment groups with overall mean age of 63.3 years, BMI of 30.4 kg/m^2, HbA_{1C} of 8.2% (66 mmol/mol), and diabetes disease duration of 11.2 years. HbA_{1C} change from baseline at week 26 was significantly greater for albiglutide than for sitagliptin (-0.83% vs. -0.52%, $P = 0.0003$). Decreases in HbA_{1C}, FPG, and weight were seen through week 52. Time to hyperglycemic rescue through week 52 was significantly longer for albiglutide than for sitagliptin ($P = 0.0017$). Results of safety assessments were similar between groups, and most adverse events (AEs) were mild or moderate. The incidences of gastrointestinal AEs for albiglutide and sitagliptin were as follows: overall 31.7%, 25.2%; diarrhea 10.0%, 6.5%; nausea 4.8%, 3.3%; and vomiting, 1.6%, 1.2%, respectively.

Thus once-weekly albiglutide therapy in renally impaired patients with T2DM provided statistically superior glycemic improvement with almost similar tolerability compared with daily sitagliptin therapy.

(Leiter LA, Carr MC, Stewart M, *et al*. *Diabetes Care*. 2014;37(10):2723–30.)

Simple Lifestyle Recommendations and the Outcomes of Gestational Diabetes: A 2×2 Factorial Randomized Trial

EDITOR'S VIEW

This study examined the effect of exercise and behavioral changes on metabolic parameters and the maternal and neonatal outcomes in 200 patients with gestational diabetes mellitus (GDM). In a randomized trial, all women were given the same diet. In addition, group D received dietary recommendations only, while group E was advised to walk briskly for 20 minutes per day, group B received behavioral dietary recommendations, and group BE was prescribed the same as groups B and E. In a multivariable regression model, exercise, but not behavioral changes, was associated with the reduction in postprandial glucose, HbA_{1C}, triglycerides, and C-reactive protein (CRP).

In patients with GDM, an acceptable exercise program reduced maternal postprandial glucose, HbA_{1C}, CRP, triglycerides, and maternal/neonatal complications, but not fasting glucose values. This study clears away the orthodox idea of keeping the GDM woman under complete rest. A simple walking is very effective.

The benefits of exercise and behavioral recommendations in gestational diabetes mellitus (GDM) are controversial. In a randomized trial with a 2×2 factorial design, the effect of exercise and behavioral recommendations on metabolic variables, and maternal/neonatal outcomes in 200 GDM patients were studied. All women were given the same diet: group D received dietary recommendations only; group E was advised to briskly walk 20 min/day; group B received behavioral dietary recommendations; group BE was prescribed the same as B + E. Dietary habits improved in all groups.

In a multivariable regression model, fasting glucose did not change. Exercise, but not behavioral recommendations, was associated with the reduction of postprandial glucose ($P < 0.0001$), glycated hemoglobin (HbA_{1C}; $P < 0.001$), triglycerides ($P = 0.02$), and C-reactive protein (CRP; $P < 0.001$) and reduced any maternal/neonatal complications (OR = 0.50; 95%CI = 0.28–0.89; $P = 0.02$). In GDM patients a simple exercise program reduced maternal postprandial glucose, HbA_{1C}, CRP, triglycerides, and any maternal/neonatal complications, but not fasting glucose values.

(Bo S, Rosato R, Ciccone G, *et al*. *Diabetes Obes Metab*. 2014;16(10)1032–5.)

Artificial Sweeteners Induce Glucose Intolerance by Altering the Gut Microbiota

EDITOR'S VIEW

So long the advice for the intake of artificial sweeteners were given without any restrictions only by keeping an account of total calories consumed from them. But in this study the effect of noncaloric artificial sweeteners (NASs) on the intestinal microbiota of mice has been shown to have alterations in the composition and function of their gut flora, leading to glucose intolerance by facilitated absorption. Fecal transplantation from NAS-consuming mice with glucose intolerance into non–NAS consuming mice led to glucose intolerance. Antibiotics reversed the effects in NAS-consuming mice. If this stands true in human trial, diabetics will have to sacrifice sweet taste totally.

Noncaloric artificial sweeteners (NASs) are among the most widely used food additives worldwide, regularly consumed by lean and obese individuals alike. This artificial sweetener consumption is considered safe and beneficial owing to their low-caloric content, yet supporting scientific data remain sparse and controversial. Here Suez *et al*. demonstrated that consumption of commonly used NAS formulations drives the development of glucose intolerance through induction of compositional and functional alterations to the intestinal microbiota.

These NAS-mediated deleterious metabolic effects are abrogated by antibiotic treatment, and are fully transferrable to germ-free mice upon fecal transplantation of microbiota configurations from NAS-consuming mice, or of microbiota anaerobically incubated in the presence of NAS. The researchers identified NAS-altered microbial metabolic pathways that are linked to host susceptibility to metabolic disease, and demonstrated similar NAS-induced dysbiosis and glucose intolerance in healthy human subjects. Collectively, these results link NAS consumption, dysbiosis, and metabolic abnormalities, thereby calling for a reassessment of massive NAS usage.

(Suez J, Korem T, Zeevi D, Zilberman-Schapira G, *et al*. *Nature*. 2014;[EPub Ahead of Print].)

Prediabetes and the Risk of Cancer: A Meta-analysis

EDITOR'S VIEW

The study group conducted a meta-analysis of 16 prospective studies, which included 891,426 participants with prediabetes to assess overall cancer risk. People with prediabetes had the highest rates of cancer in the stomach, colorectum, pancreas, liver, endometrium, and breast ($P < 0.05$). Of these, the liver, endometrium, and stomach/colorectum were the most frequent sites of cancer ($P = 0.01$). A meta-analysis of cohort studies in prediabetes shows an increase in cancer, predominately of the gut/liver, of about 15%. This study highlights that dysglycemia even at the stage of prediabetes should be seriously assessed for chances of malignancy.

For more than a decade, numerous studies have demonstrated an increased risk for cancer and cancer-related mortality in obese individuals and patients with type 2 diabetes mellitus (T2DM). This has generally been seen in all ethnic groups and for most solid tumors.

This study by Huang and colleagues is a meta-analysis of a cohort of over 860,000 individuals with prediabetes. Prediabetes was defined as either impaired fasting glucose or glucose intolerance following a glucose tolerance test.

Similar to the findings in obesity and T2DM, prediabetes is also associated with increased cancer risk for most, but not all, tumors; prostate cancer is once again less common, although mortality from prostate cancer has usually increased.

While the meta-analysis has demonstrated quite convincingly the association between prediabetes and cancer risk, no mechanism can be derived from these types of studies. Prediabetes is often associated with insulin resistance and hyperinsulinemia; the latter is clearly becoming recognized as a possible causal factor. Other factors that may be involved include hyperlipidemia, cytokines, and adipocytokines, which are usually not measured in these types of studies.

The results from prospective cohort studies of prediabetes (impaired fasting glucose and/or impaired glucose tolerance) and risk of cancer are controversial. We conducted a meta-analysis to evaluate the risk of cancer in association with impaired fasting glucose and impaired glucose tolerance.

The PubMed, EMBASE, and Cochrane Library databases were searched for prospective cohort studies with data on prediabetes and cancer. Two independent reviewers assessed the reports and extracted the data. Prospective studies were included if they reported adjusted relative risks (RRs) with 95% confidence intervals (CIs) for the association between cancer and prediabetes. Subgroup analyses were conducted according to end point, age, sex, ethnicity, duration of follow-up, and study characteristics.

Data from 891,426 participants were derived from 16 prospective cohort studies. Prediabetes was associated with an increased risk of cancer overall (RR 1.15; 95% CI 1.06, 1.23). The results were consistent across cancer end point, age, duration of follow-up, and ethnicity. There was no significant difference for the risk of cancer with different definitions of prediabetes. In a site-specific cancer analysis, prediabetes was significantly associated with increased risks of cancer of the stomach/colorectum, liver, pancreas, breast, and endometrium (all $P < 0.05$), but not associated with cancer of the bronchus/lung, prostate, ovary, kidney, or bladder. The risks of site-specific cancer were significantly different ($P = 0.01$) and were highest for liver, endometrial, and stomach/colorectal cancer.

Overall, prediabetes was associated with an increased risk of cancer, especially liver, endometrial, and stomach/colorectal cancer.

(Huang Y, Cai X, Qiu M, *et al*. *Diabetologia*. 2014.

Impact of Comorbidities on Pharmacotherapy of Painful Diabetic Neuropathy in Clinical Practice

EDITOR'S VIEW

In this 6-month observational study, the impact of comorbidities on treatment effectiveness with duloxetine and anticonvulsants was assessed on 2,575 participants with diabetic peripheral neuropathic pain (DPNP). Out of them, 89.5% reported comorbidities, which included macro- and micro-angiopathic conditions, dyslipidemias, chronic pain (including joint pain), and depression. Treatment with duloxetine was more effective in those with depression, joint pain, and higher baseline BPI scores.

This study concludes that many patients with diabetic neuropathy have additional comorbidities that can contribute to pain. Prescribers should choose a pain medication that can ideally treat more than one source of pain. Prescribers should also take care of the associated complications during treating DPNP.

Ziegler *et al*. studied the impact of baseline comorbidities on the effectiveness of duloxetine and anticonvulsants (pregabalin /gabapentin) in patients with painful diabetic neuropathy in clinical care.

In this study, the outcomes from a 6-month, observational study with 2,575 patients initiating/switching diabetic peripheral neuropathic pain (DPNP) treatment were analyzed post-hoc. Propensity scoring was used to adjust for baseline factors influencing treatment choice in 1,523 patients receiving duloxetine or anticonvulsants. Analysis of covariance models with fixed effects for baseline pain, treatment, propensity score, baseline characteristics, or comorbidities, and their interaction with treatment were used to estimate LS mean effects on brief pain inventory (BPI) average pain and interference scores.

Here 89.5% of patients reported comorbidities, including hypertension (70.5%), hyperlipidemia (39.2%), and depression (24.8%). Macrovascular complications (37.0%) and "other chronic pain" (41.5%), particularly joint pain, had an impact on both pain treatments, that is, less improvement of average pain and interference of pain. Better treatment responses with duloxetine versus anticonvulsants were observed in patients with depression, those with high baseline BPI total interference score, especially general activity, and in patients with joint pain. The conclusion of the study was that comorbidities such as macroangiopathy and depression as well as pain characteristics should be considered in the treatment of DPNP as they may predict the effectiveness of duloxetine and anticonvulsants.

(Ziegler D, Schneider E, Boess FG, *et al.*
J Diabetes Complicat. 2014;28(5)698–704.)

Impact of Age, Age at Diagnosis, and Duration of Diabetes on the Risk of Macrovascular and Microvascular Complications and Death in Type 2 Diabetes

EDITOR'S VIEW

This is a part of the ADVANCE trial where 11,140 participants with type 2 diabetes mellitus (T2DM) were enrolled to examine for the development of microvascular disease, macrovascular disease, and death as associated with age, age at diagnosis, and duration of diabetes. Microvascular events, macrovascular events, and death were all well correlated with the duration of diabetes. Macrovascular events and death were associated with age and age at diagnosis. But among the younger patients, an interaction between the diabetes duration, age, and risk for microvascular events was identified (P = 0.002), pointing toward the fact that these patients are at increased risk for microvascular complications.

Age at diagnosis predicts mortality and macrovascular disease, while microvascular disease is related to duration of diabetes.

The associations between age (or age at diagnosis), diabetes duration, and major macrovascular events, all-cause death, and major microvascular events were examined in 11,140 patients with type 2 diabetes mellitus (T2DM) randomly allocated to intensive or standard glucose control in the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial. Rates were calculated by 5-year baseline age (or age at diagnosis) and diabetes duration strata. Risks were estimated using Cox models adjusted for treatment assignment and HbA_{1C}.

The mean age (±SD) was 65.8±6.4 years, age at diagnosis was 57.8±8.7 years, and diabetes duration was 7.9±6.4 years. Diabetes duration was associated with the risk of macrovascular events (HR 1.13 [95% CI 1.08, 1.17]), microvascular events (1.28 [1.23, 1.33]), and death (1.15 [1.10, 1.20]), whereas age (or age at diagnosis) was only associated with the risk of macrovascular events (1.33 [1.27, 1.39]) and death (1.56 [1.48, 1.64]). No interaction was observed between diabetes duration, age, and the risk of macrovascular events or death (both $P > 0.4$). However, an interaction was observed between diabetes duration, age, and the risk of microvascular events (P = 0.002), such that the effects of increasing diabetes duration were greatest at younger rather than older age.

In patients with T2DM, age or age at diagnosis and diabetes duration are independently associated with macrovascular events and death, whereas only diabetes duration is independently associated with microvascular events and this effect is greater in the youngest patients.

(Zoungas S, Woodward M, Li Q, *et al*. *Diabetologia*. 2014.

Combination Therapy with Metformin Plus Sulphonylureas Versus Metformin Plus DPP-4 Inhibitors: Association With Major Adverse Cardiovascular Events and All-Cause Mortality

EDITOR'S VIEW

The study compared the differences in all-cause mortality and major adverse cardiovascular events (MACE) in diabetic patients using a metformin–sulfonylurea combination (SU; *n* = 33,983) with the patients using a metformin–DPP-4 inhibitor combination (*n* = 7,864).

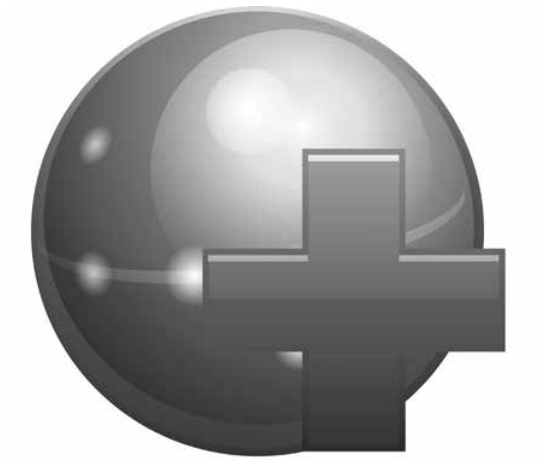
Results showed greater all-cause mortality risk (aHR = 1.357; 95% CI, 1.076–1.710) and greater risk for CV events (aHR = 1.710; 95% CI, 1.280–2.285) with a metformin–SU combination versus metformin-DPP-4 combination. This study favors the use of metformin-DPP-4 combination over the use of metformin–sulfonylurea combination.

Abstract: To compare the risk of major adverse cardiovascular events (MACE) and mortality for combination therapies with metformin and either sulphonylurea (SU) or dipeptidyl peptidase-4 inhibitor (DPP-4i).

Data were from the UK Clinical Practice Research Datalink (CPRD). Patients with type 2 diabetes mellitus (T2DM) were selected if initiated with combination therapies comprising metformin plus SU or DPP-4i 2007–2012. The coprimary end points were all-cause mortality and MACE (myocardial infarction or stroke). Times to endpoints were compared using Cox proportional hazards models. Additional analyses were performed on subsets matched directly on key characteristics and by propensity score.

A total of 33,983 patients were prescribed SU and 7,864 DPP-4i, and 5,447 patients in each cohort could be matched directly and 6,901 by propensity score. In the main analysis, there were 716 MACE events and 1,217 deaths. Crude event rates for MACE were 11.3 events per 1000 person-years (pkpy) for SU, versus 5.3 pkpy for DPP-4i. For all-cause mortality, rates were 16.9 versus 7.3 pkpy, respectively. Following adjustment, there was a significant increase in the adjusted hazard ratio (aHR) for all-cause mortality in those exposed to SU across all analytical models: aHR = 1.357 (95% CI 1.076-1.710) for all subjects, 1.850 (1.245–2.749) directly matched, and 1.497 (1.092–2.052) propensity-matched. For MACE, aHR was 1.710 (1.280–2.285) for all subjects, 1.323 (0.832–2.105) directly matched, and 1.547 (1.076–2.225) propensity-matched. There was a reduction in all-cause mortality for patients treated with metformin combined with DPP-4i versus metformin plus SU, and a similar trend for MACE.

(Morgan CL, Mukherjee J, Jenkins-Jones S, *et al. Diabetes Obes Metab*. 2014;16(10)977–83.)



Incidence of Pancreatitis and Pancreatic Cancer in a Randomized Controlled Multicenter Trial (SAVOR-TIMI 53) of the Dipeptidyl Peptidase-4 Inhibitor Saxagliptin

EDITOR'S VIEW

In this study, the incidence of pancreatitis or pancreatic cancer between the treatment group with saxagliptin and placebo groups in 16,492 patients with type 2 diabetes mellitus (T2DM) with cardiovascular disease or risk factors were evaluated. After a follow-up period of 2.1 years, no difference was observed in the incidence of pancreatitis or pancreatic cancer between the treatment and placebo groups.

These findings establish that treatment of T2DM patients with dipeptidyl peptidase-4 inhibitors such as saxagliptin likely does not increase risk for pancreatitis or pancreatic cancer. The strength of the study number of the patients is not negligible.

Raz *et al.* studied the incidence of pancreatitis and pancreatic cancer in the SAVOR-TIMI 53 trial in a total of 16,492 type 2 diabetes mellitus (T2DM) patients ≥40 years of age with established cardiovascular (CV) disease or CV risk factors. The patients were randomized to saxagliptin or placebo and followed for 2.1 years. Outcome measures were investigator reported with blinded expert adjudication of total pancreatitis (acute and chronic) and reported cases of pancreatic cancer. Trial investigators reported 35 events of pancreatitis in each treatment arm in 63 patients (33 [0.40%] in the saxagliptin arm and 30 [0.37%] in control arm), with a hazard ratio (HR) of 1.09 (95% CI 0.66–1.79, $P = 0.80$). Analysis confirmed pancreatitis in 24 patients (26 events) in the saxagliptin arm (0.29%) and 21 patients (25 events) in placebo arm (0.26%), with an HR of 1.13 (0.63–2.06, $P = 0.77$). Cases of definite acute pancreatitis were confirmed in 17 (0.2%) versus 9 (0.1%) (HR 1.88 [0.86–4.41], $P = 0.17$), definite plus possible pancreatitis in 22 versus 16 (HR 1.36 [0.72–2.64], $P = 0.42$), and chronic pancreatitis in 2 versus 6 (HR 0.33 [0.05–1.44], $P = 0.18$) in the saxagliptin and placebo arms, respectively.

No differences in time to event onset, concomitant risk factors for pancreatitis, investigator-reported causality from study medication or disease severity, and outcome were found between treatment arms. The investigators reported 5 and 12 cases of pancreatic cancer in the saxagliptin and placebo arms, respectively (HR 0.42 [0.13–1.12], $P = 0.09$). Thus the SAVOR-TIMI 53 trial showed that, within 2.1 years of follow up, risk for pancreatitis in T2DM patients treated with saxagliptin was low and apparently similar to placebo, with no sign of increased risk for pancreatic cancer. Further studies are needed to completely resolve the pancreatic safety issues with incretin-based therapy.

(Raz I, Bhatt DL, Hirshberg B, *et al. Diabetes Care*. 2014;37(9) 2435–41.)