UNDERSTANDING DIABETES CARDIOVASCULAR OUTCOME TRIALS

A New Kind of Information

David Doriguzzi, PA-C

OBJECTIVES

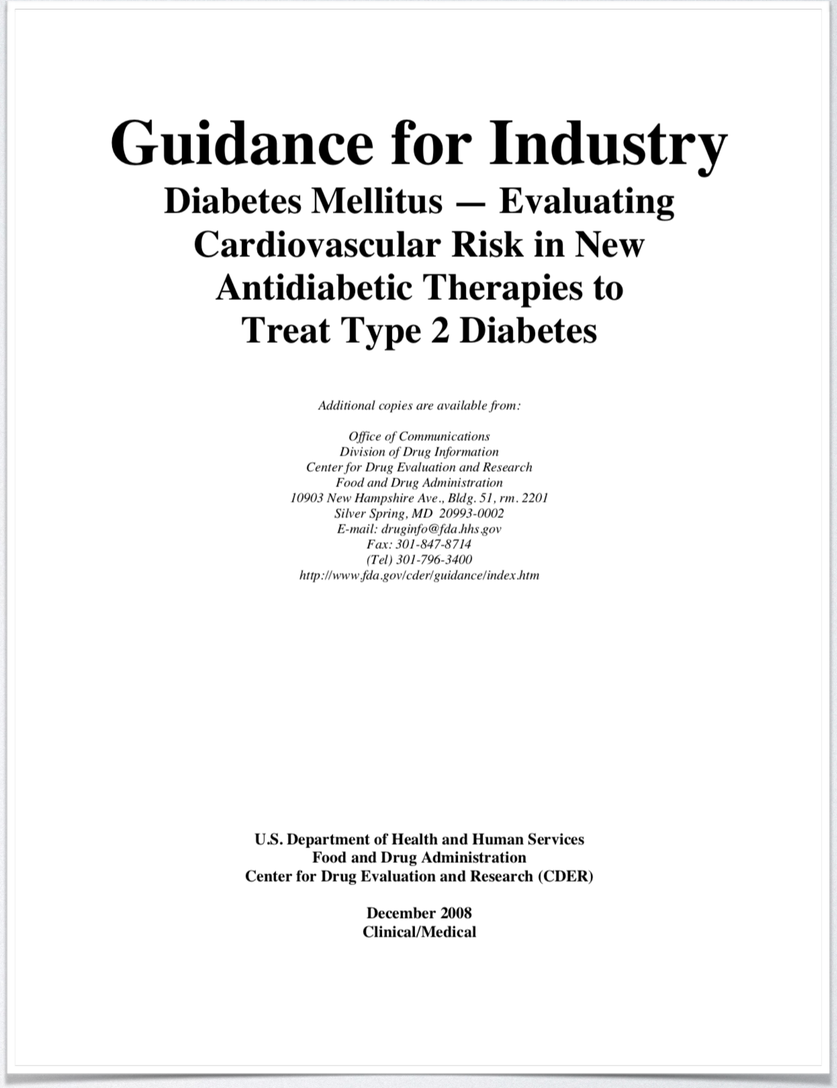
- To understand the purpose of Diabetes Cardiovascular Outcomes Trials (CVOTs)
- To have a general familiarity with the results of recent CVOTs
- To understand how CVOTs for similar drugs compare and contrast in design
- To recognize the relevance of CVOT findings in everyday clinical practice
- To understand the place of CVOT findings in recommended diabetes treatment guidelines
- To understand where future research is needed in Diabetes Cardiovascular Safety

DISCLOSURES

- Presenter serves as a speaker for Janssen Pharmaceuticals and Novo Nordisk
- Presenter served as a sub-Investigator on the SUSTAIN-6, DEVOTE, PIONEER-6, HARMONY, SELECT, and SOUL clinical trials (as an employee of the research site, without any direct compensation from the pharmaceutical sponsors)

BACKGROUND

- In December 2008, FDA issued guidance regarding new expectations to be placed on pharmaceutical developers
- Guidelines were established in response to concerns about potential increased CV risk with certain approved DM drugs, particularly rosiglitazone (Avandia)



Guidance for Industry

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

Additional copies are available from:

Office of Communications
Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 51, rm. 2201
Silver Spring, MD 20993-0002
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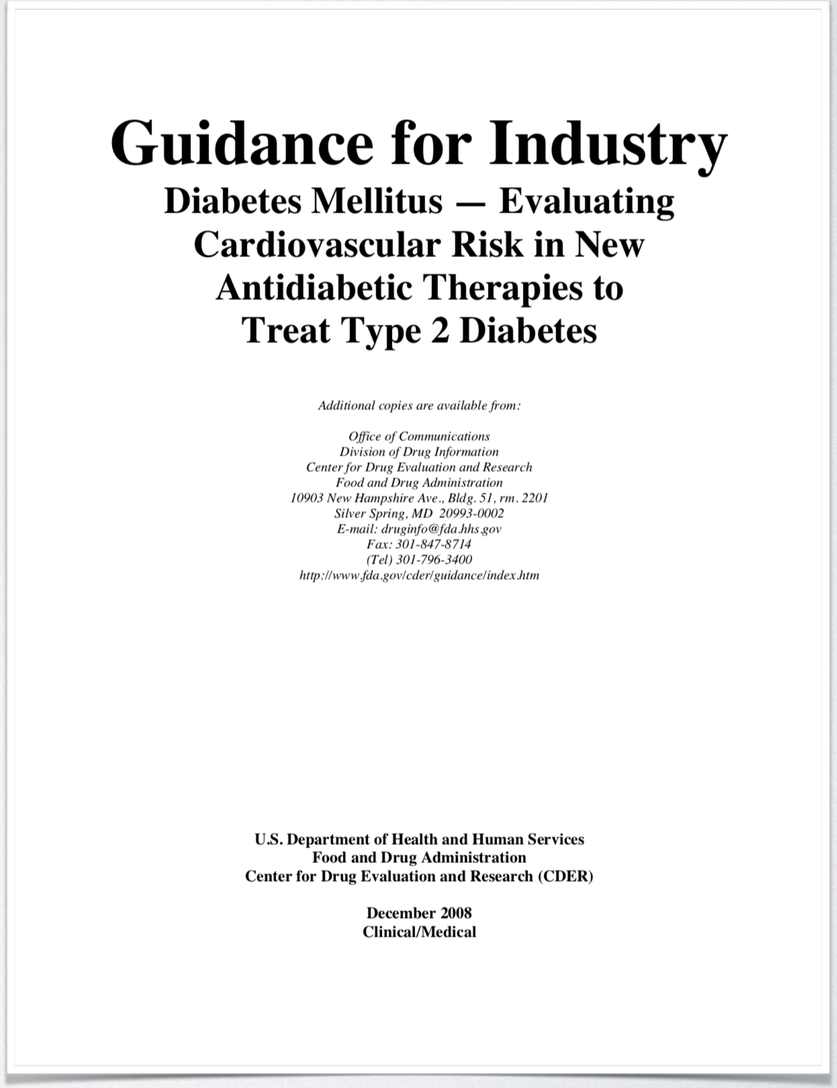
Fax: 301-847-8714
(Tel) 301-796-3400
http://www.fda.gov/cder/guidance/index.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

December 2008
Clinical/Medical

BACKGROUND

- Pharmaceutical companies would have to show that new drugs pose no significantly increased cardiovascular risk
- Guidelines on how to do this are both detailed and a bit non-specific
- Recommendations are a ***suggestion*** and not legally binding



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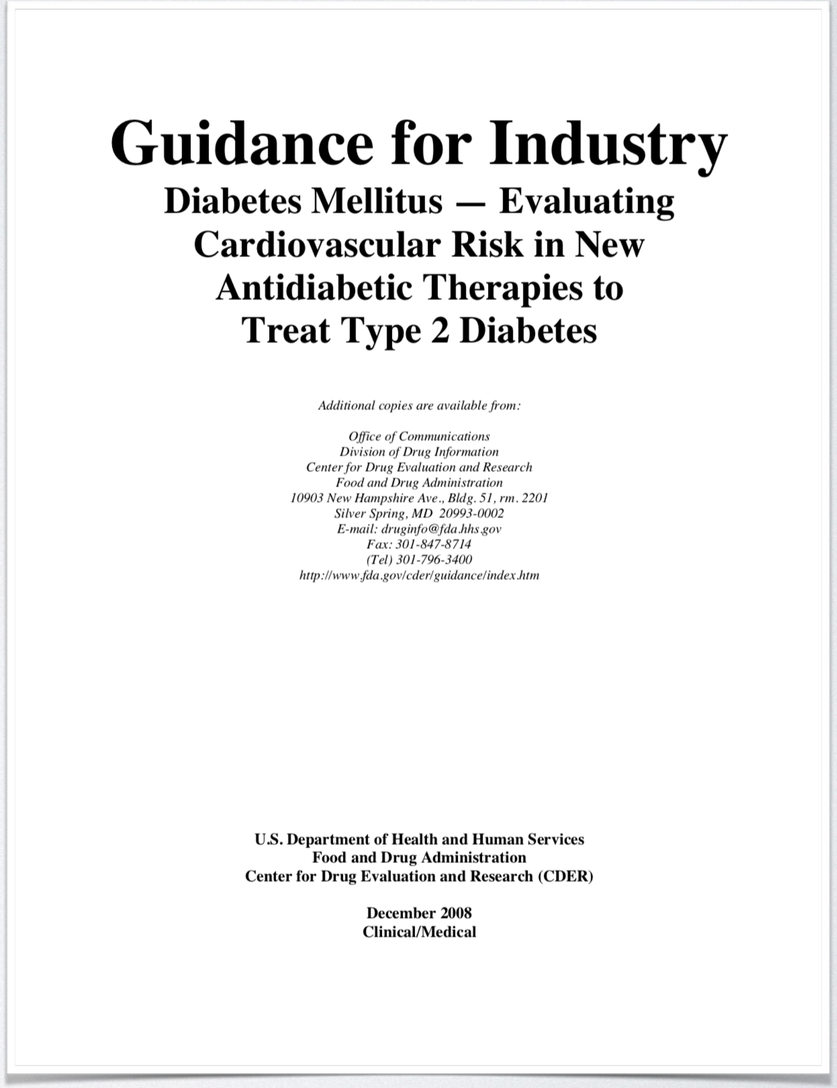
December 2008
Clinical/Medical

BACKGROUND

- Could be accomplished by meta-analysis of all phase 2 & 3 trials (if sufficient data available)
- If meta-analysis not feasible, company must perform a standalone Cardiovascular Outcomes Trial
- If non-inferiority is met, trial can then test for superiority
- Some CVOT structure specifics are not mandated



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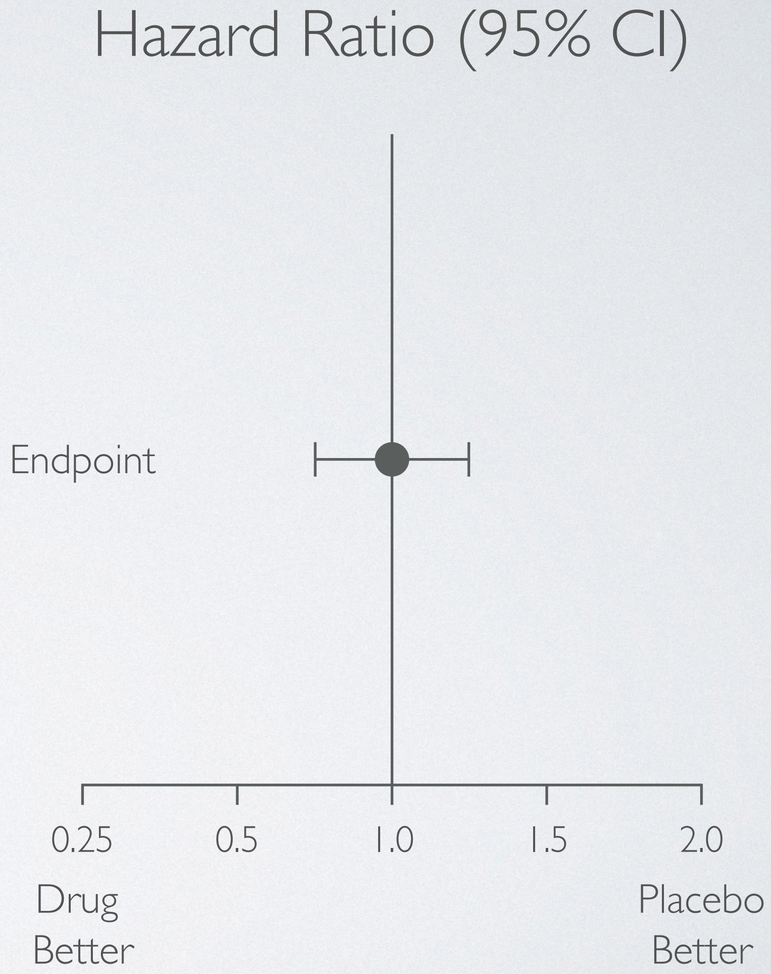
December 2008
Clinical/Medical

CVOT STRUCTURE

- CVOTs recruit large numbers of high cardiovascular risk patients who are likely to experience cardiovascular events in the upcoming years
- Subjects are assigned to placebo/standard of care or active study drug in addition to Standard of Care diabetes management

CVOT STRUCTURE

- CV events are monitored over the following years until sufficient events are captured to show the upper end of a 2-sided 95% confidence interval of the estimated hazard ratio is <1.8 (most studies set 1.3 as the target)
- Monitored CV events must include CV death, non-fatal MI, and non-fatal stroke
  - Can also include other endpoints such a hospitalization for HF, acute coronary syndrome, or revascularization procedures (bypass, stenting)



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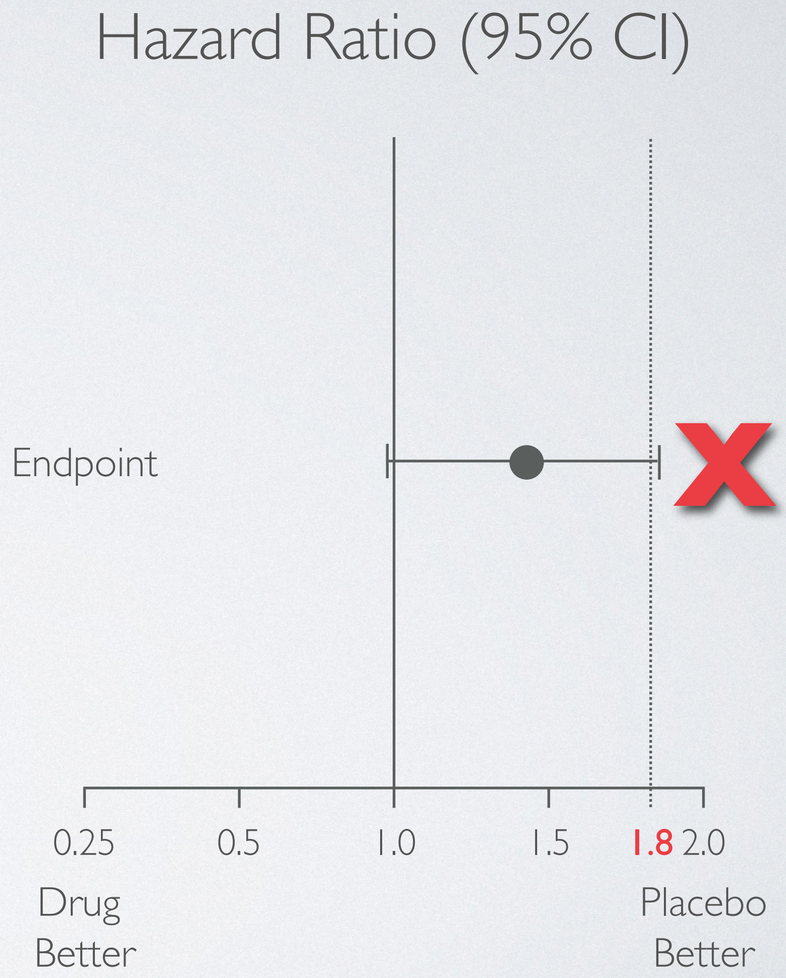


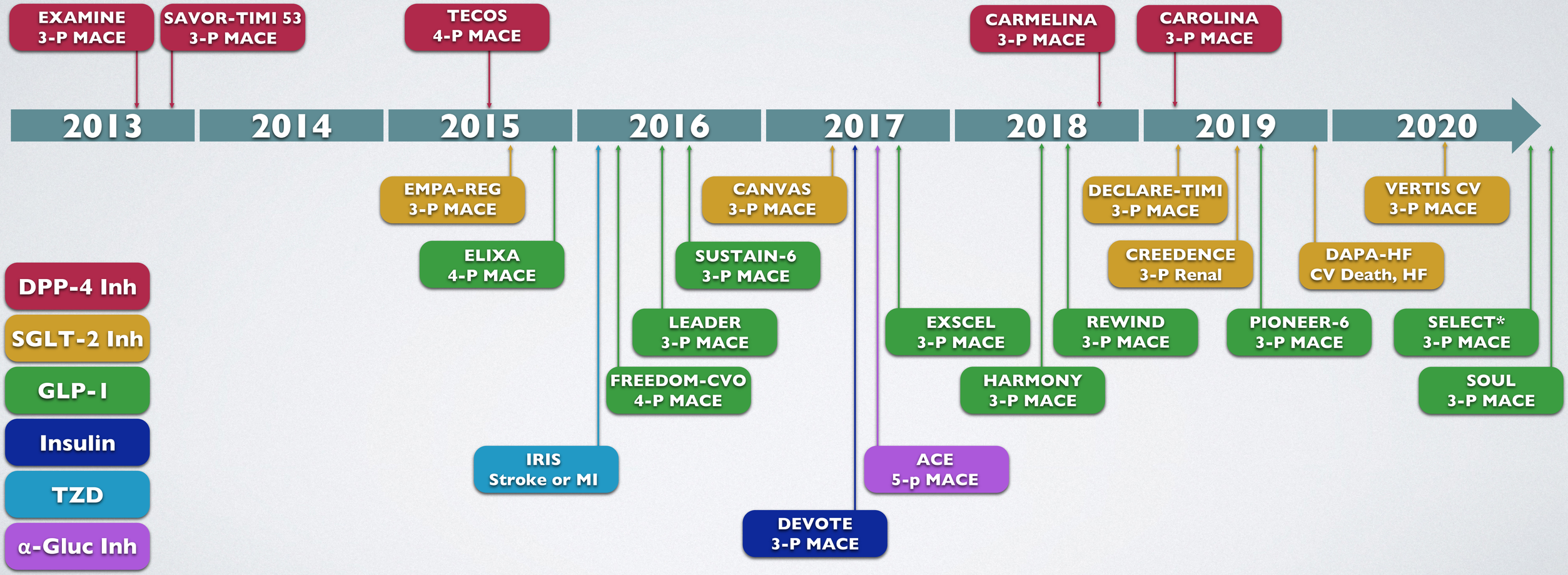
3-POINT MACE

- Large numbers of adjudicated CV events are needed to achieve a 95% confidence interval. (Usually >600 events)

- To allow a reasonable duration of the study AND collect sufficient data, most trials evaluate the 3-point Major Adverse Cardiovascular Event (MACE), which is the composite of
    1. Cardiovascular Death
    2. Non-Fatal Myocardial Infarction
    3. Non-Fatal Stroke

    - Additional endpoints such as unstable angina, HF hospitalization, etc. can be added at the discretion of the sponsor

CVOT TIMELINE



*Cardiovascular outcomes with Semaglutide in Obese patients with Cardiovascular Disease. Not a Diabetes study.

COMPARING STUDIES

STUDY A

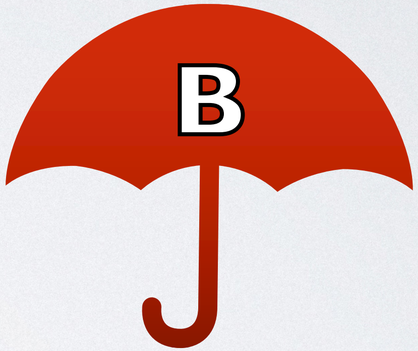
Umbrella A vs Placebo

90% reduction in wetness compared to placebo

Study conducted in Seattle, WA

STUDY B

Umbrella B vs Placebo



Non-Inferior to placebo

Study conducted in Palm Springs, CA

DPP-IV INHIBITORS

DPP-IV INHIBITORS

Five studies have been performed:

- Alogliptan (Nesina) - EXAMINE
- Saxagliptan (Onglyza) - SAVOR-TIMI 53
- Sitagliptan (Januvia) - TECOS
- Linagliptan (Tradjenta) - CARMELINA & CAROLINA

DPP-IV INHIBITORS

EXAMINE

ALOGLIPTAN (NESINA)

Patients studied -	Established CVD - Acute ACS in past 15-90 d (n=5,380)
Duration-	Median 1.5 years
Primary Endpoint-	3-point MACE
Secondary Endpoint-	4-point MACE (revascularization 2° to unstable angina)
Study Goal-	Demonstrate Non-Inferiority, Consider Superiority

N Engl J Med 2013;369:1327-1335.

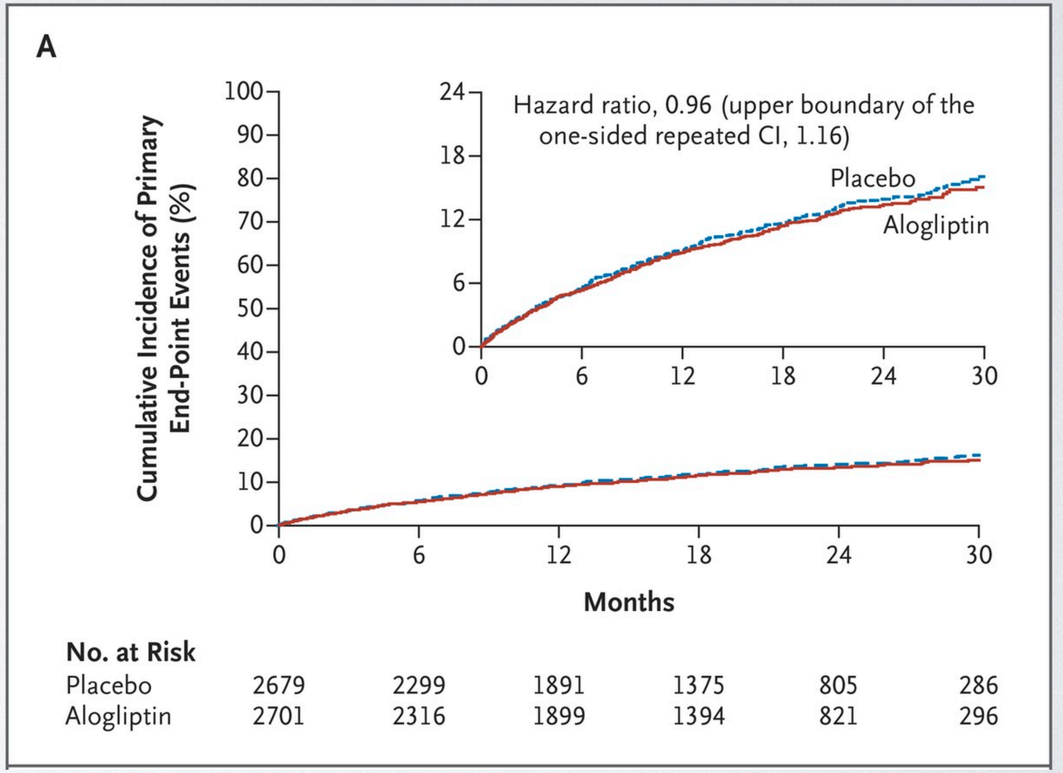
DPP-IV INHIBITORS

EXAMINE

ALOGLIPTAN (NESINA)

Key Findings-

- Alogliptan is non-inferior to placebo
- Superiority not demonstrated



N Engl J Med 2013;369:1327-1335.

DPP-IV INHIBITORS

SAVOR-TIMI 53

SAXAGLIPTAN (ONGLYZA)

Patients studied -	Established CVD or CV risk factors CVD(n=16,492)
Duration-	Median 2.1 years
Primary Endpoint-	3-point MACE
Secondary Endpoint-	4-point MACE, coronary revascularization, unstable angina
Study Goal-	Demonstrate Superiority, consider non-inferiority

N Engl J Med 2013;369:1317-1326.

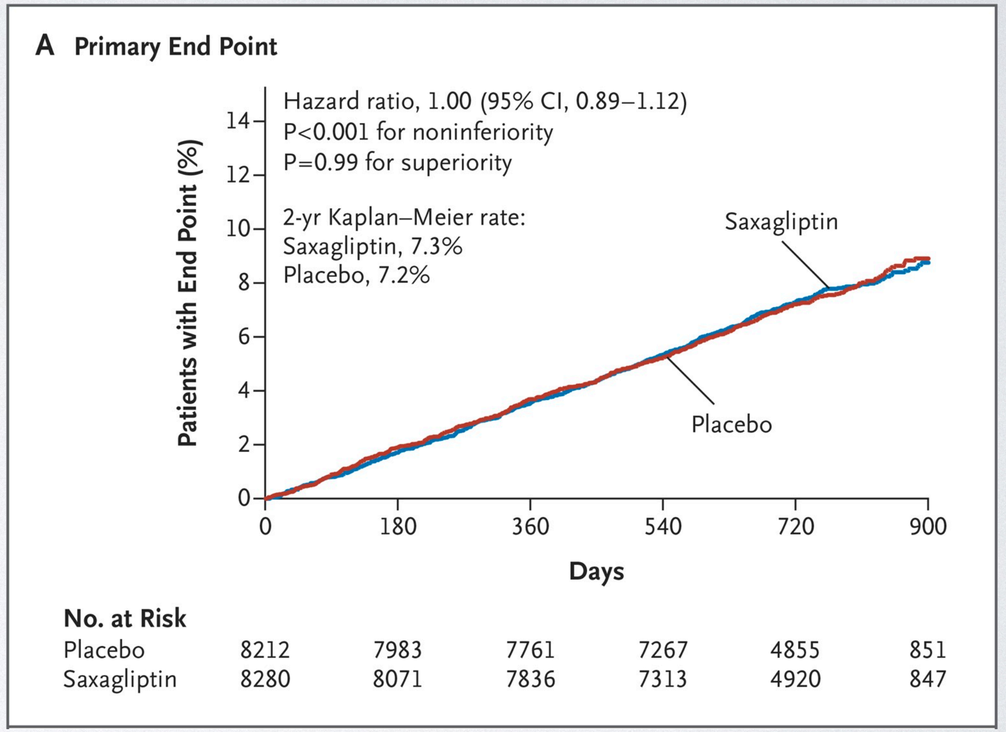
DPP-IV INHIBITORS

SAVOR-TIMI 53

SAXAGLIPTAN (ONGLYZA)

Key Findings-

- Superiority not demonstrated
- Saxagliptan is Non-inferior to placebo
- Statistically significant increase in hospitalization for Heart Failure (HR 1.27)



N Engl J Med 2013;369:1317-1326.

DPP-IV INHIBITORS

TECOS

SITAGLIPTAN (JANUVIA)

Patients studied -	Established CVD (n=14,671)
Duration-	Median 3.0 years
Primary Endpoint-	4-point MACE (added unstable angina)
Secondary Endpoints-	MI, Stroke, CV Death, Hosp for HF, Death from any cause
Study Goal-	Demonstrate Non-Inferiority, Consider Superiority

N Engl J Med 2015;373:232-242.

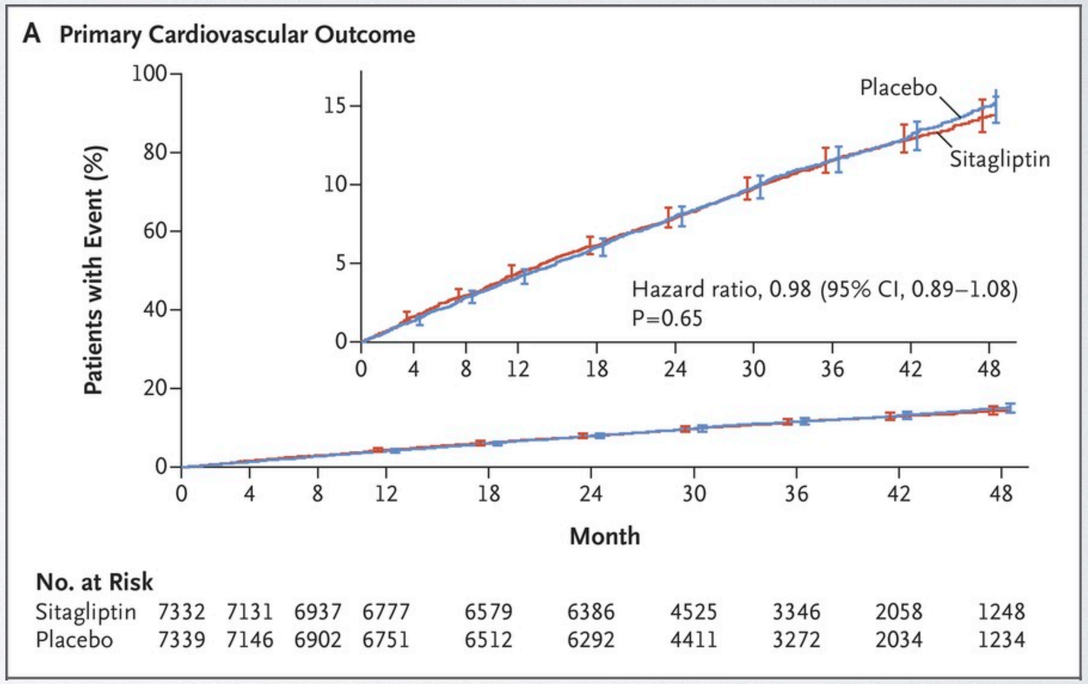
DPP-IV INHIBITORS

TECOS

SITAGLIPTAN (JANUVIA)

Key Findings-

- Sitagliptan is non-inferior to placebo
- Superiority not demonstrated
- No significant HF risk (HR 1.0)



N Engl J Med 2015;373:232-242.

DPP-IV INHIBITORS

CAROLINA

LINAGLIPTAN (TRADJENTA) VS GLIMEPIRIDE

Patients studied -	CV risk (n=6,033)
Duration-	Median 6 years
Endpoint-	3-point MACE
Study Goal-	Demonstrate Non-Inferiority
Outcome-	Linagliptan non-inferior to glimepiride

JAMA 2019;322(12):1155-1166.

DPP-IV INHIBITORS

CARMELINA

LINAGLIPTAN (TRADJENTA) VS PLACEBO

Patients studied -	High CV risk and Renal risk (n=6,991)
Duration-	Median 2.2 years
Endpoint-	3-point MACE (Secondary endpoint of renal safety)
Study Goal-	Demonstrate Non-Inferiority
Outcome-	Linagliptan is non-inferior for CV and kidney safety

JAMA 2019;321(1):69-79.

DPP-IV INHIBITORS SUMMARY

- All available DPP-IV inhibitors have been generally shown not to increase cardiovascular risk
    - Increased risk of hospitalization for heart failure with saxagliptin (Onglyza)
        - Non-significant outcomes in other studies may suggest HF signal for other DPP-IV Inhibitors

ALPHA GLUCOSIDASE INHIBITORS

ACARBOSE CARDIOVASCULAR EVALUATION (**ACE**)TRIAL

Patients studied -	Established CVD (n=6,522)
Duration-	Median 5.0 years
Endpoint-	5-point MACE (added HF & unstable angina)
Study Goal-	Demonstrate superiority (reduced events)
Outcome-	Not superior, but non-inferior to placebo

Lancet Diab Endo 2017 Nov;5(11):877-886

THIAZOLIDINEDIONES (TZD)

TZD
IRIS - PIOGLITAZONE (ACTOS)

Patients studied -	Insulin resistant (not DM) with recent stroke or TIA
Number of participants-	3,876
Duration-	Median 4.8 years
Endpoint-	MI or Stroke (fatal or nonfatal)
Study Goal-	Demonstrate risk reduction
Outcome-	24% reduction with pioglitazone vs placebo

N Engl J Med 2016;374:1321-1331.

INSULIN

INSULIN GLARGINE (LANTUS)
ORIGIN

Patients studied -	CV Risk (n=12,537)
Duration-	Median 6.2 years
Endpoint-	5-Point MACE
Study Goal-	Demonstrate Superiority
Outcome-	Glargine non-inferior to standard of care

N Engl J Med 2012;367:319-328.

INSULIN DEGLUDEC (TRESIBA)
DEVOTE

Patients studied -	Established CVD (n=7,567)
Duration-	Median 2 years
Endpoint-	3-Point MACE
Secondary Endpoint-	Severe Hypoglycemia
Study Goal-	CV Non-Inferiority, Hypoglycemia Superiority

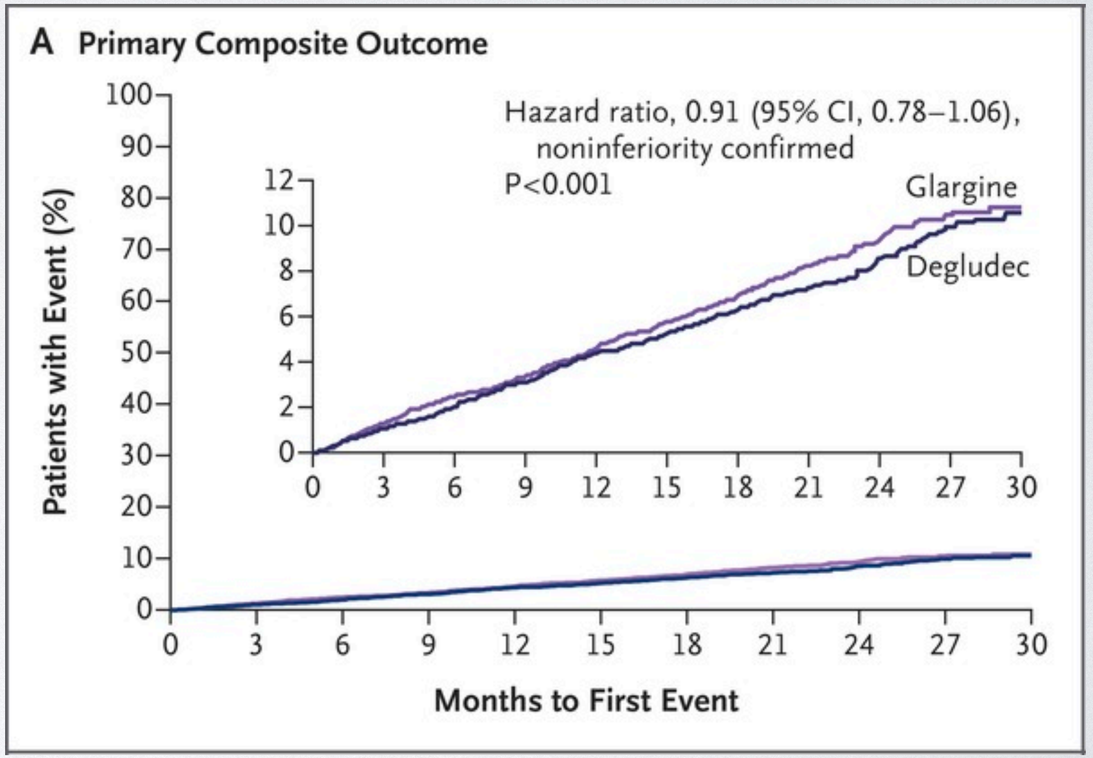
N Engl J Med 2017;377:723-32.

INSULIN DEGLUDEC (TRESIBA)
DEVOTE

Key Findings-

- Degludec is non-inferior to Glargine for CV Risk
- 40% risk reduction for severe hypoglycemia compared to Glargine

3-Point MACE



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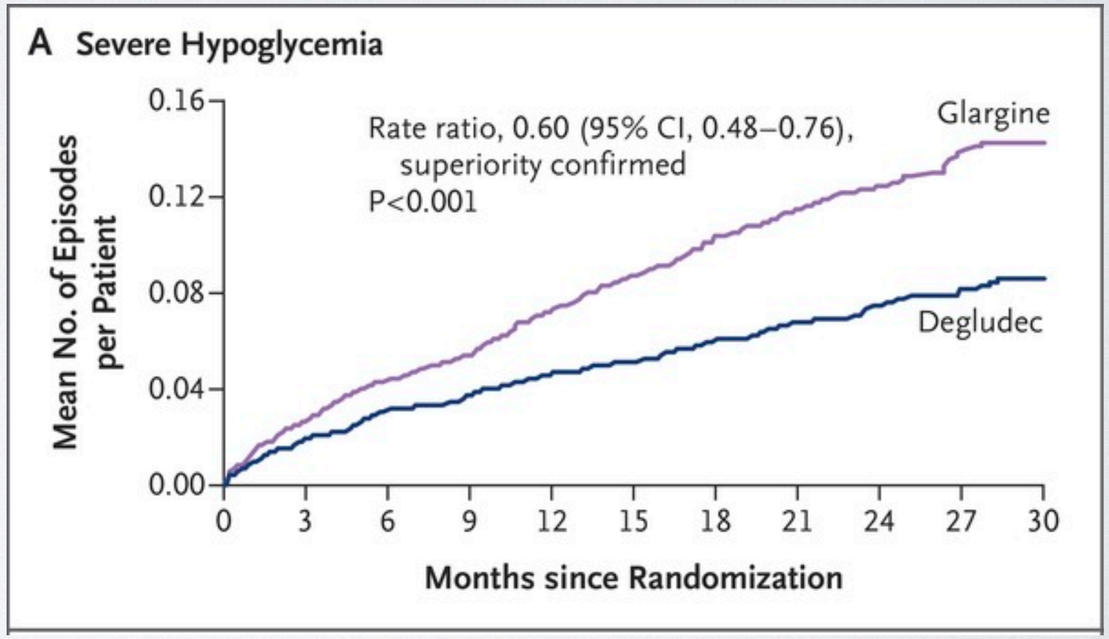
Severe Hypoglycemia



N Engl J Med 2017;377:723-32.

SGLT-2 INHIBITORS

SGLT-2 INHIBITORS

Six studies have been performed:

- Empagliflozin (Jardiance) - EMPA-REG OUTCOMES
- Canagliflozin (Invokana) - CANVAS, CREDENCE
- Dapagliflozin (Farxiga) - DECLARE-TIMI 58, DAPA-HF
- Ertrugliflozin (Steglatro) - VERTIS CV

SGLT-2 INHIBITORS

EMPA-REG

EMPAGLIFLOZIN (JARDIANCE)

Patients studied -	Established CVD (n=7,020)
Duration-	Median 3.1 years
Endpoint-	3-Point MACE
Secondary Endpoint-	4-point MACE (Hosp. For Unstable Angina)
Study Goal-	Demonstrate Non-Inferiority, Superiority

N Engl J Med 2015; 373:2117-2128

SGLT-2 INHIBITORS

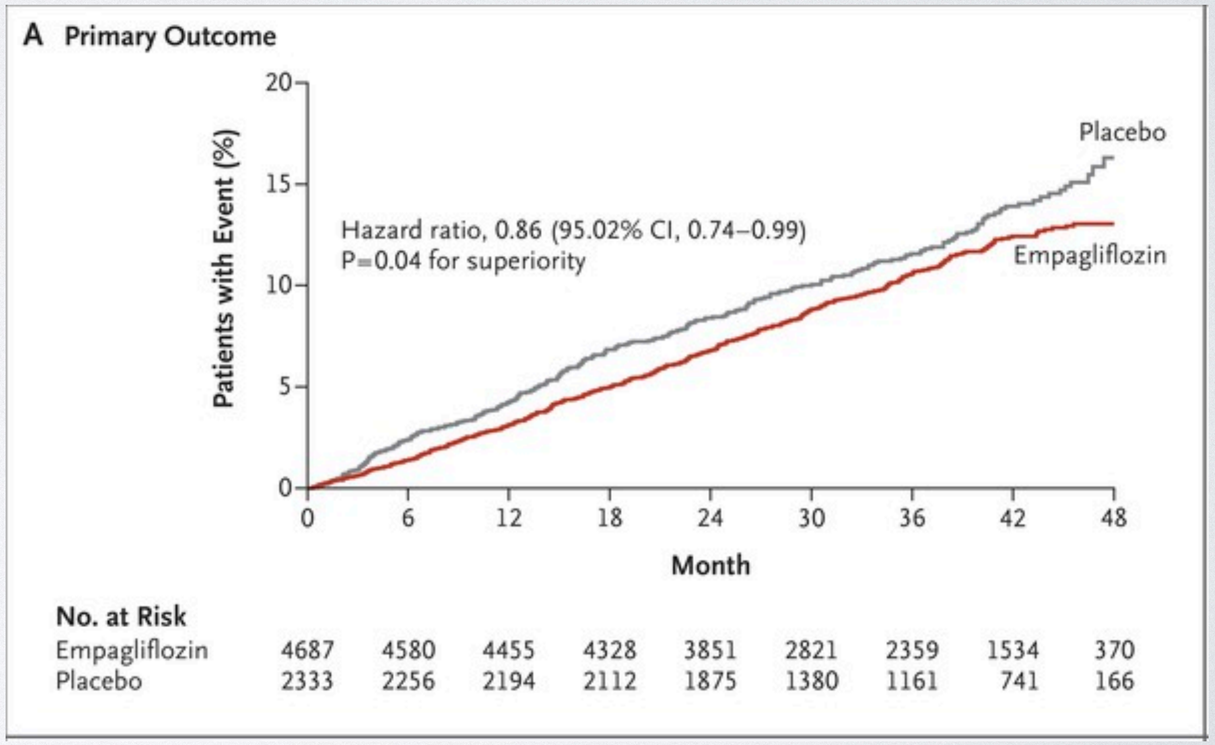
EMPA-REG

EMPAGLIFLOZIN (JARDIANCE)

Key Findings-

- 14% reduction in 3-P MACE
- 38% reduction in CV Death
- 32% reduction in All Cause Mortality
- 35% reduction in HF Hosp

3-Point MACE



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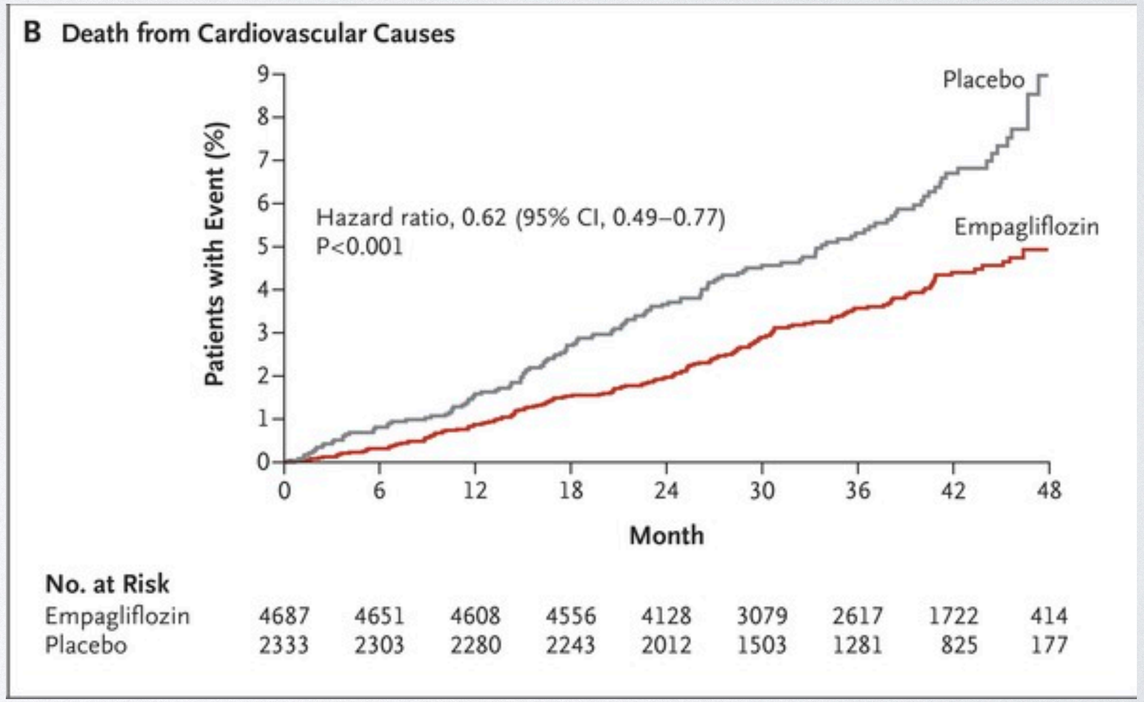
CV Death



N Engl J Med 2015; 373:2117-2128

SGLT-2 INHIBITORS

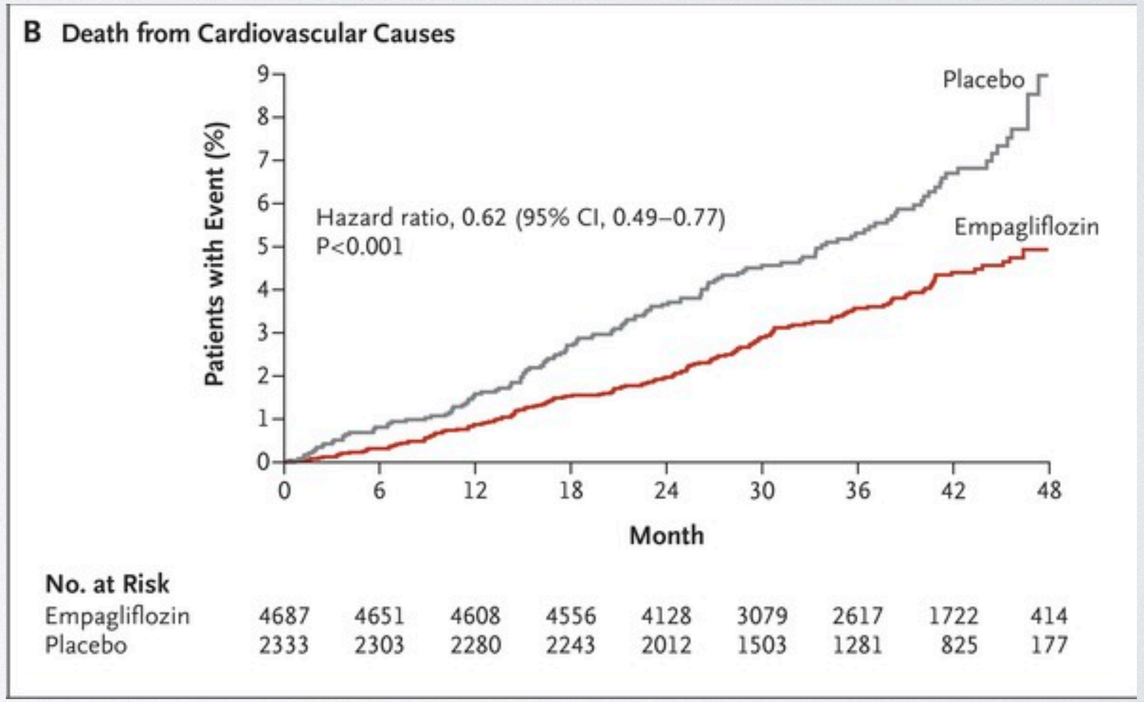
EMPA-REG

EMPAGLIFLOZIN (JARDIANCE)

Considerations

- First CVOT to show actual cardiovascular risk reduction, rather than non-inferiority to placebo
- EARLY protective effect (Kaplan-Meier curve separation after only a few months of treatment)

CV Death



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SGLT-2 INHIBITORS

CANVAS

CANAGLIFLOZIN (INVOKANA)

Patients studied -	Established CVD (n=10,142)
Duration-	Median 2.4 years
Endpoint-	3-Point MACE
Secondary Endpoint-	Renal Composite, Death any cause, HF Hosp
Study Goal-	Demonstrate Non-Inferiority, Superiority

N Engl J Med 2017;377:644-657.

SGLT-2 INHIBITORS

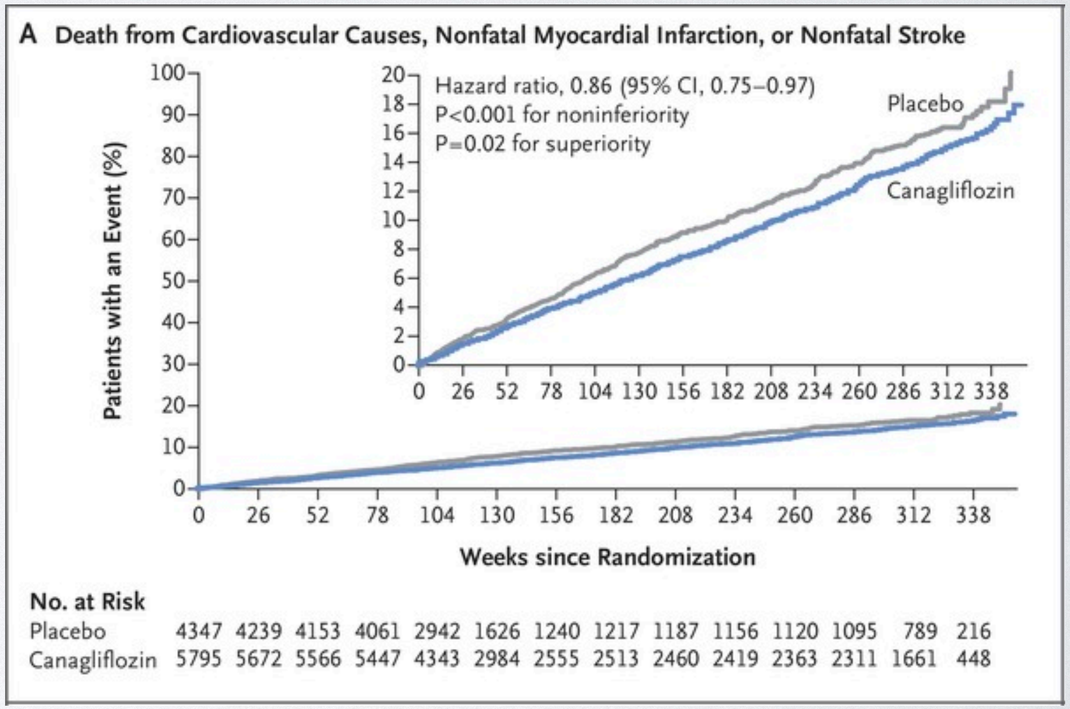
CANVAS

CANAGLIFLOZIN (INVOKANA)

Key Findings-

- 14% reduction in 3-P MACE
- 33% reduction in HF Hosp
- 27% reduction in Composite of 40% eGFR reduction, ESRD, Renal Death

3-Point MACE



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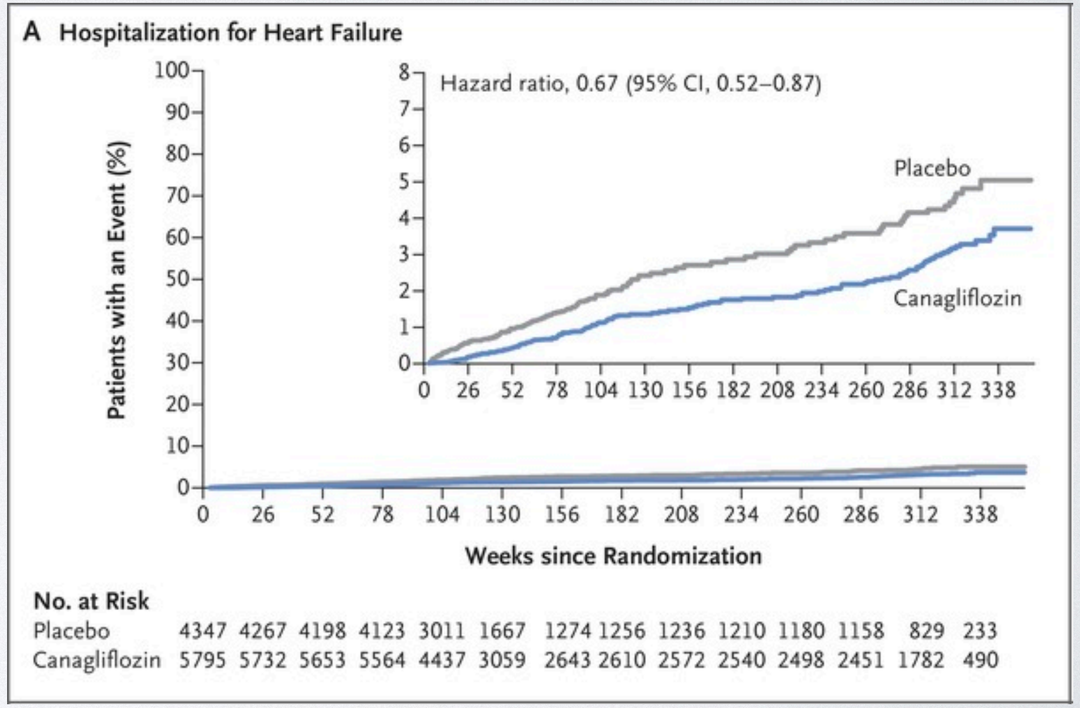
Heart Failure Hospitalization



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SGLT-2 INHIBITORS

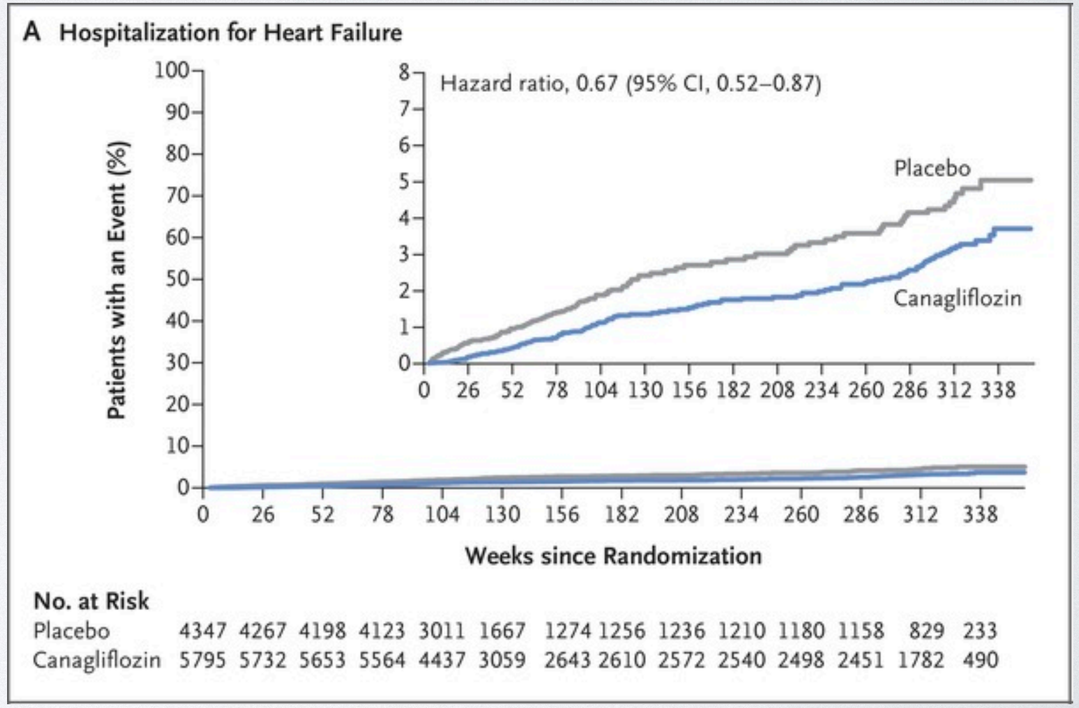
CANVAS

CANAGLIFLOZIN (INVOKANA)

Considerations

- Statistically significant increase in amputation of the lower extremity observed (6.3 vs 3.4 per 1000 pt years)
- Incidence of amputation was similar to that observed in the EMPA-REG Trial (6.5 per 1000 pt years), but the placebo group was lower in CANVAS, accounting for the statistical significance

Heart Failure Hospitalization



N Engl J Med 2017;377:644-657.

SGLT-2 INHIBITORS

CREDENCE

CANAGLIFLOZIN (INVOKANA)

Patients studied -	Established CKD (n=4,401), 50.4% also had CVD
Duration-	Median 2.62 years
Primary Endpoint-	Composite ESRD, 2x serum Creat, Renal or CV Death
Secondary Endpoint-	Composite CV Death or HF, 3-Point MACE, et al
Study Goal-	Demonstrate Superiority

N Engl J Med 2019; 380:2295-2306

SGLT-2 INHIBITORS

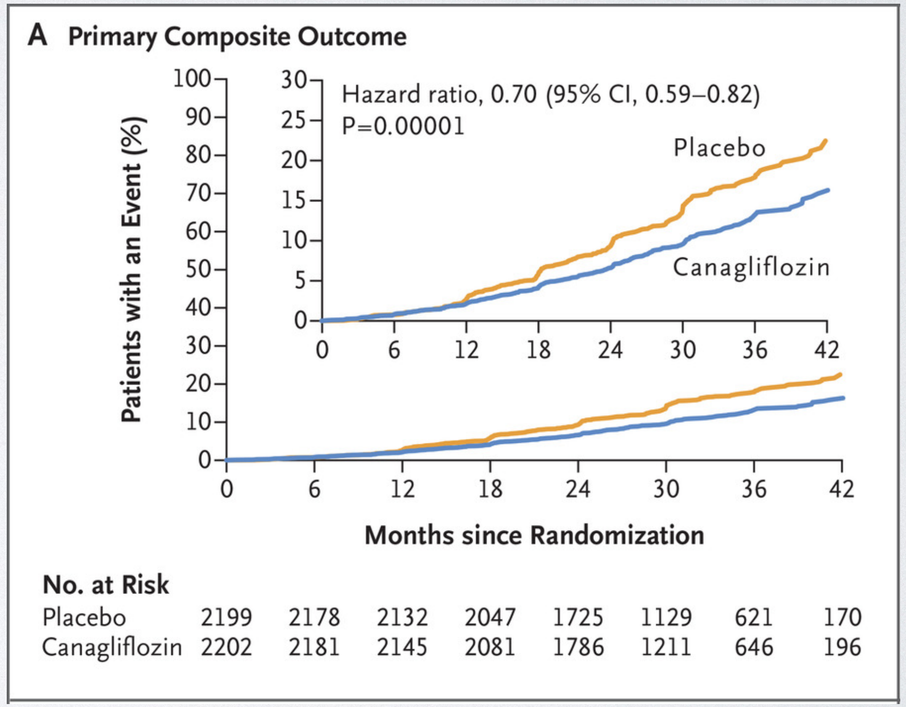
CREDENCE

CANAGLIFLOZIN (INVOKANA)

Key Findings-

- Study stopped early due to overwhelming benefit in the Canagliflozin group - 30% reduction in relative risk
- 20% reduction in 3-Point MACE
- 39% reduction in HF Hosp

Renal Composite



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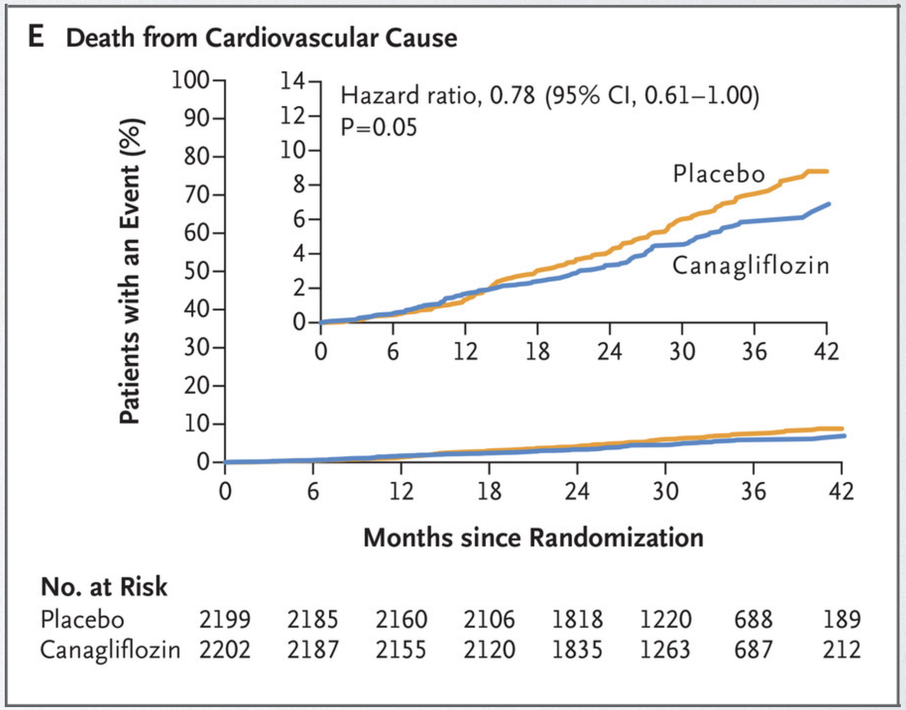
CV Death



N Engl J Med 2019; 380:2295-2306

SGLT-2 INHIBITORS

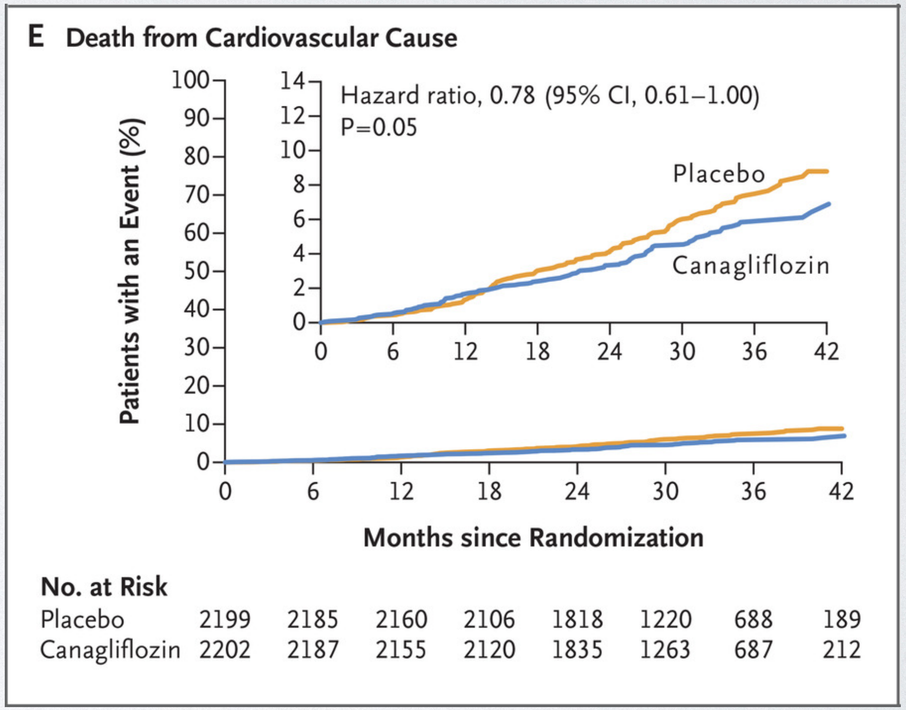
CREDENCE

CANAGLIFLOZIN (INVOKANA)

Considerations

- No statistically significant increase in amputation was observed

CV Death



N Engl J Med 2019; 380:2295-2306

SGLT-2 INHIBITORS

DECLARE TIMI-58

DAPAGLIFLOZIN (FARXIGA)

Patients studied -	Established CVD or CV risk (n=17,276) ~60% without CVD
Duration-	Median 4.2 years
Primary Endpoint-	3-Point MACE, Comp. of CV Death & HF Hosp
Secondary Endpoint-	Renal Composite, Death from Any Cause
Study Goal-	Demonstrate Non-Inferiority, Superiority

N Engl J Med 2019;380:347–357.

SGLT-2 INHIBITORS

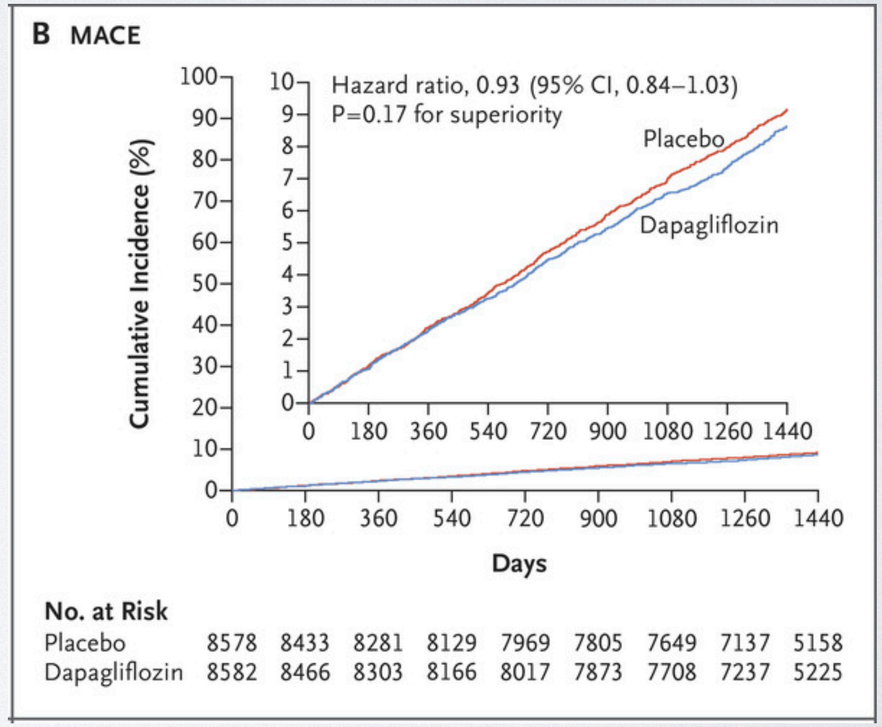
DECLARE TIMI-58

DAPAGLIFLOZIN (FARXIGA)

Key Findings-

- Non-inferior to placebo for 3-P MACE, but no significant reduction
- 27% reduction in HF Hosp.
- 24% reduction in renal composite

3-Point MACE



N Engl J Med 2019;380:347–357.

SGLT-2 INHIBITORS

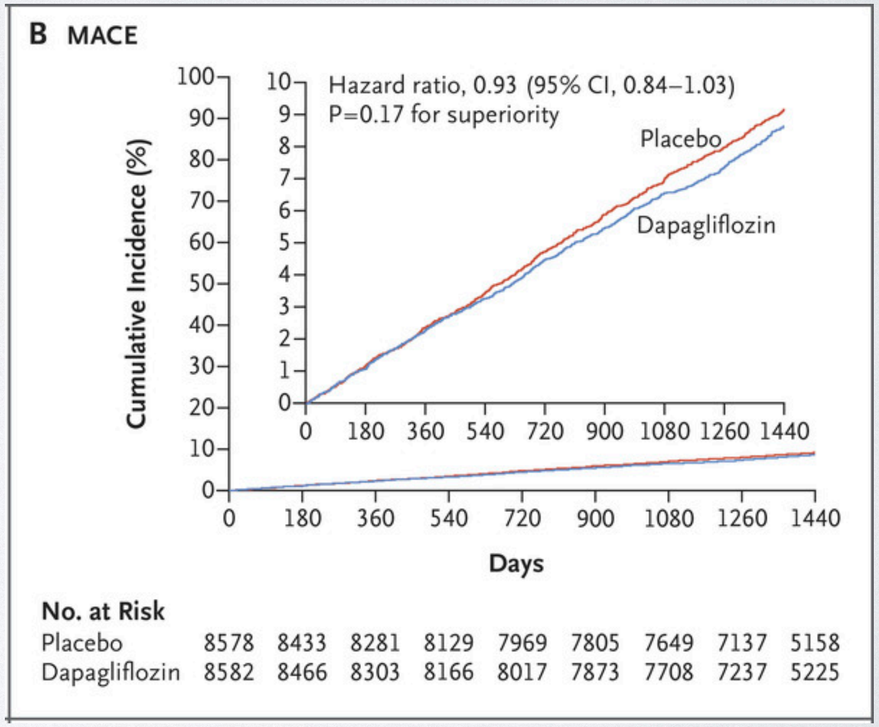
DECLARE TIMI-58

DAPAGLIFLOZIN (FARXIGA)

Considerations

- Only SGLT-2 CVOT to primarily include patients WITHOUT established cardiovascular disease
- Sub-analysis performed on the ~40% of subjects WITH cardiovascular disease also shown no statistically significant risk reduction

3-Point MACE



N Engl J Med 2019;380:347–357.

SGLT-2 INHIBITORS

DAPA-HF

DAPAGLIFLOZIN (FARXIGA)

Patients studied -	NYHA HF class II-IV (n=4,744) -With or Without Diabetes
Duration-	Median 1.5 years
Primary Endpoint-	Composite of Worsening HF or CV Death
Secondary Endpoint-	HF Hosp & CV Death, individually
Study Goal-	Demonstrate Non-Inferiority, Superiority

N Engl J Med 2019;381:1995-2008.

SGLT-2 INHIBITORS

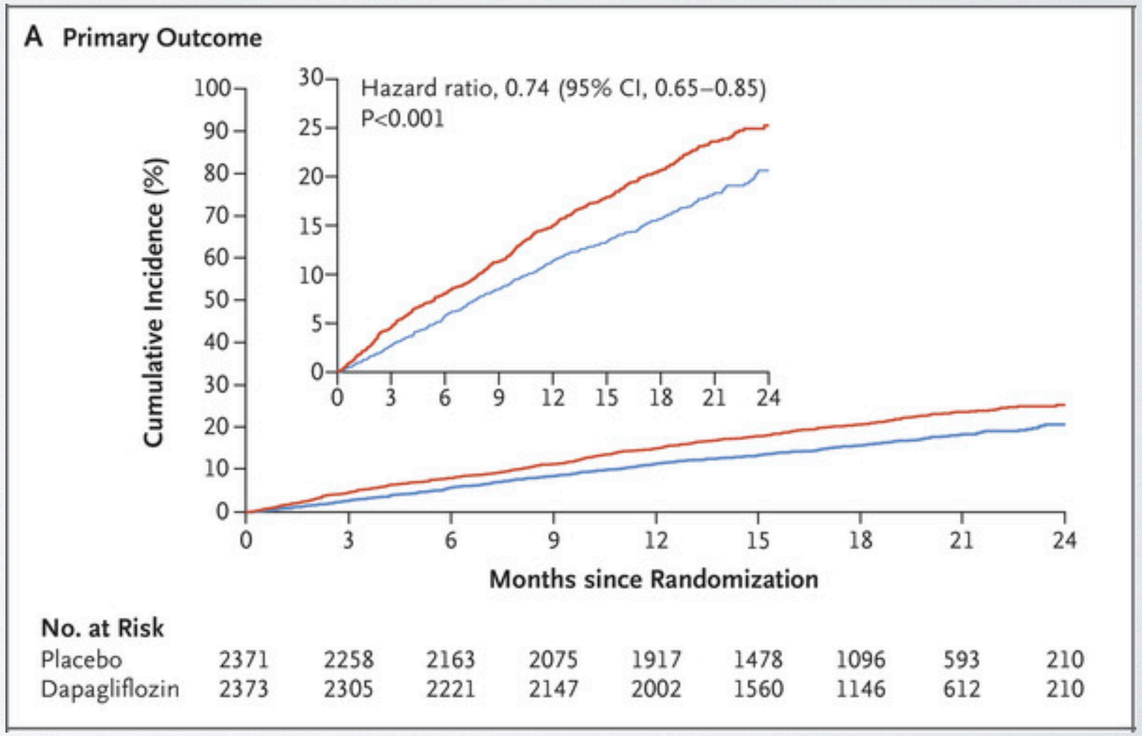
DAPA-HF

DAPAGLIFLOZIN (FARXIGA)

Key Findings-

- 26% reduction in Composite Outcome
- 30% reduction in HF Hosp.
- 18% reduction in CV Death
- 17% reduction in All-Cause Death

Worsening HF or CV Death



N Engl J Med 2019;381:1995-2008.

SGLT-2 INHIBITORS

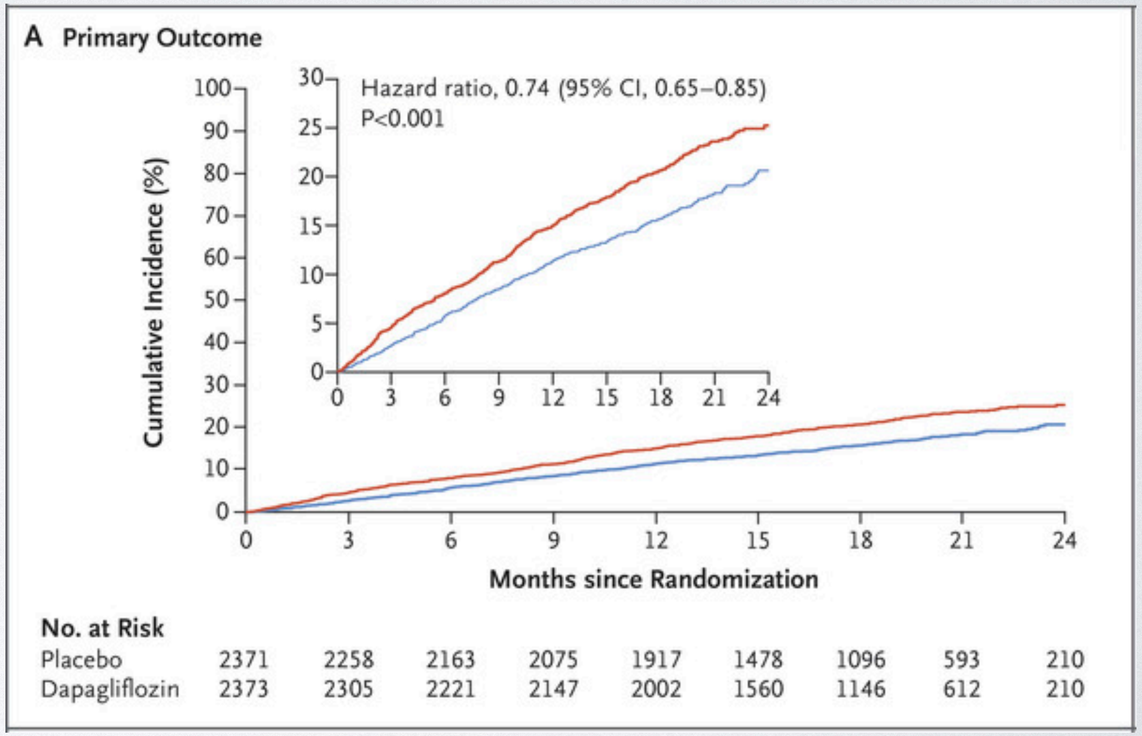
DAPA-HF

DAPAGLIFLOZIN (FARXIGA)

Considerations

- Risk reduction was similar for Diabetics and Non-Diabetics
- Risk reduction most noticeable in NYHE class II patients (much less risk reduction in class III-IV subjects), suggesting earlier intervention carries greater benefit

Worsening HF or CV Death



N Engl J Med 2019;381:1995-2008.

SGLT-2 INHIBITORS

VERTIS-CV

ERTUGLIFLOZIN (STEGLATRO)

Patients studied -	Established CVD (8,000)
Number of participants-	8,000
Duration-	Not yet reported
Endpoint-	3-Point MACE
Study Goal-	Demonstrate Non-Inferiority, Superiority
Outcome-	Not yet reported

SGLT-2 INHIBITORS SUMMARY

	CANVAS	CREDENCE	EMPA-REG	DECLARE	DAPA-HF
3-P MACE	Protective	Protective	Protective	Neutral	N/A
HF Hosp	Protective	Protective	Protective	Protective	Protective
CV Death or HF Hosp	Protective	Protective	Protective	Protective	Protective
> 40% decrease eGFR, ESRD, or Renal Death	Protective	Protective*	N/A	Protective	N/A
Death any cause	Neutral	Neutral	Protective	Neutral	Protective
Death CV cause	Neutral	Neutral	Protective	Neutral	Protective
Amputation	Increased	Neutral	N/A	Neutral	Neutral

*Actual endpoint was Doubling Serum Creatinine, ESRD, or Renal Death

GLP-1 AGONISTS

GLP-1 AGONISTS

Eight studies have been performed:

- Lixisenatide (Adlyxin) - ELIXA
- Liraglutide (Victoza) - LEADER
- Semaglutide (Ozempic) - SUSTAIN-6, PIONEER-6
- Exenatide weekly (Bydureon) - EXSCEL
- Implanted exenatide (ITCA 650) - FREEDOM CVO
- Albiglutide (Tanzeum) - HARMONY OUTCOMES
- Dulaglutide (Trulicity) - REWIND

GLP-1 AGONISTS

ELIXA

LIXISENATIDE (ADLYXIN)

Patients studied -	MI or Hosp. For Unstable Angina in prior 180 days (n=6,068)
Duration-	Median 2.1 years
Primary Endpoint-	4-Point MACE (3P + Unstable Angina)
Secondary Endpoints-	5-Point MACE (4P + HF), 6-Point (+ revasc.)
Study Goal-	Demonstrate Non-inferiority, Superiority

N Engl J Med 2015;373:2247–2257.

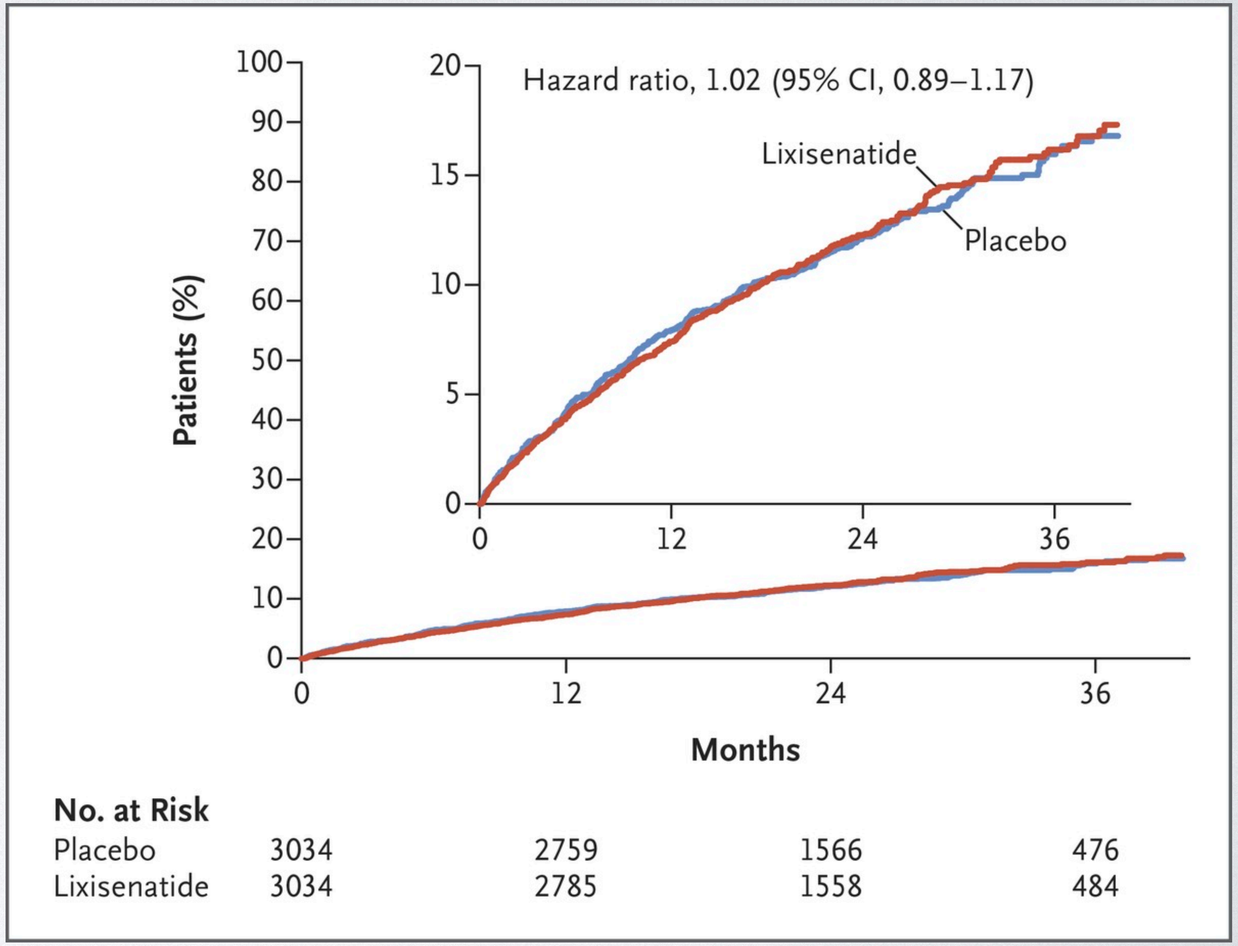
GLP-1 AGONISTS

ELIXA

LIXISENATIDE (ADLYXIN)

Key Findings-

- Non-inferior to placebo
- No significant reduction of risk for any CV outcome



N Engl J Med 2015;373:2247–2257.

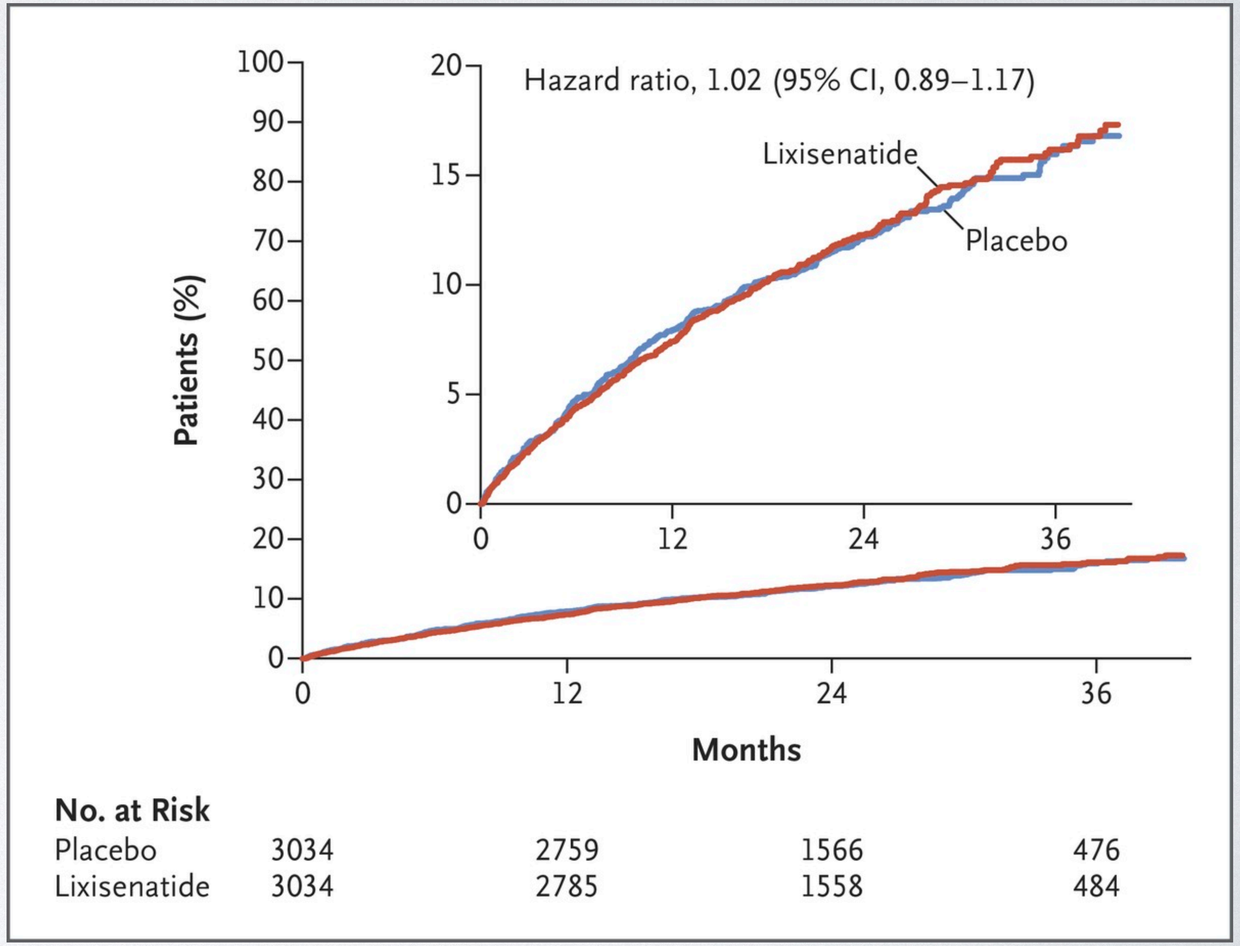
GLP-1 AGONISTS

ELIXA

LIXISENATIDE (ADLYXIN)

Considerations

- Evaluated only patients with ***recent*** acute coronary syndrome and did not include patients with chronic, established CVD or CV Risk
- Lixisenatide half life is 2-4 hours, compared to approx. 5 days in other available GLP-1 medications



N Engl J Med 2015;373:2247–2257.

GLP-1 AGONISTS

LEADER

LIRAGLUTIDE (VICTOZA)

Patients studied -	Established CVD or CV Risk (n = 9,340)
Duration-	Median 3.8 years
Primary Endpoint-	3-Point MACE
Secondary Endpoint-	5-Point MACE, Death Any Cause, neoplasms, et al
Study Goal-	Demonstrate Non-inferiority, Superiority

N Engl J Med 2016;375:311–322.

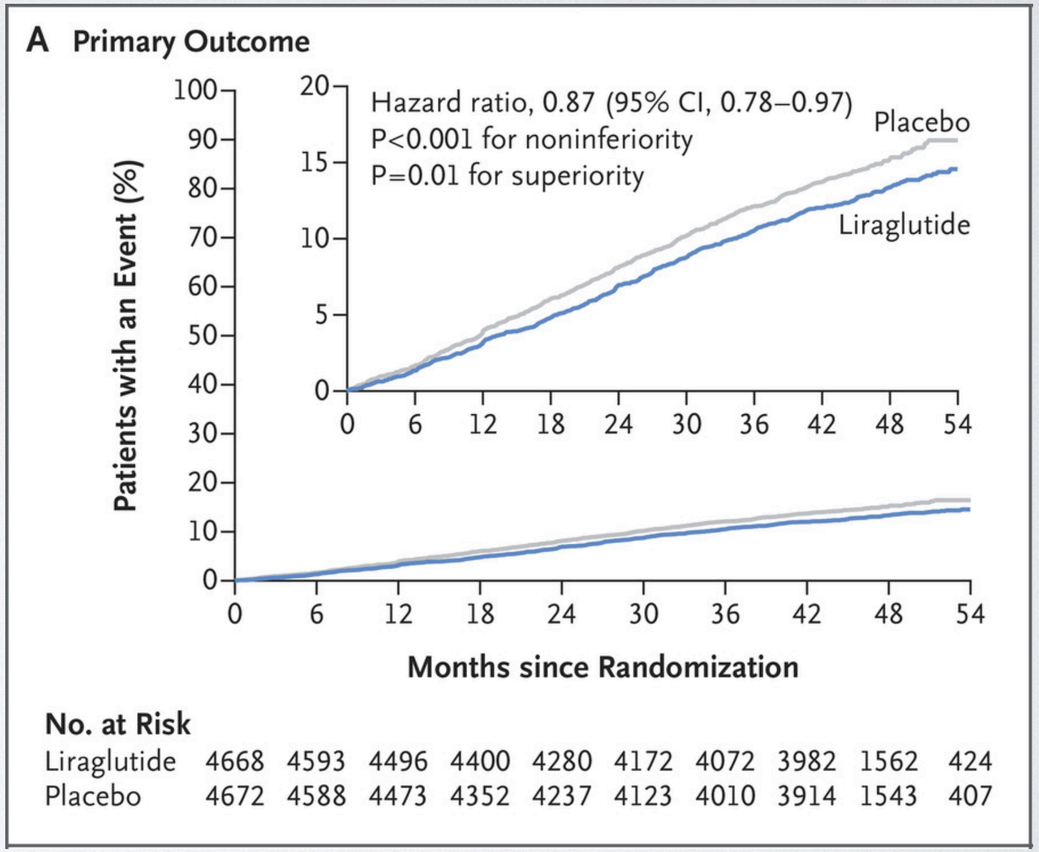
GLP-1 AGONISTS

LEADER

LIRAGLUTIDE (VICTOZA)

Key Findings-

- 13% reduction in 3-P MACE
- 22% reduction in CV Death
- 15% reduction in Death from Any Cause
- Numerical, but not statistically significant reduction in MI and Stroke



N Engl J Med 2016;375:311–322.

GLP-1 AGONISTS

SUSTAIN-6

SEMAGLUTIDE - INJECTED (OZEMPIC)

Patients studied -	Established CVD or CV Risk (n = 3,297)
Duration-	Median 2.1 years
Primary Endpoint-	3-Point MACE
Secondary Endpoint-	5-Point MACE, retinopathy, nephropathy
Study Goal-	Demonstrate Non-inferiority

N Engl J Med 2016;375:1834–1844.

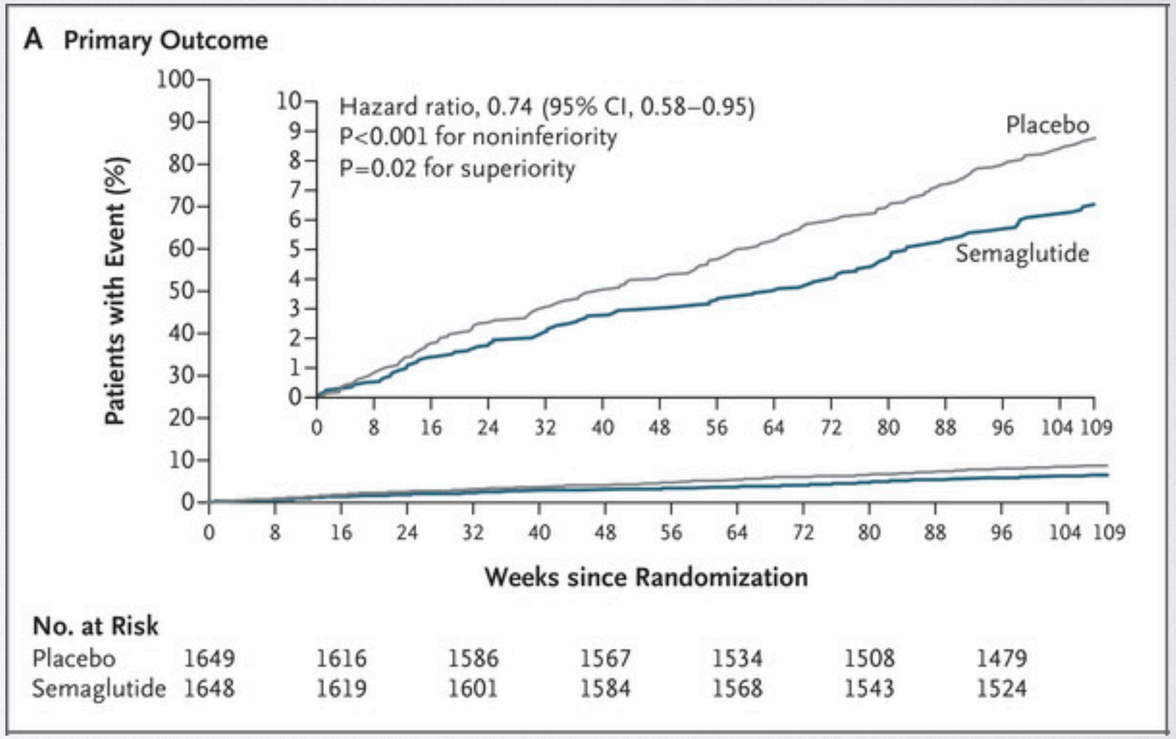
GLP-1 AGONISTS

SUSTAIN-6

SEMAGLUTIDE - INJECTED (OZEMPIC)

Key Findings-

- 26% reduction in 3-P MACE
- 39% reduction in Non-Fatal Stroke
- No significant decrease in CV Death
- Statistically significant increase in retinopathy complications (76%)
- Superiority analysis was not pre-specified



N Engl J Med 2016;375:1834–1844.

GLP-1 AGONISTS

SUSTAIN-6

SEMAGLUTIDE - INJECTED (OZEMPIC)

Key Findings-

- 26% reduction in 3-P MACE
- 39% reduction in Non-Fatal Stroke
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- Statistically significant increase in retinopathy complications (76%)
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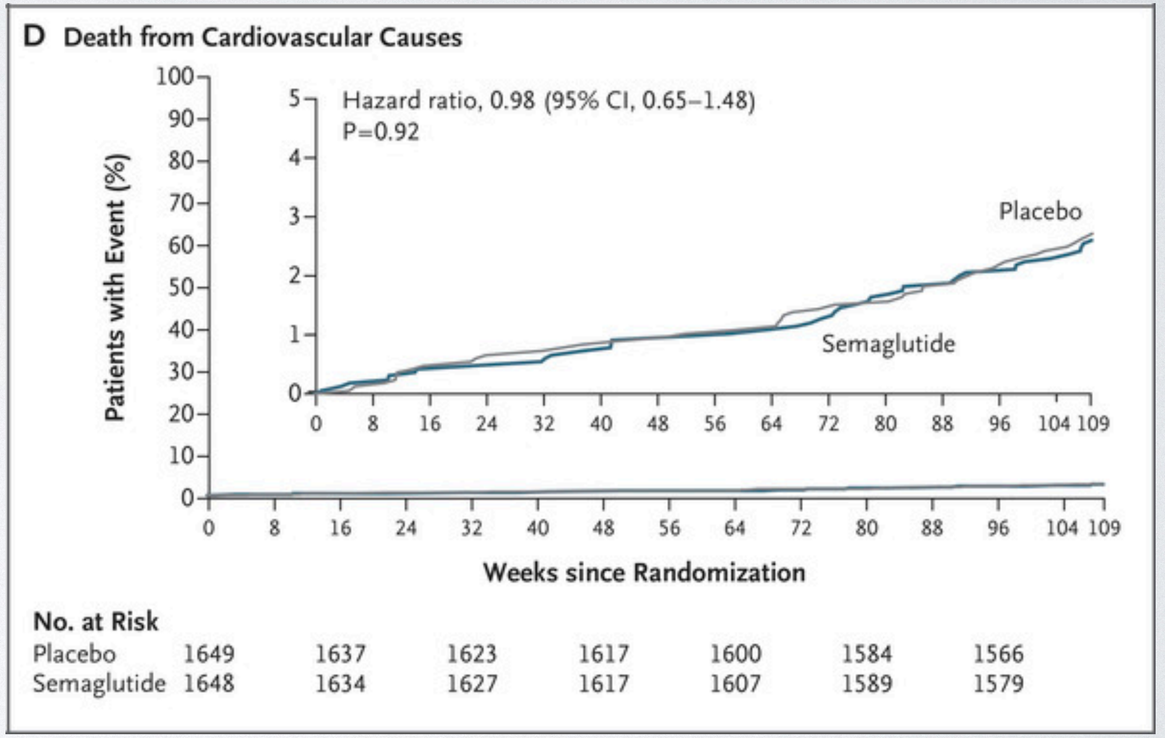


N Engl J Med 2016;375:1834–1844.

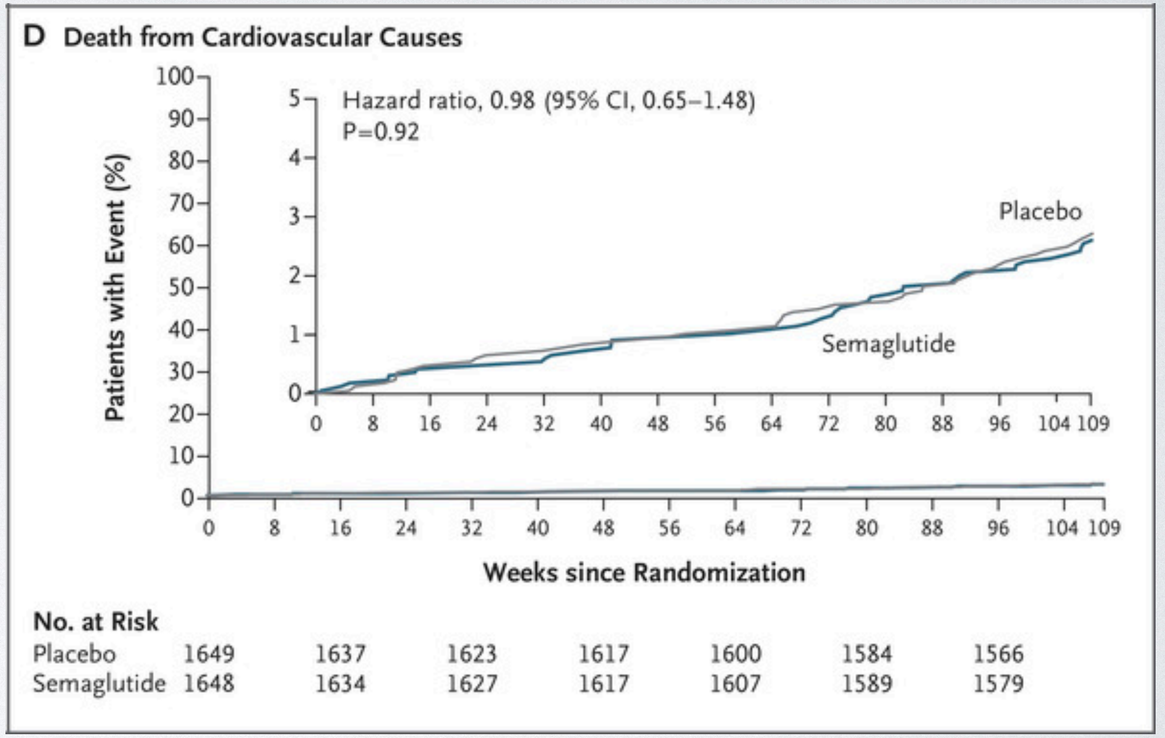
GLP-1 AGONISTS

SUSTAIN-6

SEMAGLUTIDE - INJECTED (OZEMPIC)

Considerations

- Increase in retinopathy complications was found primarily in patients with pre-existing proliferative retinopathy and driven by rapid improvement in glycemic control
  - Following this finding, patients with proliferative retinopathy requiring intervention are commonly excluded from participation in similar trials
- Superiority analysis was not pre-specified and could not be determined to be a conclusion



N Engl J Med 2016;375:1834–1844.

GLP-1 AGONISTS

PIONEER-6

SEMAGLUTIDE - ORAL (RYBELSUS)

Patients studied -	Established CVD or CV Risk (n = 3,183)
Duration-	Median 15.9 months
Primary Endpoint-	3-Point MACE
Secondary Endpoint-	5-Point MACE, individual outcomes of comp.
Study Goal-	Demonstrate Non-inferiority, Superiority

N Engl J Med 2019;381:841–851.

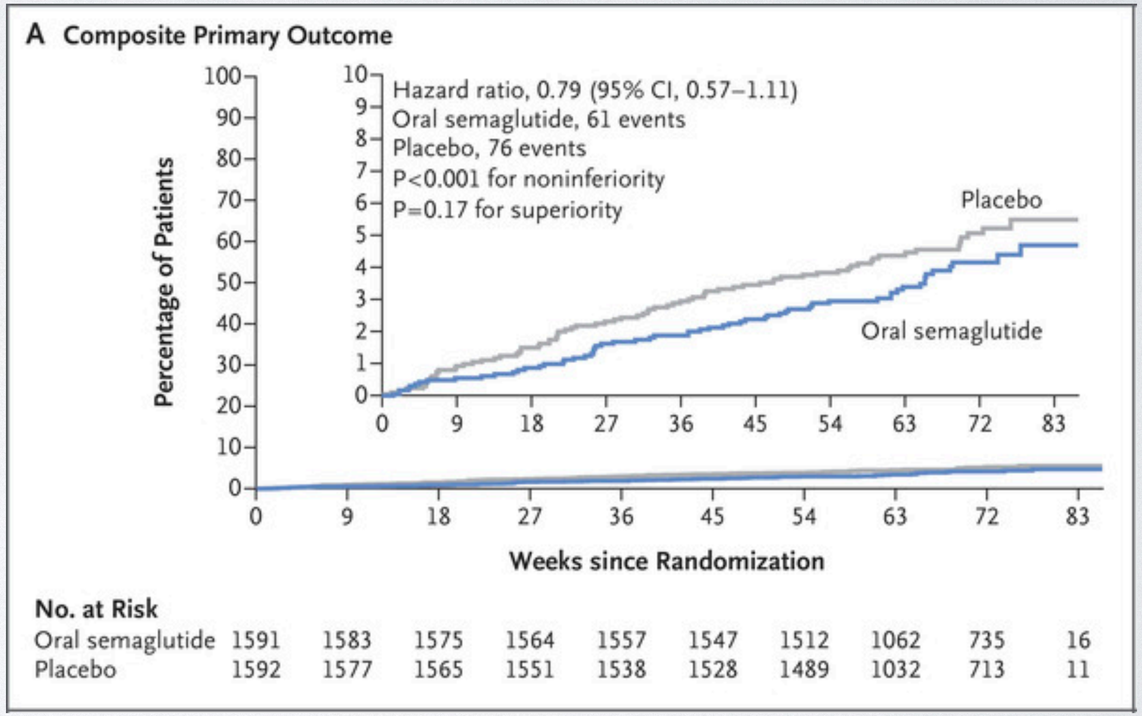
GLP-1 AGONISTS

PIONEER-6

SEMAGLUTIDE - ORAL (RYBELSUS)

Key Findings-

- Non-Inferior to placebo
- Non-Significant 21% reduction in 3-P MACE
- 49% reduction in All Cause Mortality
- 26% reduction in Non-Fatal Stroke



N Engl J Med 2019;381:841–851.

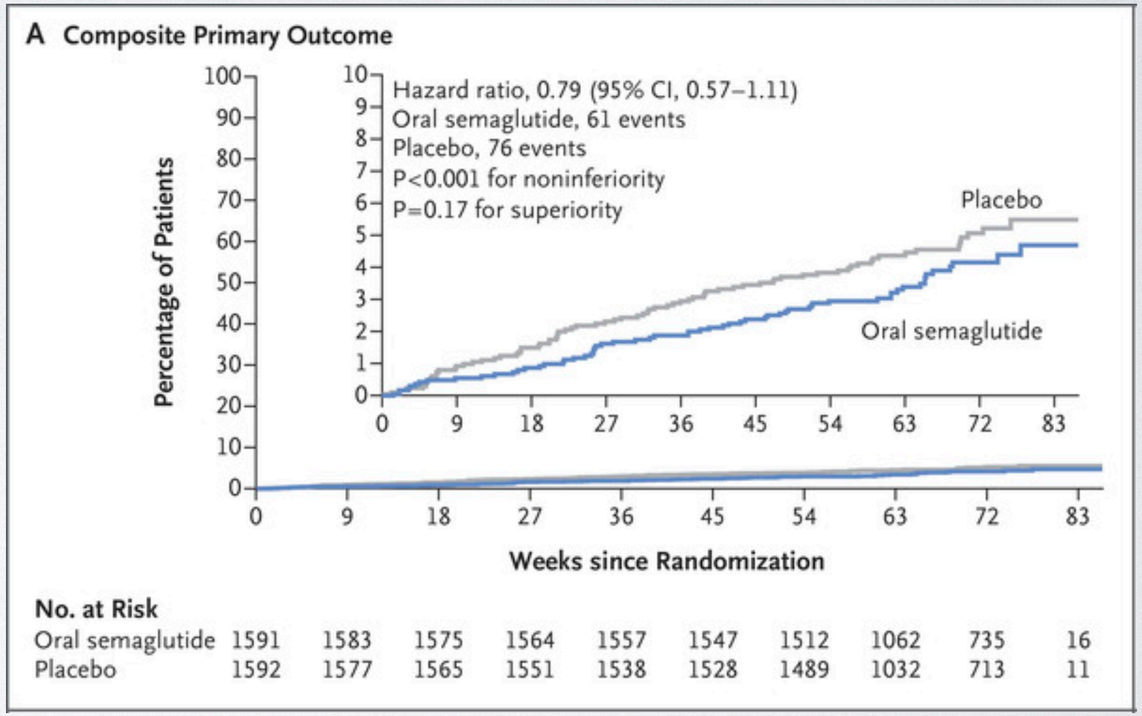
GLP-1 AGONISTS

PIONEER-6

SEMAGLUTIDE - ORAL (RYBELSUS)

Considerations

- Event-driven trial that was halted after the pre-specified number of events had occurred
  - Resulted in relatively short median follow-up time in the trial (1.3 years)
- Although statistically significant, the reductions in All Cause Mortality and Stroke is based on a small number of events
  - (68 for All Cause Mortality, 28 for Stroke)



N Engl J Med 2019;381:841–851.

GLP-1 AGONISTS

EXSCEL

EXENATIDE - WEEKLY (BYDUREON)

Patients studied -	Established CVD or CV Risk (n = 14,752)
Duration-	Median 3.2 years
Primary Endpoint-	3-Point MACE
Secondary Endpoint-	All Cause Death, CV Death, 4-P MACE
Study Goal-	Demonstrate Non-inferiority, Superiority

N Engl J Med 2017; 377:1228-1239

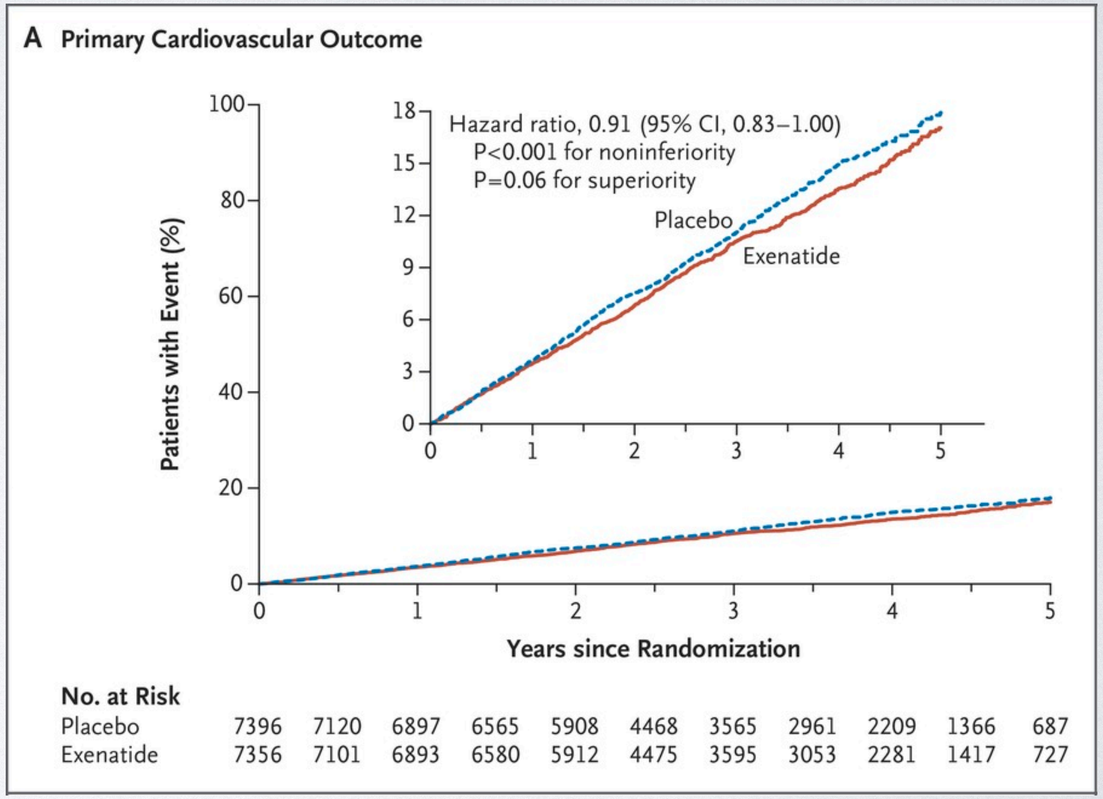
GLP-1 AGONISTS

EXSCEL

EXENATIDE - WEEKLY (BYDUREON)

Key Findings-

- Non-Inferior to placebo
- Non-Significant 9% reduction in 3-P MACE
- Significant 14% reduction in All Cause Mortality



N Engl J Med 2017; 377:1228-1239

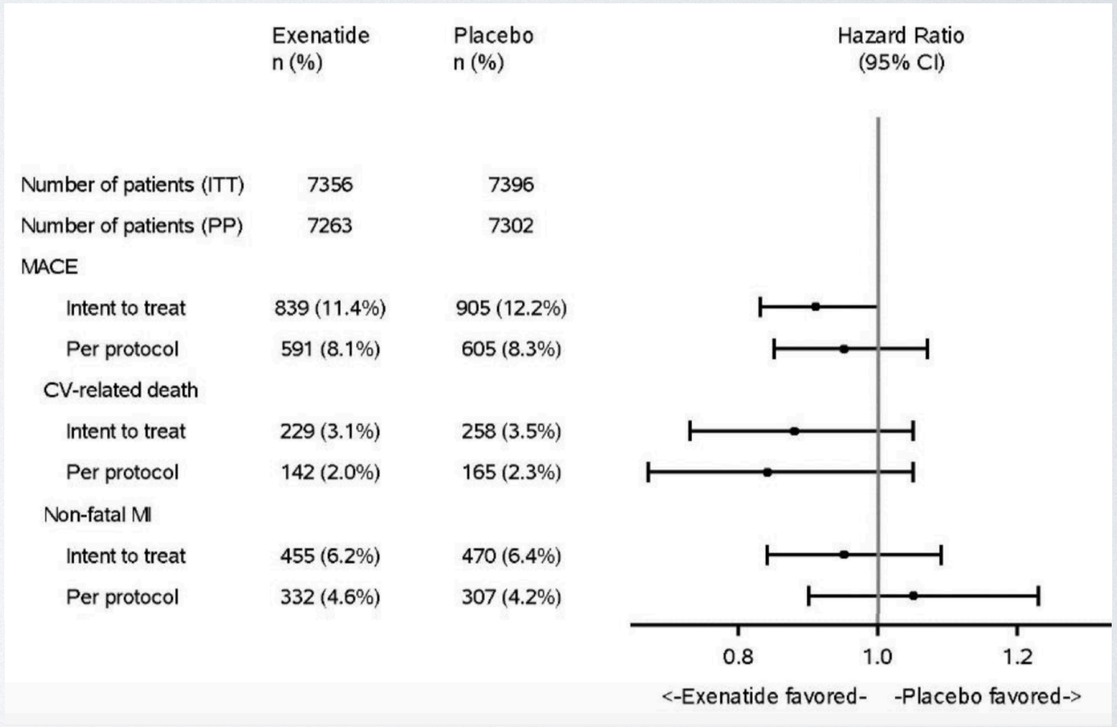
GLP-1 AGONISTS

EXSCEL

EXENATIDE - WEEKLY (BYDUREON)

Considerations-

- BARELY missed statistical significance for Superiority (0.83-1.00)
- Study was pragmatic in nature, with minimal patient visits, limited patient support
- 43% of participants discontinued study drug before trial completion
- Study utilized the original Bydureon Tray, rather than the currently available Pen or B-Cise



N Engl J Med 2017; 377:1228-1239

GLP-1 AGONISTS

FREEDOM-CVO

EXENATIDE - IMPLANTED (ITCA 650)

Patients studied -	Established CVD or CV Risk (n = >4,000)
Duration-	Median 1.2 years
Primary Endpoint-	3-Point MACE
Study Goal-	Demonstrate Non-inferiority
Findings-	Non-Inferior

Results posted on intartia.com website

GLP-1 AGONISTS

FREEDOM-CVO

EXENATIDE - IMPLANTED (ITCA 650)

Considerations

Short median exposure (1.2 years)

FDA declined to approve ITCA 650 (implanted exenatide) in September, 2017

FDA accepted resubmitted NDA in October 2019, with a targeted action date of March 2020

Results posted on intartia.com website

GLP-1 AGONISTS

HARMONY

ALBIGLUTIDE - (TANZEUM)

Patients studied -	Established CVD or CV Risk (n = 9,463)
Duration-	Median 1.6 years
Primary Endpoint-	3-Point MACE
Study Goal-	Demonstrate Non-inferiority, Superiority
Findings-	Superiority - Significant 22% risk reduction

Lancet 2018 DOI:https://doi.org/10.1016/S0140-6736(18)32261-X

GLP-1 AGONISTS

HARMONY

ALBIGLUTIDE - (TANZEUM)

Considerations

Statistically significant CV Risk reduction in spite of relatively short median exposure time (1.6 years)

Drug taken off the market as a business decision in 2017

Lancet 2018 DOI:https://doi.org/10.1016/S0140-6736(18)32261-X

GLP-1 AGONISTS

REWIND

DULAGLUTIDE - (TRULICITY)

Patients studied - Established CVD or CV Risk (n = 9,901)
31.5% with CVD, 68.5% with CV Risk

Duration- Median 5.4 years

Primary Endpoint- 3-Point MACE

Secondary Endpoint- Microvascular Composite, All Cause Mortality, et al.

Study Goal- Demonstrate Superiority

Lancet 2019 DOI:https://doi.org/10.1016/S0140-6736(19)31149-3

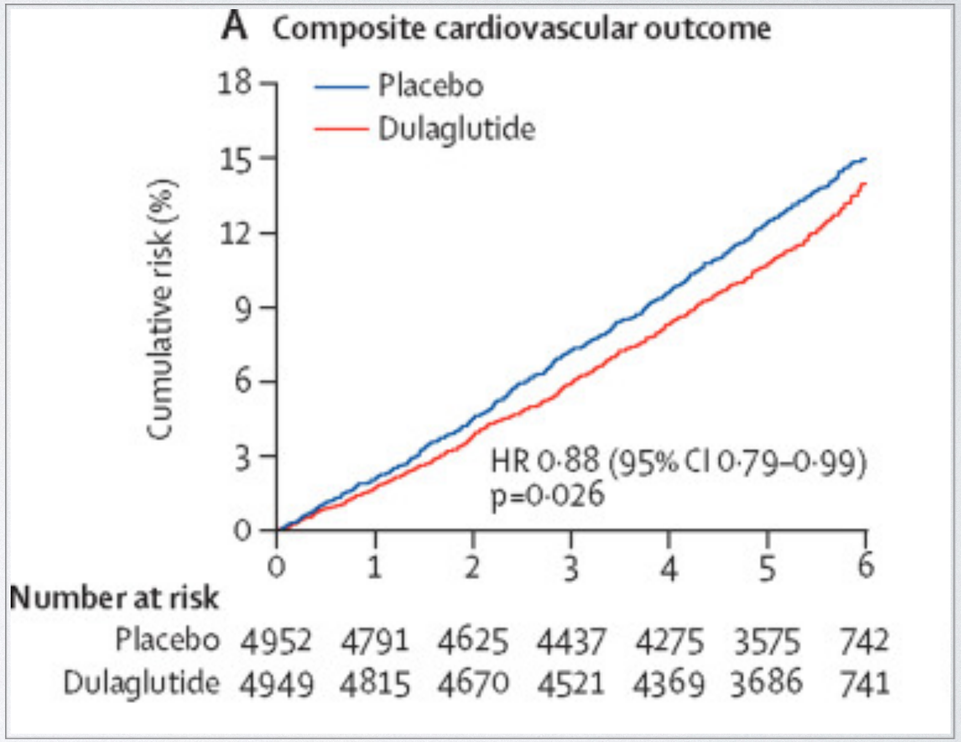
GLP-1 AGONISTS

REWIND

DULAGLUTIDE - (TRULICITY)

Key Findings-

- 12% risk reduction for 3-P MACE
- 24% risk reduction for Stroke
- No significant reduction in Myocardial Infarction, CV Death, or All Cause Mortality



Lancet 2019 DOI:https://doi.org/10.1016/S0140-6736(19)31149-3

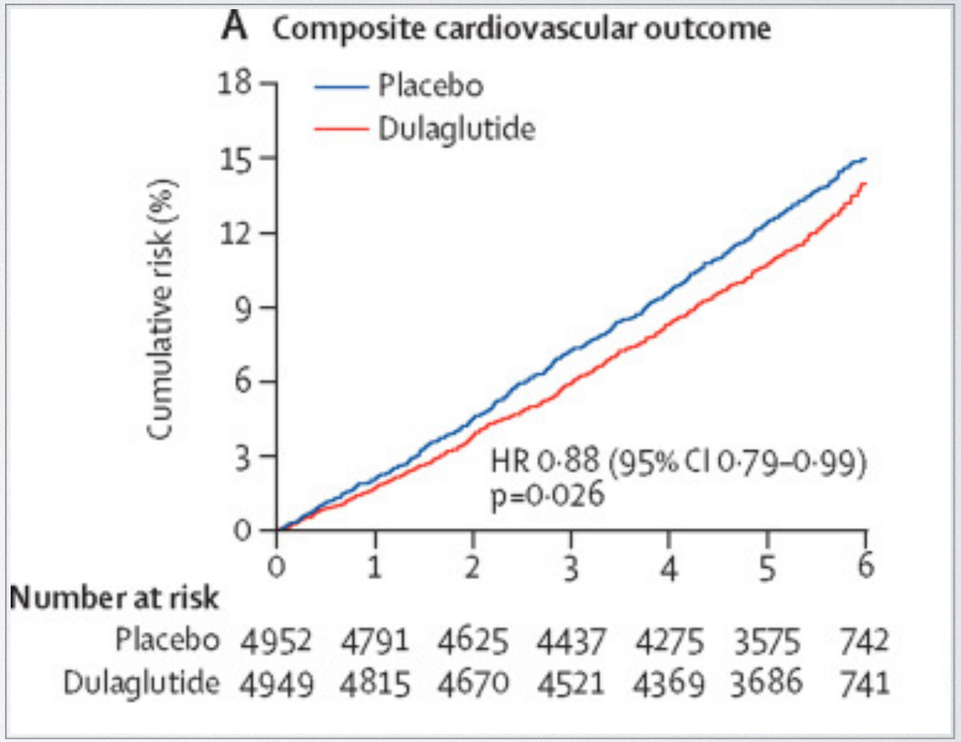
GLP-1 AGONISTS

REWIND

DULAGLUTIDE - (TRULICITY)

Considerations

- Study population consisted mostly of patients without established CVD
- Overall outcome was driven primarily by participants in Europe and Asia
  - US and Canadian participants actually had a non-significant 14% increase in hazard ratio.
- 25% of participants discontinued study drug before study conclusion
- Greater number of participants in the placebo group were also using other cardioprotective drugs



Lancet 2019 DOI:https://doi.org/10.1016/S0140-6736(19)31149-3

GLP-1 AGONISTS
RISK REDUCTION SUMMARY

	ELIXA (Adlyxin)	**LEADER** (Victoza)	**SUSTAIN-6** (Ozempic)	**PIONEER-6** (PO Semaglutide)	**EXSCEL** (Bydureon)	**REWIND** (Trulicity)
3-P MACE	Neutral	Protective	Protective	Neutral	Neutral	Protective
CV Death	Neutral	Protective	Neutral	Protective	Neutral	Neutral
Non-Fatal Stroke	Neutral	Neutral	Protective	Neutral	Neutral	Protective
Death any cause	Neutral	Protective	Neutral	Protective	Protective	Neutral
HF Hosp	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral
Non-Fatal MI	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral

GLP-1 AGONISTS
RISK REDUCTION SUMMARY

	ELIXA (Adlyxin)	**LEADER** (Victoza)	**SUSTAIN-6** (Ozempic)	**PIONEER-6** (PO Semaglutide)	**EXSCEL** (Bydureon)	**REWIND** (Trulicity)
3-P MACE	**+2%**	**-13%**	**-26%**	**-21%**	**-9%**	**-12%**
CV Death	**-2%**	**-22%**	**-2%**	**-51%**	**-12%**	**-9%**
Non-Fatal Stroke	**+12%**	**-11%**	**-39%**	**-26%**	**-15%**	**-24%**
Death any cause	**-6%**	**-15%**	**+5%**	**-49%**	**-14%**	**-10%**
HF Hosp	**-4%**	**-13%**	**+11%**	**-14%**	**-6%**	**-7%**
Non-Fatal MI	**+3%**	**-12%**	**-36%**	**+18%**	**-3%**	**-4%**

- **Statistically Significant**
- **Non-Statistically Significant**

CVOTS IN PROGRESS

SOUL

Evaluating Oral Semaglutide for Cardiovascular risk reduction in diabetic patients with CVD or CV Risk (testing for superiority)

SELECT

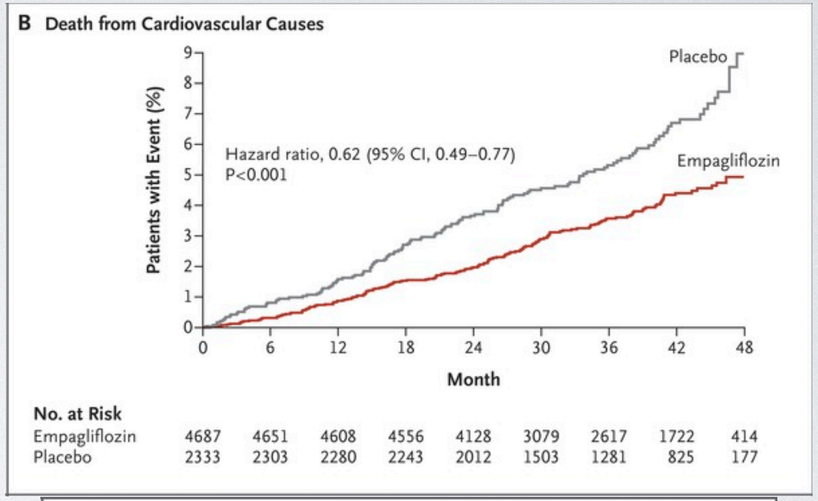
Evaluating Injected Semaglutide for Cardiovascular risk reduction in Non-Diabetic overweight or obese patients with established CVD

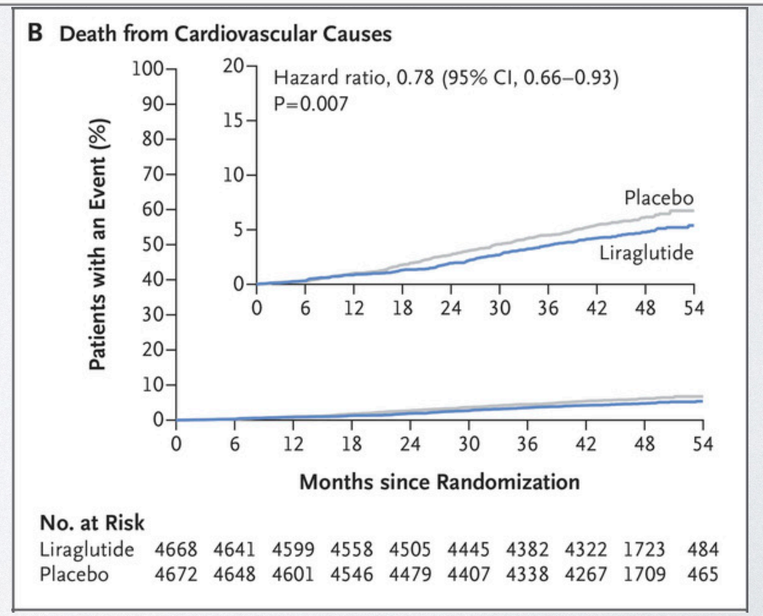
BENEFITS OF CVOTS

- All currently available have been shown to be generally safe from a cardiovascular standpoint and previously unproven benefits have been demonstrated in certain agents
- Previously unknown renal benefit has been observed with SGLT-2 and some GLP1 therapy
  - This has prompted further research on direct renal effects (CREDENCE, FLOW)
- Cardiovascular and renal benefits of GLP-1 and SGLT-2 medications appear to go beyond the effect of improved Hemoglobin A1c

WHAT HAVE WE LEARNED?

- Mechanisms of CV protection appears tp be different between SGLT-2s and GLP-1s
  - Earlier Kaplan-Meier separation in EMPA-REG vs LEADER
  - GLP-1 meds seem to affect atherosclerosis
  - SGLT-2 meds seem to affect ventricular function



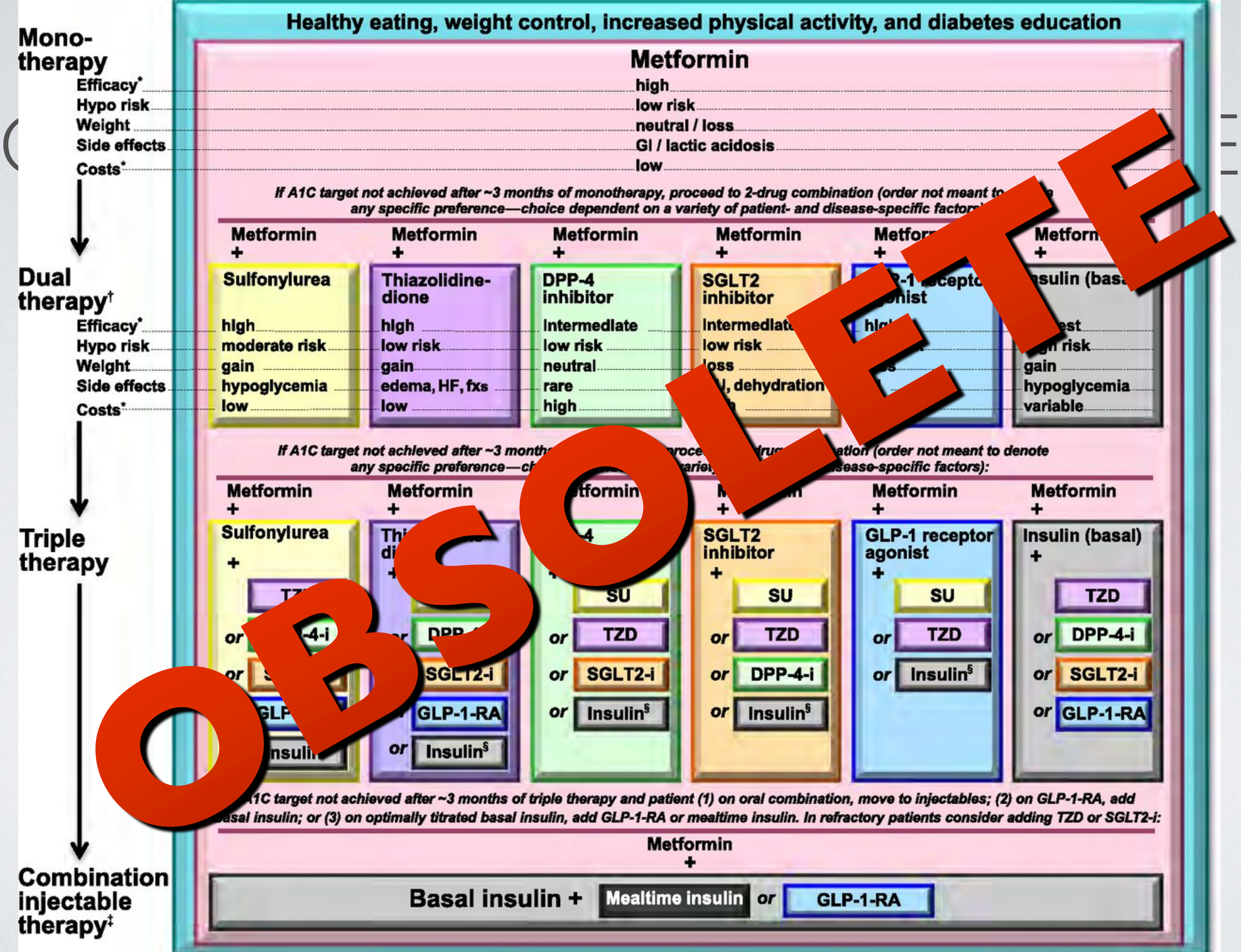


CHALLENGES OF CVOTS

- Findings may not necessarily be applicable when comparing one study to another
  - Inconsistencies amongst studies in terms of design and population
- Findings may not apply to all patients in clinical practice
- Small, easily overlooked factors can confound one's understanding of a study's findings (e.g. drug discontinuation in EXSCEL, low number of events in PIONEER 6, etc.)
- CVOTs may not be long enough to adequately study long-term effect (>5 years)

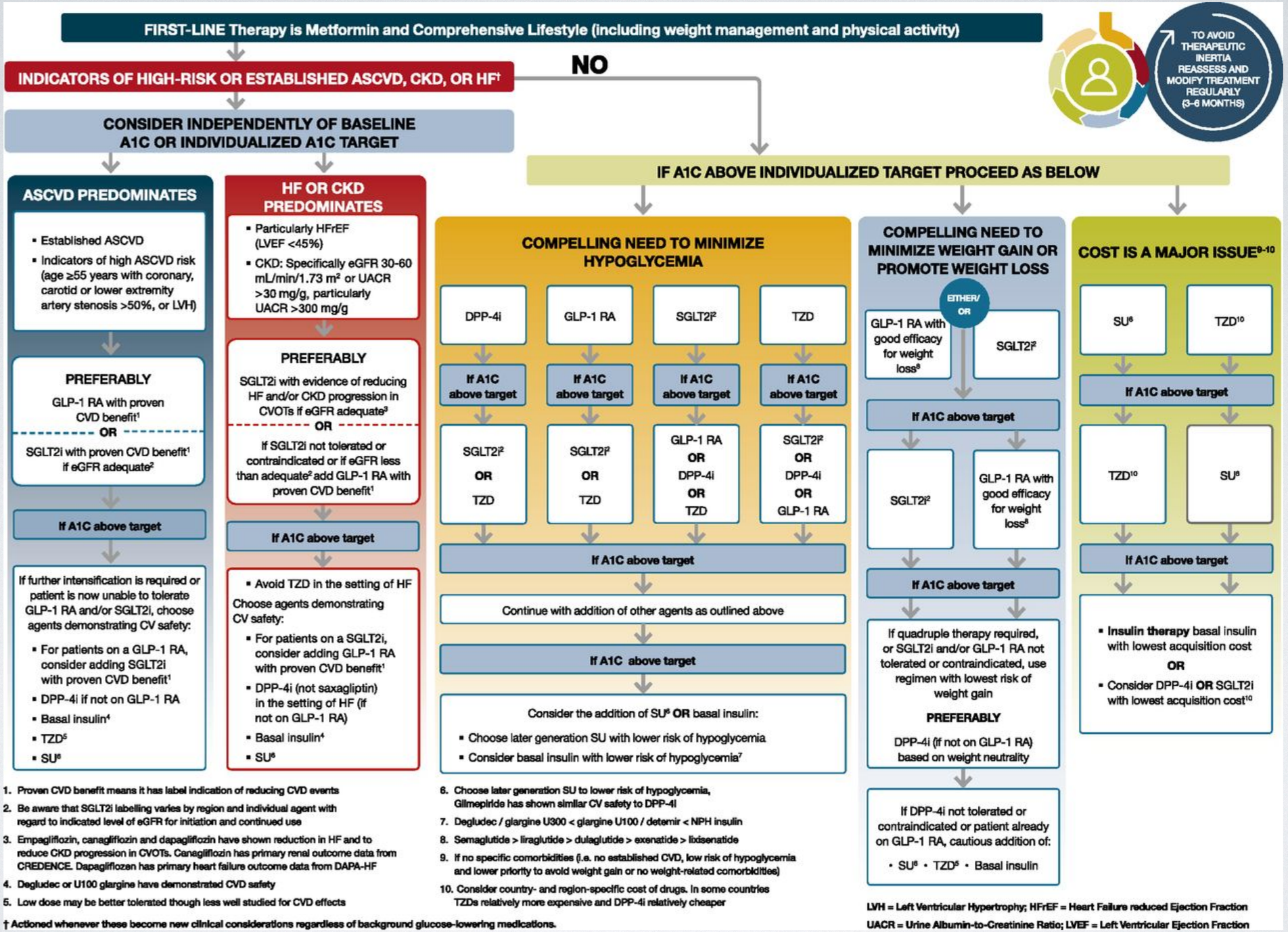
CVOT RELEVANCE IN PRACTICE

- CVOTs have changed the way we approach treatment of diabetes
- Improving A1c is important, but how we get there matters
- CVOT findings have resulted in changes in treatment algorithm recommendations from ADA


Healthy eating, weight control, increased physical activity, and diabetes education
Mono-therapy
Efficacy*
Hypo risk
Weight
Side effects
Costs*
Metformin
high
low risk
neutral / loss
GI / lactic acidosis
low
If A1C target not achieved after ~3 months of monotherapy, proceed to 2-drug combination (order not meant to
any specific preference—choice dependent on a variety of patient- and disease-specific factor
Dual therapy†
Efficacy*
Hypo risk
Weight
Side effects
Costs*
Metformin +
Sulfonylurea
high
moderate risk
gain
hypoglycemia
low
Metformin +
Thiazolidine-dione
high
low risk
gain
edema, HF, fxs
low
Metformin +
DPP-4 inhibitor
Intermediate
low risk
neutral
rare
high
Metformin +
SGLT2 inhibitor
low risk
neutral
rare
high
Metformin +
Insulin (basal)
gain
hypoglycemia
variable
If A1C target not achieved after ~3 months
any specific preference—ch
ation (order not meant to denote
ease-specific factors):
Triple therapy
Metformin +
Sulfonylurea +
or
or
Metformin +
or
or
Metformin +
SU
or TZD
or SGLT2-i
or Insulin§
Metformin +
SGLT2 inhibitor +
SU
or TZD
or DPP-4-i
or Insulin§
Metformin +
GLP-1 receptor agonist +
SU
or TZD
or Insulin§
Metformin +
Insulin (basal) +
TZD
or DPP-4-i
or SGLT2-i
or GLP-1-RA
1C target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectables; (2) on GLP-1-RA, add
asal insulin; or (3) on optimally titrated basal insulin, add GLP-1-RA or mealtime insulin. In refractory patients consider adding TZD or SGLT2-i:
Combination injectable therapy‡
Metformin +
Basal insulin + Mealtime insulin or GLP-1-RA
OBSOLETE

American Diabetes Association®

2020 Guidelines



1. Proven CVD benefit means it has label indication of reducing CVD events
2. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Empagliflozin, canagliflozin and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin has primary renal outcome data from CREDENCE. Dapagliflozen has primary heart failure outcome data from DAPA-HF
4. Degludec or U100 glargine have demonstrated CVD safety
5. Low dose may be better tolerated though less well studied for CVD effects
6. Choose later generation SU to lower risk of hypoglycemia, Glimepiride has shown similar CV safety to DPP-4i
7. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin
8. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
9. If no specific comorbidities (i.e. no established CVD, low risk of hypoglycemia and lower priority to avoid weight gain or no weight-related comorbidities)
10. Consider country- and region-specific cost of drugs. In some countries TZDs relatively more expensive and DPP-4i relatively cheaper

† Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications.

LVH = Left Ventricular Hypertrophy; HFrEF = Heart Failure reduced Ejection Fraction
UACR = Urine Albumin-to-Creatinine Ratio; LVEF = Left Ventricular Ejection Fraction

Diabetes Care 2020 Jan; 43(Supplement 1): S98-S110

NEED FOR FURTHER RESEARCH

- Longer-term follow up is needed to study life-long effect in diabetics
- A standardized study design would allow more generalizability between different studies of different drugs
- Further studies of low-risk populations would be more applicable to the average diabetic patient

FUTURE OF CVOTS?

- In March 2020 FDA revised guidelines, removing the CVOT demonstration of safety as part of pre-approval requirement

QUESTIONS

Thank you for your attention