Together 2 Goal.

AMGA Foundation National Diabetes Campaign



Monthly Campaign Webinar June 18, 2020

Today's Webinar



- Together 2 Goal® Updates
 - Webinar Reminders
 - Project ECHO Webinar
 - ADA COVID-19 Resources
- Cardiovascular Benefit of New Diabetes Medications
 - Gretchen Shull, M.D. of Mercy



- Q&A
 - Use Q&A or chat feature

Webinar Reminders



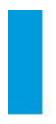
- Webinar will be recorded today and available the week of June 22nd
 - www.Together2Goal.org
- Participants are encouraged to ask questions using the "Chat" and "Q&A" functions on the right side of your screen



Project ECHO Webinar



- Topic: Identifying High-Risk Diabetes Patients for COVID-19 Triage
- Date/Time: June 24, 2020 from 12:00 1:15 pm EST
- Presenter: John Kennedy, M.D.



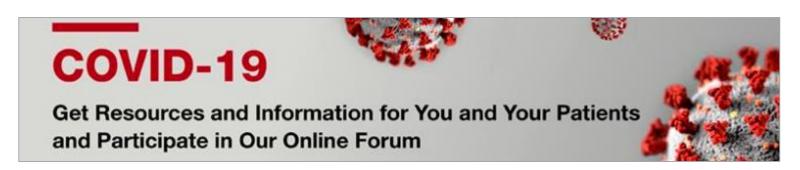




American Diabetes Association COVID-19 Resources



- ADA COVID-19 Webinar Series
- Live Virtual Events*
- COVID-19 and Diabetes Discussion Forum*
- Special Podcast Series: COVID-19 & Diabetes



https://professional.diabetes.org/content-page/covid-19

^{*}ADA membership may be required to gain full access to certain live events and/or discussion boards

Today's Featured Presenter



Gretchen Shull, M.D.



Physician Lead
Endocrinology Specialty Council
Vice President of Diabetes Care
Mercy Clinic Endocrinology - Joplin



Diabetes Treatment

Cardiovascular Considerations

Dr. Gretchen Shull, MD vice president of diabetes care Mercy

18 June 2020



No disclosures



Objectives:

- Recognize CVD as closely connected to DM2
- Revisit the evolution of treating DM2 and CVD
- Highlight current guidelines and medications
- Think about strategies to use current/relevant medications





The Growing Facts

- > 12% of the population has DM
- 9.5% of that is DM type 2
- Treatment and science of DM is constantly changing
 - 1 endocrinologist per 5200 patients
 - ½ my personal practice = DM per monthly referrals
 - Cannot simply refer
- 14 + different drug classes approved for glucose control



DM type 2 and CVD

- CVD = #1 cause of morbidity and mortality
- Complications attributed to CVD = costs
- Increase financial and physical burdens on patients and caregivers.



Intensive vs Less Intensive Rx

UKPDS (2000)

- Reduced microvascular complications
- No difference in CV mortality/ MACE

VADT (2009)

 No diff in CV mortality if A1c ≤ 6.5% but fewer CV events

ADVANCE (2008)

- Reduced microvascular risks
- No diff in CV mortality if A1c ≤ 6.5%

ACCORD (2008)

- Stat. sig ↑ in CV mortality and all cause mortality if A1c < 6%
- No sig reduction in events



2006-2009 - Conclusions

- Individualized glycemic goals are the answer
- Intense glycemic control is not enough to improve CV outcomes
- Statin > glucose medications
- 2008 CV outcomes trials (CVOTs) were mandated by FDA
 - These are conducted to rule out an unacceptable increase in CV risk for a new treatment
 - Event driven with MACE as a primary endpoint
 - DPP-4 inhibitors
 - GLP-1 agonists
 - SGLT-2 inhibitors



Cardiology vs. Diabetes CVOTs

CARDIOLOGY CVOTS



Aim: Demonstrate CV benefit

Initiation of treatment vs. active comparator



No treatment adjustment

Difference between treatment arms



Significant reduction in CV outcomes vs. active comparator

Lower CV risk vs. placebo/active comparator

DIABETES CVOTS

Aim: Demonstrate CV safety

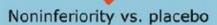
Initiation of blinded treatment/placebo

Maintain similar HbA1c levels in treatment arms



Treatment adjustment

Small/no difference in HbA1c observed between treatment arms



No unacceptable increase in CV risk vs. placebo as part of standard care



Cardiovascular Outcomes Trials

Efficacy vs. safety; superiority vs. noninferiority

EFFICACY TRIALS

Aim: Demonstrate CV benefit

Initiation of treatment vs. comparator



Difference between treatment arms (e.g., biomarkers such as HbA1c or lipids)

Significant reduction in CV outcomes vs. active comparator

Lower CV risk vs. placebo/active comparator

SAFETY TRIALS

Aim: Demonstrate CV safety

Initiation of blinded treatment/placebo

Maintain similar HbA1c levels in treatment arms



Treatment adjustment (standard of care)

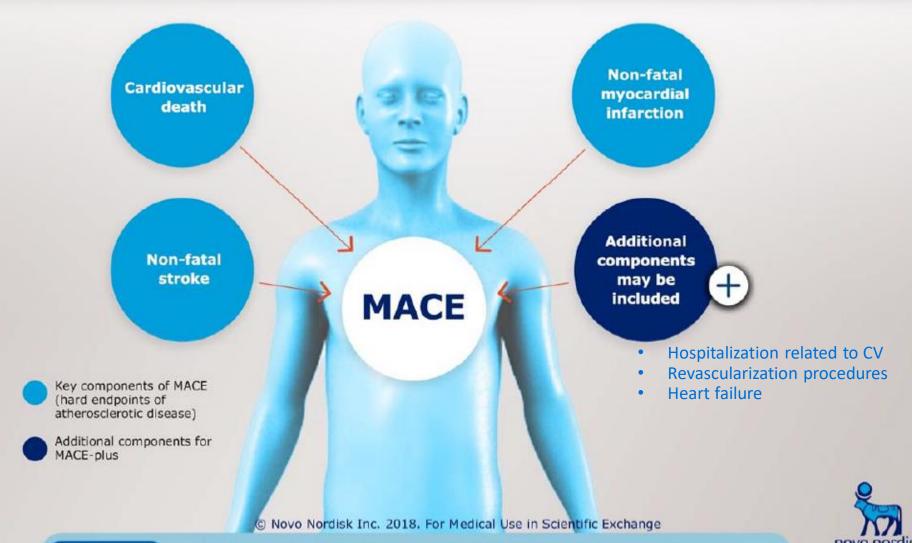
Small/no difference in biomarkers (e.g., HbA1c observed between treatment arms)

Noninferiority vs. placebo

No unacceptable increase in CV risk vs. placebo as part of standard care



Cardiovascular Outcomes: Major Adverse Cardiovascular Events (MACEs*)



Evidence – Multifactorial Interventions

Target

- Hyperglycemia
- Hypertension
- Dyslipidemia
- Obesity

Order

- Lifestyle modification
- Medications
 - A1c
 - BP
 - LDL
 - Weight
 - No harm



Look AHEAD Trial

- \geq 7% weight reduction = + impact on all CV risks
- ≥ 10% weight reduction = 21% decline in CV events



Hypoglycemia

- ACCORD & VADT
 - Severe hypoglycemia may increase risk of CVD events
 - If DM type 2 and CVD, may increase risk of death if have severe hypoglycemia
- Other studies
 - DM type 2 with CVD
 - More hypoglycemia = more arrhythmias

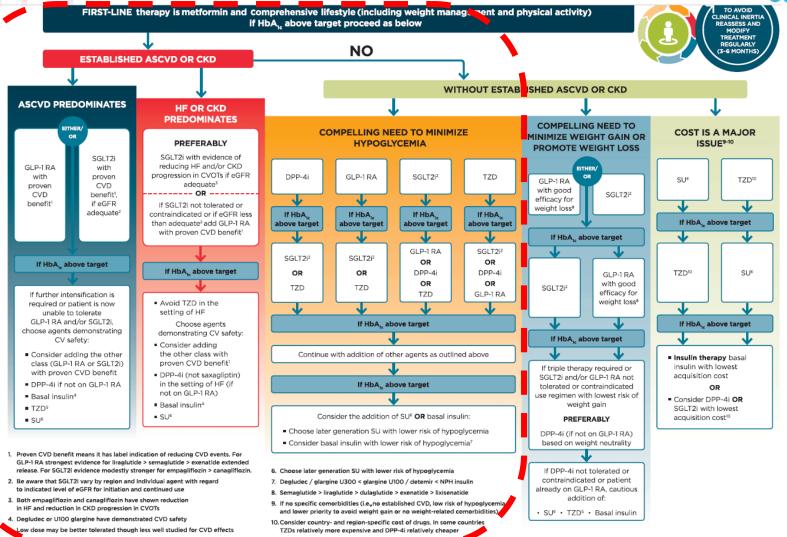


Beyond Glycemic Effects

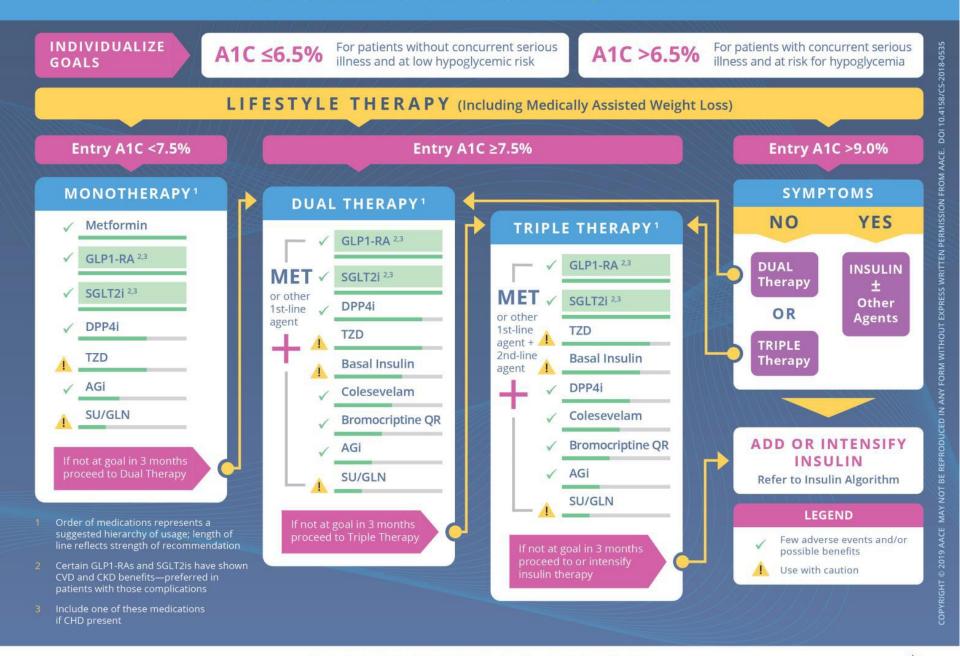
- Lifestyle management as foundation
- Newer Agents
 - Low risk of hypoglycemia
 - Neutral / beneficial effect on weight

SGLT-2 GLP-1 inhibitor agonist Weight Weight reduction reduction **Decreased BP Decreased BP** Some increase Reduction in in LDL; total; LDL and TG **HDL**

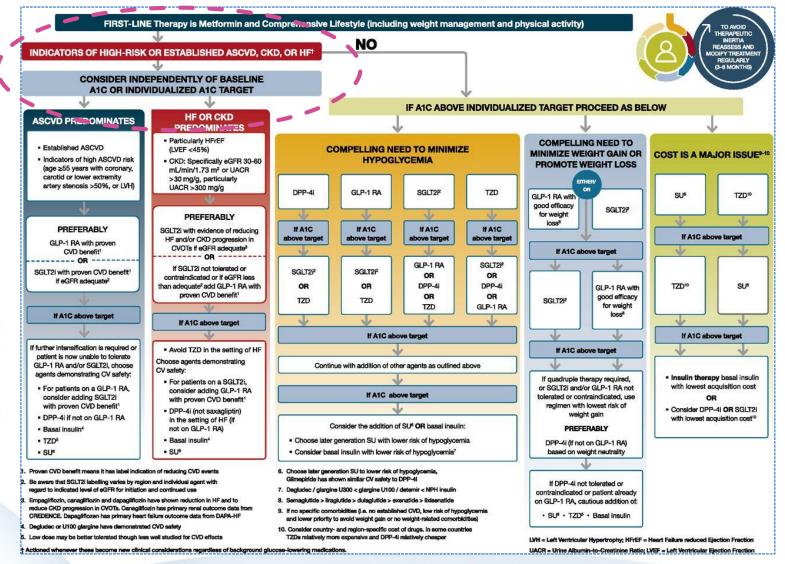




GLYCEMIC CONTROL ALGORITHM







S

GLYCEMIC CONTROL ALGORITHM

INDIVIDUALIZE For patients without concurrent serious For patients with concurrent serious A1C ≤6.5% A1C >6.5% illness and at low hypoglycemic risk illness and at risk for hypoglycemia GOALS LIFESTYLE THERAPY AND ONGOING GLUCOSE MONITORING (CGM preferred) INDEPENDENT OF GLYCEMIC CONTROL, IF ESTABLISHED OR HIGH ASCVD RISK AND/OR CKD, RECOMMEND SGLT2I AND/OR LA GLP1-RA Entry A1C >9.0% Entry A1C ≥7.5% - 9.0% TRIPLE THERAPY SYMPTOMS **DUAL THERAPY** YES NO GLP1-RA ✓ GLP1-RA Entry A1C <7.5% Independent of DUAL INSULIN SGLT2 glycemic MONOTHERAPY 13 Therapy я. MONTHS² control, if MONTHS² DPP4i ✓ Metformin established Other OR Agents ✓ GLP1-RA ASCVD or high SU/GLN risk, CKD 3, or TRIPLE SGLT2i Basal Insulin HFrEF, start LA SU/GLN Therapy DPP4i GLP1-RA or DPP4i Basal Insulin 3 m SGLT2i with TZD Colesevelam proven Colesevelam AGI efficacy* SU/GLN Bromocriptine OR Bromocriptine QR ADD OR INTENSIFY INSULIN AGI AGi Refer to Insulin Algorithm LEGEND or other agent Few adverse events and/or possible benefits 1 Order of medications represents a suggested hierarchy of usage; length of line reflects strength of recommendation 2 If not at goal in 3 months, proceed to next level therapy Use with caution *CKD 3: canagiffozin: HFrEP: dapagiffozin CKD 3 = stage 3 chronic kidney disease: HPEF = heart failure with reduced ejection fraction; LA = long-acting (>24 hour duration)

PROGRESSION OF

DISEASE

PROFILES OF ANTIHYPERGLYCEMIC MEDICATIONS

	MET	GLP1-RA	SGLT2i	DPP4i	AGi	TZD (moderate dose)	SU GLN	COLSVL	BCR-QR	INSULIN	PRAML
НҮРО	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate/ Severe Mild	Neutral	Neutral	Moderate to Severe	Neutral
WEIGHT	Slight Loss	Loss	Loss	Neutral	Neutral	Gain	Gain	Neutral	Neutral	Gain	Loss
	Contra- indicated if eGFR <30 mL/min/ 1.73 m²	Exenatide Not	Not Indicated for eGFR <45 mL/ min/1.73 m ²	Dose Adjustment Necessary (Except Linagliptin) Effective in Reducing Albuminuria	Neutral	Neutral	More Hypo Risk	Neutral	Neutral	More Hypo Risk	Neutral
RENAL / GU indicated if eGFR < mL/min/		Indicated CrCl <30	See #1 Genital Mycotic Infections								
		Potential Benefit of LA GLP1-RA	Potential CKD Benefit; See #1								
GI Sx	Moderate	Moderate	Neutral	Neutral	Moderate	Neutral	Neutral	Mild	Moderate	Neutral	Moderate
CHF	Neutral	Neutral	Prevent HF Hospitalization Manage HFrEF; See #2	See #4	Neutral	Moderate	Neutral	Neutral	Neutral	CHF Risk	
ASCVD		Potential Benefit of LA GLP1-RA	See #3			May Reduce Stroke Risk	Possible ASCVD Risk	Lowers LDL-C	Safe	Neutral	Neutral
BONE	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate Fracture Risk	Neutral	Neutral	Neutral	Neutral	Neutral
KETOACIDOSIS	Neutral	Neutral	DKA Can Occur in Various Stress Settings	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral



Use with caution

Likelihood of adverse effects

Canagliflozin indicated for eGFR ≥30 mL/min/1.73 m² in patients with CKD 3 + albuminuria.

^{2.} Dapagliflozin-potential primary prevention of HF hospitalization & demonstrated efficacy in HFrEF.

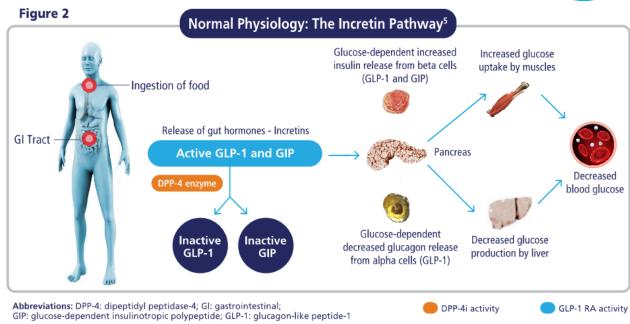
^{3.} Empagliflozin-FDA approved to reduce CV mortality. Canagliflozin-FDA approved to reduce MACE events.

^{4.} Possible increased hospitalizations for heart failure with alogliptin and saxagliptin.

TABLE 9.1 Drug-specific and patient factors to consider when selecting antihyperglycemic treatment in adults with type 2 diabetes

		Efficacy	cacy Hypoglycemia	la Weight	CV effects		Cost Oral	Oral/SQ	Renal	effects	Additional considerations
		100000000000000000000000000000000000000	INVESTMENTS.	change	ASCVD	HF	57707		Progression of DKD	Dosing/use considerations*	Applitorial considerations
Metformin	*	High	No	Neutral (potential for modest loss)	Potential benefit	Neutral	Low	Oral	Neutral	Contraindicated with eGFR <30 mL/min/1.73 m²	Gastrointestinal side effects common (diarrhea, nausea) Potential for B12 deficiency
SGLT-2 inh	ibitors	Intermediate	No	Loss	Benefit: empagliflozin†, canagliflozin	Benefit: empagliflozint, canagliflozin, dapagliflozint	High	Oral	Benefit: canagliflozins, empagliflozin,dapagliflozin	 Renal dose adjustment required (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin) 	FDA Black Box: Risk of amputation (canagliflozin) Risk of bone fractures (canagliflozin) DKA risk (all agents, rare in TZDM) Genitourinary infections Risk of volume depletion, hypotension TLDL cholesterol Risk of Fournier's gangrene
GLP-1 RAS		High	No	Loss	Neutral: lixisenatide Benefit: See label indication of reducing CVD events	Neutral	High.	SQ; oral (semaglutide)	Benefit: liragiutide	Renal dose adjustment required (exenatide, lixisenatide) Caution when initiating or increasing dose due to potential risk of acute kidney injury	FDA Black Box: Risk of thyroid C-cell tumors (liragiutide, albiglutide, dulagiutide, exenatide extended release) Gastrointestinal side effects common (nausea, vomiting, diarrhea) Injection site reactions Acute pancreatitis risk
DPP-4 inhi	lbitors	Intermediate	No	Neutral	Neutral	Potential risk: saxagliptin	High	Oral	Neutral	Renal dose adjustment required (sitagliptin, saxagliptin, alogliptin); can be used in renal impairment No dose adjustment required for linagliptin	Potential risk of acute pancreatitis Joint pain
Thiazolidir	nediones	High	No	Gain	Potential benefit: ploglitazone	Increased risk	Low	Oral	Neutral	No dose adjustment required Generally not recommended in renal impairment due to potential for fluid retention	FDA Black Box: Congestive heart failure [plog ltazone, rosiglitazone] Fluid retention (edema; heart failure) Benefit in NASH Risk of bone fractures Bladder cancer (plog ltazone) DLDLcholesterol (rosiglitazone)
Sulfonyluz (2nd gene		High	Yes	Gain	Neutral	Neutral	Low	Oral	Neutral	Glyburide: not recommended Glipizide and glimepiride: initiate conservatively to avoid hypoglycemia	FDA Special Warning on increased risk of cardiovascular mortality based on studies of an older sulfonylurea (tolbutamide)
Insulin	Human Insulin	Highest	Yes	Gain	Neutral	Neutral	Low	SQ; inhaled	Neutral	Lower insulin doses required with a decrease in eGFR; titrate	Injection site reactions Higher risk of hypoglycemia with human insulin (NPH or premised
	Analogs						High	SQ		per clinical response	formulations) vs. analogs





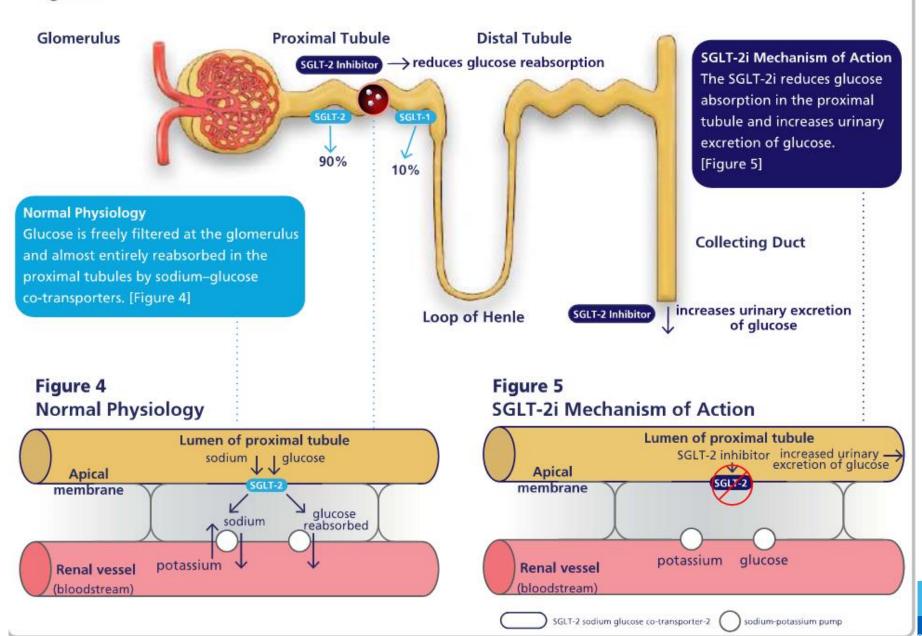
Glucagon-like peptide-1 (GLP-1) Receptor Agonists

In the presence of elevated blood glucose⁵:

- Activate GLP-1 receptors in the pancreas to increase insulin secretion
- Activate the GLP-1 receptors in the pancreas to reduce glucagon secretion, thereby reducing hepatic glucose output
- Delay gastric emptying

Pathway of Renal Glucose Reabsorption^{6,7}

Figure 3





Properties of anti-hyperglycemic agents

Class/therapies in class	Primary physiological actions	Advantages	Disadvantages/adverse e	ffects	Efficacy
Sulfonylureas Glibenclamide/ glyburide Glipizide Gliclazide* Glimepiride	• ↑ Insulin secretion	Extensive experience ↓ Microvascular risk (UKPD5) Inexpensive	Hypoglycemia † Weight Uncertain CV safety	Dose adjustment/avoidance for renal disease High rate of secondary failure	High
TZDs • Pioglitazone • Rosiglitazone [†]	• ↑ Insulin sensitivity	Low risk for hypoglycemia Durability ↑ HDL-C Triacylglycerols (pioglitazone) ASCVD events (pioglitazone: in a post-stroke insulin-resistant population and ac secondary end point in a high-risk-of-CVD diabetes population)	↑ Weight Edema/heart failure Bone loss ↑ Bone fracturec	• ↑ LDL-C (rosiglitazone) • ? Bladder cancer • ? Macular edema	High
Meglitinides (Glinides) • Repaglinide • Nateglinide	• † Insulin secretion	Postprandial glucose excursions Dosing flexibility Safe in advanced renal disease with cautious dosing (especially repaglinide) Lower cost	Hypoglycemia Weight Uncertain CV safety Frequent dosing schedule		Intermediate- high

^{*}Not licensed in the U.S. for T2D, Not licensed in Europe for T2D.

ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; CVD, cardiovascular disease; HDL-C, High-density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; UKPDS, United Kingdom Prospective Diabetes Study.

Modified from 2018 ADA EASD Type 2 Diabetes Guidelines. Diabetes Care. 2018 Oct 4. [Epub ahead of print] https://doi.org/10.2337/dci18-0033

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Incorporating into Practice



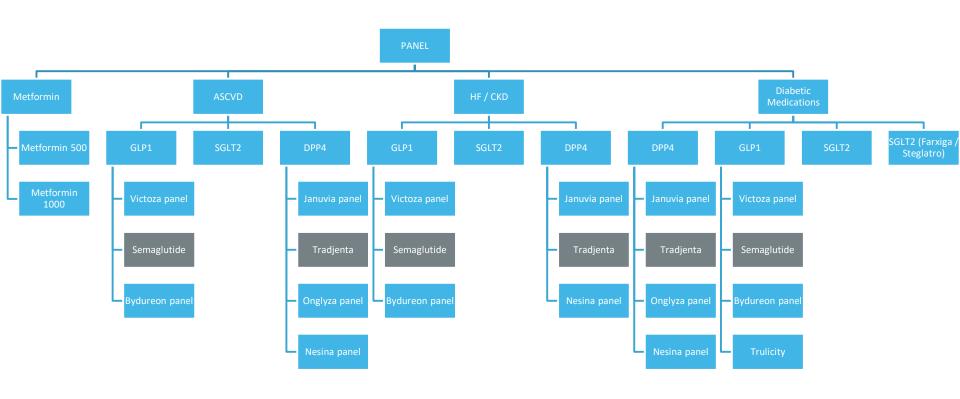


Decision-making tool

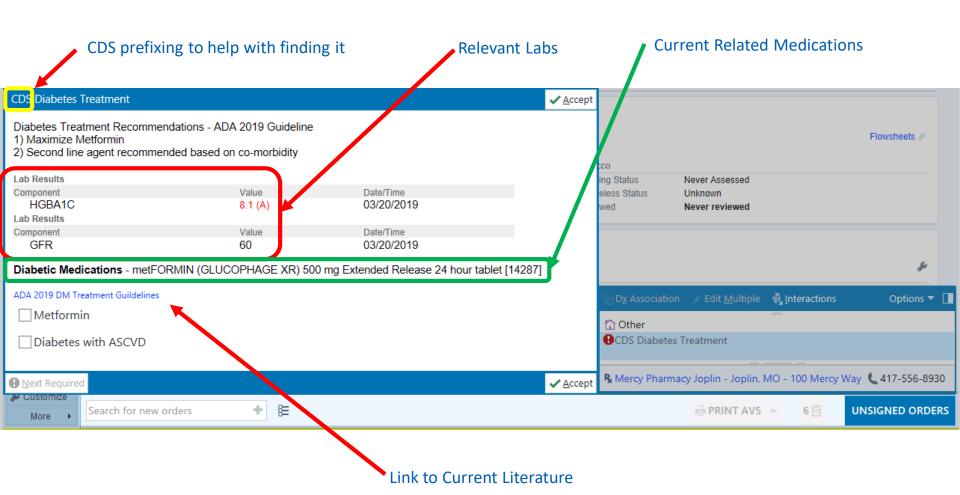
- Help clinicians stay current with latest recommendations in diabetic management
- Only display appropriate medications based on the unique parameters of each patient
- Reduce errors by pre-filtering based on GFR and common contraindications
- Reduce clicks by providing simplistic interface
- Phase 1



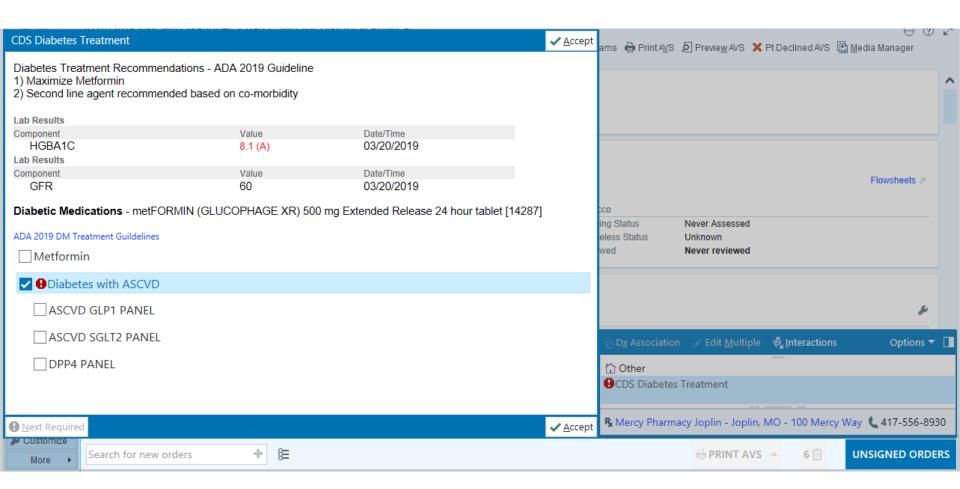
Panel Layout





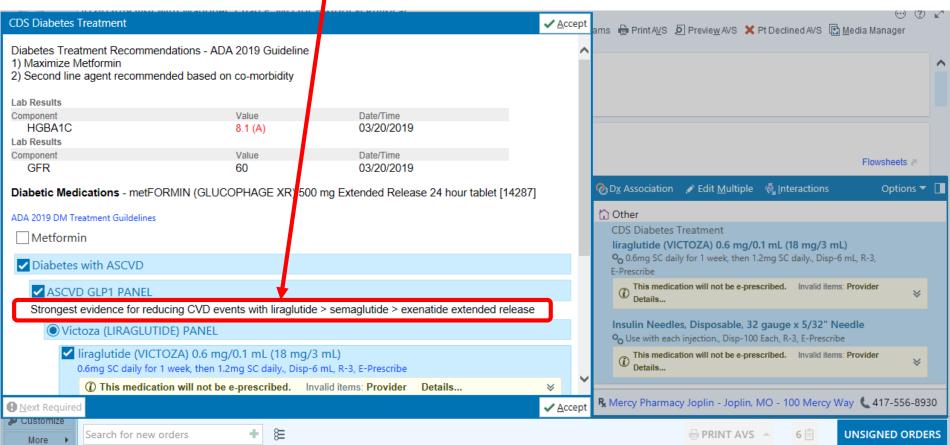




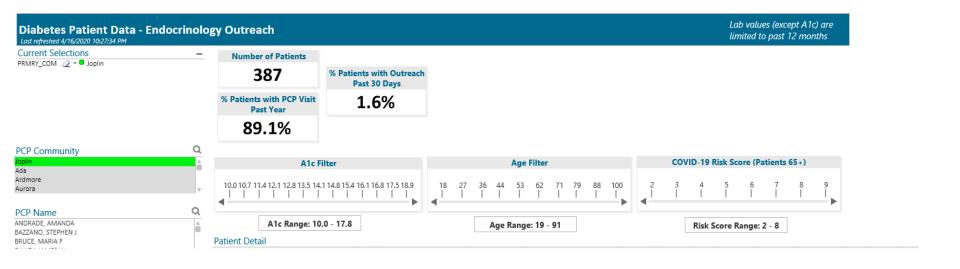




Additional instructions to guide treatment choice







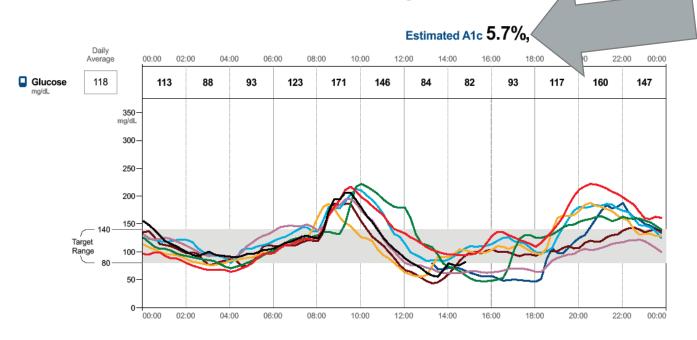
When in Doubt

Go to the sugars





Look at the blood sugars



- Metformin
- Glyburide 10 mg at 7:30 and 9 pm
- Breakfast = instant oatmeal
- Lunch and supper = mixed meals





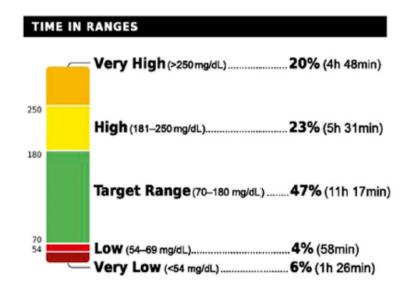


AGP Report

Glucose Variability

Name		
MRN		

26 Feb 2019-10 Mar 2019 % Time CGM is Active	13 days 99.9%	13 days 99.9%		
Glucose Ranges	Targets [% of Readings (Time/l	Day)		
Target Range 70-180 mg/dL	Greater than 70% (16h 48min)			
Below 70 mg/dL	Less than 4% (58min)			
Below 54 mg/dL	Less than 1% (14min)			
Above 180 mg/dL				
Above 250 mg/dL				
Each 5% increase in time in range (70-180 mg/dL) is clinically benefic	ial.		
Average Glucose	173 mg/	dL		
Glucose Management Ind				



Defined as percent coefficient of variation (%CV); target ≤36%

FIGURE 6.1 Sample AGP report. Adapted from Battelino T, Danne T, Bergenstal RM, et al. Diabetes Care 2019;42:1593-1603.

49.5%



Keep in mind

- Time-in-range matters
- \$
- Patient adherence leads to successful glucose control
 - Don't choose medications they will not take
- Step-wise addition of glucose lowering meds generally remains preferred to initial combination therapy
 - Insufficient evidence to suggest first-line combination is superior
 - But those needing > 1.5% A1c reduction will likely need combination
- It still takes a team to treat diabetes





July Webinar



- Date/Time: July 16, 2020 from 2-3pm Eastern
- Topic: Prediabetes Predictive Model – Delivering Patientspecific Risk Estimates at the Point-of-Care
- Presenter: AMGA Analytics



Questions



