All the New Medications: What Should I Choose for NIDDM

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changing lives for the better, *together.*

Disclosures

- None

Objectives

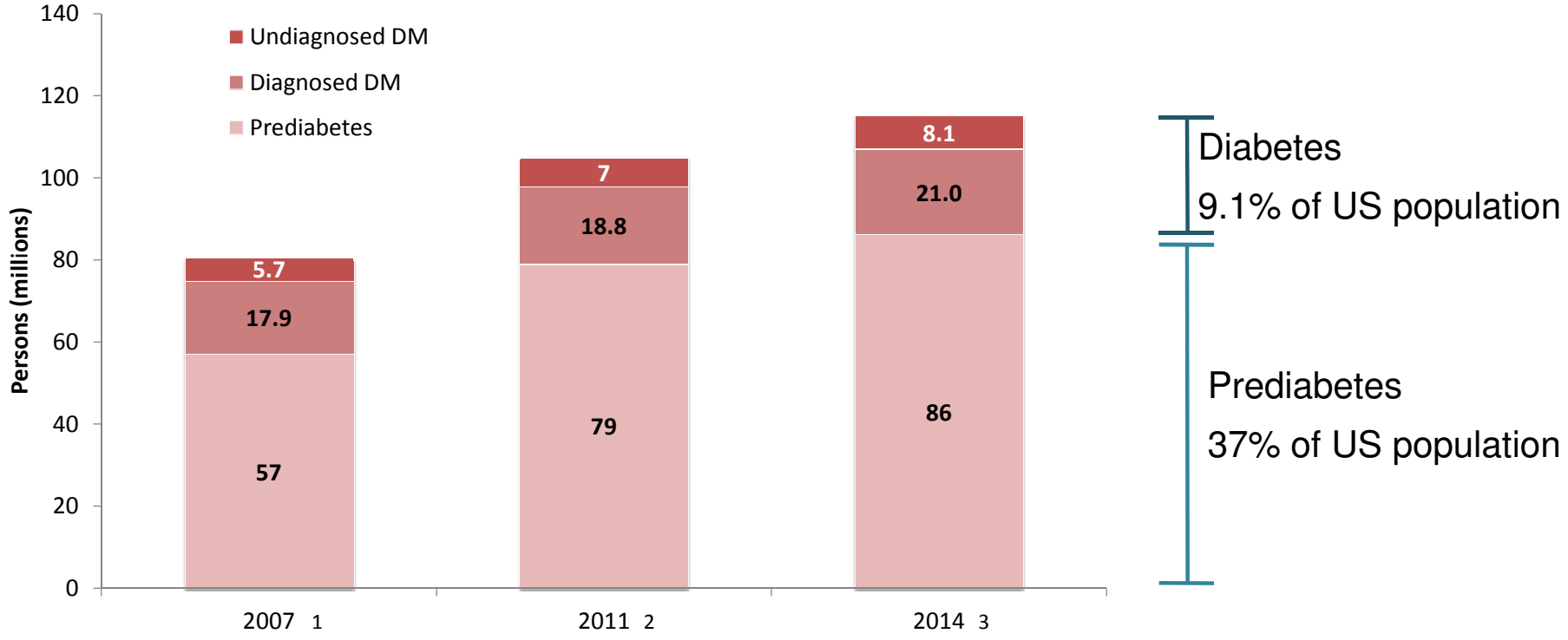
- To become familiar with the new medication classes for the treatment of Type 2 diabetes mellitus
- Become familiar with the advantages and disadvantages of the new classes of diabetes medications

Outline

- Background
- A1C Goals and Outcomes
- Case Presentation
- Review new medication classes
  - DPP4 Inhibitors
  - GLP1 Receptor Agonists
  - GLP1 Receptor Agonist + Basal insulin combined
  - SGLT2 Inhibitors
- Review case presentations
- Summary

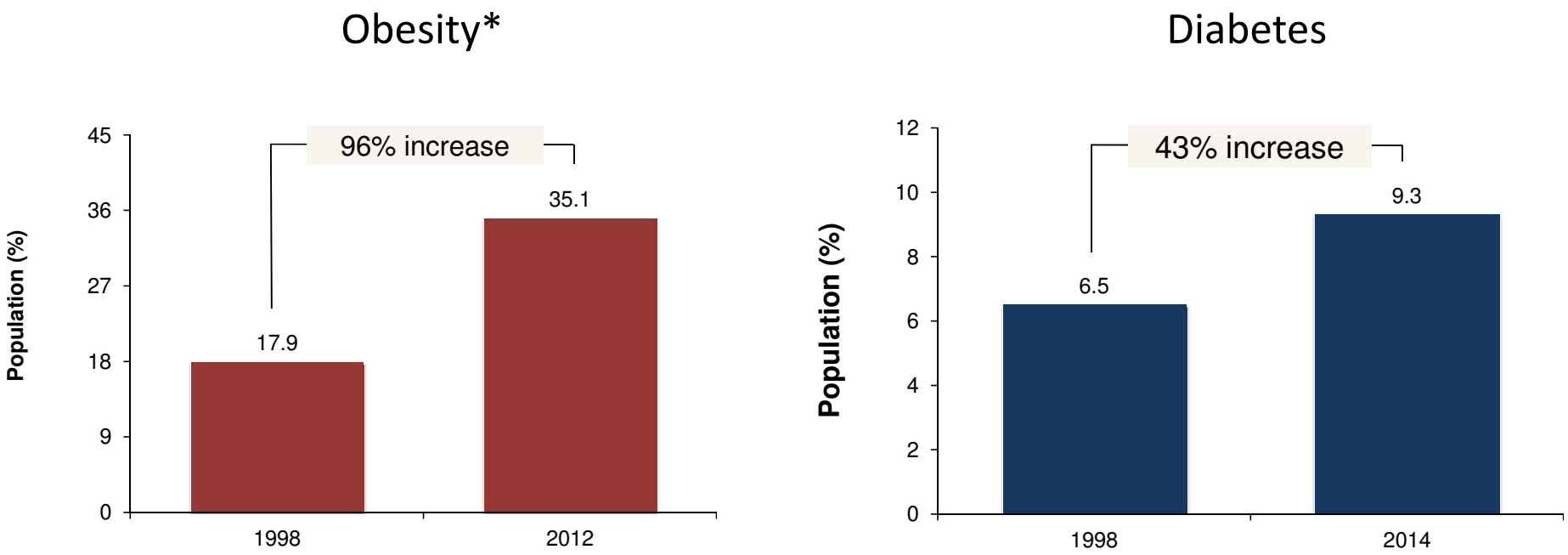
Background

Prevalence of Diabetes and Prediabetes in the United States



1. CDC. National diabetes fact sheet, 2008. http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2008.pdf.
2. CDC. National diabetes fact sheet, 2011. http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf.
3. CDC. National diabetes statistics report, 2014. http://www.cdc.gov/diabetes/pubs/statsreport14/national-diabetes-report-web.pdf

Increase in Diabetes Parallels the Increase in Obesity in the United States



*BMI ≥30 kg/m^2.

CDC. National diabetes statistics report, 2014. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention, 2014. Mokdad AH, et al. *JAMA*. 1999;282:1519-1522; Mokdad AH, et al. *Diabetes Care*. 2000;23:1278-1283; Ogden CL, et al. *JAMA*. 2014;311:806-814.

Diabetes Morbidity and Mortality

- 7th leading cause of death in US
- Leading cause of blindness
- Most frequent cause of kidney failure
- Accounts for ~60% of nontraumatic lower limb amputations
- Doubles risk of periodontal disease
- Double risk of developing depression
- Increases patients' susceptibility to acute illness
  - Worsens the prognosis of patients with acute illness

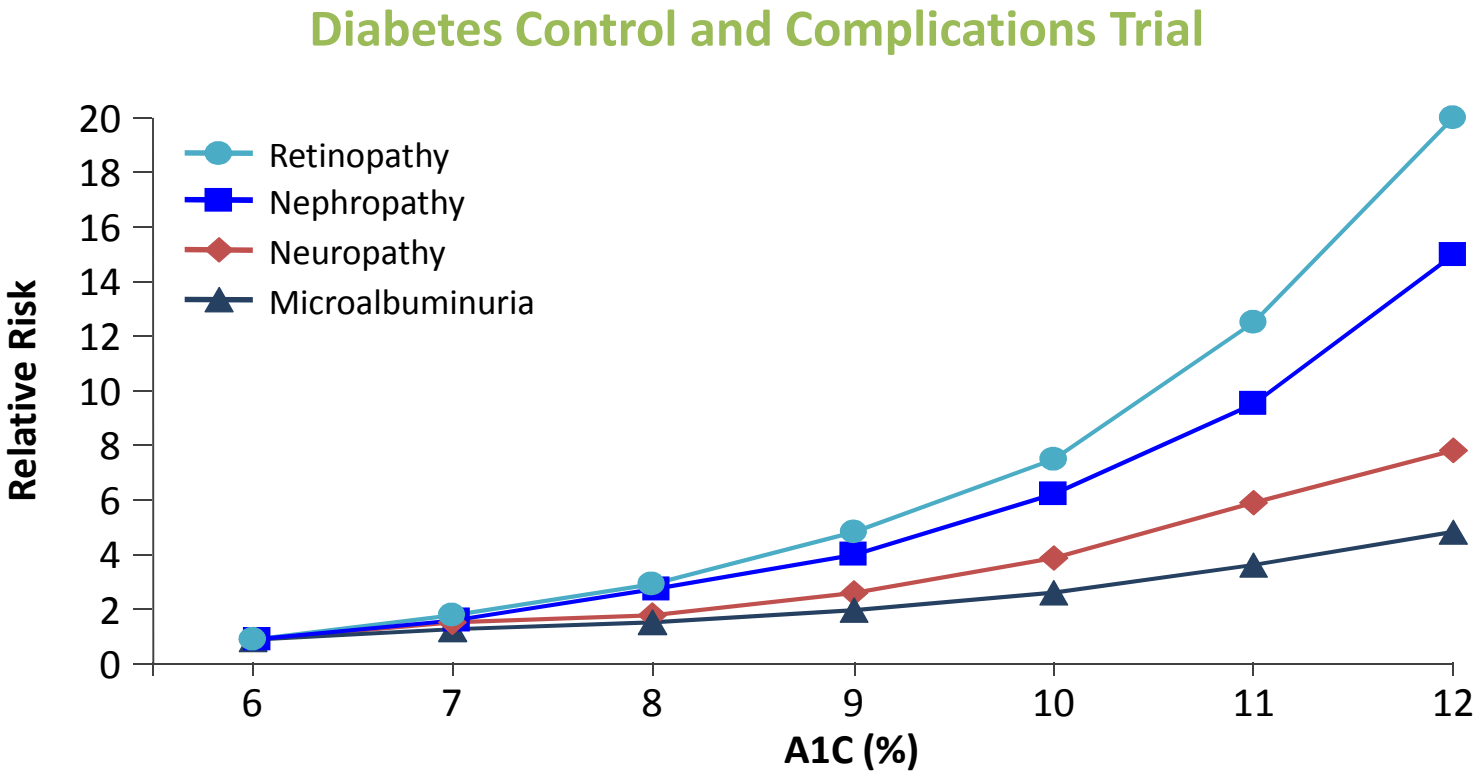
CDC. National diabetes statistics report, 2014. http://www.cdc.gov/diabetes/pubs/statsreport14/national-diabetes-report-web.pdf.
CDC. National diabetes fact sheet, 2011. http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf.

Relationship of A1C Goals and Outcome

- Microvascular complications
  - 38% reduction in risk with every 1% reduction in A1C
- Macrovascular complications
  - Reduction in risk with early, intensive treatment
  - High-risk patients, intensive control may increase risk

UKPDS Lancet 1998; Holmann New EnglJ 2008; Patel New EnglJ 2008; Stratton BMJ 2008; Gerstein New EnglJ 2011.

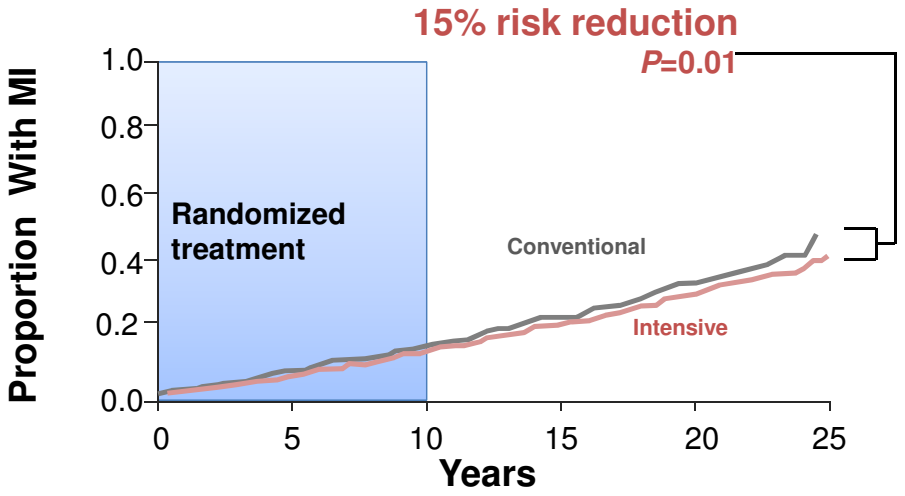
Microvascular Complications Increase With Increasing A1C



Skyler JS. *Endocrinol Metab Clin North Am*. 1996;25:243-254.

Intensive Glycemic Control Reduces Long-term Macrovascular Risk

UKPDS
T2D, newly diagnosed (N=4209)



T2D, type 2 diabetes; UKPDS, United Kingdom Prospective Diabetes Study.

Holman RR, et al. *N Engl J Med*. 2008;359:1577-1589.

GOALS FOR GLYCEMIC CONTROL

INDIVIDUALIZE GOALS

A1C ≤ 6.5%

For patients without concurrent serious illness and at low hypoglycemic risk

A1C > 6.5%

For patients with concurrent serious illness and at risk for hypoglycemia

 DOI 10.4158/EP161682.CS

Targets for Glycemic Control

Targets for Gylcemic Control

	ADA*	AACE**
HbA_{1c} (%)	<7.0	<6.5
Fasting/preprandial glucose (mg/dL)	80–120	<110
Postprandial glucose (mg/dL)	100–180	<140
Bedtime glucose (mg/dL)	100–140	100–140

*American Diabetes Association *Diabetes Care*. 2000;26[suppl 1]:S33.
**American College of Clinical Endocrinologists *Endocin Pract*. 2002;8[suppl 1]:40.

New Medication Classes

- DDP4 Inhibitors
- GLP-1 Receptor Agonist (RA)
- GLP-1 RA + Basal insulin combination
- SGLT2 Inhibitors

It is <u>now</u> possible to treat Type 2 diabetes mellitus effectively with a low risk for hypoglycemia, weight loss, robust lowering of A1C, a reduction in the need or frequency of self-monitored blood glucose levels, and even cardiac death reduction.

GLYCEMIC CONTROL ALGORITHM

LIFESTYLE THERAPY
(Including Medically Assisted Weight Loss)

Entry A1C < 7.5%

MONOTHERAPY*

- ✓ Metformin
- ✓ GLP-1 RA
- ✓ SGLT-2i
- ✓ DPP-4i
- ! TZD
- ✓ AGi
- ! SU/GLN

If not at goal in 3 months proceed to Dual Therapy

Entry A1C ≥ 7.5%

DUAL THERAPY*

MET or other 1st-line agent +

- ✓ GLP-1 RA
- ✓ SGLT-2i
- ✓ DPP-4i
- ! TZD
- ! Basal Insulin
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGi
- ! SU/GLN

If not at goal in 3 months proceed to Triple Therapy

TRIPLE THERAPY*

MET or other 1st-line agent + 2nd-line agent +

- ✓ GLP-1 RA
- ✓ SGLT-2i
- ! TZD
- ! Basal insulin
- ✓ DPP-4i
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGi
- ! SU/GLN

If not at goal in 3 months proceed to or intensify insulin therapy

Entry A1C > 9.0%

SYMPTOMS

NO	YES
DUAL Therapy OR TRIPLE Therapy	INSULIN ± Other Agents

ADD OR INTENSIFY INSULIN

Refer to Insulin Algorithm

LEGEND

- ✓ Few adverse events and/or possible benefits
- ! Use with caution

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

PROGRESSION OF DISEASE

 DOI 10.4158/EP161682.CS

Case 1

- 52 year old man here for follow-up of Type 2 DM. His diabetes was diagnosed 4 years ago. A1C is 7.2%.
- Medications:
  - Metformin 1000 mg PO BID
  - Atorvastatin 20 mg QD
  - Lisinopril 10 mg PO QD
  - ASA 81 mg PO QD
- For the last 3 months, he has been working on improving diet and increasing exercise.
- No history of pancreatitis . No personal or family history of medullary thyroid cancer. No recurrent yeast infections.

Case 1

- PMH:
  - DM2
  - HTN
  - Mixed hyperlipidemia
  - Obesity (BMI 32)
  - CAD s/p stent 2 years ago
- BP 130/75
- Normal BMP. Lipids at goal.
- Eye exam and vaccinations up-to-date
- Sensation to monofilament decreased on diabetic foot exam

Case 1

- What is next best step in his diabetes management?
  A. No change in medication. A1C at goal.
  B. Add sulfonylurea (e.g., glipizide)
  C. Add SGLT-2 Inhibitor
  D. Add DPP-4 Inhibitor
  E. Add GLP-1 Receptor Agonist

Case 2

- 47 year old woman with Type 2 DM.
- A1C is 6.9%, however, she reports frequent low blood glucose levels (40's-50's mg/dL) in the afternoon associated with missed meals at work. No lows overnight or in the morning.
- She is also very frustrated with her weight. Trying to follow a low carb diet with reduced portion sizes but has only lost 2 lbs over last 3 months.
- No history of pancreatitis. No personal or family history of medullary thyroid cancer. No history of yeast infections.

Case 2

- Medications:
  - Metformin 500 mg PO BID
  - Lantus 10 units SQ QHS
  - Glimepiride 1 mg PO QD
  - Atorvastatin 10 mg PO QD
  - Losartan 100 mg PO QD
  - ASA 81 mg PO QD

Case 2

- PMH:
  - DM2
  - HTN
  - Mixed HLD
  - Diabetic kidney disease
- BMI 34
- eGFR 40
- BP: 116/65
- Recent normal eye exam, up-to-date on vaccinations, normal diabetic foot exam

Case 2

- What would you do for this individual?
  A. No change. A1C is at goal.
  B. Stop glimepiride.
  C. Stop glimepiride. Add GLP-1 receptor agonist
  D. Stop glimeperide. Add DPP-4 Inhibitor
  E. Stop glimeperide. Add SGLT-2 Inhibitor

Case 3

- 69 year old man here for follow-up of Type 2 DM. A1C 8.4%.
- Medications:
  - Metformin 1000 mg PO BID
  - Rosuvastatin 10 mg PO BID
  - ASA 81 mg PO BID
  - Lisinopril 20 mg PO QD
- He reports a needle phobia and does not want any type of injectable therapy.
- He lives alone.
- Previously had lower A1C on SU, however, due to recurrent hypoglycemia the SU was discontinued. He reports irregular eating schedule.

Case 3

- No history of pancreatitis. No personal or family history of medullary thyroid cancer. No history of yeast infections.
- PMH:
  - DM2
  - Mild non-proliferative diabetic retinopathy, stable
  - Peripheral neuropathy
  - Mixed HLD
  - HTN
  - OSA on CPAP
  - CAD s/p CABG

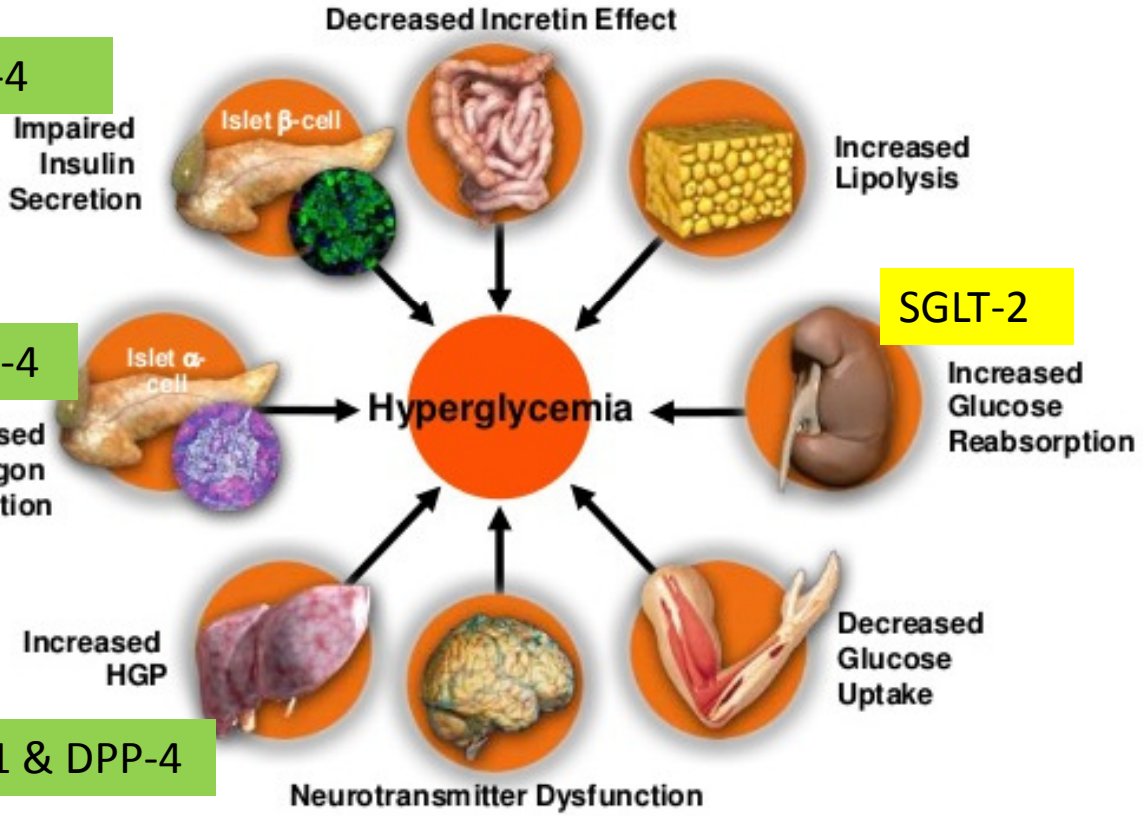
Case 3

- BP 140/80
- BMI: 42
- Normal BMP. Lipids at goal.
- Up-to-date on eye exam and vaccinations

Case 3

- What would you offer this patient?
  A. Restart SU at lower dose
  B. Start GLP-1 Agonist
  C. Start DPP-4 Inhibitor
  D. Start SGLT-2 Inhibitor
  E. Start a SGLT-2 and DPP-4 Inhibitor

Pathophysiologic Defects in Type 2 Diabetes: The Ominous Octet



DeFronzo RA. *Diabetes*. 2009;58(4):773-795.

GLP-1 & DPP-4

GLP-1 & DPP-4

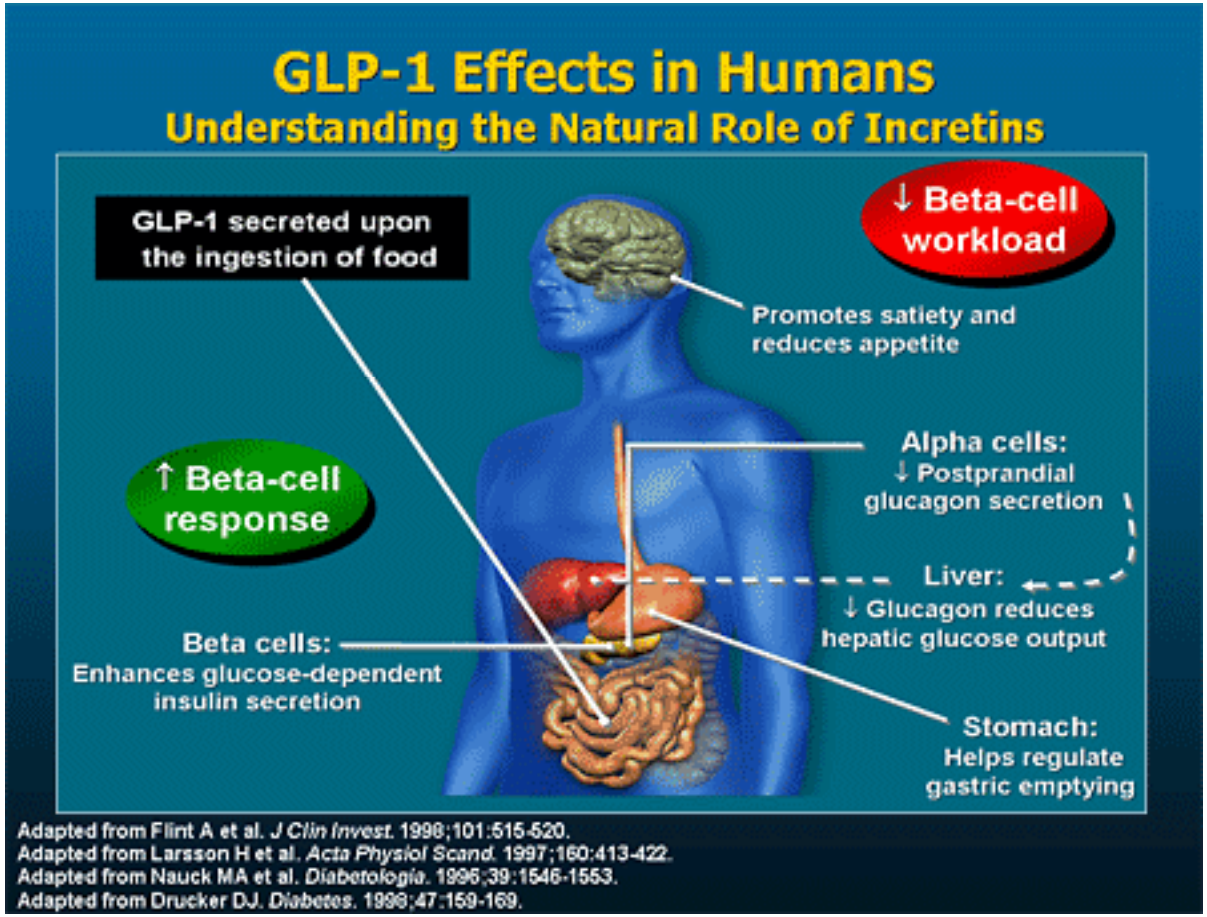
SGLT-2

GLP-1 & DPP-4

GLP-1 & DPP-4

GLP-1

Normal Physiology: GLP-1 and DPP4



DPP-4 Inhibitors

FDA-Approved Agents

- Alogliptin (Nesina)
- Linagliptin (Tradjenta)
- Saxagliptin (Onglyza)
- Sitagliptin (Januvia)

Key Features

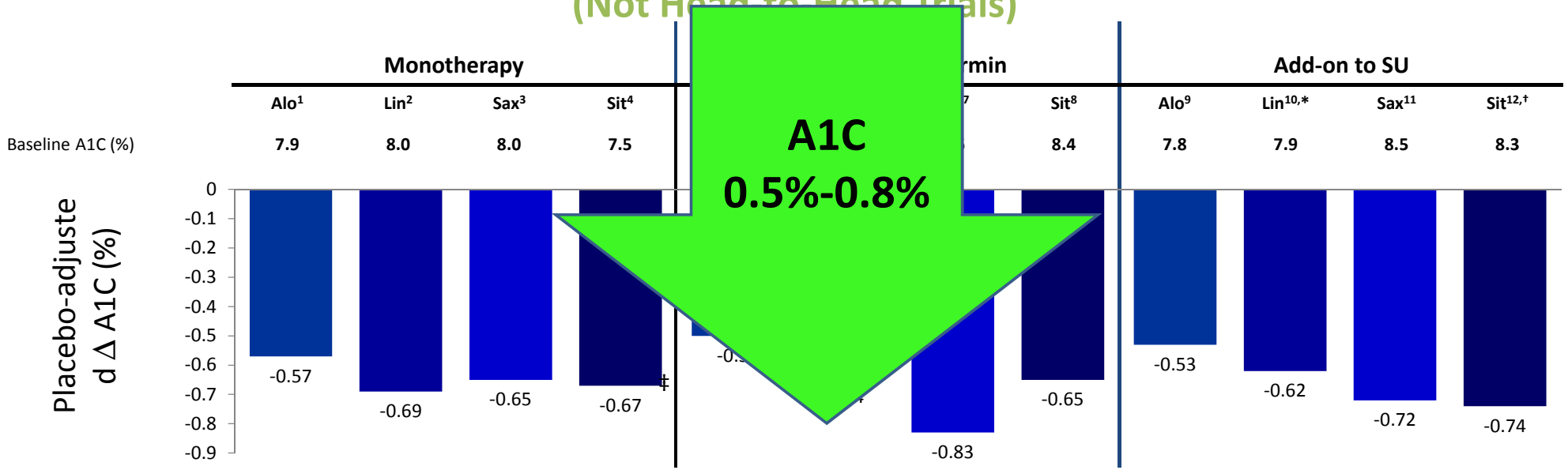
- Oral administration
- Increase endogenous GLP-1 levels
- Increase glucose-dependent insulin secretion
- Suppress glucagon production

DPP-4, dipeptidyl peptidase 4; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide 1.

Garber AJ, et al. *Endocr Pract*. 2016;22:84-113.

Glucose Control with DPP-4 Inhibitors

Placebo-Adjusted Change from Baseline (Not Head-to-Head Trials)

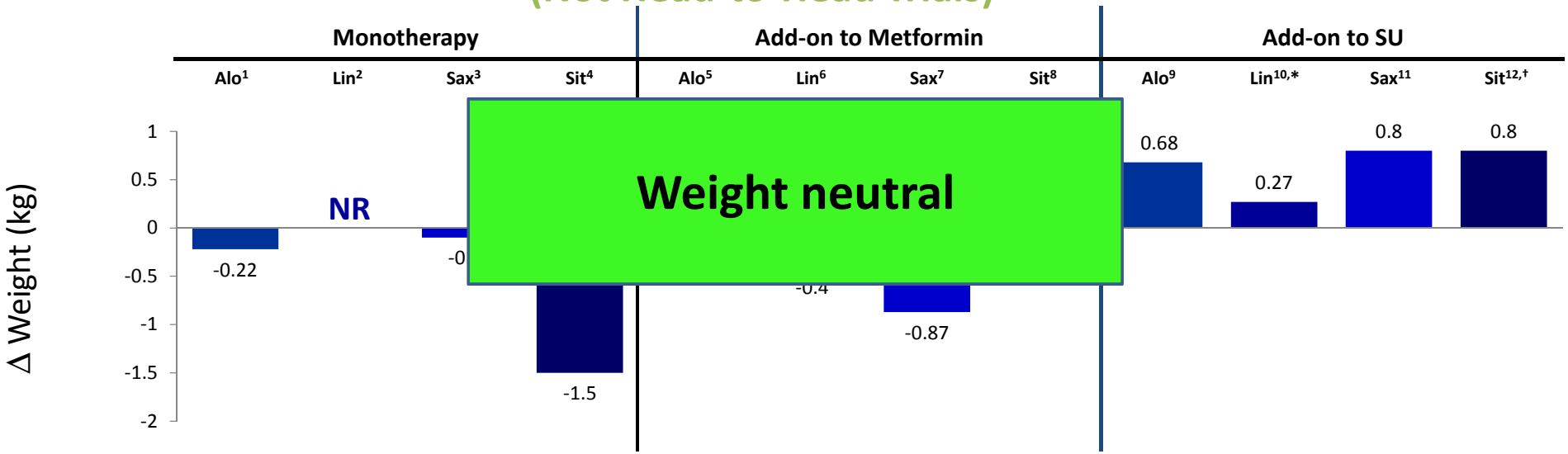


*SU + metformin. †With or without metformin. ‡Absolute change from baseline (active-controlled trial).

1. DeFronzo RA, et al. *Diabetes Care*. 2008;31:2315–2317. 2. Del Prato S, et al. *Diabetes Obes Metab*. 2011;13:258-267.
3. Rosenstock J, et al. *Curr Med Res Opin*. 2009;25:2401-2411. 4. Nauck MA, et al. *Diabetes Obes Metab*. 2007;9:194-205. 5. Nauck MA, et al. *Int J Clin Pract*. 2009;63:46-55. 6. Taskinen MR, et al. *Diabetes Obes Metab*. 2011;13:65-74. 7. DeFronzo RA, et al. *Diabetes Care*. 2009;32:1649-1655. 8. Charbonnel B, et al. *Diabetes Care*. 2006;29:2638-2643. 9. Pratley RE, et al. *Diabetes Obes Metab*. 2009;11:167-176. 10. Owens DR, et al. *Diabet Med*. 2011;28:1352-61. 11. Chacra AR, et al. *Int J Clin Pract*. 2009;63:1395-1406. 12. Hermansen K, et al. *Diabetes Obes Metab*. 2007;9:733-745.

Weight Change with DPP-4 Inhibitors

Absolute Change from Baseline (Not Head-to-Head Trials)



NR, value not reported.

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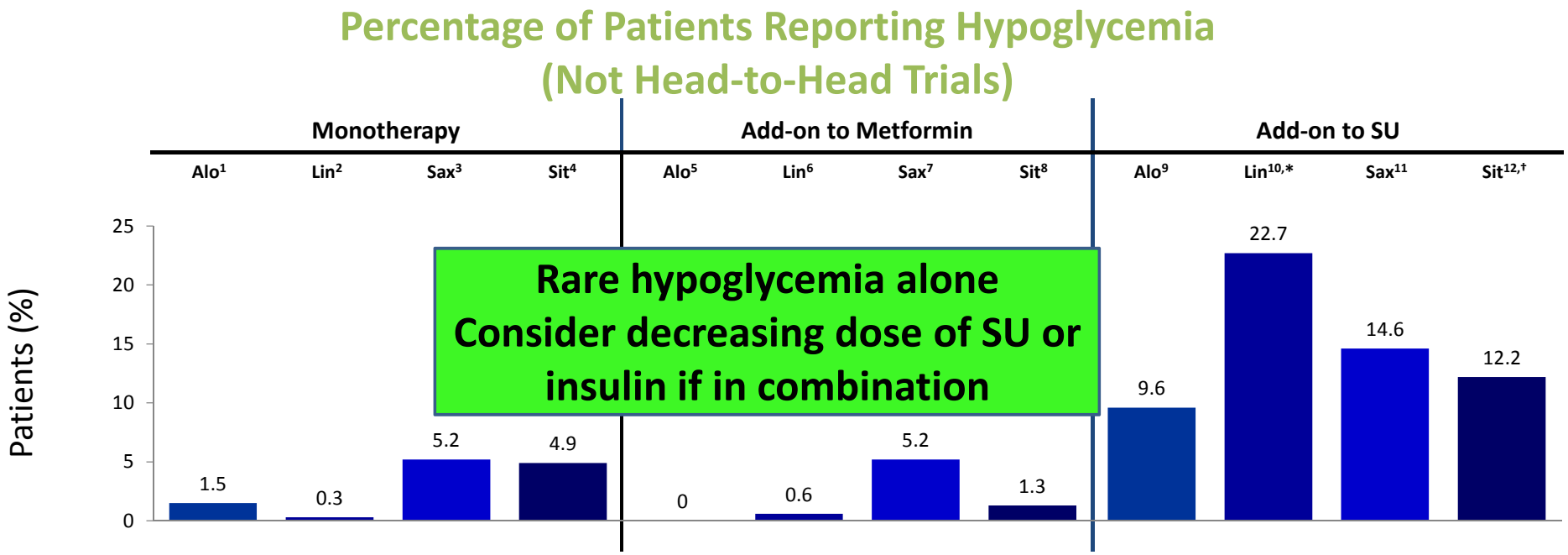
Hypoglycemia with DPP-4 Inhibitors



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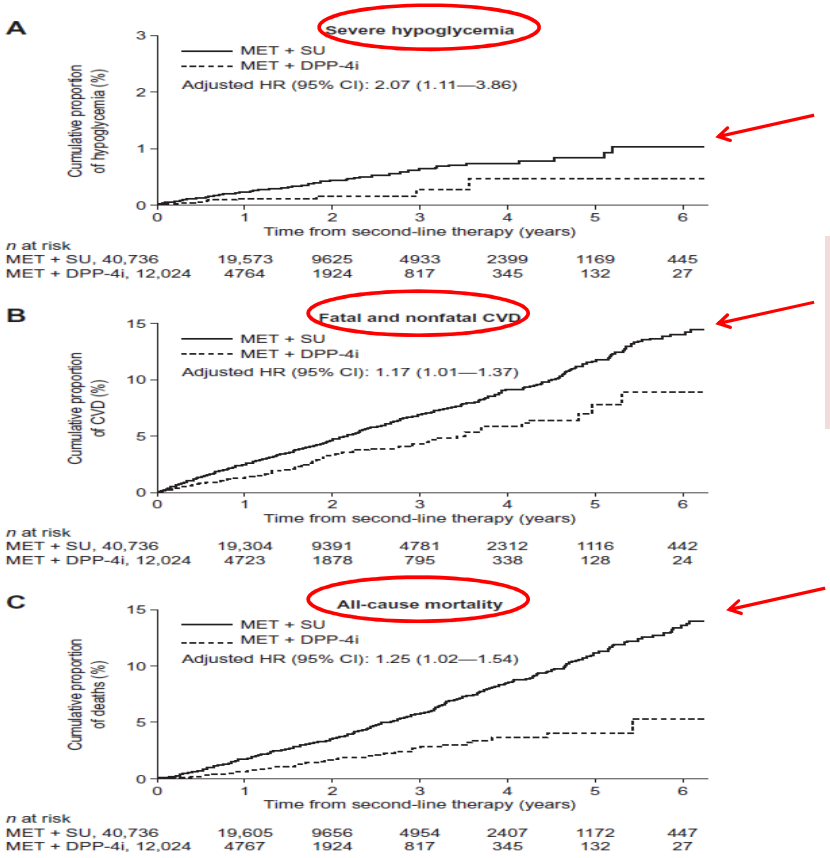
Cardiovascular Outcome Trials

DDP4 Inhibitor CV Outcome Trials

	TECOS	SAVOR-TIMI	EXAMINE	CARMELINA
MEDICATION	**Sitagliptin**	**Saxagliptin**	**Alogliptin**	**Linagliptin**
# OF PATIENTS	14,671	16,492	5,380	8,300
	DM2, established CVD	DM2, established CVD or multiple risk factors for CVD	DM2, recent acute coronary syndrome event	DM2, high risk for CV events, BMI ≤45
STUDY DESIGN	Multi-center, randomized, double-blind, open-label	Multi-center, randomized, double-blind, placebo-controlled	Multi-center, randomized, double-blind	Multi-center, randomized, double-blind, parallel assignment
PRIMARY OUTCOME	**4-point MACE:** CV death, nonfatal MI, nonfatal stroke, hospitalization for unstable angin, Noninferiority and superiority design	**3-point MACE**: CV death, nonfatal MI, nonfatal ischemic stroke. Superiority and noninferiority design	**3-point MACE:** CV death, nonfatal acute MI, nonfatal stroke. Noninferiority design	**4-point MACE:** CV death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina
RESULTS	Primary outcome: Sitagliptin 11.4%, Placebo 11.6%, Hazard ratio: 0.98 (95% CI: 0.88 to 1.09), p<0.001. Secondary Outcome: Heart failure hospitaliza[illegible] 2.8%, P[illegible] Hazard ratio: 1.00 (95% CI: 0.83-1.20), p=0.98	Primary outcome: Saxagliptin 7.3%, Placebo 7.2%, Hazard ratio: 1.0 (95% CI: 0.89-1.12), p=0.99. Secondary outcome, Heart failure hoospitalization: Saxagliptin 3.5%, Placebo 2.8%, Hazard ratio: 1.27 (95% CI: 1.07-1.51), p=0.007	Primary Outcome: Alogliptin 11.3%, Placebo 11.8%, Hazard ratio: 0.96 (95% CI: <1.16), p=0.32. Post hoc analysis: Alogliptin 3.1%, Placebo 2.9%, Hazard ratio: 1.07 (95% CI: 0.79-1.46), p=0.66	Ongoing Jan 2018
ADDITIONAL BENEFITS/RISKS	At 4 months, HbA1C .4 percentage points lower in sitagliptin group vs placebo group; sitagliptin group less like to start long-term insulin therapy	Glycemic control was lower in saxagliptin group compared [illegible] place	NT-pro-BNP concentrations decreased significantly and similar in the 2 groups. Post-hoc analysis for hospitalization for heart failure	

Sulphonylurea compared to DPP-4 Inhibitors in combination with metformin

- All T2DM patients in Sweden 2006-2013
- Model adjusted for age, sex, CVD drugs, prior CVD diagnosis
- Met + SU = 40,736
- Met + DPP4i = 12, 024



More hypoglycemia, CV events and mortality in SU-treated patients

Erikson, JW et al Diab Res Clin Pract 2016. 117; 39-47

Stay Tuned…CAROLINA TRIAL

- Cardiovascular Outcome Study of Linagliptin vs Glimepiride
- Ongoing, randomized trial
- Started date: 10/2010
- Estimated Completion date: 2/2019
- N = 6041
- Reported patient characteristics:
  - Median duration Type 2 DM: 6.2 years
  - 60% male; 40% female
  - Mean A1C 7.2%
  - 34.5% had previous CV complications

Marx, N et al. Diab Vasc Dis Res. 2015 May;12(3):164-74.

Stay Tuned…CAROLINA TRIAL

- Primary Outcome: 3 point MACE
  - CV death
  - non-fatal MI
  - non-fatal stroke

Marx, N et al. Diab Vasc Dis Res. 2015 May;12(3):164-74.

Adverse Effects of DPP-4 Inhibitors

- Generally well tolerated
- Side-effects
  - Headache
  - Nausea, diarrhea, abdominal pain
  - Peripheral edema
- Rare side-effects
  - Acute pancreatitis – sitagliptin
  - Acute renal failure
  - Bone fractures – saxagliptin
  - Angioedema

Safety Considerations with DPP-4 Inhibitors

- **Pancreatitis**
  - No causal relationship established
  - Discontinue if pancreatitis suspected
  - No evidence of increased pancreatitic risk with incretins vs other agents
- **Pancreatic cancer**
  - No evidence of increased pancreatic risk with incretins vs other agents
  - Further assessments required from long duration controlled studies or epidemiological databases
- **CHF**
  - Potentially increased risk of CHF hospitalization with alogliptin and saxagliptin
- **Renal impairment**
  - Dose adjustment and periodic monitoring of kidney function in moderate-severe CKD
    - EXCEPT linagliptin which is NOT renally excreted

Garber AJ, et al. *Endocr Pract*. 2016;22:84-113. White W, et al. *N Engl J Med*. 2013;369:1327-1335. Scirica BM, et al. *Circulation.* 2014;130:1579-1588. ADA/EASD/IDF statement concerning the use of incretin therapy and pancreatic disease [news release]. Alexandria, VA: American Diabetes Association, European Association for the Study of Diabetes, International Diabetes Federation; June 28, 2013. http://www.diabetes.org/newsroom/press-releases/2013/recommendations-for.html.

Key Points

- Once daily, oral therapy
- Clinically significant A1C reductions (0.5-0.8%)
- No/low hypoglycemia
  - Consider reduction of dose of SU or insulin if used in combination
- Complementary mechanism of action with many drugs
  - Don’t use with GLP-1 receptor agonist
- Very well tolerated
  - No weight gain, no hypoglycemia, no edema, minimal GI sx
- DPP-4 Inhibitors are safe in patients with CV disease.
  - ? Saxagliptin and alogliptin increase risk of hospitalizations for heart failure
- Need dose adjustment for moderate-severe CKD
  - Except for linagliptin

GLP-1 Receptor Agonists

FDA-Approved Agents

- Albiglutide (Tanzeum)
- Dulaglutide (Trulicity)
- Exenatide (Byetta)
- Exenatide ER (Bydureon)
- Liraglutide (Victoza)
- Lixisenatide (Aldyxin)

Key Features

- Injectable administration
- Mimic action of native GLP-1
- Increase glucose-dependent insulin secretion
- Suppress glucagon production
- Slow gastric emptying

ER, extended release; GLP-1, glucagon-like peptide 1.

Garber AJ, et al. *Endocr Pract*. 2016;22:84-113.

GLP-1 RA Dosing

Daily dosing

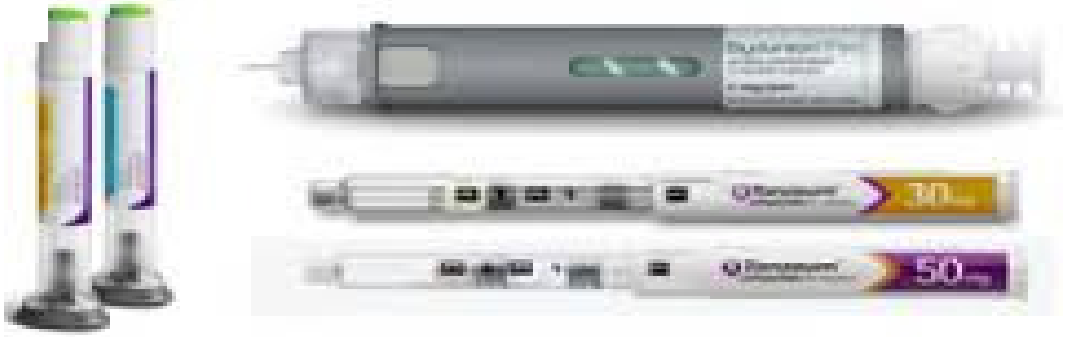
Once weekly dosing

(once weekly dosing)

QW Exenatide (Bydureon®) FDA approved 2012

Albiglutide (Tanzeum®) FDA approved 2014

Dulaglutide (Trulicity®) FDA approved 2014



Glucose Control with GLP-1 Receptor Agonists

Head-to-Head Trials

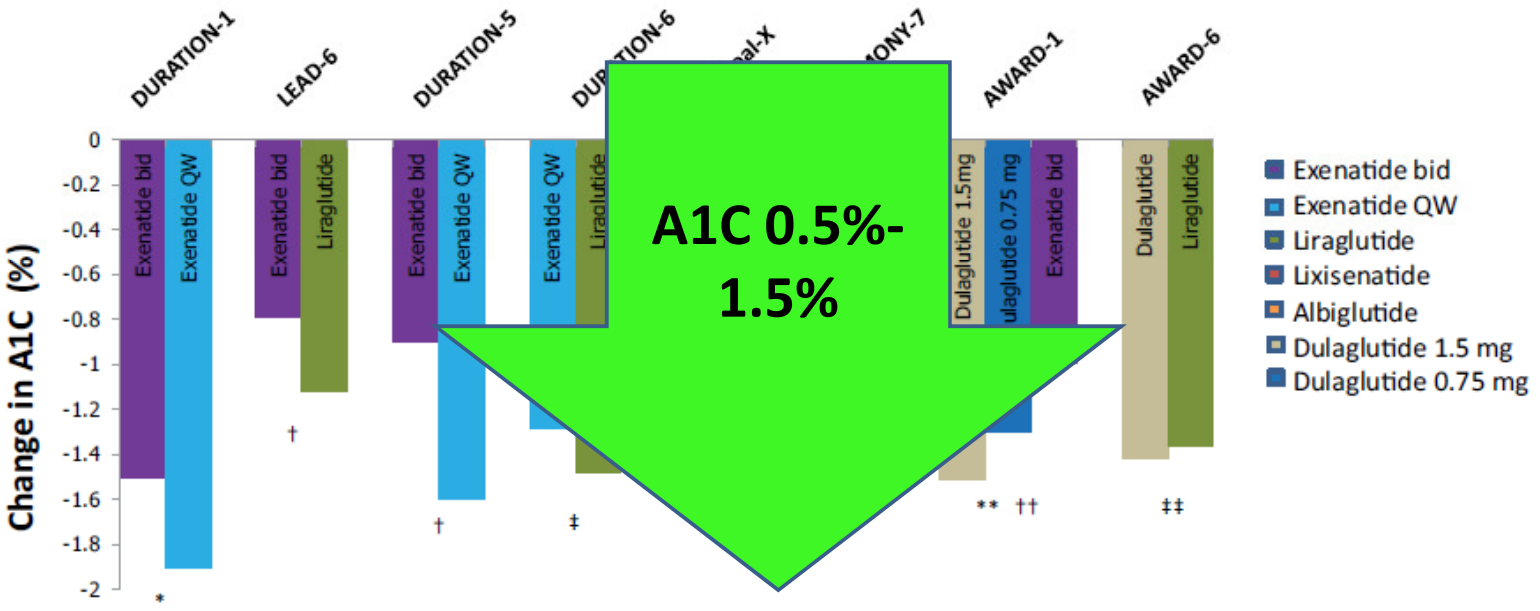


Figure 1. Changes in A1C values with glucagon-like peptide 1 receptor agonists (GLP-1 RAs) in head-to-head clinical studies.

Trujillo, J et al. T*herapeutic Advances in Endocrinology and Metabolism* 2015, 6(1): 19–28

Weight Change with GLP-1 Receptor Agonists

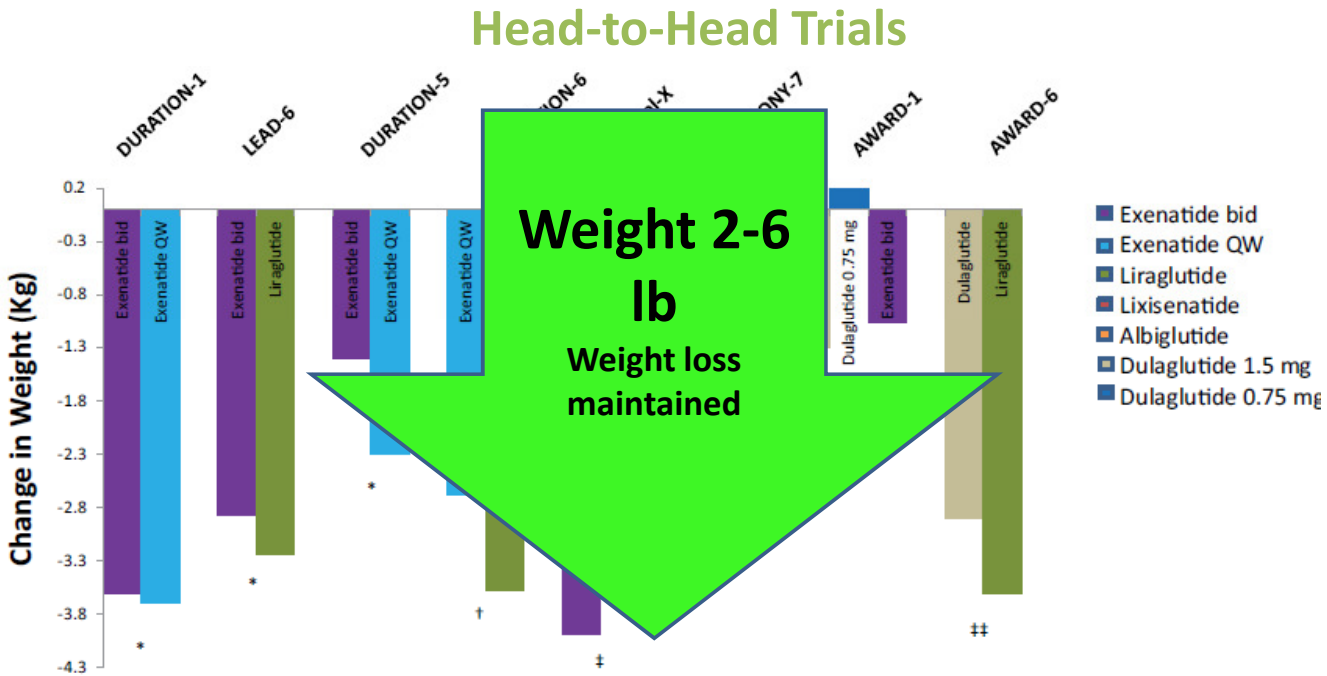
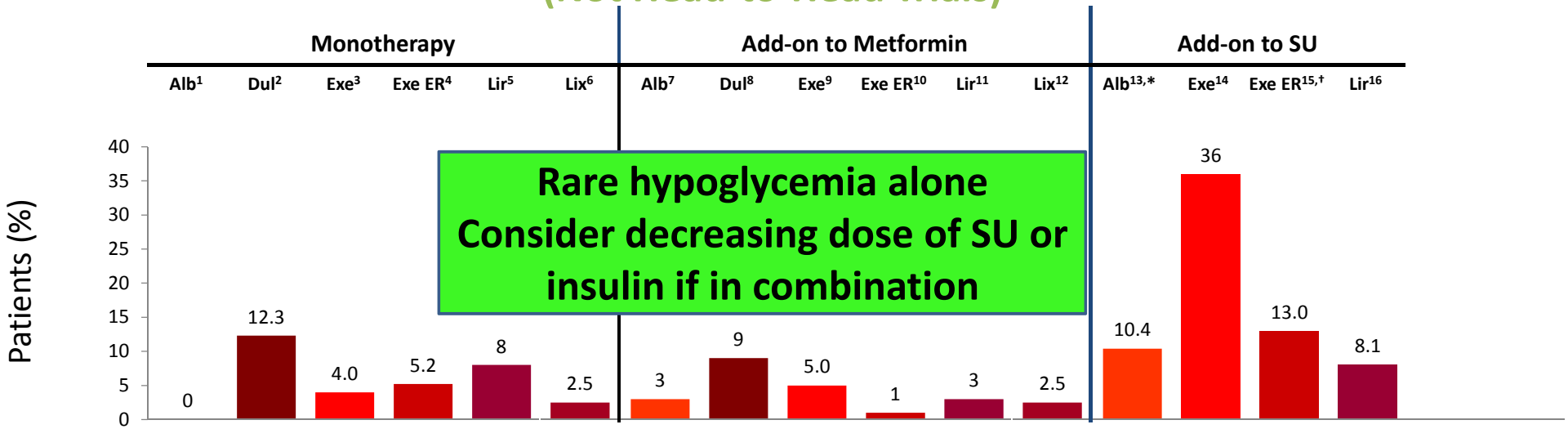


Figure 2. Changes in weight with glucagon-like peptide 1 receptor agonists (GLP-1 RAs) in head-to-head clinical studies.

Trujillo, J et al. T*herapeutic Advances in Endocrinology and Metabolism* 2015, 6(1): 19–28

Hypoglycemia with GLP-1 Receptor Agonists

Percentage of Patients Reporting Hypoglycemia (Not Head-to-Head Trials)



*Metformin with or without SU or TZD. †Metformin with or without SU.

1. Nauck M, et al. *Diabetes*. 2013;62(suppl 2): Abstr. 55-LB. 2. Umpierrez G, et al. *Diabetes Care*. 2014;37:2168-2176. 3. Moretto TJ, et al. *Clin Ther*. 2008;30:1448-1460. 4. Russell-Jones D, et al. *Diabetes Care*. 2012;35:252-258. 5. Garber A, et al. *Lancet*. 2009;373:473-481. 6. Fonseca VA, et al. *Diabetes Care*. 2012;35:1225-1231. 7. Ahrén B, et al. *Diabetes Care*. 2014;37:2141-2148. 8. Dungan KM, et al. *Lancet*. 2014;384:1349-1357. 9. DeFronzo RA et al. *Diabetes Care*. 2005;28:1092-1100. 10. Bergenstal RM, et al. *Lancet*. 2010;376:431-439. 11. Pratley RE, et al. *Lancet*. 2010;375:1447-1456. 12. Rosenstock J, et al. *Diabetes Care*. 2013;36:2945-2951. 13. Pratley RE, et al. *Lancet Diabetes Endocrinol*. 2014;2:289-297. 14. Buse JB, et al. *Diabetes Care*. 2004;27:2628-2635. 15. Diamant M, et al. *Lancet*. 2010;375:2234-2243. 16. Marre M, et al. *Diabet Med*. 2009;26:268-278.

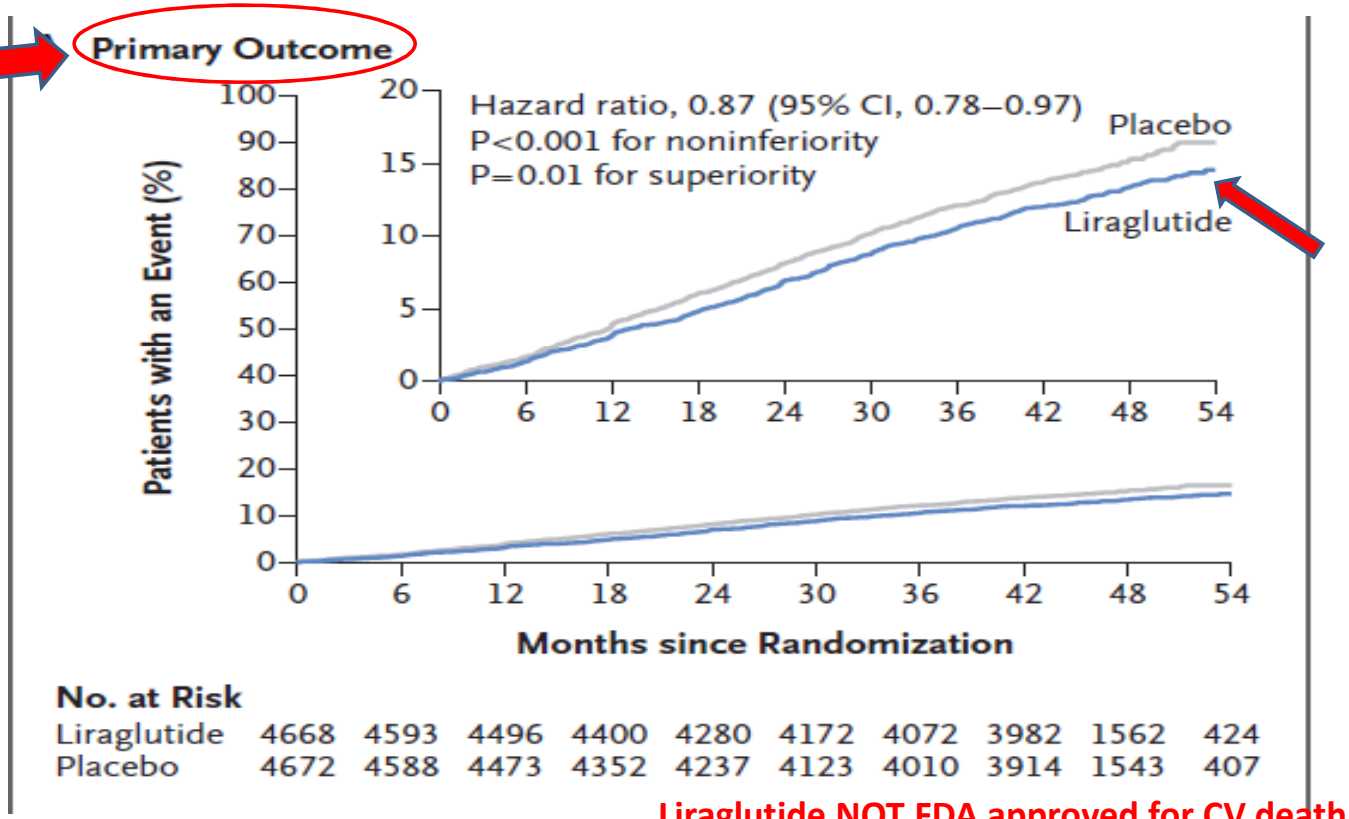
Cardiovascular Outcome Trials

Table 1. Trials With GLP-1 Therapeutics

	ELIXA	*LEADER*	*SUSTAIN-6*	*EXSCEL*	*LYDIA*
MEDICATION	Lixisenatide	Liraglutide	Semaglutide	Exenatide	Liraglutide
# PATIENTS	6,068	9,340	2,735	14,000	90
HISTORY	T2D, acute coronary event within 180 days prior to randomization	T2D, high risk CVD	T2D, high risk CVD	T2D, with prior CV events and/or with or w/o known CV risks	T2D, Obese
STUDY DESIGN	Multi-center, randomized, double-blind, placebo-controlled; Non-inferiority **Superiority**	Multi-center, double-blind, placebo-controlled; Non-inferiority **Superiority**	Multi-center, double-blind, placebo-controlled; Non-inferiority **Superiority**	Phase 3/4 multi-center, randomized, double-blind, placebo-controlled, parallel-group	Prospective, randomized, open label, blind endppoint
PRIMARY OUTCOME	4-point **MACE:** CV death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina (coronary revascularization)	3-point **MACE:** CV death, nonfatal MI, nonfatal stroke	3-point **MACE:** CV death, nonfatal MI, nonfatal stroke	**3-point MACE:** CV death, nonfatal MI, nonfatal stroke	Diastolic Fruntion (HF-NEF)
RESULTS	Lixisenatide Group: 13.4% Placebo Group: 13.2% HR 1.02; 95% CI 0.89–1.17 P<0.001 for non-inferiority P=0.81 for superiority	Liraglutide Group: 13.0% Placebo group: 14.9% HR 0.87; 95% CI 0.78-0.97 P<0.001 for non-inferiority P=0.01 for superiority	Semaglutide Group: 6.6% Placebo Group: 8.9% HR 0.74; 95% CI, 0.58 to 0.95 P<0.001 for noninferiority	Ongoing April 2018	2017
ADDITIONAL BENEFITS/RISKS		Reduction in all-cause mortality in Rx group (8.2% vs. 9.6% in placebo group; HR 0.85; 95% CI 0.74-0.97; P=0.02)	Increased risk of retinopathy in semaglutide group		Younger Popn (Ages 18-50) 28 weeks duration

LEADER (Liraglutide) Cardiovascular Outcome Trial

CV death,
MI, stroke



Liraglutide NOT FDA approved for CV death prevention

Marso, S. et al N Engl J Med 2016; 375(4): 311-22

Adverse Effects with GLP-1 RA

- GI – N/V, diarrhea or constipation
  - Common
  - Usually dose dependent and transient
  - Usually reduced with dose titration
  - Caution in patients with gastroparesis

Safety Considerations with GLP-1 RA

- **Pancreatitis**
  - No causal relationship established
  - Discontinue if pancreatitis suspected
  - No evidence of increased pancreatic risk with incretins vs. other agents
- **Pancreatic cancer**
  - No evidence of increased pancreatic risk with incretins vs. other agents
  - Further assessments required from long duration controlled studies or epidemiological databases
- **Medullary Thyroid Cancer**
  - Animal data showed increased incidence of C-cell tumors with liraglutide and exenatide ER treatment, but confirmatory population studies are lacking
  - Labeling for liraglutide and exenatide ER:
    - Patients should be counseled regarding MTC and the signs/symptoms of thyroid tumors
    - Contraindicated in patients with personal/family history of MTC or MEN Type 2
- **Renal impairment**
  - Exenatide is contraindicated in patients with severe renal insufficiency or ESRD
  - Liraglutide safe in moderate renal impairment
  - Dulaglutide is safe in renal impairment

Garber AJ, et al. *Endocr Pract*. 2016;22:84-113. White W, et al. *N Engl J Med*. 2013;369:1327-1335. Scirica BM, et al. *Circulation.* 2014;130:1579-1588. ADA/EASD/IDF statement concerning the use of incretin therapy and pancreatic disease [news release]. Alexandria, VA: American Diabetes Association, European Association for the Study of Diabetes, International Diabetes Federation; June 28, 2013. http://www.diabetes.org/newsroom/press-releases/2013/recommendations-for.html.

Key Points

- Once daily or once weekly SQ injection
- Impressive clinically significant A1C reductions (0.5-1.5%)
- Both fasting and prandial blood glucose reductions
- No hypoglycemia
  - Consider reduction of dose of SU or insulin if used in combination
- Sustained weight loss
- Slight decrease in SBP
- Beta-cell preservation
- Complementary mechanism of action with many drugs
  - Don’t use with DPP-4 Inhibitors
- GI side effects
  - Less with weekly dosing
- Don’t use if history of MTC/MEN2
- Caution if history of pancreatitis or gastroparesis

Basal insulin + GLP-1

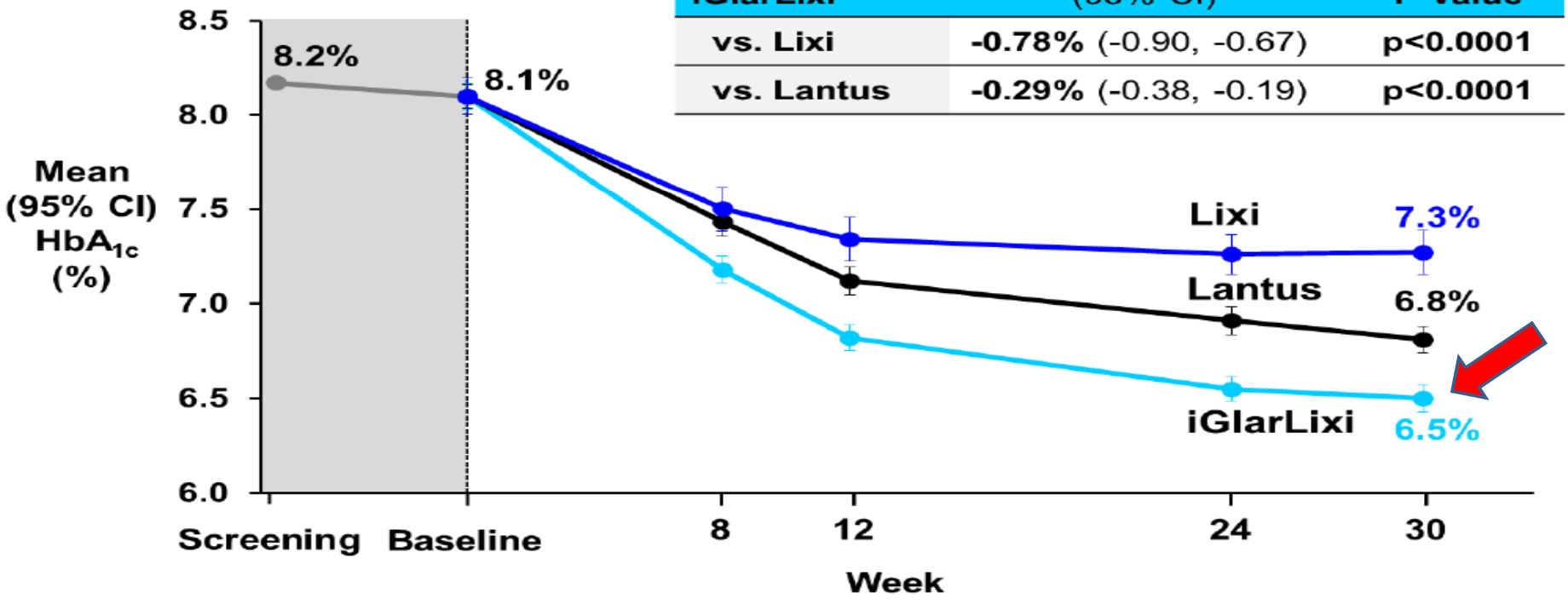
- Now available as combination injection

Basal insulin + GLP-1 Combination

- IGlarLixi (Soliqua) – released Jan 2017
- IDegLira (Xultophy) – expected released June 2017

IGlarLixi

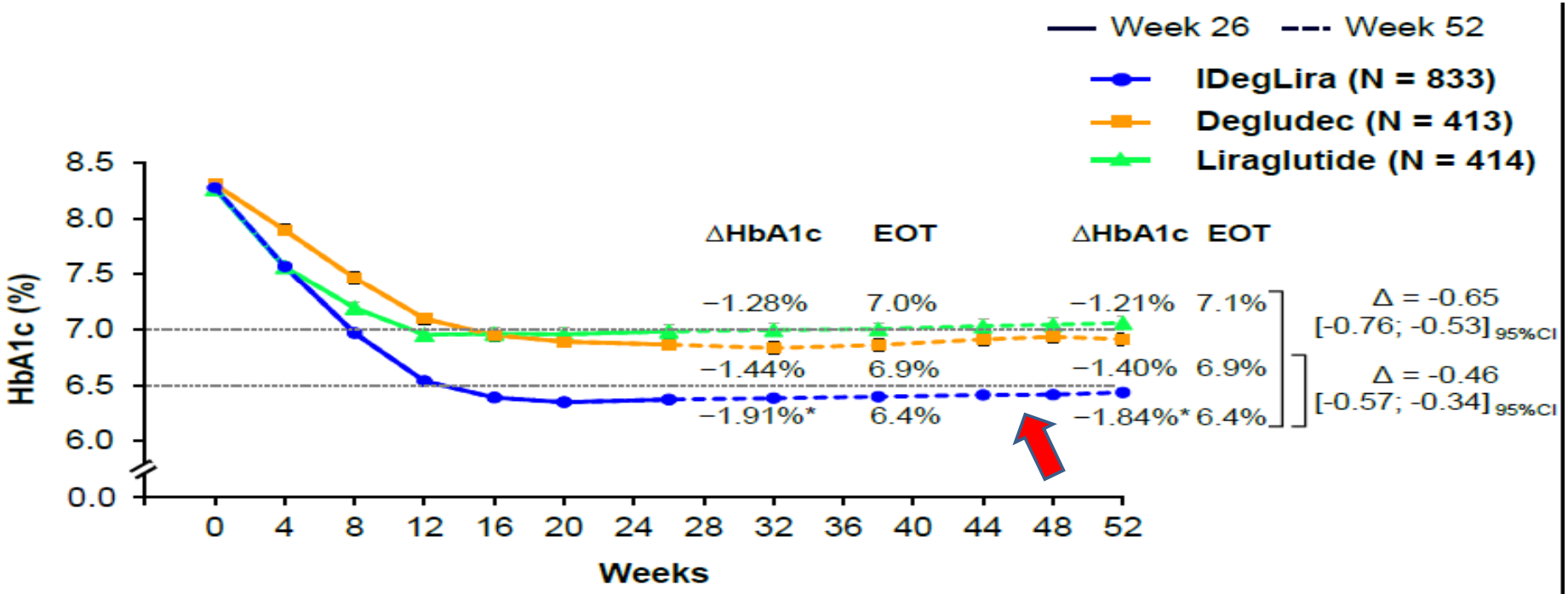
iGlarLixi	Mean Difference (95% CI)	P-Value
vs. Lixi	**-0.78%** (-0.90, -0.67)	**p<0.0001**
vs. Lantus	**-0.29%** (-0.38, -0.19)	**p<0.0001**



IGlarLixi

- 1 unit of IGlarLixi =
  - 1 unit of Lantus + 0.33 mcg lixisenatide
- Dosing:
  - If uncontrolled on basal insulin < 30 units/day
    - Start 15 units of IGlarLixi
  - If uncontrolled on basal insulin ≥ 30 units/day
    - Start 30 units of IGlarLixi
  - Max dose 60 units
- Give within 1 hour of 1st meal of the day
- Titrate weekly by 2-4 units until goal fasting glucose reached

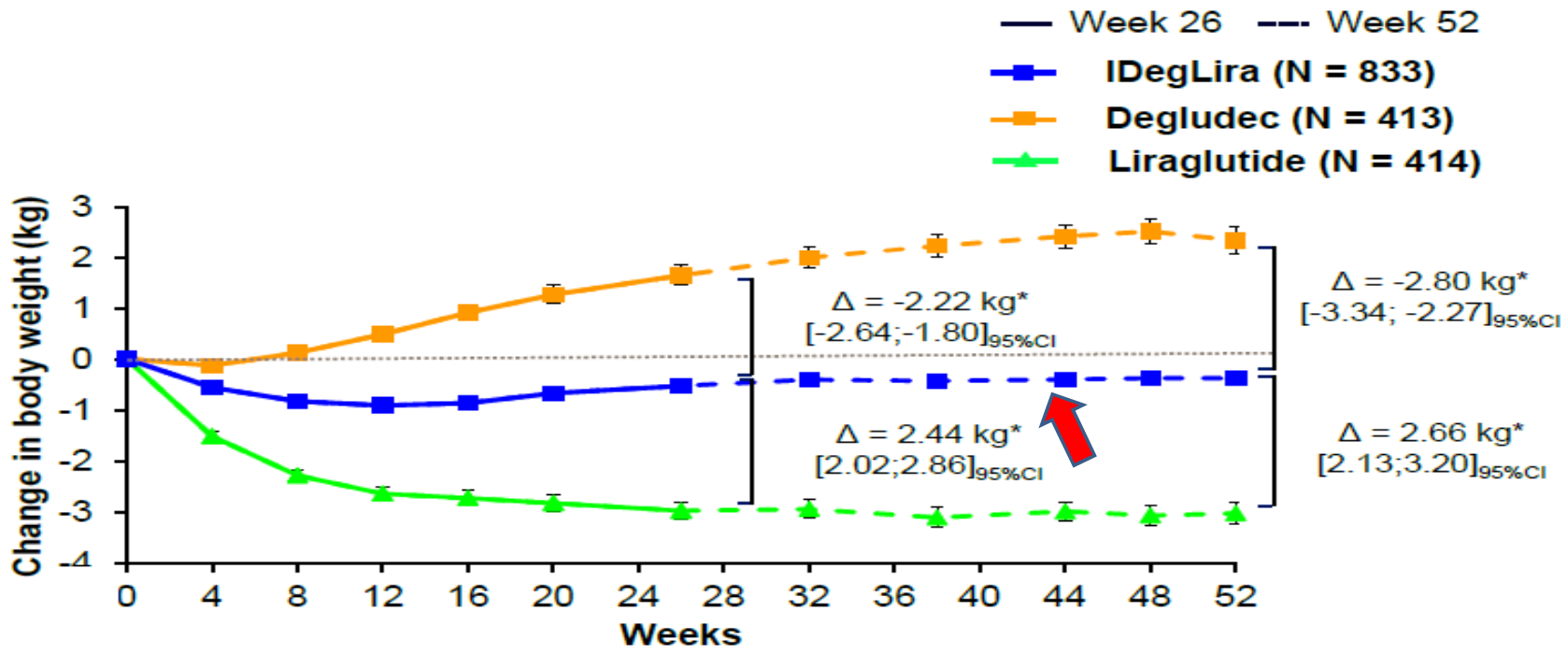
IDegLira (Xultophy) – Significant reduction in A1C relative to individual components



Full analysis set. Data are mean ± SEM. Δ = Observed change from baseline. LOCF imputation. EOT = End of treatment.

*$p<0.0001$ vs. degludec and vs. liraglutide.

No weight gain when IDegLira added to Metformin +/- Pioglitazone



Full analysis set. Data are mean ± SEM. Δ = Estimated treatment difference. LOCF imputation. Week 26 analysis adjusted for multiplicity. *$p<0.0001$

IDegLira Safety Profile

- Safety profile consistent with individual components
- Some component adverse effects mitigated
  - Confirmed hypoglycemia rates with IDegLira
    - Consistently lower than with basal insulin
    - Higher than GLP-1 RA or placebo
  - GI AEs with IDegLira
    - Lower than with GLP-1 RA
    - Higher than with basal insulin alone
  - No confirmed cases of pancreatitis
  - CV safety reflective of components
  - No cases of MTC

SGLT2 Inhibitors

SGLT2 Inhibitors

FDA-Approved Agents

- Canagliflozin (Invokana)
- Dapagliflozin (Farxiga)
- Empagliflozin (Jardiance)

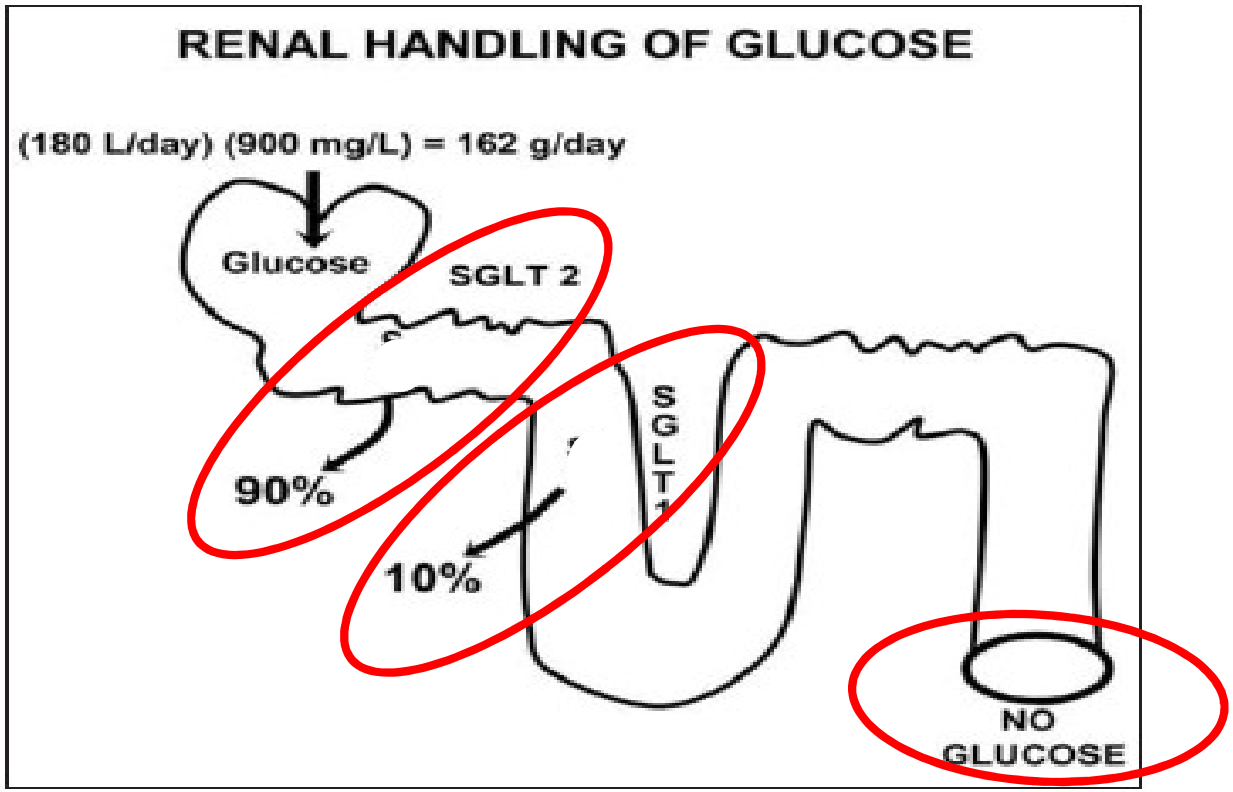
Key Features

- Oral administration
- Inhibit reabsorption of glucose into the bloodstream from renal fluid

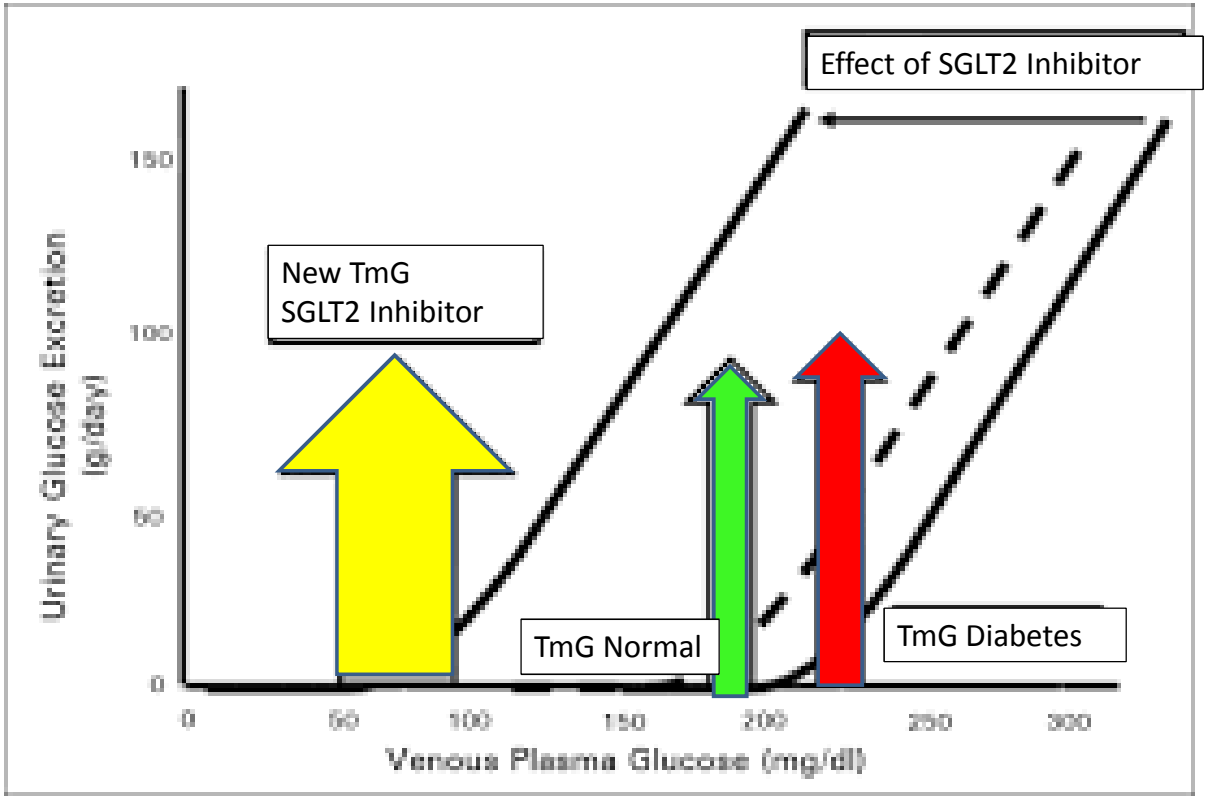
SGLT2, sodium-glucose cotransporter 2.

DeFronzo RA, et al. *Diabetes Obes Metab*. 2012;14:5-14.

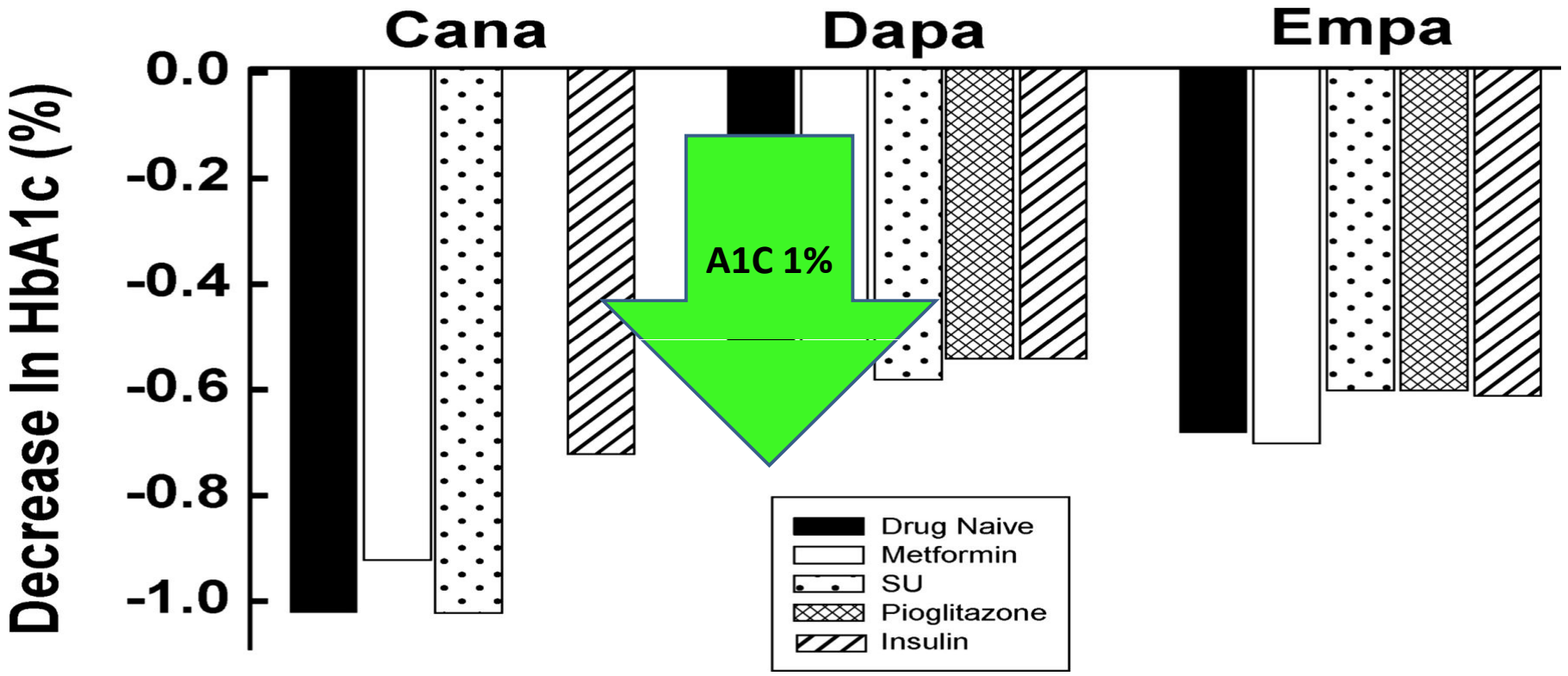
Pathophysiology



Renal Glucose Threshold



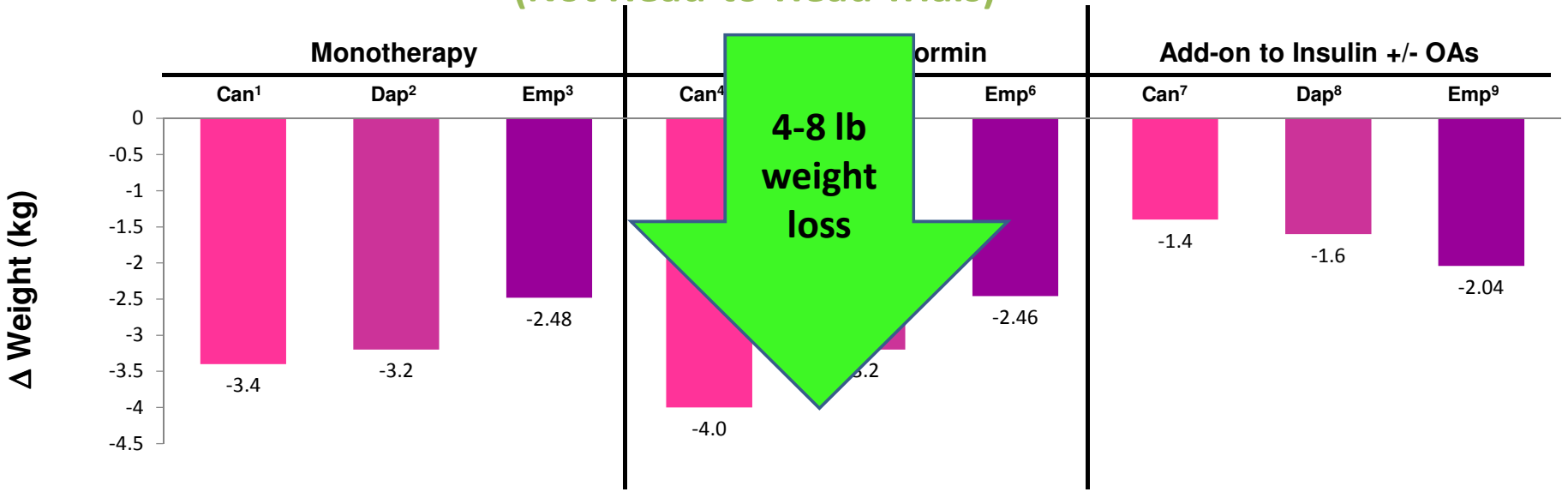
Glucose Control with SGLT2 Inhibitors



Muhammad A. Abdul-Ghani et al. Am J Physiol Renal Physiol 2015;309:F889-F900

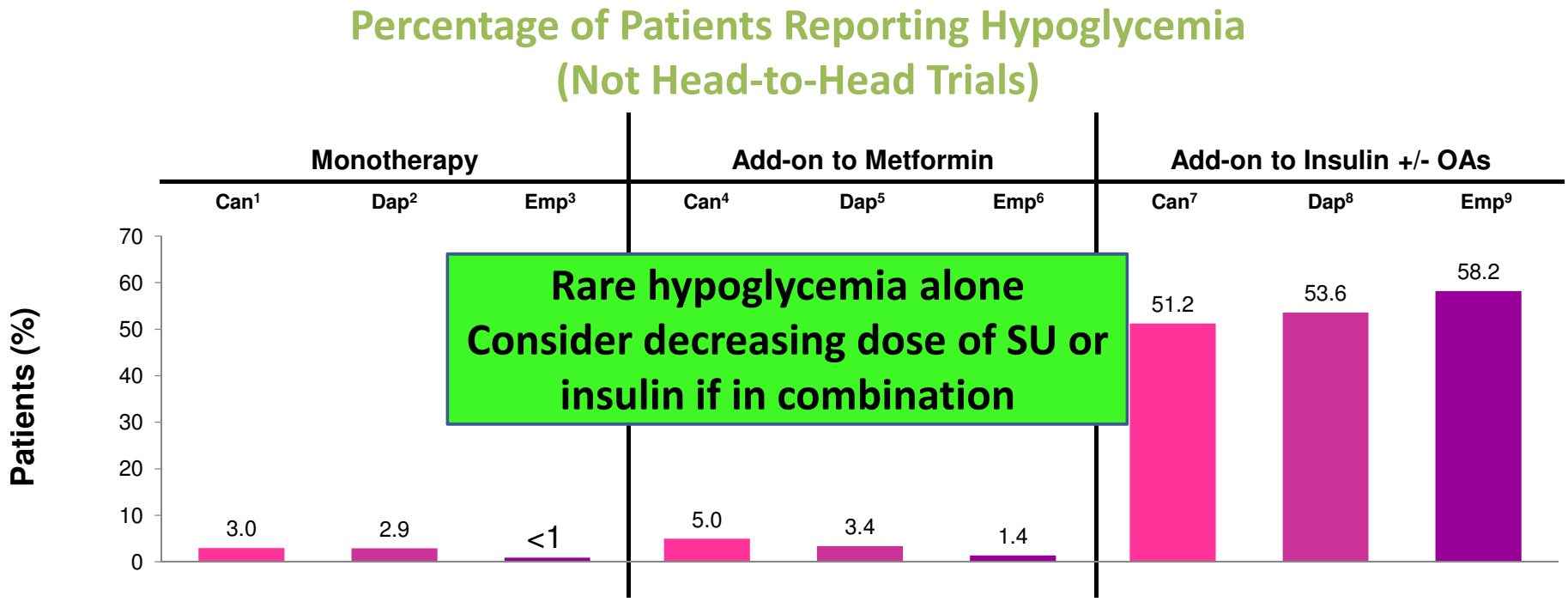
Weight Change with SGLT2 Inhibitors

Absolute Change from Baseline (Not Head-to-Head Trials)



1. Stenlof K, et al. *Diabetes Obes Metab*. 2013;15:372-382. 2. Ferrannini E, et al. *Diabetes Care*. 2010;33:2217-2224. 3. Roden M, et al. *Lancet Diabetes Endocrinol*. 2013;1:208-219. 4. Cefalu WT, et al. *Lancet*. 2013;382:941-950. 5. Nauck MA, et al. *Diabetes Care*. 2011;34:2015-2022. 6. Haring HU, et al. *Diabetes Care*. 2014;37:1650-1659. 7. Yale J-F, et al. *Diabetes Obes Metab*. 2013;15:463-473. 8. Wilding JPH, et al. *Ann Intern Med*. 2012;156:405-415. 9. Rosenstock J, et al. *Diabetes Care*. 2014;37:1815-1823.

Hypoglycemia with SGLT2 Inhibitors



1. Stenlof K, et al. *Diabetes Obes Metab*. 2013;15:372-382. 2. Ferrannini E, et al. *Diabetes Care*. 2010;33:2217-2224. 3. Roden M, et al. *Lancet Diabetes Endocrinol*. 2013;1:208-219. 4. Cefalu WT, et al. *Lancet*. 2013;382:941-950. 5. Nauck MA, et al. *Diabetes Care*. 2011;34:2015-2022. 6. Haring HU, et al. *Diabetes Care*. 2014;37:1650-1659. 7. Yale J-F, et al. *Diabetes Obes Metab*. 2013;15:463-473. 8. Wilding JPH, et al. *Ann Intern Med*. 2012;156:405-415. 9. Rosenstock J, et al. *Diabetes Care*. 2014;37:1815-1823.

Cardiovascular Outcomes Trials

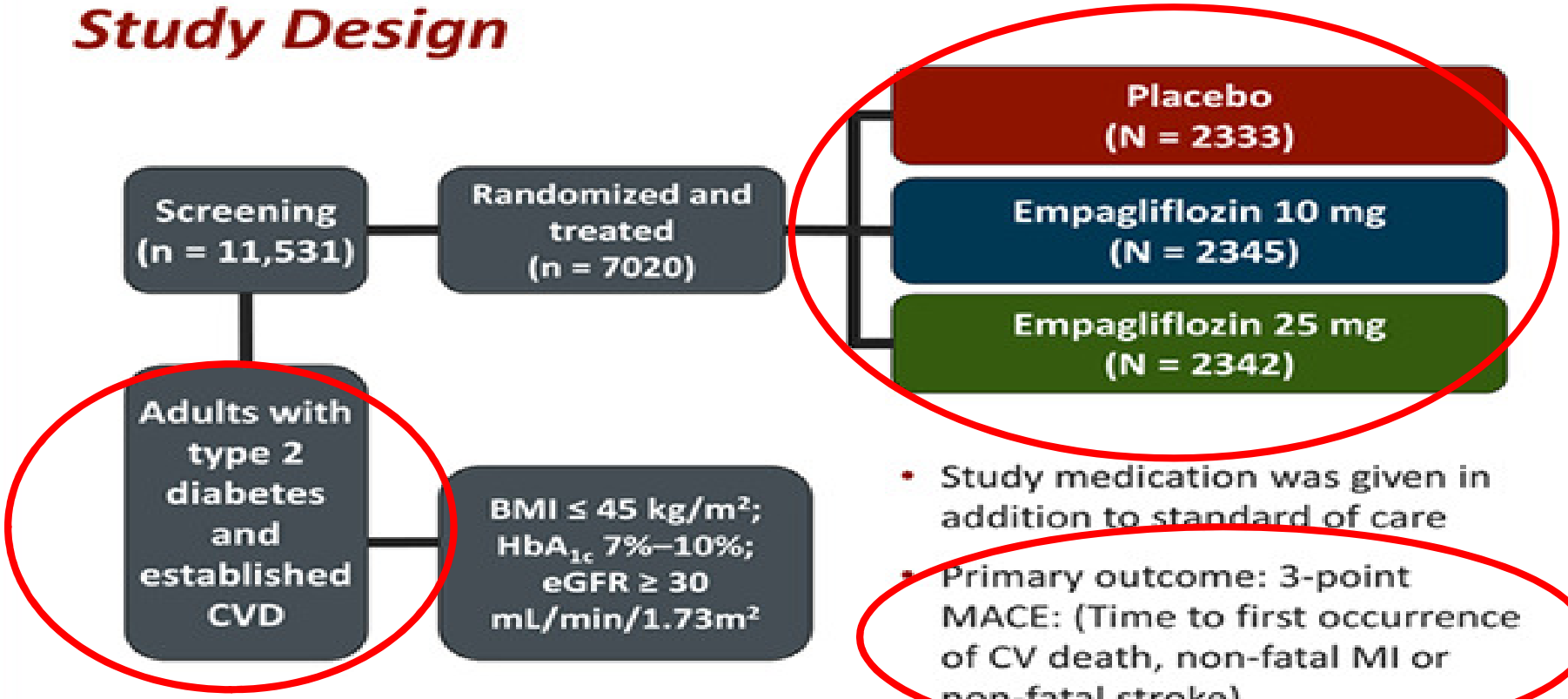
Table 2. Cardiovascular outcome trials with SGLT-2 inhibitors*

	EMPA-REG OUTCOME	CANVAS	DECLARE-TIMI 58
ClinicalTrials.gov	NCT01131676	NCT01032629	NCT01730534
Interventions (randomization)	Empagliflozin/ placebo (2:1)	Canagliflozin/ placebo (2:1)	Dapagliflozin/placebo (1:1)
Enrollment	7020	4411	17,276
Key inclusion criteria	Established vascular complications, HbA1c 7.0%–10.0%, age ≥18 years	Established vascular complications (age ≥30 years) or ≥2 CV risk factors (age >50 years), HbA1c 7.0%–10.5%	High risk for CV events, T2DM, age ≥40 years
Primary end point	CV death, nonfatal MI, nonfatal stroke	CV death, nonfatal MI, nonfatal stroke	CV death, nonfatal MI, nonfatal stroke
Estimated reporting	2015	2017	2019

HbA1c: glycosylated hemoglobin A1c; CV: cardiovascular; T2DM: type 2 diabetes mellitus; MI: myocardial infarction.
*Adapted from Inzucchi et al.[6]

EMPA-REG OUTCOME®

Study Design



- Study medication was given in addition to standard of care
- Primary outcome: 3-point MACE: (Time to first occurrence of CV death, non-fatal MI or non-fatal stroke)

Zinman B, et al. *N Engl J Med*. 2015;373:2117-2128.

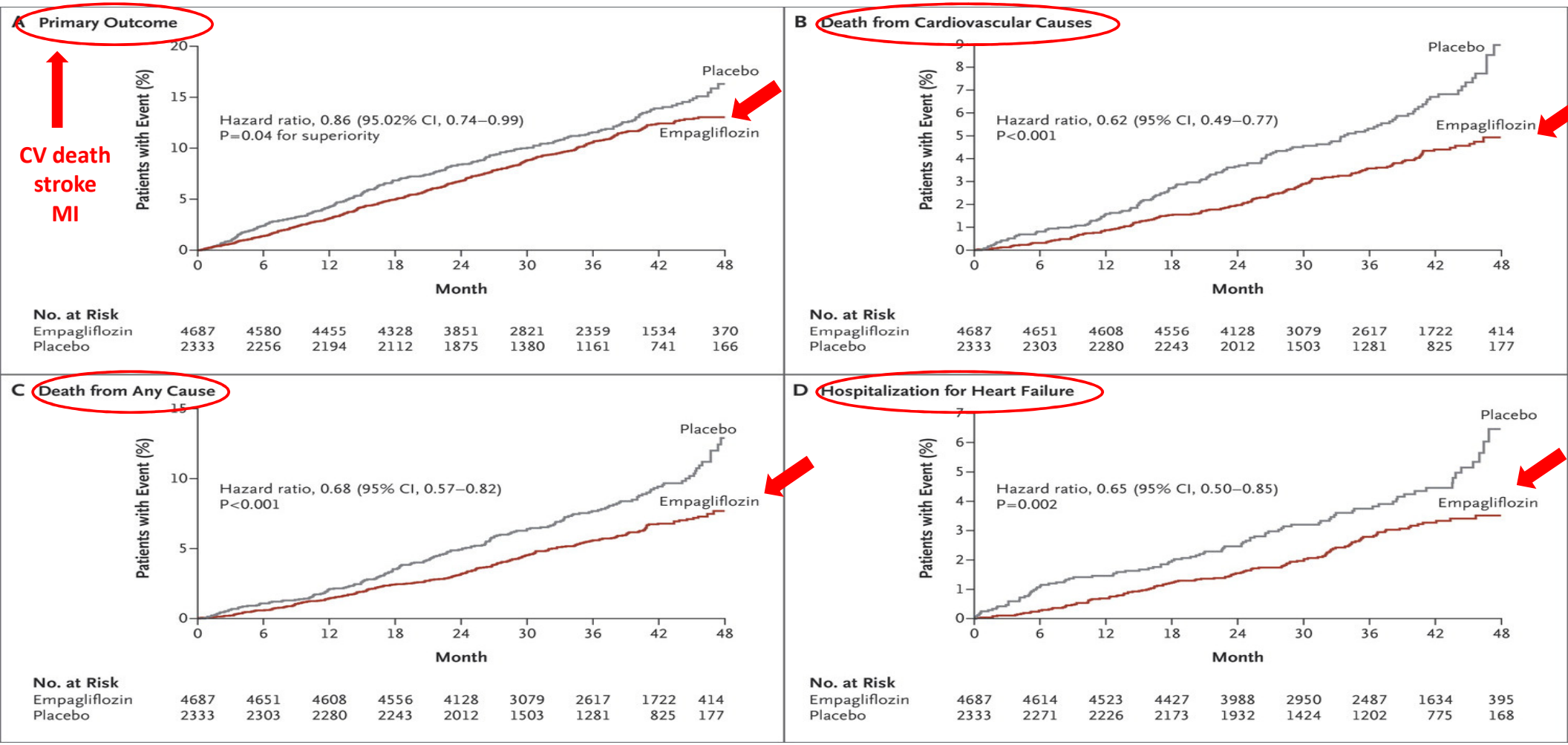
EMPA-REG Baseline Characteristics

Baseline Characteristics	Placebo N = 2, 333	Empaglafozin N = 4,687
Mean Age (years)	63 (+/- 9)	63 (+/- 9)
Male (%)	72	71
Race %	-	-
White	72	73
Asian	22	22
Black/ AfricanAmerican	5	5
Mean BMI	31 +/- 5	31 +/- 5

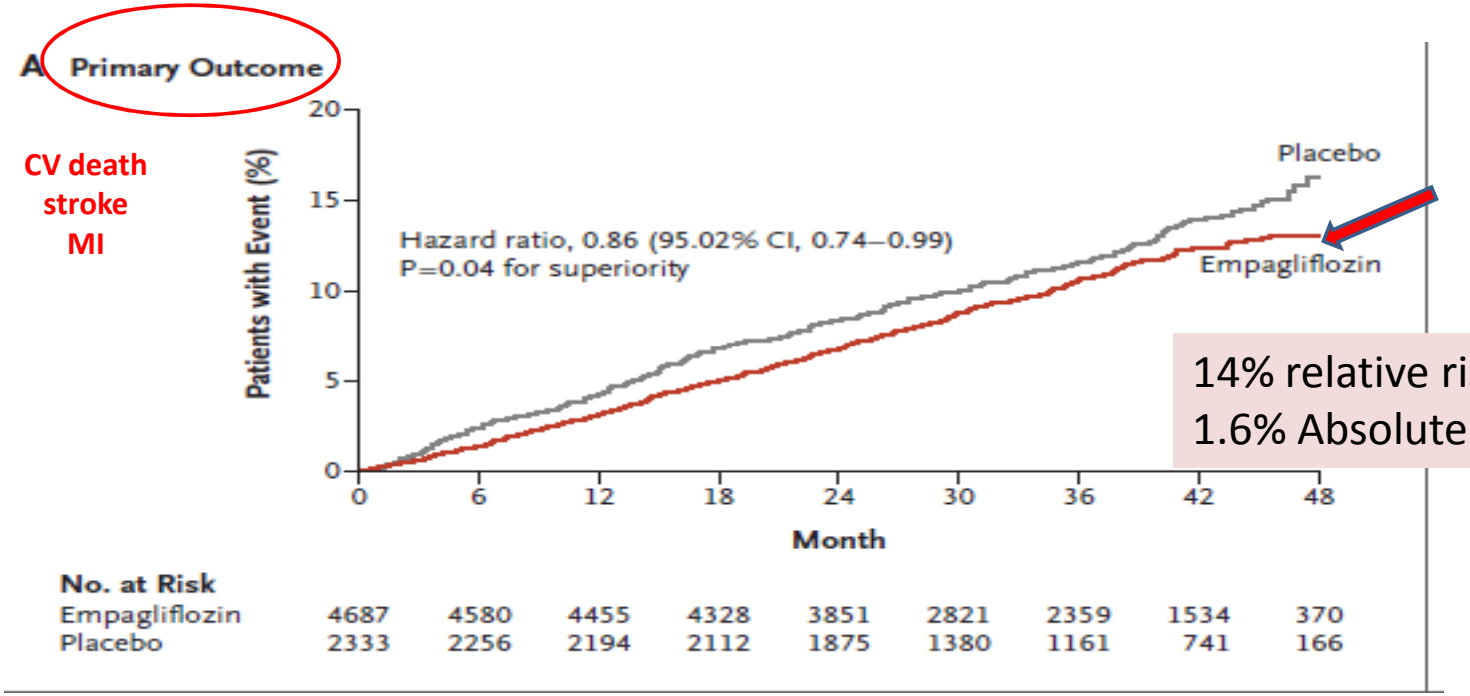
EMPA-REG Baseline Characteristics

Baseline Characteristics	Placebo N = 2, 333	Empaglafozin N = 4,687
Established CVD* (%)	99	99
CAD	76	76
History of MI	46	47
History of stroke	24	23
PAD	21	21

EMPA-REG Outcome



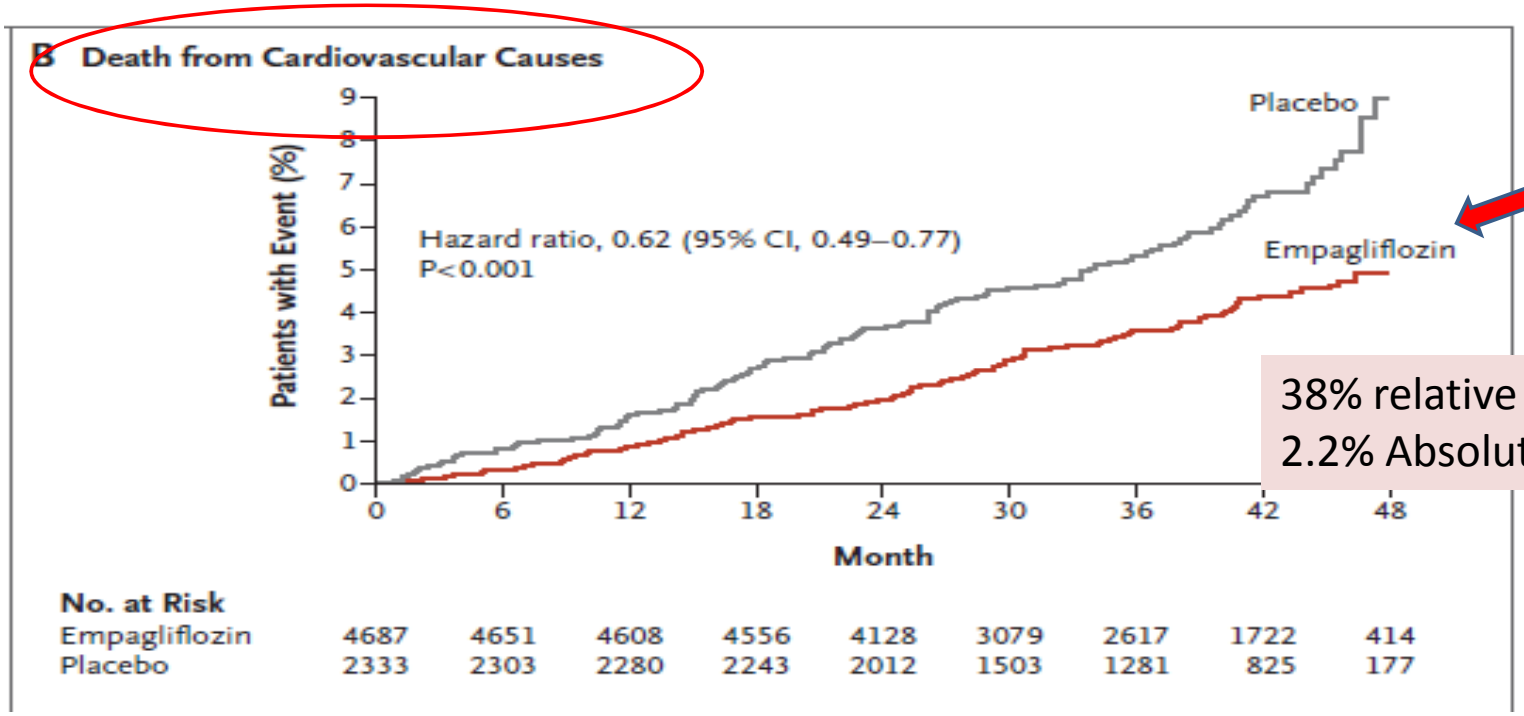
EMPA-REG Cardiovascular Outcome Study



14% relative risk reduction
1.6% Absolute risk reduction

Zinman B et al. N Engl J Med. 2015; 373: 2117-2226

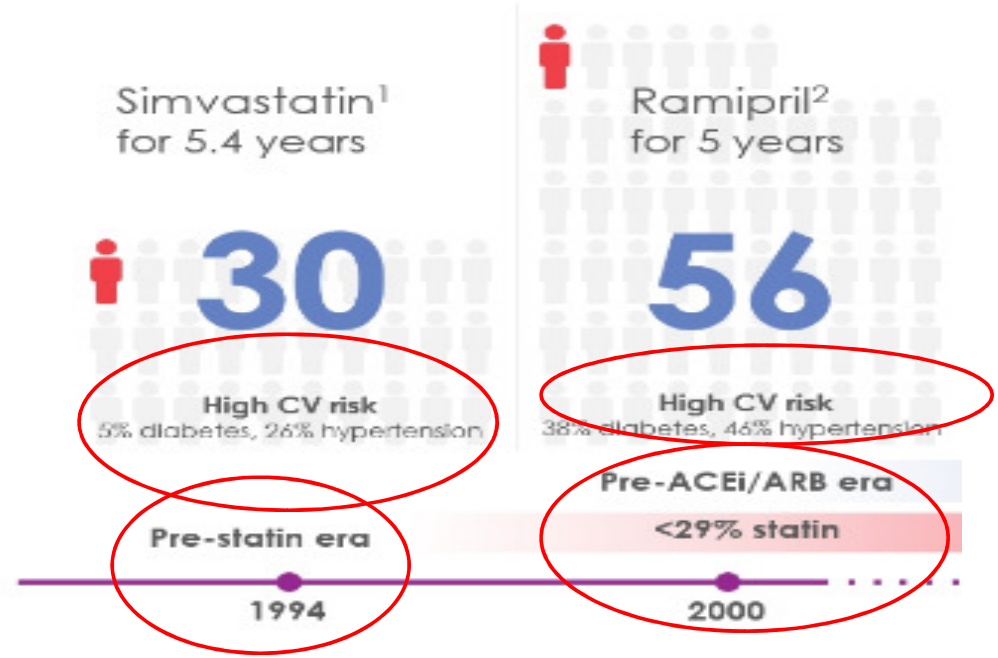
EMPA-REG Cardiovascular Outcome Study



38% relative risk reduction
2.2% Absolute risk reduction

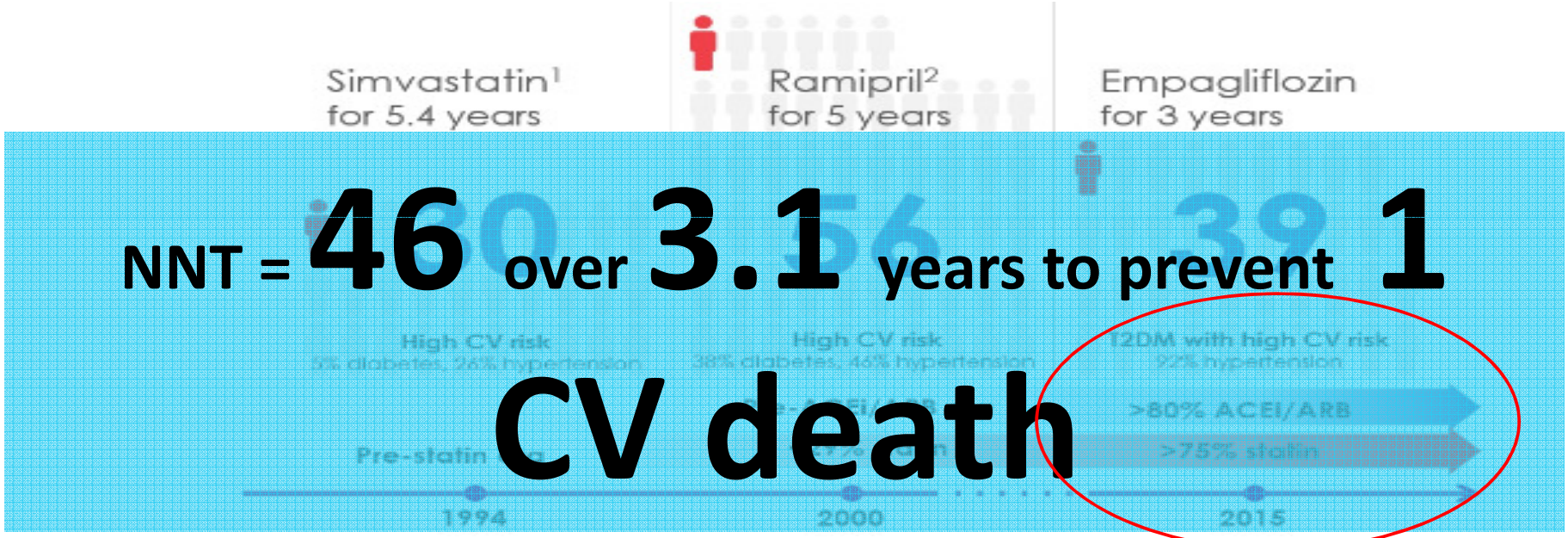
FDA approved to reduce the risk of CV death in adults with Type 2 DM and established CV disease

Number Needed to Treat
To Prevent Death in High CV risk Group



1. 4S Investigator, Lancet 1994; 344:1352-59.
2. HOPE Investigator. N Engl J Med 2000; 342: 145-53.

Number Needed to Treat
To Prevent Death



1. 4S Investigator, Lancet 1994; 344:1352-59.
2. HOPE Investigator. N Engl J Med 2000; 342: 145-53.

Is it a Class Effect?

Awaiting results of CANVAS and DECLARE, but…

CVD REAL…

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Study Objectives

ACC.17

Primary

- Compare risk of HHF in patients with Type 2 diabetes newly initiated on SGLT-2i versus other glucose-lowering drugs (oGLDs)

Secondary

- Compare risk of all-cause death between the two treatment groups
- Compare risk of HHF or all-cause death between the two treatment groups

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Data Sources: Health Records Across Six Countries

- Truven MarketScan Claims & Encounters and linked Medicare
- National full-population registries
- National full-population registries
- National full-population registries
- Clinical Practice Research Datalink (CPRD) and The Health Improvement Network (THIN)
- Diabetes Patienten Verlaufsdokumentation (DPV) initiative

HHF

All-cause death and composite HHF/all-cause death

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Inclusion/Exclusion Criteria

ACC.17

Inclusion

- New users receiving SGLT-2i or oGLDs
  - Established Type 2 diabetes on or prior to the index date
  - ≥18 years old
  - >1 year* historical data available prior to the index date

Exclusion

- Patients with Type 1 diabetes
- Patients with gestational diabetes

*In Germany, >6 months

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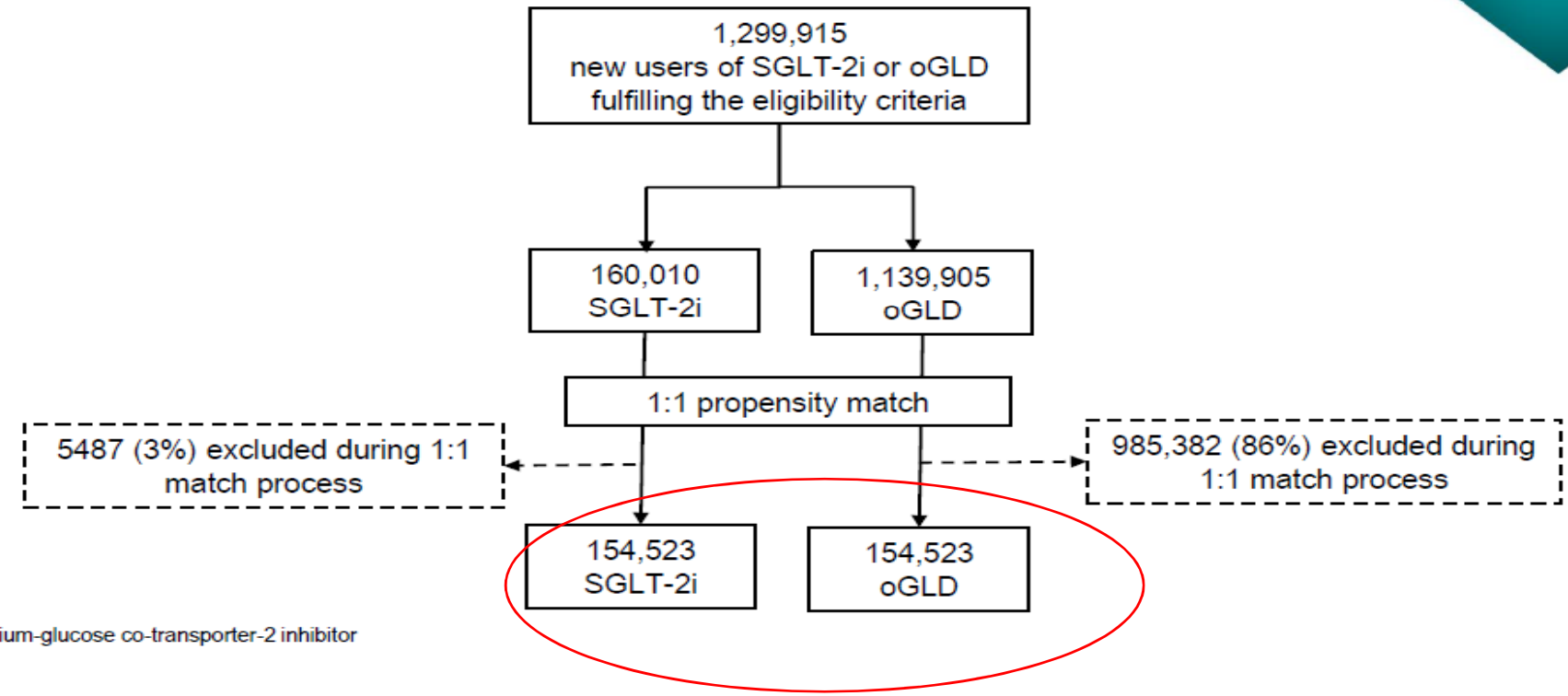
Patient Population

ACC.17



SGLT-2i=sodium-glucose co-transporter-2 inhibitor

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Baseline Characteristics for Propensity Match Cohort

	SGLT-2i* N=154,523	oGLD* N=154,523
Age, years, mean (SD)	57.0 (9.9)	57.0 (10.1)
Women	68,419 (44.3)	68,770 (44.5)
Established cardiovascular disease†	20,043 (13.0)	20,302 (13.1)
Acute myocardial infarction	3792 (2.5)	3882 (2.5)
Unstable angina	2529 (1.6)	2568 (1.7)
Heart failure	4714 (3.1)	4759 (3.1)
Atrial fibrillation	5632 (3.6)	5698 (3.7)
Stroke	6347 (4.1)	6394 (4.1)
Peripheral arterial disease	5239 (3.4)	5229 (3.4)
Microvascular disease	42,214 (27.3)	42,221 (27.3)
Chronic kidney disease	3920 (2.5)	4170 (2.7)

*Data are n (%) unless otherwise stated; †Myocardial infarction, unstable angina, stroke, heart failure, transient ischemic attack, coronary revascularization or occlusive peripheral artery disease

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Baseline Characteristics for Propensity Match Cohort

	SGLT-2i* N=154,523	oGLD* N=154,523
Cardiovascular therapies		
Antihypertensive therapy†	123,691 (80.0)	123,560 (80.0)
Loop diuretics	14,280 (9.2)	14,314 (9.3)
Thiazides	42,444 (27.5)	42,509 (27.5)
ACE inhibitors	66,812 (43.2)	67,067 (43.4)
ARBs	48,718 (31.5)	48,443 (31.4)
Statins	103,966 (67.3)	104,126 (67.4)
Diabetes therapies		
Metformin	121,496 (78.6)	123,429 (79.9)
Sufonylurea	59,405 (38.4)	59,786 (38.7)
DPP-4 inhibitor	51,398 (33.3)	50,088 (32.4)
Thiazolidinedione	13,649 (8.8)	12,970 (8.4)
GLP-1 receptor agonist	31,352 (20.3)	27,086 (17.5)
Insulin	45,570 (29.5)	45,095 (29.2)

*Data are n (%); †Includes angiotensin converting enzyme inhibitors, angiotensin receptor blockers, Ca2+ channel blockers, β-blockers, thiazides; ACEi=angiotensin-converting-enzyme; ARB=angiotensin II receptor blockers; DPP-4=Dipeptidyl peptidase-4; GLP-1=glucagon-like peptide-1

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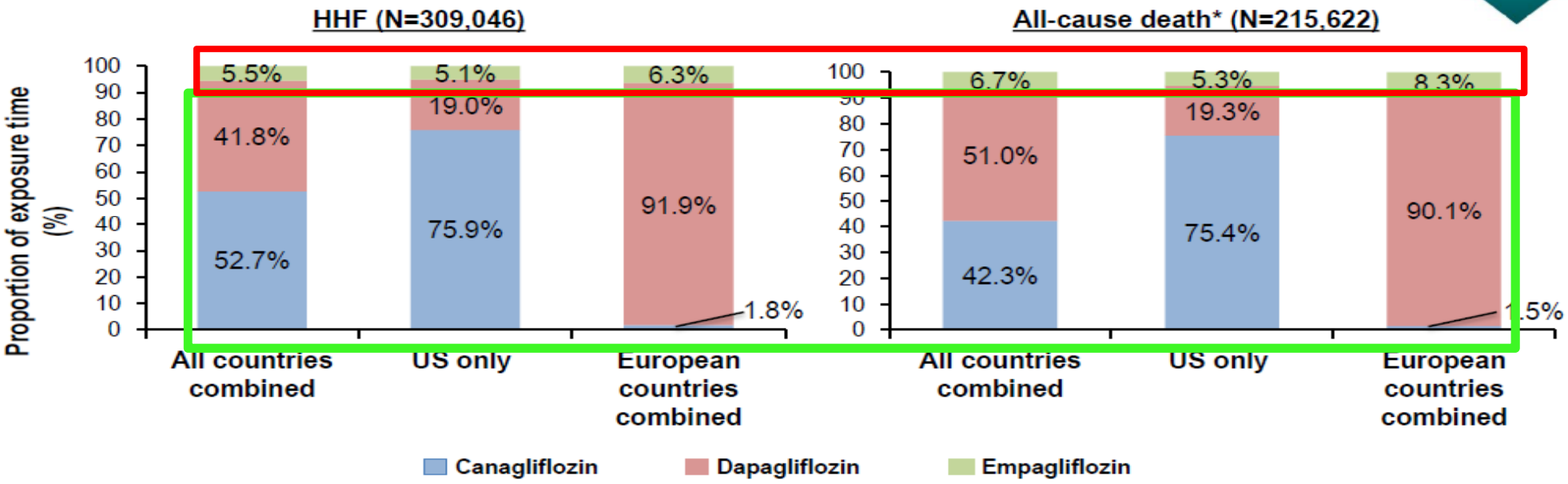
Contribution of SGLT-2i compounds



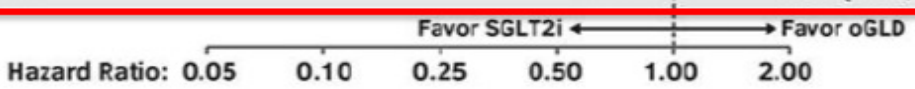
*Data shown are for all-cause death; data for HHF or all-cause death are similar

CVDREAL

HHF Primary Analysis

ACC.17

Database	N	# of events	HR (95% CI)
US	233,798	298	0.55 (0.44, 0.69)
Norway	25,050	278	0.62 (0.49, 0.79)
Denmark	18,468	167	0.77 (0.59, 1.01)
Sweden	18,378	191	0.61 (0.45, 0.82)
UK	10,462	16	0.36 (0.12, 1.13)
Germany	2900	11	0.14 (0.03, 0.68)
Total	309,056	961	0.61 (0.51, 0.73)



P-value for SGLT2i vs oGLD: <0.001

Heterogeneity p-value: 0.17

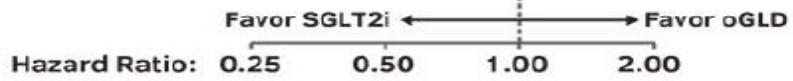
Data are on treatment, unadjusted; oGLD=other glucose-lowering drug; HR=hazard ratio

CVDREAL

All-Cause Death

ACC.17

Database	N	# of events	HR (95% CI)
US	143,264	250	0.38 (0.29, 0.50)
Norway	25,050	364	0.55 (0.44, 0.68)
Denmark	18,468	323	0.46 (0.37, 0.57)
Sweden	18,378	317	0.47 (0.37, 0.60)
UK	10,462	80	0.73 (0.47, 1.15)
Total	215,622	1334	0.49 (0.41, 0.57)



P-value for SGLT2i vs oGLD: <0.001

Heterogeneity p-value: 0.09

Data are on treatment, unadjusted; oGLD=other glucose-lowering drug; HR=hazard ratio

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Conclusions

ACC.17

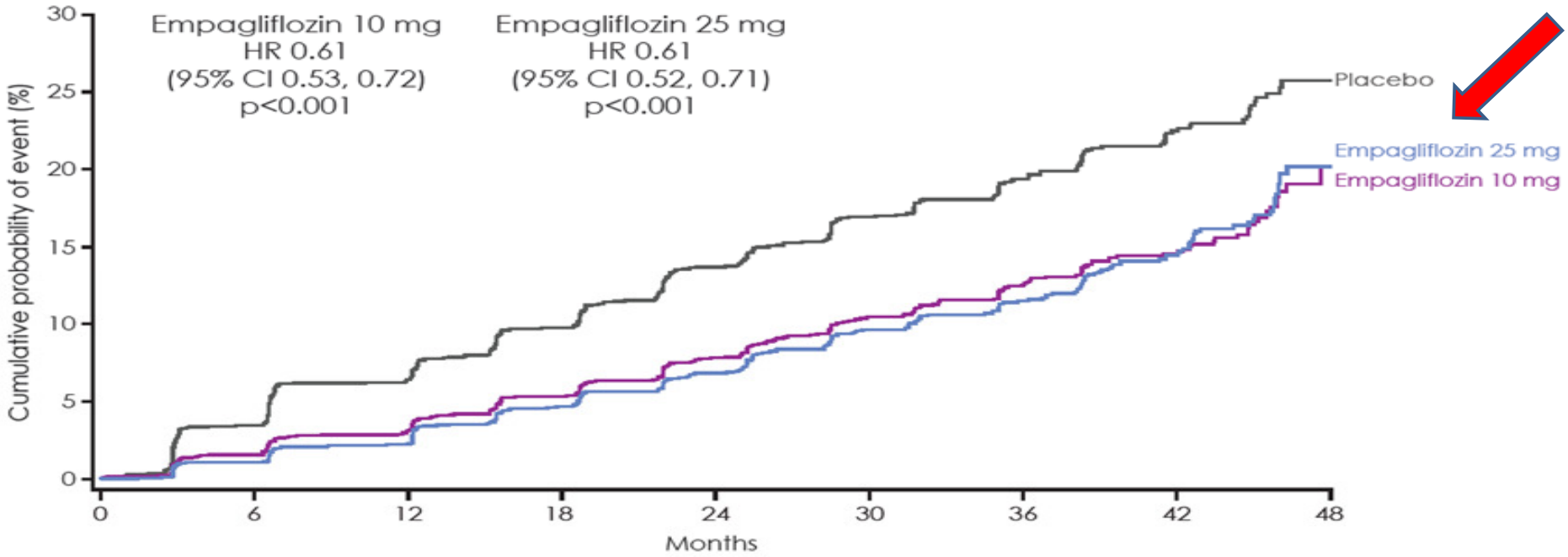
- In a large real-world study across six countries and a broad population of patients with Type 2 diabetes, treatment with SGLT-2i versus oGLDs was associated with marked reductions in:
  - Hospitalization for heart failure
  - All-cause death
  - Hospitalization for heart failure or all-cause death

Renal Benefit of SGLT2 Inhibitors?

EMPA-REG Outcome Trial

- Assessment of renal outcome was pre-specified objective
- Main renal outcomes
  - Incident or worsening nephropathy defined as:
    - Doubling of serum Cr with eGFR $\leq$ 45 ml/min/1.73m2 or
    - Initiation of renal replacement therapy or
    - Death due to renal disease

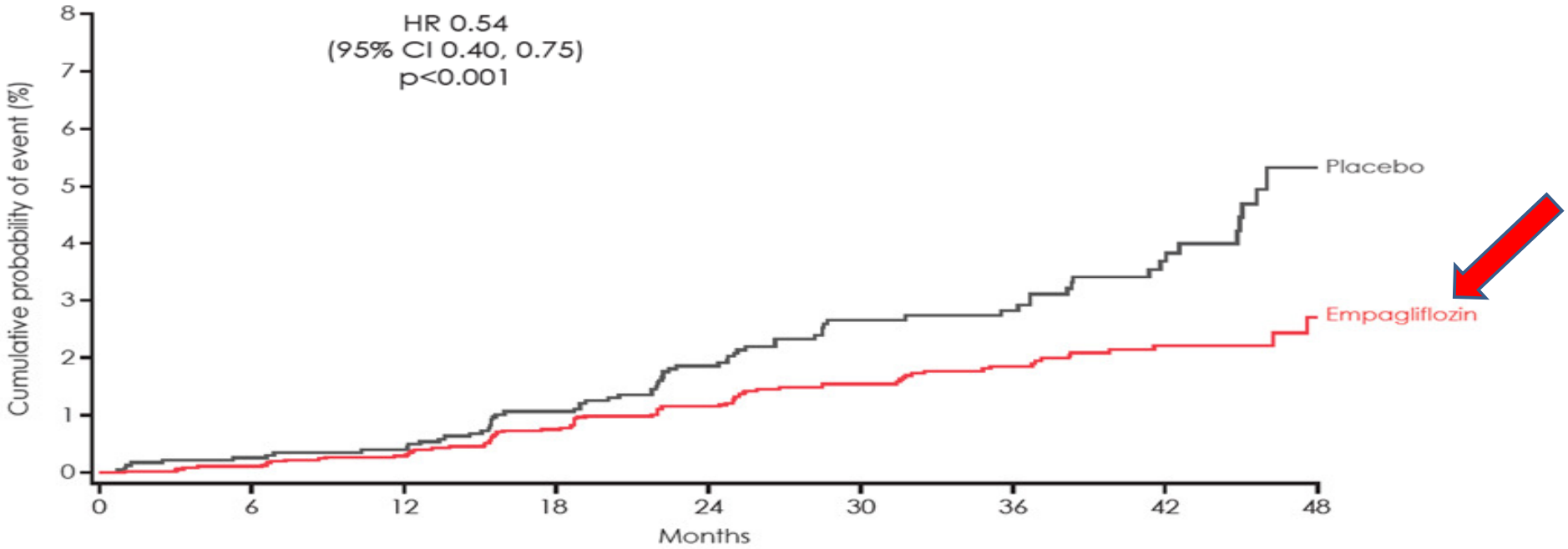
Incident or worsening nephropathy



No. of patients									
Empagliflozin 10 mg	2055	1991	1912	1825	1571	1122	922	593	136
Empagliflozin 25 mg	2069	2003	1936	1844	1600	1157	965	626	154
Placebo	2061	1946	1836	1703	1433	1016	833	521	106

Kaplan-Meier estimate. Hazard ratios based on pre-specified Cox regression analyses.

Doubling of serum creatinine*, initiation of renal replacement therapy, or death due to renal disease



No. of patients									
Empagliflozin	4645	4500	4377	4241	3729	2715	2280	1496	360
Placebo	2323	2229	2146	2047	1771	1289	1079	680	144

*Accompanied by eGFR (MDRD) ≤45 mL/min/1.73m².
Post-hoc analyses. Kaplan-Meier estimate. Hazard ratio based on Cox regression analyses.

Adverse Effects of SGLT-2 Inhibitors

- Genital Mycotic Infection (Yeast infections)
  - Empa-reg study: 6.5% developed vs. 1.8% placebo
  - Rare cause of discontinuation (0.8%)
  - Avoid use in patients with recurrent yeast infections
  - Treat if necessary
- Hypotension
  - Avoid use in patients with low blood pressure or tendency for volume depletion
  - Counsel patients to stay well hydrated
- LDL-C
  - Small increases in LDL-C have been observed

Safety Considerations SGLT-2 Inhibitors

- Renal Impairment
  - Monitor renal function
  - Dapaglifozin – Avoid use if eGFR < 60 mL/min/1.73 m^2
  - Canaglifozin – Avoid if eGFR < 45 mL/min/1.73 m^2
  - Empagliflozin – Avoid if eGFR < 45 mL/min/1.73 m^2
- Bone fractures
  - Increased incidence of bone fractures in canagliflozin and dapaglifozin clinic trials
  - Canagliflozin labeling includes specific warning about bone fractures

Safety Considerations SGLT-2 Inhibitors

- DKA
  - Potentially increased risk of diabetic ketoacidosis in patients with insulin deficiency and/or those undergoing acute metabolic stress
- Bladder cancer
  - Increased incidence of bladder cancers in patients receiving dapagliflozin
  - Dapagliflozin labeling recommends not using in patients with active bladder cancer and should be used with caution in patients with a history of bladder cancer

Key Points

- Once daily, oral therapy
- Clinically significant A1C reductions (~1%)
  - Increased reduction in more uncontrolled DM
- Significant weight loss
- Blood pressure improvements
- Empagliflozin has FDA approval for CV death prevention
  - Class effect????

Key Points

- Low risk hypoglycemia
  - Consider reduction of dose of SU or insulin if used in combination
- Complementary mechanism of action with many drugs
- Very well tolerated
  - Increased risk of GU infections: Don't use if already an issue
    - Treat if needed
- Avoid use if GFR < 45
  - Or if eGFR < 60 for dapaglifozin
- Potential renal protection??

Case 1

- 52 year old man here for follow-up of Type 2 DM. His diabetes was diagnosed 4 years ago. A1C is 7.2%.
- Medications:
  - Metformin 1000 mg PO BID
  - Atorvastatin 20 mg QD
  - Lisinopril 10 mg PO QD
  - ASA 81 mg PO QD
- For the last 3 months, he has been working on improving diet and increasing exercise.
- No history of pancreatitis . No personal or family history of medullary thyroid cancer. No recurrent yeast infections.

Case 1

- PMH:
  - DM2
  - HTN
  - Mixed hyperlipidemia
  - Obesity (BMI 32)
  - CAD s/p stent 2 years ago
- BP 130/75
- Normal BMP. Lipids at goal.
- Eye exam and vaccinations up-to-date
- Sensation to monofilament decreased on diabetic foot exam

Case 1

- What is next best step in his diabetes management?
  A. No change in medication. A1C at goal.
  B. Add sulfonylurea (e.g., glipizide)
  C. Add SGLT-2 Inhibitor
  D. Add DPP-4 Inhibitor
  E. Add GLP-1 Receptor Agonist

Case 1

- What is next best step in his diabetes management?
  A. No change in medication. A1C at goal.
  B. Add sulfonylurea
  C. Add SGLT-2 Inhibitor – Likely my first choice in this patient
  D. Add DPP-4 Inhibitor
  E. Add GLP-1 Receptor Agonist – Great alternative

Case 2

- 47 year old woman with Type 2 DM.
- A1C is 6.9%, however, she reports frequent low blood glucose levels (40's-50's mg/dL) in the afternoon associated with missed meals at work. No lows overnight or in the morning.
- She is also very frustrated with her weight. Trying to follow a low carb diet with reduced portion sizes but has only lost 2 lbs over last 3 months.
- No history of pancreatitis. No personal or family history of medullary thyroid cancer. No history of yeast infections.

Case 2

- Medications:
  - Metformin 500 mg PO BID
  - Lantus 10 units SQ QHS
  - Glimepiride 1 mg PO QD
  - Atorvastatin 10 mg PO QD
  - Losartan 100 mg PO QD
  - ASA 81 mg PO QD

Case 2

- PMH:
  - DM2
  - HTN
  - Mixed HLD
  - Diabetic kidney disease
- BMI 34
- eGFR 40
- BP: 116/65
- Recent normal eye exam, up-to-date on vaccinations, normal diabetic foot exam

Case 2

- What would you do for this individual?
  A. No change. A1C is at goal.
  B. Stop glimepiride.
  C. Stop glimepiride. Add GLP-1 receptor agonist
  D. Stop glimeperide. Add DPP-4 Inhibitor
  E. Stop glimeperide. Add SGLT-2 Inhibitor

Case 2

- What would you do for this individual?
  A. No change. A1C is at goal.
  B. Stop glimepiride.
  C. Stop glimepiride. Add GLP-1 Receptor agonist
  D. Stop glimeperide. Add DPP-4 Inhibitor
  E. Stop glimeperide. Add SGLT-2 Inhibitor

Case 3

- 69 year old man here for follow-up of Type 2 DM. A1C 8.4%.
- Medications:
  - Metformin 1000 mg PO BID
  - Rosuvastatin 10 mg PO BID
  - ASA 81 mg PO BID
  - Lisinopril 20 mg PO QD
- He reports a needle phobia and does not want any type of injectable therapy.
- He lives alone.
- Previously had lower A1C on SU, however, due to recurrent hypoglycemia the SU was discontinued. He reports irregular eating schedule.

Case 3

- No history of pancreatitis. No personal or family history of medullary thyroid cancer. No history of yeast infections.
- PMH:
  - DM2
  - Non-proliferative diabetic retinopathy
  - Peripheral neuropathy
  - Mixed HLD
  - HTN
  - OSA on CPAP
  - CAD s/p CABG

Case 3

- BP 140/80
- BMI: 42
- Normal BMP. Lipids at goal.
- Up-to-date on eye exam and vaccinations

Case 3

- What would you offer this patient?
  A. Restart SU at lower dose
  B. Start GLP-1 Agonist
  C. Start DPP-4 Inhibitor
  D. Start SGLT-2 Inhibitor
  E. Start a SGLT-2 and DPP-4 Inhibitor

Case 3

- What would you offer this patient?
  A. Restart SU at lower dose
  B. Start GLP-1 Agonist
  C. Start DPP-4 Inhibitor
  D. Start SGLT-2 Inhibitor
  E. Start a SGLT-2 and DPP-4 Inhibitor

Summary

- Goal A1C $\leq$ 6.5%, but need to individualize
- Achieving goal reduces complications
- Metformin first line
- 2nd line: GLP-1 RA, SGLT2i, DPP4i

Summary

GLP-1 Receptor Agonist

Promote weight loss

Reduce BP

Low risk hypoglycemia

Cardiac benefits?

SGLT-2 Inhibitor

Promote weight loss

Reduce BP

Low risk hypoglycemia

Cardiac death reduction

Renal protection?