Uncontrolled Type 2Diabetes

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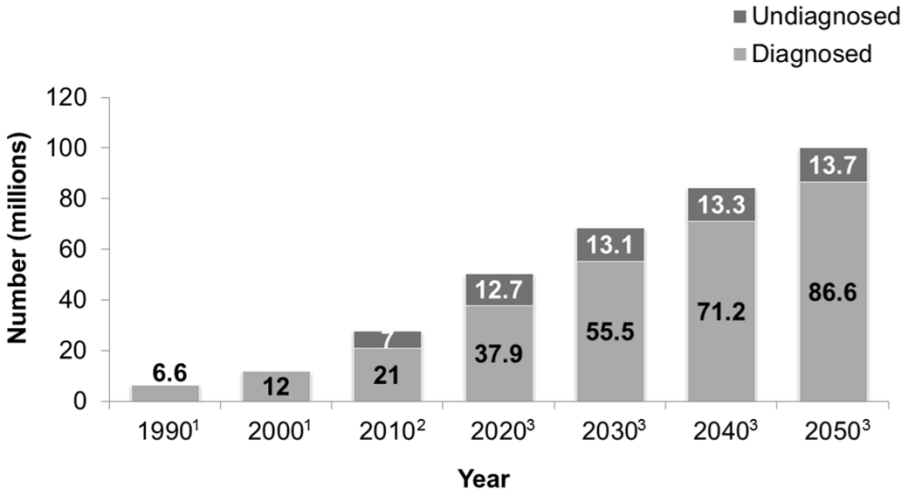
Disclosures

- **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



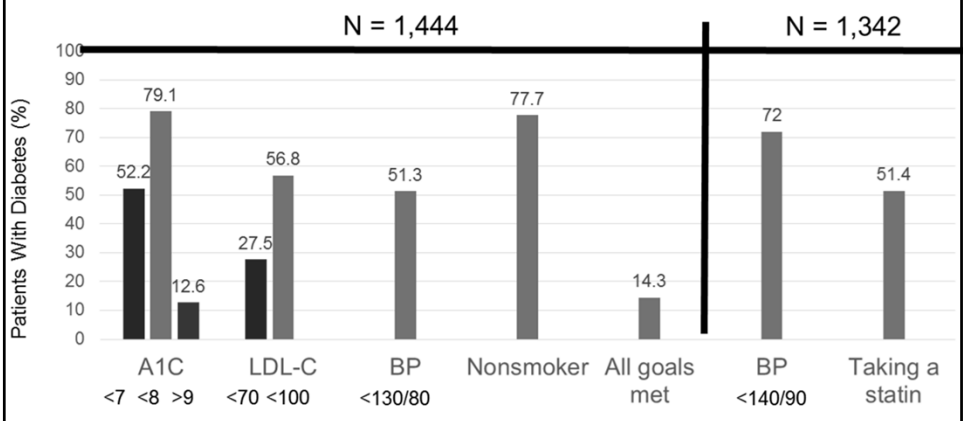
1. National Diabetes Surveillance System. http://www.cdc.gov/diabetes/statistics/prev/national/figpersons.htm. 2. CDC. National diabetes fact sheet, 2011. http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf. 3. Boyle JP, et al. *Popul Health Metr*. 2010 Oct 22;8:29.

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

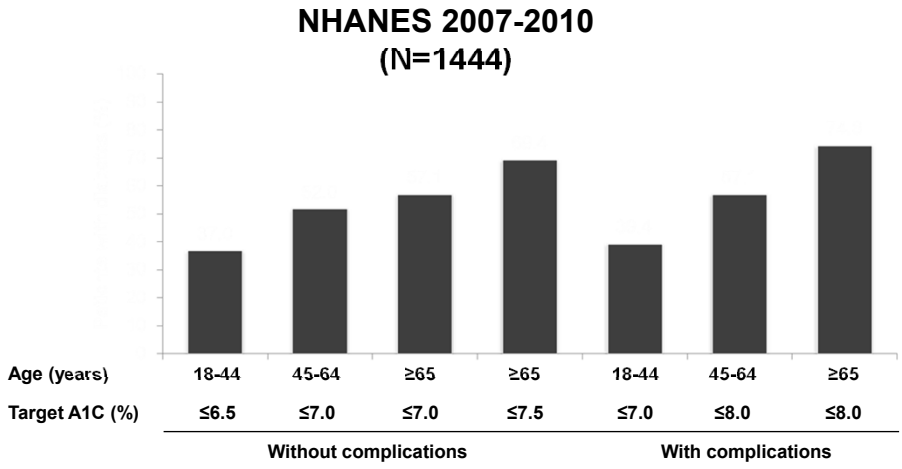
CDC. National diabetes statistics report, 2014. http://www.cdc.gov/diabetes/pubs/statsreport14/national-diabetes-report-web.pdf.
CDC. National diabetes fact sheet, 2011. http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf.

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

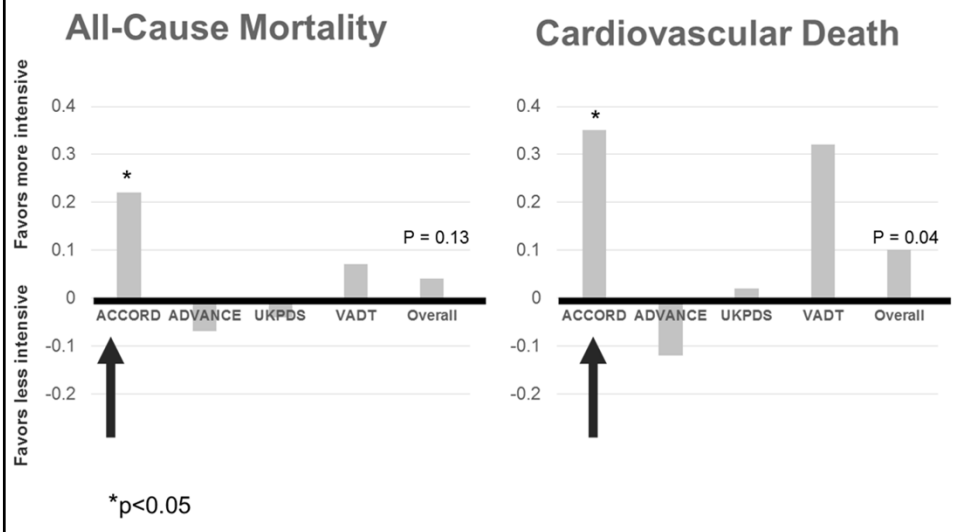
A1C Achievement by Individualized Target



NHANES, National Health and Nutrition Examination Survey.

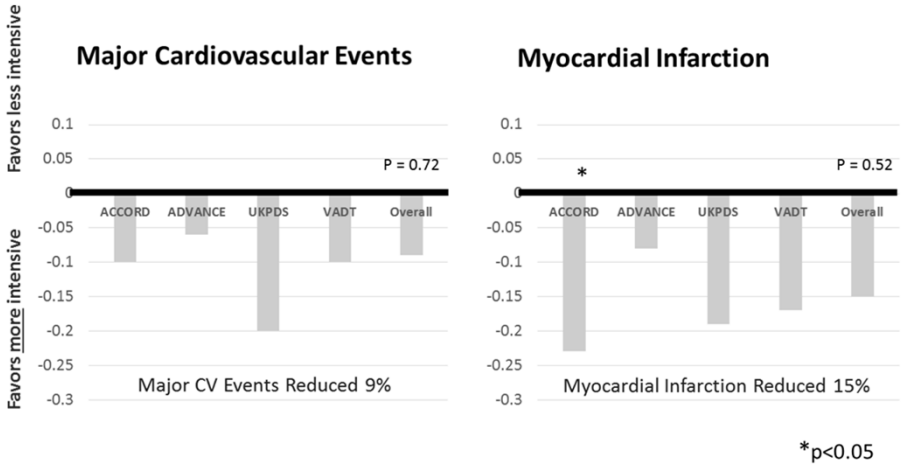
Ali MK, et al. *N Engl J Med*. 2013;368:1613-1624.

Meta-analysis: Intensive Glucose Control & Mortality



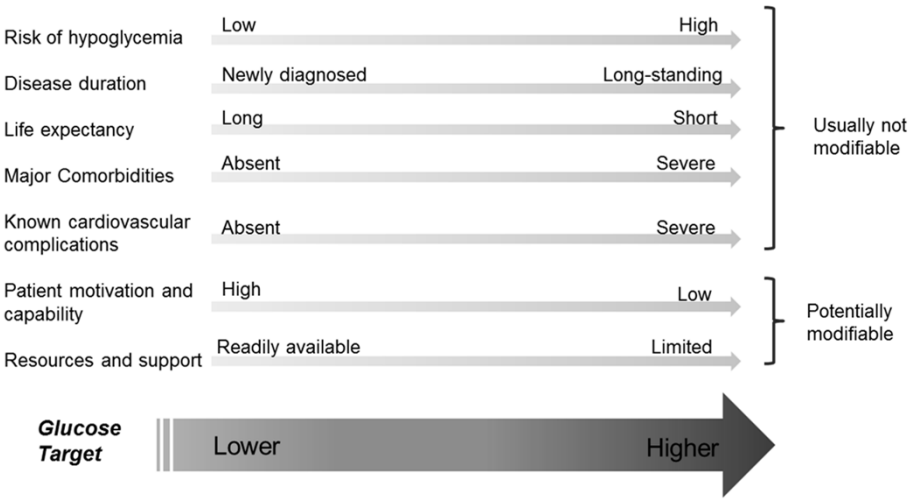
Diabetologia 2009;52:2288-98

Meta-analysis: Glucose Control & Macrovascular Disease



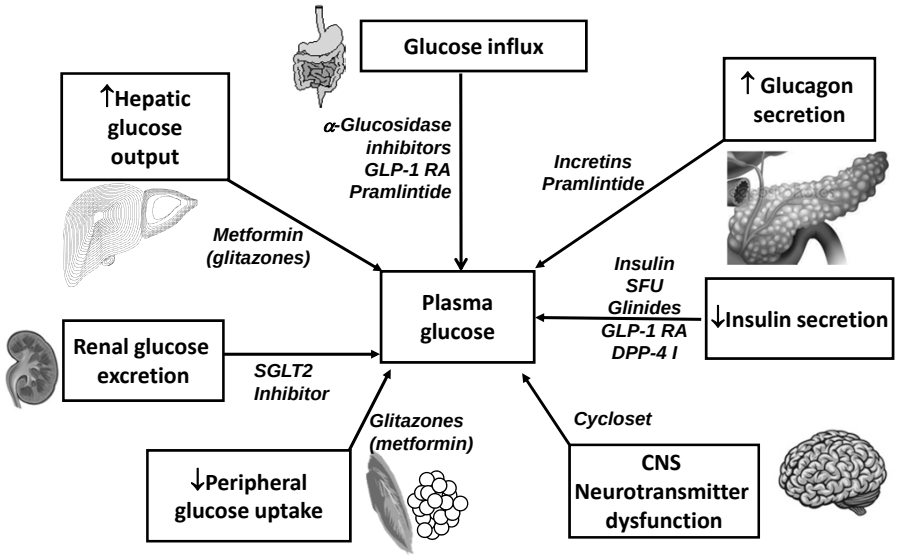
Pistrosch and Hanefeld. Curr Diab Rep 2015;15:117

ADA-Recommended Approach to Management of Hyperglycemia



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

Matching Pharmacology to Physiology

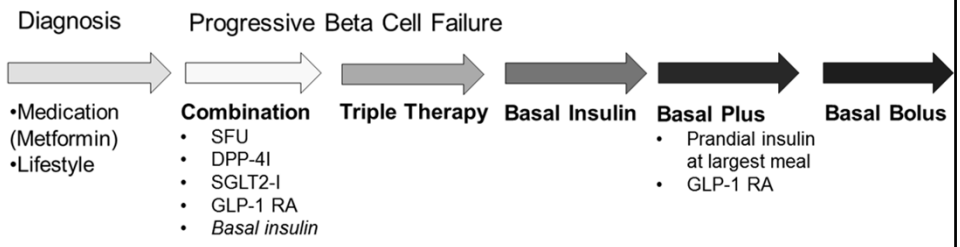


Comparison of Diabetes Medications

	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)	+++
Colesevalem	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



- Treat to Target A1c while avoiding hypoglycemia
- Add new medications rather than substitute
- Start insulin early when a patient needs it

FDA Update with Metformin

- **Renal dosing**
  - **contraindicated with eGFR <30 mL/minute/1.73 m^2.**
  - **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[1] 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[2] but not RCT

Pioglitazone

- Meta-analysis[3] 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		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

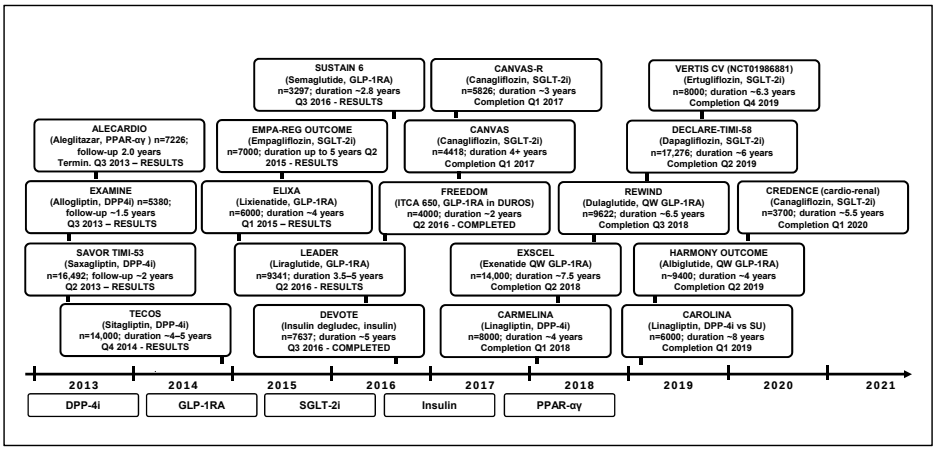
Name	% HbA1c Reduction	Starting Dose	Max Dose	Primary effect	Cautions
Canagliflozin (Invokana®)	0.5−1.0	100 mg daily	300 mg daily	Block renal glucose reabsorption	Ineffective if eGFR <45 (C, E) or <60 (D), UG infection, fluid/electrolyte, euglycemic DKA
Empagliflozin (Jardiance®)		10 mg daily	25 mg daily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

FDA Urged to Test Diabetes Drugs' Heart Risk

THE WALL STREET JOURNAL

Study: Sanofi's Lantus Insulin Has Possible Cancer Link

From The Times

May 31, 2007

GlaxoSmithKline defends Avandia as shares drop 13% in nine days

CBS NEWS

Judge sets first hearing for diabetes drug lawsuits

WebMD

Better information. Better health.

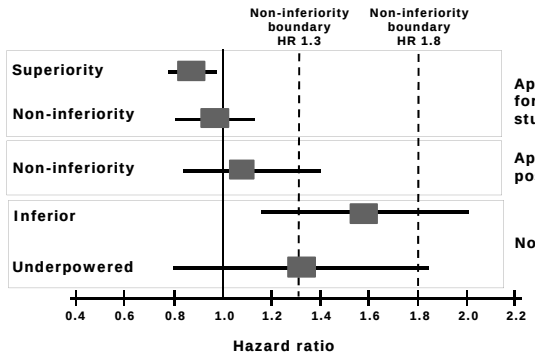
More Evidence Links Fractures to Diabetes Drugs

Avandia, Actos Boost Fracture Risk in Older Women, Study Finds

The New York Times

Diabetes drug tied to pancreatitis, deaths

FDA criteria for requirement of a postmarketing CV outcomes trial



Approvable: No need for postmarketing study

Approvable: Need for postmarketing study

Not approvable

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

Hirshberg 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

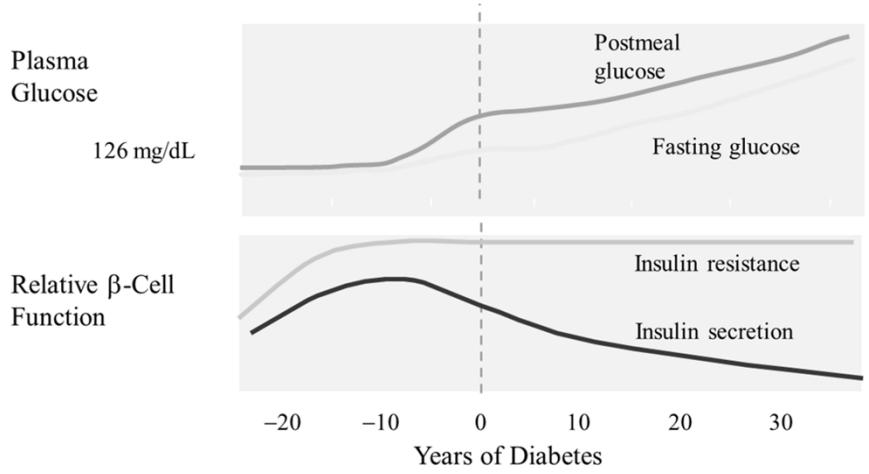
***Final CVOT pending**

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

Basal Insulin
- Continue metformin +/- other agent
- Start 10 unit/day or 0.1-0.2 unit/kg/day

Adjust 10-20% 2x/week

Not at goal after FBG target is reached or >0.5 unit/kg

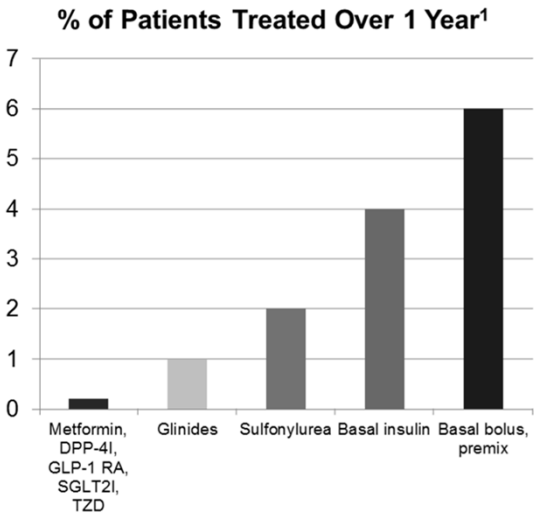
Basal Plus
- GLP-1 RA
- Prandial insulin at largest meal
  - 4 unit, 0.1 unit/kg, or 10% of basal dose
  - Consider reducing basal
- Premix
  - Divide basal dose to 2/3 AM, 1/3 PM

Adjust 10-20% 2x/week

Not at goal

Basal Bolus
- Prandial insulin at 2-3 meals
  - 4 unit, 0.1 unit/kg, or 10% of basal dose
  - Consider reducing basal

Frequency of Severe Hypoglycemia With Antihyperglycemic Agents



- HbA1c and duration of DM is not a significant predictor[2]
- Duration of insulin therapy associated with overall, nocturnal and severe hypoglycaemia

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

2) Khunti 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

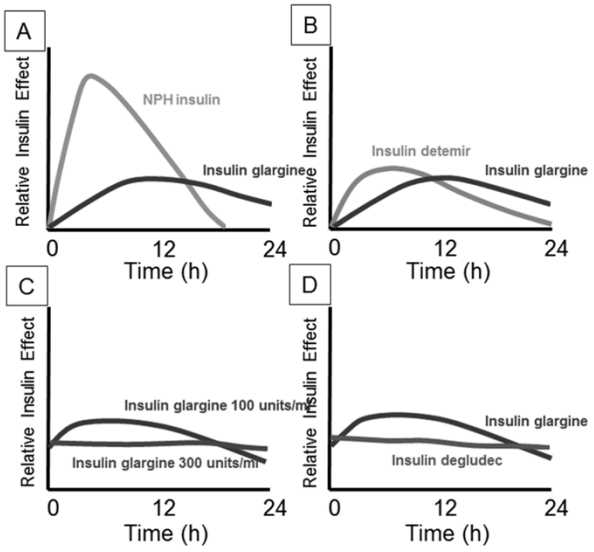
Basal insulins: *Practical Aspects*

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
Basal Insulin							
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)	6 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

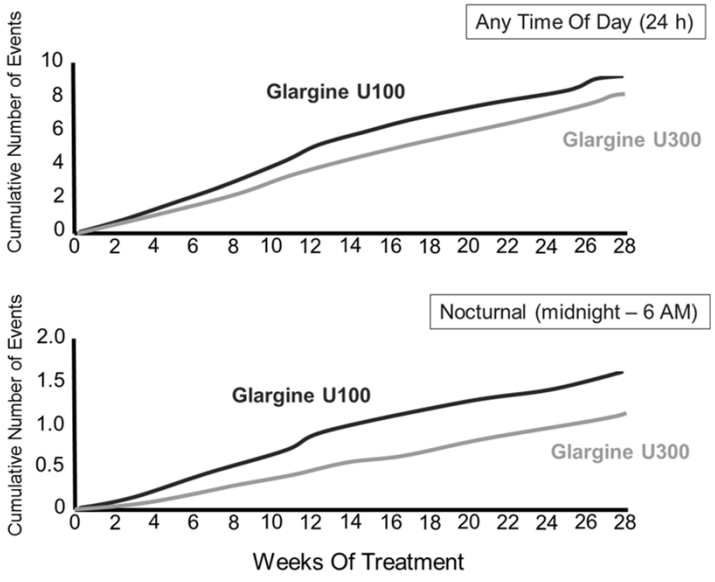
	Dur-ation	DM Type	Baseline Rx	N	Compa rator	HbA1c	Hypoglycemia (overall)	Hypoglycemia (nocturnal)	Weight Gain (kg)
EDITION 1	12	2	Basal bolus	807	G-U100	Similar	0.94 (0.89-0.99)	0.84 (0.75-0.94)	Comparable
EDITION 2	12	2	Basal	811	G-U100	Similar	0.96 (0.89-1.02)	0.84 (0.71-0.99)	0.42 vs. 1.14 , p=0.009
EDITION 3	6	2	Naïve	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

	Dur-ation	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	26	2	Naïve	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

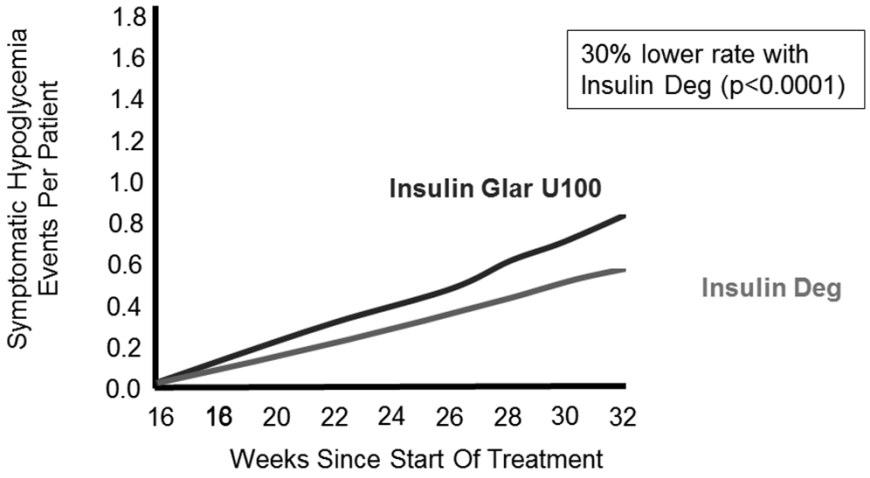
#Includes comparator group with flexible timing of daily dose
BB=basal bolus, D=degludec, DF=degludec flexible timing, G=glargine

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 Ideg v. Igla 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
Bolus Insulin							
Regular q.a.c.	30 min	2-4 hr	6-10 hr	10 mL, 1000 unit	Kwikpen: 1-60 NovoPen3 PenMate: 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	Echo: 0.5-30	0.5	Cartridge: 3 ml, 300 unit
				N/A	Flextouch: 1-60	1	Pen: 3 ml, 300 unit
Glulisine q.a.c.	5-15 min	1-2 hr	4-6 hr	10 mL, 1000 unit	Solostar pen: 1-80	1	Pen: 3 ml, 300 unit
Lispro q.a.c. (U100)	5-15 min	1-2 hr	4-6 hr	10 mL, 1000 unit	Luxura: 0.5-30	0.5	Cartridge: 3 ml, 300 unit
				N/A	Kwikpen: 1-60	1	Pen: 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

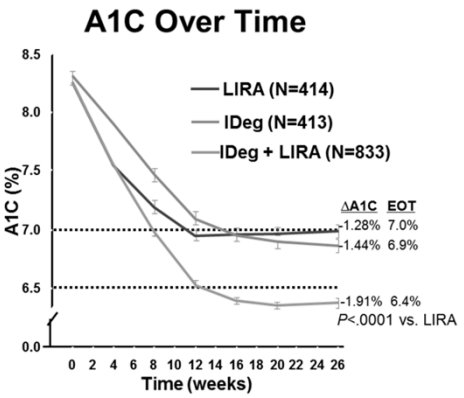
Other Insulins

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
Other							
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/m²**
  - **Age ≥18 years****

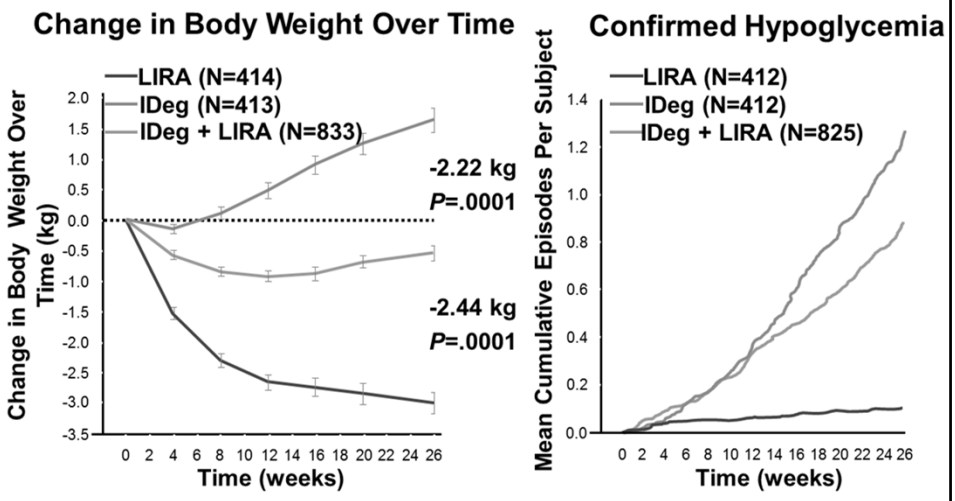
Mean values (±SEM) based on FAS and LOCF-imputed data.

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

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

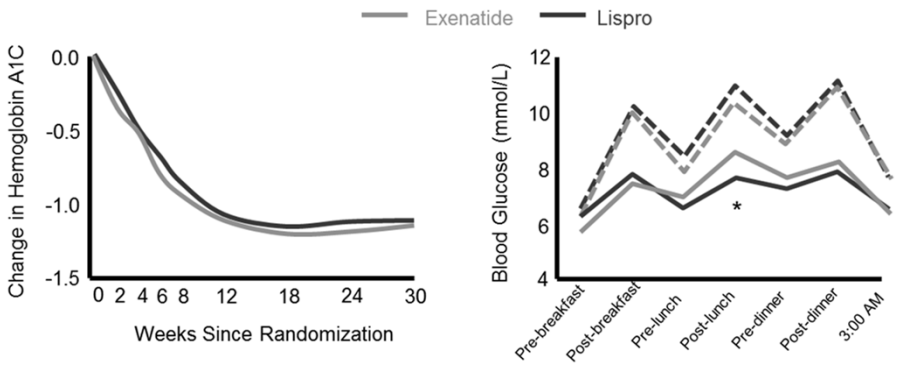
Gough SC, et al. *Lancet Diabetes Endocrinol*. 2014.

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



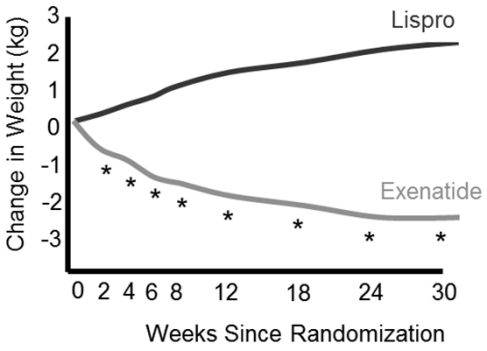
- **627 patients randomized to Exenatide BID or Lispro TID**
- **A1C non-inferior**
- **Fasting blood glucose lower with Exenatide**

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%**

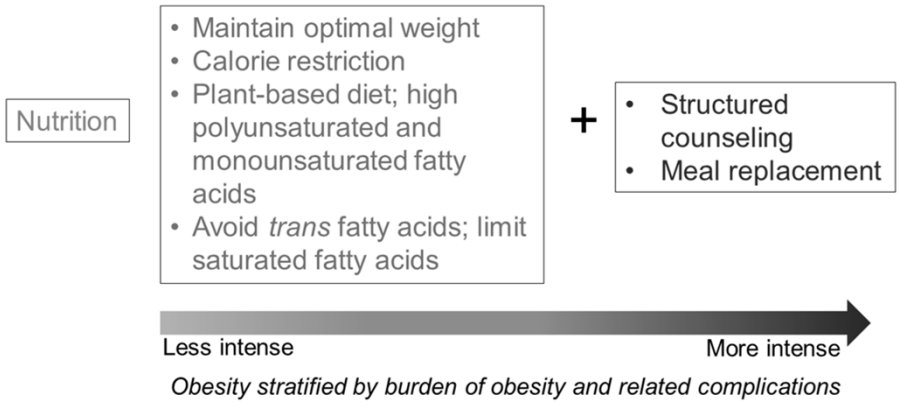


Diamant et al Diabetes Care 2014;37:2763-2773

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



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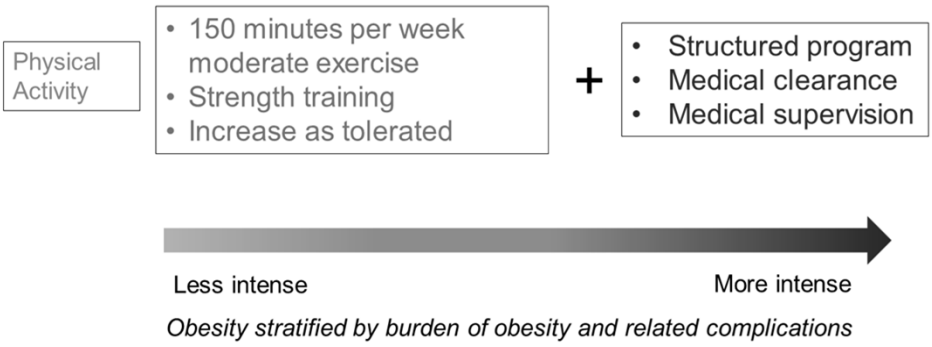
Lifestyle Therapy: risk stratification for diabetes complications



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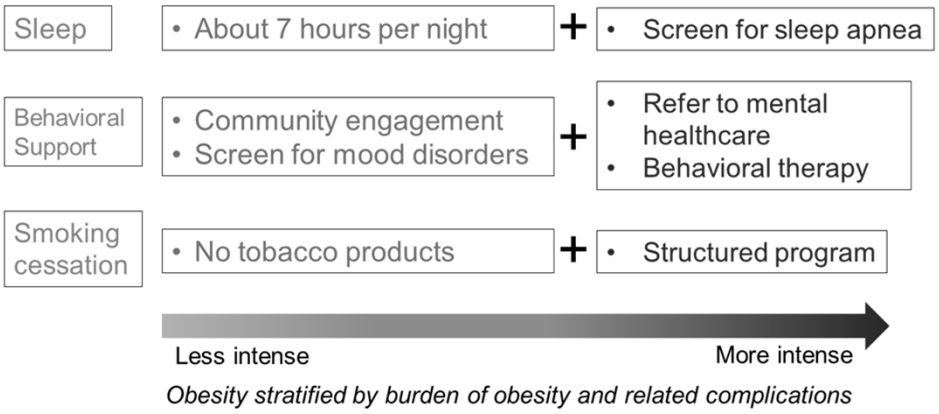
Lifestyle Therapy: risk stratification for diabetes complications



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Uncontrolled Diabetes

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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