TABLE 1. Select Clinical Trials on Basal Insulin Dosing and Titration

Clinical Trial	Design/ Primary Objective	Population	Intervention	Results	Conclusions/ Comments
Insulin glargine					
Treat-to-Target Trial, Riddle et al., 2003 (23)	RCT, parallel-group, multicenter, open-label, 24-week Percentage of subjects achieving A1C ≤7% without a single instance of symptomatic nocturnal hypoglycemia	*n* = 756 Inclusion criteria: 30–70 years of age, type 2 diabetes for ≥2 years, A1C >7.5–10%, stable dose of 1–2 OADs for ≥3 months, BMI 26–40 kg/m^2, FPG ≥140 mg/dL	*n* = 367: insulin glargine, 10 units at bedtime *n* = 389: NPH, 10 units at bedtime OADs were continued at prestudy doses	Primary end point was achieved by more subjects treated with insulin glargine than with NPH (33.2 vs. 26.7%, *P* <0.05)	Systematic titration of bedtime basal insulin added to oral therapy safely achieved a 7% A1C in the majority of patients studied. Insulin glargine causes significantly less nocturnal hypoglycemia than NPH during forced titration. This study excluded patients who previously used insulin. There was a larger percentage of Hispanics in the insulin glargine group.
AT.LANTUS trial, Davies et al., 2005 (24)	RCT, parallel-group, multicenter, open-label, 24-week Compare physician-managed vs. patient-managed insulin glargine titration algorithm in terms of incidence of severe hypoglycemia	*n* = 4,961 Inclusion criteria: ≥18 years of age, antidiabetic therapy >6 months requiring long-acting insulin, A1C >7 to <12%, BMI <40 kg/m^2	*n* = 2,493: algorithm 1, 10 units of evening insulin glargine if insulin naive or conversion to equivalent dose of glargine if previously treated with basal insulin *n* = 2,468: algorithm 2, evening insulin glargine at a dose equivalent to the highest FPG value (in mmol/L) over the previous 7 days if insulin naive or conversion to equivalent dose of glargine if previously treated with basal insulin	No significant difference in the incidence of severe hypoglycemia between a physician- and a patient-managed algorithm using insulin glargine (0.9 vs. 1.1%, [90% CI 0.3–0.7])	Both algorithms had a low incidence of severe hypoglycemia, with no incident difference. Subjects had a mean duration of type 2 diabetes of 12 years and a 5-year mean duration of insulin pretreatment. 72% of subjects were pretreated with insulin at inclusion. This study provided two simple, widely applicable treatment algorithms for insulin glargine.
INSIGHT trial, Gerstein et al., 2006 (25)	RCT, multicenter, open-label, 24-week First achievement of two consecutive A1C levels ≤6.5%	*n* = 405 Inclusion criteria: 18–80 years of age, type 2 diabetes ≥6 months, A1C 7.5–11%, 0–2 OADs	*n* = 206: insulin glargine, 10 units in the evening *n* = 199: conventional therapy OAD intensification	Patients receiving insulin glargine reached two consecutive A1C levels ≤6.5% before the conventional group and were 1.68 times more likely to achieve the end point (95% CI 1.00–2.83,	Adding insulin glargine is more likely to achieve a lower A1C level than conventional therapy with OADs.

				$P = 0.049$)	
Insulin detemir					
Detemir Treat-to-Target trial, Hermansen et al., 2006 (26)	RCT, parallel-group, multicenter, open-label, 24-week Percentage decrease in A1C at 24 weeks	$n = 453$ Inclusion criteria: ≥18 years of age, type 2 diabetes for ≥12 months, A1C 7.5–10%, BMI ≤35 kg/m^2	$n = 237$: insulin detemir, 10 units* before breakfast and in the evening (within 1 hour before dinner until bedtime) via pen injector $n = 238$ NPH, 10 units* before breakfast and in the evening (within 1 hour before dinner until bedtime) via pen injector *If initial prebreakfast or predinner plasma glucose was <126 mg/dL or BMI was <26 kg/m^2, starting doses were reduced to 6 units OADs were continued at prestudy doses	Insulin detemir: A1C decreased by 1.8 percentage points from 8.6% ($n = 237$) to 6.8% ($n = 230$) by 24 weeks NPH: A1C decreased by 1.9 percentage points, from 8.5% ($n = 237$) to 6.6% ($n = 232$) Baseline-, country-, and OAD-adjusted means of 6.58 ± 0.06 and 6.46 ± 0.06%, fulfilling criteria for noninferiority (mean difference 0.13 [95% CI 0.00–0.25])	This study confirmed the feasibility of adding basal insulin with intensive dose titration to OADs as a strategy for achieving recommended glycemic targets in patients with previously poorly controlled type 2 diabetes. The noninferiority criterion was defined as <0.4 percentage point difference in A1C. There were more women and a slightly higher mean A1C in the insulin detemir group. In each group, ~65% received combination OAD therapy, but the study excluded patients on thiazolidinediones. Classification of patients into responders and nonresponders was used for purposes of a titration schedule. The authors noted a lower risk of any hypoglycemic event and less weight gain with insulin detemir.

TABLE CONTINUED ON P. 3 →

TABLE 1. Select Clinical Trials on Basal Insulin Dosing and Titration, *continued from p. 2*

Phase 3 study, Philis-Tsimikas et al., 2006 (27)	RCT, parallel-group, three-arm, multicenter, open-label, 20-week Compare the effectiveness (mean A1C at end of study) and tolerability of insulin detemir vs. NPH administered once daily with ≥1 OAD in poorly controlled type 2 diabetes	*n* = 504 Inclusion criteria: ≥18 years of age, type 2 diabetes ≥12 months, insulin naive, A1C 7.5–11%, ≥3 months of treatment with ≥1 OAD, BMI ≤40 kg/m^2	*n* = 165: morning insulin detemir, 10 units before breakfast *n* = 169: evening insulin detemir, 10 units before dinner *n* = 164: evening NPH, 10 units before dinner	Morning insulin detemir decreased the raw mean A1C by 1.58 percentage points, whereas evening insulin detemir and evening NPH decreased the mean by 1.48 and 1.74 percentage points, respectively	Insulin detemir administered once daily in the morning or evening can be used to improve glycemic control and may offer some tolerability advantages over NPH. The noninferiority criterion was defined as <0.4 percentage point difference in A1C. Morning and evening detemir were associated with reductions in A1C similar to those seen with evening NPH. Two major hypoglycemic episodes were recorded during the study, both in the evening insulin detemir group, with none in the other groups. OAD therapy and doses remained unchanged during the study period.
PREDICTIVE 303 trial, Meneghini et al., 2007 (28)	RCT, multicenter, open-label, 26-week Efficacy of a simplified patient self-adjusted algorithm vs. standard-of-care, physician-driven adjustments with regard to A1C change and A1C change from baseline to the end of the treatment period	*n* = 5,604 Inclusion criteria: ≥18 years of age, type 2 diabetes, A1C ≤12%, BMI ≤45 kg/m^2, likely to benefit from insulin detemir	*n* = 2,787: 303 Algorithm: insulin detemir once daily in the evening *n* = 389: standard-of-care algorithm, insulin detemir once daily in the evening	Mean A1C with insulin detemir decreased from 8.5 to 7.9% in the 303 Algorithm group (P <0.0001) and decreased from 8.5 to 8% in the standard-of-care group (P <0.0001) with a significant difference between groups (P <0.0106)	Overall glycemic control achieved by the patient self-adjusted 303 Algorithm group was noninferior to that of the standard-of-care group, but the standard-of-care group experienced fewer hypoglycemic events. The study had broad inclusion criteria that closely resemble the U.S. type 2 diabetes population. This was a noninferiority trial. There were no forced titrations. Titration was focused on basal insulin for

					the first 12 weeks, and then the investigator was encouraged to adjust other antidiabetic medication(s) as needed. Only 2.3% of patients were not receiving any therapy for diabetes at randomization, and about one-third had not received any previous insulin therapy at baseline.

FPG, fasting plasma glucose; OAD, oral antidiabetic drug; RCT, randomized controlled trial.

TABLE 2. Select Clinical Trials Detailing Basal Insulin Titration Methods

Clinical Trial	Titration Algorithm
Insulin glargine	
Treat-to-Target trial, Riddle et al., 2003 (23)	Glargine and NPH: forced titration schedule with weekly adjustments based on FPG: ≥180 mg/dL, +8 units; 140–180 mg/dL, +6 units; 120–140 mg/dL +4 units, or 100–120 mg/dL, +2 units
AT.LANTUS trial, Davies et al., 2005 (24)	Algorithm 1: Physician-managed titration at weekly intervals based on FPG: 100–119 mg/dL, +0–2 units; 120–139 mg/dL, +2 units; 140–179 mg/dL, +4 units; or ≥180 mg/dL, +6–8 units Algorithm 2: Patient-managed titration every 3 days based on FPG: 100–119 mg/dL, +0–2 units; or ≥120 mg/dL, +2 units
INSIGHT trial, Gerstein et al., 2006 (25)	Glargine: self-titration of +1 unit/day if FPG was >100 mg/dL Conventional: Physician adjustment of OADs if FPG was >100 mg/dL
Insulin detemir	
Detemir Treat-to-Target trial, Hermansen et al., 2006 (26)	Detemir and NPH: Forced titration with at least weekly adjustments based on prebreakfast and predinner plasma glucose readings for the first 12 weeks, then titrations at least every 2 weeks Titrations based on whether the patient was a responder or nonresponder to previous adjustment • For responders: >180 mg/dL, +10 units; 163–180 mg/dL, +6 units; 145–162 mg/dL, +4 units; or 109–144 mg/dL, +2 units • For nonresponders: >180 mg/dL, +10 units; 163–180 mg/dL, +8 units; 145–162 mg/dL, +6 units; 127–144 mg/dL, +4 units; or 109–126 mg/dL, +2 units • Reduce dose by 2 units for members of either group if prebreakfast plasma glucose was 50–72 mg/dL or by 4 units if <56 mg/dL
Phase 3 study, Philis-Tsimikas et al., 2006 (27)	Titration once every 4 weeks based on the mean of three preprandial plasma glucose readings measured on 3 consecutive days: ≤108 mg/dL, no change; 109–144 mg/dL, +2 units; 145–162 mg/dL, +4 units; 163–180 mg/dL, +6 units; or ≥180 mg/dL, +8 units Reduce dose by 4 units or 10% if dose was >40 units if ≥1 value was <56 mg/dL without an obvious explanation, and reduce by 2 units or 5% if dose was >40 mg/dL for ≥1 value was 56–72 mg/dL without an obvious explanation
PREDICTIVE 303 trial, Meneghini et al., 2007 (28)	303 Algorithm: self-adjust every 3 days based on an average of three daily self-measured FPG values: >110 mg/dL, +3 units; 80–110 mg/dL, no change; or <80 mg/dL, –3 units Standard-of-care algorithm: doses adjusted by investigator according to the standard of care using an average FPG over the last 6 days before each scheduled visit, with no specified frequency

FPG, fasting plasma glucose; OAD, oral antidiabetic drug.

TABLE 3. Select Clinical Trials on Bolus Insulin Dosing and Titration

Clinical Trial	Design/Primary Objective	Population	Intervention	Results	Comments/Conclusions
Insulin glulisine					
OPAL trial, Lankisch et al., 2008 (30)	Stratified, 1:1 randomization, open-label, parallel-group, (per-protocol treatment group), 24-week Investigate efficacy of the addition of a glulisine injection either before breakfast or before the main meal	*n* = 316 Inclusion criteria: type 2 diabetes, ≥18 years of age, glargine + OADs for ≥3 months, able to perform SMBG	*n* = 162: breakfast injection *n* = 154: main mealtime injection No information regarding specific initiation doses provided for either group	Overall A1C improvement from 7.32 ± 0.70 to 6.99 ± 0.83%* Breakfast group: from 7.35 ± 0.71 to 7.03 ± 0.79%* Main-meal group: from 7.29 ± 0.69 to 6.94 ± 0.87%* *These results were statistically significant (P <0.0001) vs. baseline Primary efficacy analysis: breakfast treatment arm differed from main-meal arm absolute A1C by 0.0481 percentage points (P >0.0001 for equivalence)	Addition of a single daily injection of glulisine improved A1C and postprandial plasma glucose. Equivalence was shown regardless of administration meal without significant difference in hypoglycemic events.
Owens et al., 2011 (31)	Parallel-group, RCT, open-label, 3-month run-in and 3-month randomized treatment period (run-in: transferred to glargine and titrated) Investigate the efficacy of initiating and titrating a single dose of glulisine to baseline insulin glargine + OADs	*n* = 106 Inclusion criteria: type 2 diabetes 18–75 years of age, BMI 25–45 kg/m^2, A1C 7.5–9.5%, basal insulin + metformin for >3 months	*n* = 57: basal-only group *n* = 49: basal-bolus group Initial glulisine doses: postprandial glucose level after the main meal in mmol/L divided by 2 (Russia and United Kingdom); 6 units before the main meal with a 6-unit reduction in glargine dose (United States)	A1C reduction 3 months after randomization was significantly greater in basal-bolus group (–0.37 vs. –0.11%, P = 0.0290) Primary end point (A1C <7%) reached more frequently in basal-bolus group (mITT 22.4 vs. 8.8%, per-protocol population 24.4 vs. 7.8%, P <0.05 and P = 0.0254, respectively)	Addition of a single glulisine dose before the meal with largest postprandial glucose excursion significantly improved A1C. Improvement in A1C, mean daily glucose levels, diurnal glucose profile, and variability in mean daily glucose was seen with basal-bolus in comparison to basal-only regimen. Significant increases in hypoglycemia frequency or weight gain were not observed.

TABLE CONTINUED ON P. 7 →

TABLE 3. Select Clinical Trials on Bolus Insulin Dosing and Titration, *continued from p. 7*

Clinical Trial	Design/Primary Objective	Population	Intervention	Results	Comments/Conclusions
GINGER trial, Fritsche et al., 2010 (32)	Open-label, active-controlled, parallel-group using 1:1 randomization, 52-week Compare once-daily glargine plus mealtime glulisine with a twice-daily premixed insulin regimen in patients currently on premixed therapy	*n* = 287 (per-protocol population) Inclusion criteria: type 2 diabetes for ≥5 years, 18–75 years of age, A1C 7.5–11.0%, stable regimen of premixed insulin (NPH/regular, NPH/lispro, or NPH/aspart in a 70/30 or 75/25 ratio) ± metformin for ≥3 months	*n* = 141: glargine-glulisine Initial doses: • Glargine: ~50% TDD at baseline; minimum recommended dose of 16 units daily • Glulisine: ~50% TDD at baseline divided into three preprandial doses; minimum recommended mealtime dose of 6 units *n* = 146: premixed insulin Initial dose unchanged from baseline	Primary end point (change A1C from baseline) 1.31 vs. –0.80 percentage points in favor of basal-bolus; statistically significant Basal-bolus regimen maintained superiority, providing significantly better adjusted mean reductions in A1C than either premixed regimen 46.6% of basal-bolus patients achieved A1C ≤7% compared to 27.9% of premixed insulin patients	Combination of once-daily glargine plus mealtime glulisine was superior to twice-daily premixed prandial insulin over 12 months. More patients in the basal-bolus group reached the goal A1C.
Riddle et al., 2014 (33)	RCT, open-label, 60-week Determine whether basal insulin plus one prandial injection is as effective as premixed insulin; determine whether stepwise progression to basal-plus-prandial insulin at each meal is superior to premixed insulin	*n* = 582 Inclusion criteria: type 2 diabetes, 18–70 years of age, A1C ≥7.5 and ≤10%, on insulin therapy (minimum 2 injections per day) ± metformin for minimum of 3 months	*n* = 194: twice-daily premixed injections (premixed) Initial premixed dose: 5 units 15 minutes before breakfast, and 5 units 15 minutes before dinner *n* = 194: once-daily glargine plus 0–1 glulisine injection (G + 1) Initial doses: Glargine, 10 units daily; glulisine, 6 units daily; recommended reduction in glargine dose by 6 units *n* = 194: glargine plus 0–3 glulisine injections (G + 3) Initial dosing same as G + 1 group	Co-primary outcomes: • Adjusted mean change in A1C: –2.3 percentage points for G + 1 and –2.0 percentage points for premixed group; not statistically significant • Attainment of A1C <7.0%: 44.1% of participants (G + 3) compared to 38.1% (premixed)* *Statistically significant only when data from sites nonadherent to the protocol were included	Combination of once-daily glargine plus mealtime glulisine was superior to twice-daily premixed prandial insulin over 12 months. More patients in the basal-bolus group reached the goal A1C.
Insulin aspart					

Step-Wise (SimpleSTEP and ExtraSTEP) trial, Meneghini et al., 2011 (36)	RCT, parallel-group, open-label, 48-week Investigate whether the SimpleSTEP strategy is equivalent to the ExtraSTEP strategy (in terms of glycemic control and tolerability)	*n* = 296 Inclusion criteria: ≥18 years of age, type 2 diabetes for ≥6 months, A1C 7.5–10%, on basal insulin (NPH, glargine, or detemir) + 1–3 OADs	*n* = 150: SimpleSTEP Initial dosing: Detemir run-in phase; basal insulin switched to once-daily bedtime detemir unit-for-unit (exception: 20% dose reduction when converting from twice-daily NPH); minimum initial detemir dose, 10 units; aspart, 4 units per meal *n* = 146: ExtraSTEP Initial dosing same as for SimpleSTEP	Primary end point (reduction in A1C after 36 weeks): • SimpleSTEP: 1.2 percentage point decrease (7.5 ± 1.1%) • ExtraSTEP: 1.2 percentage point decrease (7.7 ± 1.2%) Estimated treatment difference: 0.06% (not statistically significant)	Sequential addition of insulin aspart improved glycemic control when intensification is needed. The SimpleSTEP method was as effective as ExtraSTEP.
FullSTEP trial, Rodbard et al., 2014 (37)	RCT, parallel-group, open-label, 32-week with 2-week screening period followed by 8-week run-in to convert and adjust detemir (dosed once daily at bedtime) Investigate the sequential, incremental addition of up to three prandial insulin injections compared to full basal-bolus insulin therapy	*n* = 401 Inclusion criteria: ≥18 years of age, type 2 diabetes for ≥12 months, A1C 7–9%, on basal insulin (NPH, glargine, or detemir) for ≥6 months before study start	*n* = 201: Stepwise 4 units aspart before largest meal; addition of bolus doses before next largest meal at weeks 11 and 22 if A1C ≥7% *n* = 200: basal-bolus 2 units aspart daily before breakfast, lunch, and dinner	Change in A1C from baseline: 0.98 percentage points (95% CI 1.09 to –0.87) for stepwise group compared to –1.12% (95% CI 1.23–1.00%) for basal-bolus group Significantly more patients in basal-bolus group reached target A1C at end of first treatment period; difference was not significant at study completion	The stepwise regimen was noninferior to full basal-bolus therapy. Hypoglycemia incidence was lower in the stepwise group. Patient satisfaction regarding treatment was higher in the stepwise group.

TABLE CONTINUED ON P. 9 →

TABLE 3. Select Clinical Trials on Bolus Insulin Dosing and Titration, *continued from p. 7*

Clinical Trial	Design/Primary Objective	Population	Intervention	Results	Comments/Conclusions
Insulin lispro					
Jain et al., 2010 (38)	RCT, open-label, active-controlled, 36-week Evaluate two approaches to starting and intensifying insulin therapy: premixed insulin progression compared to a basal-bolus regimen	*n* = 484 (randomized) Inclusion criteria: 30–80 years of age, type 2 diabetes, A1C 7.5–12.0%, on ≥2 oral diabetes medications for ≥90 days and insulin naive	*n* = 211: premixed Lispro mix 50/50: 10 units before the evening meal* *n* = 215: basal/bolus (glargine + lispro); glargine 10 units at the same time each morning* *Initial dosing 12 units if FBG ≥180 mg/dL	Change in A1C from baseline to end point: –1.76 ± 0.37 percentage points (premixed) and –1.93 ± 0.36 percentage points (glulisine + lispro); between-group difference not statistically significant (0.17%, *P* = 0.097)* *Noninferiority was not achieved based on 95% CI –0.03 to 0.37; upper limit of CI set at >0.3% Hypoglycemia difference between groups not statistically significant	Both premixed and glulisine + lispro regimens were effective in lowering A1C, although noninferiority was not demonstrated. The article includes discussion regarding barriers to increasing the number of injections vs. clinical inertia despite patients not reaching the A1C goal.
Rosenstock et al., 2008 (39)	RCT, open-label, active-controlled, 24-week, initial randomization: conservative vs. aggressive dosing algorithm, based on plasma glucose levels and total daily insulin requirement (<100 units or >100 units); initial dose based on entry glargine dose Compare two analog insulin therapies: prandial premixed therapy vs. basal-bolus therapy in patients currently treated with basal insulin	*n* = 374 (randomized) Inclusion criteria: 30–75 years, type 2 diabetes, A1C 7.5–12.0%, on insulin glargine (≥30 units/day) for ≥90 days, in combination with 1–3 OADs	*n* = 158: premixed lispro 50/50 mix three times daily with meals; investigators were allowed to switch evening dose to lispro 75/25 mix if FPG remained >110 mg/dL during the study *n* = 158: basal/bolus 50% glargine and 50% divided into three equal doses of lispro with meals	Mean reduction in A1C: –1.87 percentage points (prandial premixed therapy) and –2.9% (basal-bolus therapy); between-group difference not statistically significant (0.22% [95% CI –0.38 to –0.07])* *Noninferiority was not achieved based on upper limit of CI set at >0.3% Hypoglycemia difference between groups not statistically significant	Both prandial premixed therapy and basal-bolus therapy regimens were effective in lowering A1C, although noninferiority was not demonstrated. More patients in the basal-bolus group reached the A1C target; this may be attributable to investigator familiarity with basal-bolus therapy over prandial premixed therapy. Rates of hypoglycemia were low overall.

mITT, modified intention-to-treat; OAD, oral antidiabetic drug; RCT, randomized, controlled trial; TDD, total daily dose.

TABLE 4. Select Clinical Trials Detailing Bolus Insulin Titration Methods

Clinical Trial	Titration Algorithm
Insulin glulisine	
OPAL trial, Lankisch et al., 2008 (30)	Titration based on investigator discretion and prespecified prandial and FPG goals Glargine dose adjustments according to target FBG ≤100 mg/dL Glulisine dose adjustments according to goal of 2-hour postprandial glucose ≤135 mg/dL and FBG ≤100 mg/dL Details regarding magnitude of specific dose adjustments not provided
Owens et al., 2011 (31)	Glargine titrated per Treat-to-Target algorithm to achieve FBG ≤100 mg/dL (during run-in period) United Kingdom and Russia: weekly glulisine adjustment based on 2-hour postprandial glucose with target ≤135 mg/dL: ≤135 mg/dL, no change; 135–153 mg/dL, +1 unit; 153–180 mg/dL +2 units; or >180 mg/dL, +3 units United States: postprandial (immediately before the next meal) plasma glucose target 100–120 mg/dL or at bedtime if the main meal was dinner: 120–140 mg/dL, +1 unit; or 140–180 mg/dL, +2 units
GINGER trial, Fritsche et al., 2010 (32)	Titration targets were the same for both regimens: FBG ≤100 mg/dL and postprandial glucose ≤135 mg/dL Premixed insulin: mean of prebreakfast plasma glucose values over 2 consecutive days was used to calculate the increase in predinner dose; mean of predinner plasma glucose values over 2 consecutive days was used to calculate the increase in the prebreakfast dose. Adjustment of premixed insulin was based on the highest value of preprandial plasma glucose over 2 consecutive days: >100–120 mg/dL, +2 units; >120–140 mg/dL, +4 units; 140–160 mg/dL, +6 units; or >160 mg/dL, +8 units Glargine: adjustment was based on the highest value of FBG over 2 consecutive days: >100–120 mg/dL, +2 units; >120–140 mg/dL, +4 units; >140–160 mg/dL, +6 units; or >160 mg/dL, +8 units Glulisine: adjustment based on the highest value of postprandial plasma glucose over 2 consecutive days: >135–160 mg/dL +1 unit; >160–200 mg/dL, +2 units; or >200 mg/dL, +3 units
Riddle et al., 2013 (33)	Glargine: weekly adjustment based on median fasting 3-day SMBG: >180 mg/dL, +8 units; 140–180 mg/dL, +6 units; 120–139 mg/dL, +4 units; 110–119 mg/dL, +2 units; 101–109 mg/dL, +2 units or no change; 70–100 mg/dL, no change; or <70 mg/dL, decrease dose by 10% Premixed insulin: morning dose adjustment was based on median of prelunch or predinner SMBG. Evening dose adjustment was based on the median of before-bedtime or fasting SMBG: >180 mg/dL, +4 units; 140–180 mg/dL, +3 units; 120–139 mg/dL, +2 units; 110–119 mg/dL, +1 unit; 101–109 mg/dL, +1 unit or no change; 70–100 mg/dL, no change; or <70 mg/dL, decrease dose by 10% Glulisine: weekly adjustment based on median of three SMBG values before bedtime or premeal: >180 mg/dL, +4 units; 140–180 mg/dL, +3 units; 120–139 mg/dL, +2 units; 101–119 mg/dL, +1 unit; 70–100 mg/dL, no change; or <70 mg/dL, decrease insulin glargine dose by 10%

TABLE CONTINUED ON P. 12 →

TABLE 4. Select Clinical Trials Detailing Bolus Insulin Titration Methods, *continued from p. 10*

Insulin aspart	
Step-Wise (SimpleSTEP and ExtraSTEP) Trial, Meneghini et al., 2011 (36)	Treatment intensification with addition of aspart injection (≤3 boluses/day) every 12 weeks if A1C remained >7% SimpleSTEP: titration based on premeal plasma glucose; addition of aspart to largest meal ExtraSTEP: titration based on postmeal values; addition of aspart to meal with largest prandial plasma glucose increment Detemir: titration based on average of three FPG (prebreakfast) measurements: <56 mg/dL, –4 units; 56–71 mg/dL, –2 units; 72–108 mg/dL, no change; 109–144 mg/dL, +2 units; 145–162 mg/dL, +4 units; or >162 mg/dL, +6 units Aspart (SimpleSTEP): titration based on four daily plasma glucose measurements: <72 mg/dL premeal or at bedtime, –2 units; 72–108 mg/dL premeal or 72–144 mg/dL at bedtime, no change; 109–162 mg/dL premeal or 145–180 mg/dL at bedtime, +2 units; or >162 mg/dL premeal or >180 mg/dL at bedtime, +4 units Aspart (ExtraSTEP): titration based on six daily plasma glucose measurements: <72 mg/dL, –2 units; 72–144 mg/dL, no change; 145–180 mg/dL, +2 units; or >180 mg/dL, +4 units
FullSTEP trial, Rodbard et al., 2014 (37)	Detemir: titration based on average of three consecutive FPG (prebreakfast) measurements: ≤70 mg/dL, –3 units; 71–130 mg/dL, no change; or >130 mg/dL, +3 units Aspart: each dose was titrated independently based on premeal and/or bedtime SMBG after the bolus injection(s): ≤70 mg/dL, –1 unit; 71–130 mg/dL, no change; or >130 mg/dL, +1 unit
Insulin lispro	
Jain et al., 2010 (38)	Premix: increase to twice or three times daily; if on premix three times daily for ≥6 weeks and FPG >100 mg/dL, dinnertime 50/50 switched to lispro mix 75/25 Glargine plus lispro progression: glargine supplemented with 1–3 prandial lispro injections Glargine: titration based on average of at least two readings: <80 mg/dL, –2 units; 81–100 mg/dL, no change; 101–120 mg/dL, +2 units; 121–140 mg/dL, +4 units; 141–160 mg/dL, +6 units, or ≥161 mg/dL, +8 units Lispro mix 50/50 or insulin lispro: adjusted at least weekly for the first 10 weeks, then at least once every 2 weeks for the next 8 weeks, then every 3 weeks: <80 mg/dL at bedtime or fasting/preprandial, –2 units (starting the next day); 81–110 mg/dL at bedtime or 81–100 mg/dL preprandial, no change; 111–139 mg/dL at bedtime or 101–139 mg/dL preprandial, +2 units; 140–179 mg/dL at bedtime or 140–179 mg/dL preprandial, +4 units or ≥180 mg/dL at bedtime or fasting/preprandial, +6 units
Rosenstock et al., 2008 (39)	Conservative vs. aggressive dosing algorithm based on plasma glucose levels and TDD (<100 or ≥100 units); initial dose based on entry glargine dose Basal: stratified into TDD <100 or ≥100 units; based on preprandial plasma glucose: 110–150 mg/dL, +2 units (conservative) or +4 units (aggressive); 151–200 mg/dL, +4 units (conservative) or +8 units (aggressive); 201–250 mg/dL, +6 units (conservative) or +12 units (aggressive); 251–300 mg/dL, +8 units (conservative) or +16 units (aggressive), or >300 mg/dL, +10 units (conservative) or +20 units (aggressive) Bolus: based on preprandial plasma glucose: 110–200 mg/dL, +2 units; 201–300 mg/dL, +3 units; or >300 mg/dL, +4 units

FPG, fasting plasma glucose, SMBG, self-monitoring of blood glucose, TDD, total daily dose.