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Getting to the Heart of Antidiabetic Medication Safety and Efficacy

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&
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Disclosure

Daniel Riche

Becton Dickinson: Advisory Board; Merck: Speaker's Bureau; Novo Noordisk: Advisory Board, Speaker's Bureau

All other planners, presenters, and reviewers of this session report no financial relationships relevant to this activity.

Program Outline

- Introduction
- Case Presentation
- Introduction to Cardiovascular Safety Assessment
- Review of Clinical Trials Evaluating the Safety of T2DM Medications
- Patient Case Scenarios
- Audience Questions & Answers

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Introduction of Patient Case

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Associate Professor
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Patient Case

- 68 y/o F with history of T2DM x 12 years
  - Height: 5’4”
  - Weight: 143 lbs
  - A1c 7.9%
  - eGFR 77 mL/min
  - BGs: 212; 185; 176; 192 mg/dL
  - Medications:
    - Metformin 500 mg bid
    - Glipizide XL 10 mg daily
- PMH
  - HTN x 15 years
    - Losartan/HCTZ 50/12.5 mg daily
  - DLD x 11 years
    - Rosuvastatin 20 mg daily
  - Myocardial infarction 2 years ago
    - ASA 81 mg daily
    - Metoprolol tartrate 50 mg bid

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Introduction to Cardiovascular Safety Assessment of Type 2 Diabetes Medications & the U.S. FDA's Requirement for Clinical Trial Evidence

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Epidemiology of Diabetes Mellitus

- >29 million estimated to have type 2 diabetes mellitus (T2DM) in the U.S. in 2012
  - Another 8 million undiagnosed cases
- Total US prevalence ~ 9.3% of total population
- Projected to increase to 20% by 2050
- 95% of all DM cases classified as T2DM

CDC National Diabetes Statistics Report, 2014.
Boyle JP, et al. *Popul Health Metr*. 2010;8:29.

Type 2 DM & Cardiovascular Disease

- Risk of developing CV disease ↑ 2- to 4-fold in diabetics vs. non-diabetics
- ~2/3 of diabetes-related deaths are attributed to myocardial infarction (MI)
  - ~16% are attributed to stroke
- ~25-40% of T2DM develop heart failure
  - 2X higher risk in men (vs. non-diabetics)
  - 5X higher risk in women (vs. non-diabetics)

Azim S, Baker WL, White WB. *Curr Cardiol Rep*. 2014;16:541.
White WB, Baker WL. *Ann Rev Med*. 2016;67:245-60.

Trials Prior to December 2008

- HbA1c, as the measure of glycemic control, was the efficacy endpoint for approval of anti-diabetic therapies
- Trials supporting marketing application:
  - 6-month PC or AC with open-label extension
  - Monotherapy and combination therapy
- Patient population:
  - CVD often an exclusion criterion
  - Few patients with renal disease enrolled
  - Treatment-naïve or short duration of diabetes
  - Discontinuations for glycemic rescue medications

Consequences of a "Glucocentric" Regulatory Approach to T2DM Drugs

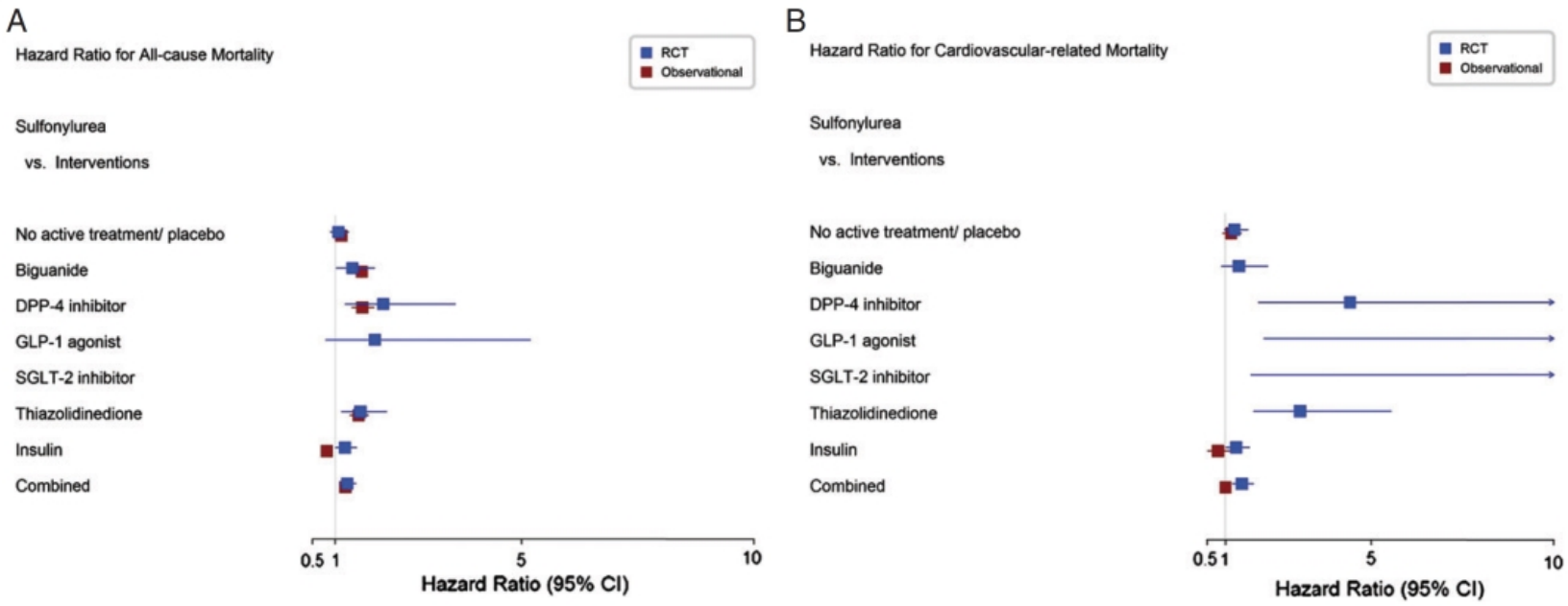
- Pre-approval studies focus on demonstrating maximal glucose lowering effects
- Patients are selected with relatively high HbA1c levels to enhance apparent "efficacy"
- Studies seek "bragging" rights – "my drug lowers blood sugar more than your drug"
- Patients at high CV risk are deliberately avoided. Why take a change of a safety signal?

Cardiovascular Safety of Sulfonylureas

- Early data from the University Group Diabetes Programme in the 1970's suggested higher CV death rates with tolbutamide vs. placebo
- Some meta-analyses support these findings
- More recent studies have seen trends for increases in adverse CV outcomes
- Large confirmatory clinical trials are unlikely

Goldner MG, et al. *JAMA*. 1971;218:1400-10; Meinert CL, et al. *Diabetes*. 1970;19:830.
Phung OJ, et al. *Diab Med*. 2013;30:1160-71.; Rados EV, et al. *PLoS Med*. 2016;13:e1001992.

Meta-Analysis Showing Increased Mortality and CV Death With SUs



Bain S, et al. *Diab Obes Metab.* 2017;19:329-35.

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Muraglitazar
(PPAR agonist)

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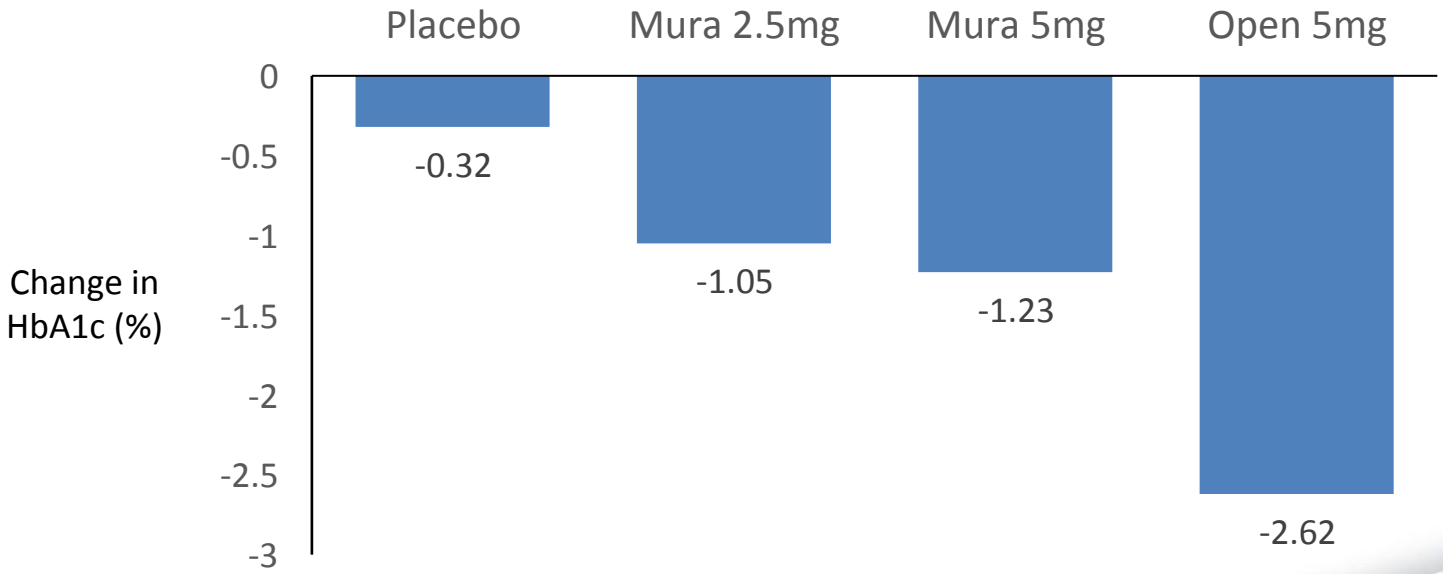
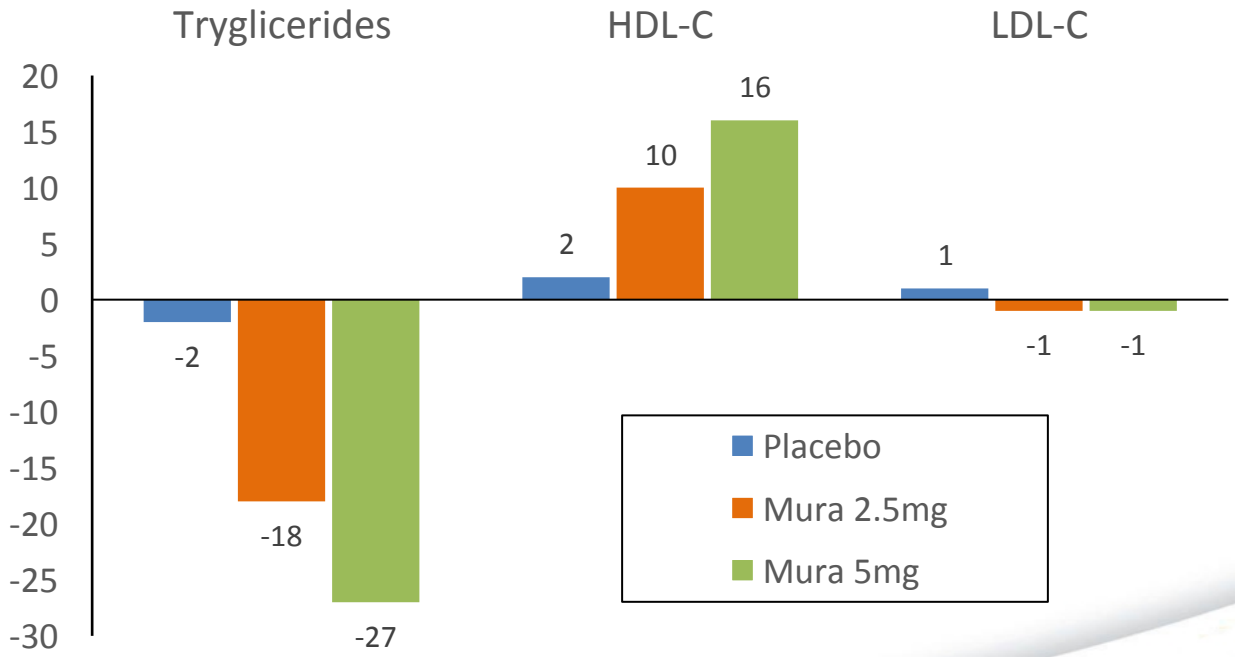
Effect of Muraglitazar on HbA1c



Buse JB, et al. *Clin Ther.* 2005;27:1181-95.

Effect of Muraglitazar on Lipids



Kendall DM, et al. *Diabetes Care*. 2006;29:1016-23.

CV Effects of Muraglitazar

Endpoint	Mura n (%)	Controls n (%)	RR	95% CI	p value
All cause mortality or nonfatal MI	27/2374 (1.14%)	7/1351 (0.52%)	2.21	0.96-5.08	0.06
CV death or nonfatal MI	19/2374 (0.80%)	5/1351 (0.37%)	2.17	0.81-5.83	0.12
All cause mortality plus nonfatal MI or stroke	35/2374 (1.47%)	9/1351 (0.67%)	2.23	1.07-4.66	0.03
CV death + nonfatal MI or Stroke	27/2374 (1.14%)	7/1351 (0.52%)	2.21	0.96-5.08	0.06
All cause mortality+nonfatal MI, stroke, TIA, or CHF	50/2374 (2.11%)	11/1351 (0.81%)	2.62	1.36-5.05	0.004
CV death + nonfatal MI, stroke, TIA, or CHF	42/2374 (1.77%)	9/1351 (0.67%)	2.69	1.30-5.53	0.007

Nissen SE, et al. *JAMA.* 2005;294:2581-6.

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Rosiglitazone (Avandia®)

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Rosiglitazone FDA Advisory Panel: CV Events (1999)

Ischemic Heart Disease Events			
RSG N=2902	Placebo N=601	Metformin N=225	SU N=626
36 (1.2%)	3 (0.5%)	3 (1.3%)	4 (0.6%)

Rosiglitazone	Comparators	Relative Risk
36/2902 (1.24%)	10/1452 (0.69%)	1.8 (0.9 to 3.6)

FDA Reviewer: “A post-marketing study to evaluate long-term safety of rosiglitazone should be required for approval”

Glycemic Durability of Rosiglitazone, Metformin, or Glyburide Monotherapy

Steven E. Kahn, M.B., Ch.B., Steven M. Haffner, M.D., Mark A. Heise, Ph.D., William H. Herman, M.D., M.P.H., Rury R. Holman, F.R.C.P., Nigel P. Jones, M.A., Barbara G. Kravitz, M.S., John M. Lachin, Sc.D., M. Colleen O'Neill, B.Sc., Bernard Zinman, M.D., F.R.C.P.C., and Giancarlo Viberti, M.D., F.R.C.P., for the ADOPT Study Group *

- Designed to show greater durability of glucose lowering with rosiglitazone (not safety)
- CV events not collected in an adjudicated manner
- Because of LDL-raising effects of Rosi, more patients received statins
- HR for MI = 1.33 (0.80 to 2.21)

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

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

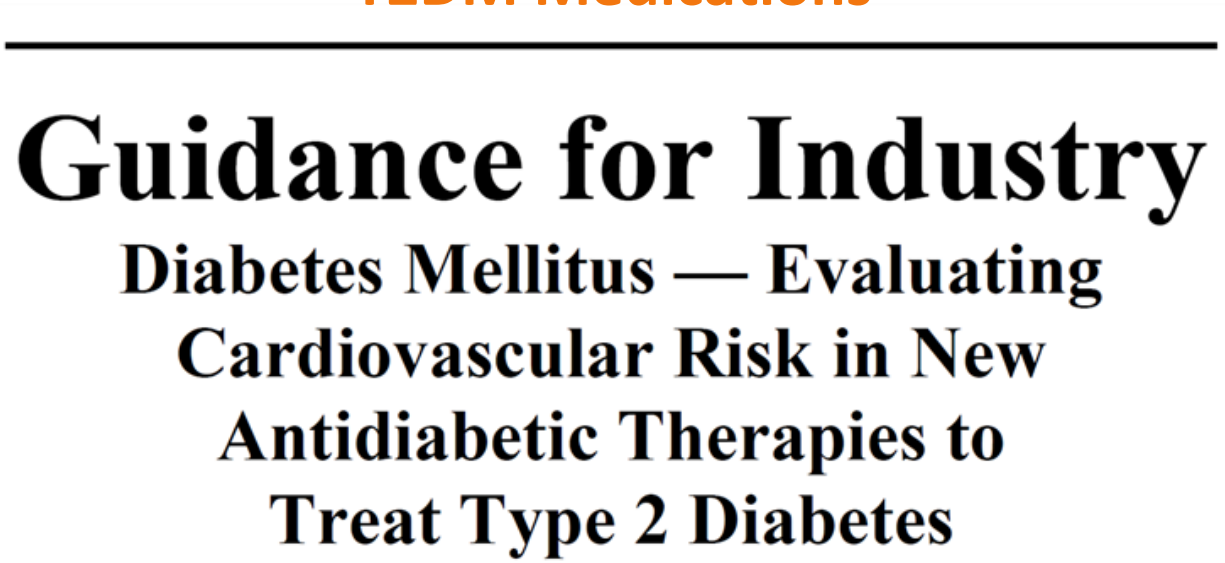
Steven E. Nissen, M.D., and Kathy Wolski, M.P.H.

Table 4. Rates of Myocardial Infarction and Death from Cardiovascular Causes.

Study	Rosiglitazone Group	Control Group	Odds Ratio (95% CI)	P Value
	no. of events/total no. (%)			
Myocardial infarction				
Small trials combined	44/10,285 (0.43)	22/6106 (0.36)	1.45 (0.88–2.39)	0.15
DREAM	15/2,635 (0.57)	9/2634 (0.34)	1.65 (0.74–3.68)	0.22
ADOPT	27/1,456 (1.85)	41/2895 (1.42)	1.33 (0.80–2.21)	0.27
Overall			1.43 (1.03–1.98)	0.03
Death from cardiovascular causes				
Small trials combined	25/6,845 (0.36)	7/3980 (0.18)	2.40 (1.17–4.91)	0.02
DREAM	12/2,635 (0.46)	10/2634 (0.38)	1.20 (0.52–2.78)	0.67
ADOPT	2/1,456 (0.14)	5/2895 (0.17)	0.80 (0.17–3.86)	0.78
Overall			1.64 (0.98–2.74)	0.06

Nissen SE & Wolski K. *N Engl J Med.* 2007;356:2457-71.

2008 FDA Industry Guidance for Evaluating CV Safety of New T2DM Medications



Guidance for Industry

Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

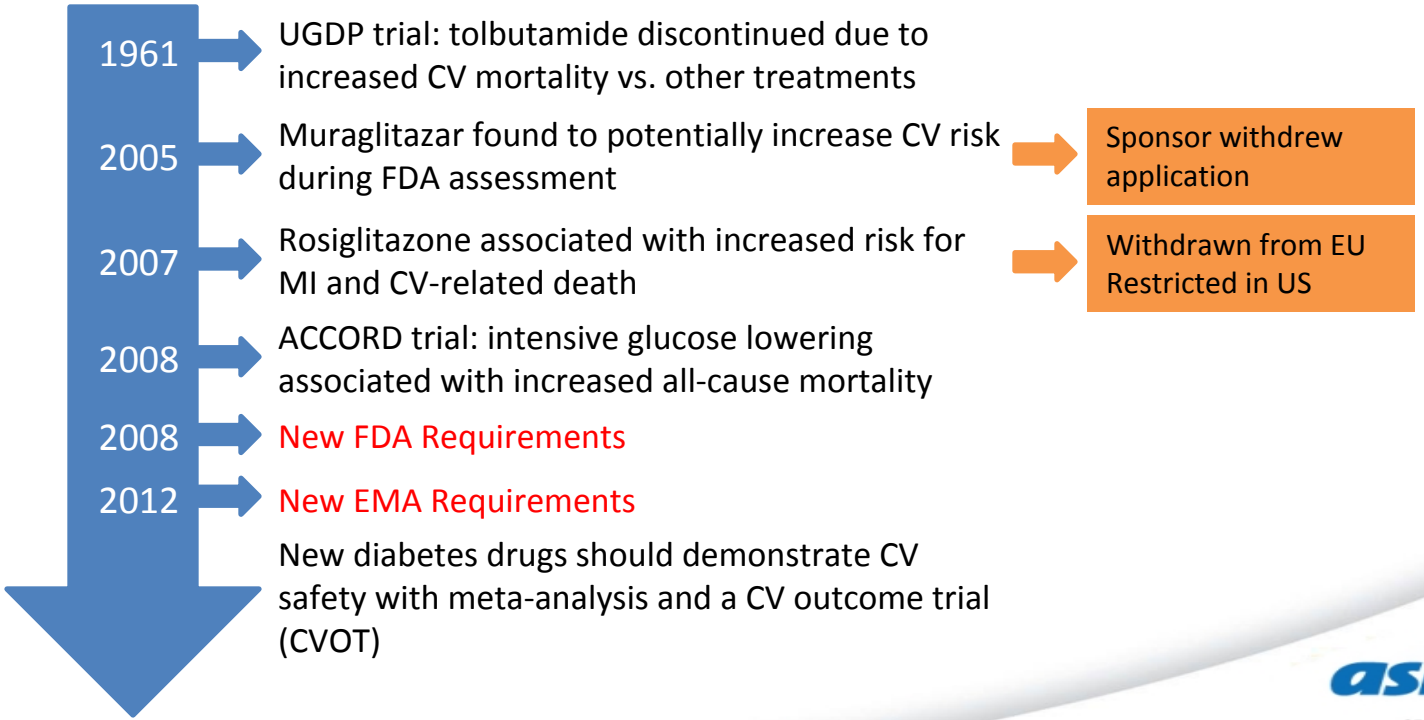
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071627.pdf.

2008 FDA Diabetes Guidance Recommendations

- Primary evidence for regulatory approval: glycemic control
- Demonstrate that therapy will not result in an unacceptable increase in CV risk (noninferiority)
- Phase 3 trials should rule out a HR of 1.8 (upper bound of 95% CI) for MACE (CV death, nonfatal MI, nonfatal stroke)
- Postmarketing (phase 4) trial, the upper bound of the 95% CI should not exceed 1.3 for MACE
- Independent committee should prospectively and blindly adjudicate MACE
- Trials should include patients at increased risk for cardiovascular disease (advanced CVD, CKD, elderly)
- Trial duration(s) should be longer than 3-6 months to obtain enough events to provide long-term data (~2 years)

http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071627.pdf.

Summary of Events That Lead to Regulatory Requirements



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Review of Clinical Trials Evaluating the Safety and Efficacy of Newly Approved Medications for Type 2 Diabetes

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University of Mississippi School of Pharmacy
Jackson, MS

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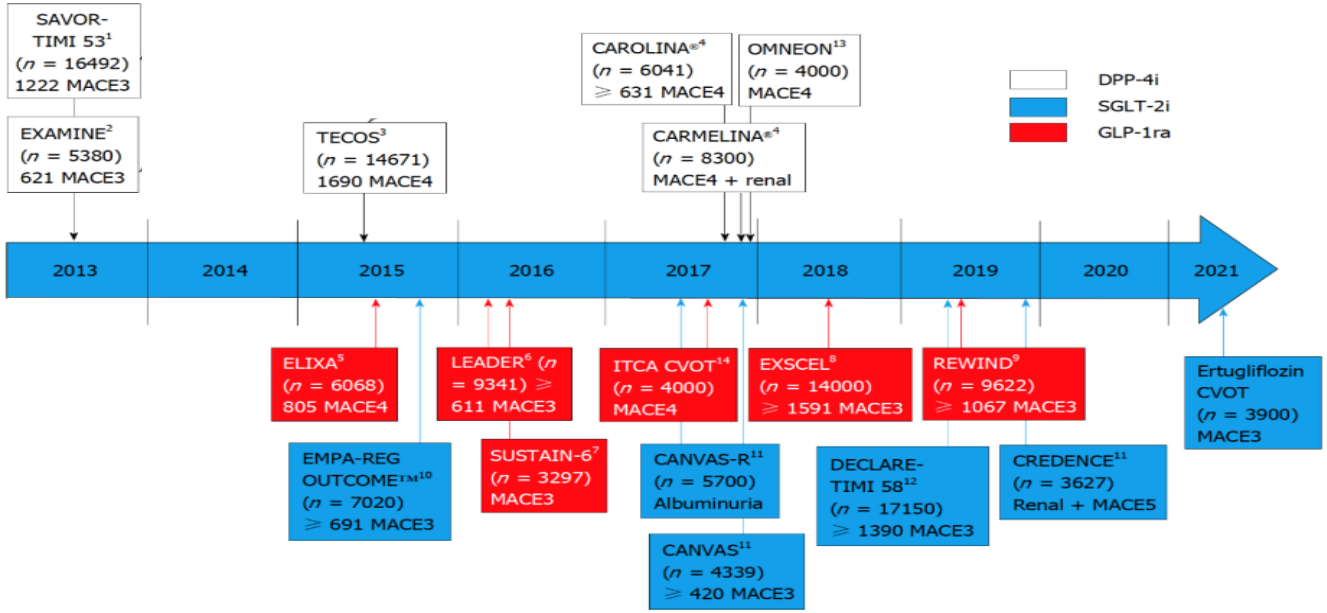
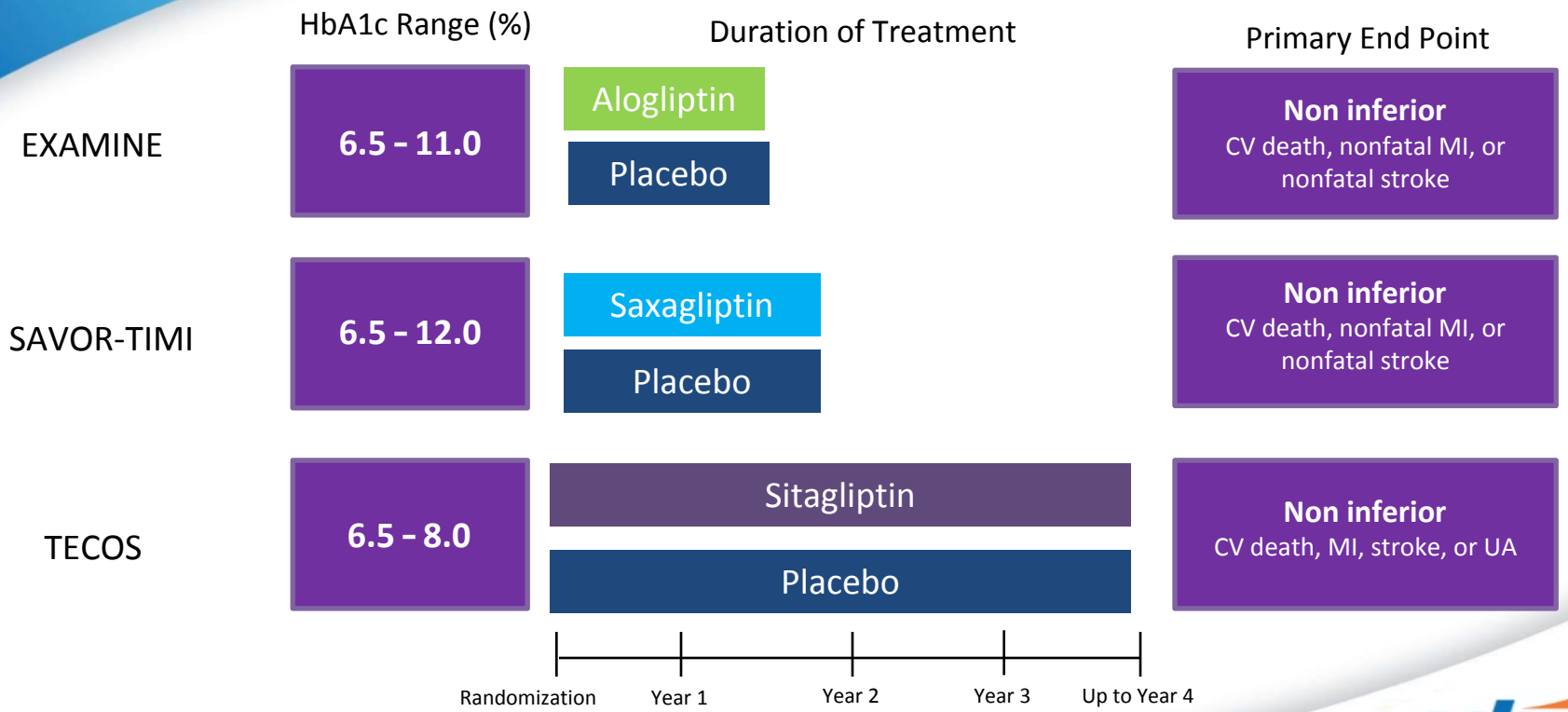
Diabetes CVOT 2013-2021



Adapted from: Johansen OK. *World J Diab.* 2015;6:1092-6.

Dipeptidyl Peptidase-4 (DPP4) Inhibitors

DPP4 Inhibitor CVOTs



White WB, et al. *N Engl J Med.* 2013;369:1327-35.
Scirca BM, et al. *N Engl J Med.* 2013;369:1317-26.; Green JP, et al. *N Engl J Med.* 2015;373:232-42.

EXAMINE Trial (Alogliptin)

Study Design

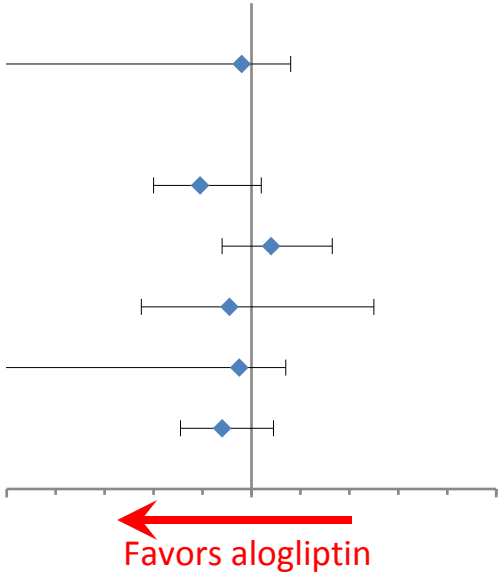
- n=5,380 patients with T2D and ACS
- Dosing: 25mg PO once daily with eGFR ≥ 60 mL/min
- Randomization
  - Alogliptin: n=2,701 Placebo: n=2,679
- Non-inferiority study predefined by hazard ratio of 1.3 for primary endpoints
  - Primary endpoint: CV death, nonfatal MI, or nonfatal stroke

Key Results

- Median follow-up: 18 months
- Least squares mean difference in A1C:
  - -0.36% (95% CI -0.43 to -0.28; *P*<0.001)
- CV outcomes reported as hazard ratios
  - Primary: 0.96 (≤1.16); *P*=0.32
- No HF at baseline subgroup
  - Admission for HF: 1.76 (1.07-2.90); p=0.026
- No difference between alogliptin and placebo in incidence of acute and chronic pancreatitis, cancer, renal impairment, angioedema, or severe hypoglycemia

White WB, et al. *N Engl J Med.* 2013;369:1327-35.

EXAMINE: Outcomes



	Hazard ratio (95% CI)	*P* value
Primary composite	0.96 (≤1.16)*	0.32
Primary endpoint components		
CV death	0.79 (0.6-1.04)	0.10
Nonfatal MI	1.08 (0.88-1.33)	0.47
Nonfatal stroke	0.91 (0.55-1.50)	0.71
Primary secondary endpoint†	0.95 (≤1.14)*	0.26
Death from any cause	0.85 (0.66-1.10)	0.21

*Upper boundary of 1-sided repeated CI, alpha level 0.01.

†CV death, nonfatal MI, nonfatal stroke, urgent revascularization for unstable angina.

CI, confidence interval; CV, cardiovascular; EXAMINE, Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care; MI, myocardial infarction.

White WB, et al. *N Engl J Med.* 2013;369:1327-35.

SAVOR-TIMI (Saxagliptin)

Study Design

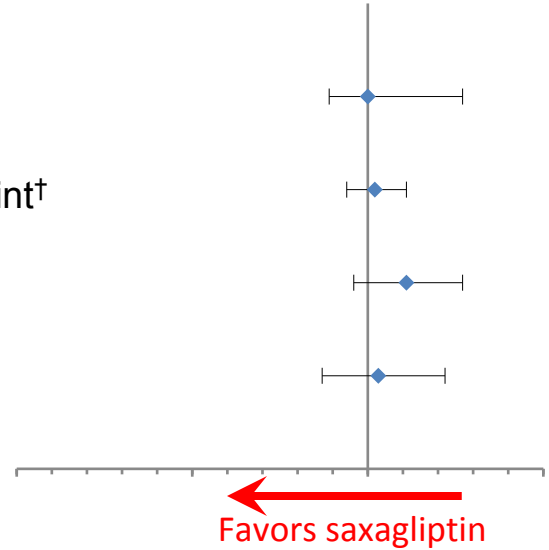
- n=16,492 patients with T2D and CVD or CVD risk
- Dosing: 5 mg or 2.5 mg PO once daily
- Randomization
  - Saxagliptin: n=8,280 Placebo: n=8,212
- Superiority study with provision to test for non-inferiority
  - Primary composite endpoint: CV death, nonfatal MI, or nonfatal ischemic stroke

Key Results

- Median follow-up: 2.1 years
- Endpoint A1C
  - Saxagliptin: 7.7% ± 1.4% (P<0.001 vs placebo)
  - Placebo: 7.9% ± 1.5%
- CV outcomes
  - Primary: 1.00 (0.89-1.27); P=0.99
- Higher incidence of HF hospitalization in saxagliptin
- No difference between groups in incidence of acute or chronic pancreatitis
  - Fewer cases of pancreatic cancer in saxagliptin group;
  - More cases of nonfatal angioedema in saxagliptin group (8 vs 1)

Scirca BM, et al. *N Engl J Med*. 2013;369:1317-26.

SAVOR-TIMI: Outcomes



	Hazard ratio (95% CI)	*P* value
Primary composite endpoint*	1.00 (0.89-1.27)	0.99
Secondary composite endpoint†	1.02 (0.94-1.11)	0.66
Death from any cause	1.11 (0.96-1.27)	0.15
CV death	1.03 (0.87-1.22)	0.52

CI, confidence interval; CV, cardiovascular; SAVOR-TIMI, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction.

Scirca BM, et al. *N Engl J Med*. 2013;369:1317-26.

TECOS (Sitagliptin)

Study Design

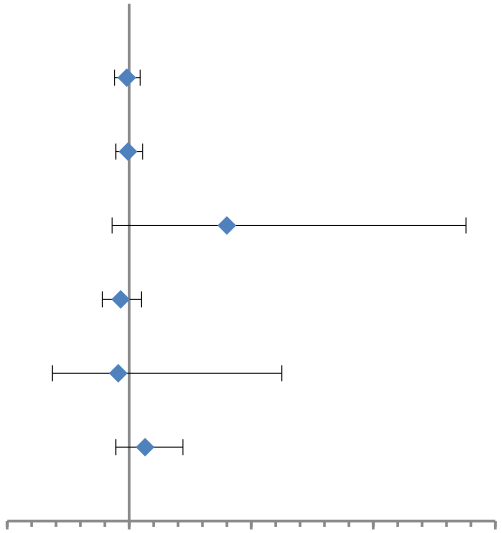
- n=14,671 patients with T2D and CVD
- Dosing: 50 mg or 100 mg (depending on renal function) PO once daily
- Randomization
  - Sitagliptin: n=7,332 (6972 completed)
  - Placebo: n=7,339 (6905 completed)
- Non-inferiority study: 1.3 marginal upper boundary of 2 -sided 95% CI
  - Primary composite outcome: cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina

Key Results

- Median follow-up: 3.0 years
- Least squares mean difference in A1C:
  - -0.29% (95% CI -0.32 to -0.27) for sitagliptin vs placebo
- Non-inferior to placebo for cardiovascular outcomes
  - Primary: 0.98 (0.88-1.09); *P*<0.001
- No difference between sitagliptin and placebo in incidence of infections, cancer, renal failure, hypoglycemia, or non-cardiovascular death

Green JP, et al. *N Engl J Med.* 2015;373:232-42.

TECOS: Primary and Secondary Outcomes



	Hazard ratio (95% CI)	*P* value
Primary composite endpoint*	0.98 (0.88-1.09)	<0.001 (NF)
Secondary composite endpoint†	0.99 (0.89-1.11)	<0.001 (NF)
Acute pancreatitis	1.80 (0.86-3.76)	0.12
Any cancer (except nonmelanoma skin cancer)	0.93 (0.89-1.44)	0.38
Pancreatic cancer	0.91 (0.37-2.25)	0.85
Severe hypoglycemia	1.13 (0.89-1.44)	0.31

*Cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina.

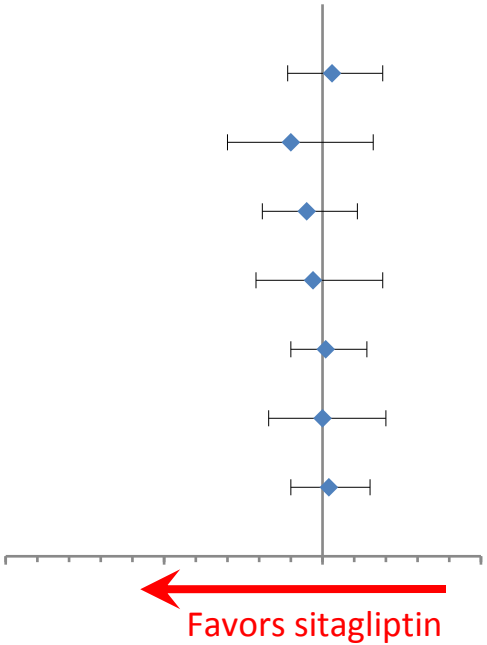
†Secondary composite: cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.

NF, non-inferiority; TECOS, Trial Evaluating Cardiovascular Outcomes with Sitagliptin.

Green JP, et al. *N Engl J Med.* 2015;373:232-42.

TECOS: Individual Secondary Outcomes

	Hazard ratio (95% CI)	*P* value
CV death	1.03 (0.89-1.19)	0.71
Hospitalization for unstable angina	0.90 (0.70-1.16)	0.42
Fatal or nonfatal MI	0.95 (0.81-1.11)	0.49
Fatal or nonfatal stroke	0.97 (0.79-1.19)	0.76
Death from any cause	1.01 (0.90-1.14)	0.88
Hospitalization for heart failure	1.09 (0.83-1.20)	0.98
Hospitalization for heart failure or CV death	1.02 (0.90-1.15)	0.74



CV, cardiovascular; MI, myocardial infarction; NF, non-inferiority; TECOS, Trial Evaluating Cardiovascular Outcomes with Sitagliptin.

Green JP, et al. *N Engl J Med.* 2015;373:232-42.

CAROLINA (Linagliptin vs. Glimepiride)

Study Design

- Ongoing multi-center, randomized, double-blind, active-controlled, Phase III clinical trial
- Investigating long-term impact on CV outcomes, relevant efficacy parameters, and safety
- 6041 patients randomized with early T2DM and increased CV risk or established complications
- A total of 631 patients with primary outcome events will be required to provide 91% power to demonstrate non-inferiority in cardiovascular safety
- Comparing the upper limit of the two-sided 95% CI for < 1.3 hazard ratio.

Study Outcomes

- Primary
  - CV death, nonfatal MI (excluding silent MI), nonfatal stroke, and hospitalization for unstable angina.
- Secondary
  - Primary outcome components (excluding hospitalization for UA), change from baseline to final visit in HbA1c, and urine albumin-to-creatinine ratio (UACR) or transition in albuminuria categories.

Rosenstock J, et al. *Diab Vasc Dis Res*. July 2013.

DPP Selectivity

Identifier	Chemical/Generic Name	Base	DPP-4	DPP-8	DPP-9
MK-0431	Sitagliptin	Piperazine	12-18	>2,660	>5,550
LAF-237	Vildagliptin	Cyanopyrrolidine	22-83	270	32
SYR-322	Alogliptin	Xanthine	6.9	>14,000	>14,000
BMS-477118	Saxagliptin	Cyanopyrrolidine	26	390	77
BI-1356	Linagliptin	Xanthine	1.7	40,000	>100,000

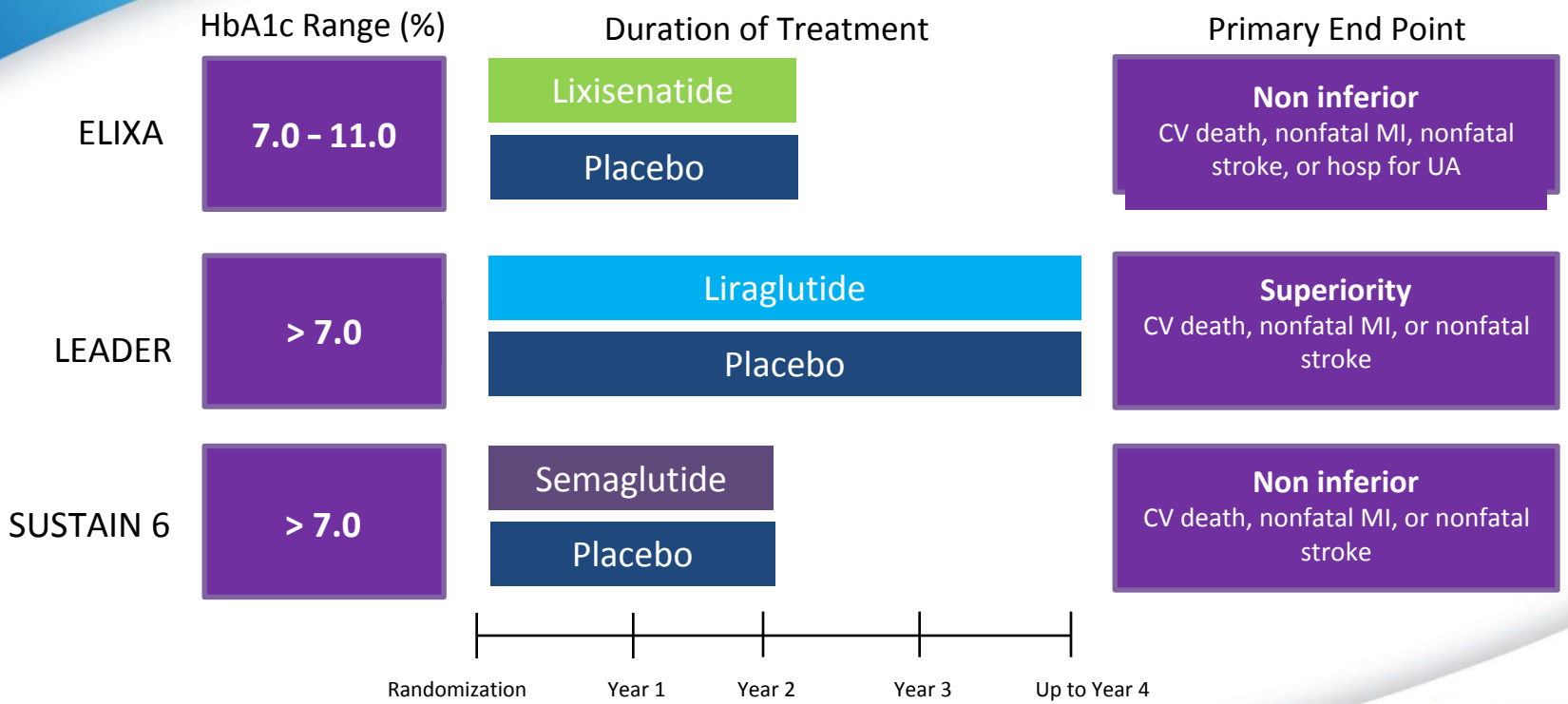
Riche DM, et al. *Lancet*. 2015;386:1443-4.

FDA Warning: February 11, 2014 (Updated April 5, 2016)

- Saxagliptin and alogliptin may increase the risk of heart failure, especially in those with pre-existing heart or kidney disease
- Precaution/warning added to label regarding risk of hospitalization for heart failure to sitagliptin and linagliptin in August 2017
- “Healthcare professionals should consider discontinuing the medicine in patients who develop heart failure and monitor their diabetes control”

Glucagon-Like Peptide-1 (GLP-1) Agonists

GLP-1 Agonist CVOTs



Pfeffer MA, et al. *N Engl J Med.* 2015;373:2247-57.
Marso SP, et al. *N Engl J Med*. 2016;375:311-32.; Marso SP, et al. *N Engl J Med.* 2016;375:1834-44.

ELIXA (Lixisenatide)

Study Design

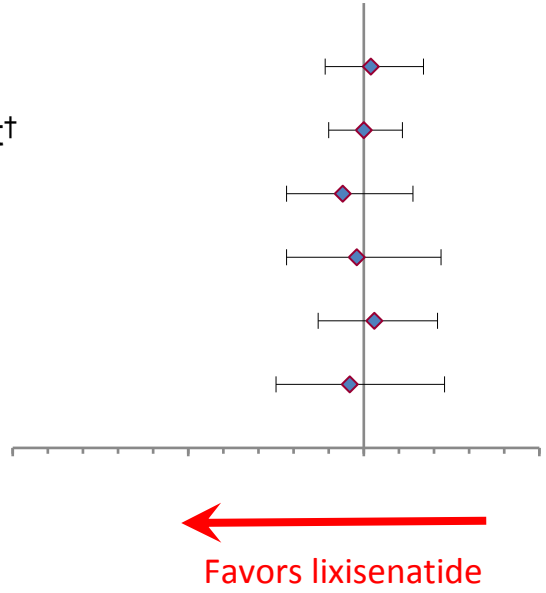
- n=6,068 patients with T2D and high CV risk
- Dosing: 10 mcg SQ once daily for 14 days. On day 15, increase dosage to 20 mcg SQ once daily
- Randomization
  - Lixisenatide: n=3,034 Placebo: n=3,034
- Non-inferiority study: pre-specified margin = 1.3 for upper bound of 95% CI of the HR for the primary endpoint
  - Primary endpoint: composite of CV death, nonfatal MI (including silent MI), or nonfatal stroke, hospitalization for UA

Key Results

- Median follow-up: 25 months
- Difference from placebo at 36 months
  - A1C: −0.27% (95% CI, −0.31% to −0.22%)
  - Weight: −0.7 kg (95% CI, −1.3 to −0.3 kg)
  - SBP: −0.8 mm Hg (95% CI, −1.3 to −0.3 mm Hg)
- CV outcomes
  - Primary: HR 1.02 (95% CI 0.89 to 1.17); *P*=0.81 for non-inferiority
- No difference between lixisenatide and placebo in incidence of heart failure hospitalizations, mortality, pancreatitis or pancreatic cancer

Pfeffer MA, et al. *N Engl J Med.* 2015;373:2247-57.

ELIXA: Outcomes



	Hazard ratio (95% CI)	*P* value
Primary composite endpoint*	1.02 (0.89-1.17)	0.81
Expanded composite endpoint†	1.00 (0.90-1.11)	0.96
Death from any cause	0.94 (0.78-1.13)	0.50
CV death	0.98 (0.78-1.22)	0.85
Fatal or nonfatal MI	1.03 (0.87-1.22)	0.71
Hospitalization for HF	0.96 (0.75-1.23)	0.75

Pfeffer MA, et al. *N Engl J Med.* 2015;373:2247-57.

LEADER (Liraglutide)

Study Design

- n=9,340 patients with T2D and high CV risk
- Dosing: max dose of 1.8mg SQ once daily
- Randomization
  - Liraglutide: n=4,672 Placebo: n=4,668
- Non-inferiority study: pre-specified margin = 1.3 for upper bound of 95% CI of the HR for the primary endpoint
  - Primary endpoint: composite of CV death, nonfatal MI (including silent MI), or nonfatal stroke
  - Secondary endpoint: composite of CV death, nonfatal MI (including silent MI), nonfatal stroke, coronary revascularization, and hospitalization for unstable angina or HF

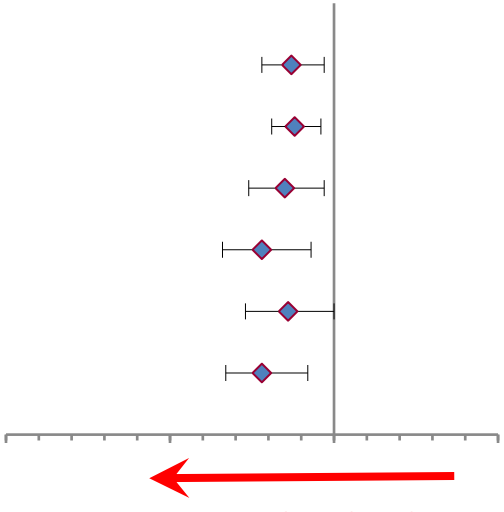
Key Results

- Median follow-up: 3.5 years
- Difference from placebo at 36 months
  - A1C: −0.40% (95% CI, −0.45% to −0.34%)
  - Weight: −2.3 kg (95% CI, −2.0 to −2.5 kg)
  - SBP: −1.2 mm Hg (95% CI, −0.5 to −1.9 mm Hg)
- CV outcomes
  - Primary: HR 0.87 (95% CI 0.78 to 0.97); *P*=0.01
  - Secondary HR: 0.88 (95% CI 0.81 to 0.96); *P*=0.005
- Significantly lower rates of all-cause death and CV death with liraglutide
- Increased rates of GI events in liraglutide patients
- Lower numerical incidence of pancreatitis in liraglutide group (not statistically significant)

Marso SP, et al. *N Engl J Med*. 2016;375:311-32.

LEADER: Outcomes

	Hazard ratio (95% CI)	*P* value
Primary composite endpoint*	0.87 (0.78-0.97)	0.01
Expanded composite endpoint†	0.88 (0.81-0.96)	0.005
Death from any cause	0.85 (0.74-0.97)	0.02
CV death	0.78 (0.66-0.93)	0.007
Fatal or nonfatal MI	0.86 (0.73-1.00)	0.046
Nephropathy	0.78 (0.67-0.92)	0.003



Marso SP, et al. *N Engl J Med*. 2016;375:311-32.

Liraglutide: New FDA Indication 8/25/17

- FDA approved new indication for liraglutide in reducing risk of myocardial infarction, stroke, and cardiovascular death in adults with T2DM who have established cardiovascular disease

SUSTAIN-6 (Semaglutide)

Study Design

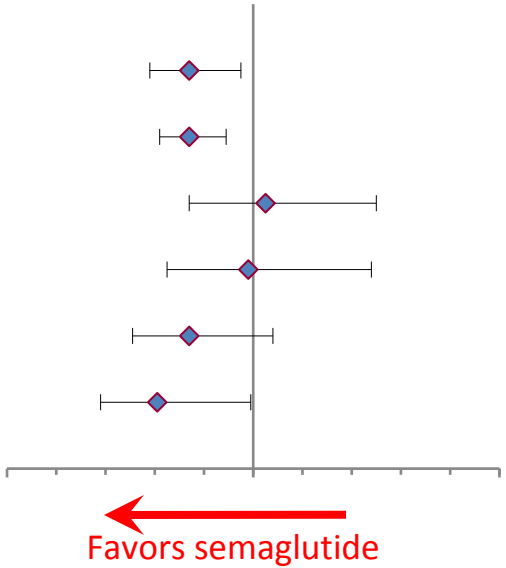
- n=3,297 patients with T2D and high CV risk
- Dosing: once weekly 0.5mg SQ OR once weekly dose of 1mg
- Randomization
  - Semaglutide: n=1,648 Placebo: n=1,649
- Non-inferiority study: pre-specified margin = 1.8 for upper bound of 95% CI of the HR for the primary endpoint
  - Primary endpoint: composite of CV death, nonfatal MI (including silent MI), or nonfatal stroke
  - Secondary endpoint: composite of CV death, nonfatal MI (including silent MI), nonfatal stroke, coronary revascularization, and hospitalization for unstable angina or HF

Key Results

- Median follow-up: 2.1 years
- Difference from placebo at 104 weeks
  - A1C: 0.5mg: −0.66% (95% CI, −0.80% to −0.52%)
    1.0mg: −1.05% (95% CI, −1.19% to −0.91%)
  - Weight: 0.5mg: −2.87 kg (95% CI, −3.47 to −2.28 kg)
    1.0mg: −4.35 kg (95% CI, −4.94 to −3.75 kg)
  - SBP: 0.5mg: −1.27 mm Hg (95% CI, −2.77 to 0.23 mm Hg)
    1.0mg: −2.59 mm Hg (95% CI, −4.09 to −1.08 mm Hg)
- CV outcomes
  - Primary: HR 0.74 (95% CI 0.58 to 0.95); *P*<0.001 for non-inferiority; *P*=0.02 for superiority
  - Secondary: HR 0.74 (95% CI 0.62 to 0.89); *P*=0.002 for superiority

Marso SP, et al. *N Engl J Med.* 2016;375:1834-44.

SUSTAIN-6: Outcomes



	Hazard ratio (95% CI)	*P* value
Primary composite endpoint*	0.74 (0.58-0.95)	0.02
Expanded composite endpoint†	0.74 (0.62-0.89)	0.002
Death from any cause	1.05 (0.74-1.50)	0.79
CV death	0.98 (0.65-1.48)	0.92
Nonfatal MI	0.74 (0.51-1.08)	0.12
Nonfatal stroke	0.61 (0.38-0.99)	0.04

*CV death, nonfatal MI (including silent MI), or nonfatal stroke; †CV death, nonfatal MI (including silent MI), nonfatal stroke, coronary revascularization, and hospitalization for unstable angina or HF.

CI, confidence interval; CV, cardiovascular; MI, myocardial infarction.

Marso SP, et al. *N Engl J Med.* 2016;375:1834-44.

EXSCEL (Exenatide)

Study Design

- n=14,752 patients with T2D +/- CVD
- Dosing: once weekly 2 mg SQ weekly
- Randomization
  - Exenatide: n=7,356 Placebo: n=7,396
- Non-inferiority study: pre-specified margin = 1.3 for upper bound of 95% CI of the HR for the primary safety endpoint
  - Primary endpoint: composite of CV death, nonfatal MI (including silent MI), or nonfatal stroke

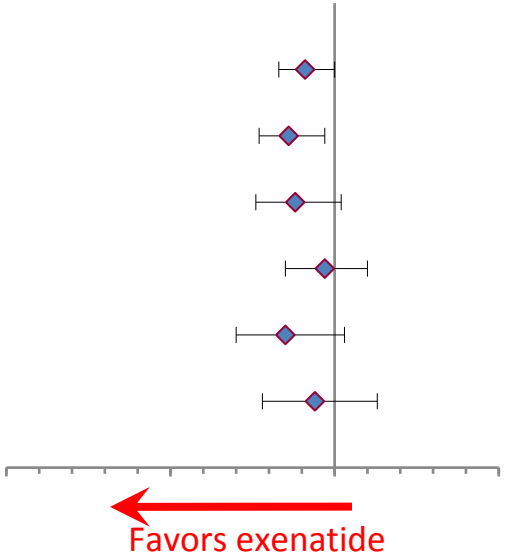
Key Results

- Median follow-up: 3.2 years
- Overall mean difference from placebo
  - A1C: −0.53% (95% CI, −0.57% to −0.50%)
  - Weight: −1.27 kg (95% CI, −1.40 to -1.13 kg)
  - SBP: −1.57 mm Hg (95% CI, −1.92 to -1.21 mm Hg)
- CV outcomes
  - Primary Composite: HR 0.91 (95% CI 0.83 to 1.00); P<0.001 for non-inferiority; P=0.06 for superiority

Holman RR, et al. *N Engl J Med.* 2017; Epub ahead of print.

EXSCEL: Outcomes

	Hazard ratio (95% CI)
Primary composite endpoint*	0.91 (0.83-1.00)
Death from any cause	0.86 (0.77-0.97)
Death from CV causes	0.88 (0.76-1.02)
Fatal or nonfatal MI	0.97 (0.85-1.10)
Fatal or nonfatal stroke	0.85 (0.70-1.03)
Hospitalization for HF	0.94 (0.78-1.13)



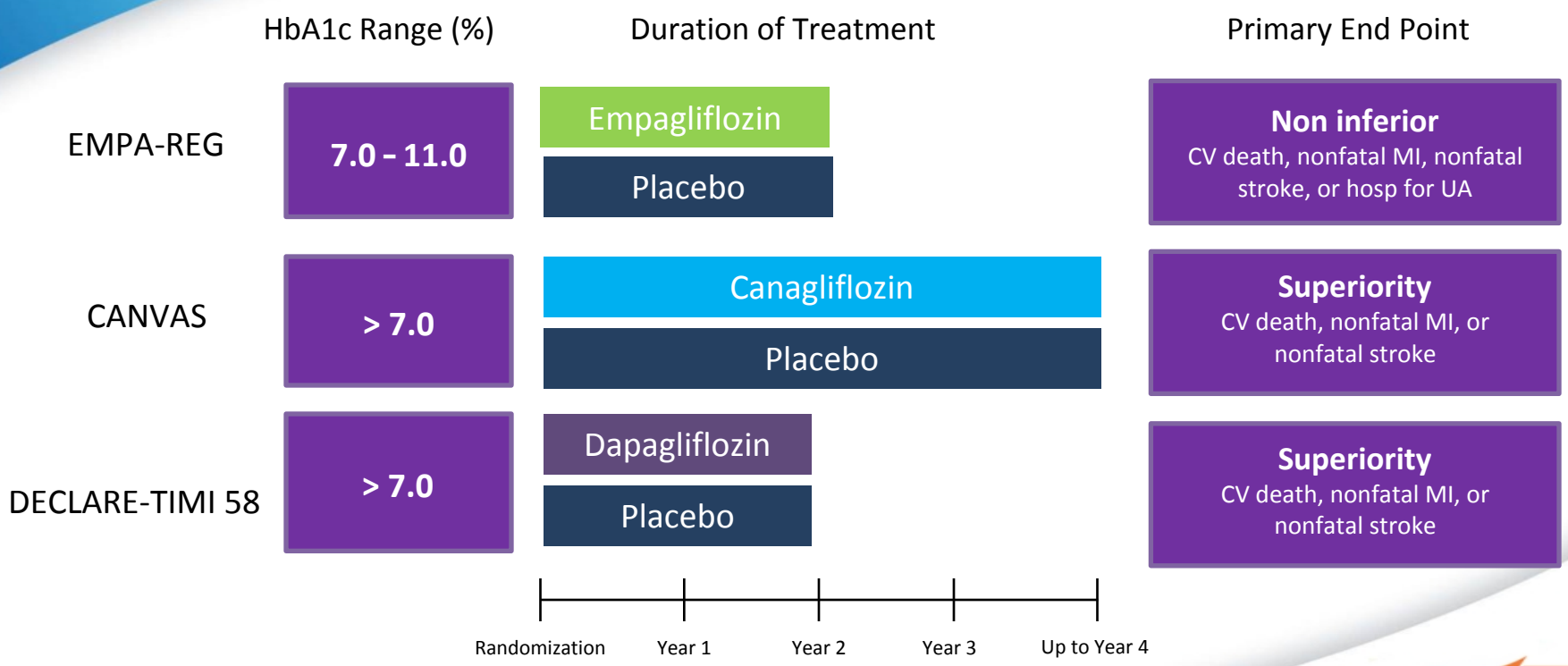
*CV death, nonfatal MI (including silent MI), or nonfatal stroke

CI, confidence interval; CV, cardiovascular; MI, myocardial infarction; HF, heart failure.

Holman RR, et al. *N Engl J Med.* 2017; Epub ahead of print.

Sodium-Glucose Co-Transporter 2 (SGLT-2) Inhibitors

SGLT-2 Antagonist CVOTs



Zinman B, et al. *N Engl J Med.* 2015;373:2117-28.

EMPA-REG (Empagliflozin)

Study Design

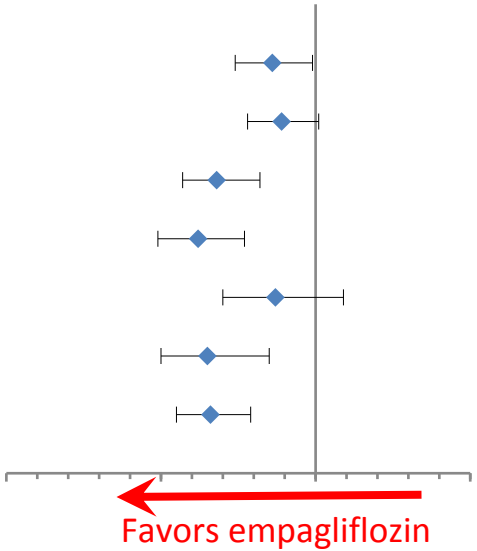
- n=7,020 patients with T2D and CVD
- Dosing: 10 mg or 25 mg PO once daily
- Randomization
  - Empagliflozin: n=4,687 Placebo: n=2,333
- Non-inferiority study: pre-specified HR margin = 1.3 for primary endpoint
  - Primary endpoint: composite of CV death, nonfatal MI (excluding silent MI), or nonfatal stroke
  - Secondary endpoint: composite of CV death, nonfatal MI (excluding silent MI), nonfatal stroke, and hospitalization for unstable angina

Key Results

- Median follow-up: 3.1 years
- Week 206 A1C, difference from placebo
  - Empagliflozin 10 mg: -0.24% (955 CI, -0.40% to -0.08%)
  - Empagliflozin 25 mg: -0.36% (95% CI, -0.51% to -0.20%)
- CV outcomes (pooled analysis)
  - Primary: HR 0.86 (95% CI 0.74 to 0.99); *P*=0.04 for superiority
  - Secondary: HR 0.89 (95% CI 0.78 to 1.01); *P*<0.001 for noninferiority and *P*=0.08 for superiority
- Significantly lower rates of all-cause death, CV death, and HF hospitalization with empagliflozin
- Increased rates of genital infections in empagliflozin -treated patients

Zinman B, et al. *N Engl J Med.* 2015;373:2117-28.

EMPA-REG: Outcomes



	Hazard ratio (95% CI)	*P* value
Primary composite endpoint*	0.86 (0.74-0.99)	0.04
Secondary composite endpoint†	0.89 (0.78-1.01)	0.08
Death from any cause	0.68 (0.57-0.82)	<0.001
CV death	0.62 (0.49-0.77)	<0.001
Fatal or nonfatal MI	0.87 (0.70-1.09)	0.23
Hospitalization for HF	0.65 (0.50-0.85)	0.002
Hospitalization for HF or CV death	0.66 (0.55-0.79)	<0.001

*CV death, nonfatal MI (excluding silent MI), or nonfatal stroke; †CV death, nonfatal MI (excluding silent MI), nonfatal stroke, and hospitalization for unstable angina.

CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; MI, myocardial infarction.

Zinman B, et al. *N Engl J Med.* 2015;373:2117-28.

Empagliflozin Approval (12/2/2016)

- First anti-diabetic medication with FDA-labeled indication for lowering CV death
- Applies to patients with T2DM and established CVD
- ADA guidelines recommend adding empagliflozin (or liraglutide) to metformin in uncontrolled T2DM for patients with established ASCVD

American Diabetes Association. *Diab Care.* 2017;40(Suppl 1):S64-S-74.
Savarese G, et al. *Int J Cardiol.* 2016;220:595-601.

CANVAS (Canagliflozin)

Study Design

- n=10,142 patients with T2D and CVD
- Dosing: 100mg or 300mg PO once daily
- Randomization
  - Canagliflozin: n=5,795 Placebo: n=4,347
- Non-inferiority study: pre-specified HR margin = 1.3 for primary endpoint
  - Primary endpoint: composite of CV death, nonfatal MI, or nonfatal stroke
  - Secondary endpoint: death from any cause, death from CV causes, progression of albuminuria, and the composite of death from CV causes and hospitalization for heart failure

Key Results

- Median follow-up: 126.1 weeks
- Mean A1C difference from placebo
  - Canagliflozin: -0.58% (95% CI, -0.61% to -0.56%)
- CV outcomes (pooled analysis)
  - Primary: HR 0.86 (95% CI 0.75 to 0.97); P<0.001 for non-inferiority and *P*=0.02 for superiority
  - Secondary HR: death from any cause with 0.87 (95% CI 0.74 to 1.01); death from CV causes with 0.87 (95% CI 0.72 to 1.06).
  - Reduces CV events by 14% and cuts the rate of renal decline by 40, but also doubles the risk for lower-limb amputation (primarily toe or metatarsal).
  - No differences between CANVAS and CANVAS-R trials for the primary, fatal, or exploratory CV outcomes.

Neal B, et al. *N Engl J Med*. 2017;377(7):644-657.

CANVAS: CV Protection at a Cost?

- CANVAS program combined data from two trials, CANVAS and CANVAS-R, involving a total of 10,142 patients with T2DM and high CVD risk.
- “CANVAS data suggests that CV and renal benefits are a class effect,” according to lead investigator (Neal *et al*.)
- Unlike EMPA-REG and LEADER, where all subjects had established CVD, only about 2/3 of CANVAS subjects did and the rest did not. CV death was not significantly reduced in CANVAS as it was in both EMPA-REG and LEADER trials
- CANVAS data revealed a significant doubling in risk for amputations, primarily of the toe and metatarsal.

DECLARE-TIMI 58 (Dapagliflozin)

- Ongoing multinational, randomized, double-blind, placebo-controlled Phase IIIB trial
- Superiority trial
  - Testing for long-term reduction in composite endpoint (CV death, MI, ischemic stroke)
  - The trial is to also seek definitively excluding unacceptable CV risk from dapagliflozin in these patients.
- Planned to randomize ~17,150 patients with T2DM and either known CVD (secondary prevention cohort) OR at least two risk factors for CVD (primary prevention cohort).
- Event-driven trial
- Estimated follow up: 4.5 years

DECLARE-TIMI58 (*clinicaltrials.gov*).

CVD-REAL

- Retrospective observational cohort
- > 300,000 patients across 6 countries were observed
  - 87% did not have a history of CVD
- Treatment with SGLT-2s (canagliflozin, dapagliflozin, and empagliflozin):
  - 39% lower risk of hospitalization for HF (HR: 0.61; 95% CI 0.51-0.73; p<0.001)
  - 51% lower risk of death from any cause (HR: 0.49; 95% CI 0.41-0.57; p<0.001)
- Composite endpoint of hospitalization for heart failure or death from any cause:
  - Treatment with SGLT-2 versus other drugs was associated with a 46% lower risk (HR 0.54; 95% CI 0.48-0.60; p<0.001)

Kosiborod M, et al. *Circulation*. 2017;136(10):1-81.

CVD-REAL: Outcomes

- Of the data reviewed, 42% of patients were on canagliflozin, 51% on dapagliflozin, and 7% on empagliflozin.
- Treatment with canagliflozin, dapagliflozin and empagliflozin was associated with a 39% lower risk of hospitalization for heart failure and 51% lower risk of death from any cause, compared with other T2D medicines.
- The results suggest that the benefits of reducing the risk of death was a class effect.
- While CVD-REAL is a large study with a robust propensity-matching technique, given its observational nature, the possibility of residual and unmeasured confounding factors cannot be definitively excluded.

Kosiborod M, et al. *Circulation*. 2017;136(10):1-81.

SGLT-2i Class Differences: Efficacy

- An analysis of 13 trials (6 dapagliflozin, 3 canagliflozin, 2 empagliflozin, along with others that are not yet FDA approved)
  - Key points from this analysis:
    - Independent network meta-analysis shows few clinically meaningful differences in the effectiveness on HbA1c, weight, and systolic blood pressure of different SGLT2 inhibitors.
    - Monotherapy with canagliflozin 300 mg ***may*** be slightly better at lowering HbA1c than the other members of this drug class, but this advantage does not hold up in dual therapy.

Shyangdan DS, et al. *BMJ Open*. 2016;6(2):1-20.

SGLT-2i Class Differences: Safety

- Amputation Hypotheses:
  - Canagliflozin causes substantial activation of 5' adenosine monophosphate protein kinase (AMPK), whereas dapagliflozin or empagliflozin were less likely *in vivo.*
  - Canagliflozin was the only SGLT2 that inhibited 2-deoxyglucose (2DG) uptake.
    - Hampers cell growth
  - Canagliflozin associated with decreasing bone mineral density

CDC. *MMWR Morb Mortal Wkly Rep. 1998;47(31)*:649-652.
Larsson J, et al. *Acta Orthopaedica Scandinavica.* 1995;66(2):181-192.
Neal B, et al. *The New England Journal of Medicine.* 2017;377:644-57.
Hawley SA, et al. *Diabetes*. 2016;65(9):2784-2794.
Alba M, et al. *Taylor & Francis*. 2016;32(8):1375-1385.

What is the most compelling CV outcomes study that may impact upcoming ADA guidelines?

A. SAVIOR-TIMI
B. EMPA-REG
C. CANVAS
D. LEADER

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Return to the Patient Case

Daniel Riche, Pharm.D., FCCP, BCPS, CDE, ASH-CHC, CLS
Associate Professor
University of Mississippi School of Pharmacy
Jackson, MS

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Patient Case

- 68 y/o F with history of T2DM x 12 years
  - Height: 5’4”
  - Weight: 143 lbs
  - A1c 7.9%
  - eGFR 77 mL/min
  - BGs: 212; 185; 176; 192 mg/dL
  - Medications:
    - Metformin 500 mg bid
    - Glipizide XL 10 mg daily
- PMH
  - HTN x 15 years
    - Losartan/HCTZ 50/12.5 mg daily
  - DLD x 11 years
    - Rosuvastatin 20 mg daily
  - Myocardial infarction 2 years ago
    - ASA 81 mg daily
    - Metoprolol tartrate 50 mg bid

Which of the medication classes covered in this presentation would you consider first in our patient?

A. DPP-4 Inhibitor
B. GLP-1
C. SGLT-2i

After starting an SGLT-2i in our patient,* what would be your next medication step?

A. Sitagliptin
B. Liraglutide
C. Insulin gargine
D. Luraglutide/Insulin degludec

* Assuming the SFU is discontinued

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Thank You for your Attention

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