2 – 3:15 pm

Noninsulin Approaches to Managing Type 2 Diabetes: Best Practices in Combination Therapy

SPEAKERS

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Presenter Disclosure Information

The following relationships exist related to this presentation:

- Eileen Egan, DNP, FNP-C, CDE: No financial relationships to disclose.
- Scott Joy, MD, MBA, FACP: Medical Advisory Board for AstraZeneca; Boehringer Ingelheim Pharmaceuticals, Inc.; Exact Sciences; and Janssen Pharmaceuticals, Inc.
- Mark Stolar, MD: Speakers Bureau for AstraZeneca and Takeda Pharmaceuticals. Medical Advisory Board for AstraZeneca; sanofi-aventis U.S.; and Takeda Pharmaceuticals.

Off-Label/Investigational Discussion

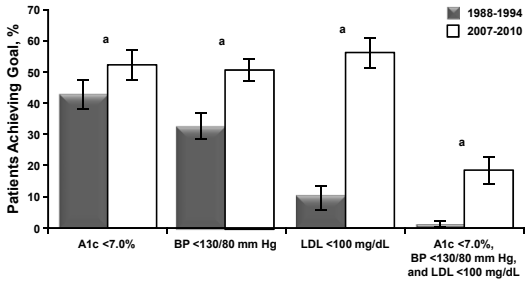
- In accordance with pmiCME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.

Educational Objectives

- Individualize therapeutic goals for patients with T2DM based on disease severity, comorbidities, treatment-related risks, and psychosocial status
- Discuss the clinical profiles of current and emerging fixed-dose combinations of antihyperglycemic medications
- Intensify multidrug noninsulin regimens for various patient types to address poor glycemic control and other relevant clinical parameters
- Engage patients in their antidiabetes management plans to motivate lifestyle changes and improve treatment adherence

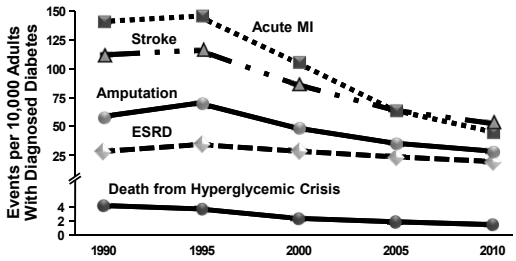
T2DM, type 2 diabetes mellitus.

Achieving Treatment Goals
Room for Improvement in T2DM



[a]*P*<0.01.
N=1497 (1988-1994) and 1447 (2007-2010) adults aged ≥20 years with a self-reported diagnosis of diabetes.
Retrospective analysis of data obtained from the National Health and Nutrition Examination Surveys.
Stark Casagrande S, et al. *Diabetes Care*. 2013;36(8):2271-2279.

Diabetes-Related Complications
Rates in the United States



Data obtained from the National Health Interview Survey, the National Hospital Discharge Survey, the US Renal Data System, and the US National Vital Statistics System.
ESRD, end stage renal disease; MI, myocardial infarction.
Gregg EW, et al. *N Engl J Med*. 2014;370(16):1514-1523.

Jerry
Case Background

- 59-year-old accountant
  - Married with 1 son at college
  - Wife attends appointment
- Dietary habits
  - Primarily pasta and red meat
  - Few fruits or vegetables
  - 1-3 alcoholic drinks/day
- Smokes 1-2 packs/week
- Medical history
  - Hypertension diagnosis 5 years ago
    - Lisinopril 40 mg daily
    - Atenolol 50 mg daily
    - Forgets medications 1-2 times weekly
- Family history
  - Father treated for T2DM and died of MI at 55 years of age
- T2DM diagnosis last week
  - Complaints of increased thirst and urination
  - Dark patches of skin behind his neck and under his arms (acanthosis nigricans)

Jerry
Recent Lab Results

- BMI, 31.0 kg/m^2 (obese)
- BP, 129/75 mm Hg
- FPG, 202 mg/dL
  - Second test, 198 mg/dL
- A1c, 8.7%
- eGFR, 84 mL/min/ 1.73 m^2
- ACR, 2.4 mg/mmol
- Lipids
  - TC, 165 mg/dL
  - TG, 150 mg/dL
  - LDL-C, 95 mg/dL
  - HDL-C, 40 mg/dL
  - ApoB, 82 mg/dL
- Sensory and eye exams unremarkable

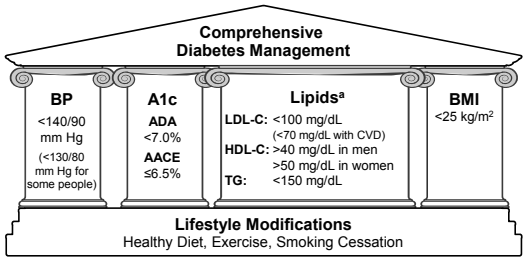
ACR, albumin/creatinine ratio; ApoB, apolipoprotein B; BMI, body mass index; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

ADA/EASD Position Statement
Setting Glycemic Goals in T2DM

More Stringent	Factors	Less Stringent
Highly motivated, adherent, excellent self-care capacities	Patient attitude and expected treatment efforts	Less motivated, nonadherent, poor self-care capacities
Low	Risks potentially associated with hypoglycemia, other adverse events	High
Newly diagnosed	Disease duration	Long-standing
Long	Life expectancy	Short
Absent	Important comorbidities	Severe
Absent	Established vascular complications	Severe
Readily available	Resources, support system	Limited

ADA, American Diabetes Association; EASD, European Association for the Study of Diabetes.
Inzucchi SE, et al. *Diabetes Care.* 2012;35:1364-1379; Ismail-Beigi F, et al. *Ann Intern Med.* 2011;154:554-559.

Reducing T2DM Complications
Multidimensional Treatment Goals



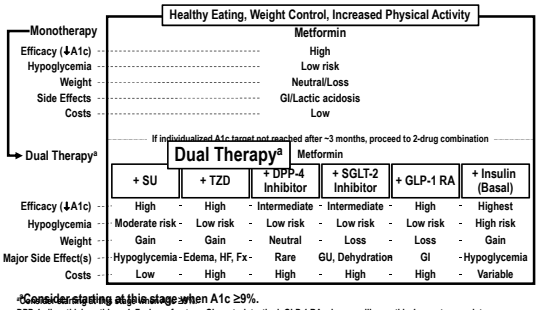
[a]2013 ACC/AHA guidelines: Treat patients aged 40-75 years with T2DM and LDL-C ≥70 mg/dL with high-intensity (lower LDL-C by ≥50% if 10-year atherosclerotic CVD risk is ≥7.5%) or moderate-intensity (lower LDL-C 30%-50% if 10-year ASCVD risk is <7.5%) statin therapy.
ACC, American College of Cardiology; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease.
ADA. *Diabetes Care.* 2015;38(suppl 1):S1-S94; Garber AJ, et al. *Endocr Pract.* 2015;21(4):438-447;
Stone NJ, et al. *Circulation.* 2014;129(25 suppl 2):S1-S45.

Diabetes Education and Lifestyle Modifications

- **Skills-Based Diabetes Education**
  - Disease process and treatment options
  - Blood glucose monitoring
  - Medication safety (eg, hypoglycemia)
  - Strategies to promote behavior change
- **Physical Activity**
  - At least 150 min/wk of moderate activity
  - Aerobic, resistance, flexibility
- **Individualized Dietary Recommendations**
  - Dehydration and nutritional deficits
  - Discuss macronutrient content and eating patterns
  - Monitor carbohydrate intake
  - Reduce calories to achieve weight loss
    - Initial moderate calorie restriction (500-1000 kcal/d)

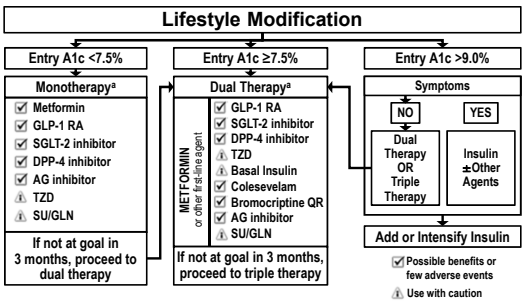
ADA. *Diabetes Care.* 2015;38(suppl 1):S1-S91; Evert AB, et al. *Diabetes Care.* 2014;37(suppl 1):S120-S143; Jensen MD, et al. *Circulation.* 2014;129(25 suppl 2):S102-S138; Haas L, et al. *Diabetes Care.* 2014;37(suppl 1):S144-S153.

ADA Recommendations
Managing Hyperglycemia in T2DM



[a]Consider starting at this stage when A1c ≥9%.
DPP-4, dipeptidyl peptidase-4; Fx, bone fracture; GI, gastrointestinal; GLP-1 RA, glucagon-like peptide-1 receptor agonist; GU, genitourinary; HF, heart failure; SGLT-2, sodium glucose cotransporter-2; SU, sulfonylurea; TZD, thiazolidinedione.
ADA. *Diabetes Care.* 2015;38(suppl 1):S1-S94.

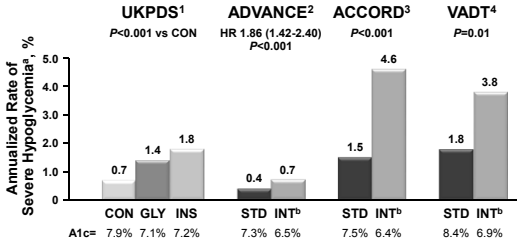
AACE/ACE Algorithm
Glycemic Control and Early Dual Therapy



[a]Order of medications listed are a suggested hierarchy of usage.
ACE, American College of Endocrinology; AG, α-glucosidase; GLN, glinide; QR, quick release.
Garber AJ, et al. *Endocr Pract.* 2015;21(4):438-447.

Hurdles to Intensive Therapy

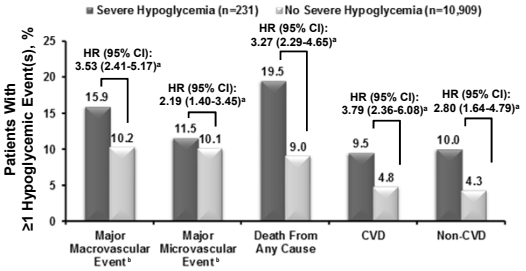
Rates of Severe Hypoglycemia



[a]Hypoglycemia requiring any assistance; [b]Intensive glycemic control was defined differently in these trials.
ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADVANCE, Action in Diabetes and Vascular Disease: PreterAx and DiamicroN MR Controlled Evaluation; CON, conventional therapy; GLY, glibenclamide; HR, hazard ratio; INS, insulin; INT, intensive therapy; STD, standard therapy; UKPDS, UK Prospective Diabetes Study; VADT, Veterans Affairs Diabetes Trial.
1. UKPDS Group. *Lancet*. 1998;352(9131):837-853; 2. Patel A, et al; [ADVANCE]. *N Engl J Med*. 2008;358(24):2560-2572; 3. Gerstein HC, et al; [ACCORD]. *N Engl J Med*. 2008;358(24):2545-2559; 4. Duckworth W, et al. *N Engl J Med*. 2009;360(2):129-139.

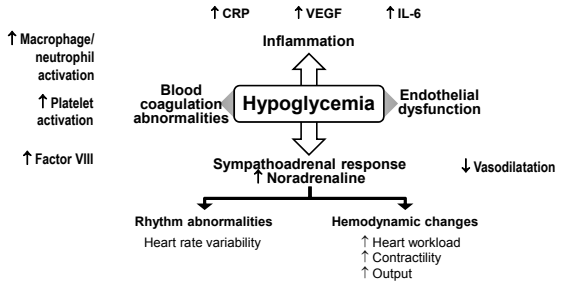
ADVANCE

Severe Hypoglycemia vs Adverse Endpoints



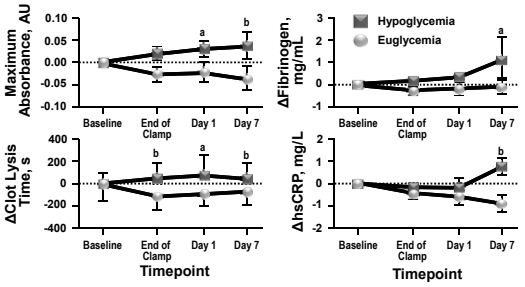
[a]Adjusted for multiple baseline covariates; [b]Primary endpoints.
Major macrovascular event=cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.
Major microvascular event=new or worsening nephropathy or retinopathy.
CI, confidence interval.
Zoungas S, et al. *N Engl J Med*. 2010;363(15):1410-1418.

Pathophysiologic Cardiovascular Consequences of Hypoglycemia



CRP, C-reactive protein; IL-6, interleukin-6; VEGF, vascular endothelial growth factor.
Desouza CV, et al. *Diabetes Care*. 2010;33:1389-1394.

Effects of Hypoglycemia on Thrombosis in T2DM



[a]P<0.05 vs euglycemia; [b]P<0.01 vs euglycemia apart (data are mean ± standard error of the mean).
N=10 patients with T2DM underwent paired hyperinsulinemic clamp stuides at least 4 weeks apart.
hsCRP, high-sensitivity CRP.
Chow EYK, et al. *Diabetologia*. 2013;56(suppl 1):S243.

Hypoglycemia

Risks of Cardiac Arrhythmias

Risks of Events During Hypoglycemia vs Euglycemia in Insulin-Treated Patients

	Day			Night		
	IRR	95% CI	*P*	IRR	95% CI	*P*
Bradycardia	NA	NA	NA	8.42	1.40-51.0	0.02
Atrial ectopic	1.35	0.92-1.98	0.13	3.98	1.10-14.40	0.04
VPB	1.31	1.10-1.57	<0.01	3.06	2.11-4.44	<0.01
Complex VPB	1.13	0.78-1.65	0.52	0.79	0.22-2.86	0.72

IRR, incident rate ratios; VPB, ventricular premature beats.
N=25 insulin-treated patients with T2DM and a history of CVD or ≥2 cardiovascular risk factors underwent simultaneous continuous interstitial glucose and ambulatory electrocardiogram monitoring.
Chow E, et al. *Diabetes*. 2014;63(5):1738-1747.

Hypoglycemia With Antidiabetes Therapies

Drug Class	Estimated A1c Reduction, %	Hypoglycemia Incidence, %
Short-acting GLP-1 RA[1,a]	0.5-0.7	3.8-10.7*
Long-acting GLP-1 RA[1,b]	0.7-1.6	0-10.9*
DPP-4 inhibitors[2,c]	0.4-0.8	0.3-5*
SGLT-2 inhibitors[3,b]	0.7	0-6*
Sulfonylureas[6]	1-2	18-30
Pioglitazone[6]	0.5-1.4	0-3.7
Basal insulin[6,d]	1.5-3.5	29.9-61.2

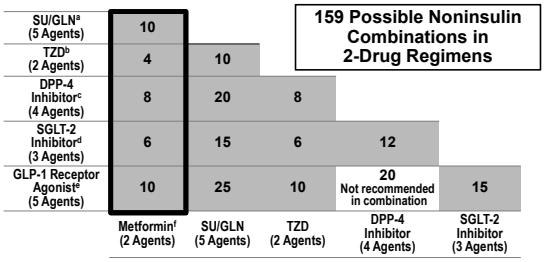
***Hypoglycemia risks are higher when agents are combined with a sulfonylurea or insulin.**

[a]Exenatide twice daily; [b]Includes liraglutide, exenatide once weekly, albiglutide, and dulaglutide; [c]Includes saxagliptin, linagliptin, and sitagliptin; [d]Includes canagliflozin, dapagliflozin, and empagliflozin; [e]Includes neutral protamine Hagedorn insulin, insulin glargine, and insulin detemir.
1. Drugs@FDA. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/; 2. Boland CL, et al. *Ann Pharmacother*. 2013;47(4):490-505; 3. Nauck MA. *Drug Des Devel Ther*. 2014;8:1335-1380.

Jerry
Initial Treatment

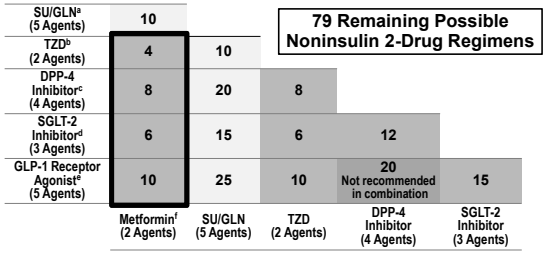
- Target A1c ≤6.5%
- His PCP engages Jerry in discussion around lifestyle modifications, including smoking cessation and weight loss
- Suggests a certified diabetes educator
  - Patient education
  - Detailed dietary and exercise recommendations
- Jerry and his PCP also review the possibility of initiating therapy with 2 antihyperglycemic agents

Noninsulin Antihyperglycemic Therapy
Potential 2-Drug Combinations in the US



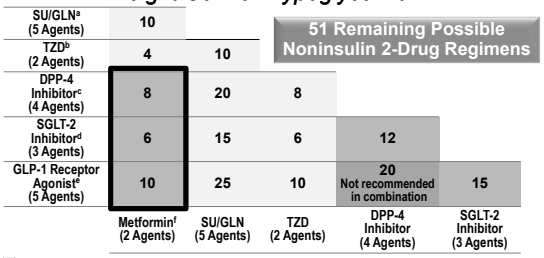
[a]Possible SUs and GLNs include glimepiride, glipizide, glyburide, nateglinide, and repaglinide; [b]Possible TZDs include pioglitazone and rosiglitazone; [c]Possible DPP-4 inhibitors include alogliptin, sitagliptin, linagliptin, and saxagliptin; [d]Possible SGLT-2 inhibitors include canagliflozin, dapagliflozin, and empagliflozin; [e]Possible GLP-1 RAs include exenatide twice daily, exenatide once weekly, liraglutide, dulaglutide, and albiglutide; [f]Possible metformin drugs include standard and extended release formulations.
ADA. *Diabetes Care*. 2015;38(suppl 1):S1-S94; Nauck M, et al. *Diabetes*. 2015;64(suppl 1):A3 [abstract 10-OR].

Noninsulin Dual Therapy
Avoiding Agents With High Hypoglycemia Risks



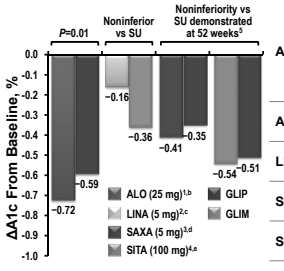
[a]Possible SUs and GLNs include glimepiride, glipizide, glyburide, nateglinide, and repaglinide; [b]Possible TZDs include pioglitazone and rosiglitazone; [c]Possible DPP-4 inhibitors include alogliptin, sitagliptin, linagliptin, and saxagliptin; [d]Possible SGLT-2 inhibitors include canagliflozin, dapagliflozin, and empagliflozin; [e]Possible GLP-1 RAs include exenatide twice daily, exenatide once weekly, liraglutide, dulaglutide, and albiglutide; [f]Possible metformin drugs include standard and extended-release formulations.
ADA. *Diabetes Care*. 2015;38(suppl 1):S1-S94; Nauck M, et al. *Diabetes*. 2015;64(suppl 1):A3 [abstract 10-OR].

Noninsulin Dual Therapy
Avoiding Agents With High Risks of Weight Gain or Hypoglycemia



[a]Possible SUs and GLNs include glimepiride, glipizide, glyburide, nateglinide, and repaglinide; [b]Possible TZDs include pioglitazone and rosiglitazone; [c]Possible DPP-4 inhibitors include alogliptin, sitagliptin, linagliptin, and saxagliptin; [d]Possible SGLT-2 inhibitors include canagliflozin, dapagliflozin, and empagliflozin; [e]Possible GLP-1 RAs include exenatide twice daily, exenatide once weekly, liraglutide, dulaglutide, and albiglutide; [f]Possible metformin drugs include standard and extended-release formulations.
ADA. *Diabetes Care*. 2015;38(suppl 1):S1-S94; Nauck M, et al. *Diabetes*. 2015;64(suppl 1):A3 [abstract 10-OR].

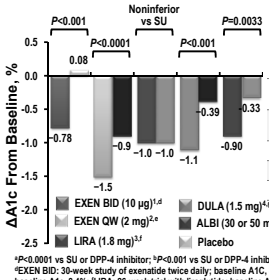
DPP-4 Inhibitors vs Sulfonylureas
Added to Metformin



Agent	Δ Weight, kg		Hypoglycemia % of patients	
	DPP-4 inhibitor	SU	DPP-4 inhibitor	SU
ALO[1,a]	−0.9[a]	+1.0	1	23
LINA[2,b]	−1.4[a]	+1.3	7[a]	36
SAXA[3,c]	−1.5	+1.3	3	38
SITA[4,d]	−1.6	+0.7	5	34

[a]P<0.001 vs SU;
[b]ALO: 104-week trial of alogliptin; baseline A1c, 7.6%; [c]LINA: 104-week trial of linagliptin; baseline A1c, 7.7%;
[d]SAXA: 104-week trial of saxagliptin; baseline A1c, 7.7%; [e]SITA: 104-week trial of sitagliptin; baseline A1c, 7.3%.
1. Del Prato S, et al. *Diabetes Obes Metab*. 2014;16:1239-1246; 2. Gallwitz B, et al. *Lancet*. 2012;380:475-483; 3. Göke B, et al. *Int J Clin Pract*. 2013;67:307-316; 4. Seck T, et al. *Int J Clin Pract*. 2010;64:562-576; 5. Nauck MA, et al. *Diabetes Obes Metab*. 2007;9:194-205.

GLP-1 RAs vs Sulfonylureas or DPP-4 Inhibitors
Added to Metformin



Agent	Δ Weight, kg		Hypoglycemia, % of patients	
	GLP-1 RA	SU/ DPP-4i	GLP-1 RA	SU/ DPP-4i
EXEN BID[1,d]	−2.8	NA	5	NA
EXEN QW[2,e]	−2.3[b]	−0.8	1[c]	3
LIRA[3,f]	−1.5[a]	+1.0	3[b]	17
DULA[4,g]	−3.0[b]	−1.5	10[c]	5
ALBI[5,h]	−1.2[a]	+1.2	3[c]	18

[a]P<0.0001 vs SU or DPP-4 inhibitor; [b]P<0.001 vs SU or DPP-4 inhibitor; [c]No statistical analysis performed;
[d]EXEN BID: 30-week study of exenatide twice daily; baseline A1C, 8.2%; [e]EXEN QW: 26-week trial of exenatide once weekly; baseline A1c, 8.4%; [f]LIRA: 26-week trial with liraglutide; baseline A1c, 8.4%; [g]DULA: 52-week trial; baseline A1c, 8.1%;
[h]ALBI: 104-week trial of albiglutide; baseline A1c, 8.1%.
1. DeFronzo RA, et al. *Diabetes Care*. 2005;28:1092-1100; 2. Bergenstal RM, et al. *Lancet*. 2010;376:431-439;
3. Nauck M, et al. *Diabetes Care*. 2009;32(1):84-90; 4. Nauck M, et al. *Diabetes Care*. 2014;37(8):2149-2158;
5. Ahrén B, et al. *Diabetes Care*. 2014;37(8):2141-2148.

Safety With Incretin-Based Agents
Acute Pancreatitis

- **Precautions**[1-5]
  - Cases have been reported
  - Consider treatments other than GLP-1 RAs in patients with history of pancreatitis
  - Unknown if pancreatitis history increases risk with DPP-4 inhibitors
- **Recommendations**[1-5]
  - Ask about pancreatitis history
  - Educate patients about signs and symptoms of pancreatitis
  - Discontinue if pancreatitis symptoms occur
  - Report cases of pancreatitis to www.fda.gov/medwatch

Pancreatitis risk is 1.5- to 3-fold higher in individuals with diabetes[6-8]

1. See Drugs@FDA (http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021773s029s030lbl.pdf); 2. See Drugs@FDA (http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022200s008lbl.pdf); 3. See Drugs@FDA (http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022341s020lbl.pdf); 4. Albiglutide prescribing information. https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Tanzeum/pdf/TANZEUM-PI-MG-IFU-COMBINED.PDF; 5. Dulaglutide prescribing information. http://pi.lilly.com/us/trulicity-uspi.pdf;
6. Girman CJ, et al. *Diabetes Obes Metab.* 2010;12(9):766-771; 7. Garg R, et al. *Diabetes Care.* 2010;33(11):2349-2354;
8. Yang L, et al. *Eur J Gastroenterol Hepatol.* 2013;25(2):225-231

Safety of Incretin Therapy
2014 FDA and EMA Analysis

- FDA and EMA conducted parallel, independent safety assessments of incretin-based drugs following postmarketing reports of pancreatitis or pancreatic cancer in treated individuals

"Assertions of a causal association are not consistent with current data"

"Product information and labeling reflect current understanding of risk"

- Both agencies continue to investigate safety signals and data from ongoing trials

EMA, European Medicines Association.
Egan AG, et al. *N Engl J Med.* 2014;370(9):794-797.

DPP-4 Inhibitors
Safety: Additional Considerations

- Generally well-tolerated[1]
- Most common adverse effects[1]
  - Nasopharyngitis
  - Headache
  - Nausea
  - Hypersensitivity
  - Skin reactions
- Recent statement from the FDA warned about the risks of joint pain that can be severe and disabling[2]
- Dose reductions are required for alogliptin, saxagliptin, and sitagliptin in patients with moderate or severe renal impairment, or ESRD (CrCl ≤50 mL/min)[1]

CrCl, creatinine clearance.
1. Grunberger G. *J Diabetes.* 2013;5:241-253;
2. US FDA: Available at www.fda.gov/Drugs/DrugSafety/ucm459579.htm; Accessed September 4, 2015.

Nausea/Vomiting With GLP-1 RAs
Pooled Results From Placebo-Controlled Trials

Medication	Nausea Incidence, %	Vomiting Incidence, %
Albiglutide[1]	11%	4%
Dulaglutide[2]	12%-21%	6%-13%
Exenatide BID[3]	8%-44%	4%-18%
Exenatide QW[4]	11%-27%	11%
Liraglutide[5]	8%-35%	6%-17%

- **Potential approaches to reduce risks for nausea and vomiting**[3,6]
  - Educate on meal size, eating pace, and dose timing relative to meals
  - Use incremental dose titration, particularly with shorter-acting agents
  - Prescribe short-term antiemetic therapy for select patients

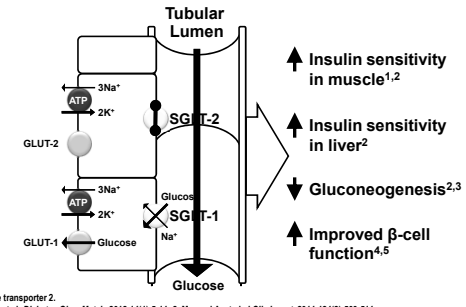
1. Albiglutide prescribing information. https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Tanzeum/pdf/TANZEUM-PI-MG-IFU-COMBINED.PDF; 2. Dulaglutide prescribing information. http://pi.lilly.com/us/trulicity-uspi.pdf; 3. Drugs@FDA (http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021773s029s030lbl.pdf); 4. Drugs@FDA (http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022200s008lbl.pdf); 5. Drugs@FDA (http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022341s020lbl.pdf); 6. Ellero C, et al. *Diabet Med.* 2010;27(10):1168-1173.

GLP-1 RAs
Safety: Additional Considerations

- Use with caution in patients with renal impairment or renal transplantation, especially when initiating or escalating doses[1-5]
  - Hypovolemia due to nausea/vomiting may worsen renal function
  - Do not use exenatide formulations in patients with severe renal impairment (CrCl <30 mL/min) or ESRD
- All long-acting GLP-1 RAs should not be used in patients with MEN2 or a personal/family history of MTC[2-5]
  - Counsel regarding MTC risk and symptoms of thyroid tumors
  - Report MTC to state cancer registry, regardless of treatment http://www.naaccr.org/Membership/MembershipDirectory.aspx

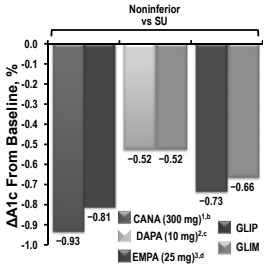
MEN2, multiple endocrine neoplasia syndrome type 2; MTC, medullary thyroid carcinoma.
1. See Drugs@FDA (http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021773s029s030lbl.pdf);
2. See Drugs@FDA (http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022200s008lbl.pdf);
3. See Drugs@FDA (http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022341s020lbl.pdf);
4. Albiglutide prescribing information. https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Tanzeum/pdf/TANZEUM-PI-MG-IFU-COMBINED.PDF;
5. Dulaglutide prescribing information. http://pi.lilly.com/us/trulicity-uspi.pdf.

SGLT-2 Inhibition
Insulin-Independent Reversal of Glucotoxicity



GLUT-2, glucose transporter 2.
1. DeFronzo RA, et al. *Diabetes Obes Metab.* 2012;14(1):5-14; 2. Merovci A, et al. *J Clin Invest.* 2014;124(2):509-514;
3. Marsenic O. *Am J Kidney Dis.* 2009;53(5):875-883; 4. Ferrannini E, et al. *J Clin Invest.* 2014;124(2):499-508;
5. Polidori D, et al. *Diabetologia.* 2014;57(5):891-901.

SGLT-2 Inhibitors vs Sulfonylureas
Added to Metformin



Agent	Δ Weight, kg		Hypoglycemia, % of patients	
	SGLT-2 Inhibitor	SU	SGLT-2 Inhibitor	SU
CANA[1,a]	−4.0[a]	+0.7	5[a]	34
DAPA[2,b]	−3.2[a]	+1.4	3[a]	41
EMPA[3,c]	−3.2[a]	+1.6	2[a]	24

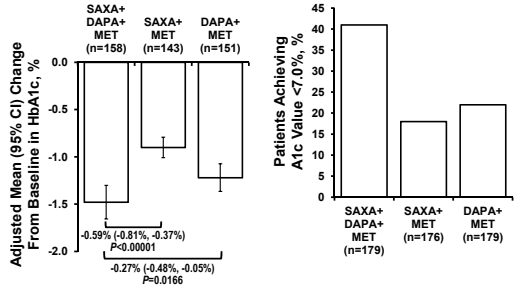
[a]*P*<0.0001 vs SU.
[b]CANA: 52-week trial of canagliflozin; baseline A1c, 7.8%; [c]DAPA: 52-week trial of dapagliflozin; baseline A1c, 7.7%;
[d] EMPA:104-week trial of empagliflozin; baseline A1c, 7.9%.
1. Cefalu WT, et al. *Lancet*. 2013;382(9896):941-950; 2. Nauck MA, et al. *Diabetes Care*. 2011;34(9):2015-2022;
3. Ridderstråle M, et al. *Lancet Diabetes Endocrinol*. 2014;2(9):691-700.

SGLT-2 Inhibitors
Safety Considerations

- Generally well-tolerated with good safety profile[1,2]
  - Most common AEs include genital mycotic infections and UTIs
- Dose-related increases in serum creatinine and decreased eGFR[3-5]
  - Evaluate renal function before initiating treatment and during therapy
  - Do not use dapagliflozin if eGFR is <60 mL/min/1.73 m^2
  - Do not use canagliflozin or empagliflozin if eGFR is <45 mL/min/1.73 m^2
- Cause intravascular volume depletion, which may lead to symptomatic hypotension[3-5]
  - At risk populations include patients on loop diuretics, elderly individuals, patients with low systolic BP, and those with eGFR <60 mL/min/1.73 m^2
  - Assess and correct volume status before initiating therapy
- Changes in plasma lipids were observed in clinical trials[3-5]
  - Monitor LDL-C and treat per standard of care
- Recent FDA warning calls out risks of euglycemic diabetic ketoacidosis as well as canagliflozin for bone fracture

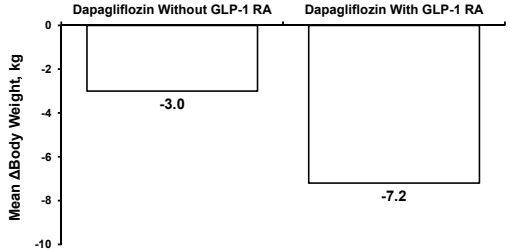
UTI, urinary tract infection.
1. Abdul-Ghani MA, Defronzo RA. *J Intern Med*. 2014 Apr 1; 2. List JF, et al. *Diabetes Care*. 2009;32(4):650-657;
3. See Drugs@FDA (www.accessdata.fda.gov/drugsatfda_docs/label/2013/204042s000lbl.pdf);
4. See Drugs@FDA (www.accessdata.fda.gov/drugsatfda_docs/label/2014/202293s000lbl.pdf);
5. See Drugs@FDA (www.accessdata.fda.gov/drugsatfda_docs/label/2015/204629s001s002s003lbl.pdf).

Saxagliptin and/or Dapagliflozin Add-on to Metformin
24-Week Data for Initial T2DM Therapy



N=534 patients with T2DM, A1c values between 8.0% and 12.0% (mean A1c, 8.9%), and an inadequate response to metformin.
Rosenstock J, et al. *Diabetes Care*. 2015;38(3):376-383.

GLP-1 RA + SGLT-2 Inhibitor
Initial Indications of Synergistic Weight Loss



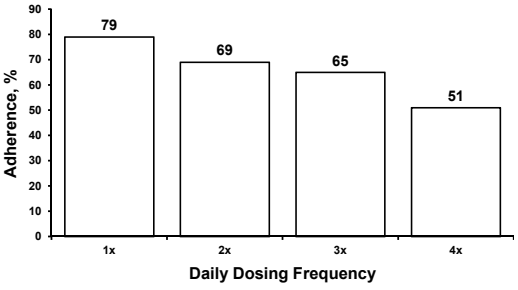
P=0.02 between groups.
N=88 subjects with T2DM started on dapagliflozin and followed for 1 year.
McGovern AP, et al. Presented at the Diabetes UK Professional Conference. March 11-13, 2015; London, UK. Abstract A6 (P143).

Jerry
Pharmacologic Treatment

- Jerry and his PCP decide to start therapy with metformin BID and an SGLT-2 inhibitor
  - Jerry is educated on risks with both drugs
  - He is assessed for volume status
  - Both medications titrated up over next 2 weeks
- At a 3-month follow-up, Jerry's A1c has fallen to 7.4%
  - Previous value, 8.7%
- Jerry often forgets which drugs he has taken each day
  - Frequently skips doses for T2DM or hypertension
- His weight is relatively unchanged
  - He reports continued bad eating habits during tax season

How can the PCP help improve Jerry's adherence to lifestyle recommendations and his medications?

Daily Doses and Adherence



Claxton AJ, et al. *Clin Ther*. 2001;23:1296-1310; Laufs U, et al. *Eur Heart J*. 2011;32:264-268.

Simplify the Regimen

Core Principles	Action
Adjust timing, frequency, amount, and dosage	• Prescribe once-daily medications
Match regimen to patient's activities of daily living	• Dose to regular activities (eg, meals)
Recommend all medications are taken together	• Consider combination formulations • Assess for drug-drug interactions and food absorption issues
Avoid medications with special requirements	• Avoid medications that should not be taken with meals
Avoid unnecessary side effects	• Evaluate all potential side effects • May need to choose among side effects

Change the *situation* rather than change the *patient!*

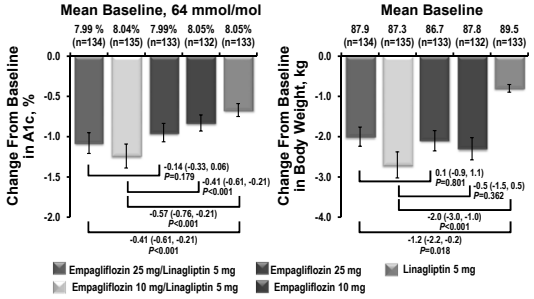
American College of Preventative Medicine. Available at: www.acpm.org/resource/resmgr/timetools-files/adherenceclinicalreference.pdf. Accessed September 3, 2015.

Oral Combination Formulations With DPP-4 Inhibitors and SGLT-2 Inhibitors

Fixed Dose Combinations	Clinical Status
DPP-4 Inhibitor + Metformin	
Sitagliptin + Metformin	Approved in the US
Sitagliptin + Metformin ER	Approved in the US
Saxagliptin + Metformin ER	Approved in the US
Linagliptin + Metformin	Approved in the US
Alogliptin + Metformin	Approved in the US
SGLT-2 Inhibitor + Metformin	
Dapagliflozin + Metformin	Approved in the US
Canagliflozin + Metformin	Approved in the US
Empagliflozin + Metformin	Approved in the US
DPP-4 Inhibitor + SGLT-2 Inhibitor	
Empagliflozin + Linagliptin	Approved in the US
Dapagliflozin + Saxagliptin	Filed in the US
Ertugliflozin + Sitagliptin	Phase 3
DPP-4 Inhibitor + TZD	
Alogliptin + Pioglitazone	Approved in the US

Empagliflozin/Linagliptin Combination

24-Week Data for Initial T2DM Therapy



N=674 individuals with T2DM who had not received diabetes therapy for ≥12 weeks (week 24 data).
Lewin A, et al. *Diabetes Care*. 2015;38(3):394-402.

Dapagliflozin/Saxagliptin Combination

24-Week Study Add-on to Metformin

Parameters	DAPA/SAXA 10/5 mg	SAXA 5 mg and PBO	DAPA 10 mg and PBO
ΔA1c from baseline, %	**-1.47**	**-0.88**	**-1.20**
Difference from combination, % [95% CI]	**N/A**	**-0.59 [-0.81, -0.37][a]**	**-0.27 [-0.48, -0.05][b]**
Patients achieving A1c <7%, %	**41**	**18**	**22**
Difference from combination, % [95% CI]		**23 [15, -32]**	**22 [10, 28]**
Hypoglycemia, %[c]	**1.1**	**0.6**	**1.1**

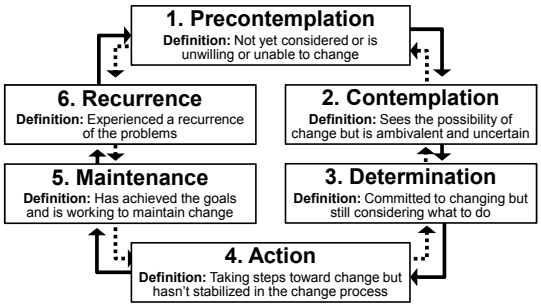
[a]$P<0.0001$; [b]$P<0.02$; [c]No major episodes of hypoglycemia.
N=534 patients with T2DM (A1c, ≥8.0% and ≤12.0%) treated with metformin XR ≥1500 mg daily.
Rosenstock J, et al. Dual add-on therapy in poorly controlled type 2 diabetes on metformin: randomized, double-blind trial of saxagliptin+dapagliflozin vs. Saxagliptin and dapagliflozin alone. Poster presented at American Diabetes Association. 74th Scientific Session; June 13-17, 2014; San Francisco, CA.

Motivational interviewing is a collaborative conversation style for strengthening a person's own motivation and commitment to change by eliciting and exploring the persons own reasons for change

Miller & Rollnick, 2013

Motivational Interviewing

Stages of Change



Jerry
Key Points

- Individualize treatment goals for patients with T2DM
  - Consider comorbidities
  - Address psychosocial factors
  - Take steps to reduce risk of hypoglycemia
- Ensure lifestyle modifications are the foundation of any treatment regimen for T2DM
- Monitor multiple metabolic targets for comprehensive management and reduction of cardiovascular risk
  - A1c, lipids, BP
- When necessary, promptly intensify antihyperglycemic therapy
  - Consider early multidrug regimens that reflect the baseline degree of hyperglycemia and other clinical parameters
  - Minimize risks of hypoglycemia
  - Use combination formulations to address multiple pathologic mechanisms in T2DM and to simplify treatment regimens

Choose-a-Case

Eileen Egan, DNP, FNP-C, CDE

Chief Nurse Practitioner
Winthrop Center for Comprehensive Diabetes Care
Winthrop Endocrine, Diabetes, & Metabolism Faculty Practice
Mineola, New York
Adjunct Faculty
Department of Graduate Studies & Advanced Practice Nursing
Stony Brook University
Stony Brook, New York

OSCAR
Background

- 53-year-old teacher
- Lives with wife and 2 daughters
- Visits you after missing last 2 appointments
- Reports feeling rundown over last 4 months
- Gets up ≥2 times nightly to urinate
- Trying to eat healthily but has found it difficult
  - 1-2 glasses of wine with dinner each night
  - Drinks caffeinated soda each day
  - Does not smoke
- No exercise other than walking 2 blocks to and from school each day

OSCAR
Patient History

- Medical history
  - Hypercholesterolemia diagnosis 9 years ago
    - Atorvastatin 20 mg once daily
- Family history
  - Father underwent bypass surgery at 74 years old
  - Mother was obese
    - Died following MI at 65 years old

OSCAR
Physical Exam and Lab Testing

- Height, 5′ 7″
- Weight, 190 lb
- BMI, 29.8 kg/m^2
  - Abdominal obesity
- Afebrile
- BP, 125/79 mm Hg
- FPG, 178 mg/dL
  - 2nd test, 176 mg/dL
- A1c, 8.8%
- Dark discolored skin around neck
- Normal sensory and fundoscopic exams
- Lipids
  - TC, 178 mg/dL
  - LDL-C, 99 mg/dL
  - HDL-C, 50 mg/dL
  - TG, 145 mg/dL
- Framingham risk, 7.3%
- Stage 2 CKD
  - eGFR, 78 mL/min/1.73 m^2
  - ACR, 28 mg/g

After educating OSCAR on his diagnoses of chronic kidney disease and T2DM, what initial steps would you take to help him manage his diabetes?

What if his eGFR was 38 mL/min/1.73 m^2?

NATALIE
Background

- 56-year-old Caucasian woman
  - Lives with her husband of 3 years
  - Unemployed, but looking for work
- Long history of alcohol abuse
  - Currently sober for past 6 months
- Returns for a follow-up 14 months after her last appointment
  - Sober at her last appointment but relapsed soon after
- Presenting symptoms
  - Fatigue
  - Increased thirst

NATALIE
Patient History

- Medical history
  - T2DM diagnosis 3 years ago
    - Previous PCP prescribed metformin and basal insulin
    - 2 episodes of severe hypoglycemia in the first 3 months after starting insulin (stopped injection)
  - Current regimen
    - Metformin 1000 mg twice daily and linagliptin 5 mg
    - Reports missing "a couple of doses each week"
    - Adherence is much worse when she is drinking
- Family history is unremarkable

NATALIE
Physical Exam and Lab Testing

- Height, 5′ 5″
- Weight, 160 lb
- BMI, 26.6 kg/m^2
- Afebrile
- BP, 134/78 mm Hg
- FPG, 170 mg/dL
  - Previous value, 130 mg/dL
- A1c, 8.4%
  - Previous value 7.5%
  - A1c goal, <7.0%
- Lipids
  - TC, 187 mg/dL
  - LDL-C, 105 mg/dL
  - HDL-C, 50 mg/dL
  - TG, 160 mg/dL
- Liver tests
  - AST, 250 IU/L
  - ALT, 100 IU/L
- eGFR, 90 mL/min/1.73 m^2
- ACR, 5.5 mg/g

ALT, alanine transaminase; AST, aspartate transaminase.

What steps would you take to help NATALIE better manage her T2DM?

NORMAN
Background

- 61-year-old Mexican-American man
  - Relocated to area 3 months ago after divorcing wife of 20 years
    - Lives alone
    - Markedly depressed since his divorce became final
  - Found you as his new PCP
- Works long office hours
  - Sedentary lifestyle
- Presenting symptoms
  - Fatigue
  - General weakness
  - Frequent urination
  - "Pins and needles" in both feet
- Symptoms started 1 year ago
  - Recently worsened

NORMAN
Patient History

- Medical history
  - T2DM diagnosis 8 years ago
    - Metformin 1000 mg twice daily
  - MDD diagnosis 20 years ago
    - 3 major episodes since then
    - Intermittent antidepressant treatment (not currently)
  - 1 pack of cigarettes daily for 30 years
    - Uses nicotine gum but still has 1-2 cigarettes daily
- Poor diet and exercises infrequently
- Reports forgetting medication "2 or 3" times/week
- Family history
  - Father died of MI at 58 years old

MDD, major depressive disorder.

NORMAN
Physical Exam and Lab Testing

- Height, 5′ 7″
- Weight, 220 lb
- BMI, 34.5 kg/m^2 (obese)
  - Abdominal obesity
- Afebrile
- BP, 139/86 mm Hg
- PHQ-9 score, 14 (moderate depression)
- Sensory neuropathy in both feet up to ankles
- FPG, 170 mg/dL
- A1c, 8.7%
- Lipids
  - TC, 191 mg/dL
  - LDL-C, 116 mg/dL
  - HDL-C, 32 mg/dL
  - TG, 215 mg/dL
- eGFR, 88 mL/min/1.73 m^2
- ACR, 2.5 mg/g

PHQ, Patient Health Questionnaire.

What steps would you take to help NORMAN better manage his T2DM?

CHARLIE
Background

- 56-year-old African American man
  - Retired postal worker
  - Lives alone
    - Wife died of breast cancer 3 years ago
- Presents for his regular check-up
- Nonsmoker
- Otherwise unhealthy lifestyle
  - Little physical activity
  - Regularly consumes fried food, red meat, and sugary soda
  - Rarely eats fruits or vegetables

CHARLIE
Patient History

- Medical history
  - Hypertension diagnosis 5 years ago
    - Lisinopril 40 mg daily and atenolol 50 mg daily
  - NSTE myocardial infarction 2 years ago
    - PCI, 12 months of ticagrelor, daily low-dose aspirin
  - T2DM diagnosis at admission for the MI
    - Metformin 1000 mg twice daily
  - Dyslipidemia diagnosis 1 year ago
    - Atorvastatin 40 mg daily
- Family history
  - Father died of MI at 68 years old
  - Mother is alive at 80 years old but has T2DM

NSTE, non ST-segment elevation; PCI, percutaneous coronary intervention.

CHARLIE
Physical Exam, Lab Testing, Interview

- Height, 5′ 10″
- Weight, 205 lb
- BMI, 29.4 kg/m^2
  - Muscular body type but some abdominal obesity
- Afebrile
- BP, 130/78 mm Hg
- FPG, 165 mg/dL
- A1c, 8.4%
  - Previous value 7.5% 6 months ago
- Lipids
  - TC, 166 mg/dL
  - LDL-C, 90 mg/dL
  - HDL-C, 46 mg/dL
  - TG, 150 mg/dL
- eGFR, 90 mL/min/1.73 m^2
- Clinical interview
  - Forgets medications 1-2 times/week
  - Does not like needles

What steps would you take to help CHARLIE better manage his T2DM?

Conclusions

- Comprehensive T2DM management requires diligent monitoring of blood sugars, lipid profile, blood pressure, and body weight
  - Treatment is founded on lifestyle and behavioral modifications
- Hypoglycemic episodes are associated with serious adverse outcomes
- Certain combinations of noninsulin agents can effectively reduce hyperglycemia with relatively low risks of hypoglycemia and potential for weight loss