

## Uncontrolled Type 2 Diabetes

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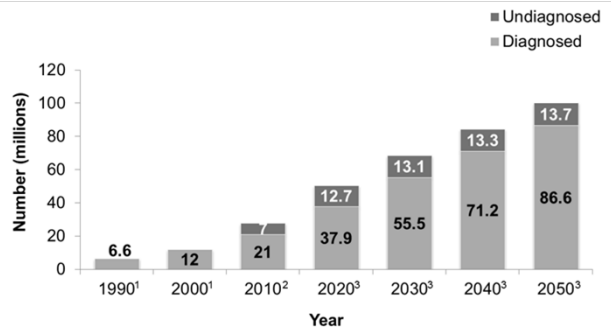
## Disclosures

- **Research:** Novo Nordisk, GSK, Astra Zeneca, Merck
- **Consultant/advisory:** GSK, Novo Nordisk, Eli Lilly, Janssen

## Case

- 53 YO M with a 5 year h/o T2DM, HTN, HLD, obesity who presents for routine visit.
- He is testing his BG irregularly
- Medications: HCTZ 25 mg daily, atorvastatin 40 mg daily, metformin 1 gm BID
- PE: BMI 34, BP 138/80, HR 85
- Labwork: HbA1c 9.1%, creatinine 0.9 mg/dl, LDLc 85, HDL 43, TG 186
- What would you advise?

## Projected Prevalence of Diabetes in the United States: 1990 to 2050



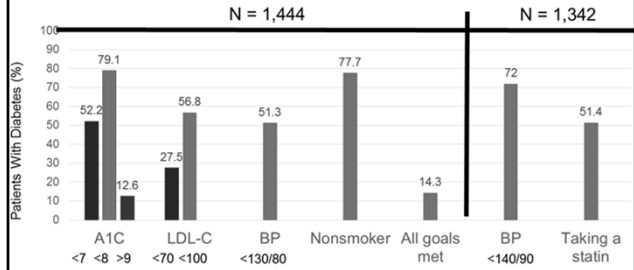
1. National Diabetes Surveillance System. <http://www.cdc.gov/diabetes/statistics/prevalence/figpersons.htm>. 2. CDC. National diabetes fact sheet, 2011. [http://www.cdc.gov/diabetes/pubs/pdf/nldr\\_2011.pdf](http://www.cdc.gov/diabetes/pubs/pdf/nldr_2011.pdf). 3. Boyle JP, et al. *Popul Health Metr*. 2010 Oct 22;8:28.

## Diabetes Morbidity and Mortality

- 7th leading cause of death in US
- Leading cause of blindness
- Most frequent cause of kidney failure
- ~60% of nontraumatic lower limb amputations occur in people with diabetes
- Diabetes also
  - Doubles the risk of periodontal disease
  - Doubles the risk of depression
    - Depression increases T2D risk by 60%
  - Increases patients' susceptibility to acute illness (eg, pneumonia and influenza)
    - Worsens the prognosis of patients with acute illnesses

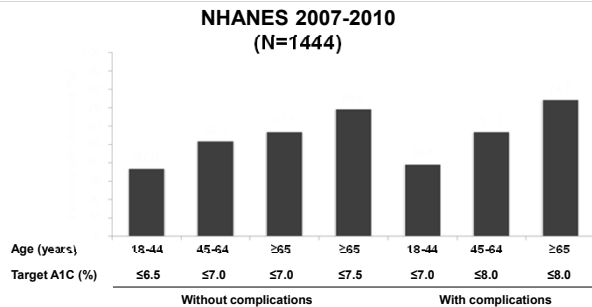
CDC. National diabetes statistics report, 2014.  
<http://www.cdc.gov/diabetes/pubs/statsreport14/national-diabetes-report-web.pdf>  
 CDC. National diabetes fact sheet, 2011.  
[http://www.cdc.gov/diabetes/pubs/pdf/ndfs\\_2011.pdf](http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf)

## Goal Achievement in Diabetes: NHANES 2007-2010



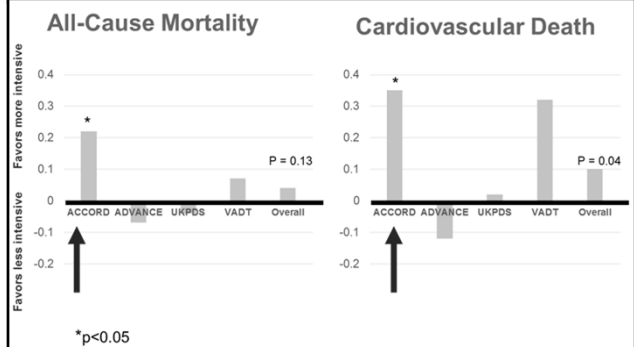
Ali MK, et al. *N Engl J Med*. 2013;368:1613-1624.  
 Stark Casagrande S, et al. *Diabetes Care*. 2013;36:2271-2279

## A1C Achievement by Individualized Target



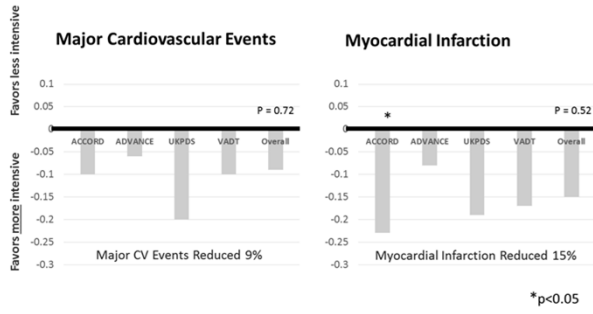
NHANES, National Health and Nutrition Examination Survey.  
 Ali MK, et al. *N Engl J Med*. 2013;368:1613-1624.

## Meta-analysis: Intensive Glucose Control & Mortality



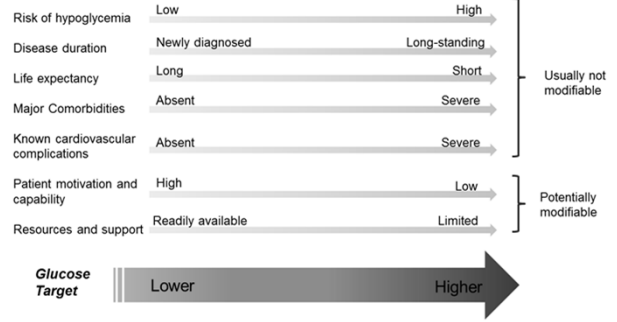
\*p<0.05  
 Diabetologia 2009;52:2288-98

## Meta-analysis: Glucose Control & Macrovascular Disease



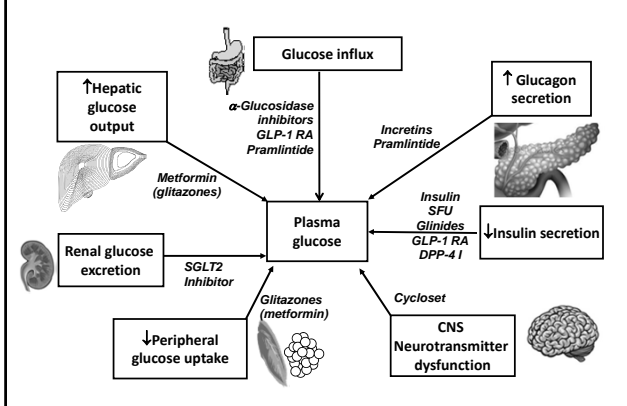
Pistrosch and Hanefeld. *Curr Diab Rep* 2015;15:117

## ADA-Recommended Approach to Management of Hyperglycemia



Inzucchi SE, et al. *Diabetes Care*. 2015;38:140-149.

## Matching Pharmacology to Physiology

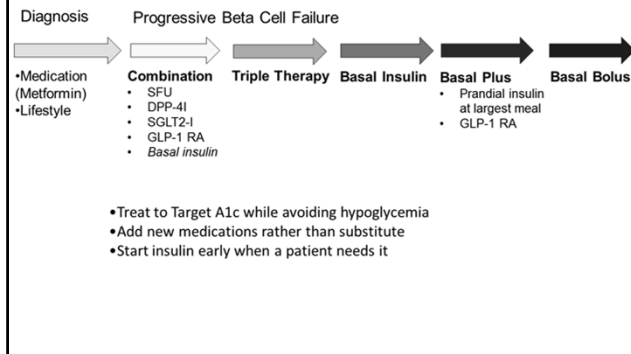


## Comparison of Diabetes Medications

	Efficacy	Hypo-glycemia	Weight Gain	Side effects/Precautions*	Cost
SFU	High	++	+	GI, elderly, renal/liver disease	+
Metformin	High	-	-	Elderly, renal, liver disease Unstable heart failure or lung disease	+
TZD	High	-	+	Heart failure, Edema, Liver#renal disease Osteoporosis?	++
Glinides	High	+	-	Renal/liver failure	++
α-glucosidase Inhibitor	Intermediate	-	-	Malabsorption syndromes	+
DPP-IV Inhibitor	Intermediate	-	-	?pancreatitis Drug interactions (linagliptin, allogliptin)	+++
Colesevaem	Intermediate	-	-	Constipation, drug interactions (LT4, OCPs, vitamins, glyburide)	+++
Cycloset	Intermediate	-	-	Orthostasis, psychotic disorder, dopamine agonist, GI	+++
SGLT-2 Inhib	Intermediate	-	Loss	GU infection, fluid/electrolyte, DKA	+++
GLP-1 agonists	High	-	Loss	GI, Gastroparesis, ?pancreatitis, medullary thyroid cancer, renal failure	+++
Insulin	Highest	++	+	Allergy	Varies

AACE Medical Guidelines for Clinical Practice for the Management of Diabetes Mellitus; *Endocr Pract*;13(Supp 1), 2007.

## Treatment Strategy



## FDA Update with Metformin

- Renal dosing
  - contraindicated with eGFR <30 mL/minute/1.73 m<sup>2</sup>.
  - Starting metformin with eGFR 30-45 not recommended.
  - Assess risks/benefits if eGFR falls <45
- Discontinue metformin before IV contrast if:
  - eGFR 30-60
  - liver disease
  - Alcoholism
  - heart failure
  - intra-arterial contrast.
  - evaluate eGFR 48 hours after the imaging procedure

## Glitazones update

### Rosiglitazone

- Meta-analysis<sup>1</sup> of small trials, DREAM and ADOPT
  - MI risk increased 43% (P=0.03)
  - Risk of CV death was double the comparator (P=0.02)
- MI risk confirmed with longer-term meta-analysis<sup>2</sup> but not RCT

### Pioglitazone

- Meta-analysis<sup>3</sup> of 19 trials
  - The primary outcome (death, non-fatal MI, non-fatal stroke) was 18% LESS common with pioglitazone (P=0.005)
- IGT trial: reduced CV events

All prescribing restrictions imposed by the FDA have been lifted, except for CHF risk, which is substantially increased with both rosiglitazone and pioglitazone (relative increase 50%-100%, absolute increase 1%-2%)

1. Nissen SE et al. *N Engl J Med.* 2007;356:2457-2471. 3. Singh S et al. *JAMA.* 2007;298:1189-1195.  
 2. Lincoff AM et al. *JAMA.* 2007;298:1180-1188.  
 3. Home et al. *RECORD Trial, Lancet.* 2009 Jun 20;373(9681):2125-35

## DPP-4 Inhibitors

Name	% HbA1c Reduction	Renal Dose	Max Dose	Primary effect	Cautions
Sitagliptin (Januvia®)	0.5-0.8	CrCl <30: 25 mg CrCl 30-50: 50 mg	100 mg daily	Increase incretin activity	Pancreatitis?
Saxagliptin (Onglyza®)		CrCl <50: 2.5 mg	5 mg daily		
Linagliptin ( Tradjenta®)		5 mg daily	5 mg daily		
Alogliptin (Nesina®)		CrCl 30-60: 12.5mg CrCl <30: 6.25 mg	25 mg daily		

No added hypoglycemia unless used with secretagogue or insulin

Weight neutral  
Well-tolerated

## GLP-1 receptor agonists

Generic Name	Brand Name	Dose forms	HbA1c Reduction	Dosing Interval	Cautions
Exenatide BID	Byetta	5, 10 µg	1-2%	BID	C-cell tumors/
Lixisenatide#	Lyxumia	10, 20 µg		QD	
Liraglutide	Victoza	1.6, 1.2, 1.8 µg	1-2%	Daily	MEN-2, advanced CKD, gastroparesis, pancreatitis?
Exenatide QW*	Bydureon	2 mg		Weekly	
Albiglutide*	Tanzeum	30, 50 mg		Weekly	
Dulaglutide	Trulicity	0.75, 1.5 mg		Weekly	

# FDA approved but not yet available  
\*Requires reconstitution, may cause injection site reactions

GLP-1 R  
Activation  
Intermittent  
Continuous

- No inherent hypoglycemia
- Modest weight and BP reduction
- Nausea/vomiting, usually self-limited

## SGLT2 Inhibitors

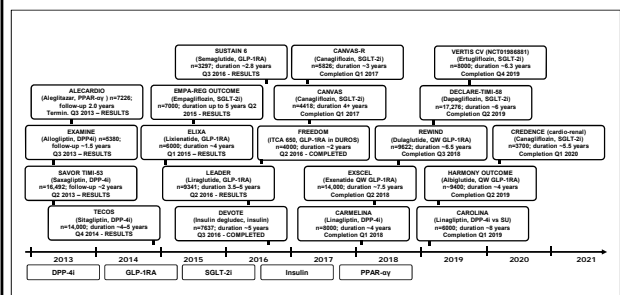
Name	% HbA1c Reduction	Starting Dose	Max Dose	Primary effect	Cautions
Canagliflozin (Invokana®)	0.5-1.0	100 mg daily	300 mg daily	Block renal glucose reabsorption	Ineffective if eGFR <45 (C, E) or <60 (D), UG infection, fluid/electrolyte, euglycemic DKA
Empagliflozin (Jardiance®)		10 mg daily	25 mg daily		
Dapagliflozin (Farxiga®)		5 mg daily	10 mg daily		

Modest blood pressure, weight reduction  
No hypoglycemia

## Case continued

- The patient reaches an HbA1c at target with medication, diet and lifestyle therapies.
- By 6 years after presentation, he is admitted with acute myocardial infarction.
- Current medications: Metformin 1 gm BID, Glimpiride 2 mg daily
- SMBG: checks 1-2 times per day, denies significant hypoglycemia
- BMI 34
- HbA1c 8.1%
- What would you do next?

## CVOTs in diabetes



Boxes with broken lines are for completed CVOTs  
CVOT, cardiovascular outcomes trial; DPP-4i, dipeptidyl peptidase 4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; GW, once weekly; SGLT-2i, sodium glucose co-transporter 2 inhibitor; SU, sulphonylurea  
Source: clinicaltrials.gov (October 2016)

**Real uncertainty about off-target effects**

**CNN**  
Can a dirt-cheap diabetes drug fight cancer?

**THE WALL STREET JOURNAL**  
Study: Sanofi's Lantus Insulin Has Possible Cancer Link

**CBS NEWS**  
Judge sets first hearing for diabetes drug lawsuits

**The New York Times**  
Diabetes drug tied to pancreatitis, deaths

**THE WALL STREET JOURNAL**  
FDA Urged to Test Diabetes Drugs' Heart Risk

**From The Times**  
May 31, 2007  
GlaxoSmithKline defends Avandia as shares drop 13% in nine days

**WebMD**  
Better information. Better health.  
**More Evidence Links Fractures to Diabetes Drugs**  
Avandia, Actos Boost Fracture Risk in Older Women, Study Finds

**FDA criteria for requirement of a postmarketing CV outcomes trial**

**All Phase 2 and 3 studies should include a prospective independent adjudication of CV events**

**A minimum of 2 years' CV safety data must be provided**

Upper limit of 95% CI  
CI, confidence interval; CV, cardiovascular; FDA, Food and Drugs Administration; HR, hazard ratio Hirschberg B and Raz I. *Diabetes Obes Metab* 2011;34(Suppl. 2):S101-S106

**Glucose-lowering effects on the combined triple endpoint of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke**

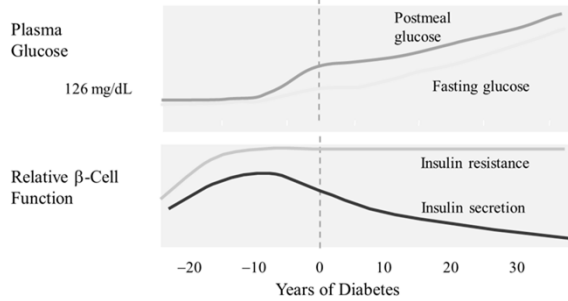
Study	Anti-Diabetic Drug	Hazard Ratio	P
PROactive	Pioglitazone	0.84	0.02
ORIGIN	Insulin glargine	1.02	NS
SAVOR	Saxagliptin	1.00	NS
EXAMINE	Alogliptin	0.96	NS
CANVAS*	Canagliflozin	1.00	NS
ELIXA	Lixisenatide	1.02	NS
TECOS	Sitagliptin	0.98	NS
EMPA-REG	Empagliflozin	0.86	0.04
LEADER	Liraglutide	0.87	0.01

\*Final CVOT pending  
J Diabetes Complications 2014;28:430-433

**Case continued**

- 10 years after presentation, your patient is seen for routine follow-up.
- Current medications: Metformin, glimepiride, empagliflozin
- SMBG: he is testing twice per day. BG running mostly in 200s.
- BMI
- HbA1c 9.1%, creatinine 1.6, eGFR 45
- Now what?

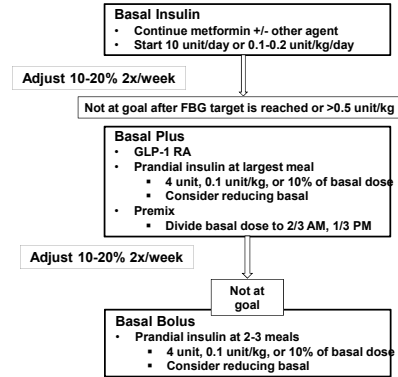
## Natural History of T2DM



- Loss of beta cell function begins before diagnosis and progresses
- Insulin resistance does not change over time

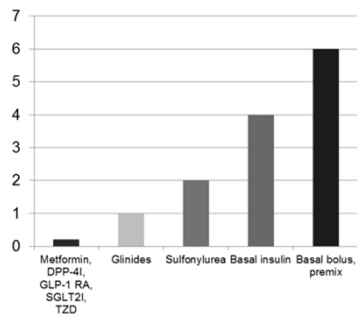
Adapted from International Diabetes Center (IDC), Minneapolis, Minnesota.

## Insulin Intensification Strategy



## Frequency of Severe Hypoglycemia With Antihyperglycemic Agents

% of Patients Treated Over 1 Year<sup>1</sup>



- HbA1c and duration of DM is not a significant predictor<sup>2</sup>
- Duration of insulin therapy associated with overall, nocturnal and severe hypoglycaemia

1) Moghissi E, et al. Endocr Pract. 2013;19:526-535.

2) Khuntia et al. Diabetes Obes Metab. 2016;18(9):907-15

## Meta-analysis of Insulin Analogue Regimens

- A1c reduction favored prandial or biphasic over basal insulin
- Overall frequency of hypoglycemia low (0.4 events/patient/30 day) but favored basal insulin
- Weight gain favored basal

Giugliano et al. Diabetes Care 34:510-517, 2011

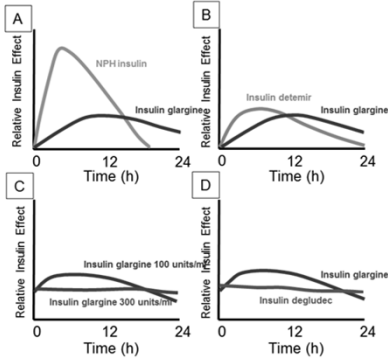
## Basal insulins: Practical Aspects

Preparation	Action Onset	Peak	Action Duration	Vial	Disposable Pens and Pen with Cartridges		
					Dosing Range per injection (Unit)	Dosing Increment per Injection (Unit)	Dispensing Amount
<b>Basal Insulin</b>							
NPH daily or bid	1-2 hr	4-8 hr	10-20 hr	10 mL, 1000 unit	Kwikpen: 1-60	1	Pen: 3 ml, 300 unit
Detemir daily or bid	3-4 hr	Nearly flat	Up to 24 hr	10 mL, 1000 unit	Flextouch: 1-80	1	Pen: 3 ml, 300 unit
Glargine daily (U100)	3-4 hr	Nearly flat	Approx 24 hr	10 mL, 1000 unit	Solostar: 1-80	1	Pen: 3 ml, 300 unit
Glargine daily (U300)	8 hr	Flat	24-30 hr	N/A	Solostar: 1-80	1	Pen: 1.5 ml, 450 unit
Degludec daily (U100)	1 hr	Flat	24-30 hr	N/A	Flextouch: 1-80	1	Pen: 3 ml, 300 unit
Degludec daily (U200)	1 hr	Flat	24-30 hr	N/A	Flextouch: 2-160	2	Pen: 3 ml, 600 unit

- Ultra-long-acting insulins should be titrated every 4 days
- Therapeutic conversion:
  - U300 glargine: Labeling recommends 1:1 though patients needed ~15% more on U300 vs. U100
  - Degludec: Labeling recommends 1:1 though patients needed ~10% less on degludec vs. glargine U100

## Does the type of basal insulin affect hypoglycemia risk?

### Ultra-Long-Acting Insulins



- Key Features:**
- Flatter profile
  - Longer duration
  - Less hypoglycemia
  - Once daily, flexible

Pettus et al. Diabetes Metab Res Rev 2015;

### U300 Glargine Clinical Trials

	Duration	DM Type	Baseline Rx	N	Comparator	HbA1c	Hypoglycemia (overall)	Hypoglycemia (nocturnal)	Weight Gain (kg)
EDITION 1	12	2	Basal bolus	807	G-U100	Similar	0.84 (0.89-0.99)	0.84 (0.75-0.94)	Comparable
EDITION 2	12	2	Basal	811	G-U100	Similar	0.96 (0.89-1.02)	0.84 (0.71-0.99)	0.42 vs. 1.14, p=0.009
EDITION 3	6	2	Naive	873	G-U100	Similar	0.88 (0.77-1.01)	0.76 (0.59-0.99)	Comparable
EDITION 4	6	1	Basal bolus	559	G-U100	Similar	1.00 (0.95-1.04)	0.98 (0.88-1.09)	0.5 vs. 1.0, p=0.04

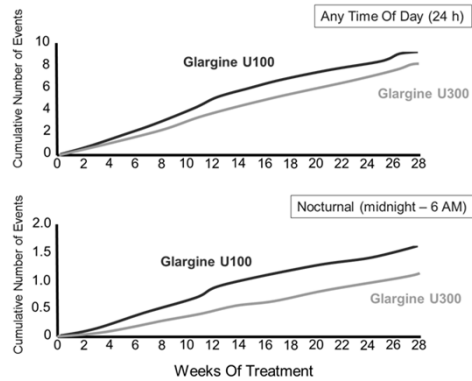


## Degludec clinical trials

	Duration	DM Type	Baseline Rx	N	Comparator	HbA1c	Hypoglycemia (overall)	Hypoglycemia (nocturnal)	Weight Gain (kg)
BEGIN BB T1	52	1	Basal bolus	D-472 G-154	G-U100	Similar	Similar	0.75 (0.59-0.96)	Similar
BEGIN BB T1	52	2	Basal	D-744 G-248	G-U100	Similar	0.82 (0.69-0.99)	0.75 (0.58-0.99)	Similar
BEGIN Flex T1	26	2	Naive	DF-229 D-228 G-230	G-U100*	Similar	Similar	0.77 (0.44-1.35)	Similar
BEGIN Flex T1	26	1	Basal bolus	DF-164 D-165 G-163	G-U100*	Similar	Similar	0.60 (0.44-0.82)	Similar
BEGIN Once Long	52	2	Naive	D-773 G-257	G-U100	Similar	Similar	0.64 (0.42-0.98)	Similar

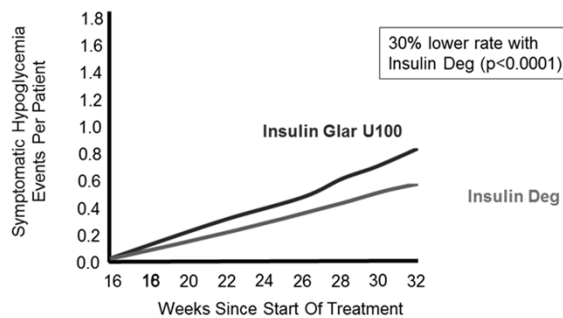
#Includes comparator group with flexible timing of daily dose  
**BB=basal bolus, D=degludec, DF=degludec flexible timing, G=glargine**

## Hypoglycemia with U300 vs U100 glargine



Ritzel et al. Diabetes Obes Metab. 2015 Sep; 17(9): 859-867

## Type 2 diabetes previously treated with basal insulin: symptomatic hypoglycemia ldeg v. lglar U100



## Bolus Insulins

Preparation	Action Onset	Peak	Action Duration	Vial	Disposable Pens and Pen with Cartridges		
					Dosing Range per injection (Unit)	Dosing Increment per Injection (Unit)	Dispensing Amount
<b>Bolus Insulin</b>							
Regular q.a.c.	30 min	2-4 hr	6-10 hr	10 mL, 1000 unit	Kwikpen: 1-60 NovoPen3 PenNite: 1-60	1	Pen: 3 mL, 300 unit Cartridge: 3 mL, 300 unit
Aspart q.a.c.	5-15 min	1-2 hr	4-6 hr	10 mL, 1000 unit N/A	Echo: 0.5-30	0.5	Cartridge: 3 mL, 300 unit
Gulisine q.a.c.	5-15 min	1-2 hr	4-6 hr	10 mL, 1000 unit	Flextouch: 1-60	1	Pen: 3 mL, 300 unit
Lispro q.a.c. (U100)	5-15 min	1-2 hr	4-6 hr	10 mL, 1000 unit	Solostar pen: 1-80 Luxura: 0.5-30	1 0.5	Cartridge: 3 mL, 300 unit
Lispro q.a.c. (U200)	5-15 min	1-2 hr	4-6 hr	N/A	Kwikpen: 1-60	1	Pen: 3 mL, 300 unit

Generally all have similar HbA1c reductions.  
 There is less hypoglycemia with insulin analogs compared to regular human insulin

# Other Insulins

Preparation	Action Onset	Peak	Action Duration	Vial	Disposable Pens and Pen with Cartridges		
					Dosing Range per injection (Unit)	Dosing Increment per Injection (Unit)	Dispensing Amount
<b>Other</b>							
70/30 regular bid	30 min	2-4 hr	10-20 hr	10 mL, 1000 unit	N/A	N/A	N/A
70/30 Aspart bid	5-15 min	1-2 hr	10-20 hr	10 mL, 1000 unit	Flextouch: 1-60	1	Pen: 3 mL, 300 unit
75/25 Lispro bid	5-15 min	1-2 hr	10-20 hr	10 mL, 1000 unit	Kwikpen: 1-80	1	Pen: 3 mL, 300 unit
Regular U500 bid or tid	30 min	4-8 hr	18-23 hr	20 mL, 10,000 unit	Kwikpen: 5-300	5	Pen: 3 mL, 1500 unit

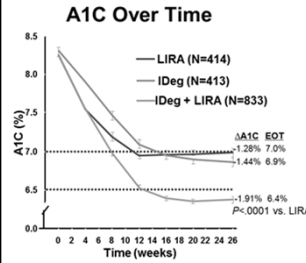
### Premix insulins:

- for patients with large insulin requirements or who are able to maintain a consistent schedule of eating, activity
- Higher risk of hypoglycemia compared with basal or basal bolus insulin

### U500 insulin

- For patients requiring >200 units/day

# Degludec + Liraglutide Combination



### Inclusion criteria

- T2DM
- Insulin-naïve, treated with metformin ± pioglitazone
- A1C 7.0%-10.0%
- BMI ≤40 kg/m<sup>2</sup>
- Age ≥18 years\*\*

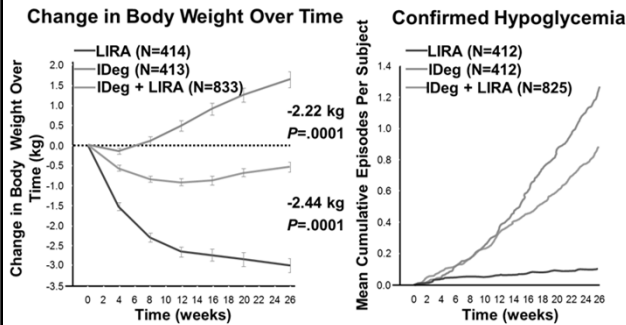
Mean values (±SEM) based on FAS and LOCF-imputed data.

ADA/EASD A1C target <7.0%. AACE A1C target ≤6.5%.

EOT=end of trial; FAS=full analysis set; LOCF=last observation carried forward

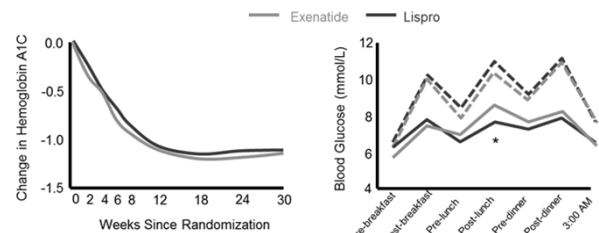
Gough SC, et al. *Lancet Diabetes Endocrinol.* 2014.

# Degludec + Liraglutide Combination: Body Weight and Hypoglycemia



Gough SC, et al. *Lancet Diabetes Endocrinol.* 2014.

# GLP-1 RA or Bolus Insulin As Add-On To Basal Insulin



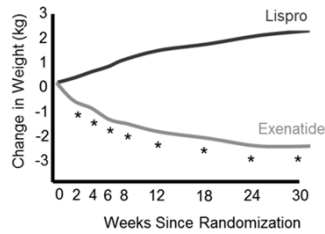
- 627 patients randomized to Exenatide BID or Lispro TID
- A1C non-inferior
- Fasting blood glucose lower with Exenatide

Diamant et al *Diabetes Care* 2014;37:2763-2773

## Exenatide or Bolus Insulin as add-on to Basal Insulin

Exenatide treatment resulted in

- Lower insulin requirements
- Better treatment satisfaction and quality of life
- More adverse events (mainly GI: 7 vs.13%)
- Less hypoglycemia
  - Minor: 41 vs. 30%
  - Confirmed non-nocturnal: 34 vs. 15%

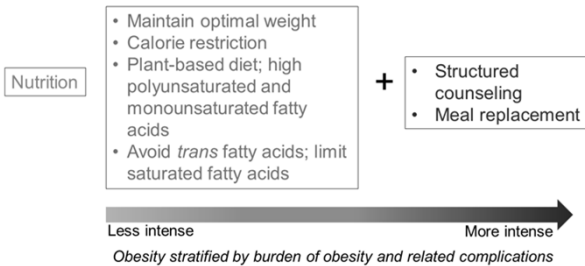


Diamant et al Diabetes Care 2014;37:2763-2773

## Optimizing your insulin

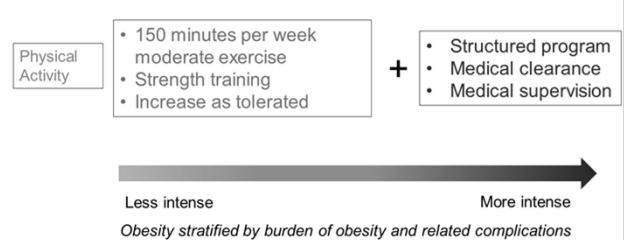
- Insulin is necessary and life-saving!
- CV safety may be limited by hypoglycemia
- Hypoglycemia mitigation
  - Manage carbohydrates, activity
  - Insulin analogues
  - Ultra-long acting insulins (if needed)
  - Combine with GLP-1 RA
  - Combine with other oral agents (DPP-4 Inhibitor or SGLT2 Inhibitor)

## Lifestyle Therapy: risk stratification for diabetes complications



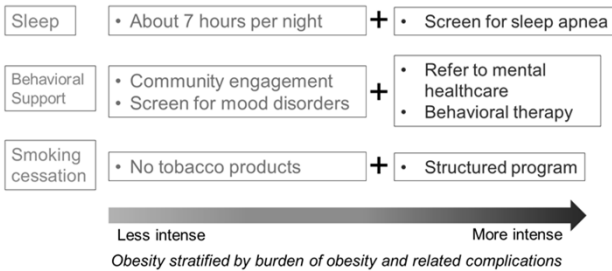
AACE 2016

## Lifestyle Therapy: risk stratification for diabetes complications



AACE 2016

## Lifestyle Therapy: risk stratification for diabetes complications



AACE 2016

## Uncontrolled Diabetes

**Janet Zappe, RN, MS, CDE**  
Clinical Program Manager  
Division of Endocrinology, Diabetes & Metabolism  
The Ohio State University Wexner Medical Center

## Partnering for Success

- Comprehensive Education
- Realistic Goals
- Relatable Information
- Acknowledging work and progress

## Comprehensive Education

- Diabetes Education is recommended every five years
- Certified programs through the American Diabetes Association or the American Association of Diabetes Educators
- Diabetes educators are specialists
- Why? Stay current with medical practices, higher motivation, tighten self care practices.

## Realistic Goals

- **Patient Involvement**
  - What will they do differently
  - When will they practice the behavior/skill
  - Where will they practice the behavior/skill
  - Why did they choose this behavior/skill
- **Physician Guidance**
  - Set a number for the goal
  - Agree on a frequency
  - Provide details on how to measure
  - Ask for progress updates

## Nutrition Tips

- Use the plate method
- Suggest one less portion per meal
- Reduce the number of fast food visits
- Reduce portion size
- Use food models to demonstrate portion
- Eat breakfast – keep this simple!
- Replace caloric drinks
- Read food labels

## Exercise and Activity

- Encourage activity over exercise
- Use the further restroom, stairs, deep knee bends, no texting at work, walk laps
- Interval walking
- No sitting longer than 90 minutes at one time
- Smart tv/computer for activity and exercise routines of all levels
- Exercise is money in their pocket
- Increase daily steps by 500 weekly

## Medicine

- Ask how often they miss a dose
  - Use pill box, put medicine near a daily activity like brushing their teeth
- What do they like least about the medicine
  - Can the medicine be taken with food
- Insulin reminders
  - Review all injection sites
  - Rotate injection site once a week
  - Dose meal time insulin before meals
  - Prime pen needle – insulin only, not necessary for GLP 1
- Use manufacturer discounts, have pharmacy check eligibility

## **Blood Glucose Monitoring**

- Oral meds and basal insulin only – ask for once a day rotating the time
- Meal time insulin before meals
- Set targets and reduce targets weekly by 25-50 points until at goal
- Must wash hands or use alcohol swabs before obtaining sample
- Require name brand meter unless cost is an issue
- Change lancet
- Look at the logbook
- Use apps such as Glooko or mysugr

## **Acknowledge Progress**

- Verbal acknowledgement of changes
- Use a reward system – works for kids!
- Review logbooks/records kept
- Ask what is the hardest part and set small goal around that problem
- Respond timely to logs sent to the office