2013 Diabetes Clinical Practice Recommendations and Treatment Algorithms: What's New!

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- The speaker has no conflict in relation to this program.

Outline

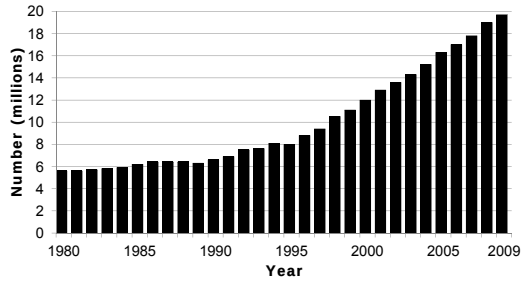
- ADA 2013 Clinical Practice Recommendations
- ADA-EASD Position Statement on Type 2 Diabetes Management
- AACE/ACE Treatment Algorithm
- New Diabetes Treatments
  - Long-acting GLP-1 Agonists
  - Ultra Long-acting Insulin
  - SGLT2 Inhibitors
- No conflicts of interest to report

Epidemiology of Diabetes

- Diabetes affects 25.8 million people of all ages
- 8.3% of the U.S. population
  - Diagnosed: 18.8 million
  - Undiagnosed: 7.0 million
- Leading cause of kidney failure, nontraumatic lower-limb amputation, new cases of blindness among adults
- Major cause of heart disease and stroke
- Seventh leading cause of death

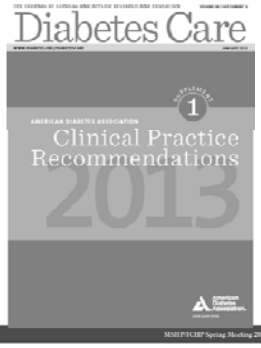
National Diabetes Information Clearinghouse. National Diabetes Statistics, 2011. Available at: http://diabetes.niddk.nih.gov/dm/pubs/statistics/

Number of Americans with Diagnosed Diabetes, 1980-2009



www.cdc.gov

STANDARDS OF MEDICAL CARE IN DIABETES—2013



ADA Evidence Grading System for Clinical Recommendations

Level of Evidence	Description
A	Clear or supportive evidence from adequately powered well-conducted, generalizable, randomized controlled trials
	Compelling nonexperimental evidence
B	Supportive evidence from well-conducted cohort studies or case-control study
C	Supportive evidence from poorly controlled or uncontrolled studies
	Conflicting evidence with the weight of evidence supporting the recommendation
E	Expert consensus or clinical experience

ADA. *Diabetes Care* 2013;36(suppl 1):S12; Table 1.

Classification of Diabetes

- Type 1 diabetes
  - β-cell destruction
- Type 2 diabetes
  - Progressive insulin secretory defect
- Other specific types of diabetes
  - Genetic defects in β-cell function, insulin action
  - Diseases of the exocrine pancreas
  - Drug- or chemical-induced
- Gestational diabetes mellitus (GDM)

ADA. I. Classification and Diagnosis. *Diabetes Care* 2013;36(suppl 1):S11.

Criteria for the Diagnosis of Diabetes

A1C ≥6.5%

OR

Fasting plasma glucose (FPG) ≥126 mg/dL

OR

2-h plasma glucose ≥200 mg/dL during an OGTT

OR

A random plasma glucose ≥200 mg/dL

ADA. I. Classification and Diagnosis. *Diabetes Care* 2013;36(suppl 1):S13; Table 2.

Prediabetes: IFG, IGT, Increased A1C

Categories of increased risk for diabetes (prediabetes)*

FPG 100–125 mg/dL: IFG

OR

2-h plasma glucose in the 75-g OGTT 140–199 mg/dL: IGT

OR

A1C 5.7–6.4%

*For all three tests, risk is continuous, extending below the lower limit of a range and becoming disproportionately greater at higher ends of the range.

ADA. I. Classification and Diagnosis. *Diabetes Care* 2013;36(suppl 1):S13; Table 3.

Criteria for Testing for Diabetes in Asymptomatic Adult Individuals

Testing should be considered in all adults who are overweight (BMI ≥25 kg/m^2*) and have additional risk factors:

- Physical inactivity
- First-degree relative with diabetes
- High-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
- Women who delivered a baby weighing >9 lb or were diagnosed with GDM
- Hypertension (≥140/90 mmHg or on therapy for hypertension)
- HDL cholesterol level <35 mg/dL and/or a triglyceride level >250 mg/dL
- Women with polycystic ovary syndrome (PCOS)
- A1C ≥5.7%, IGT, or IFG on previous testing
- Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
- History of CVD

*At-risk BMI may be lower in some ethnic groups.

ADA. Testing for Diabetes in Asymptomatic Patients. *Diabetes Care* 2013;36(suppl 1):S14; Table 4.

Recommendations: Prevention/Delay of Type 2 Diabetes

- Refer patients with IGT (A), IFG (E), or A1C 5.7–6.4% (E) to ongoing support program
  - Targeting weight loss of 7% of body weight
  - At least 150 min/week moderate physical activity
- Follow-up counseling important for success (B)
- Based on cost-effectiveness of diabetes prevention, third-party payers should cover such programs (E)

ADA. IV. Prevention/Delay of Type 2 Diabetes. *Diabetes Care* 2013;36(suppl 1):S16.

Recommendations: Prevention/Delay of Type 2 Diabetes

- Consider metformin for prevention of type 2 diabetes if IGT (A), IFG (E), or A1C 5.7–6.4% (E)
  - Especially for those with BMI >35 kg/m^2, age <60 years, and women with prior GDM (A)
- In those with prediabetes, monitor for development of diabetes annually (E)
- Screen for and treat modifiable risk factors for CVD (B)

ADA. IV. Prevention/Delay of Type 2 Diabetes. *Diabetes Care* 2013;36(suppl 1):S16.

Diabetes Care: Management

- People with diabetes should receive medical care from a team that may include
  - Physicians, nurse practitioners, physician's assistants, nurses, dietitians, pharmacists, mental health professionals
  - In this collaborative and integrated team approach, essential that individuals with diabetes assume an active role in their care
- Management plan should recognize diabetes self-management education (DSME) and on-going diabetes support

ADA. V. Diabetes Care. *Diabetes Care* 2013;36(suppl 1):S17.

Diabetes Care: Glycemic Control

- Two primary techniques available for health providers and patients to assess effectiveness of management plan on glycemic control
  - Patient self-monitoring of blood glucose (SMBG), or interstitial glucose
  - A1C

ADA. V. Diabetes Care. *Diabetes Care* 2013;36(suppl 1):S17.

Recommendations: Glucose Monitoring

- Patients on multiple-dose insulin (MDI) or insulin pump therapy should do SMBG (B)
  - At least prior to meals and snacks
  - Occasionally postprandially
  - At bedtime
  - Prior to exercise
  - When they suspect low blood glucose
  - After treating low blood glucose until they are normoglycemic
  - Prior to critical tasks such as driving

ADA. V. Diabetes Care. *Diabetes Care* 2013;36(suppl 1):S17.

Recommendations: Glucose Monitoring

- When prescribed as part of a broader educational context, SMBG results may be helpful to guide treatment decisions and/or patient self-management for patients using less frequent insulin injections or noninsulin therapies (E)
- When prescribing SMBG, ensure that patients receive ongoing instruction and regular evaluation of SMBG technique and SMBG results, as well as their ability to use SMBG data to adjust therapy (E)

ADA. V. Diabetes Care. *Diabetes Care* 2013;36(suppl 1):S16.

Recommendations: A1C

- Perform A1C test at least twice yearly in patients meeting treatment goals (and have stable glycemic control) (E)
- Perform A1C test quarterly in patients whose therapy has changed or who are not meeting glycemic goals (E)
- Use of point-of-care (POC) testing for A1C provides the opportunity for more timely treatment changes (E)

ADA. V. Diabetes Care. *Diabetes Care* 2012;35(suppl 1):S18.

Correlation of A1C with Average Glucose (AG)

A1C (%)	Mean plasma glucose mg/dL	mmol/L
6	126	7.0
7	154	8.6
8	183	10.2
9	212	11.8
10	240	13.4
11	269	14.9
12	298	16.5

These estimates are based on ADAG data of ~2,700 glucose measurements over 3 months per A1C measurement in 507 adults with type 1, type 2, and no diabetes. The correlation between A1C and average glucose was 0.92. A calculator for converting A1C results into estimated average glucose (eAG), in either mg/dL or mmol/L, is available at http://professional.diabetes.org/eAG.

ADA. V. Diabetes Care. *Diabetes Care* 2013;36(suppl 1):S19; Table 8.

Recommendations: Glycemic Goals in Adults

- Lowering A1C to below or around 7% has been shown to reduce microvascular complications and, if implemented soon after the diagnosis of diabetes, is associated with long-term reduction in macrovascular disease (B)
- Therefore, a reasonable A1C goal for many nonpregnant adults is <7% (B)

ADA. V. Diabetes Care. *Diabetes Care* 2013;36(suppl 1):S19.

Recommendations: Glycemic Goals in Adults

- Providers might reasonably suggest more stringent A1C goals (such as <6.5%) for selected individual patients, if this can be achieved without significant hypoglycemia or other adverse effects of treatment (C)
- Appropriate patients might include those with short duration of diabetes, long life expectancy, and no significant CVD (C)

ADA. V. Diabetes Care. *Diabetes Care* 2013;36(suppl 1):S19.

Recommendations: Glycemic Goals in Adults

- Less stringent A1C goals (such as <8%) may be appropriate for patients with (B)
  - History of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions
  - Those with longstanding diabetes in whom the general goal is difficult to attain despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose lowering agents including insulin

ADA. V. Diabetes Care. *Diabetes Care* 2013;36(suppl 1):S19.

Recommendations: Glycemic, Blood Pressure, Lipid Control in Adults

A1C	<7.0%*
Blood pressure	<140/80 mmHg†
Lipids: LDL cholesterol	<100 mg/dL‡ Statin therapy for those with history of MI or age >40+ or other risk factors

*More or less stringent glycemic goals may be appropriate for individual patients. Goals should be individualized based on: duration of diabetes, age/life expectancy, comorbid conditions, known CVD or advanced microvascular complications, hypoglycemia unawareness, and individual patient considerations.
†Based on patient characteristics and response to therapy, higher or lower systolic blood pressure targets may be appropriate.
‡In individuals with overt CVD, a lower LDL cholesterol goal of <70 mg/dL, using a high dose of statin, is an option.

ADA. VI. Prevention, Management of Complications. *Diabetes Care* 2013;36(suppl 1):S33; Table 10.

Recommendations: Diabetes Care in the Hospital

- Goals for blood glucose levels
  - Critically ill patients: Initiate insulin therapy for treatment of persistent hyperglycemia starting at a threshold of no greater than 140-180 mg/dL . (A)
  - More stringent goals, such as 110-140 mg/dL may be appropriate for selected patients, if achievable without significant hypoglycemia (C)
  - Critically ill patients require an IV insulin protocol with demonstrated efficacy, safety in achieving desired glucose range without increasing risk for severe hypoglycemia (E)

ADA. IX. Diabetes Care in Specific Settings. *Diabetes Care*. 2013;36(suppl 1):S45.

Recommendations: Diabetes Care in the Hospital

- Goals for blood glucose levels
  - Noncritically ill patients: No clear evidence for specific blood glucose goals
  - If treated with insulin, premeal blood glucose targets (if safely achieved)
    - Generally <140 mg/dL with random blood glucose <180 mg/dL
  - More stringent targets may be appropriate in stable patients with previous tight glycemic control
  - Less stringent targets may be appropriate in those with severe comorbidities (E)

ADA. IX. Diabetes Care in Specific Settings. *Diabetes Care*. 2013;36(suppl 1):S46.

Recommendations: Diabetes Care in the Hospital

- Scheduled subcutaneous insulin with basal, nutritional, and correction components is the preferred method for achieving and maintaining glucose control in non-critically ill patients (C)

ADA. IX. Diabetes Care in Specific Settings. *Diabetes Care*. 2013;36(suppl 1):S46.

Recommendations: Diabetes Care in the Hospital

- Initiate glucose monitoring in any patient not known to be diabetic who receives therapy associated with high-risk for hyperglycemia
  - High-dose glucocorticoid therapy, initiation of enteral or parenteral nutrition, or other medications such as octreotide or immunosuppressive medications (B)
- If hyperglycemia is documented and persistent, consider treating such patients to the same glycemic goals as patients with known diabetes (E)

ADA. IX. Diabetes Care in Specific Settings. *Diabetes Care*. 2013;36(suppl 1):S46.

Recommendations: Diabetes Care in the Hospital

- A hypoglycemia management protocol should be adopted and implemented by each hospital or hospital system (E)
- Obtain A1C for all patients (E)
  - If results within previous 2–3 months unavailable
  - With diabetes risk factors who exhibit hyperglycemia
- Patients with hyperglycemia without a diagnosis of diabetes: document plans for follow-up testing and care at discharge (E)

ADA. IX. Diabetes Care in Specific Settings. *Diabetes Care*. 2013;36(suppl 1):S46.

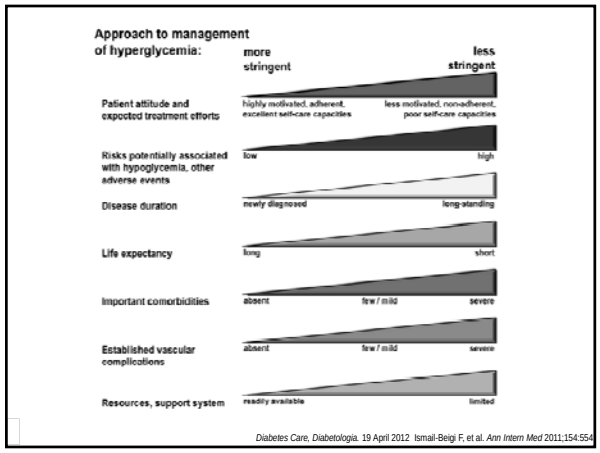
Impact of Intensive Therapy for Diabetes: Summary of Major Clinical Trials

Study	Microvasc		CVD		Mortality	
UKPDS	↓	↓	↔	↓	↔	↓
DCCT / EDIC*	↓	↓	↔	↓	↔	↔
ACCORD	↓		↔		↑	
ADVANCE	↓		↔		↔	
VADT	↓		↔		↔	

Kendall DM, Bergenstal RM. © International Diabetes Center 2009
UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;352:854.
Holman RR et al. *N Engl J Med*. 2008;359:1577. DCCT Research Group. *N Engl J Med* 1993;329:977.
Nathan DM et al. *N Engl J Med*. 2005;353:2643. Gerstein HC et al. *N Engl J Med*. 2008;358:2545.
Patel A et al. *N Engl J Med* 2008;358:2560.

* in T1DM

Initial Trial
Long Term Follow-up



Diabetes Care, Diabetologia. 19 April 2012 Ismail-Beigi F, et al. *Ann Intern Med* 2011;154:554

ADA-EASD Position Statement: Management of Hyperglycemia in T2DM

Anti-hyperglycemic Therapy

- Therapeutic options:

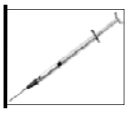
  Oral agents & non-insulin injectables

  - Metformin
  - Sulfonylureas
  - Thiazolidinediones
  - DPP-4 inhibitors
  - GLP-1 receptor agonists
  - Meglitinides
  - α-glucosidase inhibitors
  - Bile acid sequestrants
  - Dopamine-2 agonists
  - Amylin mimetics

Diabetes Care, Diabetologia. 19 April 2012

ADA-EASD Position Statement: Management of Hyperglycemia in T2DM

Anti-hyperglycemic Therapy



- Therapeutic options: Insulin
  - Neutral protamine Hagedorn (NPH)
  - Regular
  - Basal analogs (glargine, detemir)
  - Rapid analogs (lispro, aspart, glulisine)
  - Pre-mixed varieties

Diabetes Care, Diabetologia. 19 April 2012

Case: 55 yo obese man diagnosed with T2DM 10 years ago. A1C of 8.7% and fasting glucose levels of 110-170 mg/dl on metformin 1000mg BID and pioglitazone 45mg daily.
What is your next step in managing this patients diabetes?

1. Add GLP-1 receptor agonist
2. Add basal insulin
3. Add a DPP-4 inhibitor
4. Add a sulfonylurea

Current Practice Patterns of Health Care Providers in Managing Type 2 Diabetes

Case and Question	Options	FPs (n=150)	IMs (n=126)	NPs (n=125)	CDEs (n=121)
Case: 55 yo obese man diagnosed with T2DM 10 years ago. A1C of 8.7% and fasting glucose levels of 110-170 mg/dl on metformin 1000mg BID and pioglitazone 45mg daily. Question: What is your next step in managing this patients diabetes?	-Add a GLP-1 receptor agonist -Add basal insulin -Add a DPP-4 inhibitor -Add a sulfonylurea				

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Case: 49 yo woman diagnosed with T2DM 9 months ago is overweight and has an A1C of 8.0%. She is on metformin 500mg TID and needs her treatment intensified. What is your next step in managing this patients diabetes?

1. Add a GLP-1 receptor agonist
2. Add basal insulin
3. Add a DPP-4 inhibitor
4. Add a TZD
5. Add a sulfonylurea
6. Other

Current Practice Patterns of Health Care Providers in Managing Type 2 Diabetes

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Current Practice Patterns of Health Care Providers in Managing Type 2 Diabetes

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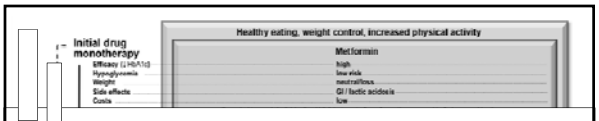
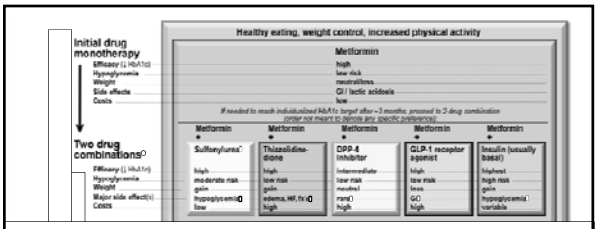


T2DM Antihyperglycemic Therapy: General Recommendations

Diabetes Care, Diabetologia. 19 April 2012



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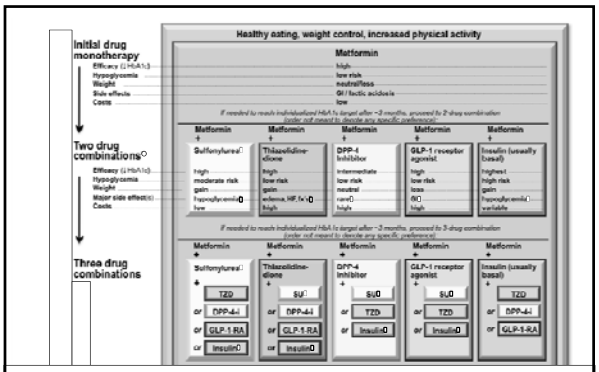

T2DM Antihyperglycemic Therapy: General Recommendations

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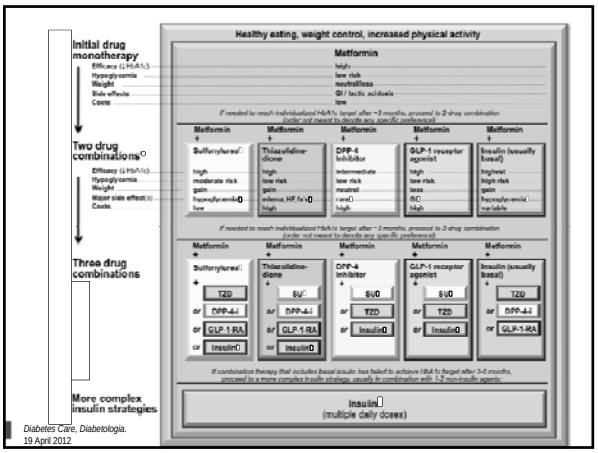
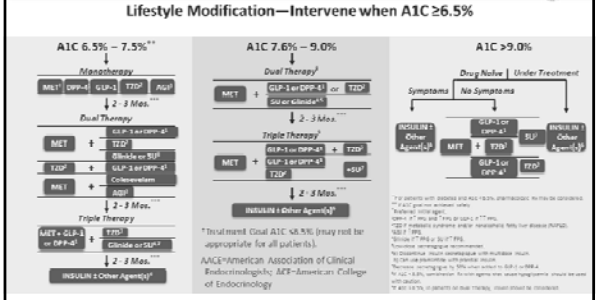


Diabetes Care, Diabetologia. 19 April 2012

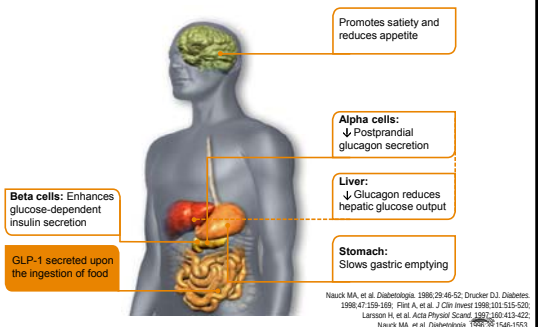
DPP-4 Inhibitors Can be Used in All Lines of Therapy: AACE/ACE Algorithm for Glycemic Control*



New Classes of Diabetes Medications in Development

- **Long-acting GLP-1 receptor agonists**
- **Ultra long-acting insulin**
- Ultra rapid-acting insulin
- Ranolazine
- **Dual & Pan PPAR agonists**
- **11 Hydroxysteroid Dehydrogenase (HSD)- 1 inhibitors**
- Fructose 1,6-bisphosphatase inhibitors
- Glucokinase activators
- G protein-coupled Receptor (GPR)- 40 & -119 agonists
- Protein Tyrosine Phosphatase (PTB)- 1b inhibitors
- Camitine- Palmitoyltransferase (CPT)- 1 inhibitors
- Acetyl COA Carboxylase (ACC)- 1 & -2 inhibitors
- **Glucagon receptor antagonists**
- Salicylate derivatives
- Immunomodulatory drugs
- **Sodium- Glucose Co-transporter (SGLT) {-1} & -2 inhibitors**

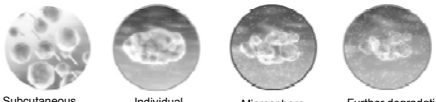
GLP-1 Effects in Humans: Glucoregulatory Role of Incretins



Nauck MA, et al. *Diabetologia.* 1986;29:46-52; Drucker DJ. *Diabetes.* 1998;47:159-169; Flint A, et al. *J Clin Invest* 1998;101:515-520; Larsson H, et al. *Acta Physiol Scand.* 1997;160:413-422; Nauck MA, et al. *Diabetologia.* 1996;39:1546-1553.

Microsphere Technology Provides a Continuous Level of Exenatide

- Patented Medisorb® microspheres* deliver a constant presence of exenatide with a once-weekly dose
- Microspheres are made of a biodegradable polymer which dissipates into CO_2 and water
- This material is also used in dissolvable sutures and other long-acting therapies



Subcutaneous injection of microsphere suspension of exenatide

Individual microspheres aggregate and there is initial release of exenatide

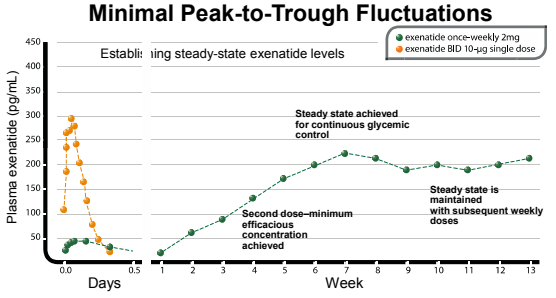
Microsphere degradation leads to continued release of exenatide

Further degradation and metabolism of microsphere polymer provide sustained levels of exenatide

* The BYDUREON microsphere is made of PLGA (polylactide co-glycolide). Medisorb is a registered trade mark of Alkermes, Inc.

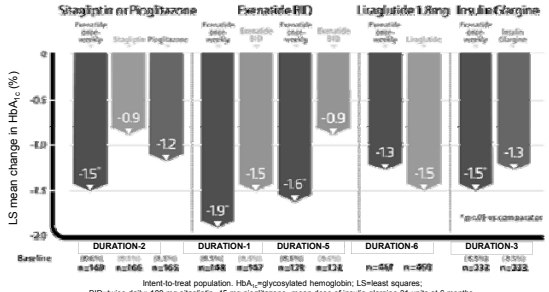
DeYoungMB, et al. *Diabetes Technol Ther.*2011;13:1145-1154

Microsphere Technology: Steady-state Exenatide Concentrations Ensuring Minimal Peak-to-Trough Fluctuations



Fineman M, et al. *Clin Pharmacokinet*. 2011;50(1):65-74;

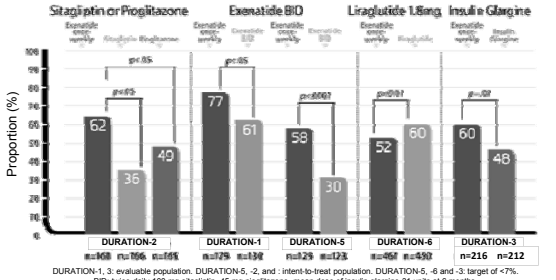
HbA_{1c} Reduction from Baseline by Exenatide Once-Weekly Ranged from 1.3% to 1.9%



Intent-to-treat population. HbA_{1c}=glycosylated hemoglobin; LS=least squares; BID=twice-daily; 100 mg sitagliptin, 45 mg pioglitazone, mean dose of insulin glargine 31 units at 6 months.

Bergenstal RM, et al. *Lancet*. 2010;376(9739):431-39; Drucker DJ, et al.*Lancet*. 2008;372(9645):1240-50; Blevins T, et al. *J Clin Endocrin Metab*. 2011; 96(5):2010-81; Buse JB, et al. *Diabetologia* 2011;54(Suppl 1):S38; Diamant M, et al. *Lancet*. 2010;375(9733):2234-43.

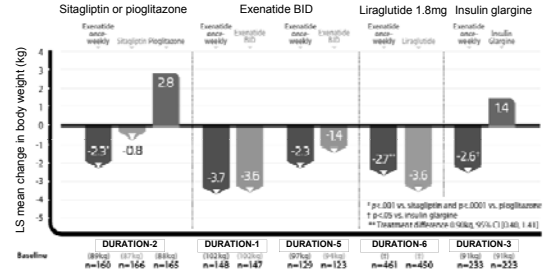
Proportion of Subjects Achieving HbA_{1c} Target of ≤7% vs Comparators



DURATION-1, 3: evaluable population. DURATION-5, -2, and : intent-to-treat population. DURATION-5, -6 and -3: target of <7%. BID: twice-daily 100 mg sitagliptin, 45 mg pioglitazone, mean dose of insulin glargine 31 units at 6 months.

Bergenstal RM, et al. *Lancet*. 2010;376(9739):431-39; Drucker DJ, et al. *Lancet*. 2008;372(9645):1240-50; Blevins T, et al. *J Clin Endocrin Metab*. 2011;96(5):2010-81; Buse JB, et al. *Diabetologia* 2011;54(Suppl 1):S38; Diamant M, et al. *Lancet*. 2010;375(9733):2234-43. Data on file, Eli Lilly and Company / Amylin Pharmaceuticals, Inc.

Exenatide Once-Weekly Changes in Body Weight vs Comparators

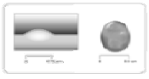


Rapid weight loss at a rate of >1.5 kg per week has been reported in patients treated with exenatide. Weight loss of this rate may have harmful consequences.

‡ Baseline weight values for individual groups are not currently published

Bergenstal RM, et al. *Lancet*. 2010;376(9739):431-39; Drucker DJ, et al. *Lancet*. 2008;372(9645):1240-50; Blevins T, et al. *J Clin Endocrin Metab*. 2011;96(5):2010-81; Buse JB, et al. *Diabetologia* 2011;54(Suppl 1):S38; Diamant M, et al. *Lancet*. 2010;375(9733):2234-43.

Subcutaneous Injection Site Nodules: Known Response to Microsphere Technology

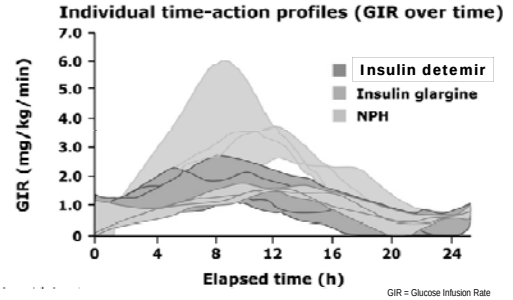


- These appear as small bumps and have been observed very frequently in clinical trials
  - These are consistent with the known properties of poly (D,L -lactide co-glycolide) polymer microsphere formulations
- Most individual nodules were asymptomatic, although some were associated with redness and itching, and resolved over 4 to 8 weeks
  - Mostly small, average size is 0.5 cm to 0.75 cm in diameter; smaller than the average pea
  - May not be detected visually
  - May not appear right away
  - More than 1 bump may be present at any given time
- In clinical trials, withdrawal due to injection site reactions occurred in <1% in exenatide once-weekly-treatment groups

Data on file, Eli Lilly and Company / Amylin Pharmaceuticals, Inc.

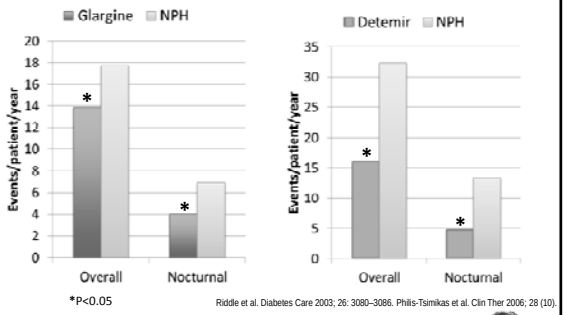
How Do the Pharmacodynamics of Basal Insulin Preparations Affect Outcomes

Biologic Activity Over 24-hours More Consistent for Basal Insulin Analogs



GIR = Glucose Infusion Rate
Heise et al. Diabetes 2004; 53 (6): 1614-1620

Less Hypoglycemia with Basal Analogs vs. NPH



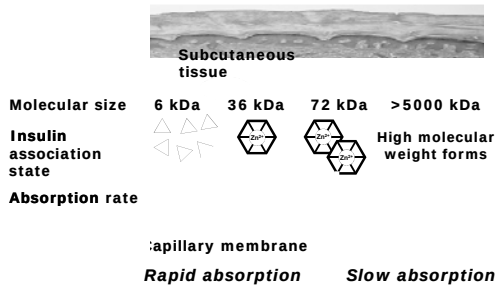
*P<0.05

Riddle et al. Diabetes Care 2003; 26: 3080–3086. Philis-Tsimikas et al. Clin Ther 2006; 28 (10).

Improving on Current Basal Insulin Analogs

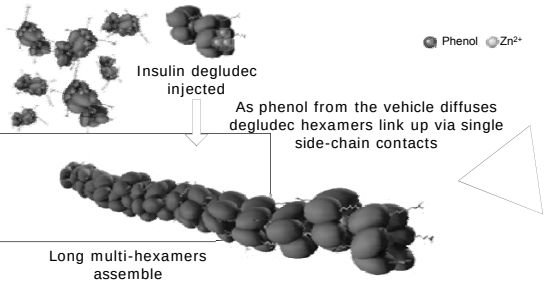
- Extend duration of action
- Flat pharmacodynamic profile
- Reduced day-to-day variability

Molecular Size Determines Rate of Subcutaneous Absorption

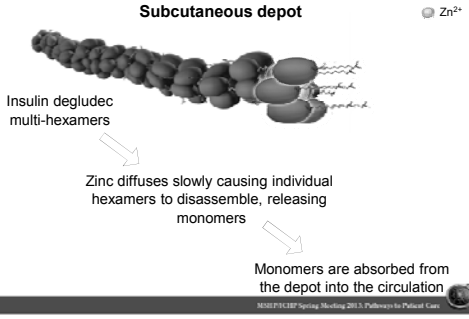


Brange *et al. Diabetes Care* 1990;13:923–54

Insulin Degludec from Solution to Subcutaneous Depot



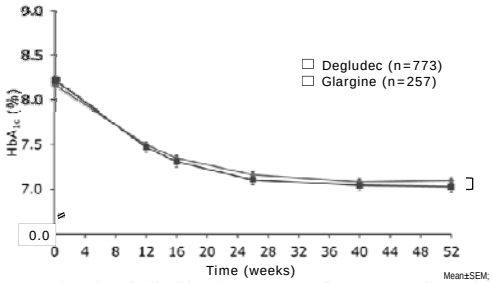
Insulin Degludec: Slow Release Following Injection



Terminal Half-life & Coefficient of Variation at Steady State

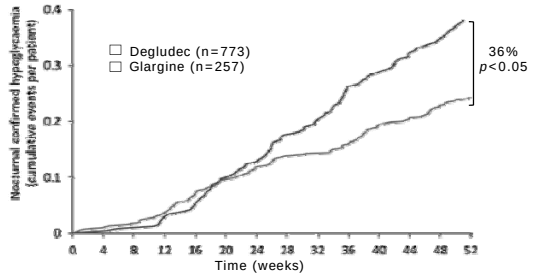
	Harmonic mean (h)	CV (%)
Terminal half-life (steady state)		
Degludec	24.5	23
Glargine	12.2	56

No Difference in HbA_{1c} Decrease over Time Between Degludec & Glargine



Mean±SEM; FAS; LOCF
Comparisons: Estimates adjusted for multiple covariates
Data on file: NN1250-3579; Accepted for presentation at ADA 2012

Lower Nocturnal Confirmed Hypoglycemia with Insulin Degludec



Comparisons: Estimates adjusted for multiple covariates
Data on file: NN1250-3579; Accepted for presentation at ADA 2012

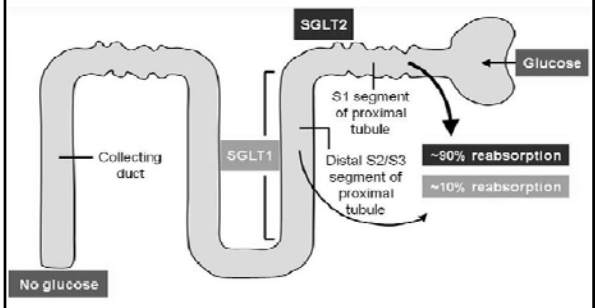
The Kidneys Play an Important Role in Glucose Control

Normal Renal Glucose Physiology

- 180 g of glucose is filtered each day
- Virtually all glucose reabsorbed in the proximal tubules & reenters the circulation
- SGLT2 reabsorbs about 90% of the glucose
- SGLT1 reabsorbs about 10% of the glucose
- Virtually no glucose excreted in urine

Mather, A & Pollock, C. *Kidney International*. 2011;79:S1-S6.

Targeting the Kidney



Chao EC, et al. *Nat Rev Drug Discovery*. 2010;9:551-559.

Rationale for SGLT2 Inhibitors

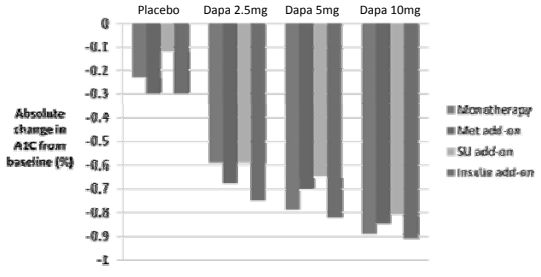
- SGLT2 is a low-affinity, high capacity glucose transporter located in the proximal tubule and is responsible for 90% of glucose reabsorption
- Selective SGLT2 inhibitors have a novel & unique mechanism of action reducing blood glucose levels by increasing renal excretion of glucose
- Decreased glycemia will decrease glucose toxicity leading to further improvements in glucose control
- Selective SGLT2 inhibition, would also cause urine loss of the calories from glucose, potentially leading to weight loss

Brooks AM, Thacker SM. *Ann Pharmacother*. 2009;42(7):1286-1293.

SGLT2 Inhibitors in Phase 3 Development

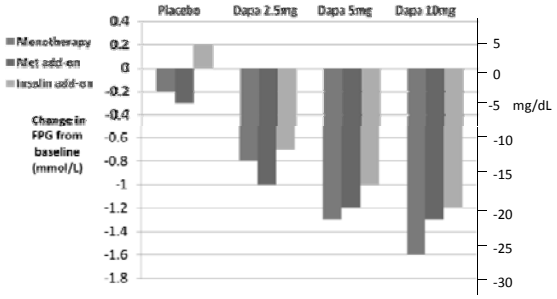
- Empagliflozin
- Canagliflozin
- Dapagliflozin
- Ipragliflozin

Changes from Baseline in A1C in Phase 3 Dapagliflozin Studies



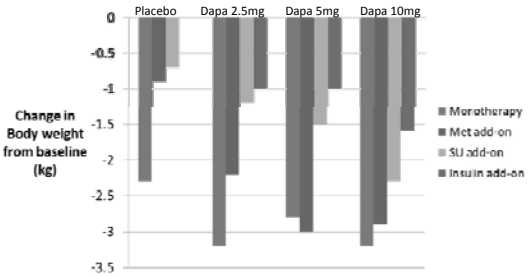
Wilding JPH, et al. Abstract 78-OR. ADA 2010; Strojek K, et al. Abstract 870. EASD 2010; Ferrannini E, et al. *Diabetes Care*. 2010;33(10):2217-2224; Bailey CJ, et al. *Lancet*. 2010;375(9733):2223-2233.

Changes from Baseline in Fasting Glucose in Phase 3 Dapagliflozin Studies



Wilding JPH, et al. Abstract 78-OR. ADA 2010; Strojek K, et al. Abstract 870. EASD 2010; Ferrannini E, et al. *Diabetes Care*. 2010;33(10):2217-2224; Bailey CJ, et al. *Lancet*. 2010;375(9733):2223-2233.

Changes from Baseline in Body Weight in Phase 3 Dapagliflozin Studies



Wilding JPH, et al. Abstract 78-OR. ADA 2010; Strojek K, et al. Abstract 870. EASD 2010; Ferrannini E, et al. *Diabetes Care*. 2010;33(10):2217-2224; Bailey CJ, et al. *Lancet*. 2010;375(9733):2223-2233.

Perspectives on SGLT2 Inhibition

- Potential advantages
  - Insulin Independence
  - Weight loss (75g urine glucose = 300kcal/day)
  - Low risk of hypoglycemia
  - Blood pressure lowering?
- Concerns
  - Polyuria
  - Electrolyte disturbances
  - Bacterial urinary tract infections
  - Fungal genital infections
  - Malignancies