

# TYPE 2 DIABETES ADULT OUTPATIENT INSULIN GUIDELINES

## GENERAL RECOMMENDATIONS

- Start insulin if A1C and glucose levels are above goal despite optimal use of other diabetes medications. (Consider insulin as initial therapy if A1C very high, such as > 10.0%)<sup>6,7,8</sup>
  - Start with **BASAL INSULIN** for most patients<sup>6,7,8</sup>
  - Consider the following goals<sup>1,6</sup>
    - ADA A1C Goals:
      - A1C < 7.0 for most patients
      - A1C > 7.0 (consider 7.0-7.9) for higher risk patients
        1. History of severe hypoglycemia
        2. Multiple co-morbid conditions
        3. Long standing diabetes
        4. Limited life expectancy
        5. Advanced complications or
        6. Difficult to control despite use of insulin
    - ADA Glucose Goals\*:
      - Fasting and premeal glucose < 130
      - Peak post-meal glucose (1-2 hours after meal) < 180
      - Difference between premeal and post-meal glucose < 50
- \*for higher risk patients individualize glucose goals in order to avoid hypoglycemia*

## BASAL INSULIN

### Intermediate-acting:

**NPH** Note: NPH insulin has elevated risk of hypoglycemia so use with extra caution<sup>6,8,15,17,25,32</sup>

### Long-acting:

**Glargine (Lantus®)**  
**Detemir (Levemir®)**

- Basal insulin is best starting insulin choice for most patients (if fasting glucose above goal).<sup>6,7,8</sup>
- Start one of the intermediate-acting or long-acting insulins listed above.<sup>6,7</sup> Start insulin at night.<sup>8</sup>
- When starting basal insulin: Continue secretagogues. Continue metformin.<sup>7,8,20,29</sup>
- Note: if NPH causes nocturnal hypoglycemia, consider switching NPH to long-acting insulin.<sup>17,25,32</sup>

## STARTING DOSE:

Start dose: **10 units**<sup>6,7,8,11,12,13,14,16,19,20,21,22,25</sup>

Consider using a lower starting dose (such as 0.1 units/kg/day<sup>32</sup>) especially if patient is thin or has a fasting glucose only minimally above goal.<sup>17,19</sup>

## TITRATE:

Teach patient to self titrate ↑ by 2 units every 2-3 days until average fasting glucose < 130<sup>\*6,7,8,13,14,30,32</sup>  
(\*Inform patient to hold titration until further evaluation if develops any hypoglycemia)

or

Titrate 1-2 times per week such as per table below until average fasting glucose < 130<sup>6,19</sup>

Fasting glucose > 200	↑ 4 units
Fasting glucose 131-200	↑ 2 units
Fasting glucose 70-130	No change in dose
Fasting glucose < 70	↓ 2-4 units or by 10%

Once fasting glucose at goal, evaluate post-meal glucose pattern<sup>6,7,8</sup>

If post-meal glucose levels > 180: **ADD PRANDIAL INSULIN**<sup>6,7,8</sup>

Note: If patient unable to do multiple daily injections, consider switching to **MIXED INSULIN** instead of adding prandial insulin. (Mixed insulin is more likely to cause hypoglycemia<sup>8,19</sup> and generally requires a fixed meal schedule<sup>8</sup>)



# TYPE 2 DIABETES ADULT OUTPATIENT INSULIN GUIDELINES

## PRANDIAL INSULIN

**Short Acting: Regular** Note: Regular insulin has longer peak and extra risk of hypoglycemia so use with caution<sup>6,8,33</sup>  
**Rapid Acting: Lispro (Humalog®)**  
**Aspart (Novolog®)**  
**Glulisine (Apidra®)**

- Add prandial insulin to basal insulin if post-meal blood glucose levels are above goal.<sup>6,7,8</sup>
- Start one of the prandial insulins listed above.<sup>6,7</sup>
- When adding prandial insulin: Stop secretagogues. Continue metformin. Continue basal insulin (may need to re-adjust dose).<sup>6,7,8</sup>
- Rapid acting insulins should be just before meal. Short acting insulin needs to be taken 30 minute before meals.<sup>5,7</sup>
- Note: after maximizing prandial and night-time basal insulin dose, may need to consider adding a morning dose of basal insulin if pre-dinner glucose remains above goal (more likely to be necessary if using NPH)<sup>18,19,26,28,30</sup>

### STARTING DOSE: 4 units qAC<sup>6,35,36,37</sup>

- May consider start with largest meal only<sup>6,7</sup>
- Instruct patients to eat carb consistent meals when first starting prandial insulin

**Alternative dose:**  
7-10% of basal insulin dose qAC<sup>7,8,36</sup>

**Alternate choice<sup>7,34</sup> if meals vary in size and patient is accurate at counting carbs**

### ALTERNATE STARTING CHOICE: 1 unit to 15 grams carbs qAC<sup>34</sup>

Note: may consider calculate insulin to carb (I:C) ratio = 500 / total daily dose (TDD) of insulin (**500 rule**)<sup>7</sup>

**Consider adding pre-meal Correction Factor (CF)<sup>7</sup>:**  
Add 1 unit for each 50 that pre-meal glucose is > 130

**Alternative method to determine pre-meal correction factor:**  
Correction factor (CF) = 1800 / total daily dose of insulin (**1800 rule**)

**Consider adding pre-meal Correction Factor (CF)<sup>7</sup>:**  
Add 1 unit for each 50 that pre-meal glucose is > 130

**Alternative method to determine pre-meal correction factor:**  
Correction factor (CF) = 1800 / total daily dose of insulin (**1800 rule**)

### TITRATE

Adjust insulin to carb ratio as appropriate per below until post-meal glucose < 180<sup>7,34</sup>

	1 unit to 15 gm	
	1 unit to 12 gm	
	1 unit to 10 gm	
	1 unit to 7 gm	
	1 unit to 5 gm	
If post-meal pattern low Back up the scale	1 unit to 4 gm	If post-meal pattern high Move down the scale
	1 unit to 3 gm	

**Alternate adjustment:**  
Adjust insulin to carb ratio per 500 rule<sup>7</sup>

### TITRATE:

Titrate 1-2 units every 2-3 days until post-meal glucose < 180<sup>6,8,34,35</sup>  
(May consider different doses for different meals)

## MIXED INSULIN

**70/30 NPH/Regular** Note: 70/30 NPH/Regular insulin has elevated risk of hypoglycemia so use with extra caution<sup>6,8</sup>  
**75/25 Lispro Mix (Humalog® Mix) or 50/50 Lispro Mix (Humalog® Mix)**  
**70/30 Aspart Mix (Novolog® Mix)**

- Mixed insulin is an option for patients who are unable to do multiple injections and who have fixed meal schedules.<sup>8</sup>
- Mixed insulin is more likely to cause hypoglycemia compared to basal and prandial insulins.<sup>8,19</sup>
- Start one of the mixed insulins listed above.
- When adding mixed insulin: Stop secretagogues. Continue metformin. Stop all other insulins.<sup>7,8</sup>

### STARTING DOSE:

**PRE-DINNER dose 6-10 units<sup>40,43,45,50</sup>**  
(may adjust depending on previous basal insulin dose<sup>42,51</sup>)

Target glucose for titration is **fasting glucose.**<sup>8,43,45,46,53</sup>  
(may also consider post-dinner glucose when titrating dose)

### STARTING DOSE:

**PRE-BREAKFAST dose: 6-10 units<sup>40,43,45,50</sup>**  
(may adjust depending on previous basal insulin dose<sup>42,51</sup>)

Target glucose for titration is **pre-dinner glucose.**<sup>8,43,45,46,53</sup>  
(may also consider post-breakfast glucose when titrating dose)

### TITRATE:

Titrate 1-2 units every 2-3 days until average target glucose < 130<sup>43,51</sup>

OR

Titrate 1-2 times per week such as per table below until average target glucose < 130<sup>43</sup>

- Target glucose > 200    ↑ by 4 units
- Target glucose 131-200    ↑ by 2 units
- Target glucose 70-130    No change
- Target glucose < 70    ↓ 2-4 units or by 10%

- May require different doses for pre-breakfast and pre-dinner
- May consider adding pre-lunch dose as well if needed<sup>42,53</sup>



# TYPE 2 DIABETES ADULT OUTPATIENT INSULIN GUIDELINES

## ADDITIONAL INFORMATION:

### Alternate self titration for basal insulin<sup>16</sup>:

May consider self titrating basal insulin by increasing dose 1 unit every day until average fasting glucose is < 130, if that is easier for the patient to understand. Self titration of small doses may be easiest for patients using insulin pens.

### Other diabetes medication in combination with insulin<sup>6,7,8,20,24,29</sup>

**Metformin** Continue if able because helps prevent weight gain when patient on insulin

**Secretagogues:** (sulfonylureas and meglitinides): Consider continuing when patient is on basal insulin only. Stop when patient is on prandial or mixed insulin.

**Other Diabetes Medications:** decision to continue or discontinue other diabetes medications should be made with consideration of multiple individual patient characteristics.

**Note:** once patient's glucose levels are controlled with insulin, it may occasionally be possible to stop insulin and continue or switch to oral medications depending of the stage of the diabetes and changes in other individual patient characteristics.<sup>6,7,8</sup>

### Example of correction factor using 1800 Rule<sup>7</sup>

Patient on 60 units basal insulin. Total Daily Dose (TDD) is 60 units. Correction Factor (CF) = 1800 / 60 = 30. If pre-meal glucose = 250, blood glucose is 150 mg/dl above goal of 100; Correction is 150/30 = 5 units. Give 5 units in addition to prandial insulin dose being used to cover meal.

### Example of carbohydrate ratio using 500 Rule<sup>7</sup>

Patient on 50 units basal insulin daily. Total Daily Dose (TDD) is 50 units. Insulin to Carbohydrate Ratio (I:C Ratio): 500/50 = 1:10 units. For a 60 gm carbohydrate meal = 60/10 = take 6 units.

### Example of Insulin with prandial starting dose of 4 units and correction factor of 1:50

Pre-meal Glucose Level	Prandial Insulin Dose
70-150	4 units
150-200	5 units
200-250	6 units
250-300	7 units
300-350	8 units
350-400	9 units
>400	10 units

### Mealtime Advice<sup>2,5</sup>

Take rapid acting prandial and mixed insulins just before a meal. At restaurants only take once food actually arrives at table. Take Regular insulin 30 minutes before meals.

### Hypoglycemia<sup>1,3</sup>

Tell patient to carry rapidly absorbed carbohydrate source at all times and teach friends and family about how to treat low glucose. Treat low glucose (<70) as per **Rule of 15's**: Give 15 gm of rapidly absorbed carbohydrate (ie: 1/2 cup juice or 4 glucose tabs). Recheck glucose level in 15 minutes. Give another 15 gm of carbohydrate if glucose still < 70. Repeat until the glucose level is > 70. Once glucose level returns to normal, consider follow with a snack or meal. Inform provider of hypoglycemia episodes at next appointment. If severe (unconscious, seizures) call 911 and give glucagon (1.0 for adult, 0.5 for child < 50 lbs) if available. Prescribe glucagon kit for high risk patient to have at home.

### Identification

Carry personal ID and wear medical ID.

### Insulin Device

Consider insulin pen if able for patients with vision, dexterity or cognition difficulties or for patient convenience. Note insulin pens cost more than insulin vials. However, total cost of insulin pen is potentially lower than vial if patient's daily insulin dose is low (since less unused insulin needs to be discarded at end of month). Insulin pens may not be covered by insurance.

### Storage<sup>2,5</sup>

Refrigerate insulin until opened. Discard after expiration date. Once opened can be kept at room temperature. Avoid heat. Replace insulin vial or pen as required per specific insulin package insert.

### Syringes and Needles<sup>2,4</sup>

For pen consider use pen needles that are 31 or 32 gauge and 5 mm to 8 mm. For vials consider use syringes that are 0.3-1.0 cc with ultrafine 5/16" 31 gauge needles. Instruct patient to leave needle in skin for 5 or more seconds after injection completed.

### Exercise<sup>9</sup>

Low glucose levels may occur during or after exercise. Carry glucose source when exercising. Check glucose before and during exercise. If patient has low glucose levels associated with exercise: consider decreasing preceding prandial insulin dose (if within several hours before exercise) and/or taking extra carbohydrates before or during exercise.

### Education<sup>1,8</sup>

All patients should receive Diabetes Self Management Training (DSMT) and Medical Nutrition Therapy (MNT) by certified diabetes educator if possible.



# TYPE 2 DIABETES ADULT OUTPATIENT INSULIN GUIDELINES

## LITERATURE SEARCH AND RATING PROCESS

The identification and rating of the body of evidence to support the Type 2 Diabetes Insulin Guidelines followed a three-step process:

1. Pertinent articles for review were identified by a Medline search including the key words: Diabetes Mellitus, Type 2/drug therapy, Hypoglycemic Agents, Insulin, Algorithms, Titrate, Titration, Bolus, and Basal. The search was limited to 2005-2010 and the language English. Older clinical trials evaluating Regular insulin were included, since none were available from 2005-2010. The most recent ADA and AACE consensus statements, position statements and technical reviews on diabetes care topics were also identified. Insulin package insert recommendations were obtained from Lexi-Comp, Online.
2. Experts in diabetes care then examined the list of articles and included only those that were identified as randomized controlled clinical trials examining the initiation and titration of insulin, the most recent general consensus statements, technical reviews, or position statements by ADA and AACE, the most recent insulin review article by the American Academy of Family Practice, and the Lexi-Comp online insulin package insert recommendations.
3. The articles were reviewed and the body of evidence was rated using a system adopted from the ADA grading system for clinical practice recommendations. *American Diabetes Association Standards of medical care in diabetes--2010. Diabetes Care. 2010 Jan;33 Suppl 1:S12.*
  - (A) Clear evidence from well-conducted, generalizable, randomized controlled trials that are adequately powered, including:
    - Evidence from a well-conducted multicenter trial
    - Evidence from a meta-analysis that incorporated quality ratings in the analysis
 Compelling non-experimental evidence, i.e., "all or none" rule developed by Center for Evidence Based Medicine at Oxford  
 Supportive evidence from well-conducted randomized controlled trials that are adequately powered, including:
    - Evidence from a well-conducted trial at one or more institutions
    - Evidence from a meta-analysis that incorporated quality ratings in the analysis
  - (B) Supportive evidence from well-conducted cohort studies:
    - Evidence from a well-conducted prospective cohort study or registry
    - Evidence from a well-conducted meta-analysis of cohort studies
 Supportive evidence from a well-conducted case-control study
  - (C) Supportive evidence from poorly controlled or uncontrolled studies
    - Evidence from randomized clinical trials with one or more major or three or more minor methodological flaws that could invalidate the results
    - Evidence from observational studies with high potential for bias (such as case series with comparison to historical controls)
    - Evidence from case series or case reports
 Conflicting evidence with the weight of evidence supporting the recommendation
  - (E) Expert consensus or clinical experience

## GENERAL INFORMATION: Consensus Statements and Reviews

1. American Diabetes Association Standards of medical care in diabetes--2010. *Diabetes Care. 2010 Jan;33 Suppl 1:S11-61.*
2. American Diabetes Association. Insulin administration. *Diabetes Care. 2004 Jan;27 Suppl 1:S106-9.*
3. Cryer PE, et al. Hypoglycemia in diabetes. *Diabetes Care. 2003 Jun;26(6):1902-12.*
4. Hofman PL, et al. Defining the ideal injection techniques when using 5-mm needles in children and adults. *Diabetes Care. 2010 Sept;33:1940-1944.*
5. Lexi-Comp, Online. Lexi-Comp, Inc. 1100 Terex Road, Hudson, OH 44236. <http://online.lexi.com/crlsql/servlet/crlonline>. August 2010.
6. Nathan DM, et al. American Diabetes Association; European Association for Study of Diabetes. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care. 2009 Jan;32(1):193-203.*
7. Ripsin CM, et al. Management of blood glucose in type 2 diabetes mellitus. *Am Fam Physician. 2009 Jan 1;79(1):29-36*
8. Rodbard HW, et al. Statement by an American Association of Clinical Endocrinologists/American College of Endocrinology consensus panel on type 2 diabetes mellitus: an algorithm for glycemic control. *Endocr Pract. 2009 Sep-Oct;15(6):540-59.*
9. Sigal RJ, et al. Physical activity/exercise and type 2 diabetes. *Diabetes Care. 2004 Oct;27(10):2518-39.*

## BASAL INSULIN (A-level evidence)

10. Bergenstal RM, et al. Adjust to target in type 2 diabetes: comparison of a simple algorithm with carbohydrate counting for adjustment of mealtime insulin glulisine. *Diabetes Care. 2008 Jul;31(7):1305-10.*
11. Bretzel RG, et al. Once-daily basal insulin glargine versus thrice-daily prandial insulin lispro in people with type 2 diabetes on oral hypoglycaemic agents (APOLLO): an open randomised controlled trial. *Lancet. 2008 Mar 29;371(9618):1073-84.*
12. Buse JB, et al. DURABILITY of basal versus lispro mix 75/25 insulin efficacy (DURABLE) trial 24-week results: safety and efficacy of insulin lispro mix 75/25 versus insulin glargine added to oral antihyperglycemic drugs in patients with type 2 diabetes. *Diabetes Care. 2009 Jun;32(6):1007-13.*
13. Davies M, et al. ATLANTUS Study Group. Improvement of glycemic control in subjects with poorly controlled type 2 diabetes: comparison of two treatment algorithms using insulin glargine. *Diabetes Care. 2005 Jun;28(6):1282-8.*
14. Davies M, et al. ATLANTUS Study Group. Initiation of insulin glargine therapy in type 2 diabetes subjects suboptimally controlled on oral antidiabetic agents: results from the ATLANTUS trial. *Diabetes Obes Metab. 2008 May;10(5):387-99.*
15. Fajardo Montañana C, et al. Less weight gain and hypoglycaemia with once-daily insulin detemir than NPH insulin in intensification of insulin therapy in overweight Type 2 diabetes patients: the PREDICTIVE BMI clinical trial. *Diabet Med. 2008 Aug;25(8):916-23.*
16. Harris S, et al. Can family physicians help patients initiate basal insulin therapy successfully?: randomized trial of patient-titrated insulin glargine compared with standard oral therapy: lessons for family practice from the Canadian INSIGHT trial. *Can Fam Physician. 2008 Apr;54(4):550-8.*
17. Hermansen K, et al. Home P. A 26-week, randomized, parallel, treat-to-target trial comparing insulin detemir with NPH insulin as add-on therapy to oral glucose-lowering drugs in insulin-naive people with type 2 diabetes. *Diabetes Care. 2006 Jun;29(6):1269-74. Erratum in: Diabetes Care. 2007 Apr;30(4):1035.*
18. Hollander P, et al. A 52-week, multinational, open-label, parallel-group, noninferiority, treat-to-target trial comparing insulin detemir with insulin glargine in a basal-bolus regimen with mealtime insulin aspart in patients with type 2 diabetes. *Clin Ther. 2008 Nov;30(11):1976-87.*
19. Holman RR, et al. 4-T Study Group. Three-year efficacy of complex insulin regimens in type 2 diabetes. *N Engl J Med. 2009 Oct 29;361(18):1736-47.*
20. Janka HU, et al. Comparison of basal insulin added to oral agents versus twice-daily premixed insulin as initial insulin therapy for type 2 diabetes. *Diabetes Care. 2005 Feb;28(2):254-9.*
21. Kennedy L, et al. GOAL A1C Team. Impact of active versus usual algorithmic titration of basal insulin and point-of-care versus laboratory measurement of HbA1c on glycemic control in patients with type 2 diabetes: the Glycemic Optimization with Algorithms and Labs at Point of Care (GOAL A1C) trial. *Diabetes Care. 2006 Jan;29(1):1-8.*
22. Liebl A, et al. PREFER Study Group. Comparison of insulin analogue regimens in people with type 2 diabetes mellitus in the PREFER Study: a randomized controlled trial. *Diabetes Obes Metab. 2009 Jan;11(1):45-52.*



# TYPE 2 DIABETES ADULT OUTPATIENT INSULIN GUIDELINES

## **BASAL INSULIN (A-level evidence), continued**

23. Masuda H, et al. Comparison of twice-daily injections of biphasic insulin lispro and basal-bolus therapy: glycaemic control and quality-of-life of insulin-naïve type 2 diabetic patients. *Diabetes Obes Metab.* 2008 Dec;10(12):1261-5.
24. Meneghini L, et al. The usage of a simplified self-titration dosing guideline (303 Algorithm) for insulin detemir in patients with type 2 diabetes--results of the randomized, controlled PREDICTIVE 303 study. *Diabetes Obes Metab.* 2007 Nov;9(6):902-13.
25. Philis-Tsimikas A, et al. Comparison of once-daily insulin detemir with NPH insulin added to a regimen of oral antidiabetic drugs in poorly controlled type 2 diabetes. *Clin Ther.* 2006 Oct;28(10):1569-81.
26. Raskin P, et al. Comparison of insulin detemir and insulin glargine using a basal-bolus regimen in a randomized, controlled clinical study in patients with type 2 diabetes. *Diabetes Metab Res Rev.* 2009 Sep;25(6):542-8.
27. Robbins DC et al. Mealtime 50/50 basal + prandial insulin analogue mixture with a basal insulin analogue, both plus metformin, in the achievement of target HbA1c and pre- and postprandial blood glucose levels in patients with type 2 diabetes: a multinational, 24-week, randomized, open-label, parallel-group comparison. *Clin Ther.* 2007 Nov;29(11):2349-64.
28. Rosenstock J, et al. A randomised, 52-week, treat-to-target trial comparing insulin detemir with insulin glargine when administered as add-on to glucose-lowering drugs in insulin-naïve people with type 2 diabetes. *Diabetologia.* 2008 Mar;51(3):408-16.
29. Schiel R, et al. Efficacy and treatment satisfaction of once-daily insulin glargine plus one or two oral antidiabetic agents versus continuing premixed human insulin in patients with Type 2 diabetes previously on long-term conventional insulin therapy: the SWITCH Pilot Study. *Exp Clin Endocrinol Diabetes.* 2008 Jan;116(1):58-64.
30. Swinnen SG, et al. Rationale, design, and baseline data of the insulin glargine (Lantus) versus insulin detemir (Levemir) Treat-To-Target (L2T3) study: A multinational, randomized noninferiority trial of basal insulin initiation in type 2 diabetes. *Diabetes Technol Ther.* 2009 Nov;11(11):739-43.
31. Swinnen, SG A 24-week randomized , treat-to-target trial comparing initiation of insulin glargine once-daily with insulin detemir twice daily in patients with type 2 diabetes inadequately controlled on oral glucose-lowering drugs. *Diabetes Care* 2010; 33(6): 1176-1178.
32. Wang XL, et al. Evaluation of the superiority of insulin glargine as basal insulin replacement by continuous glucose monitoring system. *Diabetes Res Clin Pract.* 2007 Apr;76(1):30-6.

## **PRANDIAL INSULIN (A-level evidence)**

33. Anderson J H; Brunelle R L; Koivisto V A; Pfoetzner A; Trautmann M E; Vignati L; DiMarchi R Reduction of postprandial hyperglycemia and frequency of hypoglycemia in IDDM patients on insulin-analog treatment. Multicenter Insulin Lispro Study Group. *Diabetes* Feb 1997 46 (2) p265-70.
34. Bergenstal RM, et al. Adjust to target in type 2 diabetes: comparison of a simple algorithm with carbohydrate counting for adjustment of mealtime insulin glulisine. *Diabetes Care.* 2008 Jul;31(7):1305-10.
35. Bretzel RG, et al. Once-daily basal insulin glargine versus thrice-daily prandial insulin lispro in people with type 2 diabetes on oral hypoglycaemic agents (APOLLO): an open randomised controlled trial. *Lancet.* 2008 Mar 29;371(9618):1073-84.
36. Holman RR, et al. 4-T Study Group. Three-year efficacy of complex insulin regimens in type 2 diabetes. *N Engl J Med.* 2009 Oct 29;361(18):1736-47.
37. Lankisch MR, et al. Orals Plus Apidra and LANTUS (OPAL) study group. Introducing a simplified approach to insulin therapy in type 2 diabetes: a comparison of two single-dose regimens of insulin glulisine plus insulin glargine and oral antidiabetic drugs. *Diabetes Obes Metab.* 2008 Dec;10(12):1178-85.
38. Liebl A, et al. PREFER Study Group. Comparison of insulin analogue regimens in people with type 2 diabetes mellitus in the PREFER Study: a randomized controlled trial. *Diabetes Obes Metab* 2009 Jan;11(1):45-52.
39. Masuda H, et al. Comparison of twice-daily injections of biphasic insulin lispro and basal-bolus therapy: glycaemic control and quality-of-life of insulin-naïve type 2 diabetic patients. *Diabetes Obes Metab.* 2008 Dec;10(12):1261-5.

## **MIXED INSULIN (A-level evidence)**

40. Buse JB, et al. DURAbility of basal versus lispro mix 75/25 insulin efficacy (DURABLE) trial 24-week results: safety and efficacy of insulin lispro mix 75/25 versus insulin glargine added to oral antihyperglycemic drugs in patients with type 2 diabetes. *Diabetes Care.* 2009 Jun;32(6):1007-13.
41. Clements MR, et al. Improved glycaemic control of thrice-daily biphasic insulin aspart compared with twice-daily biphasic human insulin; a randomized, open-label trial in patients with type 1 or type 2 diabetes. *Diabetes Obes Metab.* 2008 Mar;10(3):229-37.
42. Garber AJ, et al. Attainment of glycaemic goals in type 2 diabetes with once-, twice-, or thrice-daily dosing with biphasic insulin aspart 70/30 (The 1-2-3 study). *Diabetes Obes Metab.* 2006 Jan;8(1):58-66.
43. Holman RR, et al. 4-T Study Group. Three-year efficacy of complex insulin regimens in type 2 diabetes. *N Engl J Med.* 2009 Oct 29;361(18):1736-47.
44. Jacober SJ, et al. A comparison of intensive mixture therapy with basal insulin therapy in insulin-naïve patients with type 2 diabetes receiving oral antidiabetes agents. *Diabetes Obes Metab.* 2006 Jul;8(4):448-55.
45. Janka HU, et al. Comparison of basal insulin added to oral agents versus twice-daily premixed insulin as initial insulin therapy for type 2 diabetes. *Diabetes Care.* 2005 Feb;28(2):254-9.
46. Liebl A, et al. PREFER Study Group. Comparison of insulin analogue regimens in people with type 2 diabetes mellitus in the PREFER Study: a randomized controlled trial. *Diabetes Obes Metab* 2009 Jan;11(1):45-52.
47. Malone JK, et al. Twice-daily pre-mixed insulin rather than basal insulin therapy alone results in better overall glycaemic control in patients with Type 2 diabetes. *Diabet Med.* 2005 Apr;22(4):374-81
48. Masuda H, et al. Comparison of twice-daily injections of biphasic insulin lispro and basal-bolus therapy: glycaemic control and quality-of-life of insulin-naïve type 2 diabetic patients. *Diabetes Obes Metab.* 2008 Dec; 10(12):1261-5.
49. Miyashita Y, et al. Prospective randomized study for optimal insulin therapy in type 2 diabetic patients with secondary failure. *Cardiovasc Diabetol.* 2008 May 29;7:16.
50. Oyer DS, et al. INITIATEplus Study Group. A(1c) control in a primary care setting: self-titrating an insulin analog pre-mix (INITIATEplus trial). *Am J Med.* 2009 Nov;122(11):1043-9.
51. Robbins DC, et al. Mealtime 50/50 basal + prandial insulin analogue mixture with a basal insulin analogue, both plus metformin, in the achievement of target HbA1c and pre- and postprandial blood glucose levels in patients with type 2 diabetes: a multinational, 24-week, randomized, open-label, parallel-group comparison. *Clin Ther.* 2007 Nov;29(11):2349-64.
52. Schiel R, et al. Efficacy and treatment satisfaction of once-daily insulin glargine plus one or two oral antidiabetic agents versus continuing premixed human insulin in patients with Type 2 diabetes previously on long-term conventional insulin therapy: the SWITCH Pilot Study. *Exp Clin Endocrinol Diabetes.* 2008 Jan;116(1):58-64.
53. Yang W, et al. Biphasic insulin aspart 30 three times daily is more effective than a twice-daily regimen, without increasing hypoglycemia, in Chinese subjects with type 2 diabetes inadequately controlled on oral antidiabetes drugs. *Diabetes Care.* 2008 May;31(5):852-6.

