

ADA T2DM Treatment Algorithm: The Role of Insulin Intensification and New Data on Basal Bolus Management

Presented to:
Diabetes Alliance of Idaho

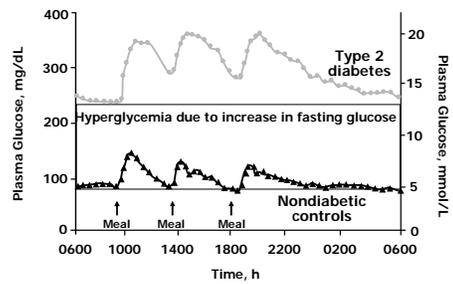
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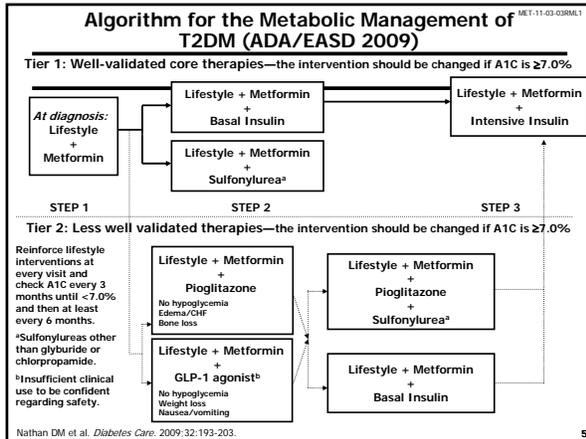
Topics of Inquiry

- Discuss the importance of basal insulin
- Review the ADA T2DM Treatment recommendations
- Simplification approaches to intensification of insulin treatment

Treating Fasting Hyperglycemia Lowers Entire 24-Hour Plasma Glucose Profile



Comparison of 24-hour glucose levels in control subjects vs patients with diabetes ($P < 0.001$). Adapted with permission from Polonsky K et al. *N Engl J Med*. 1988;318:1231-1239.



MET-11-02-11RML1

A Stepwise Approach to Insulin Therapy in Patients With Type 2 Diabetes Failing Basal Insulin Treatment

MB Davidson, P Raskin, RJ Tanenberg, A Vlahjnic, P Hollander

Davidson MB et al. [Published online ahead of print February 16, 2011.] *Endocr Pract*. doi:10.4158/EP10323.OR. Study funded by sanofi-aventis US. 6

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Study Objectives

- To determine if a basal-prandial regimen can be simplified without compromising effectiveness in patients requiring insulin intensification
- Examined whether administering 1 or 2 preprandial injections before the meals of greatest glycemic impact can be as effective as administering 3 preprandial injections
 - Based on A1C reductions and proportion of patients achieving A1C $< 7.0\%$
 - Noninferiority analyses

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Methods Study Design (cont)

- Multicenter, open-label, randomized, 3-arm, parallel-group (1:1:1) study in adult patients with T2DM
 - On a stable dose of 2 or 3 OADs
 - Had an A1C $> 8.0\%$ at screening visit
- 14-week run-in treatment phase
 - Added insulin glargine to current OAD regimen
 - Insulin glargine initiated at 10 U/d and titrated every 2 days to target FG 70-109 mg/dL
 - Patients with A1C $> 7.0\%$ at end of run-in were randomized to receive prandial injections of insulin glulisine

FG = fasting glucose; OAD = oral antidiabetic drugs.
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Methods Study Design (cont)

Randomized treatment phase

- **3 arms: Insulin glargine + insulin glulisine before**
 - The meal with greatest glycemic index (1x)
 - The 2 meals with greatest glycemic index (2x)
 - All 3 meals (3x)
- **Insulin glulisine was administered 0-15 minutes before meals**
- **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**

HS = bedtime; PPG = preprandial glucose.
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Methods Study Design

The flowchart illustrates the study design. It begins with a **Screening** phase (N=1232) involving 2 or 3 OADs. This leads to a **Run-in** phase (n=785) with insulin glargine and 2 or 3 OADs. Patients with A1C > 7.0% are excluded. The remaining patients undergo **Randomization** into three **ITT/Safety Population** arms:

- Insulin glulisine 1x/d (n=115)
- Insulin glulisine 2x/d (n=113)
- Insulin glulisine 3x/d (n=115) + Insulin glargine + Sensitizer (S) + Discontinue SU

 The timeline shows **Screening: 1 wk**, **Run-in: 14 wk**, and **Treatment: 24 wk**. Visits are marked with diamonds at weeks -16, -14, -12, -10, -8, -6, -4, -2, 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24. A **Phone Follow-up** occurs 24 hours after the final visit.

OADs = oral antidiabetic drugs; SU = sulfonylurea; ◇ = study visit.
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Methods Titration Regimen

Insulin Glargine^a

Mean Fasting 2-Day SMBG, mg/dL	Insulin Glargine Adjustments q 2 Days
>250	Increase the dose at investigator discretion
110-250	Increase 2 U
100-109	Increase 0-2 U at investigator discretion ^b
70-99	No change
<70	Decrease the dose 2-4 U at investigator discretion

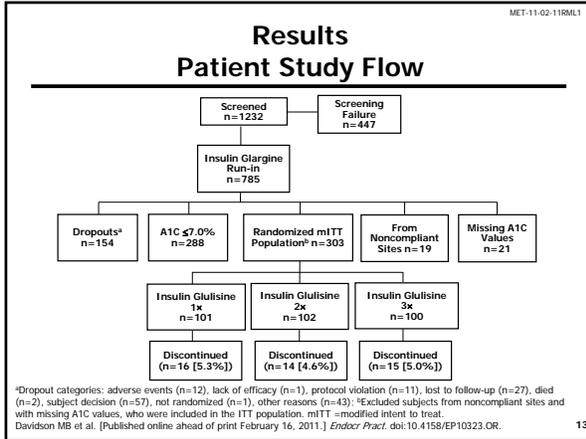
^aTitrated based on fasting SMBG; ^bInsulin glargine doses could be increased if A1C remained $\geq 7.0\%$.
SMBG = self-monitored blood glucose.
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A1C Decreases After Run-In

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

CI = confidence interval.
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Methods Titration Regimen

Insulin Glulisine^a

Mealtime Dose, U	Pattern of Low Preprandial Blood Glucose Values (≥2 Values <70 mg/dL)	Pattern of High Preprandial Blood Glucose Values (≥4 Values Above Target)
	≤10 U	Decrease by 1 U
11-20 U	Decrease by 2 U	Increase by 2 U
>20 U	Decrease by 3 U	Increase by 3 U

^aTitrated weekly based on preprandial self-monitored blood glucose.
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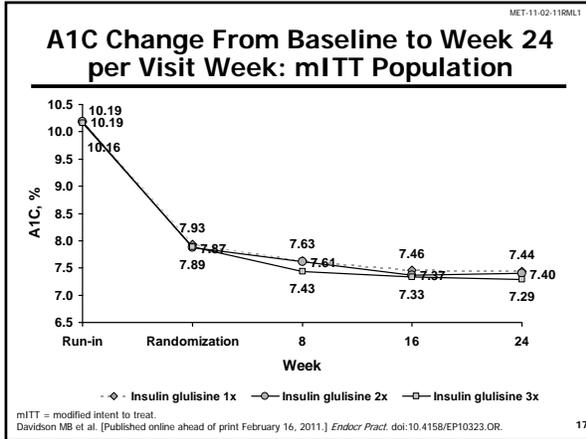
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- MET-11-02-119ML1
- ## Methods Endpoints
- **Primary endpoint**
 - Change in A1C from randomization to week 24
 - **Secondary endpoints**
 - Percentage of patients achieving A1C <7.0% at week 24
 - Changes in A1C, FPG, preprandial SMBG, and weight from randomization to week 8, 16, 24
 - **Safety**
 - AEs
 - Hypoglycemia
- AEs = adverse events; FPG = fasting plasma glucose; SMBG = self monitored blood glucose.
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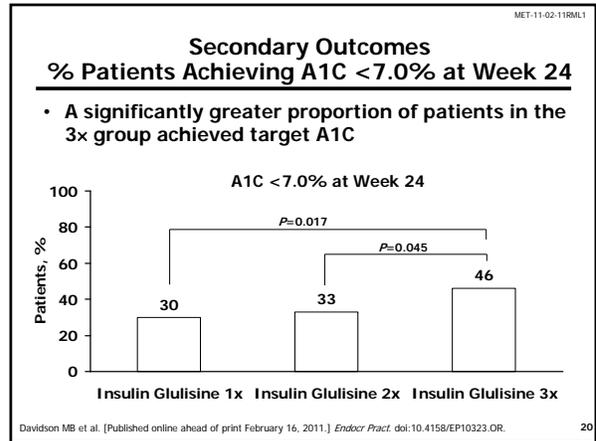
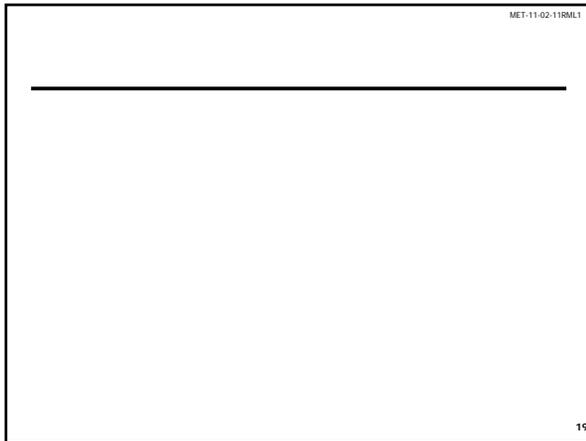


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A1C Decreases After Randomization

- Following randomization to add-on insulin glulisine
 - All 3 dosage regimens led to equivalent A1C reductions
 - A1C decreases were -0.44%, -0.36%, and -0.43% for 1x, 2x, and 3x groups, respectively
 - Noninferiority of insulin glulisine 1x and 2x vs 3x was demonstrated (adjusted mean difference [97.5%CI])
 - 1x: -0.02 (-0.39-0.36), $P=0.922$
 - 2x: 0.06 (-0.30-0.43), $P=0.695$

CI = confidence interval.
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Safety Outcomes Hypoglycemia

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- Insulin glulisine 3x group had highest incidence of hypoglycemia in all documented categories; yet none reached statistical significance
- Severe hypoglycemia occurred in twice as many patients in 3x group than the 1x or 2x groups (18 vs 8 vs 9, $P=0.099$)
- Insulin glulisine 3x group had a significantly higher event rate than the 1x group (0.64 vs 0.28, $P=0.04$)

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Summary of Study Findings

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- Nearly half (46%) of patients achieved A1C $\leq 7.0\%$ during 14 weeks of insulin glargine + OADs (run-in phase)
- In patients who did not reach goal A1C with insulin glargine + OADs alone:
 - Addition of insulin glulisine 1, 2, or 3 x daily decreased A1C approximately equally
 - More patients achieved A1C goal $< 7.0\%$ with insulin glulisine administered 3x daily vs 1x or 2x
 - However, more people taking insulin glulisine 3x daily had hypoglycemic events

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Conclusions

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- This study supports the stepwise approach of adding preprandial insulin injections in patients not controlled with a long-acting insulin
- A basal-plus insulin administration regimen^a is an easy, safe, and effective alternative to insulin intensification with a basal-bolus regimen^b
 - Not all patients will require 3 preprandial injections to achieve glycemic goals
 - May simplify insulin intensification, improve physician and patient willingness to aggressively manage diabetes, and lead to improved glycemic control for patients with T2DM

^aA long-acting insulin is in use and injections of rapid-acting insulin are added at the largest meal, then the 2 largest meals, and finally all 3 meals. ^bLong-acting insulin plus rapid-acting insulin at each meal.

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Wrap-Up

- Discuss the importance of basal insulin
- Review the ADA T2DM Treatment recommendations
- Simplification approaches to intensification of insulin treatment