Navigating Through The Latest Diabetes Clinical Trials – The Role of Newer Drugs

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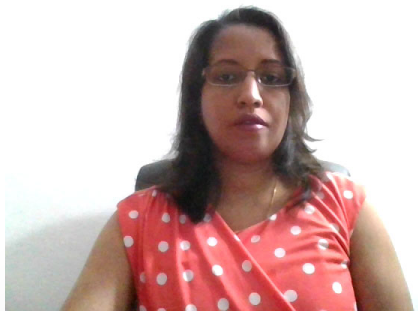
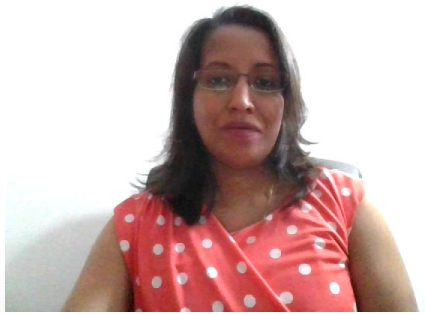


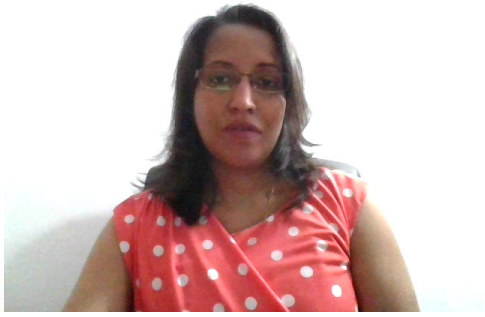
Disclosures

- Not relevant to this presentation
  - Sub-investigator for VESALIUS-CV Study
    - Sponsored by Amgen
    - PCSK9i in patients at **high risk** for CVD



Objectives

- Review landmark clinical trials and outcomes
- Evaluate the success and pitfalls of older medications
- Describe the timeline of emerging newer oral and non-insulin injectable agents
- Understand the cardiovascular and renal outcomes of newer drugs
- Summarize the role of newer drugs w practical approach to patient care



Prevalence

- Today, an estimated 9.3% of adults aged 20–79 years – **a staggering 463 million people – are living with diabetes**.

Map Prevalence of diabetes in adults (20–79 years) in IDF Regions, by age-adjusted comparative diabetes prevalence

North America & Caribbean
2045 13.0%
2030 12.3%
2019 11.1%

South & Central America
2045 9.9%
2030 9.5%
2019 8.5%

WORLD
2045 9.6%
2030 9.2%
2019 8.3%

Middle East & North Africa
2045 13.9%
2030 13.3%
2019 12.2%

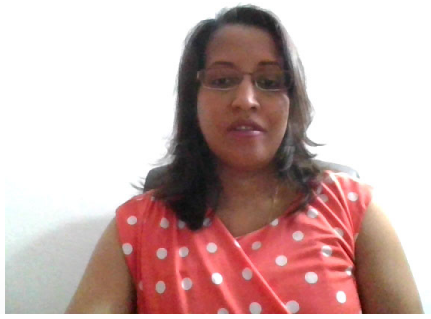
Africa
2045 5.2%
2030 5.1%
2019 4.7%

South-East Asia
2045 12.6%
2030 12.2%
2019 11.3%

Europe
2045 7.8%
2030 7.3%
2019 6.3%

Western Pacific
2045 12.8%
2030 12.4%
2019 11.4%

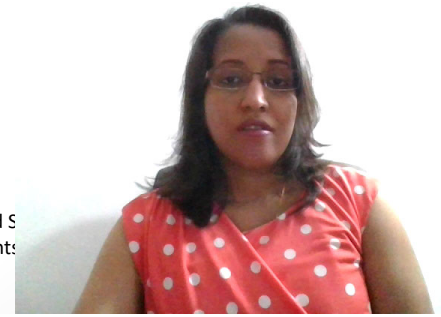
For confidence intervals, see full *IDF Diabetes Atlas*, Table 3.4.



Diabetes & Cardiovascular Disease

- Several studies have shown that **patients with diabetes have higher mortality and morbidity rates than patients without diabetes** after an acute myocardial infarction

1. Malmberg K, Ryde´n L. Myocardial infarction in patients with diabetes mellitus. Eur Heart J. 1988;9:256–264.
2. Herlitz J, Malmberg K, Karlsson B, et al. Mortality and morbidity during a five year follow-up of diabetics with myocardial infarction. Acta Med S
3. Granger C, Califf R, Young S, et al. Outcome of patients with diabetes mellitus and acute myocardial infarction treated with thrombolytic agents 1993;21:920–925.



Diabetes & Cardiovascular Disease

- The Organization to Assess Strategies for Ischemic Syndromes (OASIS) registry results provided long-term information on 8013 patients with unstable coronary artery disease from 6 different countries and 95 hospitals.
- Mean age was 65 years for patients with and without DM
- They also had significantly more previous cardiovascular events, including MI, congestive heart failure, stroke, and more revascularization procedures.

1. Malmberg K, Ryde´n L. Myocardial infarction in patients with diabetes mellitus. Eur Heart J. 1988;9:256–264.
2. Herlitz J, Malmberg K, Karlsson B, et al. Mortality and morbidity during a five year follow-up of diabetics with myocardial infarction. Acta Med S
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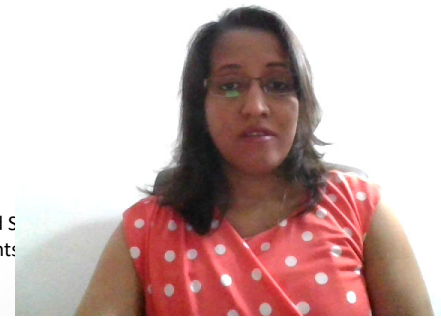
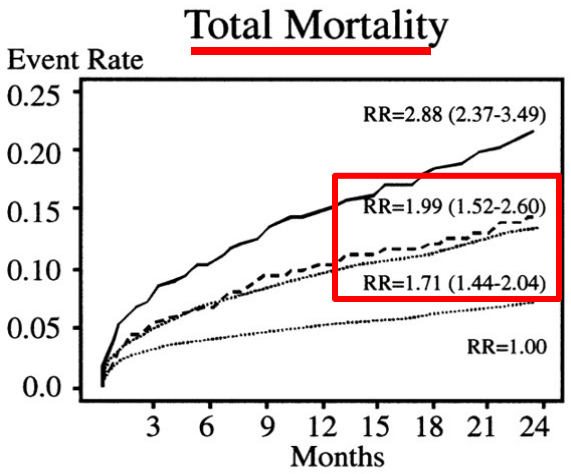
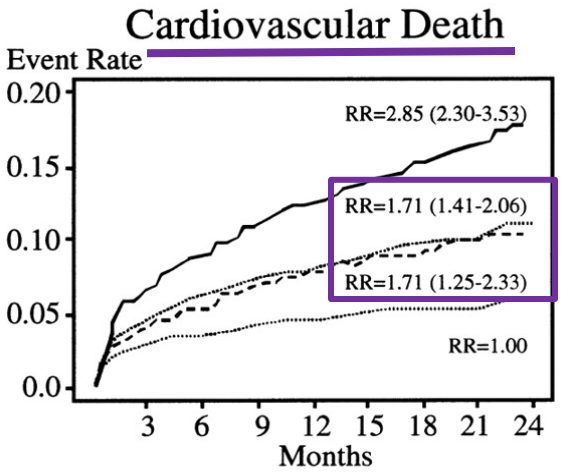
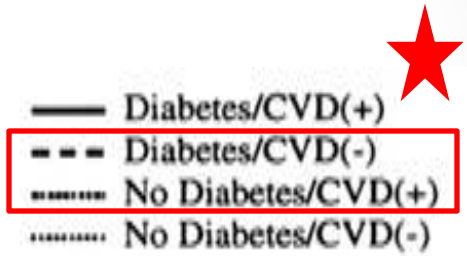
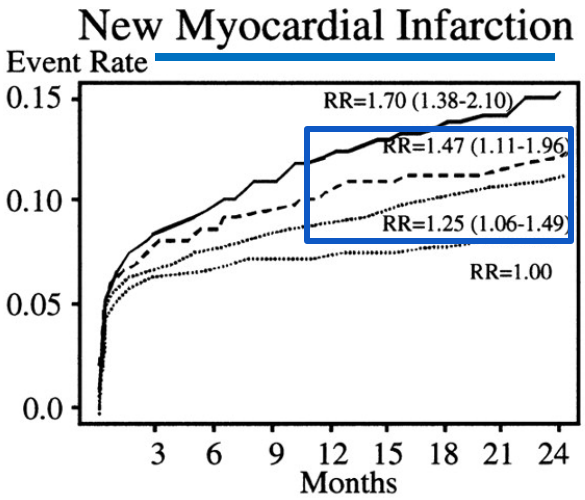


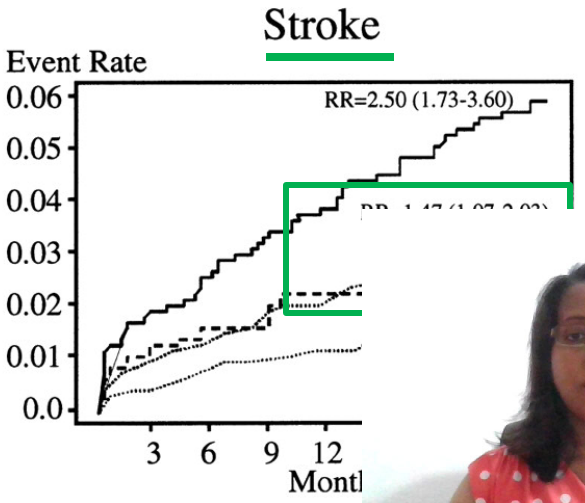
Diabetes & Cardiovascular Disease

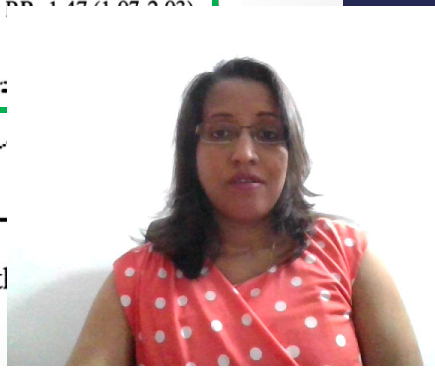






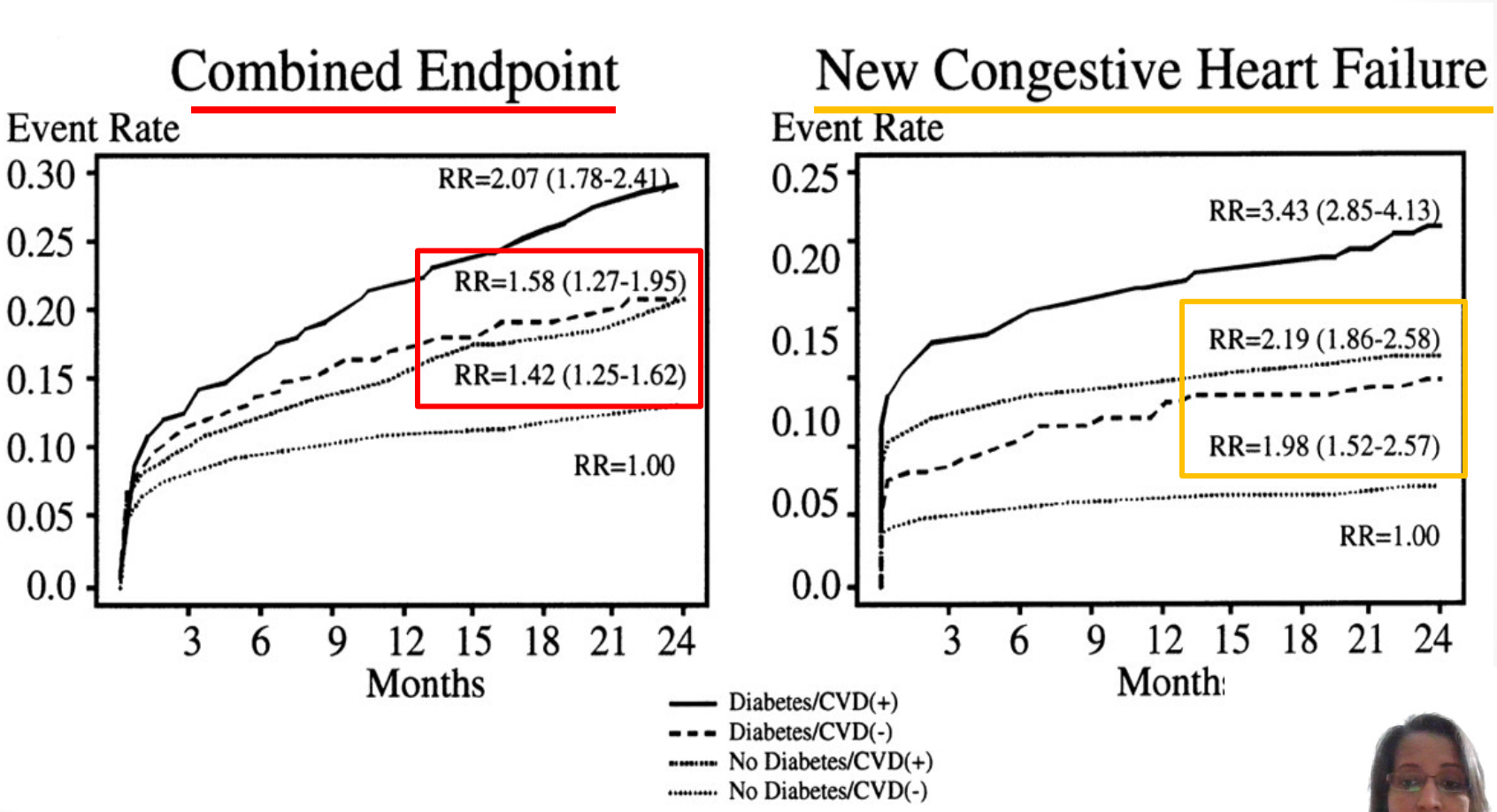


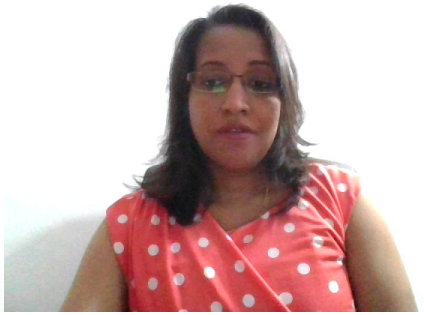




Malmberg, et al. Impact of Diabetes on CHD. Circulation. August, 2000: 1014-1019

Diabetes & Cardiovascular Disease



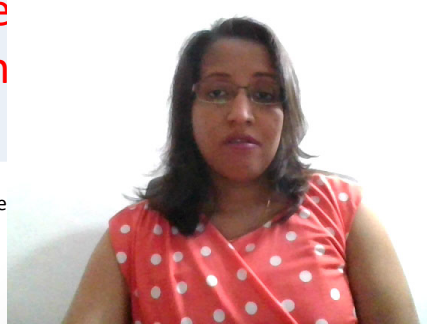


Malmberg, et al. Impact of Diabetes on CHD. Circulation. August, 2000: 1014-1019

Landmark DM Trials

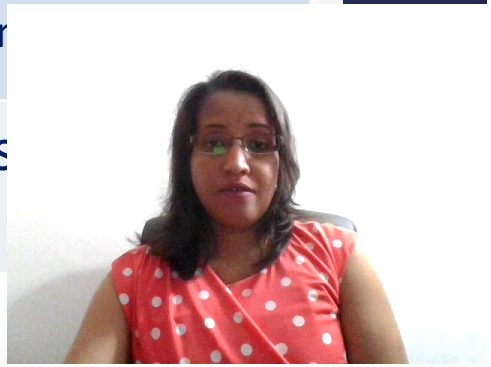
Trial	DCCT	EDIC	UKPDS	UKPDS 10-Yr
Participants	1441	1357	5102	1525
Duration	6.5 years		10 years	
Intensive Arm	Pump or MDI		SU or Insulin or Metformin	
Conventional Arm	1 or 2 daily insulin injection		Dietary therapy	
Median A1c (IA & CA)	7.4% and 9.1%		7.9% and 9.1%	
Primary Outcome	41% ↓ in major CV and PVD (NS)	42% ↓ heart disease; 57% ↓ non-fatal MI, stroke, CVD death	16% ↓ in fatal and nonfatal MI and sudden death (NS)	15% ↓ in MI; 13% ↓ in de an

1. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Inte Treatment and Cardiovascular Disease in Patients with Type 1 Diabetes. *N Engl J Med* 2005;353:2643-2653.
2. Group UKPDS. *The Lancet.* 1998;352(9131):837-853.



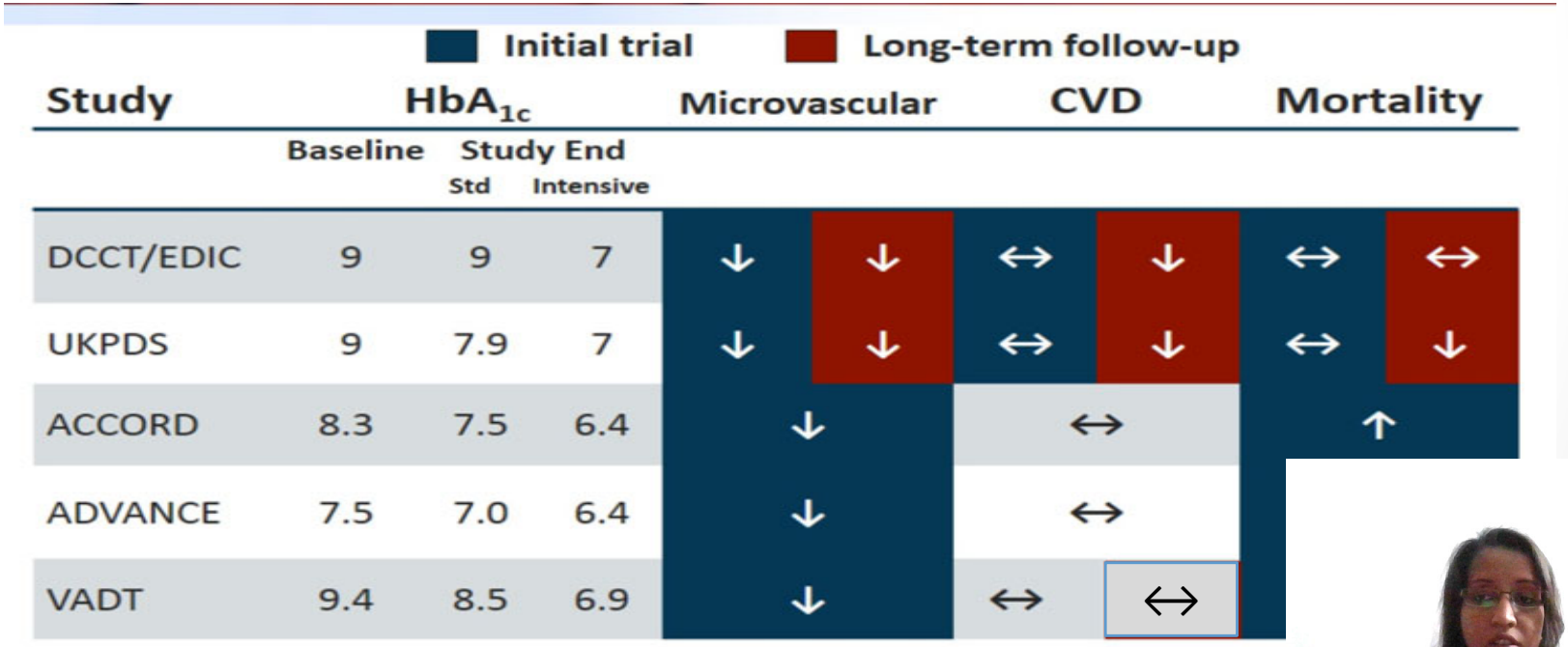
Landmark T2DM Trials

Trial	ACCORD	ADVANCE	VADT
Participants	10,251	11,140	1,791
Duration	3.4 years	5 years	5.6 years
DM Duration	10 years	7.9 years	11.5 years
Mean A1c	8.3%	7.5%	9.4%
H/o CV Event	35.2%	32.2%	40.2%
Intervention Arm	Atleast 2 hypoglycemic agents + other drugs	Gliclazide + other drugs	Glimepiride or Metformin + Roziglitazone OR insulin (max doses)
Control Arm	Diet or meds or both	Current therapy	Glimepiride or Metformin + Roziglitazor
Primary Outcome	6.9% vs. 7.2% (NS)	18% vs. 20% (S*)	29.5% vs (NS)

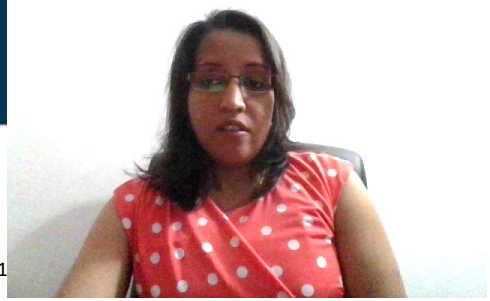


In Summary: Landmark Trials

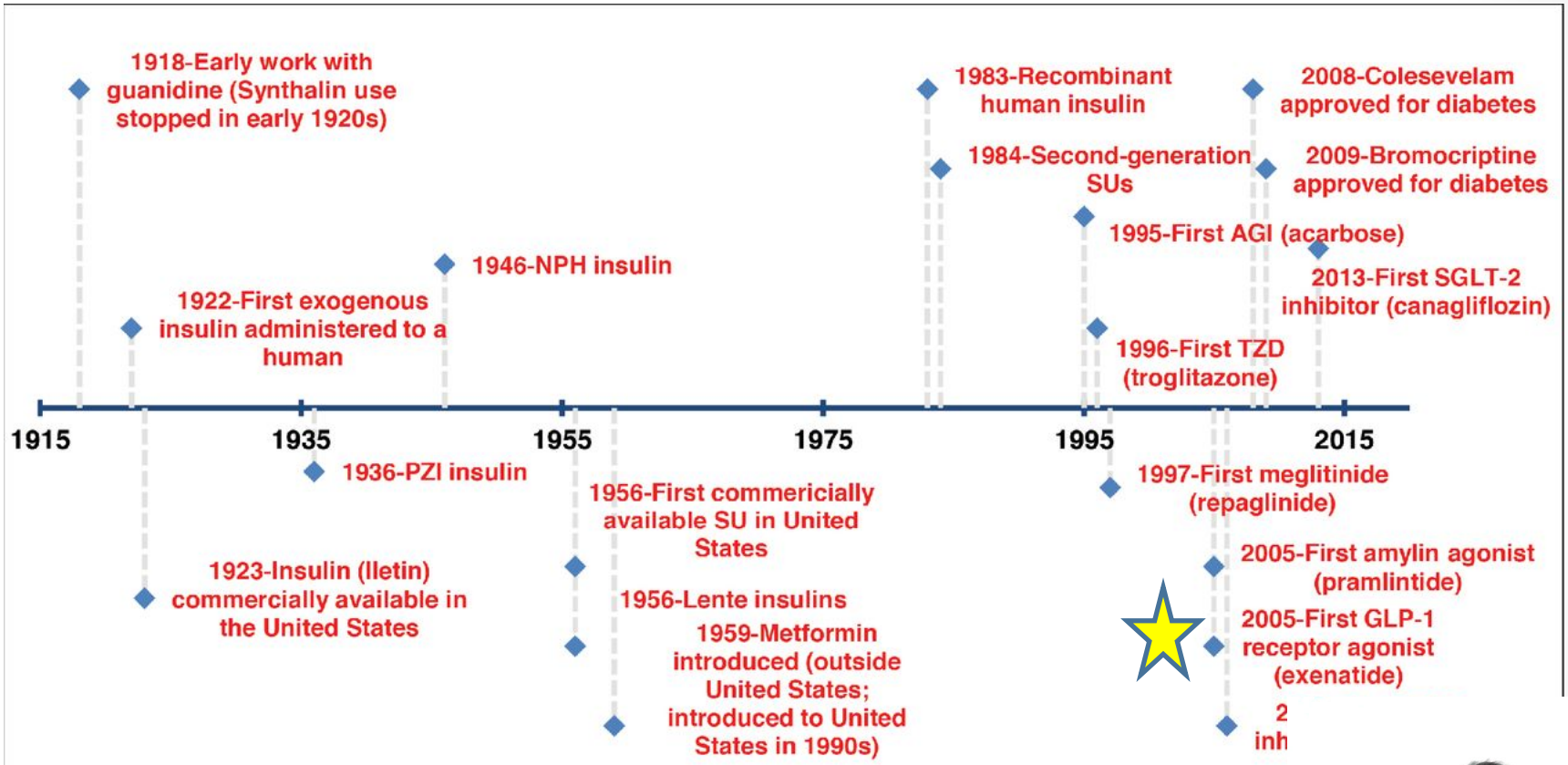
- The DCCT/EDIC and the UKPDS did not show any significant reduction in cardiovascular risk until their observational follow-up 10 years later, indicating a **"legacy effect"**

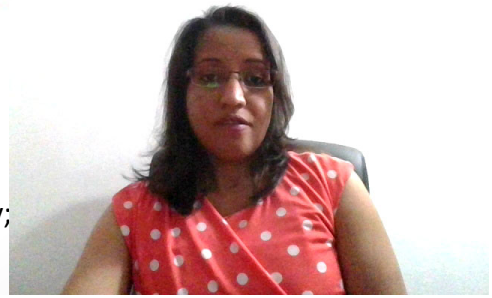


Group UKPDS. *The Lancet.* 1998;352(9131):837-853.
The Action to Control Cardiovascular Risk in Diabetes Study Group. N Engl J Med 2008; 358:2545-2559
The ADVANCE Collaborative Group. N Engl J Med 2008; 358:2560-2572
Duckworth W et al. Glucose Control and Vascular Complications in Veterans with Type 2 Diabetes. *New England Journal of Medicine.* 2009;360(2):1



Drug Discovery Timeline



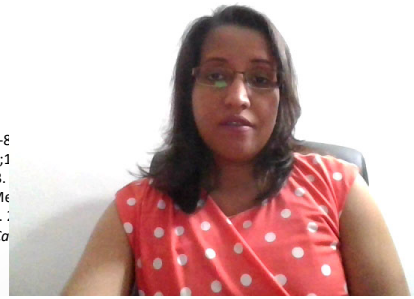


White, J. A Brief History of the Development of Diabetes Mediccations. Diabetes Spectrum 2014 May;

Existing Favorites – Metformin, Sulfonylureas, and TZDs

- Randomized controlled trials[1-3] that evaluated metformin in patients with type 2 diabetes indicated significant improvements in cardiovascular outcomes.
- There exists controversial data regarding cardiovascular disease risk with sulfonylureas[4-5].
- A meta-analysis of pioglitazone reported lower risk of recurrent MACE, stroke, or MI in patients with vascular disease. Pioglitazone did not lower the risk for all-cause mortality; however, increased the risk for new heart failure[6]

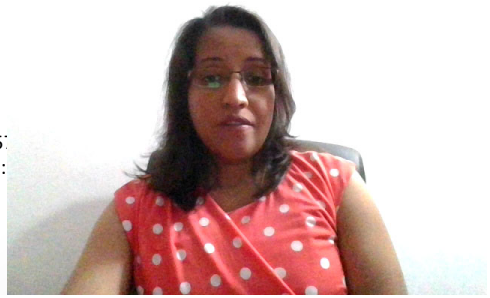
1. UK Prospective Diabetes Study Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet*. 1998;352:854-8
2. Kooy A, de Jager J, Lehert P, et al. Long-term effects of metformin on metabolism and microvascular and macrovascular disease in patients with type 2 diabetes mellitus. *Arch Intern Med*. 2009;1
3. Hong J, Zhang Y, Lai S, et al. Effects of metformin versus glipizide on cardiovascular outcomes in patients with type 2 diabetes and coronary artery disease. *Diabetes Care*. 2013;36(5):1304-1313.
4. Rados DV, et al. The Association between Sulfonylurea Use and All-Cause and Cardiovascular Mortality: A Meta-Analysis with Trial Sequential Analysis of Randomized Clinical Trials.2016: PLoSMe
5. Rosenstock J, Marx N, Kahn SE, et al. Cardiovascular outcome trials in type 2 diabetes and the sulphonylurea controversy: rationale for the active-comparator CAROLINA trial. *Diab Vasc Dis Res*.
6. de Jong M, van der Worp HB, van der Graaf Y, Visseren FLJ, Westerink J. Pioglitazone and the secondary prevention of cardiovascular disease. A meta-analysis of randomized-controlled trials. *Ca*



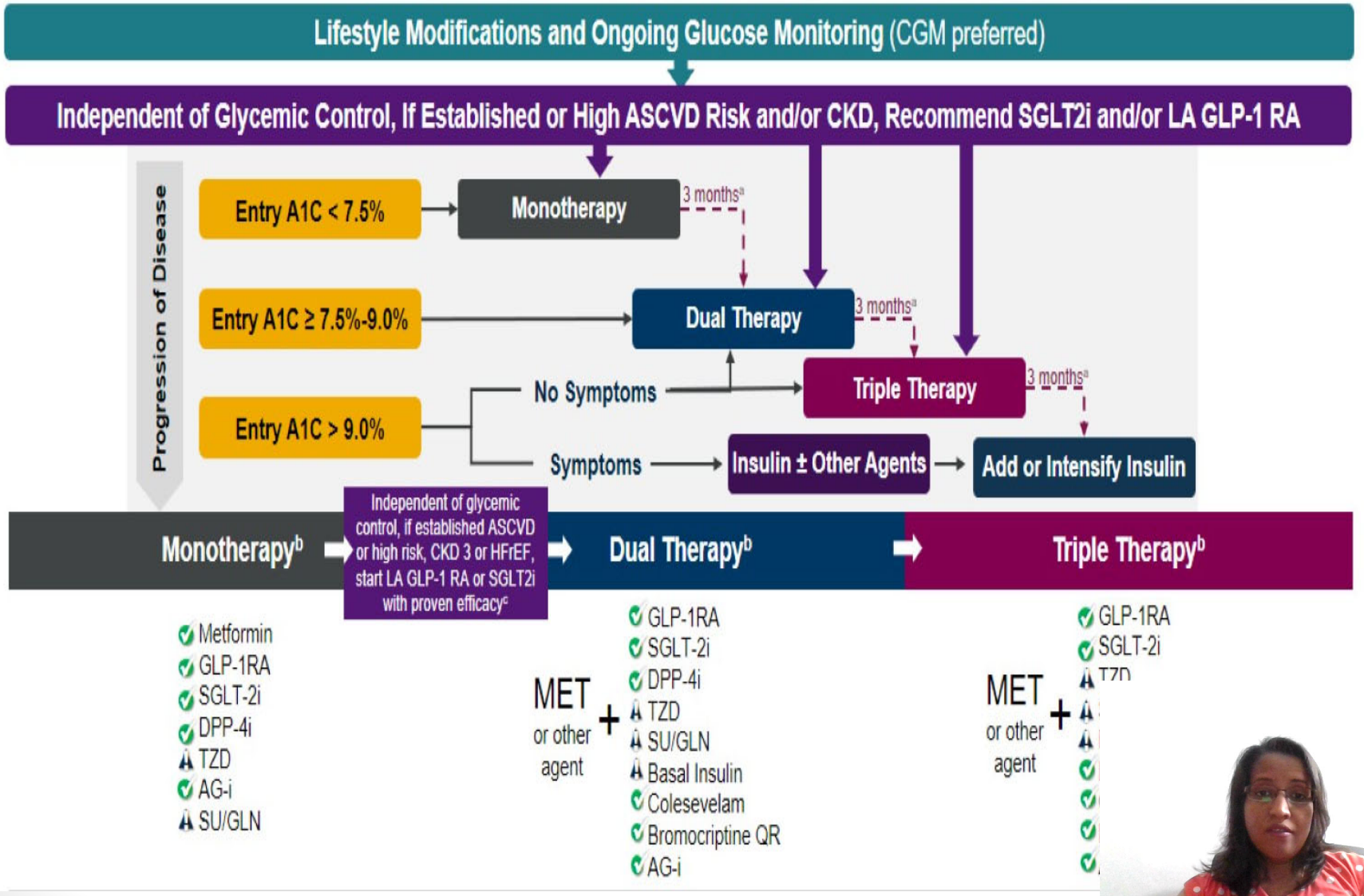
Cardiovascular Focus & DM

- In 2007, Rosiglitazone was associated with a significant increase in risk of MI
- In 2008, FDA mandated evaluation of newer DM drugs to show no increase in cardiovascular risk
- All CVOT are industry funded, multicenter, randomized, double-blinded, placebo-controlled trials

1. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med 2007;356:245
2. Sheahan KH, Wahlberg EA, Gilbert MP. An overview of GLP-1 agonists and recent cardiovascular outcomes trials. *Postgrad Med J*. 2020;96(1133):

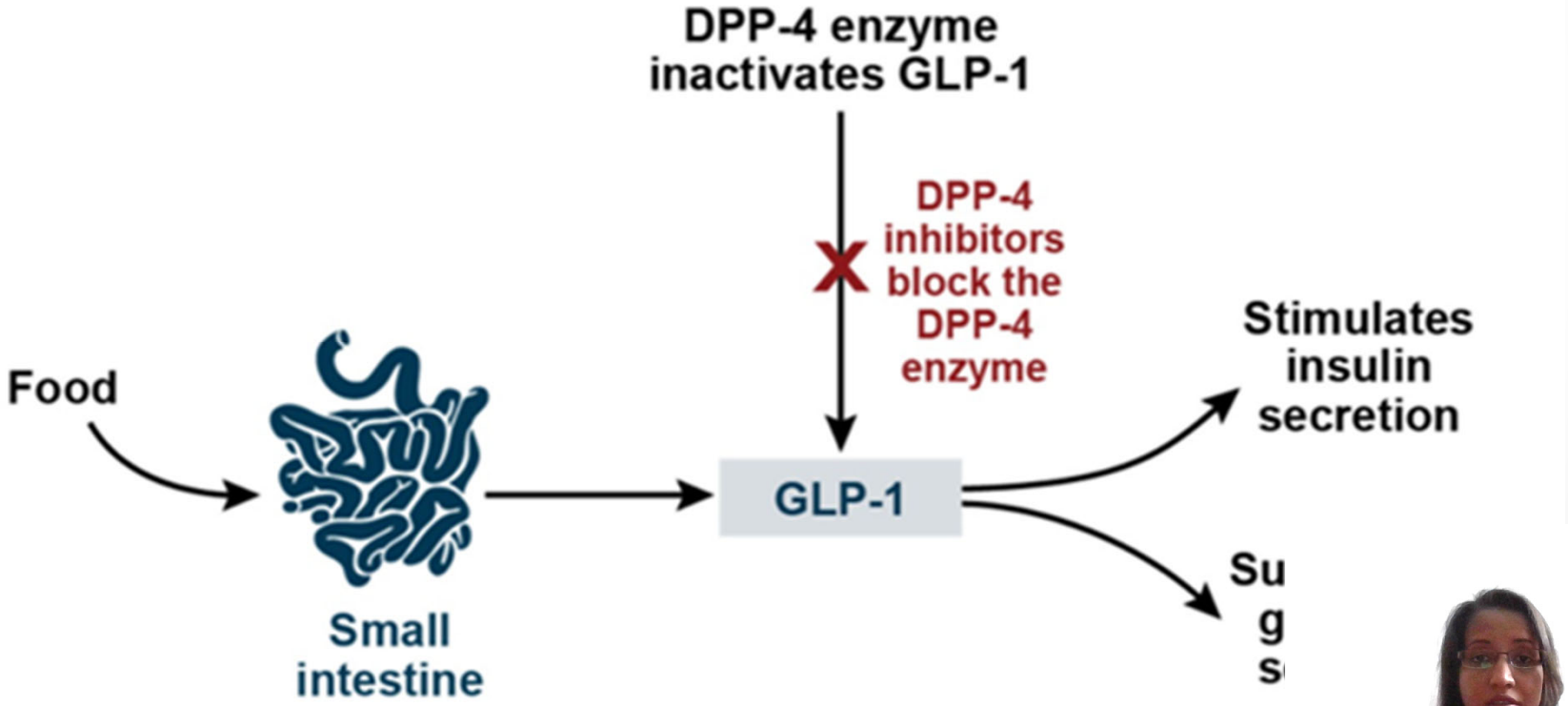


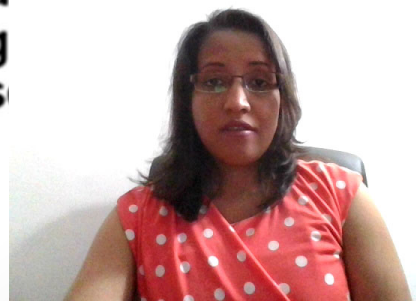
AACE/ACE 2020 Algorithm for Glycemic Management



Newer DM Drug Categories

Glucagon Like Peptide – 1 Agonists **Dipeptidyl Peptidase 4 Inhibitors**





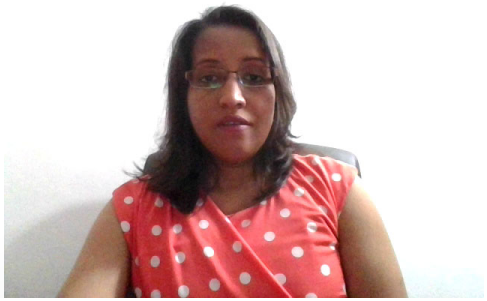
Newer DM Drug Categories

Glucagon Like Peptide – 1 Agonists

- Lixisenatide (®Adlyxin)
- Liraglutide (®Victoza)
- Semaglutide (®Ozempic)
- Exenetide (®Byetta)
- Exenatide LAR (®Bydureon)
- Dulaglutide (®Trulicity)
- Oral Semaglutide (®Rybelsus)

Dipeptidyl Peptidase 4 Inhibitors

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



GLP-1 CVOT – ELIXA

Lixisenatide (®Adlyxin)

T2DM; N = 6068; Avg A1c 7.7%; Duration = 2yrs

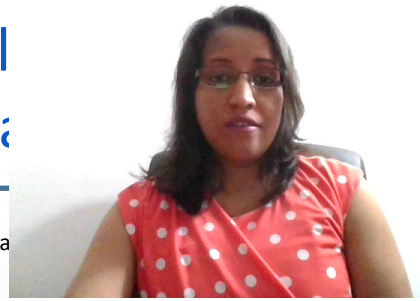
Acute coronary event – 180 days prior to screening

Run-in period of placebo injections

Lixisenatide QD	Placebo QD

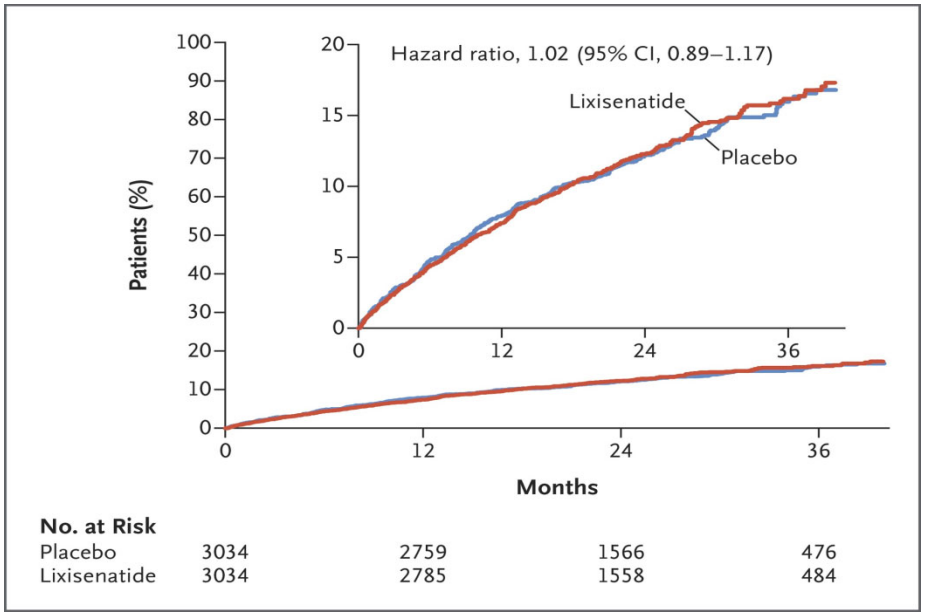
Primary Endpoint

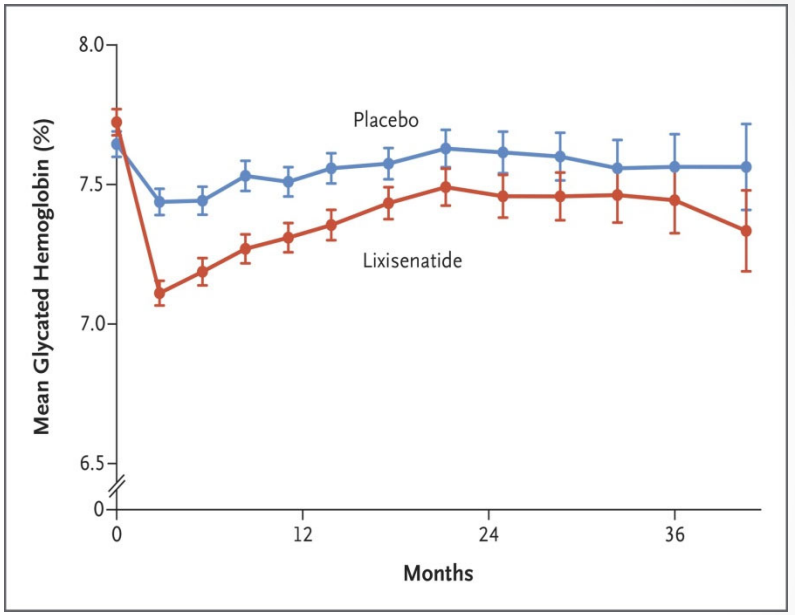
Death from CV cause, nonfatal MI, nonfatal stroke or hospitalization for unstable angina



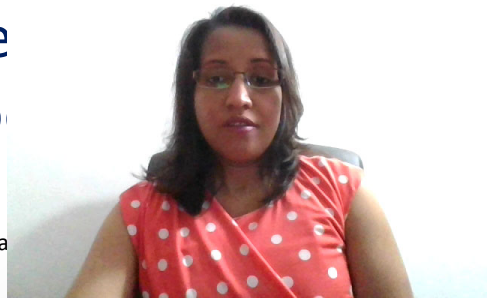
Muskiet MHA, Tonneijck L, Huang Y, et al. Lixisenatide and renal outcomes in patients with type 2 diabetes and acute coronary syndrome: a the ELIXA randomised, placebo-controlled trial. *Lancet Diabetes Endocrinol*. 2018;6(11):859-869. doi:10.1016/S2213-8587(18)30268-7

GLP-1 CVOT – ELIXA
Lixisenatide (®Adlyxin)





- Results showed non-inferiority to placebo as primary endpoints were similar in both groups.
- The reduction in HbA1c values was significantly gre among patients in the lixisenatide group vs. placeb



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GLP-1 CVOT – LEADER
Liraglutide (®Victoza)

T2DM; N = 9340; Avg A1c 8.7%; Duration = 3.5yrs

Patients with pre-existing CVD 81.3% and

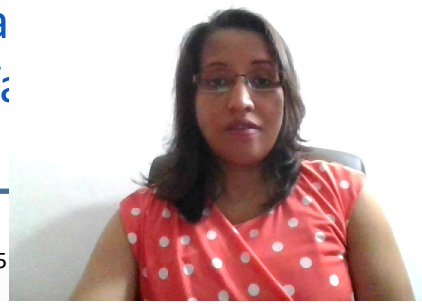
24.7% with >CKD3

Run-in period of placebo injections

Liraglutide QD

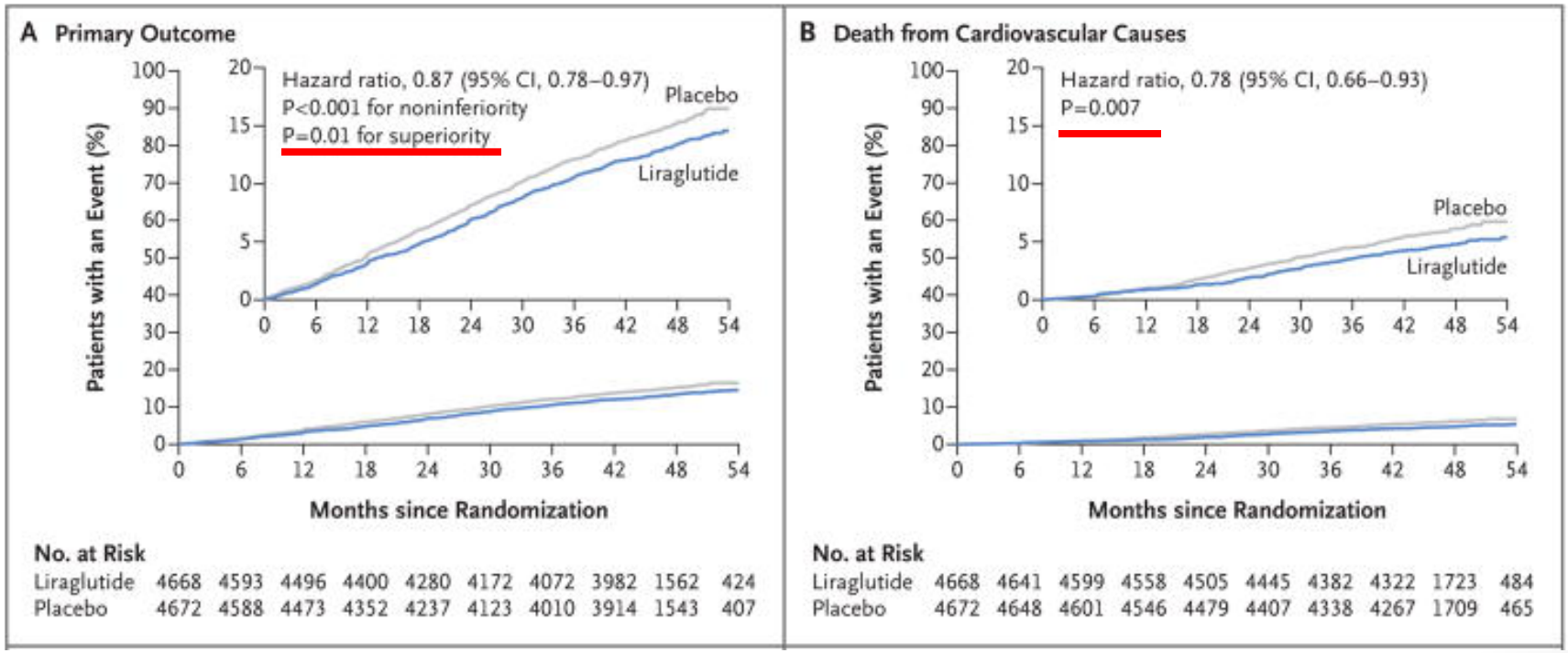
Placebo QD

The primary composite outcome in the time-to-event an
was the first occurrence of death from cardiovascular ca
nonfatal (including silent) myocardial infarction, or nonfa
stroke.



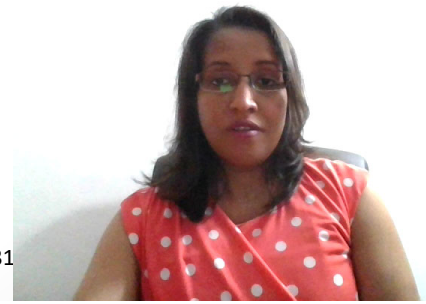
Marso SP, Daniels GH, Brown-Frandsen K, et al. . Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016;375

GLP-1 CVOT – LEADER
Liraglutide (®Victoza)



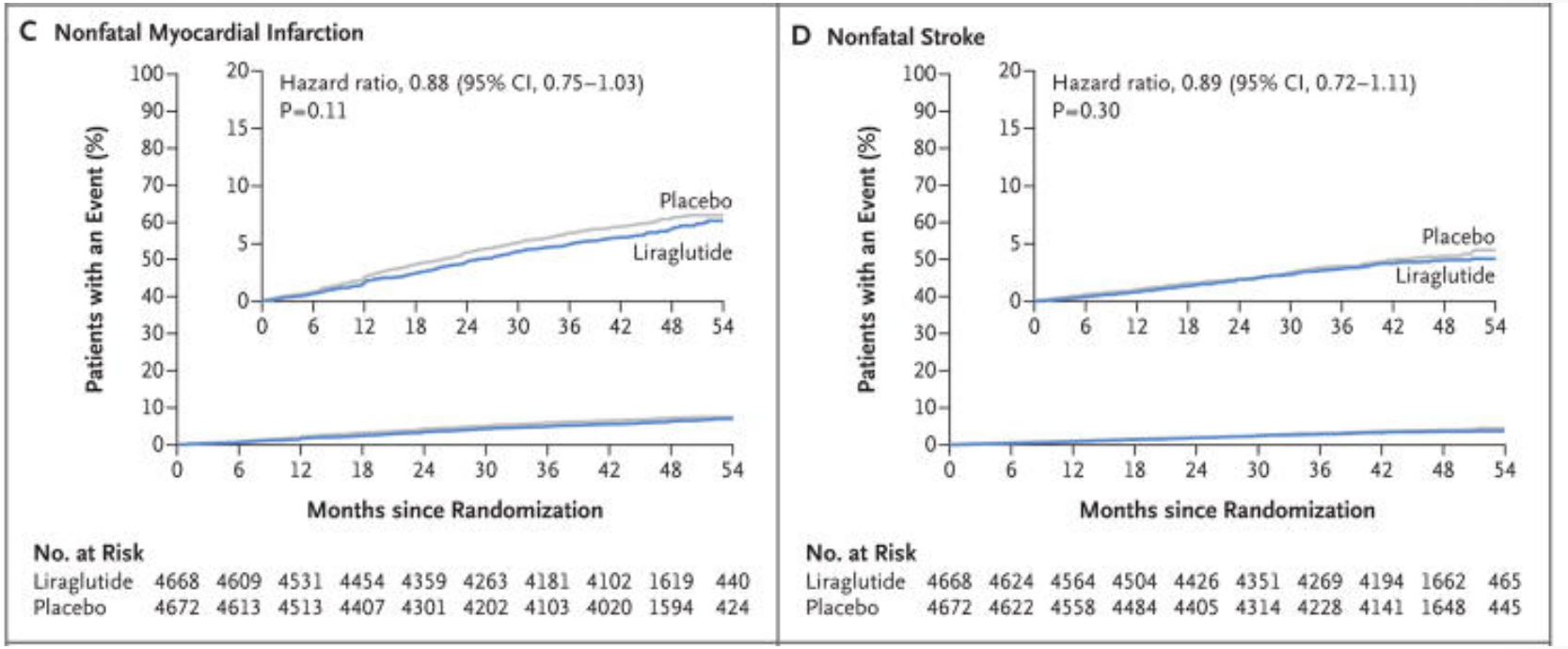
A – Primary composite outcome occurred in fewer patients in Liraglutide group (13%) vs. placebo group (14.9%)

B – Death from CV causes occurred in fewer patients in Liraglutide group (4.7%) vs. placebo group (6.9%)

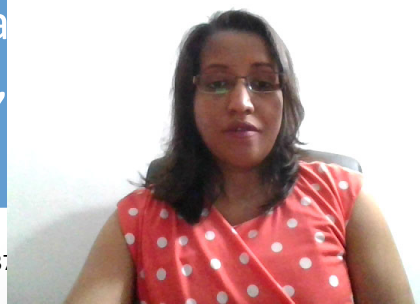


Marso SP, Daniels GH, Brown-Frandsen K, et al. . Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016;375:31

GLP-1 CVOT – LEADER
Liraglutide (®Victoza)

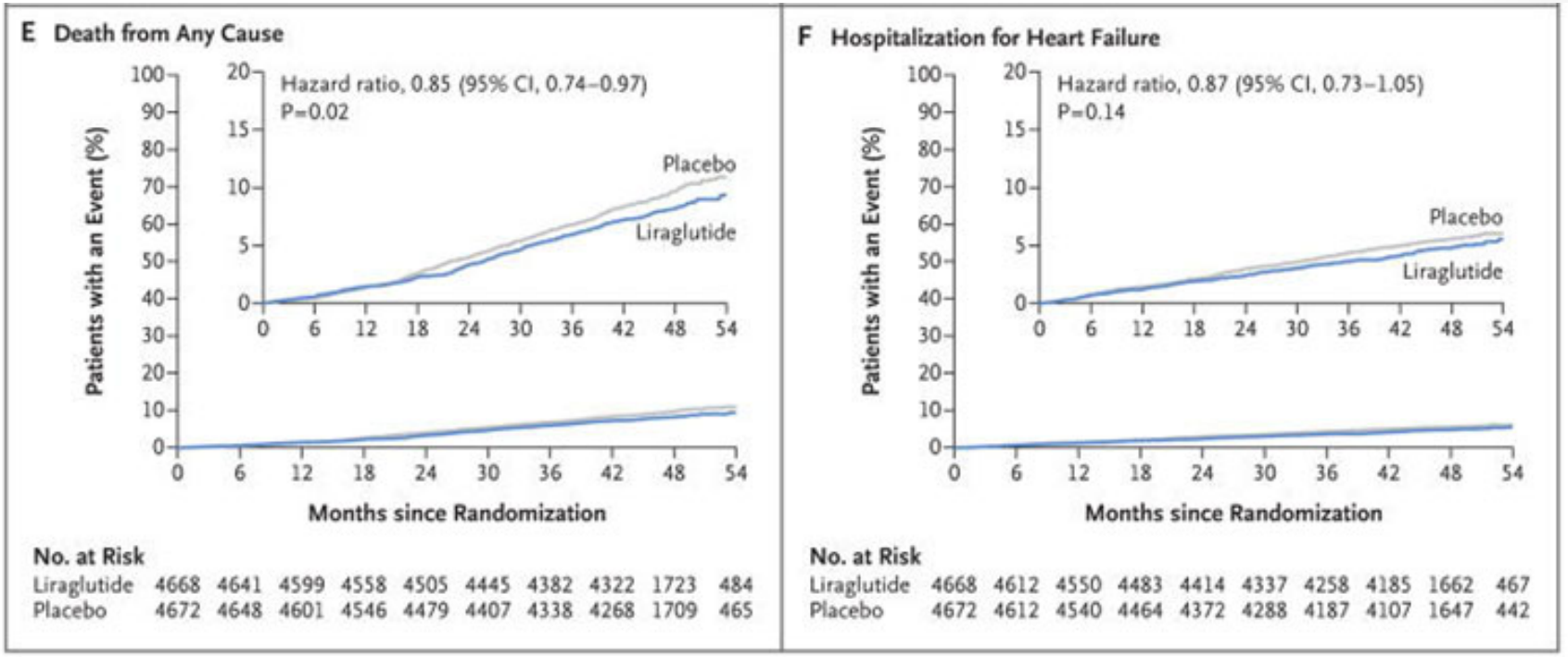


The frequencies of nonfatal myocardial infarction and nonfata
were lower in the liraglutide group than in the placebo group,
the differences were not significant



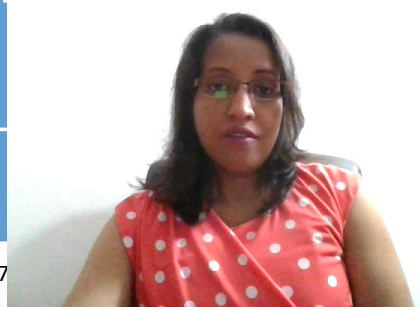
Marso SP, Daniels GH, Brown-Frandsen K, et al. . Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016;37

GLP-1 CVOT – LEADER
Liraglutide (®Victoza)



E – The rate of death from any cause was lower in the liraglut
(8.2%) vs. placebo group (9.6%)

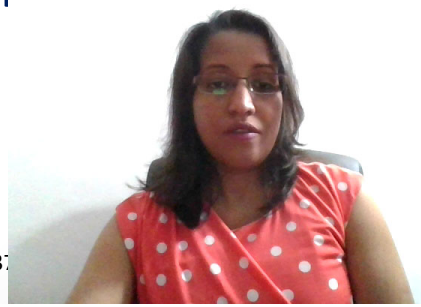
F – 18% of patients participating in this trial had NYHA Class I-
the rate of hospitalizations was not significant



Marso SP, Daniels GH, Brown-Frandsen K, et al. . Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016;37

GLP-1 CVOT – LEADER
Liraglutide (®Victoza)

- There were also significant mean differences between the liraglutide group and the placebo group in the change from baseline to 36 months in the following variables:
  - Weight loss was 2.3 kg (95% CI, 2.5 to 2.0) higher in the liraglutide group
  - The systolic blood pressure was 1.2 mm Hg (95% CI, 1.9 to 0.5) lower in the liragluti group



Marso SP, Daniels GH, Brown-Frandsen K, et al. . Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016;3

GLP-1 CVOT – SUSTAIN-6
Semaglutide (®Ozempic)

T2DM; N = 3297; Avg A1c 8.7%; Duration = 2.1yrs

83% patients had CVD and CKD3 or higher

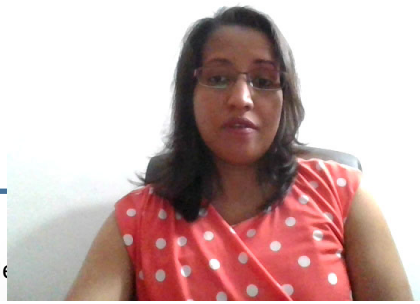
59% patients had CVD without CKD

Run-in period of placebo injections

Semaglutide 0.5 mg or 1.0 mg once/week

Matched Placebo 0.5 mg or 1.0 mg once/week

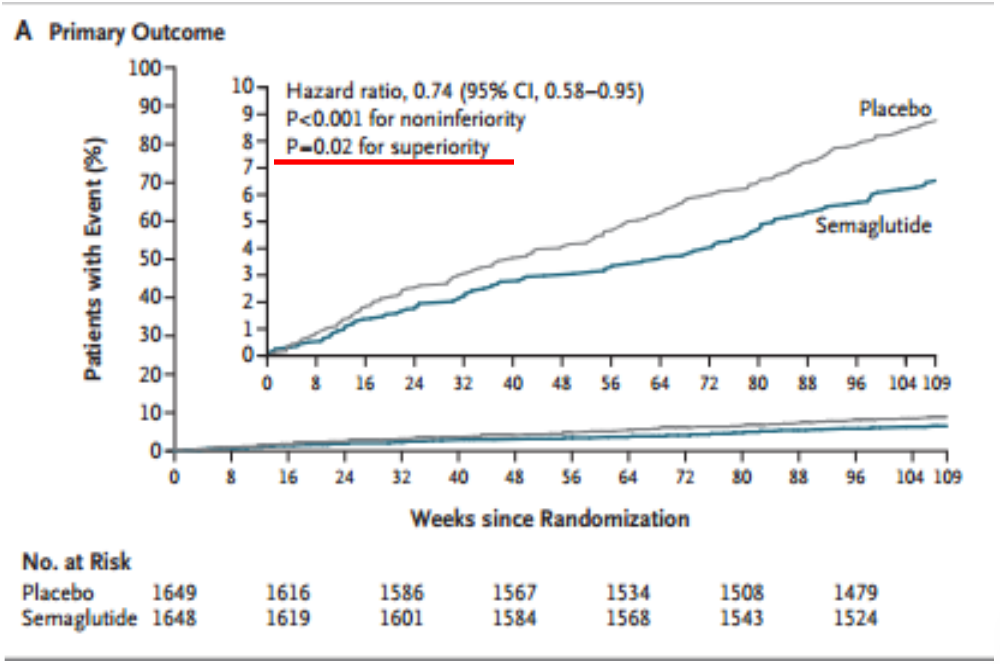
The primary composite outcome was the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction (including silent), or nonfatal stroke.

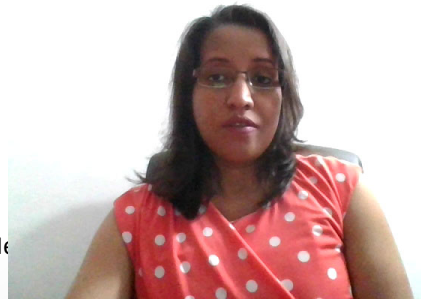


Marso SP, Bain SC, Consoli A, et al. . Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Me

GLP-1 CVOT – SUSTAIN-6 Semaglutide (®Ozempic)

The primary composite cardiovascular outcome occurred in 6.6% of patients in the semaglutide group vs. 8.9% in the placebo group, which was statistically significant.

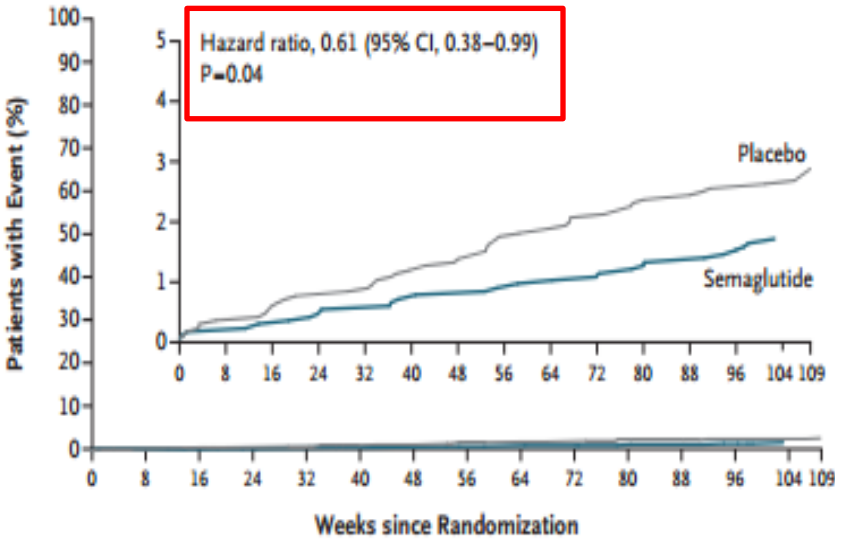




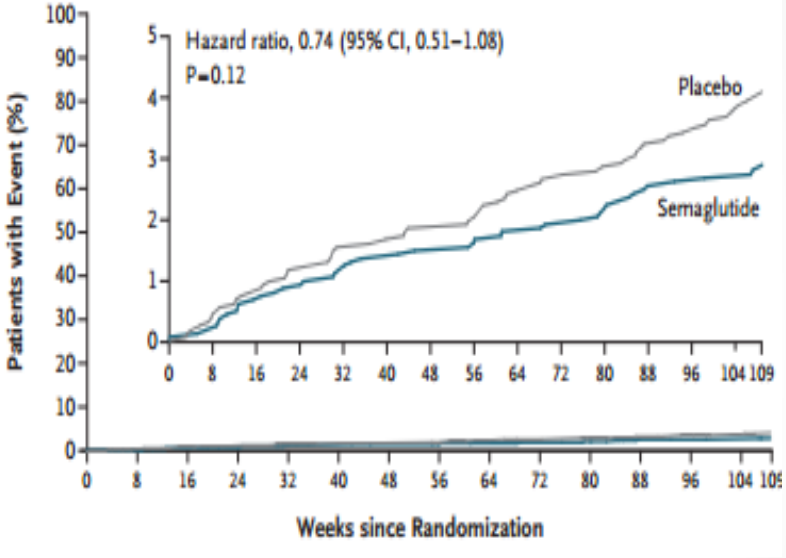
Marso SP, Bain SC, Consoli A, et al. . Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Me

GLP-1 CVOT – SUSTAIN-6
Semaglutide (®Ozempic)

Nonfatal stroke

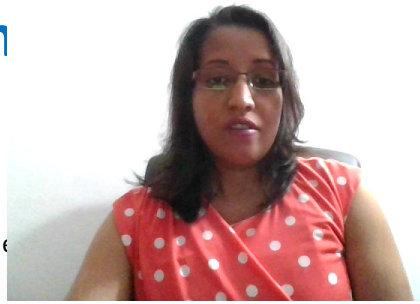


Nonfatal MI



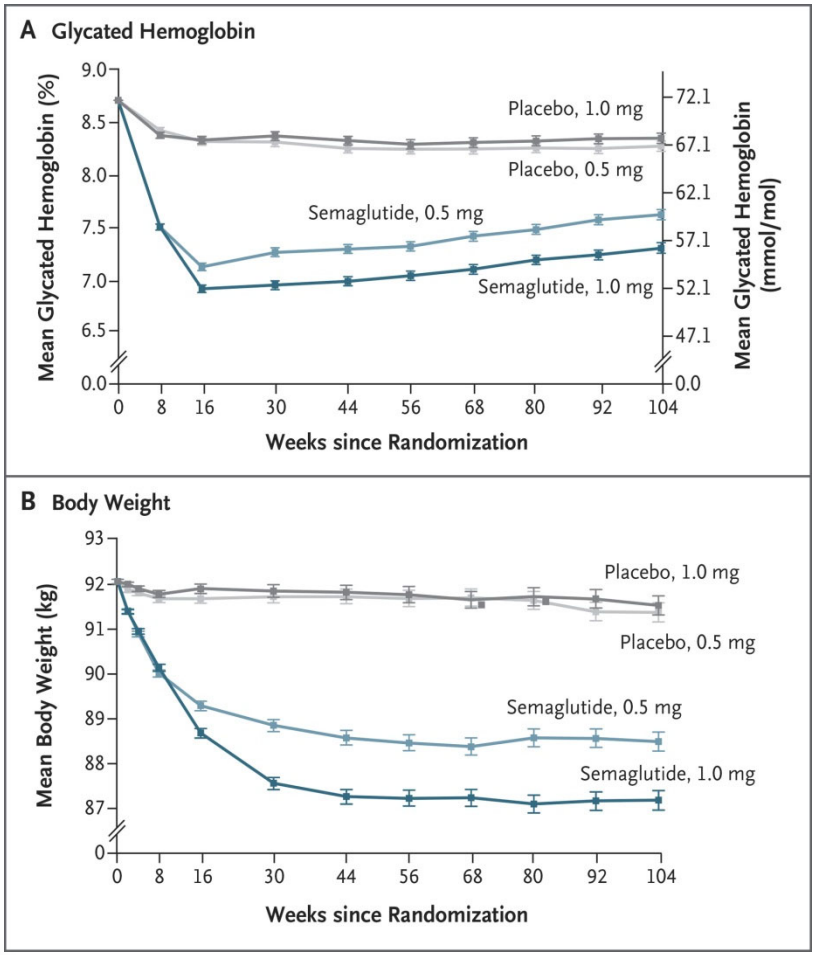
There were significantly fewer non-fatal strokes in the semaglutide group (1.6%) vs. placebo group (2.7%)

MACE reduction was primarily due to reduction in non-fatal MI and non-fatal stroke



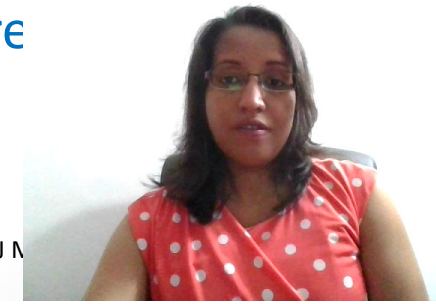
Marso SP, Bain SC, Consoli A, et al. . Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Me

GLP-1 CVOT – SUSTAIN-6
Semaglutide (®Ozempic)



The mean HbA1c level in the semaglutide group vs. placebo group, was 0.7 percentage points lower (for 0.5 mg dose) and 1.0 percentage point lower (for 1.0 mg dose), significant

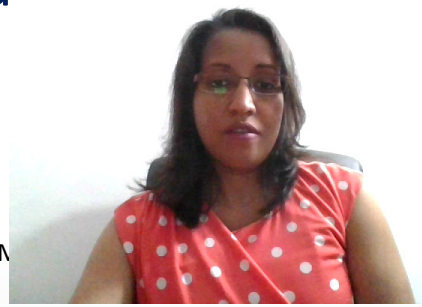
The mean body weight in the semaglutide group vs. placebo was 2.9 kg lower in the group receiving 0.5 mg and
lower in the group re
mg (P<0.001).



Marso SP, Bain SC, Consoli A, et al. . Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J M

GLP-1 CVOT – SUSTAIN-6 Semaglutide (®Ozempic)

- The mean systolic blood pressure in the semaglutide group vs. placebo was 1.3 mm Hg lower in the group receiving 0.5 mg (P=0.10) and 2.6 mm Hg lower in the group receiving 1.0 mg (P<0.001)
- New or worsening nephropathy occurred in 3.8% patients in Semaglutide group vs. 6.1% in placebo group (P=0.005)
- In contrast, diabetic retinopathy occurred in 3% patients in Semaglutide group vs. 1.8% in pla group (P=0.02)



Marso SP, Bain SC, Consoli A, et al. . Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J M

GLP-1 CVOT – EXSCEL

Exenatide LAR (®Bydureon)

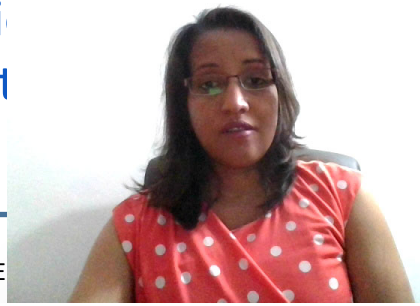
T2DM; N = 14,752; Avg A1c 8.0%; Duration = 3.2yrs

73% patients had CVD

NO run-in period of placebo injections

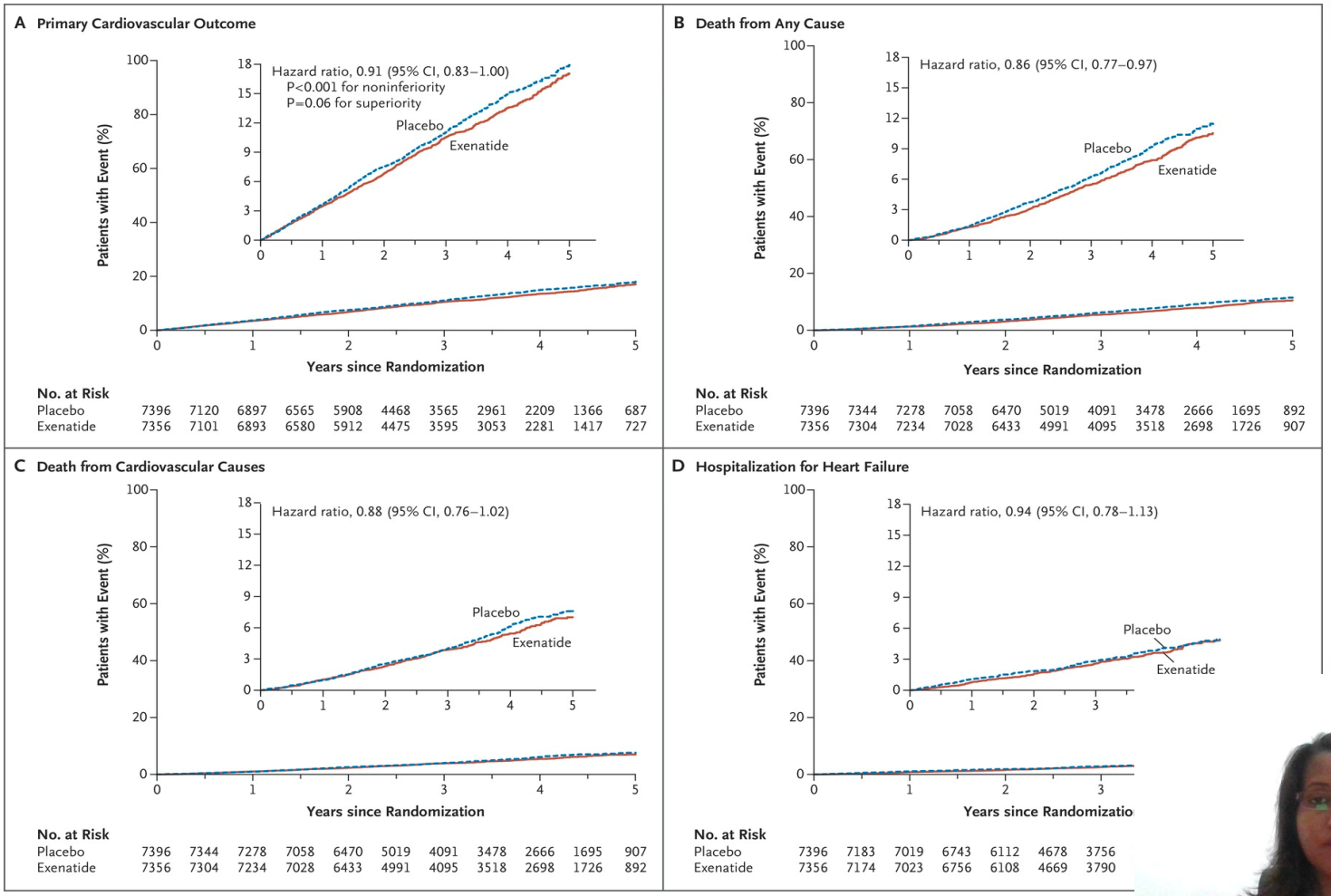
Exenatide 2 mg once/wk	Placebo 2 mg once/wk

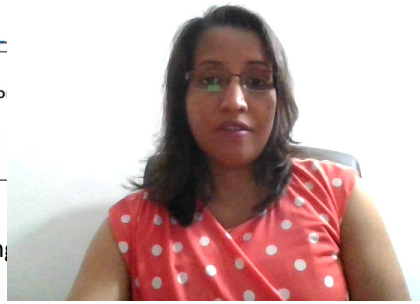
The primary outcome was defined as the first occurrence o
component of the composite outcome of death from cardi
causes, nonfatal myocardial infarction, or nonfatal stroke (t
component MACE outcome), in a time-to-event analysis.



Holman RR, Bethel MA, Mentz RJ, et al. . Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. N E

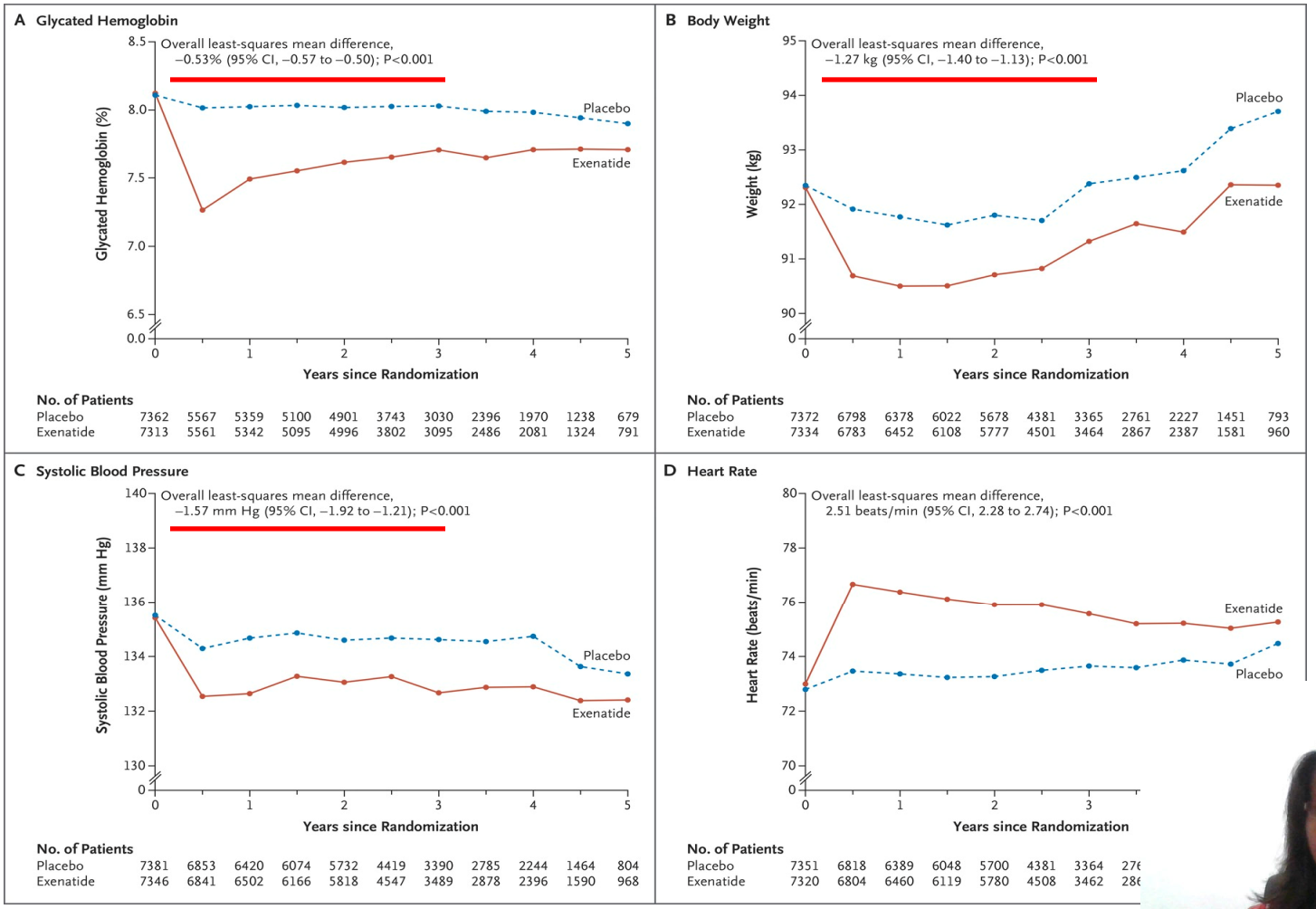
GLP-1 CVOT – EXSCEL
Exenatide LAR (®Bydureon)

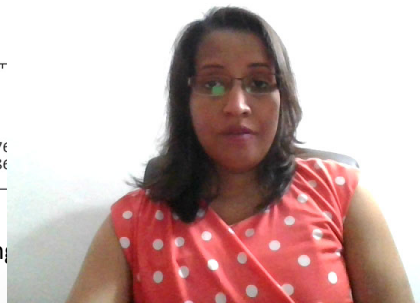




Holman RR, Bethel MA, Mentz RJ, et al. . Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. N En

GLP-1 CVOT – EXSCEL
Exenatide LAR (®Bydureon)





Holman RR, Bethel MA, Mentz RJ, et al. . Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. N En

GLP-1 CVOT – REWIND
Dulaglutide (®Trulicity)

T2DM; N = 9901; Avg A1c 7.2%; Duration = 5.4yrs

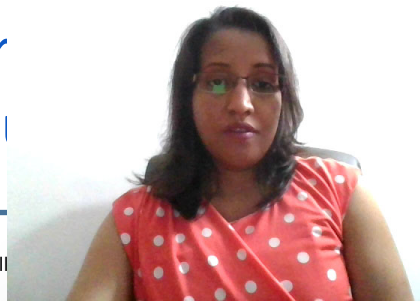
31.5% patients had CVD

3-week run-in period of placebo injections

Dulaglutide 1.5 mg once/week

Placebo 1.5 mg once/week

The primary outcome was the first occurrence of composite endpoint of non-fatal myocardial infar non-fatal stroke, or death from cardiovascular ca



Gerstein HC, Colhoun HM, Dagenais GR, et al. . Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controll

GLP-1 CVOT – REWIND
Dulaglutide (®Trulicity)

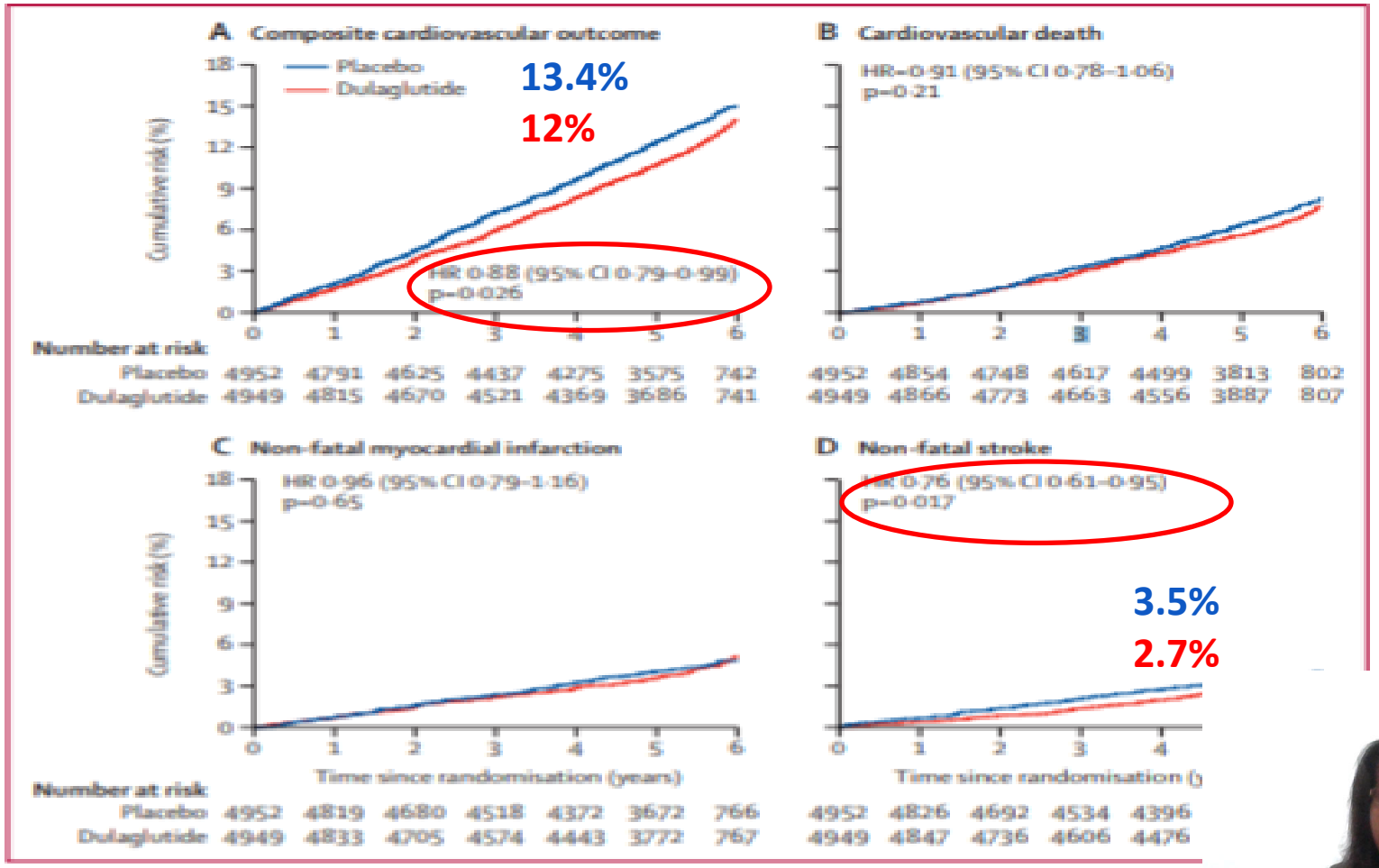
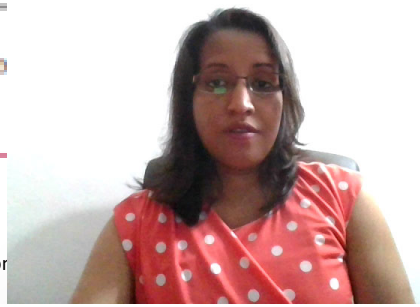


Figure 2: Cumulative incidence of cardiovascular outcomes
HR=hazard ratio. HbA_{1c}=glycated haemoglobin A_{1c}.



Gerstein HC, Colhoun HM, Dagenais GR, et al. . Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-cor
2019;394:121–30.

GLP-1 CVOT – PIONEER 6
Semaglutide (®Rybelsus)

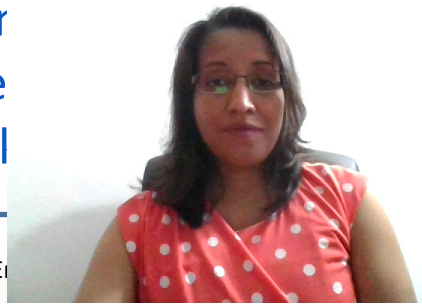
T2DM; N = 3183; Avg A1c 8.2%; Duration = 1.3yrs

84.7% patients had CVD

Semaglutide 14 mg PO QD

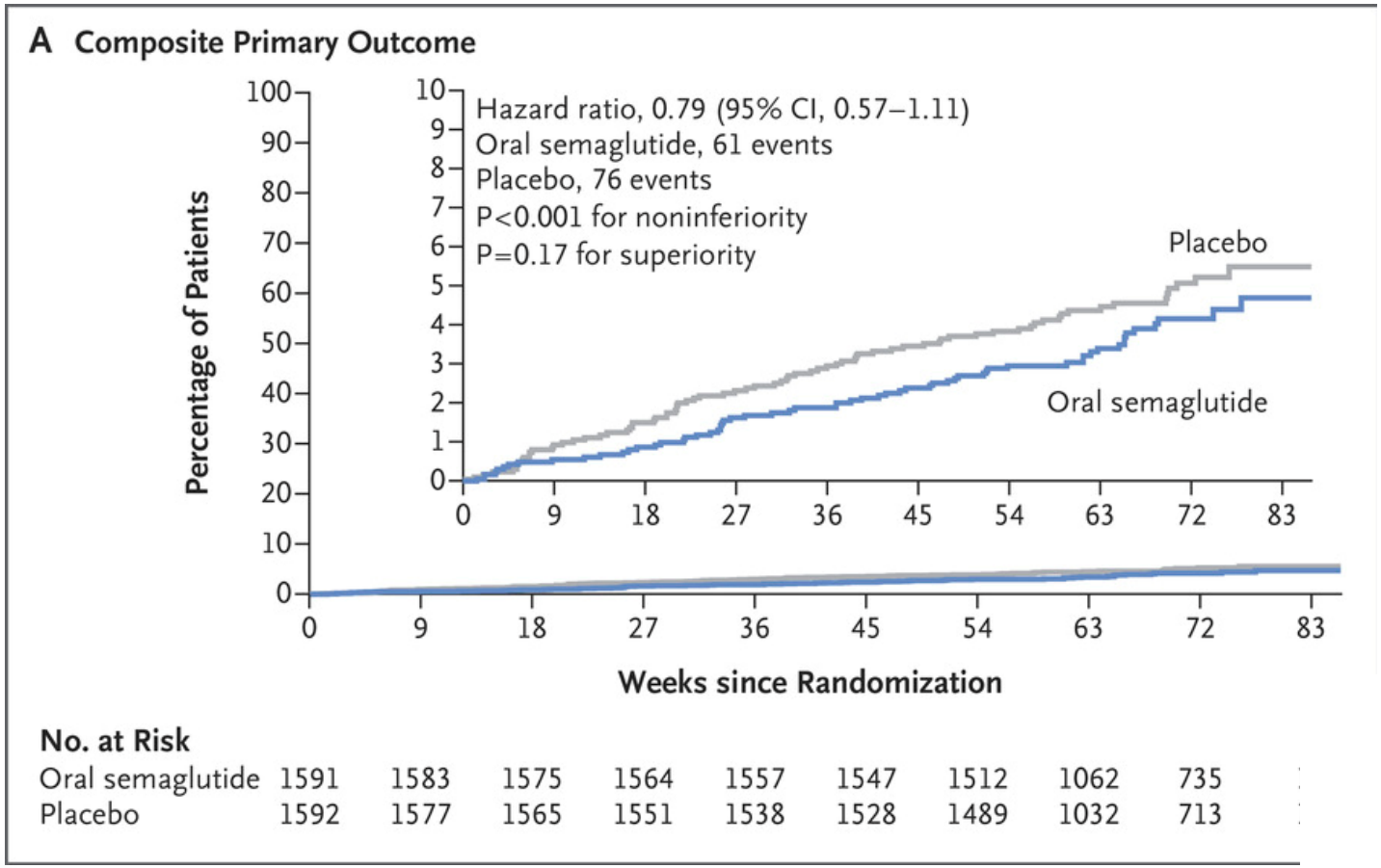
Placebo 14 mg PO QD

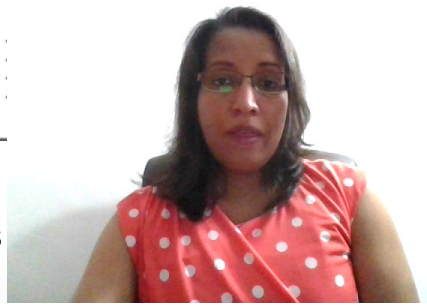
Primary Outcome: The time from randomization to the fir
occurrence of a major adverse cardiovascular event, a cor
death from cardiovascular causes (including undetermine
of death), nonfatal myocardial infarction, or nonfatal strol



Husain M, Birkenfeld AL, Donsmark M, et al. . Oral Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N E

GLP-1 CVOT – PIONEER 6
Semaglutide (®Rybelsus)

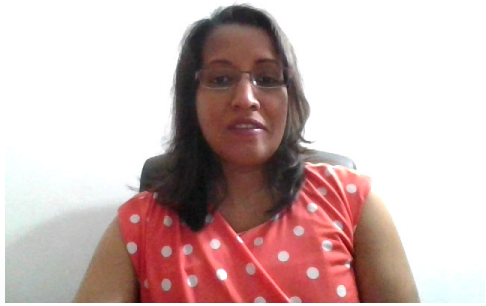




Husain M, Birkenfeld AL, Donsmark M, et al. . Oral Semaglutide and cardiovascular outcomes in patients
diabetes. N Engl J Med 2019;381:841–51

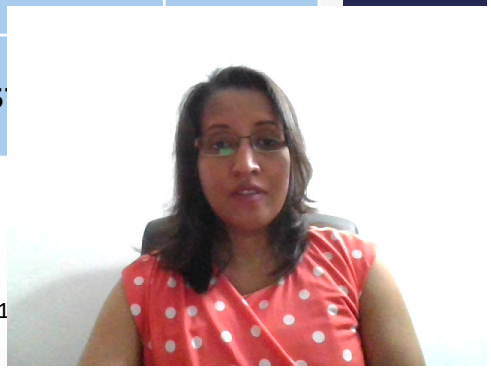
GLP-1 Agonist – Class Effects

- GLP-1 agents in general are known to significantly reduce
  - HbA1c values
  - Weight (in kg)
  - Systolic blood pressure
- Composite cardiovascular outcomes* (LEADER, SUSTAIN-6, and REWIND trials)



GLP-1 CVOT Comparison

GLP-1 RA: Study name	N	Median F/u (yrs)	% with CV disease*	% of statin use	Baseline HbA1c	Baseline BMI	Primary composite CV outcome HR (95% CI)	P value
Lixisenatide: ELIXA	6068	2.1	100%	93%	7.70%	30.1	1.02 (0.89 to 1.17)	0.81
Liraglutide: LEADER	9340	3.8	81%	72%	8.70%	32.5	0.87 (0.78 to 0.97)	0.01
Semaglutide: SUSTAIN-6	3297	2.1	60%	73%	8.70%	32.8	0.74 (0.58 to 0.95)	0.02
Exenatide QW: EXSCEL	14752	3.2	73.10%	74%	8.00%	31.8	0.91 (0.83 to 1.00)	0.06
Dulaglutide: REWIND	9901	5.4	31.50%	66%	7.20%	32.3	0.88 (0.79 to 0.99)	0.026
Semaglutide Oral: PIONEER 6	3183	1.3	84.70%	85%	8.20%	32.3	0.79 (0.5	



Sheahan KH, Wahlberg EA, Gilbert MP. An overview of GLP-1 agonists and recent cardiovascular outcomes trials. *Postgrad Med J*. 2020;96(1

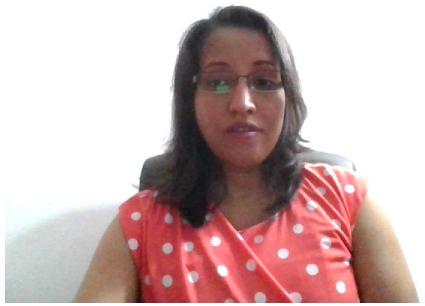
Newer DM Drug Categories

Glucagon Like Peptide – 1 Agonists

- Lixisenatide (®Adlyxin)
- Liraglutide (®Victoza)
- Semaglutide (®Ozempic)
- Exenetide (®Byetta)
- Exenatide LAR (®Bydureon)
- Dulaglutide (®Trulicity)
- Oral Semaglutide (®Rybelsus)

Dipeptidyl Peptidase 4 Inhibitors

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



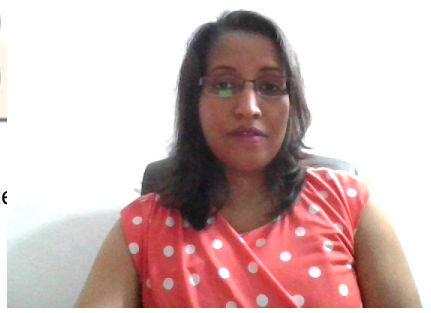
DPP4-I CVOT

- EXAMINE Trial – Alogliptin (®Nesina)

Table 3. Major Safety End Points.

End Point	Placebo (N=2679)	Alogliptin (N=2701)	Hazard Ratio for Alogliptin Group (95% CI)	P Value*
	no. (%)			
Primary end point†	316 (11.8)	305 (11.3)	0.96 (≤1.16)‡	0.32
Components of primary end point				
Death from cardiovascular causes	111 (4.1)	89 (3.3)	0.79 (0.60–1.04)	0.10
Nonfatal myocardial infarction	173 (6.5)	187 (6.9)	1.08 (0.88–1.33)	0.47
Nonfatal stroke	32 (1.2)	29 (1.1)	0.91 (0.55–1.50)	0.71
Principal secondary end point§	359 (13.4)	344 (12.7)	0.95 (≤1.14)‡	0.26
Other end points				
Death from any cause	173 (6.5)	153 (5.7)	0.88 (0.71–1.09)	
Death from cardiovascular causes¶	130 (4.9)	112 (4.1)	0.85 (0.66–1.10)	

White WB, Cannon CP, Heller SR, Nissen SE, Bergenstal RM, Bakris GL, Perez AT, Fleck PR, Mehta CR, Kupfer S, et al. Alogliptin afte
in patients with type 2 diabetes. N Engl J Med. 2013;369:1327–1335.



DPP4-I CVOT

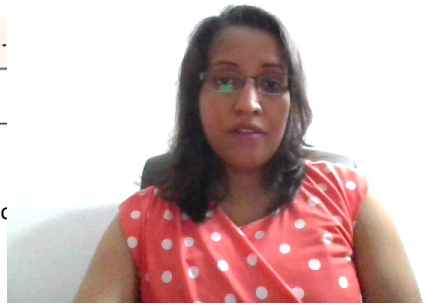
- SAVOR-TIMI 53 - Saxagliptin(®Onglyza)

Table 2. Prespecified Clinical End Points.*

End Point	Saxagliptin (N=8280)	Placebo (N=8212)	Hazard Ratio (95% CI)	P Value
	no. (%)			
Cardiovascular death, myocardial infarction, or stroke: primary efficacy end point	613 (7.3)	609 (7.2)	1.00 (0.89–1.12)	0.99
Cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, heart failure, or coronary revascularization: secondary efficacy end point	1059 (12.8)	1034 (12.4)	1.02 (0.94–1.11)	0.66
Hospitalization for heart failure	**289 (3.5)**	**228 (2.8)**	**1.27 (1.07 -1.51)**	**P=0.007**
Hospitalization for heart failure	289 (3.5)	228 (2.8)	1.27 (1.07–1.51)	0.007
Hospitalization for coronary revascularization	423 (5.2)	459 (5.6)	0.91 (0.80–1.04)	0.18
Doubling of creatinine level, initiation of dialysis, renal transplantation, or creatinine >6.0 mg/dl (530 μmol/liter)	194 (2.2)	178 (2.0)	1.08 (0.88–1.	
Hospitalization for hypoglycemia	53 (0.6)	43 (0.5)	1.22 (0.82–1.	

* Event rates and percentages are 2-year Kaplan–Meier estimates.

Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, Ohman P, Frederich R, Wiviott SD, Hoffman EB, et al. Saxagliptin and cardio
with type 2 diabetes mellitus. N Engl J Med. 2013;369:1317–1326

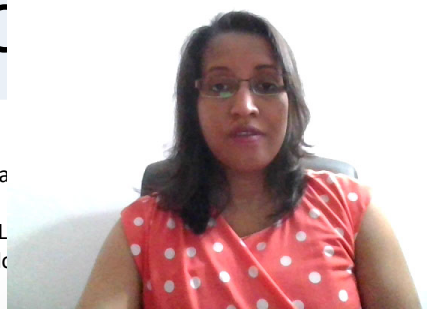


DPP4-I CVOT

- TECOS – Sitagliptin (®Januvia)
- CARMELINA – Linagliptin (®Tradjenta)

TECOS	CARMELINA
N=14671	N=6979
A1c 6.5% - 8%	A1c 6.5% - 10%
Duration = 3 years	Duration = 2.2 years
4-point MACE	3-point MAC

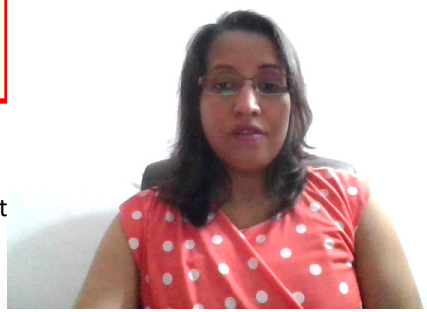
1. Green JB, Bethel MA, Armstrong PW, Buse JB, Engel SS, Garg J, Josse R, Kaufman KD, Koglin J, Korn S, et al. Effect of sitagliptin on ca outcomes in type 2 diabetes. N Engl J Med. 2015;373:232–242
2. Rosenstock J, Perkovic V, Johansen OE, Cooper ME, Kahn SE, Marx N, Alexander JH, Pencina M, Toto RD, Wanner C, et al. Effect of L placebo on major cardiovascular events in adults with type 2 diabetes and high cardiovascular and renal risk: the CARMELINA rand JAMA. 2019;321:69–79



DPP4-I CVOT

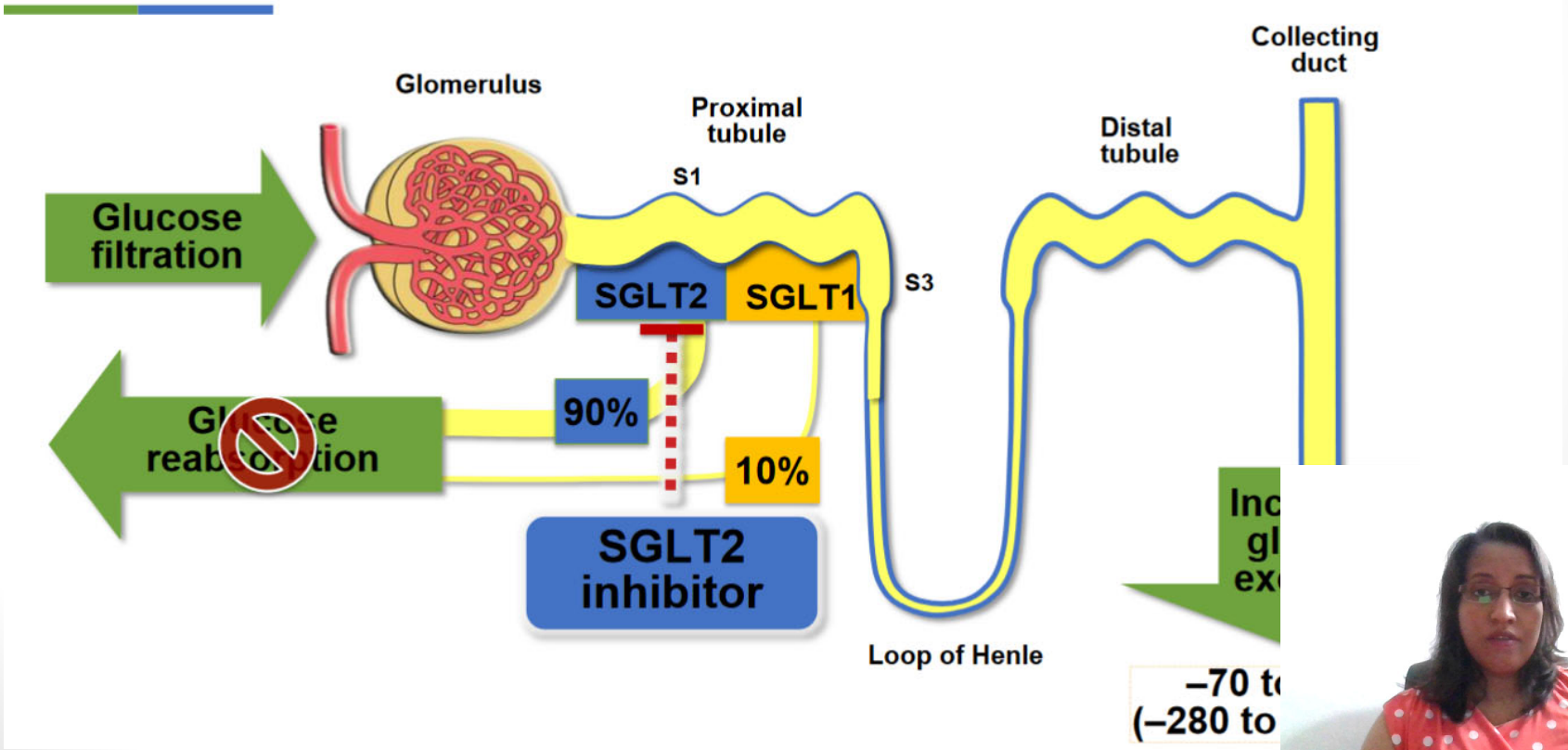
Clinical trial	Intervention	Primary outcome	CV risk	HR, OR or RR (95% CI)
DPP-4 inhibitors				
EXAMINE [8] *N* = 5380	Alogliptin versus placebo	3-point MACE	↔	HR 0.96 (≤ 1.16)[a]
SAVOR-TIMI 53 [7] *N* = 16,492	Saxagliptin versus placebo	3-point MACE	↔	HR 1.00 (0.89–1.12)
TECOS [5] *N* = 14,671	Sitagliptin versus placebo	4-point MACE	↔	HR 0.98 (0.88–1.09)
CARMELINA [6] *N* = 6979	Linagliptin versus placebo	3-point MACE	↔	

Santamarina M, Carlson CJ. Review of the cardiovascular safety of dipeptidyl peptidase-4 inhibitors and the clinical relevance of t
BMC Cardiovasc Disord. 2019;19(1):60.



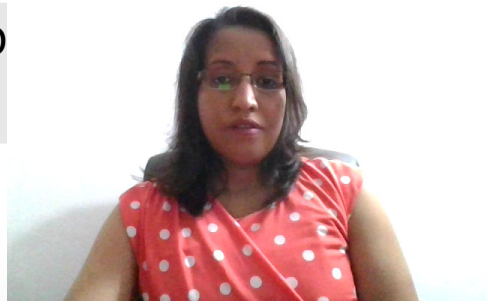
SGLT2 - Inhibitors

The kidneys play a major role in the regulation of glucose, reabsorbing 99% of the plasma glucose that filters through the renal glomerular tubules



SGLT2 - Inhibitors

	Canagliflozin (®Invokana)	Dapagliflozin (®Farxiga)	Empagliflozin (®Jardiance)	Ertugliflozin (®Steglatro)
Doses	100 mg, 300 mg	5 mg, 10 mg	10 mg, 25 mg	5 mg, 15 mg
eGFR>60	No change	No change	No change	No change
eGFR 45-60	**100 mg only**	Don't start	**No change**	Consider stopping
eGFR 30-45	Don't start	Don't start	Stop	Consider stopping
eGFR <30	Contraindicated	Contraindicated	Contraindicated	Contraindicated
FDA Approved	March 2013	January 2014	August 2014	D



SGLT2-I CVOT – CANVAS & CANVAS-R
Canagliflozin (®Invokana)

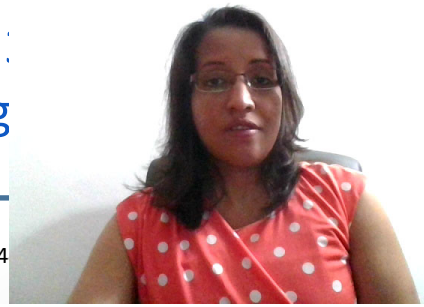
T2DM
N = 10, 142
A1c 7% - 10.5%

GFR >30 ml/min
Age 30 + symptomatic CAD
Age 50 + 2CAD/Renal risks

Duration 3.6 years

CANVAS
1:1:1
Canagliflozin 100 mg:
Canagliflozin 300 mg:
Matching Placebo

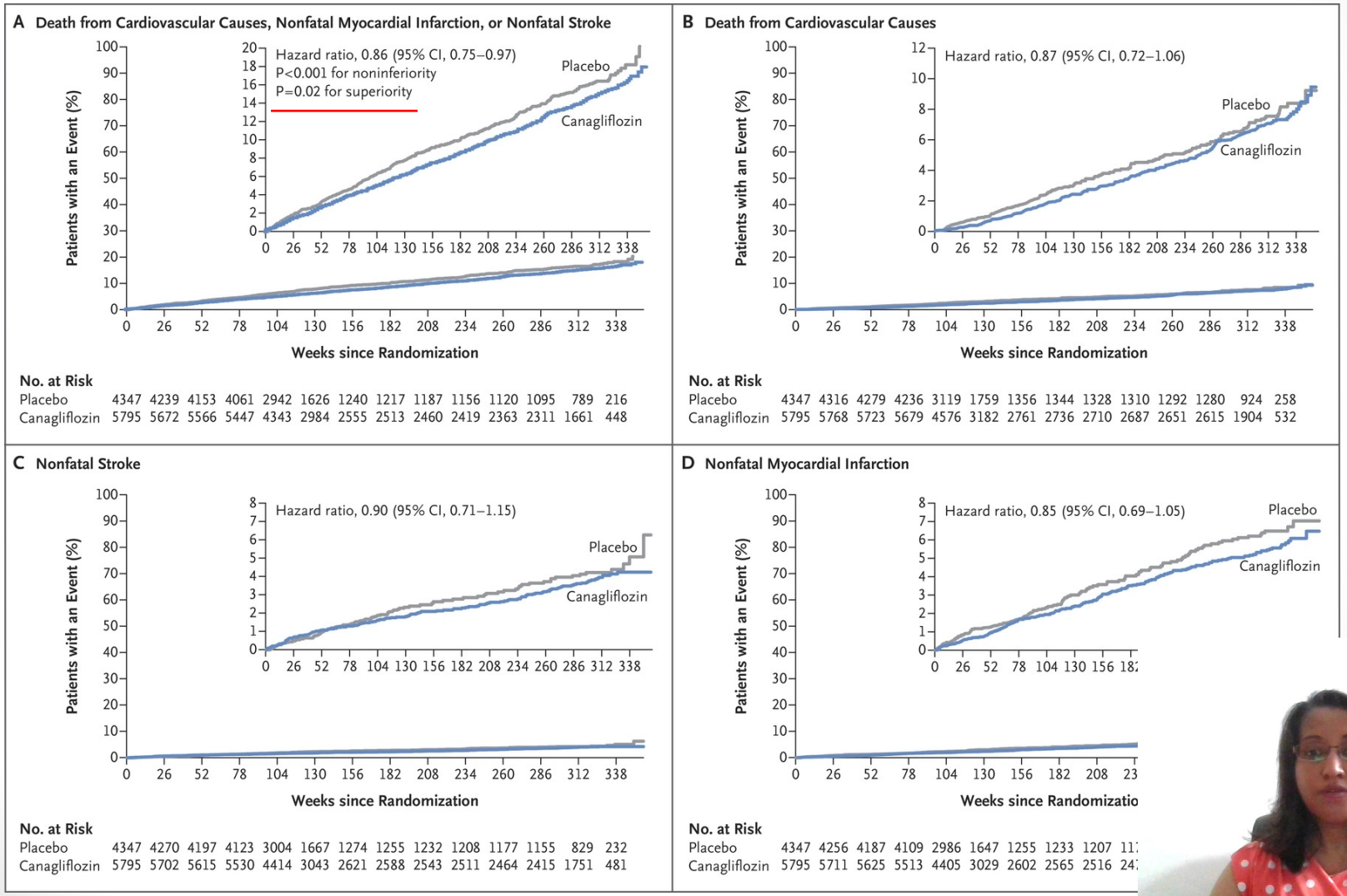
CANVAS - R
1:1
Canagliflozi
13 w >>
Matching

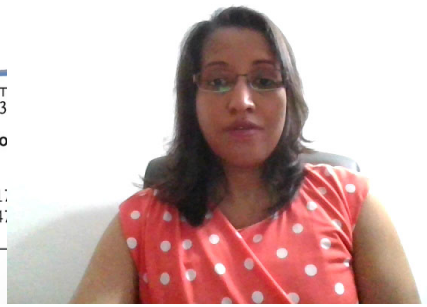


Neal B, Perkovic V, Mahaffey KW et al (2017) Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 377:64

SGLT2-I CVOT – CANVAS & CANVAS-R

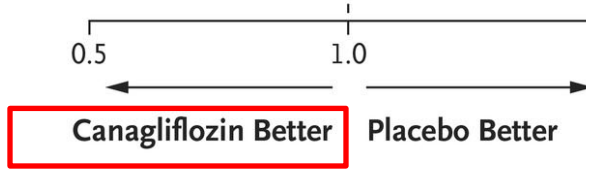
Canagliflozin (®Invokana)

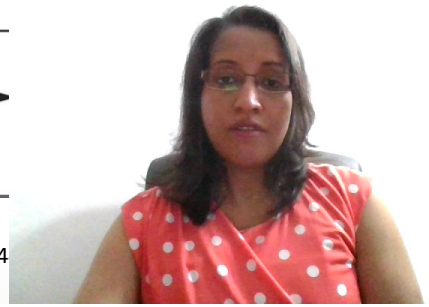




SGLT2-I CVOT – CANVAS & CANVAS-R
Canagliflozin (®Invokana)

Outcome	Canagliflozin (N=5795)	Placebo (N=4347)	Hazard Ratio (95% CI)
	no. of participants per 1000 patient-yr		
Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke	26.9	31.5	0.86 (0.75–0.97)
Death from cardiovascular causes	11.6	12.8	0.87 (0.72–1.06)
Nonfatal myocardial infarction	9.7	11.6	0.85 (0.69–1.05)
Nonfatal stroke	7.1	8.4	0.90 (0.71–1.15)
Fatal or nonfatal myocardial infarction	11.2	12.6	0.89 (0.73–1.09)
Fatal or nonfatal stroke	7.9	9.6	0.87 (0.69–1.09)
Hospitalization for any cause	118.7	131.1	0.94 (0.88–1.00)
Hospitalization for heart failure	5.5	8.7	0.67 (0.52–0.87)
Death from cardiovascular causes or hospitalization for heart failure	16.3	20.8	0.78 (0.67–0.91)
Death from any cause	17.3	19.5	0.87 (0.74–1.01)
Progression of albuminuria	89.4	128.7	0.73 (0.67–0.79)
40% reduction in eGFR, renal-replacement therapy, or renal death	5.5	9.0	

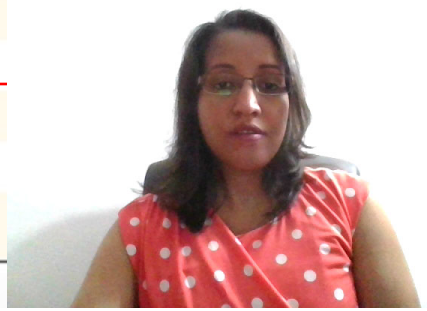




Neal B, Perkovic V, Mahaffey KW et al (2017) Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 377:64

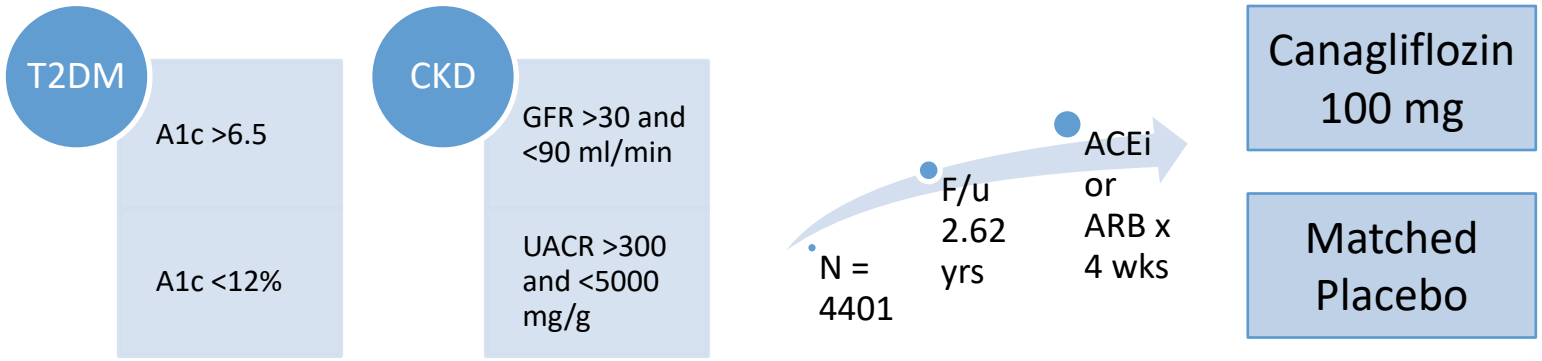
SGLT2-I CVOT – CANVAS & CANVAS-R
Canagliflozin (®Invokana)

Adverse Effects	Canagliflozin	Placebo	P value
Diabetic ketoacidosis (adjudicated)	0.6	0.3	0.14
Amputation	6.3	3.4	<0.001
Fracture (adjudicated)‡			
All	15.4	11.9	0.02
Low-trauma	11.6	9.2	0.06
Venous thromboembolic events	1.7	1.7	0.63
Infection of male genitalia§	34.9	10.8	<0.001
Serious and nonserious adverse events of interest collected in CANVAS alone¶			
Osmotic diuresis	34.5	13.3	<0.001
Volume depletion	26.0	18.5	0.009
Hypoglycemia	50.0	46.4	0.20
Acute kidney injury	3.0	4.1	0.33
Hyperkalemia	6.9	4.4	
Urinary tract infection	40.0	37.0	
Mycotic genital infection in women	68.8	17.5	
Severe hypersensitivity or cutaneous reaction	8.5	6.1	
Hepatic injury	7.4	9.1	
Renal-related (including acute kidney injury)	19.7	17.4	

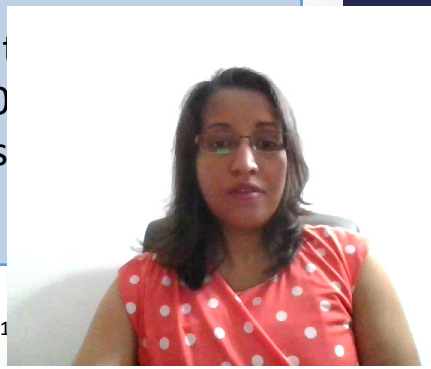


SGLT2-I CVOT – CREDENCE
Canagliflozin (®Invokana)

- The study was designed to formally test whether canagliflozin - reduced the risk of kidney failure and cardiovascular events in patients with T2DM and markers of established kidney disease compared to placebo when used in addition to standard of care.

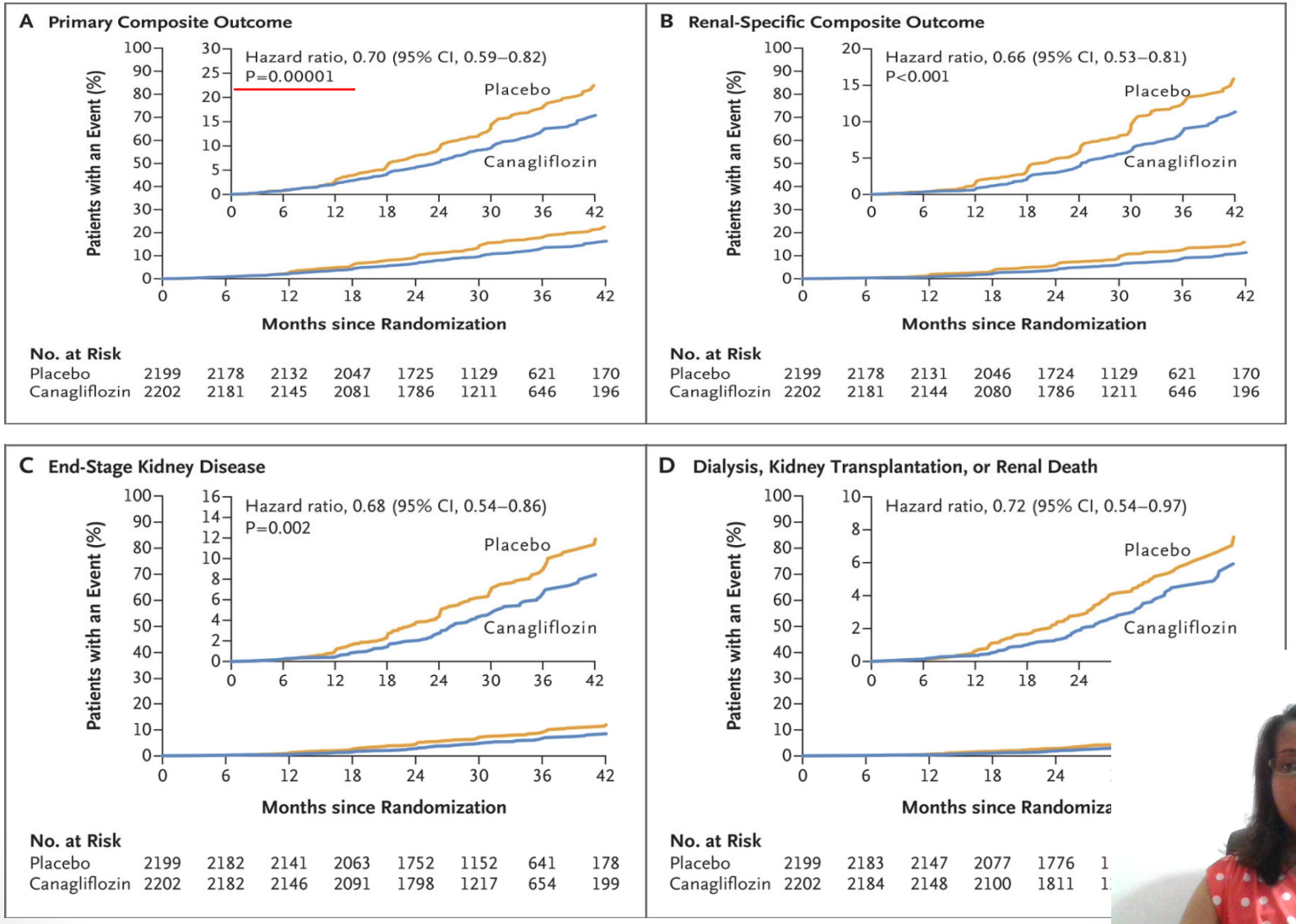


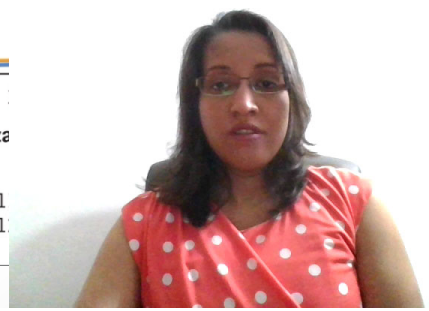
The primary outcome was a composite of
- end-stage kidney disease (dialysis for at least 30 days, kidney transplantat
  estimated GFR of <15 ml per minute per 1.73 m^2 sustained for at least 30
- doubling of the serum creatinine level from baseline sustained for at leas
- death from renal or cardiovascular disease.



Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. *N Engl J Med*. 2019;380(24):2295-2306. doi:1

SGLT2-I CVOT – CREDENCE
Canagliflozin (®Invokana)

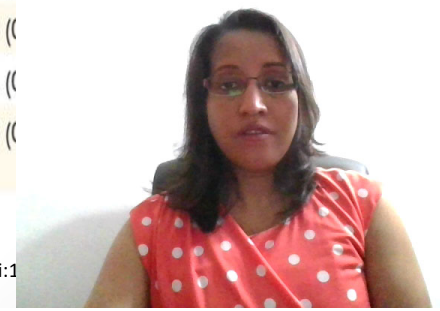




SGLT2-I CVOT – CREDENCE
Canagliflozin (®Invokana)

Table 2. Efficacy and Safety.*

Variable	Canagliflozin	Placebo	Canagliflozin	Placebo	Hazard Ratio (95% CI)	P Value
	no./total no.		*events/ 1000 patient-yr*			
Efficacy						
Primary composite outcome	245/2202	340/2199	43.2	61.2	0.70 (0.59–0.82)	0.00001
Doubling of serum creatinine level	118/2202	188/2199	20.7	33.8	0.60 (0.48–0.76)	<0.001
End-stage kidney disease	116/2202	165/2199	20.4	29.4	0.68 (0.54–0.86)	0.002
Estimated GFR <15 ml/min/1.73 m^2	78/2202	125/2199	13.6	22.2	0.60 (0.45–0.80)	NA
Dialysis initiated or kidney transplantation	76/2202	100/2199	13.3	17.7	0.74 (0.55–1.00)	NA
Renal death	2/2202	5/2199	0.3	0.9	NA	NA
Cardiovascular death	110/2202	140/2199	19.0	24.4	0.78 (0.61–1.00)	0.05
Secondary outcomes						
Cardiovascular death or hospitalization for heart failure	179/2202	253/2199	31.5	45.4	0.69 (	
Cardiovascular death, myocardial infarction, or stroke	217/2202	269/2199	38.7	48.7	0.80 (	
Hospitalization for heart failure	89/2202	141/2199	15.7	25.3	0.61 (	
End-stage kidney disease, doubling of serum creatinine level, or renal death	153/2202	224/2199	27.0	40.4	0.66 (	



Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. *N Engl J Med*. 2019;380(24):2295-2306. doi:1

SGLT2-I CVOT – EMPA-REG OUTCOMES

Empagliflozin (®Jardiance)

Adult with T2DM

BMI ≤ 45 kg/m2

Established cardiovascular disease (prior MI, CAD, stroke, unstable angina or occlusive PAD)

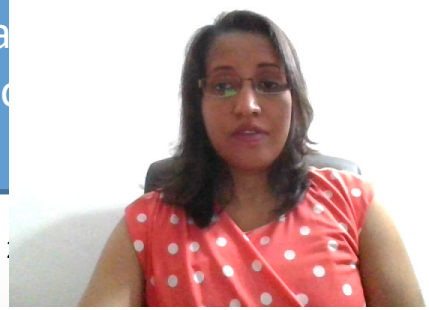
A1C 7-10%

N=7020

3.1 years

- Empagliflozin 10mg
- Empagliflozin 25mg
- Placebo

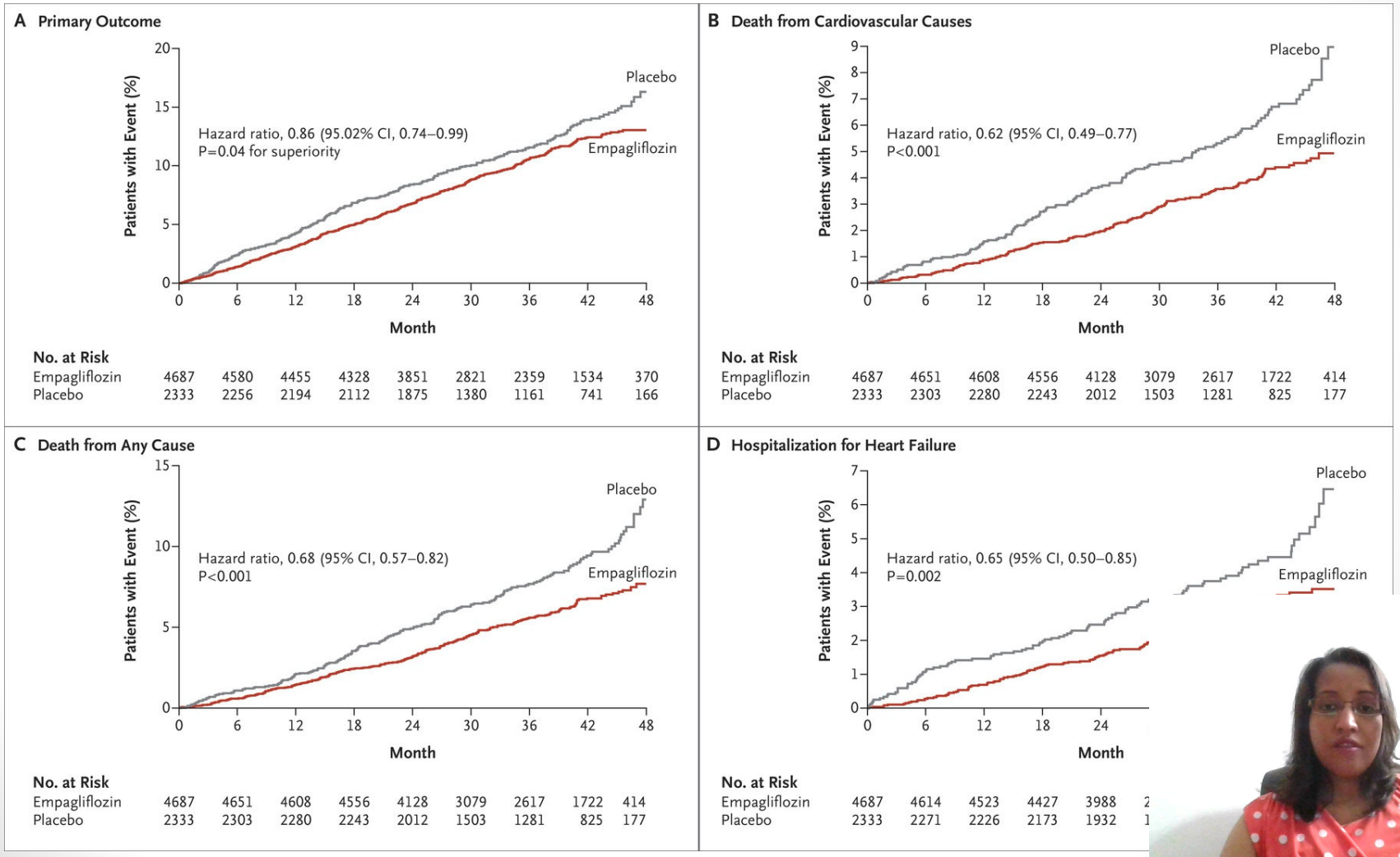
The primary outcome was a composite of death from cardiovascular ca
nonfatal myocardial infarction (excluding silent myocardial infarction), c
stroke.



Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med*.

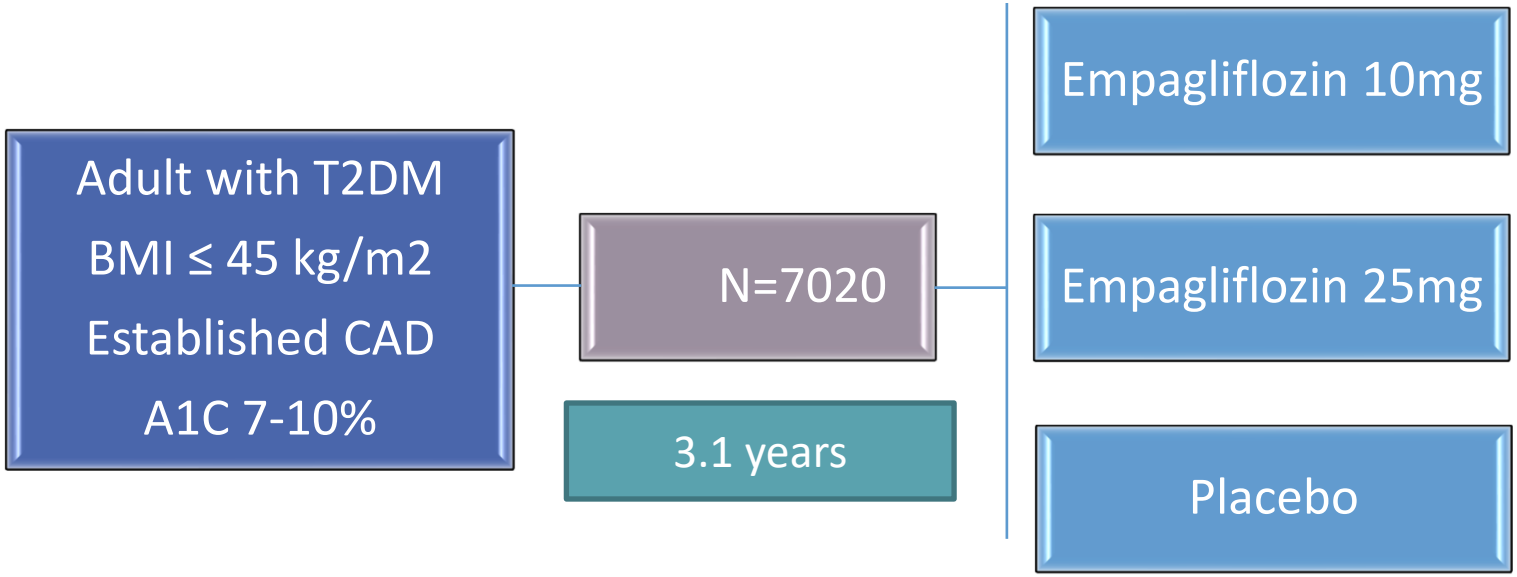
SGLT2-I CVOT – EMPA-REG OUTCOMES

Empagliflozin (®Jardiance)



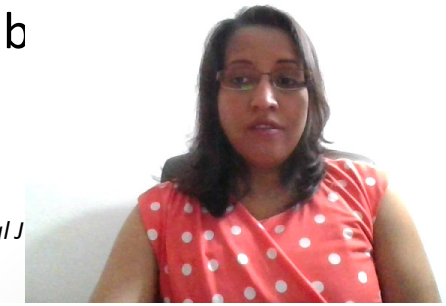
SGLT2-I Renal – EMPA-REG OUTCOMES

Empagliflozin (®Jardiance)



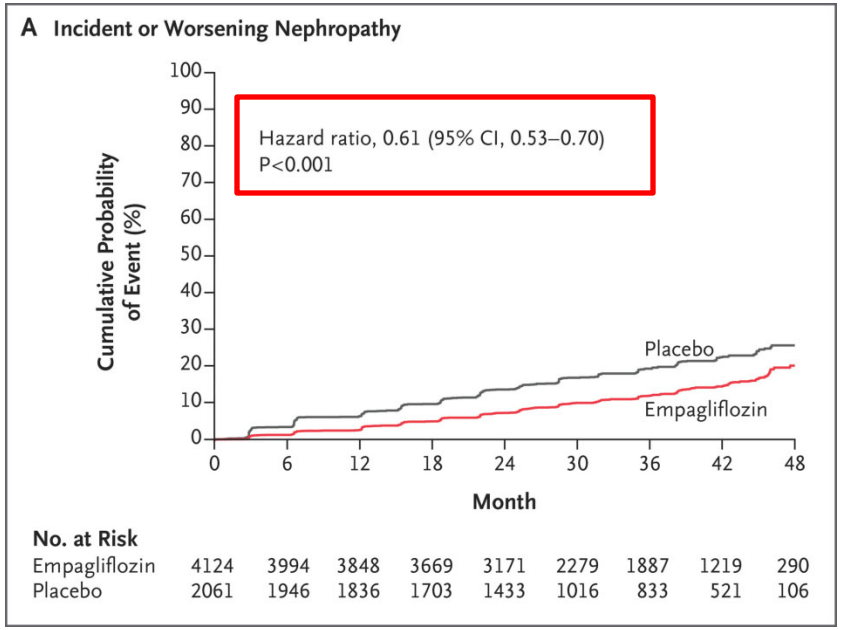
At baseline, the eGFR was 45 – 59 ml/min in 17.8% of the patients and 30 - 44 ml/min in 7.7% patients

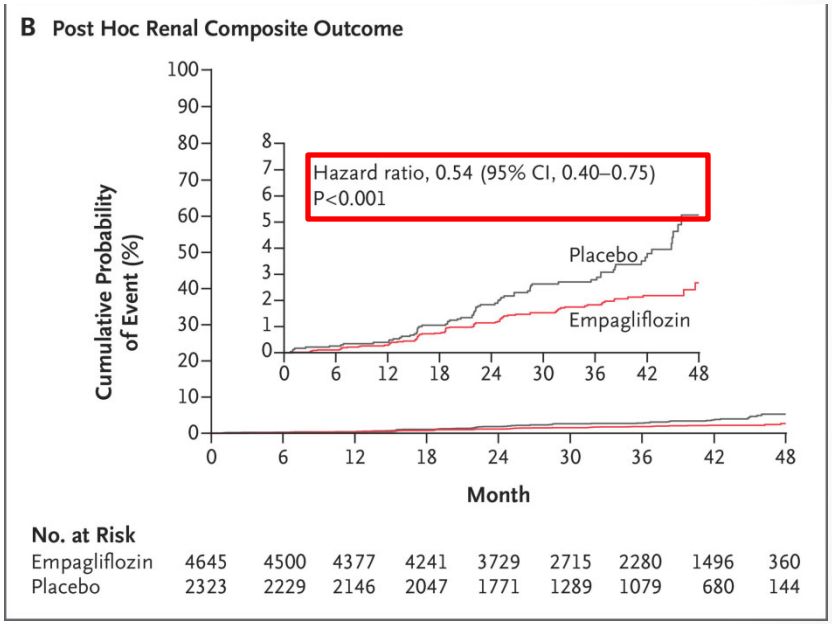
- 28.7% had microalbuminuria, and 11.0% had macroalbumin
- In total, 80.7% of the patients were taking ACEi or ARBs at b

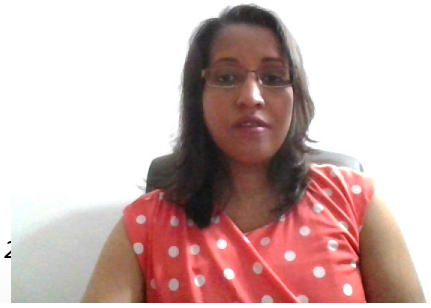


Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J* 2015;373(22):2117-2128.

SGLT2-I Renal – EMPA-REG OUTCOMES
Empagliflozin (®Jardiance)



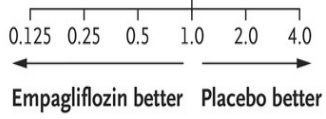


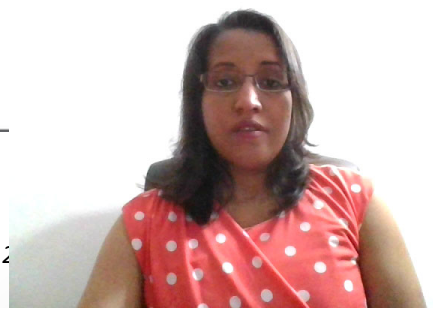


Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. N Engl J Med. 2

SGLT2-I Renal – EMPA-REG OUTCOMES
Empagliflozin (®Jardiance)

Renal Outcome Measure	Empagliflozin no. with event/ no. analyzed (%)	Empagliflozin rate/1000 patient-yr	Placebo no. with event/ no. analyzed (%)	Placebo rate/1000 patient-yr	Hazard Ratio (95% CI)	P Value
Incident or worsening nephropathy or cardiovascular death	675/4170 (16.2)	60.7	497/2102 (23.6)	95.9	0.61 (0.55–0.69)	<0.001
Incident or worsening nephropathy	525/4124 (12.7)	47.8	388/2061 (18.8)	76.0	0.61 (0.53–0.70)	<0.001
Progression to macroalbuminuria	459/4091 (11.2)	41.8	330/2033 (16.2)	64.9	0.62 (0.54–0.72)	<0.001
Doubling of serum creatinine level accompanied by eGFR of ≤45 ml/min/1.73 m^2	70/4645 (1.5)	5.5	60/2323 (2.6)	9.7	0.56 (0.39–0.79)	<0.001
Initiation of renal-replacement therapy	13/4687 (0.3)	1.0	14/2333 (0.6)	2.1	0.45 (0.21–0.97)	0.04
Doubling of serum creatinine level accompanied by eGFR of ≤45 ml/min/1.73 m^2, initiation of renal-replacement therapy, or death from renal disease	81/4645 (1.7)	6.3	71/2323 (3.1)	11.5	0.54 (0.40–0.75)	<0.001
Incident albuminuria in patients with a normal albumin level at baseline	1430/2779 (51.5)	252.5	703/1374 (51.2)	266.0	0.95 (0.87–1.04)	0.25





Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. N Engl J Med. 2

SGLT2-I CVOT – DECLARE-TIMI 58

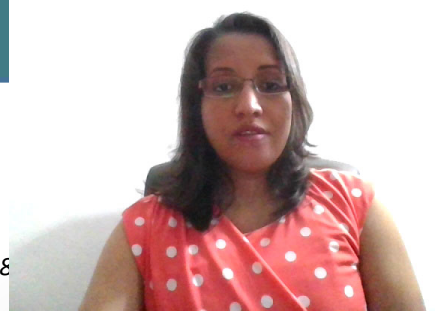
Dapagliflozin (®Farxiga)

T2DM (A1c 6.5 – 12%)
CAD or Risk
GFR > 60 ml/min
N = 17,160

Dapagliflozin
10 mg QD

Placebo

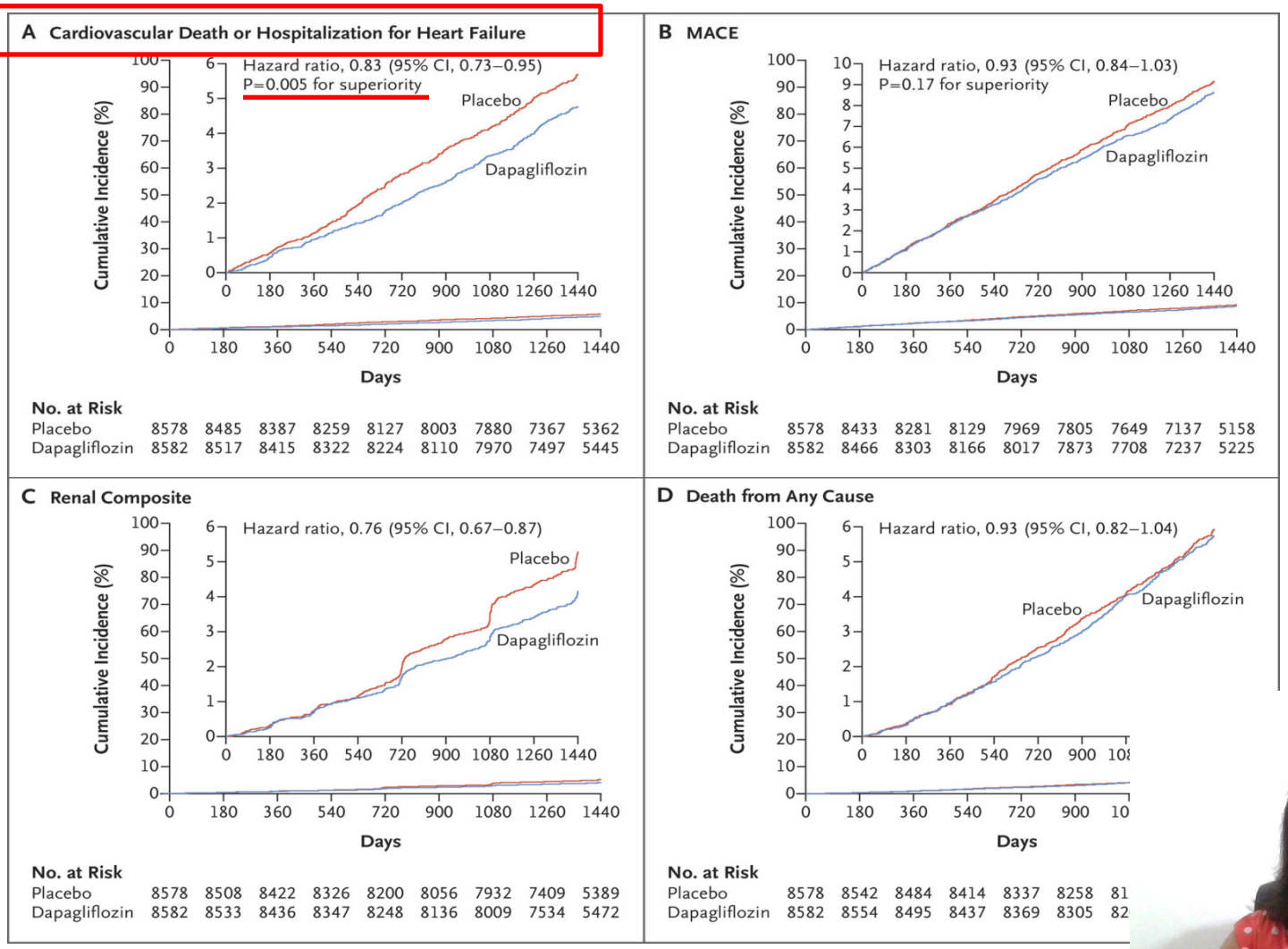
4.2 yrs



Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2018;38

SGLT2-I CVOT – DECLARE-TIMI

Dapagliflozin (®Farxiga)



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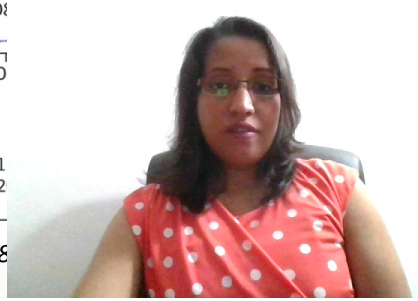
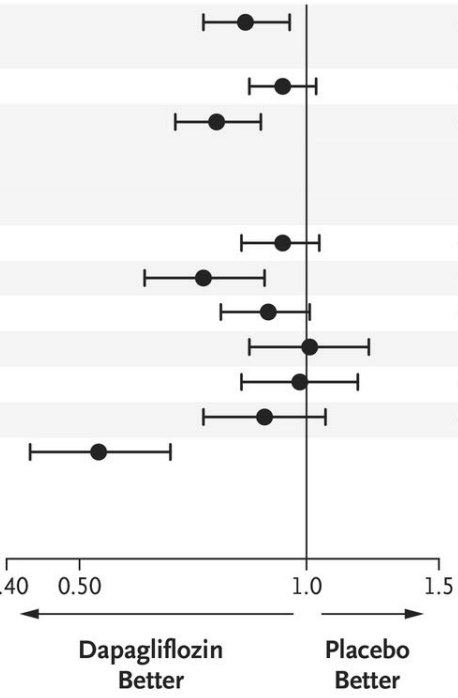
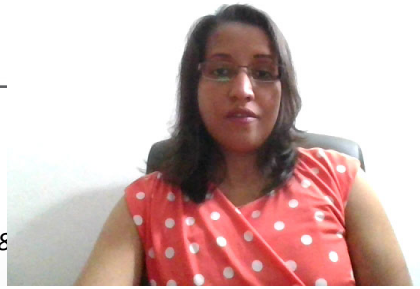


SGLT2-I CVOT – DECLARE-TIMI
Dapagliflozin (®Farxiga)

Outcome	Dapagliflozin (N=8582) no. (%)	Dapagliflozin (N=8582) rate/1000 patient-yr	Placebo (N=8578) no. (%)	Placebo (N=8578) rate/1000 patient-yr	Hazard Ratio (95% CI)	P Value
Cardiovascular death or hospitalization for heart failure	417 (4.9)	12.2	496 (5.8)	14.7	0.83 (0.73–0.95)	0.005
MACE	756 (8.8)	22.6	803 (9.4)	24.2	0.93 (0.84–1.03)	0.17
≥40% decrease in eGFR to <60 ml/min/1.73 m^2, ESRD, or death from renal or cardiovascular cause	370 (4.3)	10.8	480 (5.6)	14.1	0.76 (0.67–0.87)	
Death from any cause	529 (6.2)	15.1	570 (6.6)	16.4	0.93 (0.82–1.04)	
Hospitalization for heart failure	212 (2.5)	6.2	286 (3.3)	8.5	0.73 (0.61–0.88)	
Myocardial infarction	393 (4.6)	11.7	441 (5.1)	13.2	0.89 (0.77–1.01)	
Ischemic stroke	235 (2.7)	6.9	231 (2.7)	6.8	1.01 (0.84–1.21)	
Death from cardiovascular cause	245 (2.9)	7.0	249 (2.9)	7.1	0.98 (0.82–1.17)	
Death from noncardiovascular cause	211 (2.5)	6.0	238 (2.8)	6.8	0.88 (0.73–1.06)	
≥40% decrease in eGFR to <60 ml/min/1.73 m^2, ESRD, or death from renal cause	127 (1.5)	3.7	238 (2.8)	7.0	0.53 (0.43–0.66)	

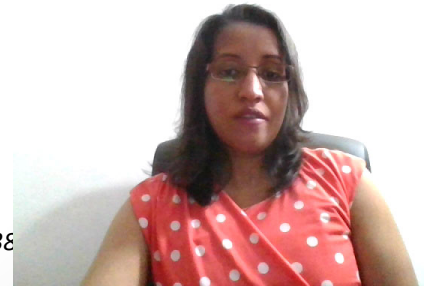




Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2018;38

SGLT2-I CVOT – DECLARE-TIMI
Dapagliflozin (®Farxiga)

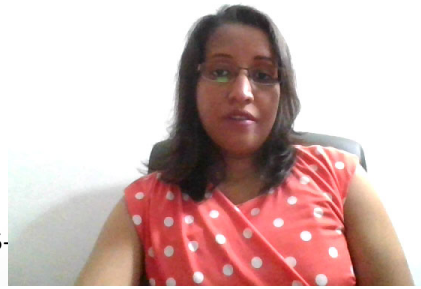
- This trial included more than 10,000 patients without evident atherosclerotic cardiovascular disease
  - Dapagliflozin prevented cardiovascular events, particularly hospitalization for heart failure, regardless of a history of atherosclerotic cardiovascular disease or heart failure.
  - Majority of patients did not have a history of heart failure, so the prevention of new clinical heart failure is notable.



Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2018;38

SGLT2-I CVOT – DAPA – HF Trial
Dapagliflozin (®Farxiga)

- In the DAPA-HF trial, 4443 patients were involved with NYHA Class II HF and EF <40%, optimally treated for HF
- Only 42% of patients in this trial had a h/o T2DM.
- Patients also completed a Kansas City Cardiomyopathy Questionnaire (23 item questionnaire)

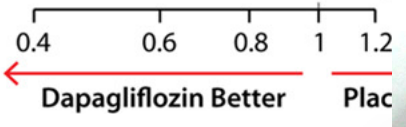


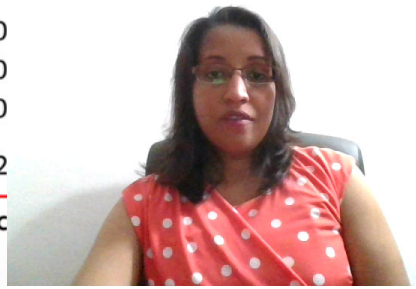
*McMurray et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med. 2019;*381:1995-

SGLT2-I CVOT – DAPA – HF Trial

Dapagliflozin (®Farxiga)

Outcome	Dapagliflozin	Placebo	HR (95% CI)	p-value
Cardiovascular Death, Hospitalization for Heart Failure or Urgent Heart Failure Visit				0.52
≤65.6 (n=1487)	162/768	209/719	0.70 (0.57, 0.86)	
65.7-87.5 (n=1564)	119/773	152/791	0.77 (0.61, 0.98)	
>87.5 (n=1392)	73/693	116/699	0.62 (0.46, 0.83)	
Cardiovascular Death or Hospitalization for Heart Failure				0.53
≤65.6 (n=1487)	160/768	205/719	0.71 (0.57, 0.87)	
65.7-87.5 (n=1564)	118/773	150/791	0.77 (0.61, 0.99)	
>87.5 (n=1392)	73/693	115/699	0.62 (0.46, 0.83)	
Hospitalization for Heart Failure or Urgent Heart Failure Visit				0.38
≤65.6 (n=1487)	99/768	134/719	0.67 (0.51, 0.86)	
65.7-87.5 (n=1564)	78/773	101/791	0.76 (0.56, 1.02)	
>87.5 (n=1392)	43/693	78/699	0.54 (0.37, 0.78)	
Hospitalization for Heart Failure				0.40
≤65.6 (n=1487)	96/768	130/719	0.67 (0.51, 0.87)	
65.7-87.5 (n=1564)	76/773	98/791	0.76 (0.56, 1.03)	
>87.5 (n=1392)	43/693	77/699	0.55 (0.38, 0.79)	
Cardiovascular Death				0.82
≤65.6 (n=1487)	107/768	121/719	0.84 (0.64, 1.09)	
65.7-87.5 (n=1564)	63/773	81/791	0.78 (0.56, 1.09)	
>87.5 (n=1392)	39/693	54/699	0	
Death from Any Cause				
≤65.6 (n=1487)	134/768	142/719	0	
65.7-87.5 (n=1564)	76/773	99/791	0	
>87.5 (n=1392)	46/693	67/699	0	





SGLT2-I CVOT – VERTIS CV
Ertugliflozin (®Steglatro)

Multicenter, randomized, double-blind, placebo-controlled, event-driven trial

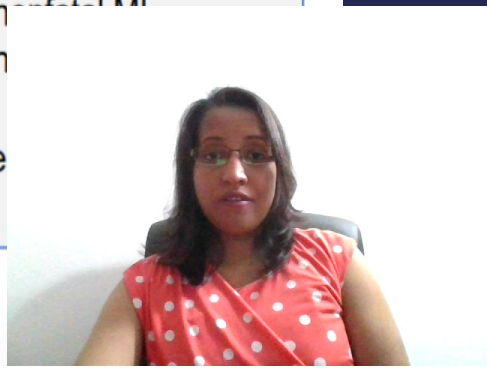
Randomization 1:1:1

Placebo | **Ertugliflozin 5 mg** | **Ertugliflozin 15 mg**

Primary endpoint (non-inferiority):
- Composite outcome of MACE (CV death, nonfatal MI, nonfatal stroke)

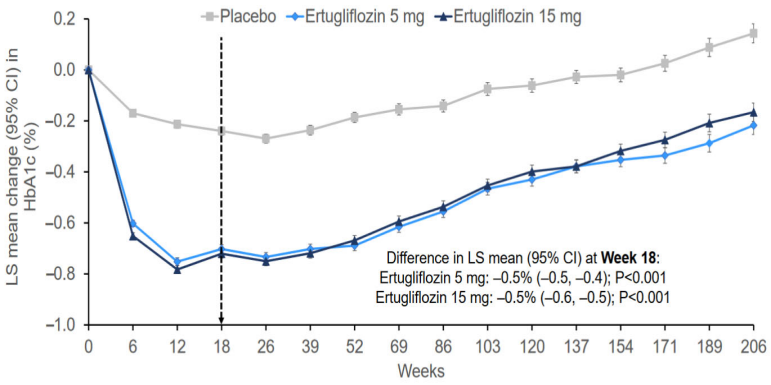
Secondary endpoints (superiority):
- Composite outcome of CV death/HHF
- CV death
- Renal composite (renal death, dialysis/transplant, doubling of serum creatinine)

Other prespecified endpoints:
- Individual components of MACE
- Composite of MACE-plus (MACE plus hospitalization for unstable angina)
- Fatal or n
- Fatal or n
- HHF
- All-cause

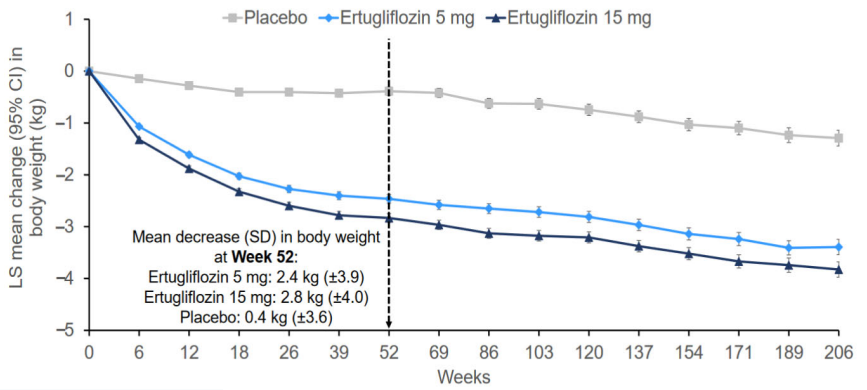


SGLT2-I CVOT – VERTIS CV
Ertugliflozin (®Steglatro)

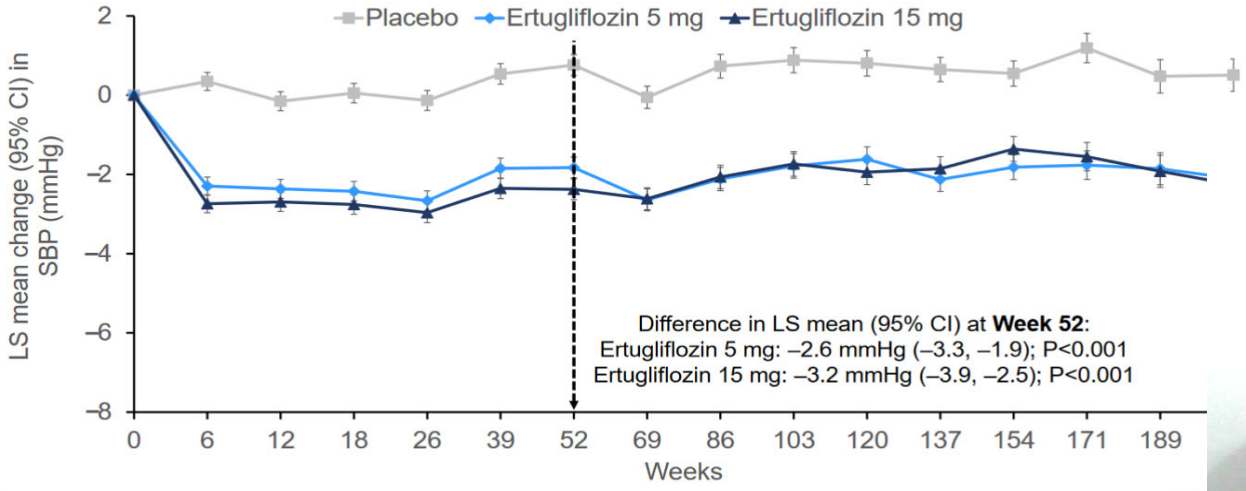
HbA1c

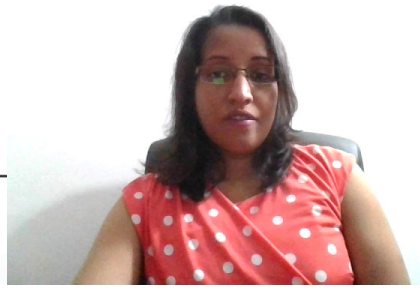


Body Weight



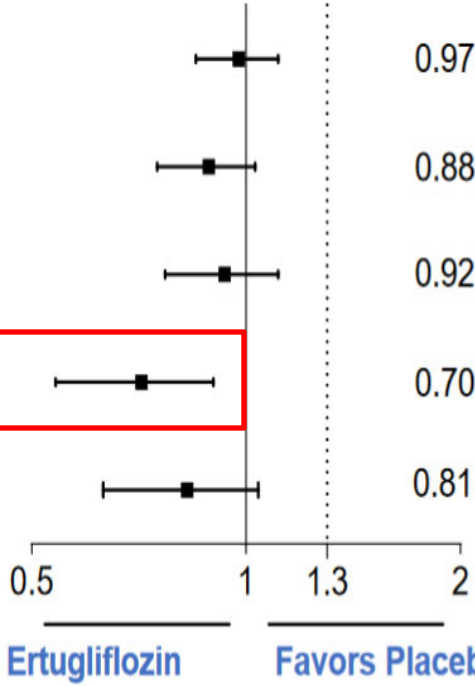
Systolic BP

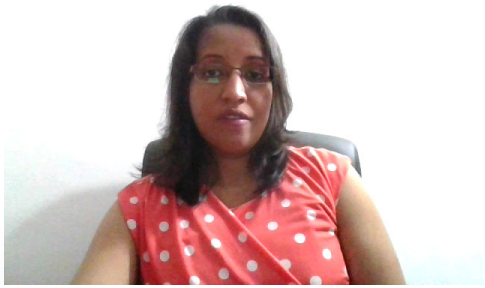




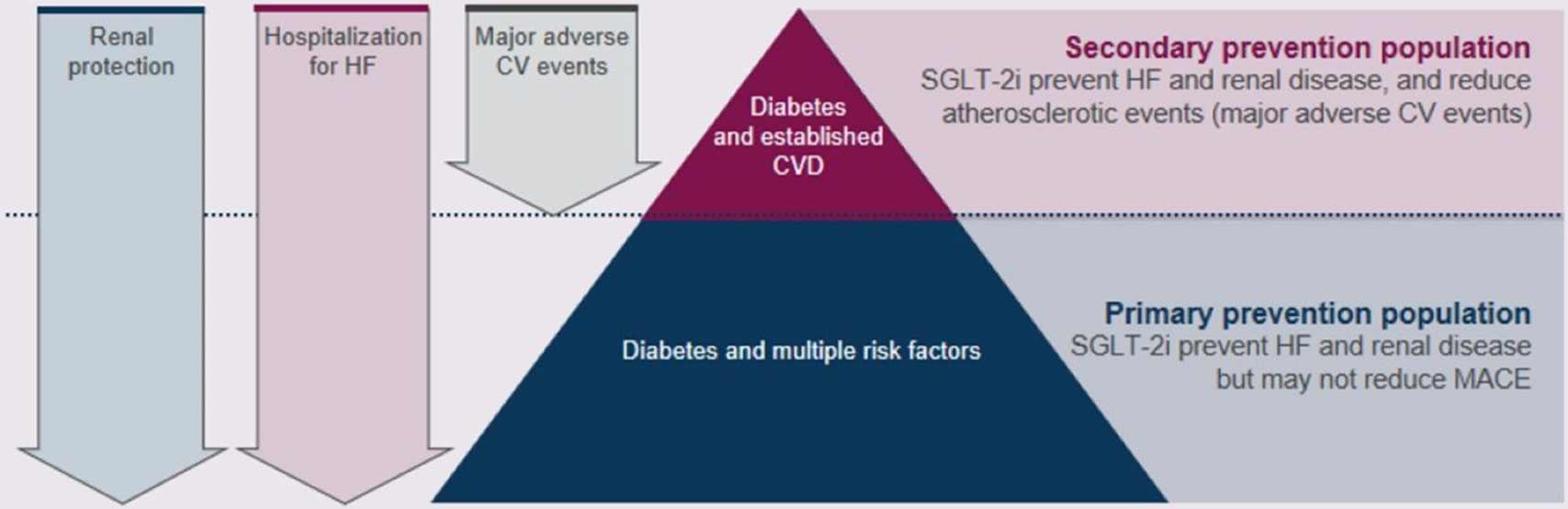
SGLT2-I CVOT – VERTIS CV Ertugliflozin (®Steglatro)

	Ertugliflozin n=5499	Placebo n=2747	HR (CI)	P Value
	Rate/100 patient-years			
MACE*	3.9	4.0	0.97 (0.85, 1.11)	<0.001 (for non-inferiority)
CV Death/HHF†	2.3	2.7	0.88 (0.75, 1.03)	0.11
CV Death†	1.8	1.9	0.92 (0.77, 1.11)	0.39
HHF†	0.7	1.1	0.70 (0.54, 0.90)	0.006
Renal Composite†	0.9	1.2	0.81 (0.63, 1.04)	

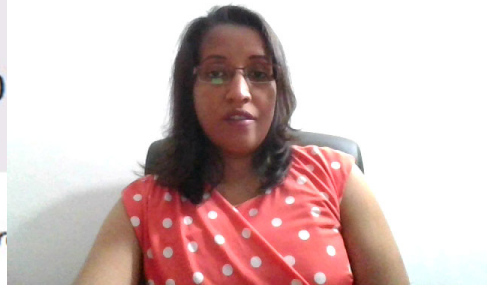




SGLT-2 Inhibition Leads to Benefits in Cardiorenal Outcome in Several Patient Populations



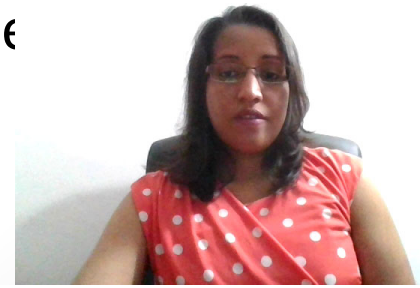
- According to a recent meta-analysis of three randomized CVOTs in patients with T2D with either established CVD or multiple risk factors (~60% with established CVD), SGLT-2i reduced the risk of[1,2]:
  - Hospitalization for HF by 31% (HR=0.69; 95% CI, 0.61-0.79; *P*<.0001)
  - CV death or hospitalization for HF by 23% (HR=0.77; 95% CI, 0.71-0.84; *P*<
  - Major MACE by 11% (HR=0.89; 95% CI, 0.83-0.96; *P*=.0014)
  - Progression of renal disease by 45% (HR=0.55; 95% CI, 0.48-0.64; *P*<.000



CVD=cardiovascular disease; CVOT=cardiovascular outcome trial; MACE=major adverse cardiovascular event.
1. Verma S, et al. *Lancet*. 2019;393(10166):3-5. 2. Zelniker TA, et al. *Lancet*. 2019;393(10166):31-39. 3. Scheen RJ. *Cir* 2019;14(1):23-32.

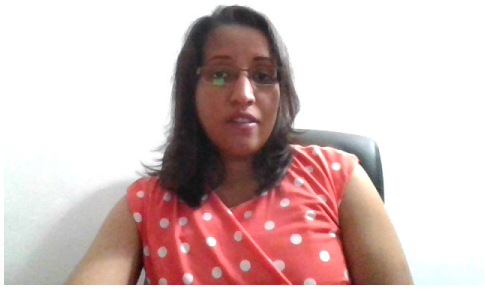
In Summary

- All the DPP4 inhibitor trials met the non-niferiority criteria but none of them met superiority criteria for CV outcomes
- Among the GLP-1 agents, Liraglutide (Victoza), Semaglutide (Ozempic), and Dulaglutide (Trulicity) showed statistically significant and real world clinically significant benefits for CV disease and nephropathy
- Among the SGLT-2 inhibitors, Canagliflozin (Invokana), Empagliflozin (Jardiance), and Dapagliflozin (Farxiga) are noted to significantly reduce hospitalizations for progression of renal disease, and MACE outcome



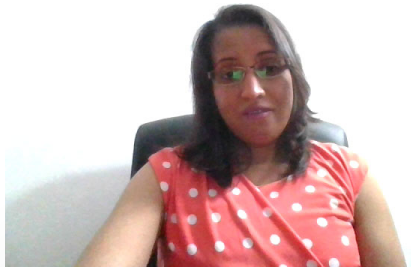
In Clinical Practice

- 65 y/o male with poorly controlled T2DM (A1c 8%) complicated with history of CAD s/p 1 stent, CHF (EF 40%), and CKD2 is referred to you by PCP for management of T2DM. His BMI is 32 kg/m2 and BP is 144/94 mm Hg. He admits to a FH of MI in his father at age 40. He is adherent to diet and exercise, takes Metformin 1000 mg BID, Lisinopril 5 mg QD, and Atorvastatin 40 mg QHS.
- **Which of the following agents would be of consideration for him in addition to Metformin?**
- Pioglitazone (Actos)
- Dulaglutide (Trulicity)
- Saxagliptin (Onglyza)
- Empagliflozin (Jardiance)



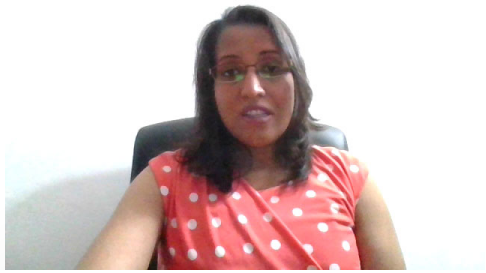
References

1. Malmberg K, Ryde´n L. Myocardial infarction in patients with diabetes mellitus. Eur Heart J. 1988;9:256–264.
2. Herlitz J, Malmberg K, Karlsson B, et al. Mortality and morbidity during a five-year follow-up of diabetics with myocardial infarction. Acta Med Scand. 1988;24:31–38.
3. Granger C, Califf R, Young S, et al. Outcome of patients with diabetes mellitus and acute myocardial infarction treated with thrombolytic agents. J Am Coll Cardiol. 1993;21:920–925.
4. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive Diabetes Treatment and Cardiovascular Disease in Patients with Type 1 Diabetes. *N Engl J Med* 2005;353:2643-2653.
5. Group UKPDS. *The Lancet.* 1998;352(9131):837-853.
6. The Action to Control Cardiovascular Risk in Diabetes Study Group. N Engl J Med 2008; 358:2545-2559
7. The ADVANCE Collaborative Group. N Engl J Med 2008; 358:2560-2572
8. Duckworth W et al. Glucose Control and Vascular Complications in Veterans with Type 2 Diabetes. *New England Journal of Medicine.* 2009;360(2):129-139.
9. White, J. A Brief History of the Development of Diabetes Mediccations. Diabetes Spectrum 2014 May; 27(2): 82-86.
10. Kooy A, de Jager J, Lehert P, et al. Long-term effects of metformin on metabolism and microvascular and macrovascular disease in patients with type 2 diabetes mellitus. *Arch Intern Med*. 2009;169(6):616-625.
11. Hong J, Zhang Y, Lai S, et al. Effects of metformin versus glipizide on cardiovascular outcomes in patients with type 2 diabetes and coronary artery disease. *Diabetes Care*. 2013;36(5):1304-1313.
12. Rados DV, et al. The Association between Sulfonylurea Use and All-Cause and Cardiovascular Mortality: A Meta-Analysis with Trial Sequential Analysis of Randomized Clinical Trials.2016: PLoSMed13(4):e1001992.
13. Rosenstock J, Marx N, Kahn SE, et al. Cardiovascular outcome trials in type 2 diabetes and the sulphonylurea controversy: rationale for the active-comparator CAROLINA trial. *Diab Vasc Dis Res*. 2013;10(4):289-301.
14. de Jong M, van der Worp HB, van der Graaf Y, Visseren FLJ, Westerink J. Pioglitazone and the secondary prevention of cardiovascular disease. A meta-an trials. *Cardiovasc Diabetol*. 2017;16(1):134.
15. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med 2007;356:2457–71.



References

1. Marso SP, Daniels GH, Brown-Frandsen K, et al. . Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016;375:311–22
2. Marso SP, Bain SC, Consoli A, et al. . Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2016;375:1834–44.
3. Holman RR, Bethel MA, Mentz RJ, et al. . Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. N Engl J Med 2017;377:1228–39
4. Gerstein HC, Colhoun HM, Dagenais GR, et al. . Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. Lancet 2019;394:121–30.
5. Husain M, Birkenfeld AL, Donsmark M, et al. . Oral Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2019;381:841–51
6. Sheahan KH, Wahlberg EA, Gilbert MP. An overview of GLP-1 agonists and recent cardiovascular outcomes trials. *Postgrad Med J*. 2020;96(1133):156-161
7. White WB, Cannon CP, Heller SR, Nissen SE, Bergenstal RM, Bakris GL, Perez AT, Fleck PR, Mehta CR, Kupfer S, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med. 2013;369:1327–1335.
8. Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, Ohman P, Frederich R, Wiviott SD, Hoffman EB, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med. 2013;369:1317–1326
9. Green JB, Bethel MA, Armstrong PW, Buse JB, Engel SS, Garg J, Josse R, Kaufman KD, Koglin J, Korn S, et al. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2015;373:232–242
10. Rosenstock J, Perkovic V, Johansen OE, Cooper ME, Kahn SE, Marx N, Alexander JH, Pencina M, Toto RD, Wanner C, et al. Effect of Linagliptin vs placebo on major cardiovascular events in adults with type 2 diabetes and high cardiovascular and renal risk: the CARMELINA randomized clinical trial. JAMA. 2019;321:69–79
11. Santamarina M, Carlson CJ. Review of the cardiovascular safety of dipeptidyl peptidase-4 inhibitors and the clinical relevance of the CAROLINA trial. *BMC Cardiovasc Disord*. 2019;19(1):60.
12. Neal B, Perkovic V, Mahaffey KW et al (2017) Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 377:644–657
13. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. *N Engl J Med*. 2019;380(24):2295-2306. doi:10.1056/NEJMoa1811744
14. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med*. 2015;373(22):2117-2128.
15. *Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2018;380:347-357.*
16. *McMurray et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med. 2019;*381:1995-2008



THANK YOU

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