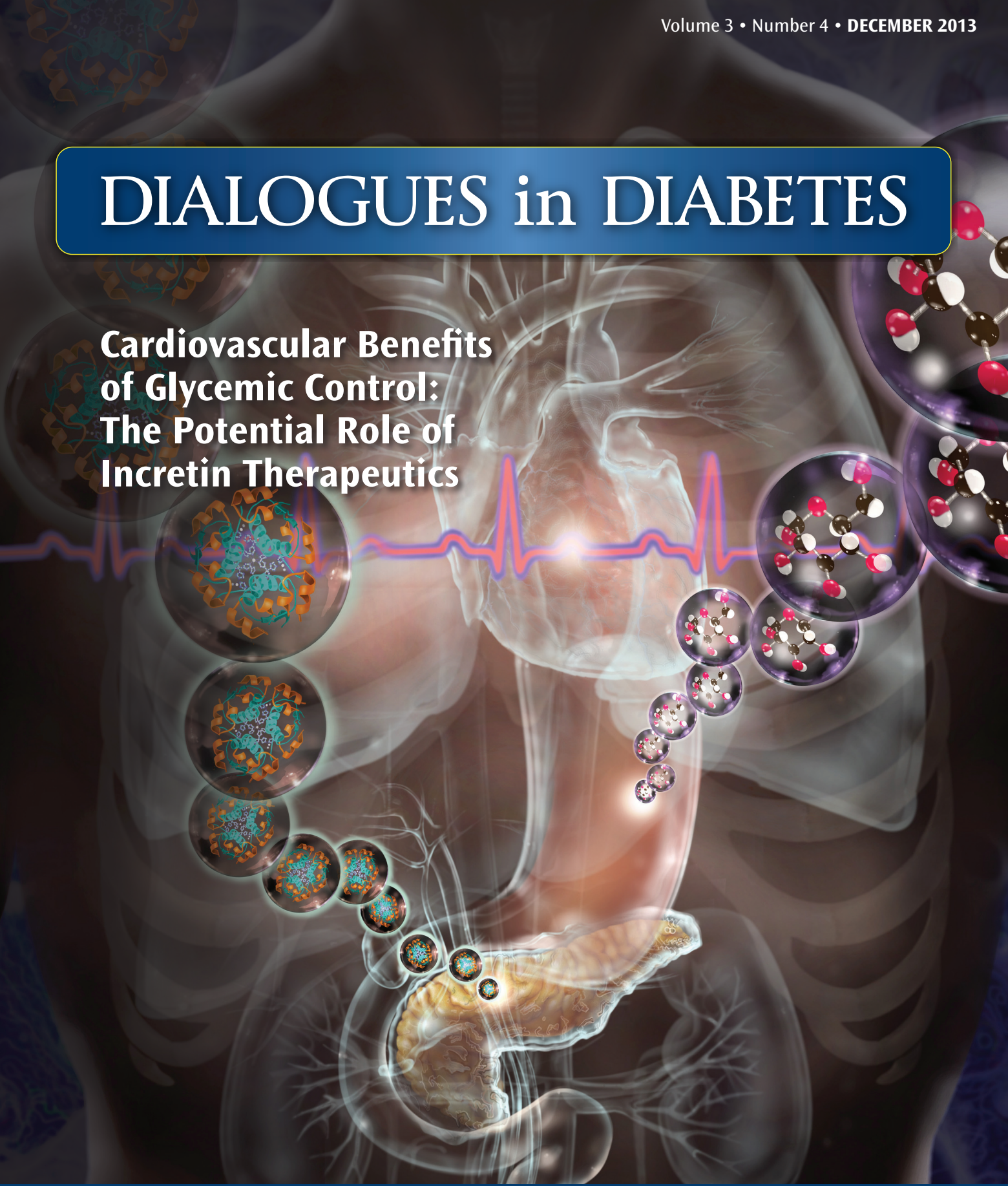
Volume 3 • Number 4 • **DECEMBER 2013**

DIALOGUES in DIABETES

Cardiovascular Benefits of Glycemic Control: The Potential Role of Incretin Therapeutics



Supplement to
Endocrine today®
CLINICAL NEWS ON DIABETES AND ENDOCRINE DISORDERS
December 2013

VINDICO medical education

DIALOGUES in DIABETES

Featured Articles

EARN **CME** CREDIT

Introduction

Reducing cardiovascular risk in patients with diabetes remains an ever challenging problem. Recent clinical trials have raised into question the value of glycemic control in reducing cardiovascular risk in this patient population, emphasizing a more comprehensive approach including lipid, hypertension, and glucose regulation.

Recent advances in incretin-based therapies have provided us with a valuable weapon in fighting the battle to reduce cardiovascular risk in patients with type 2 diabetes mellitus (T2DM). The incretin pathway is responsible for both insulin and glucagon regulation. The injectable glucagon-like peptide-1 (GLP-1) receptor agonists mimic the effects of endogenous GLP-1, which stimulates pancreatic insulin secretion in a glucose-dependent fashion, suppressing pancreatic glucagon output, slowing gastric emptying, and decreasing appetite. This action induces weight loss, which can be significant in some patients. The oral dipeptidyl peptidase-4 (DPP-4) inhibitors enhance circulating concentrations of active GLP-1 agonists by suppressing the inactivation of GLP-1 agonists by DPP-4 inhibitors. Their major effect appears to be in the regulation of insulin and glucagon secretion, as well as being weight neutral. Also of clinical interest is the impact of incretin-based therapies on plasma lipids as well as their cardiovascular effects and impact on cardiovascular risk.

This issue of Dialogues in Diabetes will explore several important clinical issues: (1) reducing cardiovascular disease risk in patients with T2DM; (2) the cardiovascular benefits of glycemic control with updates on the use of anti-diabetic medications for the prevention of cardiovascular events; and (3) the effects of incretin-based therapies on inflammatory markers and cardiovascular risk.

I would like to thank the faculty for their invaluable contribution to this issue and trust that this CME publication will assist you in managing your patients with this challenging disease.

Michael H. Davidson, MD, FACC, FACP, FNLA

This continuing medical education activity is sponsored by

VINDICO medical education

This activity is supported by an educational grant from

ADVANCING DIABETES CARE
Bristol-Myers Squibb AstraZeneca

Learning Objectives

At the conclusion of this series, participants should be able to:

- Assess the pathophysiology of hyperglycemia, its role in macrovascular and microvascular diseases, and the role of incretin pathways in type 2 diabetes mellitus.
- Examine the differences in mechanism of action, efficacy, and safety of treatment options that target the incretin pathway.
- Examine approaches to managing the obese patient with type 2 diabetes.
- Incorporate evidence-based guidelines and recommendations into practice when considering the use of incretin-based therapies for type 2 diabetes.
- Utilize GLP-1 agonists and DPP-4 inhibitors in combination with insulin and oral agents to achieve optimal glycemic control.
- Analyze the potential cardiovascular benefits of incretin therapies in addition to glycemic control.

DIALOGUES in DIABETES

Chief Medical Editor

Robert R. Henry, MD
Professor of Medicine
Division of Endocrinology & Metabolism
University of California, San Diego
Chief, Section of Diabetes, Endocrinology and Metabolism
Director, Center for Metabolic Research
VA San Diego Healthcare System
San Diego, CA

Editorial Board

Lawrence Blonde, MD, FACP, FACE
Director, Ochsner Diabetes Clinical Research Unit
Department of Endocrinology
Ochsner Medical Center
New Orleans, LA

Michael H. Davidson, MD, FACC, FACP, FNLA
Professor, Director of the Lipid Clinic
The University of Chicago, Pritzker School of Medicine
Chicago, IL

Ralph A. DeFronzo, MD
Professor of Medicine
Chief, Diabetes Division
University of Texas Health Science Center of San Antonio
Deputy Director
Texas Diabetes Institute
San Antonio, TX

Vivian A. Fonseca, MD, FRCP
Professor of Medicine and Pharmacology
Tullis–Tulane Alumni Chair in Diabetes
Chief, Section of Endocrinology
Tulane University Health Sciences Center
New Orleans, LA

Contributing Faculty

Deepak L. Bhatt, MD, MPH, FACC, FAHA, FSCAI, FESC
Professor of Medicine, Harvard Medical School
Executive Director of Interventional Cardiovascular Programs, Brigham and Women's Hospital Heart and Vascular Center
Boston, MA

Robert Chilton, MD, DO, FACC, FAHA, FACP
Professor of Medicine
Division of Cardiology
The University of Texas Health Science Center at San Antonio
San Antonio, TX

Vindico Medical Education

Medical Director
Ronald Codario, MD, FACP, FNLA, CCMEP

Vice President, Office of Medical Affairs
James T. Magrann

Director of Medical Education
Chris Rosenberg

Medical Editor
Sharon Powell

Scientific Director
Jennifer Frederick, PharmD, BCPS

Program Manager
Kristin Riday

Publication Design
Kimi Dolan
David Barker
Theresa McIntire

Accreditation

Vindico Medical Education is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Credit Designation

Vindico Medical Education designates this enduring material for a maximum of 1.25 *AMA PRA Category 1 Credit(s)*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

This enduring material is approved for 1 year from the date of original release, December 1, 2013 to December 1, 2014.

How To Participate in this Activity and Obtain CME Credit

To participate in this CME activity, you must read the objectives and articles, complete the CME posttest, and fill in the evaluation. Provide only one (1) correct answer for each question. A satisfactory score is defined as answering 70% of the posttest questions correctly. Upon receipt of the completed materials, if a satisfactory score on the posttest is achieved, Vindico Medical Education will issue an *AMA PRA Category 1 Credit(s)*™ certificate.

Reviewers

Ronald A. Codario, MD, FACP, FNLA, CCMEP
Carol H. Wysham, MD

Disclosures

In accordance with the Accreditation Council for Continuing Medical Education's Standards for Commercial Support, all CME providers are required to disclose to the activity audience the **relevant financial relationships** of the planners, teachers, and authors involved in the development of CME content. An individual has a relevant financial relationship if he or she has a financial relationship in any amount occurring in the last 12 months with a commercial interest whose products or services are discussed in the CME activity content over which the individual has control.

The authors disclose that they do have significant financial interests in any products or class of products discussed directly or indirectly in this activity, including research support.

Planning Committee and Faculty members report the following relationship(s):

Lawrence Blonde, MD, FACP, FACE
Research Grant Support: To Ochsner for his role as investigator from Eli Lilly and Company, Novo Nordisk, and Sanofi-Aventis
Speaker's Bureau: Amylin Pharmaceuticals, Inc., Bristol-Myers Squibb/AstraZeneca, Janssen Pharmaceuticals, Inc., Johnson & Johnson Diabetes Institute, L.L.C., Merck & Co. Inc., Novo Nordisk, Sanofi-Aventis, Santarus, Vivus, Inc.
Consultant: Amylin Pharmaceuticals, Inc., Eisai Inc, GlaxoSmithKline, Janssen Pharmaceuticals, Inc., Merck & Co., Inc., Novo Nordisk, Pfizer, Sanofi-Aventis, Santarus

Deepak L. Bhatt, MD, MPH, FACC, FAHA, FSCAI, FESC
Contracted Research: Amarin, AstraZeneca, Bristol-Myers Squibb, Eisai, Ethicon, Medtronic, Sanofi Aventis, The Medicines Company

Robert Chilton, MD, DO, FACC, FAHA, FACP
Consulting Fees: Bristol-Myers Squibb, Lilly, MSD, Takeda

Michael H. Davidson, MD, FACC, FACP, FNLA
Consulting Fees: AbbVie, Amgen, AstraZeneca, Daiichi-Sankyo, Esperion, Lipidemx, Merck & Co., Inc
Speakers Bureau: Merck & Co., Inc.
Ownership Interest: Prior to July 2013, ownership interest in Omthera Pharmaceuticals, Inc.

Ralph A. DeFronzo, MD
Consulting Fees: Amylin, Bristol-Myers Squibb, Janssen, Lexicon, Novo Nordisk, Takeda
Contracted Research: Amylin, Bristol-Myers Squibb, Lexicon, Takeda
Speakers Bureau: Amylin, AstraZeneca, Bristol-Myers Squibb, Janssen, Novo Nordisk

Vivian A. Fonseca, MD, FRCP
Honoraria for Consulting Fees and Lectures: Abbott, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Eli Lilly, GlaxoSmithKline, Novo Nordisk, PamLabs, Sanofi-Aventis, Takeda
Research Support (to Tulane): Abbott, Eli Lilly, Endo Barrier, Novo Nordisk, Pan American Laboratories, Rcata, Sanofi-Aventis

Robert R. Henry, MD
Grant/Research Support: AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Sanofi-Aventis
Consultant: Boehringer Ingelheim, Intarcia, Isis, Eli Lilly, Novo Nordisk, Roche/Genentech, Sanofi-Aventis
Advisory Board: Amgen, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Elcelyx, Eli Lilly, Intarcia, Johnson & Johnson/Janssen, Merck, Novo Nordisk, Roche/Genentech, Sanofi-Aventis

Reviewers report the following relationship(s):

Ronald A. Codario, MD, FACP, FNLA, CCMEP
No relevant financial relationships to disclose.

Carol H. Wysham, MD
Consulting Fees: Boehringer Ingelheim, Eli Lilly, Janssen, Sanofi-Aventis
Speaker's Bureau: AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly, Janssen, Medtronic, Novo Nordisk, Sanofi-Aventis
Contract Research: Abbott, Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly, Intarcia, Janssen, Merck & Co., Inc., Novo Nordisk, Sanofi-Aventis

Vindico Medical Education staff report the following relationship(s):
No relevant financial relationships to disclose.

Signed disclosures are on file at Vindico Medical Education, Office of Medical Affairs and Compliance.

Target Audience

The intended audience for this activity is endocrinologists and other health care professionals involved in the treatment of patients with type 2 diabetes.

Unlabeled and Investigational Usage

The audience is advised that this continuing medical education activity may contain references to unlabeled uses of FDA-approved products or to products not approved by the FDA for use in the United States. The faculty members have been made aware of their obligation to disclose such usage. All activity participants will be informed if any speakers/authors intend to discuss either non-FDA approved or investigational use of products/devices.

Created and published by Vindico Medical Education, 6900 Grove Road, Building 100, Thorofare, NJ 08086-9447. Telephone: 856-994-9400; Fax: 856-384-6680. Printed in the USA.
Copyright © 2013. Vindico Medical Education. All rights reserved. No part of this publication may be reproduced without written permission from the publisher. The material presented at or in any of Vindico Medical Education continuing medical education activities does not necessarily reflect the views and opinions of Vindico Medical Education. Neither Vindico Medical Education nor the faculty endorse or recommend any techniques, commercial products, or manufacturers. The faculty/authors may discuss the use of materials and/or products that have not yet been approved by the US Food and Drug Administration. All readers and continuing education participants should verify all information before treating patients or utilizing any product.

Addressing Challenges of Reducing CVD Risk in Patients with Type 2 Diabetes Mellitus

Michael H. Davidson, MD, FACC, FACP, FNLA

The leading cause of death for patients with type 2 diabetes mellitus (T2DM) is cardiovascular disease (CVD), and once a patient with T2DM has a cardiovascular event, long-term survival is significantly reduced. Therefore, in the field of preventive cardiology, there is intensive focus to modify cardiovascular risk factors in a patient with T2DM before the initial event. Although patients with T2DM without coronary artery disease (CAD) have a 10-year risk of future events that is lower than patients with CAD, in the latest population studies, their lifetime risk of cardiovascular events is >50%, and the new American Heart Association/American College of Cardiology (AHA/ACC) 2013 Guidelines recommends high-intensity statin therapy for those >40 years of age with risk factors to achieve low-density lipoprotein cholesterol/non-high-density lipoprotein cholesterol (LDL-C/non-HDL-C) reduction.[1] The importance of giving a maximally tolerated statin with high intensity received primary emphasis because it most accurately reflects the data that statins reduce the relative risk of atherosclerotic cardiovascular disease (ASCVD) events similarly in patients with and without diabetes and in primary and secondary prevention in those with diabetes, along with evidence that high-intensity statins reduce ASCVD risk more than moderate-intensity statins**.** Because patients with diabetes often have lower LDL–C levels than patients without diabetes, "goal" directed therapy often encourages the use of a lower statin dose, and non-statin drugs may be added on to address low HDL–C or high triglycerides, for which randomized control trial evidence of an ASCVD risk reduction benefit is lacking.[1] However, expert opinion guidelines, such as those developed by the American Association of Clinical Endocrinologists (AACE) continue to recommend combination therapy for the achievement of target goals for LDL-C/non-HDL-C and potentially low-density lipoproteins particles (LDL-P), apolipoprotein B (apoB), and triglycerides.[2] Once a patient with T2DM is diagnosed with CAD, secondary prevention strategies may still be effective, but improved survival has been difficult to demonstrate with more intensive glycemic control.[3,4] A consensus is developing that although microvascular benefits can be demonstrated with more intensive glycemic control, macrovascular benefits of the existing therapies to improve outcomes has not yet been proven in large randomized clinical trials. This has led to the evaluation of the effects of specific hypoglycemic agents on traditional cardiovascular risk factors, such as lipoproteins, blood pressure, and body weight, as well as the potential adverse effects of these therapeutic agents on cardiovascular safety. Therefore, each pharmaceutical agent that is used to improve glycemic control should also be evaluated in the context of global cardiovascular risk reduction and eventually have outcome benefits demonstrated in large randomized trials.

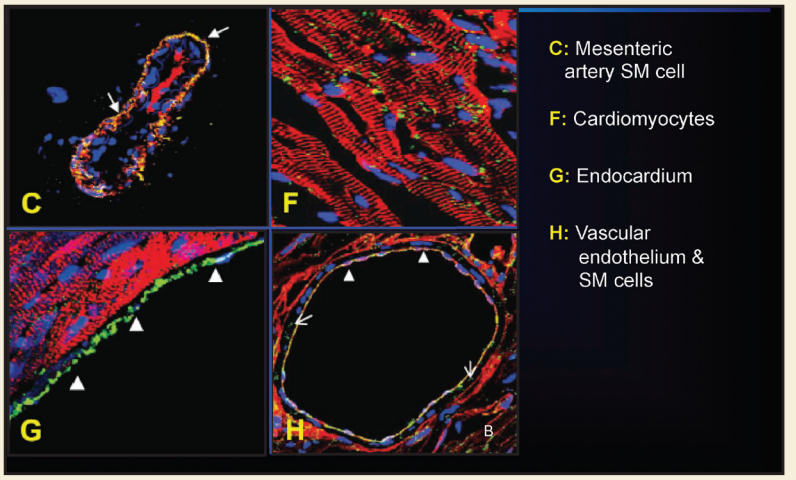
It is well acknowledged that patients with T2DM have an increased prevalence of lipid abnormalities contributing to their high risk of cardiovascular disease.

In patients with T2DM, the therapeutic approach should include diet control, physical exercise, smoking cessation, and particularly, pharmacologic interventions including antidyslipidemics (mainly statins) and hypoglycemic agents.

Evidence for the benefits of lipid-lowering therapy in patients with T2DM has been demonstrated in multiple clinical trials, and it is well acknowledged that patients with T2DM have an increased prevalence of lipid abnormalities contributing to their high risk of CVD. In patients with diabetes, there is overproduction of very-low-density lipoprotein (VLDL), mediated by an increased influx of free fatty acids into the liver. In the setting of hepatic insulin resistance, VLDL secreted by the liver has an increased triglyceride content and apolipoprotein CIII (apoCIII) synthesis is upregulated, leading to competition for apoE

receptor clearance of atherogenic remnant lipoproteins and decreased lipolysis. Increased hepatic secretion of enlarged VLDL with apoCIII results in impaired conversion of VLDL to low-density lipoprotein (LDL). Triglyceride within VLDL is transferred into LDL and high density lipoprotein (HDL) in exchange for cholesterol ester by cholesteryl ester transfer protein. After lipolysis by hepatic lipases, LDL and HDL sizes are significantly reduced. Therefore the net result of hepatic insulin resistance is increased VLDL secretion, an abundance of small dense LDL, and very low HDL-C, the hallmark features of the dyslipidemia associated with T2DM. In addition, due to impaired lipolysis of VLDL, competition develops for clearance of dietary fat, resulting in markedly enhanced postprandial lipemia. All of these factors result in increased CV risk in patients with T2DM.[5]

Figure 1. Location of GLP-1 Receptors in the Cardiovascular System



There has been speculation that GLP-1 receptor agonists may reduce markers of CVD risk.

Source: Ban K, et al. Circulation. 2008;117(18):2340-2350. Reprinted with permission from Wolters Kluwer Health.

The Role of Incretin Therapeutics

Dipeptidyl peptidase-4 (DPP-4) inhibitors have little effect on fasting lipid profiles. Although, DPP–4 inhibitors have been reported to reduce total cholesterol, results are inconsistent across trials. A recent meta-analysis of 17 clinical trials with a variety of DPP-4 inhibitors demonstrated approximately a 6 mg/dL reduction in total cholesterol compared with controls.[6]

However, DPP-4 inhibitors appear to have a significant beneficial effect on postprandial lipemia. Sitagliptin was shown to reduce the area under the curve for triglycerides and apolipoprotein B-48, as well as apolipoprotein B-100.[7] This suggests that DPP-4 inhibitors decrease postprandial plasma levels of triglyceride-rich lipoproteins of both intestinal and hepatic origin. Similar effects on postprandial lipemia have been demonstrated with other DPP-4 inhibitors, such as vildagliptin and alogliptin.[8]

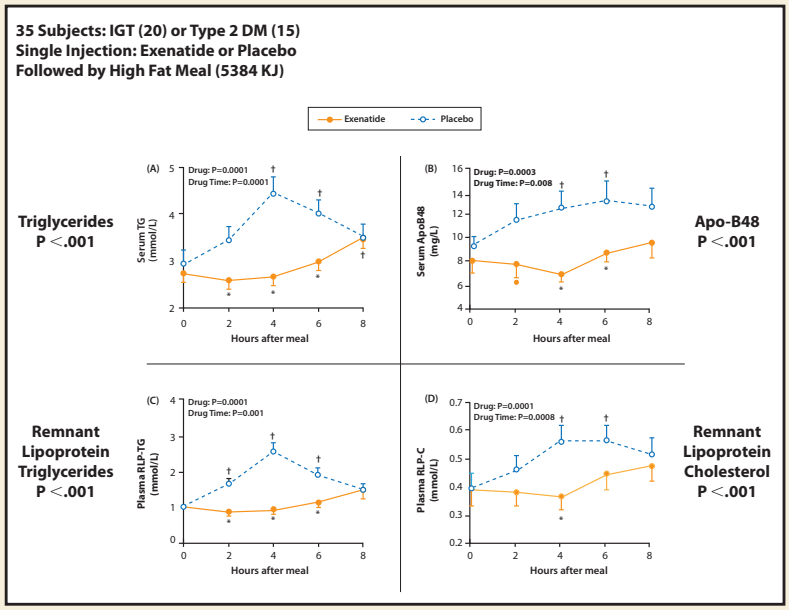
GLP-1 is a hormone that normally promotes the production and secretion of insulin from pancreatic islet-cells in a glucose-dependent manner, reduces hepatic glucose production, minimizes the release of glucagon from pancreatic islet cells, and slows gastric emptying and induces satiety, thereby promoting weight loss. Failure of secretion of the incretin hormone GLP-1 plays a prominent role in T2DM, and restoration of GLP-1 action is an important therapeutic objective. GLP-1 receptor agonists have also been identified in the heart, kidneys, and blood vessels, leading

Table. Effect of GLP-1 Agonists on Lipids

Parameter	Liraglutide	Rosiglitazone	Glimepiride	Glargine	Exenatide	Placebo
TC (mmol/L)	-5.07	11.31	-1.95	0.78	-1.95	0.39
LDL-C (mmol/L)	-7.8	2.34	-4.68	-2.73	-5.85	-5.07
VLDL (mmol/L)	3.9	8.58	4.68	4.68	6.24	6.24
HDL-C (mmol/L)	-1.56	0.78	1.56	1.56	1.95	-1.59
FFA (mmol/L)	-2.34	N/A	-1.33	N/A	-0.8	-1.59
TG (mmol/L)	-17.8	-4.45	-14.24	-13.35	-4.45	1.78

Source: Plutzky J, et al. Diabetologia. 2009;52(Suppl 1):S299-S300.

Figure 2. Exenatide and Postprandial Lipemia



Liraglutide and exenatide suppresses postprandial elevations in lipids and proteins.

Source: Reprinted from Schwartz EA, et al. Atherosclerosis. 2010;212(1):217-222 with permission from Elsevier.

to the hypothesis that GLP-1 receptor agonists may reduce markers of CVD risk (Figure 1, see page 5).[9] GLP-1 receptor agonists appear to have the greatest effects on triglyceride-rich lipoproteins compared with other hypoglycemic agents, potentially because of their beneficial effects on body weight. GLP-1 receptor agonists lower levels of total cholesterol by 5% (Table, see page 5).[6] The effect of the GLP-1 receptor agonists, liraglutide and exenatide on reducing postprandial lipemia, has also been established with respect to the suppression of postprandial elevations in lipids and lipoproteins (Figure 2).[10]

Findings from the SAVOR and EXAMINE trials demonstrate that DPP-4 inhibition with either saxagliptin or alogliptin neither increases nor decreases the rate of ischemic events over a median 2-year period.

Recent CV Safety Trials with Incretin Therapies

Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53) randomized 16,492 patients with T2DM and a history of established cardiovascular disease or multiple risk factors for vascular disease to either saxagliptin, doses ranging from 2.5 to 5 mg daily, or placebo. The primary endpoint – a composite of cardiovascular death, myocardial infarction, or ischemic stroke – occurred at similar rates in 613 patients randomized to receive saxagliptin treatment and 609 patients randomized to receive placebo (7.3% and 7.2%, respectively) at a median followup of 2.1 years. A major secondary endpoint, a composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, coronary revascularization, or heart failure, also occurred at similar rates in the treatment and placebo groups (12.8% and 12.4%, respectively). However, more patients in the treatment group than in the placebo group were hospitalized for heart failure (3.5% vs. 2.8%). The etiology of the excess risk of heart failure is uncertain.[11]

Similarly, the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) trial with another DPP-4 inhibitor, alogliptin, with patients with T2DM and a recent acute myocardial infarction or unstable angina requiring hospitalization showed that the primary endpoint, a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, did not occur significantly more often at a median followup of 18 months in 2,679 patients randomized to receive treatment, compared with 2,701 patients randomized to receive placebo (11.3% vs. 11.8%, respectively). For both studies, it was reassuring that there was not an increase in pancreatitis or pancreatic cancer in the patients treated with a DPP-4 inhibitor compared to control. The findings from the SAVOR and EXAMINE trials demonstrate that DPP-4 inhibition with either saxagliptin or alogliptin neither increases nor decreases the rate of ischemic events over a median 2-year period, although longer duration of treatment may have resulted in a different outcome. Without significant changes in lipid levels or blood pressure it was unlikely that a very modest difference in A1C would have resulted in a cardiovascular benefit after such a short treatment period.[12]

There are currently 3 large, randomized controlled trials investigating cardiovascular outcomes in patients with T2DM with GLP-1 therapies.

The Exenatide Study of Cardiovascular Event Lowering (EXSCEL) trial is an ongoing multicenter trial randomizing more than 9,500 patients with T2DM on stable doses of oral glucose-lowering agents to once-weekly exenatide injections or placebo with a followup of 4 years for major macrovascular events. The Evaluation of Cardiovascular Outcomes in Patients With Type 2 Diabetes After Acute Coronary Syndrome During Treatment With AVE0010 (Lixisenatide) (ELIXA) trial is another ongoing multicenter trial that will randomize an estimated 6,000 patients with T2DM to lixisenatide or placebo after ACS and followup for major cardiovascular events. Finally, the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results—A Long Term Evaluation (LEADER) trial has randomized 9,341 patients with hemoglobin A1C levels >7% to receive liraglutide or placebo and will followup for major cardiovascular events until 2016.[13]

The GLP-1 receptor agonists are a promising class of glucose-lowering agents given their weight-loss properties and the improvements in surrogates, such as blood pressure and cholesterol. These trials are therefore more likely to demonstrate a CV outcome benefit if the improvement in weight loss induced risk factors can be sustained over the length of the multiple years of the studies.

Conclusion

Evidence-based approaches for reducing cardiovascular risk in patients with diabetes include statins regardless of baseline LDL-C. Therefore the new AHA/ACC Guidelines are now consistent with the ADA Guidelines which recommends high-intensity statin therapy for those >40 years of age with risk factors. In regards to the selection of the most appropriate drug to add to metformin to reduce A1C, DPP-4 inhibitor-based therapies provide an option that have demonstrated safety but as of yet have not been shown to reduce CV events despite the promise of some of the earlier clinical trials. However, the SAVOR and EXAMINE outcome trials with saxagliptin and alogliptin respectively may have been too short of treatment duration and/or with insufficient differences in A1C and other cardiovascular risk factor effects to result in a clinically meaningful benefit. The GLP-1 receptor agonists provide an additional improvement in risk factor reduction, such as lower fasting triglycerides, increases in HDL-C, and reduced blood pressure (which may be weight loss mediated) and therefore still hold out promise for cardiovascular event reduction in the high-risk patient with diabetes population.

References

1. Stone NJ, et al. *J Am Coll Cardiol*. 2013;pii:S0735-1097(13)06028-2. [Epub ahead of print]
2. Garber AJ, et al. *Endocr Pract.* 2013; 19(2):327-336.
3. The Diabetes Control and Complications Trial Research Group. *N Engl J Med.* 1993;329(14):977-986.
4. Stratton IM, et al. *BMJ.* 2000; 321(7258):405-412.
5. David MH. *Am J Cardiol*. 2012;110(9 Suppl):43B-49B.
6. Plutzky J, et al. *Diabetologia.* 2009; 52(Suppl 1):A762-P.
7. Tremblay AJ, et al. *Diabetes Obes Metab.* 2011;13(4):366–373.
8. Matikainen N, et al. *Diabetologia.* 2006; 49(9):2049–2057.
9. Ban K, et al. *Circulation*. 2008;117(18): 2340-2350.
10. Schwartz EA, et al. *Atherosclerosis.* 2010;212(1):217–222.
11. Scirica BM, et al. *N Engl J Med.* 2013; 369(14):1317-1326.
12. White WB, et al. *N Engl J Med.* 2013; 369(14):1327-1335.
13. Marso SP, et al. *Am Heart J.* 2013; 166(5):823-830.

Full references are available at www.healio.com/endocrinology/education-lab.

Cardiovascular Benefits of Glycemic Control

Robert J. Chilton, MD, DO, FACC, FAHA, FACP

Patients with type 2 diabetes mellitus (T2DM) are at a 2-fold to 4-fold increased risk for cardiovascular disease (CVD) and mortality.[1] Commonly, T2DM clusters with other major cardiovascular risks such as dyslipidemia, obesity, and hypertension. Despite advances in current armamentarium for the treatment of T2DM, half of patients with T2DM still fail to reach the goal of A1C <7%,[2] and even fewer attain the more rigid goal of <6.5%. Fewer patients (18.8%) achieve all three ABCs (A1C, blood pressure, and cholesterol) goals. The importance of tight glycemic control in T2DM to reduce the risk of microvascular diseases has been well established,[3] while the impact on macrovascular disease is still a matter of debate.

The glycemic control of the incretin-based agents is comparable to other antidiabetic agents but without the weight gain and weight loss and with a low risk of hypoglycemia.

Hyperglycemia

Experimental work has shown repeatedly that a hyperglycemic milieu bolsters multiple mechanisms to accelerate atherosclerosis. Hyperglycemia is associated with endothelial dysfunction, impaired fibrinolysis, increased platelets aggregation, dysfunctional arterial remodeling, oxidative stress, and increased production of advanced glycosylation end products. The belief that lowering glucose is inextricably linked to a reduction in cardiovascular morbidity and mortality was recently challenged by observational findings that rosiglitazone-treated patients were at increased risk for acute myocardial infarction (MI). This led to the 2008 FDA guidance which required all new glucose lowering agents to conduct large cardiovascular safety trials. Additionally, large randomized controlled trials evaluating the effect of tight glycemic control on cardiovascular event rates in people with T2DM[4,5,6,7,8] all failed to show a cardiovascular benefit of the intensive glucose management. There are several caveats to interpreting the results of the trials: (1) pharmacotherapeutic interventions; (2) the patient population studied (especially with respect to age, duration of diabetes, and preexisting CVD); (3) the baseline A1C; (4) the glycemic goals; and (5) duration of followup. Evidence from these studies confirm that intensive approach to glucose control (using older agents) invariably results in higher risk of hypoglycemia and weight gain which may mask the favorable effects of glucose lowering on the cardiovascular system.

Incretin-based Therapies

The availability of the incretin-based therapies dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists raised the hope that while the older agents had failed to alter the course of cardiovascular disease, the incretins could potentially modify the disease process. The glycemic control of the incretin-based agents is comparable to other antidiabetic agents but is achieved without weight gain (DPP-4 inhibitor) or even weight loss (GLP-1 receptor agonist) and with a low risk of hypoglycemia. Furthermore, incretin-based agents have demonstrated in clinical trials beneficial effects on several well-known cardiovascular biomarkers (Table 1).

DPP-4 is a widely expressed protease and has been localized on the kidney, small intestine, liver, and heart tissue.[9] In clinical trials, DPP-4 inhibitors result in a mean decrease in A1C ranging from 0.3% to 1%,[10] are weight neutral with no increased risk of hypoglycemia unless combined with insulin or sulfonylureas, show modest reduction in systolic blood pressure,[11,12] improve postprandial lipids,[13] and result in favorable changes in endothelial cell function and markers of inflammation. The potential cardiovascular protective role of DPP-4 inhibitors potentially involves both GLP-1 dependent and independent mechanisms. Overall, the knowledge about the effect of this class on cardiac structure and function is limited to experimental models. Only small clinical studies of short duration, mostly assessing cardiovascular biomarkers, exist. The majority of the evidence regarding the cardiovascular impact of incretin-

Table 1. Effects of Antidiabetics on Glycemic Control and Cardiovascular Biomarkers

Drug	FPG	PPG	Lipids	Weight	Blood Pressure	Hypoglycemia	Hs-CRP
SFU	↓↓	↔	↔	↑↑	↔	↑↑	↔
TZD	↓↓	↔	↓	↑↑	↔	↔	↓↓
Metformin	↓↓	↔	↓	↔	↔	↔	↓
AGI	↓	↓↓	↔	↔	↔	↔	↓
DPP-4 Inh	↓↓	↓↓	↔	↔	↓	↔	↓
Insulin	↓↓ ↓	↓↓ ↓	↔	↑↑↑	↔	↑↑ ↑	↔
GLP-1 RA	↓↓ ↓	↓↓ ↓	↓	↓↓	↓↓	↔	↓↓

SFU: sulfonylurea, TZD: thiazolidinedione, AGI: alpha-glucosidase inhibitors, DPP-4: dipeptidyl peptidase-4 inhibitor, GLP-1 RA: glucagon-like peptide-1 receptor agonist, FPG: fasting plasma glucose, PPG: postprandial plasma glucose, hs-CRP: high-sensitivity C-reactive protein

Source: Ginsberg H, et al. *J Cardiovasc Risk.* 1999;6(5):337-346; Lehrke M, et al. *Rev Diabet Stud.* 2011;8(3):382-391.

based therapies is derived from administering native GLP-1 receptor agonists or its analogs.

GLP-1 receptor agonists are widely expressed in the human heart and are found in cardiomyocytes, endocardium, and coronary endothelium.[14] In clinical trials, when compared with DPP-4 inhibitors, GLP-1 receptor agonists result in more robust A1C reduction in weight loss, blood pressure, and lipids improvement. Depending on background glucose-lowering therapy, a weight loss of 1 to 4 kg is generally observed in patients treated with a GLP-1 receptor agonist. The reduction in systolic blood pressure ranges from 1 to 7 mm Hg in patients otherwise normotensive. The greatest change in lipid profile is seen on the triglycerides levels with average reductions around 10% to 15%. GLP-1 receptor agonists have also been shown to significantly improve a number of emerging cardiovascular risk markers (lipoprotein subfractions, anti-inflammatory markers, oxidative stress, endothelial function, etc). Growing evidence suggests a significant role for GLP-1 receptor agonists on the cardiovascular system, such as effects on vascular tone, myocardial contractility, and remodeling. Two clinical studies have focused on the potential cardioprotective effects of GLP-1 receptor agonists on ischemia-reperfusion injury.[15,16] Although the mechanism in ischemia is unknown, experimental data indicate that the effect is independent of glycemic control and may involve activation of prosurvival kinases (PI3K, Akt, glycogen synthase kinase-3b, p70s6 kinase, ERK1/2 and p38 MAPK).[17]

Pharmacology

In a Pharmacological Postconditioning (POSTCON II) trial, investigators randomized 387 ST-elevation myocardial infarction (STEMI) patients (with or without diabetes) undergoing percutaneous coronary intervention (PCI), who presented within 12 hours of symptoms and had thrombolysis in myocardial infarction (TIMI) flow grade 0/1 to intravenous exenatide or placebo. The infusion began at least 15 minutes before primary PCI and lasted 6 hours after the procedure. At 3 months, cardiac MRI demonstrated significantly higher myocardial salvage index and reduced infarct size in both patients with diabetes and patients without diabetes.[15]

In a similar study, investigators evaluated the effect of a slightly lower dose of exenatide in 71 patients without diabetes with STEMI undergoing PCI.[16] At 3 months, a trend towards higher myocardial salvage index was also reported in the exenatide treated group. Several other studies are ongoing to better understand the best dose and timing of exenatide infusion to confer the most cardioprotection during reperfusion.

Growing evidence suggests a significant role for GLP-1 receptor agonists on the cardiovascular system, such as effects on vascular tone, myocardial contractility, and remodeling.

There is no doubt that incretin-based agents offer unique attributes (weight loss/neutrality, limited risk of hypoglycemia, improvement in lipids, and blood pressure) beyond glycemic control, whether this will translate to

Table 2. Large Cardiovascular Outcome Trials of Incretin-based Therapies

Trial Name/ Drug	N	Primary Endpoint
EXAMINE[1] **Examination of Cardiovascular Outcomes with Alogliptin vs. Standard of Care**	5,380	MACE
SAVOR TIMI-53[2] **Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus**	16,492	MACE
TECOS[3] **Trial Evaluating Cardiovascular Outcomes with Sitagliptin**	14,000	MACE + unstable angina
CAROLINA[4] **Cardiovascular Outcome Study of Linagliptin vs. Glimepiride in Patients with Type 2 Diabetes**	6,000	MACE + unstable angina
LEADER[5] **Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcomes Results - A Long-term Evaluation**	9,000	MACE
EXSCEL[6] **Exenatide Study of Cardiovascular Event Lowering Trial**	12,000	MACE
ELIXA[7] **Evaluation of Cardiovascular Outcomes in Patients with Type 2 Diabetes After Acute Coronary Syndrome During Treatment with Lixisenatide**	6,000	MACE + unstable angina
REWIND[8] **Researching Cardiovascular Events with a Weekly Incretin in Diabetes**	9,600	MACE

Source:
[1]White WB, et al. Am Heart J. 2011;162(4):620-626.
[2]Scirica BM, et al. N Engl J Med. 2013;369(14):1317-1326.
[3]TECOS Study. http://clinicaltrials.gov/show/NCT00790205. Accessed November 18, 2013.
[4]CAROLINA Study. http://clinicaltrials.gov/ct2/show/NCT01243424. Accessed Novermber 18, 2013.
[5]LEADER Study. http://clinicaltrials.gov/ct2/show/NCT01179048? term=LEADER&rank=4. Accessed November 18, 2013.
[6]EXSCEL Study. http://clinicaltrials.gov/ct2/show/NCT01144338? term=EXSCEL&rank=1. Accessed November 18, 2013.
[7]ELIXA Study. http://clinicaltrials.gov/ct2/show/NCT01147250?term=ELIXA&rank=1. Accessed November 18, 2013.
[8]REWIND Study. http://clinicaltrials.gov/ct2/show/NCT01394952?term=REWIND& rank=1. Accessed November 18, 2013.

reduction in cardiovascular morbidity and mortality is still unknown. Recently, 2 large random controlled trials partially elucidated the impact of DPP-4 inhibitors on cardiovascular morbidity and mortality.

SAVOR TIMI 53 and EXAMINE Trials

The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53 (SAVOR TIMI 53) trial investigators randomized 16,492 patients with T2DM and preexisting cardiovascular disease or multiple cardiovascular risk factors.[18] The patients were assigned to either saxagliptin or a matching placebo for 2 years. The primary endpoint was a composite of cardiovascular death, nonfatal MI, or nonfatal ischemic stroke. The secondary endpoint was the primary endpoint plus hospitalization for heart failure, coronary revascularization, or unstable angina. The patients were mostly white obese males with T2DM for about 10 years with a baseline A1C around 8%. Approximately 75% of the patients received aspirin, a statin, and only 50% were on an angiotensin-converting-enzyme inhibitor.

The primary endpoint occurred in 7.3% of patients assigned to saxagliptin compared to 7.2% in the placebo group (HR, 1.0; 95% CI, 0.89 to 1.12). Similarly there was no significant difference between the groups for the secondary endpoint (12.8% vs. 12.4% for placebo). More patients in the saxagliptin treated group were hospitalized for heart failure than in the placebo group (3.5% vs. 2.8%, HR, 1.27; 95% CI, 1.07 to 1.51). At the end of the trial, the between group A1C difference was 0.2% (P<0.001 vs. placebo).

The Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) trial investigators randomized 5,380 patients with T2DM and either recent acute MI or unstable angina requiring hospitalization.[19] The patient were assigned to either alogliptin or matching placebo for 18 months. The primary endpoint was similar to the SAVOR trial. The secondary endpoint was the primary endpoint plus urgent revascularization due to unstable angina.

The patients were mostly white overweight males with T2DM for about 7 years and a baseline A1C around 8%. More than 90% of the patients were on aspirin and statin. The primary endpoint occurred in 11.3% patients assigned to alogliptin compared to 11.8% in the placebo group (HR, 0.96; P=0.32). Similarly, there was no significant difference between the two groups for the secondary endpoint (12.7% vs. 13.4% for placebo, P=0.26). At the

end of the trial, the between group difference for A1C was -0.36%.

Because of the small A1C difference between groups, the causal relationship between glucose control and CVD cannot be inferred by these trials. The promising preclinical and retrospective evidence suggesting potential cardioprotective effect of DPP-4 inhibitors in patients with T2DM did not translate in these randomized control trials. Several caveats should be considered when interpreting the results: (1) the studies were of short duration; (2) patients had diabetes for 7 to 10 years, most likely representing a population with a high atherosclerotic plaque burden; and (3) the 0.7% absolute increased risk in hospitalization for heart failure in the saxaglitin-treated group needs to be confirmed in other trials.

These two large cardiovascular outcome studies provide evidence that saxagliptin and alogliptin used to control glycemia in patients with T2DM do not increase the risk for cardiovascular events in an otherwise high-risk population. Several ongoing cardiovascular safety trials of other incretin-based therapies will provide, in the near future, further evidence to guide clinical practice (Table 2).

CONCLUSION

There is robust evidence that normalizing glycemia results in reduced risk for kidney disease, blindness, and amputations. The same causal relationship is lacking for cardiovascular disease despite the evidence from epidemiological and experimental studies. The optimal approach to reduce cardiovascular risk in patients with T2DM remains the well proven strategies of adopting an active healthy eating lifestyle, maintaining a normal weight, reducing blood pressure, lowering LDL-cholesterol, and smoking cessation.

The 2 recent large trials with DPP-4 inhibitors establish the short-term cardiovascular safety of these glucose-lowering agents for patients with T2DM at high risk for cardiovascular events. Based on clinical trials in acute MI setting, could GLP-1 receptor agonists be the glucose-lowering agents with dual properties that could prevent microvascular and macrovascular disease? Only large randomized control trials will confirm this assumption.

References

1. Emerging Risk Factors Collaboration, et al. *Lancet*. 2010;375(9733): 2215-2222.
2. Stark Casagrande S, et al. *Diabetes Care.* 2013;36(8):2271-2279.
3. Hemmingsen B, et al. *Cochrane Database Syst Rev.* 2011;(6):CD008143.
4. Raz I, et al. *Diabetes Care*. 2009; 32(3): 381-386.
5. ACCORD Study Group, et al. *N Engl J Med.* 2010; 362(17):1575-1585.
6. ADVANCE Collaborative Group, et al. *N Engl J Med*. 2008;358(24):2560-2572.
7. Duckworth W, et al. *N Engl J Med*. 2009; 360(2):129-139.
8. ORIGIN Trial Investigators, et al. *N Engl J Med*. 2012;367(4):319-328.
9. Mentlein R. *Regul Pept*. 1999;85(1):9-24.
10. Amori RE, et al. *JAMA*. 2007;298(2); 194-206.
11. Russell-Jones D, et al. *Diabetes Care*. 2012;35(2):252-258.
12. Bergenstal RM, et al. *Lancet*. 2010; 376(9739):431-439.
13. Eliasson B, et al. *Diabetologia*. 2012; 55(4):915-25.
14. Wei Y, et al. *FEBS Lett*. 1995;358(3): 219-224.
15. Bernink FP, et al. *Int J Cardiol*. 2012; 167(1):289-290.
16. Lønborg J, et al. *Eur Heart J*. 2012; 33(12):1491-1499.
17. Ban K, et al. *Circulation*. 2008; 117(18): 2340-2350.
18. Scirica BM, et al. *N Engl J Med*. 2013; 369(14):1317-1326.
19. White WB, et al. *N Engl J Med*. 2013; 369(14): 1327-1335.

Full references are available at www.healio.com/endocrinology/education-lab.

Evaluation of Cardiovascular Effects of Incretin Therapy for Type 2 Diabetes Mellitus

Deepak L. Bhatt, MD, MPH, FACC, FAHA, FSCAI, FESC

Two large cardiovascular outcome trials of diabetes medications have recently been completed. These 2 trials provide great insight into dipeptidyl peptidase-4 (DPP-4) inhibitors and their cardiovascular and overall safety profile. The results of these 2 trials will be discussed and context will be provided to evaluate these findings in the broad world of cardiovascular risk reduction.

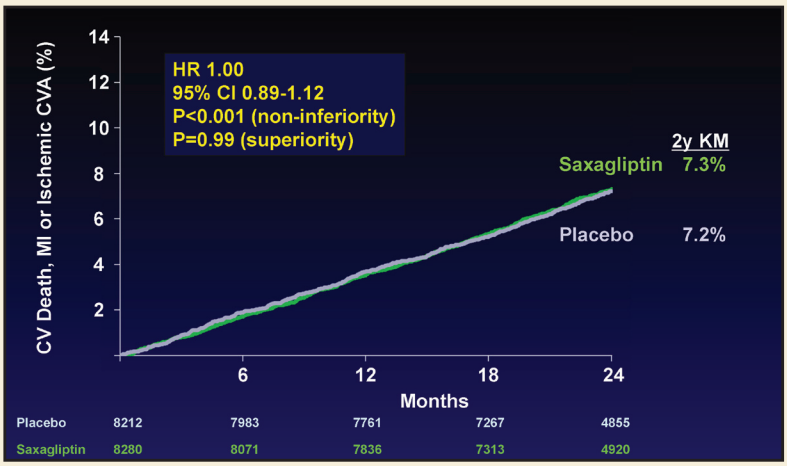
An extensive amount of preclinical data suggested that there might be a cardiovascular benefit to incretins. A large meta-analysis of DPP-4 inhibitors suggested lower rates of major adverse cardiac events in relatively healthy patients with diabetes. These potential benefits seemed to occur early. This suggested that there may be benefits of DPP-4 inhibition beyond glycemic control due to pleiotropic effects.

As these provocative data were accruing, the Food and Drug Administration (FDA) issued a requirement that all new diabetes drugs provide reassurance of their cardiovascular safety if they are to be allowed on the market or to stay on the market. Specifically, the upper bound of the 95% confidence interval for the hazard ratio for ischemic events would need to be demonstrated to be less than 1.3. In response to this requirement, several large cardiovascular outcome trials were launched.

SAVOR-TIMI 53 Trial

The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53) trial randomized a total of 16,492 patients with type 2 diabetes and either established cardiovascular disease or multiple cardiovascular risk factors to receive either the DPP-4 inhibitor saxagliptin or placebo. The hazard ratio (HR) for cardiovascular death, myocardial infarction (MI), or ischemic stroke was 1.00 (95% confidence interval = 0.89 to 1.12, *P* value for non-inferiority < 0.001, *P* value for superiority = 0.99) (Figure 1).[1] Very consistent, the hazard ratio for the more expansive secondary cardiovascular endpoint which, in addition to the primary endpoint, included hospitalization for unstable angina, heart failure, or revascularization was 1.02 (95% confidence interval = 0.94 to 1.11, *P* value for non-inferiority <0.001) (Figure 2).[1] Unexpectedly and contrary to the *a priori* hypothesis, there was an excess in hospitalization for heart failure. It is important to acknowledge that hospitalization for heart failure was only one component of a secondary endpoint that was overall neutral. Also, while statistically significant, in absolute terms, the excess rate of hospitalization for heart failure was only 0.7% over two years, and importantly, there did not appear to be any significant excess in mortality associated with this finding. Several analyses are ongoing to further

Figure 1. Primary Endpoint from SAVOR-TIMI 53



Primary endpoint HR for cardiovascular death, MI, or ischemic stroke: 1.00.

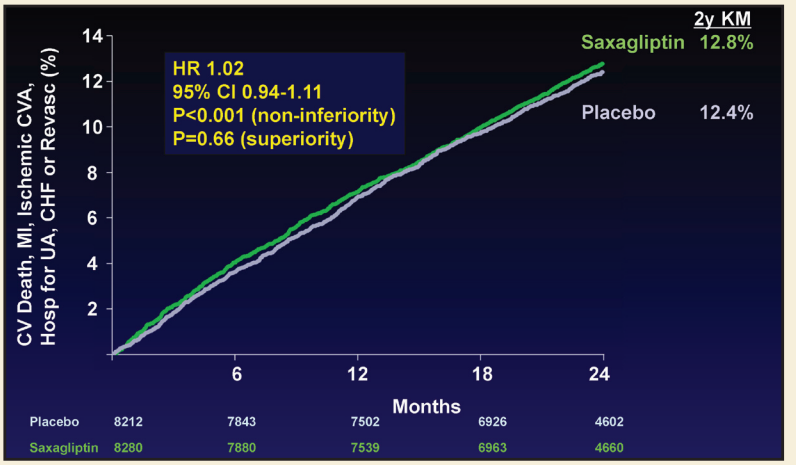
Source: From Scirica BM, et al. N Engl J Med. 2013;369(14):1317-1326. Reprinted with permission from Massachusetts Medical Society.

explore this observation, including detailed analyses of multiple biomarkers, including a b-type natriuretic peptide (BNP) blood test, that were obtained at baseline and at 2-year followup.

EXAMINE Trial

The Cardiovascular Outcomes Study of Alogliptin in Subjects With Type 2 Diabetes and Acute Coronary Syndrome (EXAMINE) trial randomized 5,380 patients with type 2 diabetes with a recent acute coronary syndrome to either the DPP-4 inhibitor alogliptin or placebo. The hazard ratio for the primary endpoint of cardiovascular death, myocardial infarction, or stroke for alogliptin vs. placebo was 0.96 (upper boundary of the one-sided repeated confidence interval = 1.16, *P* value for non-inferiority <0.001, *P* value for superiority = 0.32) (Figure 3).[2] There was no significant increase in hospitalization for heart failure in the EXAMINE trial, though directionally, there was a similar increase as seen in the SAVOR-TIMI 53 trial. As the EXAMINE trial had a little less than one third the number of patients as did the SAVOR-TIMI 53 trial and also a shorter median duration of followup, it is possible that the EXAMINE trial was underpowered to see a significant effect on hospitalization for heart failure. Potentially, the differences could be due to the different drugs studied, though there is no good reason to think one would cause heart failure and the other would not. Much more likely, if the heart failure signal is real, it is a class effect. Alternatively, the finding of heart failure in the SAVOR-TIMI 53 trial may be spurious and the by-product of multiple comparisons of different safety endpoints. An increase in heart failure has been noted with the use of thiazolidinediones, rosiglitazone, and pioglitazone. Therefore, it is important to evaluate the potential for incretins to cause heart failure and future studies should carefully adjudicate this outcome.

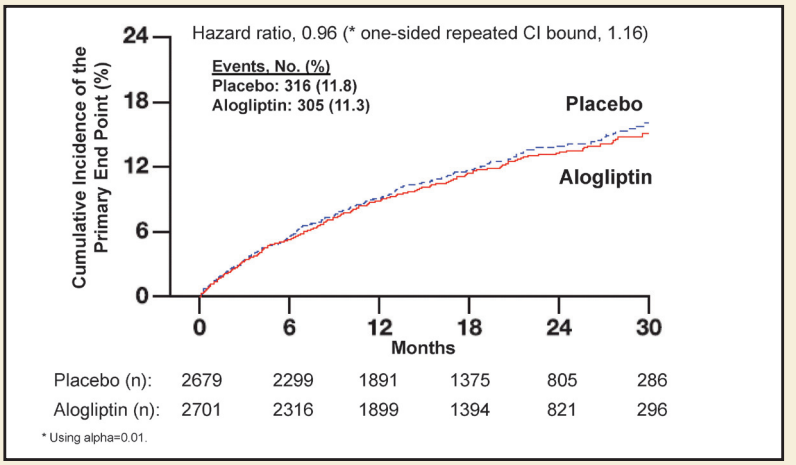
Figure 2. Secondary Endpoint from SAVOR-TIMI 53



Secondary endpoint HR, including unstable angina, heart failure, or revascularization: 1.02.

Source: From Scirica BM, et al. N Engl J Med. 2013;369(14):1317-1326. Reprinted with permission from Massachusetts Medical Society.

Figure 3. Primary Endpoint from EXAMINE



Primary endpoint HR of cardiovascular death, MI, or stroke: 0.96.

Source: From White WB, et al. N Engl J Med. 2013;369(14):1327-1335. Reprinted with permission from Massachusetts Medical Society.

Comparison

In the SAVOR-TIMI 53 trial, an increase in hypoglycemic events was found with saxagliptin vs. placebo. Fortunately, there was no increase in hospitalization for hypoglycemic events. However, in the EXAMINE trial, no increase in hypoglycemia was reported. It is unlikely that this difference in trial outcomes was due to differences in the drugs. Much more likely, these differences were due to the differing trial populations studied as well as the more sensitive definition of hypoglycemia used in the SAVOR-TIMI 53 trial.

A major concern that had been raised in the endocrinology literature was whether DPP-4 inhibitors

increase the risk of pancreatitis and pancreatic cancer. These concerns were based on observational analyses and animal data. Reassuringly, neither of these two large randomized, blinded trials found a significant difference in pancreatitis or excess in pancreatic (or other) cancers. In fact, in the SAVOR-TIMI 53 trial, a careful prespecified blinded adjudication process was used to categorize pancreatitis and there was no evident signal associated with saxagliptin. Furthermore, various safety concerns that have been raised with other classes of diabetes medications (eg, liver failure, fractures) were not noted to be associated with DPP-4 inhibitors in these 2 trials.

Both trials showed that DPP-4 inhibitors significantly improved glycemic control. In the SAVOR-TIMI 53 trial, the hemoglobin A1C at a 2-year followup was 7.5% in the saxagliptin treated patients and 7.8% in the control patients ($P<0.001$). It is important to realize this reduction was in the context of a significant reduction in the need for add-on diabetes therapy in the saxagliptin arm vs. placebo arm. Similarly, in the EXAMINE trial, there was a 0.36% reduction in hemoglobin A1C for alogliptin vs. placebo ($P<0.001$). Thus, both these trials of DPP-4 inhibitors were quite concordant overall, demonstrating safe glycemic control.

There are other large ongoing cardiovascular outcome trials of DPP-4 inhibitors in patients at elevated cardiovascular risk that should increase the understanding of diabetes medications substantially.

Neither trial was designed to examine microvascular outcomes that are associated with levels of glycemic control. However, the SAVOR-TIMI 53 trial did find that categories of microalbuminuria significantly improved and worsening of microalbuminuria was significantly lessened with saxagliptin vs. placebo. Whether this would translate into a reduction in actual progression to renal failure would have required a much longer study.

Why did the prior meta-analyses find a reduction in major adverse cardiovascular events while two large randomized clinical trials did not? Of course, one explanation is that the meta-analyses were spurious and misleading. The very early benefits seen in those analyses were attributed to pleiotropic effects. An alternative explanation is that the very early treatment effects (prior to any potential significant impact on glycemic control) were implausible. Another explanation is that the findings were accurate, but only applicable to patients with much earlier stages of diabetes and without the additional cardiovascular and medical comorbidities in the higher risk populations tested in the SAVOR-TIMI 53 and EXAMINE trials. The only way to definitively address this uncertainty would be with further large-scale randomized clinical trials in patients with diabetes who are much healthier. The practical problem with that approach is the likely low event rates would necessitate a very large and very long study if it is to be adequately powered.

Other Trials

Other large cardiovascular outcome trials of DPP-4 inhibitors in patients at elevated cardiovascular risk are ongoing. The Sitagliptin Cardiovascular Outcome Study (TECOS)[3] trial which is underway is randomizing patients with diabetes to placebo or sitagliptin, a very commonly used DPP-4 inhibitor. The TECOS trial will have a longer duration of follow-up than either the SAVOR-TIMI 53 or EXAMINE trials. This may allow a cardiovascular benefit to be seen, if one really does exist and if it was not observed in either the SAVOR-TIMI 53 trial or the EXAMINE trial due to an insufficiently long period of differential glycemic control between the active treatment and placebo arms. Alternatively, any potential safety signal regarding hospitalization for heart failure may also be confirmed (or refuted) in TECOS.

Additional large-scale trials of DPP-4 inhibitors are also ongoing. The Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus at High Vascular Risk (CARMELINA)[4] trial is randomizing patients with diabetes to placebo or linagliptin, while the Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients With Type 2 Diabetes (CAROLINA)[5] trial is randomizing patients with diabetes to glimepiride or linagliptin. With the use of placebo in one trial and with an active control as the comparator in the other trial, these two trials should provide great insight into whether any cardiovascular effects are due to a comparison with placebo or are independent of glycemic effects.

There are also ongoing cardiovascular outcome trials with glucagon-like peptide-1 (GLP-1) receptor agonists. GLP-1 receptor agonists are much more potent inhibitors of DPP-4 than the oral DPP-4 inhibitors. Therefore, any potential cardiovascular benefit (or harm, with respect to the heart failure signals) may be magnified. A number of large randomized clinical trials are comparing placebo to GLP-1 receptor agonists: ELIXA[6] is testing lixisenatide, EXSCEL[7] is

testing exenatide, LEADER[8] is testing liraglutide, SUSTAIN[9] is testing semaglutide, and REWIND[10] is testing dulaglutide. Thus, all together there are thousands of patients being studied in outcome trials of the incretins. Furthermore, there are cardiovascular outcome trials of sodium-glucose cotransporter 2 (SGLT-2) inhibitors ongoing as well. As these trials complete, our understanding of diabetes medications should increase substantially.

References

1. Scirica BM, et al. *N Engl J Med.* 2013; 369(14):1317-1326.
2. White WB, et al. *N Engl J Med.* 2013;369(14):1327-1335.
3. Sitagliptin Cardiovascular Outcome Study (MK-0431-082) (TECOS). http://clinicaltrials.gov/show/NCT00790205. Accessed November 18, 2013.
4. Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus at High Vascular Risk (CARMELINA). http://clinicaltrials.gov/ct2/show/NCT01897532. Accessed November 18, 2013.
5. Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients With Type 2 Diabetes (CAROLINA). http://clinicaltrials.gov/ct2/show/NCT01243424. Accessed Novermber 18, 2013.
6. Evaluation of Cardiovascular Outcomes in Patients With Type 2 Diabetes After Acute Coronary Syndrome During Treatment With AVE0010 (Lixisenatide) (ELIXA). http://clinicaltrials.gov/ct2/show/NCT01147250?term=ELIXA&rank=1. Accessed November 18, 2013.
7. Exenatide Study of Cardiovascular Event Lowering Trial (EXSCEL). http://clinicaltrials.gov/ct2/show/NCT01144338?term=EXSCEL&rank=1. Accessed November 18, 2013.
8. Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results - A Long Term Evaluation (LEADER). http://clinicaltrials.gov/ct2/show/NCT01179048?term=LEADER&rank=4. Accessed November 18, 2013.
9. Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes (SUSTAIN 6). http://clinicaltrials.gov/ct2/show/NCT01720446? term=SUSTAIN+semaglutide&rank=1. Accessed November 18, 2013.
10. Researching Cardiovascular Events With a Weekly Incretin in Diabetes (REWIND) http://clinicaltrials.gov/ct2/show/NCT01394952?term=REWIND&rank=1. Accessed November 18, 2013.

Full references are available at www.healio.com/endocrinology/education-lab.

Reducing CVD Risk in Patients with T2DM: Utilizing Incretin Therapeutics

Case 1

A 60-year-old man with an 11-year history of type 2 diabetes mellitus (T2DM) and hypertension presents to your office for a second opinion. He is a non-smoker that admits being noncompliant with his diet, but is concerned about his rising A1C and that he is always hungry. BP: 138/98 mm Hg; BMI: 31 kg/m^2. He is currently taking: glipizide 5 mg BID, pioglitazone 30 mg OD, simvastatin 20 mg OD, amlodipine 10 mg OD, olmesartan 20 mg OD, and ASA 325 mg OD.

LDL-C:	146 mg/dL
HDL-C:	40 mg/dL
Triglycerides:	314 mg/dL
Non-HDL-C:	219 mg/dL
Total cholesterol:	249 mg/dL
A1C:	8.2%

DISCUSSION

This 60-year-old obese hypertensive man with T2DM, noncompliant with his diet, with metabolic syndrome is at very high cardiovascular risk, with a low-density lipoprotein cholesterol (LDL-C) goal of <70 mg/dL being a prudent choice given his multiple risk factors. Therapeutic lifestyle changes and dietary counseling are needed along with tighter glycemic control, with the addition of a long-acting GLP-1 receptor agonist to reduce his A1C, decrease his weight, reduce his hunger, and have a beneficial effect on postprandial glucose and lipemia. Lipid therapy needs adjusting since simvastatin at 20 mg is clearly not getting him to goal. The substitution of a more potent statin like rosuvastatin 20 mg or atorvastatin 80 mg would bring him closer to his LDL-C goal. Another option would be switching to atorvastatin 80 mg or 20 mg of rosuvastatin and add ezetimibe or fenofibrate. Data from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, support microvascular benefits with the addition of fenofibrate to statin therapy, in addition to lowering triglycerides. Evaluation for sleep apnea and weight reduction would also be of significant value in evaluating and treating this patient. Weight reduction from 5% to 10% through diet and exercise will have a beneficial impact on this patient's blood pressure, lipids, and A1C.

Case 2

A 54-year-old overweight man with type 2 diabetes mellitus (T2DM) presents to the ER with non-ST segment elevation myocardial infarction (NSTEMI), demonstrating non-specific ST-T wave changes on ECG with CK-MB and troponin T elevations. He smokes 1 pack of cigarettes daily. BP: 136/86 mm Hg; BMI: 29 kg/m^2; WC: 41 inches. He is currently taking: ASA 81 mg OD, ramipril 10 mg OD, metformin 1000 mg BID, sitagliptin 100 mg OD, glimepiride 2 mg daily, and simvastatin 20 mg OD.

LDL-C:	**128 mg/dL**
HDL-C:	**40 mg/dL**
Triglycerides:	**195 mg/dL**
Non-HDL-C:	**167 mg/dL**
Total cholesterol:	**207 mg/dL**
A1C:	**7.9%**
FBG:	**148 mg/dL**

Discussion

Several factors prominently stand out to indicate that this patient is at high risk for cardiovascular events. First, his cigarette smoking increases his risk of a second myocardial infarction since a patient with T2DM is already at very high risk for a major cardiac event. His increased BMI and waist circumference (WC) also increase this risk. Not only is obesity now recognized as a disease, but also represents a major modifiable risk factor for cardiovascular disease, second only to cigarette smoking. Excess weight and obesity markedly increase the risk for hypertension, diabetes, coronary artery disease, and congestive heart failure in both men and women as the BMI increases beyond 25 kg/m^2.[1] The elevated TG/HDL-C ratio of almost 5.0 is not only a marker of insulin resistance and increased risk for MI (which he has already experienced), but also small LDL size, likely accompanied by elevated apoB and increased LDL-P. His LDL-C is not optimally controlled at 128 mg/dL. Although new guidelines have not specified treatment

goals, NCEP-ATP III goals applicable to patients at very high risk, such as this patient, would require an LDL-C <70 mg/dL.

Non-HDL-C has been shown to be a better predictor of risk rather than LDL-C. Optimal non-HDL-C in this patient would be <100 mg/dL (30 mg/dL greater than LDL-C goal). In this patient an additional 45 to 50 mg/dL (35% to 40%) reduction in LDL-C would be required to approach the desired goal. In the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) trial, 80 mg of atorvastatin was effectively utilized in a similar patient population to reduce CV risk. This could provide an additional 20% reduction in LDL-C compared to his present 20 mg dose of simvastatin, while doubling the statin dose would result in only a 6% LDL-C reduction. Rosuvastatin at 20 mg would also provide a similar LDL-C reduction. Despite the use of more potent statins, combination therapy should be considered to achieve LDL-C goals. Subset analysis of patients in Action to Control Cardiovascular Risk in Diabetes (ACCORD) Lipid and Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trials have suggested a benefit in patients with mildly elevated triglycerides and decreased HDL-C.

Colesevelam could provide an additional 18% to 25% reduction in LDL-C when added to a statin, while reducing A1C by up to 0.8%. Better glycemic control could be achieved with the subsitution of a glucagon-like peptide-1 (GLP-1) receptor agonist for the dipeptidyl peptidase-4 (DPP-4) inhibitor, which can also decrease weight and improve blood pressure. Enhanced glycemic control will result in better prandial and postprandial lipid regulation.

Not to be overlooked is the value of therapuetic lifestyle changes in reducing weight, improving glycemic control, and attenuating dyslipidemia with weight reductions of 5% to 10% having a significant impact on improving surrogate markers of cardiovascular risk. These lifestyle changes should begin with smoke cessation guidance and counseling, supplemented by diet as well as judicious use of exercise.

Reference

1. Sharma AM. *Growth Horm IGF Res*. 2003;13(Suppl A): S10-S17.

CME Posttest

CME Instructions

1. Review the activity learning objectives stated on the front cover.
2. Read the articles, including the tables and illustrative materials.
3. Proceed to the CME Registration Form. Type or print your name, address, and date of birth in the spaces provided.
4. Answer each test question by circling the letter corresponding to the correct answer or by entering it in the space provided on the Registration Form. Be sure to retain a copy of your answers for your records.
5. Complete the evaluation portion of the CME Registration Form. CME Registration Forms will be returned to you if the evaluation is not completed.
6. CME Registration Forms will not be accepted after the expiration date. Return the CME Registration Form before the test expires to:

   Vindico Medical Education
   PO Box 36
   Thorofare, NJ 08086-0036
   Or Fax to: 856-384-6680

7. The CME test will also be available online (within 1 month of mailing date) at:

   www.healio.com/endocrinology/education-lab

1. The leading cause of death in patients with T2DM is:

A. Hyperglycemia
B. Renal Failure
C. Electrolyte imbalance
D. Cardiovascular disease

2. A 66-year-old male is being seen in your office for hypertension, dyslipidemia, obesity, and T2DM. His BMI is 29 kg/m^2 and A1C is 8.0% and is always hungry. He currently takes a sulfonylurea, metformin, statin, ACE inhibitor, and a thiazide diuretic. He is concerned about his increasing weight and increasing A1C. Which is the best strategy to reduce his A1C, help him lose weight, and reduce his hunger?

A. Add a GLP-1 receptor agonist
B. Add bedtime NPH insulin
C. Add a long-acting analog insulin
D. Add a thiazolidinedione

3. The lifetime risk for cardiovascular events in patients with T2DM is:

A. >50%
B. <50%
C. <40%
D. >90%

4. The new American Heart Association/American College of Cardiology (AHA/ACC) 2013 Guidelines recommends high-intensity statin therapy for patients with T2DM, who are?

A. >30 years of age
B. >35 years of age
C. >40 years of age
D. Regardless of age

5. GLP-1 receptor agonists appear to have the greatest effects on which of the following?

A. Free fatty acid levels
B. HDL-C levels
C. Fasting lipid levels
D. Postprandial lipemia

6. Which of the following best describes GLP-1 receptor agonist therapy on plasma lipids?

A. Increases free fatty acids
B. Increases LDL-C
C. Increases HDL-C
D. Decreases triglycerides

7. In SAVOR-TIMI 53, saxagliptin

A. significantly reduced the rate of cardiovascular death, MI, or stroke.
B. significantly increased the rate of cardiovascular death, MI, or stroke.
C. significantly improved glycemic control.
D. significantly increased pancreatitis.

8. In EXAMINE, alogliptin

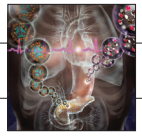
A. significantly reduced the rate of cardiovascular death, MI, or stroke.
B. significantly increased the rate of cardiovascular death, MI, or stroke.
C. significantly increased hypoglycemia.
D. significantly improved glycemic control.

9. In SAVOR-TIMI 53, saxagliptin

A. significantly raised the risk of fractures.
B. significantly increased the risk of cancer.
C. significantly raised the risk of liver failure.
D. significantly raised the risk of hospitalization for heart failure.

10. In SAVOR-TIMI 53, saxagliptin

A. significantly raised the risk of hospitalization for hypoglycaemia.
B. significantly raised the risk of any hypoglycaemia.
C. significantly worsened microalbuminuria categories.
D. significantly increased severe infections.



CME Registration Form

Questions about CME? Call us at 856-994-9400 ext. 504, Fax 856-384-6680

DIALOGUES in DIABETES

Volume 3 • Number 4

POSTTEST

1	2	3	4	5	6	7	8	9	10

***Time spent on this activity: Hours ☐ Minutes ☐**
(reading articles and completing the learning assessment and evaluation)
This information MUST be completed in order for the quiz to be scored.

Release date: December 1, 2013
Expiration date: December 1, 2014

PRINT OR TYPE

Last Name First Name Degree

Mailing Address

City State Zip Code

Date of Birth (used for tracking credits ONLY)

Phone Number FAX Number E-mail

Degree: *Please select one*

❑ MD ❑ PA
❑ PhD ❑ NP
❑ DO ❑ Other_____

Specialty: *Please select one*

❑ Primary Care ❑ Diabetes
❑ Endocrinology ❑ Obesity
❑ Other_____

EVALUATION (must be completed for your CME Quiz to be scored)

Please circle answers neatly and write legibly.

1. The content covered was useful and relevant to my practice. Yes No
2. The activity was presented objectively and was free of commercial bias. Yes No
   [Please use the additional comments field below to provide further information.]
   Additional comments regarding bias: _____
3. Based on the information I learned during this activity, I feel more confident in treating patients within my practice. Yes No
4. Knowledge acquired from this activity will be utilized to improve outcomes in my patients. Yes No
5. Future activities concerning this subject matter are necessary. Yes No
6. I plan to make the following changes to my practice:

Y = Yes N = No 2 = I Already Do This in My Practice 1 = Not Applicable

Examine more closely the differences, efficacy, and safety of treatment options that target glycemic control.	Y N 2 1
Assess the pathophysiology of incretin pathways in type 2 diabetes mellitus.	Y N 2 1
Examine approaches to managing the obese patient with type 2 diabetes.	Y N 2 1
Analyze the potential cardiovascular benefits of incretin therapies in addition to glycemic control.	Y N 2 1

Other - *Please explain:*

7. These are the barriers I face in my current practice setting that may impact patient outcomes:

Lack of evidence-based guidelines	Yes No
Lack of applicable guidelines for my current practice/patients	Yes No
Lack of time	Yes No
Organizational/institutional	Yes No
Insurance/financial	Yes No
Patient adherence/compliance	Yes No
Treatment-related adverse events	Yes No

Other - *Please explain:*

8. This activity supported achievement of each of the learning objectives. Yes No

   Please explain:

9. I see the following number of patients per week with type 2 diabetes mellitus:

   A. <10
   B. 10 to 25
   C. 26 to 50
   D. >50

10. Please list CE/CME topics that would be of value to you.

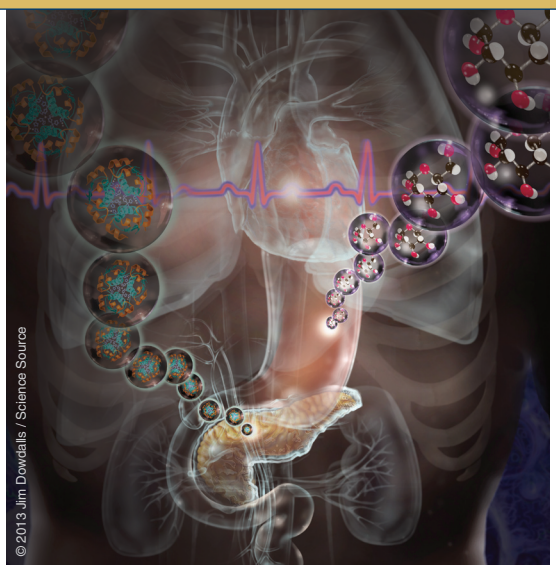
CME ACTIVITY REQUEST

❑ Yes, I would like the opportunity to earn CME credits through activities sponsored by Vindico Medical Education.

***Required Field**

OFFICE USE ONLY
Enduring material: Other
December 2013 ET-J26D

DIALOGUES in DIABETES



VINDICO
medical education

6900 Grove Road, Bldg 100, Thorofare, NJ 08086 USA
phone: 856-994-9400 • fax: 856-384-6680 • VindicoMedEd.com