Cardiovascular Outcome Trials of Anti-diabetic Drugs

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Agenda

- Concepts of Cardiovascular Outcome Trials (CVOTs).
- Landmark trials for each anti-diabetic drug.
- Conclusion.

Concept of CVOTs

- Before 2008 cardiovascular adverse effects of antidiabetic drugs were made out from the events that occur during the course of the trial.
- These cardiovascular events were not pre-specified.
- Since the subjects included in these trials were younger, of low CV risk, shorter duration of both disease and the trial, the number of CV events occurred during the the trial were low.
- The low event rates lead to poor estimates of CV safety of these agents.

- In 2007, a meta-analysis that caused some controversy was published. The analysis included 42 rosiglitazone trials involving 27843 patients and reported an increased risk of MI (RR: 1.43, 95% CI: 1.03–1.98, P =0.03) with the use of rosiglitazone.

Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med 2007;356:2457-2471

- That made FDA to issue a guidance in 2008 recommended that a new anti-diabetic drug should not increase cardiovascular risk to an unacceptable extent.

Requirements

1. **An upper bound of the 95% CI for the hazard ratio of important CV events should be less than 1.3.**
2. **Study patients must include individuals with advanced disease, elderly patients, and patients with degree of renal impairment.**
3. **A minimum of 2 years' CV safety data must be provided.**
4. **All studies should include a prospective independent CV events. Events should include CV mortality, MI, and stroke and can include hospitalization for ACS, urgent revascularization procedures, and possibly other end points.**
5. **The analysis of CV events may include a meta-analysis of all placebo controlled trials, add-on trials (i.e., drug vs. placebo, each added to standard therapy)**

Landmark Trials for each Anti-diabetic Drug

1.Metformin

- Metformin provided statistically significant reductions in the risk of all-cause mortality, diabetes- related mortality (p = 0.017), and any end-point related to diabetes (p = 0.002), but not in myocardial infarction (p = 0.052)

Prospective Diabetes Study (UKPDS) Group: Lancet 1998, 352(9131):854-865

- The UKPDS post-trial reported significant and persistent risk reductions for any diabetes-related end point (21%, p = 0.01), myocardial infarction (33%, p = 0.005), and death from any cause (27%, p = 0.002).

Holman RR, et al: 10-year follow up of intensive glucose control in type 2 diabetes.N Engl J Med 2008, 359:1577-1589.

Metformin subsequent studies showed similar effects

- Johnson JA, Majumdar SR, Simpson SH: Decreased mortality associated with the use of metformin compared with sulfonylurea Monotherapy in type 2 diabetes. Diabetes Care 2002, 25:2244-2248.
- Kao J, Tobis J, Mc Clelland RL: Relation of metformin treatment to clinical events in diabetic patients undergoing percutaneous intervention. Am J Cardiol 2004, 93:1347-1350.
- Kooy A, de Jager J, Lehert P: Long-term effects of metformin on metabolism and microvascular and macrovascular disease in patients with type 2 diabetes mellitus. Arch Intern Med 2009, 169:616- 625.
- Jadhav S, Ferrell W, Greer IA, Petrie JR, Cobbe SM, Sattar N: Effects of metformin on microvascular function and exercise tolerance in women with angina and normal coronary arteries. J Am Coll Cardiol 2006, 48:956-963.
- Boussageon R, Supper I, Bejan-Angoulvant T: Reappraisal of metformin efficacy in the treatment of type 2 diabetes: a meta-analysis of randomised controlled trials. PLoS Med 2012, 9(4):e1001204

European Heart Journal (2016) 37, 2129–2200
doi:10.1093/eurheartj/ehw128

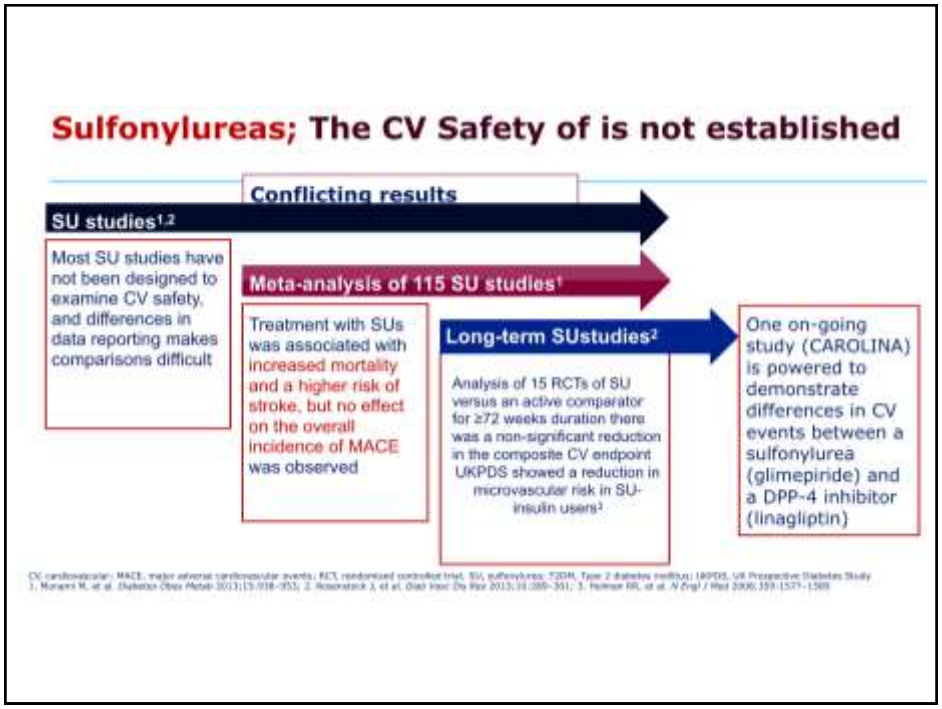
ESC GUIDELINES

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

Diabetes			
Metformin should be considered as a first-line treatment of glycaemic control in patients with diabetes and HF, unless contra-indicated.	IIa	C	440 ,441

2. Sulfonylureas



3.Thiazolidindiones(Glitazones)

Rosiglitazone

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

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

CONCLUSIONS

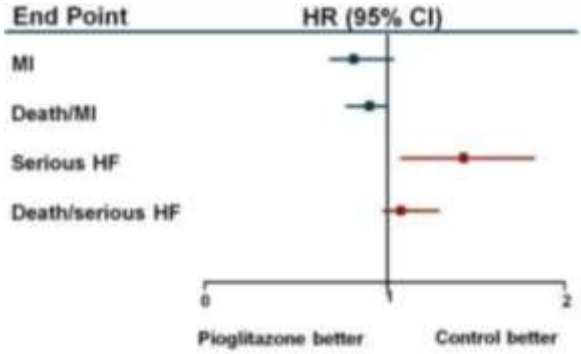
Rosiglitazone was associated with a significant increase in the risk of myocardial infarction and with an increase in the risk of death from cardiovascular causes that had borderline significance.

Record trial

- Finding:Heart failure hospitalization or CV death occurred in 61 people in the rosiglitazone group and 29 in the control group (HR 2·10, 1·35–3·27)
- Interpretation:Addition of rosiglitazone to glucose-lowering therapy in people with type 2 diabetes is confirmed to increase the risk of heart failure.

Pioglitazone

- Meta-analysis 2007



Lincoff AM, et al. Pioglitazone and Risk of Cardiovascular Events in Patients With Type 2 Diabetes MellitusA Meta-analysis of Randomized Trials. JAMA. 2007;298(10):1180–1188.

- Meta-analysis 2017

Pioglitazone was associated with reduced risk of MACE in people with DM. However, the risks of heart failure, bone fracture, oedema and weight gain were increased.

Liao H, Saver JL, Wu Y, et al Pioglitazone and cardiovascular outcomes in patients with insulin resistance, pre-diabetes and type 2 diabetes: a systematic review and meta-analysis BMJ Open 2017;7:e013927.

European Heart Journal (2016) 37, 2129–2200
doi:10.1093/eurheartj/ehw128

ESC GUIDELINES

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

Treatments (or combinations of treatments) that may cause harm in patients with symptomatic (NYHA Class II–IV) heart failure with reduced ejection fraction

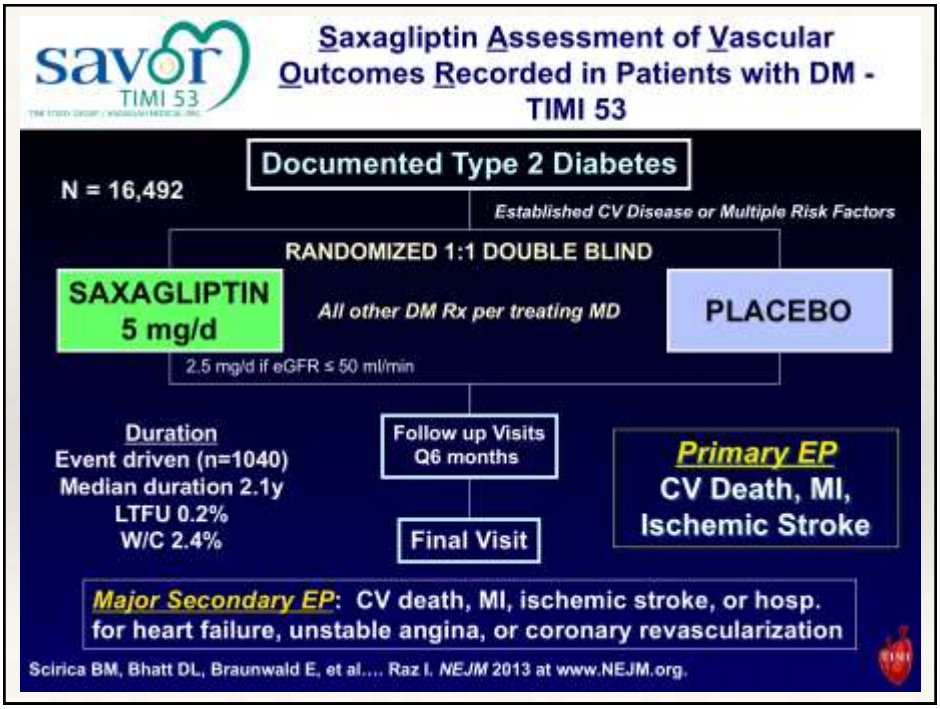
Recommendations	Class[a]	Level[b]	Ref[c]
Thiazolidinediones (glitazones) are not recommended in patients with HF, as they increase the risk of HF worsening and HF hospitalization.	III	A	209, 210

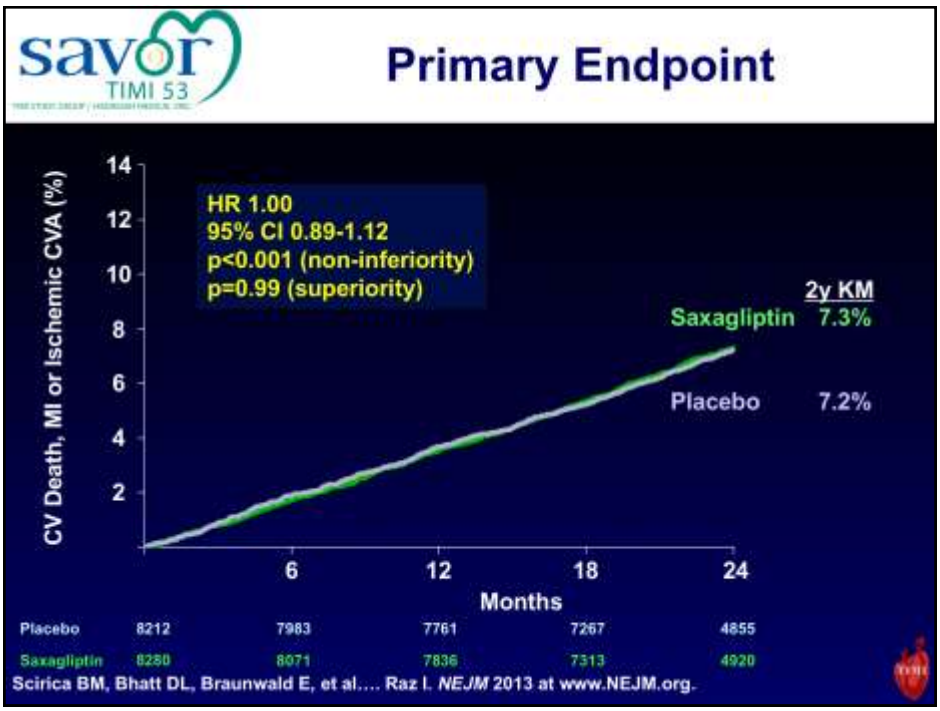
4.DPP4 inhibitors

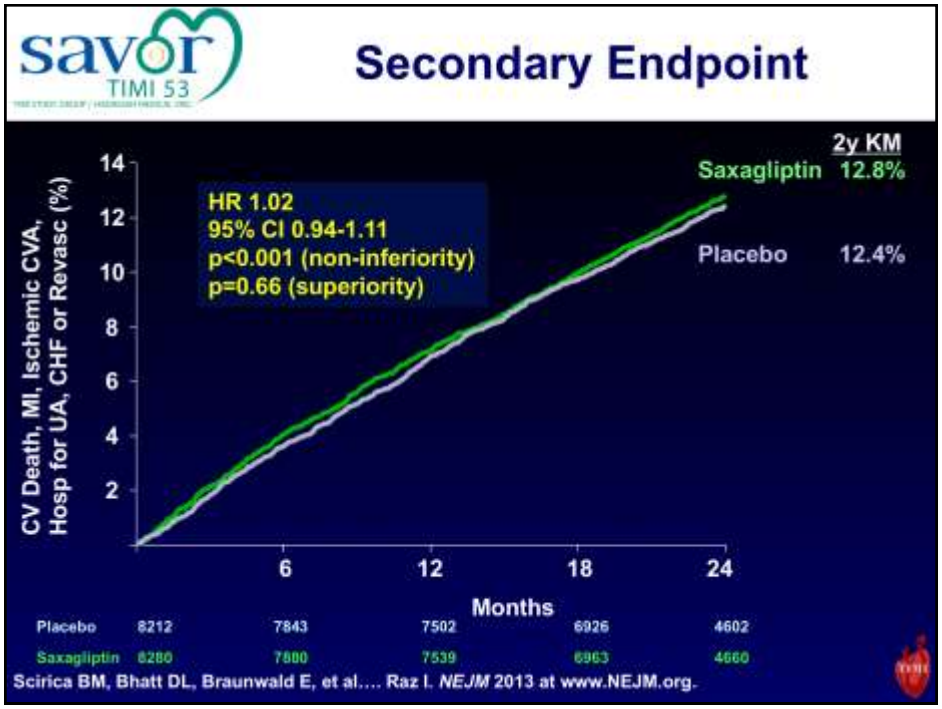
savor TIMI 53 — Saxagliptin

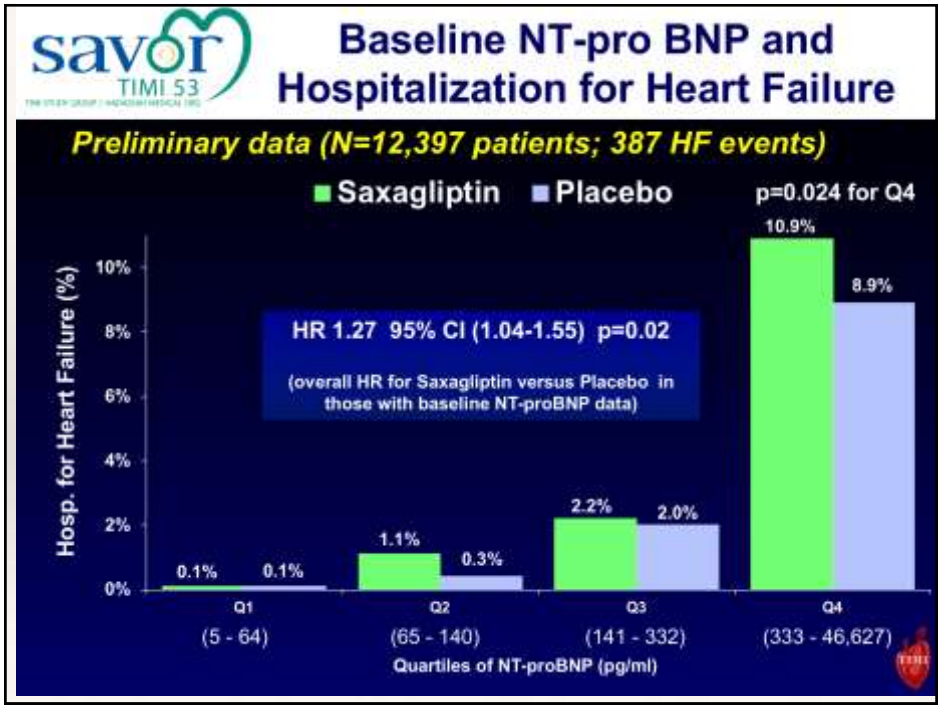
EXAMINE — Alogliptin

TECOS TRIAL EVALUATING CARDIOVASCULAR OUTCOMES WITH SITAGLIPTIN — Sitagliptin


savor TIMI 53
Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with DM - TIMI 53
Documented Type 2 Diabetes
N = 16,492
Established CV Disease or Multiple Risk Factors
RANDOMIZED 1:1 DOUBLE BLIND
SAXAGLIPTIN 5 mg/d
All other DM Rx per treating MD
PLACEBO
2.5 mg/d if eGFR ≤ 50 ml/min
Duration
Event driven (n=1040)
Median duration 2.1y
LTFU 0.2%
W/C 2.4%
Follow up Visits Q6 months
Final Visit
Primary EP
CV Death, MI, Ischemic Stroke
Major Secondary EP: CV death, MI, ischemic stroke, or hosp. for heart failure, unstable angina, or coronary revascularization
Scirica BM, Bhatt DL, Braunwald E, et al.... Raz I. NEJM 2013 at www.NEJM.org.


savor TIMI 53
Primary Endpoint
CV Death, MI or Ischemic CVA (%)
14
12
10
8
6
4
2
HR 1.00
95% CI 0.89-1.12
p<0.001 (non-inferiority)
p=0.99 (superiority)
2y KM
Saxagliptin 7.3%
Placebo 7.2%
6
12
18
24
Months
Placebo 8212 7983 7761 7267 4855
Saxagliptin 8280 8071 7836 7313 4920
Scirica BM, Bhatt DL, Braunwald E, et al.... Raz I. NEJM 2013 at www.NEJM.org.


savor TIMI 53
Secondary Endpoint
2y KM
Saxagliptin 12.8%
Placebo 12.4%
HR 1.02
95% CI 0.94-1.11
p<0.001 (non-inferiority)
p=0.66 (superiority)
CV Death, MI, Ischemic CVA, Hosp for UA, CHF or Revasc (%)
14
12
10
8
6
4
2
6
12
18
24
Months
Placebo 8212 7843 7502 6926 4602
Saxagliptin 8280 7880 7539 6963 4660
Scirica BM, Bhatt DL, Braunwald E, et al.... Raz I. NEJM 2013 at www.NEJM.org.


savor TIMI 53
Baseline NT-pro BNP and Hospitalization for Heart Failure
Preliminary data (N=12,397 patients; 387 HF events)
Saxagliptin
Placebo
p=0.024 for Q4
HR 1.27 95% CI (1.04-1.55) p=0.02
(overall HR for Saxagliptin versus Placebo in those with baseline NT-proBNP data)
Hosp. for Heart Failure (%)
10%
8%
6%
4%
2%
0%
0.1%
0.1%
1.1%
0.3%
2.2%
2.0%
10.9%
8.9%
Q1
Q2
Q3
Q4
(5 - 64)
(65 - 140)
(141 - 332)
(333 - 46,627)
Quartiles of NT-proBNP (pg/ml)

Conclusions

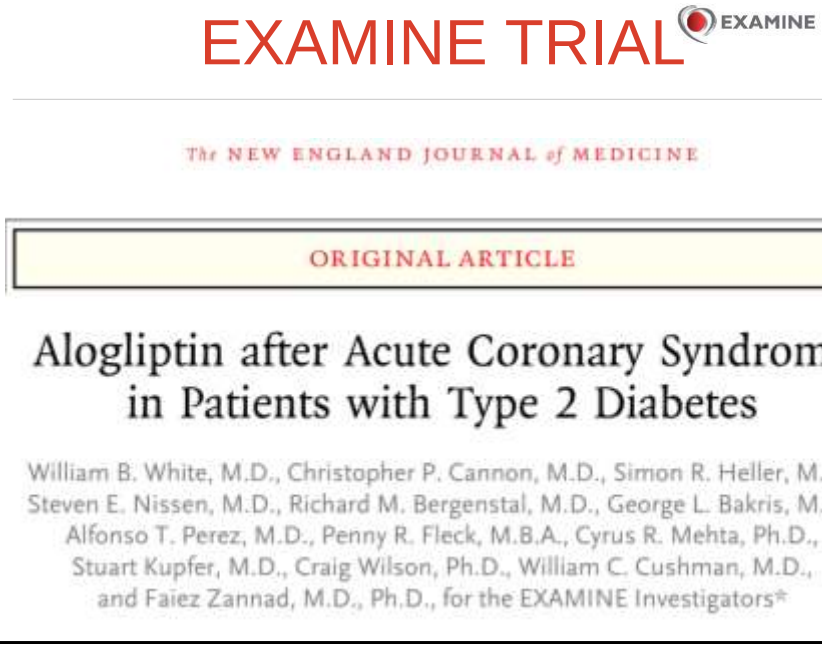
- When added to standard of care in patients with T2DM at high CV risk, saxagliptin neither reduced nor increased the risk of the primary composite endpoint of CV death, MI, or ischemic stroke.

Scirica BM, Bhatt DL, Braunwald E, et al.… Raz I. *NEJM* 2013 at www.NEJM.org.

Conclusions (Heart Failure)

- The higher incidence of hospitalization for heart failure was unexpected, but it was a pre-defined, adjudicated endpoint.
- It merits further evaluation given the history of other diabetic agents and heart failure.

EXAMINE TRIAL



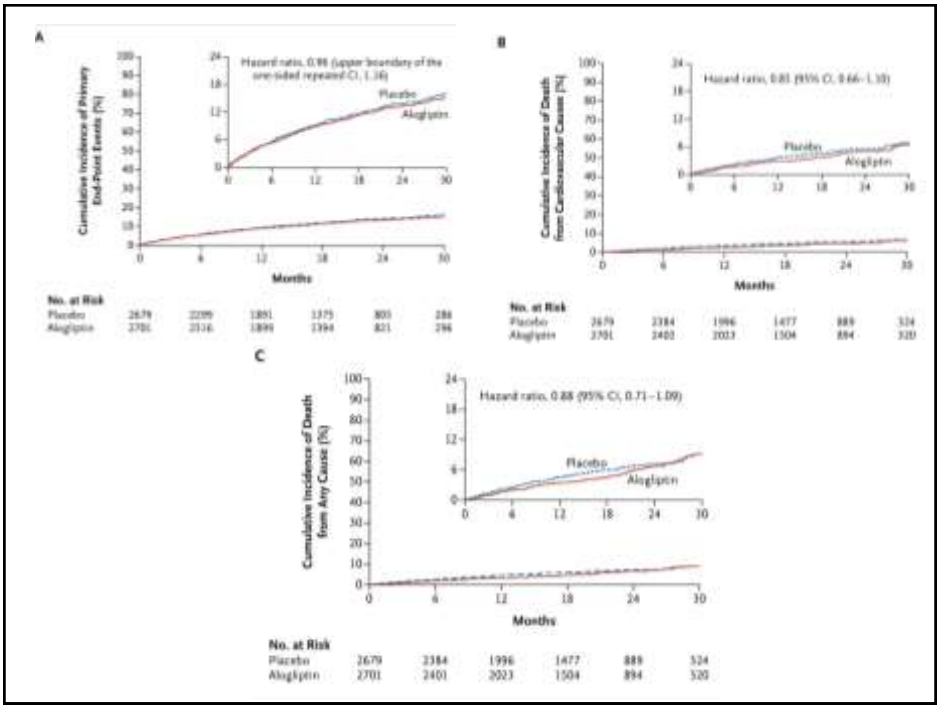
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Alogliptin after Acute Coronary Syndrome in Patients with Type 2 Diabetes

William B. White, M.D., Christopher P. Cannon, M.D., Simon R. Heller, M.D., Steven E. Nissen, M.D., Richard M. Bergenstal, M.D., George L. Bakris, M.D., Alfonso T. Perez, M.D., Penny R. Fleck, M.B.A., Cyrus R. Mehta, Ph.D., Stuart Kupfer, M.D., Craig Wilson, Ph.D., William C. Cushman, M.D., and Faiez Zannad, M.D., Ph.D., for the EXAMINE Investigators*

- They assigned 5380 patients with type 2 diabetes and either an acute myocardial infarction or unstable angina requiring hospitalization within the previous 15 to 90 days to receive alogliptin or placebo .
- Primary and secondary end points were nearly the same as SAVOR TIMI trial.



- Conclusion of EXAMINE:
- The rates of major adverse cardiovascular events were not increased with the DPP-4 inhibitor Alogliptin as compared with placebo.
- There was slight increase in HF hospitalization events compared to placebo (but not statistically significant).

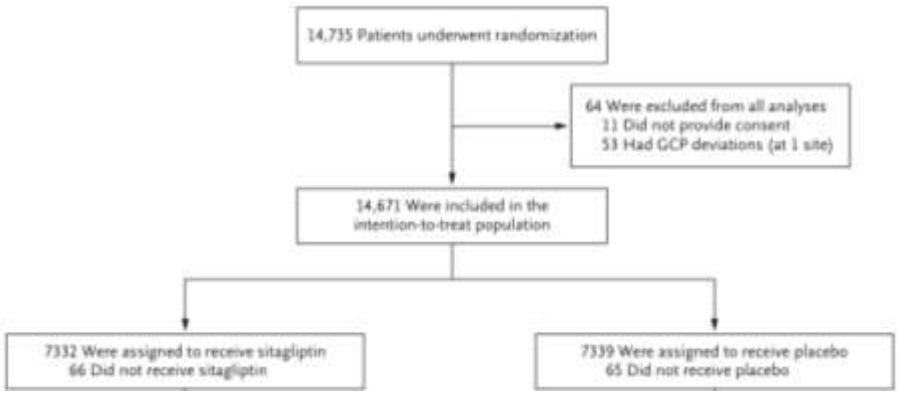
TECOS TRIAL

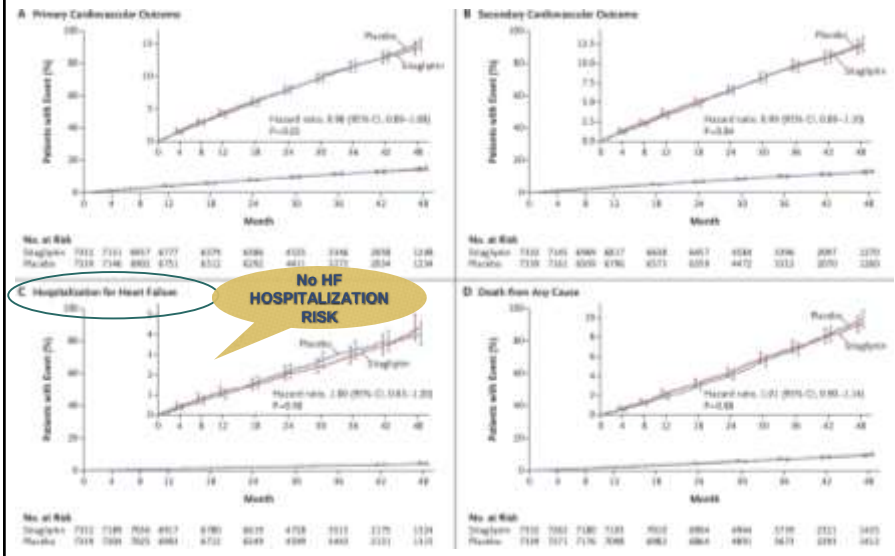
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes

Jennifer B. Green, M.D., M. Angelyn Bethel, M.D., Paul W. Armstrong, M.D., John B. Buse, M.D., Ph.D., Samuel S. Engel, M.D., Jyotsna Garg, M.S., Robert Josse, M.B., B.S., Keith D. Kaufman, M.D., Joerg Koglin, M.D., Scott Korn, M.D., John M. Lachin, Sc.D., Darren K. McGuire, M.D., M.H.Sc., Michael J. Pencina, Ph.D., Eberhard Standl, M.D., Ph.D., Peter P. Stein, M.D., Shailaja Suryawanshi, Ph.D., Frans Van de Werf, M.D., Ph.D., Eric D. Peterson, M.D., M.P.H., and Rury R. Holman, M.B., Ch.B., for the TECOS Study Group*



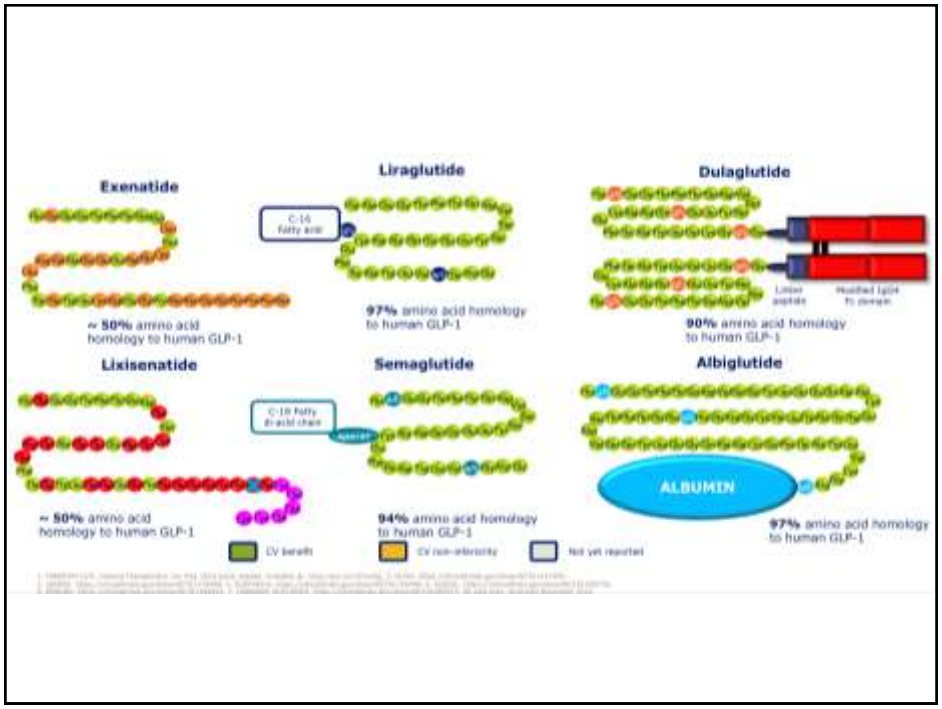


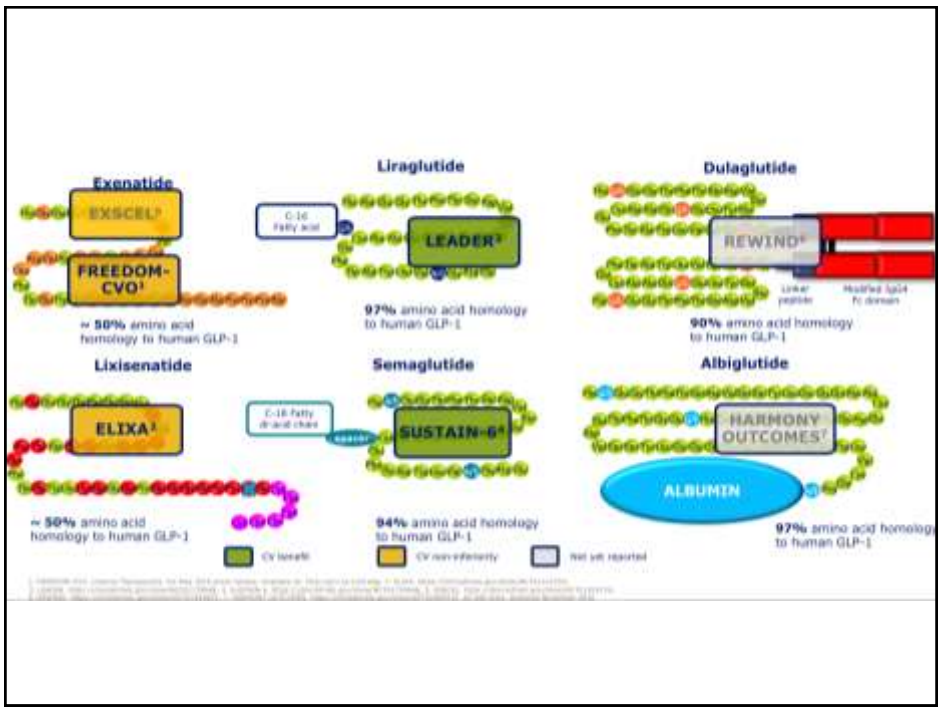
- Conclusion of TECOS
- Sitagliptin did not appear to increase the risk of MACE, hospitalization for heart failure, or other adverse events.
- This provides reassurance that even if the increased HF signal seen with Saxagliptin in SAVOR trial is true, it is not a 'class effect' associated with all DPP-4 drugs – especially TECOS had a larger sample size and longer follow up.

ALL DPP4 INHIBITORS SEEMED TO BE SAFE BUT WHY NOT CARDIOVASCULAR PROTECTIVE????

- Many of theses studies are relatively too short to be able to show a CV benefit.
- Because of the slow nature of the atherosclerotic process, we may need a longer duration of exposure before we know whether any of these compounds have an intrinsic, beneficial effect on CV events.

5.GLP1 Receptor Agonist


Exenatide
~ 50% amino acid homology to human GLP-1
Liraglutide
C-16 Fatty acid
97% amino acid homology to human GLP-1
Dulaglutide
Linker peptide
Modified IgG4 Fc domain
90% amino acid homology to human GLP-1
Lixisenatide
~ 50% amino acid homology to human GLP-1
Semaglutide
C-18 Fatty di-acid chain
94% amino acid homology to human GLP-1
Albiglutide
ALBUMIN
97% amino acid homology to human GLP-1
CV benefit
CV non-inferiority
Not yet reported


Exenatide
EXSCEL²
FREEDOM-CVO¹
~ 50% amino acid homology to human GLP-1
Liraglutide
C-16 Fatty acid
LEADER³
97% amino acid homology to human GLP-1
Dulaglutide
REWIND⁴
Linker peptide
Modified IgG4 Fc domain
90% amino acid homology to human GLP-1
Lixisenatide
ELIXA⁵
~ 50% amino acid homology to human GLP-1
Semaglutide
C-18 Fatty di-acid chain
SUSTAIN-6⁶
94% amino acid homology to human GLP-1
Albiglutide
HARMONY OUTCOMES⁷
ALBUMIN
97% amino acid homology to human GLP-1
CV benefit
CV non-inferiority
Not yet reported

Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular outcome Results LEADER®

- S.P. Marso, G.H. Daniels, K.B. Frandsen,
- P. Kristensen, J.F.E. Mann, M.A. Nauck, S.E. Nissen, S. Pocock, N.R. Poulter, L.S. Ravn, W.M. Steinberg, M. Stockner, B. Zinman, R.M. Bergenstal, and J.B. Buse
- **The LEADER Steering Committee on behalf of the LEADER Trial Investigators**

The NEW ENGLAND JOURNAL of MEDICINE

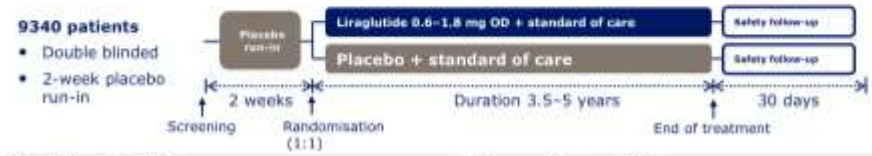
ORIGINAL ARTICLE

Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

Steven P. Marso, M.D., Gilbert H. Daniels, M.D., Kirstine Brown-Frandsen, M.D., Peter Kristensen, M.D., E.M.B.A., Johannes F.E. Mann, M.D., Michael A. Nauck, M.D., Steven E. Nissen, M.D., Stuart Pocock, Ph.D., Neil R. Poulter, F.Med.Sci., Lasse S. Ravn, M.D., Ph.D., William M. Steinberg, M.D., Mette Stockner, M.D., Bernard Zinman, M.D., Richard M. Bergenstal, M.D., and John B. Buse, M.D., Ph.D., for the LEADER Steering Committee on behalf of the LEADER Trial Investigators*

June 13, 2016, at NEJM.org. DOI: 10.1056/NEJMoa1603827

LEADER: Study design



Key inclusion criteria

- T2DM, HbA_{1c} ≥7.0%
- Antidiabetic drug naive; OADs and/or basal/premix insulin
- **Age ≥50 years and established CV disease or chronic renal failure**
  or
- **Age ≥60 years and risk factors for CV disease**

Key exclusion criteria

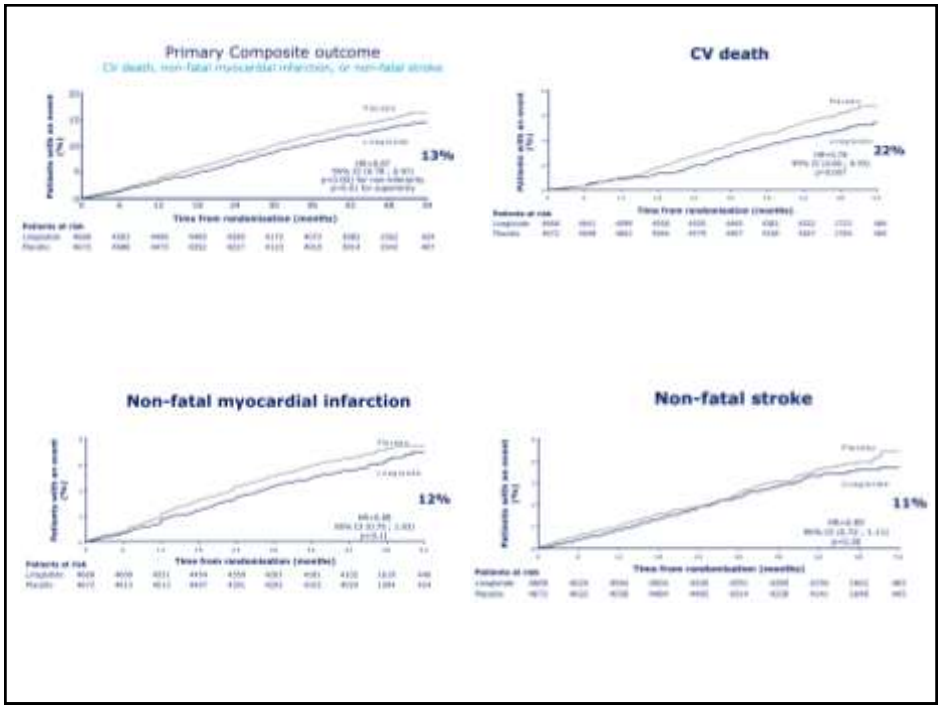
- T1DM
- Use of GLP-1RAs, DPP-4i, pramlintide, or rapid-acting insulin
- Familial or personal history of MEN-2 or MTC

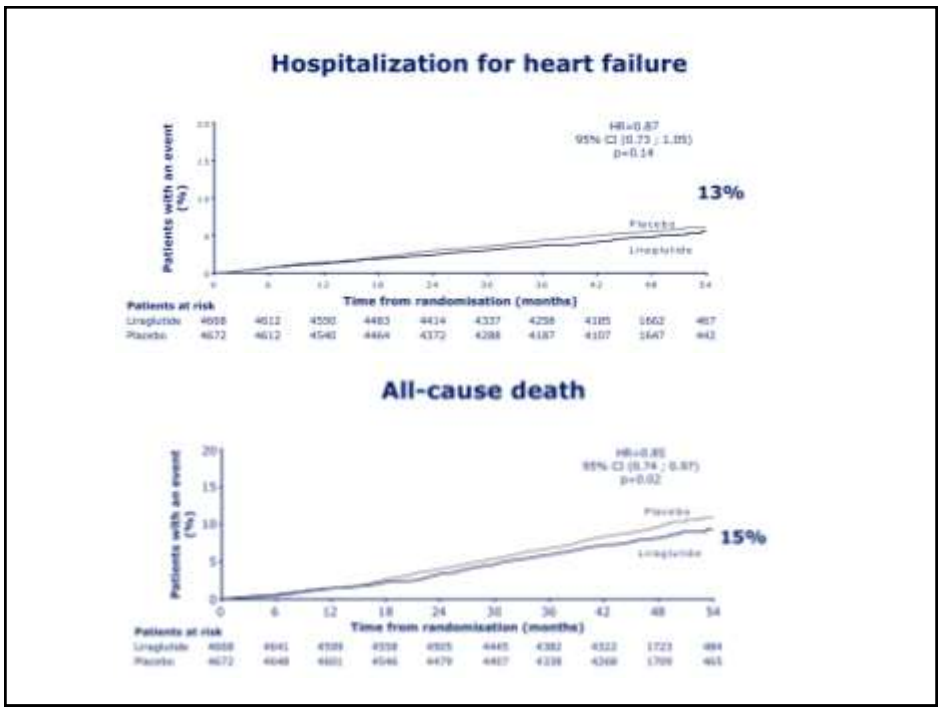
CV, cardiovascular; HbA_{1c}, glycosylated haemoglobin; OAD, oral antidiabetic drug; OD, once daily; T2DM, type 2 diabetes mellitus.
Marso SP et al. *N Engl J Med* 2016. DOI: 10.1056/NEJMoa1603827.

Primary and key secondary outcomes

Primary outcome	**Time to first MACE composed of** • CV death • Non-fatal MI • Non-fatal stroke
Key secondary outcomes	**Time to first occurrence of** • Expanded composite CV outcome (CV death, non-fatal MI, non-fatal stroke, coronary revascularisation, unstable angina pectoris requiring hospitalisation, or hospitalisation for heart failure) • All-cause death • Each individual component of expanded composite CV outcome

CV, cardiovascular; MACE, major adverse cardiovascular event; MI, myocardial infarction.
Marso SP et al. *N Engl J Med* 2016. DOI: 10.1056/NEJMoa1603827.


Primary Composite outcome
CV death, non-fatal myocardial infarction, or non-fatal stroke
13%
CV death
22%
Non-fatal myocardial infarction
12%
Non-fatal stroke
11%


Hospitalization for heart failure
HR=0.87
95% CI (0.73 ; 1.05)
p=0.14
13%
Patients with an event (%)
Placebo
Lixisenatide
Time from randomisation (months)
Patients at risk
Lixisenatide 4858 4612 4500 4403 4414 4337 4258 4185 1662 467
Placebo 4672 4612 4540 4464 4372 4288 4187 4107 1647 442
All-cause death
HR=0.85
95% CI (0.74 ; 0.97)
p=0.02
15%
Patients with an event (%)
Placebo
Lixisenatide
Time from randomisation (months)
Patients at risk
Lixisenatide 4858 4641 4599 4558 4505 4445 4382 4322 1723 484
Placebo 4672 4648 4601 4546 4479 4407 4338 4268 1709 465

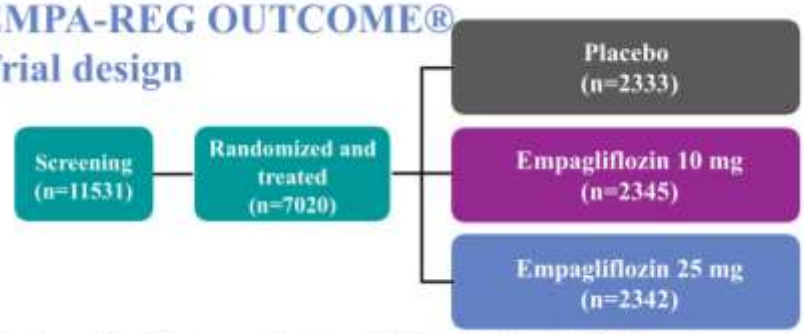
- The trial met criteria for both noninferiority and superiority for all three of the end-point components.
- Liraglutide not only safe but also shows CVS protection.
- Mechanism is not clearly understood....

6.SGLT2 INHIBITORS

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

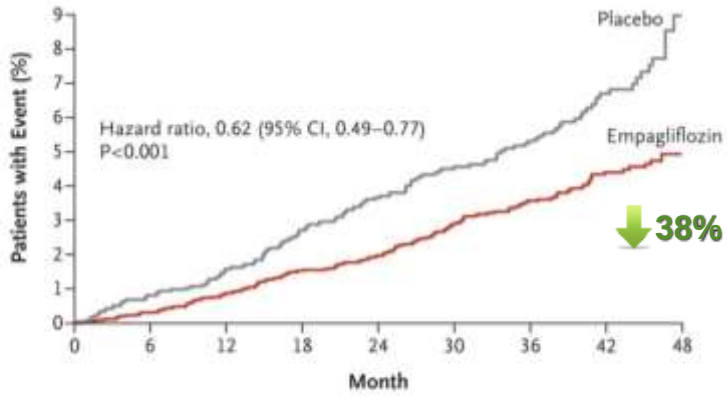
HbA1c: glycosylated hemoglobin A1c; CV: cardiovascular; T2DM: type 2 diabetes mellitus; MI: myocardial infarction.
*Adapted from Inzucchi et al.[6]

EMPA-REG OUTCOME® Trial design



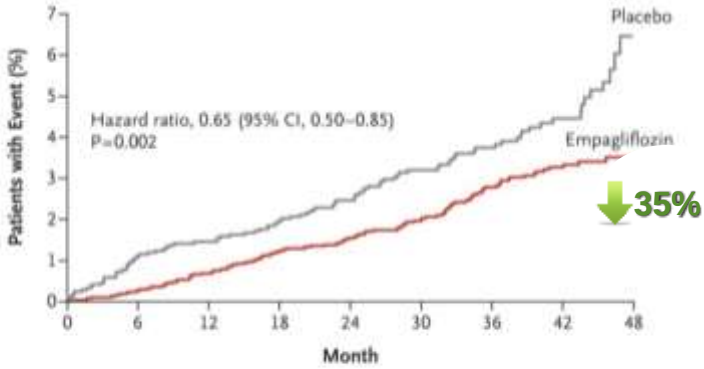
- Study medication was given in addition to standard of care.
- Key inclusion criteria:
  - Adults with type 2 diabetes and CV disease (heart attack, stroke, etc.)
  - HbA1c 7–10%; eGFR ≥30 mL/min/1.73m2 (MDRD)
- 1° outcome = '3-point MACE' (CV death, non-fatal MI, non-fatal stroke)

EMPA-REG OUTCOME: CV death



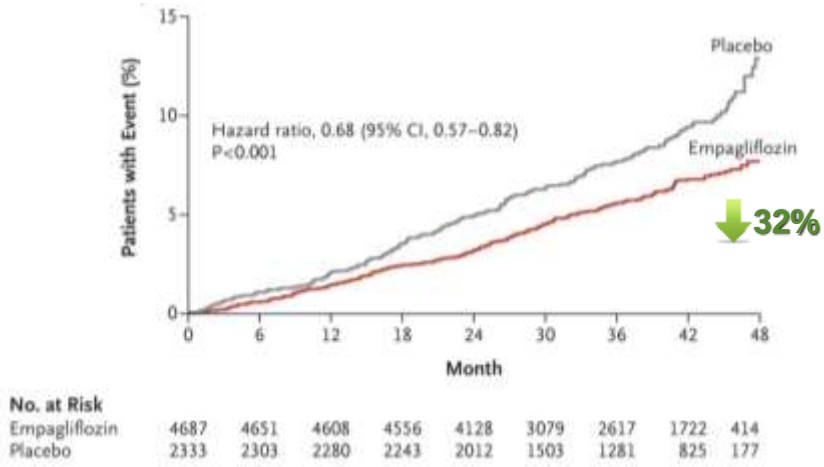
No. at Risk									
Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722	414
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

EMPA-REG OUTCOME: HF Hospitalizations



No. at Risk									
Empagliflozin	4687	4614	4523	4427	3988	2950	2487	1634	395
Placebo	2333	2271	2226	2173	1932	1424	1202	775	168

EMPA-REG OUTCOME: All cause death



- Robust CVS benefit ,especially mortality and HF
- CVS benefits occurred within first few weeks(early divergence of the curves).
- Exact mechanisms not fully understood and could not be explained by glycemic control only.
- Possible mechanisms:BP control, decrease arterial stiffness and weight reduction….
- Seems to be class effect after supporting evidence of Canagliflozin in CANVAS trial in 2017

- In patients with long-standing suboptimally controlled type 2 diabetes and established atherosclerotic cardiovascular disease, empagliflozin or liraglutide should be considered as they have been shown to reduce cardiovascular and all-cause mortality when added to standard care. Ongoing

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ESC GUIDELINES

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

Recommendations to prevent or delay the development of overt heart failure or prevent death before the onset of symptoms		
Empagliflozin should be considered in patients with type 2 diabetes in order to prevent or delay the onset of HF and prolong life.	IIa	B

Conclusion

- Clinical research in the field of type-2 diabetes is facing many challenging issues.
- Several areas of uncertainty remain. These include time of follow-up for future trials; contribution of adverse effects such as hypoglycaemia or weight gain to observed clinical outcomes.

- It is entirely reasonable to take a "first, do no harm." approach in approving new therapies. Patients take theses drugs lifelong!!!
- Modern CVOTs are designed to demonstrate safety!!!