



ACC Middle East
Conference 2018

In partnership with:



جمعية القلب السعودية
Saudi Heart Association

CV outcomes Studies and Implications for diabetes management

Seraj Abualnaja, MD, FRCPC

Consultant Interventional cardiologist
DSFH



Case

- 49 y female with the following medical problems
- DM typ2
- Hypertension
- Dyslipidemia
- CKD , GFR 40
- CAD s/p PCI 2 times , all related to angina
- Preserved LVEF 50%



ACC Middle East
Conference 2018

In partnership with:



•Her diabetic complications includes the following:

- 1- Diabetic retinopathy
- 2- CKD with FGR of 40
- 3- Vasculopathy :
- 4- CAD s/p PCI times
- 5- PVD , with moderate atherosclerosis in lower limb arterial system
- 6- Recurrent admission to the hospital for CHF



ACC Middle East
Conference 2018



- Her labs are as follow :
- HBA1C is almost always above 10
- LDL is always controlled below 70 mg/dL , last one was 60
- She has normocytic anemia , Hg is always above 10
- ECG : normal
- Echo : LVEF 52 % , no significant valve pathology



ACC Middle East
Conference 2018

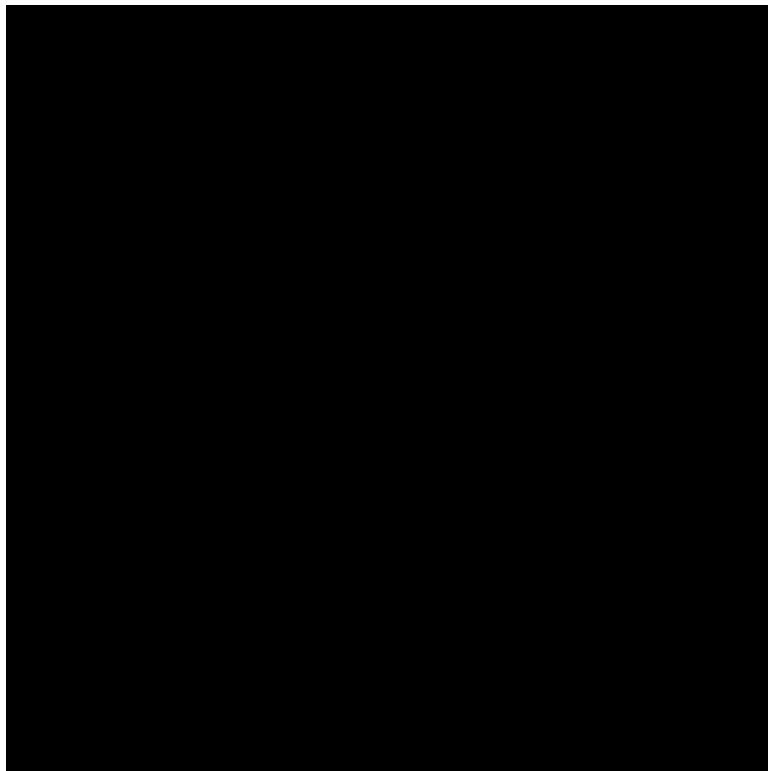


- She presented with atypical and +ve MPI in inferior wall
- She has PCI to LAD and RCA before (twice in RCA) and once in LAD
- All are DES
- She is on the following meds :
 - ASA and plavix for the last 3 years
 - Metformin , Sitagliptin and Insulin
 - Lipitor of 40 mg daily
 - Concor 10 mg daily
 - Amlodipine 10 mg daily



ACC Middle East
Conference 2018

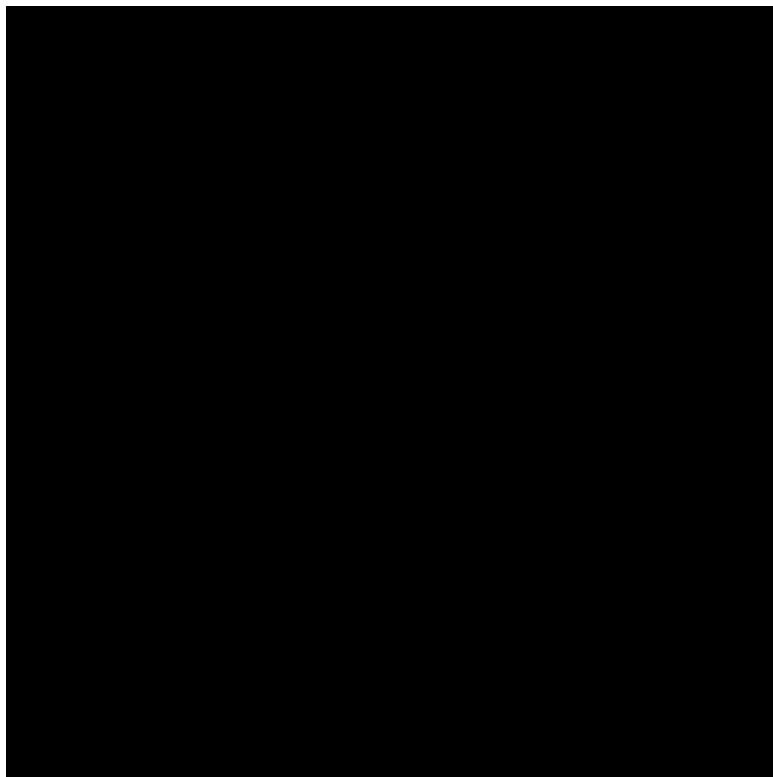




ACC Middle East
Conference 2018

In partnership with:





ACC Middle East
Conference 2018

In partnership with:



- So this time she was booked for CABG which was done for her LAD , OM and PDA
- She has prolonged ICU staying
- She was discharged after 3 weeks
- She was readmitted with sternal wound infection , debridement was done
- Another prolonged admission in the hospital but eventually she was discharged
- Another readmission for CHF symptoms and worsening creatinine
- She had aggressive diuresis and improved
- Still preserved LV function
- Creatinine is back to the base line (1.5)



ACC Middle East
Conference 2018



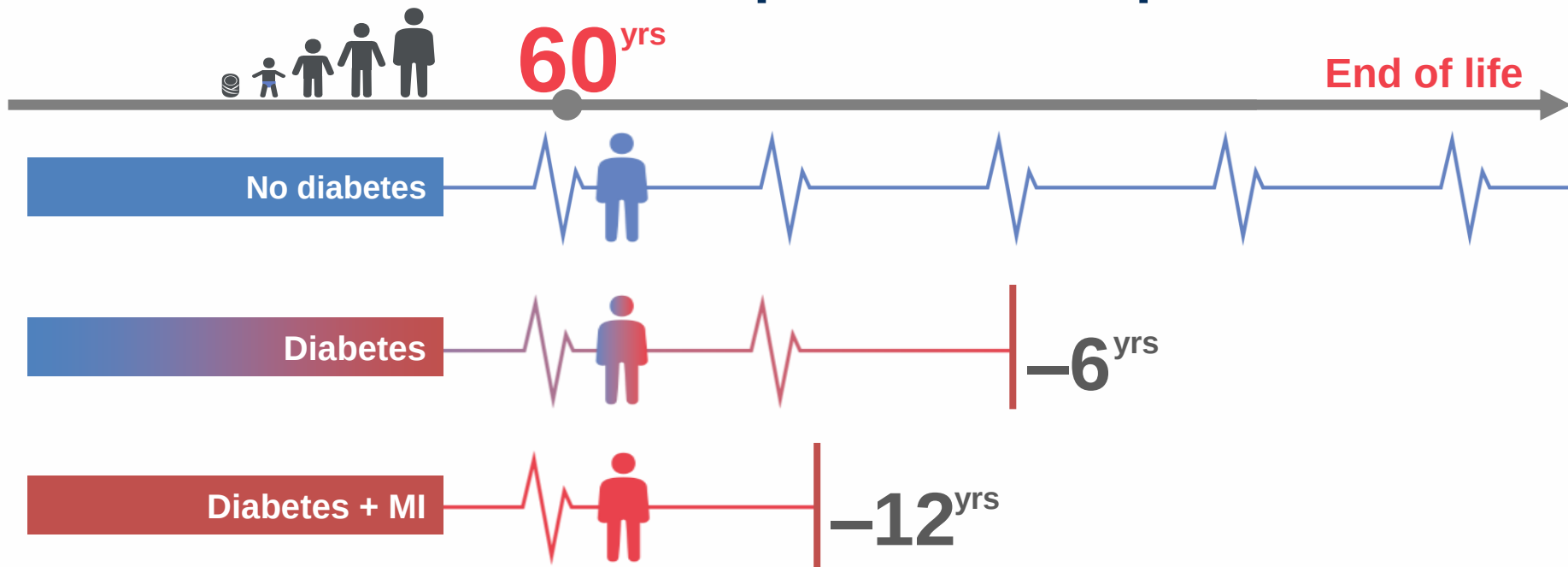
- Endocrine consultation was done for her blood sugar control
- Sitagliptin was stopped
- Empagliflozin was started as well as Insulin
- In follow up last week :
 - She is euvolemic . She is NYHA class I-II . CCS class I
 - BP is 130/60 .
 - HBA1C is 8.1



ACC Middle East
Conference 2018



Life expectancy is reduced by 12 years in diabetes patients with previous CVD*



In this case, CVD is represented by MI or stroke.
*Male, 60 years of age with history of MI or stroke.
CVD, cardiovascular disease; MI, myocardial infarction.
The Emerging Risk Factors Collaboration. *N Engl J Med*. 2015;314:52.



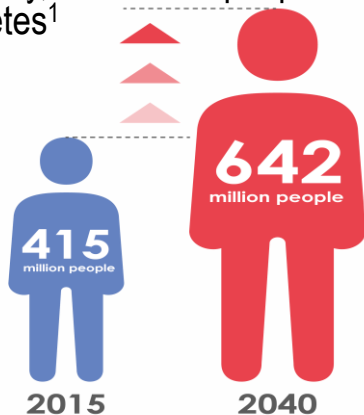
ACC Middle East
Conference 2018

In partnership with:



Type 2 diabetes is increasingly prevalent

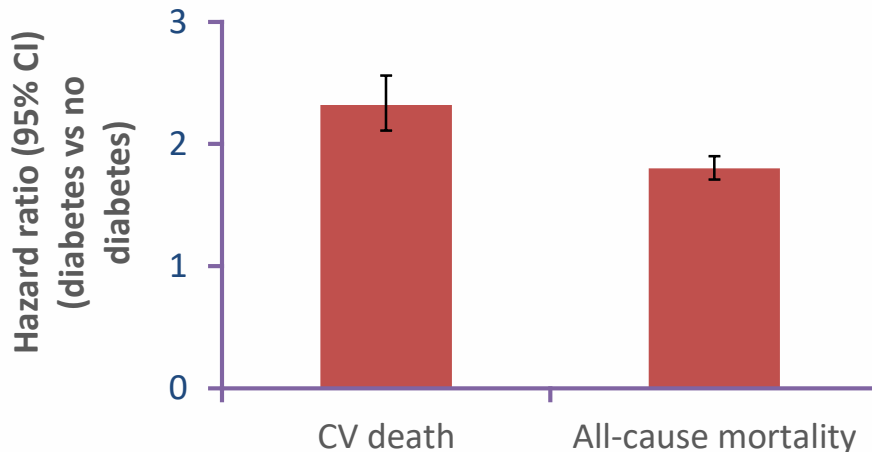
- Globally, 415 million people are living with diabetes¹



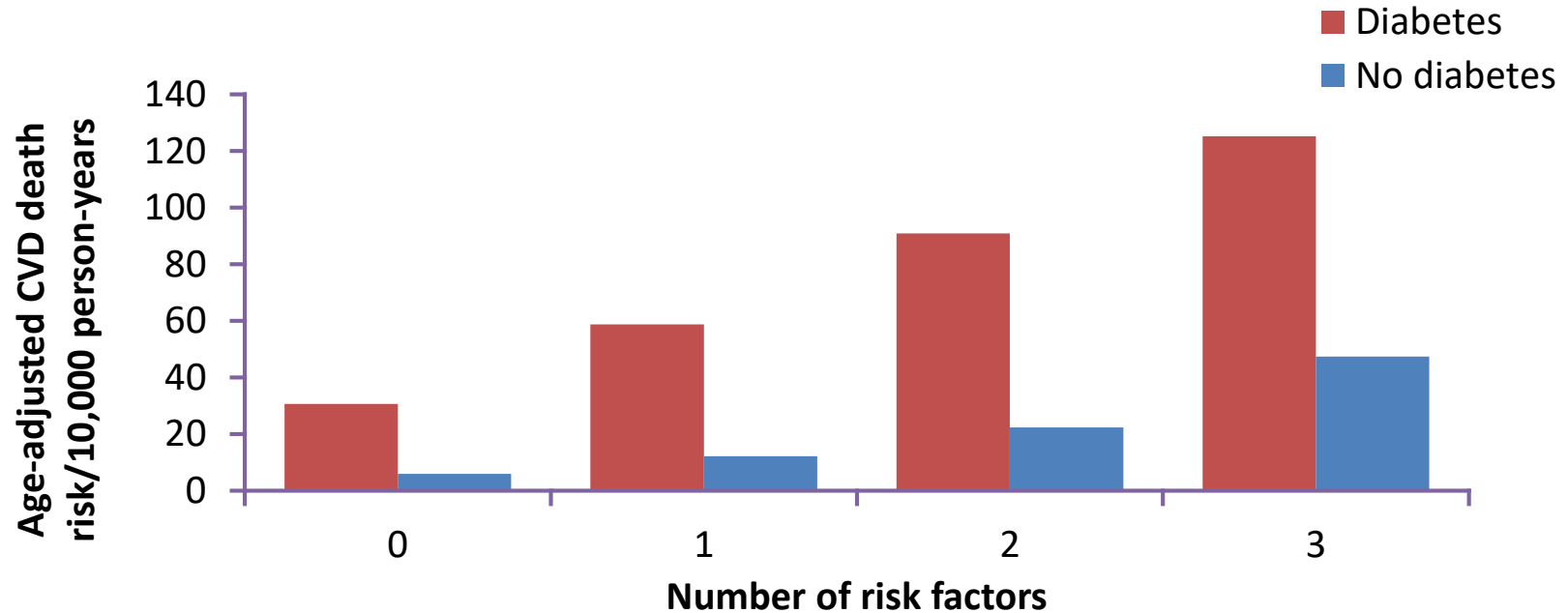
↑↑↑ This will rise to **642** million by 2040¹ ↑↑↑

- At least 68% of people >65 years with diabetes die of heart disease²

Mortality risk associated with diabetes (n=820,900)³



CV death is increased in patients with diabetes and multiple risk factors



Risk factors were serum cholesterol ≥ 200 mg/dl, current smoker, SBP ≥ 120 mmHg

CV, cardiovascular;

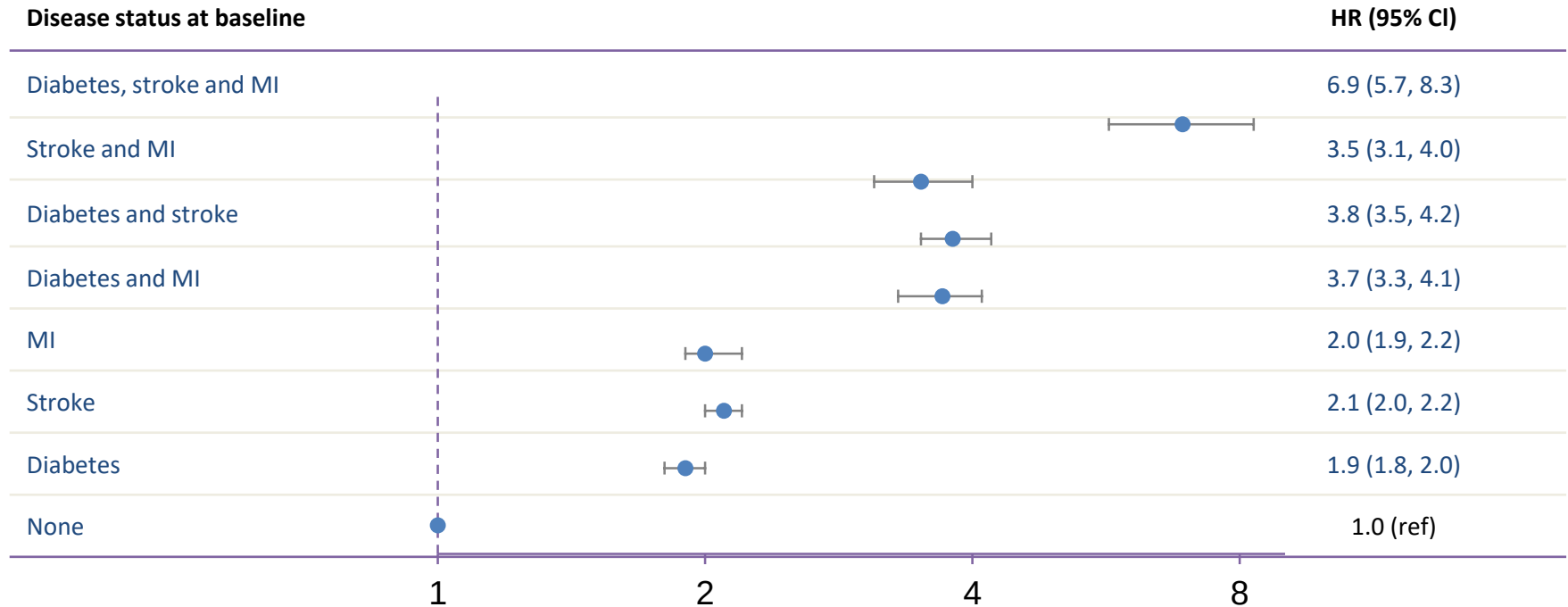


ACC.18

Despite advances in therapies, life expectancy is reduced by multiple morbidities of T2D, stroke and MI



All-cause mortality by disease status of participants at baseline

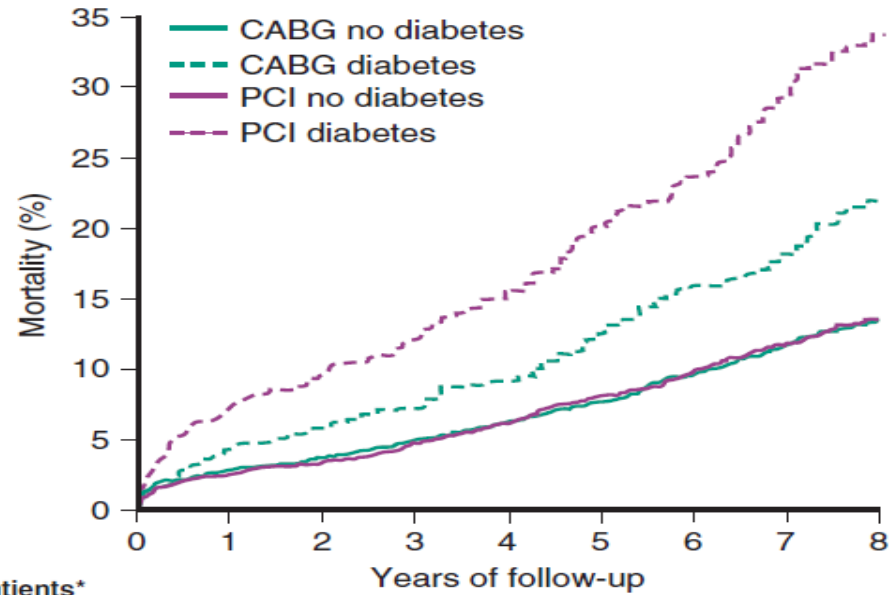


CI, confidence interval; HR, hazard ratio; MI, myocardial infarction; T2D, type 2 diabetes

The Emerging Risk Factors Collaboration. *JAMA* 2015;314:52



ACC.18



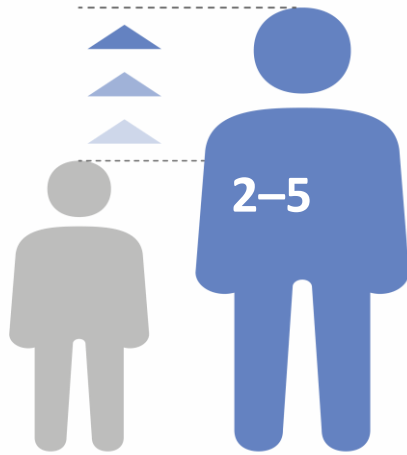
Hlatky et al, lancet, 2009,373;1190-1197



ACC Middle East
Conference 2018



People with diabetes are at increased risk of heart failure



People with diabetes have a 2- to 5-fold higher risk of developing HF¹



Diabetes confers a 60–80% greater probability of CV death and all-cause mortality in those with established HF^{2,3*}

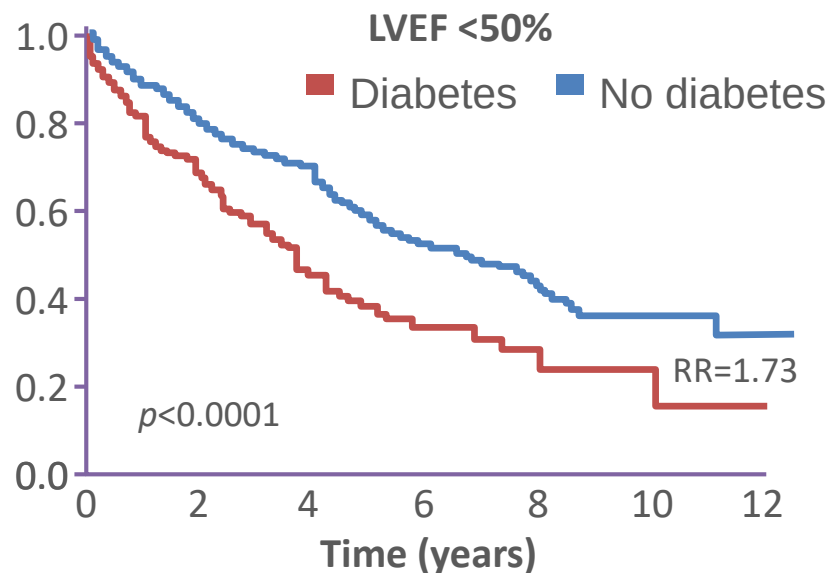
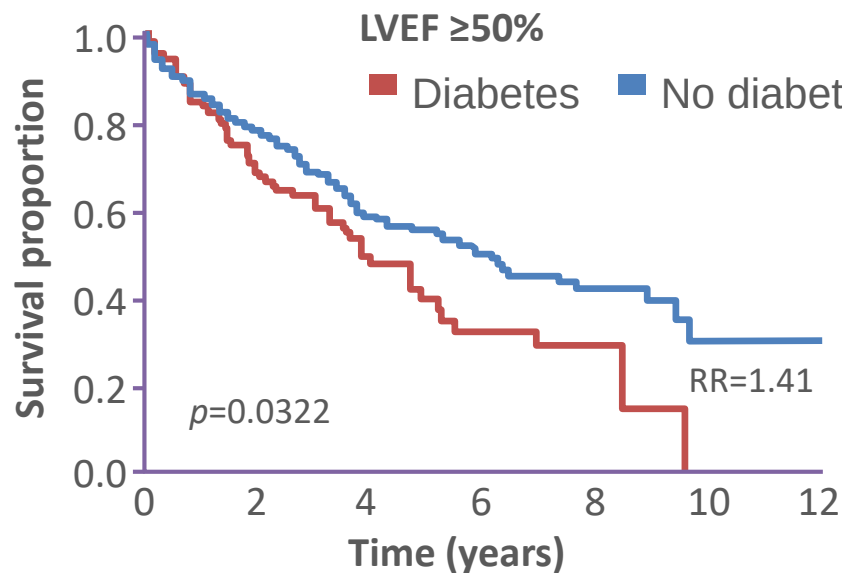


ACC Middle East
Conference 2018



Diabetes worsens heart failure prognosis

Poorer HF survival with diabetes than without diabetes



- Kaplan-Meier survival curves of HF patients hospitalised with LVEF $\geq 50\%$ (n=498) and $< 50\%$ (n=754)

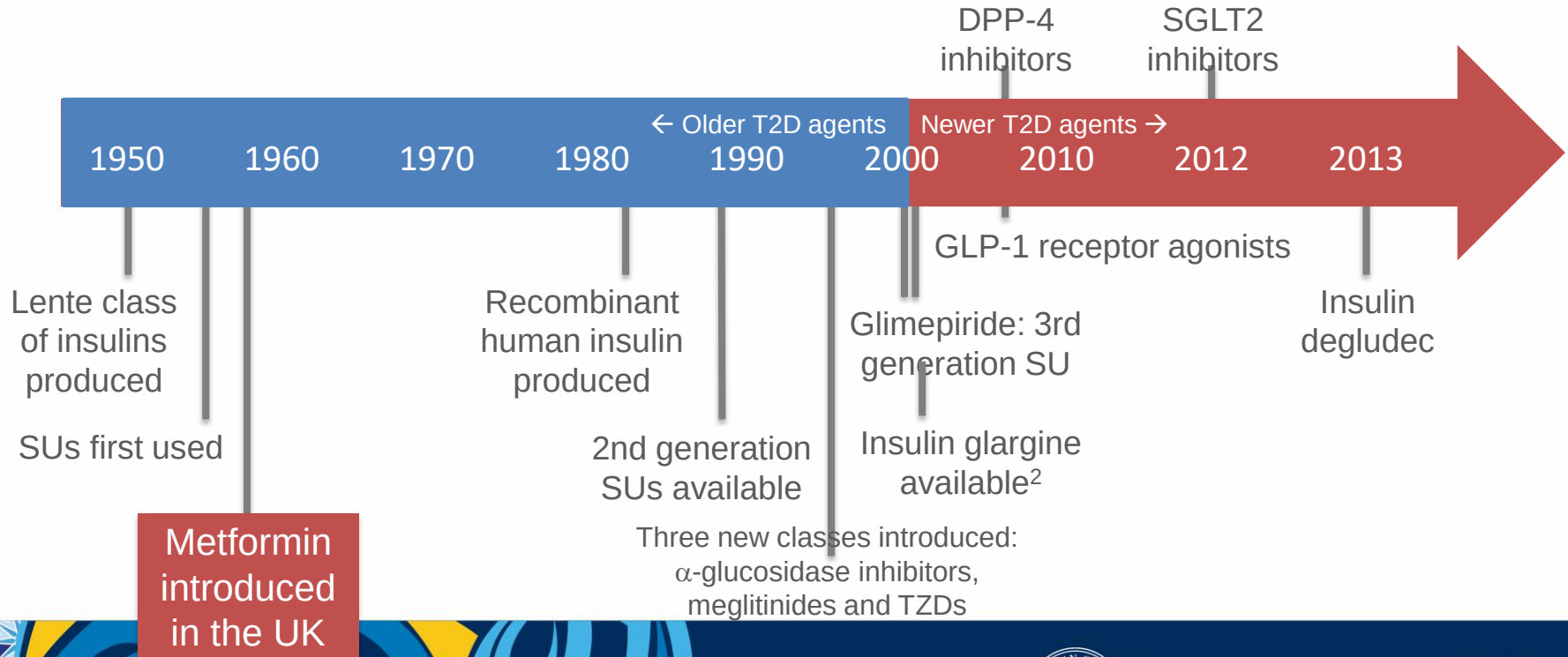
HF, heart failure; LVEF, left ventricular ejection fraction

Varela-Roman A et al. *Eur J Heart Failure* 2005;7:859



ACC.18

Evolution of T2D agents



DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SGLT2, sodium-glucose cotransporter-2; SU, sulfonylurea



ACC Middle East
Conference 2018



Antidiabetic treatments & cardiovascular disease: the evolution

- Antidiabetic treatments & relation to cardiovascular disease

(tolbutamide, rosiglitazone)

- Antidiabetic treatments that does not increase cardiovascular disease

(DPP-4 I , saxagliptin)

- ????can antidiabetic treatments reduce cardiovascular disease

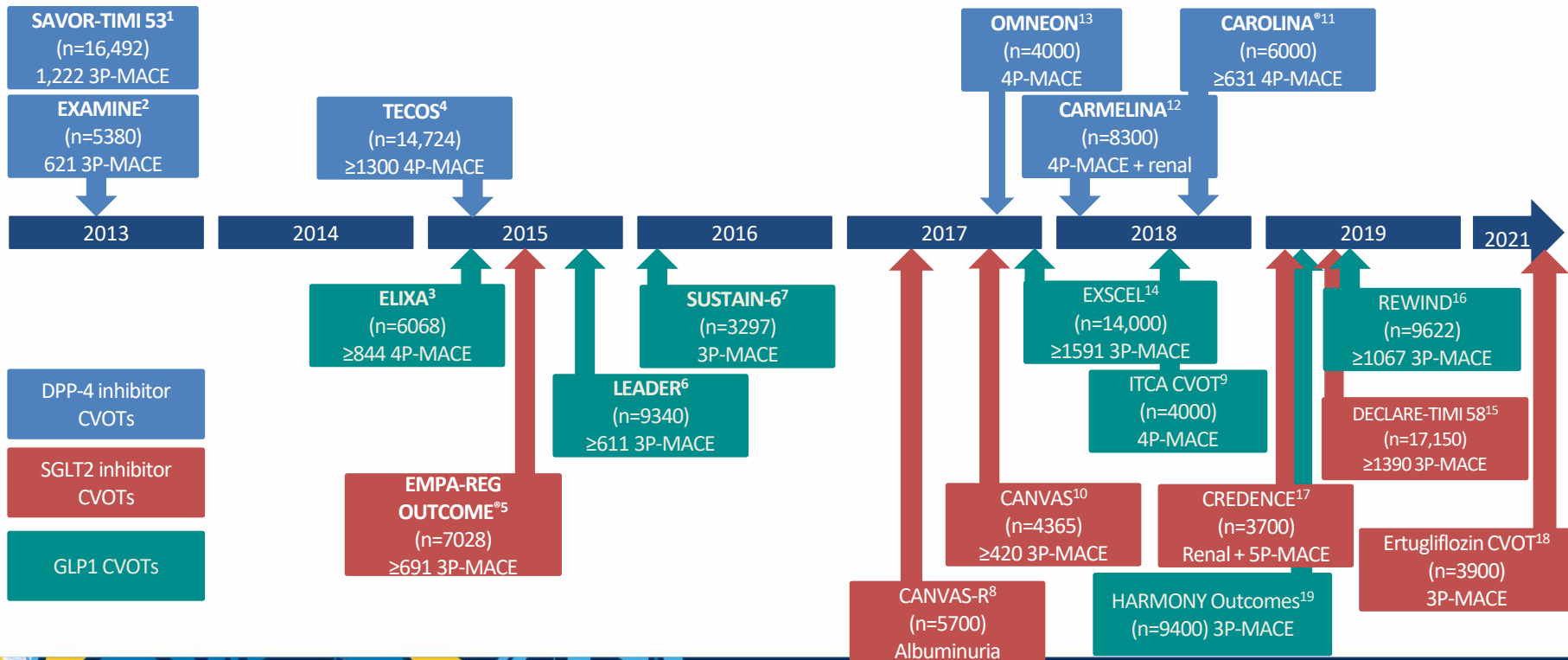
(SGLT2 inhibitors, GLP-1RA)



ACC Middle East
Conference 2018



Overview of CVOTs of glucose-lowering drugs

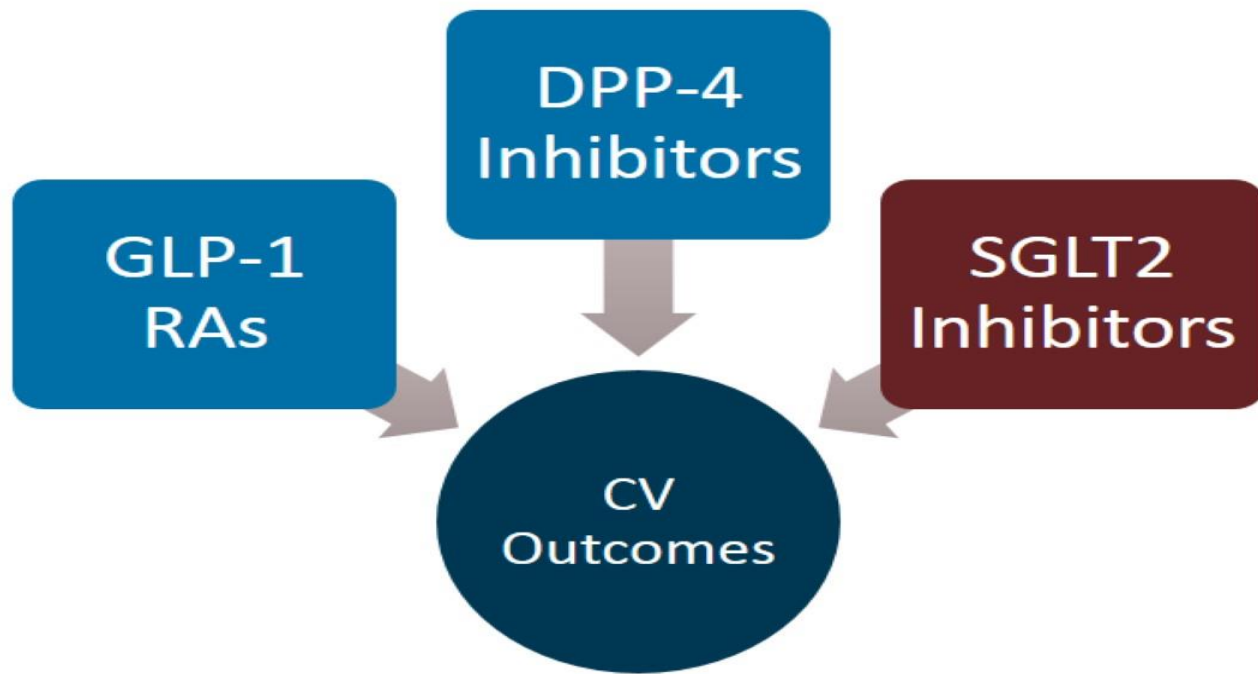


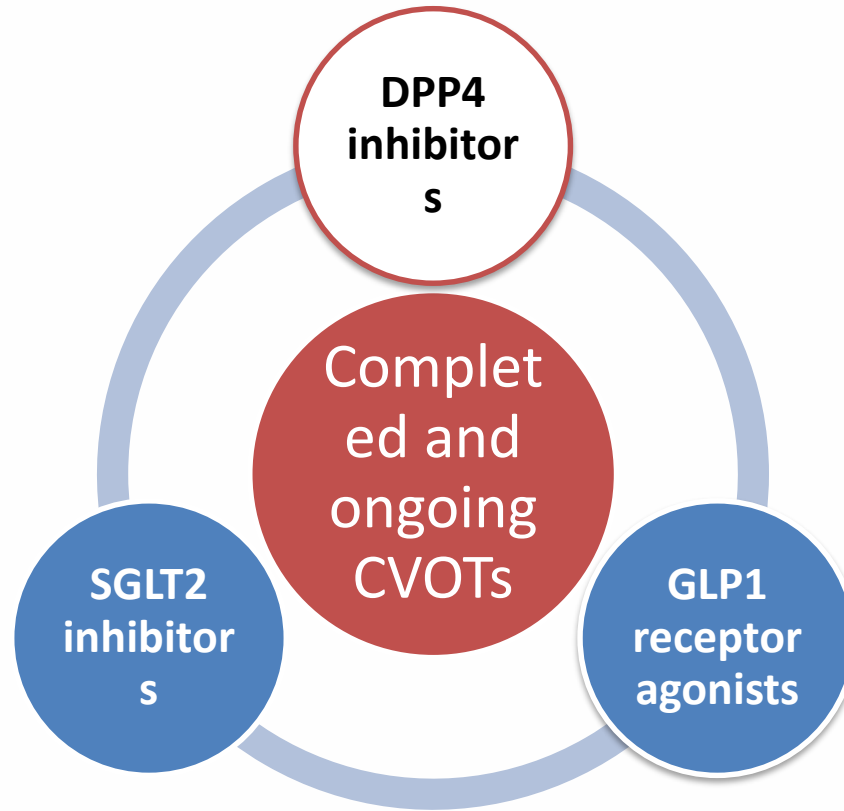
ACC Middle East
Conference 2018

In partnership with:

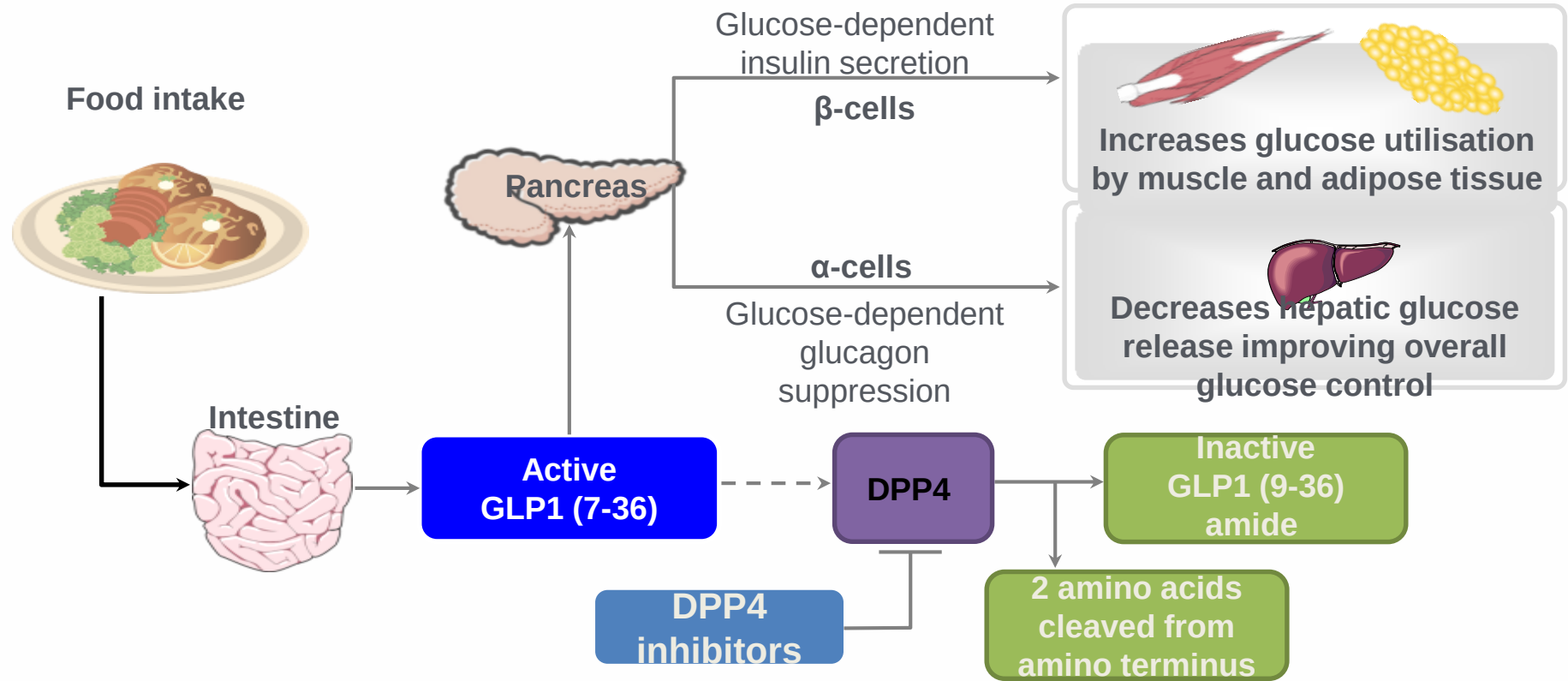


CVOTs With Glucose-Lowering Agents



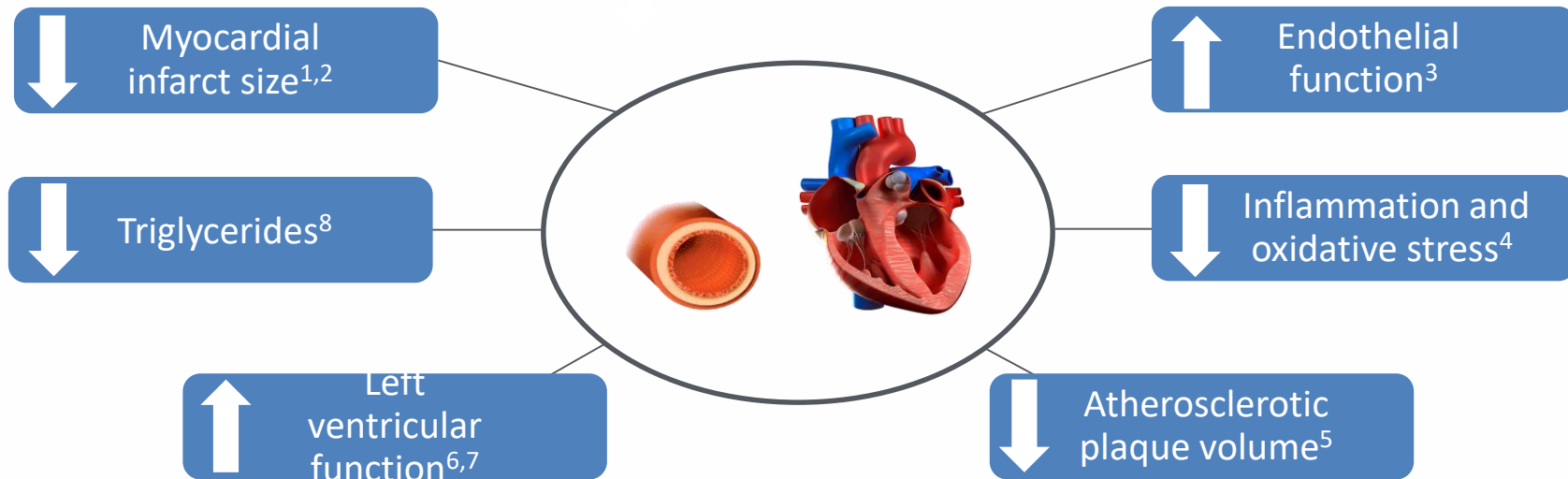


DPP4 inhibitors: Mechanism of action



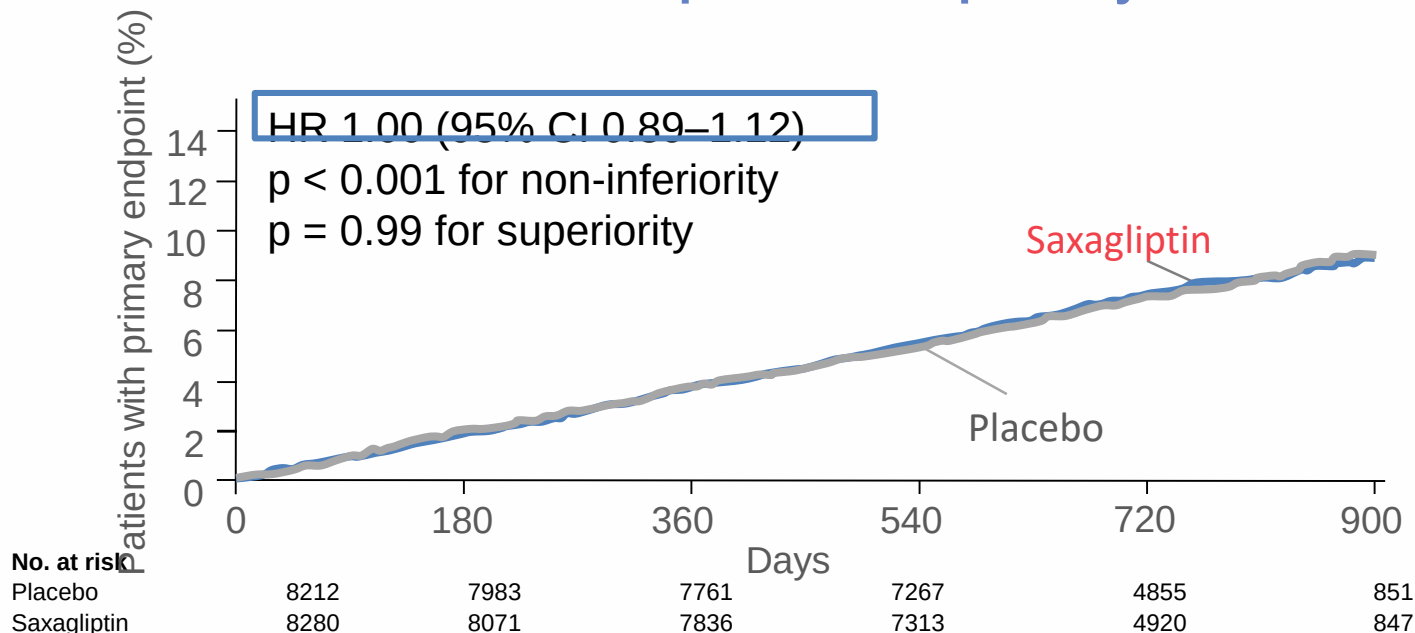
Adapted from Drucker, Expert Opin Invest Drugs 2003;12:87–100 and Ahren Curr Diab Rep. 2003;3:365–372.

Selected mechanistic trials indicate potential CV effects of the DPP4 inhibitor class



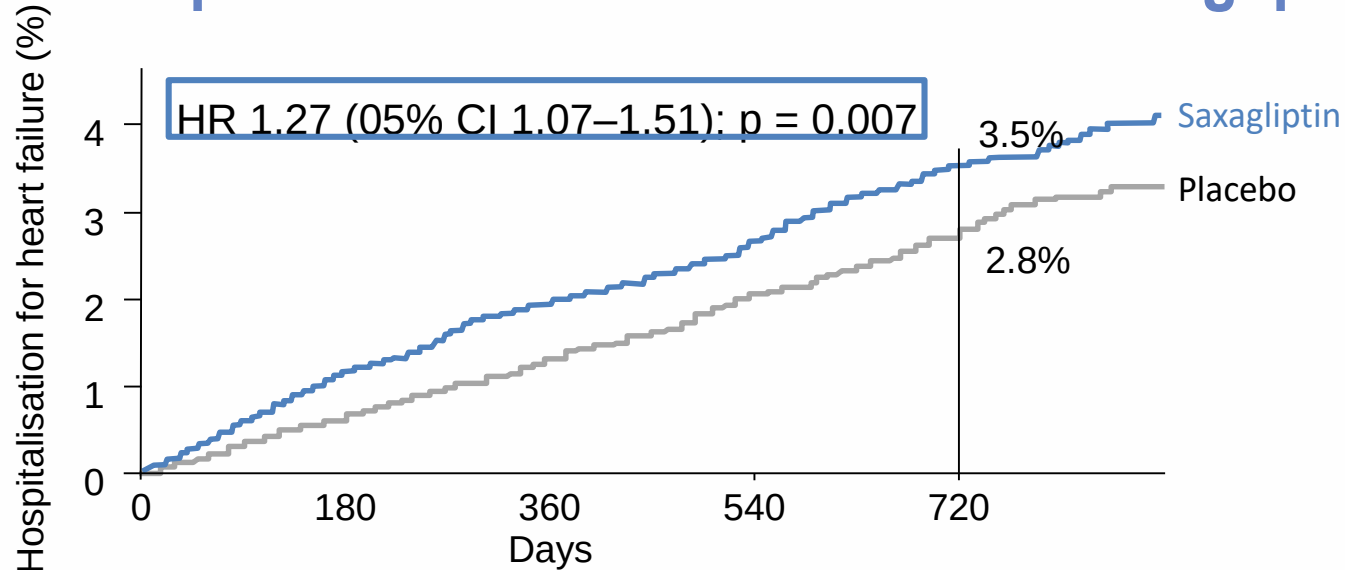
1. Ye et al. Am J Physiol Heart Circ Physiol 2010;298:H1454–65. 2. Hocher et al. Int J Cardiol 2013;167:87–93.
3. van Poppel et al. Diabetes Care 2011;34:2072–77. 4. Kröller-Schön et al. Cardiovasc Res 2012;96:140–9.
5. Ta et al. J Cardiovasc Pharmacol 2011;58:157–66. 6. Sauvé et al. Diabetes 2010;59:1063–73.
7. Read et al. Circ Cardiovasc Imaging 2010;3:195–201. 8. Matikainen et al. Diabetologia 2006;49:2049–57.

SAVOR-TIMI 53: Saxagliptin was non-inferior to placebo on primary 3P-MACE endpoint



Scirica et al. N Engl J Med 2013;369:1317–26.

SAVOR-TIMI 53: Increased risk of hospitalisation for heart failure in saxagliptin arm



Placebo	8212	8036	7856	7389	4959
Saxagliptin	8280	8064	7867	7375	4978

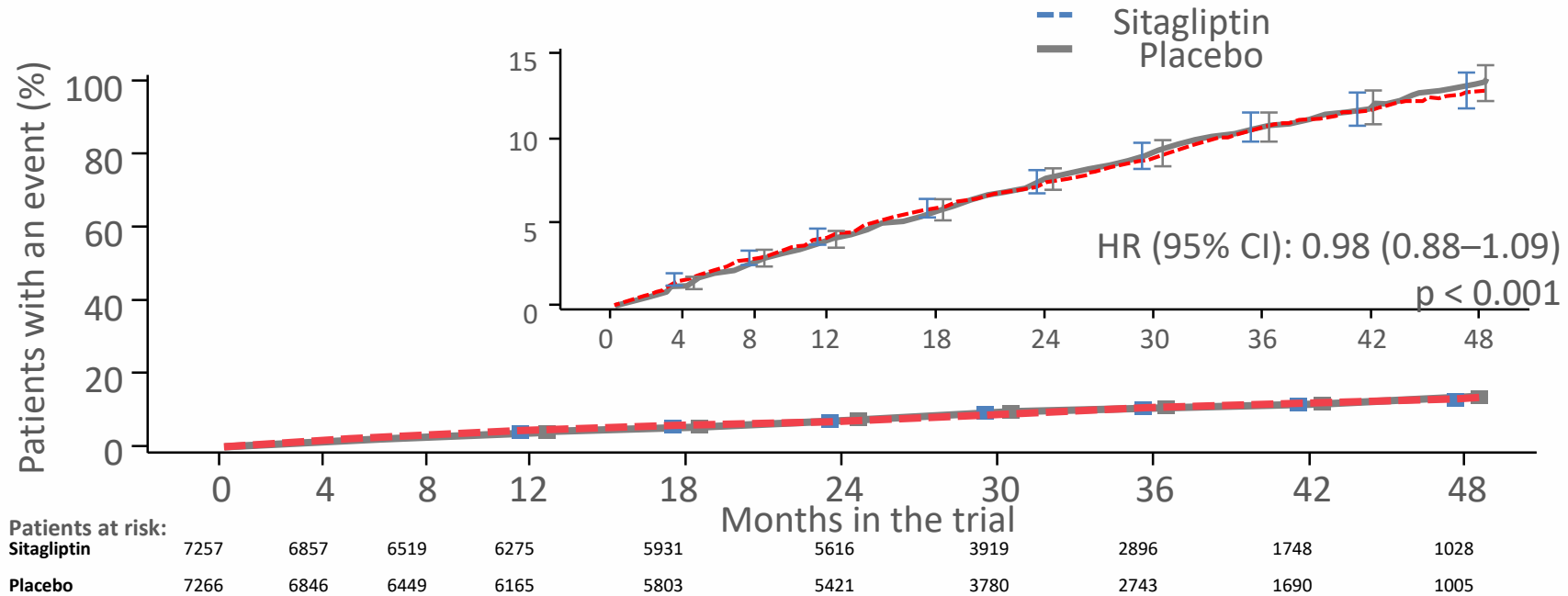
Scirica et al. Circulation 2014;130:1579–88

ACC

East
018



TECOS: Sitagliptin was non-inferior to placebo on primary 4P-MACE endpoint



*CV death, non-fatal MI, non-fatal stroke, hospitalisation for unstable angina.

Green et al. N Engl J Med 2015; DOI: 10.1056/NEJMoa1501362.

TECOS: No significant difference in rate of hospitalisation for heart failure (ITT analysis)

Outcome	Placebo	Sitagliptin	HR (95% CI)
HHF*	228 (3.1%) 1.07/100 pt-y	228 (3.1%) 1.09/100 pt-y	1.00 (0.83–1.20) p = 0.98
CV Death + HHF*	525 (7.2%) 2.50/100 pt-y	538 (7.3%) 2.54/100 pt-y	1.02 (0.90–1.15) p = 0.74

ITT population. Adjusted for history of heart failure at baseline *Pre-specified analyses

Green et al. N Engl J Med 2015; DOI: 10.1056/NEJMoa1501352

SAVOR-TIMI 53, EXAMINE, and TECOS: HHF



*Statistically significant increase in HHF associated with saxagliptin use in SAVOR-TIMI

a. Scirica BM, et al. *N Engl J Med*. 2013;369:1317-1326.

b. White WB, et al. *N Engl J Med*. 2013;369:1327-1335.

c. Green JB, et al. *N Engl J Med*. 2015;373:232-242.

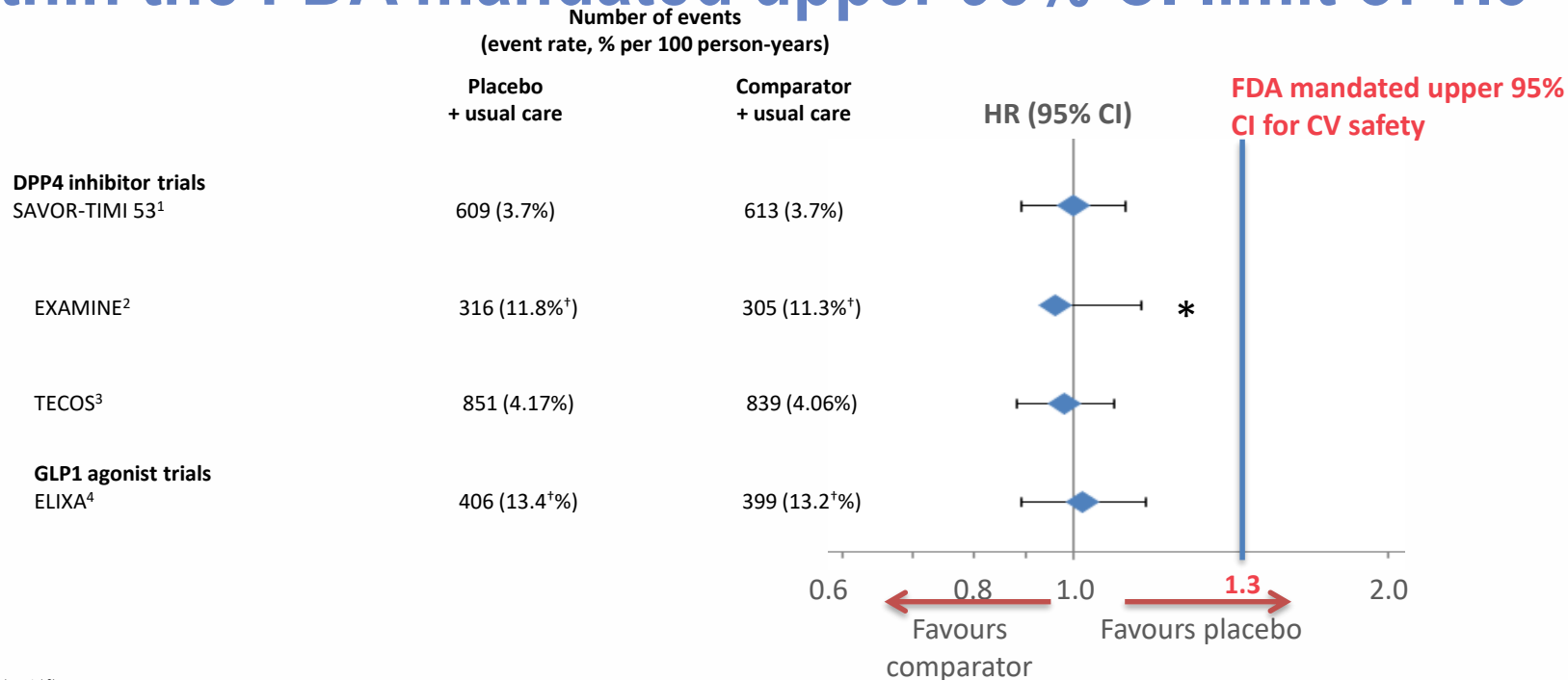
Summary of CV outcomes trials with DPP4 inhibitors

	SAVOR-TIMI 53 ¹	EXAMINE ²	TECOS ³	CAROLINA ^{®4}	CARMELINA ^{®5}
Intervention	Saxagliptin/ placebo	Alogliptin/ placebo	Sitagliptin/ placebo	Linagliptin/ glimepiride	Linagliptin/ placebo
Main inclusion criteria	History of or multiple risk factors for CVD	ACS within 15–90 days before randomisation	CVD	≥ 2 specified traditional CV risk factors or manifest CVD	High risk of CV events (e.g. albuminuria, prior CVD)
No. of patients	16,492	5380	14,671	6041	8300
Primary outcome	3P-MACE	3P-MACE	4P-MACE	4P-MACE	4P-MACE
Key secondary outcome	Expanded MACE	4P-MACE	3P-MACE	3P-MACE	3P-MACE; renal composite
Target no. of events	1040 ⁶	650	1300	631	625 ⁷
Median follow-up (y)	2.1	1.5	3.0	6–7*	4* ⁷
Estimated completion	Completed	Completed	Completed	2018 ⁸	2018

*Ongoing.

1. Scirica et al. N Engl J Med 2013;369:1317–26. 2. White et al. N Engl J Med 2013;369:1327–35. 3. Green et al. N Engl J Med 2015; DOI:10.1056/NEJMoa1501352. 4. Marx et al. Diabetes Vasc Dis Res 2015;12:164–74. 5. NCT01897532. 6. Scirica et al. Am Heart J 2011;162:818–25.e6. 7. Data on file (BI trial no. 1218.22 trial protocol). 8. NCT01243424.

For the primary outcome, all completed CVOTs fall within the FDA mandated upper 95% CI limit of 1.3



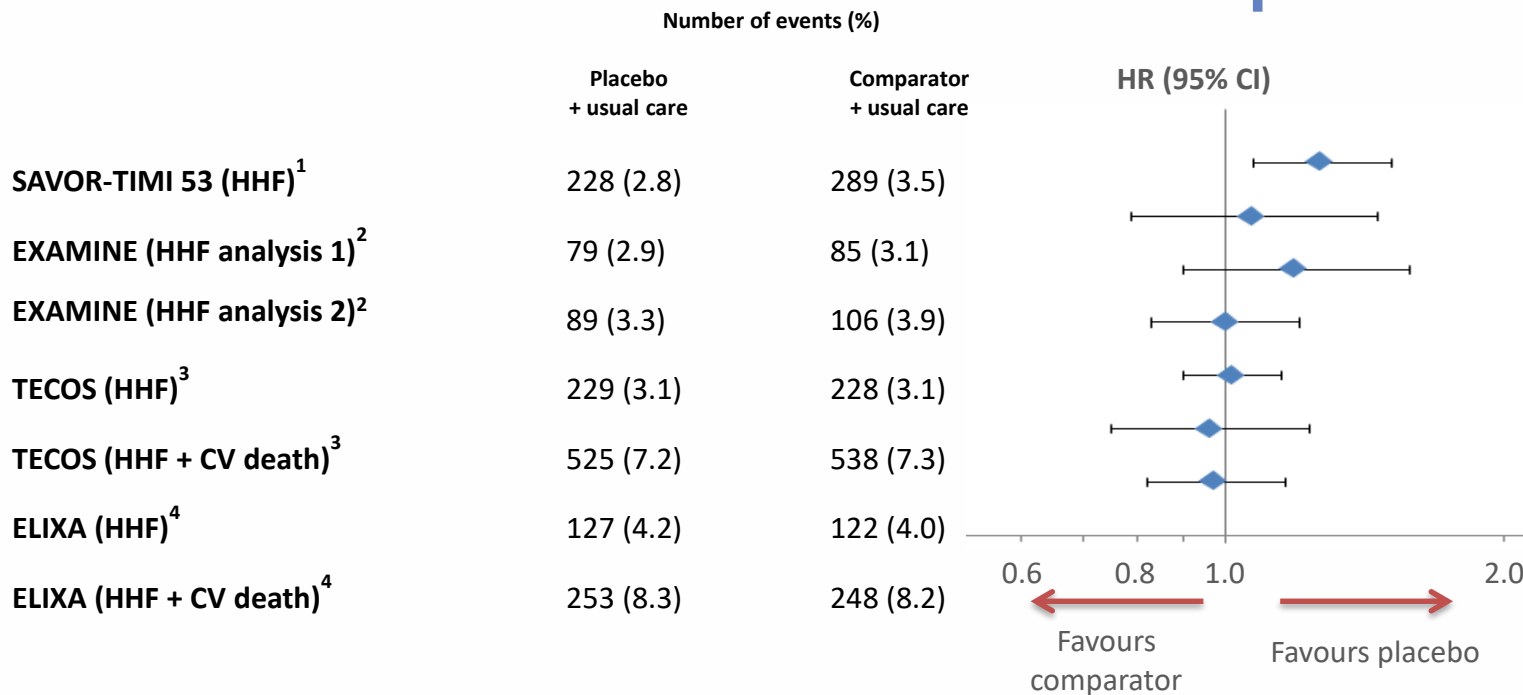
*Upper boundary of 1-sided repeated CI.

[†]Total event rate, %.

1. Schirmer et al. N Engl J Med 2013; 369:1519–26. 2. White et al. N Engl J Med 2013; 369:1327–35.

3. Chaffin et al. N Engl J Med 2015; 372:10. 10.1056/NEJMOA1501362. 4. Platter et al. ADA 68 Jun 2015, Boston, USA (oral presentation).

Hospitalisation for heart failure (HHF) data for all completed CVOTs

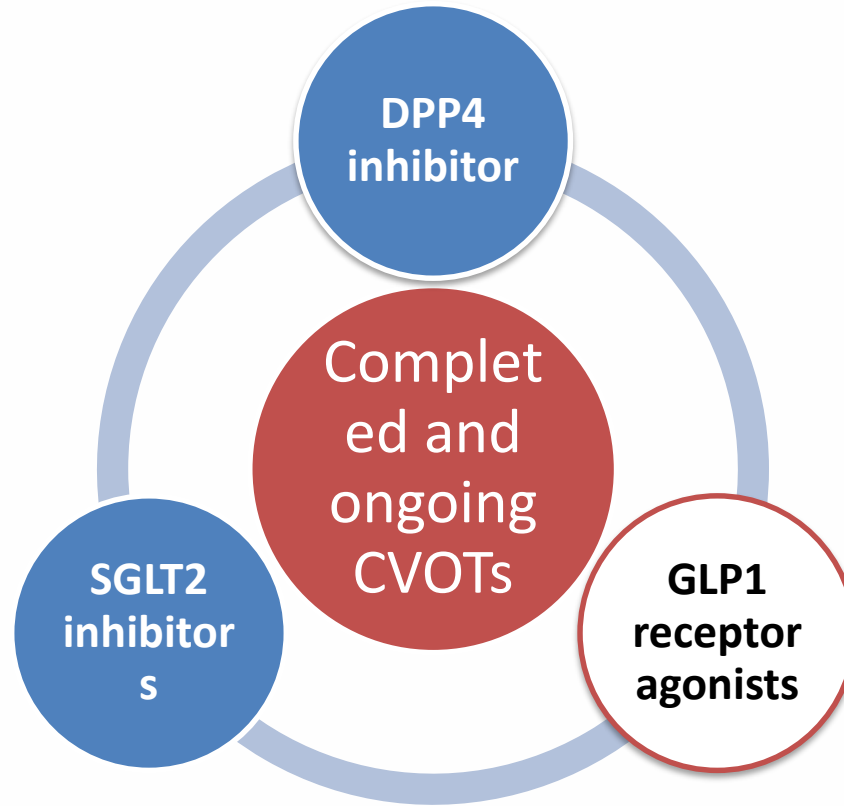


Analysis 1 = as component of expanded MACE

Analysis 2 = as component of post-hoc composite of CV death and HHF

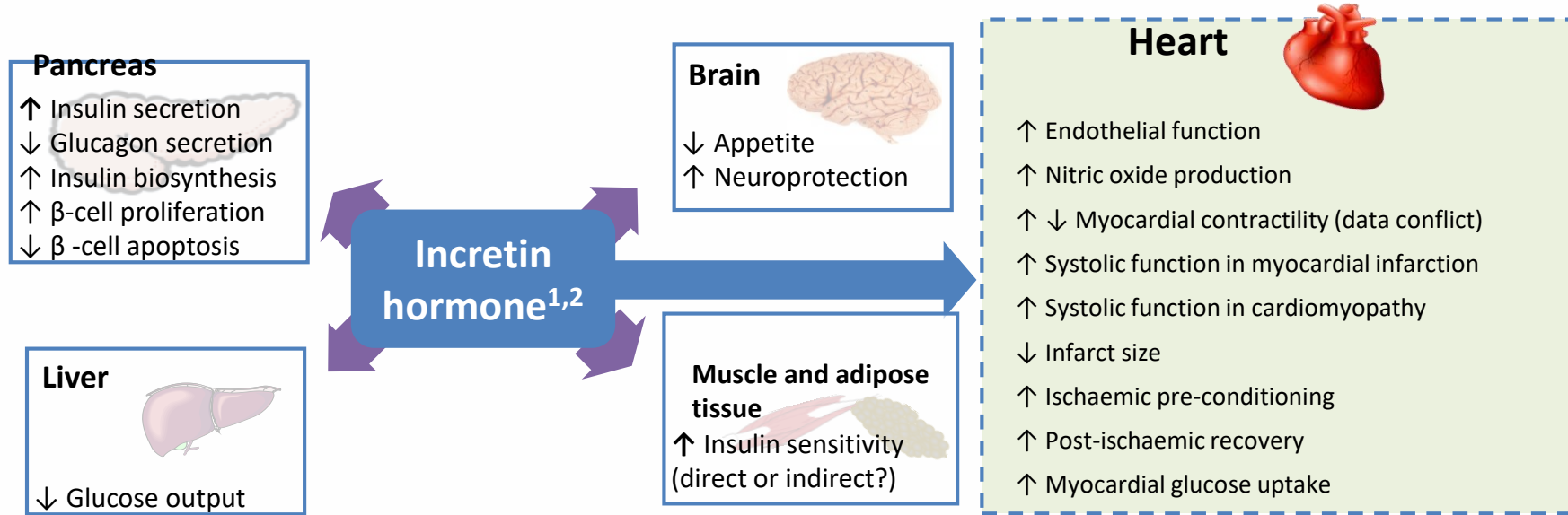
1. Scirica et al. N Engl J Med 2015; 369:1361–70. 2. White et al. N Engl J Med 2015; 369:1327–35.

3. Cannon et al. N Engl J Med 2015; 372:10. 1056/NEJMA1501352. 4. Pasterkamp et al. ACC 2015, Boston, USA (oral presentation).



GLP1 has various potential effects on the CV system:

Data derived from non-clinical and mechanistic proof-of-concept studies



Clinical trial data show that GLP1 receptor agonists are associated with small increases in heart rate and modest reductions in body weight and blood pressure³

Summary of CV outcomes trials with GLP1 receptor agonists

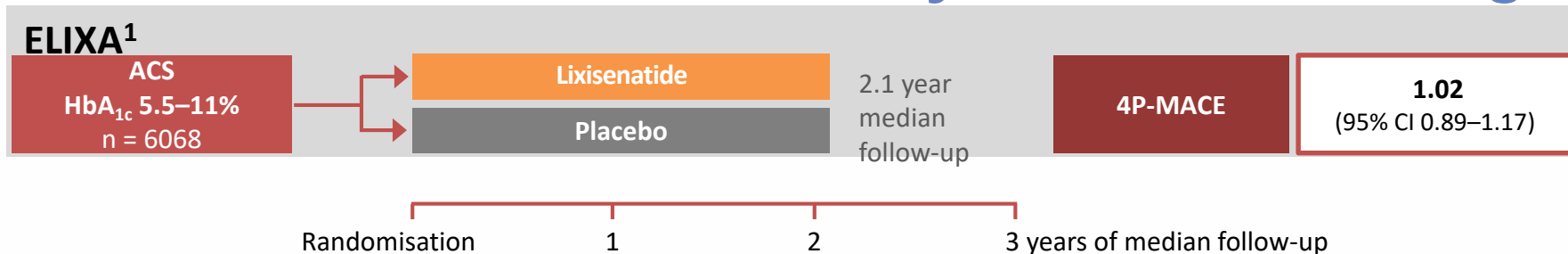
	Intervention	Main inclusion criteria	No. of patients	Primary outcome	Key 2° outcome	Target no. of events	Estimated follow-up	Estimated completion
ELIXA^{1,2}	Lixisenatide/ placebo	History of ACS	6068	4P-MACE	Expanded MACE	844	2.1 years median	Completed
LEADER³	Liraglutide/ placebo	Vascular disease, or risk factors, or CRF, or CHF	9340	3P-MACE	Expanded MACE	> 611	Up to ~5 years	Nov-15
SUSTAIN-6^{™4}	Semaglutide/ placebo	Evidence of CV disease	3297	3P-MACE	Expanded MACE	Not specified	Up to ~3 years	Jan-16
EXSCEL⁵	Exenatide ER*/ placebo	No CV criteria specified	14,000	3P-MACE	All-cause mortality; HHF	Not specified	Up to ~7.5 years	Apr-18
REWIND⁶	Dulaglutide/ placebo	Pre-existing vascular disease or ≥2 CV risk factors	9622	3P-MACE	Microvascular composite	Not specified	Up to ~6.5 years	Apr-19
HARMONY OUTCOMES⁷	Albiglutide/ placebo	Established CVD	9400	3P-MACE	Expanded MACE	Not specified	3–5 years	May-19

*Once weekly.

1. NCT01147250. 2. Bentley-Lewis et al. Am Heart J 2015;0:1-8.e7. 3. Marso et al. Am Heart J 2013;166:823–30.e5. 4. NCT01720446.

5. NCT01144338. 6. NCT01394952. 7. NCT02466515

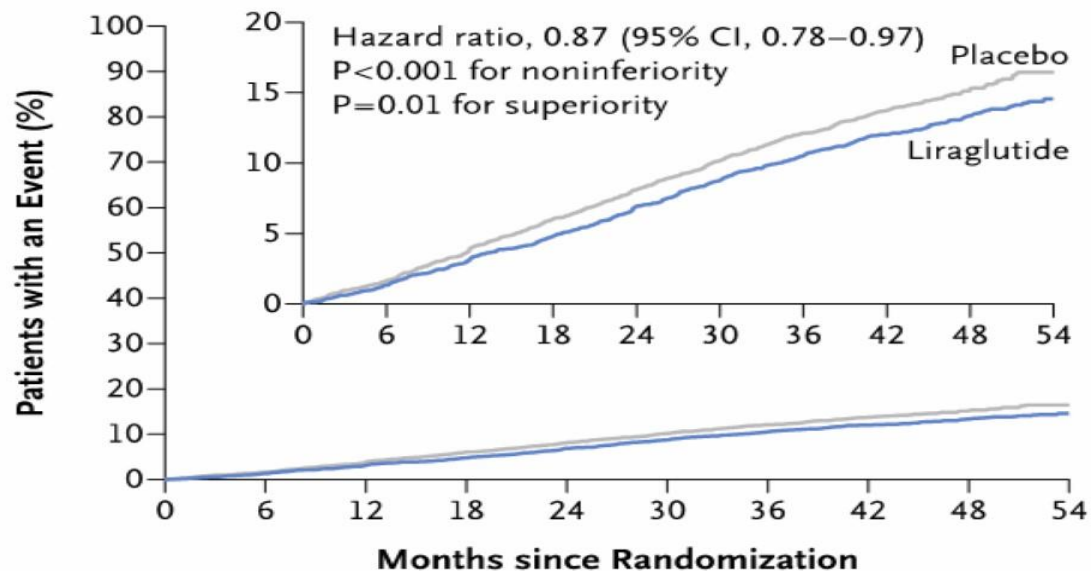
Summary of ELIXA findings



- **No difference in 4P-MACE with lixisenatide vs placebo**
 - HR 1.02 (95% CI 0.89–1.17)
- **No difference in HHF with lixisenatide vs placebo**
 - HR 0.96 (95% CI 0.75–1.23)
- **No difference in CV death + HHF with lixisenatide vs placebo**
 - HR 0.97 (95% CI 0.82–1.16)

¹ Pfeffer et al. ADA, 8 Jun 2015, Boston, USA (oral presentation).

LEADER: Primary Outcome Measure*



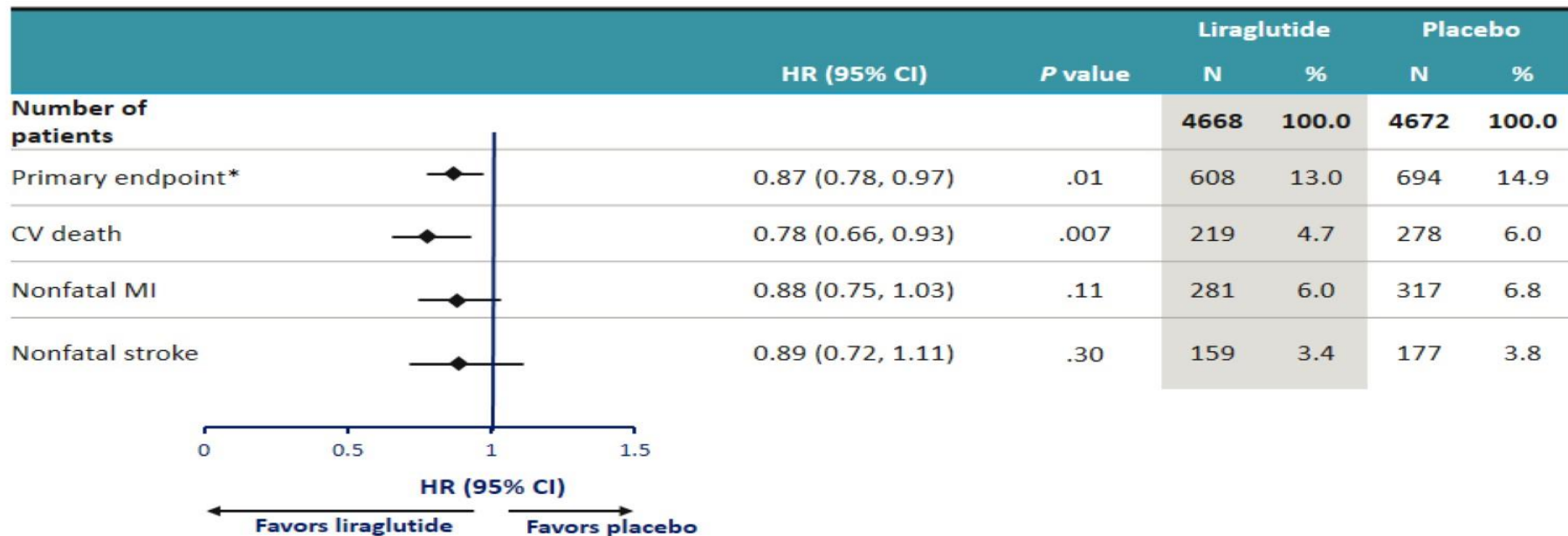
No. at Risk

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

*3-point MACE consisting of CV death, nonfatal MI, or nonfatal stroke.

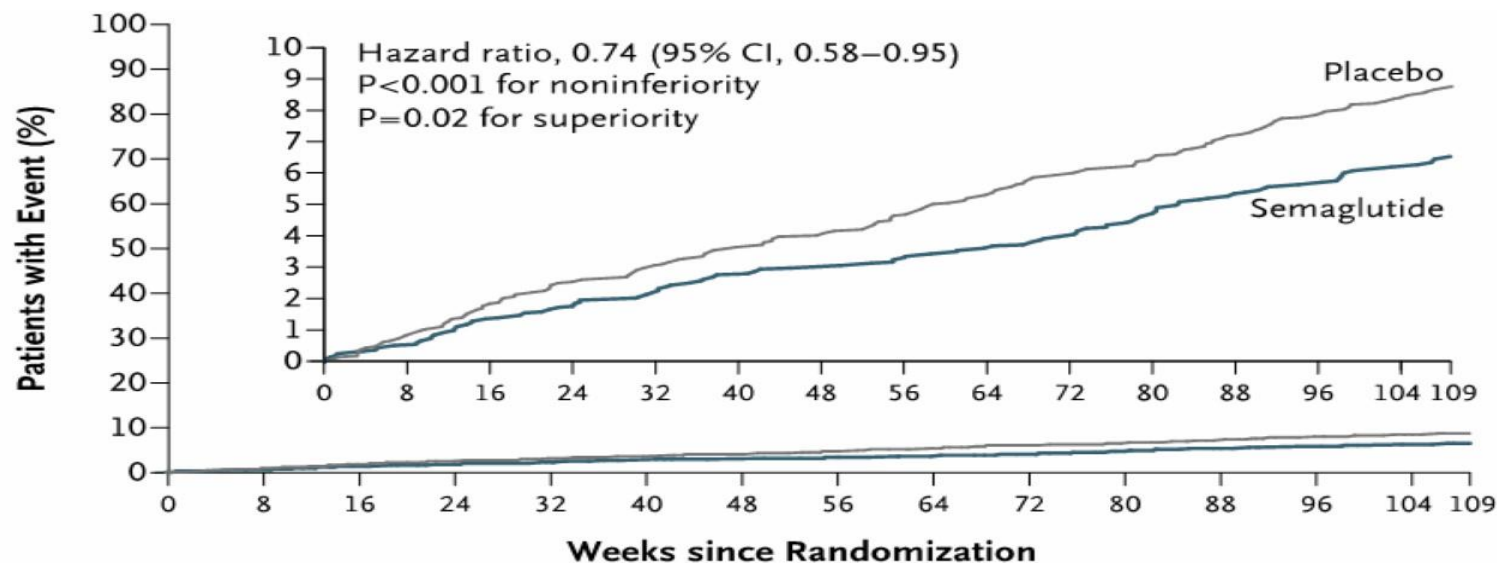
Marso SP, et al. *N Engl J Med.* 2016;375:311-322.

LEADER: Individual Components of the Primary Endpoint



*3-point MACE consisting of CV death, nonfatal MI, or nonfatal stroke.
 Marso SP et al. *N Engl J Med.* 2016;375:311-322.

SUSTAIN-6: Primary Outcome Measure*

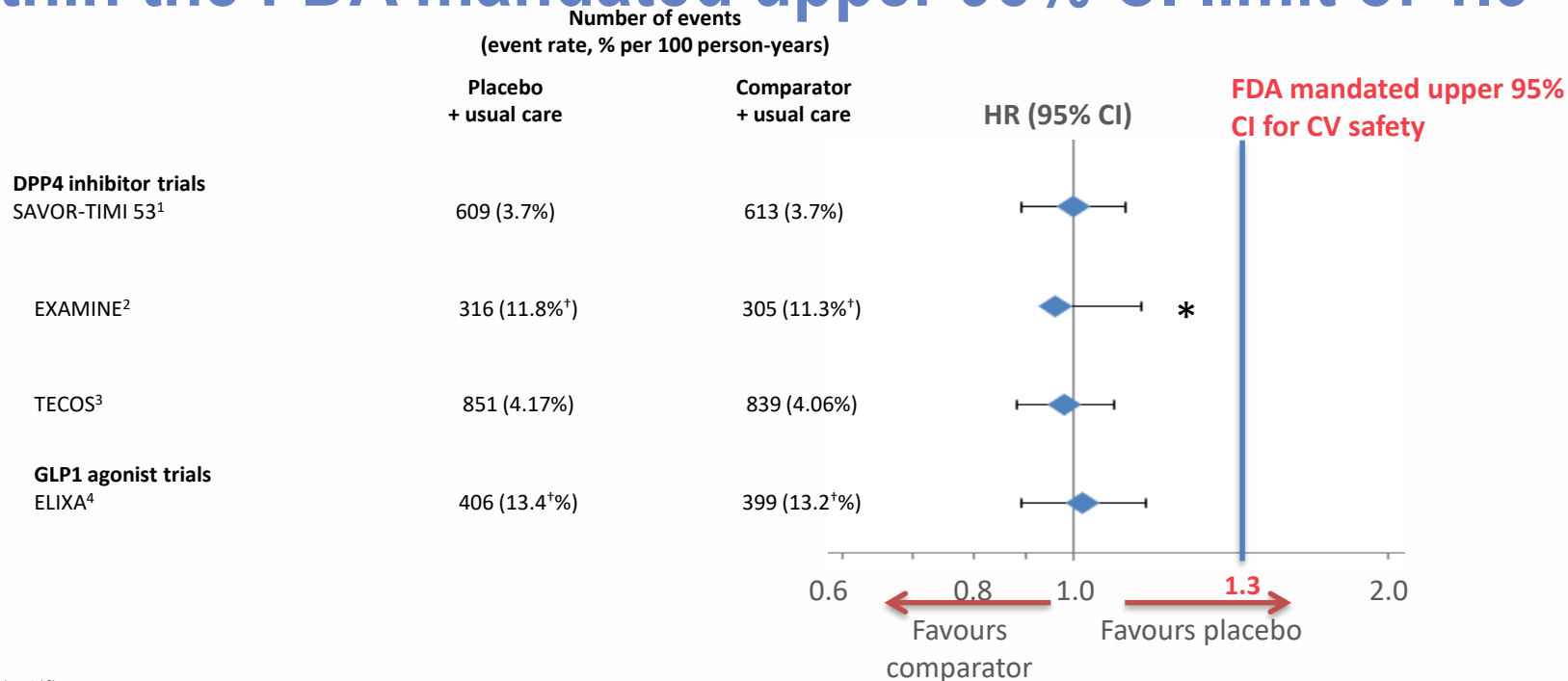


No. at Risk

Placebo	1649	1616	1586	1567	1534	1508	1479
Semaglutide	1648	1619	1601	1584	1568	1543	1524

*Composite of CV death, nonfatal MI, or nonfatal stroke
Marso SP, et al. *N Engl J Med*. 2016;375:1834-1844.

For the primary outcome, all completed CVOTs fall within the FDA mandated upper 95% CI limit of 1.3



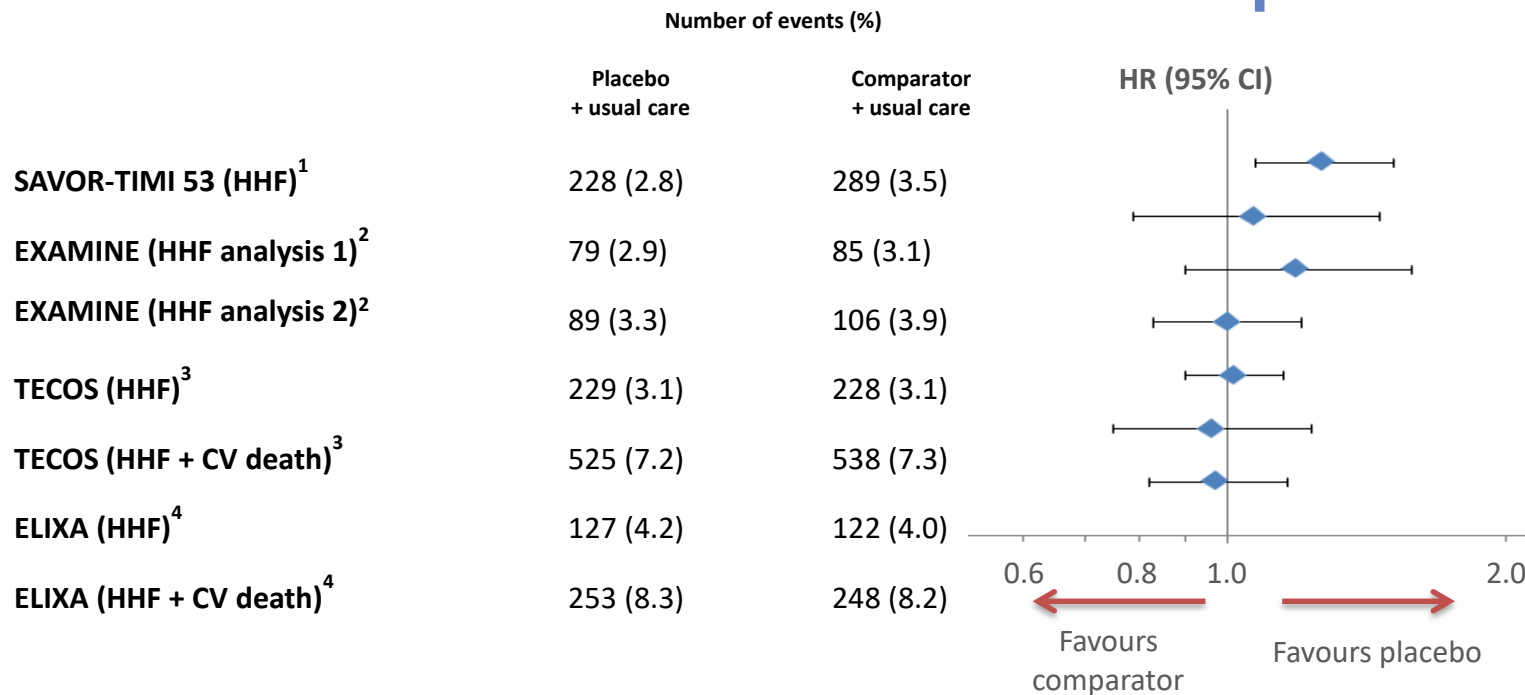
*Upper boundary of 1-sided repeated CI.

[†]Total event rate, %.

1. Schirmer et al. N Engl J Med 2013; 369:1519–26. 2. White et al. N Engl J Med 2013; 369:1327–35.

3. Chilton et al. N Engl J Med 2015; 372:10. 10.1056/NEJMOA1501362. 4. Pflaumer et al. ADA 68 Jun 2015, Boston, USA (oral presentation).

Hospitalisation for heart failure (HHF) data for all completed CVOTs



Analysis 1 = as component of expanded MACE

Analysis 2 = as component of post-hoc composite of CV death and HHF

1. Schirmer et al. N Engl J Med 2015; 369:1369–76. 2. White et al. N Engl J Med 2015; 369:1327–35.

3. Gattuso et al. N Engl J Med 2015; 369:1369–76. 4. Pasterkamp et al. JAMA 2015; 314:1369–76. (oral presentation)

CVOTs With GLP-1 RAs (cont)

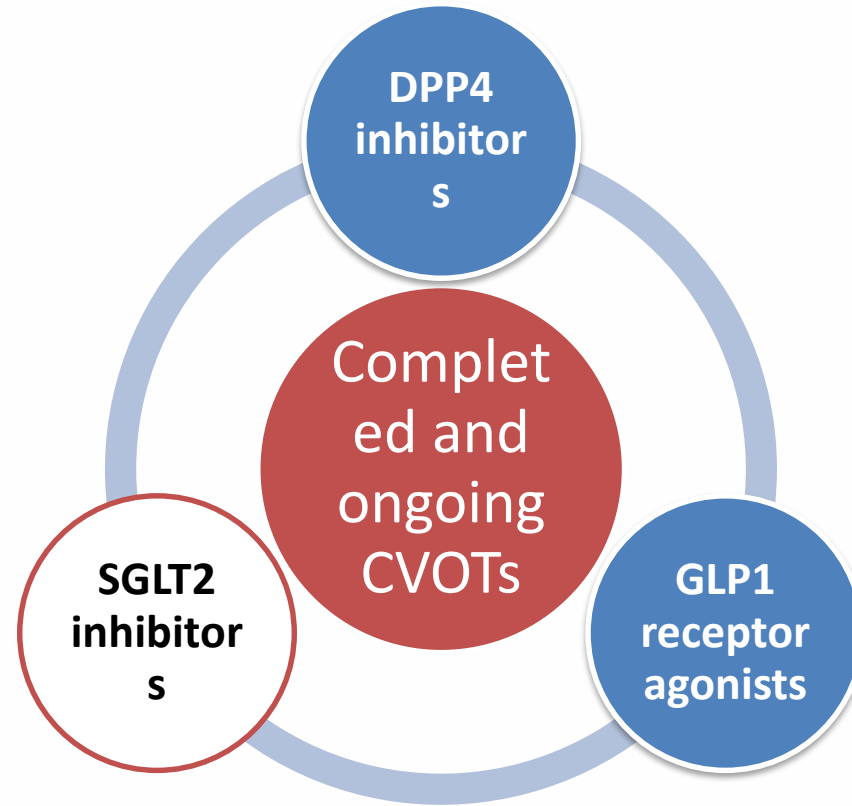
CVOT	Agent	Established CV Safety	Demonstrated Beneficial Effects on CV Endpoints
LEADER ^[a]	Liraglutide	Yes	Yes
ELIXA ^[b]	Lixisenatide	Yes	No
SUSTAIN-6 ^[c]	Semaglutide	Yes	Yes
EXSCEL ^[d]	Exenatide once weekly	Yes	No

a. Marso SP, et al. *N Engl J Med*. 2016;372:311-322.

b. Pfeffer MA, et al. *N Engl J Med*. 2015;33:2247-2257.

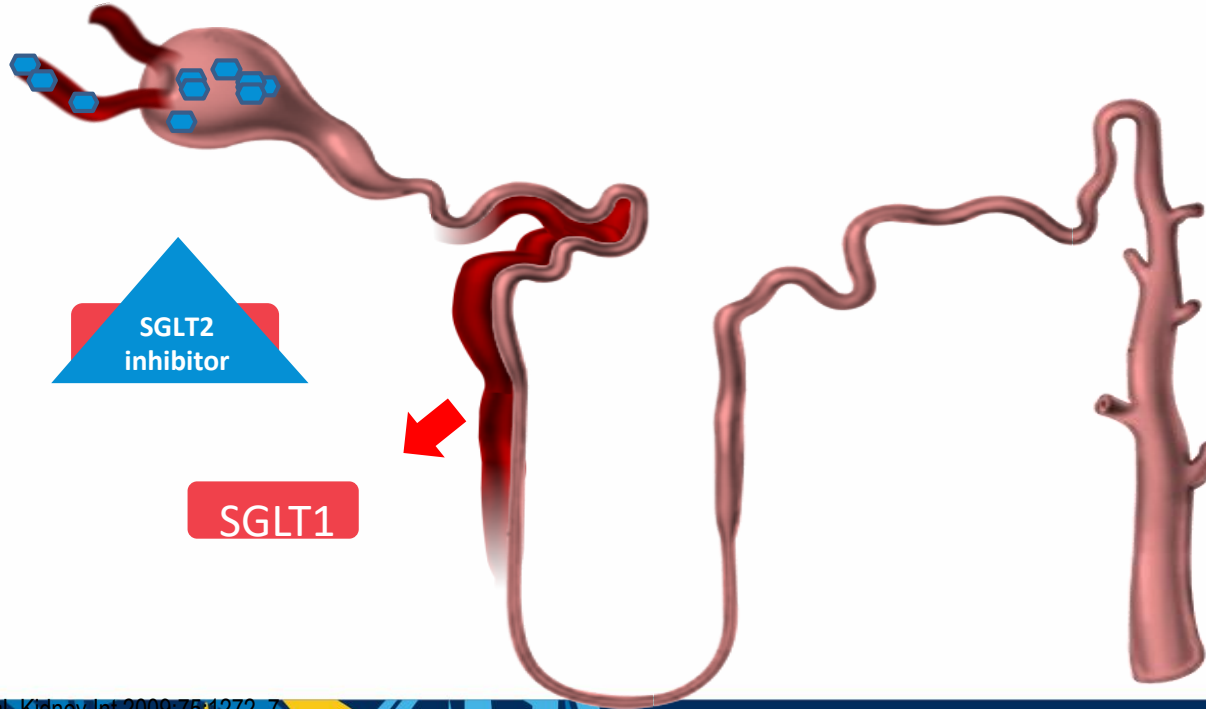
c. Marso SP, et al. *N Engl J Med*. 2016;375:1834-1844.

d. AstraZeneca website, 2017. Primary safety objective.



Urinary glucose excretion via SGLT2 inhibition¹

Filtered glucose load >
180 g/day

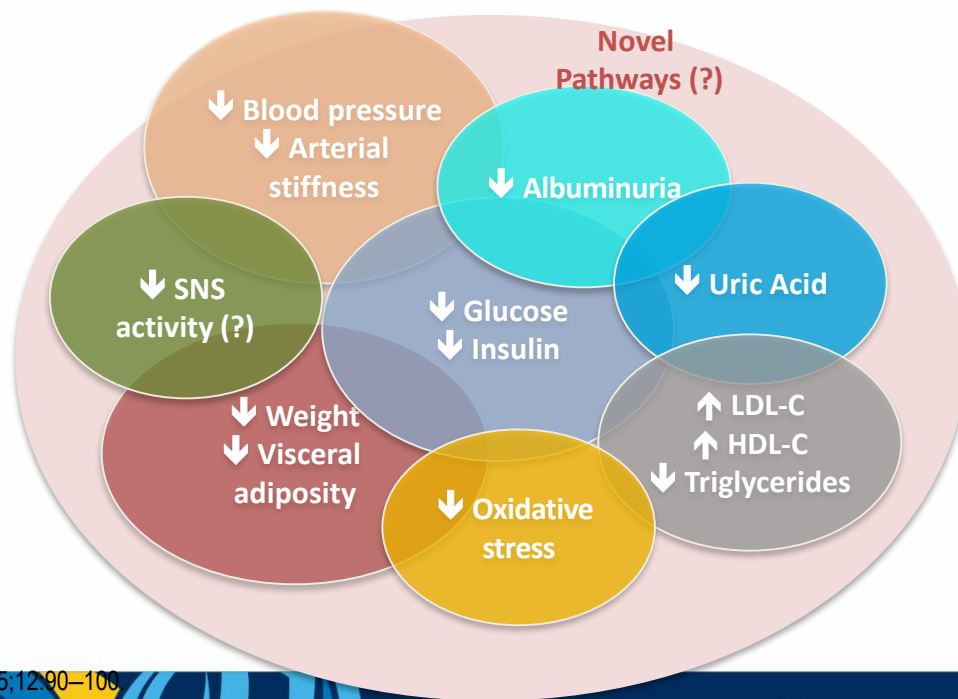


SGLT2 inhibitors
reduce glucose
reabsorption
in the proximal
tubule, leading to
urinary glucose
excretion* and
osmotic diuresis

¹ Bakris et al. Kidney Int 2009;75:1272-7.

SGLT2 inhibitors modulate a range of factors related to CV risk

Based on clinical and mechanistic studies



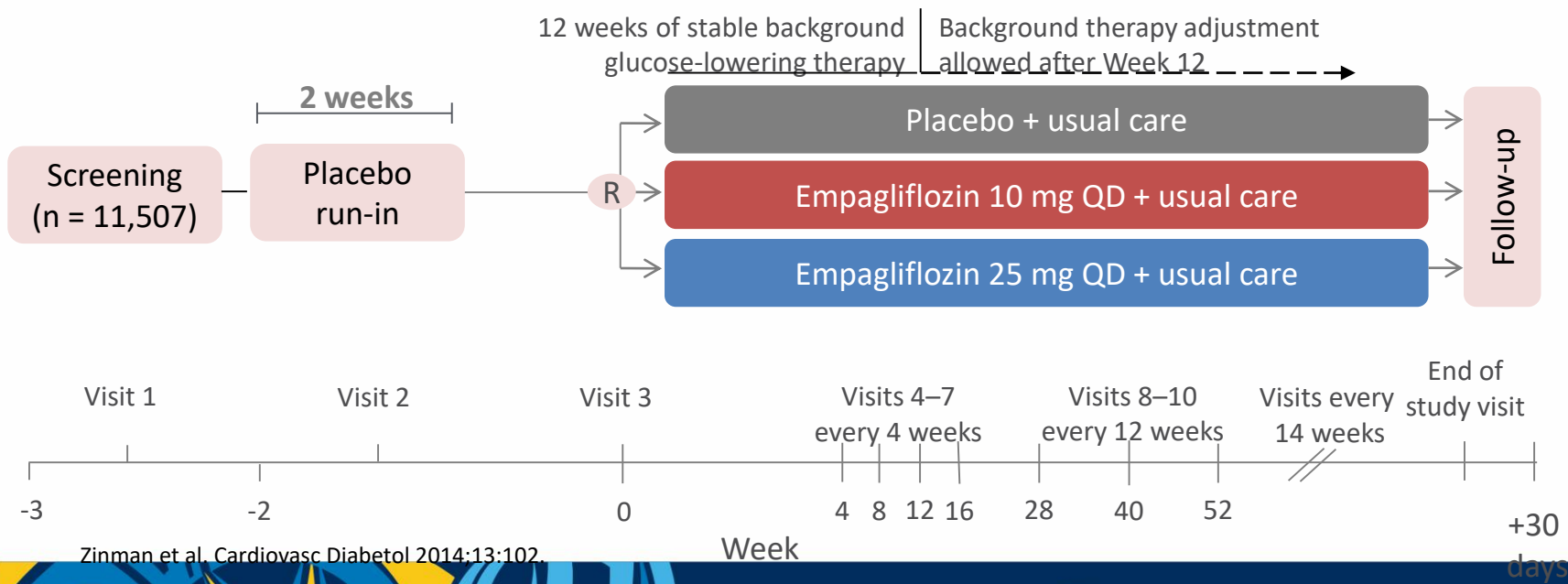
Inzucchi et al. Diab Vasc Dis Res 2015;12:90–100

EMPA-REG OUTCOME®: Study design

Aim

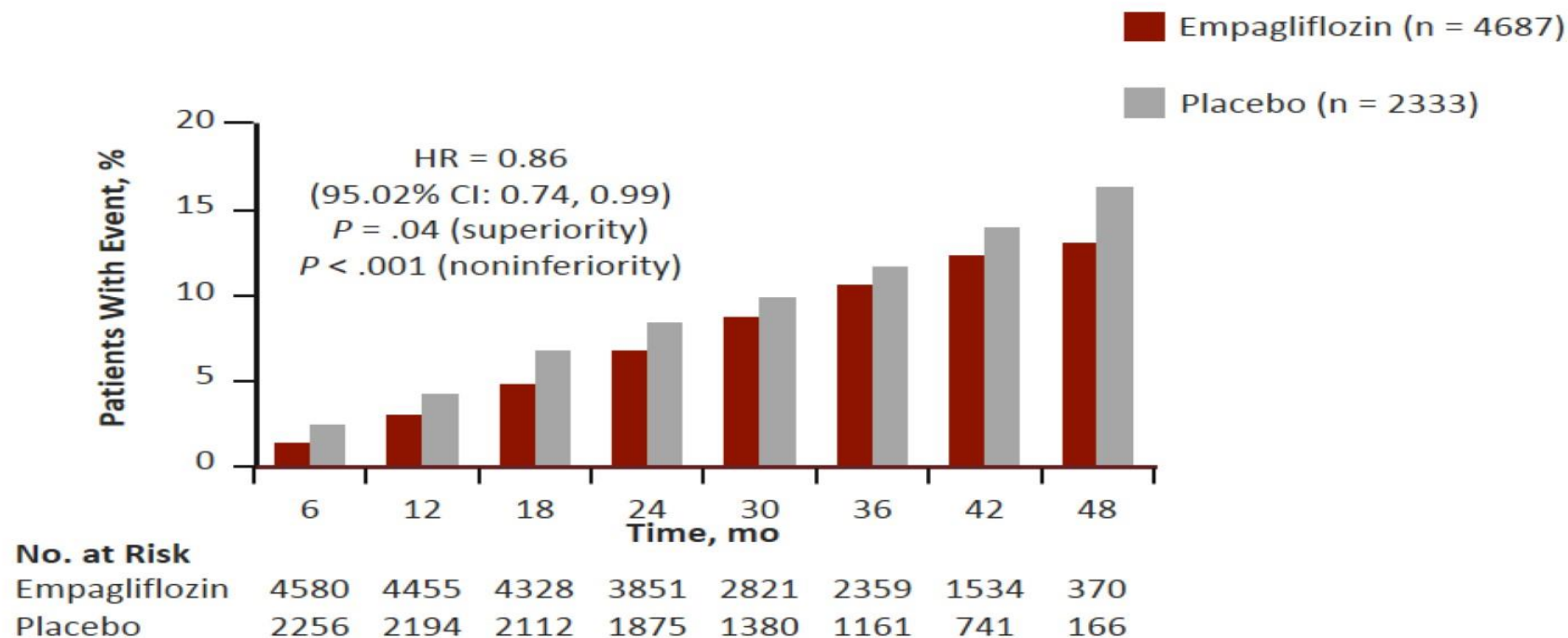
Compound-specific

To determine CV safety of empagliflozin vs placebo + usual care for glycaemic control and CV risk in patients with T2D and high CV risk

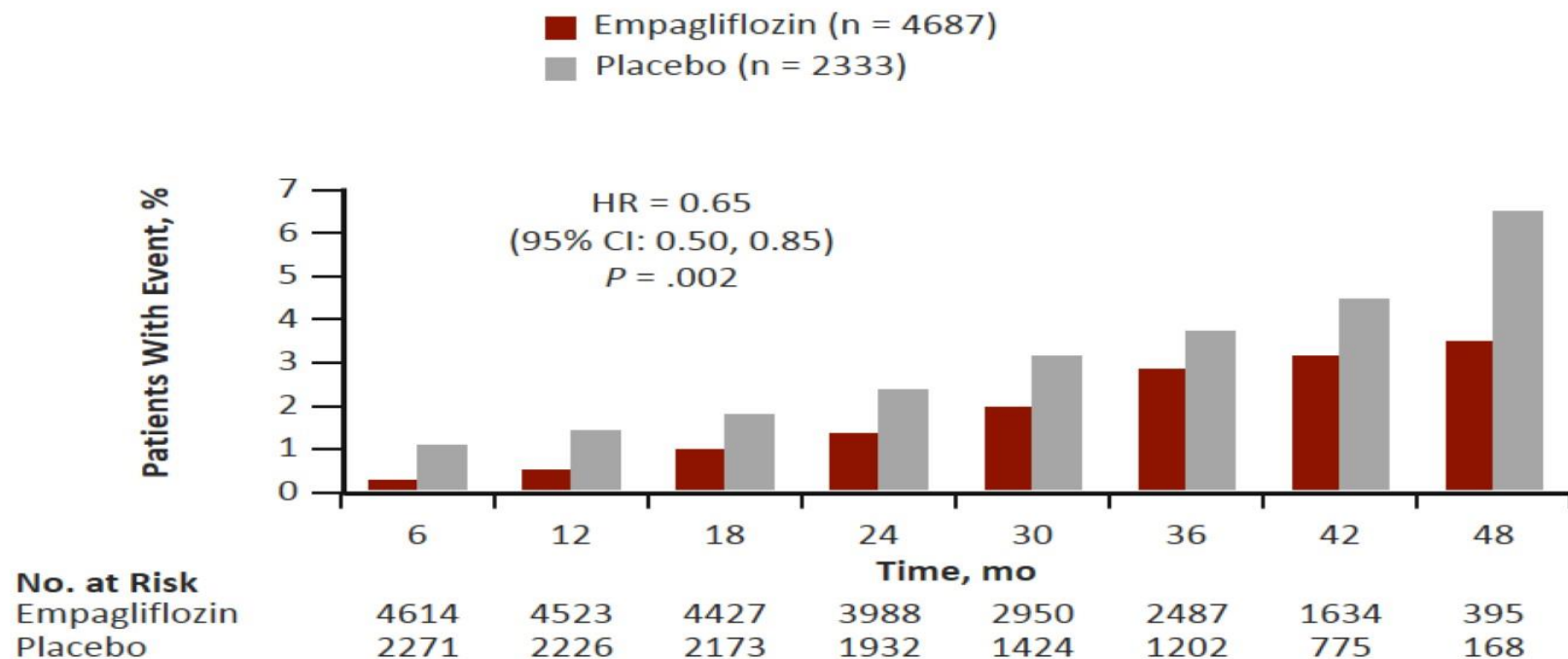


EMPA-REG OUTCOME: Empagliflozin

Primary MACE Outcome



EMPA-REG OUTCOME: Empagliflozin *Hospitalization for HF*



EMPA-REG OUTCOME[®] summary

- Empagliflozin in addition to standard of care reduced CV risk and improved overall survival in adults with T2D and established CV disease

Relative risk reduction:

3P-MACE



↓14%

CV death



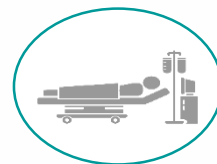
↓38%

All-cause mortality



↓32%

HHF



↓35%

The overall safety profile of empagliflozin was consistent with previous clinical trials and current label information



Conclusions

Novel glucose-lowering agents, including the GLP-1 RAs, liraglutide and semaglutide, and the SGLT2 inhibitor, empagliflozin, have demonstrated significant improvements in CV outcomes in patients with T2DM.

- Reductions in all-cause mortality, CV mortality, HHF, nonfatal stroke, nonfatal MI
 - Each agent has its own CV benefit profile

It is important for practicing cardiologists to be aware of the effects of these agents on CV risk in their patients with T2DM and facilitate their use, where appropriate.

*Thank
you*



ACC Middle East
Conference 2018

In partnership with:

