Insulin Therapy in Type 2 Diabetes:

When and How Do We Start?
When Do We Add?
How do The Guidelines Guide Us?

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What Are the Rationales for Different Glycemic Targets?

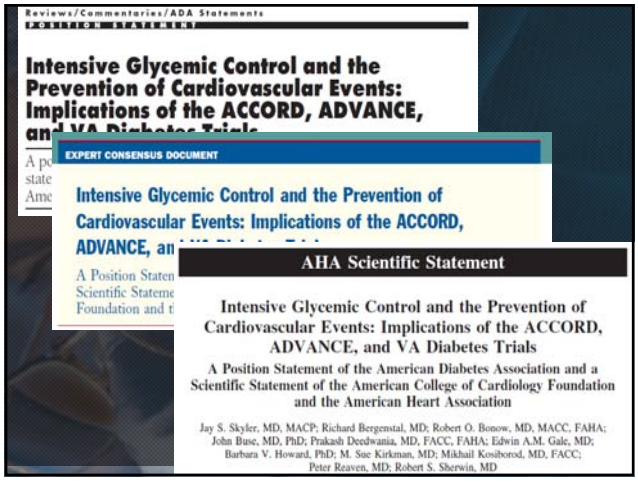
Target	Rationale
A1C ≤ 6.5%[1]	• AACE general glycemic goal • "Threshold" for the development of microvascular complications
A1C < 7%[2]	• ADA general glycemic goal • Epidemiological analysis of DCCT and UKPDS
A1C < 8%[3]	• ADA less-stringent glycemic target for selected patients • Outcomes from ACCORD, ADVANCE, and VADT studies cited in support of less-stringent goal

1. AACE/ACE consensus statement; https://www.aace.com/sites/default/files/GlycemicControlAlgorithm.pdf;
2. ADA/EASD consensus statement. *Diabetes Care*. 2009;32:193-203;
3. American Diabetes Association. *Diabetes Care*. 2012;35(suppl 1):S11-S63.

Dr. Guillermo Umpierrez, Personal/Professional Financial Relationships with Industry

External Industry Relationships *	Company Name(s)	Role
Equity, stock, or options in biomedical industry companies or publishers	None	
Board of Directors or officer	None	
Royalties from from external entity	None	
Industry funds to Emory for my research	Sanofi-Aventis Merck	Investigator-Initiated Research Projects

*Consulting, scientific advisory board, industry-sponsored CME, expert witness for company, FDA representative for company, publishing contract, etc.



Hypoglycemia Frequency, Not Severity, *Before* Enrollment in ACCORD, Increased Risk of Mortality

Crude, Annualized Mortality Rates and Hazard Ratios Within Treatment Groups

	Mortality rate (n = 451 deaths)		Hazard ratio for no previous events vs at least 1 event, stratified by glycemia arm[a] (HR [95% CI])
	No previous events	≥ 1 previous event	
Hypoglycemic events requiring any assistance, medical or nonmedical (% per year)[b]			
Intensive	1.2%	2.8%	Unadj: 1.79 (1.32 to 2.44) Adj: 1.41 (1.03 to 1.93)
Standard	1.0%	3.7%	Unadj: 2.93 (1.86 to 4.63) Adj: 2.30 (1.46 to 3.65)
Hypoglycemic events requiring medical assistance (% per year)[c]			
Intensive	1.3%	2.8%	Unadj: 1.72 (1.19 to 2.47) Adj: 1.28 (0.88 to 1.85)
Standard	1.0%	4.9%	Unadj: 3.88 (2.35 to 6.40) Adj: 2.87 (1.73 to 4.76)

[a] Hazard ratios are adjusted for the following: age, gender, smoking status, history of CVD, history of HF, peripheral neuropathy, albumin to creatinine ratio, HR, QT score, visual acuity score, statin use, sulfonylurea use, glycemia intervention, enrolled in lipid vs BP trial, intensive BP control group, and fibrate group.
[b] *P* = .076 for interaction between history of hyperglycemia requiring any assistance and glycemic intervention.
[c] *P* = .009 for interaction between history of hyperglycemia requiring medical assistance and glycemic intervention.

Bonds DE. et al. *BMJ*. 2010;340:b4909.

Evidence-Based[a] Recommendations for Individualization of Glycemic Targets in T2DM

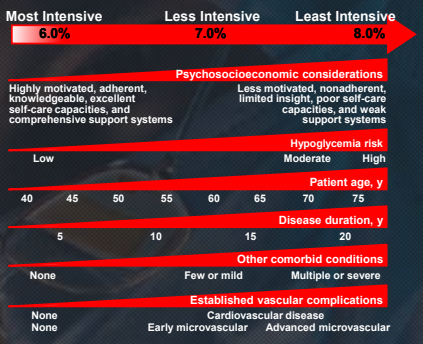
Approximate A1C Targets Determined by Clinical Characteristics (In the Absence of Severe Hypoglycemia)[b]

Age	Duration of Disease	Complications			Treatment Intensity (A1C Target)[c]
		Macrovascular		Microvascular	
< 45 y	Any	None	and	None or early	Most intensive (≤ 6.5%)
	Any	Established	and/or	Advanced	Less intensive (≈ 7.0%)
45-65 y	Short[d]	None	and	None or early	Intensive (6.5% - 7.0%)
	Long[e]	None	and	None or early	Less intensive (≈ 7.0%)
	Any	Established	and/or	Advanced	Not intensive (7.0% - 8.0%)
> 65 y	Short[d]	None	and	None or early	Less intensive (≈ 7.0%)
	Long[e]	None	and	None or early	Not intensive (7.0% - 8.0%)
	Any	Established	and/or	Advanced	Moderated (≈ 8.0%)[f]
> 75 y or infirm at any age	Any	Any	and/or	Any	Moderated (≈ 8.0%)[f]

[a] Evidence base consists of 4 major RCTs: UKPDS, ACCORD, ADVANCE, and VADT.
[b] Patient characteristics should be considered sequentially from left to right.
[c] Target blood glucose level should be increased following a severe hypoglycemic episode.
[d]

Ismail-Beigi F, et al. *Ann Intern Med*. 2011;154:554-559.

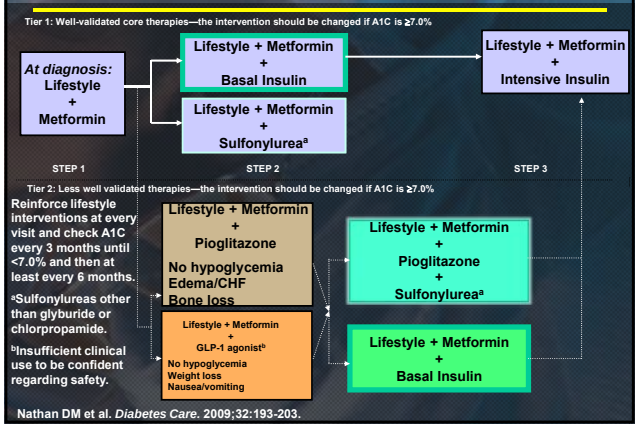
What Glycemic Targets Should We Aim For? Recommendations Based on Landmark Clinical Trials in T2DM



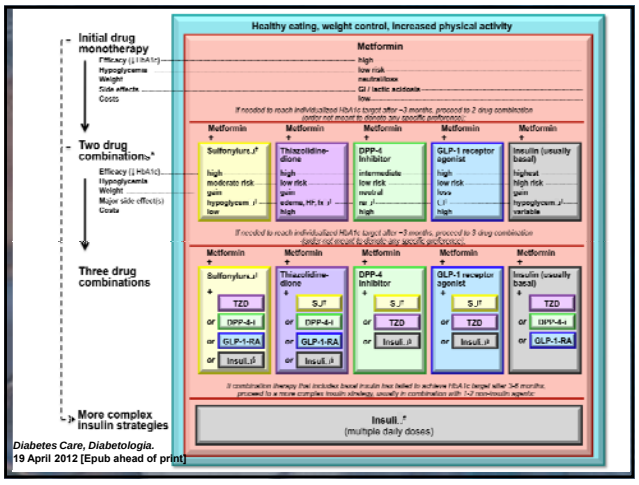
Considerations based on UKPDS, ACCORD, ADVANCE, and VADT.

Ismail-Beigi F, et al. *Ann Intern Med*. 2011;154:554-559.

Algorithm for the Metabolic Management of T2DM (ADA/EASD 2009)



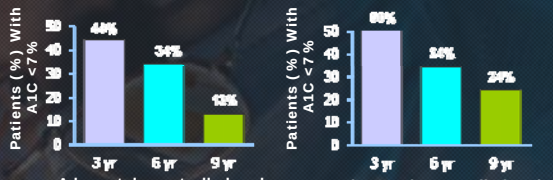
Nathan DM et al. *Diabetes Care*. 2009;32:193-203.



Diabetes Care, Diabetologia.
19 April 2012 [Epub ahead of print]

Glycemic Control Declines Over Time With Traditional Monotherapy

Most patients on traditional therapies will require another agent to maintain long-term glycemic control



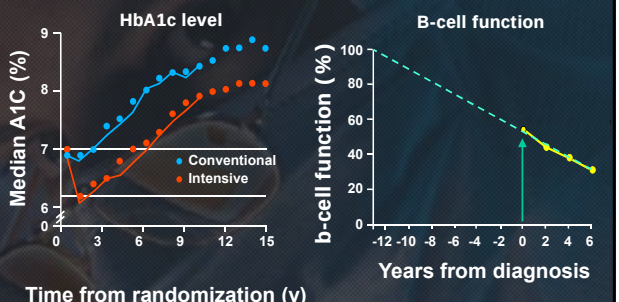
*Overweight drug-naïve patients
†Normal weight and overweight drug-naïve patients

Turner RC et al. *JAMA*. 1999;281:2005

Type 2 Diabetes Oral Medication Choices Experience and Potency

Medication	Route	Year	Efficacy as monotherapy: % ↓ in HgbA1c
Metformin	Oral	1995	1.5
Sulfonylureas	Oral	1946	1.5
Glinides	Oral	1997	1.0-1.5
TZDs	Oral	1999	0.8-1.0
α-glucosidase inhibitors	Oral	1995	0.5-0.8
DPP-IV Inhibitors	Oral	2006	0.5-0.8
Colesevelam	Oral	2008	0.5
Bromocriptine mesylate	Oral	2009	0.2-0.4

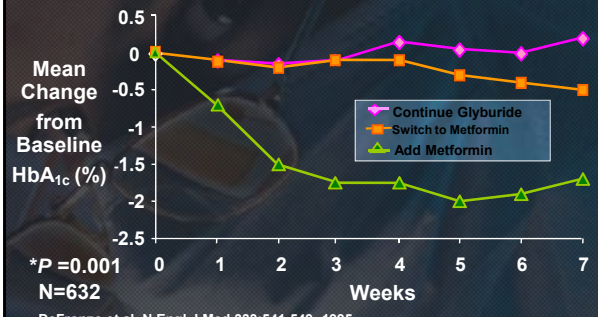
UKPDS: Progressive Deterioration in Glycemic Control Over Time



UKPDS Group. *Lancet*. 1998;352:837-853.

Holman RR. *Diabetes Res Clin Pract*. 1998;40(suppl):S21-S25.

Effects of Metformin on HbA_{1c} in Glyburide-Treated Patients



DeFronzo et al. N Engl J Med 333:541-549, 1995

Treatment Paradigm

Diet & exercise → Monotherapy → Combination oral agents → Insulin

Secondary Failure of Oral Combination Therapy

Lab: FPG >150 mg/dL, HbA_{1c} >7%

Treatment Paradigm

Diet & exercise → Monotherapy → Combination oral agents → Insulin

Treatment Paradigm

Diet & exercise → Monotherapy → Combination oral agents → Insulin

Secondary Failure of Oral Combination Therapy

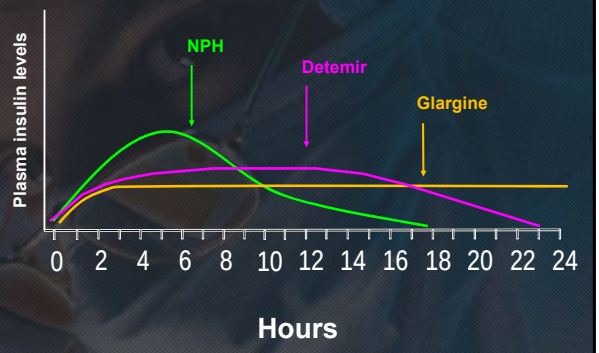
Lab: FPG >150 mg/dL, HbA_{1c} >7%

Causes
- Decreasing β-cell function
- Non-adherence to treatment
- Obesity
- Insufficient exercise
- Intercurrent illness

Insulin Therapy in Type 2 Diabetes

- Combination oral agents plus basal insulin
  - Bedtime NPH
  - Glargine
  - Detemir
- Insulin Therapy
  - Conventional approach (split-mixed NPH plus Regular insulin)
  - MDI- multi-dose insulin protocols
  - Basal/bolus insulin therapy

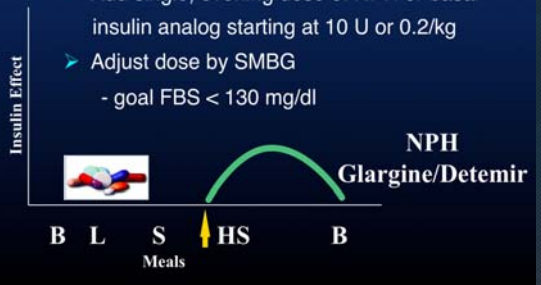
Profiles of Long-Acting Human Insulins

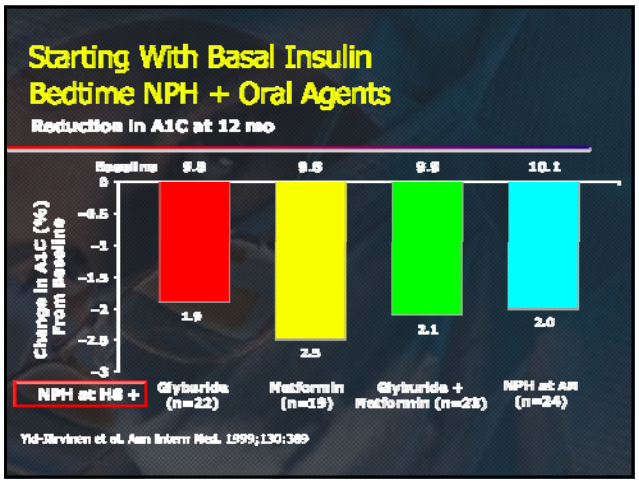


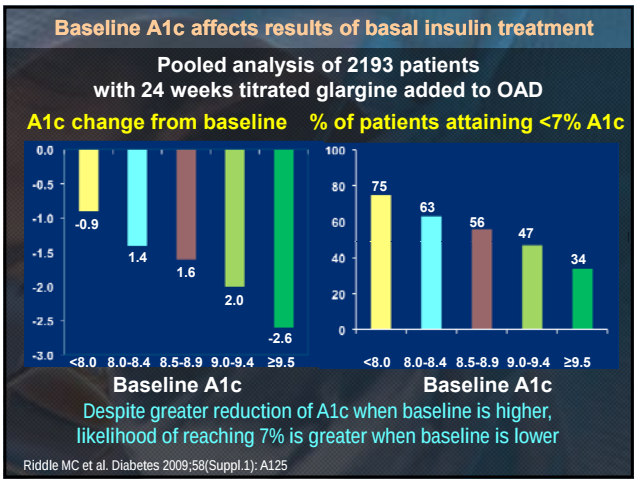
Basal Insulin Therapy – Concept and Physiology

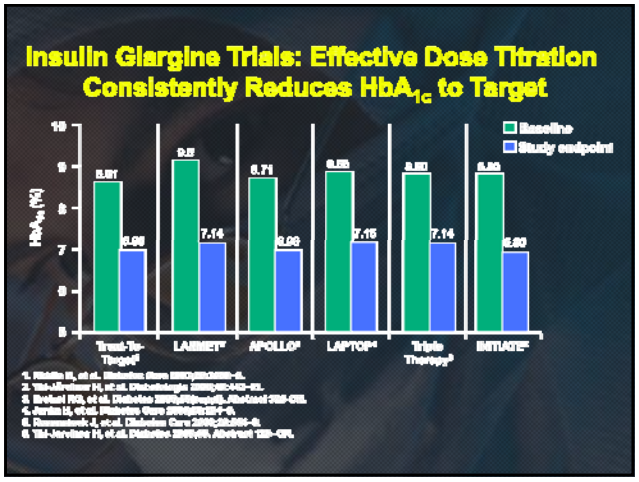
Oral agents plus NPH or Basal Insulin

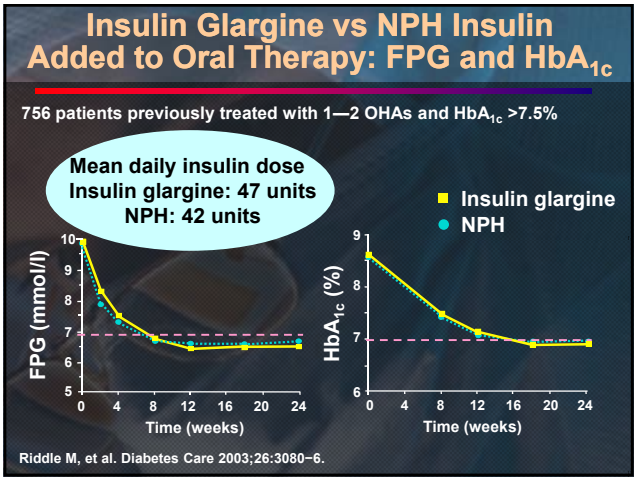
- Continue oral agent(s) at same dosage
- Add single, evening dose of NPH or basal insulin analog starting at 10 U or 0.2/kg
- Adjust dose by SMBG
  - goal FBS < 130 mg/dl



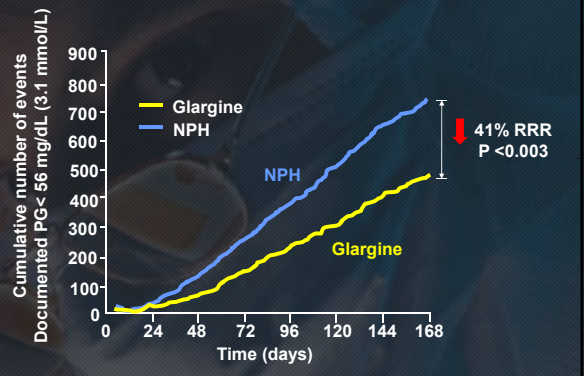

Starting With Basal Insulin
Bedtime NPH + Oral Agents
Reduction in A1C at 12 mo
Change in A1C (%) From Baseline
Baseline
9.8
9.6
9.5
10.1
-0.5
-1
-1.5
-2
-2.5
-3
1.9
2.5
2.1
2.0
NPH at HS +
Glyburide (n=22)
Metformin (n=19)
Glyburide + Metformin (n=23)
NPH at AM (n=24)
Yki-Järvinen et al. Ann Intern Med. 1999;130:389


Baseline A1c affects results of basal insulin treatment
Pooled analysis of 2193 patients
with 24 weeks titrated glargine added to OAD
A1c change from baseline
% of patients attaining <7% A1c
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
-0.9
1.4
1.6
2.0
-2.6
100
80
60
40
20
0
75
63
56
47
34
<8.0 8.0-8.4 8.5-8.9 9.0-9.4 ≥9.5
<8.0 8.0-8.4 8.5-8.9 9.0-9.4 ≥9.5
Baseline A1c
Baseline A1c
Despite greater reduction of A1c when baseline is higher,
likelihood of reaching 7% is greater when baseline is lower
Riddle MC et al. Diabetes 2009;58(Suppl.1): A125


Insulin Glargine Trials: Effective Dose Titration
Consistently Reduces HbA1c to Target
Baseline
Study endpoint
HbA1c (%)
10
9
8
7
6
8.81
8.08
9.17
7.14
8.71
8.08
8.85
7.15
8.81
7.14
8.85
8.00
Treat-To-Target
LANMET
APOLLO
LAPTOP
Triple Therapy
INITIATE


Insulin Glargine vs NPH Insulin
Added to Oral Therapy: FPG and HbA1c
756 patients previously treated with 1—2 OHAs and HbA1c >7.5%
Mean daily insulin dose
Insulin glargine: 47 units
NPH: 42 units
Insulin glargine
NPH
FPG (mmol/l)
10
9
8
7
6
5
0 4 8 12 16 20 24
Time (weeks)
HbA1c (%)
9
8
7
6
0 4 8 12 16 20 24
Time (weeks)
Riddle M, et al. Diabetes Care 2003;26:3080–6.

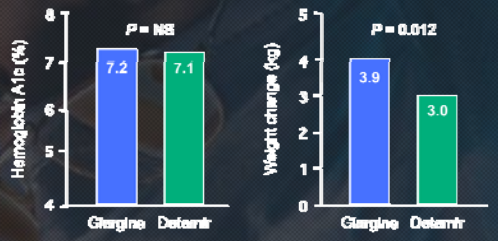
Treat to Target Trial: Frequency of Hypoglycemia



Riddle MC, et al. Diabetes Care. 2003;26:3080-3086

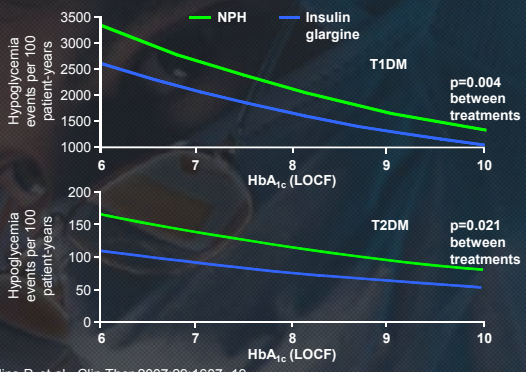
Head to Head Comparison of Glargine Versus Detemir in Type 2 Diabetes

52-weeks. Once daily Glargine or Detemir - could be titrated to BID Detemir (55%). Baseline A1c 8.6% *n* = 582



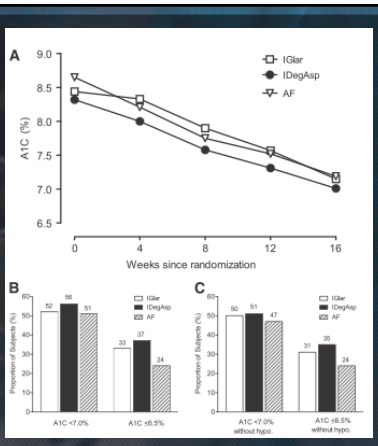
Rosenstock J et al. Diabetologia 51: 408-416, 2008

Less Hypoglycemia with Insulin Glargine vs NPH



Mullins P, et al. Clin Ther 2007;29:1607–19.

Basal Insulin Therapy with Glargine versus Degludec In T2DM



Heise et al. Diabetes Care 34:669–674, 2011

Simple Way to Start Basal Insulin

Bedtime or morning long-acting insulin OR
Bedtime intermediate-acting insulin
Daily dose: 10 units or 0.2 units/kg

Check FBG daily

Increase dose by 2 units every 3 days until FBG is 70–130 mg/dL

If FBG is >180 mg/dL, increase dose by 4 units every 3 days

In the event of hypoglycemia or FBG level <70 mg/dL

Reduce bedtime insulin dose by 4 units, or by 10% if >60 units

Continue regimen and check HbA_{1c} every 3 months

Nathan D, et al. Diabetologia 2006;49:1711–21.

Treat-to-target simply: LANMET study

- Insulin-naïve T2DM patients (n=110) failed on oral agents
- HbA_{1c} 9.5 ± 0.1%

OHAs
- **Insulin glargine + metformin**
- **NPH insulin + metformin**

Yki-Jarvinen H, et al. Diabetologia 49(3):442-51, 2006

Keys to Success with Basal Insulin Therapy

- **Use patient-driven algorithms**

Treat-to-target simply: LANMET study

- Insulin-naïve T2DM patients (n=110) failed on oral agents
- HbA_{1c} 9.5 ± 0.1%

OHAs
- **Insulin glargine + metformin**
- **NPH insulin + metformin**

Measure FPG daily for 3 days

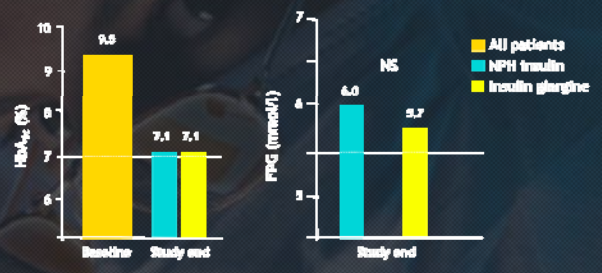
If mean of FPG measurements >100 mg/dl
ADD 2 UNITS OF BASAL INSULIN

No increase in dose if FPG <72 mg/dl

Yki-Jarvinen H, et al. Diabetologia 49(3):442-51, 2006

LANMET study: HbA_{1c} reduction between treatment groups

Bedtime NPH vs insulin glargine, plus metformin 2 g



Yki-Järvinen H, et al. Diabetologia 49(3):442-51, 2006

What if Basal Insulin is Not Enough?

Combined Effects of Metformin with Insulin Therapy in Type 2 Diabetes

Table 1. Studies showing the benefits of using metformin with insulin in type 2 diabetes*

	Yki-Järvinen et al. [26]		Avilés-Santa et al. [29]		Strowig et al. [30]		Wulffelé et al. [31]	
	Insulin	Insulin + metformin	Insulin	Insulin + metformin	Insulin	Insulin + metformin	Insulin	Insulin + metformin
Subject, *n*	24	19	22	21	31	27	182	171
Duration, mo	12	12	6	6	4	4	4	4
Insulin dose at end, U	53	36	120	92	135	82	71	64
HbA_{1c} at end, %	7.9	7.2	7.6	6.5	7.0	7.1	7.6	6.9
Weight gain, kg	4.6	0.9	3.2	0.5	4.4	0.5	1.2	-0.4

*All of the studies compared subjects on insulin versus metformin and insulin. All found less weight gain, a lower insulin dosage, and mostly a lower HbA_{1c}. HbA_{1c}—hemoglobin A_{1c}.

Sasali A and Leahy JL. *Curr Diab Rep* 3:378-385, 2003

Insufficiency of oral + basal insulin treatment

- **50% of patients with basal insulin do not reach HbA_{1c} target at initiation, with titration of the dose**

Riddle M, *et al. Treat To Target. Diabetes Care* 2003.

Insufficiency of oral + basal insulin treatment

- 50% of patients with basal insulin do not reach HbA_{1c} target at initiation, with titration of the dose

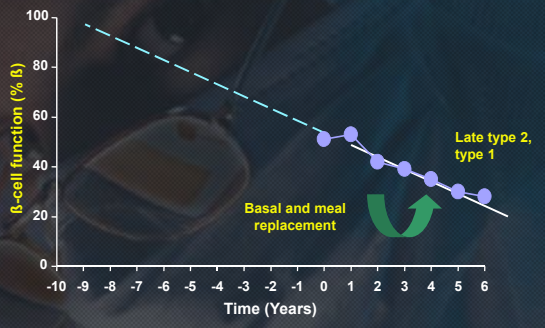
Riddle M, *et al. Treat To Target. Diabetes Care* 2003.

- Natural history of pancreatic disease in type 2 diabetes, with expected further degradation of glycemic control
- Hypoglycemic risk during titration of basal insulin, making difficult to reach FBG target
- Very high dose of basal insulin without significant effect on FBG

Monnier *et all. Diab Metab* 2006.

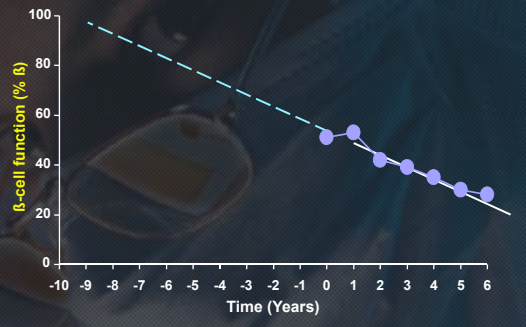
- Weight gain

Progressive Loss of ß-Cell Function in Type 2 Diabetes



DeFronzo RA. Diabetes Rev. 1997;5:178-269.

Progressive Loss of ß-Cell Function in Type 2 Diabetes



DeFronzo RA. Diabetes Rev. 1997;5:178-269.

Review article

Treatment regimens with insulin analogues and haemoglobin A1c target of <7% in type 2 diabetes: A systematic review

29 trials, with 17,588 patients

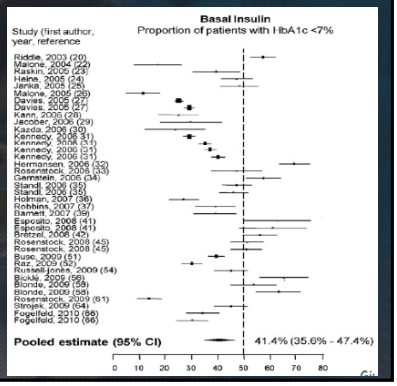
HbA1c < 7% was achieved in 41.4% (95% CI, 35.6–47.4%).

First insulin treatment, lower insulin and use of 2 oral drugs were predictors of response.

Hypoglycemia ranged from 0 to 4.71 events/patient/30 days

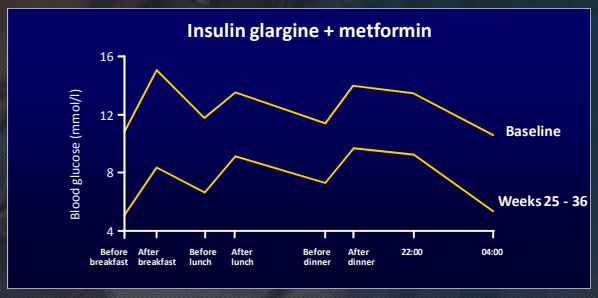
Weight gain ~1.75 kg

Giugliano et al. Diabetes Research & Clinical Practice 92 (2011) 1–10



Postprandial hyperglycemia persists despite treatment of FBG using basal insulin

- Basal insulin therapy reduces the entire 24-hour blood glucose profile, but postprandial hyperglycemia persists



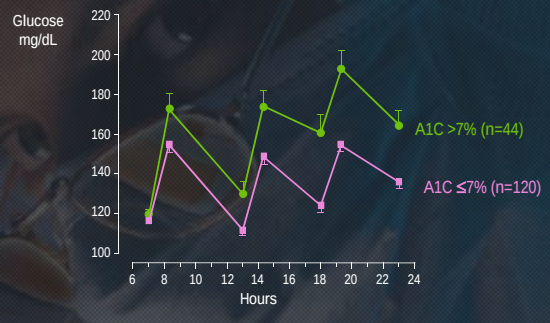
Yki-Järvinen H, *et al.* - LANMET study data. *Diabetologia* 2006;49:442-51.

When basal insulin is not enough: What strategy?

- In clinical practice:
  - Premix insulins
  - Basal plus (stepwise basal-bolus)
  - Basal-bolus
  - Insulin in combination with other hormones

Postprandial hyperglycemia persists after basal therapy

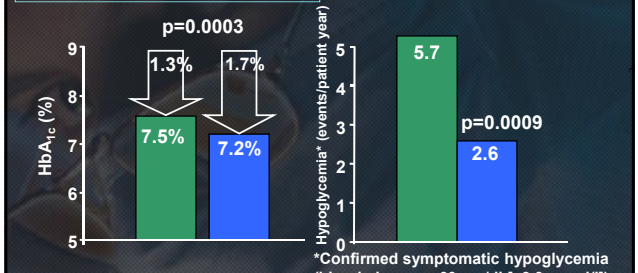
164 patients with baseline A1c ≥7.5% on diet, oral agents, or insulin
Mealtime hyperglycemia persists after 3 months of intensive treatment



Woerle HJ et al. Diabetes Res Clin Pract 2007;78:280-85

Insulin Glargine vs 70/30 Premixed Insulin in OHA Failures

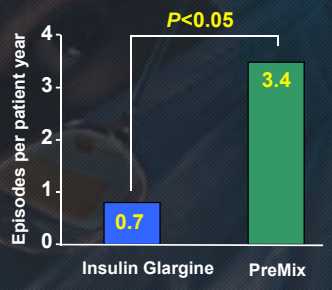
N=371 insulin-naïve patients
Insulin Glargine + OADs vs twice-daily human NPH insulin (70/30)
Follow-up: 24 weeks



*Confirmed symptomatic hypoglycemia (blood glucose <60 mg/dl [<3.3 mmol/l])

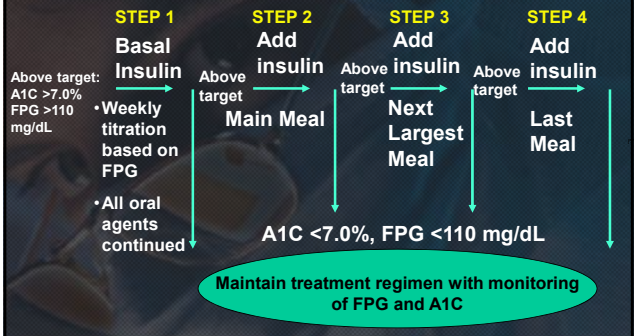
Janka H, et al. *Diabetes Care* 2005;28:254–259.

Hypoglycemia
Documented Hypoglycemic Episodes (<56 mg/dL)



Raskin P. *Diabetes Care* 2005;28:260-265.

Steps in Transition From Basal to Basal-Bolus Insulin Therapy in T2DM



Karl DM. *Curr Diab Rep.* 2004:4352-357.
American Association of Clinical Endocrinologists. *Endocr Pract.* 2007;13(suppl 1):3-68.

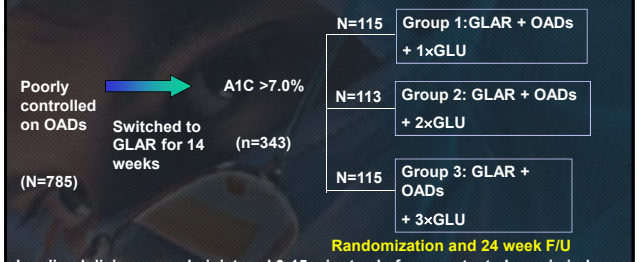
Premix insulins

- Efficient on HbA_{1c}, but very few clinical studies available
- Mainly to simplify the protocols ++
- Many disadvantages with:
  - Lack of flexibility
  - Risk of hypos
  - Poor reproducibility

Studies to Support the Basal Plus Strategy

Study	Purpose	Design	Primary endpoint	Lead country
ELEONOR	Evaluation of Basal Plus strategy in T2DM on OADs using Telecare system	Lantus® + Met + 1x Apidra® measured by SMBG vs Lantus® + Met + 1 Apidra® using Telecare assistance	Change in HbA_{1c}	ITA
1,2,3 (Lantus® + Apidra®)	Efficacy of Basal Plus strategy in persons with T2DM on TZDs	Lantus® + TZD + 1x Apidra® vs Lantus® + TZD + 2x Apidra® vs Lantus® + TZD + 3x Apidra®	Change in HbA_{1c}	USA
OSIRIS	Non-inferiority of Basal Plus strategy compared with basal—bolus regimen	Lantus® + 1,2,3x Apidra® + Met +/– SU vs Lantus® + 3x Apidra®	Change in HbA_{1c}	17 countries
All-to-Target	Basal/Basal Plus strategy more effective than premixed insulin	Lantus® + 1,2,3 Apidra® vs 2 premix	% subjects HbA_{1c} <7%	USA

Stepwise Intensification: 1-2-3 Study Design



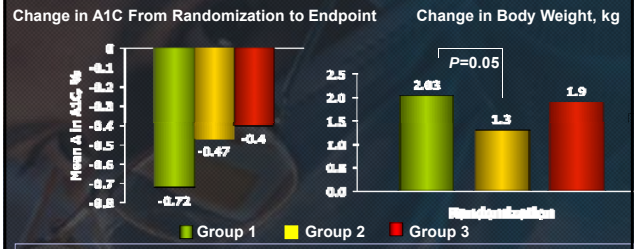
- Insulin glulisine was administered 0-15 minutes before greatest glycemic index meal
- Initial glulisine dose was 1/10th of the glargine does at randomization
- Weekly titration to target PPG 70-109 mg/dL and HS level 70-129 mg/dL

OADs were continued.

GLAR = insulin glargine; GLU = insulin glulisine; OADs=oral antidiabetic agents.

Davidson MB et al. *Endocr Pract*. February 16, 2011.

Stepwise Intensification: Change in A1C and Weight



Group 1: GLAR + MET + 3×GLU

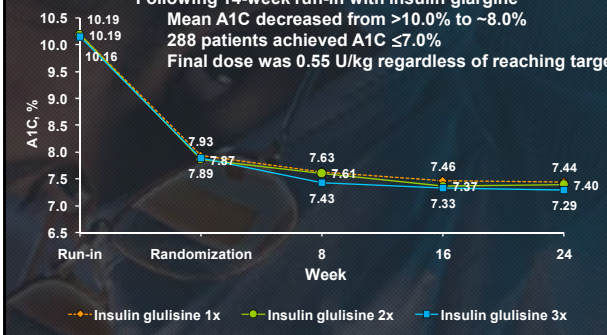
Group 2: GLAR + MET + 1, 2, or 3×GLU

Group 3: GLAR + MET + SU + 1, 2, or 3×GLU

Raccah D et al. [ADA abstract 555-P]. *Diabetes*. 2010;59(suppl 1):A151.

A1C Change From Baseline to Week 24

Following 14-week run-in with insulin glargine
Mean A1C decreased from >10.0% to ~8.0%
288 patients achieved A1C ≤7.0%
Final dose was 0.55 U/kg regardless of reaching target



mITT = modified intent to treat.

Davidson MB et al. *Endocr Pract* 2011

Matching treatment to disease progression using a stepwise approach

Basal Bolus: once-daily basal insulin plus rapid-acting insulin before meals

Basal Bolus
Add prandial insulin before each meal

Basal Plus
Add prandial insulin at main meal

Basal
Add basal insulin and titrate

Lifestyle changes plus metformin (± other agents)

Progressive deterioration of β-cell function

*Raccah D, *et al. Diabetes Metab Res Rev* 2007;23:257–64.

Basal Bolus Insulin: Percent of patients with HbA1c < 7%

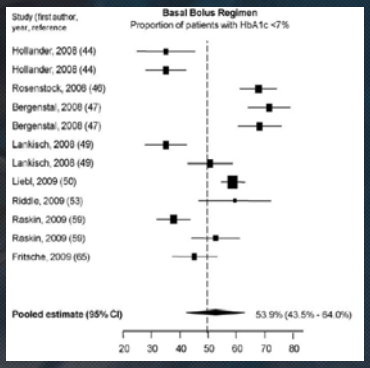
12 trials, with 2114 patients

HbA1c < 7% was achieved in 53.9% (95% CI, 43.5–64)

Hypoglycemic events (mean/patient/30 days): 0.88 (0.35-1.3)

Weight gain ~2.75 kg (1.8-3.7)

Final insulin dose: 0.89 U/kg (0.78-1.3)



Giugliano et al. Diabetes Research & Clinical Practice 92 (2011) 1–10

Insulin in Combination With Other Hormones

- Insulin + DPP-4 inhibitors
- Insulin + GLP-1 receptor agonists

Basal Bolus Insulin: Percent of patients with HbA1c < 7%

12 trials, with 2114 patients

HbA1c < 7% was achieved in 53.9% (95% CI, 43.5–64)

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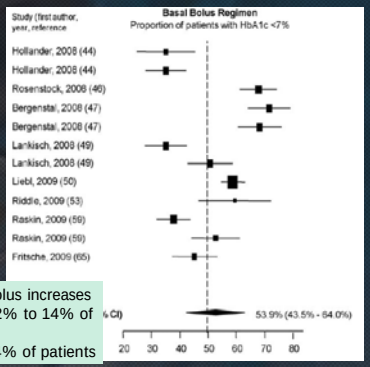
Weight gain ~2.75 kg (1.8-3.7)

Final insulin dose: 0.89 U/kg (0.78-1.3)

Escalation from basal to basal-bolus increases success rate in an additional ~12% to 14% of patients
- HbA1c < 7% is achieve in ~54% of patients



Giugliano et al. Diabetes Research & Clinical Practice 92 (2011) 1–10

US FDA-Approval Status: Incretin-Based Therapies Combined With Insulin

Class	Agents With FDA Approval for Use in Combination With Insulin
DPP-4 inhibitors[1]	Sitagliptin Saxagliptin
GLP-1 RAs[1]	Exenatide BID •Trial in combination with insulin glargine •Not studied in combination with prandial insulin Liraglutide •Trial in combination with insulin detemir •Not studied in combination with prandial insulin

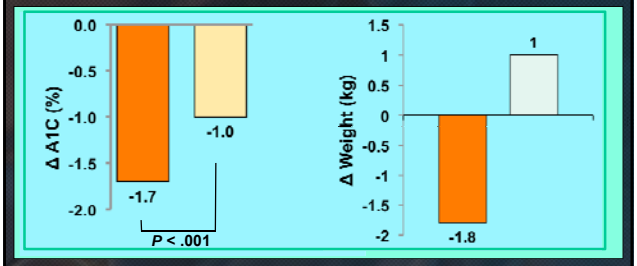
Clinical trials are in progress for the DPP-4 inhibitor, linagliptin, and the GLP-1 RA, exenatide ER.[2]

1. US FDA. Drugs@FDA Web site. http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA/.
2. US National Institutes of Health. http://www.clinicaltrials.gov/ct2/home.

Exenatide BID Added to Insulin Glargine

EXN BID or PBO Added to GLAR 30-week trial

GLAR + EXN BID (n = 137) GLAR + PBO (n = 122)



Similar rates of minor hypoglycemia in EXN BID (25%) and PBO (29%) groups

More discontinued due to AEs in EXN BID (9%) vs PBO (1%) group ($P < .01$).

Buse JB, et al. *Ann Intern Med*. 2011;154:103-112.

US FDA-Approval Status for Insulin-GLP-1 RA Combinations

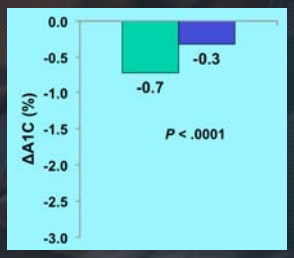
Agent	Approval Status for Combination with Insulin
Exenatide	Approved in combination with insulin glargine[1]
Liraglutide	NDA filed in 2011; awaiting response from the US FDA[2]
Lixisenatide*	Not FDA approved; studied in combination with insulin glargine[3]

*Not FDA approved.
1. Byetta [prescribing information] San Diego, CA: Amylin Pharmaceuticals, Inc; 2011. 2. Reuters. 2011. http://uk.reuters.com/article/2011/06/28/novonordisk-idUKLDE71F09U20110628. 3. http://www.clinicaltrials.gov/ct2/results?term=Lixisenatide. Accessed March 5, 2012.

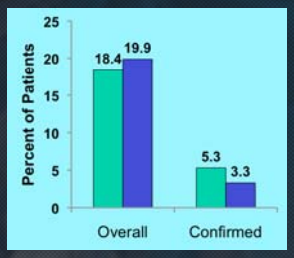
Saxagliptin Improves Glycemic Control With Low Rates of Hypoglycemia Over 24 Weeks in T2DM

SAXA + INS (n = 304) PBO + INS (n = 151)

Efficacy



Hypoglycemia



Hypoglycemia threshold not defined.

Charbonnel B, et al. *Diabetes*. 2011;60(suppl 1):A304 [abstr 1108-P].

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EXN BID or PBO Added to GLAR 30-week trial

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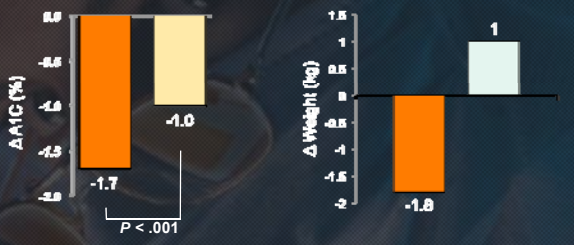

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Buse JB, et al. *Ann Intern Med*. 2011;154:103-112.

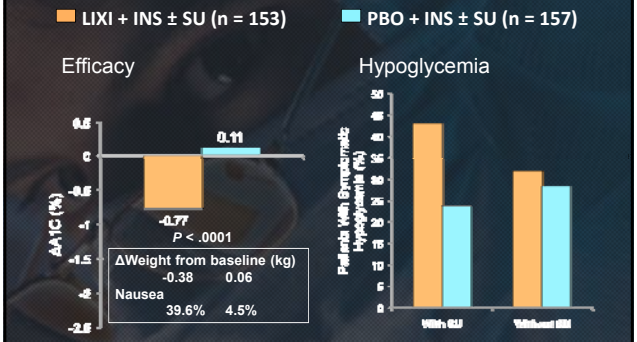
Use of Twice-Daily Exenatide in Basal Insulin–Treated Patients With T2DM

Adults with T2DM and A1C = 7.1% to 10.5% receiving GLAR MET PIO were randomized to EXN (10 g BID) or PBO for 30 weeks.

[a] *P* < .001.

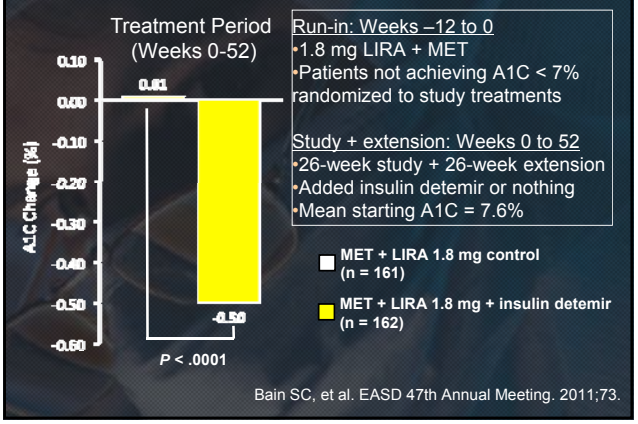
Buse JB, et al. *Ann Intern Med.* 2011;154:103-112.

Lixisenatide Combined With Basal Insulin Improves Glycemic Control With Less Weight Gain in T2DM Over 24 Weeks



Seino Y, et al. *Diabetes.* 2011;60(suppl 1):A76 [abstr 278-OR].

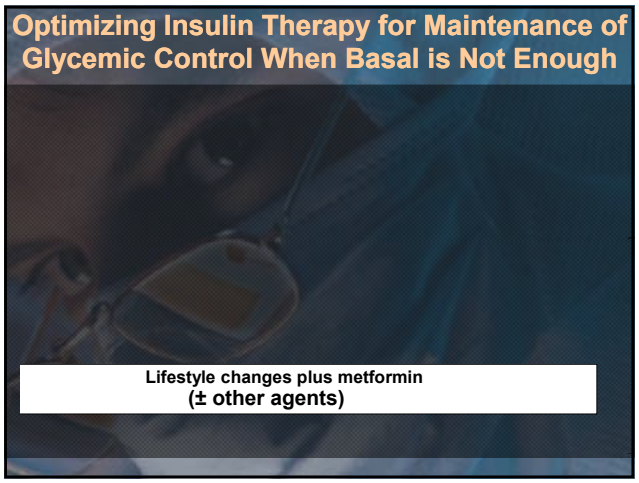
Insulin Detemir Added to Liraglutide

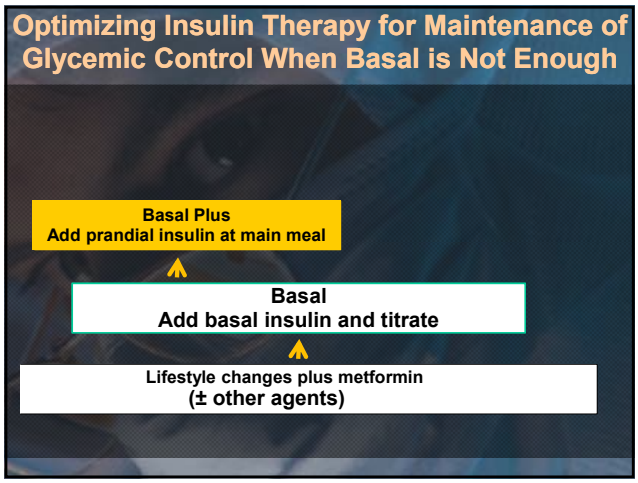


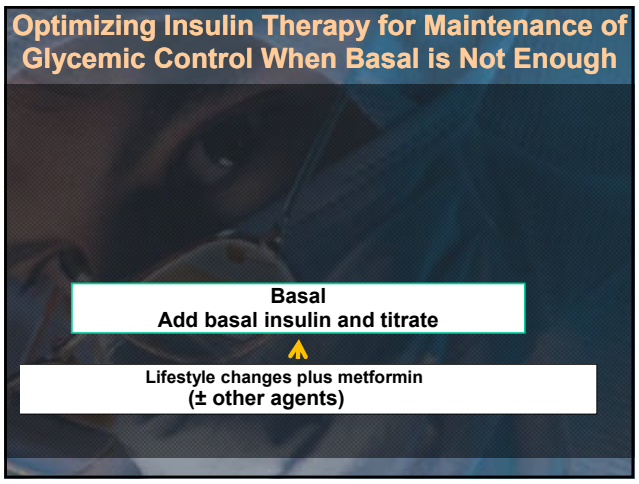
Bain SC, et al. EASD 47th Annual Meeting. 2011;73.

Summary

- Insulin + DPP-4 inhibitor combination therapy in T2DM improves glycemic control, reduces hypoglycemia, and is typically considered weight-neutral
- Insulin + GLP-1 RA combination therapy in T2DM improves glycemic control, reduces hypoglycemia, and can induce weight loss
- Insulin + GLP-1 RA combination therapy is being very actively investigated in T1DM and T2DM


Optimizing Insulin Therapy for Maintenance of Glycemic Control When Basal is Not Enough
Lifestyle changes plus metformin
(± other agents)


Optimizing Insulin Therapy for Maintenance of Glycemic Control When Basal is Not Enough
Basal Plus
Add prandial insulin at main meal
Basal
Add basal insulin and titrate
Lifestyle changes plus metformin
(± other agents)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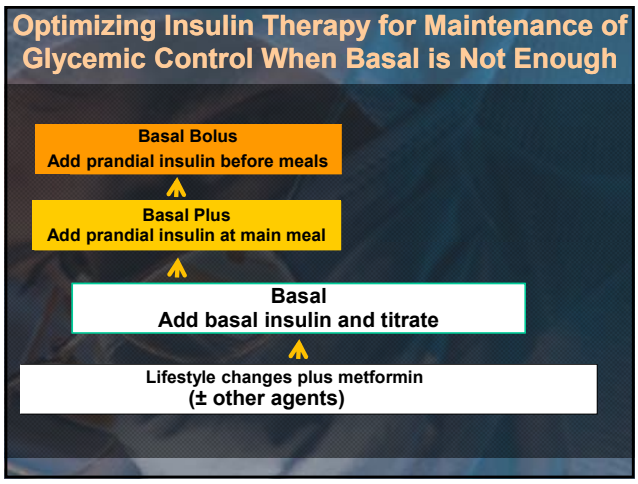
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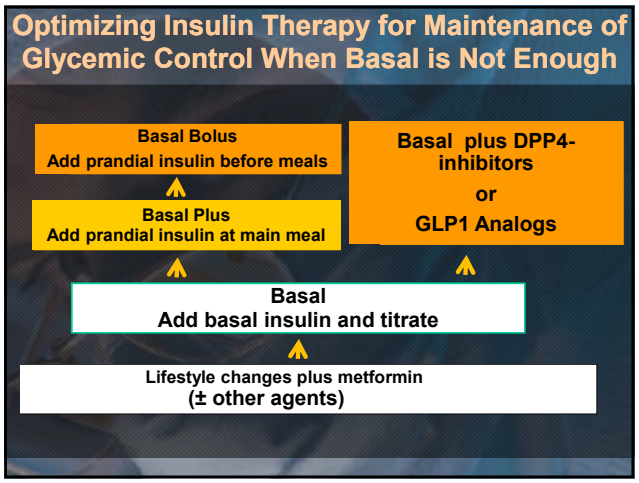
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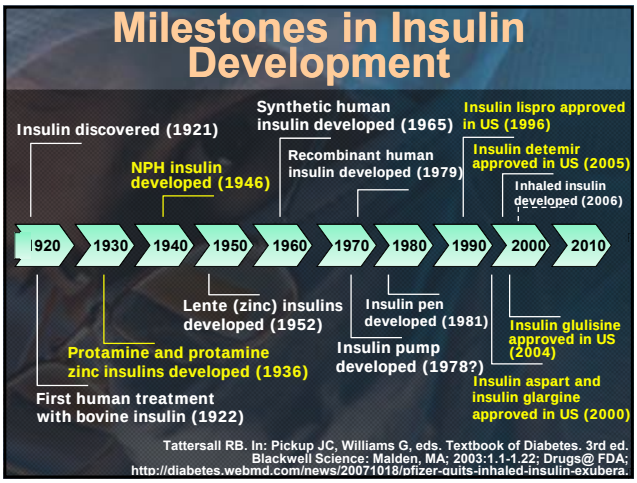
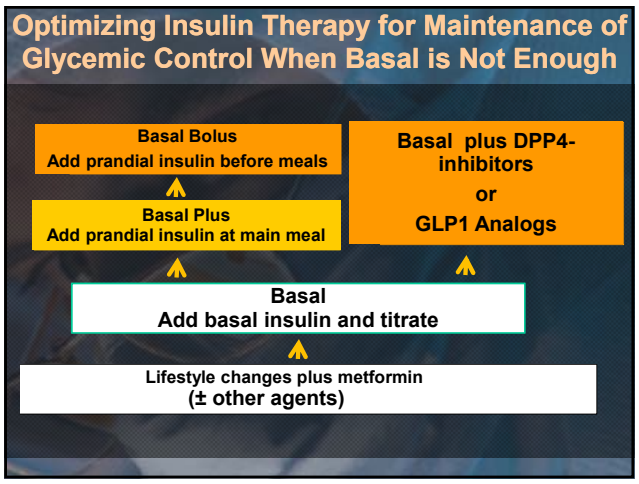
Basal Bolus
Add prandial insulin before meals
Basal Plus
Add prandial insulin at main meal
Basal plus DPP4-inhibitors
or
GLP1 Analogs
Basal
Add basal insulin and titrate
Lifestyle changes plus metformin
(± other agents)


Milestones in Insulin Development
Insulin discovered (1921)
NPH insulin developed (1946)
Synthetic human insulin developed (1965)
Recombinant human insulin developed (1979)
Insulin lispro approved in US (1996)
Insulin detemir approved in US (2005)
Inhaled insulin developed (2006)
1920
1930
1940
1950
1960
1970
1980
1990
2000
2010
Lente (zinc) insulins developed (1952)
Protamine and protamine zinc insulins developed (1936)
Insulin pen developed (1981)
Insulin pump developed (1978?)
Insulin glulisine approved in US (2004)
Insulin aspart and insulin glargine approved in US (2000)
First human treatment with bovine insulin (1922)
Tattersall RB. In: Pickup JC, Williams G, eds. Textbook of Diabetes. 3rd ed. Blackwell Science: Malden, MA; 2003:1.1-1.22; Drugs@ FDA; http://diabetes.webmd.com/news/20071018/pfizer-quits-inhaled-insulin-exubera.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