Glycemic Management in a Patient with Type 2 Diabetes.
See article at www.nejm.org/doi/full/10.1056/NEJMclde1311497.

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RESULTS IN Diabetes

The Most-Viewed Articles about Diabetes from October to December 2013

ORIGINAL ARTICLE

Bardoxolone Methyl in Type 2 Diabetes and CKD

Dick de Zeeuw, M.D., Ph.D., and others

ABSTRACT

BACKGROUND
Although inhibitors of the renin–angiotensin–aldosterone system can slow the progression of diabetic kidney disease, the residual risk is high. Whether nuclear 1 factor (erythroid-derived 2)–related factor 2 activators further reduce this risk is unknown.

METHODS
We randomly assigned 2185 patients with type 2 diabetes mellitus and stage 4 chronic kidney disease (estimated glomerular filtration rate [GFR], 15 to <30 ml per minute per 1.73 m2 of body-surface area) to bardoxolone methyl, at a daily dose of 20 mg, or placebo. The primary composite outcome was end-stage renal disease (ESRD) or death from cardiovascular causes.

RESULTS
The sponsor and the steering committee terminated the trial on the recommendation of the independent data and safety monitoring committee; the median follow-up was 9 months. A total of 69 of 1088 patients (6%) randomly assigned to bardoxolone methyl and 69 of 1097 (6%) randomly assigned to placebo had a primary composite outcome (hazard ratio in the bardoxolone methyl group vs. the placebo group, 0.98; 95% confidence interval [CI], 0.70 to 1.37; P=0.92). In the bardoxolone methyl group, ESRD developed in 43 patients, and 27 patients died from cardiovascular causes; in the placebo group, ESRD developed in 51 patients, and 19 patients died from cardiovascular causes. A total of 96 patients in the bardoxolone methyl group were hospitalized for heart failure or died from heart failure, as compared with 55 in the placebo group (hazard ratio, 1.83; 95% CI, 1.32 to 2.55; P<0.001). Estimated GFR, blood pressure, and the urinary albumin-to-creatinine ratio increased significantly and body weight decreased significantly in the bardoxolone methyl group, as compared with the placebo group.

CONCLUSIONS
Among patients with type 2 diabetes mellitus and stage 4 chronic kidney disease, bardoxolone methyl did not reduce the risk of ESRD or death from cardiovascular causes. A higher rate of cardiovascular events with bardoxolone methyl than with placebo prompted termination of the trial. (Funded by Reata Pharmaceuticals; BEACON ClinicalTrials.gov number, NCT01351675.)

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INSIDE

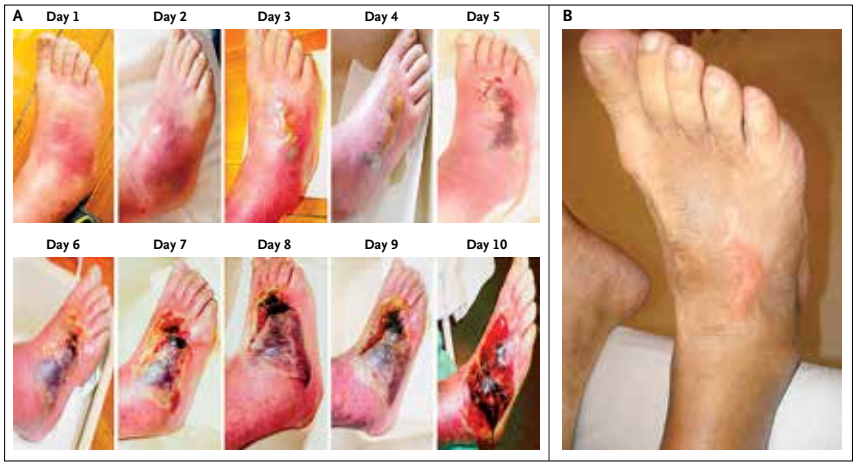
IMAGES IN CLINICAL MEDICINE

Evolution of a Diabetic Foot Infection

Mickaël Tobalem, M.D., and Ilker Uçkay, M.D.

An obese 50-year-old man with no known medical history presented with a necrotizing infection of his right foot that had begun 10 days previously with lesions that he attributed to wearing new shoes. He was found to have diabetes (glycated hemoglobin level, 10.5%) with peripheral neuropathy; he was afebrile, without leukocytosis or radiographic evidence of bone involvement in his right foot. The patient had photographed the lesion twice daily, thinking it would heal spontaneously (Panel A). The preoperative photographs show erythema (day 1), blisters (day 3), a necrotizing abscess (day 6), and wound infection requiring surgery (day 10). The patient underwent operative débridement; tissue cultures grew Enterobacter cloacae and Streptococcus agalactiae. He was treated with antibiotic agents for 3 weeks. The infection resolved, with no recurrence or sequelae during 3 years of follow-up (Panel B); during this period, the infection-related swelling disappeared and the patient lost a considerable amount of weight. Diabetic foot infection may evolve rapidly, especially in patients with neuropathy.

From the University Hospitals of Geneva, Geneva, Switzerland. **Full content, including all tables and figures, can be found at www.nejm.org/doi/full/10.1056/NEJMicm1211053.**



EDITORIAL

New Therapies for Diabetic Kidney Disease

Jonathan Himmelfarb, M.D., and Katherine R. Tuttle, M.D.

Fueled by a global pandemic of obesity, diabetic kidney disease is a pressing public health challenge. Diabetic kidney disease is the most common cause of chronic kidney disease, leading to premature death and end-stage renal disease (ESRD) in the developed and developing worlds. Remarkably, the excess risk of death from any cause in type 1 or 2 diabetes is associated almost entirely with the presence of kidney disease. In the absence of diabetic kidney disease, the risk of death among persons with diabetes is similar to that in the general population.[1,2]

The management of diabetic kidney disease focuses on the treatment of hyperglycemia and hypertension with a foundation of inhibition of the renin–angiotensin–aldosterone system.[3] The incidence of ESRD that is attributable to diabetes has stabilized during the past decade, which has been heralded as therapeutic success. However, the overall number of people with diabetic kidney disease continues to rise in parallel with the prevalence of type 2 diabetes.[4]

Clinical trials intensifying the control of conventional risk factors have not shown improved outcomes. Intensifying the management of glycemia to lower glycated hemoglobin targets in older people with type 2 diabetes (glycated

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Type 2 diabetes mellitus is the most important cause of progressive chronic kidney disease in the developed and developing worlds. Various therapeutic approaches to slow progression, including restriction of dietary protein, glycemic control, and control of hypertension, have yielded mixed results.[1-3] Several randomized clinical trials have shown that inhibitors of the renin–angiotensin–aldosterone system significantly reduce the risk of progression,[4-6] although the residual risk remains high.[7] None of the new agents tested during the past decade have proved effective in late-stage clinical trials.[8-12]

Oxidative stress and impaired antioxidant capacity intensify with the progression of chronic kidney disease.[13] In animals with chronic kidney disease, oxidative stress and inflammation are associated with impaired activity of the nuclear 1 factor (erythroid-derived 2)–related factor 2 (Nrf2) transcription factor. The synthetic triterpenoid bardoxolone methyl and its analogues are the most potent known activators of the Nrf2 pathway. Studies involving humans,[14] including persons with type 2 diabetes mellitus and stage 3b or 4 chronic kidney disease, have shown that bardoxolone methyl can reduce the serum creatinine concentration for up to 52 weeks.[15]

We designed the Bardoxolone Methyl Evaluation in Patients with Chronic Kidney Disease and Type 2 Diabetes Mellitus: the Occurrence of Renal Events (BEACON) trial to test the hypothesis that treatment with bardoxolone methyl reduces the risk of end-stage renal disease (ESRD) or death from cardiovascular causes among patients with type 2 diabetes mellitus and stage 4 chronic kidney disease.

METHODS

STUDY DESIGN AND OVERSIGHT

The BEACON trial was a phase 3, randomized, double-blind, parallel-group, international, multicenter trial of once-daily administration of bardoxolone methyl (at a dose of 20 mg in an amorphous spray-dried dispersion formulation), as compared with placebo. Participants were receiving background conventional therapy that included inhibitors of the renin–angiotensin–aldosterone system, insulin or other hypoglycemic agents, and, when appropriate, other cardiovascular medications. The trial design and the characteristics of the trial participants at baseline have been described previously.[16,17]

Reata Pharmaceuticals sponsored the trial. The trial was jointly designed by employees of the sponsor and the academic investigators who were members of the steering

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hemoglobin, <6.0 to 6.5% in persons typically >60 years of age, depending on the study) produced small reductions in the risk of albuminuria onset or progression but has been associated with episodes of severe hypoglycemia that occur two to four times as frequently as with conventional glycemic management; in addition, these targets have not decreased the risk of death, cardiovascular disease, or ESRD.[5] Another disappointment has been maximal inhibition of the renin–angiotensin–aldosterone system. Dual-blockade strategies (an angiotensin-converting–enzyme inhibitor plus an angiotensin-receptor blocker or one of those agents plus a renin inhibitor) have lowered the risk of albuminuria but have increased the risk of adverse events without reducing the risk of ESRD.[6] Thus, new therapeutic agents are urgently needed.

Abundant experimental evidence indicates that oxidative stress and inflammation are important mediators in diabetic kidney disease. Bardoxolone methyl is a small molecule that activates nuclear 1 factor (erythroid-derived 2)–like 2 factor (Nrf2)), a transcription factor regulating antioxidant genes. In 2011, the results of the phase 2 52-week Bardoxolone Methyl Treatment: Renal Function in CKD/Type 2 Diabetes trial showed that bardoxolone methyl increased the estimated glomerular filtration rate in participants with moderate-to-severe diabetic kidney disease.[7] However, the bardoxolone methyl groups had an increased rate of albuminuria, unintended weight loss, and more adverse events than the placebo group.

The results of the phase 3 Bardoxolone Methyl Evaluation in Patients with Chronic Kidney Disease and Type 2 Diabetes Mellitus: the Occurrence of Renal Events (BEACON) trial, which involved patients with advanced diabetic kidney disease, are now reported in the [December 26] issue of the *Journal* [N Eng J Med 2013;369].[8] The BEACON trial was terminated prematurely on the recommendation of the independent data and safety monitoring committee, after achieving full enrollment but with only a median of 9 months of follow-up. The reasons for termination were the strong adverse safety signals associated with bardoxolone methyl treatment, as compared with placebo, including increased rates of heart failure and cardiovascular events; higher levels of blood pressure, heart rate, and albuminuria; unintentional weight loss; and more gastrointestinal and muscle-related symptomatology. The reasons for these adverse events are unclear. The authors speculate that fluid retention, increased afterload, and higher heart rate contributed to heart failure in patients in the bardoxolone methyl group. In addition, direct toxic effects are possible.

What lessons can be learned from the bardoxolone methyl studies? First, more extensive analysis of preclinical data might have led to greater caution before clinical trials were conducted with this agent. Notably, in one study, the administration of bardoxolone analogues to diabetic rats was associated with increased occurrences of kidney injury, hypertension, proteinuria, and weight loss, which is analogous to some clinical trial findings.[9] However, these data were published only after the BEACON trial was terminated. Second, it is not surprising that a potent activator of a transcription factor might have off-target effects. In addition to Nrf2, bardoxolone methyl activates peroxisome proliferator–activated receptor γ, which may contribute to fluid retention and heart failure, especially in persons with advanced diabetic kidney disease. Third, caution should be exercised whenever any drug for diabetic kidney disease increases, rather than decreases, the degree of albuminuria.

Unfortunately, the failure rate of new drug therapies in clinical trials is extraordinarily high, exceeding 90% overall; even in phase 3 trials, it is still approximately 50%. In addition to bardoxolone methyl, a series of other new therapies for diabetic kidney disease have foundered over the course of drug development. Examples include inhibitors of advanced glycation end products, aldose reductase inhibitors, sulodexide, antifibrotic treatments, and inhibitors of protein kinase C. Increasing the success rate for drug development requires reengineering how we translate discovery science into clinical trials.[10] Efforts are under way to increase thorough reporting of preclinical studies, and the development of new tools such as human "organs on microchips" may augment the assessment of potential off-target toxic effects. Additional key areas for focus are rigorous evaluations of dosing, suitable biomarkers for disease processes and therapeutic responses, and business and regulatory environments that foster innovation. If new therapies for diabetic kidney disease are to benefit patients, fresh approaches will be critical. Given the escalating human and societal costs of diabetic kidney disease, efforts to find new safe and effective therapies remain vital.

From the Kidney Research Institute and Division of Nephrology, University of Washington School of Medicine, Seattle (J.H., K.R.T.), and Providence Sacred Heart Medical Center and Children's Hospital, Spokane (K.R.T.) — both in Washington. **Full content, including all tables and figures, can be found at www.nejm.org/doi/full/10.1056/NEJMe1313104.**

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NEJM GROUP

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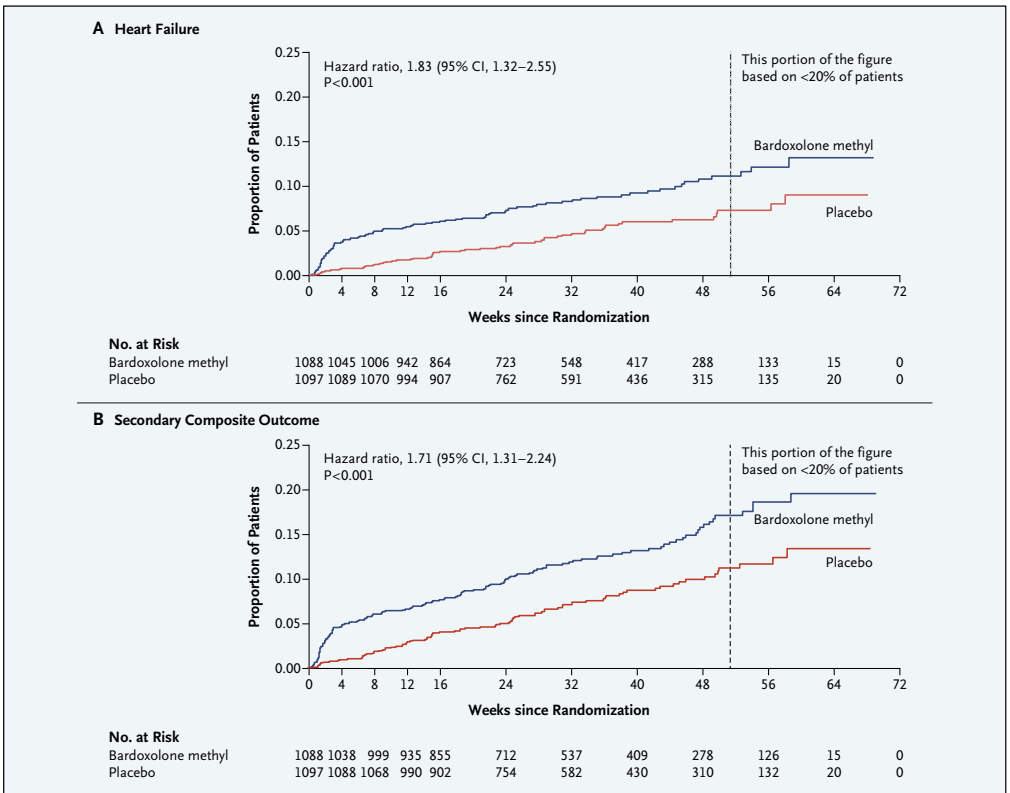
committee. The steering committee, which was led by the academic investigators and included members who were employees of the sponsor, supervised the trial design and operation. An independent data and safety monitoring committee reviewed interim safety data every 90 days or on an ad hoc basis on request. The sponsor collected the trial data and transferred them to independent statisticians at Statistics Collaborative. The sponsor also contracted a second independent statistical group (Axio Research) to support the independent data and safety monitoring committee. The trial protocol was approved by the institutional review board at each participating study site. The protocol and amendments are available with the full text of this article at NEJM.org. The steering committee takes full responsibility for the integrity of the data and the interpretation of the trial results and for the fidelity of the study to the protocol. The first and last authors wrote the first draft of the manuscript. All the members of the steering committee made the decision to submit the manuscript for publication.



Kaplan–Meier Plots of the Time to the First Event of the Discrete Secondary Outcomes.

Panel A shows the time to the first event of heart failure, defined as death due to heart failure or hospitalization for heart failure, among patients in the bardoxolone methyl group and those in the placebo group. Panel B shows the time to the first event of the secondary composite outcome (nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure, or death from cardiovascular causes) in the two study groups. The first event was nonfatal myocardial infarction in 17 patients in the bardoxolone methyl group and 11 in the placebo group, nonfatal stroke in 12 patients in the bardoxolone methyl group and 8 in the placebo group, hospitalization for heart failure in 91 patients in the bardoxolone methyl group and 54 in the placebo group, and death from cardiovascular causes in 19 patients in the bardoxolone methyl group and 13 in the placebo group.

STUDY POPULATION

Briefly, we included adults with type 2 diabetes mellitus and an estimated glomerular filtration rate (GFR) of 15 to <30 ml per minute per 1.73 m² of body-surface area. Persons with poor glycemic control, uncontrolled hypertension, or a recent cardiovascular event (≤12 weeks before randomization) or New York Heart Association class III or IV heart failure were excluded. Additional inclusion and exclusion criteria are listed in Table S1 in the Supplementary Appendix, available at NEJM.org. All the patients provided written informed consent.

RANDOMIZATION AND INTERVENTION

Randomization was stratified according to study site with the use of variable-sized blocks. The steering committee, sponsor, investigators, and trial participants were unaware of the group assignments. After randomization, patients received either bardoxolone methyl or placebo. The prescription of all other medications was at the discretion of treating physicians, who were encouraged to adhere to published clinical-practice guidelines. Patients underwent event ascertainment and laboratory testing according to the study schema shown in Figure S1 in the Supplementary Appendix. Ambulatory blood-pressure monitoring was performed in a substudy that included 174 patients (8%).

The statistical analysis plan defined the study period as the number of days from randomization to a common study-termination date. In the case of patients who were still receiving the study drug on the termination date, data on vital events were collected for an additional 30 days.

OUTCOMES

The primary composite outcome was ESRD or death from cardiovascular causes. We defined ESRD as the need for maintenance dialysis for 12 weeks or more or kidney transplantation. If a patient died before undergoing dialysis for 12 weeks, the independent events-adjudication committee adjudicated whether the need for dialysis represented ESRD or acute renal failure. Patients who declined dialysis and who subsequently died were categorized as having had ESRD. All ESRD events were adjudicated. Death from cardiovascular causes was defined as death due to either cardiovascular or unknown causes.

The trial had three prespecified secondary outcomes — first, the change in estimated GFR as calculated with the use of the four-variable Modification of Diet in Renal Disease study equation, with serum creatinine levels calibrated to an isotope-dilution standard for mass spectrometry; second, hospitalization for heart failure or death due to heart failure; and third, a composite outcome of nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure, or death from cardiovascular causes. The events-adjudication committee, whose members were unaware of the study assignments, evaluated whether ESRD events, cardiovascular events, neurologic events, and deaths met the prespecified criteria for primary and secondary outcomes (described in detail in the Supplementary Appendix).

STATISTICAL ANALYSIS

We calculated that we needed to enroll 2000 patients on the basis of the following assumptions: a two-sided type I error rate of 5%, an event rate of 24% for the primary composite outcome in the placebo group during the first 2 years of the study, a hazard ratio of 0.68 (bardoxolone methyl vs. placebo) for the primary composite outcome, discontinuation of the study drug by 13.5% of the patients in the bardoxolone methyl group each year, and a 2.5% annual loss to follow-up in each group. Under these assumptions, if 300 patients had a primary composite outcome, the statistical power would be 85%.

We collected and analyzed all outcome data in accordance with the intention-to-treat principle. We calculated Kaplan–Meier product-limit estimates of the cumulative incidence of the primary composite outcome. We computed hazard ratios and 95% confidence intervals with the use of Cox proportional-hazards regression models with adjustment for the baseline estimated GFR and urinary albumin-to-creatinine ratio. We performed analogous analyses for secondary time-to-event outcomes. Given the abundance of early adverse events, we also report discrete cumulative incidences at 4 weeks and 52 weeks.

For longitudinal analyses of estimated GFR, we performed mixed-effects regression analyses using study group, time, the interaction of study group with time, estimated GFR at baseline, the interaction of baseline estimated GFR with time, and urinary albumin-to-creatinine ratio as covariates, and we compared the means between the bardoxolone methyl group and the placebo group. We adopted similar approaches when examining the effects of treatment on other continuous measures assessed at multiple visits. Since the between-group difference in the primary composite outcome was not significant, secondary and other outcomes with P values of less than 0.05 were considered to be nominally significant. Statistical analyses were performed with the use of SAS software, version 9.3 (SAS Institute). Additional details of the statistical analysis are provided in the Supplementary Appendix.

RESULTS

PATIENTS

From June 2011 through September 2012, a total of 2185 patients underwent randomization, including 1545 (71%) in the United States, 334 (15%) in the European Union, 133 (6%) in Australia, 87 (4%) in Canada, 46 (2%) in Israel, and 40

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PERSPECTIVE

The Cardiovascular Safety of Diabetes Drugs — Insights from the Rosiglitazone Experience

William R. Hiatt, M.D., and others

The management of type 2 diabetes has been challenged by uncertainty about possible cardiovascular effects related to treatment intensity and choice of drug. Although the Food and Drug Administration (FDA) considers a decrease in glycated hemoglobin an approvable end point, very intensive glycemic control is associated with increased cardiovascular and all-cause mortality.[1] The safety of specific drugs for type 2 diabetes — particularly the thiazolidinediones — has also been questioned. After rosiglitazone had been approved in the United States in 1999 and in Europe in 2000, a highly publicized meta-analysis in 2007 reported a 43% increase in myocardial infarction (P=0.03) and a 64% increase in death from cardiovascular causes (P=0.06).[2] This report and subsequent FDA advisory committee reviews led to a boxed warning of myocardial ischemia in 2007 and highly restricted access to rosiglitazone in 2010. In 2010, the FDA placed a full clinical hold on the Thiazolidinedione Intervention with Vitamin D Evaluation (TIDE) trial (ClinicalTrials.gov number, NCT00879970), a large cardiovascular-outcome trial designed to evaluate the benefit of rosiglitazone and pioglitazone as compared with placebo (superiority hypothesis) and the safety of rosiglitazone as compared with pioglitazone (noninferiority hypothesis). In part owing to the rosiglitazone experience, the FDA issued an updated Guidance for Industry in 2008 requiring that preapproval and postapproval studies for all new antidiabetic drugs rule out excess cardiovascular risk, defined as an upper bound of the two-sided 95% confidence interval for major adverse cardiovascular events (MACE) of less than 1.80 and less than 1.30, respectively.[3] Regardless of the presence or absence of preclinical or clinical signals of cardiovascular risk, the guidance has been applied broadly to all new diabetes drugs, creating substantial challenges in the drug development and approval process.

On June 5 and 6, 2013, the FDA held a joint meeting of the Endocrinologic and Metabolic Drugs Advisory Committee (on which we serve) and the Drug Safety and Risk Management Advisory Committee to further evaluate the cardiovascular safety of rosiglitazone. When rosiglitazone was approved in Europe, the European Medicines Agency raised concern about the cardiovascular risks of the thiazolidinedione class, including fluid retention, heart failure, and increased levels of low-density lipoprotein cholesterol. This concern led to a postmarketing requirement that cardiovascular-outcome trials be conducted for both pioglitazone and rosiglitazone, and these were reviewed at subsequent FDA meetings. Although the results of the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) study (NCT00379769) did not suggest an increased risk of MACE,[4] issues with trial design and data integrity led the FDA to require the sponsor to perform an independent readjudication of the data. This extensive exercise, performed by the Duke Clinical Research Institute, had a minimal effect on the overall point estimates and confidence intervals for MACE, which remained at less than 1.30. The result was consistent with the FDA guidance and provided reassurance that rosiglitazone was not associated with excess cardiovascular risk.

Two groups of authors (Scirica et al. and White et al.) now report in the *Journal* the results of large, placebo-controlled, cardiovascular-outcome trials, these involving saxagliptin and alogliptin, members of the incretin drug class. Neither of these drugs had shown increased cardiovascular risk in its development program. Both trials were designed to first rule out excess cardiovascular risk by means of noninferiority testing; if that was shown, superiority testing followed, on the assumption that better glycemic control might yield cardiovascular benefit. Both trials clearly met the FDA 2008 guidance for cardiovascular safety, but neither showed a reduction in cardiovascular events. Saxagliptin was associated with an unexpected increased risk of hospitalization for heart failure and a high frequency of hypoglycemia. Neither trial showed any increased risk of pancreatic adverse events, including cancer.

Before rosiglitazone, the cardiovascular safety of diabetes drugs had not been well studied. The initial concern with rosiglitazone

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ORIGINAL ARTICLE

Saxagliptin and Cardiovascular Outcomes

Benjamin M. Scirica, M.D., M.P.H., and others

BACKGROUND

The cardiovascular safety and efficacy of many current antihyperglycemic agents, including saxagliptin, a dipeptidyl peptidase 4 (DPP-4) inhibitor, are unclear.

METHODS

We randomly assigned 16,492 patients with type 2 diabetes who had a history of, or were at risk for, cardiovascular events to receive saxagliptin or placebo and followed them for a median of 2.1 years. Physicians were permitted to adjust other medications, including antihyperglycemic agents. The primary end point was a composite of cardiovascular death, myocardial infarction, or ischemic stroke.

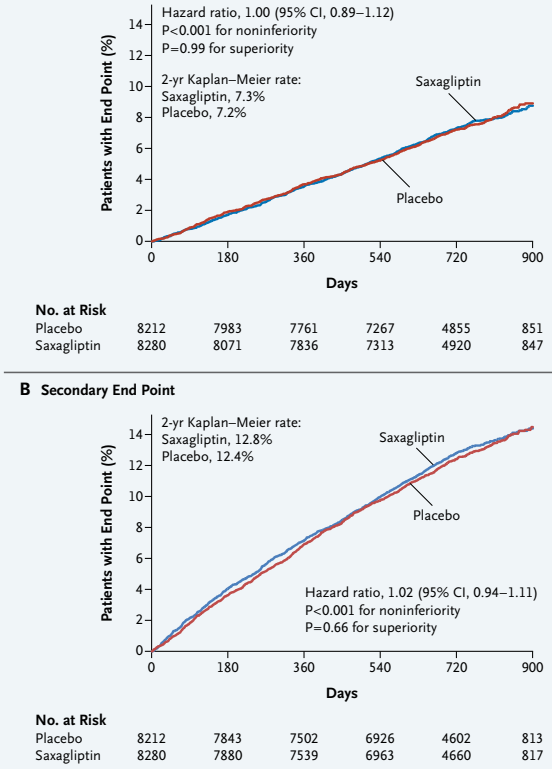
RESULTS

A primary end-point event occurred in 613 patients in the saxagliptin group and in 609 patients in the placebo group (7.3% and 7.2%, respectively, according to 2-year Kaplan–Meier estimates; hazard ratio with saxagliptin, 1.00; 95% confidence interval [CI], 0.89 to 1.12; P=0.99 for superiority; P<0.001 for noninferiority); the results were similar in the "on-treatment" analysis (hazard ratio, 1.03; 95% CI, 0.91 to 1.17). The major secondary end point of a composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, coronary revascularization, or heart failure occurred in 1059 patients in the saxagliptin group and in 1034 patients in the placebo group (12.8% and 12.4%, respectively, according to 2-year Kaplan–Meier estimates; hazard ratio, 1.02; 95% CI, 0.94 to 1.11; P=0.66). More patients in the saxagliptin group than in the placebo group were hospitalized for heart failure (3.5% vs. 2.8%; hazard ratio, 1.27; 95% CI, 1.07 to 1.51; P=0.007). Rates of adjudicated cases of acute and chronic pancreatitis were similar in the two groups (acute pancreatitis, 0.3% in the saxagliptin group and 0.2% in the placebo group; chronic pancreatitis, <0.1% and 0.1% in the two groups, respectively).

CONCLUSIONS

DPP-4 inhibition with saxagliptin did not increase or decrease the rate of ischemic events, though the rate of hospitalization for heart failure was increased. Although saxagliptin improves glycemic control, other approaches are necessary to reduce cardiovascular risk in patients with diabetes. (Funded by AstraZeneca and Bristol-Myers Squibb; SAVOR-TIMI 53 ClinicalTrials.gov number, NCT01107886.)

From the TIMI Study Group, Cardiovascular Division, Brigham and Women's Hospital, and Harvard Medical School (B.M.S., D.L.B., E.B., S.D.W., E.B.H., M.A.C., J.A.U., N.R.D.), and the VA Boston Healthcare System (D.L.B.) — all in Boston; and other sources. **Full content, including all tables and figures, can be found at www.nejm.org/doi/full/10.1056/NEJMoa1307684.**



Kaplan–Meier Rates of the Primary and Secondary End Points.

The primary end point (Panel A) was a composite of death from cardiovascular causes, myocardial infarction, or ischemic stroke. The secondary end point (Panel B) was a composite of death from cardiovascular causes, myocardial infarction, ischemic stroke, hospitalization for unstable angina, coronary revascularization, or heart failure.

ORIGINAL ARTICLE

Alogliptin in Type 2 Diabetes

William B. White, M.D., and others

BACKGROUND

To assess potentially elevated cardiovascular risk related to new antihyperglycemic drugs in patients with type 2 diabetes, regulatory agencies require a comprehensive evaluation of the cardiovascular safety profile of new antidiabetic therapies. We assessed cardiovascular outcomes with alogliptin, a new inhibitor of dipeptidyl peptidase 4 (DPP-4), as compared with placebo in patients with type 2 diabetes who had had a recent acute coronary syndrome.

METHODS

We randomly assigned patients with type 2 diabetes and either an acute myocardial infarction or unstable angina requiring hospitalization within the previous 15 to 90 days to receive alogliptin or placebo in addition to existing antihyperglycemic and cardiovascular drug therapy. The study design was a double-blind, noninferiority trial with a prespecified noninferiority margin of 1.3 for the hazard ratio for the primary end point of a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.

RESULTS

A total of 5380 patients underwent randomization and were followed for up to 40 months (median, 18 months). A primary end-point event occurred in 305 patients assigned to alogliptin (11.3%) and in 316 patients assigned to placebo (11.8%) (hazard ratio, 0.96; upper boundary of the one-sided repeated confidence interval, 1.16; P<0.001 for noninferiority). Glycated hemoglobin levels were significantly lower with alogliptin than with placebo (mean difference, −0.36 percentage points; P<0.001). Incidences of hypoglycemia, cancer, pancreatitis, and initiation of dialysis were similar with alogliptin and placebo.

CONCLUSIONS

Among patients with type 2 diabetes who had had a recent acute coronary syndrome, the rates of major adverse cardiovascular events were not increased with the DPP-4 inhibitor alogliptin as compared with placebo. (Funded by Takeda Development Center Americas; EXAMINE ClinicalTrials.gov number, NCT00968708.)

From the University of Connecticut School of Medicine, Farmington (W.B.W.); Brigham and Women's Hospital and Harvard Medical School (C.P.C.) and Harvard School of Public Health (C.R.M.) — all in Boston; and other sources. **Full content, including all tables and figures, can be found at www.nejm.org/doi/full/10.1056/NEJMoa1305889.**

Major Safety End Points.

End Point	Placebo (N=2679)	Alogliptin (N=2701)	Hazard Ratio for Alogliptin Group (95% CI)	P Value*
	no. (%)			
Primary end point†	316 (11.8)	305 (11.3)	0.96 (≤1.16)‡	0.32
Components of primary end point				
Death from cardiovascular causes	111 (4.1)	89 (3.3)	0.79 (0.60–1.04)	0.10
Nonfatal myocardial infarction	173 (6.5)	187 (6.9)	1.08 (0.88–1.33)	0.47
Nonfatal stroke	32 (1.2)	29 (1.1)	0.91 (0.55–1.50)	0.71
Principal secondary end point§	359 (13.4)	344 (12.7)	0.95 (≤1.14)‡	0.26
Other end points				
Death from any cause	173 (6.5)	153 (5.7)	0.88 (0.71–1.09)	0.23
Death from cardiovascular causes¶	130 (4.9)	112 (4.1)	0.85 (0.66–1.10)	0.21

* P values for testing the superiority of alogliptin to placebo were calculated with the use of a Cox regression analysis.
† The primary end point was a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.
‡ The parenthetical value is the upper boundary of the one-sided repeated CI, at an alpha level of 0.01.
§ The secondary end point was a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or urgent revascularization due to unstable angina within 24 hours after hospital admission.
¶ Included are deaths that occurred as primary end-point events and deaths that occurred after a nonfatal primary end-point event.

Hiatt — continued

arose from observational and case–control epidemiologic studies that generated a legitimate signal of possible cardiovascular harm, but every study had substantial methodologic shortcomings, including multiplicity, which meant that a statistically positive finding might be a false positive result.[5] Meta-analyses were also performed with preapproval studies that had been designed to show a positive glycemic effect as the primary end point. These studies enrolled patients at low cardiovascular risk, were short in duration, used both placebo and active controls, and did not prospectively adjudicate cardiovascular safety events. In such situations, comparison of a new drug with an active agent is challenged by the uncertain cardiovascular risk of the active comparator. In contrast, a placebo-controlled design may lead to imbalances in background therapy (as was the case with saxagliptin) that could influence the cardiovascular outcomes. Meta-analyses of these premarketing trials from phase 3 development programs were therefore relatively insensitive in assessing cardiovascular risk, making dedicated postmarketing cardiovascular-outcome trials such as the RECORD study necessary to substantiate any risk signals. But the design of the RECORD study had substantial limitations that precluded a complete assessment of the cardiovascular safety of rosiglitazone.

In 2010, the FDA took a cautious stance and limited exposure to rosiglitazone, given the numerous alternative therapies that were available. But this position did not acknowledge the uncertainty of cardiovascular risk associated with other diabetes drugs on the market, and the FDA decision may have had unintended consequences. The intense publicity about the ischemic cardiac risk of rosiglitazone may have diverted attention from the better-established risk of heart failure that is common to the drug class. Restricted access led patients to switch from rosiglitazone to other diabetes drugs of unproven cardiovascular safety. Patients who had a myocardial infarction while taking rosiglitazone may have concluded that the drug was the cause, adversely affecting their perceptions of their doctor, drug companies, and the FDA. And placing a hold on the TIDE trial, although arguably justifiable, prevented any further clarification of the cardiovascular risks or benefits of the thiazolidinedione drug class. The rosiglitazone experience also raises the question of how to define a regulatory standard for withdrawing drugs from the market. New drug approvals are based on "substantial evidence" of drug safety and efficacy. But there is little guidance on what constitutes substantial evidence of harm that is sufficient to justify market withdrawal or the imposition of severe market restrictions.

What have we learned from the rosiglitazone experience? Clearly, the presumed cardiovascular risks of rosiglitazone led to a major change in FDA policy regarding the approval of all new diabetes drugs. From a cardiovascular perspective, rosiglitazone, saxagliptin, and alogliptin appear to be relatively safe. It is disappointing, however, that neither intensive glycemic control nor the use of specific diabetes medications is associated with any suggestion of cardiovascular benefit. Thus the evidence does not support the use of glycated hemoglobin as a valid surrogate for assessing either the cardiovascular risks or the cardiovascular benefits of diabetes therapy.

Patients with type 2 diabetes and their physicians currently have numerous treatment options, and additional drugs are in development. Perhaps the recent experience with rosiglitazone will allow the FDA to become more targeted in its adjudication of the cardiovascular safety of new diabetes drugs, focusing the considerable resources needed to rule out a cardiovascular concern only on drugs with clinical or preclinical justification for that expenditure. New therapies targeting glycemic control may have cardiovascular benefit, but this has yet to be shown. The optimal approach to the reduction of cardiovascular risk in diabetes should focus on aggressive management of the standard cardiovascular risk factors rather than on intensive glycemic control.

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(2%) in Mexico. Figure S2 in the Supplementary Appendix shows the disposition of the study participants.

As shown in Table 1, available at NEJM.org, the patients were diverse with respect to age, sex, race or ethnic group, and region of origin; diabetic retinopathy and neuropathy were common conditions among the patients, as was overt cardiovascular disease. See Table S2 in the Supplementary Appendix for a more detailed description of the characteristics of the patients at baseline; Figure S3 in the Supplementary Appendix shows the distribution of baseline estimated GFR and urinary albumin-to-creatinine ratio.

DRUG EXPOSURE

The median duration of exposure to the study drug was 7 months (interquartile range, 3 to 11) among patients randomly assigned to bardoxolone methyl and 8 months (interquartile range, 5 to 11) among those randomly assigned to placebo. Figure S4 in the Supplementary Appendix shows the time to discontinuation of the study drug. Table S3 in the Supplementary Appendix shows the reasons that patients discontinued the study drug and the reasons that patients discontinued the study. The median duration of follow-up was 9 months in both groups.

OUTCOMES

Primary Composite Outcome

A total of 69 of 1088 patients (6%) randomly assigned to bardoxolone methyl and 69 of 1097 (6%) randomly assigned to placebo had a primary composite outcome (hazard ratio in the bardoxolone methyl group vs. the placebo group, 0.98; 95% confidence interval [CI], 0.70 to 1.37; P=0.92). Death from cardiovascular causes occurred in 27 patients randomly assigned to bardoxolone methyl and in 19 randomly assigned to placebo (hazard ratio, 1.44; 95% CI, 0.80 to 2.59; P=0.23). ESRD developed in 43 patients randomly assigned to bardoxolone methyl and in 51 randomly assigned to placebo (hazard ratio, 0.82; 95% CI, 0.55 to 1.24; P=0.35). One patient in each group died from cardiovascular causes after the development of ESRD. The mean (±SD) estimated GFR before the development of ESRD was 18.1±8.3 ml per minute per 1.73 m^2 in the bardoxolone methyl group and 14.9±4.0 ml per minute per 1.73 m^2 in the placebo group.

Secondary Outcomes

During the study period, 96 patients in the bardoxolone methyl group had heart-failure events (93 patients with at least one hospitalization due to heart failure and 3 patients who died from heart failure without hospitalization), as compared with 55 in the placebo group (55 patients with at least one hospitalization due to heart failure and no patients who died from heart failure without hospitalization) (hazard ratio, 1.83; 95% CI, 1.32 to 2.55; P<0.001) (see figure on page 3, panel A). A total of 139 patients in the bardoxolone methyl group, as compared with 86 in the placebo group, had a composite outcome event of nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure, or death from cardiovascular causes (hazard ratio, 1.71; 95% CI, 1.31 to 2.24; P<0.001) (see figure on page 3, panel B).

Incidences of Composite Outcomes and Rates of Death from Any Cause

The cumulative incidences of the primary composite outcome and of the two secondary composite outcomes at 4 weeks and at 52 weeks are shown in Table S4 in the Supplementary Appendix. The rates of death from any cause are shown in Figure S5 in the Supplementary Appendix. From the time of randomization to the end of follow-up, 75 patients died: 44 patients in the bardoxolone methyl group and 31 in the placebo group (hazard ratio, 1.47; 95% CI, 0.93 to 2.32; P=0.10). The causes of death are listed in Table S5 in the Supplementary Appendix.

Estimated GFR

Patients randomly assigned to placebo had a significant mean decline in the estimated GFR from the baseline value (–0.9 ml per minute per 1.73 m^2; 95% CI, –1.2 to –0.5), whereas those randomly assigned to bardoxolone methyl had a significant mean increase from the baseline value (5.5 ml per minute per 1.73 m^2; 95% CI, 5.2 to 5.9). The difference between the two groups was 6.4 ml per minute per 1.73 m^2 (95% CI, 5.9 to 6.9; P<0.001).

Physiological Variables

Physiological variables are shown in Table S6 in the Supplementary Appendix. The mean body weight remained stable in the placebo group but declined steadily and substantially in the bardoxolone methyl group. There was a significantly smaller decrease from baseline in mean systolic blood pressure in the bardoxolone methyl group than in the placebo group (between-group difference, 1.5 mm Hg [95% CI, 0.5 to 2.5]), and the mean diastolic blood pressure increased from baseline in the bardoxolone methyl group whereas it decreased in the placebo group (between-group difference, 2.1 mm Hg [95% CI, 1.6 to 2.6]). Blood-pressure results from the substudy in which ambulatory blood-pressure monitoring was performed were similar in direction but were more pronounced (between-group difference of 7.9 mm Hg [95% CI, 3.8 to 12.0] in systolic blood pressure and 3.2 mm Hg [95% CI, 1.3 to 5.2] in diastolic blood pressure). Heart rate also increased significantly in the bardoxolone methyl group, as compared with the placebo group (between-group difference, 3.8 beats per minute; 95% CI, 3.2 to 4.4).

Other Laboratory Variables

Data on laboratory variables are shown in Table S7 in the Supplementary Appendix. The urinary albumin-to-creatinine ratio increased significantly in the bardoxolone methyl group, as compared with the placebo group. Serum magnesium, albumin, hemoglobin, and glycated hemoglobin levels decreased significantly in the bardoxolone methyl group, as compared with the placebo group. The level of B-type natriuretic peptide increased significantly by week 24 in the bardoxolone methyl group, as compared with the placebo group.

ADVERSE EVENTS

The rates of serious adverse events are summarized in Table 2, available at NEJM.org. Serious adverse events occurred more frequently in the bardoxolone methyl group than in the placebo group (717 events in 363 patients vs. 557 events in 295 patients). There were 11 neoplastic events in the bardoxolone methyl group and 10 in placebo group. The most commonly reported adverse events are summarized in Table S8 in the Supplementary Appendix.

DISCUSSION

The current trial was designed to determine whether bardoxolone methyl, an activator of the cytoprotective Nrf2 pathway, would reduce the risk of ESRD among patients with type 2 diabetes mellitus and stage 4 chronic kidney disease who were receiving guideline-based conventional therapy. The trial was terminated early because of safety concerns, driven primarily by an increase in cardiovascular events in the bardoxolone methyl group. Bardoxolone methyl did not lower the risk of ESRD or of death from cardiovascular causes, although too few events occurred during the trial to reliably determine the true effect of the drug on the primary composite outcome.

Given the truncated duration of the trial and the number of adjudicated events (46% of the events planned), and assuming no change in any of the original assumptions, we estimated the conditional power of the trial to be less than 40%. Although patients treated with bardoxolone methyl had a significant increase in the estimated GFR, as compared with those who received placebo, there was a significantly higher incidence of heart failure and of the composite outcome of nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure, or death from cardiovascular causes in the bardoxolone methyl group. There were numerically more deaths from any cause among patients treated with bardoxolone methyl than among those in the placebo group.

Bardoxolone methyl is among the first orally available antioxidant Nrf2 activators. A small previous study showed that bardoxolone methyl reduced inflammation and oxidative stress[13] and induced a decline in the serum creatinine level. In the 52-Week Bardoxolone Methyl Treatment: Renal Function in CKD/Type 2 Diabetes (BEAM) trial,[15] 227 patients with type 2 diabetes mellitus and an estimated GFR of 20 to 45 ml per minute per 1.73 m^2 had a significant increase in the estimated GFR (mean change, 8.2 to 11.4 ml per minute per 1.73 m^2, depending on the dose group) that was sustained over the entire trial period. Muscle spasms and hypomagnesemia were the most common adverse events; there was no increase in the rate of heart failure or other cardiovascular events.

The current trial was designed to determine whether the change in estimated GFR that we anticipated on the basis of the results of the BEAM trial would translate into a slower progression toward ESRD. Although in the current trial ESRD developed in fewer patients in the bardoxolone methyl group than in the placebo group, the early termination of the trial precludes conclusion of the effect on ESRD events.

The mechanism linking bardoxolone methyl to heart failure is unknown. Since an excess in heart-failure events was unanticipated, echocardiography was not performed routinely before randomization. Although weight declined significantly in the bardoxolone methyl group, we were unable to determine whether there was loss of body fat, intracellular (skeletal muscle) water, or extracellular (interstitial) water. The fall in serum albumin and hemoglobin levels may reflect hemodilution caused by fluid retention.

Bardoxolone methyl also increased blood pressure. An increase in preload due to volume expansion and an increase in afterload (as reflected by increased blood pressure), coupled with an increase in heart rate, constitute a potentially potent combination of factors that are likely to precipitate heart failure in an at-risk population. The rise in the level of B-type natriuretic peptide with bardoxolone methyl is consistent with an increase in left ventricular wall stress owing to one or more of these mediators or to unrecognized factors such as impaired diastolic filling of the left ventricle. After recognizing the initial increase in heart-failure events, the independent data and safety monitoring committee tried to identify clinical characteristics that were associated with patients who were at elevated risk for heart failure after the initiation of bardoxolone methyl therapy (with the possibility of modifying eligibility criteria or otherwise altering the trial), but the committee was unable to do so. Other, noncardiovascular adverse events were also observed

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more frequently among patients exposed to bardoxolone methyl than among those who received placebo. Whether the effects of Nrf2 activation, or one or more counterregulatory responses, rendered this particular population vulnerable, is unknown. Zoja et al.[18] found an increase in albuminuria and blood pressure along with weight loss in Zucker diabetic fatty rats treated with an analogue of bardoxolone methyl; these effects were not observed in other studies in Zucker diabetic fatty rats or other rodent models or in 1-year toxicologic studies in monkeys.[19-21]

Why were these adverse effects identified in the current trial and not in the BEAM trial? First, the number of patient-months of drug exposure in the current trial was roughly 10 times that in the BEAM trial. Second, the population in the present trial had more severe chronic kidney disease than did the population in the BEAM trial. Observational studies have shown significantly higher rates of death and cardiovascular events, including heart failure, among patients with stage 4 chronic kidney disease than among patients with stage 3 chronic kidney disease.[22] Finally, our trial used an amorphous spray-dried dispersion formulation of bardoxolone methyl at a fixed dose rather than at an adjusted dose. We chose the 20-mg dose and the specific formulation used in the BEACON trial on the basis of four phase 2 studies of chronic kidney disease (three studies used the crystalline formulation, and one used the amorphous formulation), a crossover pharmacokinetics study involving humans that used both formulations, and several studies in animals that used both formulations (Meyer C: personal communication), to provide an activity and safety profile that was similar to that observed with 75 mg of the crystalline formulation, which was one of the dose levels tested in the BEAM trial.

In conclusion, among patients with type 2 diabetes mellitus and stage 4 chronic kidney disease, bardoxolone methyl did not reduce the risk of the primary composite outcome of ESRD or death from cardiovascular causes. Significantly increased risks of heart failure and of the composite cardiovascular outcome (nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure, or death from cardiovascular causes) prompted termination of the trial.

From the University of Groningen, Groningen, the Netherlands (D.Z., H.J.L.H.); Showa University School of Medicine, Tokyo (T.A.); and other sources. **Full content, including all tables and figures, can be found at www.nejm.org/doi/full/10.1056/NEJMoa1306033.**

ORIGINAL ARTICLE

Combined Angiotensin Inhibition in Diabetes

Linda F. Fried, M.D., M.P.H., and others

BACKGROUND

Combination therapy with angiotensin-converting–enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) decreases proteinuria; however, its safety and effect on the progression of kidney disease are uncertain.

METHODS

We provided losartan (at a dose of 100 mg per day) to patients with type 2 diabetes, a urinary albumin-to-creatinine ratio (with albumin measured in milligrams and creatinine measured in grams) of at least 300, and an estimated glomerular filtration rate (GFR) of 30.0 to 89.9 ml per minute per 1.73 m² of body-surface area and then randomly assigned them to receive lisinopril (at a dose of 10 to 40 mg per day) or placebo. The primary end point was the first occurrence of a change in the estimated GFR (a decline of ≥30 ml per minute per 1.73 m² if the initial estimated GFR was ≥60 ml per minute per 1.73 m² or a decline of ≥50% if the initial estimated GFR was <60 ml per minute per 1.73 m²), end-stage renal disease (ESRD), or death. The secondary renal end point was the first occurrence of a decline in the estimated GFR or ESRD. Safety outcomes included mortality, hyperkalemia, and acute kidney injury.

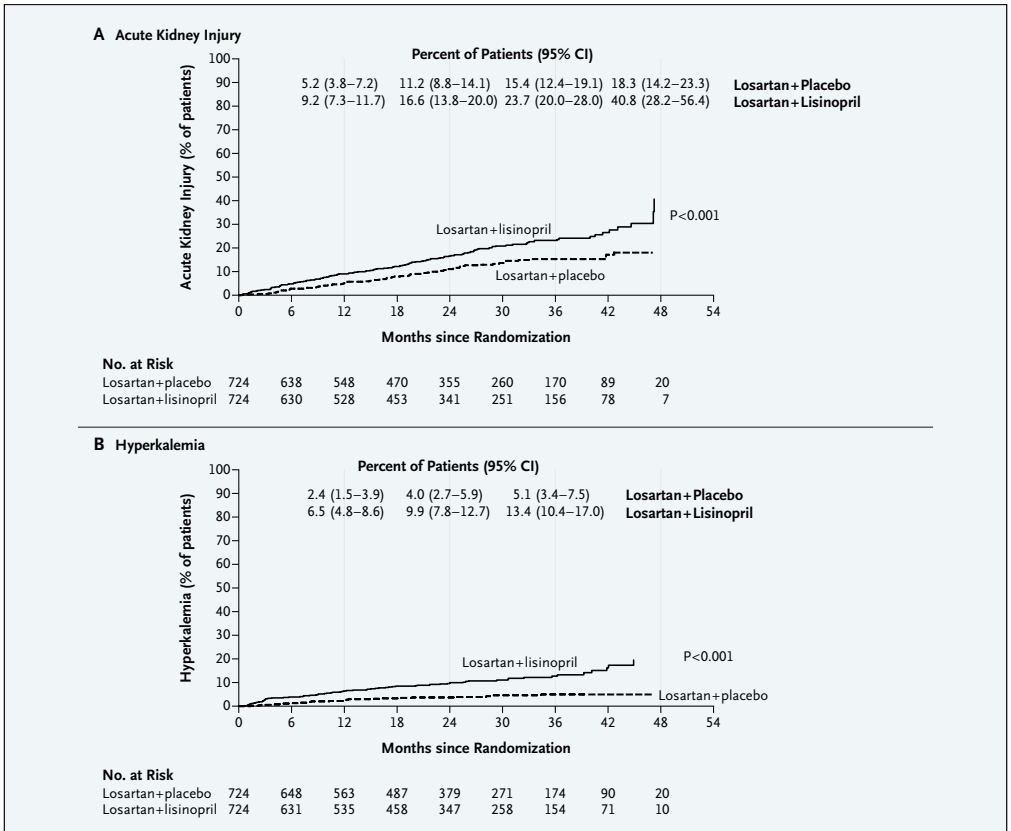
RESULTS

The study was stopped early owing to safety concerns. Among 1448 randomly assigned patients with a median follow-up of 2.2 years, there were 152 primary end-point events in the monotherapy group and 132 in the combination-therapy group (hazard ratio with combination therapy, 0.88; 95% confidence interval [CI], 0.70 to 1.12; P=0.30). A trend toward a benefit from combination therapy with respect to the secondary end point (hazard ratio, 0.78; 95% CI, 0.58 to 1.05; P=0.10) decreased with time (P=0.02 for nonproportionality). There was no benefit with respect to mortality (hazard ratio for death, 1.04; 95% CI, 0.73 to 1.49; P=0.75) or cardiovascular events. Combination therapy increased the risk of hyperkalemia (6.3 events per 100 person-years, vs. 2.6 events per 100 person-years with monotherapy; P<0.001) and acute kidney injury (12.2 vs. 6.7 events per 100 person-years, P<0.001).

CONCLUSIONS

Combination therapy with an ACE inhibitor and an ARB was associated with an increased risk of adverse events among patients with diabetic nephropathy. (Funded by the Cooperative Studies Program of the Department of Veterans Affairs Office of Research and Development; VA NEPHRON-D ClinicalTrials.gov number, NCT00555217.)

From the Veterans Affairs (VA) Pittsburgh Healthcare System and University of Pittsburgh School of Medicine, Pittsburgh (L.F.F., P.M.P.); Hines VA Hospital, Hines, and Loyola University Medical Center, Maywood — both in Illinois (N.E., D.J.L.); and other sources. **Full content, including all tables and figures, can be found at www.nejm.org/doi/full/10.1056/NEJMoa1303154.**



Kaplan–Meier Plot of Cumulative Probabilities of Acute Kidney Injury and Hyperkalemia.

Acute kidney injury was defined as acute kidney injury requiring hospitalization or occurring during a hospitalization. Hyperkalemia was defined as a potassium level that was more than 6.0 mmol per liter or that required an emergency room visit, hospitalization, or dialysis. The P values were calculated with the use of a stratified log-rank test.

Target the incretin system in your type 2 patient not at goal

- Control glycaemia with a low risk of hypoglycaemia[1]
- Sustain reductions in HbA_{1c} in patients not at goal on metformin[2,3]

A choice between two effective incretin-based treatment options:

onglyza (saxagliptin) 5 mg tablets

- Once-daily oral administration[5]
- Weight neutral[4]

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- Twice daily SC injections[6]
- Promotes weight loss[4]

Earlier and more frequent use of incretin-based therapies is recommended*, especially for those in whom excess weight or hypoglycaemia are problematic[1,4]

*Recommended by the AACE/ACE.

AstraZeneca

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