Get Your

CE IN THE MIDDAY

A Midday Symposium and Live Webinar conducted at the 2018
Midyear Clinical Meeting and Exhibition

Individualizing Therapy for Type 2 Diabetes Mellitus to Overcome Clinical Inertia: Clinical Case Vignettes

Wednesday, December 5, 2018
11:30 a.m. – 1:00 p.m.

Anaheim, California

Agenda

11:30 a.m. – 11:35 a.m.
Welcome and Introductions
Curtis L. Triplitt, Pharm.D., CDE, *Activity Chair*

11:35 a.m. – 11:55 a.m.
Current Guidelines: Choosing the Right Medication for Your Patient
Eric L. Johnson, M.D.

11:55 a.m. – 12:50 p.m.
Clinical Case Vignettes: Individualizing Therapy and Overcoming Clinical Inertia
Curtis L. Triplitt, Pharm.D., CDE and Eric L. Johnson, M.D.

12:50 p.m. – 1:00 p.m.
Panel Discussion: Questions and Answers

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Individualizing Therapy for Type 2 Diabetes Mellitus to Overcome Clinical Inertia: Clinical Case Vignettes

CE IN THE MIDDAY

Individualizing Therapy for Type 2 Diabetes Mellitus to Overcome Clinical Inertia: Clinical Case Vignettes

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  - AstraZeneca; Boehringer Ingelheim; Eli Lilly; Janssen – Speakers Bureau
  - Merck – Consultant
- Eric L. Johnson
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Learning Objectives

- Identify the current guidelines and the latest evidence for appropriate therapy in patients with type 2 diabetes mellitus and with or without comorbidities.
- Identify patient and provider barriers to overcoming clinical inertia.
- Devise interprofessional team-based strategies to maximize patient engagement in developing a diabetes care plan and achieving individualized treatment goals.
- Apply and individualize the current treatment guidelines for type 2 diabetes mellitus using patient vignettes.

Abbreviations

- AACE=American Association of Clinical Endocrinologists
- ACCORD=Action to Control Cardiovascular Risk in Diabetes trial
- ACE=American College of Endocrinology
- ACP=American College of Physicians
- ADA=American Diabetes Association
- ADVANCE=Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation trial
- ASCVD=atherosclerotic cardiovascular disease
- BMI=body mass index
- BP=blood pressure
- BUN=blood urea nitrogen
- CHF=chronic heart failure
- CV=cardiovascular
- CVD=cardiovascular disease
- DCCT=Diabetes Control and Complications Trial
- DKA=diabetic ketoacidosis
- eGFR=estimated glomerular filtration rate
- GFR=glomerular filtration rate
- GI=gastrointestinal
- HR=hazard ratio
- PCP=primary care provider
- SBP=systolic blood pressure
- SCr=serum creatinine
- T2DM=type 2 diabetes mellitus
- UKPDS=United Kingdom Prospective Diabetes Study
- UTI=urinary tract infection
- VADT=Veterans Affairs Diabetes Trial

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Prevalence and Costs of Diabetes in the U.S.

- 30.3 million Americans have diabetes
- 84.1 million Americans have prediabetes
- Costs are $327 billion

Centers for Disease Control and Prevention. National diabetes statistics report, 2017. www.diabetes.org/assets/pdfs/basics/cdc-statistics-report-2017.pdf.
American Diabetes Association. *Diabetes Care*. 2018; 41:917-28.

Medications for T2DM

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Considerations with Common Noninsulin Diabetes Medications

- **Metformin**
  - Cheap, initial for most, no hypoglycemia, positive long-term data, GI and renal considerations, weight neutral/loss
- **Sulfonylureas (SUs)**
  - Cheap, potent, weight gain, hypoglycemia, renal considerations
- **Thiazolidinediones (TZDs)**
  - Weight gain, CHF, edema, no hypoglycemia
- **Dipeptidyl peptidase (DPP)-4 inhibitors (gliptins)**
  - Weight neutral, no hypoglycemia, renal considerations for some patients, CHF signal with saxagliptin and alogliptin
- **Sodium glucose cotransporter (SGLT)-2 inhibitors**
  - Potent, weight loss, no hypoglycemia, renal considerations, UTI/yeast infection risk, lower BP (watch for orthostasis), positive CVD benefit with empagliflozin, canagliflozin, dapagliflozin (amputation risk with canagliflozin), DKA (can be normoglycemic)
- **Glucagon-like peptide (GLP)-1 agonists**
  - Injectable, potent, weight loss, pancreatitis risk, thyroid C-cell tumor risk, no hypoglycemia, positive CVD benefit with liraglutide, semaglutide, abliglutide

Garber AJ et al. *Endocr Pract*. 2018; 24:91-120. American Diabetes Association. *Diabetes Care*. 2018; 41(Suppl 1):S73-S85.

Look at these meds another way…..

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A1C Lowering

- Most oral agents 0.5% - 0.8%
- Injectable GLP-1 agonists 0.5% - 1.5%
- A1C lowering with insulin limited only by hypoglycemia

*not necessarily head to head comparisons

Garber AJ et al. *Endocr Pract*. 2018; 24:91-120.
American Diabetes Association. *Diabetes Care*. 2018; 41(Suppl 1):S73-S85.

Fasting Plasma Glucose vs. Postprandial Plasma Glucose

- **Medications primarily acting on fasting plasma glucose (FPG):**
  - Metformin
  - Basal (long-acting) insulin
  - TZDs
- **Medications primarily acting on postprandial (post-meal) glucose (PPG) :**
  - Sulfonylureas (both FPG and PPG)
  - DPP-4 inhibitors
  - GLP-1 agonists (both FPG and PPG)
  - SGLT-2 inhibitors
  - Bolus insulin (rapid-acting)

Both FPG and PPG must be treated for most patients to reach target

Garber AJ et al. *Endocr Pract*. 2018; 24:91-120.
American Diabetes Association. *Diabetes Care*. 2018; 41(Suppl 1):S73-S85.

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Weight Favorable Agents

- SGLT-2 inhibitors
- GLP-1 agonists (probably the most favorable)
- Weight neutral or small reduction
  - Metformin
  - DPP-4 inhibitors (gliptins)

Garber AJ et al. *Endocr Pract*. 2018; 24:91-120.
American Diabetes Association. *Diabetes Care*. 2018; 41(Suppl 1):S73-S85.

Avoid In Moderate to Severe Renal Disease (GFR <30-60 mL/min/1.73 m^2)

- Metformin
- GLP-1 agonists
- SGLT-2 inhibitors
- Sulfonylureas

- DPP-4 inhibitors- some have renal dosing adjustments

Garber AJ et al. *Endocr Pract*. 2018; 24:91-120.
American Diabetes Association. *Diabetes Care*. 2018; 41(Suppl 1):S73-S85.

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Risk For Hypoglycemia and Weight Gain

- Sulfonylureas
- Insulin (lower risk with basal insulin than with shorter-acting insulins)
- Start with lower dose
  - Organ dysfunction
  - Severe comorbidities
  - Elderly

Garber AJ et al. *Endocr Pract*. 2018; 24:91-120.
American Diabetes Association. *Diabetes Care*. 2018; 41(Suppl 1):S73-S85.

Older Adults

- Avoid sulfonylureas
- Consider age-related renal disease
- Be mindful of polypharmacy
- Single daily injection of basal insulin may work for many patients
- Stringent glycemic control usually not needed

Garber AJ et al. *Endocr Pract*. 2018; 24:91-120.
American Diabetes Association. *Diabetes Care*. 2018; 41(Suppl 1):S73-S85.

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Medication "Placement"

So…

How do we use these different medications with different mechanisms?

Using These Medications for T2DM

- For most, metformin first
- Any other agent as second- or third-line therapy
- Consider combination therapy initially with higher A1C (>7.5% AACE/ACE, >%9 ADA) especially with symptoms-perhaps even insulin
- Medications with cardiac benefit should be considered in those with established ASCVD after metformin

Garber AJ et al. *Endocr Pract*. 2018; 24:91-120.
American Diabetes Association. *Diabetes Care*. 2018; 41(Suppl 1):S73-S85.

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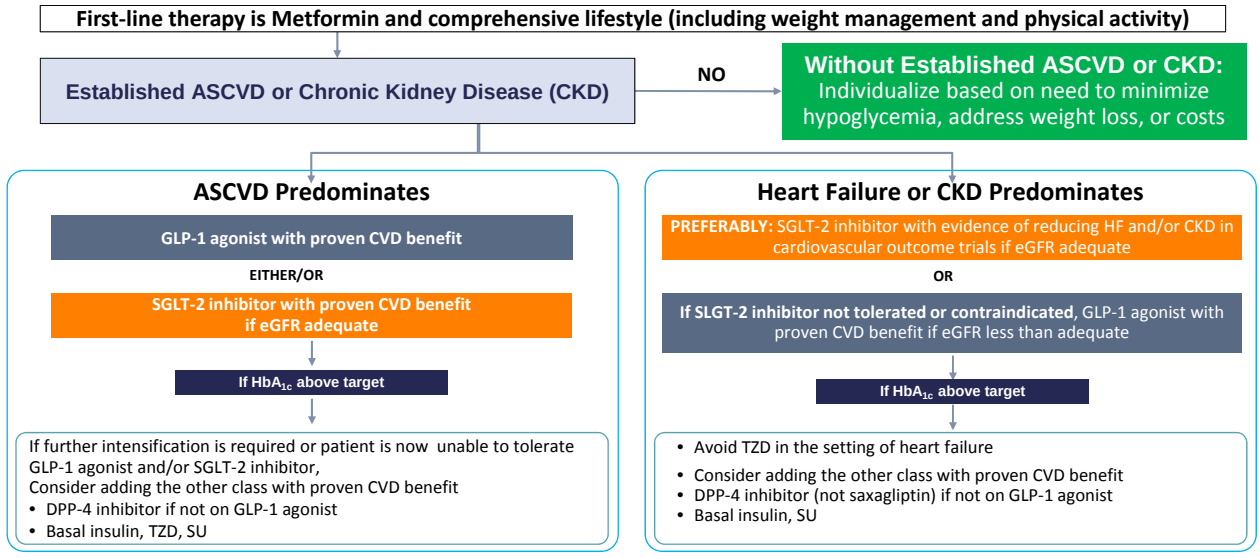
Individualizing Therapy for Type 2 Diabetes Mellitus to Overcome Clinical Inertia: Clinical Case Vignettes

2018 ADA/EASD Consensus Statement
Antihyperglycemic Medication in T2D: Overall Approach



Davies MJ et al. *Diabetes Care*. [published online October 5, 2018].

Common Combinations with Metformin: Individualization of Therapy

	Efficacy	Hypoglycemia risk	Weight	Renal outcome	Other compelling reasons
Metformin	High	No	Decrease	Neutral	
SGLT-2 inhibitor	Intermediate	No	Decrease	Improve#	CHF, CAD Wt, SBP
GLP-1 agonist	High	No	Decrease	Improve*	CAD*, Wt, SBP
DPP-4 inhibitor	Intermediate	No	Neutral	Neutral	Well tolerated
TZD	High	No	Increase	Neutral	Insulin Sensitizer, beta cell +
SU	High	Yes	Increase	Neutral	Cost
Insulin	Highest	Highest	Increase	Neutral	If symptoms of hyperglycemia

*Liraglutide, semaglutide #Empagliflozin, canagliflozin

American Diabetes Association. *Diabetes Care*. 2018; 41(Suppl 1):S73-S85.

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Algorithms/Tables

- If you know the algorithms and the tables of patient- and medication-specific factors for choosing drug therapy...
- You know a lot!

Avoid Clinical Inertia-
Advance Therapy Every 3 Months
If Not At Target

Case Studies

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Case 1: JW

- JW is a 42-year-old male who presents for an annual work physical. He denies any specific symptoms or concerns. A couple of years ago he was told he had "prediabetes" and that he should lose weight. There was a class he could take but he has not found the time to do this.
- Medical/surgical history: none
- Current medications: omeprazole 20 mg orally once a day as needed
- Drug allergies: none
- Social history: married, 3 children, all healthy
- Family history: mother with T2DM and hypertension (HTN)- alive at 71 years old with mild renal disease

Case 1: JW

- Vital Signs: normal except BP 144/88 mmHg
- Physical exam
  - Obese male BMI 32 kg/m^2
  - Mild athlete's foot
  - Exam otherwise normal
- Labs
  - A1C 8.5%
  - Glucose (fasting) 172 mg/dL
  - Triglycerides 258 mg/dL, HDL 28 mg/dL, and LDL 94 mg/dL
  - Other laboratory values pending

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Case 1: Question 1

What is your A1C goal for this patient?
Discuss at your table

a. Less than or equal to 6.5%
b. Less than 7.5%
c. Less than 8.0%
d. Less than 8.5%

Glycemic Goals by Major Organization

	AACE	ADA	ACP	Evidence "Weight"
A1C	≤6.5%	<7%	7-8%	**AACE:** weighed observational microvascular reduction data more **ADA:** Less on observational, more on UKPDS and DCCT and follow up of both studies **ACP:** weighed ACCORD, ADVANCE, and VADT to greater extent, less UKPDS
FPG	<110 mg/dL	80-130 mg/dL		
PPG	<140 mg/dL	<180 mg/dL		

All guidelines have language regarding individualizing care

American Diabetes Association. *Diabetes Care*. 2018; 41(Suppl 1):S55-64.
Garber AJ et al. *Endocr Pract*. 2018; 24:91-120.
Qaseem A et al. *Ann Intern Med*. 2018; 168:569-76.

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Treatment Intensification to Achieve and Maintain Appropriate Glycemic Levels

- Intensification approach should be individualized
- **More stringent or less stringent** based on:
  - Risks for and potential consequences of hypoglycemia and other adverse drug effects
  - Disease duration
  - Life expectancy
  - Relevant comorbidities
  - Established vascular complications
  - Patient attitude and expected treatment efforts
  - Patient resources and support system

American Diabetes Association. *Diabetes Care.* 2018; 41(suppl 1):S55-S64.

AACE/ACE Comprehensive Type 2 DM Management Algorithm

- Individual glycemic goal based on age, life expectancy, comorbid conditions, duration of diabetes, risk of hypoglycemia or adverse consequences from hypoglycemia, patient motivation, and adherence.
- In general, the A1C goal for most patients is ≤6.5%
- Drug therapy should be individualized based on:
  - -Mechanism of action
  - -Risk of inducing hypoglycemia
  - -Risk of weight gain
  - -Other adverse effects
  - -Tolerability
  - -Ease of use
  - -Likelihood of adherence
  - -Cost
  - -Safety or risk reduction in heart, kidney, or liver disease

Garber AJ et al. *Endocrine Pract*. 2018; 24:91-120.

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ACP Guidance Statements: T2DM

1. Personalize the glycemic goal
   - benefits and harms of pharmacotherapy, preferences, general health and life expectancy, treatment burden, and costs of care.
2. Achieve an A1C level between 7% and 8%
3. Deintensify pharmacologic therapy if A1C levels <6.5%.
4. Minimize symptoms related to hyperglycemia and avoid targeting an A1C level in selected patients in whom harm outweighs benefit
   - life expectancy less than 10 years due to advanced age (80 years or older)
   - residence in a nursing home, or chronic conditions (such as dementia, cancer, end-stage kidney disease, or severe chronic obstructive pulmonary disease or congestive heart failure)

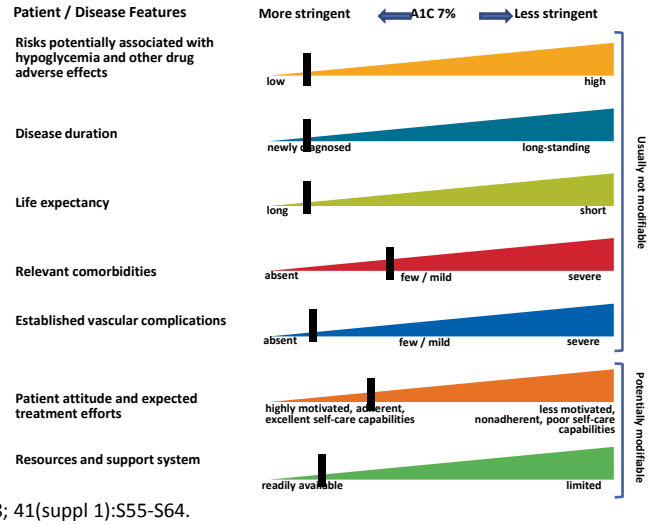
Qaseem A. *Ann Intern Med*. 2018; 168:569-76.

Treatment Intensification to Achieve and Maintain Appropriate Glycemic Levels

- Intensification approach should be ***individualized***

▌= Estimation for JW

Approach to the Management of Hyperglycemia



American Diabetes Association. *Diabetes Care.* 2018; 41(suppl 1):S55-S64.

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Case 1: JW

- Newly diagnosed T2DM
- 42 years old
- HTN is the only comorbidity, how long?
- No CVD documented, long-life expected
- Motivation and resources: JW did not attend classes, but can't classify yet- probably has social support/resources
- Would benefit from interprofessional, team-based diabetes self-management education/support (DSME/S)

A1C Goal

ADA: <7% at a minimum, although lower OK

AACE: ≤6.5%

Case 1: Question 2

- Develop a disease related treatment plan for JW
- Prioritize therapeutic goals
- Discuss at your table

TIME IS UP!

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What did you prioritize?

Treatment Plan for JW

1. **T2DM new diagnosis (by FPG and A1C)**
   - Refer to diabetes education, dietician for diabetes self-management education/support
   - What are JW's priorities?
   - Assess motivation to improve diabetes control
   - Start metformin 500 mg orally twice a day with meals, titrate to 1000 mg twice a day as tolerated
2. **HTN**
   - This is JW's first visit, so this is his first documented high BP reading
   - Recommend patient monitor BP at home and counsel on lifestyle. Assess next visit
   - OR, if we can document pattern of elevated BP >140/90 mmHg by history- we could start therapy today
3. **Dyslipidemia**
   - Patient is >40 years old with CVD risk factors, start atorvastatin 20 mg orally once a day
4. **Obesity**
   - Consider diabetes medication that may also address weight

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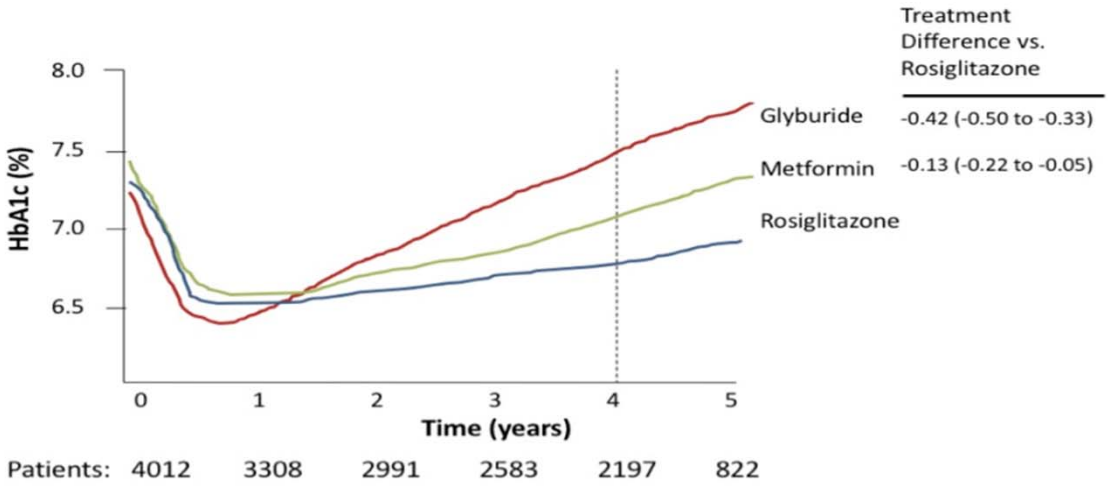
ADOPT



Kahn S et al. *N Engl J Med.* 2006; 355: 2427-43.

Case 1: Question 3

Which of the following drug classes is the preferred second-line ORAL therapy after metformin, according to the AACE/ACE glycemic control algorithm?

a. Sulfonylureas
b. GLP-1 agonists
c. SGLT-2 inhibitors
d. DPP-4 inhibitors

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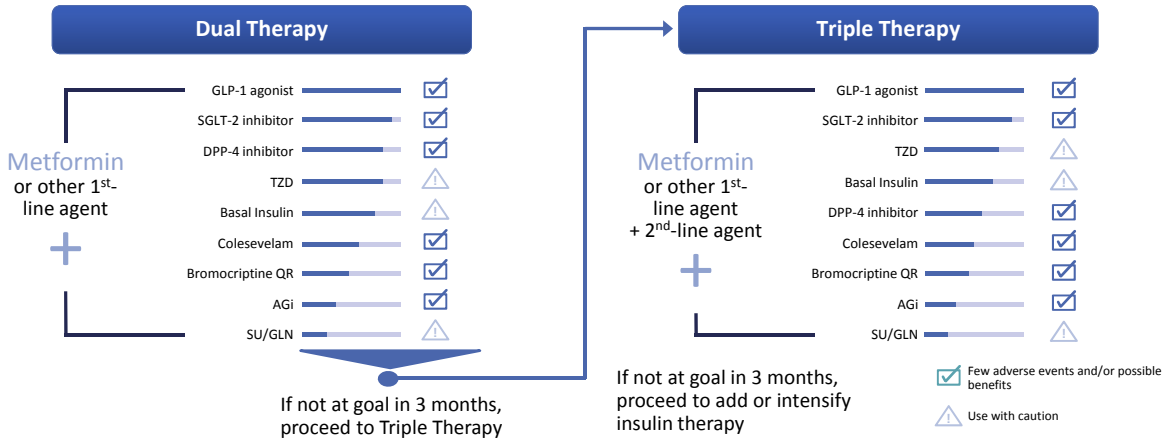
Individualizing Therapy for Type 2 Diabetes Mellitus to Overcome Clinical Inertia: Clinical Case Vignettes

AACE/ACE Guidelines Recommend Early Initiation of SGLT-2 Inhibitors

Patients with A1C ≥7.5%



Order of medications represents a suggested hierarchy of usage; length of line reflects strength of recommendation

AGi=α-glucosidase inhibitor, GLN=glinides, QR= quick release

Garber AJ et al. *Endocr Pract*. 2018; 24:91-120.

2018 ADA/EASD Consensus Statement Antihyperglycemic Medication in T2D: Overall Approach

First-line therapy is Metformin and comprehensive lifestyle (including weight management and physical activity)

Established ASCVD or Chronic Kidney Disease (CKD)

NO

Without Established ASCVD or CKD: Individualize based on need to minimize hypoglycemia, address weight loss, or costs

ASCVD Predominates

GLP-1 agonist with proven CVD benefit

EITHER/OR

SGLT-2 inhibitor with proven CVD benefit if eGFR adequate

If HbA_{1c} above target

If further intensification is required or patient is now unable to tolerate GLP-1 agonist and/or SGLT-2 inhibitor, Consider adding the other class with proven CVD benefit

- DPP-4 inhibitor if not on GLP-1 agonist
- Basal insulin, TZD, SU

Heart Failure or CKD Predominates

PREFERABLY: SGLT-2 inhibitor with evidence of reducing HF and/or CKD in cardiovascular outcome trials if eGFR adequate

OR

If SLGT-2 inhibitor not tolerated or contraindicated, GLP-1 agonist with proven CVD benefit if eGFR less than adequate

If HbA_{1c} above target

- Avoid TZD in the setting of heart failure
- Consider adding the other class with proven CVD benefit
- DPP-4 inhibitor (not saxagliptin) if not on GLP-1 agonist
- Basal insulin, SU

Davies MJ et al. *Diabetes Care*. [published online October 5, 2018].

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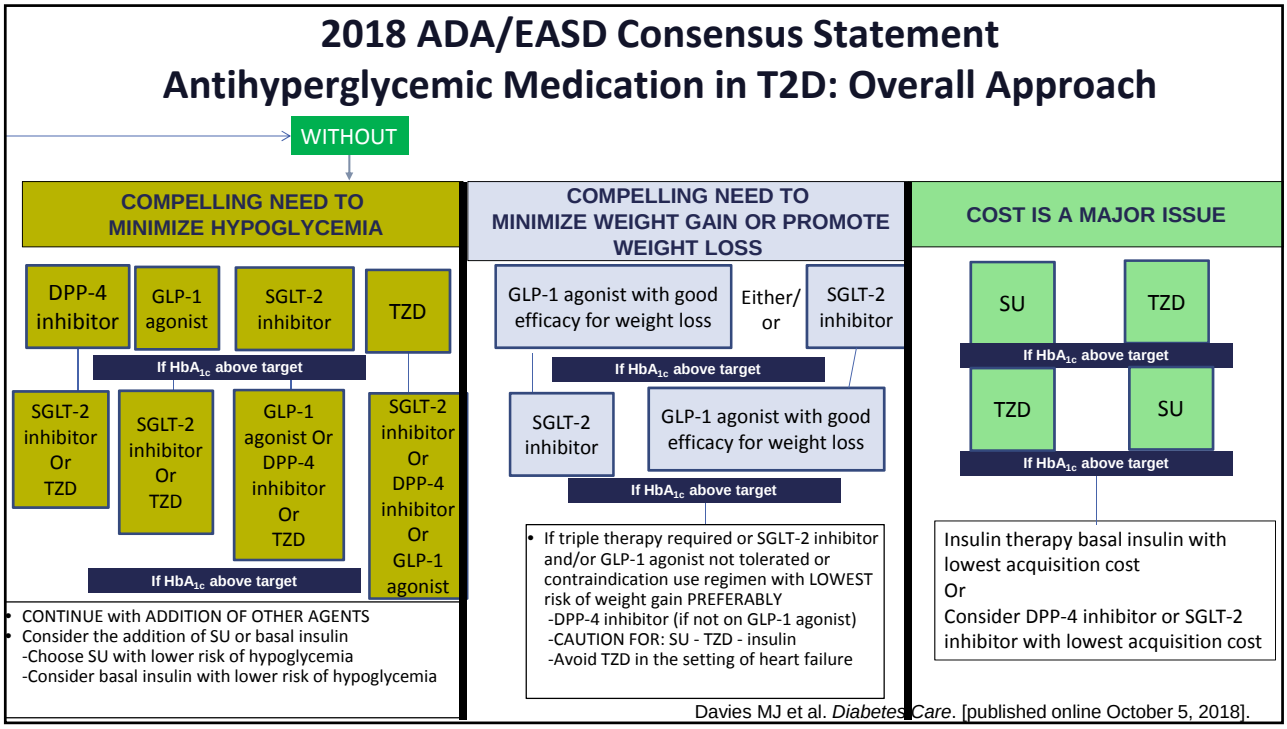

Davies MJ et al. *Diabetes Care*. [published online October 5, 2018].

Case 1: Question 4

What is THE BEST way for JW to limit clinical inertia?

a. Tell him to watch his diet
b. Call the 1-800 number if issues
c. Start metformin/SGLT-2 inhibitor combination
d. Exercise 150 minutes a week

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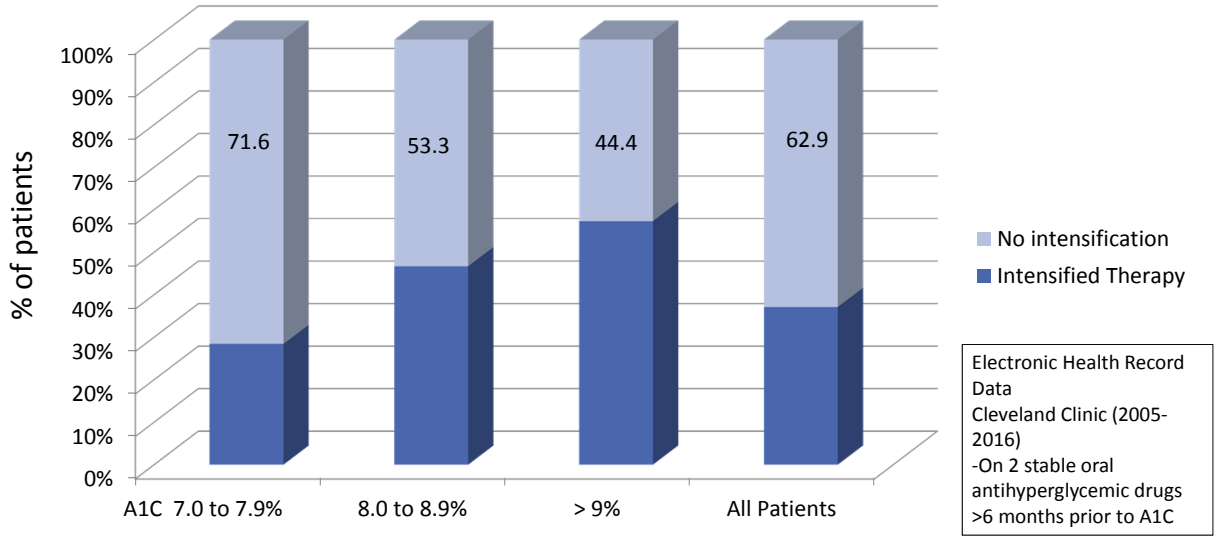
Clinical Inertia in Treating T2DM Real-World Data



Pantalone KM et al. *Diabetes Care.* 2018; 41:e113-4.

Evidence for Interventions that Help Overcome Clinical Inertia and Improve Quality of Care

Ranking of Quality Improvement Strategies for Lowering A1C			
Rank	**Intervention**	**Number of Trials**	**Mean Difference in A1C (95% CI)**
1	Promotion of self-management	60	-0.57 (-0.83 to -0.31)
2	Team changes	47	-0.57 (-0.71 to -0.42)
3	Case management	57	-0.50 (-0.65 to -0.36)
4	Patient education	52	-0.48 (-0.61 to -0.34)
5	Facilitated relay of clinical data	32	-0.46 (-0.60 to -0.33)
6	Electronic patient registry	27	-0.42 (-0.61 to -0.24)
7	Patient reminders	21	-0.39 (-0.65 to -0.12)
8	Audit and feedback	8	-0.26 (-0.44 to -0.08)
9	Clinician education	15	-0.19 (-0.35 to -0.03)
10	Clinician reminders	18	-0.16 (-0.31 to -0.02)
ALL		**120**	**-0.37 (-0.45 to -0.28)**

Ackroyd SA, Wexler DJ. *Curr Diab Rep*. 2014; 14:471. Tricco AC et al. *Lancet*. 2012; 379:2252-61.

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Major Organizational Recommendations for Combination Drug Therapy

(In Addition to Lifestyle Modification)

American Diabetes Association

Combination therapy if:

- **A1C ≥9.0%**
  - Recommend: Dual therapy
- **A1C ≥10%, blood glucose ≥300 mg/dL, or patient is symptomatic**
  - Recommend combination injectable therapy

AACE/ACE

Combination therapy if:

- **A1C ≥7.5%**
  - Recommend dual therapy
- **A1C >9.0% No Symptoms**
  - Recommend: Dual or Triple Therapy
- **A1C >9.0% + Symptomatic**
  - Recommend: insulin (± other drugs)

American Diabetes Association. *Diabetes Care*. 2018; 41(Suppl 1):S73-85. Garber AJ et al. *Endocr Pract*. 2018; 24:91-120.

Factors to Consider in Choosing Early Combination Drug Therapy over Monotherapy

- Is it pathophysiologically sound? Complementary mechanisms of action
- Would patient be unlikely to get to glycemic goal with monotherapy?
- Would combination therapy slow the deterioration of glycemic control?
- Does combination therapy allow assessment response for each component?
  - Can each component of the combination be adjusted?
- Are the costs appropriate?
  - Is there a cost advantage to the patient?
- Is the risk-to-benefit ratio acceptable?
  -Would the risk of a negative outcome be increased?
- Would combination therapy improve unmet clinical needs, such as weight issues, problems with hypoglycemia, CVD risk, and renal outcomes?
- Would adherence/compliance suffer?

Cahn A et al. *Diabetes Care.* 2016; 32(Suppl 2):S137-S145.

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Overcoming Clinical Inertia: JW

1. **Important to ask JW about his questions and concerns**
   - Family life?- who cooks, opportunities for physical activity
   - Work life?- how it affects his diabetes
   - Concerns? - side effects, cost, marital relations, his children, long-term complications, etc.
2. **Refer for interprofessional team-based diabetes self management education/support**
3. **Consider dual antidiabetes drug therapy from the beginning**
   - Risk-to-benefit ratio appears to be positive if effects of medications on lifestyle can be minimized
   - Choose combination therapy that has:
     - Low risk of hypoglycemia
     - Weight neutral or weight loss
     - May help with blood pressure

Common Combinations with Metformin: Individualization of Therapy

	Efficacy	Hypoglycemia risk	Weight	Renal outcome	Other compelling reasons
Metformin	High	No	Decrease	Neutral	Low Cost
SGLT-2 inhibitor	Intermediate	No	Decrease	Improve#	CHF, CAD Wt, SBP
GLP-1 agonist	High	No	Decrease	Improve*	CAD*, Wt, SBP if elevated
DPP-4 inhibitor	Intermediate	No	Neutral	Neutral	Well tolerated
TZD	High	No	Increase	Neutral	Insulin Sensitizer, beta cell +
SU	High	Yes	Increase	Neutral	Cost
Insulin	Highest	Highest	Increase	Neutral	If symptoms of hyperglycemia

*Liraglutide, semaglutide #Empagliflozin, canagliflozin

American Diabetes Association. *Diabetes Care*. 2018; 41(Suppl 1):S73-S85.

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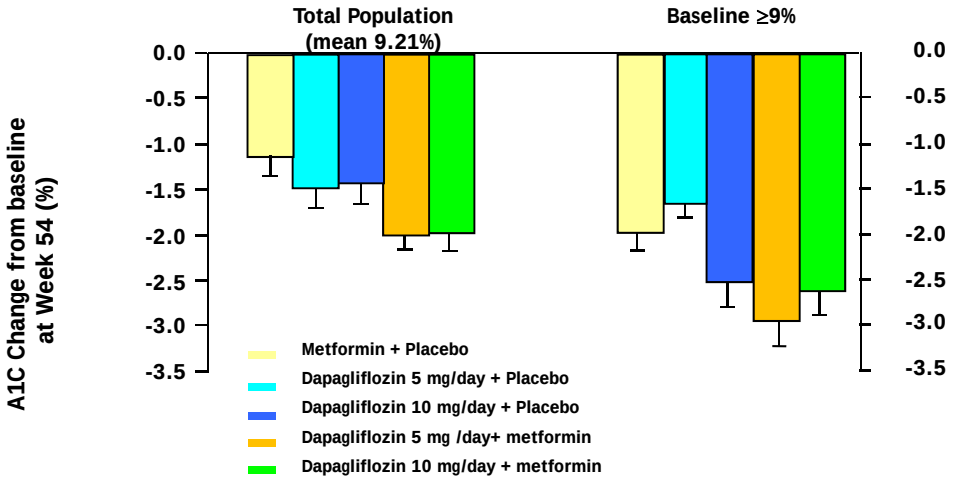
Initial Combination Therapy with Dapagliflozin and Metformin: A1C Change From Baseline at Week 24



*Mean change ± SE. All medications given orally.
Henry RR et al. *Int J Clin Pract*. 2012; 66:445-456.

Case 1: JW

- JW comes back to see you after 6 months. He saw his PCP about 3 months ago. He had gastrointestinal upset each time he tried to increase the dose of immediate release metformin past 1000 mg daily and had an A1C of 7.5%.
- His PCP started metformin XR 500 mg/canagliflozin 150 mg twice a day
- HTN is controlled (129/76 mm Hg) on lisinopril 40 mg orally once a day and canagliflozin, but his eGFR was pending at his PCP visit and is now noted to be 49 mL/min/1.73m^2
- Microalbuminuria (spot random 130 mg/g) is noted on his urine spot random microalbumin screen
- His A1C is now 6.7%

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Case 1: Question 5

How should we modify JW's treatment plan?

a. Decrease lisinopril to 20 mg daily
b. Stop canagliflozin, start basal insulin
c. Stop metformin
d. Decrease canagliflozin to 100 mg daily

Type 2 DM Medications: Compelling Indications

	Metformin	Sulfonylurea	SGLT-2 inhibitors	GLP-1 agonists	TZD Pioglitazone	DPP-4 inhibitors
Primary Compelling Indications						
CAD, stroke, and death	↓	↔	↓↓#	↓↓*	↓	↔
CHF	↔	↔	↓↓	↔	↑	↑ (saxagliptin, alogliptin)
Cardiac stent restenosis	↔	↔	↔	↔	↓	↔
Renal protection	↔	↔	↑↑#	↑↑*	↔	↔
Secondary Indications						
Weight	↓	↑	↓↓	↓↓	↑↑	↔
BP change	↔	↔	↓↓	↓	↓	↔
Cost	Low	Low	High	High	Moderate	High

2' prevention: *Liraglutide, semaglutide #Empagliflozin, canagliflozin

Garber AJ et al. *Endocr Pract*. 2018; 24:91-120.

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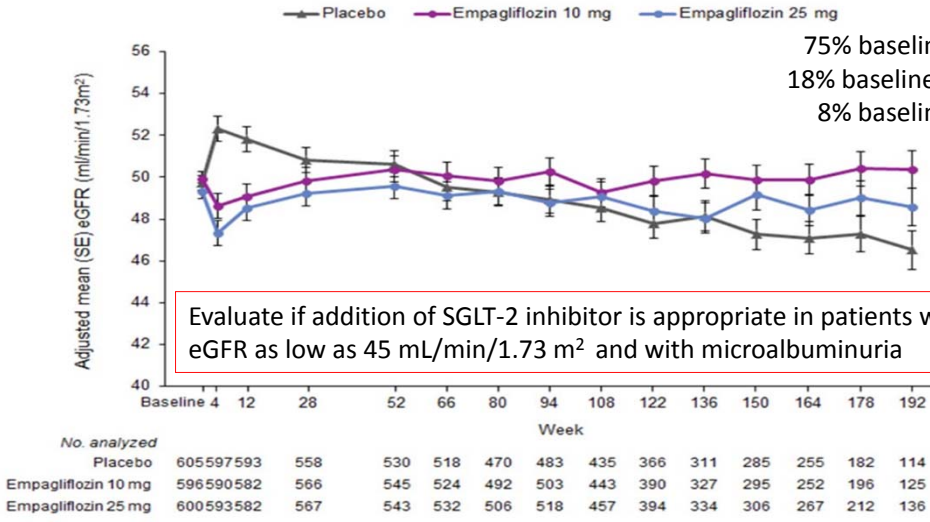
Renal Outcomes with Empagliflozin over 3.2 Years

	HR (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 mL/min	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 mL/min, 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

*Compared with placebo in patients with normal albuminuria at baseline.

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

EMPA-REG: Baseline eGFR < 60 mL/min/1.73 m^2



75% baseline eGFR > 60 mL/min
18% baseline eGFR 45-59 mL/min
8% baseline eGFR < 45 mL/min
81% on ACEI or ARB

Evaluate if addition of SGLT-2 inhibitor is appropriate in patients with eGFR as low as 45 mL/min/1.73 m^2 and with microalbuminuria

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

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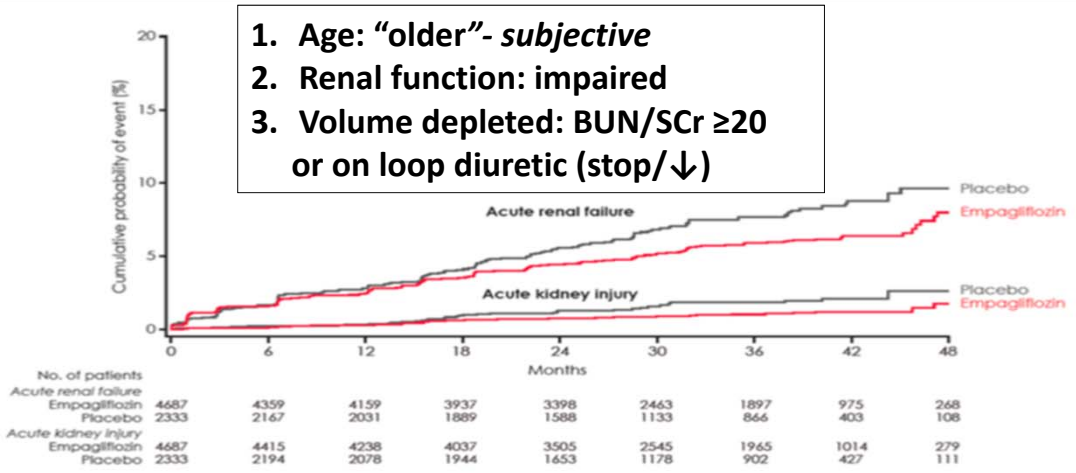
EMPA-REG: Acute Renal Injury/Failure

Risk factors for acute renal injury or failure

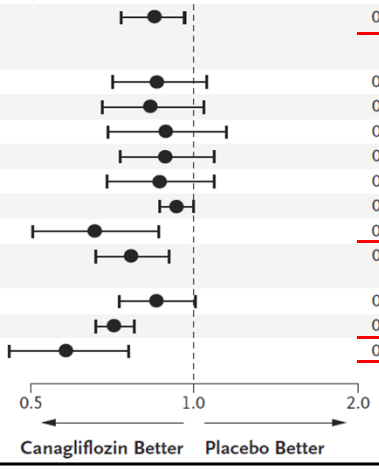
1. **Age: "older"- *subjective***
2. **Renal function: impaired**
3. **Volume depleted: BUN/SCr ≥20 or on loop diuretic (stop/↓)**



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

CANVAS: Effects of Canagliflozin

Outcome	Canagliflozin (N=5795)	Placebo (N=4347)	Hazard Ratio (95% CI)
	no. of participants per 1000 patient-yr		
Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke	26.9	31.5	0.86 (0.75–0.97)
Death from cardiovascular causes	11.6	12.8	0.87 (0.72–1.06)
Nonfatal myocardial infarction	9.7	11.6	0.85 (0.69–1.05)
Nonfatal stroke	7.1	8.4	0.90 (0.71–1.15)
Fatal or nonfatal myocardial infarction	11.2	12.6	0.89 (0.73–1.09)
Fatal or nonfatal stroke	7.9	9.6	0.87 (0.69–1.09)
Hospitalization for any cause	118.7	131.1	0.94 (0.88–1.00)
Hospitalization for heart failure	5.5	8.7	0.67 (0.52–0.87)
Death from cardiovascular causes or hospitalization for heart failure	16.3	20.8	0.78 (0.67–0.91)
Death from any cause	17.3	19.5	0.87 (0.74–1.01)
Progression of albuminuria	89.4	128.7	0.73 (0.67–0.79)
40% reduction in eGFR, renal-replacement therapy, or renal death	5.5	9.0	0.60 (0.47–0.77)



Neal B et al. *N Engl J Med*. 2017; 377:644-57.

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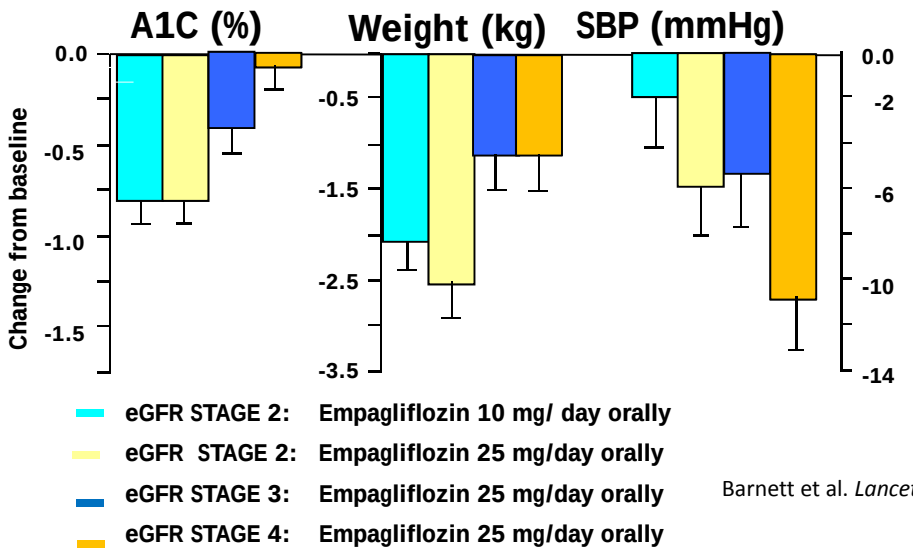
LEADER Trial: Renal Outcomes* with Liraglutide

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]

*This slide depicts urinary albumin to creatinine ratio from baseline to 3 years data for liraglutide vs.placebo
MDRD=Modification of Diet in Renal Disease

Mann J et al. *N Engl J Med.* 2017; 377:839-48.
Marso S et al. *N Engl J Med*. 2016; 375:311-22.

Empagliflozin in Renal Insufficiency 52 week data



Baseline A1C:
~8.0%

Barnett et al. *Lancet Diabetes Endocrinol.* 2014; 2:369-85.

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Diabetes Medications and Comorbidities in JW

1. **Treatment of T2DM**
   - Metformin- consider reduction of dose if eGFR <45mL/min/1.73m^2
     - May continue to use until eGFR is 30 mL/min/1.73m^2
   - GLP-1 agonist- may help with nephropathy
     - Efficacy should not be significantly effected by eGFR
     - Recommended to choose a longer-acting GLP-1 agonist (daily or weekly)
   - SGLT-2 inhibitor- may help with nephropathy
     - Glycemic efficacy diminishes as eGFR is reduced
     - A1C reduction may be close but not guaranteed to get to goal
2. **Treatment of Nephropathy/HTN**
   - Optimize ACE inhibitor or angiotensin receptor blocker (ARB) for BP control and renal protection (already on lisinopril)
   - Control HTN now (controlled)

Case 1: JW Summary

- Glycemic control IS IMPORTANT, but consider antidiabetic medications that not only address glycemic control but also comorbidities when possible
- Compelling indications with diabetes medication: - CVD, CHF, renal disease, and secondarily for weight, blood pressure, and cost
- Always remember to consider patient related issues- patient centered care can help to improve outcomes (You don't know until you ask)

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Case 2: MT

- MT is a 58-year-old Hispanic female
- T2DM x 11 years with dyslipidemia, HTN, albuminuria, non-painful peripheral neuropathy, obesity, non-alcoholic fatty liver disease (NAFLD), history of myocardial infarction (MI) 3 years ago
- Current medications:
  - Metformin 1000 mg orally twice a day
  - Glipizide 10 mg orally once daily
  - Pioglitazone 30 mg orally once daily
  - Lisinopril 20 mg orally once daily
  - Metoprolol XL 25 mg orally once daily
  - Atorvastatin 80 mg orally once daily
  - Aspirin 81 mg orally once daily

Case 2: Question 1

In this patient with established ASCVD, what should we consider beyond initial metformin therapy?

a. TZD

b. DPP-4 inhibitor

c. GLP-1 agonist (liraglutide, semaglutide, abiglutide) or SGLT-2 inhibitor (canagliflozin, empagliflozin, dapagliflozin)

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Case 2: MT

- **Physical exam**
  - Nonproliferative retinopathy, normal heart and lung sounds, obese, decreased vibratory and filament sensation in otherwise healthy appearing feet
- **Concerns**
  - Many blood sugars in 200-300s mg/dL , but occasional less than 70 mg/dL
  - Fatigue
  - Difficulty losing weight
  - Urinary frequency
- **Labs**
  - A1C 10.2%
  - Lipids in target range (on high statin dose), serum creatinine 0.9 mg/dL, GFR 54, hepatic function revealing minor transaminase elevation, urine albumin 110 mg/24 hr (normal <30)

What next?

Case 2: MT

- Recall current standards of care recommend a SGLT-2 inhibitor (empagliflozin, canagliflozin, dapagliflozin) or a GLP-1 agonist (liraglutide, semaglutide, abiglutide) in the patient with established cardiovascular disease
- One of patient's main complaints is difficulty losing weight, both of these drug classes are weight-neutral or may promote weight loss
- Basal insulin could also be considered here- A1C greater than 10% with symptoms

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Case 2: MT

- **Could do any of the following in the patient with established CVD**
  - Add liraglutide, semaglutide, or abiglutide (drug class: GLP-1 agonist)
  - Add empagliflozin, canagliflozin, or dapagliflozin (drug class: SGLT-2 inhibitor)
  - Using both GLP-1 agonist or SGLT-2 inhibitor for maximal weight loss
- **Would definitely**
  - Continue metformin (renal function is OK)
  - Refer to diabetes educator and dietician for interprofessional team care
  - Review physical activity level/exercise prescription
  - Stop glipizide
  - Stop pioglitazone

Case 2: MT

- What if A1C was not at target in 3 months?
  - If not on insulin yet, would definitely consider
- Advance therapy, avoid clinical inertia
- Remember appropriate interprofessional team-based diabetes self management education and support

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Case 3: GM

- GM is a 64-year-old white male
- Diagnosed with T2DM after 2 fasting blood sugars of 154 mg/dL and 142 mg/dL, respectively, and A1C of 6.8%
- Saw diabetes educator and dietician at diagnosis
- Preexisting conditions
  - HTN (on lisinopril 10 mg orally once daily)
  - Dyslipidemia (on atorvastatin 40 mg orally once daily)
  - No history of ASCVD
- Aspirin 81 mg orally daily (over 50 years-old + diabetes)

Case 3: GM

- Physical Exam
  - BP 132/78 mm Hg, pulse 80 bpm
  - Fundi normal
  - Obese, BMI 34 kg/m^2
  - Feet healthy appearing other than benign calluses
- Lipids in target range (measure of compliance), hepatic and renal chemistries all normal

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Case 3: GM

- Current diabetes medications:
  - Metformin 1000 mg orally twice a day
  - Glimepiride 4 mg orally once daily
  - Basal insulin 40 units subcutaneously daily
- Current glycemic measures
  - A1C 8.2%
  - FPG values 110-120s
  - 2-hour PPG 220-250s
- What next?

Case 3: Question 1

What would be an appropriate choice for this patient?

a. Adding a GLP-1 agonist
b. Increased dose of basal insulin
c. Increased dose of metformin
d. Increased dose of sulfonyurea

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Case 3: GM

- Add GLP-1 agonist
- Or switch to combination GLP-1 agonist + basal insulin
  - liraglutide + insulin degludec or lixisenatide + insulin glargine

Case 3: GM

- Options
  - Add rapid-acting insulin to largest meal of the day

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My Preferred Choices

- Basal insulin + GLP-1 agonist over basal + mealtime insulin
  - Studies show as good or almost as good for glycemic control, may have weight loss
- Don't split basal insulin into two doses
- If administering 2 injections a day, basal insulin + GLP-1 agonist is better (some are available as combinations)
- Remember CVD benefit of liraglutide, semaglutide, and abiglutide

Yamamoto S et al. *Diabetes Res Clin Pract*. 2018; 140:339-46. Nuffer W et al. *Ther Adv Endocrinol Metab*. 2018; 9: 69–79. Billings LK et al. *Diabetes Care*. 2018; 41:1009-16. Porcellati F et al. *Diabetes Metab*. 2015; 41(6 Suppl 1):6S16-6S20.

Case 3: GM

- Patient should see the Diabetes Educator (again) and Dietician for regimen change/instruction and lifestyle evaluation
- If not reaching targets, consider multiple daily injections of insulin per algorithm
- Could consider stopping glimepiride, the sulfonylurea may not be adding a lot of benefit, or could contribute to hypoglycemia
- Avoid clinical inertia by moving forward every 3 to 6 months

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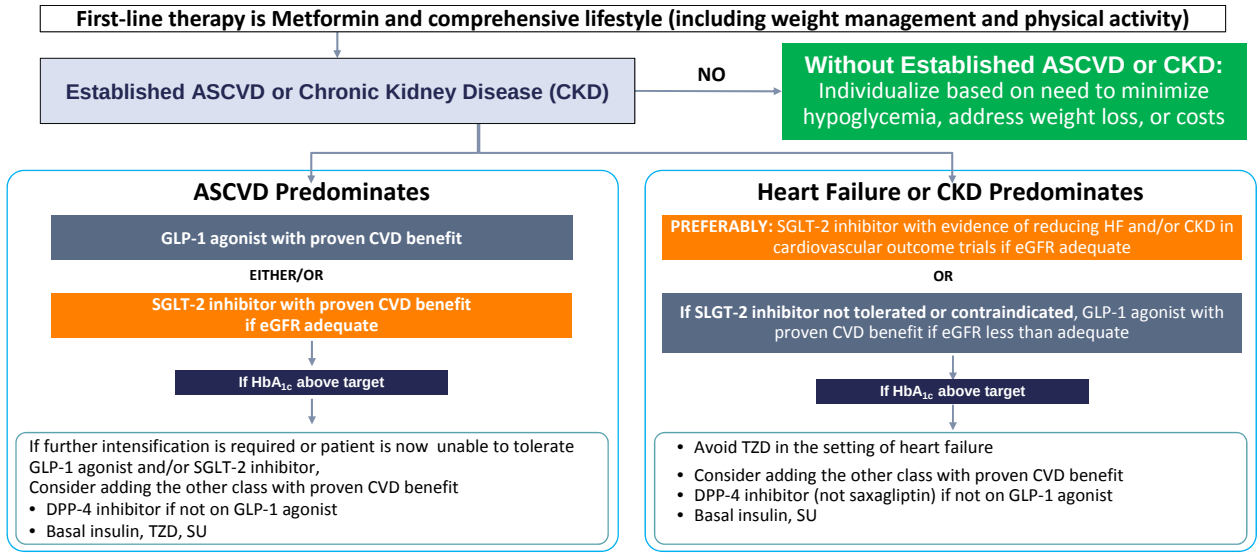
2018 ADA/EASD Consensus Statement Antihyperglycemic Medication in T2D: Overall Approach



Davies MJ et al. *Diabetes Care*. [published online October 5, 2018].

Key Takeaways

- T2DM treatment guidelines from authoritative groups vary because of different weighting of evidence
- A1C goals have not changed for the majority of T2DM patients (no greater than 7%)
- An understanding of the "profiles" for diabetes medications (i.e., efficacy, benefits, harms) facilitates optimization of drug therapy recommendations and outcomes in patients with T2DM
- Many patients benefit from interprofessional team-based care
- Clinical inertia in treating T2DM is common and has multiple possible causes
  - Individualize when significant comorbidity or short life expectancy foretell harm or a lack of benefit from intensive glycemic control
  - Lessening the time above goal via a proactive glycemic control approach may improve outcomes
  - Early combination therapy has been shown to increase the likelihood of achieving glycemic goals

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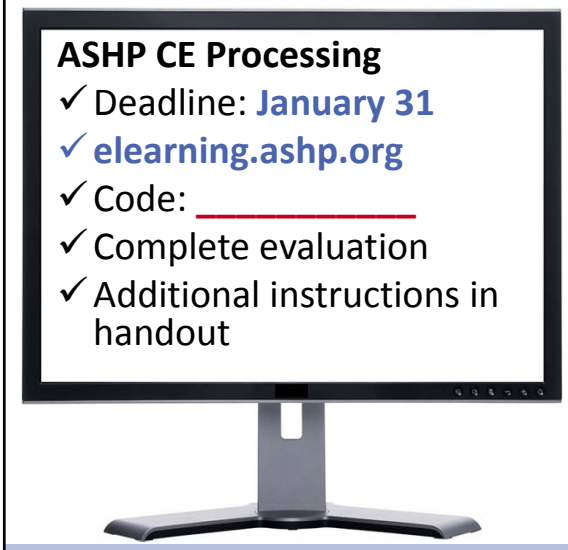
Consider these practice changes. Which will you make?

- Read the current diabetes guidelines.
- Compare the current guidelines to my institutional and personal protocols.
- Consider the role of stepwise and combination therapy.
- Discuss with colleagues the importance of avoiding clinical inertia.
- Look for opportunities to collaborate with your interprofessional colleagues to overcome clinical inertia.
- Consider patient factors in individualizing treatment plans.

Thank You for Joining Us



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About the Faculty

Curtis L. Triplitt, Pharm.D., CDE,
Activity Chair

Clinical Associate Professor
Medicine/Diabetes
University of Texas Health Science Center at San Antonio

Associate Director
Diabetes Research Unit
Texas Diabetes Institute, University Health System
San Antonio, Texas

Curtis L. Triplitt, Pharm.D., CDE, is Clinical Associate Professor of Medicine, Division of Diabetes and Clinical Assistant Professor of Pharmacy at the University of Texas Health Science Center at San Antonio. Dr. Triplitt practices at the Texas Diabetes Institute, where he manages patients with an endocrinologist and is involved with diabetes and metabolism research.

Dr. Triplitt received his doctor of pharmacy from the University of Texas Health Science Center at San Antonio and the University of Texas at Austin. He completed an ASHP-accredited primary-care residency at the William S. Middleton Memorial Veterans Hospital in Madison, Wisconsin.

Dr. Triplitt is Vice-Chair of the Texas Diabetes Council, Texas Department of State Health Services. He is a current Associate Editor and future Editor-in-Chief of *Diabetes Spectrum.* Dr. Triplitt has served as an investigator on multiple clinical trials focusing on the effects of medications on insulin sensitivity in overweight and obese subjects with hypertension and type 2 diabetes, as well as many type 2 diabetes medication trials and has published over 50 peer-reviewed articles and 8 book chapters on diabetes. In 2008 he was honored as Pharmacy Preceptor of the Year for the University of Texas. He lectures at both the national and statewide levels concerning diabetes and has been involved with the development of multiple clinical treatment algorithms for the prevention and treatment of diabetes in the State of Texas.

Eric L. Johnson, M.D.

Associate Professor, Department of Family and Community Medicine
University of North Dakota School of Medicine and Health Sciences

Assistant Medical Director
Altru Diabetes Center
Altru Health System
Grand Forks, North Dakota

Eric L. Johnson, M.D., is Associate Professor in the Department of Family and Community Medicine and Director of Interprofessional Education at the University of North Dakota School of Medicine and Health Sciences in Grand Forks, N.D. He also serves as Assistant Medical Director at Altru Diabetes Center, also in Grand Forks.

A graduate of University of Nebraska Medical Center, Dr. Johnson completed his residency at the University of North Dakota Family Practice Program in Fargo and is Board Certified in Family Medicine. His clinical areas of expertise are outpatient management of diabetes, long-term care, and tobacco cessation/control. His research interests include tobacco cessation, fatty liver disease, and celiac disease in diabetes. He has served as the principal investigator for several clinical trials through Altru Health System.

Dr. Johnson is a member of the American Diabetes Association (ADA) Primary Care Advisory Group. He also is President of the American Diabetes Association – North Dakota and President of Tobacco Free North Dakota.

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