EDITORIAL

Incretin-Based Therapies: Facing the Realities of Benefits Versus Side Effects

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INCRETIN-BASED THERAPIES for the treatment of type 2 diabetes include (1) inhibitors of the dipeptidyl peptidase-4 (DPP-4) enzyme, which lead to two- to threefold increases in endogenous glucagon-like peptide 1 (GLP-1) secretion, and (2) GLP-1 receptor agonists. The principal advantages of these drugs in treating type 2 diabetes are an increase in meal-mediated insulin secretion and a decrease in meal-mediated glucagon secretion. The unique features are that both effects are glucose-dependent (i.e., they occur in the presence of hyperglycemia and are absent in the presence of normal or low blood glucose). Pharmacologic effects of GLP-1 receptor agonists include increase in satiety, reduced food intake with weight loss, and beneficial effects in cardiovascular diseases. Many surrogate, although few clinical, outcomes have supported the beneficial effects of incretin-based therapies. Nausea and vomiting, worse initially and decreasing with duration of treatment, have been consistent side effects of GLP-1 receptor agonists, whereas the DPP-4 inhibitors cause few and minor side effects.

Shortly after the introduction of exenatide, the first GLP-1 agonist, into widespread clinical use, sporadic cases of acute pancreatitis were sent to the Food and Drug Administration's (FDA's) Adverse Event Reporting System (AERS) database or reported in the literature.^{1,2} This introduced a signal, which subsequently has raised the question whether these therapies are causally related to increased acute pancreatitis.^{3–9} Some authors have recently extended this concern to pancreatic cancer. Disparate and confusing data in experimental animals on the effects of incretin-based therapies on pancreatic exocrine and ductal cells^{10–13} and recent controversial data on human islet pathology in a very small sample of donor pancreases from individuals who had received incretin-based therapies (sitagliptin, $n=7$; exenatide, $n=1$) have fueled this controversy about incretin-based therapies in patients with type 2 diabetes and theoretically increases in acute pancreatitis and pancreatic carcinoma.^{14,15} In a recent feature article in *BMJ*, the Investigations Editor, Deborah Cohen, has gone to great lengths to develop an argument, based on the *BMJ*'s evaluation of unpublished information and published literature, that the pancreatic safety issues of incretin-based therapies have been underplayed.¹⁶

Concerns about the safety of antidiabetes drugs has a long history, starting with the controversy about cardiovascular

safety of sulfonylurea drugs and extending to the removal from the market of phenformin for lactic acidosis on November 15, 1978 and troglitazone for liver toxicity on March 21, 2000, and the marked restriction of the use of rosiglitazone for cardiovascular toxicity on November 18, 2011. Sixty years after the introduction of sulfonylureas, the clinical data on cardiovascular safety are still controversial, and the drugs are still widely prescribed. Phenformin and troglitazone toxicities were established on the bases of clinical data. The rosiglitazone decision, which was based on meta-analyses and statistical analyses of large health insurance databases, has been recently challenged by recent analyses of two large, validated randomized, controlled clinical trials, RECORD^{17,18} and BARI-2D.¹⁹

Two fundamental questions need to be evaluated when assessing whether a drug has significant safety concerns in human beings. The first is the source, quality, and relevance of the data implicating a causative relationship between the agent and the putative toxic side effect. The second and equally important consideration is whether benefits of the agent significantly exceed the putative toxic effects. The concerns that have been raised about incretin-based therapies and acute pancreatitis and pancreatic cancer need to be evaluated from these perspectives.

The quality of data is critical when making conclusions about incretin-based therapies and their safety. Published human data consist of case reports,^{1–4,6–9} the FDA AERS database, meta-analyses of published clinical studies,^{20,21} statistical mining of large health insurance or pharmacy databases,^{22–28} and large, randomized controlled clinical trials that compare the drug with a placebo or a comparator treatment.^{29–34} The case report and the FDA AERS database only raise concern about the potential signal of a side effect. They can never give a definitive answer because they represent two types of reporting bias, as there are only individual cases with no denominator of the entire population at risk and no comparable control population.^{35,36} This results in both ascertainment bias and notoriety bias, the latter from individual cases “piling on.” Meta-analyses provide a statistical attempt to combine data from many different studies to provide an overall assessment. Because the data included are derived from different populations with variable characteristics and

different experimental designs, their results can only provide a hypothesis to be tested and cannot be considered conclusive evidence.³⁷ The mining of data from large healthcare databases suffers from the lack of comparability between the patients taking the drug and the comparator group. Healthcare professionals use drugs based on the characteristics of the individual patients and the known side effects of drugs. The groups being compared are statistically different in many known and unknown parameters. No statistical manipulation can make the groups comparable, and therefore any presumed differences between a drug and its comparator can only generate a hypothesis that needs to be tested in a more scientifically designed study.³⁶ The only studies that can show a true difference between a drug and a placebo or comparator are large randomized, controlled clinical trials that are adequately designed to eliminate patient and healthcare provider bias.

Case reports of the association of incretin-based therapies and acute pancreatitis began appearing in the literature in 2006.¹ From then until now these reports have implicated the incretin-based therapies, exenatide, liraglutide, sitagliptin, and vildagliptin.^{1-4,6-9} Adverse events reported to the FDA's AERS database raised concerns that incretin-based therapies such as exenatide, liraglutide, and sitagliptin might be associated with an increase in acute pancreatitis. In response to this concern the FDA has mandated that the incretin-based therapies should have instructions in their labels that the drugs should not be given to patients with a history of acute pancreatitis and should be discontinued if patients taking the medications should develop symptoms suggestive of acute pancreatitis. The FDA, however, has repeatedly asserted that evidence for any causative role of these agents remains inconclusive. Elashoff et al.⁵ reported in 2011 that they had analyzed the FDA's AERS database and concluded that sitagliptin and exenatide use in diabetes patients was associated with a highly significant increase in both acute pancreatitis (sixfold increase, $P < 2 \times 10^{-16}$) and pancreatic carcinoma ($P < 0.008$, $P < 9 \times 10^{-5}$) compared with other therapies. However, in the editorial accompanying the publication, Spranger et al.,³⁵ from the Drug Commission of the German Medical Association, detailed the serious limitations of trying to derive meaningful conclusions from such a database. These include the following: reporting bias (both ascertainment and notoriety) is likely to exist for a new drug or one that has been suggested to have certain side effects; analysis of spontaneous reports does not allow adjustment for known risk factors; and databases on spontaneous adverse drug reports generally lack detailed information on patient characteristics and cannot quantify the number of patients being exposed to the drug. Their conclusion was, "Incidence rates cannot be calculated and although an association with an adverse event might be detected by spontaneous reports, the nature and extent of the problem cannot be addressed with certainty."³⁵

In order to examine whether incretin-based therapies are associated with acute pancreatitis, analyses of large healthcare databases have been examined by various statistical methods. Dore et al.²² analyzed the i3 Drug Safety, Waltham, MA AperioTM drug surveillance system for patients from June 2005 through June 2008. The study population was 27,996 exenatide initiators, 16,276 sitagliptin initiators, and equal numbers of matched comparators starting metformin or

glyburide. One-year incidence of acute pancreatitis for exenatide and its comparator was 0.13%, and that for sitagliptin and its comparator was 0.12%, with no differences among these four drugs.²² In a recent analysis of the IMS (Danbury, CT) LifeLinkTM database for over 65 million unique patient lives from 98 U.S. health plans, it was found that for 24,237 eligible patients initiating exenatide twice daily from June 1, 2005 to March 31, 2009, the odds ratio for acute pancreatitis was 0.95 (95% confidence interval 0.65–1.38) compared with 457,797 patients initiating other antidiabetes treatments.²⁶ A secondary analysis showed no increased risk of acute pancreatitis with exenatide twice daily regardless of current, recent, or past exposure. Similar results showing no association between exenatide use and either hospitalization for acute pancreatitis or pancreatic cancer were reported in a privately insured population of 268,561 patients in an acute pancreatitis analysis.²⁷

A population-based matched case control study from a large administrative U.S. database (February 1, 2005–December 11, 2008) identified 1,269 type 2 diabetes patients hospitalized for acute pancreatitis and 1,269 control diabetes subjects matched for age, sex, enrollment pattern, and diabetes complications.²⁸ Despite the fact that the cases were more likely than the control population to have hypertriglyceridemia, alcohol use, gallstones, tobacco abuse, obesity, biliary or pancreatic cancer, cystic fibrosis, or any neoplasm, the authors claimed that after adjusting for all the confounders, current use (within 30 days) and recent use (past 30 days to 2 years) of GLP-1-based therapies had an adjusted odds ratio of 2.24 and 2.01, respectively, of hospitalization for acute pancreatitis compared with the control population.²⁸

The use of these large databases with their statistical adjustments for all the differences between the incretin-based treatment cohort and the control population is insufficient to do anything more than suggest a hypothesis to be tested.³⁶ This is particularly true because retrospective cohort and pharmacy claims analyses have shown that type 2 diabetes patients have a 2.83-fold (95% confidence interval 1.26–3.06) greater risk of pancreatitis and a 1.91-fold (95% confidence interval 1.84–1.99) greater risk of biliary disease compared with patients without diabetes.²³ Despite the limitations of the large database analyses, most of them have reported that exenatide and sitagliptin treatments are not associated with either acute pancreatitis or pancreatic cancer^{22,24-27} with one exception.²⁸

The only valid scientific method for determining either efficacy or safety of a treatment is the randomized, controlled, clinical trial comparing the treatment in question with either placebo or a comparator. Preferably the study should be double-blinded. Existing clinical data for the incretin-based therapies are meta-analyses of the available Phase 2, 3, and 4 clinical trials (Table 1) and data from the very large randomized, controlled, blinded adjudicated cardiovascular safety trials that are being conducted for many of the DPP-4 inhibitors and the GLP-1 agonists (Table 1), some of which are also being adjudicated for pancreatitis.

A pooled analysis of 19 randomized, controlled clinical trials comprising 10,246 patients treated with sitagliptin versus a comparator or placebo for up to 2 years revealed incidence rates of pancreatitis of 0.08 events per 100 patient-years for sitagliptin and 0.10 events per 100 patient-years for those not treated with sitagliptin.²⁹ An updated analysis

TABLE 1. INCIDENCE OF ACUTE PANCREATITIS IN PATIENTS WITH TYPE 2 DIABETES TREATED WITH INCRETIN-BASED THERAPIES

	Number of patients	Cases/100 patient-years of exposure	
		No incretins	Incretin treatment
Population without diabetes ^a	337,067	0.149	
Type 2 diabetes population ^a	337,067	0.422	
Healthcare databases			
Wenten et al. ²⁶			
Other antidiabetes agents	457,797	0.133	
Exenatide	24,237		0.132
Garg et al. ²⁴			
Other antidiabetes agents	16,244	0.57	
Exenatide	6,545		0.55
Sitagliptin	15,826		0.55
Randomized, controlled clinical trials			
Sitagliptin (19 clinical trials) ²⁹	10,246	0.10	0.08
Sitagliptin (25 clinical trials) ³¹	14,611	0.08	0.09
Liraglutide clinical trials ³²	>6,500	0.07	0.18
Exenatide (19 clinical trials) ³⁰	5,594	0.18	0.27
Saxagliptin (SAVOR-TIMI 53) ³³	16,500	0.05	0.13
Alogliptin (EXAMINE) ³⁴	5,380	0.21	0.30

^aFrom a 1999–2005 large geographically diverse U.S. healthcare claims database.

involving 14,611 patients from 25 randomized clinical trials followed up for a mean of 274 days presented at the recent National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) conference on pancreatitis, diabetes, and pancreatic cancer showed similar results (sitagliptin and comparator, 0.08 and 0.09 events/100 patient-years of exposure, respectively) and additionally indicated that the rates for pancreatic cancer were 0.05 and 0.06 cases per 100 patient-years of exposure for sitagliptin and comparator treatments, respectively.³¹

The recent data from liraglutide clinical trials presented at the NIDDK conference showed a rate of pancreatitis in more than 6,500 patients followed up for more than 5,000 patient-years of 1.8/1,000 patient-years of exposure compared with a reported rate in diabetes patients not on incretin-based therapies of 0.7/1,000 patient-years of exposure.³² Data from 19 controlled clinical trials involving 3,261 exenatide-treated patients and 2,333 comparator-treated patients showed incidence rates of pancreatitis of 0.27 and 0.18 cases/100 patient-years of exposure, respectively.³⁰

Nine large cardiovascular safety trials of incretin-based therapies (four with DPP-4 inhibitors and five with GLP-1 agonists) involving close to 80,000 patients who are being treated for 2–5 years are being conducted, many of which are monitoring adjudicated cases of pancreatitis and pancreatic cancer. Two of these trials are completed, and the results have been published. The SAVOR-TIMI 53 trial randomized 16,492 patients with type 2 diabetes to saxagliptin or placebo for a median follow-up of 2.1 years³³; definite or possible acute pancreatitis occurred in 22 (0.3%) of the saxagliptin-treated patients and 16 (0.2%) of the placebo-treated patients ($P=0.42$). The EXAMINE study recruited 5,380 patients with type 2 diabetes and acute coronary syndrome and randomized them to alogliptin or placebo³⁴; during a median follow-up of 18 months, 12 patients (0.3%) on alogliptin developed acute pancreatitis compared with eight (0.2%) on placebo ($P=0.50$). In both trials there were nearly identical numbers of

cases of chronic pancreatitis and total malignancies in the DPP-4 inhibitor and placebo groups. These data suggest that DPP-4 inhibitors are unlikely to cause significant increases in acute pancreatitis. Obviously a composite analysis of pancreatitis in the nine studies, when completed, should give a definitive answer.

What conclusions can we draw from the available data? The preclinical studies are of limited value because of conflicting data and known differences in rodent and human pancreatic biology. The difficulty in interpreting the data from the histologic studies of the human donor pancreases from the incretin-treated versus non-incretin-treated diabetes patients has been addressed in the editorial by Kahn¹⁵ that accompanied the report and in a detailed critique by Harja et al.³⁷ It is interesting that several commentaries on incretin-based therapies and pancreatic safety have given much more credibility to the database analysis of Singh et al.,²⁸ which argues for the hypothesis that incretin-based therapies increase acute pancreatitis while discounting all of the other database analyses that found no effect on incretin-based therapies.^{22–26} This appears to be based more on the source of funding rather than proof of superior scientific quality.^{38–40} In the final analysis the question of the pancreatic safety of incretin-based therapies can only be answered by adequately powered clinical trial data, not by debates in the literature. Table 1 summarizes the currently available clinical data and indicates that there is as yet no substantial evidence to implicate incretin-based therapies as causing an increase in acute pancreatitis. The concern about incretin-based therapies and an increase in pancreatic cancer has primarily been a speculation and is not supported by any available clinical data.⁴¹

The benefits of incretin-based therapies on clinical outcomes in type 2 diabetes have been questioned by some.^{39,40} DPP-4 inhibitors, like other therapies for type 2 diabetes, have not been shown to reduce cardiovascular events, although several additional trials are yet to be completed. GLP-1 agonists have been shown to have beneficial effects in established

cardiovascular disease⁴²; however, their ability to reduce new cardiovascular events is currently still being evaluated in five large clinical trials. There is, however, no doubt that incretin-based therapy improves glycemic control without increasing weight and with little or no hypoglycemia.⁴³ Based on our current knowledge, one can anticipate with reasonable expectations that the use of these agents will help to reduce microvascular and neuropathic disease in millions of patients with type 2 diabetes. The magnitude of this presumed effect will require completion of long-term studies.

It is the responsibility of the regulatory agencies to require the appropriate studies and to objectively evaluate the data to determine the pancreatic safety of incretin-based therapies. Up to the present time, both the Endocrinologic and Metabolic Drugs Advisory Committee and the FDA's Division of Metabolism and Endocrinology Products have not felt that sufficient evidence is available to conclude that incretin-based therapies cause acute pancreatitis or pancreatic cancer. A similar conclusion appeared to be reached by the recent NIDDK workshop on pancreatitis, diabetes, and pancreatic cancer. The regulatory agencies continue with their ongoing evaluations and vigilance. The value of the ongoing debates in the literature and in the press is questionable. Management of type 2 diabetes is markedly impacted by patient compliance and physician commitment. These are both undermined by continuing media emphasis on presumed but not proven side effects or on overemphasis of side effects rather than benefit/side effect ratios of effective antidiabetes drugs. The magnitude of the problem of decreasing the increased mortality and morbidity of the world's 350 million diabetes patients is not benefited by continually undermining their confidence in our dedication to their safe and effective treatments.

Author Disclosure Statement

H.E.L. is currently on the Scientific Advisory Boards of Biocon Ltd., Intarcia Pharma, Metacure, and Poxel Pharmaceuticals. He serves occasionally as a consultant for AstraZeneca, Bristol Myers Squibb, and Janssen Pharmaceuticals. He owns shares of Abbott, Abbvie, and Merck.

References

- Denker PS, Dimarco PE: Exenatide (exendin-4)-induced pancreatitis. A case report. *Diabetes Care* 2006;29:471.
- Ayoub WA, Kumar AA, Naguib HS, Taylor HC: Exenatide-induced acute pancreatitis. *Endocr Pract* 2010;16:80–83.
- Girgis CM, Champion BL: Vildagliptin-induced acute pancreatitis. *Endocr Pract* 2011;17:e48–e50.
- Lee PH, Stockton MD, Franks AS: Acute pancreatitis associated with liraglutide. *Ann Pharmacother* 2011;45:e22.
- Elashoff M, Matveyenko AV, Gier B, Elashoff R, Butler PC: Pancreatitis, pancreatic and thyroid cancer with glucagon-like peptide-1-based therapies. *Gastroenterology* 2011;141:150–156.
- Iyer SN, Drake AJ, West RI, Mendez CE, Tanenberg RJ: Case report of acute necrotizing pancreatitis associated with combination treatment of sitagliptin and exenatide. *Endocr Pract* 2012;18:10–13.
- Franks AS, Lee PH, George CM: Pancreatitis: a potential complication of liraglutide? *Ann Pharmacother* 2012;46:1547–1553.
- Famularo G, Gasbarrone L, Minisola G: Pancreatitis during treatment with liraglutide. *JOP* 2012;13:540–541.
- Sue M, Yoshihara A, Kuboki K, Hiroi N, Yoshino G: A case of severe acute necrotizing pancreatitis after administration of sitagliptin. *Clin Med Insights Case Rep* 2013;6:23.
- Koehler JA, Baggio LL, Lamont BJ, Ali SD, Drucker DJ: Glucagon-like peptide-1 receptor activation modulates pancreatitis-associated gene expression but does not modify the susceptibility to experimental pancreatitis in mice. *Diabetes* 2009;58:2148–2161.
- Nachnani JS, Bulchandani DG, Nookala A, Herndon B, Molteni A, Pandya P, Taylor R, Quinn T, Weide L, Alba LM: Biochemical and histological effects of exendin-4 (exenatide) on the rat pancreas. *Diabetologia* 2010;53:153–159.
- Tatarkiewicz K, Smith PA, Sablan EJ, Polizzi CJ, Aumann DE, Villescaz C, Hargrove DM, Gedulin BR, Lu MGW, Adams L, Whisenant T, Roy D, Parkes DG: Exenatide does not evoke pancreatitis and attenuates chemically induced pancreatitis in normal and diabetic rodents. *Am J Physiol Endocrinol Metab* 2010;299:E1076–E1086.
- Nyborg NC, Moick AM, Madsen LW, Knudsen LB: The human GLP-1 analog liraglutide and the pancreas: evidence for the absence of structural pancreatic changes in three species. *Diabetes* 2012;61:1243–1249.
- Butler AE, Campbell-Thompson M, Gurlo T, Dawson DW, Atkinson M, Butler PC: Marked expansion of exocrine and endocrine pancreas with incretin therapy in humans with increased exocrine pancreas dysplasia and the potential for glucagon-producing neuroendocrine tumors. *Diabetes* 2013;62:2595–2604.
- Kahn SE: Incretin therapy and islet pathology—a time for caution. *Diabetes* 2013;62:2178–2180.
- Cohen D: Has pancreatic damage from glucagon suppressing drugs been underplayed? *BMJ* 2013;346:f3680.
- Lopes RD, Dickerson S, Hafley G, Burns S, Tourt-Uhlig S, White J, Newby LK, Komajda M, McMurray J, Bigelow R, Home PD, Mahaffey KW: Methodology of a reevaluation of cardiovascular outcomes in the RECORD trial: study design and conduct. *Am Heart J* 2013;166:208–216.
- Mahaffey KW, Hafley G, Dickerson S, Burns S, Tourt-Uhlig S, White J, Newby LK, Komajda M, McMurray J, Bigelow R, Home PD, Lopes RD: Results of a reevaluation of cardiovascular outcomes in the RECORD trial. *Am Heart J* 2013;166:240–249.
- Bach RG, Brooks MM, Lombardero M, Genuth S, Donner TW, Garber A, Kennedy L, Morad S, Pop-Busui R, Kelsey SF, Frye RL: Rosiglitazone and outcomes for patients with diabetes and coronary artery disease in the Bypass Angioplasty Revascularization Investigation 2 diabetes trial. *Circulation* 2013;128:785–794.
- Labuzek K, Kozlowski M, Szkudlowski D, Sikorska P, Kozlowska M, Okopien B: Incretin-based therapies in the treatment of type 2 diabetes—more than meets the eye. *Eur J Intern Med* 2013;24:207–212.
- Scheen A: Gliptins (dipeptidyl peptidase-4 inhibitors) and risk of acute pancreatitis. *Expert Opin Drug Saf* 2013;12:545–557.
- Dore DD, Seeger JD, Chan KA: Use of a claims-based active drug safety surveillance system to assess the risk of acute pancreatitis with exenatide or sitagliptin compared to metformin or glyburide. *Curr Res Med Opin* 2009;25:1019–1027.
- Noel RA, Braun DK, Patterson RE, Bloomgren GI: Increased risk of acute pancreatitis and biliary disease observed in

- patients with type 2 diabetes. A retrospective cohort study. *Diabetes Care* 32:834–838.
24. Garg R, Chen W, Pendergrass M: Acute pancreatitis in type 2 diabetes treated with exenatide or sitagliptin. A retrospective observational pharmacy claims analysis. *Diabetes Care* 2010;33:2349–2354.
 25. Dore DD, Bloomgren GL, Wenten M, Hoffman C, Clifford CR, Quinn SG, Braun DK, Noel RA, Seeger JD: A cohort study of acute pancreatitis in relation to exenatide use. *Diabetes Obes Metab* 2011;13:559–566.
 26. Wenten M, Gaebler JA, Hussein M, Pelletier EM, Smith DB, Girase P, Noel RA, Braun DK, Bloomgren GL: Relative risk of acute pancreatitis in initiators of exenatide twice daily compared with other anti-diabetic medication: a follow-up study. *Diabet Med* 2012;29:1412–1418.
 27. Romley JA, Goldman DP, Solomon M, McFadden D, Peters AL: Exenatide therapy and the risk of pancreatitis and pancreatic cancer in a privately insured population. *Diabetes Technol Ther* 2012;14:904–911.
 28. Singh SS, Chang H-Y, Richards TM, Weiner JP, Clark JM, Segal JB: Glucagonlike peptide-1-based therapies and risk of hospitalization for acute pancreatitis in type 2 diabetes mellitus. *JAMA Intern Med* 2013;173:534–539.
 29. Engel SS, Williams-Herman DE, Golm GT, Clay RJ, Machotka SV, Kaufman KD, Goldstein BJ: Sitagliptin: review of preclinical and clinical data regarding incidence of pancreatitis. *Int J Clin Pract* 2010;64:984–990.
 30. MacConell L, Brown C, Gurney K, Han J: Safety and tolerability of exenatide twice daily in patients with type 2 diabetes: integrated analysis of 5594 patients from 19 placebo-controlled and comparator-controlled clinical trials. *Diabetes Metab Syndr Obes* 2012;5:29–41.
 31. Engel SS: Incidence of pancreatitis and PDCA in clinical studies of sitagliptin. Presented at the NIDDK Pancreatitis–Diabetes–Pancreatic Cancer Workshop, June 12–13, 2013; NIH Campus, Bethesda, MD, p 84.
 32. Moses AC, Rasmussen M, Knudsen LB: No evidence of a risk of pancreatitis or PDAC with liraglutide therapy. Presented at the NIDDK Pancreatitis–Diabetes–Pancreatic Cancer Workshop, June 12–13, 2013; NIH Campus, Bethesda, MD, p 83.
 33. Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, Ohman P, Frederick R, Wiviott SD, Hoffman EB, Cavender MA, Udell JA, Desai NR, Mozenon O, McGuire DK, Ray KK, Leiter LA, Raz I; the SAVOR-TIMI 53 Steering Committee and Investigators: Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med* 2013 Sep 2 [Epub ahead of print]. doi: 10.1056/NEJMoa1307684.
 34. White WB, Cannon CP, Heller SR, Nissen SE, Bergenstal RM, Bakris GL, Perez AT, Fleck PR, Mehta CR, Kupfer S, Wilson C, Cushman WC, Zannad F; the EXAMINE Investigators: Alogliptin after acute coronary syndrome in patients with type 2 diabetes mellitus. *N Engl J Med* 2013 Sep 2 [Epub ahead of print]. doi: 10.1056/NEJMoa1305889.
 35. Spranger J, Gündert-Remy U, Stammerschulte T: GLP-1 based therapies: the dilemma of uncertainty. *Gastroenterology* 2011;141:150–156.
 36. Iyasu S: FDA's approach to addressing a pancreatic safety signal with incretin mimetics: pharmacovigilance and pharmacoepidemiology. Presented at the NIDDK Pancreatitis–Diabetes–Pancreatic Cancer Workshop, June 12–13, 2013; NIH Campus, Bethesda, MD, pp 90–91.
 37. Harja E, Lord J, Skyler JS: An analysis of characteristics of subjects examined for incretin effects on pancreatic pathology. *Diabetes Technol Ther* 2013;15:609–618.
 38. Gier B, Butler PC: Glucagonlike peptide-1 based drugs and pancreatitis. Clarity at last, but what about pancreatic cancer. *JAMA Intern Med* 2013;173:539–541.
 39. Cohen D: Two drugs for type 2 diabetes seem to raise risk of acute pancreatitis, study shows. *BMJ* 2013;346:f1304.
 40. Gale EAM: GLP-1 based agents and acute pancreatitis. Drug safety falls victim to the three monkey paradigm. *BMJ* 2013;346:f1263.
 41. Butler PC, Elashoff M, Elashoff R, Gale EA: A critical analysis of the clinical use of incretin-based therapies: are the GLP-1 therapies safe? *Diabetes Care* 2013;36: 2118–2125.
 42. Woo JS, Kim W, Ha SJ, Kim JB, Kim SJ, Kim WS, Seon HJ, Kim KS: Cardioprotective effects of exenatide in patients with ST-segment-elevation myocardial infarction undergoing primary percutaneous coronary intervention: results of exenatide myocardial protection in revascularization study. *Arterioscler Thromb Vasc Biol* 2013;33:2252–2260.
 43. Nauck M: A critical analysis of the clinical use of incretin-based therapies. The benefits far outweigh the potential risks. *Diabetes Care* 2013;36:2126–2132.

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