1 – 2:15pm

Optimizing Insulin Therapy for Patients with Type 2 Diabetes: Existing Challenges and New Opportunities for Improved Care

SPEAKERS
Lawrence Blonde, MD, FACP, FACE
Luigi Meneghini, MD, MBA

Presenter Disclosure Information

The following relationships exist related to this presentation:

- Lawrence Blonde, MD, FACP, FACE: Consultant for AstraZeneca; GlaxoSmithKline; Intarcia Theraputics, Inc.; Janssen Pharmaceuticals, Inc.; Merck & Co., Inc.; Novo Nordisk Inc.; Quest Diagnostics; and sanofi-aventis U.S. Speakers Bureau for AstraZeneca; Janssen Pharmaceuticals, Inc.; Merck & Co., Inc; Novo Nordisk Inc.; and sanofi-aventis U.S.
- Luigi Meneghini, MD, MBA: Advisory Board for Novo Nordisk Inc. and sanofi-aventis U.S.

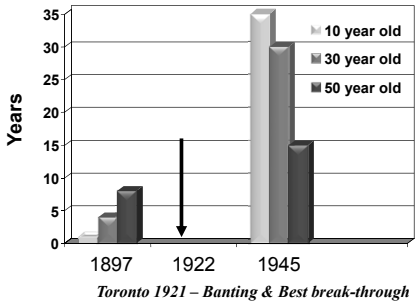
Off-Label/Investigational Discussion

- In accordance with pmiCME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.

Learning Objectives

- Better identify and understand pathophysiologic defects contributing to postprandial hyperglycemia and its impact on managing glycemic burden in type 2 diabetes patients
- Incorporate assessment of postprandial glucose as part of diagnostic and treatment plan so as to target therapy to better manage hyperglycemia and prevent potential complications in patients with type 2 diabetes mellitus
- Overcome both clinician and patient resistance to appropriate initiation and intensification of insulin therapy to best manage postprandial hyperglycemia, while lowering risk for adverse events
- Better distinguish conventional, new, and emerging prandial insulin therapies for appropriate treatment selection in patients with T2DM so as to properly integrate in to care and improve outcomes

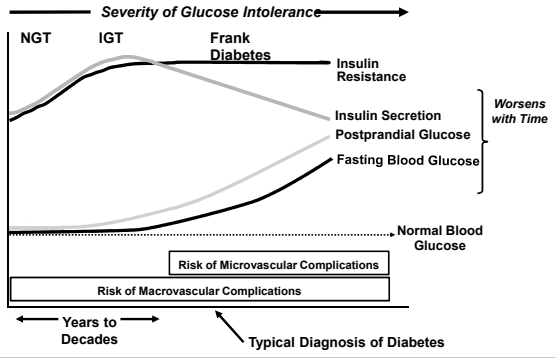
The History of Diabetes Survival



Toronto 1921 – Banting & Best break-through

Bliss M. The Discovery of Insulin. University of Chicago Press. 1984. 11-20
Photographs courtesy of the National Library of Medicine

Natural History of Type 2 Diabetes



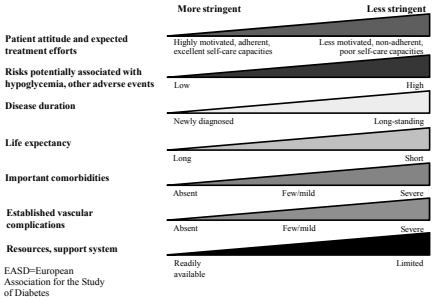
Glycemic Target Goals for Patients with Type 2 Diabetes

Treatment Goal	ADA	AACE
HbA_{1C} (%)	< 7	≤ 6.5
FPG (mg/dL)	80-130	<110
Preprandial glucose (mg/dL)	80–130	< 110
Postprandial glucose (mg/dL)	< 180*	< 140**

HbA_{1C} is "gold standard" measure of diabetes control over previous 2–3 months

* Peak PPG; ** 2 Hr PPG
American Diabetes Association. *Diabetes Care.* 2015; 38(suppl 1):S33-S40.
Handelsman, Y., et al. (2015). Endocr Pract 21(0): 1-87.

ADA/EASD: Approach to the Management of Hyperglycemia



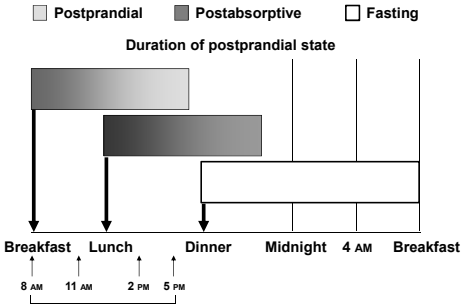
EASD=European Association for the Study of Diabetes

Inzucchi, S. E., et al. (2015). Diabetes Care 38(1): 140-149.

To achieve a normal or near normal A1C, both FPG and PPG levels must be normal or near normal.

Thus both FPG and PPG must be targets for therapy

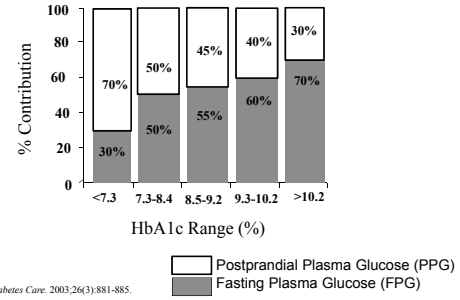
T2DM Patients Can Spend More Than 12 Hrs/day in the Postprandial State



Adapted from Monnier L. *Eur J Clin Invest.* 2000;30(suppl 2):3-11.

Fasting vs Postprandial Glucose: Relationship to A1C Level

PPG contribution to HbA1c is greater when HbA1c is lower



Monnier L et al. *Diabetes Care.* 2003;26(3):881-885.

Case: Poorly Controlled T2DM Patient on OAD meds

- 55-yr old African American male with T2DM diagnosis since age 45 on OADs and poorly controlled T2DM
- Hx: HTN, mixed dyslipidemia adequately controlled with medications
  - Employed as heavy machine operator, married with 2 children in college
  - Relatively active with exercise 3 times per week for 30 minutes daily. Tennis occasionally.
  - EtoH & tobacco (negative)

Current Exam & Treatment

Current exam:

- Wt 208 lbs, Ht 68", BMI 31.6
- A1C 8.2%, Cr 0.9 mg/dL
- eGFR: 90 mL/min/1.73 m^2

Current treatment:

- Metformin 1000 mg BID
- Glimepiride 4 mg QD
- Sitagliptin 50 mg QD
- Atorvastatin 20 mg QD
- Lisinopril 10 mg QD

Current Presentation, cont.

- A1C is 8.2% and FPG averages ~ 182 mg/dL
  Random BG after breakfast ~ 210 mg/dL
- He has fear of needles and dreads having to inject himself, particularly at his work as a heavy machine operator.
- Concerned about increase in weight despite fairly strict diet and exercise. Has gained 10 lbs since last visit 6 months ago.

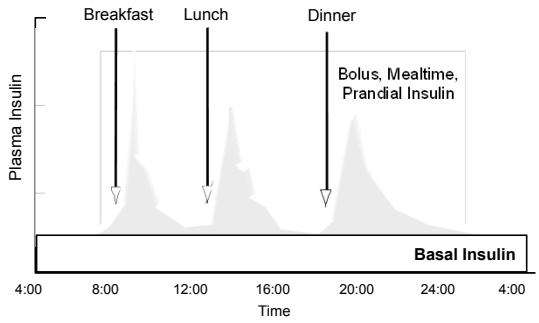
When to Consider Insulin in a Person with Type 2 Diabetes

- When combination of non-insulin antihyperglycemic medications are unable to achieve A1C, FPG and/or PPG targets
- Unacceptable side effects from non insulin medications
- Advanced hepatic or renal disease
- Special considerations (steroids, infection, pregnancy)
- Hyperglycemia in a hospitalized patient
- "Severely" uncontrolled diabetes*

Nathan DM, et al. *Diabetes Care*. 2009; volume 32,193-203.
Inzucchi SE, et al. *Diabetes Care*. 2012;35(6):1364-1379.
ADA *Diabetes Care*. 2014:37(Suppl 1):S14-S80.

* Random Glucose > 300 mg/dL, A1C > 10%, Ketonuria, Symptomatic polyuria/polydipsia, weight loss

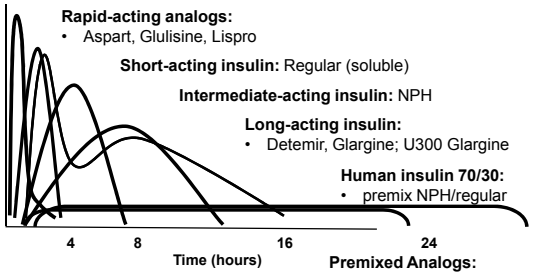
Physiologic Insulin Secretion



Adapted from Kruszynska Y, et al. *Diabetologia*. 1987; 30:16.

Types of Insulin

Ultra-Rapid-acting:
- Inhaled human insulin



Premixed Analogs:
Insulin lispro mix 75/25, 50/50
- Biphasic insulin aspart 70/30

Adapted from Hirsch I. *N Engl J Med*. 2005;352:174-183.

Currently Available Insulin Products

Insulin*	Onset	Peak	Effective Duration
Ultra-Rapid Acting technosphere inhaled (TI) human insulin	7.5 -10 minutes	12-15 minutes	28-180 minutes
Rapid-Acting Aspart, glulisine, lispro	5-15 minutes	30-90 minutes	<5 hours
Short-Acting Regular, U-500	30-60 minutes	2-3 hours	Regular: 5-8 hours U-500: 12 hours
Intermediate (basal) NPH	2-4 hours	4-10 hours	10-16 hours
Long-Acting (basal) Glargine, detemir U300 Glargine onset develops over 6 hours; Flatter profile; Duration longer than 24 hours	2-4 hours**	Modest peak	20-24 hours
Premixed 75% NPL/25% lispro 50% NPL/50% lispro 70% aspart protamine/30% aspart 70% NPH/30% regular/NPH	5-15 minutes 5-15 minutes 5-15 minutes 30-60 minutes	Dual Dual Dual Dual	10-16 hours 10-16 hours 10-16 hours 10-16 hours

*Assumes 0.1-0.2 units/kg/injection. Onset and duration may vary significantly by injection site
** Time to steady state

NPL=Neutralized Protamine Lispro;
NPH=Neutralized Protamine Hagedorn
TI = technosphere inhaled human insulin

DeWitt DE, et al. *JAMA*. 2003;289:2254-2264;
Hirsch IB, et al. *Clin Diabetes*. 2005;23:78-86
Adapted from Afrezza Technosphere PI FDA document-

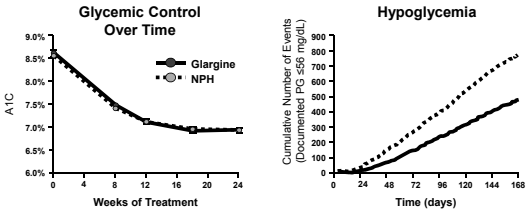
Advantages of Basal Insulin Analogs Over Human Insulin

- Longer-acting (up to 24 hours or longer)
  - Once-daily administration
  - Less variability from day to day
- Flatter biological activity (less peak)
  - Lower risk of nocturnal and overall hypoglycemia
- Less weight gain (insulin detemir)

Hirsch IB. *N Engl J Med*. 2005;352(2):174-183.
Meneghini L. et al. *Diabetes Obes Metab*. 2007;9(6):902-913.
Monami M, et al. *Diabetes Res Clin Pract*. 2008;81(2):184-189.

Addition of Basal Insulin to Oral Therapy: Treat-to-Target Trial

756 Patients with Type 2 Diabetes on 1 or 2 Oral Agents



PG = plasma glucose

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

Basal Insulin Analogs in Development

- Insulin Degludec U100 & U200
- PEGylated insulin lispro

Heise T, et al. Diabetes Obes Metab. 2012;14:944-950
Becker R, et al. European Patent EP 2 387 989 A2. 2011
Bergenstal RM, et al. Diabetes Care. 2012;35:2140-2147.

When It May Be Time to Stop Titrating Basal Insulin Therapy in T2DM?

- Individual is not meeting glycemic targets on basal insulin[1,2]
  - A1C still not at goal with ≈0.5 U/kg/day of daily basal insulin
  - A1C not at goal despite target fasting plasma glucose (FPG) with basal insulin
  - FPG with basal insulin is at target, but PPG is persistently above goal
- Large glucose drops overnight or between meals (suggesting excessive amounts of basal insulin)
- Presence of nocturnal hypoglycemia[1,2] or when further increases in basal insulin result in hypoglycemia

1. Inzucchi S, et al. *Diabetes Care*. 2012;35:1364-1379. 2. ADA. Practical Insulin: A Handbook for Prescribing Providers. 3rd ed. 2011:1-68.; Holman RR, et al. *N Engl J Med*. 2007;357:1716-1730.
Davidson MB, et al. *Endocr Pract*. 2011;17:395-403.

Options When Basal Insulin + Oral Antihyperglycemic Agents Do Not Achieve Target Glycemia?

- Add GLP-1 receptor agonist (GLP-1 RA) or DPP-4 inhibitor
- Add SGLT-2 inhibitor
- Substitute premix insulin
- Add bolus, mealtime (prandial) insulin
- Add inhaled technosphere insulin

Noninsulin Treatments for Postprandial Hyperglycemia

GLP-1 RA (exenatide bid, liraglutide, albiglutide)

- Injectable agents that enhance insulin secretion and inhibit glucagon release, both in a glucose-dependent manner[1,2-3]
- Shorter-acting GLP-1 RAs have greater impact on PPG levels while longer acting GLP-1RAs tend to have greater effect on FPG levels[3]
- Associated weight[2,3] and BP reduction[2] and improved lipid levels
- Exenatide QW and dulaglutide have not been studied with basal insulin; dulaglutide has been studied as add on to prandial insulin

1. Campbell JE, et al. *Cell Metab*. 2013;17:819-837. 2.Garber AJ. *Diabetes Care*. 2011;34(suppl 2):s279-s284.
3. Cross LB, Brunell S. *Am J Pharm Benefits*. 2013:5:e139-e150.

Noninsulin Treatments to Improve Postprandial Glucose

- DPP-4 inhibitors (sitagliptin, linagliptin, saxagliptin, alogliptin)[1]
  - Oral agents with moderate A1C improvement, especially when combined with metformin
  - Weight neutral
  - Adjustments for renal impairment except linagliptin
- SGLT2 Inhibitors (canagliflozin, dapagliflozin, empagliflozin)[2,3]
  - Oral antihyperglycemic agents
  - Associated with reduced systolic BP/diastolic BP and weight
  - Limited use in patients with significant chronic kidney disease; none are approved for patients with eGFR <45 ml/min

1. Deacon CF, Holst JJ. *Expert Opin Pharmacother*. 2013;14:2047-2058. 2. Yale J, et al. *Diabetes Obes Metab*. 2013;15:463-473.
3. Ghosh RK, et al. *J Clin Pharmacol*. 2012;52:457-463.

Noninsulin Treatments for Postprandial Hyperglycemia

- Incretins and SGLT2 inhibitors have a low risk for hypoglycemia unless they are given in combination with agents that themselves can cause hypoglycemia (sulfonylureas; glinides or insulin)
- When using such combinations clinicians should consider reducing dose of insulin or insulin secretagogues in order to reduce the risk for hypoglycemia

1. Campbell JE, et al. *Cell Metab*. 2013;17:819-837. 2.Garber AJ. *Diabetes Care*. 2011;34(suppl 2):s279-s284.
3. Cross LB, Brunell S. *Am J Pharm Benefits*. 2013:5:e139-e150.

However, many type 2 diabetes patients will require the addition of a prandial insulin to achieve glycemic goals

Role for Premixed Insulin

- Advantages
  - Both basal and prandial components in a single insulin preparation
  - Can cover insulin requirements through most of day
- Disadvantages
  - Not physiologic
  - Requires consistent meal and exercise pattern,
  - Cannot separately titrate individual insulin components [1]
  - ↑ risk for nocturnal hypoglycemia[2,3]
  - ↑ risk for fasting hyperglycemia if basal component does not last long enough[3]
  - Often requires accepting higher A1C goal (≤7.5% or ≤8%)[2,3]

1. Inzucchi S. et al. ADA, EASD Position Statement. *Diabetes Care*. 2012;35;1364-1379. 2. Janka HU, et al. *Diabetes Care*. 2005;28:254-259. 3. Fritsche A, et al. *Diab Obes Metab*. 2010;12:115-123.

Advantages of Rapid-Acting Insulin Analogs Over Regular Human Insulin

- More rapid onset of action
  - Facilitates more convenient mealtime administration
  - Offers potential for better postprandial glucose control
- More rapid return to basal insulin levels
  - Potentially less hypoglycemia
- Greater predictability

Hirsch IB. *N Engl J Med*. 2005;352:174-183.

Physician Roadblocks to Timely Insulin Initiation

When Do Physicians Consider Using Insulin Therapy?	
Multiple medication failure	75%
A1C > 8.5%	41%
Worsening of microvascular complications	15%
Unintentional weight loss	12%
Repeated fasting glucose > 200 mg/dL	9%

Physician Concerns About Starting Insulin Therapy	
Poor patient adherence	92%
Hypoglycemia	80%
Pain from glucose monitoring	54%
Pain from insulin injections	48%
Patient is too old	47%
No experience with insulin	27%
Weight gain	26%
Diabetes is too severe	13%

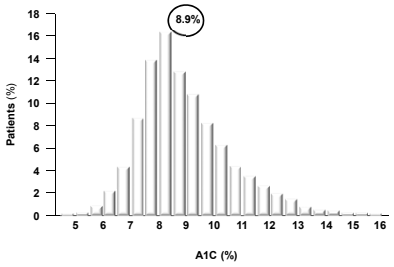
Nakar S, et al. *J Diabetes Complications*. 2007;21:220-226.

Patient Concerns About Insulin

- Self-blame due to perception that adherence to therapy should have been better.
- Avoidance/fear of injections
- Concerns of risk
  - Hypoglycemia
  - Weight gain
  - Complexity of regimens
  - Misconceptions about complications
- Skepticism of need for insulin or its efficacy
- Negative impact on social life

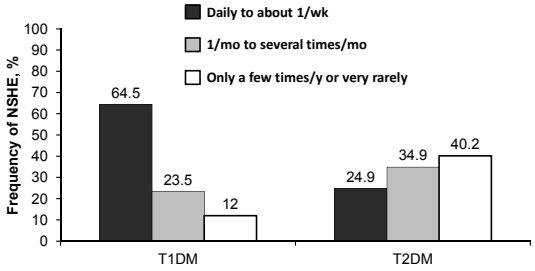
Karter A, et al. *Diabetes Care*. 2010;33:733-735;
Peyrot M, et al. *Diabetes Care*. 2005;28:2673-2679.

SOLVE: Baseline A1C Distribution at Insulin Initiation



Khunti K, et al for the SOLVE Study Group. *Diabetes*. 2011;6 (Suppl 1):A306.

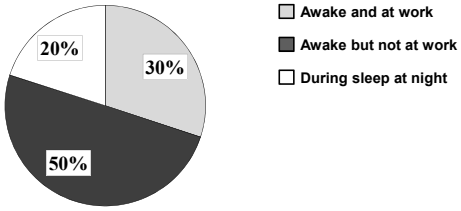
How Often Does Hypoglycemia Occur in Diabetes Patients?



NSHE, nonsevere hypoglycemic events.
Survey 409 US patients with T1DM (n = 200) and with T2DM (n = 209).

Brod M, et al. *Value Health*. 2011;14:665-671.

When Does Hypoglycemia Occur With Diabetes?

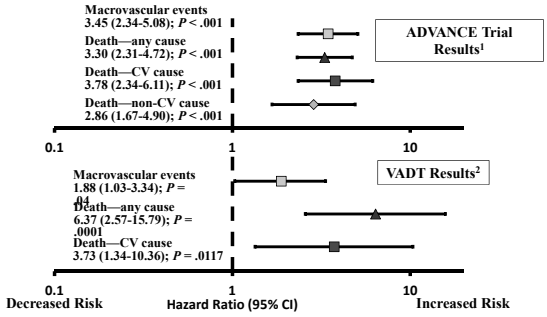


1/5 of all nonsevere hypoglycemia occurs nocturnally

NSHE, nonsevere hypoglycemic events.
Survey 409 US patients with T1DM (n = 200) and with T2DM (n = 209).

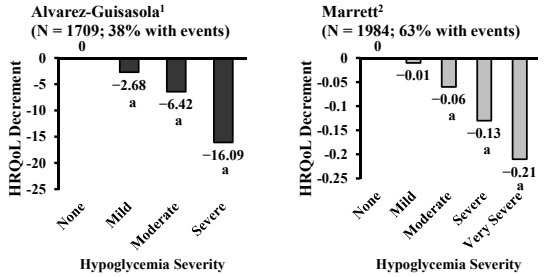
Brod M, et al. *Value Health*. 2011;14:665-671.

Severe Hypoglycemia Increases the Risk of Mortality and CV Events



1. Zoungas S, et al; ADVANCE Collaborative Group. *N Engl J Med*. 2010;363:1410-1418.
2. Duckworth W, et al; VADT Investigators. VA Diabetes Trial (VADT) update. ADA 70th Scientific Sessions. 2010: http://webcasts.prous.com/netadmin/webcast_viewer/Preview.aspx?type=0&lid=9473&pv=2&preview=False&idcl=0.

All Hypoglycemia Negatively Affects Quality of Life in Patients With T2DM



Hypoglycemia is also associated with lower treatment satisfaction, poorer adherence, and greater resource utlization[3]

* *P* < .05 vs no reported hypoglycemia.

1. Alvarez-Guisasola F, et al. *Health Qual Life Outcomes*. 2010;8:86.
2. Marrett E, et al. *BMC Res Notes*. 2011;4:251.
3. Williams S, et al. *Diabetes Res Clin Pract*. 2011;91:363-370.

Practical Tips for Treating Hypoglycemia

- **Patient, family, and friends should be aware of hypoglycemia signs and symptoms**
- **Have a plan to manage hypoglycemia (eg, Rule of 15)**
  - **Test BG, if possible**
  - **Treat hypoglycemia with 15 grams of sugar or carbohydrates (eg, ½ cup juice, 2-3 glucose tablets)**
  - **Wait 15 minutes and test BG again**
  - **Take additional 15 grams if necessary**
  - **Follow treatment of hypoglycemia with protein**
  - **Resume activity when feeling better and BG > 100 mg/dL**

ADA. Hypoglycemia (low blood glucose). http://www.diabetes.org/living-with-diabetes/treatment-and-care/blood-glucose-control/hypoglycemia-low-blood.html.

Guidelines for Preventing Hypoglycemia

AACE[1-4]

- Address in each patient contact
- If problematic, adjust regimen by:
  - Reviewing/applying diabetes self-management
  - Frequent SMBG
  - Flexible, appropriate insulin regimens
  - Individualized glycemic goals
  - Ongoing professional guidance and support
- Consider each of the known risk factors for hypoglycemia

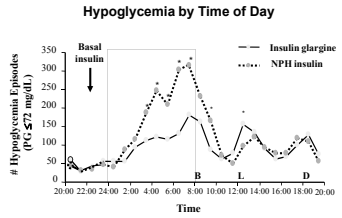
ADA[5]

- Reevaluate SMBG skills periodically
- Avoid aggressive targets in advanced disease
- Limit alcohol intake
  - ≤ 1 drink/day in adult women
  - ≤ 2 drinks/day in adult men
- Add carbohydrate before exercising if BG < 100 mg/dL
- Strict avoidance of hypoglycemia for several weeks partly resolves repeated severe hypoglycemia, hypoglycemia unawareness

SMBG, self-monitoring of blood glucose.

1. Cryer PE, et al. *J Clin Endocrinol Metab*. 2009;94:709-728.
2. Cooperberg BA, et al. *Diabetes Care*. 2008;31:2271-2272.
3. Raju B, et al. *J Clin Endocrinol Metab*. 2006;91:2087-2092.
4. Taplin CE, et al. *J Pediatr*. 2010;157:784-788.
5. American Diabetes Association. *Diabetes Care*. 2015;38(suppl 1):S38-39

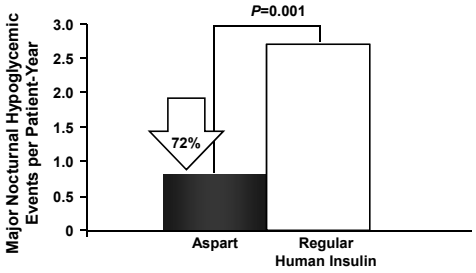
Treat-to-Target Trial: Timing and Frequency of Hypoglycemia



*P<.05 (between treatment)
PG=plasma-referenced glucose

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

Fewer Nocturnal Hypoglycemic Events in Patients Treated With Aspart vs Regular Human Insulin



Adapted from Heller SR et al. *Diabet Med*. 2004;21:769-775.

Summary

- Many type 2 diabetes patients will require insulin for glycemic control
- Whether basal insulin or a GLP-1 receptor agonist should be the 1st injectable should be individualized
- Insulin analogs have several advantages over human insulin products
- When FPG is at goal but A1C is elevated, PPG needs to be assessed
- Multiple options for addressing elevated PPG but ultimately many patients may require prandial insulin

Luigi Meneghini, MD, MBA

Professor of Internal Medicine
Division of Endocrinology
University of Texas Southwestern Medical Center
Executive Director
Global Diabetes Program
Parkland Health and Hospital System
Atlanta, GA.

Controlling Glucose is Difficult

- Self-monitoring of blood glucose > 4 times daily
- Measurement of A1C every 3-4 months
- Dietary modification
- Rigorous diet / exercise program
- No existing drug that consistently controls blood glucose levels
- Mealtime glucose excursions are poorly controlled

Case: Poorly Controlled T2DM Patient on Basal Insulin at HS

- 58-yr old African American male with T2DM diagnosis since age 45, now on basal insulin at HS for past 3 yrs returns for follow-up.
- Hx: HTN, mixed dyslipidemia adequately controlled with medications
  - Recently widowed, but children live nearby
  - Physically active with regular exercise 4 X/wk for 30-45 minutes daily. Tennis at least once each week
  - EtoH & tobacco (negative)

Current Exam & Treatment

Current exam:

- Wt 228 lbs, Ht 68", BMI 34.7
- A1C 8.2%, Cr 1.2, C-peptide 2.9 ng/mL
- eGFR: 50 mL/min/1.73 m^2

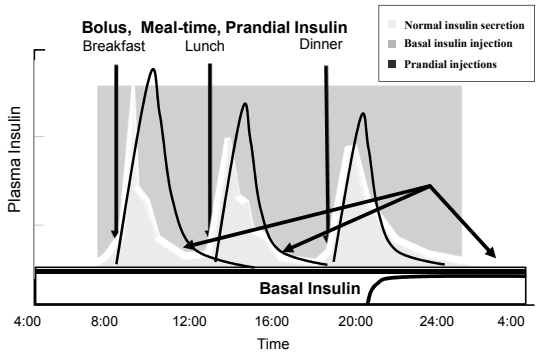
Current treatment:

- Metformin 1000 mg BID
- Sitagliptin 100 mg QD
- Glargine insulin 47 U HS
- Atorvastatin 20 mg QD
- Lisinopril 10 mg QD

Current Presentation, cont.

- A1C is 8.2% and FPG averages ~ 119 mg/dL
- At his physician's request he recorded his glucose values which showed modestly increased post-lunch and pre-bedtime glucose values.
- He is concerned about hypoglycemia, especially since he lives alone and has had 3 documented instances of hypoglycemia over past year.
- Also concerned about recent weight gain (8 lbs), which seems to have also worsened over time..

Need for Better Coverage?

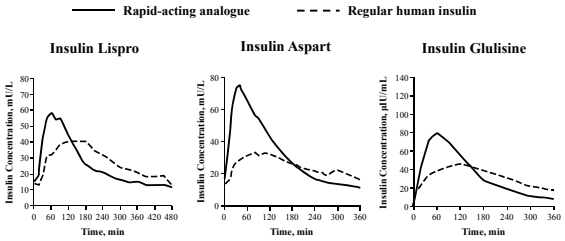


Adapted from Kruszynska Y, et al. *Diabetologia.* 1987; 30:16.

Limitations of Human Regular Insulin

- **Slow onset of action**
  - Requires inconvenient administration:
    20 to 40 minutes prior to meal
  - Risk of hypoglycemia if meal is further delayed
  - Mismatch with postprandial hyperglycemic peak
- **Long duration of activity**
  - Up to 12 hours' duration
  - Increased at higher dosages
  - Potential for late postprandial hypoglycemia

Prandial Insulins: Rapid-Acting Analogues vs. Regular Human Insulin



Rapid-acting analogues have more rapid onset and shorter time to peak than regular human insulin

http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA;
ADA *Practical Insulin: A Handbook for Prescribing Providers*. 3rd ed. 2011:1-68.

Clinical features of Rapid-acting Analogues

- **Insulin profile more closely mimics normal physiology**
- **Convenient administration immediately prior to meals**
- **Faster onset of action**
- **Limit postprandial hyperglycemic peaks**
- **Shorter duration of activity**
  - Reduced late postprandial and nocturnal ***hypoglycemia***
  - But more frequent late postprandial ***hyperglycemia***
- **Need for basal insulin replacement revealed**

6-27

Comparing 2 Methods of Stepwise Prandial Insulin Intensification

Parameter/ Characteristic	SimpleSTEP	ExtraSTEP
Basal insulin titration	Based on average of 3 pre-breakfast plasma glucose readings	
Prandial dose addition (every 12 weeks, if needed)	• Added to perceived largest meal	• Added to meal with highest postmeal plasma glucose increase
Prandial insulin titration	Based on ***PREMEAL*** plasma glucose	Based on ***POSTMEAL*** plasma glucose
SMBG	3 × 4-point profiles • Before each meal • Bedtime	3 × 6-point profiles • Before each meal • 2 h after each meal

Meneghini L, et al. *Endocr Pract.* 2011;17:727-736.

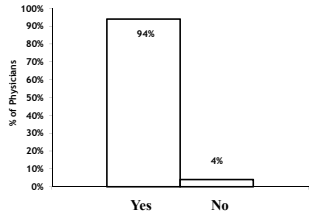
STEPwise Study Conclusions

- Overall reduction in A1C of 1.2% was achieved with the addition of prandial insulin.
- Greatest A1C reductions were achieved with the first and second bolus injections.
- Improvement in glycemic control was comparable in both groups.
- Number of hypoglycemic episodes increased with increasing number of prandial injections.
- Basal-bolus treatment can be introduced in a more patient-friendly approach, using simple stepwise addition of prandial insulin.

Meneghini, et al. *Endocr Pract.* 2011;17:727-736

Physicians Confirm Need for a Faster Insulin

"We need insulins that work faster than current rapid-acting analogs."



Source: Close Concerns, Diabetes Close Up; HCP Survey ADA 2010

Ideal Prandial Insulin

Desirable Characteristics

Predictable time-action profile

Rapid onset of action

Short duration of action

Benefits

Precise dosing

Improve post-meal

Reduced risk of hypoglycemia (day & night)

Less weight gain

Approaches to Accelerate the Time Action Profiles of Fast-Acting Insulins

- Faster insulins
  - Linjeta - Biodel (Phase 3)
  - Adocia – Biochaperone (Phase 2)
  - Faster-acting Aspart - Novo Nordisk (Phase 3)
- Co-formulate with hyaluronidase
  - Halozyme (Phase 4)
- Warming the infusion site
  - InsuPad- InsuLine Medical
- Alternate Routes
  - Inhaled Insulin: Afrezza-MannKind (FDA Approved)
  - Intra-dermal: Micro-needle infusion sets-BD
  - Intra-peritoneal: DiaPort-Roche

Challenges of Previous Inhaled Human Insulin

- Challenges
  - Size of device
  - Difficult dose adjustment
  - Dosage form inconsistencies
  - Risk of lung disease
  - Insurance barriers
  - Withdrawn from the market in 2007

Mack GS. *Nat Biotechnol.* 2007 Dec;25(12):1331-2.

Novel Delivery of Insulin

Human insulin produced by recombinant DNA technology

Technosphere insulin consists of fumaryl diketopiperazine (FDKP)

- Biologically inert excipient
- Self-assembles into microcrystals 2-4 µm (~ 2.5µm in diameter)
- Ideal size for inhalation into the deep lung
- FDKP has no metabolic activity in man
- FDKP excreted intact in the urine

www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/endocrinologicandmetabolicdrugsadvisorycommittee/ucm390865.pdf

Rapid Absorption and Short Duration of Action

MKC-TI-177

Compared to subcutaneous rapid acting insulin analog (RAA),

TI shows:

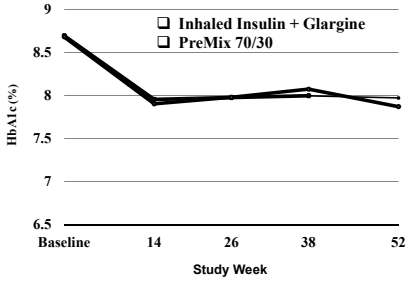
- More rapid absorption :
  - Time to peak serum insulin conc. (T_{max})
  - **⇒ ~ 14 min after TI inhalation**
  - **⇒ ~ 60 minutes after SC RAA**
- Faster elimination
  - ⇒ ~ 180 minutes for TI
  - ⇒ ~ 300 minutes for RAA

/www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/endocrinologicandmetabolicdrugsadvisorycommittee/ucm390865.pdf

Clinical Application of Inhaled human Insulin

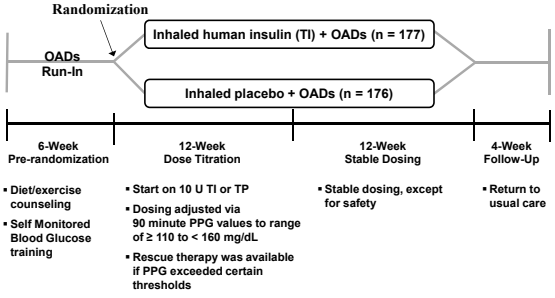
- Indications:
  - A rapid-acting, pre-meal time insulin for patients with Type 1 and 2 diabetes.
- Place in therapy:
  - An inhaled alternative to vial and syringe for meal-time insulins. Type 1 diabetes patients wtill need a long-acting insulin in addition to prandial insulin.

Non-Inferior Glycemic Control A1C Change - Baseline to Week 52



Rosenstock J, Lancet, 2010

T2DM Trial Design (Trial 175)



Insulin–naïve patients with inadequate glycemic control (HbA1c 7.5% to 10%) on optimal or maximally-tolerated doses of either metformin monotherapy or ≥ 2 OADs

www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/endocrinologicandmetabolicdrugsadvisorycommittee/ucm390865.pdf

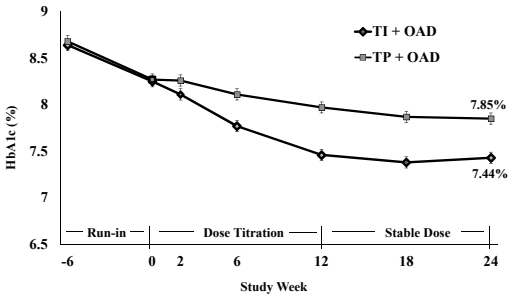
Primary Endpoint: HbA1c Change from Baseline to Week 24

Drug	N	HbA1c			Treatment Difference
		Baseline	Week 24	Change	
TI + OAD	177	8.25%	7.43%	-0.82%	-0.40% p<0.0001
TP + OAD	176	8.27%	7.85%	-0.42%	

Treatment Difference 95% CI: (-0.57, -0.23)

www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/endocrinologicandmetabolicdrugsadvisorycommittee/ucm390865.pdf

Change in HbA_{1c} Over Time



TI N:	177	176	174	163	159	149	139
TP N:	176	176	167	163	147	137	129

www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/endocrinologicandmetabolicdrugsadvisorycommittee/ucm390865.pdf

Adverse Effects

Inhaled Insulin vs. Placebo vs. Non-placebo In Type 2 DM patients	Inhaled Insulin vs SC insulin In Type 1 DM patients
Headache: 3.1% (2.8%) [1.8%]	**Headache:** 4.7% [2.8%]
Cough: 25.6% (19.7%) [5.4%]	**Cough:** 29.4% [4.9%]
Throat pain / irritation: 4.4% (3.8%) [0.9%]	**Throat pain / irritation:** 5.5% [1.9%]
Severe hypoglycemia: 5.1% (1.7%)	**Bronchitis:** 2.5% [2.0%]
Hypoglycemia: 67% (30%)	**Urinary tract infection**: 2.3% [1.9%]
FEV1 decline >15%: 6% [3%]	

www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/endocrinologicandmetabolicdrugsadvisorycommittee/ucm390865.pdf

Safety

- Well tolerated
- Most common adverse events were cough and hypoglycemia
- Small non-progressive, clinically insignificant changes in pulmonary function
- Significant reduction in the risk of mild, moderate and severe hypoglycemia compared with SC insulins
- No increased cardiovascular risk
- No increased cancer risk observed

Limitations / Contraindications

❑Limitations:

- Inhaled insulin is not a substitute for long-acting insulin.
- Not recommended for the treatment of diabetic ketoacidosis
- Not recommended in patients who smoke or who have stopped smoking in last 6 months.

❑Contraindications:

- During episodes of hypoglycemia
- In patients who have chronic lung disease such as COPD or asthma

www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/endocrinologicandmetabolicdrugsadvisorycommittee/ucm390865.pdf

Warnings and Precautions

- Decline in pulmonary function observed over time
- Incidence of lung cancer was observed in controlled and uncontrolled trials
- More patients using inhaled insulin experienced ketoacidosis
- Life-threatening hypokalemia

www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/endocrinologicandmetabolicdrugsadvisorycommittee/ucm390865.pdf

Black Box Warning

- Acute bronchospasms reported in patients with asthma and COPD using inhaled insulin.
  - REMS established to ensure benefits outweigh risk
- Contraindication in patients with chronic lung disease
- Before initiating inhaled insulin all patients need detailed medical history, PE and spirometry to identify potential lung disease

www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/endocrinologicandmetabolicdrugsadvisorycommittee/ucm390865.pdf

Monitoring Parameters

- **Efficacy Monitoring**:
  - Blood glucose, A1C
- **Toxicity Monitoring:**
  - Pulmonary function tests before initiating, after 6 months of therapy and annually, even in absence of pulmonary symptoms.
  - Fluid retention and heart failure with concomitant use of thiazolidinediones
  - Hypokalemia

www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/endocrinologicandmetabolicdrugsadvisorycommittee/ucm390865.pdf

Risk Management Plan

Label	REMS	Post- Approval Studies	Pharmacovigilance Plan
Contraindication: **Patients with asthma, COPD, or other chronic lung conditions**	**Communication Plan to inform HCPs of potential risk with TI** **Screening for lung disease prior to starting TI** · **Lung function decline over time** · **Use by inappropriate patient populations (smokers, chronic lung disease)**	**Prospective, long-term, observational study to evaluate risk of:** · **Lung cancer** · **Other malignancies** · **Respiratory events** · **Hypoglycemia requiring medical interventions** · **Serious allergic events**	**Proactively identify, evaluate, and monitor targeted medical events such as respiratory events, malignancies, CV events, hypoglycemia requiring medical intervention, DKA, medication errors and product complaints, etc.** **Signal detection and evaluation**
Warnings and Precautions: · **Screening for potential lung disease before starting TI** · **Not recommended in smokers**	**Additional voluntary measures outside of REMS** **Instructions for Use** **Medication Guide** **Starter Kits**		

COPD=chronic obstructive pulmonary disease; CV=cardiovascular; DKA=diabetic ketoacidosis; HCP=health care providers; REMS=Risk Evaluation and Mitigation Strategy

Afrezza FDA approval data on file

Insulin Naïve & Conversion Dosing

Insulin Naïve Individuals:
Start on 4 units of inhaled insulin at each meal.

Individuals Using Subcutaneous Mealtime (Prandial) Insulin:
Determine the appropriate inhaled dose for each meal by converting from the injected dose using table.

www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/endocrinologicandmetabolicdrugsadvisorycommittee/ucm390865.pdf

Mealtime Dose Adjustment

- Adjust the dosage of inhaled insulin based on the individual's metabolic needs, blood glucose monitoring results and glycemic control goal.
- Dosage adjustments may be needed with changes in physical activity, changes in meal patterns, changes in renal or hepatic function or during acute illness
- Carefully monitor blood glucose control in patients requiring high doses of inhaled insulin. If blood glucose control is not achieved with increased inhaled doses, consider use of subcutaneous mealtime insulin.

Switching from SC Pre-mixed Insulin:

- Estimate the mealtime injected dose by dividing half of the total daily injected pre-mixed insulin dose equally among the three meals of the day.
- Convert each estimated injected mealtime dose to an appropriate inhaled dose using chart.
- Administer half of the total daily injected pre-mixed dose as an injected basal insulin dose.

Clinical Case Scenario

- A 58 y/o man with T2DM of 6 yrs duration presents to his primary care provider for follow-up.
  - History of HTN, mixed dyslipidemia, obesity
  - Recently widowed, but children live nearby
  - Physically active with regular exercise at least 4 times /week for 30-45 minutes daily. Tennis at least once each week
- He is currently taking metformin, sitagliptin and insulin glargine and not at goal

Clinical Case Scenario, cont.

- A1C is 8.2% and FPG averages ~ 119 mg/dL
- At his physician's request he recorded his glucose values which showed modestly increased post lunch and pre-bedtime glucose values.
- He is concerned about hypoglycemia, especially since he lives alone and has had 3 documented instances of hypoglycemia over past year.
- Also concerned about recent weight gain (8 lbs), which seems to have also worsened over time..

Current Labs & Medications

Labs:

- Blood pressure: 136/85 mmHg
- BMI: 33.5
- LDL-C: 80 mg/dL
- TC: 182 mg/dL
- eGFR: 50 mL/min/1.73 m^2

Medications

- metformin 1,000 mg BID
- sitagliptin 100mg QD
- glargine insulin 47 U SC
- atorvastatin 20 mg QD

Conclusions

- Many type 2 diabetes patients will require insulin for glycemic control
- When FPG is at goal, but A1C is elevated, PPG needs to be assessed
- Multiple options for addressing elevated PPG but ultimately many patients may require prandial insulin
- Wide range of prandial insulins are available for both SC and inhaled delivery
- Hypoglycemia can be minimized and treated

More Conclusions

- Inhaled insulin is indicated for use as meal time insulin in patients with type 1 and type 2 diabetes
- Inhaled insulin has quicker onset and shorter duration than other rapid-acting insulins resulting in improved postprandial control with less risk of hypoglycemia and weight gain
- Adding 3 x daily inhaled insulin to existing oral therapy is generally more effective over a 12-24 week period than adding a second oral agent taken once or twice a day
- Should be avoided in smokers, patients with chronic pulmonary disease and patients with bronchospasm or asthma
- Most suitable for patients with A1C levels that remain elevated after FPG have been controlled with a basal insulin