Treatment: Concepts and New Developments

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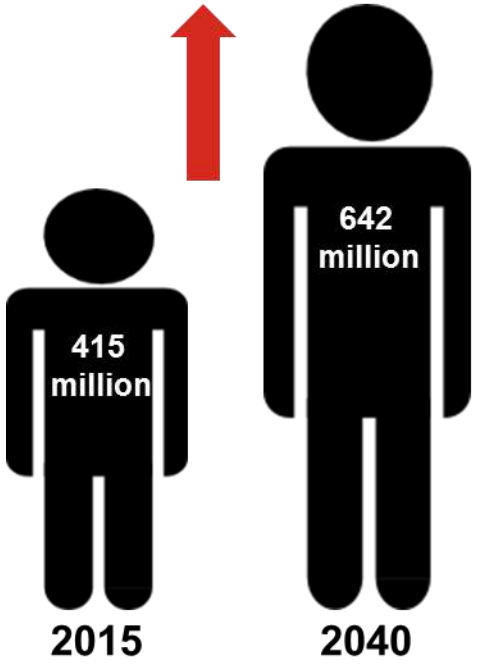
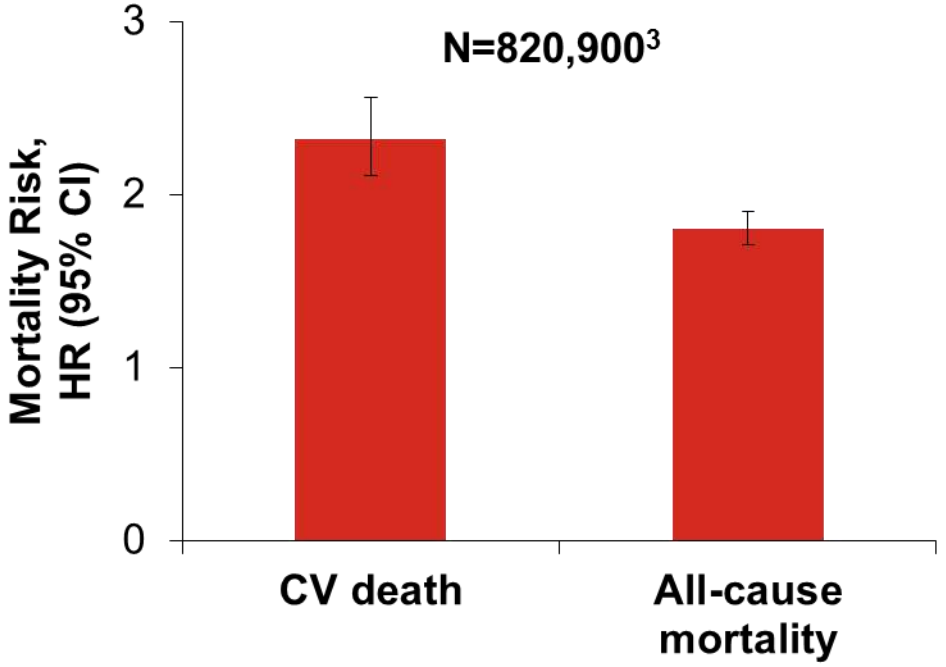
Disclosures

- None

Prevalence of Type 2 Diabetes Mellitus Is Increasing

- Globally, 415 million people were living with diabetes in 2015; this will rise to 642 million by 2040[1]
- CV death rates are higher among adults with diabetes when compared to those without diabetes[2]

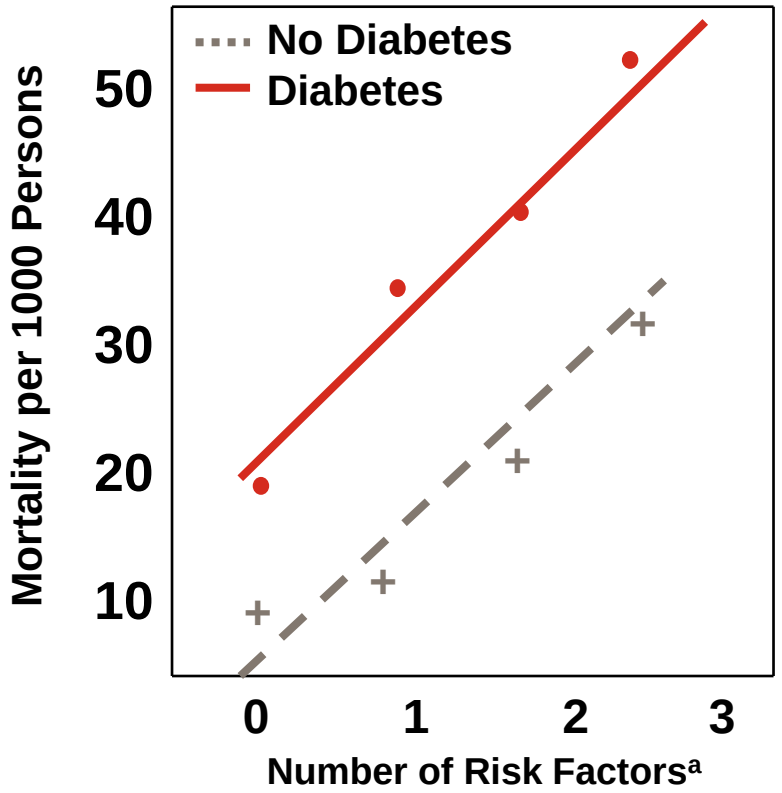




http://www.diabetesatlas.org/
National diabetes statistics report, 2014
Seshasai SR et al. *N Engl J Med* 2011;364:829-41

Impact of Diabetes on Cardiovascular Mortality

Mortality rate by number of diabetes risk factors[1]

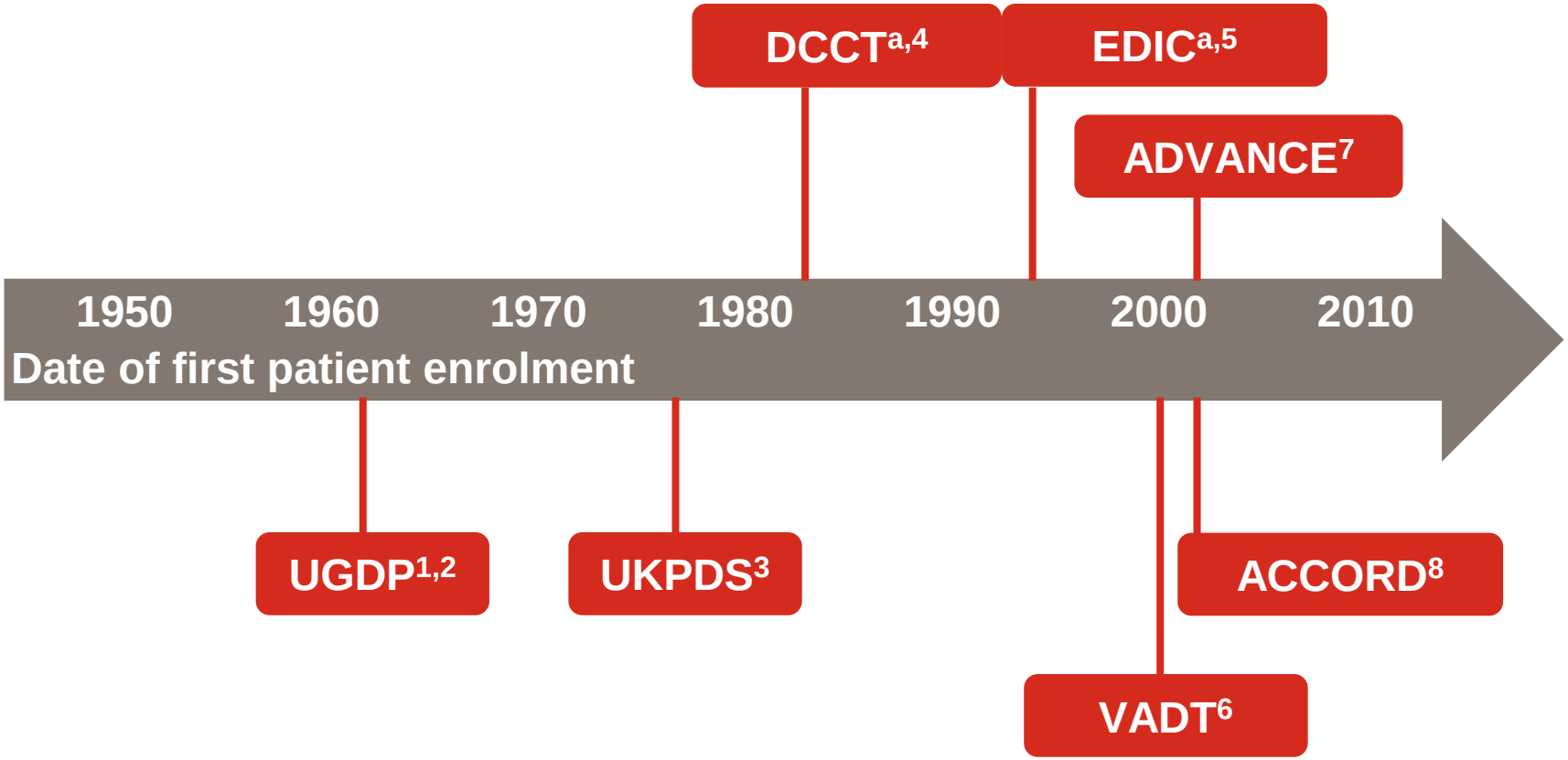


- CV disease is the major cause of morbidity and mortality for individuals with diabetes[2]
- Presence of these risk factors[a] in diabetic patients results in increased incidence of coronary heart disease, CV disease, and mortality in this population[1]

[a]Risk factors analyzed were smoking, dyslipidemia, and hypertension

1. Data from ADA. *Diabetes Care* 1989;12:573-9
2. ADA. *Diabetes Care* 2016;39(Suppl 1):S60-71

Major Historic CV Outcomes Trials: Intensive vs. Conventional Glycemic Control

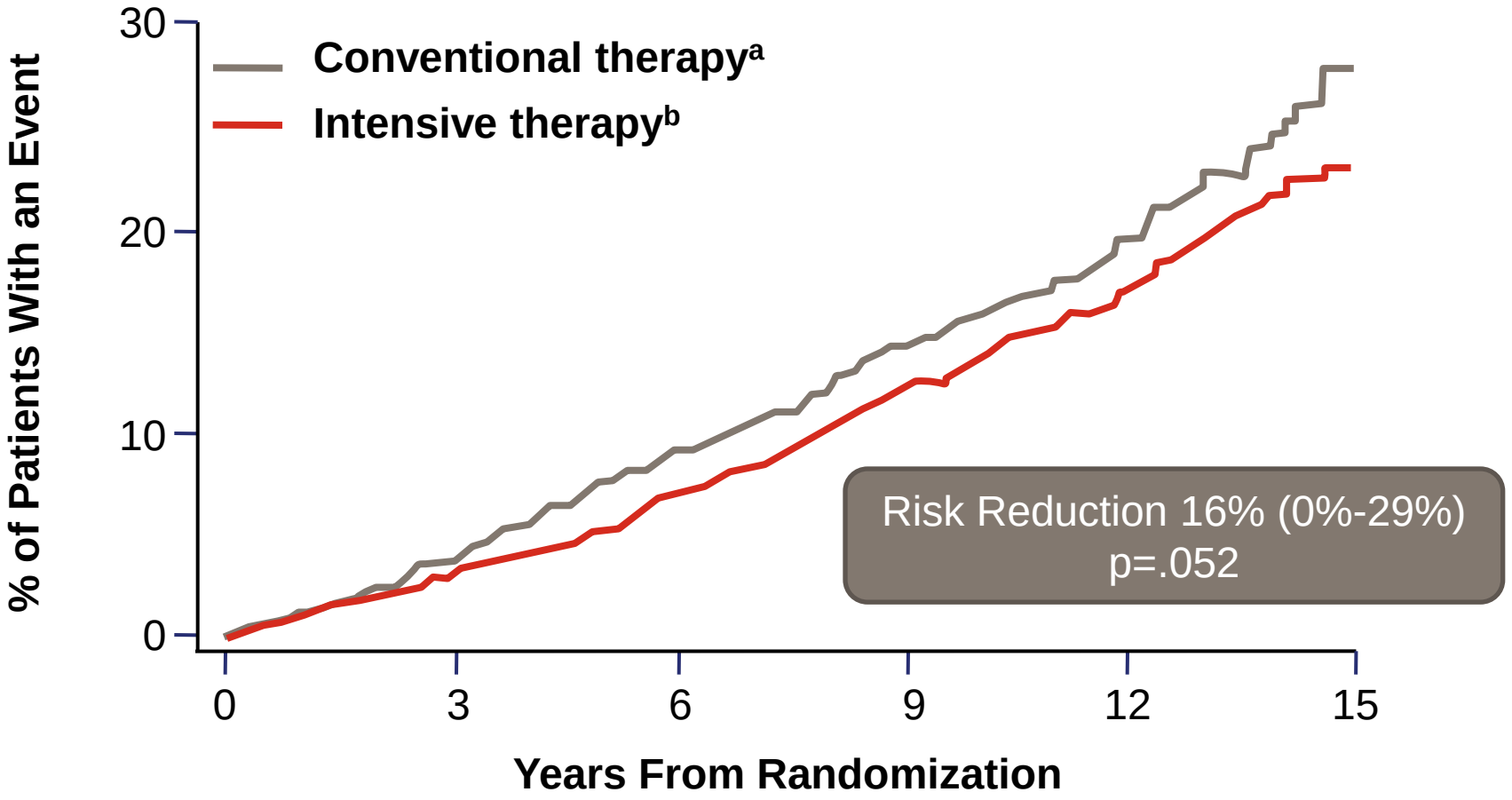


[a]DCCT/EDIC study included patients with T1DM; all other studies included patients with T2DM

1. Meinert et al. *Diabetes* 1970;19(Suppl):789-830
2. Schwartz TB and Meinert CL. *Perspect Biol Med* 2004;47(4):564-74
3. UKPDS Group. *Lancet* 1998;352:837-53 (updated 354:602)
4. DCCT Research Group. *N Engl J Med* 1993;329:977-86
5. EDIC. *Diabetes Care* 1999;22:99-111
6. Duckworth et al. *N Engl J Med* 2009;360:129-39
7. ADVANCE Collaborative Group. *N Engl J Med* 2008;358:2560-72
8. ACCORD. *N Engl J Med* 2008;358:2545-59

UKPDS: Myocardial Infarction

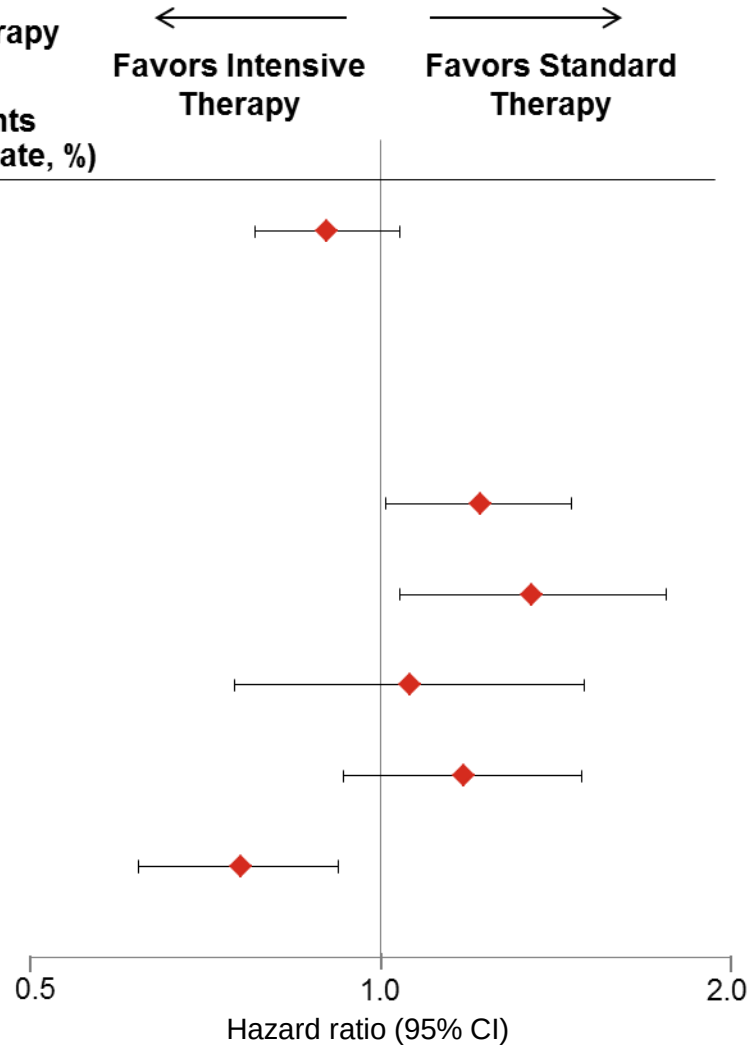
Fatal or Nonfatal MI, Sudden Death 573 of 3867 Patients (15%)



[a]Conventional policy: Patients received dietary advice to maintain FPG <15 mmol/L and near-normal body weight
[b]Intensive policy: Patients received insulin or SU with an aim to maintain FPG <6 mmol/L
Data from UKPDS Group. *Lancet* 1998;352:837-53

ACCORD: Intensive Glucose Lowering Associated With Higher Mortality vs. Standard Therapy

Outcome	Intensive Therapy (n=5128) No. of Patients (Annual Event Rate, %)	Standard Therapy (n=5123) No. of Patients (Annual Event Rate, %)
Primary outcome[a]	352 (2.11)	371 (2.29)
Secondary outcome		
Death		
Any cause	257 (1.41)	203 (1.14)
CV cause	135 (0.79)	94 (0.56)
Nonfatal stroke	67 (0.39)	61 (0.37)
Fatal or nonfatal CHF	152 (0.90)	124 (0.75)
Nonfatal MI	186 (1.11)	235 (1.45)

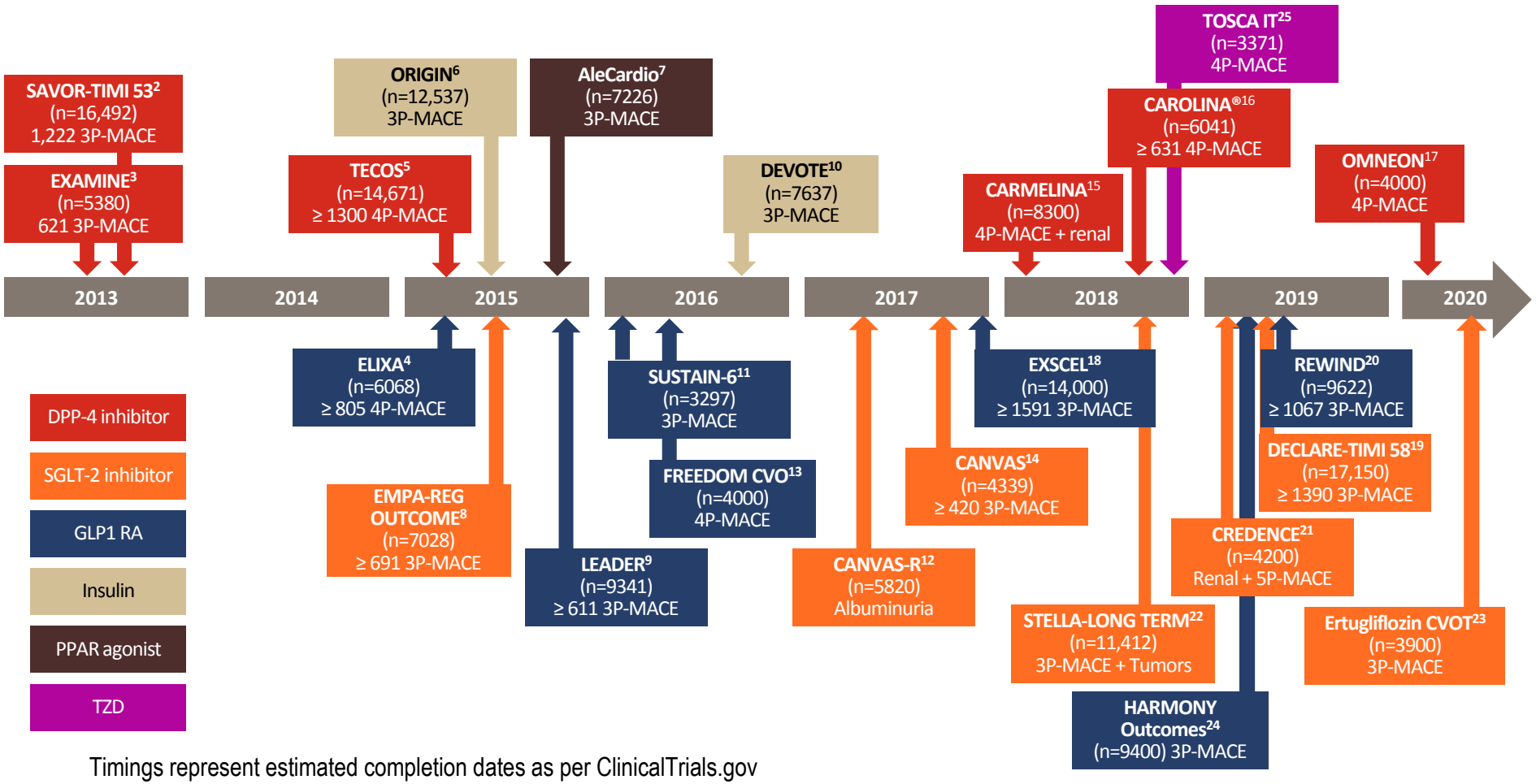


[a]First occurrence of nonfatal MI or nonfatal stroke or death from CV causes

Intensive therapy arm was terminated early (after 3.5 years) due to higher mortality

Gerstein et al. *N Engl J Med* 2008;358:2545-59

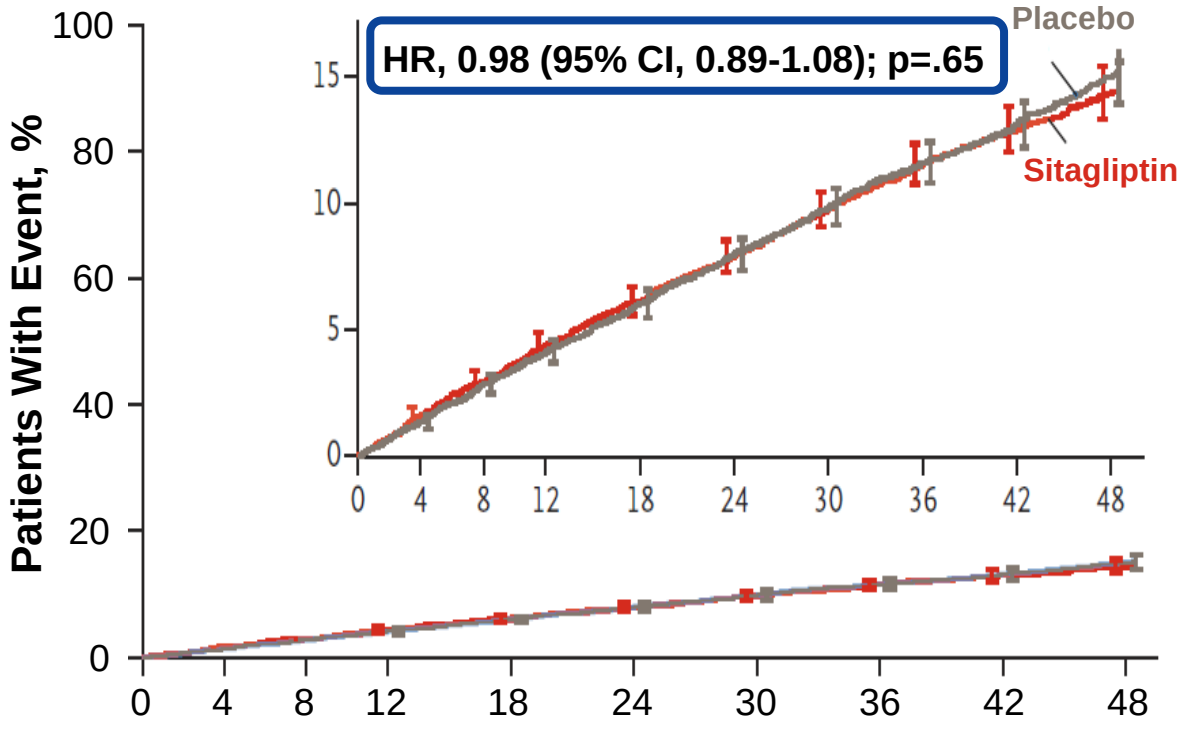
Overview of CVOTs of Glucose-lowering Drugs[1]



Timings represent estimated completion dates as per ClinicalTrials.gov

1. Johansen OE. 2015
2. Scirica BM et al. 2013
3. White WB et al. 2013
4. Pfeffer MA et al. 2015
5. Green JB et al. 2015
6. ORIGIN. 2012
7. Lincoff AM et al. 2014
8. Zinman B et al. 2015
9. Marso SP et al. 2016
10. NCT01959529
11. NCT01720446
12. NCT01989754
13. NCT01455896
14. NCT01032629
15. NCT01897532
16. NCT01243424
17. NCT01703208
18. NCT01144338
19. NCT01730534
20. NCT01394952
21. NCT02065791
22. NCT02479399
23. NCT01986881
24. NCT02465515
25. NCT00700856

TECOS: Primary CV Outcome[a]



No. at Risk:

Sitagliptin	7332	7131	6937	6777	6579	6386	4525	3346	2058	1248
Placebo	7339	7146	6902	6751	6512	6292	4411	3272	2034	1234

CI upper limit <1.3
Sitagliptin met the noninferiority criterion (did not increase the risk of CV events versus placebo) (primary objective)

CI upper limit >1.0
Sitagliptin did not demonstrate superiority (did not reduce the risk for CV events vs. placebo)

- There was no significant between-group difference in the primary composite CV outcome[a]

[a]Primary endpoint was composite of CV death, nonfatal MI, nonfatal stroke, or hospitalization for UA

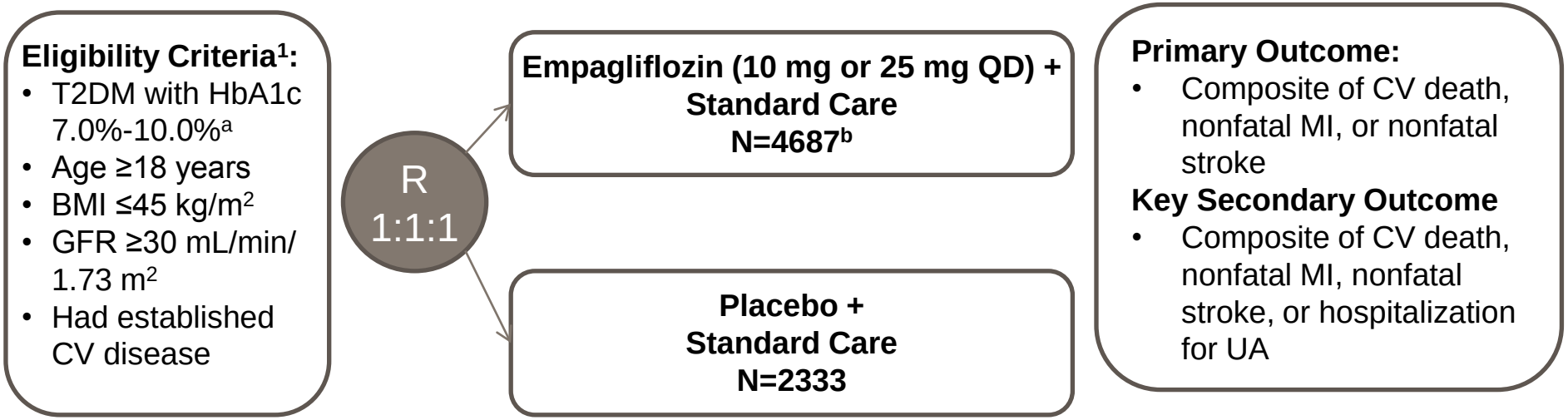
Data from Green JB et al. *N Engl J Med* 2015;373:232-42 (updated: 373:586)

Cardiovascular Outcome Trials for SGLT-2 Inhibitors

Study Identifier	SGLT-2 inhibitor	Study Phase	Completion Date
EMPA-REG OUTCOME[1]	Empagliflozin	3	2015
CANVAS[2]	Canagliflozin	3	2017
CANVAS-R[3]	Canagliflozin	4	2017
STELLA LONGTERM[4]	Ipragliflozin	Observational	2018
DECLARE-TIMI 58[5]	Dapagliflozin	3	2019
CREDENCE[6]	Canagliflozin	3	2020
Ertugliflozin CVOT[7]	Ertugliflozin	3	2020

1. Zinman B et al. *N Engl J Med* 2015;373:2117-28
2. https://clinicaltrials.gov/ct2/show/NCT01032629
3. https://clinicaltrials.gov/ct2/show/NCT01989754
4. https://clinicaltrials.gov/ct2/show/NCT02479399
5. https://clinicaltrials.gov/ct2/show/NCT01730534
6. https://clinicaltrials.gov/ct2/show/NCT02065791
7. https://clinicaltrials.gov/ct2/show/NCT01986881

EMPA-REG OUTCOME: Study Design and Objectives

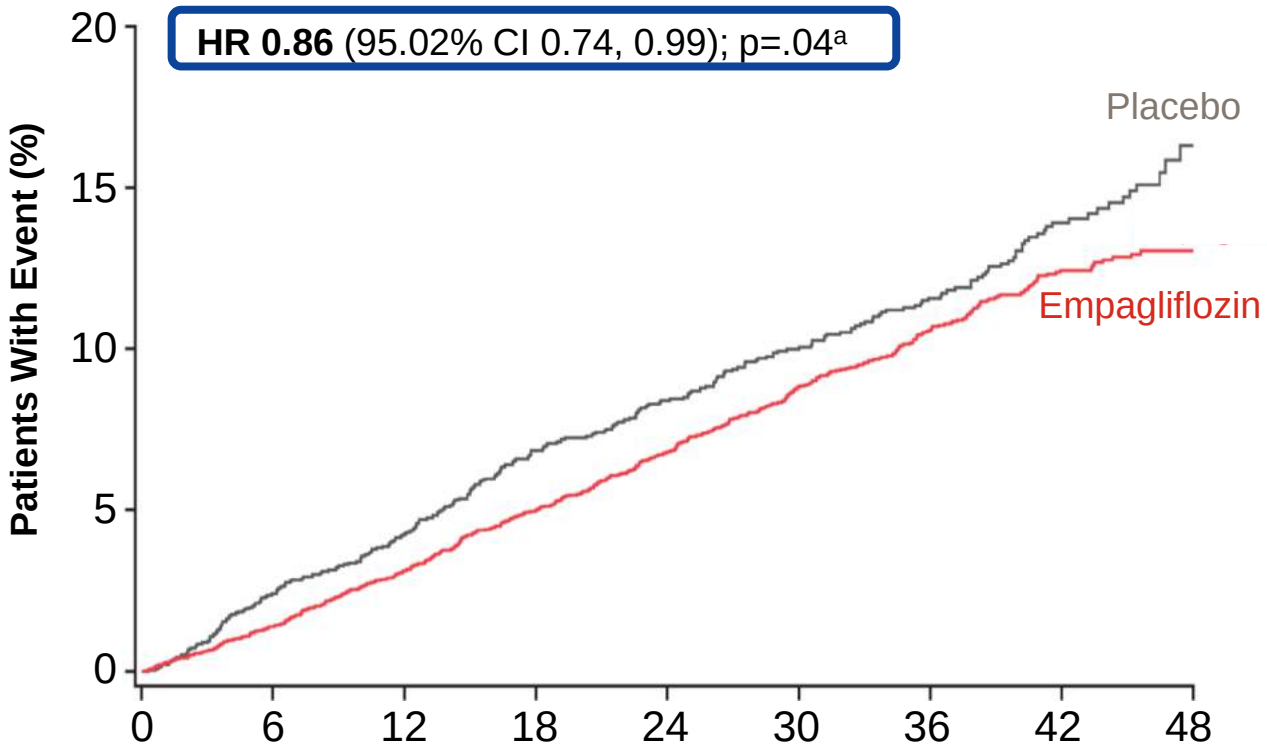


- **Study design:** Multicenter, randomized, double-blind, placebo-controlled study
- **Primary objective:** To assess the effects of empagliflozin vs. placebo on CV morbidity and mortality in patients with T2DM who were at high risk for CV events and were receiving standard care

[a]HbA1c 7.0%-9.0% in patients who did not receive any glucose lowering agents ≥12 weeks prior to randomization
[b]Pooled empagliflozin group

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

EMPA-REG OUTCOME: Primary Outcome (3-point MACE)



No. at Risk:									
Empagliflozin	4687	4580	4455	4328	3851	2821	2359	1534	370
Placebo	2333	2256	2194	2112	1875	1380	1161	741	166

Cumulative incidence function

[a]Two-sided tests for superiority were conducted (statistical significance was indicated if p≤.0498)

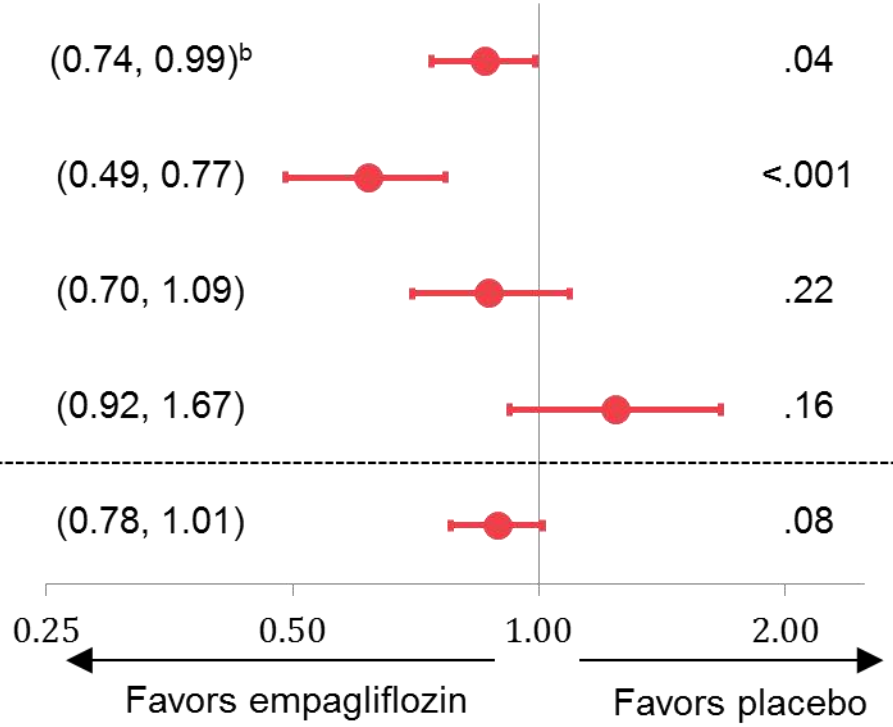
Data from Zinman B et al. *N Engl J Med* 2015;373:2117-28

CI upper limit <1.3
Empagliflozin met the noninferiority criterion (did not increase the risk of CV events versus placebo) (primary objective)

CI upper limit <1.0
Empagliflozin met the superiority criterion (reduced risk for CV events vs. placebo)

EMPA-REG OUTCOME: 3-point MACE and 4-point MACE

	Empagliflozin n/N	Placebo n/N	HR	(95% CI)	p-value
3-point MACE[a]	490/4687	282/2333	0.86	(0.74, 0.99)[b]	.04
CV death	172/4687	137/2333	0.62	(0.49, 0.77)	<.001
Nonfatal MI	213/4687	121/2333	0.87	(0.70, 1.09)	.22
Nonfatal stroke	150/4687	60/2333	1.24	(0.92, 1.67)	.16
4-point MACE[c]	599/4687	333/2333	0.89	(0.78, 1.01)	.08

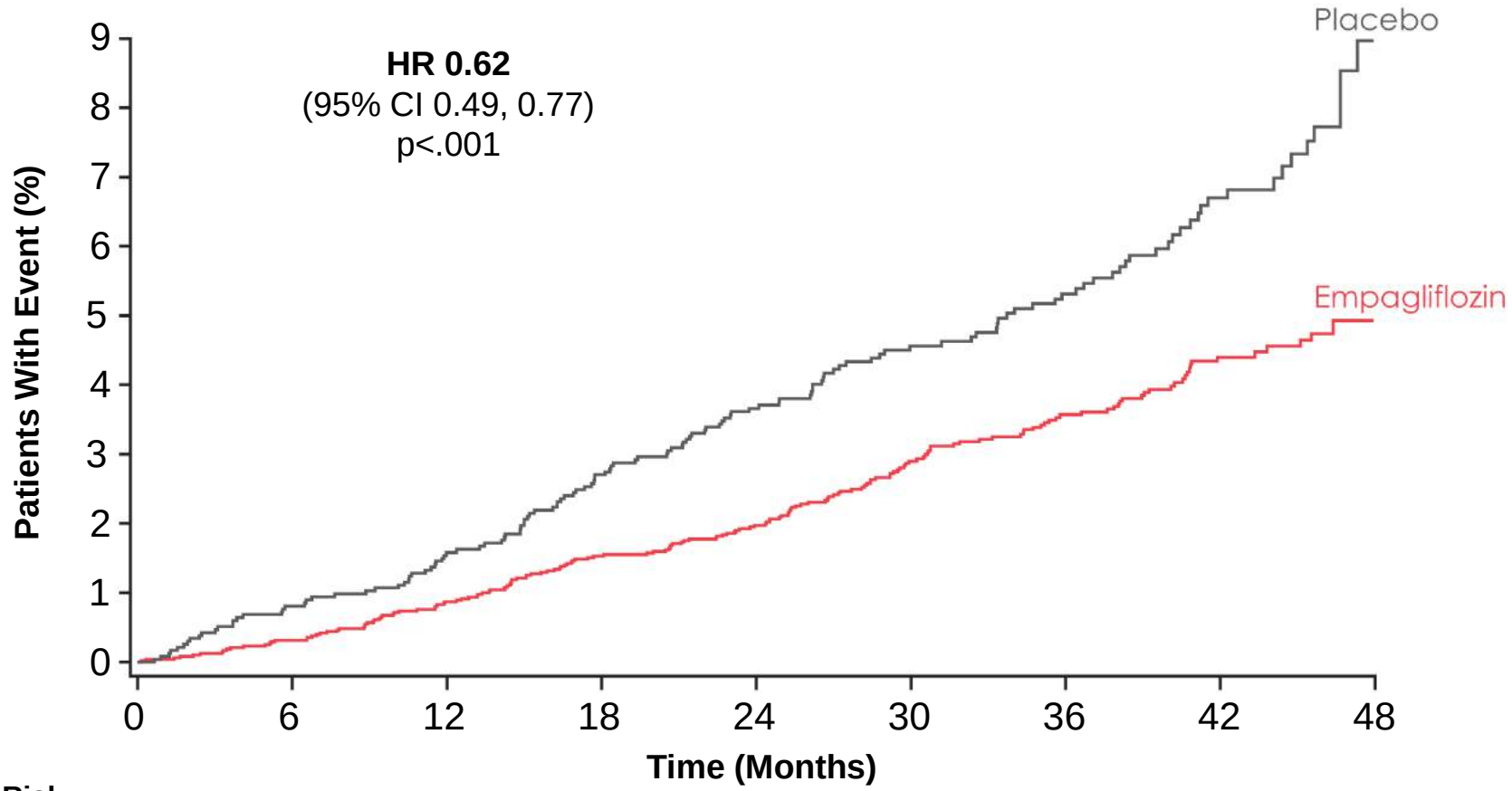


Cox regression analysis

[a]Primary outcome: Composite of CV death, nonfatal MI, and nonfatal stroke; [b]95.02% CI
[c]Secondary outcome: Composite of CV death, nonfatal MI, nonfatal stroke, or hospitalization for UA

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

EMPA-REG OUTCOME: CV Death



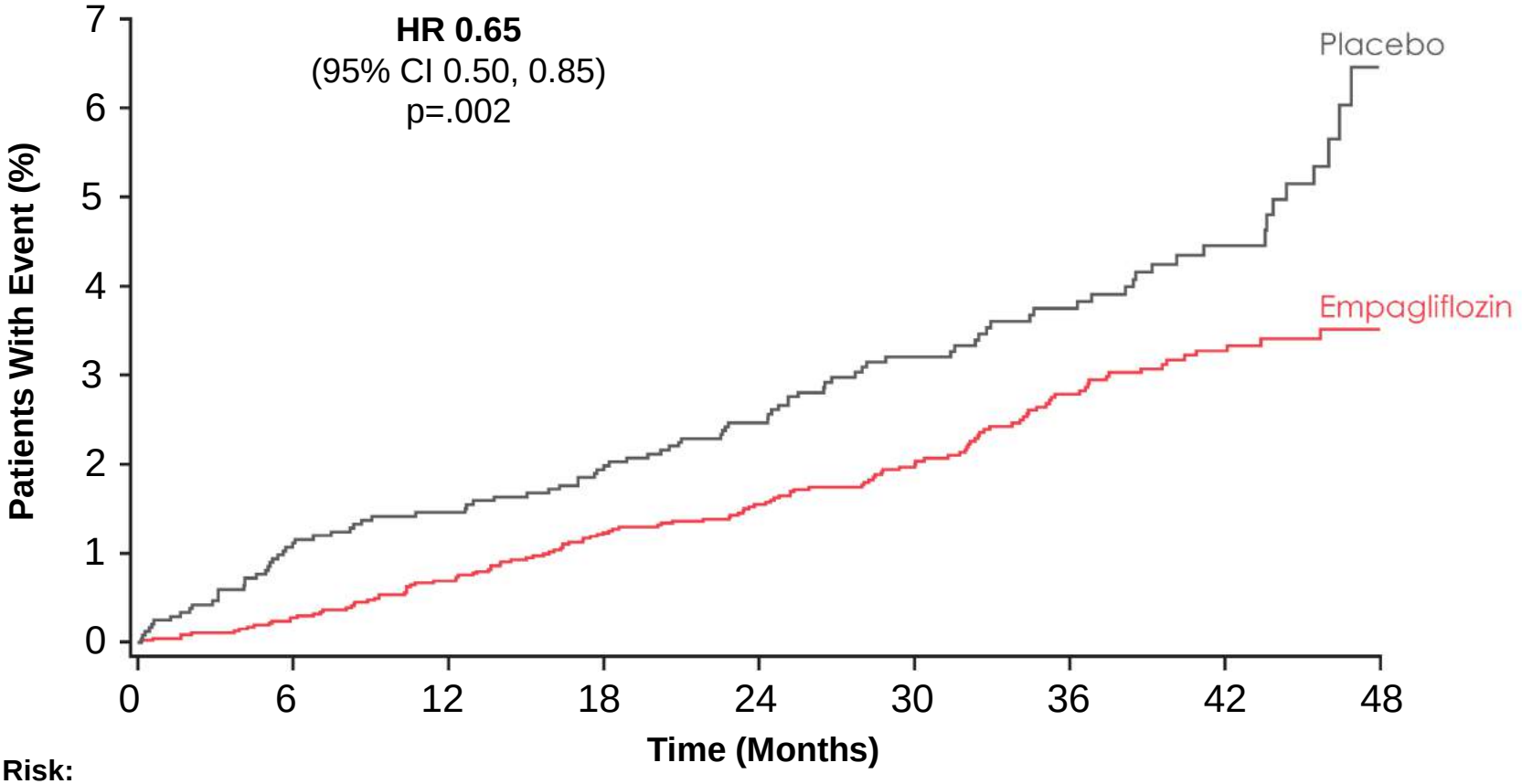
No. at Risk:

Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722	414
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

Cumulative incidence function

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

EMPA-REG OUTCOME: Hospitalization for Heart Failure



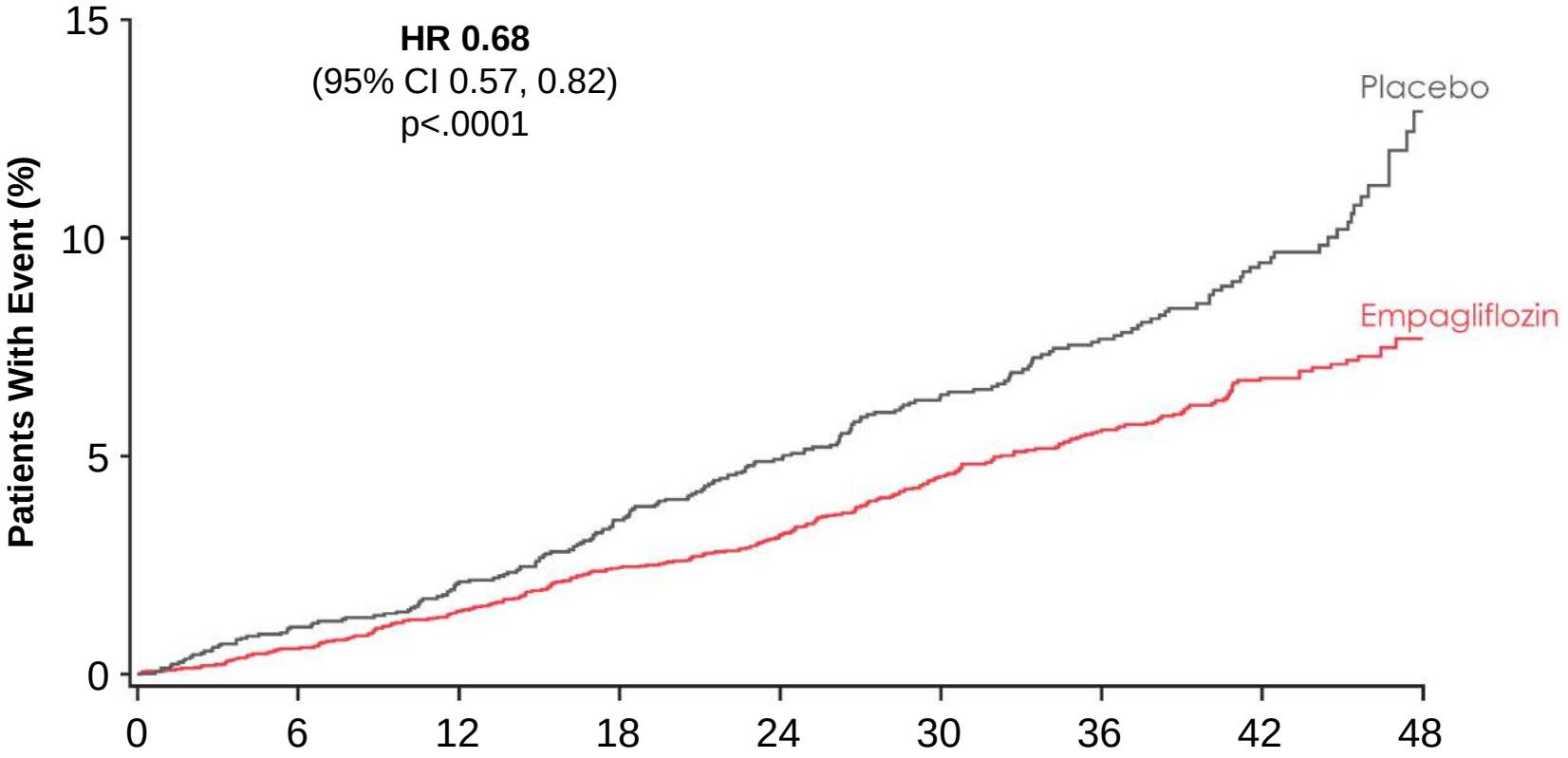
No. at Risk:

Empagliflozin	4687	4614	4523	4427	3988	2950	2487	1634	395
Placebo	2333	2271	2226	2173	1932	1424	1202	775	168

Cumulative incidence function

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

EMPA-REG OUTCOME: All-cause Mortality



No. at Risk:

Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722	414
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

Cumulative incidence function

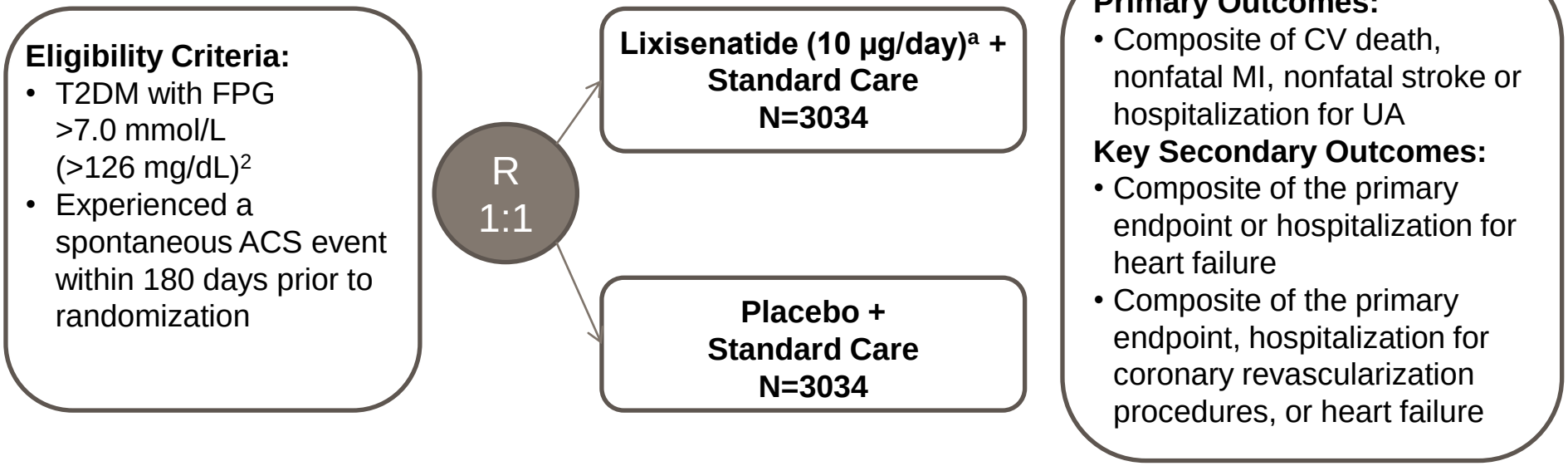
Data from Zinman B et al. *N Engl J Med* 2015;373:2117-28

EMPA-REG OUTCOME: Conclusions

- In patients with T2DM who are at high risk for CV events, empagliflozin added to standard care, compared to placebo, is associated with lower rates of
  - The primary composite CV outcome
    - This was driven by the significant reduction in CV death, with no significant between-group difference in risk of MI or stroke
  - Death from any cause
  - Hospitalization for heart failure
- Proportion of patients reporting AEs, SAEs, and AEs leading to discontinuation was similar in the two groups

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

ELIXA: Study Design and Objectives[1]

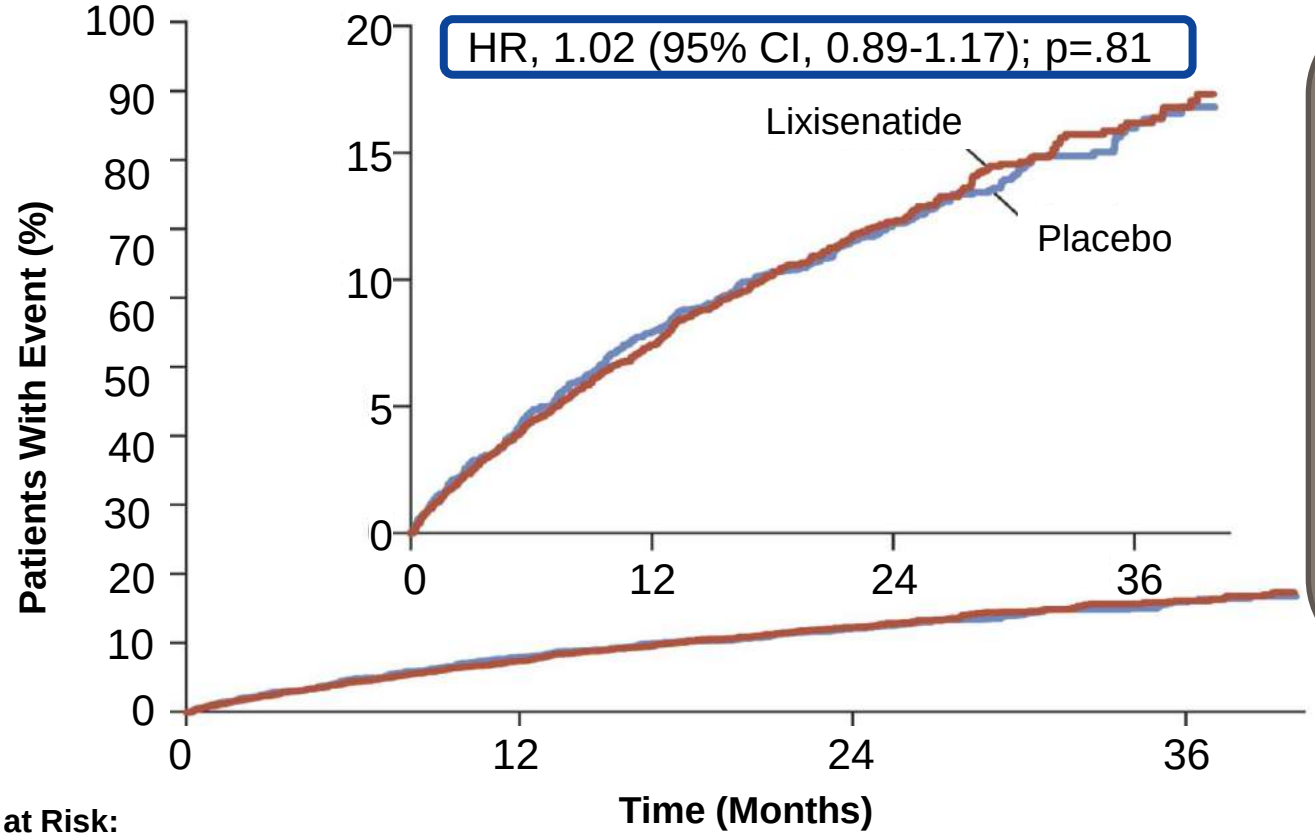


- **Study design:** Multicenter, randomized, double-blind , parallel-group, placebo-controlled study
- **Primary objective:** To evaluate the effects of lixisenatide on CV morbidity and mortality [composite endpoint of CV death, nonfatal MI, nonfatal stroke, hospitalization for UA] compared to placebo in T2DM patients who recently experienced an ACS event

[a]Dose could be increased to a maximum of 20 µg/day at the investigator's discretion

1. Pfeffer MA et al. *N Engl J Med* 2015;373:2247-57
2. Bentley-Lewis R et al. *Am Heart J* 2015;169:631-638.e7

ELIXA: Primary Outcome (CV Death, MI, Stroke, or UA)



No. at Risk:

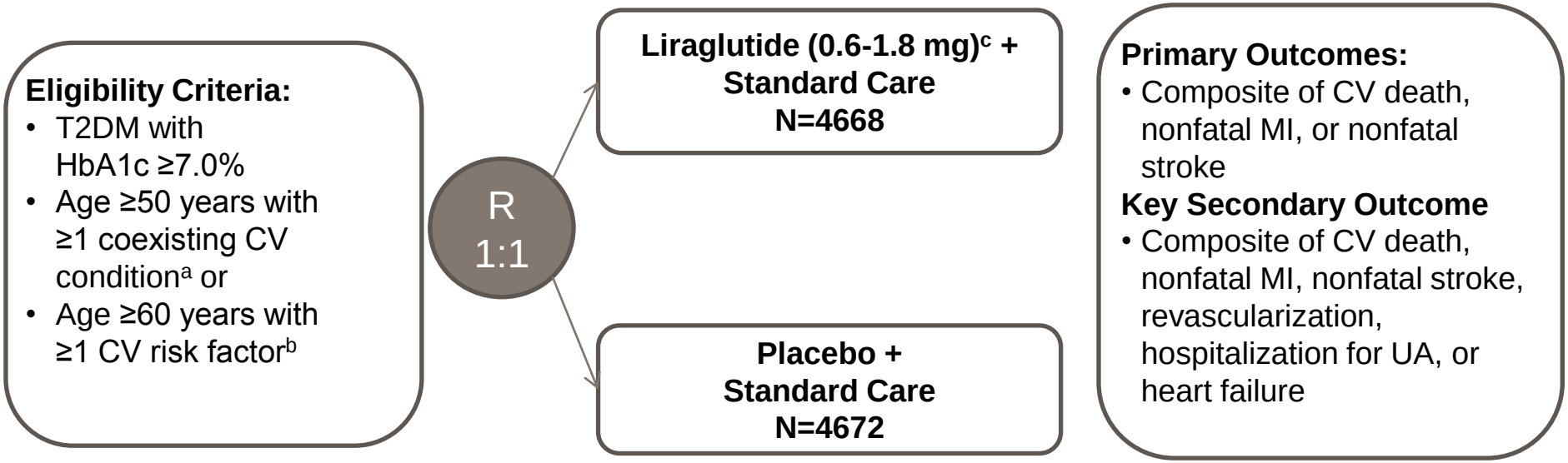
Lixisenatide	3034	2785	1558	484
Placebo	3034	2759	1566	476

CI upper limit <1.3
Lixisenatide met the noninferiority criterion (did not increase the risk of CV events versus placebo) (primary objective)

CI upper limit >1.0
Lixisenatide did not demonstrate superiority (reduced risk for CV events vs. placebo)

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

LEADER:
Study Design and Objectives



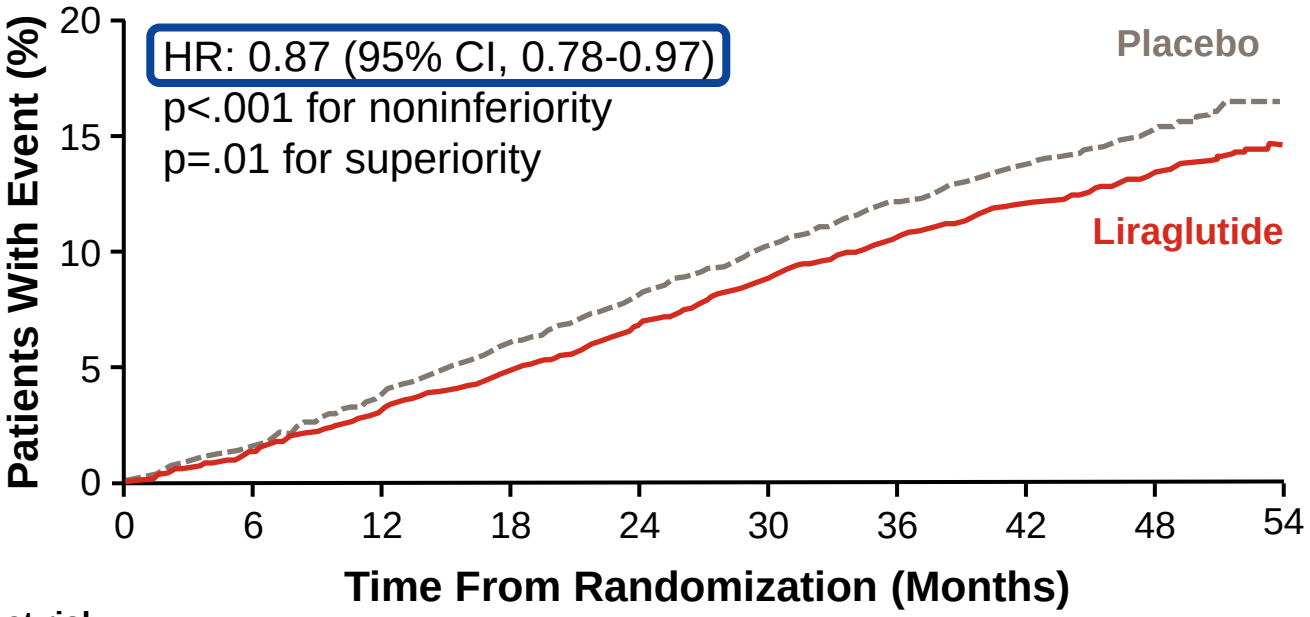
- **Study design:** International, randomized, placebo-controlled study
- **Primary objective:** To evaluate the effect of liraglutide compared to placebo on the incidence of CV events in adults with type 2 diabetes

[a]Coronary heart disease, cerebrovascular disease, peripheral vascular disease, CKD stage ≥3, chronic heart failure NYHA class II/III
[b]Microalbumiuria or proteinuria, hypertension and left ventricular hypertrophy, left ventricular systolic or diastolic dysfunction, or an ankle-brachial index (the ratio of the systolic BP at the ankle to the systolic BP in the arm) of <0.9
[c]Liraglutide was administered at 0.6 mg daily for 1 week, 1.2 mg/day for an additional week, and a potential maximum dosage of 1.8 mg/day thereafter

Marso SP et al. *Am Heart J* 2013;166:823-30.e5

LEADER: Primary Outcome[a]

CV Death, Nonfatal MI, or Nonfatal Stroke



No. at risk

Liraglutide	4668	4593	4496	4400	4280	4172	4072	3982	1562	424
Placebo	4672	4588	4473	4352	4237	4123	4010	3914	1543	407

CI upper limit <1.3
Liraglutide met the noninferiority criterion (did not increase the risk of CV events vs. placebo) (primary objective)

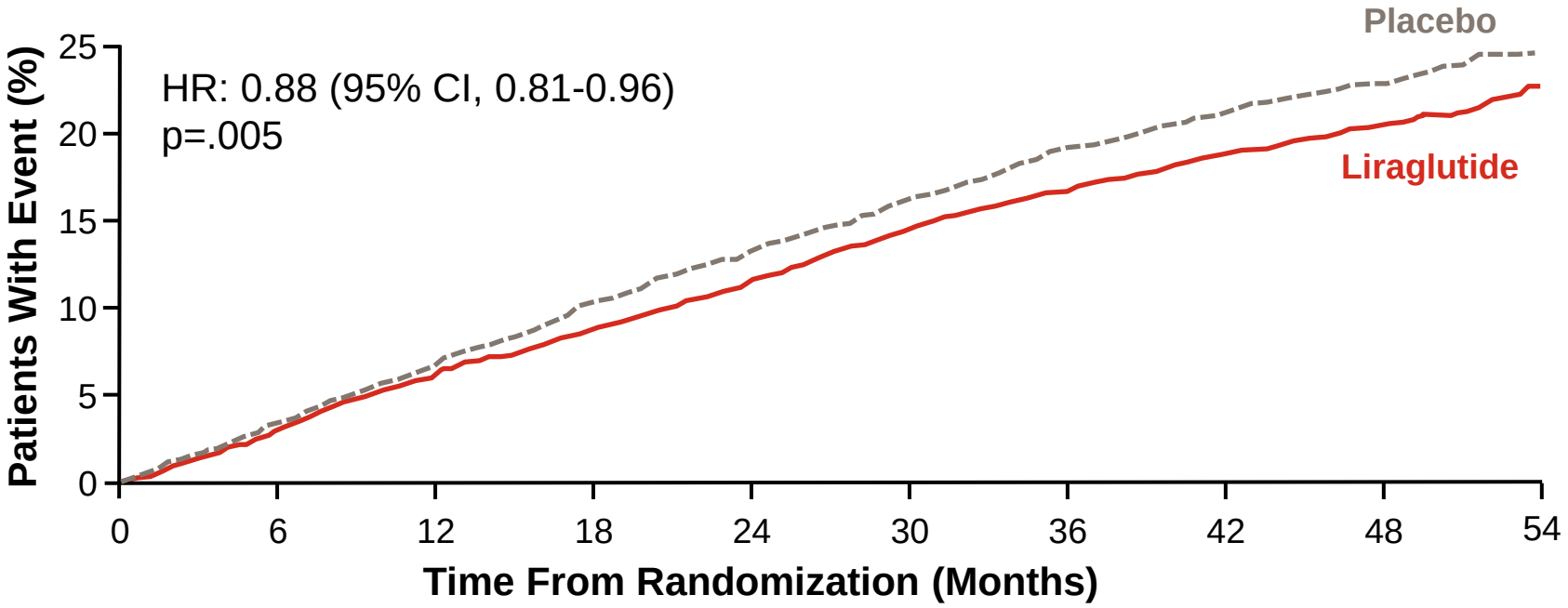
CI upper limit <1.0
Liraglutide demonstrated superiority (reduced risk for CV events) vs. placebo

[a]The primary composite outcome in the time-to-event analysis was the first occurrence of CV death, nonfatal MI, or nonfatal stroke
The cumulative incidences were estimated with the use of the Kaplan-Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model
The data analyses were truncated at 54 months, because <10% of the patients had an observation time beyond 54 months

Marso SP et al. *N Engl J Med* 2016;(Ahead of print)

LEADER: Expanded MACE[a]

CV Death, Nonfatal MI, Nonfatal Stroke, Coronary Revascularization, or Hospitalization for UA



No. at risk										
Liraglutide	4668	4515	4356	4221	4063	3914	3793	3682	1452	395
Placebo	4672	4506	4336	4157	4002	3857	3697	3581	1410	366

[a]The expanded composite CV outcome included CV death, nonfatal MI, nonfatal stroke, coronary revascularization, or hospitalization for UA or heart failure

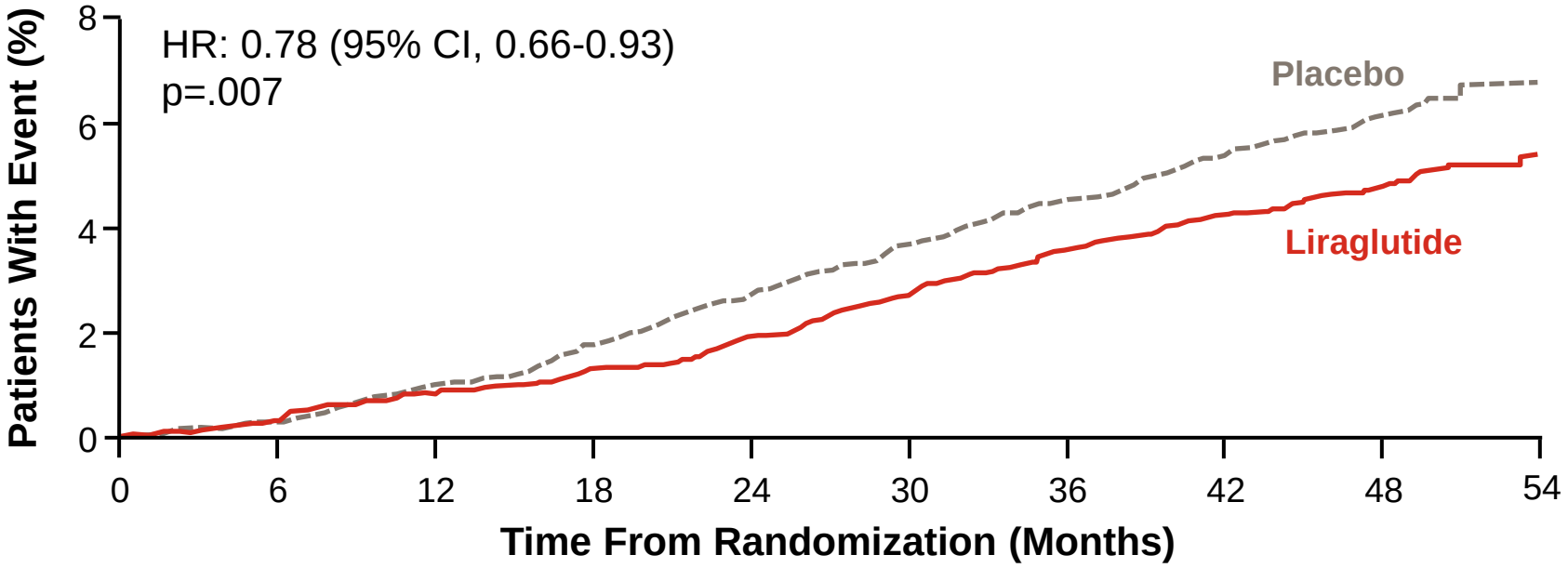
The cumulative incidences were estimated with the use of the Kaplan-Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model

The data analyses were truncated at 54 months, because less than 10% of the patients had an observation time beyond 54 months

Marso SP et al. *N Engl J Med* 2016;(Ahead of print)

LEADER: CV Death

Time-to-Event Analysis



No. at risk

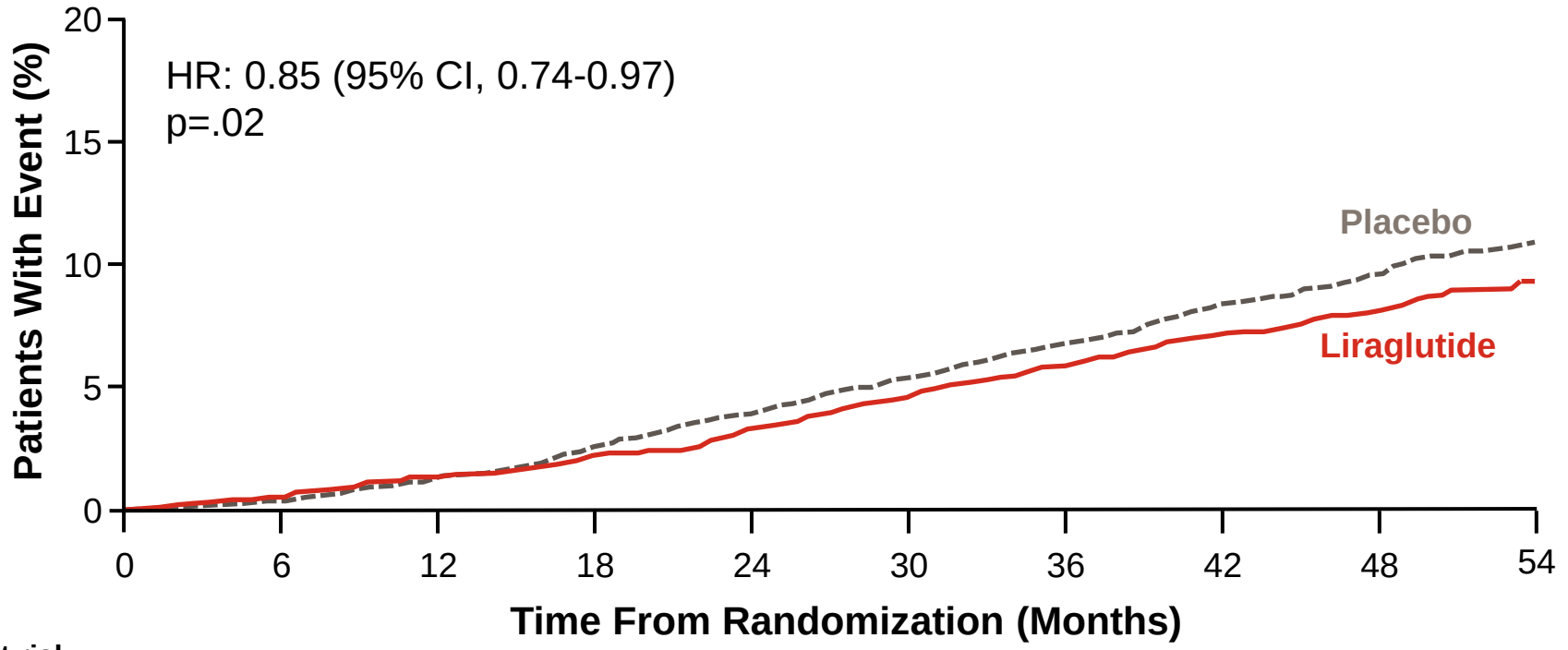
Liraglutide	4668	4641	4599	4558	4505	4445	4382	4322	1723	484
Placebo	4672	4648	4601	4546	4479	4407	4338	4267	1709	465

The cumulative incidences were estimated with the use of the Kaplan-Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model

The data analyses were truncated at 54 months, because less than 10% of the patients had an observation time beyond 54 months

Marso SP et al. *N Engl J Med* 2016;(Ahead of print)

LEADER: All-cause Death



No. at risk

Liraglutide	4668	4641	4599	4558	4505	4445	4382	4322	1723	484
Placebo	4672	4648	4601	4546	4479	4407	4338	4268	1709	465

The cumulative incidences were estimated with the use of the Kaplan-Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model

The data analyses were truncated at 54 months, because less than 10% of the patients had an observation time beyond 54 months

Marso SP et al. *N Engl J Med* 2016;(Ahead of print)

LEADER: Summary

- Liraglutide added to standard of care demonstrated noninferiority, as well as superiority, vs. placebo + standard of care for the primary endpoint[a]
  - Liraglutide reduced the risk for 3-point MACE by 13%
- Nonfatal MI, nonfatal stroke and hospitalization for heart failure were numerically lower in the liraglutide group
- Liraglutide reduced the risk of CV death and all-cause death by 22% and 15%, respectively

[a]The primary composite outcome included CV death, nonfatal MI, or nonfatal stroke

Marso SP et al. *N Engl J Med* 2016;(Ahead of print)

Thesis

The role of ketone measurements which have been ignored in recent recommendations on diabetes care need to be reassessed.

Species of Ketones

- Beta Hydroxybutyrate (<0.3mmol/L)
- Acetoacetate (<0.1 mmoles/L)
- Acetone (undetectable)

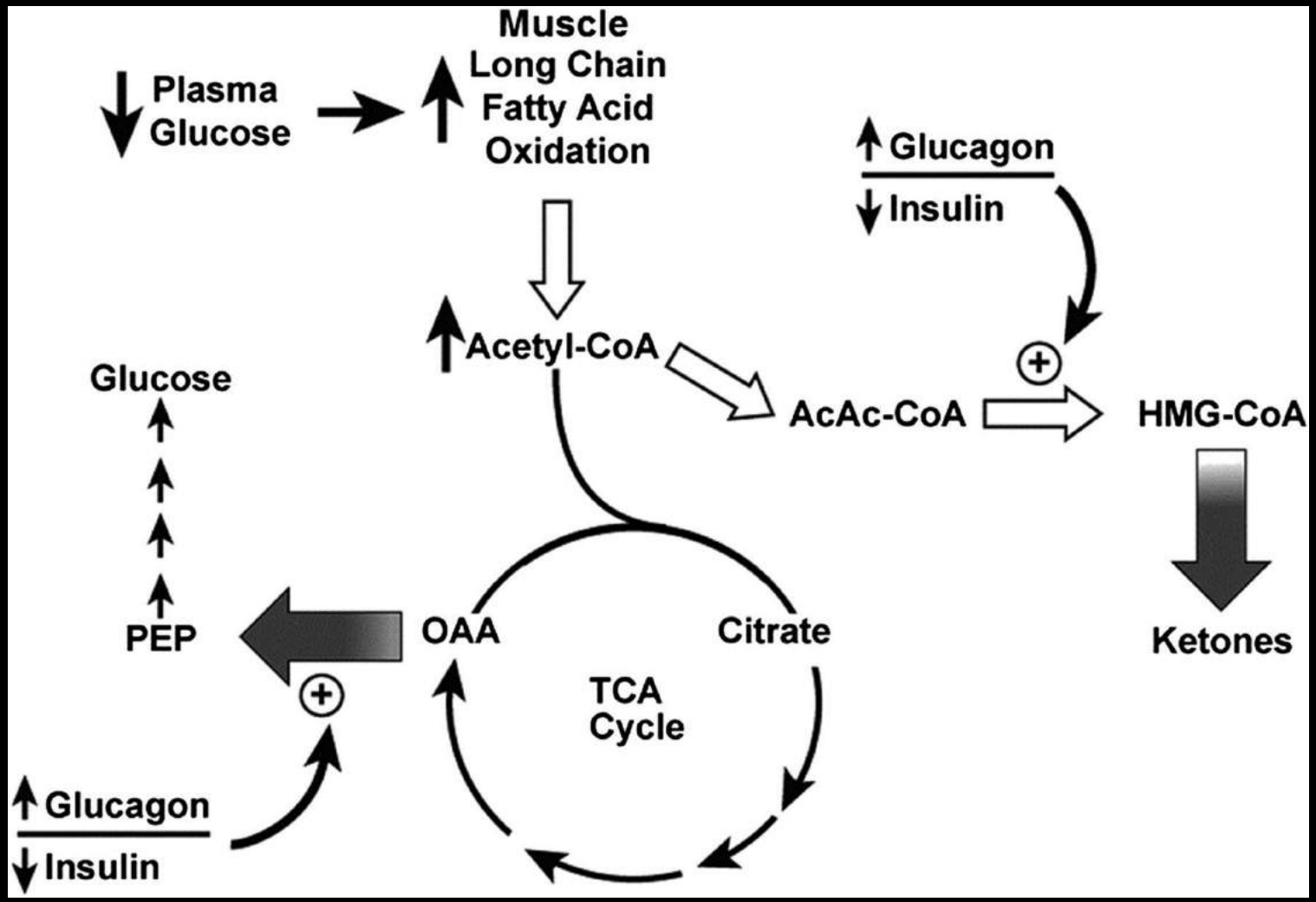
Standard urine ketone and serum testing only measured acetoacetate and acetone. Beta hydroxybutyrate is not measured.

Role of Ketone Measurements

Nutritional Status

Recognition and treatment of DKA

Cardiac impact



American Diabetes Association.

The phenomenon of near euglycemic diabetic ketoacidosis

Individuals on SGLT-2 inhibitors with diabetes supposedly, Type 1 and Type 2, have presented with diabetic ketoacidosis despite serum glucose levels often less than 200 mg/dl. This has been confirmed by the presence of an anion gap acidosis and elevated ketone levels.

Glucose Clamps Studies in Patients on Dapaglifozin

- Increased Glucose Disposal by 36% $p<0.01$
- Decreased Glucose Oxidation
- Increased Glycogen Formation
- Increased Lipid Oxidation
- Increased Ketone Formation (0.05mmol/L to 0.20 mmole/L $p<0.01$)
- Increased Glucagon (77 to 94 $p<0.01$)

Diabetes Care 39:2036-2041, 2016

EMPA-REG Outcomes -Questions

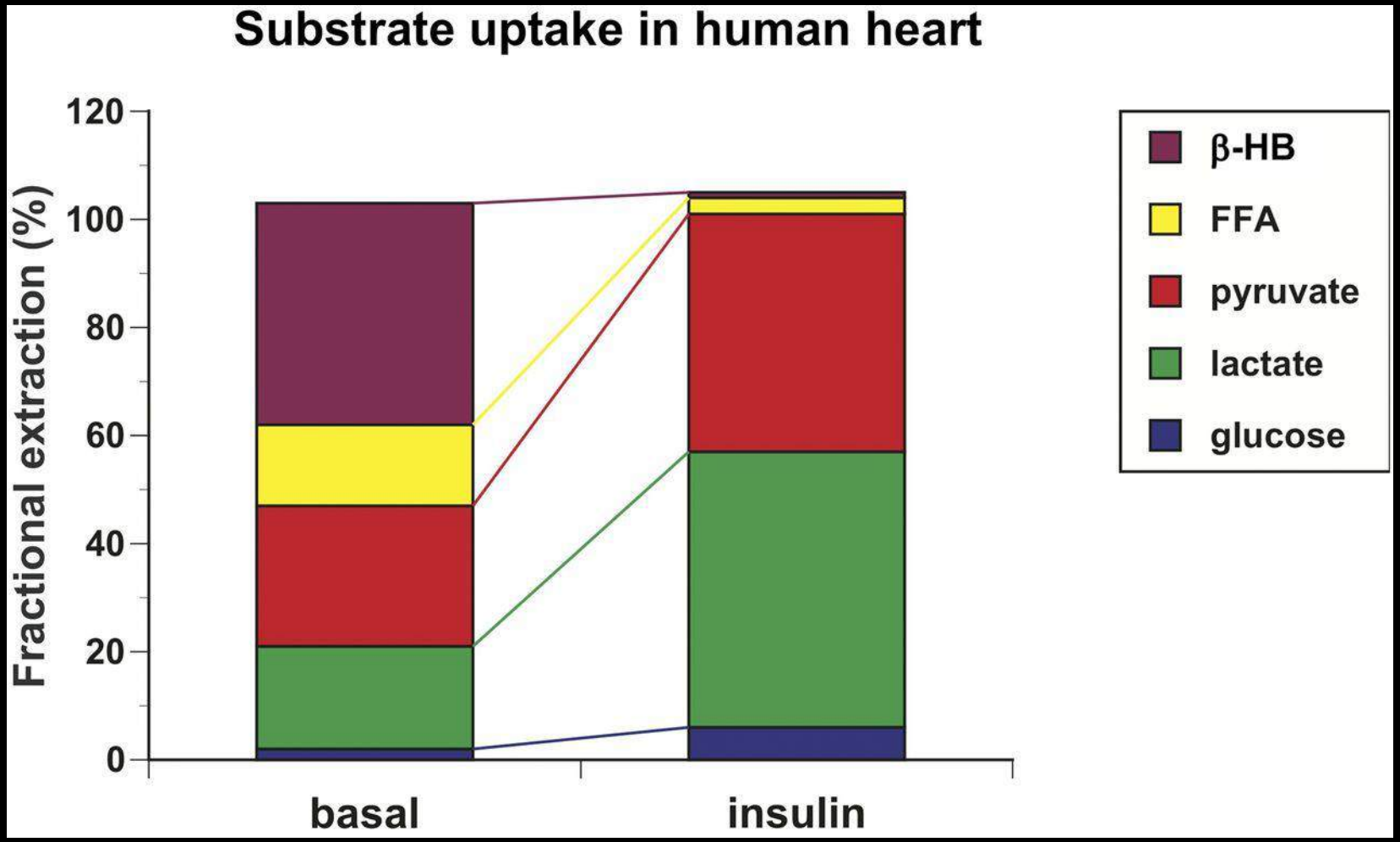
- Game changer? Or incredibly preliminary?
- Class effect or drug specific?
- What happens with primary prevention?
- What is the mechanism?
- If osmotic diuresis is the mechanism, should Empagliflozin/SGLT2 be studied in non-diabetic patients with fluid overload states?
- Are the Glitazars (mura, tesa and aleglitazar) an acceptable comparator?

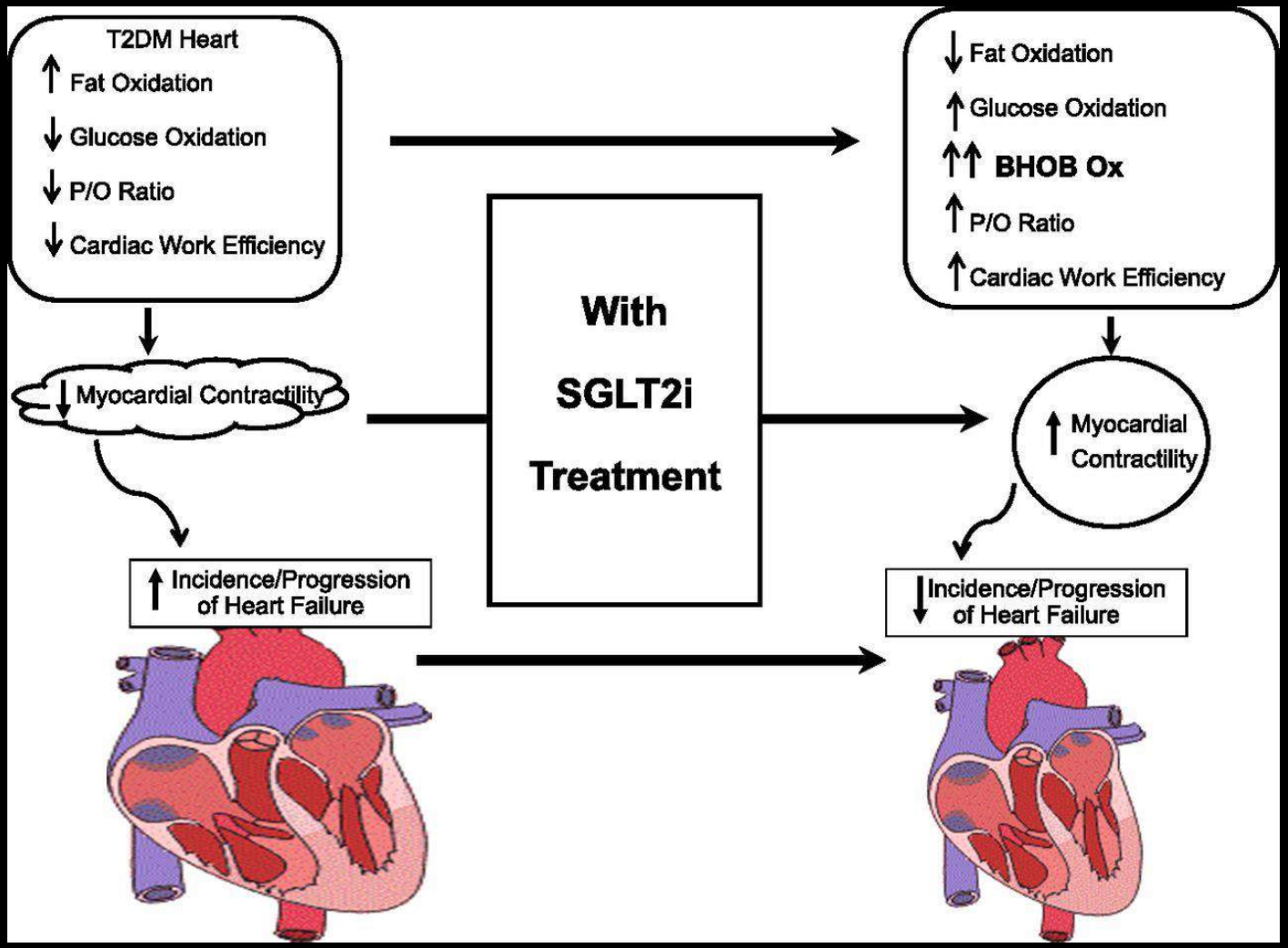
EMPA-REG POSSIBLE EXPLANATIONS

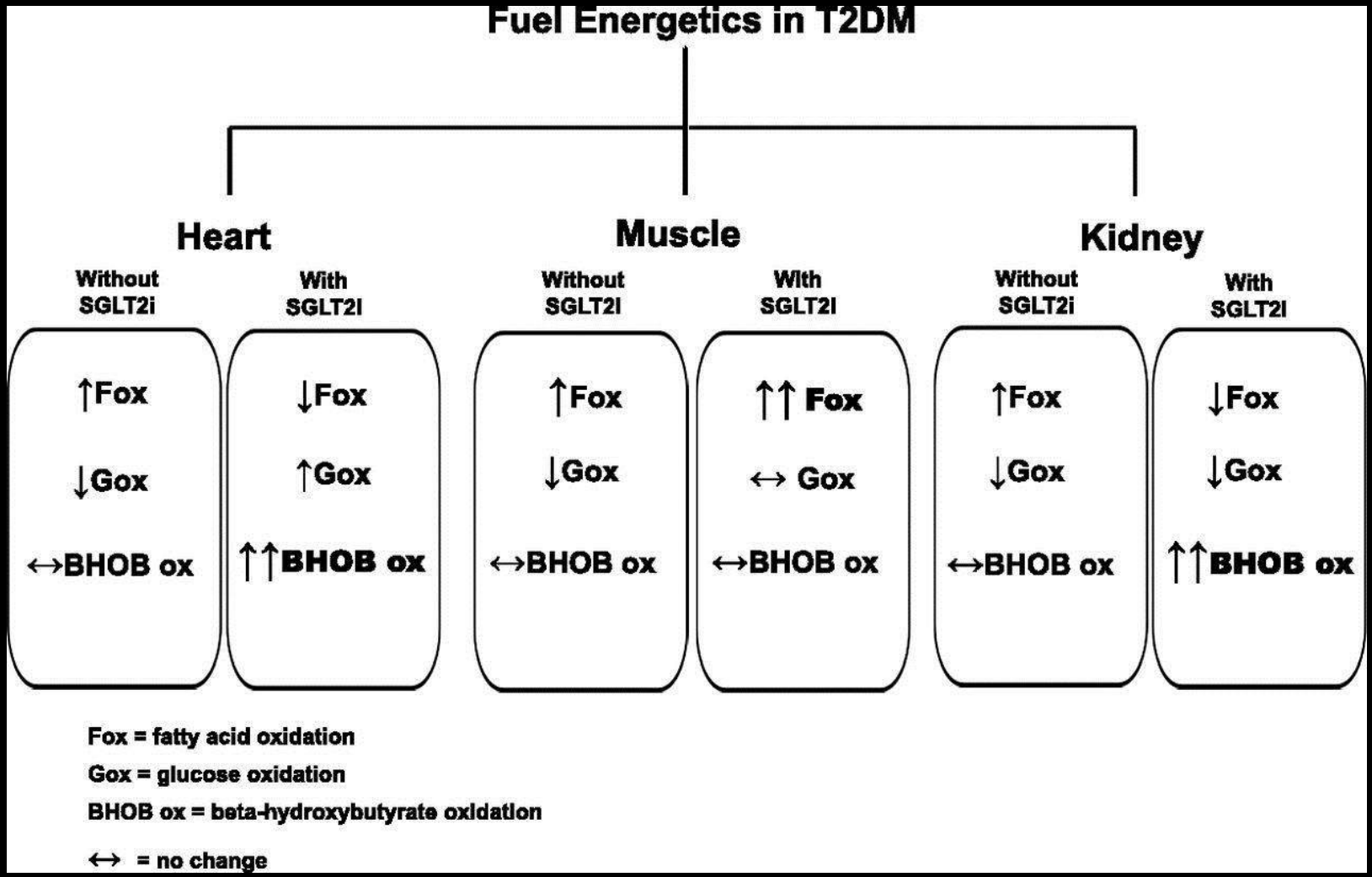
- Diuretic Effect
- Blood Pressure Effect
- Improved Glycemic control
- Weight Loss
- Decreased glucose fluctuations
- Increased levels and use of beta hydroxybutyrate as cardiac substrate

Effect of beta Hydroxybutyrate on Cardiac Myocytes

- Beta Hydroxybutyrate uptake is insulin independent
- Fractional extraction of 40%
- Contributes 15% of energy expenditure overnight
- Decreases lipid oxidation and subsequent oxygen demand







HYPOTHESIS

Should beta Hydroxybutyrate measurements be done routinely with the goal of preventing ketoacidosis in individuals with Type 1 diabetes if and when SGLT2 therapy is indicated and should these measurements also be done on individuals with Type 2 diabetes and cardiac disease to achieve safe but desirable levels of beta hydroxybutyrate?

Differences Between EMPA-REG and Leader

- Time to initial benefit
- Impact on Stroke
- Impact on Heart Failure
- Impact on Pulse Rate

Analysis of EMPA-REG and Leader

- Primary vs Secondary Prevention
- Same phenomenon or different
- Synergistic ?

Thougths and Recommendations

- SGLT2 Treatment for all Diabetics with Heart Failure
- Testing for occult Heart Failure in all Diabetics
- Harm of GLP1 treatment on the benefits of SGLT2 treatment
- Need for Primary Prevention Study of both agents