Diabetes2017

From the 77th Annual Scientific Sessions of the American Diabetes Association ■ San Diego, CA

2014 2015 2016 **2017** 2018 2019 2020

Sponsored by **Yale School of Medicine**, Department of Internal Medicine, Section of Endocrinology

Volume **35** ■ June 11, 2017 ■ Issue **2**

Important data on diabetes presented at the 77th Annual Scientific Sessions of the American Diabetes Association come to you in **Diabetes 2017**, a newsletter CME program that is being offered to you by Yale School of Medicine. After receiving the newsletters by e-mail, please go to www.cme.yale.edu and take the CME quiz. You will qualify for up to 5.0 *AMA PRA Category 1 Credits™* to be issued by Yale School of Medicine.

Diabetes 2017 is being offered to physicians practicing in the United States. After successfully completing this program, participants will be able to:

- Explain the pathogenesis of Type 2 diabetes, especially the coexisting roles of insulin resistance, abnormal insulin secretion, and derangements in the incretin axis.
- Highlight new discoveries in the immunopathogenesis of Type 1 diabetes.
- Describe the evolving cellular mechanisms associated with the progression of diabetes and its complications.
- Implement strategies for the early diagnosis and treatment of diabetes.
- Recognize the clinical manifestations of the macrovascular and microvascular complications of diabetes and describe appropriate therapeutic interventions.
- Recognize the interrelationship between insulin resistance, hyperglycemia, inflammation, and atherosclerosis in patients with Type 2 diabetes.
- Underscore the importance of lifestyle change, exercise, and dietary interventions in the management of diabetes.
- Compare the mechanisms of actions of a growing array of oral and injectable pharmacologic agents for the treatment of diabetes, their risks and benefits, and their proper evidence-based role in the management of this disease.
- Identify evolving and emerging management strategies for diabetes (e.g., combination therapies, new insulin delivery systems, new glucose monitoring techniques, novel drugs).
- Describe the approach to managing dyslipidemia, hypertension, and cardiovascular risk factors in patients with diabetes.
- Identify unique management issues among special sub-populations of patients with diabetes.
- Discuss the impact of diabetes on healthcare systems.

Yale School of Medicine is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education to physicians.

Yale School of Medicine designates this enduring material for a maximum of 10 *AMA PRA Category 1 Credits™* (5.0 credit hours per test). Physicians should claim only the credit commensurate with the extent of their participation in the activity.

This CME program is supported in part through educational grants from Eli Lilly and Company and Merck & Co., Inc. It is understood that supporters will in no way control the content of this program.

EMPA-REG OUTCOME Update

The most recent glucose-lowering category for the management of Type 2 diabetes is the SGLT-2 inhibitors. These oral agents reduce blood glucose levels through the induction of glucosuria via inhibition of a sodium-glucose cotransporter in the proximal nephron that is normally responsible for the reclamation of glucose from the glomerular filtrate. In addition to a modest effect on HbA1c (approximately -0.6% to -0.8%), drugs in this class are associated with mild improvements in blood pressure, body weight, triglycerides, and albuminuria. Their main side effects are urinary frequency and genitourinary infections. One member, canagliflozin, has also been linked to a small increased risk of lower extremity amputations (mainly toes) and bone fractures. All SGLT-2 inhibitors could potentially result in acute kidney injury, due to changes in plasma volume and renal blood flow, as well as reductions in intraglomerular pressures. Long-term, however, they likely have renal benefits.

There has been growing interest in this drug class since the results of EMPA-REG OUTCOME were reported in 2015. That cardiovascular (CV) outcome trial found, for the first time in high-risk patients with Type 2 diabetes, a 14% relative risk reduction in major adverse CV events (MACE) in patients treated with empagliflozin vs. placebo on top of standard care. This was driven mainly by a surprising 38% reduction in CV mortality and 32% reduction in all-cause mortality. Moreover, there were 35% fewer hospitalizations for heart failure, likely related to the drug's diuretic effect. In contrast, an explanation for the mortality benefit has remained elusive.

At the ADA Scientific Sessions this week, the EMPA-REG investigators presented interesting updates from their trial. The first two presentations in a moderated poster session sought to determine the impact of CV disease risk factor control on the SGLT-2 inhibitor's effect on CV mortality and heart failure hospitalizations, respectively. In two corresponding abstracts, Zinman *et al.* (abstract 1173-P) and Fitchett *et al.* (abstract 1172-P) demonstrated that adjusting for optimal control of blood pressure (<140/90), LDL-cholesterol (C) (<100 mg/dL), and HbA1c (<7.5%) had absolutely no effect on the hazard ratio (HR) for study drug vs. placebo on these outcomes (Figure 1). The consistency of the benefit was striking. As Dr. Zinman mentioned in his comments, this should not be surprising since the effect of empagliflozin on these variables (lower blood pressure and HbA1c and higher LDL-C) was quite modest.

In a related presentation, Inzucchi *et al.* (abstract 1174-P) delved further into the effect of HbA1c. The investigators conducted several analyses for CV mortality. The first was by baseline HbA1c. Here, there was no statistical heterogeneity in the treatment response for patients who started the trial with HbA1c <7.0%, 7.0-7.9%, 8.0-8.9%, or ≥9.0% (p=0.41). In the second analysis, the data were adjusted for HbA1c control (<7.5% vs. >7.5%) at baseline and during the trial. The HR's for CV death were also essentially superimposable at 0.62 (0.49-0.77) and 0.62 (0.49-0.78), respectively. In the third analysis, adjustments were made for the change from baseline to the last HbA1c obtained during the trial. The HR for treatment benefit was 0.60 (0.44-0.80) for patients experiencing any reduction in HbA1c vs. 0.64 (0.45-0.91) for those experiencing no change or an increase in HbA1c. Similar findings were reported in the fourth analysis, which adjusted for HbA1c change from baseline at week 12 (during which time adjustments in background therapy could not be made).

These data indicate that HbA1c is very unlikely to be an important mediator of the reduction in CV mortality from empagliflozin. Moreover, it suggests that clinical decision making about continuing therapy should not necessarily be based solely on the drug's glucose-lowering effects. Of course, more extensive work is necessary before we can come to such a provocative conclusion.

Wanner *et al.* presented updated renal data from the trial (abstract 1175-P). The study group had previously reported a 39% reduction in the secondary outcome of progression of nephropathy. This composite consisted of persistent macroalbuminuria, doubling of serum creatinine,

Continued on page 2

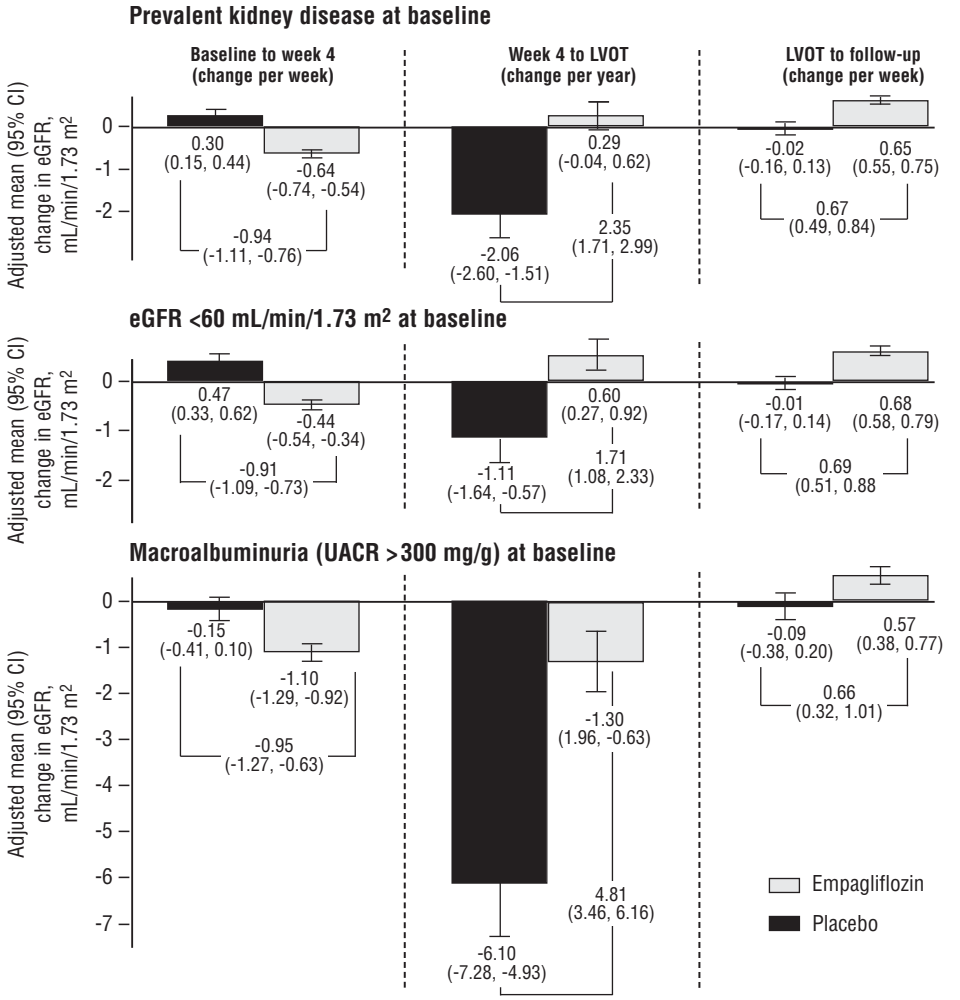
EMPA-REG OUTCOME Update

Continued from page 1

and the need for renal replacement therapy, with each component contributing to the risk reduction. Renal functional 'slope analyses' have also shown an initial dip in eGFR in the empagliflozin group, followed by long-term stabilization of renal function. For the current study, the investigators explored the impact of the SGLT-2 inhibitor on eGFR in patients at high risk for progressive kidney disease. The average rates of loss of renal function were measured in 3 subgroups of patients: (1) prevalent kidney disease (eGFR <60 ml/min/1.73m^2 and/or macroalbuminuria), (2) eGFR <60 ml/min/1.73m^2, and (3) macroalbuminuria. At baseline, these subgroups comprised 32%, 26%, and 11% of patients, respectively. Each subgroup randomized to active therapy experienced the expected initial decrease in eGFR from study drug between baseline and week 4 (Figure 2). Consistently, however, this was then followed by long-term stabilization of renal function through the last dose of medication taken. Importantly, after the drug was stopped, eGFR rapidly moved toward baseline. In contrast, there was a progressive decline in eGFR in the placebo group after week 4. Most notably (bottom, middle panel), the annualized loss of eGFR in the macroalbuminuric patients on placebo was about 6 ml/min/1.73 m^2, translating to an approximate loss of 18 ml/min/1.73 m^2 during the course of the 3-year study. These data suggest that empagliflozin has the potential to slow renal function decline in patients at high risk for progression of their kidney disease.

We look forward to the CANVAS results being presented tomorrow in San Diego to determine whether the SGLT-2 inhibitor canagliflozin has effects similar to those demonstrated by empagliflozin.

Figure 2. Annualized Changes in eGFR: Empagliflozin vs. Placebo during 3 Time Periods of EMPA-REG OUTCOME



eGFR=estimated glomerular filtration rate, UACR=urine albumin:creatinine ratio, LVOT=last visit on treatment.

Figure 1. Effect of Empagliflozin on CV Death and Hospitalization for Heart Failure after Adjustment for CV Risk Factor Control

Cardiovascular Death	*Hazard Ratio (95% CI)*	*p-value*	*Hazard Ratio (95% CI)*
Primary analysis	0.62 (0.49, 0.77)	p<0.0001	
Adjusted for time-dependent control of blood pressure	0.61 (0.49, 0.76)		
Adjusted for time-dependent control of LDL-C	0.59 (0.47, 0.75)		
Adjusted for time-dependent control of HbA1c	0.62 (0.49, 0.78)		
Adjusted for time-dependent control of blood pressure, LDL-C and HbA1c	0.61 (0.48, 0.76)		

Hospitalization for Heart Failure	*Hazard Ratio (95% CI)*	*p-value*	*Hazard Ratio (95% CI)*
Primary analysis	0.65 (0.50, 0.85)	p=0.0017	
Adjusted for time-dependent control of blood pressure	0.67 (0.51, 0.87)		
Adjusted for time-dependent control of LDL-C	0.65 (0.50, 0.86)		
Adjusted for time-dependent control of HbA1c	0.64 (0.49, 0.83)		
Adjusted for time-dependent control of blood pressure, LDL-C, and HbA1c	0.66 (0.50, 0.86)		

T2DM

Predict, Prevent, Protect

T1DM

The diabetes epidemic has prompted multiple avenues of investigation into factors that predict as well as ways to prevent the disease. We summarize the results of several such studies presented at this year's ADA Scientific Sessions, involving risks for several forms of diabetes: Type 1, Type 2, and gestational.

Metabolic Risk Factors Identified Decades Before Type 2 Diagnosis

Malmström and associates from Sweden and the US noted that Type 2 diabetes is associated with subtle elevations of glucose and lipids many years before diagnosis (abstract 250-OR). In a nested-design study, the investigators identified 47,997 new Type 2 diabetes cases from 1985-2012 in the Swedish AMORIS cohort (n =537,119) that were each matched by sex, age, and calendar date with 5 controls. Risk factors (fasting glucose, triglycerides, total cholesterol, and BMI) were measured at clinical examinations between 1985 to 1996. The 20-year risk for diabetes based on age, sex, BMI, and trajectory (yearly mean over time) for glucose and triglycerides was estimated using logistic regression.

Cases of Type 2 diabetes had higher trajectory for glucose and triglycerides compared to controls, long before diagnosis (Figure 3). The 20-year risk of diabetes was high in obese subjects even at low-to-moderate glucose levels. Triglycerides ≥124 mg/dL increased the risk, irrespective of BMI and trajectory of glucose. Women showed at least the same risk of developing diabetes as men at corresponding risk factor levels.

These findings suggest that diabetogenic processes, presumably related to chronic insulin resistance, predate a Type 2 diabetes diagnosis by decades.

Table 1. Risk Reduction for Diabetes After 15 Years of Metformin

	*DM by Glucose**			*DM by HbA1c†*		
	DM Incidence, % per year		*DM Risk Reduction‡*	*DM Incidence, % per year*		*DM Risk Reduction‡*
	Metformin	*Placebo*	*(95% CI)*	*Metformin*	*Placebo*	*(95% CI)*
All patients	*5.9*	*7.1*	***17 (7, 27)***	*2.9*	*4.5*	***36 (25, 45)***
Age (yrs)						
25-44	*6.0*	*8.2*	***27 (9, 42)***	*3.5*	*5.2*	***32 (10, 48)***
45-59	*5.7*	*7.0*	***18 (4, 31)***	*2.7*	*4.3*	***35 (19, 48)***
≥60	*6.3*	*5.9*	*-4 (-38, 22)*	*2.2*	*4.3*	***45 (18, 63)***
BMI (kg/m²)						
22 - <30	*5.2*	*5.8*	*10 (-13, 28)*	*2.1*	*3.6*	***40 (19, 56)***
30 - <35	*5.6*	*6.8*	*17 (-3, 34)*	*2.7*	*4.4*	***38 (18, 54)***
≥35	*6.8*	*8.7*	***22 (6, 35)***	*3.9*	*5.7*	***30 (11, 45)***

DM = diabetes mellitus

** Fasting plasma glucose ≥126 mg/dL or 2-hr OGTT plasma glucose ≥200 mg/dL*

† HbA1c ≥6.5%

‡ Metformin vs. placebo.

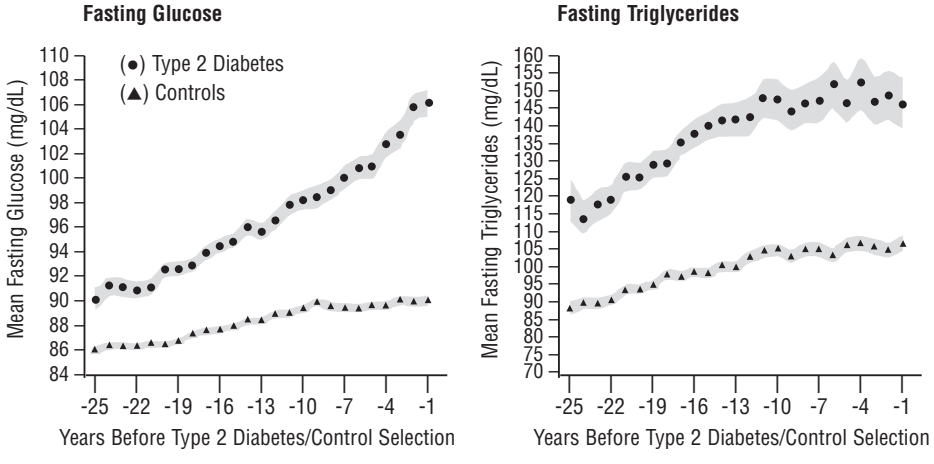
Note: p<0.05 noted in bold.

Metformin for Diabetes Prevention

In the landmark trial conducted by the Diabetes Prevention Program (DPP) Research Group, metformin reduced the 3-year development of diabetes by 31% (95% CI: 17%, 43%), compared with placebo, in a high-risk cohort (fasting plasma glucose 95-125 mg/dL and overweight or obese) (*N Engl J Med* 2002; 346:393-403). Participants who, at baseline, were younger than 60 years, had a BMI ≥35 kg/m², and women with a history of gestational diabetes mellitus (GDM) had the greatest responses to metformin, with 44%, 53%, and 51% reductions in diabetes development, respectively.

Today at the ADA 2017 Scientific Sessions, Nathan and DPP investigators reported results of the DPP follow-up, known as the DPP Outcomes Study (DPPOS) in which placebo was discontinued and the original metformin group received open-label metformin and lifestyle intervention (abstract 169-OR). Over 15 years, metformin treatment continued to confer beneficial effects on the prevention of diabetes (defined by fasting plasma glucose, 2-hour OGTT criteria, or by HbA1c ≥6.5%) in participants of younger age and greater BMI (Table 1). In addition, metformin decreased diabetes development in women with a prior history of GDM (n=233) by 40.6% (95% CI: 16%, 58%), compared with 9.7% (-6%, 23%) in parous women with no GDM history (n=1223). These results inform the discussion of whether and in whom to use metformin for diabetes prevention. Clearly, long-term benefits can be expected with proper patient selection.

Figure 3. Risk Factors Predate Type 2 Diabetes Diagnosis



Early Pregnancy HbA1c Screening for GDM?

Lawrence and coworkers from California identified GDM in a diverse obstetric population of women (91,855 deliveries from 2012-2015) who had first trimester HbA1c screening (mean age 30.8 years, mean pre-pregnancy BMI 26.8 [±6.2] kg/m², 51% Latina) (abstract 207-OR).

Continued on page 4

Predict, Prevent, Protect

Continued from page 3

GDM was identified by applying the newer (and still controversial) International Association of Diabetes in Pregnancy Study Group's (IADPSG) or the older and standard Carpenter & Coustan (C&C) criteria to 75- or 100-gram OGTT results, respectively. Relative risks (RR) and 95% CI were reported from log binomial models.

In the study cohort, 16.7% had prediabetes defined by HbA1c (5.7-6.4%), and 0.1% had overt diabetes, with HbA1c ≥6.5%. Of 87,373 who underwent testing, 11.6% had GDM. Women with prediabetes by this measure had more than a 50% greater risk (RR=1.54; 95% CI: 1.51, 1.57) of GDM than those with normal HbA1c, after adjusting for age, race/ethnicity, pre-pregnancy BMI, GDM test results (C&C vs. IADPSG), and delivery year. Obesity, age ≥40 years, and Asian race each had similar risk of GDM, as elevated HbA1c. These data suggest that HbA1c screening early in pregnancy might be a convenient way to identify women at increased risk for GDM.

Using Autoantibodies to Predict Type 1 Diabetes Risk

The risk of developing Type 1 diabetes is extremely high among young children (5-year risk 44%, 10-year risk 70%) with multiple (≥2) autoantibodies (Abs), but this is far less studied in older individuals. Using Cox regression analysis, Jacobsen and coworkers from the US and Australia, examined the impact of the Diabetes Prevention Trial Risk Score (DPTRS), types of autoantibodies, and age upon the risk of Type 1 diabetes (abstract 249-OR). They used data from 1,896 participants in the TrialNet Pathway to Prevention study (mean±SD age: 13.5±10.7 years; range 1-45 years); Abs measured were IAA, GADA, IA-2A, ICA, and ZnT8.

Overall, in those with normal glucose levels and DPTRS of 6.5 or greater, the 5-year risk of developing Type 1 diabetes was 49% and 57% with 2 Abs and >2 Abs, respectively. For those with lower DPTRS, the corresponding risk was only 12% and 21%, respectively. After adjusting for Ab number, those with positive GADA as one of their ≥2 autoantibodies had lower risk (HR: 0.337 [0.281, 0.505]; p<0.001) and those with positive IA-2A had higher risk (HR: 1.78 [1.33, 2.38]; p<0.001). The investigators also found that risk for developing Type 1 diabetes in a diversely-aged population with ≥2 Abs decreased by 4.5% (95% CI: 3.3%, 5.6%) with each year of aging (p<0.001).

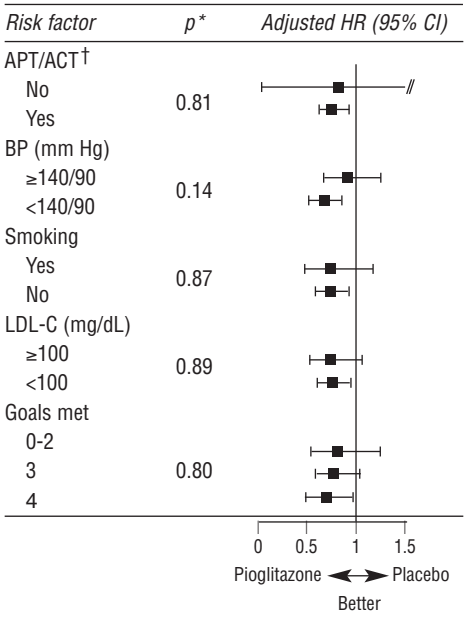
Taken together, these results suggest that a considerable proportion of diversely aged individuals with ≥2 Abs appear unlikely to progress to Type 1 diabetes over a 5-10 year period and that this risk declines as they age.

Pioglitazone — Worth a Second Look?

The thiazolidinediones have certainly fallen onto hard times over the past decade. Once a very popular class of glucose-lowering drugs for Type 2 diabetes, increasing concerns and, to some degree, confusion about their risks have resulted in their relegation to almost niche status. However, despite prior concerns raised by a 2007 meta-analysis of Phase 3 data, rosiglitazone was eventually vindicated as a drug that does *not* increase myocardial infarction (MI) in the RECORD trial (Home *et al., Lancet* 2009). Also, pioglitazone was eventually found *not* to increase the risk of bladder cancer in a 10-year prospective study from Kaiser-Permanente (Lewis J *et al., JAMA* 2016). So, the class may be safer than currently considered by most clinicians, particularly pioglitazone. More recently, two clear and important benefits of pioglitazone have also been confirmed — a significant reduction in CV events and a major improvement in non-alcoholic steatohepatitis (NASH). Three abstracts this week dealt with these advantages of pioglitazone. Will their recognition result in a resurgence of interest in this now inexpensive generic agent?

In the recent *Insulin Resistance Intervention after Stroke* (IRIS) trial (Kernan *et al. NEJM* 2016), pioglitazone, an insulin-sensitizing thiazolidinedione, reduced the primary composite outcome of fatal/non-fatal MI or stroke vs. placebo in 3876 insulin-resistant, but non-diabetic patients with a recent stroke or transient ischemic attack (TIA). In a follow-up study from IRIS, Inzucchi and international colleagues wondered if the benefits of pioglitazone could be mitigated by standard secondary prevention strategies used at baseline by the IRIS cohort (abstract 416-P). Control of the following risk factors were assessed: use of anti-platelet and/or anti-coagulant therapy ("anti-thrombotic therapy"), blood pressure control (<140/90), LDL-C control (<100 mg/dL), and non-smoking status. Cox model HRs for pioglitazone vs. placebo and Kaplan-Meier cumulative outcome-free rates were then calculated.

Figure 4. Stroke/MI 5-Year Risk by Treatment Group, Based on Control of Risk Factors at Baseline



* p-value for test of interaction between treatment and hazard ratio.

† Antiplatelet (APT) or anticoagulant (ACT) use.

Primary outcome HRs did not differ significantly for patients who had vs. had not achieved the above 4 secondary prevention goals: (1) anti-thrombotic therapy, 0.76 vs. 0.84 (interaction p=0.96); (2) blood pressure, 0.67 vs. 0.94 (p=0.09); LDL-C, 0.78 vs. 0.73 (p=0.77); and non-smoking status, 0.73 vs. 0.86 (p=0.49). Results were similar after adjustment for baseline risk features (Figure 4). Results were also unchanged in two sensitivity analyses, the first for LDL-C above or below 70 mg/dL and the second for baseline statin therapy (yes/no). HRs were also consistent in those meeting all 4 vs. 3 or fewer of the goals (0.69 vs. 0.81, p=0.47) as well as in those meeting 3-4 vs. 0-2 of the goals (0.74 vs. 0.87, p=0.51).

So, in insulin-resistant but non-diabetic patients with recent stroke or TIA, use of the thiazolidinedione, pioglitazone, decreased the risk of MI and recurrent stroke irrespective of prevalent risk factor management, suggesting an incremental benefit of this insulin-sensitizing drug.

Stroke was also the topic of an inquiry by Morgan and Welsh colleagues who used a National Health System (NHS) database from the

Continued on page 5

Pioglitazone — Worth a Second Look?

Continued from page 4

UK to determine whether users of pioglitazone between 2000-2012 experienced less stroke events than those taking other glucose-lowering drugs (abstract 457-P). Cases with at least 90 days of pioglitazone exposure were found, with the index date being that of the first prescription of the drug. Those with a heart failure diagnosis were excluded because the drug is contraindicated in that disorder. Non-exposed controls were then found, matched for age, sex, HbA1c, diabetes duration, history of prior stroke, a variety of co-morbidities, and prior glucose-lowering therapy. The primary outcome was the risk of incident stroke, with time to event evaluated using the Cox proportional hazards model adjusted for potential confounders, including atrial fibrillation. 4,484 matched pairs were identified. For the 98% of patients with no prior history of stroke, there were 42 (4.1 per 1,000 patient-years) stroke events during pioglitazone exposure vs. 71 (8.2 per 1,000 patient-years) in the control group. Corresponding values during the entire follow-up period were 140 (5.7 per 1,000 patient-years) vs. 184 (8.5 per 1,000 patient-years). After adjustments, the HRs were 0.489 (95% CI, 0.329-0.727) on treatment and 0.661 (0.524-0.833) for the entire follow-up period for pioglitazone vs. placebo. For the 2% of patients with prior history of stroke, there appeared to be a similar treatment effect but the data were non-significant, likely due to much smaller numbers (HR 0.607 [0.277-1.331] on treatment and 0.597 [0.354-1.007] for entire follow-up period). These data are consistent with the IRIS findings and further underscore the benefit of pioglitazone in patients with or at risk for stroke.

Bril and American colleagues have been interested in the effects of pioglitazone to reduce non-alcoholic fatty liver disease (NAFLD) (abstract 245-OR). The group recently reported major histological improvement in this group of patients treated with the thiazolidinedione over a period of 36 months (Cusi *et al., Ann Intern Med* 2016). This benefit appeared to correlate with the drug's insulin-sensitizing activity. They had randomized 101 patients with diabetes or prediabetes and NASH (age: 50±1 years, 70% male, BMI: 34.4±0.5 kg/m^2) to pioglitazone or placebo for 18 months. The primary outcome was an improvement in the NAFLD activity score of 2 points or more without worsening of fibrosis on liver biopsy. Secondary outcomes included resolution of NASH on histology, intrahepatic triglyceride (IHTG) content by magnetic resonance spectroscopy, and insulin sensitivity as assessed during a euglycemic hyperinsulinemic clamp procedure. Both groups were equally matched at baseline.

In San Diego this week, the investigators presented some new data, comparing the effects of pioglitazone among the two major sub-groups —those who had pre-existing Type 2 diabetes and those with just prediabetes. Treatment effect for the primary outcomes was comparable between the two groups: 48% of patients with diabetes vs. 46% of patients with prediabetes, although complete resolution of NASH seemed greater in those with diabetes (44% vs. 26%). Significant improvement in fibrosis was also only observed in the diabetic group (p=0.035). Other intermediate parameters were similar between the groups, including changes in liver fat content (-11±2% vs. -9±2%, p=0.62), plasma ALT levels (-50±10 vs. -36±5 U/L, p =0.22), and the improvement in both hepatic (p=0.49) and peripheral (p=0.32) insulin sensitivity.

The investigators summarized that pioglitazone results in histological and metabolic benefits for NAFLD in both those with prediabetes or Type 2 diabetes. This suggests that the drug's benefits are likely not mediated through glucose lowering. The drug should now be studied in a larger cohort of patients and, if the data are confirmed, it may become standard therapy for NASH—a potentially lethal condition that predisposes patients to cirrhosis and also hepatocellular carcinoma.

Will these recent positive reports about pioglitazone's benefits alter the diminishing popularity of this drug? The answer to this question is not clear. Of course, the drug still has major concerns, including its association with weight gain, edema, increased risk of heart failure (due to fluid retention), and bone fracture. As with all our therapies, it is important to weigh both the risks and the benefits, while also including patients in this decision-making.

New Data from LEADER

At last year's ADA Scientific Sessions in New Orleans, data from the second CV outcome trial with a GLP-1 receptor agonist (RA) were revealed. Previously, another member of this class, lixisenatide, had actually shown neutral results for MACE in a high-risk group of patients with recent acute coronary syndrome (ELIXA trial; see *Diabetes 2015*, vol 31, p 20). In New Orleans last June, the *Liraglutide Effect and Action in Diabetes: Evaluation of CV Outcome Results* or LEADER trial was presented (see *Diabetes 2016*, vol 33, p 15). 9,340 patients were randomized from 32 countries and 410 sites to the once daily injectable liraglutide (force titration to 1.8 mg) or placebo and followed for about 4 years. Inclusion criteria were Type 2 diabetes and either established CV disease (CVD) with age ≥50 years (~80% of the study population) or age >60 years with multiple CVD risk factors (~20%). Key baseline features included a mean age of 64 years, BMI 32.5 kg/m^2, diabetes duration of about 13 years, and HbA1c of 8.7%. The primary outcome (3-point MACE: composite of CV death, non-fatal MI and non-fatal stroke) was reduced in the active therapy arm by 13% (HR 0.87 [95% CI, 0.78-0.97]; p<0.001 for non-inferiority and p=0.01 for superiority) (Figure 5). The components of this composite all contributed with HRs <1.00 for CV death (0.78 [0.66-0.93]), MI (0.88 [0.75-1.03]), and stroke (0.89 [0.72-1.11]), although only the first was statistically significant. Also, there was borderline statistical heterogeneity (p=0.04) between the CVD risk categories, with the HR in the CVD risk factor only group being 1.20—suggesting that the drug had a benefit only in those with established CVD.

Dr. Richard Pratley of Florida Hospital in Orlando presented new LEADER data at a trial update on Sunday morning. He focused his initial comments on recurrent events—i.e., those CV outcomes that occurred after the first event. This is an increasingly important outcome in clinical CV trials since they contribute significantly to disease burden and costs. In some circumstances, such as in heart failure trials, their inclusion may increase the event rates by more than 50%. In most clinical trials, however, with their classical time-to-first-event analyses, recurrent events are often ignored. In LEADER, the recurrent events analysis presented by Dr. Pratley was entirely consistent with the previously reported primary outcome: 735 total events in the liraglutide group and 870 in the placebo group, with a HR of 0.86 [0.78-0.95]).

Next, statistical analyses were presented that attempted to determine the precise mediator or mediators of the CV benefit from the GLP-1 RA during the trial. First he showed data controlling for a variety of background CV therapies (statins, RAS inhibitors, beta-blockers, aspirin) and glucose-lowering therapies (metformin, sulfonylureas, insulin). Briefly, there appeared to be no effect, either positive or negative, of any of these on the benefit of liraglutide during the trial. Since patients in the placebo group were more likely to have additional diabetes drugs added to their

Continued on page 6

New Data from LEADER

Continued from page 5

regimen (in order to achieve HbA1c targets), this was also examined as a potential cause of harm in that arm of the study. Once again, however, there appeared to be no statistical association between their addition and the effect on MACE from liraglutide. Similarly, although severe hypoglycemia proved more common in the placebo group (HR in favor of liraglutide, 0.69 [0.51-0.92]), this, too, did not appear to influence the results. Finally, in a preliminary analysis examining the effect of HbA1c during LEADER, the CV benefits of liraglutide did not appear to be linked to on-trial changes in this parameter. While not presented, similar inquiries examining blood pressure, BMI, and lipids, each modestly improved in the liraglutide patients, failed to identify the reason for the MACE reduction.

Dr. Pratley therefore concluded that the benefits of this GLP-1 RA were not likely to have been mediated through the drug's effect on HbA1c, body weight, blood pressure, or lipids and proposed that there may be a specific effect on either the heart or blood vessels that was resulting in lower atherosclerotic events. This aspect to GLP-1 RA therapy is certainly deserving of further study, especially since there now appears to be significant heterogeneity within the class for CV benefit. As mentioned, lixisenatide had no CV effect in ELIXA and, recently, top-line results from EXSCEL, which tested long-acting exenatide, were similarly neutral (complete results to be presented at this September's *EASD* meeting in Lisbon, Portugal).

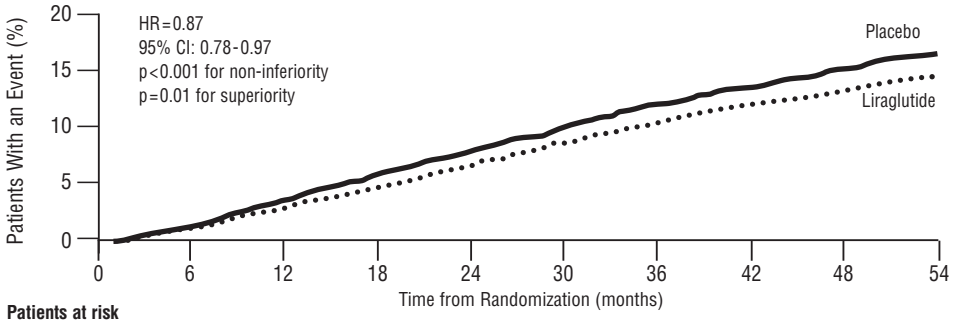
In a follow-up presentation at this symposium, Dr. Steven Nissen from the Cleveland Clinic addressed "A Triumph of Evidence Based Medicine." Dr. Nissen was one of the most vocal original proponents for large CV outcome trials in diabetes. His efforts in the mid-2000s prompted the FDA to release their 2008 "Guidance to Industry", requiring the demonstration of CV safety of any new diabetes therapeutic entering the market. The upper bound of the confidence interval for MACE (<1.8 to get to market and <1.3 to stay on the market), as suggested by Nissen and later adopted by the FDA, essentially mandated that several thousand high-risk patients needed to be exposed for at a minimum of 2-3 years. Only thereby could enough clinical events be generated to make any firm conclusions about safety. The FDA guidance has resulted in an explosion of CV outcome trials in diabetes, into which more than 100,000 patients are current enrolled.

The initial trials involving the DPP-4 inhibitors were routinely neutral, with one surprise finding of potential harm from saxagliptin in SAVOR-TIMI, which found an increase in heart failure events in the active therapy arm. Since then, however, a series of trials (EMPA-REG, LEADER, SUSTAIN-6) have finally demonstrated not only CV safety but also CV benefit. Dr. Nissen felt that these results not only vindicated the somewhat controversial FDA decision in 2008 to compel these trials, but have also fostered in a new era of diabetes management. We can now base clinical decisions on actual data—never before possible given the FDA's prior myopic regulatory focus on glycemic reduction alone.

Finally, Dr. Nissen criticized professional societies, which have lagged behind the data in terms of their clinical practice guidelines. He pointed specifically to the most recent ADA guidelines (*Diabetes Care* 2017; Suppl 1), which merely suggest that either empagliflozin or liraglutide 'be considered' as second-line therapy after metformin in those with prevalent CVD. Dr. Nissen obviously prefers a more proscriptive approach, essentially directing clinicians to these therapies algorithmically.

We certainly admire Dr. Nissen's passion and appreciate his seminal role in the history of the CV assessment of diabetes drugs. However, we would point out that the management of hyperglycemia is a complex undertaking, with every patient presenting a unique set of circumstances. Accordingly, being overly dogmatic in terms of which drug to use after metformin may be counterproductive. Drug choices must be personalized to each patient after carefully weighing their risks, benefits, and costs. Yet we fully agree that treatment guidelines must be updated rapidly to incorporate these exciting emerging data.

Figure 5. Composite Primary Outcome: Time to First Occurrence of CV Death, Non-Fatal MI, or Non-Fatal Stroke



Patients at risk

Liraglutide	4668	4593	4496	4400	4280	4172	4072	3982	1562	424
Placebo	4672	4588	4473	4352	4237	4123	4010	3914	1543	407

So Many Posters, So Little Time....

Metformin and B_{12} Deficiency

Alharbi and coworkers from Saudi Arabia estimated the prevalence and risk of vitamin B_{12} deficiency in 412 patients with Type 2 diabetes (mean age: 57.8±0.6 years) who were being treated with metformin (n=319) or were not (n=93) (abstract 557-P). They determined the overall prevalence of B_{12} deficiency (defined as <156 pmol/l) to be 7.8% (2 non-metformin users and 30 metformin users). In adjusted multivariate logistic regression analyses, duration of metformin exposure exceeding 4 years and metformin dose >2 gm increased the risk of B_{12} deficiency by approximately 6-fold (OR=6.35, p<0.01) and 22-fold (OR=21.67, p<0.01), respectively. Higher dietary B_{12} intake was positively associated with higher serum B_{12} levels, although the level of intake did not protect from B_{12} deficiency associated with metformin usage. From their study results the investigators suggested targeted screening for B_{12} deficiency in patients treated with a metformin dose exceeding 2 grams for more than 4 years.

Silvio E. Inzucchi, MD
Robert S. Sherwin, MD

Editors, Yale University, New Haven, Connecticut