EDUCATIONAL AFFAIRS

TO REDUCE OR NOT TO REDUCE? INSULIN DOSE ADJUSTMENTS UPON STARTING GLP-1 RECEPTOR AGONISTS

Abigail T. Elmes, PharmD, BCPS
Research Fellow in Academia and Family Medicine; University of Illinois at Chicago College of Pharmacy - Chicago, IL

Daphne E. Smith Marsh, PharmD, BC-ADM, CDCES
Clinical Assistant Professor/Clinical Pharmacist; Dept. of Pharmacy Practice College of Pharmacy/Mile Square Health Center, UI Health - Chicago, IL

Brianna M. McQuade, PharmD, BCACP, MHPE
Clinical Assistant Professor; University of Illinois at Chicago College of Pharmacy, Mile Square Center - Chicago, IL

Jennie B. Jarrett, PharmD, BCPS, MMedEd, FCCP
Assistant Professor; Clinical Pharmacist, Family Medicine, University of Illinois at Chicago College of Pharmacy - Chicago, IL

The development of glucagon-like peptide-1 receptor agonists (GLP-1RAs), such as exenatide, liraglutide, dulaglutide, lixisenatide, and semaglutide, led to major significant advances in type 2 diabetes (T2DM) management. GLP-1RAs improve insulin secretion in a glucose-dependent manner, slow gastric emptying, increase satiety, increase glucose uptake by the muscles, decrease gluconeogenesis in the liver, and reduce postprandial glucagon secretion.[1] These agents offer many advantages given their significant reduction of hemoglobin A1c (A1C)[2], promotion of weight loss[3], reduced risk of hypoglycemia, and reduced major adverse cardiovascular outcomes[4–6] and reduced progression of nephropathy.[7]

The American Diabetes Association recommends initiating GLP-1RAs in patients with T2DM after implementing lifestyle modifications and metformin therapy if promoting weight loss, minimizing weight gain, or decreasing hypoglycemia is desired.[8] GLP-1RAs with proven cardiovascular disease benefits (dulaglutide, liraglutide, or semaglutide) are recommended in patients with atherosclerotic cardiovascular disease (ASCVD) or chronic kidney disease without albuminuria. Additionally, GLP-1RAs are the preferred injectable agent over insulin for patients on oral therapy needing intensification.[8] Insulin should be prioritized over a GLP-1RA in patients with A1C >10% or blood glucose levels >300 mg/dL or weight loss AND symptoms of hyperglycemia.[8]

For patients on basal insulin, GLP-1RAs are the preferred addition over prandial insulin due to clearer dose titration and patient education and as well as a reduced risk of hypoglycemia and fluctuations in blood glucose.[8,9] Combination products like Xultophy™ (insulin degludec/liraglutide) and Soliqua™ (insulin glargine/lixisenatide) offer the advantage of reduced administrations by combining basal insulin and a GLP-1RA in a single injection.[10]

Due to their extended time on the receptor, longer-acting GLP-1RAs have a greater effect on FBG and PPG compared to shorter-acting agents, which have targeted effects on PPG (**Table 1**).[9] Some clinical trials have described anticipatory reductions in basal insulin dose by 10-20% when initiating a GLP-1RA in more adequately controlled patients (A1C <8%). These adjustments are based on clinical knowledge and are not consistent or well-studied.[9] **Table 2** outlines clinical trials and recommendations for insulin adjustments with GLP-1RAs. However, best practices are needed for insulin adjustments when initiating a GLP-1RA.

In 2015, researchers at the Oxford Centre for Diabetes Endocrinology and Metabolism released recommendations for a 10% reduction in basal insulin and 30-40% reduction in prandial insulin upon addition of a GLP-1RA.[11] Few studies specifically evaluating insulin dose adjustments in GLP-1RA initiation have been published since this recommendation. A randomized, double-blind, placebo-controlled trial in Sweden evaluated the addition of once-daily liraglutide to patients inadequately controlled on basal-bolus insulin therapy.[12] Because patients had suboptimal glycemic control at baseline (A1C ≥7.5%), insulin doses were not preemptively

TABLE 1. INSULIN ADJUSTMENTS UPON GLP-1 RA INITIATION IN PATIENTS WITH A1C≤8%

	Insulin Regimen (pre-initiation)	
GLP-1 RA Type	**Basal-only**	**Basal-bolus**
Short-acting[a]	No dose adjustments	Consider 30-50% bolus dose reduction
Long-acting[b]	Consider initial 10-20% basal dose reduction	Consider 10-20% basal dose reduction and 30-50% bolus dose reduction

[a]Exenatide, lixisenatide [b]Dulaglutide, exenatide XR, liraglutide, semaglutide; Key: GLP-1RA: glucagon-like peptide-1 receptor agonist

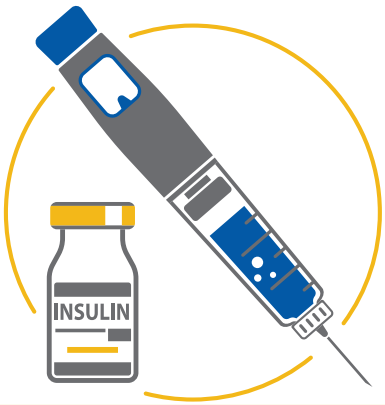
TABLE 2. PRESCRIBING INFORMATION RECOMMENDATIONS FOR INSULIN ADJUSTMENTS UPON GLP-1RA INITIATION

Drug	Prescribing Information Recommendation[17–26]	Significant Trials[a]
Liraglutide	• Has not been studied in combination with prandial insulin • Consider insulin dose reduction when starting liraglutide	**LIRA-RENAL**[27] Population: Patients with T2DM and moderate renal impairment inadequately controlled on basal or premixed insulin and/or metformin and/or SU and/or TZD Intervention: Liraglutide versus placebo Dose Adjustment: Insulin dose was reduced by 20% at randomization for patients with baseline A1C ≤8%
Exenatide	• Has not been studied and is not recommended in combination with prandial insulin • Consider insulin dose reduction when starting exenatide	**Buse et al.**[28] Population: Patients with T2DM inadequately controlled on insulin glargine with or without metformin and/or TZD Intervention: Exenatide versus placebo Dose Adjustment: Insulin glargine dose was reduced by 20% at randomization for patients with baseline A1C ≤8%
		Diamant et al.[29] Population: Patients with T2DM inadequately controlled on optimized insulin glargine and metformin Intervention: Exenatide versus titrated insulin lispro Dose Adjustment: After basal insulin optimization, insulin glargine dose was reduced "by at least 10%" for patients in the exenatide arm with A1C ≤8%
Exenatide ER	• Has not been studied in combination with prandial insulin • Consider insulin dose reduction when starting exenatide ER	**DURATION-7**[30] Population: Patients with T2DM inadequately controlled on insulin glargine with or without metformin Intervention: Exenatide ER versus placebo Dose Adjustment: No insulin dose adjustments noted in the study
Dulaglutide	• Consider insulin dose reduction when starting dulaglutide	**AWARD-9**[31] Population: Patients with T2DM inadequately controlled on insulin glargine with or without metformin Intervention: Dulaglutide versus placebo Dose Adjustment: Insulin glargine dose was reduced by 20% at randomization for patients with baseline A1C ≤8%
Semaglutide injection	• Consider insulin dose reduction when starting semaglutide	**SUSTAIN 5**[32] Population: Patients with T2DM inadequately controlled with basal insulin with or without metformin Intervention: Semaglutide versus placebo Dose Adjustment: Basal insulin dose was reduced by 20% at screening for patients with baseline A1C ≤8%
Semaglutide tablet	• Consider insulin dose reduction when starting semaglutide	**PIONEER 5**[33] Population: Patients with T2DM and moderate renal impairment inadequately controlled on metformin alone, SU alone, basal insulin alone, or metformin in combination with either SU or basal insulin Intervention: Semaglutide versus placebo Dose Adjustment: Basal insulin dose was reduced by 20% at randomization regardless of baseline A1C
		PIONEER 8[34] Population: Patients with T2DM inadequately controlled on insulin (basal, basal/bolus, or premixed) with or without metformin Intervention: Semaglutide versus placebo Dose Adjustment: Insulin dose was reduced by 20% at randomization for all patients
Lixisenatide	• Has not been studied in and is not recommended in combination with prandial insulin • Consider insulin dose reduction when starting lixisenatide	**GetGoal-L**[35] Population: Patients with T2DM inadequately controlled on diet, exercise, and basal insulin with or without metformin Intervention: Lixisenatide versus placebo Dose Adjustment: No mention of dose reduction
		GetGoal-L-Asia[36] Population: Asian Patients with T2DM inadequately controlled on diet, exercise, and basal insulin with or without SU Intervention: Lixisenatide versus placebo Dose Adjustment: No mention of dose reduction
		GetGoal-Duo[37] Population: Patients with T2DM inadequately controlled on diet, exercise, insulin glargine, and metformin with or without TZD Intervention: Lixisenatide versus placebo Dose Adjustment: No mention of dose reduction
Albiglutide[b]	• Has not been studied in combination with prandial insulin • Consider insulin dose reduction when starting albiglutide	**HARMONY 6**[38] Population: Patients with T2DM inadequately controlled on >20 daily units insulin glargine Intervention: Albiglutide versus insulin lispro at mealtimes Dose Adjustment: No mention of dose reduction
Insulin degludec/ liraglutide	• Has not been studied in combination with prandial insulin	*Insulin naïve patients:* 10 units daily *Patients taking basal insulin:* start at 16 units daily
Insulin glargine/ lixisenatide	• Has not been studied in combination with prandial insulin	*Insulin or GLP-1RA naïve patients:* 15 units daily *Patients taking < 30 units basal insulin:* 15 units daily *Patients taking 30 to 60 units basal insulin:* 30 units daily

[a]Not an all-inclusive list, [b]Removed from the U.S. market in 2017
Key: GLP-1RA: glucagon-like peptide-1 receptor agonist; T2DM: type 2 diabetes; SU: sulfonylurea; TZD: thiazolidinedione; A1C: hemoglobin A1c

reduced. If FBG or pre-prandial glucose levels were normal or close to normal for two consecutive days, then dose reductions were considered. After 24 weeks, reductions were found between liraglutide versus placebo for A1C (-1.13 [95% CI -1.45 to -0.81]), body weight (-3.81 kg [95% CI -4.87 to -2.76]), and total daily insulin dose (-15.8 units [95% CI -23.1 to -8.5]). There was no difference in hypoglycemia between the groups.[12]

A 26-week, randomized, open-label, active-control, multicenter, treat-to-target study compared patients with T2DM with an A1C 7.0 to 9.5% with or without metformin on a basal-bolus insulin regimen (<140 units/day and at least 3 three injections/day) versus the addition of albiglutide and reduction of prandial insulin. All patients were standardized on once-daily insulin glargine and three times-daily insulin lispro before randomization. In the albiglutide and insulin glargine (AIG) group, the insulin lispro dose was reduced by 50% and subsequently discontinued at week 4 for the remainder of the treatment period. After week 8, insulin lispro was reintroduced in patients with average PPG >180 mg/dL. The insulin glargine-lispro (IGL) arm served as the active control, and insulin lispro dose adjustments were made following an algorithm. The AIG group was non-inferior to the IGL group for change in A1C from baseline (0.06% [95% CI -0.05 to 0.17]). The proportion of patients achieving A1C <7% was similar between groups (OR 1.0 [95% CI 0.7-1.3]). In the AIG group, 72% of patients either did not require insulin lispro reintroduction or decreased the insulin lispro without increasing A1C, and 54% completely replaced insulin lispro with albiglutide at the study conclusion. There were no differences in baseline characteristics between the patients in the AIG group who did or did not require reintroduction of insulin lispro.



Reductions were found between AIG versus IGL for average weekly injections (-16.0 ± 7.9), body weight (-4.4 kg [95% CI -4.9 to -3.8]), total daily insulin dose (-61.8 units [95% CI -65.9 to -57.8]), and hypoglycemic rate (OR 0.43 [95% CI .031-0.60]). Of note, albiglutide was removed from the U.S. market in 2017 for economic reasons unrelated to safety or efficacy.[13,14] The study showed a similar mean insulin glargine dose between groups with a lower FBG in the AIG group, emphasizing the impact of long-acting GLP-1RAs on both FBG and PPG.[15] Therefore, basal insulin dose reductions may be more appropriate with long-acting agents versus short-acting agents. **Table 1** outlines recommendations for short- and long-acting GLP-1RAs initiation with various insulin regimens.

In diabetes management, a patient-centered approach and strong clinical judgment are imperative. For example, in patients at higher risk of hypoglycemia, (longer duration of diabetes, concomitant secretagogues, erratic eating patterns, and kidney disease), more substantial insulin dose reductions may be appropriate.[16] Consider the patient case outlined in **Figure 1**. GLP-1RA initiation is appropriate in this patient, given their elevated A1C, obesity, and ASCVD. Because the A1C is relatively close to the patient's goal, a 10-20% reduction in basal insulin dose and a 30-50% reduction in prandial insulin dose is appropriate upon starting a long-acting GLP-1RA. If the patient were less adequately controlled, less aggressive insulin dose adjustments could be considered, if at all. Close monitoring of FBG, PPG, and signs/symptoms of hypo- and hyperglycemia is warranted in patients on insulin starting any GLP-1RA.

REFERENCES:

1. Collins L, Costello RA. Glucagon-like peptide-1 receptor agonists. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2020. http://www.ncbi.nlm.nih.gov/books/NBK551568/. Accessed November 18, 2020.
2. Htike ZZ, Zaccardi F, Papamargaritis D, Webb DR, Khunti K, Davies MJ. Efficacy and safety of glucagon-like peptide-1 receptor agonists in type 2 diabetes: A systematic review and mixed-treatment comparison analysis. Diabetes Obes Metab. 2017;19(4):524-536. doi:10.1111/dom.12849
3. Shyangdan DS, Royle P, Clar C, Sharma P, Waugh N, Snaith A. Glucagon-like peptide analogues for type 2 diabetes mellitus. Cochrane Database Syst Rev. 2011;(10):CD006423. doi:10.1002/14651858.CD006423.pub2
4. Varin EM, McLean BA, Lovshin JA. Glucagon-like peptide-1 receptor agonists in adult patients with type 2 diabetes: review of cardiovascular outcome trials. Can J Diabetes. 2020;44(1):68-77. doi:10.1016/j.jcjd.2019.08.011
5. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2016;375(4):311-322. doi:10.1056/NEJMoa1603827
6. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2016;375(19):1834-1844. doi:10.1056/NEJMoa1607141
7. Dicembrini I, Nreu B, Scatena A, et al. Microvascular effects of glucagon-like peptide-1 receptor agonists in type 2 diabetes: a meta-analysis of randomized controlled trials. Acta Diabetol. 2017;54(10):933-941. doi:10.1007/s00592-017-1031-9
8. American Diabetes Association. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes—2021. Diabetes Care. 2021;44(Supplement 1):S111-S124. doi:10.2337/dc21-S009
9. Anderson SL, Trujillo JM. Basal insulin use with GLP-1 receptor agonists. Diabetes Spectr. 2016;29(3):152-160. doi:10.2337/diaspect.29.3.152
10. Nuffer W, Guesnier A, Trujillo JM. A review of the new GLP-1 receptor agonist/basal insulin fixed-ratio combination products. Ther Adv Endocrinol Metab. 2018;9(3):69. doi:10.1177/2042018817752315
11. Artigas CF, Stokes V, Tan GD, Theodorakis MJ. Insulin dose adjustments with add-on glucagon-like peptide-1 receptor (GLP-1R) agonists in clinical practice. Expert Opin Pharmacother. 2015;16(10):1417-1421. doi:10.1517/14656566.2015.1052740
12. Lind M, Hirsch IB, Tuomilehto J, et al. Liraglutide in people treated for type 2 diabetes with multiple daily insulin injections: randomised clinical trial (MDI Liraglutide trial). BMJ. 2015;351. doi:10.1136/bmj.h5364
13. Walmsley E. GlaxoSmithKline investor event. Presented at the: GSK Investor Event; July 26, 2017; London, UK.
14. Rosenstock J, Nino A, Soffer J, et al. Impact of a weekly glucagon-like peptide 1 receptor agonist, albiglutide, on glycemic control and on reducing prandial insulin use in type 2 diabetes inadequately controlled on multiple insulin therapy: a randomized trial. Diabetes Care. 2020;43(10):2509-2518. doi:10.2337/dc19-2316
15. Bolli GB, Porcellati F, Meier JJ. Switching from insulin bolus treatment to GLP-1 RAs added to continued basal insulin in people with type 2 diabetes on basal-bolus insulin. Diabetes Care. 2020;43(10):2333-2335. doi:10.2337/dci20-0038
16. Silbert R, Salcido-Montenegro A, Rodriguez-Gutierrez R, Katabi A, McCoy RG. Hypoglycemia among patients with type 2 diabetes: epidemiology, risk factors, and prevention strategies. Curr Diab Rep. 2018;18(8):53. doi:10.1007/s11892-018-1018-0
17. Victoza (liraglutide) prescribing information. Plainsboro, NJ: Novo Nordisk Inc; 2020 Aug.
18. Byetta (exenatide) prescribing information. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2020 Feb.
19. Bydureon (exenatide extended-release) prescribing information. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2020 Feb.

FIGURE 1. PATIENT CASE

58 year old male presenting to the clinic for diabetes management. His home blood glucose log indicates an average FBG 125 mg/dL and PPG 220 mg/dL.

Past medical history: type 2 diabetes x 14 years, hypertension x 10 years, MI in 2014

Current Medication list:

- Metformin 1000 mg by mouth twice daily
- Insulin glargine 42 units subcutaneously daily
- Insulin aspart 14 units subcutaneously with meals
- Lisinopril 20 mg by mouth daily
- Metoprolol succinate 50 mg by mouth daily
- Atorvastatin 80 mg by mouth daily
- Aspirin 81 mg by mouth daily

	Today	3 months ago	6 months ago
HbA1c (%)	7.9	7.9	7.8
Random BG (mg/dL)		213	
Na (mmol/L)		139	
K (mmol/L)		4.4	
Cl (mmol/L)		105	
CO2 (mmol/L)		26	
Ca (mg/dL)		9.9	
SCr (mg/dL)		0.86	
BUN (mg/dL)		12	
eGFR (mL/min/1.73*m^2)		91	
Weight (kg)	98.5	98.5	98.3
Height (cm)	180.3	180.3	180.3
BMI (kg/m^2)	30.3	30.3	30.2

The patient's A1C goal is <7%. You are considering starting a GLP-1 RA for your patient given his past ASCVD and need for further A1C reduction. You decide to start an agent with proven CVD benefits, preferably once weekly, based on insurance coverage.

What considerations should be made to the patient's insulin regimen if…

Starting a long-acting agent?

Long-acting agents like dulaglutide, exenatide XR, liraglutide, semaglutide lower FBG and PPG. Because the patient is on a basal-bolus regimen and the A1C is relatively close to the patient's goal, a 10-20% reduction in basal insulin dose and a 30-50% reduction in prandial insulin dose is appropriate.

Starting a short-acting agent?

Short-acting agents like exenatide and lixisenatide have limited effects on FBG. Because the patient is on a basal-bolus regimen and the A1C is relatively close to the patient's goal, 30-50% reduction in prandial insulin dose is appropriate.

The patient's A1C was 9%?

Patients less adequately controlled on insulin therapy are at a lower risk of hypoglycemia. If this patient's A1C was 9%, less aggressive insulin dose reductions may be appropriate, if at all.

20. Trulicity (dulaglutide) prescribing information. Indianapolis, IN: Lilly USA, LLC; 2020 Sept.
21. Ozempic (semaglutide injection) prescribing information. Plainsboro, NJ: Novo Nordisk Inc; 2020 Sept.
22. Rybelsus (semaglutide tablets) prescribing information. Plainsboro, NJ: Novo Nordisk Inc; 2020 Jan.
23. Adlyxin (lixisenatide) prescribing information. Bridgewater, NJ: Sanofi-Aventis U.S. LLC; 2019 Jan.
24. Tanzeum (albiglutide) prescribing information. Research Triangle Park, NC: GlaxoSmithKline LLC; 2017 Sept.
25. Xultophy (insulin degludec and liraglutide) prescribing information. Plainsboro, NJ: Novo Nordisk Inc; 2019 Nov.
26. Soliqua (insulin glargine and lixisenatide) prescribing information. Bridgewater, NJ: Sanofi-Aventis U.S. LLC; 2019 Nov.
27. Davies MJ, Bain SC, Atkin SL, et al. Efficacy and safety of liraglutide versus placebo as add-on to glucose-lowering therapy in patients with type 2 diabetes and moderate renal impairment (LIRA-RENAL): a randomized clinical trial. Diabetes Care. 2016;39(2):222-230. doi:10.2337/dc14-2883
28. Buse JB, Bergenstal RM, Glass LC, et al. Use of twice-daily exenatide in basal insulin–treated patients with type 2 diabetes. Ann Intern Med. 2011;154(2):103-112. doi:10.7326/0003-4819-154-2-201101180-00300
29. Diamant M, Nauck MA, Shaginian R, et al. Glucagon-like peptide 1 receptor agonist or bolus insulin with optimized basal insulin in type 2 diabetes. Diabetes Care. 2014;37(10):2763-2773. doi:10.2337/dc14-0876
30. Guja C, Frías JP, Somogyi A, et al. Effect of exenatide QW or placebo, both added to titrated insulin glargine, in uncontrolled type 2 diabetes: The DURATION-7 randomized study. Diabetes Obes Metab. 2018;20(7):1602-1614. doi:10.1111/dom.13266
31. Pozzilli P, Norwood P, Jódar E, et al. Placebo-controlled, randomized trial of the addition of once-weekly glucagon-like peptide-1 receptor agonist dulaglutide to titrated daily insulin glargine in patients with type 2 diabetes (AWARD-9). Diabetes Obes Metab. 2017;19(7):1024-1031. doi:10.1111/dom.12937
32. Rodbard HW, Lingvay I, Reed J, et al. Semaglutide added to basal insulin in type 2 diabetes (SUSTAIN 5): a randomized, controlled trial. J Clin Endocrinol Metab. 2018;103(6):2291-2301. doi:10.1210/jc.2018-00070
33. Mosenzon O, Blicher TM, Rosenlund S, et al. Efficacy and safety of oral semaglutide in patients with type 2 diabetes and moderate renal impairment (PIONEER 5): a placebo-controlled, randomised, phase 3a trial. Lancet Diabetes Endocrinol. 2019;7(7):515-527. doi:10.1016/S2213-8587(19)30192-5
34. Zinman B, Aroda VR, Buse JB, et al. Efficacy, safety, and tolerability of oral semaglutide versus placebo added to insulin with or without metformin in patients with type 2 diabetes: the PIONEER 8 trial. Diabetes Care. 2019;42(12):2262-2271. doi:10.2337/dc19-0898
35. Riddle MC, Aronson R, Home P, et al. Adding once-daily lixisenatide for type 2 diabetes inadequately controlled by established basal insulin: a 24-week, randomized, placebo-controlled comparison (GetGoal-L). Diabetes Care. 2013;36(9):2489-2496. doi:10.2337/dc12-2454
36. Seino Y, Min KW, Niemoeller E, Takami A, EFC10887 GETGOAL-L Asia Study Investigators. Randomized, double-blind, placebo-controlled trial of the once-daily GLP-1 receptor agonist lixisenatide in Asian patients with type 2 diabetes insufficiently controlled on basal insulin with or without a sulfonylurea (GetGoal-L-Asia). Diabetes Obes Metab. 2012;14(10):910-917. doi:10.1111/j.1463-1326.2012.01618.x
37. Riddle MC, Forst T, Aronson R, et al. Adding once-daily lixisenatide for type 2 diabetes inadequately controlled with newly initiated and continuously titrated basal insulin glargine: a 24-week, randomized, placebo-controlled study (GetGoal-Duo 1). Diabetes Care. 2013;36(9):2497-2503. doi:10.2337/dc12-2462
38. Rosenstock J, Fonseca VA, Gross JL, et al. Advancing basal insulin replacement in type 2 diabetes inadequately controlled with insulin glargine plus oral agents: a comparison of adding albiglutide, a weekly GLP-1 receptor agonist, versus thrice-daily prandial insulin lispro. *Diabetes Care.* 2014;37(8):2317-2325. doi:10.2337/dc14-0001 ■