MEDX
MEDICAL EDUCATION EXCHANGE

Type 2 Diabetes Management
Case 1: Reducing Hypoglycemic Risk
Case 2: Reducing Cardiovascular Risk

M. Susan Burke, MD, FACP
Clinical Associate Professor of Medicine
Sidney Kimmel Medical College at
Thomas Jefferson University
Senior Advisor, Lankenau Medical Associates
Lankenau Medical Center
Wynnewood, PA

Ellen H. Miller, MD
Professor of Science Education & Medicine
Hofstra Northwell School of Medicine
Senior Medical Director
North Shore - LIJ CareConnect
East Hills, NY

MEDX
MEDICAL EDUCATION EXCHANGE

Case 1:
Reducing Hypoglycemic Risk

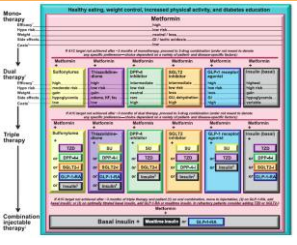
Case 1: Sophie

- Sophie is 87 years old and has had T2DM for 15 years
  - Managed with glyburide 10mg BID since then with fairly good HbA1C levels
- Current concerns
  - Recent episodes of confusion/dizziness
  - Occasionally forgets medication and meals
  - Home glucose monitoring shows multiple hypoglycemic episodes throughout day; ? wrong dose of medication, ? missing meals

Case 1: Sophie – cont'd

- Physical examination
  - Frail appearance (BMI: 19.0 kg/m^2)
  - Rales at both lung bases posteriorly
  - Bilateral 1+ pitting pedal edema
- Laboratory evaluation
  - Random glucose: 68 mg/dL; HgbA1C: 6.1%
  - SCr 1.7; eGFR: 28 mL/min/1.73 m^2

ADA/EASD Position Statement



Inzucchi SE et al. *Diabetes Care*. 2015;38:140-149. Used for Educational Purposes Only.
*AACE guidelines: Garber AJ et al. *Endocr Pract*. 2016;22:84-113.

Expected HbA1C Reduction of Antihyperglycemic Agents

Drug Class	Expected HbA1C Reduction
Biguanide	1%-2%
SU (2nd Generation)	1%-2%
TZD	1%-1.5%
GLP-1 RA	0.5%-1.5%
DPP-4 inhibitor	0.5%-1%
SGLT-2 inhibitor	0.5%-1%

Mayo Foundation for Medical Education and Research. Diabetes medication choice, 2014. Available at: http://shareddecisions.mayoclinic.org.
Allen J, Freitas S. Comparison chart of glucose-lowering agents for management of type 2 diabetes mellitus. October 2015.

Type 2 Diabetes Management:
Case 1: Reducing Hypoglycemic Risk
Case 2: Reducing Cardiovascular Risk

Case 1: Sophie
What Should You Consider?

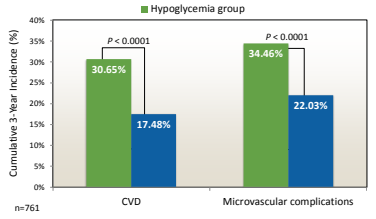
- Her hypoglycemia risk
  - Risk factors?
  - Drug classes to avoid?
- Her renal insufficiency
  - Drug classes to avoid?
  - Required dose adjustments?
- Her preferences regarding route of administration

Hypoglycemia Risk Factors in Elderly Patients with T2DM

- Advanced age
- Polypharmacy
- Sulfonylurea or insulin use
- Poor nutrition or fasting
- Intercurrent illness
- Chronic renal disease
- Chronic liver disease
- Prolonged physical exercise
- Alcohol ingestion
- Endocrine deficiencies (thyroid, adrenal, pituitary)
- Loss of normal counter-regulation
- Hypoglycemic unawareness

Mathieu C et al. *Int J Clin Pract.* 2007;61(suppl 154):29-37

The Association Between Medication-related Hypoglycemia and Vascular Risk



Zhao Y et al. *Diabetes Care.* 2012;35:1126-1132.

Sulfonylureas in Patients with Renal Impairment

- SUs are a leading cause of ER evaluations for adverse drug reactions
- Some SUs have prolonged half-life (glyburide, glimepiride)
- Some SUs have active metabolites that are renally excreted (glyburide)
- Safest may be glipizide (shortest acting and inactive metabolites)
- Consider glinides (eg, repaglinide, nateglinide) – rapid-acting secretagogues
- Dose any secretagogue cautiously in CKD due to the fact that insulin itself is renally cleared

Physicians' Desk Reference. 66th ed. Montvale, NJ: PDR Network; 2012.

What about Metformin?
FDA Changes Labeling for Metformin Use in T2DM Patients with Impaired Renal Function

- In T2DM patients with impaired renal function, use of metformin previously contraindicated[1]
- 2014 systematic review assessing metformin-associated lactic acidosis risk in T2DM with impaired renal function: no increased rate of lactic acidosis, along with macrovascular outcome benefit[1]
- FDA: can use metformin safely in patients with mild renal impairment and in some with moderate renal impairment[2]
- FDA new labeling changes[2]
  - Obtain eGFR before starting metformin, then annually; assess more frequently if risk for renal impairment (eg, elderly)[2]
  - Starting metformin in patients with eGFR of 30 mL/min/1.73 m^2 not recommended
  - Contraindicated in patients with eGFR of <30 mL/min/1.73 m^2
  - Assess benefit and risk if eGFR decreases to <45 mL/min/1.73 m^2; discontinue if eGFR decreases to <30 mL/min/1.73 m^2

1. Inzucchi SE et al. *JAMA.* 2014;312:2668-2675.
2. FDA Drug Safety Communication, 4-8-16; http://www.fda.gov/downloads/Drugs/DrugSafety/UCM494140.pdf.

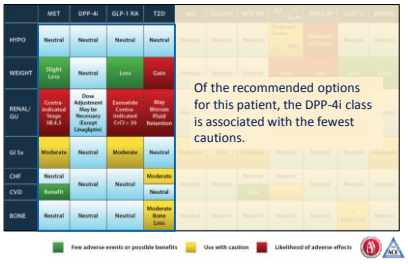
Diabetes and Renal Impairment

- **Metformin:** contraindicated when eGFR <30, do not start if 30-45
- **SU:** dose reduction or replacement for renal insufficiency; do not use glyburide
- **Insulin:** dose reduction for renal insufficiency
- **GLP-1 receptor agonists**
  - Exenatide: do not use if eGFR <30
  - Others: use with caution
- **DPP-4 inhibitors**
  - Sitagliptin, saxagliptin, alogliptin require dose adjustment
  - Linagliptin: no dose adjustment
- **SGLT-2 inhibitors**
  - Canagliflozin: lower dose for eGFR 45-60; discontinue/do not initiate if eGFR <45; **contraindicated** <30
  - Dapagliflozin do not initiate if eGFR <60; discontinue if persistently <60; **contraindicated** in severe renal impairment, ESRD, dialysis
  - Empagliflozin: do not initiate if eGFR <45; discontinue if persistently <45; **contraindicated** in severe renal impairment, ESRD, dialysis

Physicians' Desk Reference. Montvale, NJ: PDR Network; 2014; FDA http://www.fda.gov/Drugs/DrugSafety/ucm493244.htm
FDA Drug Safety Communication, 4-8-16; http://www.fda.gov/downloads/Drugs/DrugSafety/UCM494140.pdf.

Type 2 Diabetes Management:
Case 1: Reducing Hypoglycemic Risk
Case 2: Reducing Cardiovascular Risk

Profiles of Antidiabetic Medications



Sitagliptin vs Glipizide Added on to Metformin

	Baseline ± sd	Week 52 ± sd	Change in A1C from Baseline	Hypoglycemia	Weight
Glipizide 10mg twice daily (n=584)	7.52 ± 0.85	6.86 ± 0.69	-0.67%	32% (657 events)	+1.1 kg*
Sitagliptin 100mg once daily (n=588)	7.48 ± 0.76	6.84 ± 0.66)	-0.67%	5% (50 events)*	-1.5 kg

*$P<0.001$ between treatment

Nauck MA, et al. *Diabetes Obes Metab.* 2007;9:194-205.

Comparison of DPP-4 Inhibitors

	Sitagliptin	Saxagliptin	Linagliptin	Alogliptin
Dosage	25, 50, 100 mg once daily	2.5, 5.0 mg once daily	5 mg once daily	25 mg once daily
Half-life ($t_{1/2}$)	12.4 h	2.2 to 3.8 h	>113 h	21 h
24-h DPP-4 inhibition	≈ 80%	5 mg: ≈ 55%	>90%	>80%
Elimination	Kidney (mostly unchanged)	Liver and kidney active metabolite	Liver, <5% renal	Renal
Dose adjustments for renal impairment	Yes	Yes	None	Yes
Drug interaction potential	Low	Strong CYP3A4/5 inhibitors	Strong CYP3A4/5 inhibitors	Low

Summary

- Factors to consider when selecting a therapy:
  - Hypoglycemia
    - Risk factors: older age, concurrent medications (SUs, insulin), comorbidities
    - Drug classes to avoid: SUs, insulin
  - Comorbidity: Renal Insufficiency
    - Metformin contraindicated
    - SGLT-2 inhibitors not effective
    - DPP-4 inhibitors: acceptable, require dose adjustment (linagliptin exception)
    - GLP-1-RAs use cautiously
  - Route of administration: injectable vs oral

MEDX
MEDICAL EDUCATION EXCHANGE

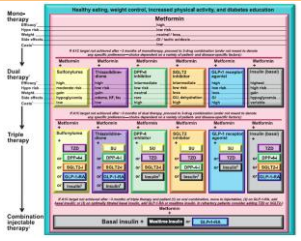
Case 2: Reducing Cardiovascular Risk

Case 2: Manuel

56-year-old man with newly diagnosed T2DM

- Physical examination
  - Patient is overweight (BMI: 31 kg/m^2)
- Laboratory evaluation
  - Blood pressure: 153/87 mm Hg
    - 10-year history of uncontrolled hypertension; patient is not compliant with prescribed antihypertensive medication
  - FPG: 145 mg/dL
  - HbA1C: 8.9%
  - eGFR: 60

ADA/EASD Position Statement



Inzucchi SE et al. *Diabetes Care.* 2015;38:140-149. Used for Educational Purposes Only.
*AACE guidelines: Garber AJ et al. *Endocr Pract.* 2016;22:84-113.

Case 2: Manuel – Treatment

- Patient is placed on metformin (500 mg BID) and a TZD

Case 2: Manuel – cont'd

- Patient experiences an MI
- Laboratory evaluation immediately following MI:
  - Blood pressure: 155/85 mm Hg
  - Total cholesterol: 246 mg/dL
  - HbA1C: 8.5%
  - Decline in renal function to 52
- Also showing signs of CHF: chest pain, dyspnea, fatigue, persistent cough with phlegm production, ankle edema
- What is the next step regarding treatment for T2DM based on CV event?

Would you stop the metformin and/or the TZD?

T2DM Agents: CV Advantages and Disadvantages

Class	CV 'Advantages'	CV 'Disadvantages'
SUs		? ↑ CVD events ↓ischemic preconditioning
Biguanides	↓ LDL, ↓ CRP, ↓insulin	
TZDs	↑ HDL; ↓ TG, ↓ insulin, ↓CRP, ↓CVD events (pio)	↑ HF, ↑ LDL, ↑?CVD events (rosi)
GLP-1 RAs	↓ weight, ↓ BP, ↓ TG, ↓ CRP, ? direct cardiac effect	↑ HR
DPP-4 inhibitors	? direct cardiac effect (via GLP-1)	? ↑ HF

Courtesy, S. Inzucchi, Yale University

Large CV Outcomes Trials in Diabetes

Study	SAVOR	EXAMINE	TECOS	CAROLINA	CARMELINA
DPP-4-inhibitors	saxagliptin	alogliptin	sitagliptin	linagliptin	linagliptin
Comparator	placebo	placebo	placebo	sulfonylurea	placebo
n	16,500	5,400	14,700	6,000	8,300
Results	2013	2013	2015	2017	2017
NEUTRAL		NEUTRAL	NEUTRAL		

Study	EMPA-REG	CANVAS	DECLARE	VERTIS CV Study
SGLT-2 inhibitors	empagliflozin	canagliflozin	dapagliflozin	ertugliflozin
Comparator	placebo	placebo	placebo	placebo
n	7,000	4,300	22,200	8,000
Results	2015	2017	2019	2019
CV BENEFIT				

Study	LEADER	ELIXA	SUSTAIN 6	EXSCEL	REWIND
GLP-1 RA	liraglutide	lixisenatide	semaglutide	exenatide LR	dulaglutide
Comparator	placebo	placebo	placebo	placebo	placebo
n	9,300	6,000	3,700	5,400	8,300
Results	2015	2015	2016	2018	2019
CV BENEFIT		NEUTRAL	CV BENEFIT		

EMPA-REG Study

- 7,034 T2DM patients at high CVD risk randomized to empagliflozin or placebo[1]
- Empagliflozin reduced primary major adverse cardiac event endpoint (CV death, nonfatal myocardial infarction, nonfatal stroke) by 14%[1]
  - 38% reduction in CV mortality
  - 35% reduction in hospitalization for heart failure
- Multiple metabolic benefits: decreases in HbA1C, weight, and BP; increase in HDL[1]
- Also associated with slower progression of renal disease[2]

1. Abdul-Ghani M. *Diabetes Care.* 2016;39:717-725; 2. Wanner C et al. *N Engl J Med.* 2016;Jun 14. [Epub ahead of print].

Other Considerations with SGLT-2 Inhibitors

Genital infections
- Patients treated with antifungal or antibiotic agents

Fracture
- Use of dapagliflozin in moderate renal impairment leads to increased fractures

Bladder cancer?
- Only seen in dapagliflozin study; groups had higher than expected risk of bladder cancer; possibly b/c GU SE led to increased cancer detection

Serious urinary tract infections
- FDA warning due to reported cases of urosepsis

Ketoacidosis
- Insulin-deficient patients at higher risk
- 12/2015: FDA recommends stopping the drug and immediately seeking treatment for symptoms of ketoacidosis

Acute kidney injury
- Recent label change; 101 cases reported

Leg/foot amputations
- **FDA warning:** canagliflozin associated with increased leg/foot amputations

Liraglutide Decreases CVD in High-risk Patients with T2DM in the LEADER Trial

- 9,340 adults with T2DM at high risk of major CVD randomized to liraglutide or placebo
- Results: liraglutide reduced primary endpoint by 13% (composite outcome of first occurrence of CV death, non-fatal MI, or non-fatal stroke)
  - 15% reduction in all-cause death
  - 22% reduction in CV death
  - 14% relative risk reduction in MI
  - 14% relative risk reduction in stroke
  - 22% reduction in renal events
  - Metabolic benefits: decreases in HbA1C, weight, BP

Marso SP et al. *N Engl J Med.* 2016;Jun 13. [Epub ahead of print]. Presentation at ADA Scientific Sessions, June 13, 2016, session 3-CT-SY24.

Short-, Long-, and Very Long-acting GLP-1 RAs

Parameters	Short-acting	Long-acting	Very Long-acting
Compounds	Exenatide	Liraglutide, Lixisenatide	Albiglutide, Dulaglutide, Exenatide QW
Half-life	2-5 hours	12-14 hours	>1 week
Frequency of administration	Twice daily	Once daily	Once weekly
HbA1C reduction	0.7%–1.7%	0.8%–1.8%	0.8%-0.9% albiglutide 0.7%–1.6% dulaglutide 1.3%-1.9% exenatide QW
FBG levels reduction	Modest	Strong	Strong
PP hyperglycemia	Strong	Modest	Modest
Glucagon secretion	Reduction	Reduction	Reduction
Gastric emptying rate	Deceleration	Some deceleration	Some deceleration
Blood pressure	Reduction	Reduction	Reduction
Body weight reduction	1-5 kg	2-4 kg	0.6-2.5 kg

FBG = fasting blood glucose; PP = postprandial; QW = once weekly

Meier JJ. *Nat Rev Endocrinol.* 2012;8:728-742. *Physician's Desk Reference.* Montvale, NJ. Thomson PDR; 2013.

Other Considerations with Incretin Agents

- No added hypoglycemia unless used with secretagogue or insulin
- Pancreatitis:
  - FDA: available data do not confirm causal relationship between GLP-1 therapies and increased risk for pancreatic side effects
  - Conclusion of meta-analysis of case-controlled and retrospective cohort studies (1,324,515 patients): no suggestion that acute pancreatitis is associated
- C-cell hyperplasia and medullary cancer in rodents
- Side effect with GLP-1 RA: nausea/vomiting

FDA. FDA Drug Safety Communication. 3-14-2013. Available at: www.fda.gov/drugs/drugsafety/ucm343187.htm.
Brooks M. FDA sides with EMA on incretin diabetes drugs. 8-1-2013. Available at: www.medscape.com/viewarticle/808830.
Wang T et al. *Diabetes Obes Metab.* 2015;17:32-41. Chang CH et al. *Medicine (Baltimore).* 2016;95:e2603.

Is insulin the best choice for this overweight patient, with CV history and increased hypoglycemia risk?

Deciding about First Injectable Drug for Patients Not Controlled by Oral Agents

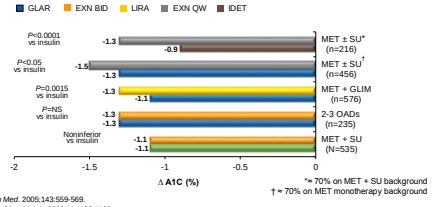
- DURATION-3 trial of once-weekly exenatide vs insulin glargine as first injectable therapy

3-year endpoint	Exenatide (n=233)	Insulin glargine (n=223)	*P* Value
Change in A1C	-1.01%	-0.81%	0.03
Change in body weight	-5.5 lbs	+4.4 lbs	<0.001
Hypoglycemia (exposure-adjusted events)	0.3 events per patient-year	0.9 events per patient-year	NR

NR = not reported.

Diamant M et al. *Lancet.* 2014;2:464-473.

A1C: Effects of Adding GLP-1 RAs vs Basal Insulin to Multiple Oral Agents



Heine R et al. *Ann Intern Med*. 2005;143:559-569.
Davies M et al. *Diabetes Obes Metab*. 2009;11:1153-1162.
Russell-Jones D et al. *Diabetologia*. 2009;52:2046-2055.
Diamant M et al. *Lancet*. 2010;375:2234-2243.
Davies M et al. *Diabetes Care*. 2013;36:1368-1376.

Case 2: Manuel – cont'd

- Dose of metformin increased to 1000 BID
- Patient placed on liraglutide 0.6 mg per day for first 2 weeks, then increased to 1.2 mg
- Patient started on new antihypertensive medication and agent for dyslipidemia by cardiologist
- Laboratory values at 3 months:
  - Blood pressure: 135/79 mm Hg
  - Total cholesterol: 210 mg/dL
  - HbA1C: 7.9%
  - Weight loss: 18 lb

What does the endocrinologist expect of the PCP regarding the ongoing management of this patient?

Summary

Antihyperglycemic agents have variable effects on CV outcomes in T2DM

- SGLT-2 inhibitors
  - Associated with weight loss, BP reduction
  - Empaglifozin: favorable CV outcomes
- DPP-4 inhibitors
  - Neutral CV effects
- GLP-1 RAs
  - Effective lowering of A1C (except albiglutide)
  - Weight loss, BP reductions, small improvements in lipids
  - Liraglutide demonstrated CV risk reduction