Is Incretin-Based Therapy Ready for the Care of Hospitalized Patients With Type 2 Diabetes?

The time has come for GLP-1 receptor agonists!

Significant data suggest that overt hyperglycemia, either observed with or without a prior diagnosis of diabetes, contributes to an increase in mortality and morbidity in hospitalized patients. In this regard, goal-directed insulin therapy has remained as the standard of care for achieving and maintaining glycemic control in hospitalized patients with critical and noncritical illness. As such, protocols to assist in the management of hyperglycemia in the inpatient setting have become commonplace in hospital settings. Clearly, insulin is a known entity, has been in clinical use for almost a century, and is effective. However, there are limitations to its use. Based on the observed mechanisms of action and efficacy, there has been a great interest in using incretin-based therapy with glucagon-like peptide-1 (GLP-1) receptor agonists instead of, or complementary to, an insulin-based approach to improve glycemic control in hospitalized, severely ill diabetic patients. To provide an understanding of both sides of the argument, we provide a discussion of this topic as part of this two-part point-counterpoint narrative. In this point narrative as presented below, Drs. Schwartz and DeFronzo provide an opinion that now is the time to consider GLP-1 receptor agonists as a logical consideration for inpatient glycemic control. It is important to note the recommendations they propose under "incretin-based approach" with these agents represent their opinion for use and, as they point out, well-designed prospective studies comparing these agents with insulin will be required to establish their efficacy and safety. In the counterpoint narrative following Drs. Schwartz and DeFronzo's contribution, Drs. Umpierrez and Korytkowski provide a defense of insulin in the inpatient setting as the unquestioned gold standard for glycemic management in hospitalized settings.

—William T. Cefalu
Editor in Chief, *Diabetes Care*

Controversy exists concerning the role of intensified glycemic control in critically ill, hospitalized diabetic patients (1,2). Results with insulin therapy largely have been disappointing. In the current point-counterpoint debate, we advocate and provide evidence to support the use of glucagon-like peptide-1 (GLP-1) analogs because of their ability to control stress-induced hyperglycemia with minimal side effects, especially hypoglycemia.

Poor glycemic control predicts increased mortality in hospitalized patients —In noncritically ill medical/surgical patients and in patients in intensive care units, hyperglycemia is frequent, occurring in >30–50% of individuals (3,4). Hyperglycemia is an independent risk marker of in-hospital mortality in patients with undiagnosed diabetes and in individuals without diabetes (4,5), and even mild glucose elevations (fasting plasma glucose >110 mg/dL) are associated with increased (threefold) mortality in patients undergoing percutaneous coronary intervention (5). Because hyperglycemia is a predictor of adverse outcome, it logically follows that hospitalized patients would benefit from improved glycemic control.

Insulin therapy fails to reduce mortality—In hyperglycemic patients hospitalized for acute myocardial infarction (MI) (6,7) and in the surgical intensive care unit (ICU) (8) and burned pediatric ICU (9) patients, improved glycemic control with insulin has been shown to be associated with reduced mortality in some studies. However, most studies in ICU patients have failed to demonstrate any benefit on mortality with intensive insulin therapy (10–12), and two large randomized trials (13,14) with insulin in ICU patients were stopped prematurely because of increased hypoglycemia and lack of benefit. Hypoglycemia is a serious complication of insulin therapy and has been shown to be associated with negative outcomes (15). Hypoglycemia exerts many deleterious effects on the cardiovascular system including *1*) prolonged QT interval, which lasts for an extended period and 2) stimulation of catecholamine release, which can precipitate angina, cause electrocardiogram abnormalities, and ischemic electrocardiogram changes, induce arrhythmias, and cause sudden death.

Incretin therapy has multiple benefits over insulin in the management of critically ill, hospitalized patients—GLP-1 receptor analogs exert a number of metabolic effects that make them attractive agents for the treatment of hyperglycemia in critically ill, hospitalized patients including *1*) glucose-dependent stimulation of insulin secretion (16), thereby preventing hypoglycemia (15); 2) inhibition of glucagon secretion; 3) suppression of hepatic glucose production secondary to enhanced insulin secretion and inhibition of glucagon secretion; *4*) enhanced tissue sensitivity to insulin (17,18); 5) beneficial effects on cardiovascular risk factors (reduced systolic/diastolic blood pressure, triglycerides, LDL cholesterol, high-sensitivity C-reactive protein, B-type natriuretic peptide, inflammatory cytokines, and oxidative stress); and 6) improved cardiovascular and endothelial function (19) (Table 1). Further, in preclinical studies GLP-1 has been shown to reduce infarct size (reviewed in reference 20).

In contrast, in critically ill, hospitalized patients insulin therapy is associated with an unacceptably high incidence of hypoglycemia (11,14,15), aggravates the underlying insulin resistance (21), may adversely affect cardiovascular risk factors and endothelial function (22,23), does not reduce cardiovascular events (23–25), and most importantly does not improve mortality (11–14). In contrast, meta-analysis of patients in the exenatide database showed a hazard ratio for cardiovascular events of 0.69 (95% CI 0.46–1.04) (26).

Table 1—*Benefits/risks of GLP-1 receptor agonist and insulin therapy*

	GLP-1 receptor agonists	Insulin
Glycemic control	Very good	Very good
Hypoglycemia	Minimal	Significant
Improved mortality and cardiovascular outcomes	To be determined	Controversial, many negative studies
Specifically counteracts stress-induced hyperglycemia	Yes	No
Gastrointestinal side effects	Small	None
Therapeutic approach	Simple, little dose titration can obviate need for insulin	Complicated, requires significant dose titration

Cardiovascular benefits of incretin hormones—Recent reviews (20) have examined the cardiovascular benefits of incretin therapy including enhanced cardiac myocyte viability after ischemic injury, increased systolic function in preclinical models and humans, coronary arterial vasodilatation, improved endothelial function, increased sodium excretion, and protection of neural cells against hyperglycemic injury. Both exenatide and liraglutide exert these effects.

A 72-h GLP-1 infusion in acute MI patients with and without diabetes significantly improved left ventricular ejection fraction (27). Improved left ventricular function also has been observed in congestive heart failure patients who received a 5-week GLP-1 infusion following acute MI (28). GLP-1 infusion has been shown to improve myocardial functional recovery in the peri-infarct zone following an MI (28) and in patients undergoing coronary artery bypass graft surgery (27,29). GLP-1 therapy reduced the need for vasopressors, decreased the incidence of arrhythmias, and improved glycemic control in the pre- and perioperative periods (95 vs. 140 mg/dL, $P < 0.02$) despite 45% less insulin compared with the control group (29). Similar results after cardiac surgery have been reported by others (30).

β-Cell function, incretins, and stress diabetes—In response to stress, the body releases counter-regulatory hormones (cortisol, glucagon, catecholamines, growth hormone) that cause insulin resistance in muscle and stimulate hepatic glucose production (31). Catecholamines also impair insulin secretion via α−adrenergic receptor activation, while glucocorticoids exert a potent inhibitory effect on insulin secretion and augment glucagon secretion (32,33). Glucocorticoids also induce β-cell apoptosis, an effect that requires expression of Pdx-1 and can be prevented by GLP-1 (34). Importantly, these stress-induced hormones act synergistically to raise the blood glucose concentration (31,35).

Hyperglucagonemia commonly is observed in the postsurgical setting and in critically ill patients (36) and causes glucose intolerance by stimulating hepatic glucose production (37). Further, physiologic hyperglucagonemia for as little as 3 days causes severe insulin resistance in peripheral (muscle) tissues (37). GLP-1 is a potent inhibitor of glucagon secretion and reduces elevated plasma glucagon levels (17) that occur in postsurgical patients. GLP-1 analogs also counteract the negative effect of steroids on insulin secretion and prevent the development of hyperglycemia (32).

After major surgery in type 2 diabetic patients, intravenous GLP-1 has been shown to normalize blood glucose levels in association with increased insulin and reduced plasma glucagon concentrations without causing hypoglycemia (38). When administered post–coronary artery bypass surgery, GLP-1 was as effective as insulin in normalizing blood glucose without causing hypoglycemia (30) and reduced glucose levels from 162 to 124 mg/dL following angioplasty in patients with acute MI (28). In type 2 diabetic patients undergoing coronary artery bypass surgery (30), GLP-1 infusion decreased the amount of insulin required to achieve glycemic control. Importantly, gastrointestinal side effects, nausea, and vomiting have not been a problem in the studies described above. In the studies by Müssig et al. (30) and Sokos et al. (29), no nausea was observed in any patient.

GLP-1 receptor agonists in the intensive care setting—The use of GLP-1 analogs in treating critically ill patients in medical/surgical ICUs is of great interest because they can restore normoglycemia without causing hypoglycemia and have potential cardiovascular benefit (20). In a preliminary study, Marso et al. (39) reported excellent results with intravenous exenatide (bolus = 0.05 μg/min for 30 min followed by 0.025 μg/min) in 40 adults admitted to the cardiac ICU. It took 3.9 h to reduce and maintain plasma glucose from 199 to 140 mg/dL for the subsequent 48 h. Blood glucose levels <70 mg/dL were uncommon. We (S.S.) have administered placebo ($n = 10$), low-dose exenatide (0.27 ng/kg · min), and high-dose exenatide (0.41 0.27 ng/kg · min) intravenously during cardiac ($n = 12$) and noncardiac ($n = 18$) surgical procedures in diabetic and nondiabetic patients with normalization of blood glucose levels and decreased glycemic excursions (40). At 150 min after the start of surgery, the median blood glucose was 187, 144, and 141 mg/dL in subjects treated with placebo, low-dose exenatide, and high-dose exenatide, respectively. There were no episodes of hypoglycemia or adverse effects in any group. Twice-daily subcutaneous administration of exenatide has been studied in severely burned patients, and a significant reduction in insulin requirement with earlier withdrawal of insulin therapy has been observed (41).

Many critically ill patients require insulin, often in large doses, to restore normoglycemia. GLP-1 analogs safely can be combined with insulin. Since diabetic—as well as nondiabetic—critically ill patients often require insulin, the use of incretins and insulin may need to be combined. Garber et al. (42) have estimated that 85% of in-hospital patient hypoglycemia is because of bolus insulin therapy and 15% because of basal insulin therapy. It is the authors' experience that by combining a GLP-1 analog with basal insulin, the need for bolus insulin therapy can be largely obviated, thereby markedly reducing the incidence of hypoglycemia.

In-hospital treatment of type 2 diabetes

Screening for diabetes and hyperglycemia

Hyperglycemia is an independent risk factor for all-cause mortality in critically ill, hospitalized medical and surgical

patients (5,6). Insulin currently represents the standard of care for seriously ill patients in the perioperative period, in ICUs, and on general medical/surgical wards (1). From a theoretical standpoint, one would expect tight glycemic control to improve outcomes in these critically ill patients. However, the American College of Physicians has recommended avoiding *intensive* insulin therapy in critically ill patients (2) because recent studies have failed to show benefit on morbidity or mortality (11–14) and have demonstrated an increased incidence of side effects, especially hypoglycemia (15). It is possible that the underlying disease process is so severe that it obscured the benefit of intensified glycemic control with insulin in these severely ill patients. Alternatively, side effects associated with intensified insulin therapy could have offset any potential benefit on morbidity/mortality. The risks associated with insulin-induced hypoglycemia are well documented and include sympathetic nervous system activation, increased stroke volume and myocardial oxygen consumption, arrhythmias, hypokalemia, and hypophosphatemia. Approaches to reduce the frequency and severity of these side effects have been developed (43). Nonetheless, the incidence of side effects with insulin therapy, especially hypoglycemia, remains high and presents a barrier to achieving tight glycemic control in critically ill, hospitalized patients (42).

Incretin-based approach—As an alternative approach, we recommend that critically ill patients receive incretin-based therapy (liraglutide, 0.6–1.2 mg/day s.c. or exenatide, 5–10 μg bid s.c.) to achieve blood glucose levels in the 90–130 mg/dL range, while avoiding hypoglycemia.

The following approach is both simple and practical. In hyperglycemic patients without prior diabetes history, i.e., stress-induced diabetes, start with or have an incretin onboard pre-, peri-, and postoperatively or in the ICU and continue incretin therapy throughout hospitalization. A number of insulin infusion protocols have been developed for the treatment of hospitalized patients with hyperglycemia (43). If necessary, incretin therapy can be supplemented with insulin using any of these published protocols (43). Incretin therapy has the potential to avoid completely the need for insulin, decrease the amount of basal insulin, avoid insulin boluses, prevent hypoglycemia, and reduce glycemic variability. In patients previously on insulin, the GLP-1 analog will allow the insulin dose to be reduced or discontinued completely, avoid the need for bolus insulin dosing, and decrease glycemic variability.

In prediabetic and well-controlled type 2 diabetic patients treated with oral antidiabetic agents and who undergo cardiac catheterization or elective surgical procedures, the oral antidiabetic agents (metformin, sulfonylurea, pioglitazone) should be held on the day of surgery/cardiac catherization. Ideally, incretin therapy should be started prior to admission and given in the morning of the day of surgery. Postoperatively, most of these patients can be managed with incretin therapy alone. If hyperglycemia is excessive (>150–160 mg/dL), a small amount of insulin, using established protocols, can be added.

Insulin-treated type 2 diabetic patients should be instructed to take their usual dose of basal insulin (glargine, levemir) on the day/night prior to surgery and incretin therapy administered preoperatively and postoperatively as described above.

In poorly controlled diabetic patients on admission or in newly discovered diabetic patients in whom surgery cannot be delayed, intravenous GLP-1 (as per Marso et al. [39]) or subcutaneous GLP-1 receptor agonist therapy should be started and the dose adjusted to achieve the desired level of glycemic control (<120–140 mg/dL). Postoperatively, GLP-1 receptor agonist therapy should be continued and, if necessary, insulin therapy added.

In the medical/surgical ICU, excessive hyperglycemia—whether in previously diagnosed or new-onset diabetic patients or secondary to stress-induced hyperglycemia—can be controlled with an intravenous GLP-1 infusion or GLP-1 analog given subcutaneously without causing hypoglycemia. Stress-induced hyperglycemia responds well to GLP-1 receptor agonist therapy. The need for supplemental insulin can be discerned quickly after starting GLP-1 therapy.

Although gastrointestinal side effects are a potential concern with GLP-1 agonist therapy, the dropout rate in the studies mentioned above has been low (29,30,39). In nondiabetic subjects treated with exenatide, the incidence of nausea can be reduced with ondansetron or metoclopramide (44).

Conclusions—A pathophysiological rationale for intensive glycemic control in critically ill, hospitalized patients exists. However, the benefit of aggressive glycemic control with insulin on morbidity/mortality has been difficult to demonstrate and may be offset by side effects, especially hypoglycemia. We believe that optimizing glycemic control while minimizing hypoglycemia still remains the goal of therapy. In this point-counterpoint debate, we suggest an alternate pharmacologic approach with GLP-1 receptor agonists, for which clinical data continue to accumulate and support their use for the treatment of hyperglycemia in critically ill, hospitalized patients by virtue of their: *1*) glucose-dependent release of insulin and glucagon suppression, thereby minimizing hypoglycemia; *2*) ability to reverse stress-induced (glucagon and glucocorticoid) hyperglycemia; *3*) potential to reduce cardiovascular-related morbidity (Table 1). Although considerable evidence supports the use of GLP-1 receptor analogs in critically ill hospitalized patients with hyperglycemia, well-designed prospective studies comparing these agents with insulin will be required to establish their efficacy and safety.

STANLEY SCHWARTZ, MD, FACP, FACE[1]
RALPH A. DEFRONZO, MD[2]

From the [1]Main Line Health System, University of Pennsylvania, Philadelphia, Pennsylvania; and the [2]Diabetes Division, The University of Texas Health Science Center at San Antonio, San Antonio, Texas.

Corresponding author: Ralph A. DeFronzo, albarado@uthscsa.edu.

DOI: 10.2337/dc12-2060

Acknowledgments—S.S. has served on the advisory boards for Lilly, Amylin, Santarus, Janssen, Merck, and Sanofi and on the speakers' bureaus for Lilly, Amylin, Santarus, Merck, Sanofi, Novo Nordisk, Boehringer Ingelheim, Bristol-Myers Squibb, and AstraZeneca. R.A.D. has served on the advisory boards for Takeda, Amylin, Bristol-Myers Squibb, Boehringer Ingelheim, Novo Nordisk, Janssen, and Lexicon and on the speakers' bureaus for Novo Nordisk. He has received grants from Takeda and Bristol-Myers Squibb. No other

potential conflicts of interest relevant to this article were reported.

The authors are indebted to Amy Richardson and Lorrie Albarado (Diabetes Division, The University of Texas Health Science Center, San Antonio, Texas) for secretarial assistance in preparation of the manuscript.

References

1. ACE/ADA Task Force on Inpatient Diabetes. American College of Endocrinology and American Diabetes Association consensus statement on inpatient diabetes and glycemic control. Diabetes Care 2006;29:1955–1962
2. Qaseem A, Humphrey LL, Chou R, Snow V, Shekelle P; Clinical Guidelines Committee of the American College of Physicians. Use of intensive insulin therapy for the management of glycemic control in hospitalized patients: a clinical practice guideline from the American College of Physicians. Ann Intern Med 2011;154:260–267
3. Levetan CS, Passaro M, Jablonski K, Kass M, Ratner RE. Unrecognized diabetes among hospitalized patients. Diabetes Care 1998;21:246–249
4. Falciglia M, Freyberg RW, Almenoff PL, D'Alessio DA, Render ML. Hyperglycemia-related mortality in critically ill patients varies with admission diagnosis. Crit Care Med 2009;37:3001–3009
5. Muhlestein JB, Anderson JL, Horne BD, et al.; Intermountain Heart Collaborative Study Group. Effect of fasting glucose levels on mortality rate in patients with and without diabetes mellitus and coronary artery disease undergoing percutaneous coronary intervention. Am Heart J 2003;146:351–358
6. Kosiborod M, Inzucchi SE, Krumholz HM, et al. Glucose normalization and outcomes in patients with acute myocardial infarction. Arch Intern Med 2009;169:438–446
7. Malmberg K, Rydén L, Efendic S, et al. Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI study): effects on mortality at 1 year. J Am Coll Cardiol 1995;26:57–65
8. van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. N Engl J Med 2001;345:1359–1367
9. Vlasselaers D, Milants I, Desmet L, et al. Intensive insulin therapy for patients in pediatric intensive care: a prospective, randomised controlled study. Lancet 2009;373:547–556
10. Malmberg K, Rydén L, Wedel H, et al.; DIGAMI 2 Investigators. Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on mortality and morbidity. Eur Heart J 2005;26:650–661
11. van den Berghe G, Wilmer A, Hermans G, et al. Intensive insulin therapy in the medical ICU. N Engl J Med 2006;354:449–461
12. Finfer S, Chittock DR, Su SY, et al.; NICE-SUGAR Study Investigators. Intensive versus conventional glucose control in critically ill patients. N Engl J Med 2009;360:1283–1297
13. Brunkhorst FM, Engel C, Bloos F, et al.; German Competence Network Sepsis (SepNet). Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med 2008;358:125–139
14. Preiser JC, Devos P, Ruiz-Santana S, et al. A prospective randomised multi-centre controlled trial on tight glucose control by intensive insulin therapy in adult intensive care units: the Glucontrol study. Intensive Care Med 2009;35:1738–1748
15. Turchin A, Matheny ME, Shubina M, Scanlon JV, Greenwood B, Pendergrass ML. Hypoglycemia and clinical outcomes in patients with diabetes hospitalized in the general ward. Diabetes Care 2009;32:1153–1157
16. Nauck MA, Vardarli I, Deacon CF, Holst JJ, Meier JJ. Secretion of glucagon-like peptide-1 (GLP-1) in type 2 diabetes: what is up, what is down? Diabetologia 2011;54:10–18
17. Cervera A, Wajcberg E, Sriwijitkamol A, et al. Mechanism of action of exenatide to reduce postprandial hyperglycemia in type 2 diabetes. Am J Physiol Endocrinol Metab 2008;294:E846–E852
18. Degn KB, Juhl CB, Sturis J, et al. One week's treatment with the long-acting glucagon-like peptide 1 derivative liraglutide (NN2211) markedly improves 24-h glycemia and alpha- and beta-cell function and reduces endogenous glucose release in patients with type 2 diabetes. Diabetes 2004;53:1187–1194
19. Courrèges JP, Vilsbøll T, Zdravkovic M, et al. Beneficial effects of once-daily liraglutide, a human glucagon-like peptide-1 analogue, on cardiovascular risk biomarkers in patients with type 2 diabetes. Diabet Med 2008;25:1129–1131
20. Chilton R, Wyatt J, Nandish S, Oliveros R, Lujan M. Cardiovascular comorbidities of type 2 diabetes mellitus: defining the potential of glucagonlike peptide-1-based therapies. Am J Med 2011;124(Suppl):S35–S53
21. Del Prato S, Leonetti E, Simonson DC, Sheehan P, Matsuda M, DeFronzo RA. Effect of sustained physiologic hyperglycaemia on insulin secretion and insulin sensitivity in man. Diabetologia 1994;37:1025–1035
22. Rensing KL, Reuwer AQ, Arsenault BJ, et al. Reducing cardiovascular disease risk in patients with type 2 diabetes and concomitant macrovascular disease: can insulin be too much of a good thing? Diabetes Obes Metab 2011;13:1073–1087
23. Arcaro G, Cretti A, Balzano S, et al. Insulin causes endothelial dysfunction in humans: sites and mechanisms. Circulation 2002;105:576–582
24. Gerstein HC, Miller ME, Byington RP, et al.; Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358:2545–2559
25. Patel A, MacMahon S, Chalmers J, et al.; ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008;358:2560–2572
26. Ratner R, Han J, Nicewarner D, Yushmanova I, Hoogwerf BJ, Shen L. Cardiovascular safety of exenatide BID: an integrated analysis from controlled clinical trials in participants with type 2 diabetes. Cardiovasc Diabetol 2011;10:22–32
27. Nikolaidis LA, Mankad S, Sokos GG, et al. Effects of glucagon-like peptide-1 in patients with acute myocardial infarction and left ventricular dysfunction after successful reperfusion. Circulation 2004;109:962–965
28. Sokos GG, Nikolaidis LA, Mankad S, Elahi D, Shannon RP. Glucagon-like peptide-1 infusion improves left ventricular ejection fraction and functional status in patients with chronic heart failure. J Card Fail 2006;12:694–699
29. Sokos GG, Bolukoglu H, German J, et al. Effect of glucagon-like peptide-1 (GLP-1) on glycemic control and left ventricular function in patients undergoing coronary artery bypass grafting. Am J Cardiol 2007;100:824–829
30. Müssig K, Oncü A, Lindauer P, et al. Effects of intravenous glucagon-like peptide-1 on glucose control and hemodynamics after coronary artery bypass surgery in patients with type 2 diabetes. Am J Cardiol 2008;102:646–647
31. Shamoon H, Hendler R, Sherwin RS. Synergistic interactions among antiinsulin hormones in the pathogenesis of stress hyperglycemia in humans. J Clin Endocrinol Metab 1981;52:1235–1241
32. van Raalte DH, van Genugten RE, Linssen MM, Ouwens DM, Diamant M. Glucagon-like peptide-1 receptor agonist treatment prevents glucocorticoid-induced glucose intolerance and islet-cell dysfunction in humans. Diabetes Care 2011;34:412–417
33. van Raalte DH, Nofrate V, Bunck MC, et al. Acute and 2-week exposure to prednisolone impair different aspects of beta-cell function in healthy men. Eur J Endocrinol 2010;162:729–735
34. Ranta F, Avram D, Berchtold S, et al. Dexamethasone induces cell death in insulin-secreting cells, an effect reversed by exendin-4. Diabetes 2006;55:1380–1390

35. DeFronzo RA, Sherwin RS, Felig P. Synergistic interactions of counterregulatory hormones: a mechanism for stress hyperglycemia. Acta Chir Scand Suppl 1980; 498:33–42
36. Ortega AE, Peters JH, Incarbone R, et al. A prospective randomized comparison of the metabolic and stress hormonal responses of laparoscopic and open cholecystectomy. J Am Coll Surg 1996;183: 249–256
37. Del Prato S, Castellino P, Simonson DC, DeFronzo RA. Hyperglucagonemia and insulin-mediated glucose metabolism. J Clin Invest 1987;79:547–556
38. Meier JJ, Weyhe D, Michaely M, et al. Intravenous glucagon-like peptide 1 normalizes blood glucose after major surgery in patients with type 2 diabetes. Crit Care Med 2004;32:848–851
39. Marso SP, Al-Amoodi M, Riggs L, et al. Administration of intravenous exenatide to patients with sustained hyerglycemia in the coronary ICU (Abstract). Diabetes 2011;60(Suppl. 1):A75
40. Kohl B, Hammond M, Schwartz S, Ochroch A. Intravenous exenatide (Byetta) for the treatment of perioperative hyperglycemia (Abstract). Society of Critical Care Medicine's 40th Critical Care Congress, 15–19 January 2011
41. Mecott GA, Herndon DN, Kulp GA, et al. The use of exenatide in severely burned pediatric patients. Crit Care 2010;14:R153
42. Garber AJ, King AB, Del Prato S, et al.; NN1250-3582 (BEGIN BB T2D) Trial Investigators. Insulin degludec, an ultralongacting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin apart in type 2 diabetes (BEGIN Basal-Bolus Type 2): a phase 3, randomised, open-label, treat-to-target noninferiority trial. Lancet 2012;379:1498–1507
43. Inzucchi SE, Siegel MD. Glucose control in the ICU–how tight is too tight? N Engl J Med 2009;360:1346–1349
44. Ellero C, Han J, Bhavsar S, et al. Prophylactic use of anti-emetic medications reduced nausea and vomiting associated with exenatide treatment: a retrospective analysis of an open-label, parallel-group, single-dose study in healthy subjects. Diabet Med 2010;27:1168–1173