Treating Type 2 Diabetes with Glucose-Lowering Drugs: Which Drug and When

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1

Disclosure

Consultant: Bayer; Boehringer Ingelheim; Corcept Therapeutics; DIASOME; Eli Lilly; Merck; Novo Nordisk; Sanofi

Research Grant: Bayer; Eli Lilly; Merck; Novo Nordisk; Twin Health

Speaker's Bureau: AstraZeneca; Corcept Therapeutics; Novo Nordisk

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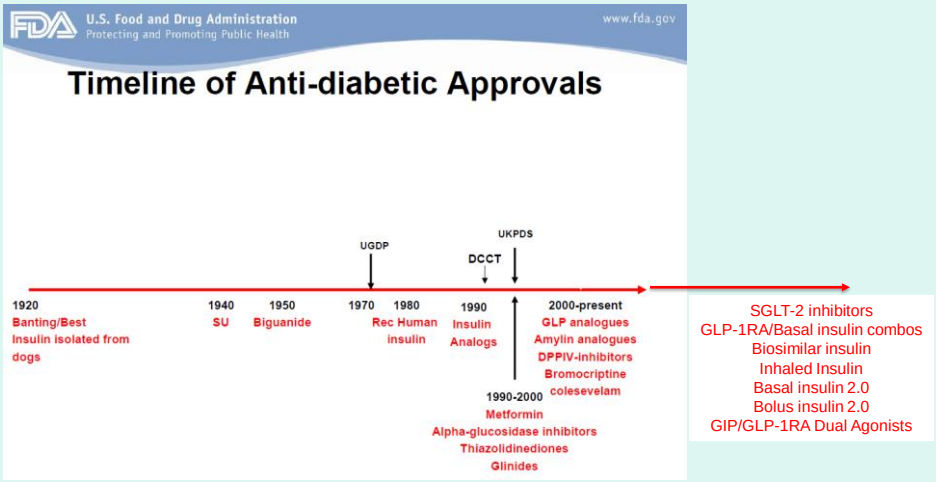
2

Oral Anti-diabetic Agents

- Used to be two main categories:
  - Insulin sensitizers
  - Insulin secretagogues
- The new agents do not fit nicely into these two categories
  - Many of the new oral (and injectable) T2D medications work by novel mechanisms

3

Available Medications



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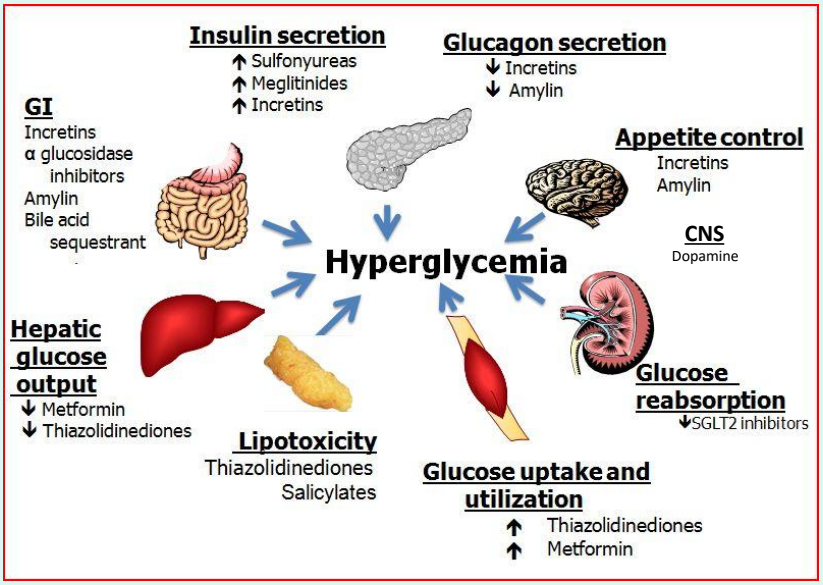
Anti-diabetic Agents: **Major Sites of Action**



endotext.org

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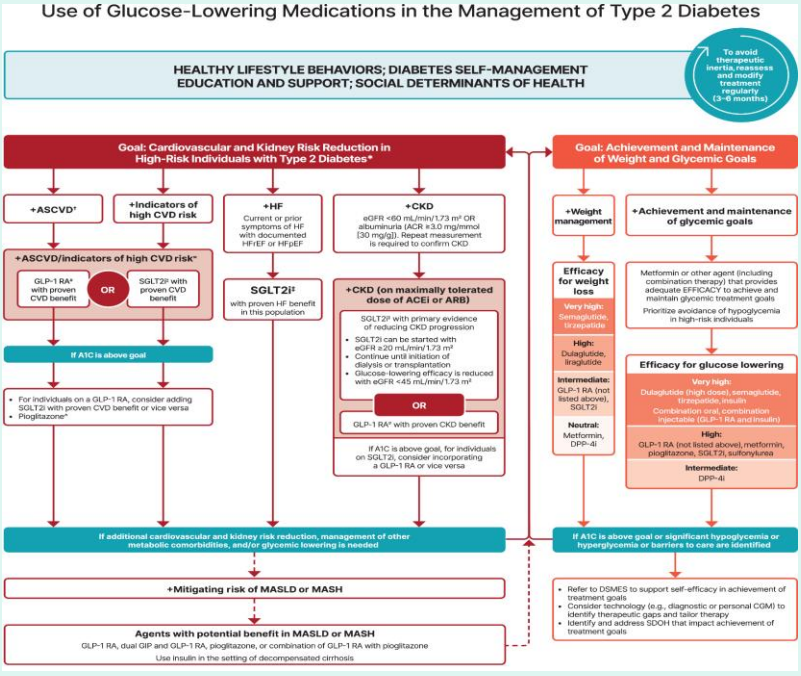


*In people with HF, CKD, established CVD, or multiple risk factors for CVD, the decision to use a GLP-1RA or SGLT-2i with proven benefit should be made irrespective of background use of metformin or A1C

9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes—2025; Diabetes Care 2025;48(Supplement_1):S181–S206.

6

Treat-to-Target (and Outcome)

- Glucose-centric approach is evolving to an outcome-based approach
- Glycemic goal attainment is still important, but how one gets there must be considered
- A1C goal attainment is still important to reduce risk of DM-related complications (particularly microvascular complications)
  - CGM and time-in-range (TIR) are becoming ever more important
- Carefully review patient comorbidities which will influence which therapies are prescribed to individuals with T2D
  - CKD, CHF, CVD

7

Biguanides: Metformin

- Metformin improves hyperglycemia primarily by
  - Suppressing hepatic gluconeogenesis
  - ? Insulin sensitizer
- The "average" person with type-2 diabetes has three times the normal rate of gluconeogenesis; metformin treatment reduces this by over one third
- 1st line therapy for most

Kirpichnikov D. Ann Intern Med. 2002;137(1):25–33.
Hundal R. Diabetes. 2000;49(12):2063–9.

8

Metformin

- Still considered by most to be the 1st line agent of choice, in the absence of contraindications
- Contraindications/Concerns include:
  - CHF
    - Unstable or acute heart failure at risk of hypoperfusion
  - Hepatic Impairment
  - ARF/CKD
  - Stress-related states
    - Decreased tissue perfusion or hemodynamic instability due to infection or other causes
  - Active Alcohol Abuse
  - IV contrast exposure

9

Metformin

- eGFR <30 mL/min/1.73 m^2
  - Metformin is contraindicated
- eGFR between 30-45 mL/min/1.73 m^2
  - Initiating metformin in patients with an is not recommended (but you can do it)
  - Some advocate limiting daily dose to 1,000 mg
- For patients taking metformin whose eGFR falls below 45 mL/min/1.73 m^2
  - The R vs. B of continuing metformin should be assessed
  - Metformin should be discontinued if the eGFR falls below 30 mL/min/1.73 m^2
- Metformin associated lactic acidosis is rare

Salpeter SR et al. Cochrane Database Syst Rev 2010; :CD002967.
Lazarus B et al. JAMA Intern Med 2018; 178:903.
Up-to-Date: Metformin in the treatment of adults with type 2 diabetes mellitus. This topic last updated: Jan 09, 2025.

10

Metformin

- Common side effects:
  - Abdominal bloating, diarrhea, nausea
- Weight neutral
- No hypoglycemia
- Don’t forget about metformin XR!!!!!

Tan J et al. Front Pharmacol. 2021 May 17;12:669814.
https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/020357s031,021202s016lbl.pdf

11

Sulfonylureas (SFUs)

- Insulin secretagogue
  - glyburide, glimepiride, glipizide
- Fallen out of favor in recent years
- Contraindications/Concerns:
  - Use in elderly
  - Caution should be used in patients with liver or kidney dysfunction or in patients who often skip meals

12

SFUs

- Common side effects
  - Hypoglycemia
    - Glipizide XL
  - Risk of cross-reaction exists in patients with sulfa allergy; avoid use when previous reaction has been severe
- Weight gain

13

SFUs

- University Group Diabetes Program (UGDP) 1975
  - Sulfonylurea (tolbutamide) may increase the risk of cardiovascular death
  - FDA mandated warning labels regarding an increased risk of cardiovascular-related mortality be added to all sulfonylureas
  - Currently all sulfonylureas approved for use within the United States are accompanied with this warning

NOT supported by the UKPDS which followed

University Group Diabetes Program (UGDP). Diabetes. 1970; 19(Suppl 2):747-830.

14

CAROLINA CVOT
Linagliptin vs. Glimepiride (N=6,033)

- The median duration of diabetes for the population was 6.3 years, 42% had established CVD, 0% were on insulin, and 83% were on metformin
- HR 0.98, 95% CI: 0.84-1.14
  - P<0.0001 for non-inferiority, P=0.76 for superiority
  - A **very** neutral finding
- Any form of hypoglycemia experienced
  - 37.7% Glimepiride vs. 10.6% Linagliptin
  - HR 0.23, 95% CI: 0.21-0.26, p<0.0001

New introduction of Glucose-lowering medications post-baseline:

	Glimepiride	Linagliptin
Any glucose lowering therapy	40%	41%
Non-insulin therapies	29%	31%
insulin	19%	18%

Rosenstock J et al. JAMA doi: 10.1001/jama.2019.13772. https://doi.org/10.1001/jama.2019.13772

15

Thiazolidinediones (TZDs)

- TZDs are agonists of peroxisome proliferator-activated receptor gamma (PPARγ)
  - Pioglitazone (Actos®)
  - Rosiglitazone (Avandia®)
- Primarily enhance insulin sensitivity of muscle and fat, and mildly of the liver

Yki-Järvinen H. N Engl J Med. 2004 Sep 9;351(11):1106-18.

16

TZDs

- Contraindications/Concerns include:
  - These agents should be avoided in patients with functional class III or IV heart failure
- Common side effects:
  - Weight gain, with an increase in subcutaneous adiposity
  - Fluid retention, which typically manifests as peripheral edema, but heart failure has been shown to occur on occasion
- No hypoglycemia
- Work great where insulin resistance is very high:
  AA, American Indians, Asians

Reasner CA. Diabetes Metab Res Rev. 2002 Mar-Apr:18 Suppl 2:S30-5.
https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021073s043s044lbl.pdf

17

Pioglitazone

- Has favorable effect on lipids: lowering triglycerides, increasing HDL, and increasing the LDL particle size
- CV risk reduction (PROactive)?
- Bladder Cancer
  - Literature has suggested the possibility of an increased risk of bladder cancer in patients exposed to pioglitazone
  - Risk may be increased with duration of use

Lewis JD et al. Diabetes Care. 2011 Apr;34(4):916-22.
Azoulay L et al. BMJ. 2012 May 30;344:e3645.
Dormandy JA et al. Lancet 2005; 366: 1279–1289.
https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021073s043s044lbl.pdf
Davidson MB. Diabetes Research and Clinical Practice. 2018;135:102–110.
Tang H et al. Cancer Med. 2018 Apr; 7(4): 1070–1080.

18

Pioglitazone

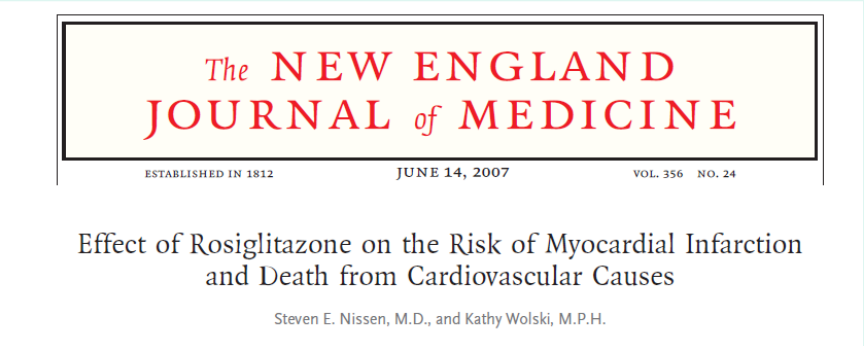
- Has favorable effect on lipids: lowering triglycerides, increasing HDL, and increasing the LDL particle size
- CV risk reduction (PROactive)?
- Bla
  - L sk of b
  - Risk may be increased with duration of use

In August 2011, the FDA approved an update to the Actos warning label to publicize the possible link between extended use of Actos (≥12 months) and an increased risk of developing bladder cancer

Lewis JD et al. Diabetes Care. 2011 Apr;34(4):916-22.
Azoulay L et al. BMJ. 2012 May 30;344:e3645.
Dormandy JA et al. Lancet 2005; 366: 1279–1289.
https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021073s043s044lbl.pdf
Davidson MB. Diabetes Research and Clinical Practice. 2018;135:102–110.
Tang H et al. Cancer Med. 2018 Apr; 7(4): 1070–1080.

19

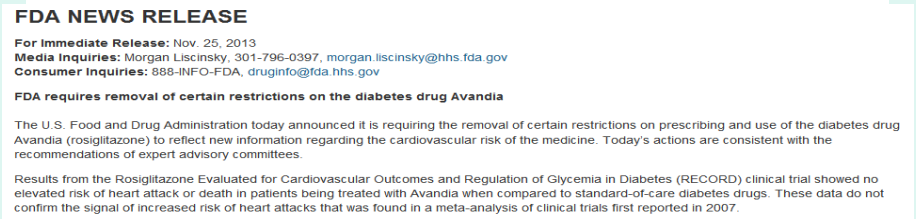
Rosiglitazone


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 14, 2007 VOL. 356 NO. 24

Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

Steven E. Nissen, M.D., and Kathy Wolski, M.P.H.


FDA NEWS RELEASE

For Immediate Release: Nov. 25, 2013
Media Inquiries: Morgan Liscinsky, 301-796-0397, morgan.liscinsky@hhs.fda.gov
Consumer Inquiries: 888-INFO-FDA, druginfo@fda.hhs.gov

FDA requires removal of certain restrictions on the diabetes drug Avandia

The U.S. Food and Drug Administration today announced it is requiring the removal of certain restrictions on prescribing and use of the diabetes drug Avandia (rosiglitazone) to reflect new information regarding the cardiovascular risk of the medicine. Today's actions are consistent with the recommendations of expert advisory committees.

Results from the Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycemia in Diabetes (RECORD) clinical trial showed no elevated risk of heart attack or death in patients being treated with Avandia when compared to standard-of-care diabetes drugs. These data do not confirm the signal of increased risk of heart attacks that was found in a meta-analysis of clinical trials first reported in 2007.

Nissen SE and Wolski K. N Engl J Med. 2007 Jun 14;356(24):2457-71.

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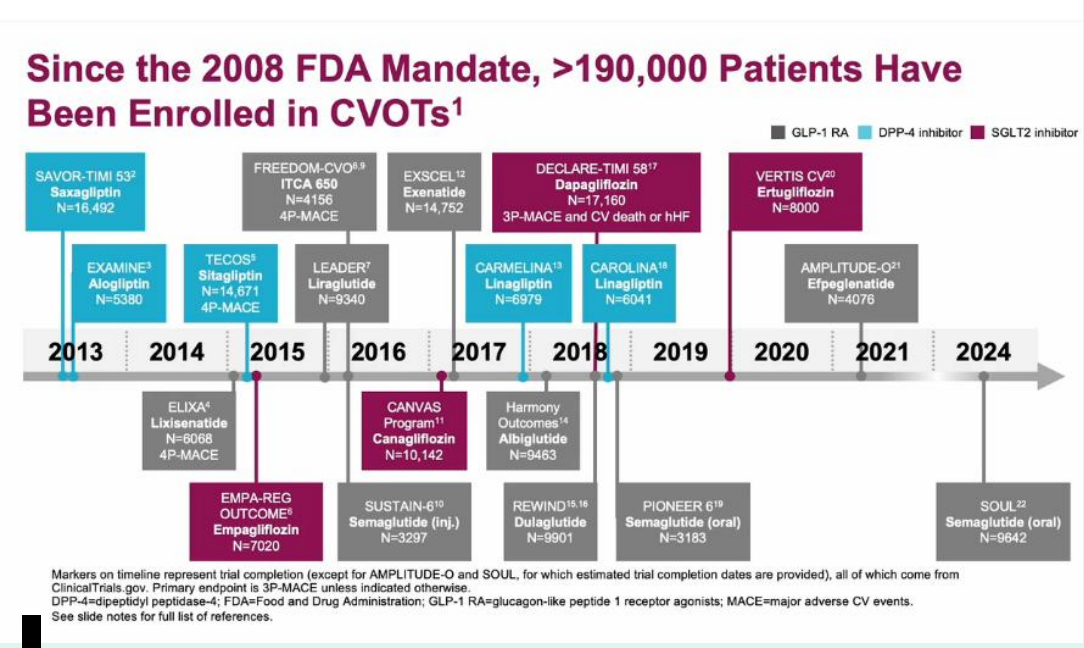


21

CV Risk Reduction with Pioglitazone

- CV risk reduction has been observed
- PROactive
  - Primary Composite Endpoint:
    - Composite of all-cause mortality, non fatal myocardial infarction (including silent myocardial infarction), stroke, acute coronary syndrome, endovascular or surgical intervention in the coronary or leg arteries, and amputation above the ankle.
      - HR 0.90, 95% CI 0.80-1.02, p=0.095
  - Secondary Composite Endpoint:
    - Pioglitazone reduces the composite of all-cause mortality, non-fatal myocardial infarction, and stroke in patients with type 2 diabetes who have a high risk of macrovascular events
    - 301 patients in the pioglitazone group and 358 in the placebo group reached this endpoint
      - HR 0.84, 0.72-0.98, p=0.027

Dormandy JA et al. Lancet. 2005 Oct 8;366(9493):1279-89.
Kernan WN et al. N Engl J Med. 2016 Apr 7;374(14):1321-31.
de Jong M et al. Cardiovasc Diabetol. 2017; 16: 134.

22

Pioglitazone

- Lower-dose therapy (e.g., pioglitazone 15–30 mg) mitigates weight gain and edema
- But, the broader benefits and harms of low-dose TZD therapy have not been evaluated

Davies MJ et al. Diabetes Care 2018 Dec; 41(12): 2669-2701.

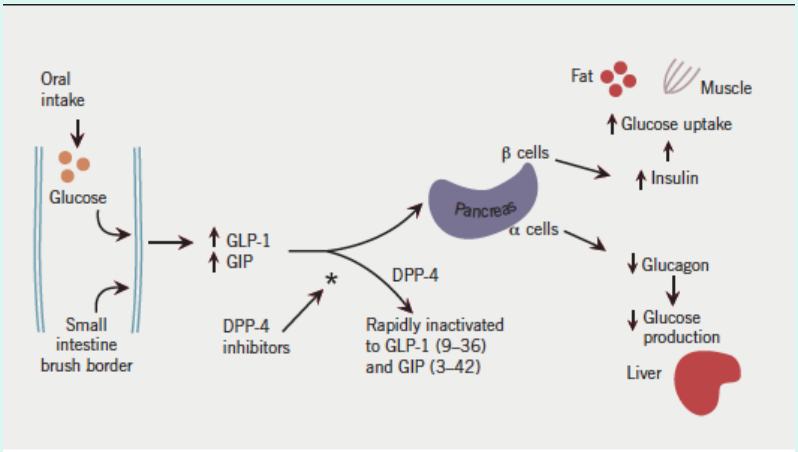
23

Dipeptidyl Peptidase-4 Inhibitors

- Dipeptidyl peptidase-4 (DPP-4) is a cell membrane protein that rapidly degrades GLP-1 and glucose-dependent insulinotropic polypeptide (GIP)
  - Sitagliptin (Januvia®)
  - Saxagliptin (Onglyza®)
  - Linagliptin (Tradjenta®)
  - Alogliptin (Nesina®)

24

DPP-4i
Mechanism of Action



McDougall C, McKay GA, Fisher M Br J Cardiol 2011;18 (3):130–2.

25

DPP-4 Inhibitors

- Generally well tolerated
  - Most common side effect is headache
  - An increase in nasopharyngitis has also been reported
  - ? Bullous Pemphigoid (rare)
  - ? Increase risk of HF (Saxagliptin, Alogliptin)
- Weight neutral
- No hypoglycemia
- CV safety (but NO CV benefit)
- Renal Adjustment
  - Sitagliptin, Saxagliptin, and Alogliptin, Linagliptin does not

Scirica BM et al. N. Engl. J. Med. 2013;369:1317-26.
White WB et al. N. Engl. J. Med. 2013;369:1327-35.
Green JB et al. N Engl J Med. 2015 Jul 16;373(3):232-42.
Rosenstock J et al. JAMA. 2018 Nov 9. doi: 10.1001/jama.2018.18269. [Epub ahead of print]

26

Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitor

- Block the glucose reabsorption function of the kidney, resulting in the excretion of excess glucose—up to 10% of daily calorific intake—in patients' urine

- Dapagliflozin (Farxiga®)
- Canagliflozin (Invokana®)
- Empagliflozin (Jardiance®)
- Ertugliflozin (Steglatro®)
- Bexagliflozin (Brenzavvy®)

Dokken B. Diabetes Spectr. 2012;25:29-36.

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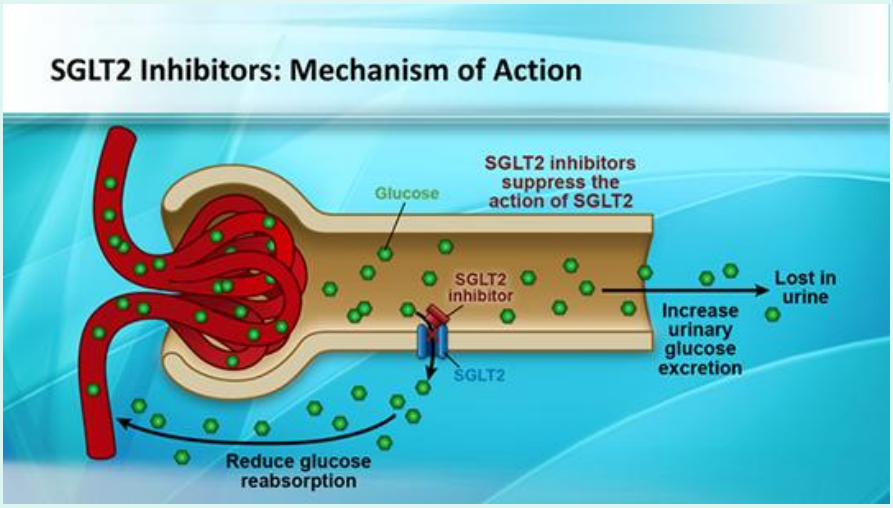


Combo SGLT2 and DPP-4 Inhibitors: Complementary Mechanisms of Action
Authors: John Anderson, MD; Vivian Fonseca, MD, FRCP
https://www.medscape.org/viewarticle/837818_transcript

28

SGLT-2 Inhibitors

- Benefits
  - Weight loss
  - Low (no) risk of hypoglycemia
  - Improved glycemic control
    - Particularly post-prandial hyperglycemia
  - Reduction in systolic BP (~ 5 mmHg)
  - CV, CKD, and HF benefits

29

SGLT-2 Inhibitors

- **Renal risk reduction/Kidney Protection**
  - Canagliflozin: Reduction in risk of ESKD, doubling of serum Cr, CV death, and hospitalization for heart failure (hHF) in adults with T2D and diabetic nephropathy, albuminuria > 300 mg/day, with T2D
  - Dapagliflozin: Reduction in risk of sustained eGFR decline, ESKD, CV death, and hospitalization for heart failure (hHF) in adults with chronic kidney disease at risk of progression, with or without T2D
  - Empagliflozin: Reduction in risk of sustained decline in eGFR, ESKD, CV death, and hospitalization in adults with chronic kidney disease at risk of progression, with or without T2D
- **CV Risk Reduction**
  - Reduction in CV death risk (Empagliflozin)
  - Reduction in CV events: CV death, nonfatal MI, nonfatal stroke (Canagliflozin)
  - Reduction in hHF (Dapagliflozin)
- **Heart Failure**
  - Reduction in CV death and hHF in patients with HF, with or without diabetes (Dapagliflozin)
  - Reduction in CV death and hHF in patients with HF, with or without diabetes (Empagliflozin)

Zinman B et al. N Engl J Med. 2015 ;373(22):2117-2128.
Neal B et al N Eng J Med. N Engl J Med 2017; 377:644-657.
Wiviott SD et al. N Engl J Med. 2018 Nov 10.
Anker SD et al. N Engl J Med 2021; 385:1451-1461.
McMurray J et al. N Engl J Med. 2019 Nov 21;381(21):1995-2008.
Percovik V et al. N Engl J Med. 2019 Jun 13;380(24):2295-2306.
Packer M et al. N Engl J Med 2020; 383:1413-1424.
Heerspink HJL et al. N Engl J Med 2020; 383:1436-1446.
Soloman SD et al. N Engl J Med August, 2022. N Engl J Med 2022;387:1089-1098.
EMPA-KIDNEY Collaborative Group. N Engl J Med 2023;388:117-127.

30

SGLT-2 Inhibitors

- Risks/Negatives
  - Slight increase in LDL cholesterol
  - Hypotension
    - Intravascular volume contraction
  - UTIs, genital mycotic infections
  - Fournier's gangrene (???)
  - Increase risk of DKA
  - Bone loss and increase in fracture risk (Canaglifl
  - Amputations (Canagliflozin ????)

FDA removes Boxed Warning about risk of leg and foot amputations for the diabetes medicine canagliflozin (Invokana, Invokamet, Invokamet XR)

Based on our review of new clinical trial data

This information is an update to the FDA Drug Safety Communication: FDA confirms increased risk of leg and foot amputations with the diabetes medicine canagliflozin (Invokana, Invokamet, Invokamet XR) issued on May 16, 2017.

Drug Safety Communication (PDF - 58KB)

8-26-2020 FDA Drug Safety Communication

Based on a U.S. Food and Drug Administration (FDA) review of new data from three clinical trials, we have removed the *Boxed Warning* about amputation risk from the diabetes medicine canagliflozin (Invokana, Invokamet, Invokamet XR) prescribing information.

We required the *Boxed Warning* in 2017 based on our assessment that the risk of amputations was very serious in relation to the potential benefit of canagliflozin, which was initially approved to be used with diet and exercise to lower blood sugar in adults with

Zinman B et al. N Engl J Med. 2015 ;373(22):2117-2128.
Neal B et al N Eng J Med. N Engl J Med 2017; 377:644-657.
Wiviott SD et al. N Engl J Med. 2018 Nov 10.
https://www.acc.org/latest-in-cardiology/clinical-trials/2020/06/16/11/24/vertis

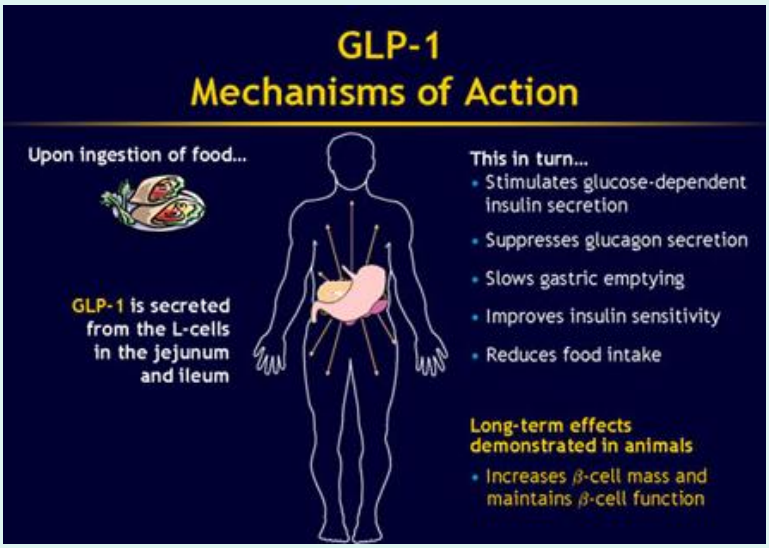
McMurray J et al. N Engl J Med. 2019 Nov 21;381(21):1995-2008.
Percovik V et al. N Engl J Med. 2019 Jun 13;380(24):2295-2306.
https://www.fda.gov/news-events/press-announcements/fda-approves-new-treatment-type-heart-failure
https://www.fda.gov/drugs/drug-safety-and-availability/fda-removes-boxed-warning-about-risk-leg-and-foot-amputations-diabetes-medicine-canagliflozin

31

Non-insulin Injectable Therapies

- Amylin analogue (Pramlintide)
  - Rarely used
- GLP-1RA
  - Multiple new formulations
  - Twice daily>>>Once daily>>>Once weekly
  - Oral GLP-1RA
- Combination products with long-acting insulin and GLP-1 combined in same pen
  - iDegLira [insulin degludec + Liraglutide (GLP-1)] Xultophy®
  - iGlarLixi [insulin glargine + Lixisenatide (GLP-1)] Soliqua®
- GIP/GLP-1RA
  - Tirzepatide

32



Drucker DJ. Diabetes Care. 2003;26:2929-2940.

33

GLP-1RA & GIP/GLP-1RA Therapies Which One to Choose?

- Among the long-acting agents, patient preference and payer coverage are important considerations
- Glycemic control appears to be similar with liraglutide and dulaglutide
- Semaglutide appears to have the greatest A1C lowering and weight loss among the GLP-1RAs
- Oral Semaglutide
- Tirzepatide appears to have the greatest A1C lower and weight loss vs. GLP-1RA, but head-to-head studies of their highest doses are lacking in T2D space

Buse JB et al. Lancet. 2013;381(9861):117-24.
Pratley RE et al. Lancet Diabetes Endocrinol. 2014;2(4):289-97.
Dungan KM et al. Lancet. 2014;384(9951):1349-57.
Ahmann AJ et al. Diabetes Care. 2018 Feb;41(2):258-266.
Pratley RE et al. Lancet Diabetes Endocrinol. 2018;6(4):275-286.

34

Long-acting GLP-1RA Other Considerations

- CV Risk Reduction
  - Currently liraglutide, dulaglutide, and semaglutide are the only GLP-1RA that have the FDA label indication for CV risk reduction
  - Oral semaglutide recently demonstrated CV risk reduction but is not yet FDA approved for CV risk reduction
  - Tirzepatide CVOT just finished, should have results soon
- Renal Risk Reduction
  - sc semaglutide
- Tolerability
- Means of injection
  - Differences in device
- GFR
  - Commonly used long-acting GLP-1RA and GIP/GLP-1RA do not require renal dose adjustment
    - Exenatide products are not recommended in patients with CrCl <30 mL/minute or end-stage renal disease (ESRD)
    - Lixisenatide Not studied ESRD (eGFR <15 mL/min/1.73 m²); use not recommended

Gerstein HC et al Lancet. 2019;394(10193):121-130.
Marso SP et al. N Engl J Med. 2016;375(19):1834-1844.
Marso SP et al. N Engl J Med. 2016;375(4):311-22.
McGuire DK et al. N Engl J Med. 2025 Mar 29. doi: 10.1056/NEJMoa2501006.
Perkovic V et al. N Engl J Med. 2024 Jul 11;391(2):109-121

35

GLP-1RA Therapy

- Benefits
  - Weight loss
  - Low (no) risk of hypoglycemia
  - Improved glycemic control
  - Reduction in systolic BP
  - Reduce CV risk (MACE)
    - FDA Approved Labels of liraglutide, sc semaglutide, dulaglutide in patients with established CVD
    - Dulaglutide (primary and secondary prevention)
  - Renal risk reduction (sc semaglutide)
    - Reduce the risk of worsening kidney disease, kidney failure, and death due to cardiovascular disease in adults with type 2 diabetes (T2D) and chronic kidney disease (CKD)
  - ? In-vivo increase B-cell growth/replication
- Side Effects/Adverse Reactions/Warnings
  - Nausea, vomiting, diarrhea, injection site reactions
  - Acute pancreatitis
  - Thyroid C-cell tumors, including medullary thyroid carcinoma (MTC)

36

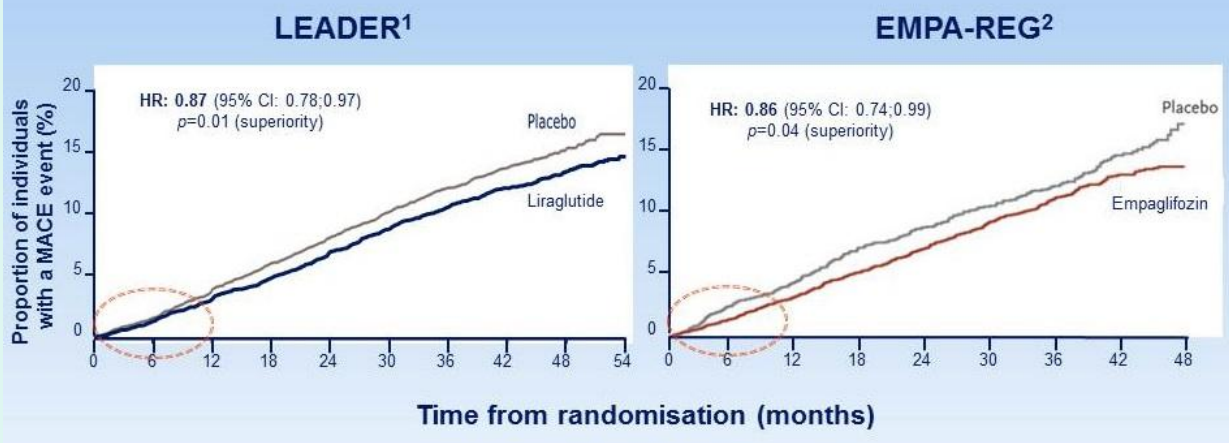
MOA-CV Risk Reduction

SGLT-2i and GLP-1RA

37

Primary outcomes in LEADER and EMPA-REG

3 Point MACE improvement not driven by glycemic efficacy!



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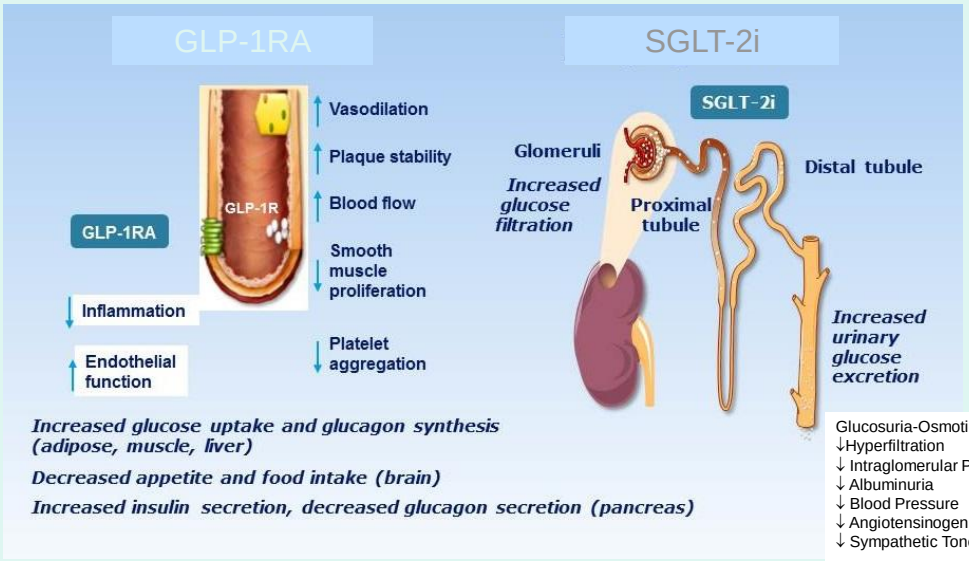
Proposed Cardioprotective Mechanisms of GLP-1 RAs and SGLT-2 Inhibitors



Glucosuria-Osmotic Diuresis
↓Hyperfiltration
↓ Intraglomerular Pressure
↓ Albuminuria
↓ Blood Pressure
↓ Angiotensinogen
↓ Sympathetic Tone
……..

http://medpagetoday.realcme.com/cms/play/819430#31

39

Thrifty-Substrate Hypothesis: SGLT-2i

- Survival benefit in setting of ischemic event
- Mild persistent hyperketonemia
  - β-hydroxybutyrate is freely taken up by the heart (among other organs) and oxidized in preference to fatty acids
- ↑HCT

Ferrannini E et al. Diabetes Care. 2016 Jul;39(7):1108-14.

40

SELECT Trial
GLP-1RA (Semaglutide)

- CV risk reduction is not all related to weight loss
- Significant early reduction in MACE was observed with semaglutide 2.4 mg sc once weekly in adults with overweight/obesity with established CVD prior to what is typically considered significant weight loss
- Established CVD was defined as a prior MI, CVA, or symptomatic PAD

Lincoff MA et al. *N Engl J Med*. 2023;389:2221-2232.

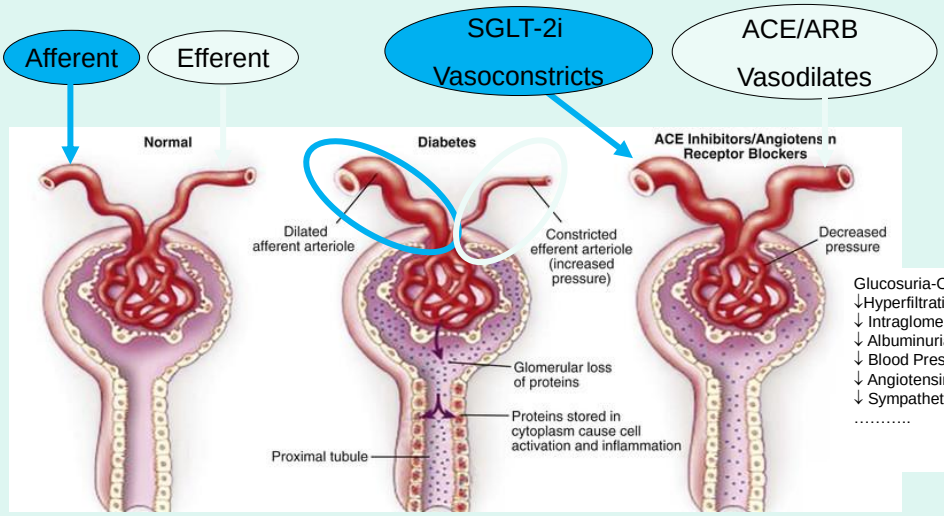
Plutzky J et al. Oral presentation presented at the European Congress on Obesity; 11-14 May 2025; Palacio De Ferias Y Congresos De Málaga, Magala, Spain. Presentation AD15.04.

41

MOA-Renal Risk Reduction

SGLT-2i

42



The increased sodium and chloride is sensed by the macula densa, resulting in tubule-glomerular feedback which causes renal afferent arteriolar vasoconstriction. This vasoconstriction will decrease glomerular filtration and glomerular hypertension.

Wolf G. Pathogenesis of DM. Abdominal Key. 2016
Sawaf H et al. J Clin Med. 2022;11(2):378

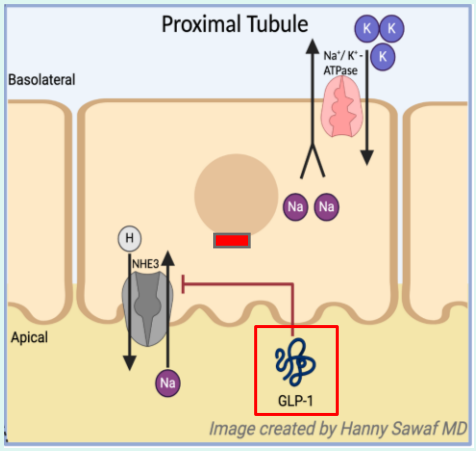
43

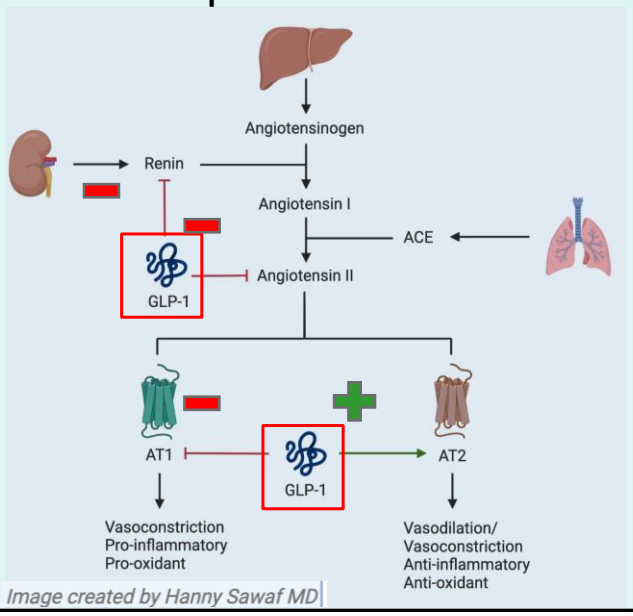
MOA: Renal Risk Reduction

GLP-1RA

44

GLP-1RA MOA for Kidney Benefit
Natriuresis and RAAS Impacts

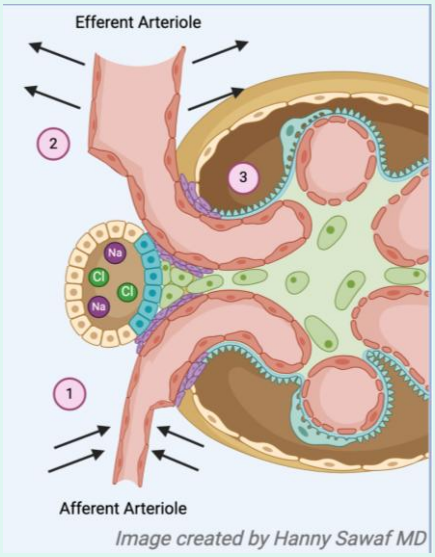




Farah LX et al. Am J Physiol Renal Physiol. 2016
Rico-Fontalvo J et al. J Bras Nephrol. 2024
Gutzwiller JP et al. J Clin Endocrinol Metab. 2004
Martins FL et al. Hypertension. 2020
Bai F et al. Eur J Pharmacol. 2020
Gutzwiller JP et al. J Clin Endocrinol Metab. 2004
Asmar A et al. Am J Physiol Endocrinol Metab. 2015

45

Cumulatively……



1. Through the action of NHE3, GLP-1 increases the delivery of sodium and chloride to the macula densa which results in **afferent arteriolar vasoconstriction** through tubuloglomerular feedback
2. GLP-1 decreases angiotensin II and endothelin-1 which results in **efferent arteriolar vasodilation**
3. Efferent arteriolar vasodilation and afferent arteriolar vasoconstriction both result in **decreased glomerular hypertension** and **decreased glomerular filtration**

Dhaun N et al. Br J Pharmacol. 2012
Bai F et al. Eur J Pharmacol. 2020
Puglsi S et al. Front Endocrinol. 2021

46

Less Common T2D Medications

47

Meglitinides "Glinides"

- Stimulate insulin secretion
  - Work in a manner similar to SFUs
    - Nateglinide (Starlix®)
    - Repaglinide (Prandin®)
- More-rapid onset of action and a shorter duration of action vs. SFUs
  - They are a good option for patients with erratic timing of meals
  - Work through lowering of post-prandial hyperglycemia vs. SFUs which have most profound effect on lower fasting BG
  - When used as monotherapy, nateglinide can lower HbA1c by approximately 0.5-1%

https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020741s035lbl.pdf
https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021204s014lbl.pdf

48

Glinides

- They have a lower risk of hypoglycemia than SFUs
- Similar to slightly lower-risk of weight gain vs. SFUs
- Caution must be used in patients with liver dysfunction (not studied)
- Dosing is before meals
- Reduced compliance taking 2-3 times per day timed with meals
- Not as cheap as generic SFU

Caroll MF et al. JCEM 2003; 88 (11): 5248–5254.
Guardado-Mendoza R et al. Arch Med Sci 2013 Apr 30;9(5):936–943.

49

Nateglinide

Aspect	Details
Drug Class	Non-sulfonylurea insulin secretagogue
Mechanism of Action	Stimulates pancreatic beta cells to release insulin in response to meals
Onset of Action	Rapid (within 30 minutes)
Duration of Action	Short (approximately 2-4 hours)
Primary Use	Control of postprandial hyperglycemia
Efficacy	Effective in lowering postprandial blood glucose levels and improving overall glycemic control
Combination Therapy	Can be used alone or in combination with other antidiabetic agents (e.g., metformin)
Benefits	Relatively low risk of hypoglycemia compared to sulfonylureas; may contribute to weight management
Common Side Effects	Hypoglycemia, gastrointestinal symptoms, potential weight gain
Long-Term Effects	Generally well-tolerated; long-term efficacy and safety continue to be evaluated in ongoing studies
Patient Population	Suitable for patients with postprandial hyperglycemia and those needing additional glycemic control
Dosing	Typically taken before meals; dose adjustments based on individual patient response
Contraindications	Not recommended in patients with type 1 diabetes or diabetic ketoacidosis
Recent Studies	Show continued effectiveness in managing postprandial glucose with a good safety profile

Ravindra Sali S et al. medtigo J Pharmacol.Published Date: Sep 24, 2024.https://doi.org/10.63096/medtigo3061115

50

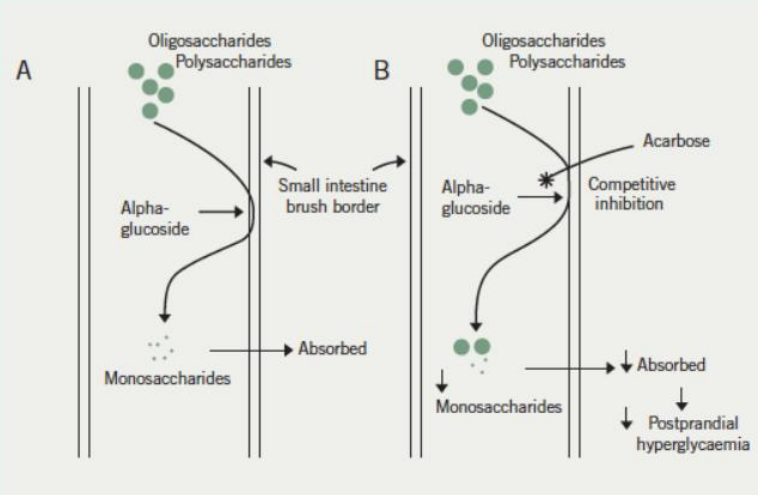
α-glucosidase Inhibitors

- Competitively block the enzyme α-glucosidase in the brush borders of the small intestine
- Inhibition of these enzyme systems reduces the rate of digestion of carbohydrates
- Less glucose is absorbed because the carbohydrates are not broken down into monosaccharides (glucose)
  - Acarbose (Precose®) and Meglitol (Glyset®)
  - Acarbose inhibits pancreatic alpha-amylase in addition to alpha-glucosidase
- Dosing must be prior to carbohydrate-containing meals

https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020482s024lbl.pdf
https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020682s010lbl.pdf

51

MOA: Acarbose

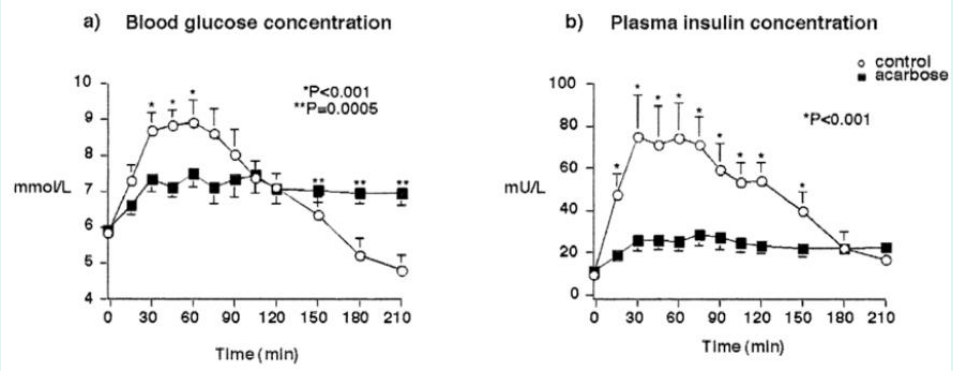


Arungarinathan G et al. Br J Cardiol 2011;18:78−81.

52

Acarbose 100 mg

180 mg/dL
162 mg/dL
144 mg/dL
126 mg/dL



Gentilcore D et al. The American Journal of Medicine (2005) 118, 1289.e5-1289.e11

53

α-glucosidase Inhibitors

- No hypoglycemia
  - But if a patient were to develop hypoglycemia while taking the medication, they should eat something containing monosaccharides, such as glucose tablets!
- Common side effects include GI complaints
  - Bloating, abdominal cramps, flatulence, and diarrhea
- Use should be avoided in patients with chronic intestinal diseases associated with marked disorders of digestion or absorption, or with conditions that may deteriorate as a result of increased gas formation in the intestine
- Still good drugs in patients with high CHO diets (Asians)

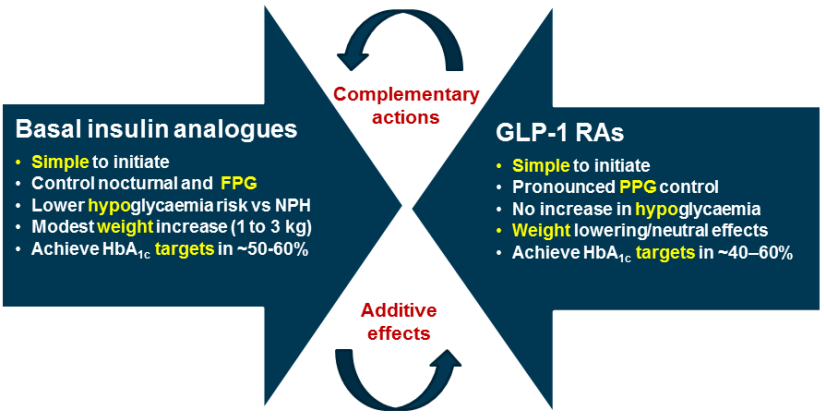
https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020482s024lbl.pdf
https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020682s010lbl.pdf

54

Thank You

55

Scientific Logic of Combining Basal Insulin With a GLP-1 Agonist



Courtesy of Julio Rosenstock, MD.
Holst JJ, Vilsbøll T. *Diabetes Obes Metab*. 2013;15:3-14.

56

Xultophy®: iDegLira

Soliqua®: iGlarLixi

1 Unit of SOLIQUA 100/33 contains 1 Unit of Lantus® and 0.33 mcg of lixisenatide

Lantus® (Units)	Lixisenatide (mcg)
15	5
30	10
40	13.3
50	16.7
60	20

57

DUAL-1: IDegLira,* A Fixed-Ratio Combination in Patients with T2D

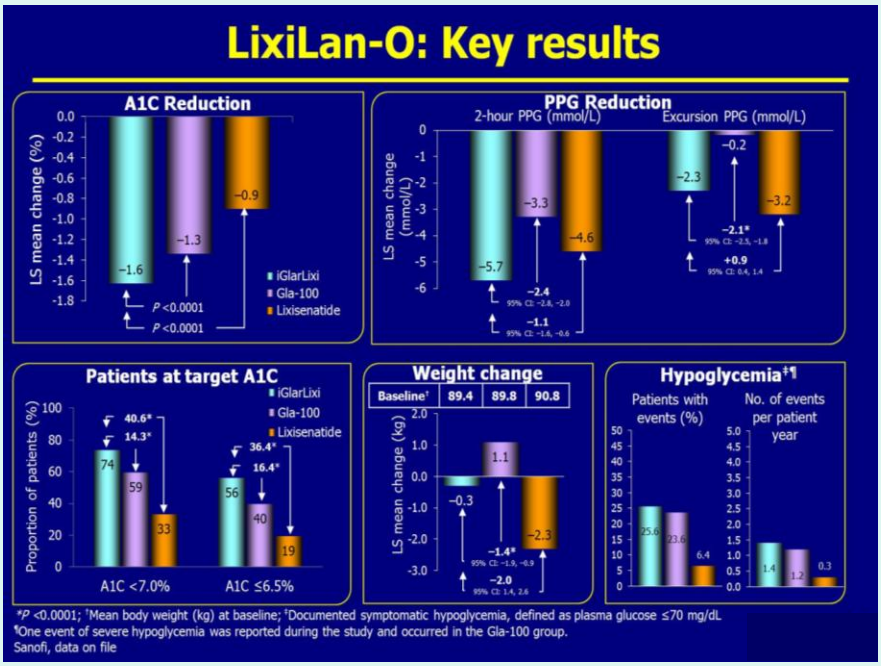
- **Study:** fixed ratio combination of insulin degludec (IDeg) and liraglutide (Lira)
- **Objective:** evaluate safety and efficacy of IDegLira compared with degludec or liraglutide alone

	IDegLira* (n=834)	Degludec (n=414)	Liraglutide (n=415)
Δ HbA_{1c}	-1.9%	-1.4%	-1.3%
Proportion achieving HbA_{1c} <7.0%	81%	65%	60%
FPG	100 mg/dL	104 mg/dL	131 mg/dL
Δ body weight	-0.5 kg	+1.5 kg	-2.9 kg

- **Conclusion:** IDegLira improves glycemic control with a low risk of hypoglycemia, weight gain, or GI complaints

Gough SC et al. Lancet Diabetes Endocrinol. 2014 Nov;2(11):885-93.

58



Rosenstock J et al. Diabetes Care. 2016 Nov;39(11):2026-2035.

59

Rarely Used T2D Medications

60

Bile Acid Sequestrant

- The exact mechanism by which bile acid sequestrants improve glycemic control is unknown
  - Colesevelam (Welchol®)
- Specifically indicated as an adjunct to diet and exercise to improve glycemic control in adults with type-2 diabetes mellitus

Fonseca VA et al. Diabetes Obes Metab. 2010 May; 12(5): 384–392.
Handelsman Y. Diabetes Care 2011 May; 34(Supplement 2): S244-S250.
https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022362s007lbl.pdf

61

Colesevelam

- Common side effect : Constipation
- Contraindications/Concerns:
  - GI disease: Use with caution in patients with GI motility disorders, or a history of major GI tract surgery
    - Secondary to the constipating effects of colesevelam
  - Hypertriglyceridemia: Use with caution in patients with serum triglyceride concentrations >300 mg/dL
    - Discontinue if triglyceride concentrations exceed 500 mg/dL or if hypertriglyceridemia-induced pancreatitis occurs

https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022362s007lbl.pdf

62

Dopamine Agonist

- Bromocriptine QR (Cyloset®)
- The exact mechanism by which Bromocriptine QR improves glycemic control is unknown
  - Centrally acting insulin sensitizer
- Morning administration of Bromocriptine QR improves glycemic control in patients with type-2 diabetes without increasing plasma insulin concentrations

https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020866lbl.pdf

63

Dopamine Agonist

- Bromocriptine QR should be administered once daily within two hours upon awakening in the morning
  - Should be taken with food to potentially reduce gastrointestinal side effects such as nausea
  - quick acting formulation of bromocriptine which results in an increase in circulating levels of bromocriptine for 4-5 hours after administration
  - Can not simply use generic bromocriptine
- Not frequently used

Chamarthi B and Cincotta AH. Postgrad Med. 2017 May;129(4):446-455.

64

Side Effects

- No hypoglycemia
- Weight neutral
- Common side effects:
  - Nausea
  - Hypotension
    - Including orthostatic hypotension
  - Somnolence

https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020866lbl.pdf

65

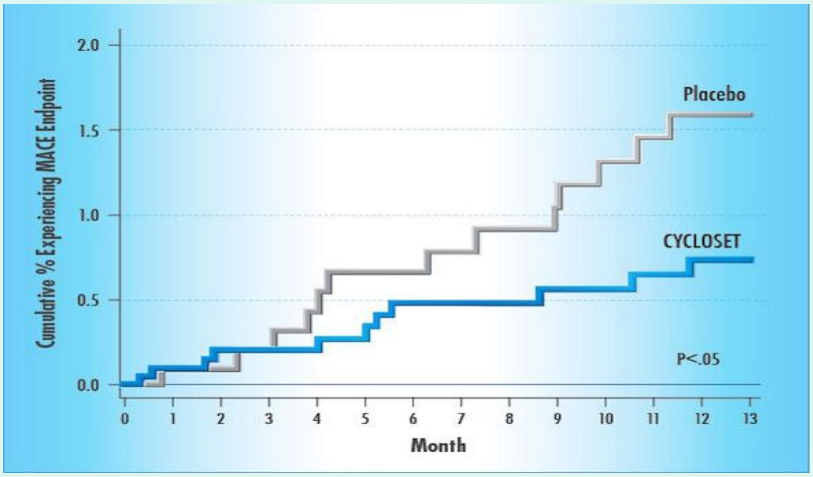
Cautions/Concerns

- Hypotension
  - Use caution in patients taking anti-hypertensive medications
- Psychosis
  - May exacerbate psychotic disorders
  - **Beware** of possible interaction with dopamine receptor antagonists (antipsychotics)
  - **Beware** of possible interaction with other dopamine agonist therapies
    - Used in the treatment of Parkinson's disease, hyperprolactinemia, restless leg syndrome, etc.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020866lbl.pdf

66

CV Risk Reduction?

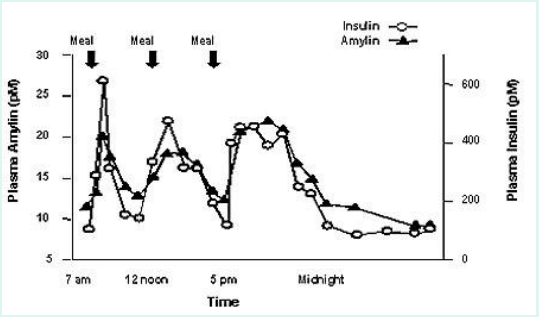


Gaziano JM et al. J Am Heart Assoc. 2012 Oct;1(5):e002279.

67

Amylin

- Co-secreted with insulin from the pancreatic β-cells



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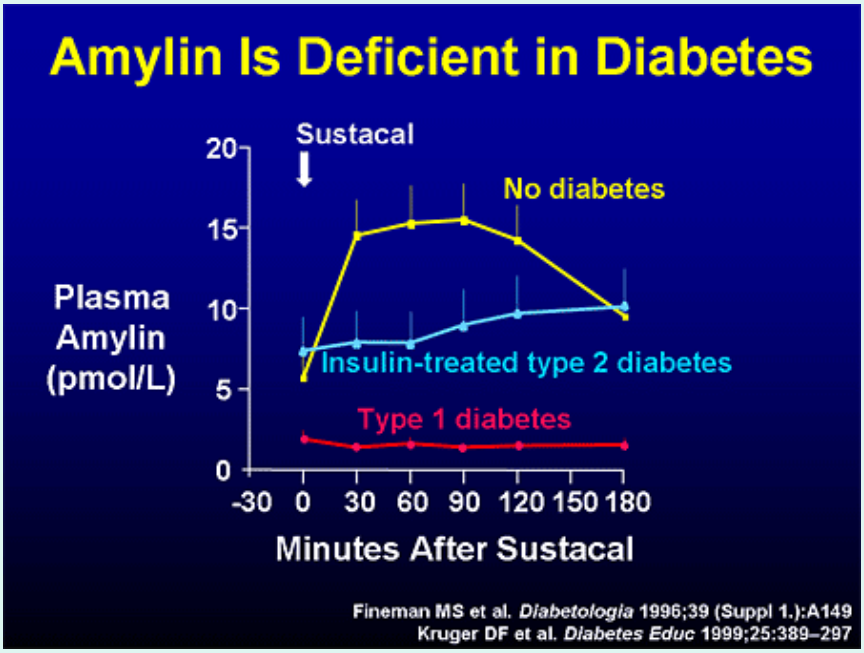

69

Amylin

- Amylin affects the rate of postprandial glucose appearance through a variety of mechanisms:
  - Slows gastric emptying
  - Suppresses glucagon secretion (not normalized by insulin alone), which leads to suppression of endogenous glucose output from the liver
  - Amylin also regulates food intake due to the centrally-mediated modulation of appetite

Schmitz O et al. Diabetes 2004 Dec; 53(suppl 3): S233-S238.

70

Pramlintide

- Pramlintide (Symlin®), by acting as an amylinomimetic agent, exhibits these effects
- Is an anti-hyperglycemic injectable drug for use in patients with diabetes treated **with** insulin
  - Given at the same time as prandial insulin
  - May help decrease insulin requirements, suppress appetite, improve blood sugar control, and assist with weight loss
- Can/has been used off-label in patients not on prandial insulin
- Never "caught on" with patients and physicians
  - Difficult to take 3 additional injections on top of the 3-5 injections of insulin per day
  - Sometimes used only at the largest meal
  - Most reasonable to try in those using insulin pump therapy
  - GLP-1 RA therapy is more practical in T2D patients

https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021332s007_S016.pdf

71

Pramlintide

- Nausea/vomiting most common side effects
- Modest efficacy
  - Usually ~ 0.2-0.5% drop in A1C
- Watch for hypoglycemia closely
  - Because of use with insulin
  - Suppressed appetite

https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021332s007_S016.pdf

72