Ask the Experts: Beyond the Basics in Managing Insulin and Other Antihyperglycemic Therapies for Type 2 Diabetes

Presented as a Live Webinar

Thursday, March 23, 2017
2:00 PM – 3:00 PM ET

On-demand Activity

Live webinar recorded and archived to be watched at your convenience
Available after May 15, 2017

www.ashpadvantage.com/go/type2

Planned by ASHP Advantage

Supported by an educational grant from Novo Nordisk Inc.

Activity Overview

In this activity, the faculty will use clinical case vignettes to address advanced challenges related to the use of insulin and other antihyperglycemic agents in the management of type 2 diabetes, such as the influence of comorbidities. The content for this activity is based on questions and comments from participants at a recent educational symposium on this topic.

Learning Objectives

At the conclusion of this application-based educational activity, participants should be able to

- Summarize key challenges related to the use of insulin and other antihyperglycemic agents in patients with type 2 diabetes with a high burden of comorbidities.
- Apply strategies to improve glycemic management in patients with type 2 diabetes.

Continuing Education Accreditation

ASHP is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

This activity provides 1.0 hour (0.1 CEU – no partial credit) of continuing pharmacy education credit.

Live activity ACPE #: 0204-0000-17-403-L01-P

On-demand activity #: 0204-0000-17-403-H01-P

Participants will process CPE credit online at http://elearning.ashp.org/my-activities. CPE credit will be reported directly to CPE Monitor. Per ACPE, CPE credit must be claimed no later than 60 days from the date of the live activity or completion of a home-study activity.

List of Abbreviations

For a list of abbreviations used in this activity, please see page 24.

Webinar Information

Visit www.ashpadvantage.com/go/type2/ate to find

- Webinar registration link
- Group viewing information and technical requirements
- CPE webinar processing information

Faculty

Curtis L. Triplitt, Pharm.D., CDE, *Initiative Chair*
Associate Director, Diabetes Research Center, Texas Diabetes Institute
Associate Professor, Department of Medicine, Division of Diabetes
University of Texas Health Science Center at San Antonio
San Antonio, Texas

Curtis L. Triplitt, Pharm.D., CDE, is Associate Professor and Certified Diabetes Educator at the University of Texas Health Science Center at San Antonio (UTHSCSA) where he oversees many diabetes research projects. In addition, he clinically manages people with diabetes with an endocrinologist at the Texas Diabetes Institute.

Dr. Triplitt earned his Bachelor of Science degree in pharmacy from the University of Iowa and his Doctor of Pharmacy degree from the University of Texas at Austin and the Health Science Center at San Antonio. He completed an ASHP-accredited primary-care residency at William S. Middleton Veteran Administration's Hospital in Madison, Wisconsin.

Dr. Triplitt has published more than 40 peer-reviewed articles in the diabetes and metabolism field, as well as eight book chapters on diabetes mellitus. He is an associate editor for the ADA publication *Diabetes Spectrum* and serves on the editorial board for *Clinical Diabetes*, *AADE in Practice*, and several other diabetes journals. In addition, Dr. Triplitt is Vice-Chair of the Texas Diabetes Council (TDC), which is legislatively mandated to develop and implement a state plan for diabetes prevention, treatment, education, and training. In 2008, he was honored with the Pharmacy Preceptor of the Year Award from The University of Texas.

Ask the Experts: Beyond the Basics in Managing Insulin and Other Antihyperglycemic Therapies for Type 2 Diabetes

Joshua J. Neumiller, **Pharm.D., CDE, FASCP**
Vice Chair and Associate Professor
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Joshua J. Neumiller, Pharm.D., CDE, FASCP, is Vice Chair and Associate Professor in the Department of Pharmacotherapy at Washington State University College of Pharmacy in Spokane, Washington.

Dr. Neumiller earned a Bachelor of Science degree in general science and a Doctor of Pharmacy degree from Washington State University in Spokane, Washington. He is a certified diabetes educator (CDE) and a fellow of the American Society of Consultant Pharmacists (ASCP).

Dr. Neumiller's research interests involve the management of diabetes and prevention of adverse drug events during transitions in care. He is Editor-in-Chief for *Diabetes Spectrum*, a journal of the American Diabetes Association (ADA). He also is a contributing author for the ADA books, *Medications for the Treatment of Diabetes*, *Practical Insulin*, and *American Diabetes Association Guide to Nutrition Therapy for Diabetes*.

Dr. Neumiller is a member of ADA, ASCP, American Association of Diabetes Educators, American Pharmacists Association, and Washington State Pharmacy Association. He was recently awarded the 2016 Albert B. Prescott Pharmacy Leadership Award from the Pharmacy Leadership and Education Institute.

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- Joshua J. Neumiller, Pharm.D., CDE, FASCP, declares that he has served as a consultant for Eli Lilly and Sanofi and on a speakers bureau for Novo Nordisk Inc. He has also received research grants from AstraZeneca, Johnson & Johnson, and Novo Nordisk Inc.
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Additional Educational Opportunities about Type 2 Diabetes

This Ask the Experts activity is just one component of the educational initiative, "Individualization of Insulin Therapy for Type 2 Diabetes Mellitus: What You Need to Know," which includes e-newsletters, faculty interviews, and other home-study CPE activities.

To access these activities and sign up for updates

www.ashpadvantage.com/go/type2

Ask the Experts: Beyond the Basics in Managing Insulin and Other Antihyperglycemic Therapies for Type 2 Diabetes

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1.0 hr CPE

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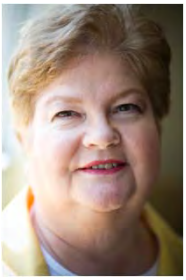
- Summarize key challenges related to the use of insulin and other antihyperglycemic agents in patients with type 2 diabetes with a high burden of comorbidities.
- Apply strategies to improve glycemic management in patients with type 2 diabetes.

Case Vignette 1: SS

- SS is a 60-year-old woman with T2DM of 11 years duration
- **Past medical history**
  - Type 2 diabetes mellitus
  - Hypertension
  - Hyperlipidemia
  - Peripheral neuropathy
- **Chief complaint**
  - Evening hyperglycemia and occasional morning hypoglycemia



Case Vignette 1: SS

- **Current medications**
  - Metformin 1000 mg PO BID
  - U-100 insulin glargine 94 units SC once daily at bedtime via vial and syringe
  - Lisinopril 20 mg PO once daily
  - Hydrochlorothiazide 12.5 mg PO once daily
  - Rosuvastatin 20 mg PO once daily
  - Duloxetine 60 mg PO once daily

Case Vignette 1: SS

- **Vital signs**
  - BP 132/90 mmHg
  - Pulse 66 bpm, regular
  - Weight 198 lb (90 kg)
- **Labs (fasting)**
  - Glucose 125 mg/dL
  - A1c 7.6%

Case Vignette 1: SS's Blood Glucose Log

- SS currently checks her BG twice daily in the morning and at bedtime

Day	Morning (Fasting)	Bedtime
Monday	141 mg/dL	180 mg/dL
Tuesday	130 mg/dL	192 mg/dL
Wednesday	141 mg/dL	210 mg/dL
Thursday	150 mg/dL	205 mg/dL
Friday*	141 mg/dL	121 mg/dL
Saturday	62 mg/dL	230 mg/dL
Sunday	173 mg/dL	202 mg/dL

*SS went shopping at the mall in the evening and ate a light dinner.

Case Vignette 1: SS

- Upon further discussion with SS, the following is discovered
  - She has been self titrating her basal insulin to target a fasting blood glucose target of 80-130 mg/dL
  - She reports often snacking during the day due to feeling "shaky"
    - She generally does not check her blood glucose during the day to save money on test strips
  - She reports occasional nocturnal and morning hypoglycemia
  - SS is frustrated that her A1c is not < 7.0%

Based on SS's blood glucose trends, which of the following do you suspect?

a. Basal insulin dose too low

b. Basal insulin dose too high

c. Nonadherence to her insulin therapy

Case Vignette 1: SS's Blood Glucose Log

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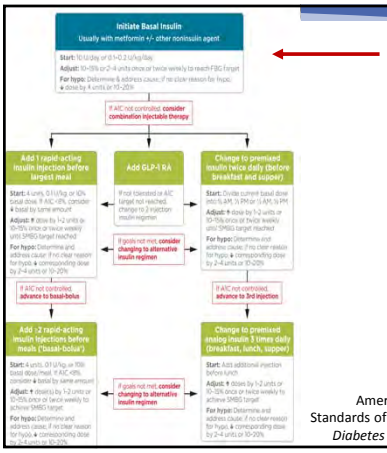
Overbasalization

- Occurs when fasting blood glucose is not controlled with up-titration of basal insulin and A1c targets remain elusive
- Has been suggested that maximal amounts of basal insulin should not comprise more than 50% of the total daily insulin dose calculation
  - TDD for insulin resistant T2DM patient = 1.0 to 1.5 units/kg/day
    - For SS: 90 kg x 1.5 units = 135 total units/day
    - 135 units/2 = 68 units of basal

TDD = total daily dose

LaSalle JR et al. *J Am Osteopath Assoc*. 2012; 113:152-62.

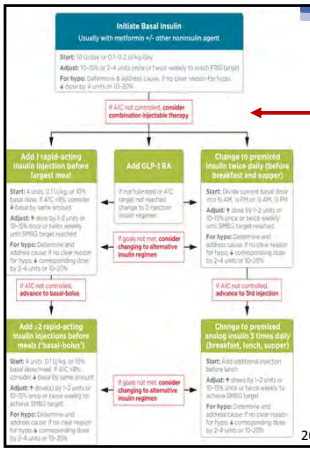


Basal Insulin Initiation in T2DM

- Start with 10 units/day or 0.1-0.2 units/kg/day
- Adjust 10-15% or 2-4 units once or twice weekly to reach **FBG** target
- Assess and adjust if hypoglycemia

American Diabetes Association (ADA). Standards of medical care in diabetes – 2017. *Diabetes Care*. 2017; 40(suppl 1):S1-S135.

See page 19 for enlarged view



Once FBG optimized, start addressing PPG excursions

- Add GLP-1 RA **or**
- Add 1 rapid-acting insulin injection to largest meal **or**
- Change to premixed insulin twice daily

GLP-1 RA = glucagon-like peptide-1 receptor agonist

ADA. Standards of medical care in diabetes – 2017. *Diabetes Care*. 2017; 40(suppl 1):S1-S135.

See page 19 for enlarged view

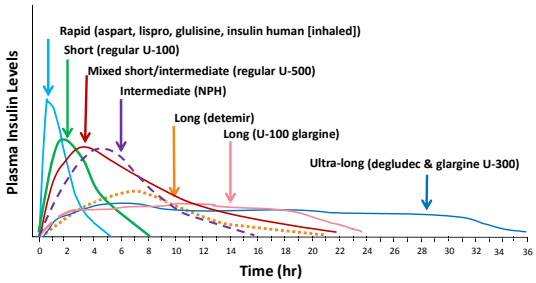
Case Vignette 1: SS

- It is recommended that SS's basal insulin be decreased and a medication to assist with postprandial blood glucose be added
- Over the next several months, SS's primary care provider (PCP) makes the following changes
  - Down titrates her U-100 insulin glargine to 60 units SC at bedtime
  - Initiates and titrates liraglutide to 1.8 mg SC daily

Case Vignette 1: SS Follow-Up

- 6 months later SS's primary care provider would like to switch her from U-100 insulin glargine to U-300 insulin glargine
  - SS's evening blood glucose readings remain slightly elevated despite her morning fasting blood glucose values generally being at target
  - SS's PCP suspects she may be experiencing some end-of-dose "wearing off" and would like to use a longer-acting basal insulin

Pharmacokinetic Profile of Currently Available Insulins



Hirsch IB. *N Engl J Med*. 2005; 352:174-83.
Flood TM. *J Fam Pract*. 2007; 56(suppl 1):S1-S12.
Becker RH et al. *Diabetes Care*. 2015; 38:637-43.

See page 20 for enlarged view

SS is currently stabilized on 60 units of U-100 insulin glargine at bedtime. Per the prescribing information, what would be an appropriate starting dose of U-300 insulin glargine?

a. 48 units once daily
b. 60 units once daily
c. 72 units once daily
d. 30 units twice daily

U-300 Insulin Glargine: Dosing Recommendations in T2DM

Prior Treatment:	Start with:
Once-daily basal insulin	1:1 conversion
Twice-daily NPH	80% of total daily NPH dose
No current basal insulin	0.2 units/kg

Available in pens only

- 300 units/mL, 1.5 mL
- Dose per injection is 1-80 units with current pen
- Dial the prescribed dose, no conversion needed

Toujeo (insulin glargine U-300 injection) prescribing information. 2015 Sep.

Case Vignette 1: SS Follow-Up

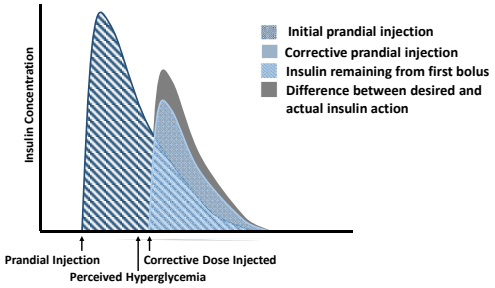
- In counseling SS, she states that she read on the internet that her new basal insulin has a "very long action" in the body and she is concerned about the insulin "building up" and causing hypoglycemia.

Insulin Stacking vs. Therapeutic Accumulation

- "Insulin stacking" is the excessive accumulation of insulin within the circulation
  - Typically occurs with the administration of rapid-acting insulin to correct hyperglycemia
  - Described as
    - "…the practice of providing correctional doses of insulin before a prior dose of prandial insulin (or the peak action of neutral protamine Hagedorn, [NPH]) has had its full effect."[1]
    - "…previously infused insulin still has an effect on future glucose values."[2]

[1]Hirsch IB. *N Engl J Med*. 2005; 352:174-83.
[2]Bequette BW. *J Diabetes Sci Technol*. 2009; 3:1005-13.

Potential for Insulin Stacking with Rapid-acting Insulin



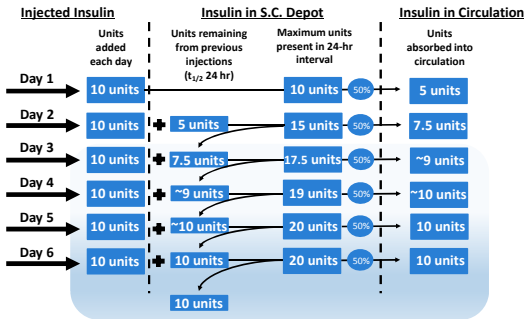
Heise T, Meneghini LF. *Endocr Pract*. 2014; 20:75-83.

Insulin Stacking vs. Therapeutic Accumulation

- Therapeutic, or steady-state accumulation is a normal part of the PK process
  - Enables long-acting insulin to reach a stable, steady-state condition
  - Important to dose the basal insulin in appropriate amounts and titrate at appropriate time intervals to allow for steady-state accumulation and avoid "overshooting" the target fasting blood glucose

Heise T, Meneghini LF. *Endocr Pract*. 2014; 20:75-83.

Therapeutic Accumulation with Long-acting Insulin



Heise T, Meneghini LF. *Endocr Pract*. 2014; 20:75-83.

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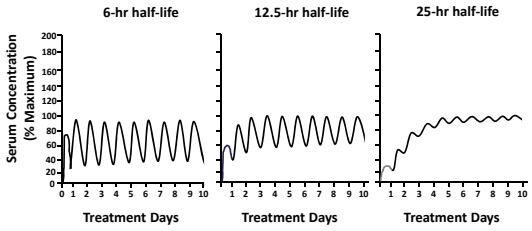
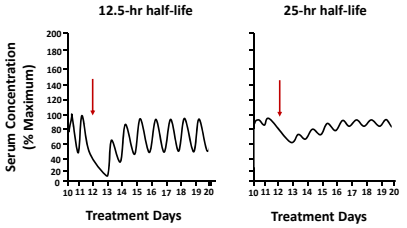
Therapeutic Accumulation with Once Daily Administration of Long-Acting Insulin



Heise T, Meneghini LF. *Endocr Pract*. 2014; 20:75-83.

Therapeutic Accumulation with Once Daily Administration of Long-acting Insulin: Impact of a Missed Dose



Heise T, Meneghini LF. *Endocr Pract*. 2014; 20:75-83.

Case Vignette 2: RD

- RD is a 57-year-old man with T2DM of 14 years duration
- **Past medical history**
  - Type 2 diabetes mellitus
  - Hypertension
  - Coronary artery disease (CAD)
  - Obesity (BMI = 42.3 kg/m^2)
  - CKD

Case Vignette 2: RD

- **Current medications**
  - Metformin 1000 mg PO BID
  - U-100 insulin glargine 80 units SC BID
  - Insulin aspart 25 units SC TID with meals
  - Metoprolol succinate 100 mg PO daily
  - Amlodipine 10 mg PO daily
  - Atorvastatin 40 mg PO at bedtime
  - Aspirin 81 mg daily

Case Vignette 2: RD

- **Vital signs**
  - BP 138/90 mmHg
  - Pulse 56 bpm, regular
  - Weight 312 lb (~142 kg)
  - BMI: 42.3 kg/m^2
- **Labs (fasting)**
  - Glucose 230 mg/dL
  - A1c 9.3%

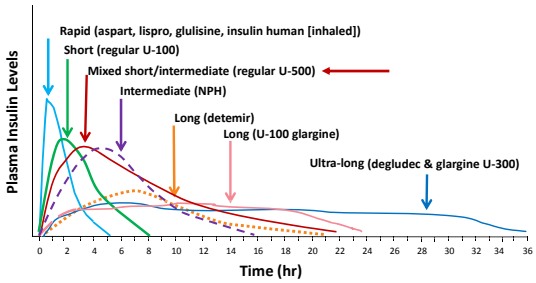
RD's physician would like to convert RD to a U-500 regular insulin regimen and would like initiation and titration assistance from pharmacy

U-500 Regular Insulin

- **Human insulin**
  - 20-mL vials
    - U-500 insulin syringes
  - 3-mL pen (1,500 units/pen)
- **Reduced hexamer formation leads to faster dissociation and absorption**
  - Time to peak: 30 minutes
  - Duration: ~7 hours
  - Half-life: ~4 hours
- **Indication**
  - Patients requiring > 200 units of insulin/day

Lamos EM et al. *Ther Clin Risk Manag*. 2016; 12:389-400.

Pharmacokinetic Profile of Currently Available Insulins



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Flood TM. *J Fam Pract*. 2007; 56(suppl 1):S1-S12.
Becker RH et al. *Diabetes Care*. 2015; 38:637-43.

See page 20 for enlarged view

Steps for Initiating U-500 Insulin

- Total daily dose determination

1 month prior: A1c >8% & Within 1 week prior: BG ≥183 mg/dL	1 month prior: A1c ≤8% OR Within 1 week prior: BG <183 mg/dL
TDD: 100% of U-100 dose	TDD: 80% of U-100 dose

- Dose proportion determination

	Before Breakfast	Before Lunch	Before Dinner
BID regimen	60%	0%	40%
TID regimen	40%	30%	30%

Hood RC et al. *Endocr Pract*. 2015; 21:782-93.

U-500 Insulin Titration: BID Regimen

Insulin Dose to Adjust	Blood Glucose Value Reviewed	Blood Glucose Value (mg/dL)	Action
Prebreakfast	Median predinner *OR* median prelunch	≤70	↓10%
	Median predinner	71-130	No change
		131-180	↑5%
		181-220	↑10%
		>220	↑15%
Predinner	Median prebreakfast, median bedtime, *OR* 3 AM value	≤70	↓10%
	Median prebreakfast	71-130	No change
		131-180	↑5%
		181-220	↑10%
		>220	↑15%

Hood RC et al. *Endocr Pract*. 2015; 21:782-93.

U-500 Insulin Titration: TID Regimen

Insulin Dose to Adjust	Blood Glucose Value Reviewed	Blood Glucose Value (mg/dL)	Action
Prebreakfast	Median prelunch	≤70	↓10%
		71-130	No change
		131-180	↑5%
		181-220	↑10%
		>220	↑15%
Prelunch	Median predinner	≤70	↓10%
		71-130	No change
		131-180	↑5%
		181-220	↑10%
		>220	↑15%
Predinner	Median prebreakfast, median bedtime, *OR* 3 AM value	≤70	↓10%
	Median prebreakfast	71-130	No change
		131-180	↑5%
		181-220	↑10%
		>220	↑15%

Hood RC et al. *Endocr Pract*. 2015; 21:782-93.

You are asked to calculate an initial BID U-500 regimen for RD. His most recent A1c was 9.3% (with multiple SMBG readings >183 mg/dL). His current TDD of U-100 insulin is 235 units. Which of the following would be the most appropriate recommendation?

a. 188 units given as 60% (112 units) prebreakfast, 40% (76 units) predinner
b. 188 units given as 40% (76 units) prebreakfast, 60% (112 units) predinner
c. 235 units given as 60% (140 units) prebreakfast, 40% (95 units) predinner
d. 235 units given as 40% (95 units) prebreakfast, 60% (140 units) predinner

RD Follow-Up

- RD was started on a BID regimen of U-500 insulin
  - 140 units before breakfast
  - 95 units before dinner
- RD's insulin was titrated per the BID dosing algorithm and he was stabilized on 165 units before breakfast and 120 units before dinner
- 6 months later, RD's A1c was 7.3%

Addressing Complex Patients with Type 2 Diabetes

Case Vignette: DG

- Age 62, with T2DM X 14 years
- PMH significant for
  - MI X 2: has had 2 stents placed in his LAD
    - Last cardiac cath: diffuse plaques throughout, LVEF= 31%
  - Microalbuminuria: persistent
  - Moderate nonproliferative background retinopathy
  - Dyslipidemia
  - Obesity
- PSH
  - Cholecystectomy 34 yr ago
  - L tibia fx from skiing 25 yr ago
- Social Hx
  - Married X 41 years, works as a maintenance supervisor in an apartment complex, 3 children-no chronic diseases
  - Smoker, 10 cigarettes a day now, has tried quitting "at least 10 times'" but stress of work and 2 AM calls, 50 pack-year history EtOH- 2-3 beers 12 oz. on the weekend

Case Vignette: DG

- Age 62, with T2DM X 14 years
- Current medications
  - Metformin 1000 mg PO BID with meals
  - Saxagliptin 5 mg PO daily
  - Insulin glargine (U-100) 78 units SC at bedtime
  - Lisinopril 40 mg PO daily
  - Amlodipine 5 mg PO daily
  - Metoprolol ER 200 mg PO daily
  - Atorvastatin 80 mg PO daily
  - Enteric-coated aspirin 81 mg PO daily
  - Clopidogrel 75 mg PO daily
- Vitals: BMI: 33 kg/m^2, BP 139/78 mmHg, HR 61 BPM, Temp WNL
- Laboratory: A1c 8.1%, FPG 142 mg/dL
- Spot random microalbumin/creatinine ratio = 210 mg/g
- TC 156 mg/dL
- LDL 62 mg/dL
- HDL 52 mg/dL
- TG 210 mg/dL

137*	100*	24$^+$	MDRD eGFR 68 mL/min/1.73m^2
4.1*	26*	1.1$^+$	

CBC WNL

*mmol/L $^+$mg/dL

What are the major issues with DG?

- CVD: stable
  - Dyslipidemia: High potency statin, LDL "at goal"
  - ASA: taking as per patient
- HTN: on lisinopril 40 mg/day, beta-adrenergic blocking agent, and calcium-channel blocking agent, BP controlled
- Microalbuminuria: stable on above medications
- Obesity: continues
- T2DM: uncontrolled (metformin, glargine, saxagliptin)
- Recommendations to improve his glycemic control?

Which of the following interventions to improve DG's glycemic control would be reasonable? Select all that apply.

a. Up titrate insulin glargine to FPG goal

b. Add pioglitazone 15 mg PO daily

c. Add dulaglutide 0.75 mg SC weekly

d. Add empagliflozin 10 mg PO daily

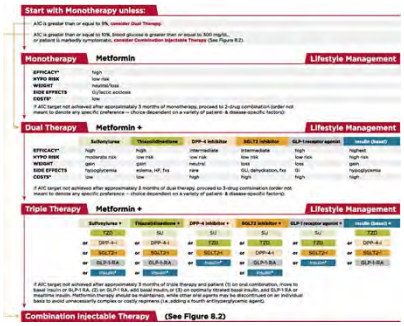
e. Do nothing – DG is complex and he is at A1c goal

Selection of Glucose-Lowering Therapy: Factors that Influence…

- Well established
  - Mechanism of action
  - Contraindications
    - Comorbidities
    - Special population
  - Side effects
  - Efficacy
  - Long-term safety
  - Ease-of-use
  - Cost
- Less well established "Nonglycemic effects"
  - Cardiovascular outcomes
    - Positive or negative?
  - Weight effects
  - Lipids effects
  - Blood pressure effects
  - β-cell effects
    - Positive or negative?

Adapted from Nathan DM et al. *Diabetes Care*. 2006; 29:1963-72.

Antihyperglycemic Therapy in Type 2 Diabetes: General Recommendations



American Diabetes Association. *Diabetes Care*. 2017; 40(suppl 1):S64-S74.

See page 21 for enlarged view

Metformin: FDA Renal Impairment Recommendations

- Obtain the patient's eGFR before starting and reassess at least annually
  - In patients at increased risk of renal impairment (e.g., elderly), renal function should be assessed more frequently.
- If eGFR falls below 45 mL/minute/1.73 m^2, assess the benefits and risks of continuing treatment
- Starting metformin with an eGFR between 30-45 mL/minute/1.73 m^2 is not recommended
- Metformin is contraindicated in patients with an eGFR below 30 mL/minute/1.73 m^2
- No reduction in dose is mentioned

FDA Drug Safety Communication: FDA revises warnings regarding use of the diabetes medicine metformin in certain patients with reduced kidney function. April 8, 2016. ww.fda.gov/Drugs/DrugSafety/ucm493244.htm (accessed 2017 Mar 1).

Metformin-associated Lactic Acidosis

- Pooled data
  - 347 comparative trials and cohort studies
- No cases of fatal or nonfatal lactic acidosis in 70,490 patient-years of metformin use or in 55,451 patient-years in non-metformin group
- True incidence of lactic acidosis per 100,000 patient-years
  - 4.3 cases in metformin group
  - 5.4 cases in non-metformin group
- No difference in lactate levels, either as mean treatment levels or as a net change from baseline, for metformin compared to non-metformin therapies

Salpeter SR et al. *Cochrane Database Syst Rev*. 2010 Jan 20;(1):CD002967.

New Metformin and Vitamin B12 Monitoring Recommendations

- ADA RECOMMENDS PERIODIC MONITORING- Level Evidence A
  a. Longstanding therapy
  b. Those with peripheral neuropathy or anemia
- Facts to know

1. MOA: Metformin effects on calcium channels, which is used to absorb B12-intrinsic factor complex
2. Metformin-induced B12 reduction easily treated with B12 supplementation or calcium supplements
3. DPP/DPPOS metformin in prediabetes study
   - Length of therapy was main association with risk of B12 deficiency
   - Slightly more anemia and neuropathy with metformin vs. placebo

ADA. Standards of medical care in diabetes – 2017. *Diabetes Care*. 2017; 40(suppl1):S64-S74.
Aroda VR et al. *J Clin Endocrinol Metab*. 2016; 101:1754-61.

DPP-4 Inhibitors

- Side effect profile very good (few call backs)
  - No known consequences if dosage adjustments for remain impairment are not made
  - Once daily dosing
  - Where to use DPP-4 inhibitors to optimize therapy?
  - Use when appropriate
    1) Close to goal (Remember that goal can be A1c 6-8.5%)
    2) When GLP-1 RAs are not a good option
    3) In elderly
    4) Renal insufficiency or failure
  - When NOT to use: CHF (except sitagliptin)

DPP-4 = dipeptidyl peptidase-4

DPP-4 Inhibitors: A1c Reduction Lesson

A1c	Reduction (%)	95% CI	P value
<7.5%	-0.43	-0.91, 0.04	0.07
7.5-8%	-0.53	-0.82, -0.23	0.0005
8-<9%	-0.61	-0.38, -0.40	<0.00001
≥9%	-0.84	-1.18, -0.50	<0.00001

Shallow A1c reduction at different baseline A1c values—Many contribute to clinical inertia

Singh-Franco D et al. *Diabetes Obes Metab*. 2012; 14:694-708.

Saxagliptin "Study 14": Time to Need for Rescue Therapy or Discontinuation*

	Saxagliptin 2.5 mg, 5 mg, or 10 mg daily + Metformin	Metformin+ Placebo
30-50 weeks in study, A1c >8.0%	16%	30%
63-76 weeks in study, A1c >7.5%	40%	60%
89-193 weeks in study, A1c>7.0%	53%	80%

*All values estimated from Rosenstock, Figure 1.

Durability is fair at best

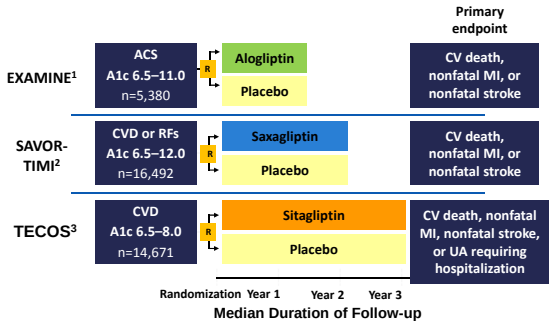
Rosenstock J et al. *Diabet Med*. 2013; 30:1472-6.

Cardiovascular Outcomes Trials: Diabetes

- Gliptins
  - Saxagliptin TIMI-53
  - Alogliptin EXAMINE
  - Sitagliptin TECOS
  - Linagliptin CAROLINA, CARMELINA
- GLP-1 receptor agonists
  - Lixisenatide ELIXA
  - Liraglutide LEADER
  - Exenatide EXSCEL
  - Dulaglutide REWIND
  - Albiglutide HARMONY
  - Semiglutide SUSTAIN-6
- SGLT-2 inhibitors
  - Empagliflozin EMPA-REG
  - Canagliflozin CANVAS
  - Dapagliflozin DECLARE-TIMI-58
- Insulin
  - Insulin glargine ORIGIN
  - Insulin degludec DEVOTE
- Thiazolidinediones (TZDs)
  - Pioglitazone ProActive, IRIS
  - Rosiglitazone RECORD

SGLT-2 = sodium glucose cotransporter-2

Gliptin CV Outcomes Trials



[1]White WB et al. *N Engl J Med*. 2013; 369:1327-35.
[2]Scirica BM et al. *N Engl J Med*. 2013; 369:1317-26.
[3]Green JB et al. *N Engl J Med*. 2015; 373:232-42.

See page 21 for enlarged view

"Gliptin" Cardiovascular Outcome Trials: Good Background Treatment of CVD Risk

Study	Insulin N (%)	Metformin N (%)	SU N (%)	ASA N (%)	Statin N (%)	Anti-Platelet/ Anti-Coagulant N (%)	β-Blocker N (%)	ACEI/ ARB N (%)
SAVOR-TIMI53 Saxagliptin	6,757 (40.9)	11,094 (67.4)	6,332 (38.5)	12,390 (75.2)	12,892 (78.3)	13,386 (81.3)	10,117 (61.4)	12,935 (78.5)
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See page 22 for enlarged view

Gliptins: CVD PRIMARY OUTCOMES

	SAVOR-TIMI Saxagliptin		EXAMINE Alogliptin		TECOS Sitagliptin	
		HR (95% CI) P value		HR (95% CI) P value		HR (95% CI) P value
Primary composite MACE	CV death, MI, or stroke	1.00 (0.89-1.12) P=0.99	CV death, MI, or stroke	0.96 (≤1.16) P=0.315	CV death, MI, UA, or stroke	0.98 (0.89–1.08) P=0.65
CV death	Primary endpoint	1.03 (0.87–1.22) P=0.72	Primary endpoint	0.85 (0.66–1.10) P=0.212	Primary endpoint	1.03 (0.89–1.19) P=0.71
Myocardial infarction	Primary endpoint	0.95 (0.80–1.12) P=0.52	Primary endpoint	1.08 (0.88–1.33) P=0.47	Primary endpoint	0.95 (0.81–1.11) P=0.49
Stroke	Primary endpoint	1.11 (0.88–1.39) P=0.38	Primary endpoint	0.91 (0.55–1.50) P=0.71	Primary endpoint	0.97 (0.79–1.19) P=0.76

White WB et al. *N Engl J Med*. 2013; 369:1327-35. Scirica BM et al. *N Engl J Med*. 2013; 369:1317-26. Green JB et al. *N Engl J Med*. 2015; 373:232-42.

See page 22 for enlarged view

Hospitalization for Heart Failure

SAVOR-TIMI Saxagliptin		EXAMINE Alogliptin		TECOS Sitagliptin	
	HR (95% CI) P value		HR (95% CI) P value		HR (95% CI) P value
Secondary endpoint	1.27 (1.07–1.51) P=0.007	Extended primary endpoint	1.19 (0.90-1.58) P=0.220	Secondary endpoint	1.00 (0.83–1.20) P=0.98

Higher risk with saxagliptin and trend with alogliptin. FDA placed warning on the package insert of both.

White WB et al. *N Engl J Med*. 2013; 369:1327-35. Scirica BM et al. N Engl J Med. 2013; 369:1317-26. Green JB et al. *N Engl J Med*. 2015; 373:232-42. McGuire DK et al. *JAMA Cardiol*. 2016; 1:126-35. White WB et al. *Diabetes Care*. 2016; 39:1267-73.

Do we need to adjust DG's saxagliptin therapy based on this information?

a. DG has CVD, NOT CHF: continue current therapy
b. DG has CHF: saxagliptin is neutral, continue current therapy
c. DG has CVD: switch because of increased CVD with DPP-4 inhibitors
d. DG has CHF: switch to sitagliptin

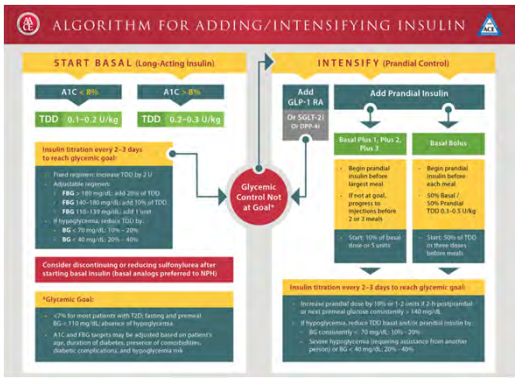
DG: Saxagliptin and Heart Failure

- PMH significant for
  - MI X 2: has had 2 stents placed in his LAD
  - Last cardiac cath: diffuse plaques throughout, LVEF= 31%
- This is indicative of systolic heart failure
- We would not recommend saxagliptin
- Choices
  - Sitaglitpin
  - Another class of medication

Pioglitazone

- Reasons to use in DG
  - Best insulin sensitizer: May decrease amount of insulin DG has to take
  - Generic
- Reasons to NOT use in DG
  - Weight: DG is obese, may contribute more weight
  - CHF: May exacerbate fluid retention and potentially CHF
  - Smoking: Higher bladder cancer risk
    - Smokers have a fourfold higher chance in their lifetime
    - FORMER smokers have a twofold higher chance in lifetime
    - Pioglitazone: bladder cancer listed on prescribing information
    - Risk is very small, perhaps 15 extra cancers in 100,000 patient-years

Lewis JD et al. *JAMA*. 2015 ;314:265-77.



Reprinted with permission from AACE © 2016 AACE. Garber AJ et al. *Endocr Pract*. 2016; 22:84-113.

See page 23 for enlarged view

Clinical Findings: Safety of SGLT-2 Inhibitors

Advantages

- Weight loss: modest
- Blood pressure reduction: modest

Disadvantages and adverse effects

- Genital mycotic infections: possible F>M
  - Risk for female if past infections, male if uncircumcised
- Osmotic diuresis: may help with CHF
  - Orthostatic changes, syncopal symptoms possible
- Others
  - UTIs: small increase in risk
  - Urosepsis: small increase in risk
  - Increases LDL (~3-10% unknown long-term effect)

SGLT-2 Inhibitors: Renal Dosing

Agent	Dosing in CKD stages 3, 4 and 5 (nondialysis)
Canagliflozin	• **eGFR 45-59 mL/min/1.73 m²** Do not exceed 100 mg/day PO • **eGFR < 45 mL/min/1.73 m²** Do not initiate and discontinue in patients currently receiving drug
Dapagliflozin	• **eGFR <60 mL/min/1.73 m²** Do not initiate and/or discontinue
Empagliflozin	• **eGFR < 45 mL/min/1.73 m²** Do not initiate and discontinue in patients currently receiving drug; no limit on dosing

- Glycemic efficacy becomes less pronounced with decreasing eGFR
- If the kidney doesn't filter as much glucose, the SGLT-2 inhibitor can't prevent reabsorption

Invokana (canagliflozin) prescribing information. 2017 Feb.
Farxiga (dapagliflozin) prescribing information. 2016 Jul.
Jardiance (empagliflozin) prescribing information. 2016 Dec.

See page 23 for enlarged view

Diabetic Ketoacidosis with SGLT-2 Inhibitors Is RARE

- Canagliflozin 0.5-0.8 per 1000 patient-years
- Dapagliflozin and empagliflozin <0.1%
  - Practical: 1 in 5000?
- Triggers
  - Dehydration: Check DG's BUN/Cr prior to use
  - Alcohol use: DG's okay here unless "fibbing"
  - Concomitant illness: if can't eat or drink, temporarily discontinue SGLT-2 inhibitor therapy
  - Diabetes mellitus with low insulin levels
  - Aggressive reduction of insulin dose upon initiation

Rosenstock J et al. *Diabetes Care*. 2015; 38:1638-42.

SGLT-2 Inhibitors: Combination with Insulin

Empagliflozin (EMPA) given daily or placebo given daily

Added to multiple daily injections in obese T2DM
52 week data
A1c 8.3% BMI 34.8 kg/m^2 Mean insulin dose 92 units/day
Insulin was titrated to maximize effect, but stayed stable (+/-10%) from week 40-52

	Placebo	EMPA 10 mg	EMPA 25 mg	Significance
A1c (Δ) from baseline	-0.81%	-1.18%	-1.27%	P<0.001 vs. placebo
A1c (%)	7.5	7.2	7.1	
Weight (Δ kg)	0.44	-1.95	-2.04	P<0.001 vs. placebo
Insulin/day (Δ units)	10.2	1.3	-1.1	NR
SBP (Δ mmHg)	-2.9	-3.4	-3.8	NS
DBP(Δ mmHg)	-0.5	-1.2	-2.5	NS

Rosenstock AJ et al. *Diabetes Care*. 2014; 37:1815-23.

Clinical Outcomes with Empagliflozin

EMPA-REG OUTCOME (N=7020)

Study Design

- Patients with T2D and CVD
- Randomization
  - Empagliflozin n=4687
  - Placebo n=2333
- Noninferiority study: prespecified HR margin = 1.3 for primary endpoint
  - Primary endpoint: composite of CV death, nonfatal MI (excluding silent MI), or nonfatal stroke
  - Secondary endpoint: composite of CV death, nonfatal MI (excluding silent MI), nonfatal stroke, and hospitalization for unstable angina

Key Results

- Median follow-up: 3.1 years
- Week 206 A1c, difference from placebo
  - Empagliflozin 10 mg daily: -0.24% (95% CI -0.40% to -0.08%)
  - Empagliflozin 25 mg daily: -0.36% (95% CI -0.51% to -0.20%)
- Increased rates of genital infections in empagliflozin-treated patients

Zinman B et al. *N Engl J Med*. 2015; 373:2117-28.

Clinical Outcomes with Empagliflozin

EMPA-REG OUTCOME Pooled Analysis (N=7020)

	Hazard Ratio (95% CI)	P value
Primary composite endpoint*	0.86 (0.74-0.99)	0.04
Secondary composite endpoint†	0.89 (0.78-1.01)	0.08
Death from any cause	0.68 (0.57-0.82)	<0.001
CV death	0.62 (0.49-0.77)	<0.001
Fatal or nonfatal MI	0.87 (0.70-1.09)	0.23
Hospitalization for HF	0.65 (0.50-0.85)	0.002
Hospitalization for HF or CV death	0.66 (0.55-0.79)	<0.001

*CV death, nonfatal MI (excluding silent MI), or nonfatal stroke
†CV death, nonfatal MI (excluding silent MI), nonfatal stroke, and hospitalization for unstable angina

Zinman B et al. *N Engl J Med*. 2015; 373:2117-28.

Renal Outcomes with Empagliflozin over 3.2 Years

	Hazard Ratio (95% CI)	P value
Incident or worsening nephropathy or CV death	0.61 (0.55-0.69)	<0.001
Incident or worsening nephropathy	0.61 (0.53-0.70)	<0.001
Progression to macroalbuminuria	0.62 (0.54-0.72)	<0.001
Doubling of SCr + eGFR ≤45	0.56 (0.39-0.79)	<0.001
Initiation of renal replacement therapy	0.45 (0.21-0.97)	0.04
Doubling of SCr + eGFR ≤45, renal replacement therapy, or renal disease death	0.54 (0.40-0.75)	<0.001
Incident albuminuria*	0.95 (0.87-1.04)	0.25

*In patients with normal albuminuria at baseline

Wanner C et al. *N Engl J Med*. 2016; 375:323-34.

EMPA-REG: Would DG Benefit from Empagliflozin?

- All-cause mortality reduction in T2DM patients with CVD
  - ✓DG would potentially benefit
- ALL subsets explored got about the same benefit
  - ✓Of special interest—heart failure reduction: YES
  - ✓Renal disease: YES if renal disease at baseline
- Negatives: DG is currently dehydrated, BUN/Cr ratio=22
  - ✓Rehydrate prior to starting—discontinue loop diuretics (DG is currently not taking)

ALL T2DM patients with atherosclerotic disease and/or renal disease (including DG) are potential candidates

GLP-1 Receptor Agonist vs. Basal-Bolus Therapy

Primary Endpoints	Weighted Mean Difference (95% CI)	Relative Risk (RR) (95% CI)	Cochran-Q (p-value)
Reduction in A1c vs. basal-bolus insulin	-0.10% (-0.17 to -0.02)		0.470
Reduction in weight vs. basal-bolus insulin	-5.66 kg (-9.80 to -1.51)		<0.0001
Proportion achieving A1c less than 7% vs. basal-bolus insulin	---	1.07 (0.91-1.26)	0.287
Incidence of hypoglycemia vs. basal-bolus insulin	---	0.67 (0.56-0.80)	0.526

Eng C et al. *Lancet*. 2014; 384:2228-34.

Clinical Outcomes with Liraglutide

LEADER TRIAL (N=9340)

• Study Design

- Patients with T2DM and high CV risk
- Randomization
  - Liraglutide: n=4672
  - Placebo: n=4668
- Noninferiority study: prespecified margin = 1.3 for upper bound of 95% CI of the HR for the primary endpoint
  - Primary endpoint: composite of CV death, nonfatal MI (including silent MI), or nonfatal stroke
  - Secondary endpoint: composite of CV death, nonfatal MI (including silent MI), nonfatal stroke, coronary revascularization, and hospitalization for unstable angina or HF

• Key Results

- Median follow-up: 3.5 years
- Difference from placebo at 36 months
  - A1c: −0.40% (95% CI, −0.45% to −0.34%)
  - Weight: −2.3 kg (95% CI, −2.0 to −2.5 kg)
  - SBP: −1.2 mm Hg (95% CI, −0.5 to −1.9 mm Hg)
- Increased rates of gastrointestinal events in liraglutide-treated patients
- Lower incidence of pancreatitis in liraglutide group (not statistically significant)

Marso SP et al. *N Engl J Med*. 2016; 375:311-22.

LEADER Trial: Primary and Secondary CV Outcomes

Outcome	Liraglutide (%)	Placebo (%)	Hazard Ratio (95% CI)	P value
Primary outcome	608 (13.0)	694 (14.9)	0.87 (0.78-0.97)	0.01
Death from CV causes	219 (4.7)	278 (6.0)	0.78 (0.66-0.93)	0.007
Death from any cause	381(8.2)	447 (9.6)	0.85 (0.74-0.97)	0.02
Myocardial infarction	292 (6.3)	339 (7.3)	0.86 (0.73-1.00)	0.046
Stroke	173 (3.7)	199 (4.3)	0.86 (0.71-1.06)	0.16
Hospitalization for heart failure	218 (4.7)	248 (5.3)	0.87(0.73-1.05)	0.14

Marso SP et al. *N Engl J Med*. 2016; 375:311-22.

LEADER Trial: Renal Outcomes

Level of Renal Impairment	Estimated Treatment Ratio [95% CI]
Baseline renal function	0.81 [0.76 to 0.86]
Without renal impairment (MDRD eGFR ≥90 mL/min/1.73m^2)	0.78 [0.70 to 0.87]
Mild renal impairment (MDRD eGFR ≥60 mL/min/1.73m^2)	0.80 [0.73 to 0.89]
Moderate renal impairment (MDRD eGFR ≥30 to <60 mL/min/1.73m^2)	0.82 [0.72 to 0.95]
Severe renal impairment (MDRD eGFR ≤30 mL/min/1.73m^2)	0.83 [0.55 to 1.26]

Marso SP et al. *N Engl J Med*. 2016; 375:311-22.
Mann J et al. European Association for the Study of Diabetes Annual Meeting. Munich, Sep 2016.

LEADER Trial: Would DG Benefit from Liraglutide?

- Could be added to basal insulin?
  - ✓DG could possibly benefit
- Possibly decrease risk of CVD?
  - ✓DG could possibly benefit
- Possibly benefit his renal situation?
  - ✓DG could possibly benefit

Summary

- Many high CV risk patients with T2DM
  - Incorporation of CVD outcomes with antihyperglycemic agents is important as 2/3 of DM patients die from CVD
  - Addition of meal-time or prandial insulin provides no known CVD benefit beyond improving glycemic control

	SGLT-2 Inhibitors	GLP-1 Receptor Agonists
A1c efficacy	Moderate	High
Weight	Reduction	Reduction
BP	Reduction	Modest reduction
Ease of use	Easy	Moderate
CVD reduction	Robust for death	Fairly robust
Renal outcomes	Very promising	Promising
CHF	Very promising	Likely neutral

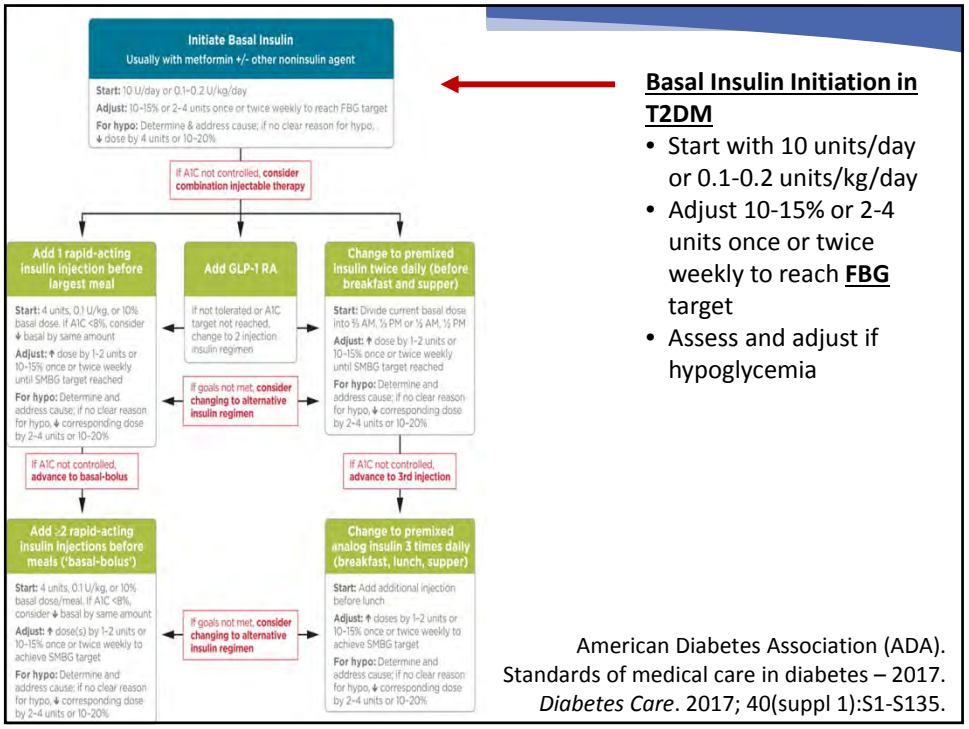
ORIGIN investigators. *N Engl J Med*. 2012; 367:319-28.

What will you do as a follow-up to today's program? Select all that apply.

a. Recognize signs of potential overbasalization
b. Distinguish insulin stacking from therapeutic accumulation
c. Formulate a plan for initiating and titrating U-500 insulin in appropriate patients
d. Apply updated 2017 ADA algorithm to challenging patients
e. Consider comorbidities when recommending therapy for T2DM

Select References

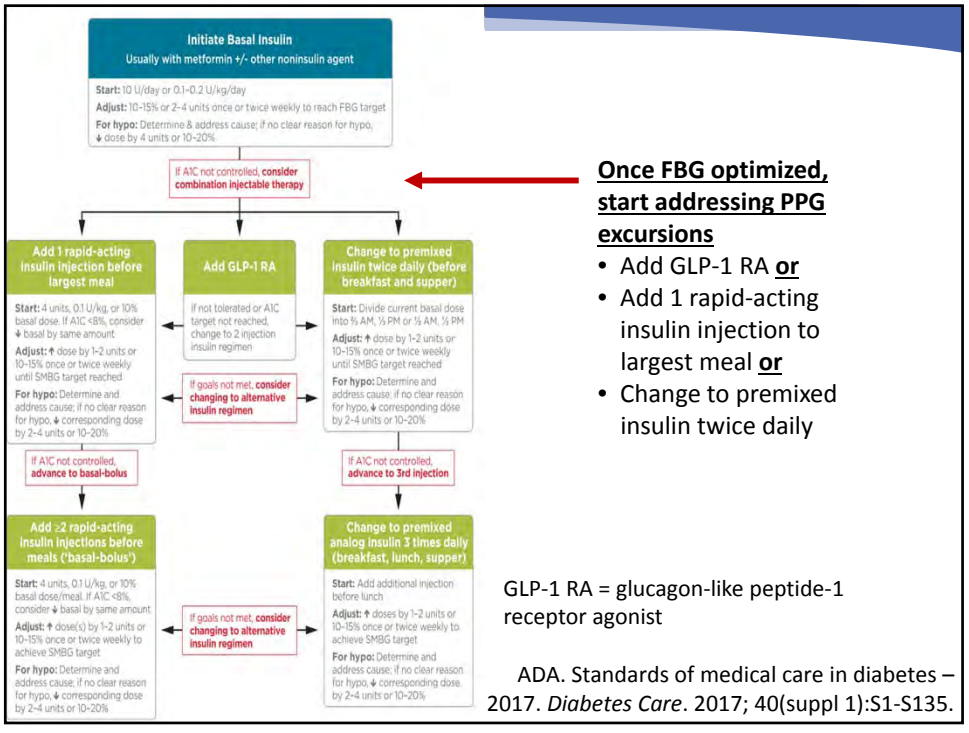
- American Diabetes Association. Pharmacologic approaches to glycemic treatment. Standards of medical care in diabetes – 2016. *Diabetes Care*. 2016; 39(suppl 1):S64-74.
- Heise T, Meneghini LF. Insulin stacking versus therapeutic accumulation: understanding the differences. *Endocr Pract*. 2014; 20:75-83.
- Hood RC, Arakaki RF, Wysham C et al. Two treatment approaches for human regular U-500 insulin in patients with type 2 diabetes not achieving adequate glycemic control on high-dose U-100 insulin therapy with or without oral agents: a randomized, titration-to-target clinical trial. *Endocr Pract.* 2015; 21:782-905.



Basal Insulin Initiation in T2DM

- Start with 10 units/day or 0.1-0.2 units/kg/day
- Adjust 10-15% or 2-4 units once or twice weekly to reach **FBG** target
- Assess and adjust if hypoglycemia

American Diabetes Association (ADA). Standards of medical care in diabetes – 2017. *Diabetes Care*. 2017; 40(suppl 1):S1-S135.



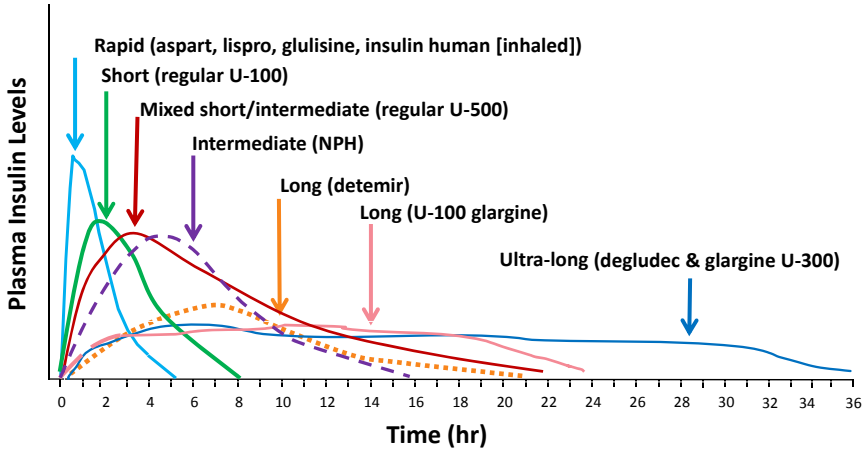
Once FBG optimized, start addressing PPG excursions

- Add GLP-1 RA **or**
- Add 1 rapid-acting insulin injection to largest meal **or**
- Change to premixed insulin twice daily

GLP-1 RA = glucagon-like peptide-1 receptor agonist

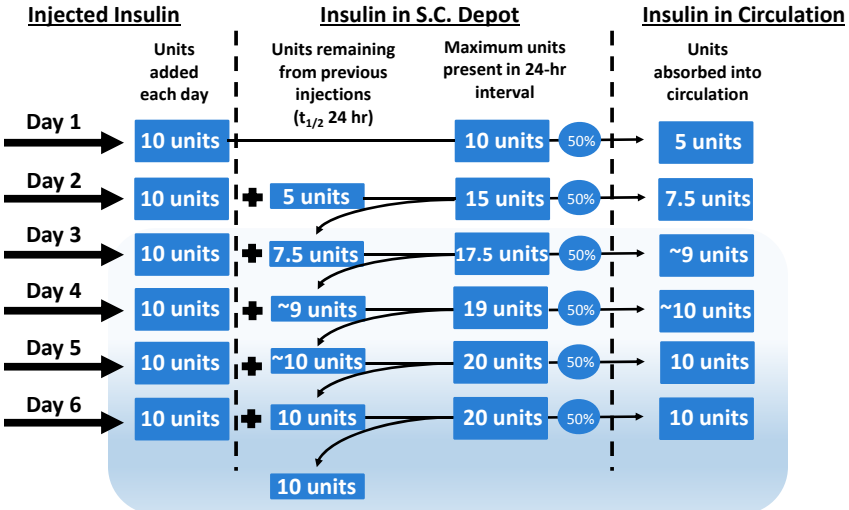
ADA. Standards of medical care in diabetes – 2017. *Diabetes Care*. 2017; 40(suppl 1):S1-S135.

Pharmacokinetic Profile of Currently Available Insulins



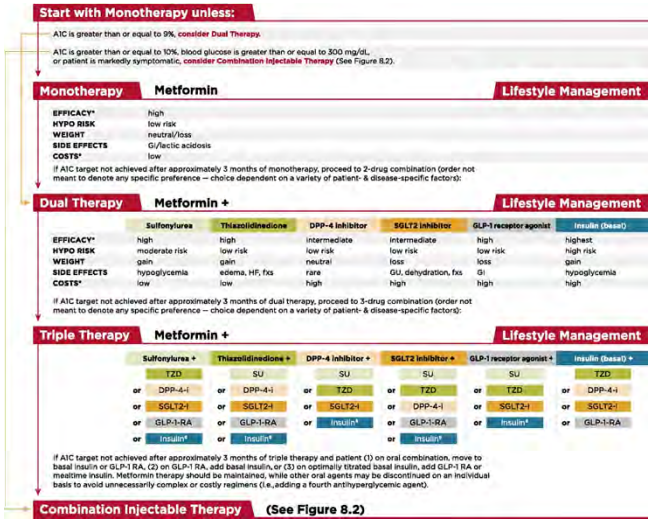
Hirsch IB. *N Engl J Med*. 2005; 352:174-83.
Flood TM. *J Fam Pract*. 2007; 56(suppl 1):S1-S12.
Becker RH et al. *Diabetes Care*. 2015; 38:637-43.

Therapeutic Accumulation with Long-acting Insulin



Heise T, Meneghini LF. *Endocr Pract*. 2014; 20:75-83.

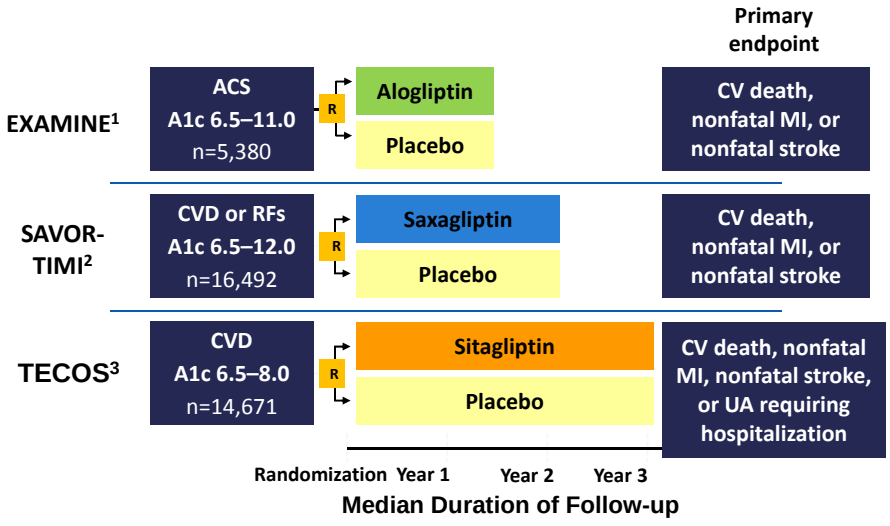
Antihyperglycemic Therapy in Type 2 Diabetes: General Recommendations



American Diabetes Association. *Diabetes Care*. 2017; 40(suppl 1):S64-S74.

American Diabetes Association.

Gliptin CV Outcomes Trials



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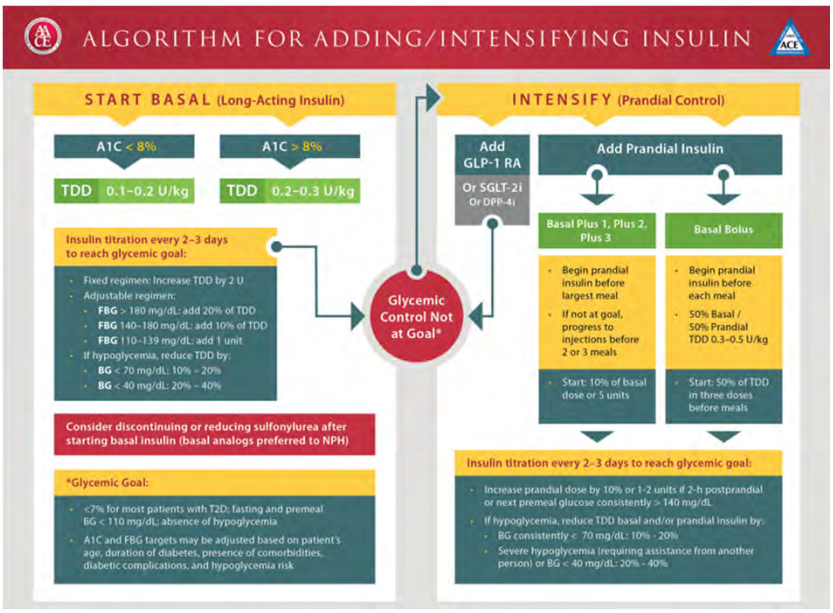
Gliptins: CVD PRIMARY OUTCOMES

	SAVOR-TIMI Saxagliptin		EXAMINE Alogliptin		TECOS Sitagliptin	
		HR (95% CI) P value		HR (95% CI) P value		HR (95% CI) P value
Primary composite MACE	CV death, MI, or stroke	1.00 (0.89-1.12) P=0.99	CV death, MI, or stroke	0.96 (≤1.16) P=0.315	CV death, MI, UA, or stroke	0.98 (0.89–1.08) P=0.65
CV death	Primary endpoint	1.03 (0.87–1.22) P=0.72	Primary endpoint	0.85 (0.66–1.10) P=0.212	Primary endpoint	1.03 (0.89–1.19) P=0.71
Myocardial infarction	Primary endpoint	0.95 (0.80–1.12) P=0.52	Primary endpoint	1.08 (0.88–1.33) P=0.47	Primary endpoint	0.95 (0.81–1.11) P=0.49
Stroke	Primary endpoint	1.11 (0.88–1.39) P=0.38	Primary endpoint	0.91 (0.55–1.50) P=0.71	Primary endpoint	0.97 (0.79–1.19) P=0.76

White WB et al. *N Engl J Med*. 2013; 369:1327-35. Scirica BM et al. *N Engl J Med*. 2013; 369:1317-26. Green JB et al. *N Engl J Med*. 2015; 373:232-42.



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SGLT-2 Inhibitors: Renal Dosing

Agent	Dosing in CKD stages 3, 4 and 5 (nondialysis)
Canagliflozin	• **eGFR 45-59 mL/min/1.73 m²** Do not exceed 100 mg/day PO • **eGFR < 45 mL/min/1.73 m²** Do not initiate and discontinue in patients currently receiving drug
Dapagliflozin	• **eGFR <60 mL/min/1.73 m²** Do not initiate and/or discontinue
Empagliflozin	• **eGFR < 45 mL/min/1.73 m²** Do not initiate and discontinue in patients currently receiving drug; no limit on dosing

- Glycemic efficacy becomes less pronounced with decreasing eGFR
- If the kidney doesn't filter as much glucose, the SGLT-2 inhibitor can't prevent reabsorption

Invokana (canagliflozin) prescribing information. 2017 Feb.
Farxiga (dapagliflozin) prescribing information. 2016 Jul.
Jardiance (empagliflozin) prescribing information. 2016 Dec.

Abbreviations Used in Presentation

ACEI	angiotensin-converting enzyme inhibitor
ADA	American Diabetes Association
ARB	angiotensin receptor blocker
ASA	aspirin
BG	blood glucose
BID	twice daily
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
CAD	coronary artery disease
CBC	complete blood count
CHF	congestive heart failure
CI	confidence interval
CKD	chronic kidney disease
Cr	creatinine
CV	cardiovascular
CVD	cardiovascular disease
DBP	diastolic blood pressure
DPP	Diabetes Prevention Program
DPP-4	dipeptidyl peptidase-4
DPP-4i	dipeptidyl peptidase-4 inhibitor
DPPOS	Diabetes Prevention Program Outcomes Study
eGFR	estimated glomerular filtration rate
EMPA	empagliflozin
ER	extended release
EtOH	alcohol
FBG	fasting blood glucose
FPG	fasting plasma glucose
fx	fracture
GLP-1	glucagon-like peptide-1
GLP-1 RA	glucagon-like peptide-1 receptor agonist
HDL	high-density lipoprotein
HF	heart failure
HR	hazard ratio
HR	heart rate
HTN	hypertension
Hx	history
hypo	hypoglycemia
LAD	left anterior descending

LDL	low-density lipoprotein
LVEF	left-ventricular ejection fraction
MACE	major adverse coronary event
MDRD	Modification of Diet in Renal Disease
MI	myocardial infarction
MOA	mechanism of action
NPH	neutral protamine Hagedorn
NS	not significant
PCP	primary care provider
PMH	past medical history
PO	by mouth
PPG	postprandial plasma glucose
PSH	past surgery history
RR	relative risk
SBP	systolic blood pressure
SC	subcutaneous
SCr	serum creatinine
SGLT-2	sodium glucose cotransporter-2
SGLT-2i	sodium glucose cotransporter-2 inhibitor
SMBG	self-monitored blood glucose
SU	sulfonylurea
$t_{1/2}$	half-life
T2DM	type 2 diabetes mellitus
TC	total cholesterol
TDD	total daily dose
TG	triglyceride
TID	three times daily
TZD	thiazolidinedione
UA	unstable angina
UTI	urinary tract infection
WNL	within normal limits

Self-assessment Questions

1. A patient is currently being treated for type 2 diabetes with metformin plus basal insulin administered at bedtime. Upon review of her blood glucose profile, you notice that her blood glucose is dropping substantially between bedtime and morning. Which of the following do you suspect is the most likely cause of the overnight drop in blood glucose?

    a. Non-adherence with her insulin.
    b. Overbasalization.
    c. Metformin overdose.
    d. Basal insulin dose too low.

2. Of the following insulin products, which one would most likely be associated with insulin stacking?

    a. U-300 insulin glargine.
    b. Insulin degludec.
    c. Insulin detemir.
    d. Insulin aspart.

3. Which of the following would be the most important medication to adjust or discontinue when starting a sodium glucose cotransporter-2 (SGLT-2) inhibitor?

    a. Insulin therapy.
    b. Loop diuretic.
    c. Sulfonylurea.
    d. Angiotensin-converting enzyme inhibitor.

4. A patient's primary care provider asked you to recommend a glucagon-like peptide-1 (GLP-1) receptor agonist for a patient with type 2 diabetes who is at risk for cardiovascular disease and whose estimated glomerular filtration rate is 70 mL/min/1.73m^2). Which of the following GLP-1 receptor agonists would you recommend?

    a. Dulaglutide.
    b. Exenatide.
    c. Liraglutide.
    d. Lixisenatide.

Answers

1. b
2. d
3. b
4. c