

# The Use of Non-Insulin Anti-Diabetic Agents to Improve Glycemia Without Hypoglycemia in the Hospital Setting: Focus on Incretins

Stanley Schwartz · Ralph A. DeFronzo

Published online: 12 February 2014  
© Springer Science+Business Media New York 2014

**Abstract** Patients with hyperglycemia in hospital have increased adverse outcomes compared with patients with normoglycemia, and the pathophysiological causes seem relatively well understood. Thus, a rationale for excellent glyce-mic control exists. Benefits of control with intensive insulin regimes are highly likely based on multiple published studies. However, hypoglycemia frequency increases and adverse out-comes of hypoglycemia accrue. This has resulted in a ‘push’ for therapeutic nihilism, accepting higher glyce-mic levels to avoid hypoglycemia. One would ideally prefer to optimize glycemia, treating hyperglycemia while minimizing or avoiding hypoglycemia. Thus, one would welcome therapies and processes of care to optimize this benefit/ risk ratio. We review the logic and early studies that suggest that incretin therapy use in-hospital can achieve this ideal. We strongly urge randomized prospective controlled studies to test our proposal and we offer a process of care to facilitate this research and their use in our hospitalized patients.

**Keywords** In-hospital diabetes control · Incretins · DPP-4 inhibitors · GLP-1 receptor agonists · Intensive insulin therapy · Noninsulin anti-diabetic agents · Glycemia · Hypoglycemia

---

This article is part of the Topical Collection on *Hospital Management of Diabetes*

---

R. A. DeFronzo  
Diabetes Division, UTHSCSA, San Antonio, TX, USA

S. Schwartz  
Main Line Health System, University of Pennsylvania, Philadelphia, PA, USA

S. Schwartz (✉)  
Suite 305, 233 E. Lancaster Ave, Ardmore, PA 19003, USA  
e-mail: stschar@gmail.com

## Introduction

Type 2 diabetes mellitus continues to increase at epidemic rates and, as a result, the proportion of hospitalized patients who have stress-induced hyperglycemia and overt diabetes is increasing [1–3]. Several recent studies [4–6] have failed to show any benefit of intensive glyce-mic control on mortality in critically ill, hospitalized patients, and some studies [7–9] have demonstrated an increased incidence of side effects, especially hypoglycemia. This has resulted in an active debate about the risk/benefit ratio of aggressive glucose control in critically ill, hospitalized patients. One can make a strong argument that these negative findings largely resulted from processes of care and use of anti-diabetic agents (insulin and sulfonylureas) that cause undue hypoglycemia, thereby oblit-erating any potential benefit of the intervention. Although unproven, one could argue that intensive glyce-mic control is appropriate in hospitalized patients with hyperglycemia as long as one employs processes of care and anti-diabetic agents that do not cause, or minimize, undue hypoglycemia. We will briefly review this debate and focus on data, where it exists, and logic [10], of using anti-diabetic agents that would obviate the need for sulfonylureas and possibly insulin in hospitalized patients, while potentially reducing the detrimental effects of hyperglycemia, glyce-mic variability, cardiovascular (CV) risk, and adverse outcomes in these patients.

## Risks/Benefits of Intensive Therapy in Diabetic Patients: Intensive Insulin Therapy in Hospitalized and Critically Ill Patients

Hospitalized patients with stress-induced diabetes and overt type 2 diabetes mellitus experience adverse outcomes at a rate that rises in proportion to the severity of hyperglycemia [3, 11, 12]. Although some studies have demonstrated the benefit of

tight glyceemic control with insulin on mortality/morbidity in hospitalized critically ill patients including individuals undergoing CABG [13], patients in the surgical intensive care unit [14], and postmyocardial infarction patients [15]. However, these results have not been consistent. VISEP [7], Glucontrol [8], and NICE-Sugar [6] trials have found increased mortality/morbidity in patients treated with intensive insulin regimens. Hypoglycemia has been a major side effect in all studies that have attempted to achieve tight glyceemic control with insulin in hospitalized, severely ill patients and this adverse event may account for the negative outcomes seen in the above trials [5, 6, 8, 9, 16–21]. Hypoglycemia has many potential deleterious effects on the CV system [22], including prolongation of the QT- interval [23], which can last for extended periods of time [24]. Hypoglycemia stimulates catecholamine release [24], and this can precipitate angina, cause ischemic EKG changes, and arrhythmias [25, 26], and result in sudden death [23, 27]. Not surprisingly, insulin is the most common cause of drug-related medication errors in hospitalized patients [28]. Not surprisingly, considerable debate exists concerning in-hospital glyceemic goals and the value of intensive insulin therapy. The ADA/EASD consensus conference advocates a plasma glucose concentration between 140–180 mg% as a reasonable goal to balance the risks (primarily hypoglycemia) and benefits of intensive insulin therapy in hospitalized patients [29]. However, many experts believe that tighter glyceemic control would be beneficial if it could be achieved without undue hypoglycemia [30].

### Insulin as Standard of Care

At the present time, insulin represents the standard-of-care for hospitalized patients [31–33]. However, targeting tight glyceemic control with intensified insulin therapy to achieve a BG target within normal limits produces unacceptable rates of hypoglycemia. With the advent of basal-bolus insulin approaches using insulin analogs, a reduction in the incidence of hypoglycemia has been achieved. Avoidance of sliding scales [34, 35] has further improved the benefit/risk ratio in achieving good control without hypoglycemia. In addition, basic principles of care—careful glucose monitoring, timing of insulin boluses in relation to meals have been shown to reduce the risk of hypoglycemia.

Given the above considerations, newer glyceemic goals of therapy have been defined. The newest guidelines from the Critical Care Society and Endocrine Society are a very reasonable synthesis [32, 33] and states that initiation of therapy occur with >180 mg/dL, aim for <140–150 mg /dL, and assiduously avoid numbers <70 mg/dL.

However, we believe that there is room for improvement, and propose medications and processes of care that have the

potential to further reduce in-hospital hypoglycemia and overall morbidity and mortality.

### Alternative Therapies To Insulin - Key Principles

The ideal characteristics of any medication proposed to replace insulin include: (I) rapid onset and offset of action; (II) effectively reduce hyperglycemia by correcting the underlying abnormalities responsible for stress-induced hyperglycemia and diabetes; (III) obviate the need for insulin completely and be complementary to insulin if insulin is required; (IV) engender no undue hypoglycemia in absence of insulin or a sulfonyleurea; (V) not increase cardiovascular risk and possibly reduce CV risk; (VI) have acceptable and manageable side effects; (VII) be easy to use by physicians and nursing personnel. The incretin class of drugs most closely fulfills these characteristics.

#### Incretin Therapies

Incretin-based therapy (glucagon-like peptide-1 [GLP-1] receptor agonists and DPP-4 inhibitors) satisfy the key principles described above and can be used throughout the continuum of care of hospitalized patients with hyperglycemia, ranging from severely ill patients with diabetes in the intensive care unit to hospitalized patients on noncritical floors, as well as in hospitalized patients with stress-induced hyperglycemia.

GLP-1 is secreted by the L-cells of the gastrointestinal tract and, in conjunction with glucose-dependent insulinotropic polypeptide (GIP), accounts for >90 % of the ‘incretin effect’, ie, the 2–3-fold greater release of insulin from beta cells following oral vs intravenous glucose administration [36]. In T2DM patients the incretin effect is markedly reduced due to beta cell resistance to the stimulatory effect of GLP-1 (and GIP) on insulin secretion [37]. The stimulatory effect of GLP-1 on insulin secretion, as well as its inhibitory effect on glucagon secretion, is glucose dependent [36]. Thus, as the plasma glucose concentration declines to normoglycemic levels, the stimulatory effect of GLP-1 on insulin secretion wanes, as does its inhibitory effect on glucagon secretion. This provides a normal physiologic mechanism to prevent hypoglycemia.

Of particular note, in the hospitalized patient undergoing significant pathophysiological stress, it’s been shown that the adverse hyperglycemic effects of steroids, both endogenous as well as exogenous, occur in part through a mechanism that can be overcome by the GLP-1 pathway in the beta-cell [38, 39]. Thus, incretins offer unique value to patients with ‘stress-induced’ and ‘steroid-induced’ hyperglycemia. Moreover, considerable data indicate that GLP-1 exerts beneficial effects on the heart [40, 41], and preliminary analyses suggest that

incretin therapy may reduce cardiovascular outcomes in diabetic patients [42–45].

Because the half-life of GLP-1 is short, ~2 minutes, incretin-based therapies rely upon administration of exogenous GLP-1 receptor agonists that are resistant to DPP4 or the inhibition of dipeptidyl peptidase 4, the enzyme that inactivates endogenously secreted GLP-1. Three GLP-1 receptor agonists (exenatide bid, exenatide qw, liraglutide) and 5 DPP4 inhibitors (sitagliptin, saxagliptin, linagliptin, vildagliptin, alogliptin) currently are available. The increase in plasma GLP-1 levels with DPP4 inhibitors is quite modest compared with the fold greater increase observed with the GLP-2 analogues [46]. Not surprisingly, the GLP-1 receptor agonists are more potent in reducing HbA1c than the DPP4 inhibitors [47].

### Incretins in Hospital: Pilot Study Data

In hospitalized patients with stress-induced and steroid-induced diabetes, as well as in patients with overt diabetes, we have found that GLP-1 receptor agonists and DPP-4 inhibitors (I) effectively reduce the mean blood glucose level while minimizing the risk of hypoglycemia; (II) decrease excessive glycemic excursions that result from the release of stress hormones (glucagon and glucocorticoids); (III) reduce or eliminate the need for insulin (both the basal insulin requirement and the need for prandial insulin boluses); (IV) reduce glycemic variability, which has been postulated to increase adverse outcomes in hospitalized patients; and (V) have no undue cardiovascular side effects [48–50].

These impressions are supported by multiple pilot studies looking at glycemic and CV benefits of incretins in the hospital.

#### GLP-1 Infusion

As early as 2004 [50], GLP-1 infusion was used to control hyperglycemia in patients undergoing major surgery and showed increases in insulin and C-peptide, a decrease in plasma glucagon concentration and improved glycemic control with no undue nausea. We treated 40 patients (36 nondiabetic and 4 diabetic) undergoing cardiac surgery and observed a 15 mg/dL decrease in plasma glucose during the procedure in those that concentrations without significant nausea [48].

A 72-hour infusion of GLP-1 added to standard therapy in patients with acute MI and without diabetes ( $n=10$ ) significantly improved left ventricular ejection fraction (LVEF) from 29 % to 39 % ( $P<0.01$ ) compared with controls ( $n=11$ ), measured by echocardiogram, after reperfusion [51]. Further, GLP-1 infusion in the peri-MI has been shown to improve regional functional recovery in the peri-infarct zone in humans ( $n=10$ ) [51]. Sokos et al [52] investigated the effect of a

continuous 48-hour infusion of GLP-1 beginning 12 hours before coronary artery bypass graft (CABG) surgery in 10 patients with coronary heart disease and preserved LV function. This resulted in a reduced need for vasopressors, decreased incidence of arrhythmias, and significantly better glycemic control in the pre- and perioperative periods (95 mg/dL vs 140 mg/dL,  $P<0.02$ ), despite a 45 % reduction in insulin requirement compared with the control group ( $n=10$ ) and no undue nausea [52]. Similar results were reported by Mussig following cardiac surgery [53]. GLP-1 infusion also has been shown to markedly attenuate the glycemic response to small intestinal nutrition [54, 55] and in-hospital test meals [56]. Deane [57] and others [58, 59] have reviewed the use of glucagon-like peptide-1 in the critically ill.

Exenatide, which is approved for the treatment of type 2 diabetes mimic the effects of native GLP-1.

Marso et al [60] administered intravenous exenatide as a prime (0.05 ug/min for 30 minutes)-and then continuous (0.025 ug/min) infusion to 40 adults admitted to the cardiac ICU. It took 3.9 hours to reduce and maintain the plasma glucose from 199 mg/dL to 140 mg/dL for the subsequent 48 hours. Blood glucose levels <70 mg/dL were uncommon. Lonberg used IV exenatide peri-MI and showed reduced infarct size [61]. Subcutaneous exenatide has been shown to treat critically ill pediatric burn patients with improved glycemic control and a significant reduction in insulin requirement [62]. In G1 Japanese type 2 diabetic patients scheduled for elective surgery, institution of liraglutide therapy prior to admission resulted in good pre-, peri- and postoperative glycemic control without any cases of hypoglycemia [63].

In a seminal paper, Umpierrez et al [64] compared the efficacy of 3 regimens in noncritically ill diabetic patients (patients on diet, oral agents or low-dose insulin ( $\leq 0.4$  u/kg/day with moderately elevated blood glucose levels, <180 mg/dL, and A1c <7.5 % on admission) admitted to general medical and surgical wards: (I) sitagliptin alone; (II) sitagliptin plus supplemental insulin boluses; (III) basal-bolus insulin therapy. There were no differences in glycemic control following randomization and ~50 % of those in the sitagliptin-only group were able to avoid insulin altogether. Since the patient population treated in this study account for about half of all diabetic patients admitted to the hospital, this therapeutic approach has the potential to avoid the use of bolus insulin and associated hypoglycemia in a large number of diabetic patients. Though in patients with significant hyperglycemia the combination of sita+glargine achieved a better mean daily BG and less treatment failures, this is a remarkable achievement. Using Garber's [65] calculation that 12 % in-hospital daily hypoglycemia is due to basal therapy and 88 % is related to bolus therapy, it can be estimated that ~50 % of in-hospital hypoglycemia can be avoided by using a GLP-1 analogue to minimize/avoid bolus insulin therapy. It should be emphasized that the patient population studied by Umpierrez et al

did not include critically ill, ICU patients and his promising results DPP4 inhibitors should not be extrapolated to this patient population. Rather, we factor the use of GLP-1 analogue therapy to control hyperglycemia in this severely ill group of patients.

### Incretin Therapy in Hospital Patients: Process of Care

When using incretin therapy (exenatide, liraglutide) in hospitalized patients, the following approach is both simple and practical. We recommend that patients with prediabetes ( $HbA1c \geq 5.7\%$ , fasting plasma glucose = 100–125 mg/dL, 2-hour or random postprandial glucose = 140–199 mg/dL) who can be expected to become hyperglycemic in the diabetic range with the stresses of the admission/ surgery, those with previously undiagnosed diabetes, or those with known diabetes be identified before elective admission and be started on incretin therapy and continued if previously treated with them. For new starts, it can be done long enough prior to admission to assure tolerability. Thus, the incretin will be ‘on-board’ pre-, peri- and postoperatively, or in the ICU). Incretin therapy should be continued throughout the hospitalization and after discharge. We favor the use of a GLP-1 receptor agonist, especially in patients who are more critically ill.

If one decides to use a DPP4 inhibitor, the renal-adjusted dose should be administered. DPP4 inhibitors can be given orally or via nasogastric tube, all are approved in combination with insulin and they are not associated with any clinically important side effects. When starting a GLP-1 one can use exenatide, 5  $\mu$ g bid, with titration as necessary, based on efficacy of this lower dose, (do not use if creatinine clearance is  $<30$  ml/min) or liraglutide, 0.6 mg/day, titrated to 1.2 mg daily the next day (off label) if the first dose of 0.6 mg is well tolerated (no renal adjustment is necessary). Patients on exenatide QW prior to admission should be maintained on the agent; there is no decrement in efficacy if 1 weekly dose is missed while patient is in hospital. Exenatide (Byetta) and liraglutide work quickly with the first dose. Exenatide once weekly (Bydureon) takes several weeks before its hypoglycemic effect becomes manifest and is not effective if started at the time of or after admission to the hospital. Exenatide normally is given by subcutaneous injection but also can be given as a continuous intravenous infusion as described by Marso (68). Exenatide and liraglutide have been approved for use in combination with basal insulin and can be used, albeit ‘off-label’, with a rapid-acting insulin analog. During the initial 24 hours after initiating GLP-1 analogue therapy, a supplemental order for a rapid acting insulin can be included and after 24 hours this can be changed to a single basal injection of insulin if necessary.

In our clinical experience, as well as in published in-hospital-use studies [52, 53, 66], the incidence of nausea/

vomiting with GLP-1 receptor agonists is low. Hospitalized patients eat less and more slowly, their diet is not high in fat and fiber content, and they should be advised to stop eating when they have the first sense of fullness. Those patients who do report gastrointestinal upset or nausea can be managed with metoclopramide or ondansetron [67]. Incretin use should be avoided in patients with a history of pancreatitis or operative procedures that carry a risk of pancreatitis (ie, Whipple procedure).

Based upon the results of Umpierrez (66), one might select a DPP4 inhibitor in patients who are not critically ill and who are being treated with diet, oral antidiabetic agents, or low doses of insulin, ie, the patient population studied by Umpierrez.

Insulin-treated diabetic patients should be instructed to start incretin therapy prior to hospitalization, and, once their insulin therapy is adjusted, to take their usual dose of basal insulin (glargine, levemir) on the night/day prior to surgery. If incretin therapy is started in the hospital, the dose of insulin can be down titrated to optimize glycemic control while avoiding hypoglycemia. In many patients addition of the GLP-1 analogue may allow insulin to be discontinued. In the face of stress, the glucose lowering efficacy of the DPP-4 inhibitors is equal to ~20–30 units of insulin, while the GLP-1 receptor agonists are equal to ~40–60 units [48]. Thus, for the insulin-treated patient, one must make appropriate reductions in their usual at home insulin dosage regimens. If these prior insulin-treated patients are placed on an insulin drip, the protocols automatically will compensate for the efficacy of the background incretin therapy.

It should be emphasized that incretin therapy can be supplemented with insulin using any protocol/regimen that routinely is employed at one’s institution. Thus, our suggested process of care concerning incretin use in the hospital does not require any change of existing insulin protocols or order-sets in order to implement.

### Conclusions

Recent clinical trials have failed to demonstrate a benefit in mortality/morbidity in critically ill, hospitalized patients treated with insulin-based therapy. In part, the failure to observe benefit with these intensified insulin regimens can be attributed to side effects of insulin therapy, especially hyperglycemia. In hospitalized patients, both those admitted to general medical/surgical wards, as well as those who are critically ill in intensive care units, we describe an alternate approach utilizing incretinometric agents.

Incretin therapy can achieve normo-/near normoglycemic control (80–140 mg/dL) in hospitalized patients while minimizing the risk of hypoglycemia and capturing those cardiovascular benefits that accrue by achieving tight glycemic

control and that are intrinsic to the incretins themselves. The approach is simple and practical, is not associated with significant side-effects, and does not require alteration of existing in-hospital protocols if concomitant insulin therapy is required. We look forward to, and encourage more clinical research to further validate and gain more experience with our recommended incretin-based therapeutic approach. Based upon (I) evidence-based practice, (II) knowledge about the pathophysiology of stress-induced hyperglycemia in critically ill, hospitalized patients, (III) the known mechanism of action of incretin hormones, (IV) the excellent benefit-risk ratio of incretin therapy, and (V) encouraging published results with incretin-based therapy, we believe that this approach has significant advantages (especially the lack of hypoglycemia) over (and if necessary, in combination with) insulin therapy.

### Compliance with Ethics Guidelines

**Conflict of Interest** Stanley Schwartz serves on the Advisory Boards for Lilly, Bristol-Myers Squibb, Astra-Zeneca, Amylin, Santarus, J&J, Merck, Sanofi-Aventis, Genesis Biotechnology Group, Takeda. He serves on the Speaker's Bureaus for Lilly, Amylin, Santarus, Merck, Sanofi-Aventis, Novo-Nordisk, Boehringer Ingelheim, Bristol Myers Squibb, Astra-Zeneca, Abbvie, Takeda. He has received grant support from CHOP-NIH for Genetics of LADA. He has received honoraria from Delaware ACP, N. Car. AACE. Ralph A. DeFronzo serves on the Advisory Boards: Amylin, Takeda, Bristol-Myers Squibb, Boehringer-Ingelheim, Lexicon, Novo-Nordisk, Janssen. He serves on the Speaker's Bureaus for Novo-Nordisk, Bristol-Myers Squibb, Janssen, Novo-Nordisk. He has grants from Amylin, Takeda, Bristol-Myers Squibb, Boehringer-Ingelheim, Bristol Myers Squibb

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

### References

Papers of particular interest, published recently, have been highlighted as:

- Of importance

1. CDC Website. Available at: <http://www.cdc.gov/diabetes/statistics/dmany/fig1.htm>. Accessed 18 May 2013.
2. Hogan P, Dall T, Nikolov P. American Diabetes Association. Economic costs of diabetes in the US in 2002. *Diabetes Care*. 2003;26:917–32.
3. Clement S, Braithwaite SS, Magee MF, Ahmann A, Smith EP, Schafer RG, et al. American Diabetes Association Diabetes in Hospitals Writing Committee. Management of diabetes and hyperglycemia in hospitals. *Diabetes Care*. 2004;27:553–91.
4. Malmberg K, Rydén L, Wedel H, Birkeland K, Bootsma A, Dickstein K, 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;26:650–61.
5. van den Berghe G, Wilmer A, Hermans G, Meersseman W, Wouters PJ, Milants I, et al. Intensive insulin therapy in the medical ICU. *N Engl J Med*. 2006;354:449–61.
6. Finfer S, Chittock DR, Su SY, et al. NICESUGAR Study Investigators. Intensive vs conventional glucose control in critically ill patients. *N Engl J Med*. 2009;360:1283–97.
7. 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;358:125–39.
8. Preiser JC, Devos P, Ruiz-Santana S, Mélot C, Annane D, Groeneveld J, 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;35:1738–48.
9. 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;32:1153–7.
10. Duggal R, Menkes DB. Evidence-based medicine in practice. *Int J Clin Pract*. 2011;65:639–44.
11. 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;37:3001–9.
12. Muhlestein JB, Anderson JL, Horne BD, Lavasani F, Maycock A, Bair TL, 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;146:351–8.
13. Furnary AP, Wu Y. Clinical effects of hyperglycemia in the cardiac surgery population: the Portland Diabetic Project. *Endocr Pract*. 2006;12 Suppl 3:22–6.
14. Van Den B, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med*. 2001;345:1359–67.
15. Malmberg K, Rydén L, Wedel H, Birkeland K, Bootsma A, Dickstein K, 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;26:650–61.
16. Griesdale DE, de Souza RJ, van Dam RM, Heyland DK, Cook DJ, Malhotra A, et al. Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data. *Can Med Assoc J*. 2009;180:821–7.
17. Wiener RS, Wiener DC, Larson RJ. Benefits and risks of tight glucose control in critically ill adults: a meta-analysis. *JAMA*. 2008;300:933–44.
18. Egi M, Bellomo R, Stachowski E, French CJ, Hart GK, Taori G, et al. Hypoglycemia and outcome in critically ill patients. *Mayo Clin Proc*. 2010;85:217–24.
19. Asadollahi K, Hastings IM, Beeching NJ, Gill GV. Laboratory risk factors for hospital mortality in acutely admitted patients. *Q J Med*. 2007;100:501–7.
20. Pinto DS, Skolnick AH, Kirtane AJ, Murphy SA, Barron HV, Giugliano RP, et al. TIMI Study Group J. U-shaped relationship of blood glucose with adverse outcomes among patients with ST-segment elevation myocardial infarction. *J Am Coll Cardiol*. 2005;46:178–80.
21. Kosiborod M, Inzucchi SE, Krumholz HM, Xiao L, Jones PG, Fiske S, et al. Glucometrics in patients hospitalized with acute myocardial infarction: defining the optimal outcomes-based measure of risk. *Circulation*. 2008;117:1018–27.
22. Desouza CV, Bolli GB, Fonseca V. Hypoglycemia, diabetes, and cardiovascular events. *Diabetes Care*. 2010;33:1389–94.

23. Gill GV, Woodward A, Casson IF, Weston PJ. Cardiac arrhythmia and nocturnal hypoglycemia in type 1 diabetes—the ‘dead in bed’ syndrome revisited. *Diabetologia*. 2009;52:42–5.
24. Tremblay A, Pinsard D, Coveney S, Catellier C, Laferriere G, Richard D, et al. Counter-regulatory response to insulin-induced hypoglycemia in trained and non-trained humans. *Metabolism*. 1990;39:1138–43.
25. Desouza C, Salazar H, Cheong B, Murgu J, Fonseca V. Association of hypoglycemia and cardiac ischemia: a study based on continuous monitoring. *Diabetes*. 2003;26:1485–9.
26. Lindstrom T, Jorfeldt L, Tegler L, Arnqvist HJ. Hypoglycemia and cardiac arrhythmias in patients with type 2 diabetes mellitus. *Diabetes Med*. 1992;9:536–41.
27. Heller SR. Abnormalities of the electrocardiogram during hypoglycemia: the cause of the dead in bed syndrome? *Int J Clin Pract*. 2002;129(Suppl):27–32.
28. <http://www.psych.com/Julyaugust-2009/164%20data-trends-july-august-2009.html>.
29. The ACE/ADA Task Force on In-patient Diabetes. American College of Endocrinology and American Diabetes Association Consensus statement on inpatient diabetes and glycemic control. *Diabetes Care*. 2006;29:1955–62.
30. Inzucchi SE, Siegel MD. Glucose control in the ICU—how tight is too tight? *N Engl J Med*. 2009;26:1346–9.
31. Umpierrez GE, Korytkowski M. Is incretin-based therapy ready for the care of hospitalized patients with type 2 diabetes? Insulin therapy has proven itself and is considered the mainstay of treatment. *Diabetes Care*. 2013;36:2112–7.
32. Jacobi J et al. Guidelines for the use of an insulin infusion for the management of hyperglycemia in critically ill patients. *Crit Care Med*. 2012;40:3251–76.
33. Umpierrez GE, Hellman R, Korytkowski MT, Kosiborod M, Maynard GA, Montori VM, et al. Management of hyperglycemia in hospitalized patients in noncritical care setting: an endocrine society clinical practice guideline. *Endocrine Society. J Clin Endocrinol Metab*. 2012;97:16–38.
34. Umpierrez GE, Smiley D, Zisman A, Prieto LM, Palacio A, Ceron M, et al. Randomized study of basal-bolus insulin therapy in the inpatient management of patients with type 2 diabetes (RABBIT 2 trial). *Diabetes Care*. 2007;30:2181–6.
35. Umpierrez GE, Smiley D, Jacobs S, Peng L, Temponi A, Mulligan P, et al. Randomized study of basal-bolus insulin therapy in the inpatient management of patients with type 2 diabetes undergoing general surgery (RABBIT 2 surgery). *Diabetes Care*. 2011;34:256–61.
36. Nauck MA, Vilsbøll T, Gallwitz B, Garber A, Madsbad S. Incretin-based therapies: viewpoints on the way to consensus. *Diabetes Care*. 2009;32:S223–31.
37. 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;54:10–8.
38. 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;34:412–7.
39. Ranta F, Avram D, Berchtold S, Dufer M, Drews G, Lang F, et al. Dexamethasone induces cell death in insulin-secreting cells, an effect reversed by exendin-4. *Diabetes*. 2006;55:1380–90.
40. 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:S35–53.
41. Fadini G. Cardiovascular effects off DPP-4 Inhibition. *Vasc Pharmacol*. 2011;55:10–3.
42. Ratner R, Han J, Nicewarmer 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.
43. Sanon S, Patel R, Eshelbrenner C, Sanon VP, Alhaddad M, Oliveros R, et al. Acute coronary syndrome in patients with diabetes mellitus: perspectives of an interventional cardiologist. *Am J Cardiol*. 2012;110(9 Suppl):13B–23B.
44. Read PA, Khan FZ, Heck PM, Hoole SP, Dutka DP. DPP-4 inhibition by sitagliptin improves the myocardial response to dobutamine stress and mitigates stunning in a pilot study of patients with coronary artery disease. *Circulation*. 2010;3:195–201.
45. Monami M, Cremasco F, Lamanna C, Colombi C, Desideri CM, Iacomelli I, et al. Glucagon-like peptide-1 receptor agonists and cardiovascular events: a meta-analysis of randomized clinical trials. *Exp Diabetes Res*. 2011;2011:215764.
46. DeFronzo RA, Okerson T, Viswanathan P, Guan X, Holcombe JH, MacConnell L. Effects of exenatide vs sitagliptin on postprandial glucose, insulin and glucagon secretion, gastric emptying, and caloric intake: a randomized, cross-over study. *Curr Med Res Opin*. 2008;24:2943–52.
47. Pratley RE, Nauck M, Bailey T, Montanya E, Cuddihy R, Filetti S, et al. Liraglutide vs sitagliptin for patients with type 2 diabetes who did not have adequate glycemic control with metformin: a 26-week, randomized, parallel-group, open-label trial. *Lancet*. 2010;375:147–56.
48. Schwartz S, Kohl BA. Type 2 diabetes mellitus and the cardiometabolic syndrome: impact of incretin-based therapies. *Diabetes Metab Syndr Obes*. 2010;3:227–42.
49. Schwartz S, Kohl BA. Intraoperative glycemic control with intravenous GLP-1 in cardiac surgery. Presented ASCCA; 2010. [Abstract].
50. Meier JJ, Weyhe D, Michaely M, Senkal M, Zumbobel V, Nauck MA, et al. Intravenous glucagon-like peptide 1 normalizes blood glucose after major surgery in patients with type 2 diabetes. *Crit Care Med*. 2004;32:848–51.
51. Nikolaidis LA, Mankad S, Sokos GG, Miske G, Shah A, Elahi D, et al. Effects of glucagonlike peptide-1 in patients with acute myocardial infarction and left ventricular dysfunction after successful reperfusion. *Circulation*. 2004;109:962–5.
52. Sokos GG, Bolukoglu H, German J, Hentosz T, Magovern GJ Jr, Maher TD, 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;100:824–9.
53. Mussig K, Oncu A, Lindauer P, Heininger A, Aebert H, Unertl K, 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;102:646–7.
54. Nauck MA, Walberg J, Vethacke A, El-Ouaghli A, Senkal M, Holst JJ, et al. Blood glucose control in healthy subject and patients receiving intravenous glucose infusion or total parenteral nutrition using glucagon-like peptide 1. *Regul Pept*. 2004;118:89–97.
55. Deane AM, Chapman MJ, Fraser RJ, Burgstad CM, Besanko LK, Horowitz. The effect of exogenous glucagon-like peptide-1 on the glycemic response to small intestinal nutrient in the critically ill: a randomized double-blind placebo-controlled cross over study. *Crit Care*. 2009;13:R67.
56. Sourij H, Schmörlzer I, Kettler-Schmut E, Eder M, Pressl H, Decampo A, et al. Efficacy of a continuous GLP-1 infusion compared with a structured insulin infusion protocol to reach normoglycemia in nonfasted type 2 diabetic patients: a clinical pilot trial. *Diabetes Care*. 2009;32:1669–71.
57. Deane AM, Chapman MJ, Horowitz M. The use of glucagon-like peptide-1 analogues in the critically ill. *Crit Care*. 2010;14:1004–7.
58. Kovalaske MA, Gandhi GY. Incretins in the ICU: is insulin on its way out? *Crit Care*. 2009;13:161. *Proposal from others on same*

- topic, albeit without understanding mechanism of effectiveness based on overcoming suppression of insulin secretion by steroids and calmodulin inhibitors.*
59. De Caterinal R, Madonna R, Sourij H, Wascher T. Glycaemic control in acute coronary syndromes: prognostic value and therapeutic options. *Eur Heart J*. 2010;31:1557–64.
  60. Marso SP, Al-Amoodi M, Riggs L, House J, Peterman D, Kennedy K, et al. Administration of intravenous exenatide to patients with sustained hyperglycemia in the coronary ICU. *Diabetes*. 2011;60:A75.
  61. Lonborg J, Vejlstrop N, Kelbæk H, Bøtker HE, Kim WY, Mathiasen AB, et al. Exenatide reduces reperfusion injury in patients with ST-segment elevation myocardial infarction. *Eur Heart J*. 2012;33:1491–9.
  63. Mecott GA, Herndon DN, Kulp GA, Brooks NC, Al-Mousawi AM, Kraft R, et al. The use of exenatide in severely burned pediatric patients. *Crit Care*. 2010;14(4):R153. doi:10.1186/cc9222. *Best study of clinically available GLP-1 in hospital, illustrated proposed benefits outlined in our article.*
  63. Katagiri N. Peri-operative therapy for Japanese subjects with T2DM; ADA Poster #1039-P. Chicago; 2013.
  65. Umpierrez GE, Gianchandani R, Smiley D, Jacobs S, Wesorick DH, Newton C, et al. Safety and efficacy of sitagliptin therapy for the inpatient management of general medicine and surgery patients with type 2 diabetes: a pilot, randomized controlled study *Diabetes Care*. 2013;36(11):3430–5. doi: 10.2337/dc13-0277. *Only randomized prospective trial using incretin in-hospital.*
  65. Garber AJ, King AB, Del Prato S, Sreenan S, Balci MK, Muñoz-Torres M, et al. NN1250-3582 (BEGIN BB T2D) Trial Investigators. Insulin degludec, an ultra-long acting basal insulin, vs insulin glargine in basal-bolus treatment with mealtime insulin as part in type 2 diabetes (BEGIN Basal-Bolus Type 2): a phase 3, randomized, open-label, treat-to-target non-inferiority trial. *Lancet*. 2012;379:1498–507.
  66. Abuannadi M, Kosiborod M, Riggs L, House JA, Hamburg MS, Kennedy KF, et al. Management of hyperglycemia with the administration of intravenous exenatide to patients in the cardiac intensive care unit. *Endocr Pract*. 2013;19:81–90.
  67. Ellero C, Han J, Bhavsar S, Cirincione BB, Deyoung MB, Gray AL, 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. *Diabetes Med*. 2010;27:1168–73.