2019 Type 2 Diabetes Care Update

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1

Disclosures

- Dr. Kowalyk is on the speaker's bureau of Novo Nordisk.

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2

GOALS

- Review the current American Diabetes Association's glucose / CV risk based treatment goals
- Highlight current treatment algorithms
- Update diabetes therapeutic options

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4

Diabetes In The US

- Leading cause of kidney failure, nontraumatic lower-limb amputation, adult blindness
- Major cause of heart disease and stroke
- **Glycemic improvement has not reduced the risk for macrovascular disease and mortality**

www.cdc.gov/diabetes/data/statistics/2014StatisticsReport.html.
www.phdmc.org/images/uploads/CHA_ID_final.pdf ~1/2014.

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5

Diabetes increases risk of cardiovascular disease

- 2x increase in coronary disease
- 5x increased risk of 1st MI + worse prognosis
- 2x increased risk ischemic CVA
- 2-4x increased risk CV death
- 2-5x increased risk HF

Despite use of statins, ACE/ARBs

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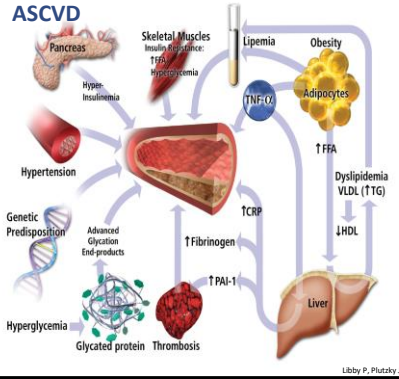
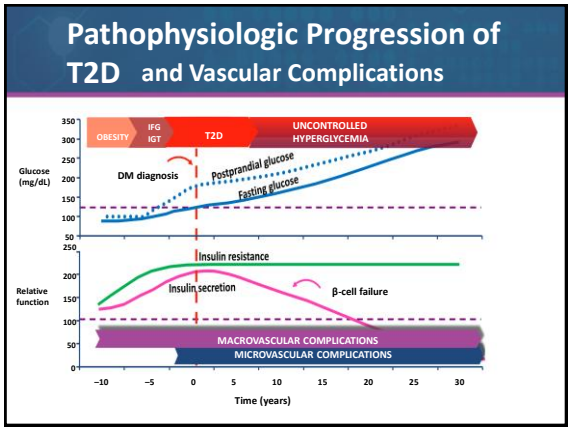
6

Proposed Links between DM and ASCVD

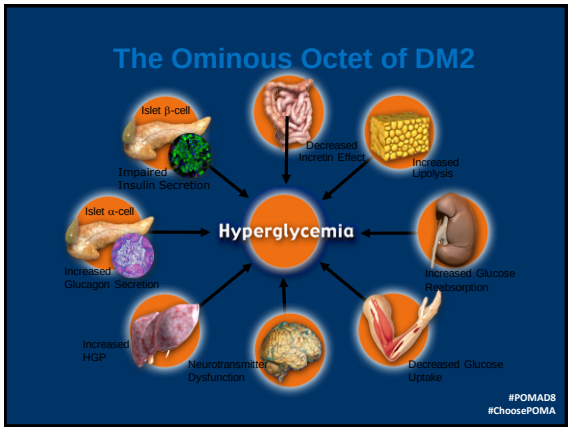


Libby P, Plutzky J. *Circulation.*

7


Pathophysiologic Progression of T2D and Vascular Complications
OBESITY
IFG
IGT
T2D
UNCONTROLLED HYPERGLYCEMIA
Glucose (mg/dL)
DM diagnosis
Postprandial glucose
Fasting glucose
Insulin resistance
Insulin secretion
β-cell failure
Relative function
MACROVASCULAR COMPLICATIONS
MICROVASCULAR COMPLICATIONS
Time (years)

8


The Ominous Octet of DM2
Islet β-cell
Impaired Insulin Secretion
Decreased Incretin Effect
Increased Lipolysis
Islet α-cell
Hyperglycemia
Increased Glucagon Secretion
Increased Glucose Reabsorption
Increased HGP
Neurotransmitter Dysfunction
Decreased Glucose Uptake
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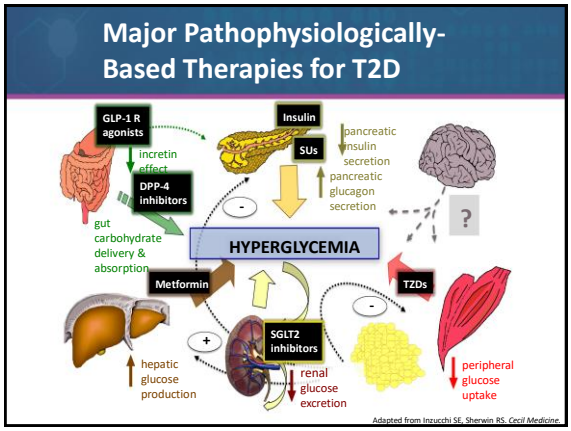
9


Major Pathophysiologically-Based Therapies for T2D
GLP-1 R agonists
incretin effect
DPP-4 inhibitors
gut carbohydrate delivery & absorption
Insulin
SUs
pancreatic insulin secretion
pancreatic glucagon secretion
?
HYPERGLYCEMIA
Metformin
TZDs
SGLT2 inhibitors
hepatic glucose production
renal glucose excretion
peripheral glucose uptake
Adapted from Inzucchi SE, Sherwin RS. Cecil Medicine.

10

Negative aspects of older DM agents

- "Metformin for Sulfonylureas Boosts CV Risk in Type 2 Diabetes, Study Finds"
- "Sulfonylureas, basal insulin linked to higher risk of heart disease"
- Black box CV warning on sulfonylureas
  - SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY (Diabetes, 19, supp. 2: 747–830, 1970).

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11

Previous 2015 ADA-EASD Position Statement Summary

- HbA1c < 7.0% (MPG ~150 mg/dL)
- Pre-prandial PG 80-130 mg/dL
- Post-prandial PG <180 mg/dL
- Avoidance of hypoglycemia
- Individualization is key:
  - More stringent (6.0-6.5%) - short disease duration, healthier, **no CVD**
  - Less stringent (7.5-8.0%+) – comorbidities, complications, hypoglycemia, short life expectancy, limited resources, support or motivation

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Diabetes Care Jan 2017, 40 (Supplement 1) S64-S74;

12

Choosing diabetes medications

- Paradigm shift for the treatment of T2DM
- Increased focus on CV risk reduction
- Despite similar antihyperglycemic effects 2 classes of therapeutic agents have shown clear beneficial effects on CV outcomes:
  - glucagon-like peptide receptor agonists-GLP1 RAs
  - sodium-glucose cotransporter -2 receptor inhibitors-SGLT2is

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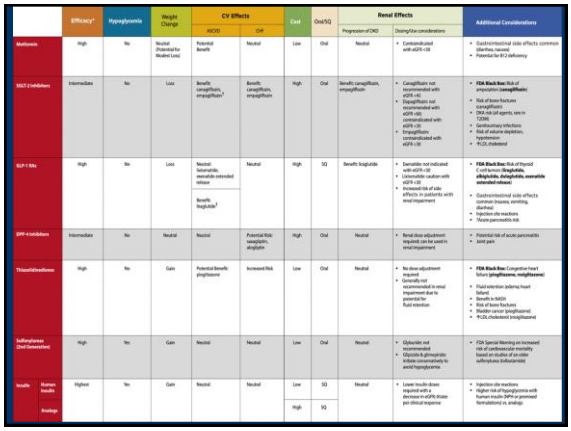
13



	Efficacy*	Hypoglycemia	Weight Change	CV Effects		Cost	Oral/SQ	Renal Effects		Additional Considerations
				ASCVD	CHF			Progression of CKD	Dosing/Use considerations	
Metformin	High	No	Neutral (Potential for Modest Loss)	Potential Benefit	Neutral	Low	Oral	Neutral	• Contraindicated with eGFR <30	• Gastrointestinal side effects common (diarrhea, nausea) • Potential for B12 deficiency
SGLT-2 Inhibitors	Intermediate	No	Loss	Benefit: canagliflozin, empagliflozin[1]	Benefit: canagliflozin, empagliflozin	High	Oral	Benefit: canagliflozin, empagliflozin	• Canagliflozin not recommended with eGFR <45 • Dapagliflozin not recommended with eGFR <60 • Not indicated with eGFR <30 • Empagliflozin contraindicated with eGFR <30	• **FDA Black Box:** Risk of amputation (**canagliflozin**) • Risk of bone fractures (canagliflozin) • Class (all agents; see in T2DM) • Genitourinary infections • Risk of volume depletion, hypotension • ↑LDL cholesterol
GLP-1 RAs	High	No	Loss	Neutral: lixisenatide, exenatide extended release Benefit: liraglutide[1]	Neutral	High	SQ	Benefit: liraglutide	• Exenatide: not indicated with eGFR <30 • Lixisenatide: caution with eGFR <30 • Increased risk of side effects in patients with renal impairment	• **FDA Black Box:** Risk of thyroid C-cell tumors (**liraglutide, albiglutide, dulaglutide, exenatide extended-release**) • Gastrointestinal side effects common (nausea, vomiting, diarrhea) • Injection site reactions • Acute pancreatitis risk
DPP-4 Inhibitors	Intermediate	No	Neutral	Neutral	Potential Risk: saxagliptin, alogliptin	High	Oral	Neutral	• Renal dose adjustment required; can be used in renal impairment	• Potential risk of acute pancreatitis • Joint pain
Thiazolidinediones	High	No	Gain	Potential Benefit: pioglitazone	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 (**pioglitazone, rosiglitazone**) • Fluid retention (edema; heart failure) • Benefit in NASH • Risk of bone fractures • Bladder cancer (pioglitazone) • ↑LDL cholesterol (rosiglitazone)
Sulfonylureas (2nd Generation)	High	Yes	Gain	Neutral	Neutral	Low	Oral	Neutral	• Glyburide: not recommended • Glipizide & 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	Neutral	• Lower insulin doses required with a decrease in eGFR titrate per clinical response	• Injection site reactions • Higher risk of hypoglycemia with human insulin (NPH or premixed formulations) vs. analogs
Insulin: Analogs						High	SQ			

14

CVD active antidiabetic agent classes

- Sodium glucose transporter 2 inhibitors
  - empagliflozin(Jardiance)
  - canagliflozin(Invokana)
  - dapagliflozin(Farxiga)
  - ertugliflozin(Steglatro)

- GLP-1 receptor agonists:
  - liraglutide(Victoza)
  - semaglutide(Ozempic)
  - dulaglitide(Trulicity)
  - lixisenatide(Adlyxin)

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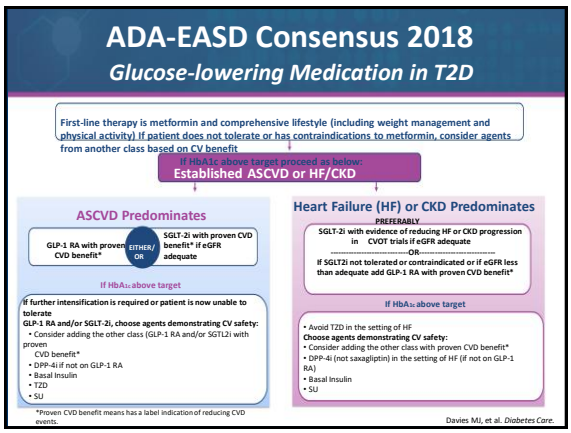
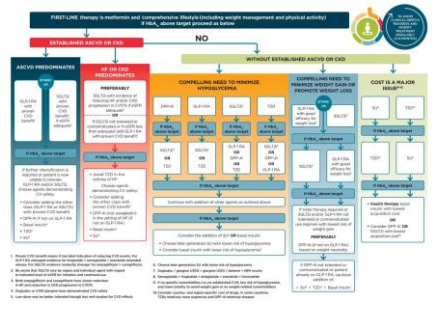
15



16

Glucose-lowering medication in type 2 diabetes: overall approach.



American Diabetes Association Clin Diabetes 2019;37:11-34

American Diabetes Association.

17

FDA Indications and Doses for SGLT2 Inhibitors with positive Cardiovascular Outcomes Trial Data-Jardiance and Invokana

	Empagliflozin(Jardiance)	Canagliflozin(Invokana)
Doses	•▪ 10 mg PO daily •▪ 25 mg PO daily	•▪ 100 mg PO daily •▪ May increase to 300 mg daily if needed in those who have an eGFR ≥60
FDA-approved Indications	•▪ Improve glycemic control in adults with T2D •▪ Reduce risk of CV death in adults with T2D and CV disease	▪ Improve glycemic control in adults with T2D -reduce the risk of heart attack, stroke, and CV death in adults with T2DM and CV disease
Dose modifications*	•▪ eGFR ≥45 : No dose adjustment required. •▪ eGFR <45 : Do not initiate; discontinue if eGFR persistently below 45	•▪ eGFR ≥60 : No dose adjustment required. •▪ eGFR 45 to 59 : Do not exceed 100 mg/day. •▪ eGFR <45: Do not initiate; discontinue if eGFR persistently below 45

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18

What about dapagliflozin(Farxiga)?

- Dapagliflozin was not beneficial for the outcome of CV death, MI and stroke, while risk for CV death and hospitalization for HF was improved overall and in the subsets with CV disease and with multiple risk factors
- ?HF primary prevention

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19

SGLT2 associated negative effects

- "glucose diuretic"
- Increased risk volume related events- frequency, hypotension(?fracture related),
- GU glucose effects- GMI, UTI, ?prostatitis
- Hypoglycemia- only if added to SFU, insulin, meglitinides
- DKA
- Invokana-increased amputation risk 0.34 vs 0.63 events per 100 patient years
- Fournier's gangene
- Initial small decrease GFR-then renal protection

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20

GLP-1 RA associated negative effects

- GI-nausea vomiting
- Acute kidney injury-volume related
- Pancreatitis
- Medullary carcinoma thyroid(rodent studies)

- Start low dose titrate slowly

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21

CV active DM medications

- SGLT2 inhibitors –proven secondary no primary CVD prevention (suggestive for heart failure)
- Rapid onset CV protective effect of SGLT2s(weeks-hemodynamic effects) vs GLP1s(years-? antiatherogenic)
- GLP1 agonists-secondary and emerging evidence of primary CVD prevention
- SGLT2-future use in lower GFR for renal/CV protection
- SGLT2-?primary prevention of heart failure

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22

Reducing CV risk in T2DM

- Increased use of empagliflozin(Jardiance), canagliflozin(Invokana) and liraglutide(Victoza), ?semaglutide(Ozempic)
- Heart failure risk reduced by all SGLT2is
- Additional benefits of GLP1 s and SGLT2i s for renal disease
- Selection of SGLT2i vs GLP1-
  - HF-SGLT2i
  - if obesity, GU infections, low GFR-GLP1

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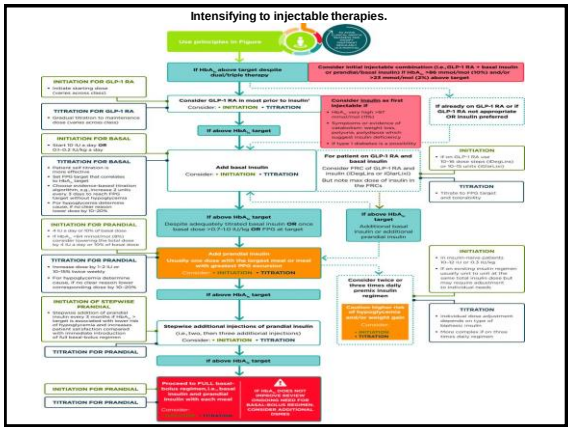
23



24

What about insulin 2018?

- Rapid onset prandial insulin-Fiasp("fast Novolog")
- Increasing use combination GLP1 RA/basal insulin
- Increasing use non traditional basal bolus insulin administration vs MDI

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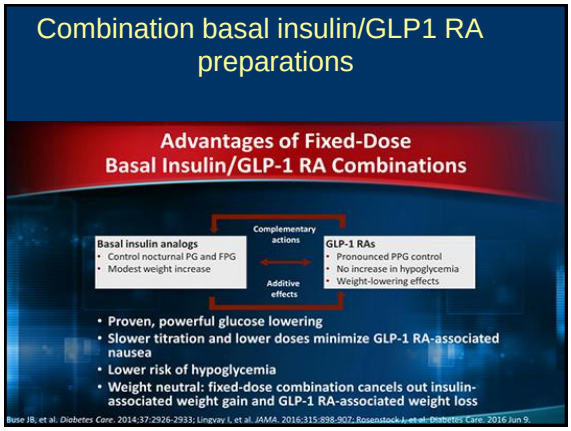
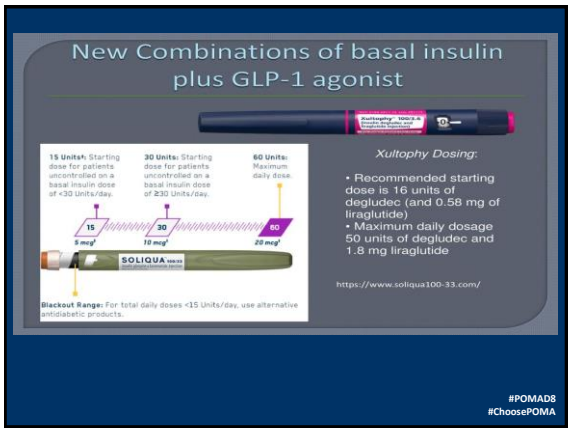
25


Combination basal insulin/GLP1 RA preparations
Advantages of Fixed-Dose Basal Insulin/GLP-1 RA Combinations
Basal insulin analogs
• Control nocturnal PG and FPG
• Modest weight increase
Complementary actions
Additive effects
GLP-1 RAs
• Pronounced PPG control
• No increase in hypoglycemia
• Weight-lowering effects
• Proven, powerful glucose lowering
• Slower titration and lower doses minimize GLP-1 RA-associated nausea
• Lower risk of hypoglycemia
• Weight neutral: fixed-dose combination cancels out insulin-associated weight gain and GLP-1 RA-associated weight loss
Buse JB, et al. Diabetes Care. 2014;37:2926-2933; Lingvay I, et al. JAMA. 2016;315:898-907; Rosenstock J, et al. Diabetes Care. 2016 Jun 9.

26


New Combinations of basal insulin plus GLP-1 agonist
15 Units*: Starting dose for patients uncontrolled on a basal insulin dose of <30 Units/day.
30 Units: Starting dose for patients uncontrolled on a basal insulin dose of ≥30 Units/day.
60 Units: Maximum daily dose.
15
30
60
5 mcg†
10 mcg†
20 mcg†
SOLIQUA
Blackout Range: For total daily doses <15 Units/day, use alternative antidiabetic products.
Xultophy Dosing:
• Recommended starting dose is 16 units of degludec (and 0.58 mg of liraglutide)
• Maximum daily dosage 50 units of degludec and 1.8 mg liraglutide
https://www.soliqua100-33.com/
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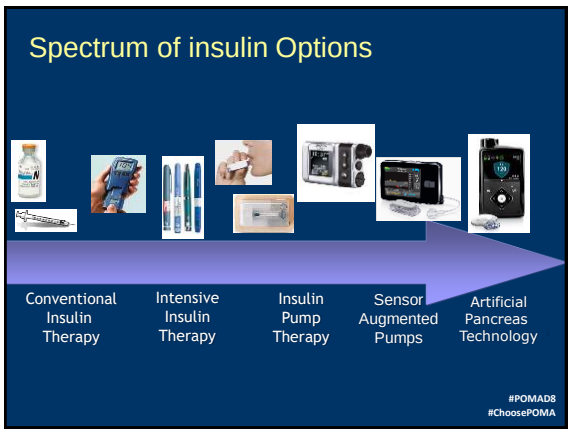
27


Spectrum of insulin Options
Conventional Insulin Therapy
Intensive Insulin Therapy
Insulin Pump Therapy
Sensor Augmented Pumps
Artificial Pancreas Technology
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28

Alternatives to multiple daily injections

- "I think it's great to have alternative, simplistic ways to deliver insulin in a basal-bolus methodology"
- VGO patch/pump(mechanical , not electronic, no tubing , 24hr wear)
- Basal insuln + inhaled insulin(Afrezza)

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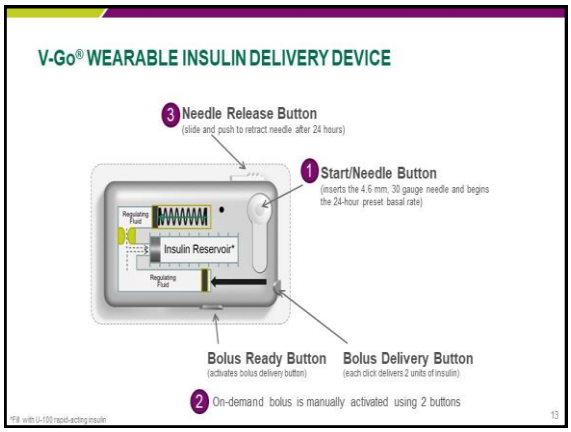
29



30

Select insulin preparations differences

- Standard insulin pens(Novolog,Humalog, Lantus, Levemir, Basaglar -80 units maximum dose
- Toujeo U300 450 units/pen max single dose 80 units 1 unit increments
- Toujeo max pen- 900 units/pen max single dose 160 units 2 unit increments
- Tresiba U100 300 units/pen-max single dose 80 units 1 unit increments
- Tresiba U200-600 units/pen max single dose 160 units 2 unit increments

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31

T2DM treatment philosophy

- Reduce microvascular burden-neuropathy, nephropathy, retinopathy-glucose management
- Reduce CV risk-75% of persons with diabetes die form cardiovascular disease-obesity, lipids, HTN
- "blood sugar, blood pressure, cholesterol"
- Use medications with "additional benefit": NO hypoglycemia, (++)weight loss, (++) CV effects,renal protection
- Now consider addition of CVD risk reducing agents even if glycemic goals are reached

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32

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33