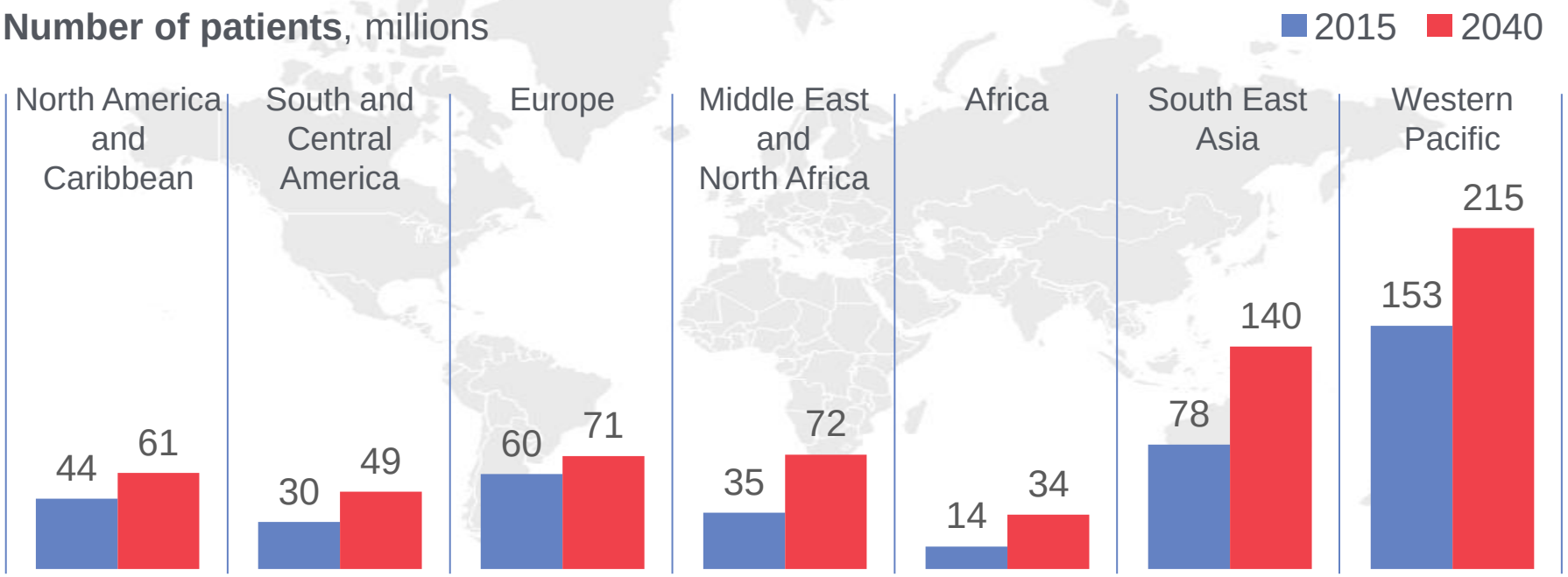
Σακχαρώδης διαβήτης τύπου 2 και καρδιαγγειακή νόσος: η ταυτόχρονη θεραπευτική πρόκληση και ο ρόλος της εμπαγλιφλοζίνης

Δημήτριος Σκούτας
Ειδικός Παθολόγος-Διαβητολόγος
Διδάκτωρ Ιατρικής Σχολής ΔΠΘ

Every 10 seconds, 3 people develop diabetes

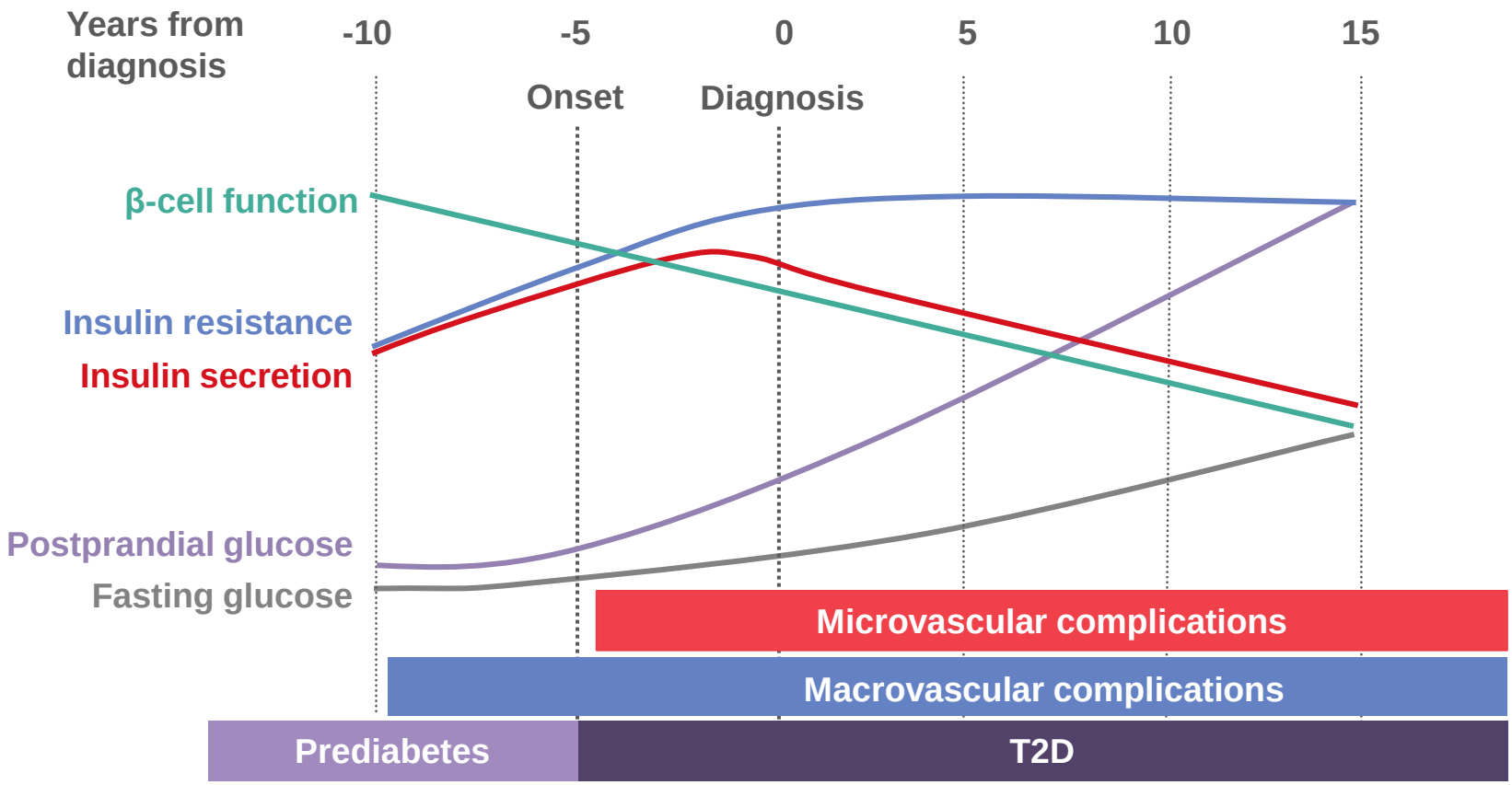
The number of patients with diabetes worldwide is expected to increase from 415 million in 2015 to 642 million in 2040



International Diabetes Federation. IDF Diabetes Atlas, 7th edn, 2015. www.diabetesatlas.org/component/attachments/?task=download&id=116 (accessed Feb 2017)

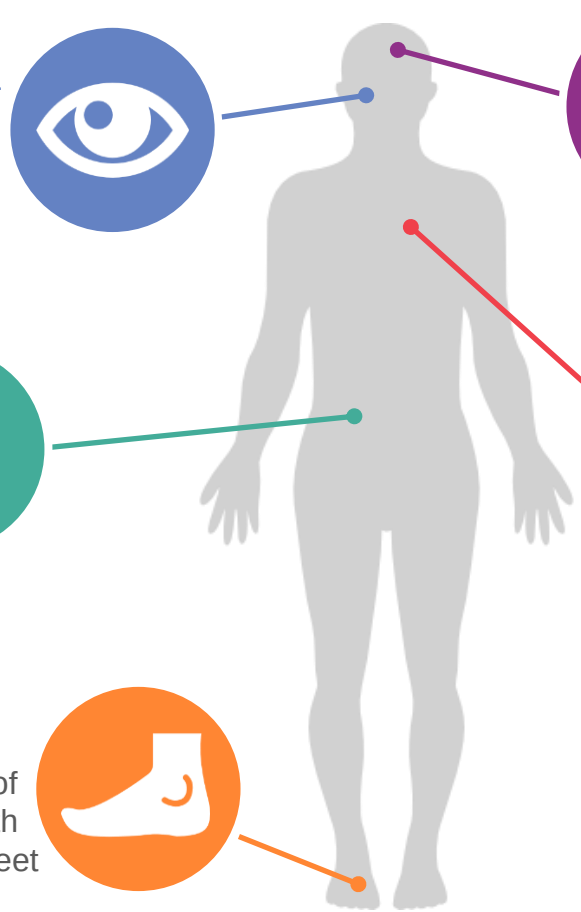
T2D is a chronic disease that worsens over time

Onset of vascular complications may begin even before T2D diagnosis



T2D, type 2 diabetes
Figure adapted from: AACE Diabetes Resource Center. http://outpatient.aace.com/type-2-diabetes/clinical-presentation-of-type-2-diabetes-mellitus (accessed May 2017)

Preventing vascular complications is a major challenge in diabetes management



Diabetic retinopathy[1]
A leading cause of preventable blindness

Stroke[1,2]
2−6 times increased risk of ischaemic attacks compared with adults without diabetes

Renal disease[1]
A leading cause of dialysis and kidney transplant

Cardiovascular disease[1,2]
2−4 times increased risk of developing cardiovascular disease compared with adults without diabetes

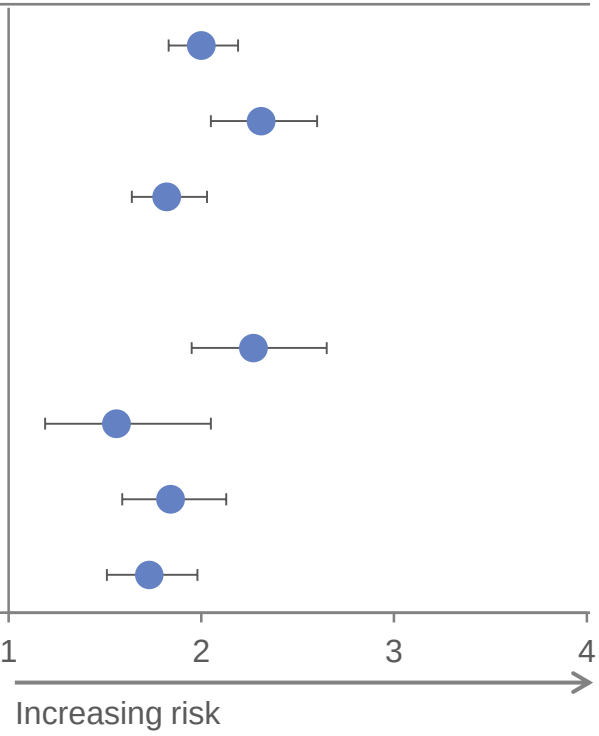
Diabetic neuropathy[1,3]
The most common complication of diabetes; up to 50% of people with T2D have neuropathy and at-risk feet

T2D, type 2 diabetes

1. World Health Organization. About diabetes. 2016. www.who.int/diabetes/action_online/basics/en/index3.html (accessed June 2017); 2. World Heart Federation. Diabetes. 2017. www.world-heart-federation.org/cardiovascular-health/cardiovascular-disease-risk-factors/diabetes (accessed June 2017); 3. Bakker K *et al. Diabetes Metab Res Rev* 2012;28:225

Diabetes doubles the risk of macrovascular events...

Outcome	Number of cases	HR (95% CI)
Coronary heart disease	26,505	2.00 (1.83, 2.19)
Coronary death	11,556	2.31 (2.05, 2.60)
Non-fatal MI	14,741	1.82 (1.64, 2.03)
Cerebrovascular disease		
Ischaemic stroke	3799	2.27 (1.95, 2.65)
Haemorrhagic stroke	1183	1.56 (1.19, 2.05)
Unclassified stroke	4973	1.84 (1.59, 2.13)
Other vascular deaths	3826	1.73 (1.51, 1.98)



MI, myocardial infarction
Sarwar N *et al. Lancet* 2010;375:2215

…and CV disease is the leading cause of death in T2D[1]

__Sixty-five percent__ of people with diabetes in the US die from heart attacks or strokes.
Unfortunately, most of them are __not aware__ of the link between __diabetes and heart disease__.[2]

CV, cardiovascular; T2D, type 2 diabetes
1. Morrish NJ *et al. Diabetologia* 2001;44(Suppl 2):S14; 2. Kappagoda CT. *Prev Cardiol* 2003;6:5

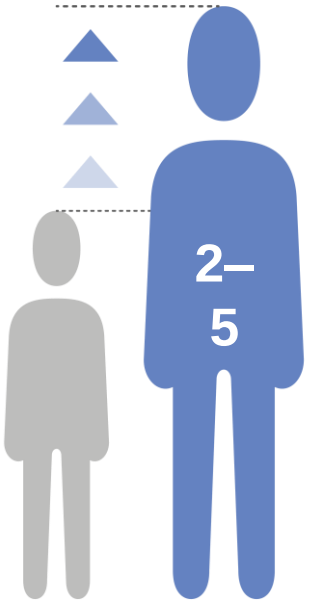
Heart failure: an introduction

- HF is a condition in which the heart is unable to pump sufficiently to maintain the metabolic needs of tissues in the body[1,2]
- Myocardial infarction and hypertension are the most common causes[2]
- HF is a major cause of morbidity and mortality[3]
  - Affects 1–2% of the adult population[3]
    - More prevalent in the elderly (affects 6–10% of people aged >65 years)[3]

HF, heart failure

1. Coronel R *et al. Cardiovasc Res* 2001;50:419; 2. Yancy CW *et al*. *Circulation* 2013;128:e240; 3. McMurray JJ & Pfeffer MA. *Lancet* 2005;365:1877

People with diabetes are at increased risk of heart failure



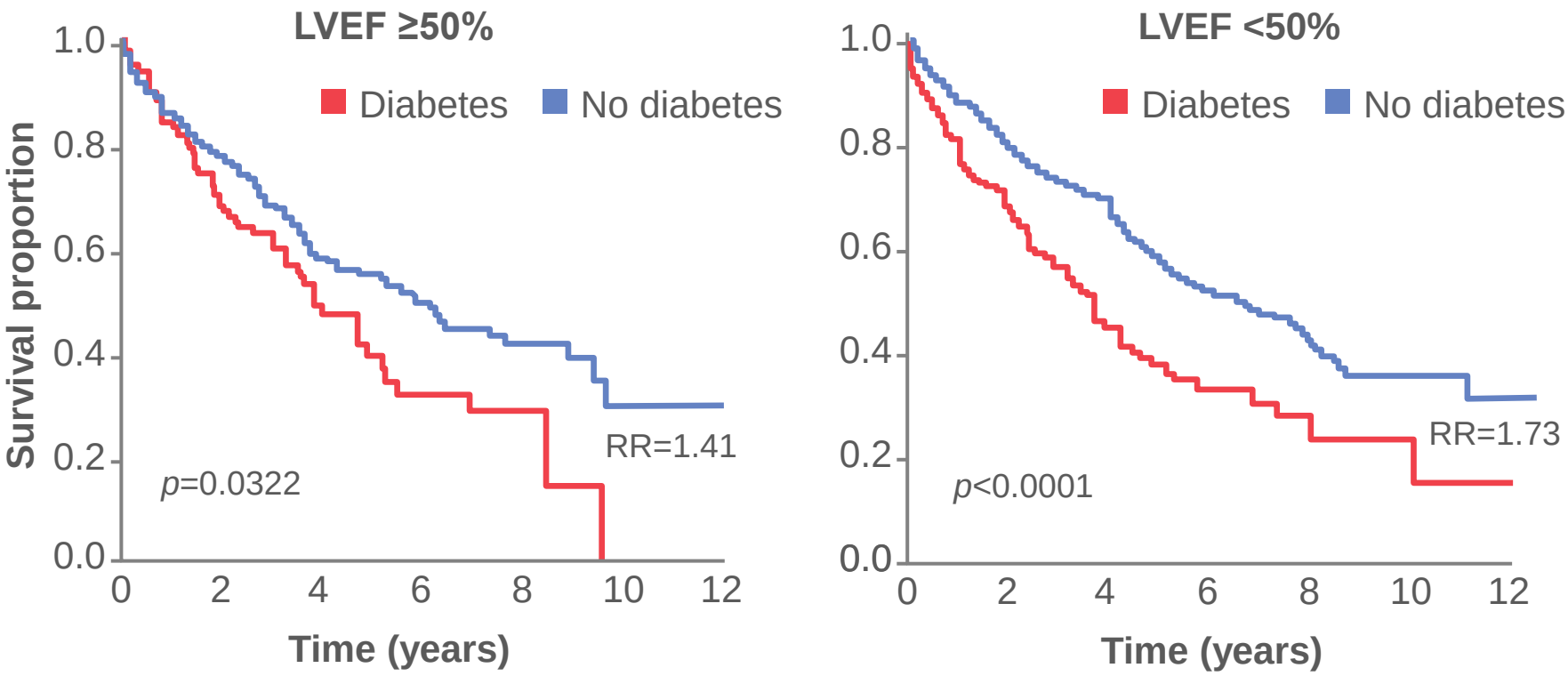
Άτομα με διαβήτη έχουν 2 έως 5 φορές υψηλότερο κίνδυνο ανάπτυξης HF[1]

Ο Διαβήτης αυξάνει κατά 60–80% την πιθανότητα για CV θάνατο και κάθε αιτιολογίας θάνατο σε ασθενείς με εγκατεστημένη HF[2,3]*

*Synthesised based on data from two clinical studies – see Notes for details
CV, cardiovascular; HF, heart failure
1. Kannel WB *et al. Am J Cardiol* 1974;34:29; 2. Cubbon RM *et al. Diab Vasc Dis Res* 2013;10:330; 3. MacDonald MR *et al. Eur Heart J* 2008;29:1377

Diabetes worsens heart failure prognosis

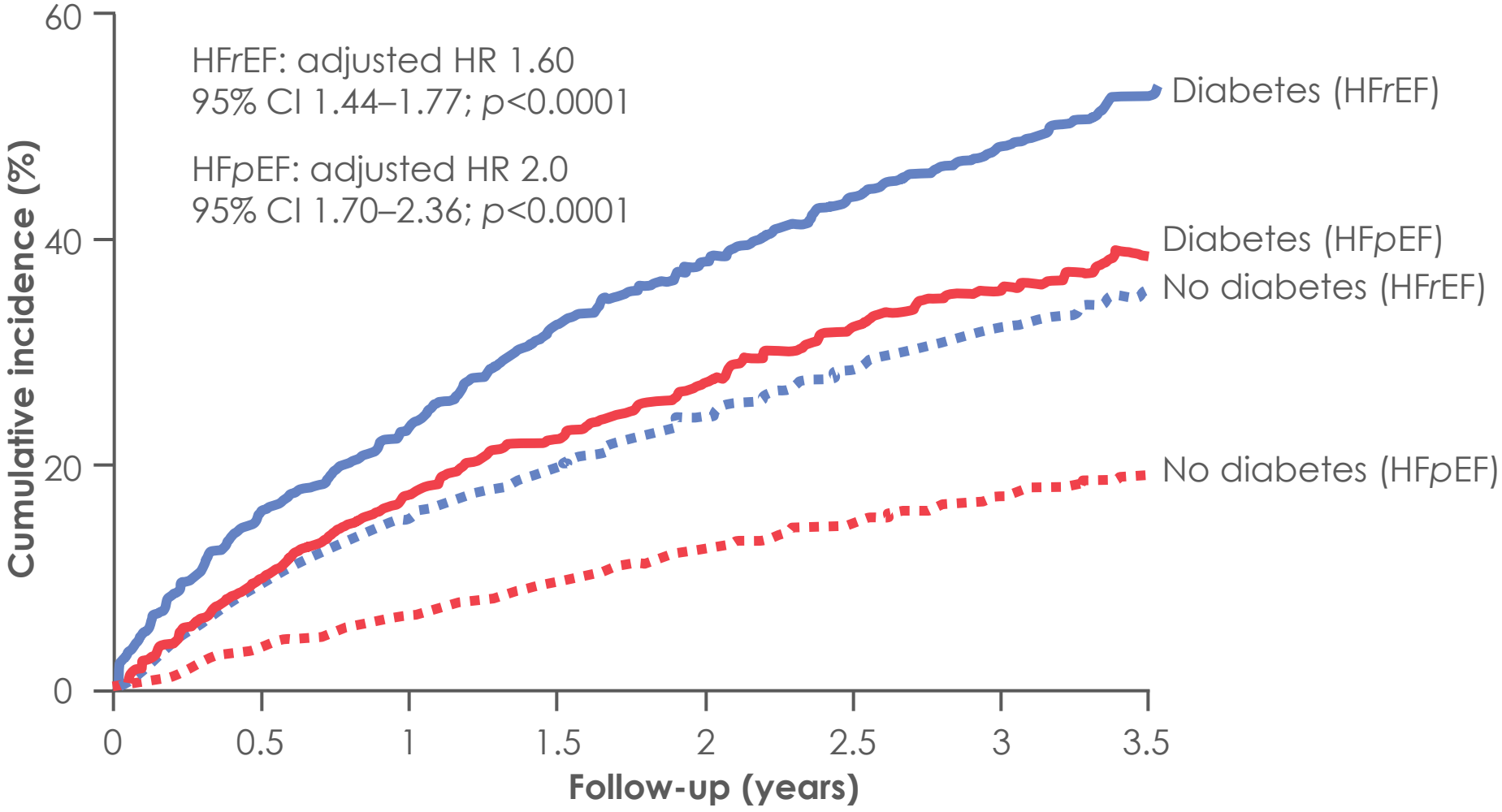
Poorer HF survival with diabetes than without diabetes



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

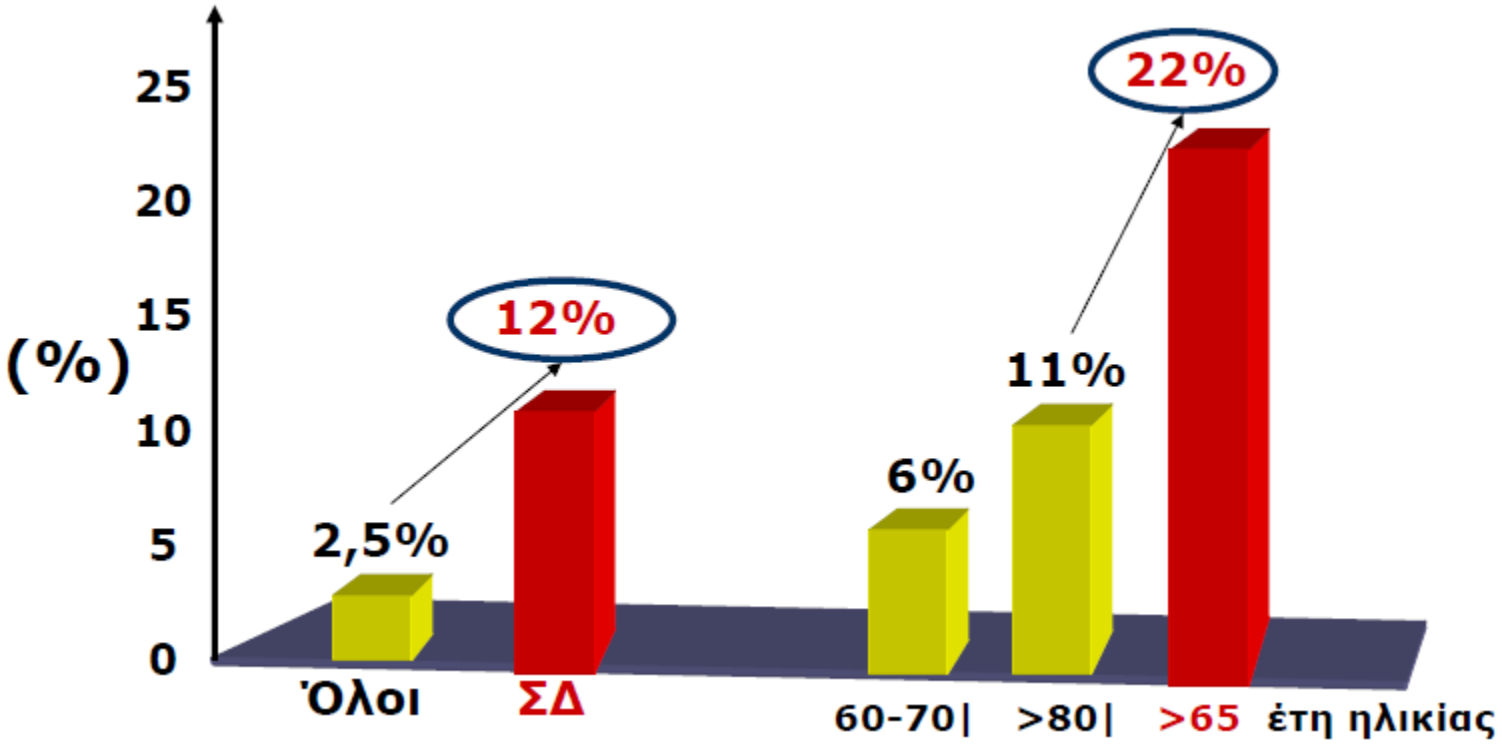
HF, heart failure; LVEF, left ventricular ejection fraction
Varela-Roman A *et al. Eur J Heart Failure* 2005;7:859

Diabetes increases risk of hospitalization or death due to heart failure



HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction.
MacDonald et al. Eur Heart J 2008;29:1377-85.

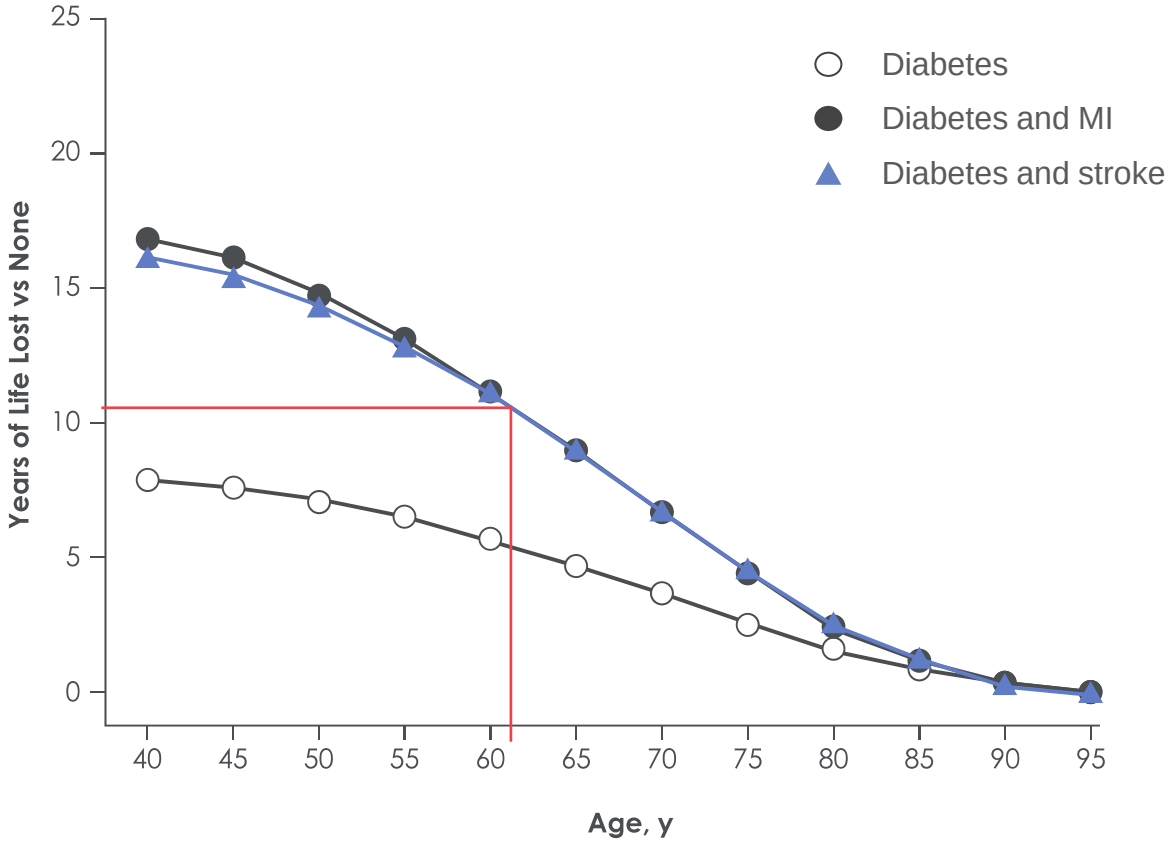
Prevalence of HF in Diabetic Patients



Circulation 2008;117;e25-e146, European Heart Journal 2008 29, 1224–1240
Diabetes Care 699–703, 2004, Diabetes Care 1614–1619, 2001, Diabetes Care 612–616, 2005

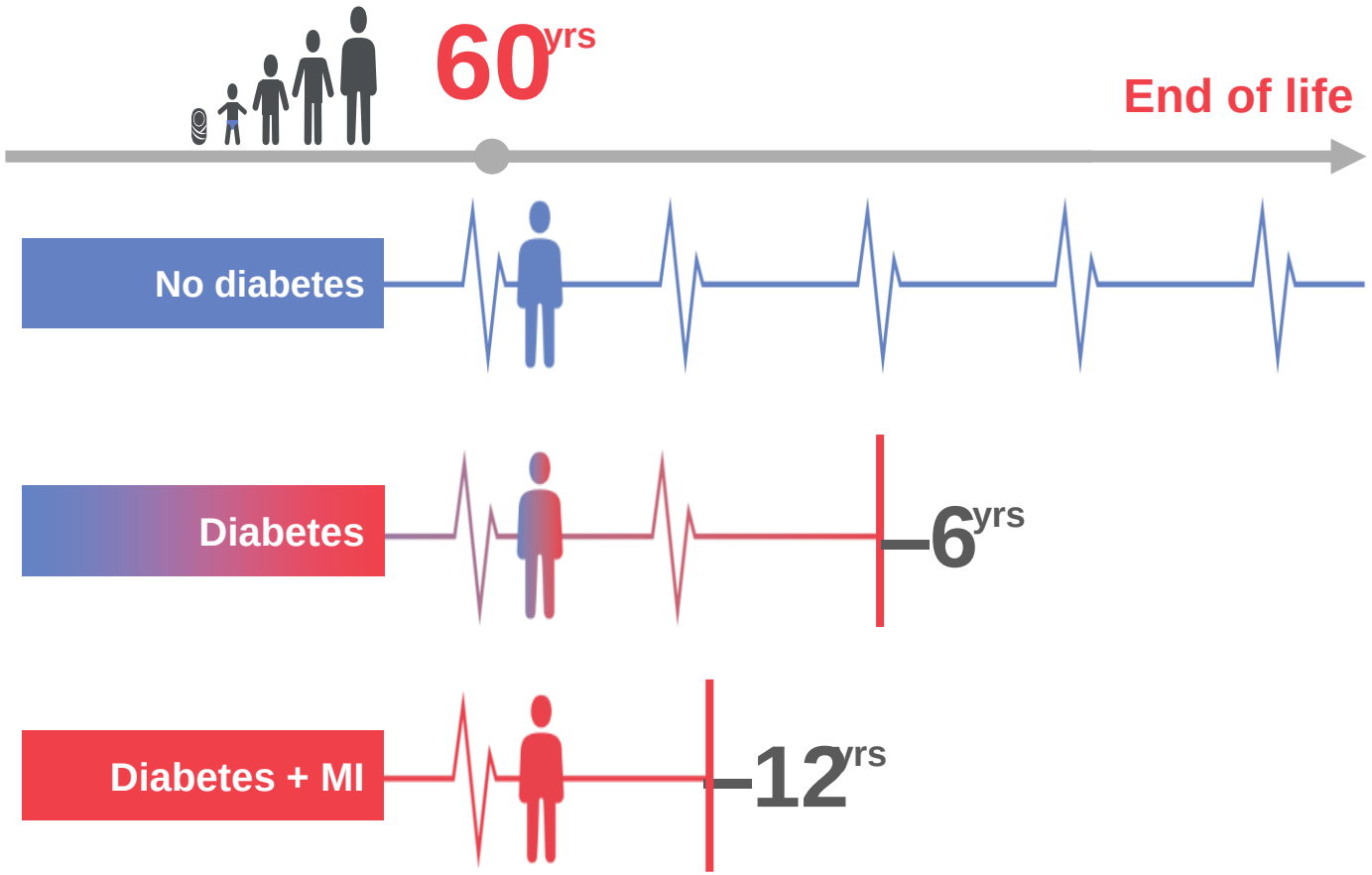
Life expectancy is reduced by ~12 years in diabetes patients with previous CVD*

Modelling of years of life lost by disease status of participants at baseline compared with those free of diabetes, stroke and MI



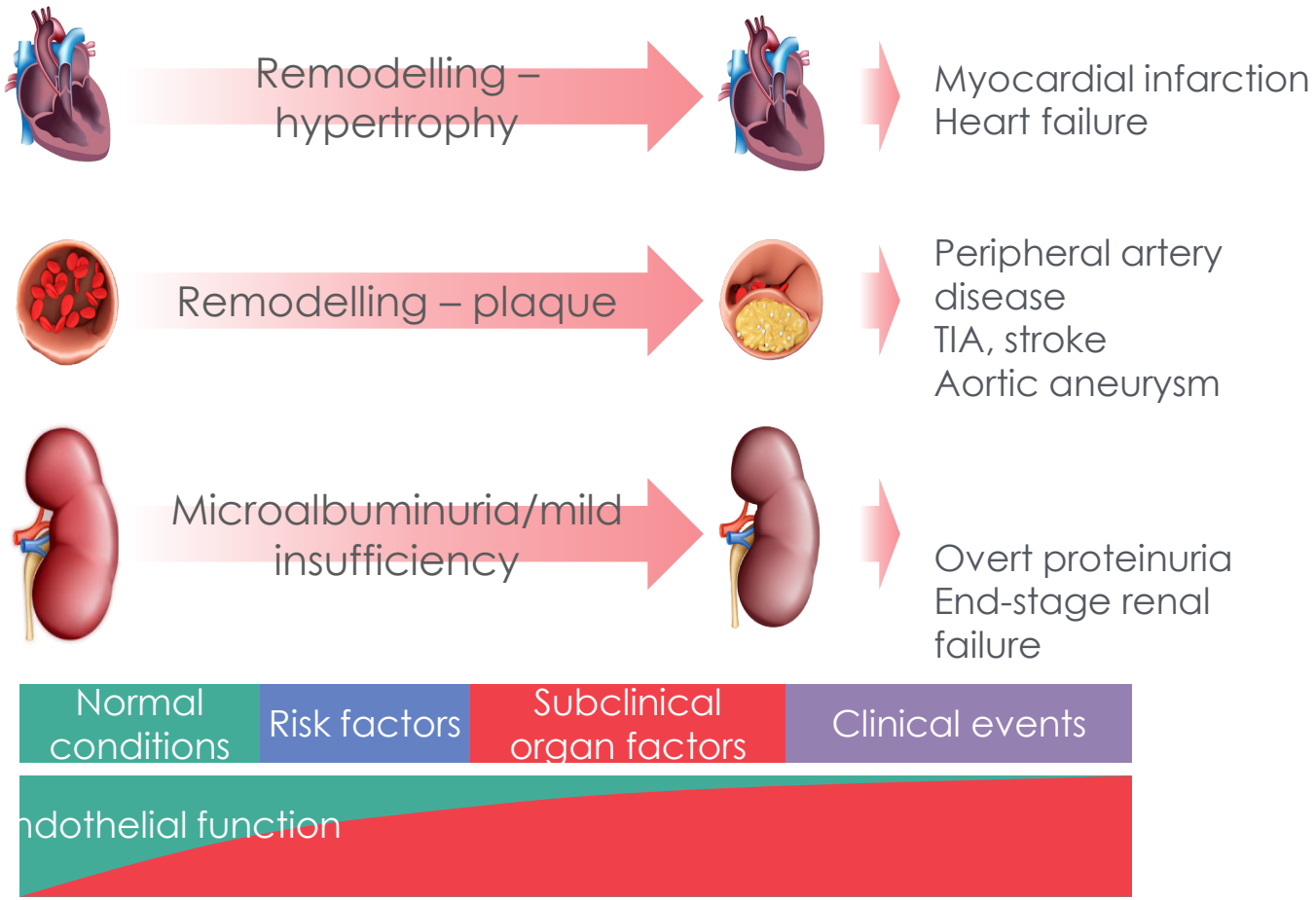
*Male, 60 years of age with history of MI or stroke
CVD, cardiovascular disease; MI, myocardial infarction; None, population free from T2D, stroke and MI
The Emerging Risk Factors Collaboration. *JAMA* 2015;314:52

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. *JAMA* 2015;314:52

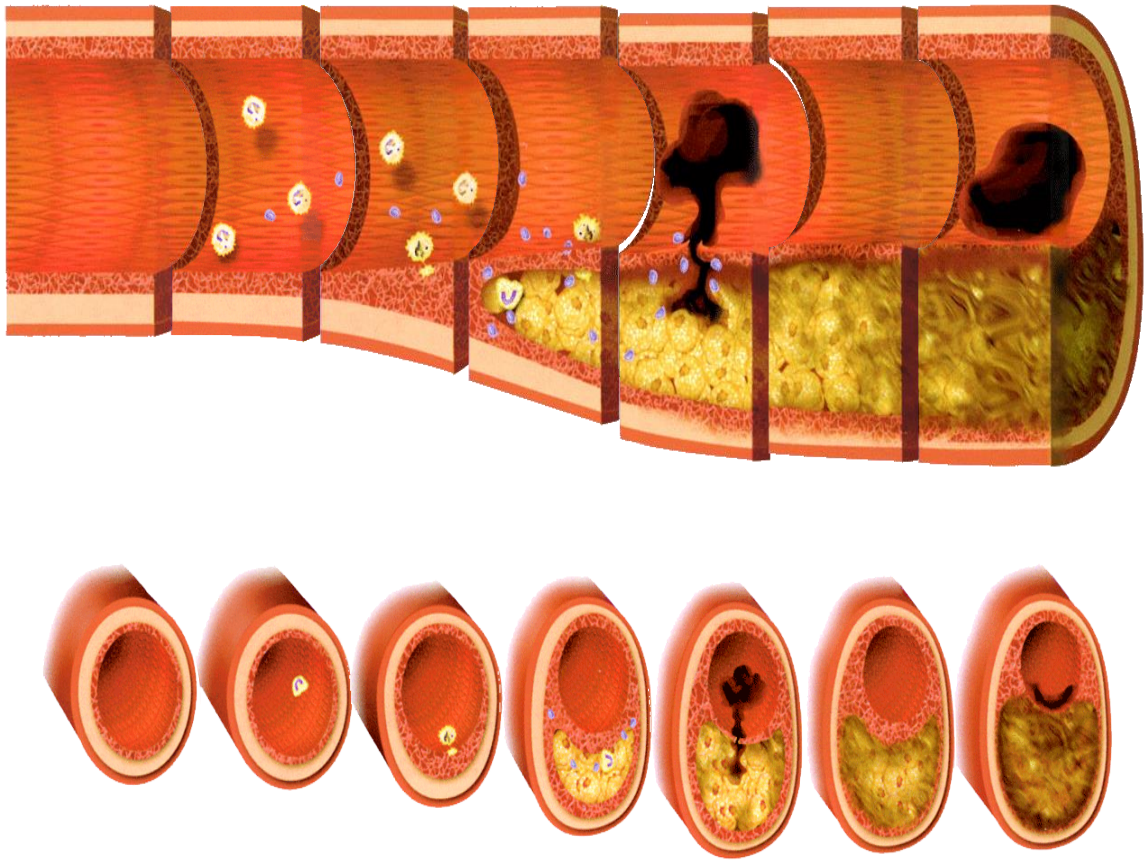
Endothelial dysfunction is common to microvascular and macrovascular events



TIA, transient ischaemic attack

Versari D *et al. Diabetes Care* 2009;32(suppl 2):S314

Endothelial dysfunction drives atherosclerotic progression

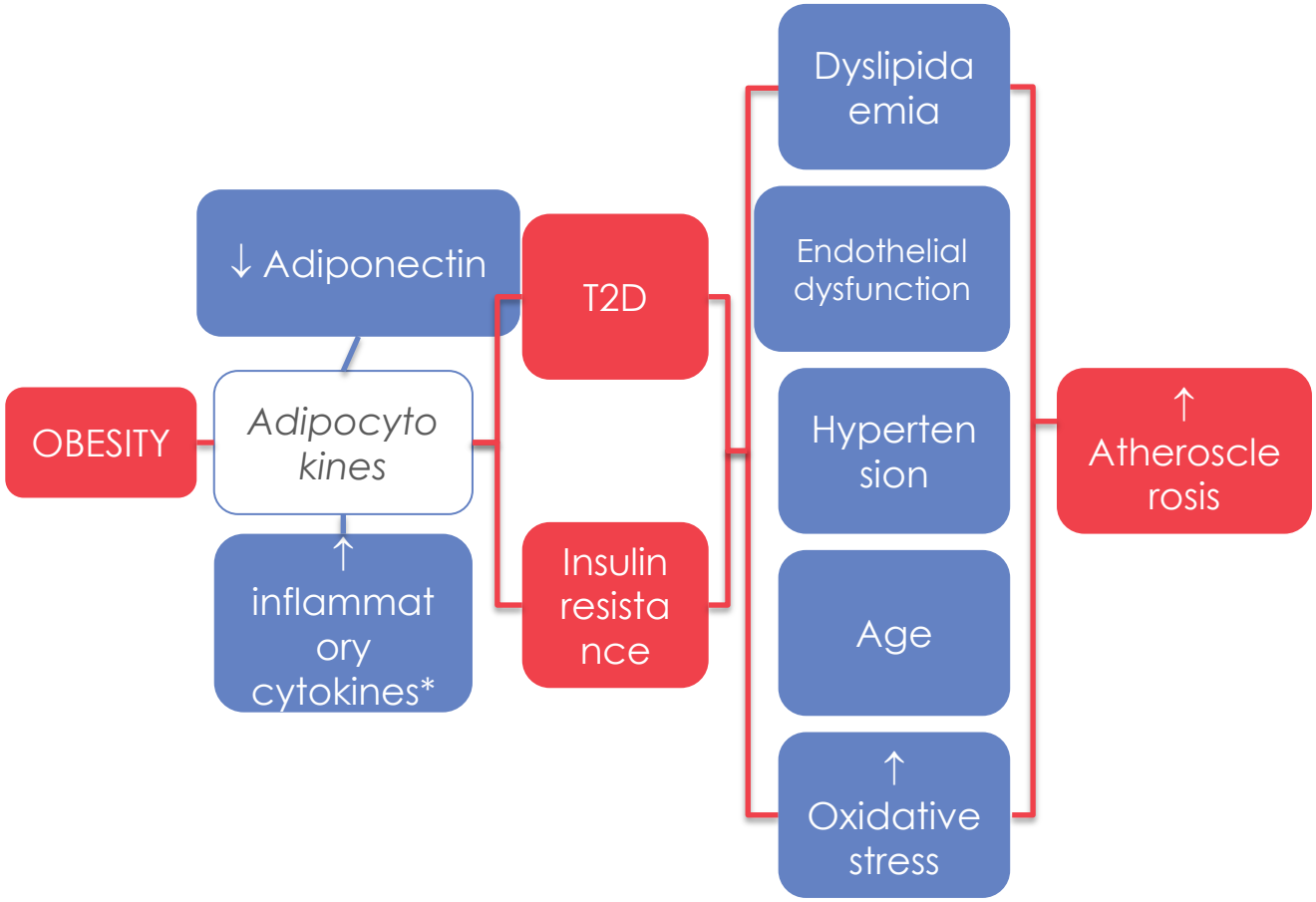


Atherosclerosis is accelerated in T2D by
hyperglycaemia,
insulin resistance, inflammation and diabetic dyslipidaemia

T2D, type 2 diabetes
Figure adapted from Libby P. *Circulation* 2001;104:365
Zeadin MG *et al. Can J Diabetes* 2013;37:345e350

Visceral adiposity is related to inflammation, insulin resistance, dyslipidaemia and atherosclerosis

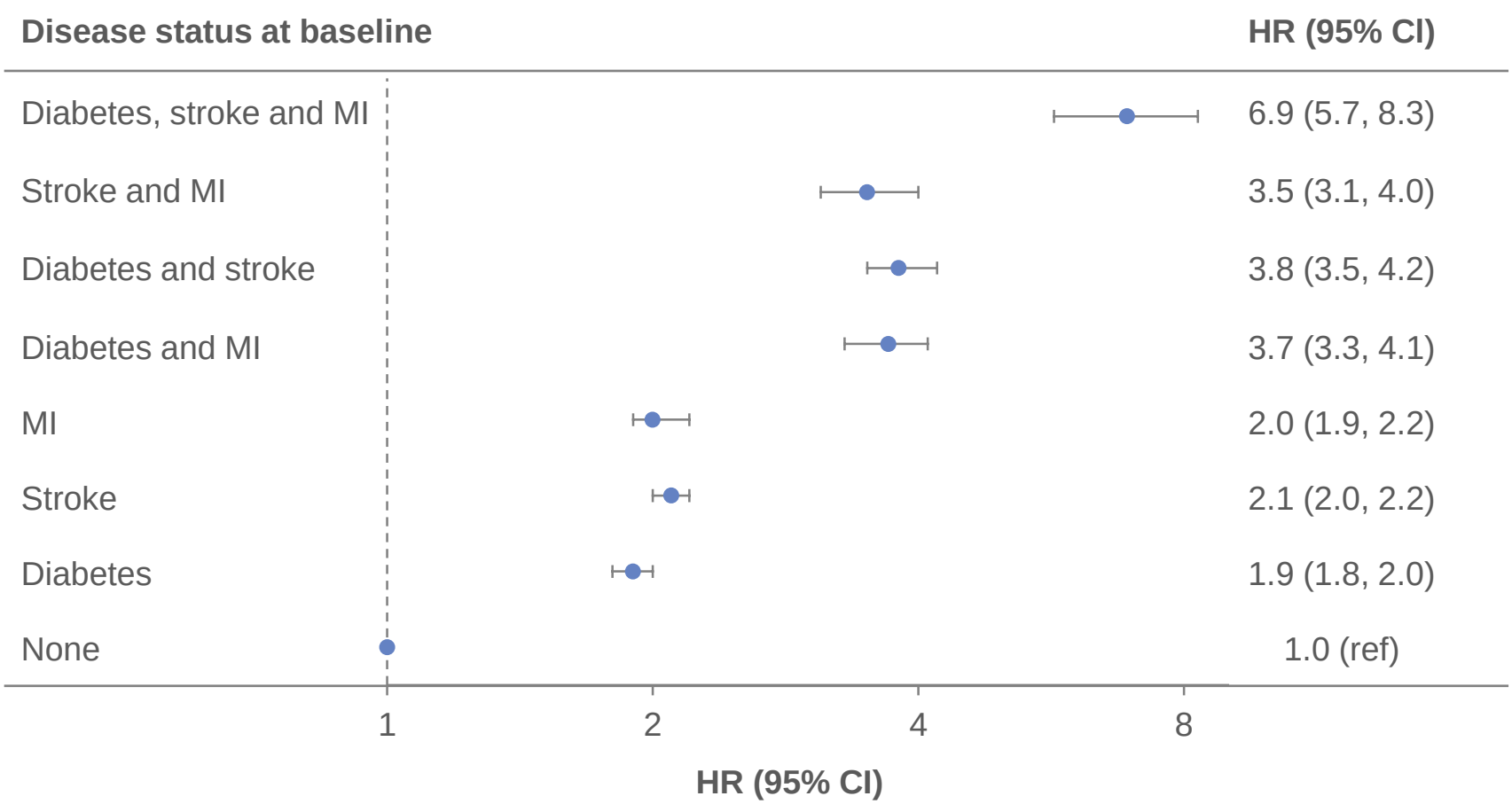
Interactions are complex, inter-related and not necessarily causal



*Including: TNFa, IL-6, resistin, PAI-1, angiotensinogen
IL-6, interleukin 6; PAI-1, plasminogen activator inhibitor-1; T2D, type 2 diabetes
Lau DCW *et al. Am J Physiol Heart Circ Physiol* 2005;288:H2031

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

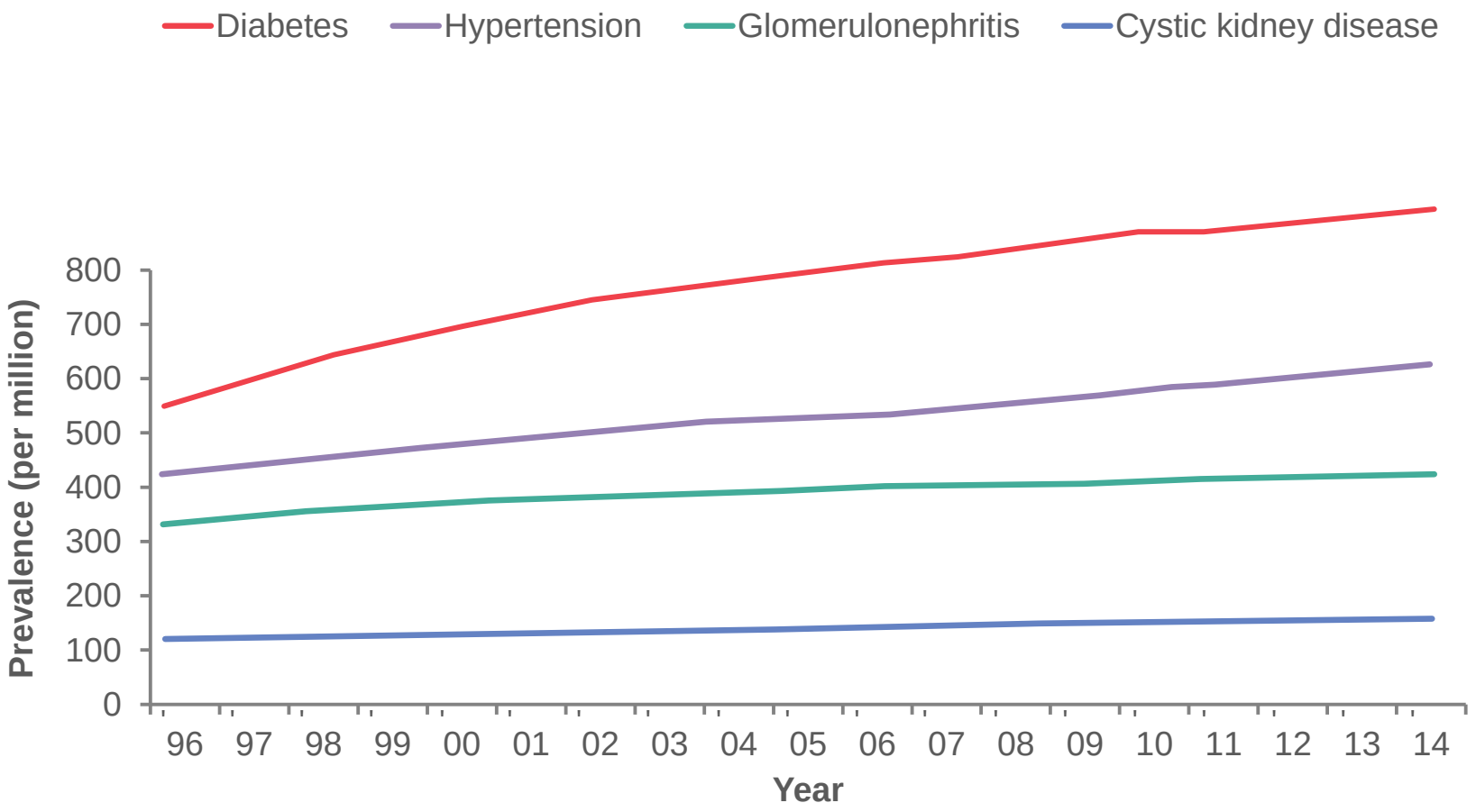


CI, confidence interval; HR, hazard ratio; MI, myocardial infarction; T2D, type 2 diabetes

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

Diabetes is the leading cause of end-stage renal disease in many parts of the world[1,2]

US annual incident cases of ESRD by primary cause[3]



ESRD, end-stage renal disease

1. Toth-Manikowski S & Atta MG. *J Diabetes Res* 2015;2015:697010; 2. Thomas MC *et al. Nat Rev Nephrol* 2016;12:73;
3. US Renal Data System. Annual data report 2016. www.usrds.org/adr.aspx (accessed May 2017)

Preventing vascular complications is the main aim of treatment for patients with T2D

European Society of Cardiology[1]

*Patients with "**diabetes, and at least one other CV risk factor** or target organ damage, should be considered to be at **very high risk**…*

*…**Most other people with diabetes** […] **are categorised as high risk**…*

*…High risk persons […] may be candidates for **drug treatment**."*

Diabetes Canada[2]

"Diabetes promotes both the development and adverse impact of CV disease risk factors...

*…**All adults with diabetes require** chronic disease care strategies that include […] for many individuals, **pharmacological vascular protection**…"*

CV, cardiovascular; T2D, type 2 diabetes

1. Piepoli MF *et al. Eur Heart J* 2016;37:2315; 2. Canadian Diabetes Association. *Can J Diabetes* 2013;37:S100

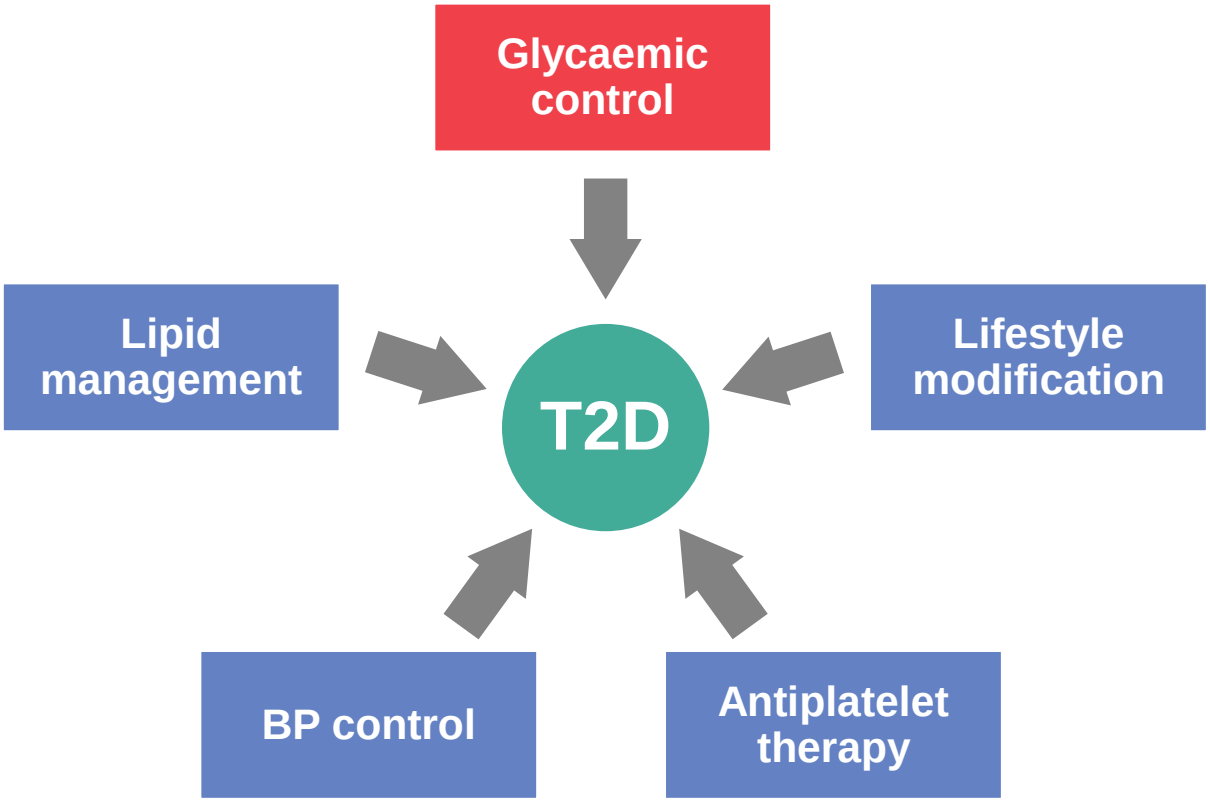
Intensive glucose-lowering has been shown to reduce risk of microvascular complications, but shows mixed results on macrovascular outcomes

Study[1]	Baseline HbA1c Control vs intensive	Mean duration of diabetes at baseline (years)	Microvascular		CVD		Mortality	
UKPDS[2]	8.4% → 7.9% vs 7.0%	Newly diagnosed	↓	↓	↔	↓	↔	↓
ACCORD[3]	8.1% → 7.5% vs 6.4%	10.0	↓*		↔		↑	
ADVANCE[4]	7.5% → 7.3% vs 6.5%	8.0	↓	↔†	↔	↔	↔	↔
VADT[5]	9.4% → 8.4% vs 6.9%	11.5	↓	NA	↔	↓	↔	↔

Long-term follow-up[1,4,5]

*No change in primary microvascular composite but significant decreases in micro/macroalbuminuria[2,3]
†No change in major clinical microvascular events but significant reduction in ESRD (p=0.007)[5]
CVD, cardiovascular disease; ESRD, end-stage renal disease; HbA1c, glycated haemoglobin; NA, not available
Table adapted from: 1. Bergenstal RM *et al. Am J Med* 2010;123:374.e9; 2. Holman RR *et al. N Engl J Med* 2010;359:1577;
3. Ismail-Beigi F *et al. Lancet* 2010;376:419; 4. Zoungas S *et al. N Engl J Med* 2014;371:1392; 5. Hayward RA *et al. N Engl J Med* 2015;372:2197

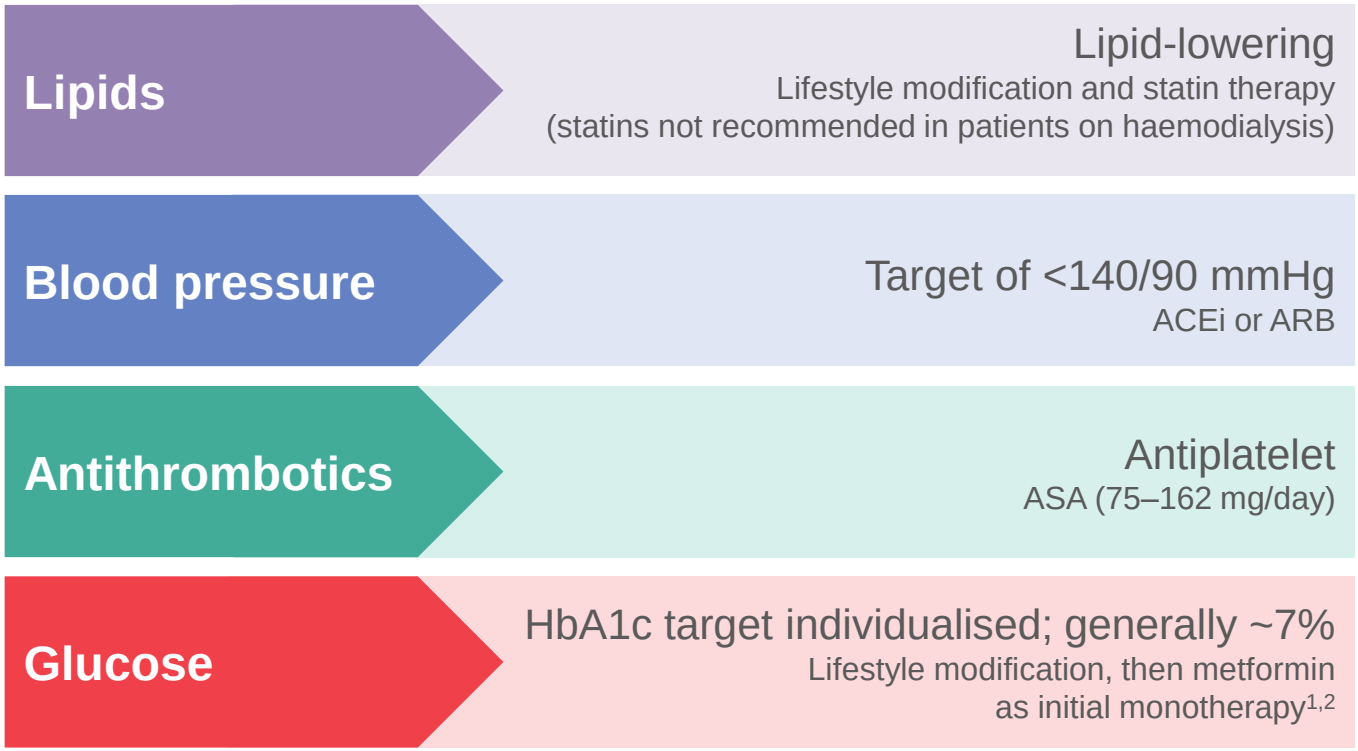
Effective management of T2D therefore extends beyond glycaemic control



BP, blood pressure; T2D, type 2 diabetes
Ryden L *et al. Eur Heart J* 2013;34:3035

CV and renal risk reduction in T2D is achieved by targeting multiple risk factors

Diabetes and cardiology treatment guidelines recommend:[1,2]

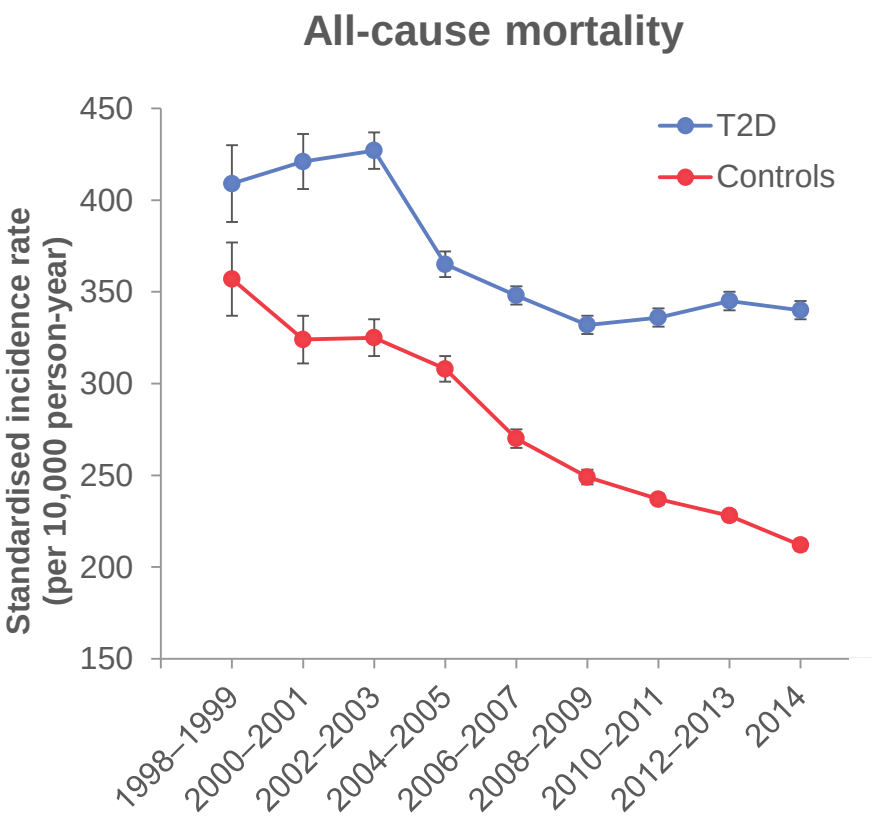


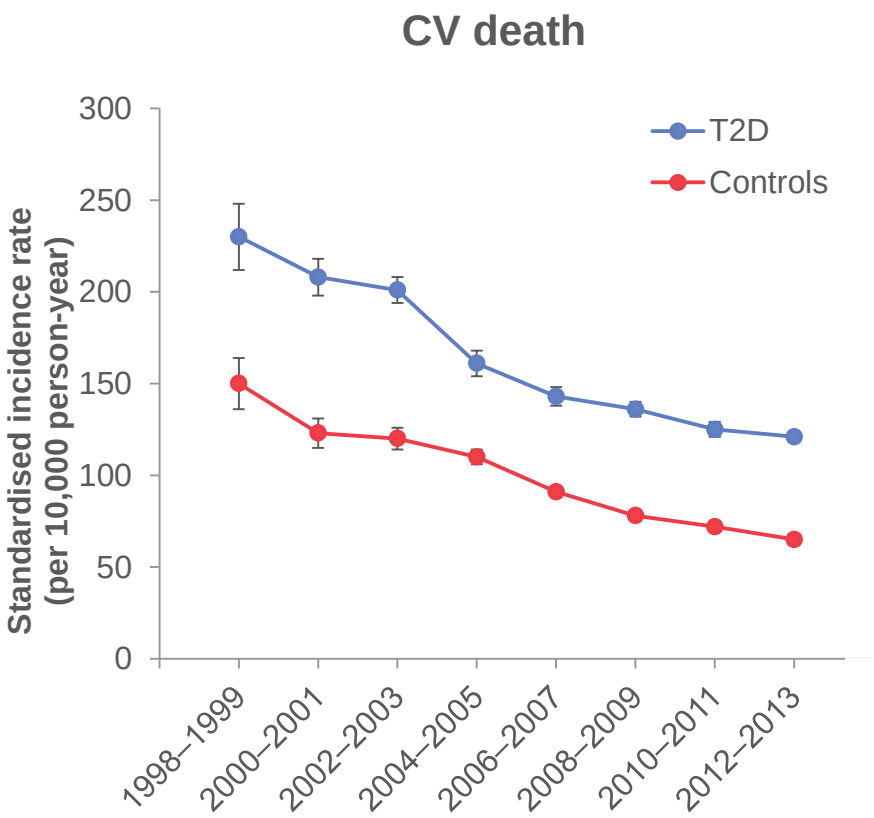
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ASA, acetylsalicylic acid; CV, cardiovascular; HbA1c, glycated haemoglobin; T2D, type 2 diabetes

1. American Diabetes Association. *Diabetes Care* 2017;40(Suppl 1):S1; 2. Rydén L *et al. Eur Heart J* 2013;34:3035

Despite advances in standard of care, patients with T2D remain at significant risk of CV mortality

Data from 457,473 patients with T2D from the Swedish National Diabetes Register



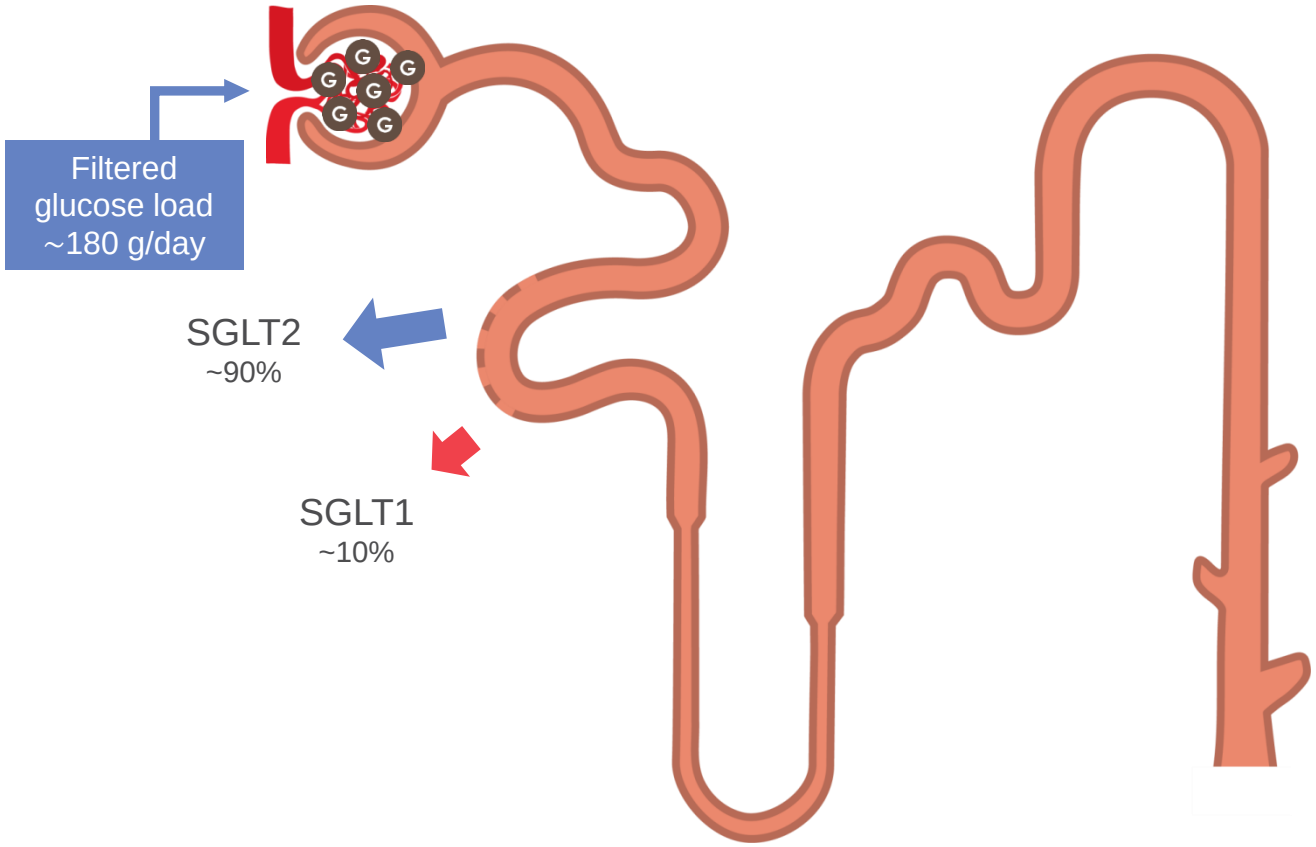


CV, cardiovascular; T2D, type 2 diabetes

Rawshani A *et al. N Engl J Med* 2017;376:1407

Rationale for SGLT2 inhibition and introduction to empagliflozin

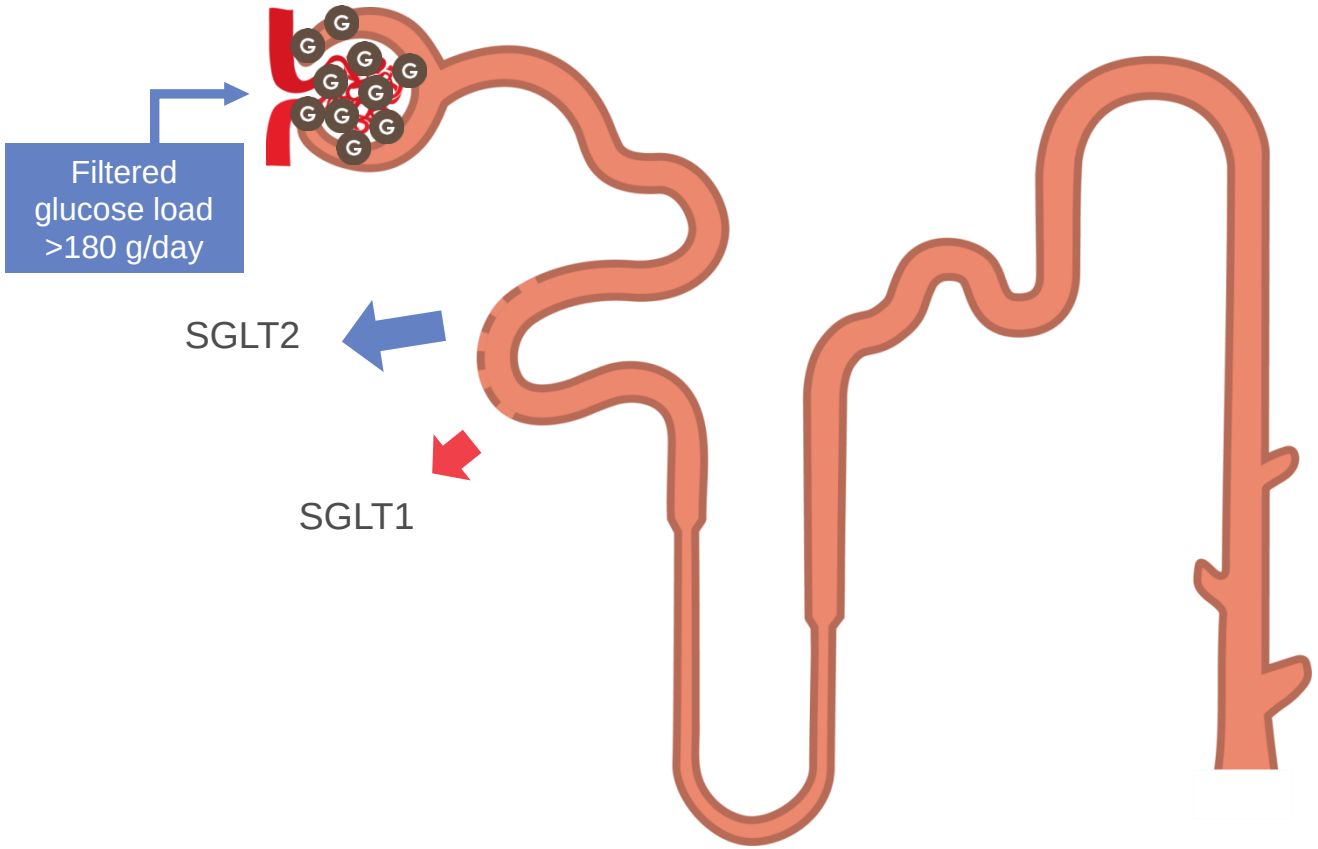
In healthy individuals, glucose is reabsorbed by the kidneys



Virtually all of the filtered glucose is reabsorbed in the proximal tubules through SGLT2 and SGLT1, with SGLT2 accounting for ~90% in the S1 and S2 segments and SGLT1 accounting for ~10% in the S3 segment

SGLT, sodium-glucose co-transporter
Gerich JE *Diabet Med* 2010;27:136

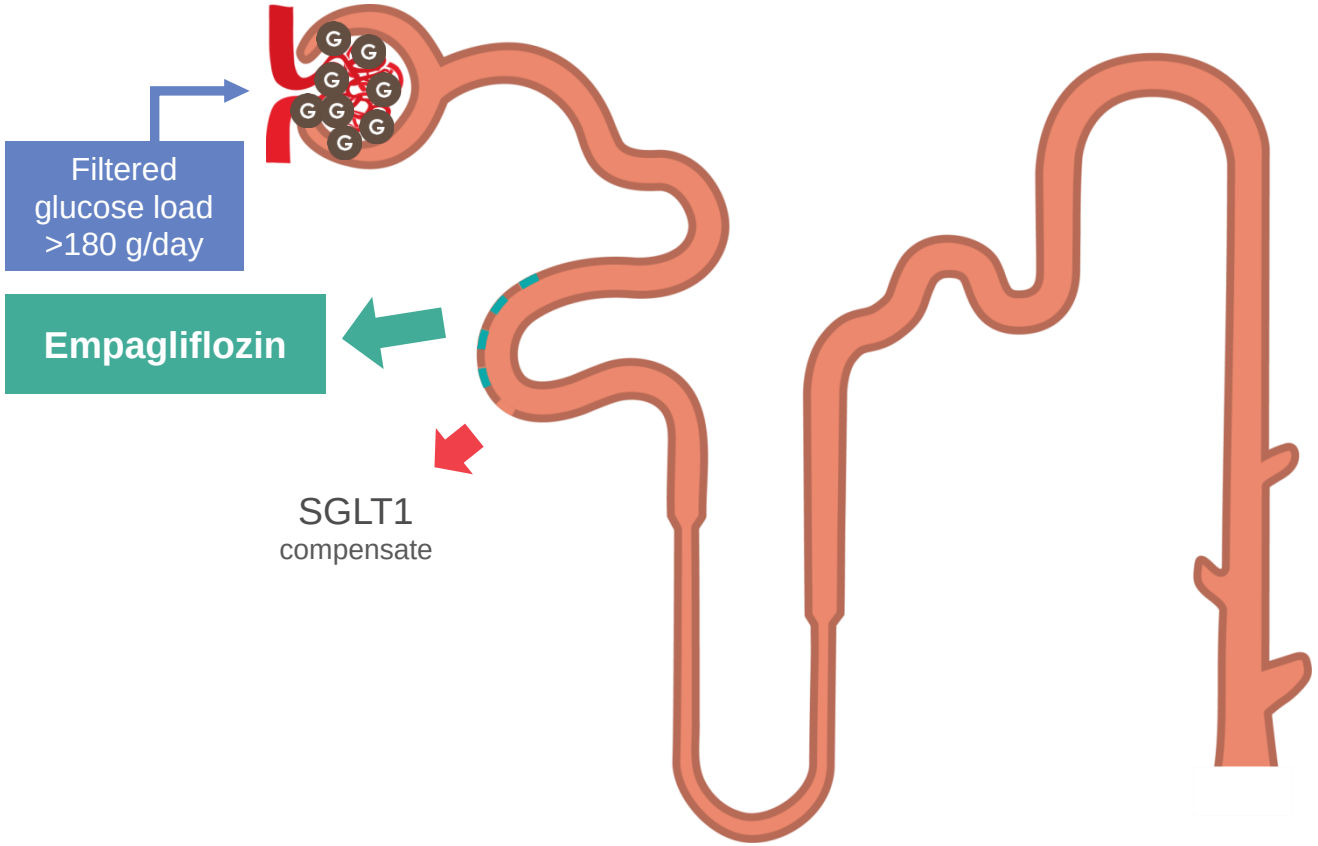
In the presence of hyperglycaemia, the renal reabsorption capacity is exceeded, resulting in urinary glucose excretion



When blood glucose increases above the renal threshold (>~10 mmol/l or >180 mg/dl), the capacity of SGLTs is exceeded, resulting in urinary glucose excretion

SGLT, sodium-glucose co-transporter
Gerich JE *Diabet Med* 2010;27:136

By inhibiting SGLT2, empagliflozin prevents sodium and glucose reabsorption, increasing urinary glucose excretion

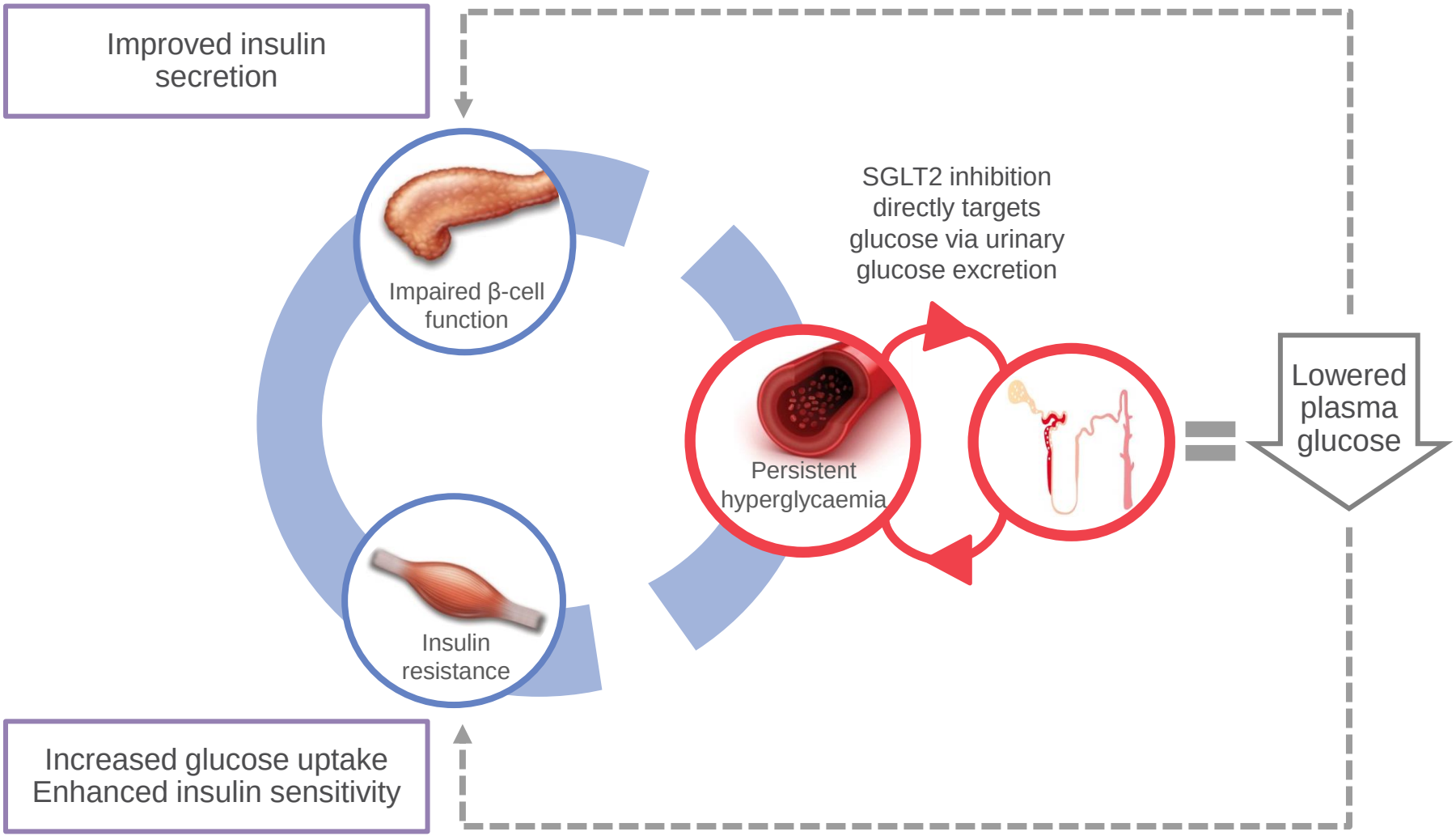


Empagliflozin reduces glucose reabsorption in the proximal tubule, leading to urinary glucose excretion* and osmotic diuresis

~80 g of glucose

*Loss of ~80 g of glucose per day = 240 cal/day
SGLT, sodium-glucose co-transporter
Bakris GL *et al. Kidney Int* 2009;75:1272

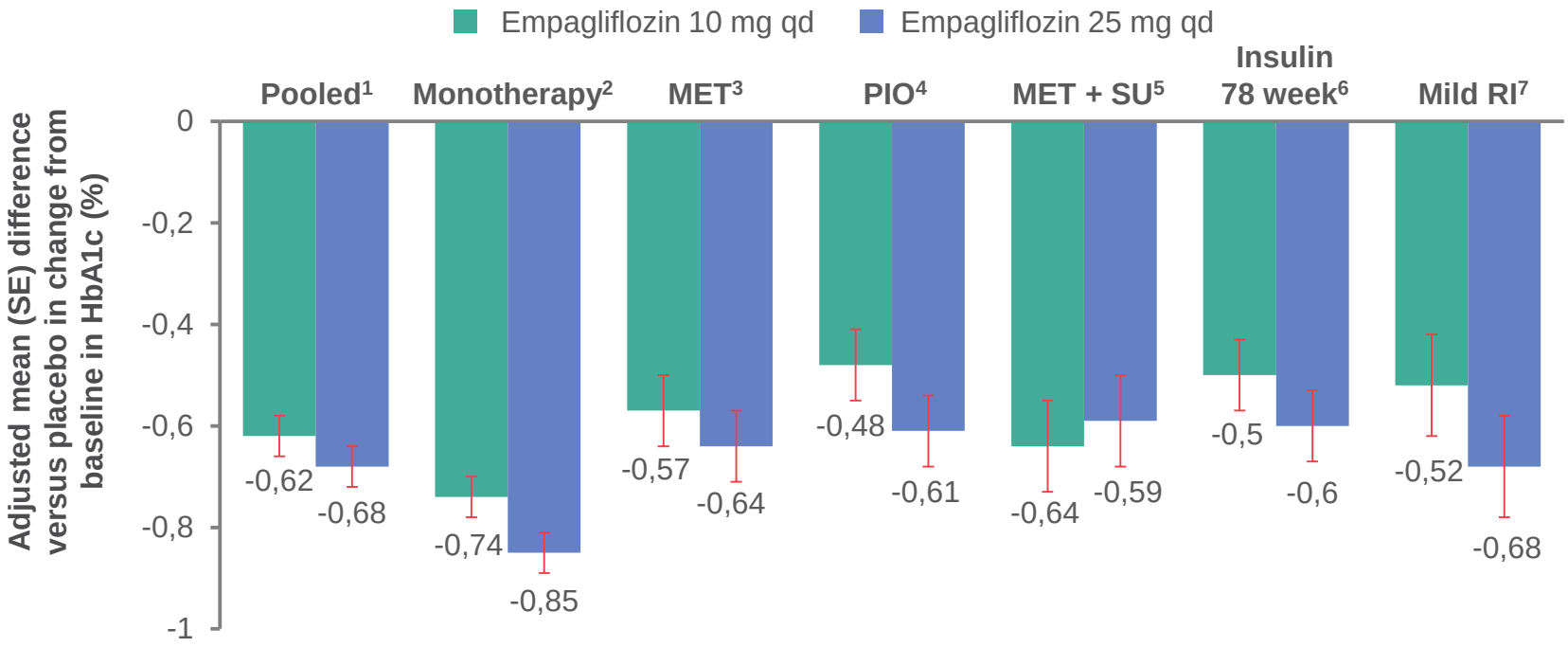
SGLT2 inhibition lowers glycaemia independently of β-cell function and insulin resistance



SGLT2, sodium-glucose co-transporter-2
Figure adapted from: DeFronzo RA. *Diabetes Obes Metab*. 2012;14:5; Del Prato S. *Diabet Med*. 2009;26:1185

Empagliflozin is the most selective SGLT2 inhibitor and provides effective glycaemic control in patients with T2D[1–8]

Placebo-corrected change* from baseline in HbA1c



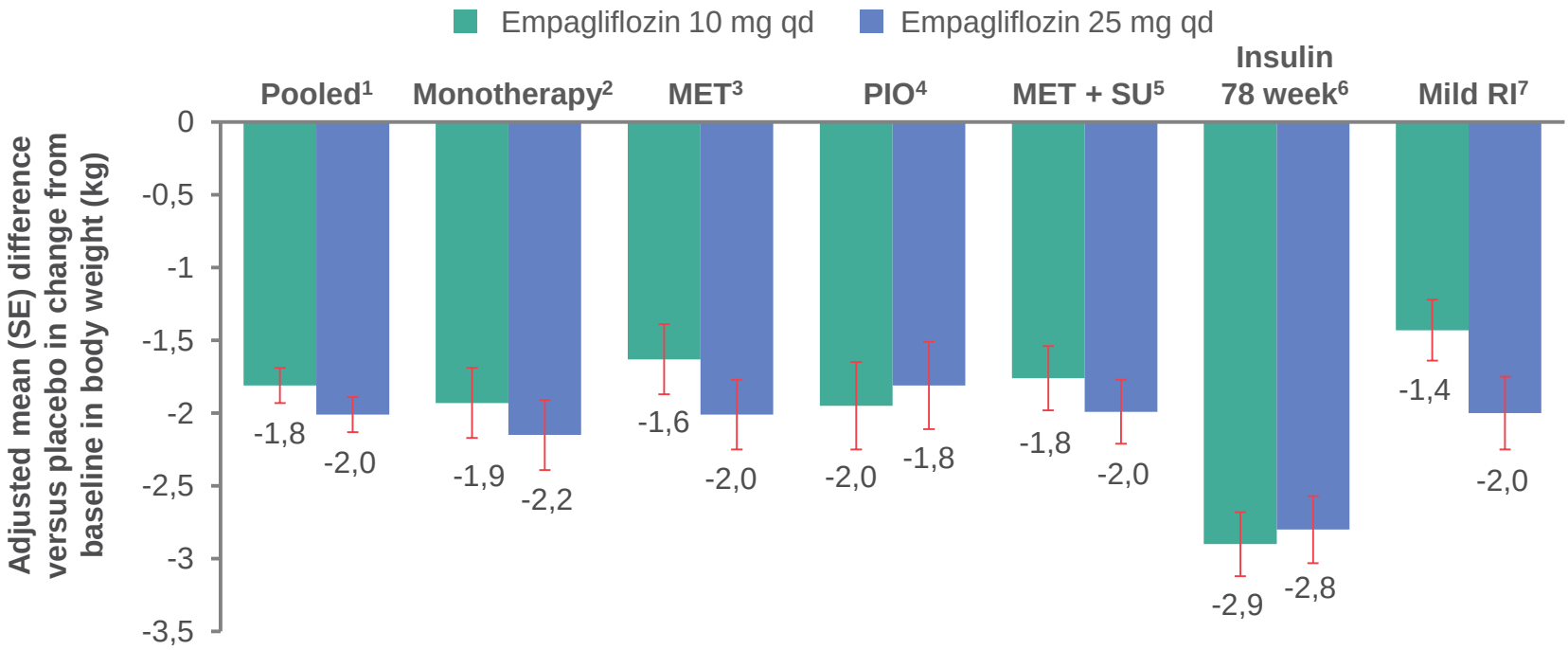
	Pooled[1]		Monotherapy[2]		MET[3]		PIO[4]		MET + SU[5]		Insulin 78 week[6]		Mild RI[7]	
Patients (n)	831	821	224	224	217	213	165	168	225	216	169	155	98	97
Baseline HbA1c (%)	7.98	7.96	7.87	7.86	7.94	7.86	8.07	8.06	8.07	8.10	8.27	8.27	8.02	7.96

*All statistically significant. HbA1c, glycated haemoglobin; MET, metformin; PIO, pioglitazone; RI, renal impairment; SE, standard error; SGLT2, sodium-glucose co-transporter-2; SU, sulphonylurea; T2D, type 2 diabetes

1. Hach T *et al. Diabetes* 2013;62(suppl 1A):A21(P69-LB); 2. Roden M *et al. Lancet Diabetes Endocrinol* 2013;1:208; 3. Häring HU *et al. Diabetes Care* 2014;37:1650; 4. Kovacs C *et al. Diabetes Obes Met* 2014;16:147; 5. Häring HU *et al. Diabetes Care* 2013;36:3396; 6. Rosenstock J *et al. Diabetes Obes Metab* 2015;17:936; 7. Barnett A *et al. Lancet Diabetes Endocrinol* 2014;2:369; 8. Data on file

Empagliflozin provides additional weight loss benefit[1–8]

Placebo-corrected change* from baseline in body weight



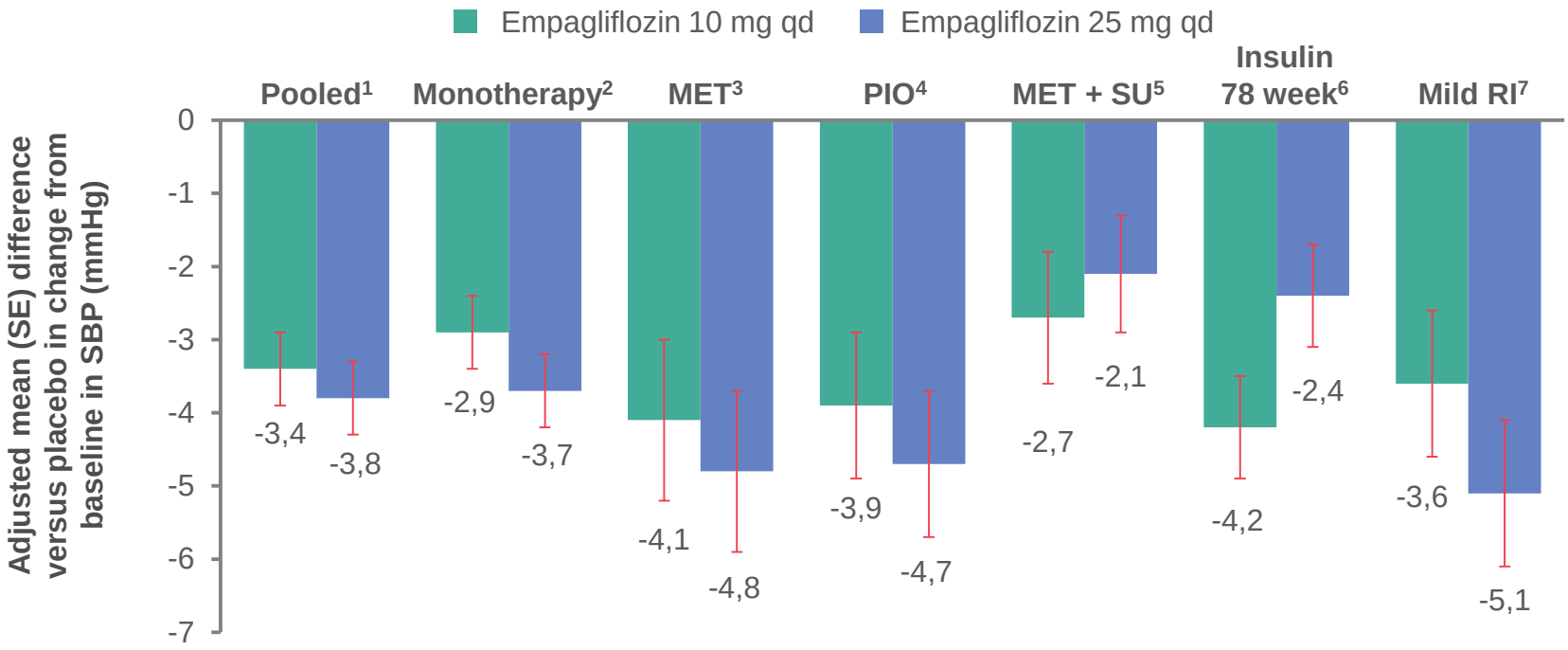
	Pooled[1]		Monotherapy[2]		MET[3]		PIO[4]		MET + SU[5]		Insulin 78 week[6]		Mild RI[7]	
Patients (n)	831	821	224	224	217	213	165	168	225	216	169	155	98	97
Baseline body weight (kg)	78.8	79.1	78.4	77.8	81.6	82.2	78.0	78.9	77.1	77.5	91.6	94.7	83.2	82.9

*All statistically significant. MET, metformin; PIO, pioglitazone; RI, renal impairment; SE, standard error; SU, sulphonylurea

1. Hach T *et al. Diabetes* 2013;62(suppl 1A):A21(P69-LB); 2. Roden M *et al. Lancet Diabetes Endocrinol* 2013;1:208; 3. Häring HU *et al. Diabetes Care* 2014;37:1650 (manuscript and supplementary appendix); 4. Kovacs C *et al. Diabetes Obes Met* 2014;16:147; 5. Häring HU *et al. Diabetes Care* 2013;36:3396; 6. Rosenstock J *et al. Diabetes Obes Metab* 2015;17:936; 7. Barnett A *et al. Lancet Diabetes Endocrinol* 2014;2:84; 8. Data on file

Empagliflozin reduces systolic blood pressure[1–8]

Placebo-corrected change* from baseline in SBP



	Pooled[1]		Monotherapy[2]		MET[3]		PIO[4]		MET + SU[5]		Insulin 78 week[6]		Mild RI[7]	
Patients (n)	831	821	224	224	217	213	165	168	225	216	169	155	98	97
Baseline SBP (mmHg)	129.6	129.0	133.0	129.9	129.6	130.0	126.5	125.9	128.7	129.3	132.4	132.8	137.4	133.7

*All statistically significant. MET, metformin; PIO, pioglitazone; RI, renal impairment; SBP, systolic blood pressure; SE, standard error; SU, sulphonylurea

1. Hach T *et al. Diabetes* 2013;62(suppl 1A):A21(P69-LB); 2. Roden M *et al. Lancet Diabetes Endocrinol* 2013;1:208; 3. Häring HU *et al. Diabetes Care* 2014;37:1650; 4. Kovacs C *et al. Diabetes Obes Met* 2014;16:147; 5. Häring HU *et al. Diabetes Care* 2013;36:3396; 6. Rosenstock J *et al. Diabetes Obes Metab* 2015;17:936; 7. Barnett A *et al. Lancet Diabetes Endocrinol* 2014;2:84; 8. Data on file

The cardiovascular effects of EMPA-REG OUTCOME®

EMPA-REG OUTCOME® was a **randomised, double-blind, placebo-controlled CV outcomes trial**[1]

7020 Patients **42** Countries **3.1** Years Median observation time

Results were achieved on top of standard of care[1]
Patients' CV risk factors, including glucose, were actively managed in placebo and empagliflozin treatment arms

95%* Antihypertensive therapy[1]

81%* Lipid-lowering therapy[1]

89%* Anticoagulants[1]

98%* Glucose-lowering medications[2]

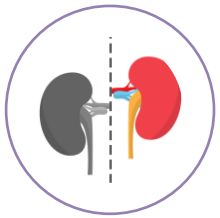
*Patients receiving therapy at baseline

1. Zinman B *et al. N Engl J Med* 2015;373:2117; 2. Zinman B *et al. Cardiovasc Diabetol* 2014;13:102

In a dedicated CV outcomes trial, empagliflozin significantly reduced CV and renal risk

- In the EMPA-REG OUTCOME® study, empagliflozin reduced CV and renal risk compared with placebo in patients with T2D and established CV disease who were already receiving standard of care therapy[1,2]

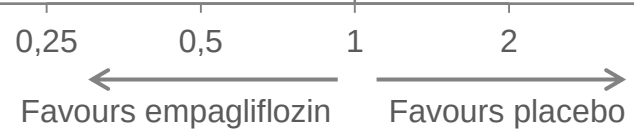
Relative risk reduction

3P-MACE	CV death	All-cause mortality	HHF	Incident or worsening nephropathy
				
↓14%	↓38%	↓32%	↓35%	↓39%

Empagliflozin is not indicated in all countries for CV risk reduction, and is not indicated for the treatment of heart failure or kidney disease
3P-MACE, 3-point major adverse cardiovascular events; CV, cardiovascular; HHF, hospitalisation for heart failure; T2D, type 2 diabetes
1. Zinman B *et al. N Engl J Med* 2015;373:2117; 2. Wanner C *et al. N Engl J Med* 2016;375:323

CV benefit with empagliflozin was driven by a significant 38% reduction in CV death

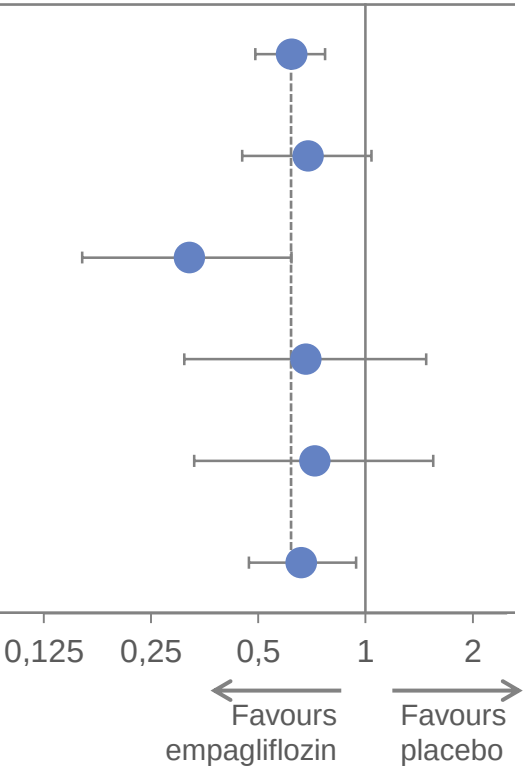
	Number of events			
	Empagliflozin (n=4687)	Placebo (n=2333)	HR (95% CI)	*p*-value
3P-MACE				
Intention-to-treat analysis*	490	282	0.86 (0.74, 0.99)†	0.04
CV death				
Intention-to-treat analysis*	172	137	0.62 (0.49, 0.77)	<0.001‡
Non-fatal MI				
Intention-to-treat analysis*	213	121	0.87 (0.70, 1.09)	0.22‡
Non-fatal stroke				
Intention-to-treat analysis*	150	60	1.24 (0.92, 1.67)	0.16‡



Prespecified analysis
*In patients who received ≥1 dose of study drug, including events observed from randomisation to the end of the study; †95.02% CI and two-sided *p*-value; ‡Nominal *p*-value
3P-MACE, 3-point major adverse cardiovascular events; CV, cardiovascular; MI, myocardial infarction
Zinman B *et al*. *N Engl J Med* 2015;373:2117

All modes of CV death were consistently reduced with empagliflozin

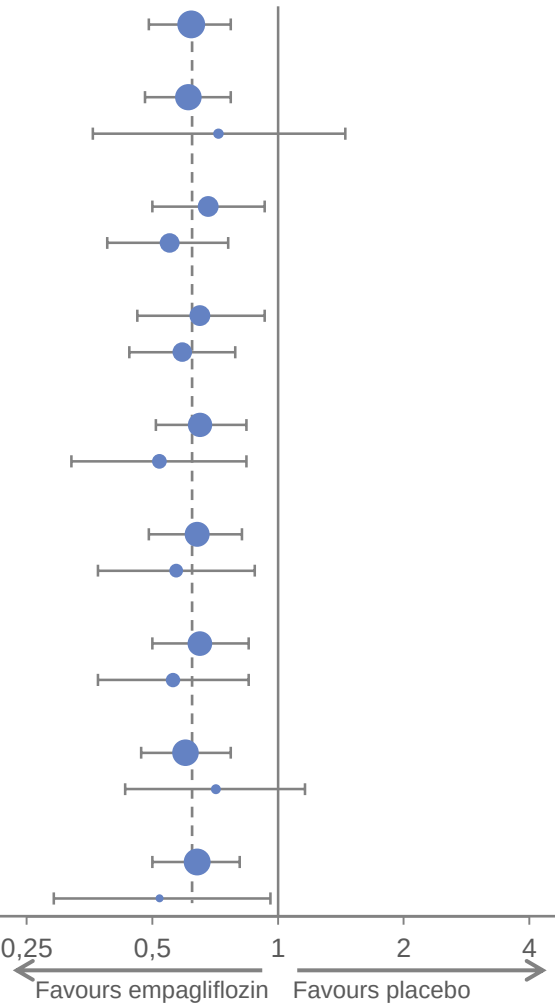
	Patients with event (%)		
	Empagliflozin (n=4687)	Placebo (n=2333)	HR (95% CI)
CV death	172 (3.7%)	137 (5.9%)	0.62 (0.49, 0.77)
Sudden death	53 (1.1%)	38 (1.6%)	0.69 (0.45, 1.04)
Worsening of heart failure or cardiogenic shock	14 (0.3%)	22 (0.9%)	0.32 (0.16, 0.62)
Acute MI	15 (0.3%)	11 (0.5%)	0.68 (0.31, 1.48)
Stroke	16 (0.3%)	11 (0.5%)	0.72 (0.33, 1.55)
Other*	74 (1.6%)	55 (2.4%)	0.66 (0.47, 0.94)



Empagliflozin is not indicated in all countries for CV risk reduction. Cox regression analysis
*1.5% on empagliflozin and 2.3% on placebo were presumed CV deaths (insufficient data for the adjudication committee to categorise cause of death)
CV, cardiovascular; MI, myocardial infarction
Fitchett D *et al. ACC* 2016; session #913; oral presentation

Reduction in CV death was consistent across all types of baseline CV disease

	Patients with event/analysed (%)		HR (95% CI)	*p*-value for interaction
	Empagliflozin	Placebo		
All patients	172/4687 (3.7)	137/2333 (5.9)		
Single vessel coronary artery disease				0.65
No	152/4189 (3.6)	124/2094 (5.9)		
Yes	20/498 (4.0)	13/238 (5.5)		
Multi-vessel coronary artery disease				0.33
No	101/2508 (4.0)	71/1233 (5.8)		
Yes	71/2179 (3.3)	66/1100 (6.0)		
History of MI				0.67
No	71/2497 (2.8)	55/1250 (4.4)		
Yes	101/2190 (4.6)	82/1083 (7.6)		
History of coronary artery bypass graft				0.40
No	137/3512 (3.9)	105/1770 (5.9)		
Yes	35/1175 (3.0)	32/563 (5.7)		
Peripheral artery disease				0.67
No	128/3704 (3.5)	101/1853 (5.5)		
Yes	44/982 (4.5)	36/479 (7.5)		
History of stroke				0.56
No	125/3603 (3.5)	93/1779 (5.2)		
Yes	47/1084 (4.3)	44/553 (8.0)		
Heart failure*				0.56
No	134/4225 (3.2)	110/2089 (5.3)		
Yes	38/462 (8.2)	27/244 (11.1)		
History of atrial fibrillation†				0.56
No	151/4440 (3.4)	116/2191 (5.3)		
Yes	21/247 (8.5)	21/142 (14.8)		



Cox regression analysis in patients treated with ≥1 dose of study drug. *p*-values for interaction of subgroup by treatment are presented
*Based on narrow standardised MedDRA query 'cardiac failure'; †Based on one MedDRA preferred term. CV, cardiovascular; MI, myocardial infarction
Zinman B *et al. AHA* 2016; poster S2044

Reduction in CV death was consistent across all patient subgroups and analyses

In EMPA-REG OUTCOME®, patients treated with empagliflozin were at reduced risk of CV death, regardless of:

Age[1,2]

Baseline medications[3]

Insulin use[4]

Heart failure at baseline[5]

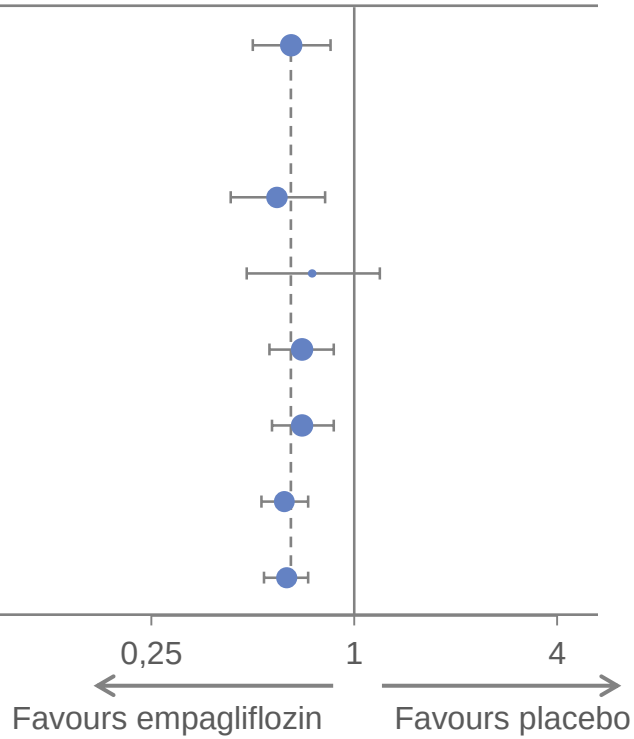
Kidney disease at baseline[6]

CV, cardiovascular

1. Monteiro P *et al. ADA* 2016; poster 1116-P; 2. Fitchett D. *ESC* 2016; oral presentation 5803; 3. Zinman B *et al. N Engl J Med* 2015;373:2117;
4. Jurišic-Eržen D *et al. EASD* 2016; ePoster 732; 5. Fitchett D *et al. ESC* 2016; oral presentation 2236; 6. Wanner C *et al. ASN* 2015; oral presentation

Empagliflozin reduced the risk of hospitalisation for HF, and HF-related conditions

	Patients with event/analysed (%)	
	Empagliflozin	Placebo
HHF, all patients[1]	126/4687 (2.7)	95/2333 (4.1)
HHF, HF at baseline[2]		
No	78/4225 (1.8)	65/2089 (3.1)
Yes	48/462 (10.4)	30/244 (12.3)
Investigator-reported HF*[1]	204/4687 (4.4)	143/2333 (6.1)
HHF or investigator-reported HF*[1]	217/4687 (4.6)	151/2333 (6.5)
Introduction of loop diuretics[1]	340/3962 (8.6)	262/1969 (13.3)
Introduction of loop diuretics or HHF[1]	411/4027 (10.2)	313/2013 (15.5)



Empagliflozin is not indicated in all countries for CV risk reduction, and is not indicated for the treatment of HF
Cox regression analysis in patients treated with ≥1 dose of study drug
*Investigator-reported HF was based on the narrow standardised MedDRA query 'cardiac failure'
CV, cardiovascular; HF, heart failure; HHF, hospitalisation for heart failure
1. Fitchett D *et al. ESC* 2016; oral presentation 2236; 2. Fitchett D *et al. Eur Heart J* 2016;37:1526

Reduction in hospitalisation for heart failure was consistent across all patient subgroups and analyses

In EMPA-REG OUTCOME®, patients treated with empagliflozin were at reduced risk of hospitalisation for heart failure, regardless of:

Age

Baseline medications

Insulin use

CV disease at baseline, including heart failure

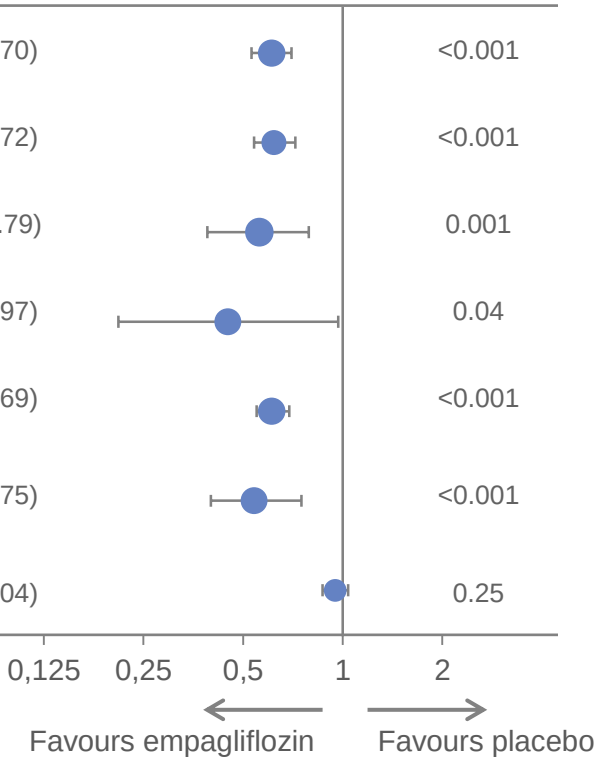
Kidney disease at baseline

CV, cardiovascular

Fitchett D *et al. Eur Heart J* 2016;37:1526

Empagliflozin reduced the risk of clinically relevant renal endpoints

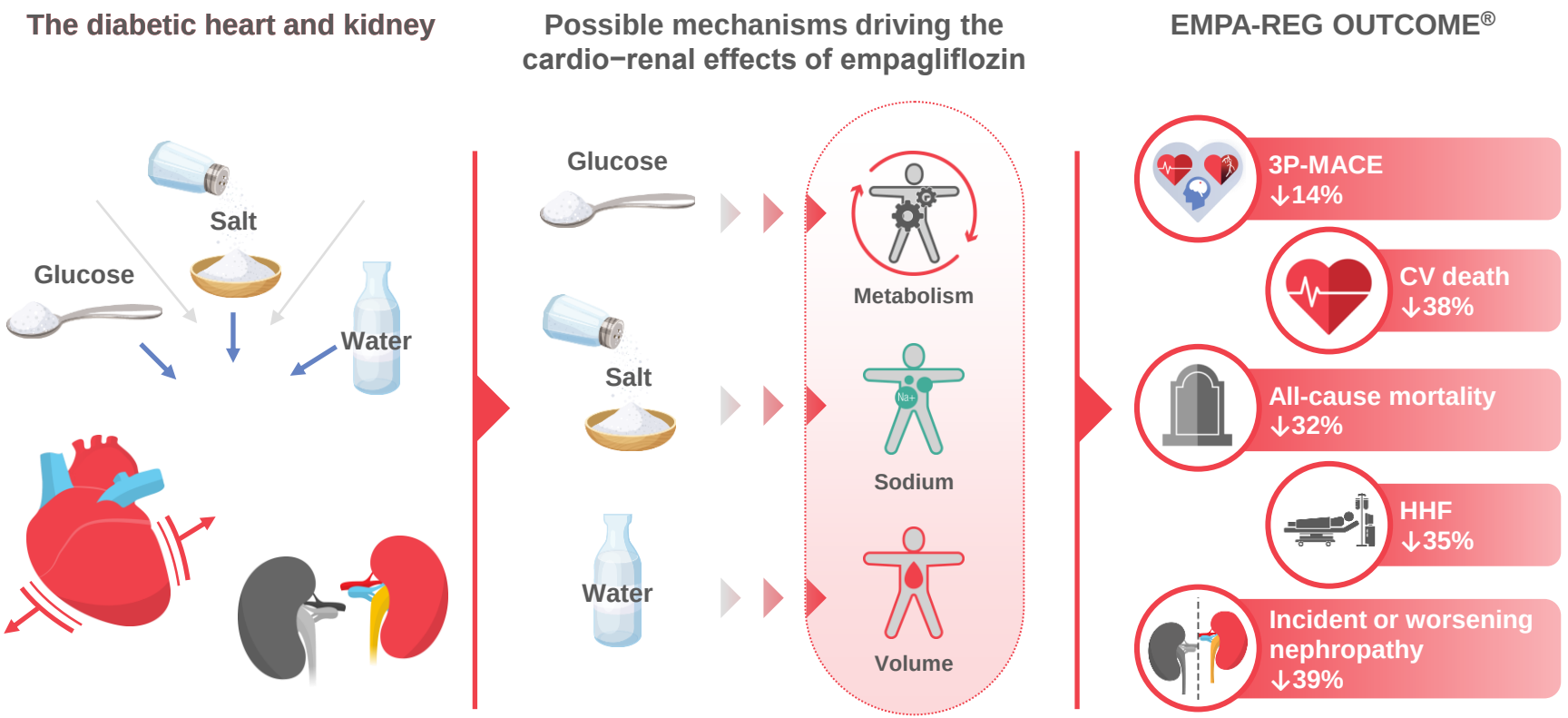
	Patients with event/analysed (%)			
	Empagliflozin	Placebo	HR (95% CI)	*p*-value*
Incident or worsening nephropathy†	525/4124 (12.7)	388/2061 (18.8)	0.61 (0.53, 0.70)	<0.001
Progression to macroalbuminuria	459/4091 (11.2)	330/2033 (16.2)	0.62 (0.54, 0.72)	<0.001
Doubling of serum creatinine‡	70/4645 (1.5)	60/2323 (2.6)	0.56 (0.39 , 0.79)	0.001
Initiation of renal replacement therapy	13/4687 (0.3)	14/2333 (0.6)	0.45 (0.21, 0.97)	0.04
Incident or worsening nephropathy or CV death	675/4170 (16.2)	497/2102 (23.6)	0.61 (0.55, 0.69)	<0.001
Doubling of serum creatinine,‡ initiation of renal replacement therapy or death due to kidney disease	81/4645 (1.7)	71/2323 (3.1)	0.54 (0.40, 0.75)	<0.001
Incident albuminuria in patients with normoalbuminuria at baseline§	1430/2779 (51.5)	703/1374 (51.2)	0.95 (0.87, 1.04)	0.25



Empagliflozin is not indicated in all countries for CV risk reduction, and is not indicated for the treatment of kidney disease
Prespecified analyses, with the exception of the composite of doubling of serum creatinine, initiation of renal replacement therapy or death due to kidney disease
*Nominal *p*-values; †HR for renal death was not calculated due to the low number of events (3 in the empagliflozin group, none in the placebo group); ‡Accompanied by eGFR (MDRD) ≤45 ml/min/1.73 m^2; §UACR <30 mg/g
CV, cardiovascular; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; UACR, urine albumin-to-creatinine ratio
Wanner C *et al. N Engl J Med* 2016;375:323

Empagliflozin enhances the excretion of glucose, sodium and water into the urine, which may unload the heart in T2D

These effects may contribute to the early and sustained CV death reduction observed in EMPA-REG OUTCOME®

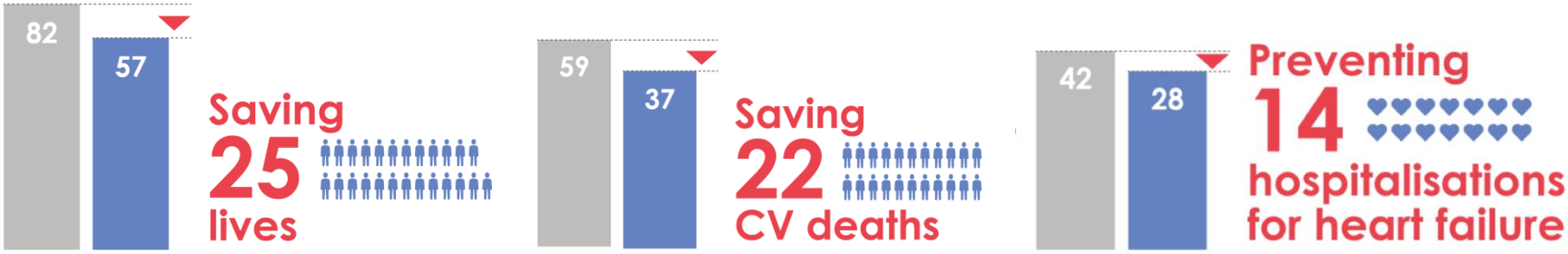


3P-MACE, 3-point major adverse cardiovascular events; CV, cardiovascular; HHF, hospitalisation for heart failure; T2D, type 2 diabetes

Heise T *et al. Diabetes Obes Metab* 2013;15:613; Ferrannini G *et al. Diabetes Care* 2015;38:1730; Zinman B *et al. N Engl J Med* 2015;373:2117; Heise T *et al. Clin Ther* 2016;38:2265

EMPA-REG OUTCOME®: treating 1000 patients with T2D at high CV risk with empagliflozin for 3 years

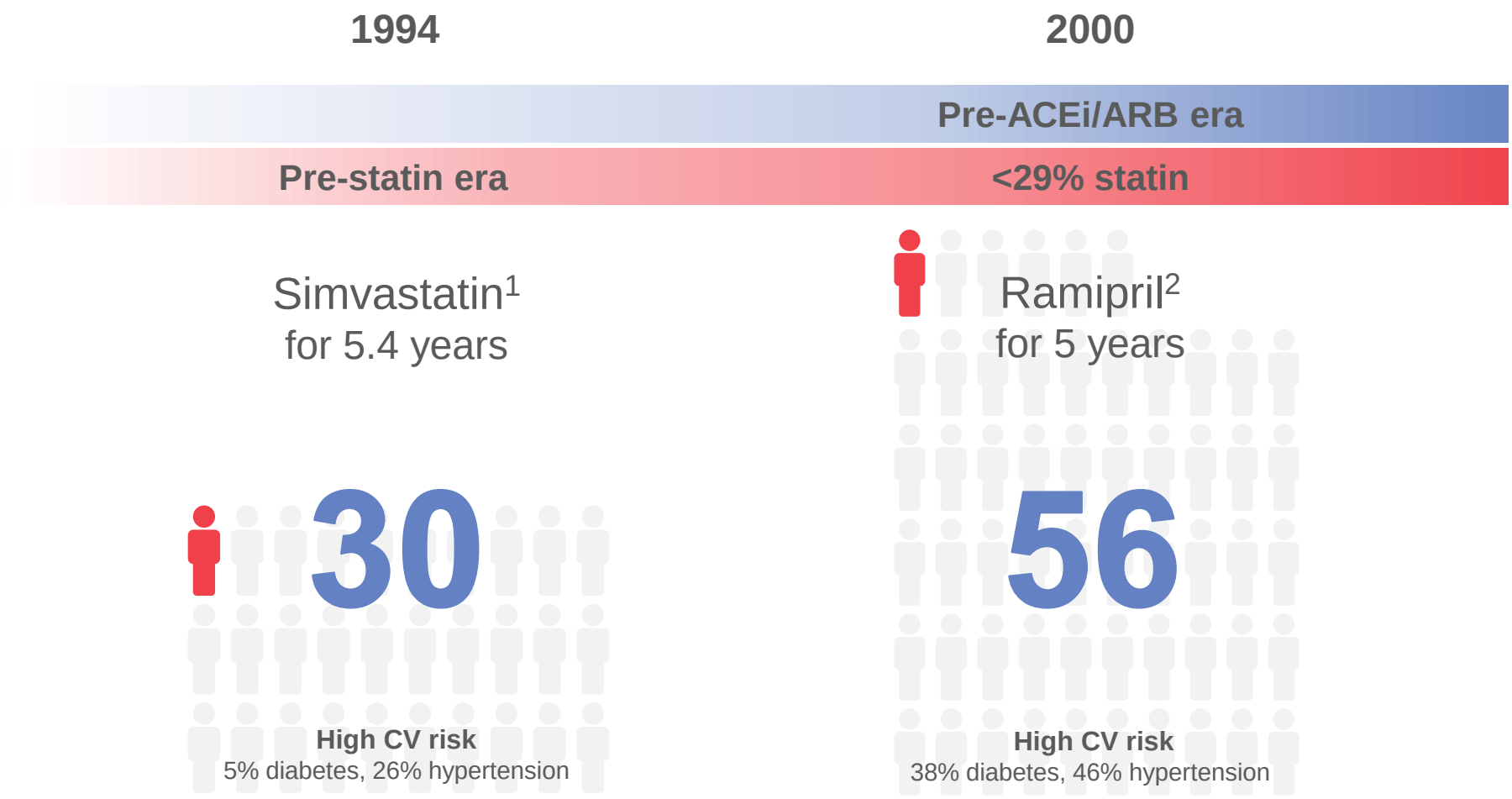
Benefits



Risks

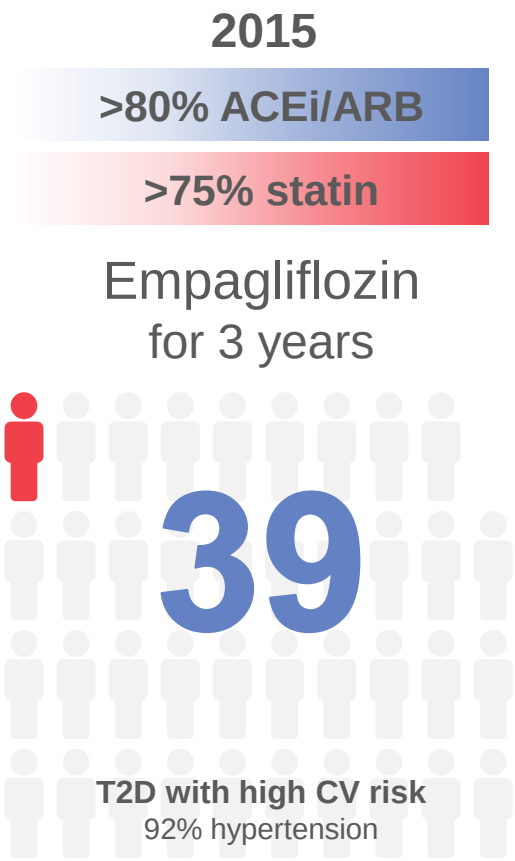
Based on 1000 adults with T2D and high CV risk receiving empagliflozin on top of standard of care for 3 years
CV, cardiovascular; T2D, type 2 diabetes
Zinman B *et al. N Engl J Med* 2015;373:2117; Zinman B. *EASD* 2015; oral presentation

Number needed to treat to prevent one death in landmark trials in patients with high CV risk



Absolute risk reduction cannot be directly compared across different outcome trials
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CV, cardiovascular
1. 4S investigators. *Lancet* 1994;344:1383; 2. HOPE investigators. *N Engl J Med* 2000;342:145

Number needed to treat to prevent one death with empagliflozin added to standard of care in patients with high CV risk



ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CV, cardiovascular; T2D, type 2 diabetes

Zinman B *et al. N Engl J Med* 2015;373:2117; Zinman B. *EASD* 2015; oral presentation

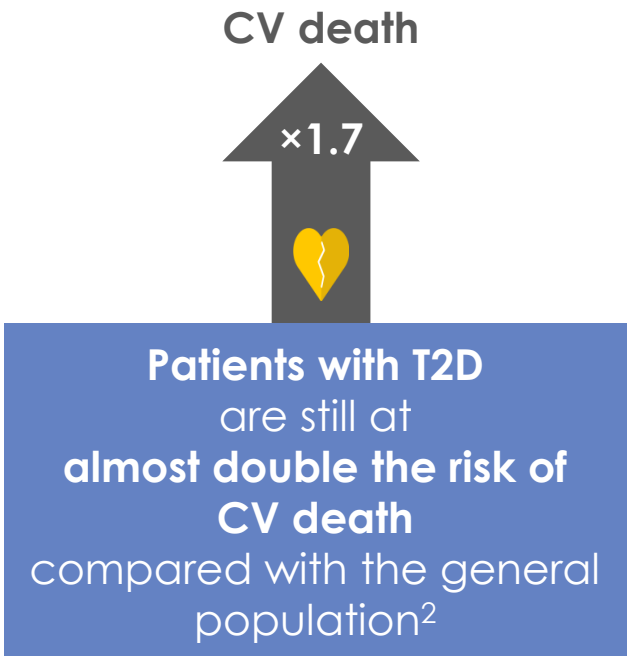
Despite receiving standard treatment, patients with type 2 diabetes and established cardiovascular disease * are still at risk and need additional cardiac protection

CV risk management[1]

- Lipid management (e.g. statins)
- Blood pressure control (e.g. ACEi/ARBs)
- Antithrombotic agents (e.g. ASA)

Glucose control[1]

- Achieve blood glucose levels of ~7%† (e.g. metformin, DPP-4i, SGLT2i, insulin)



*Including coronary artery disease, peripheral artery disease, or a history of MI or stroke; †Reasonable goal for non-pregnant adults

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ASA, acetylsalicylic acid; CV, cardiovascular;
DPP-4i, dipeptidyl peptidase-4 inhibitor; MI, myocardial infarction; SGLT2i, sodium-glucose co-transporter-2 inhibitor; T2D, type 2 diabetes 1. American Diabetes Association. *Diabetes Care* 2016;39(Suppl 1):S1; 2. Centers for Disease Control and Prevention. National Diabetes Statistics Report. 2014. www.cdc.gov/diabetes/pubs/statsreport14/national-diabetes-report-web.pdf

Latest CV disease prevention and diabetes treatment guidelines reflect the impact of empagliflozin on CV risk reduction in T2D

Empagliflozin is recommended by diabetes and cardiology guidelines to reduce risk of CV mortality in patients with T2D and CV disease[1–4]

- ESC: Guidelines on diagnosis and treatment of acute and chronic HF and CV disease prevention in clinical practice
- DC: Pharmacologic management of T2D: 2016 interim update
- AACE/ACE: Comprehensive T2D management algorithm 2017
- ADA: Standards of medical care in diabetes 2017

AACE, American Association of Clinical Endocrinologists; ACE, American College of Endocrinology; ADA, American Diabetes Association; CV, cardiovascular; DC, Diabetes Canada; ESC, European Society of Cardiology; HF, heart failure; T2D, type 2 diabetes

1. American Diabetes Association *Diabetes Care* 2017;40:S1; 2. Canadian Diabetes Association *Can J Diabetes* 2016;40:193;
3. American Association of Clinical Endocrinologists and American College of Endocrinology *Endocr Pract* 2016;22:84;
4. European Society of Cardiology *Eur Heart J* 2016;37:2315; 5. European Society of Cardiology *Eur Heart J* 2016;37:2129

Empagliflozin now has a new label indication

Empagliflozin is the only oral glucose-lowering agent approved by the FDA to reduce CV mortality risk

----------INDICATIONS AND USAGE[1]----------

JARDIANCE is a sodium-glucose co-transporter 2 (SGLT2) inhibitor indicated:

- as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus,
- to reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and established cardiovascular disease. (1)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

4.1 Therapeutic indications[2]

Jardiance is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise

- as monotherapy when metformin is considered inappropriate due to intolerance
- in addition to other medicinal products for the treatment of diabetes

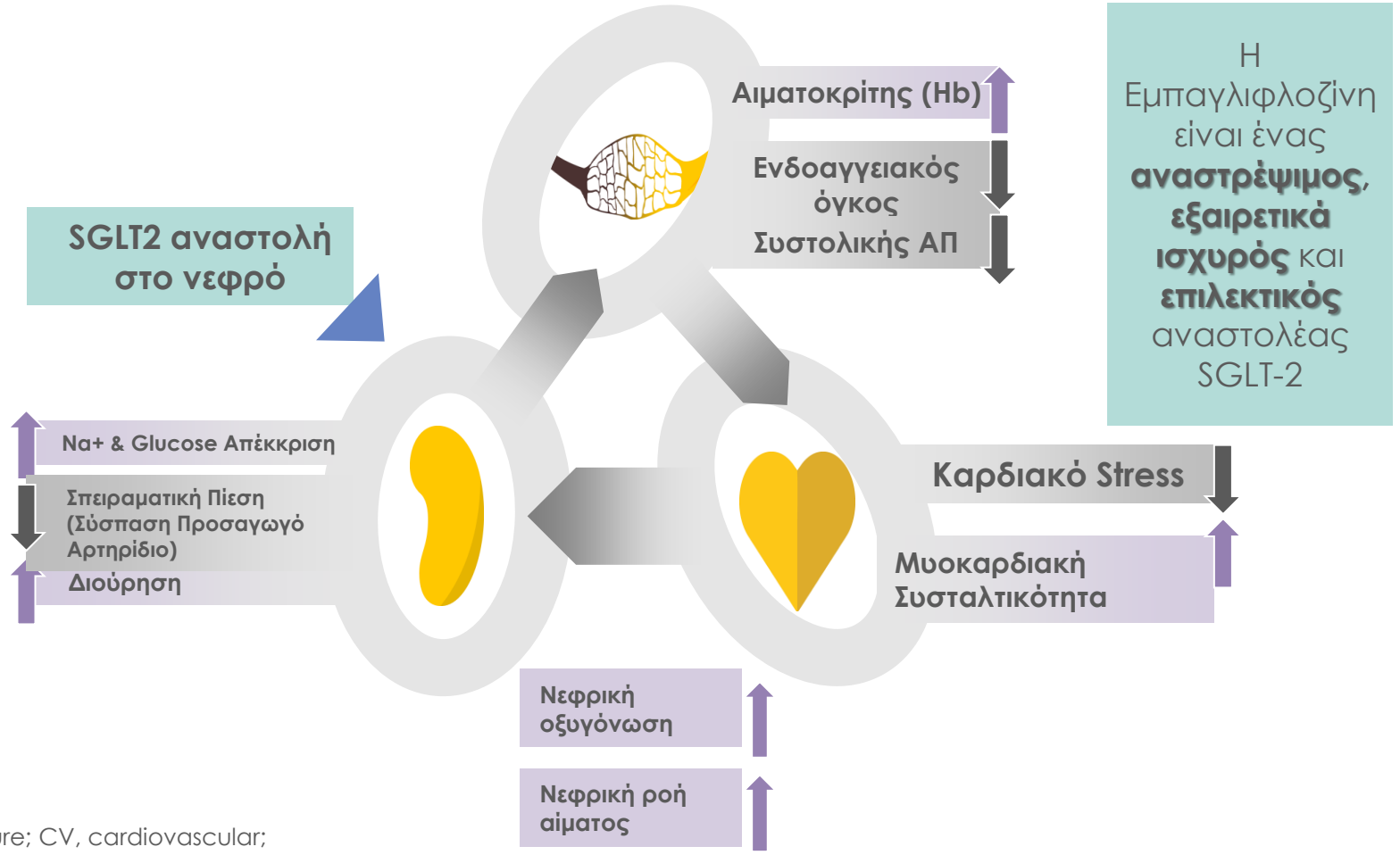
For study results with respect to combinations, effects on glycaemic control and cardiovascular events, and the populations studied, see sections 4.4, 4.5 and 5.1.

Empagliflozin is not indicated in all countries for CV risk reduction

1. Boehringer Ingelheim and Eli Lilly. Jardiance® (empagliflozin) Product Information. 2016
2. Boehringer Ingelheim . Jardiance® (empagliflozin) summary of product characteristics. 2017

The possible mechanisms explaining the CV benefits of Empagliflozin are multifactorial

Η **Empagliflozin** ρυθμίζει διάφορους παράγοντες που σχετίζονται με τον κίνδυνο CV[1]



BP, blood pressure; CV, cardiovascular;
SGLT2, sodium-glucose co-transporter-2

1. Sattar N *et al. Diabetologia* 2016;59:1333;
2. Boehringer Ingelheim Jardiance® (empagliflozin) summary of product characteristics. 2017

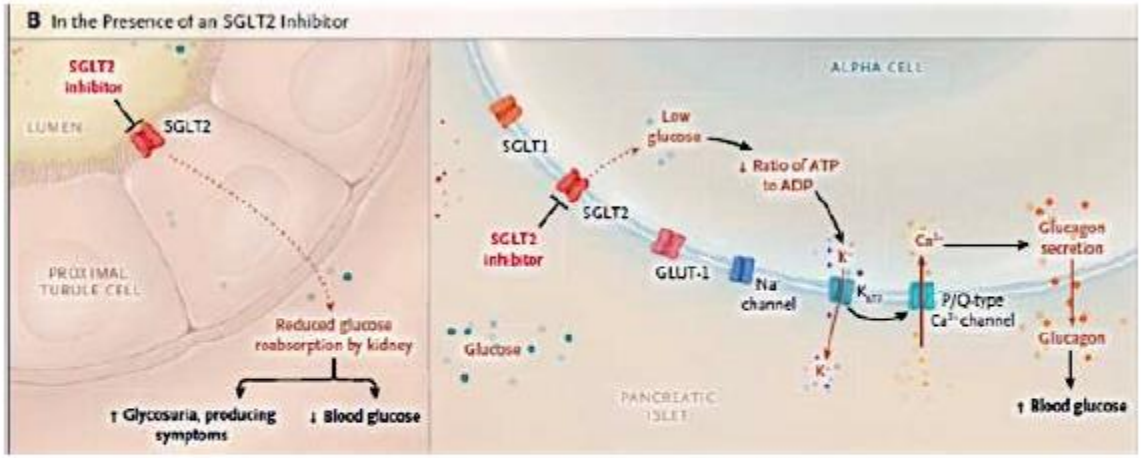
CV Protection in the EMPA-REG OUTCOME Trial: A "Thrifty Substrate" Hypothesis

Ele Ferrannini,[1] Michael Mark,[2] and Eric Mayoux[2]

Diabetes Care 2016;39:1108–1114 | DOI: 10.2337/dc16-0330

"We hypothesize that under conditions of mild, persistent hyperketonemia, such as those that prevail during treatment with SGLT2 inhibitors, β-hydroxybutyrate is freely taken up by the heart (among other organs) and oxidized in preference to fatty acids. This fuel selection improves the transduction of oxygen consumption into work efficiency at the mitochondrial level. "

The role of glucagon



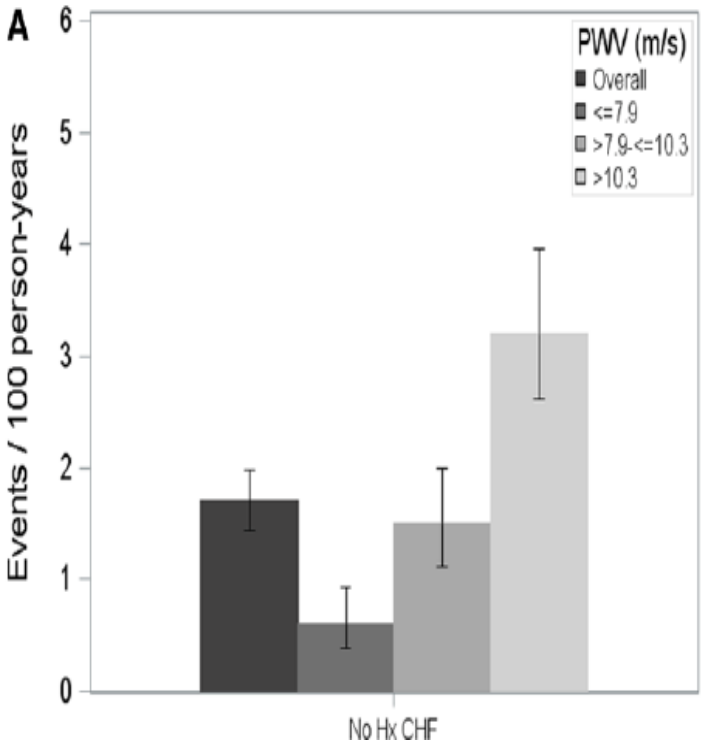
Η μείωση της πρόσληψης γλυκόζης στα α κύτταρα μειώνει την ενδοκυττάρια αναλογία του ATP προς το ADP, οδηγώντας σε άνοιγμα των διαύλων K_{ATP}, ενεργοποιώντας τα κανάλια ασβεστίου τυπου P/Q-type Ca2+, και αυξάνοντας την έκκριση γλυκαγόνης.

1. Αυξάνει την οξείδωση του λίπους και την κετονογένεση.
2. Αυξάνει κατανάλωση ενέργειας και την θερμογένεση καθώς και την αιματική ροή στο φαιό λίπος.
3. Μειώνει την πρόσληψη τροφής και επηρεάζει την έκκριση άλλων ορμονών.
4. Οξεία χορήγηση : Αύξηση «απόδοσης» της καρδιάς. Στην φυσιολογική καρδιά αυξάνει την καρδιακή συχνότητα χωρίς αύξηση της καρδιακής παροχής. Στην ανεπαρκούσα καρδιά, αυξάνει την συχνότητα και την παροχή μαζί με αύξηση της στεφανιαίας ροής. Σε χρόνια και βαρειά ΚΑ οι δράσεις είναι λιγότερο εμφανείς.
5. Οι ινότροπες δράσεις πλέον εμφανείς στις κοιλίες.
6. Ευοδώνει την κολποκοιλιακή αγωγή και ασκεί αντιαρρυθμικές δράσεις.

Ceriello et al. Cardiovasc Diabetol (2016) 15:123

Arterial Stiffness and incident HF

2602 CKD patients (CRIC cohort), 3.5 years



Chirinos JA, et al. *Circ Heart Fail 2014*

2539 Framingham Study subjects, 10.1 years

Model	Age- and Sex-Adjusted		Multivariable-Adjusted	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
iCFPWV, s/m	1.50 (1.21–1.85)	<0.001	1.29 (1.02–1.64)	0.037
Central pulse pressure, mm Hg	1.20 (1.06–1.37)	0.006	1.10 (0.93–1.29)	0.28
Forward wave amplitude, mm Hg	1.15 (1.01–1.31)	0.036	1.02 (0.88–1.19)	0.79
Augmentation index, %	1.10 (0.95–1.29)	0.21	1.11 (0.95–1.31)	0.19

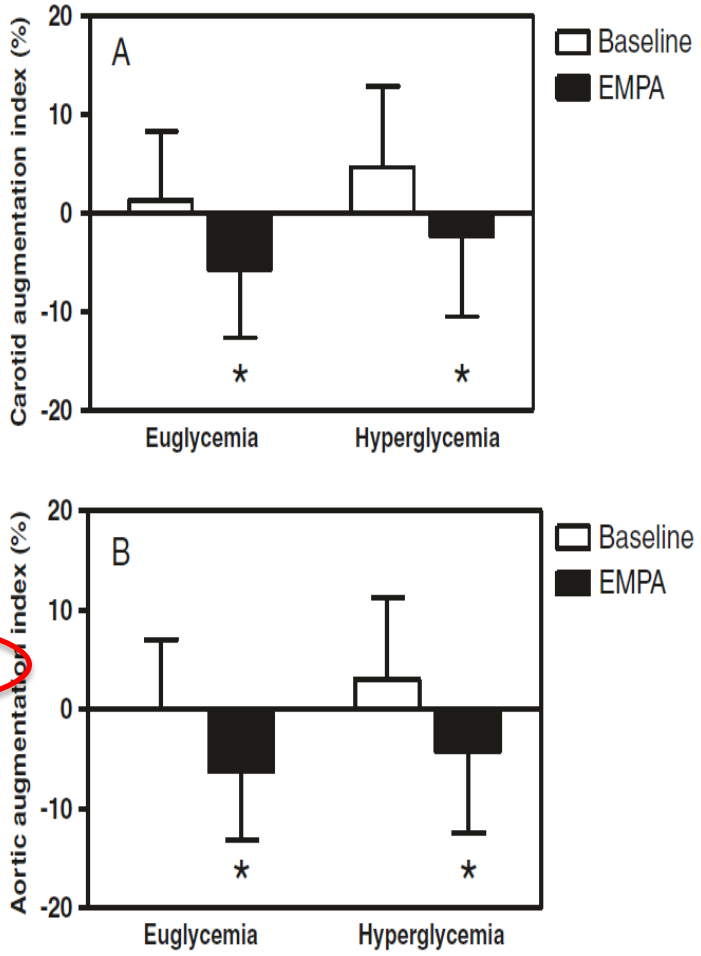
Tsao CW, et al. *J Am Heart Assoc 2016*

Empagliflozin and Arterial Stiffness

open-label, single-arm, 8 weeks

40 DM Type 1 patients during euglycemic and hyperglycemic clamp

	Euglycemia			Hyperglycemia		
	Baseline	Empagliflozin	p-value	Baseline	Empagliflozin	p-value
Blood pressure						
Systolic blood pressure (mmHg)	111.2 ± 8.9	108.5 ± 8.7	0.02	112.1 ± 9.8	110.6 ± 9.8	0.2797
Diastolic blood pressure (mmHg)	63.6 ± 8.5	63.1 ± 8.1	0.6191	65.2 ± 8.3	63.8 ± 7.3	0.2497
Pulse (beats per minute)	74.2 ± 13.1	71.8 ± 13.8	0.1885	72.0 ± 11.0	70.8 ± 12.8	0.4919
Vascular parameters						
Radial augmentation index (%)	−52.0 ± 16.1	−57.0 ± 16.7	0.0001	−47.9 ± 17.3	−52.1 ± 17.6	0.0190
Carotid radial pulse wave velocity (m/s)	7.3 ± 1.1	6.7 ± 0.9	0.0001	7.9 ± 1.1	6.9 ± 0.9	<0.0001
Carotid femoral pulse wave velocity (m/s)	5.5 ± 0.9	5.3 ± 1.0	0.1366	5.7 ± 1.1	5.2 ± 0.9	0.0017



Cherney et al. *Cardiovascular Diabetology* 2014

Reduction of myocardial cytoplasmic Na+

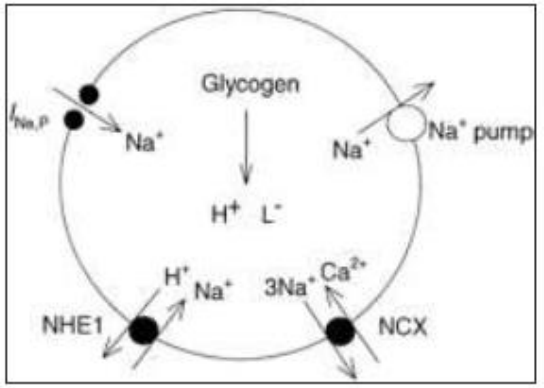
Diabetologia
DOI 10.1007/s00125-016-4134-x

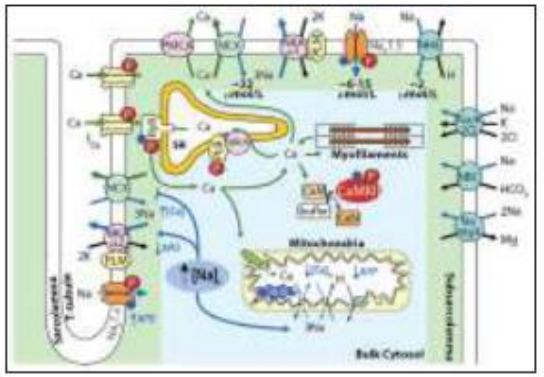
SHORT COMMUNICATION

Empagliflozin decreases myocardial cytoplasmic Na^+ through inhibition of the cardiac Na^+/H^+ exchanger in rats and rabbits

Antonius Baartscheer[1] · Cees A. Schumacher[1] · Rob C. I. Wüst[2,3] · Jan W. T. Fiolet[1] · Ger J. M. Stienen[2,4] · Ruben Coronel[1,5] · Coert J. Zuurbier[6]

.....An increase in extracellular glucose, from 5.5 mmol/l to 11 mmol/l, resulted in increased [Na+]c and [Ca2+]c levels. EMPA treatment directly inhibited NHE flux, caused a reduction in [Na+]c and [Ca2+]c and increased [Ca2+]m.....



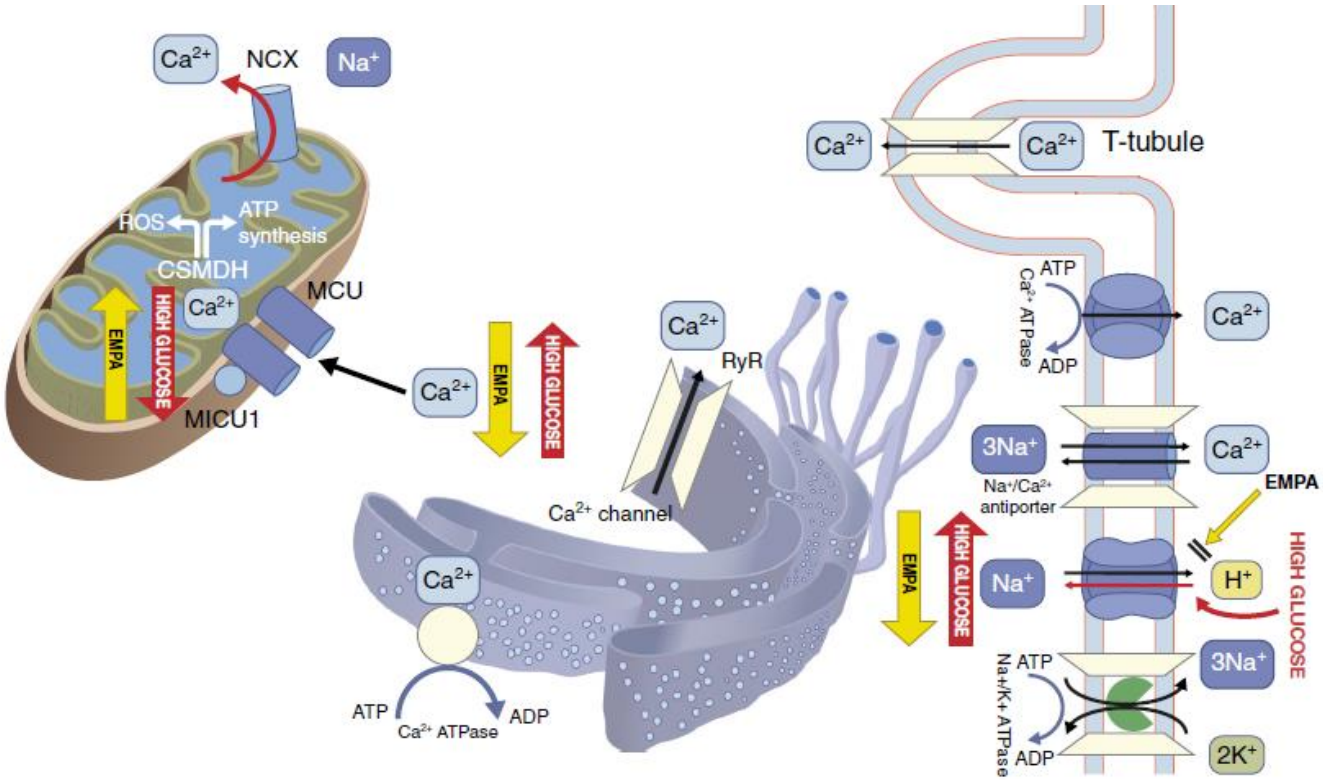


EMPA has direct cardiac effects,decreases cardiac [Na+]c and [Ca2+]c and increases cardiac [Ca2+]m via inhibition of the cardiac NHE.

Diabetologia (2017) 60:568–573

The cardiovascular benefits of empagliflozin: SGLT2-dependent and -independent effects

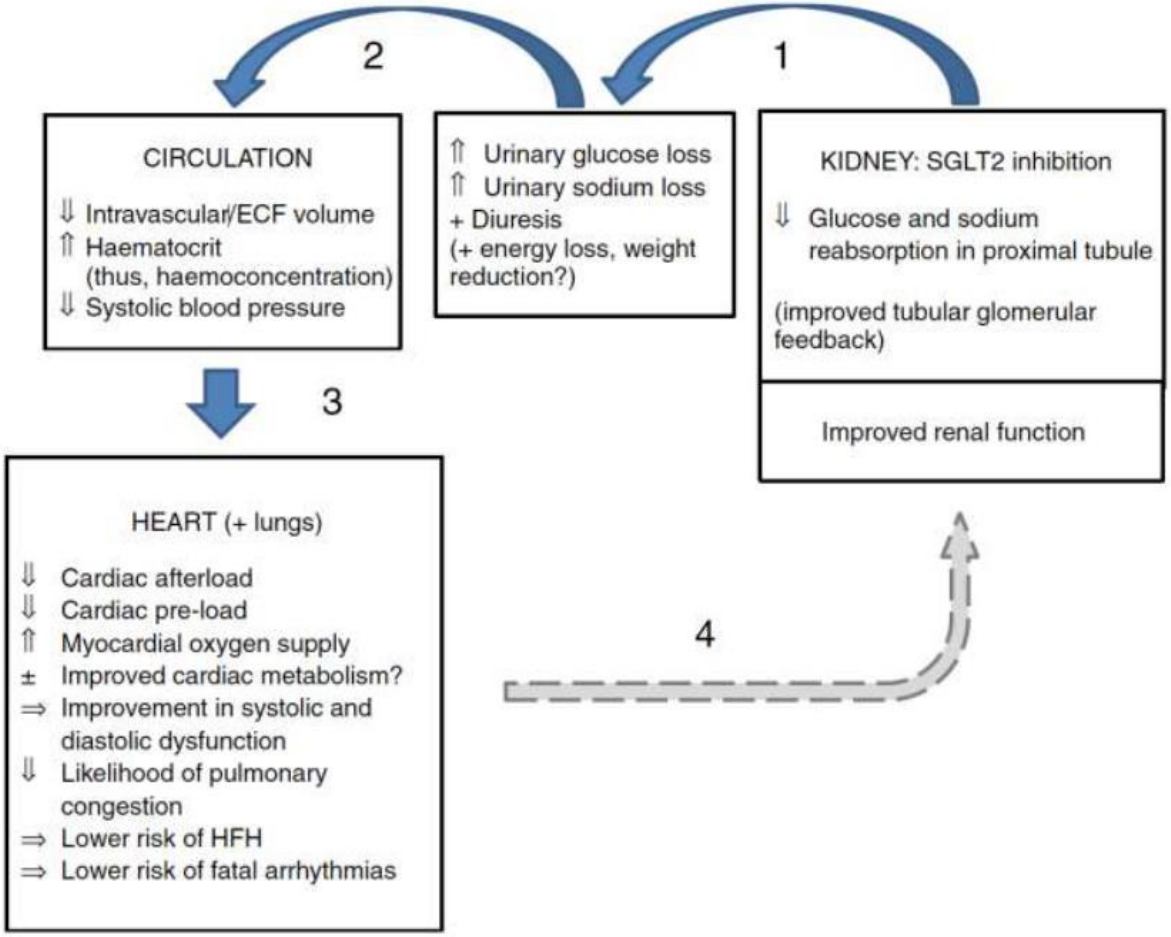
Roberto Vettor [1] · Silvio E. Inzucchi [2] · Paola Fioretto [1]



EMPA treatment directly inhibits NHE, causing a reduction of [Na+]c and [Ca2+]c, and an increase of [Ca2+]m, thus improving mitochondrial activity and ATP generation.

Diabetologia (2017) 60:395–398

Mechanisms of action of empagliflozin



Sattar et al. Diabetologia (2016) 59:1573–1574

Introduction

- In an analysis of pooled safety data from clinical trials based on >9000 patient-years' exposure, empagliflozin 10 mg and 25 mg were well tolerated in patients with T2DM.[1]
- Empagliflozin was not associated with an increased risk of hypoglycemia versus placebo, except in patients on background sulfonylurea and/or insulin.[1]
- Adverse events consistent with genital infections were reported in greater proportions of patients on empagliflozin than placebo. The incidences of events consistent with urinary tract infection, volume depletion, bone fractures, cancer, and decreased renal function were not increased with empagliflozin.[1] An increased risk of diabetic ketoacidosis was not observed in clinical trials of empagliflozin.
- **This paper describes the safety and tolerability of empagliflozin based on a large pool of patients with T2DM who were randomized 1:1:1 to empagliflozin 10 mg, empagliflozin 25 mg, or placebo in 15 Phase I–III clinical trials, including the EMPA-REG OUTCOME® trial.**

1. Kohler S, et al. Clin Ther 2016;38:1299–313.

Participants

- Data were pooled from 14 trials of 8 days to 78 weeks' duration;[1-14] the 52-week extensions to the Phase III trials of empagliflozin given as monotherapy, or as add on to metformin, metformin plus sulfonylurea, and pioglitazone with or without metformin;[15-18] and the cardiovascular outcomes trial EMPA-REG OUTCOME® (median duration of treatment 2.6 years).[19]

1. Heise T, et al. Diabetes Obes Metab 2013;15:613–21. 2.
2. Ferrannini E, et al. Diabetes Obes Metab 2013;15:721–28.
3. Rosenstock J, et al. Diabetes Obes Metab 2013;15:1154–60.
4. Rosenstock J, et al. Diabetes Obes Metab 2015;17:936–48.
5. Kanada S, et al. J Diabetes Investig 2013;4:613–17.
6. Kovacs CS, et al. Diabetes Obes Metab 2014;16:147–58.
7. Roden M, et al. Lancet Diabetes Endocrinol 2013;1:208–19.
8. Häring H-U, et al. Diabetes Care 2014;37:1650–59.
9. Häring H-U, et al. Diabetes Care 2013;36:3396–404.
10. Nishimura R, et al. Cardiovasc Diabetol 2015;14:11.
11. Barnett AH, et al. Lancet Diabetes Endocrinol 2014;2:369–84.
12. Kadowaki T, et al. Adv Ther 2014;31:621–38.
13. Tikkanen I, et al. Diabetes Care 2015;38:420–28.
14. Rosenstock J, et al. Diabetes Care 2014;37:1815–23.
15. Häring H-U, et al. Diabetes Res Clin Pract 2015;110:82–90.
16. Kovacs CS, et al. Clin Ther 2015;37:1773–88.
17. Merker L, et al. Diabet Med 2015;32:1555–67.
18. Roden M, et al. Cardiovasc Diabetol 2015;14:154.
19. Zinman B, et al. N Engl J Med 2015;373:2117–28.

Assessments

- Assessments were based on AEs reported by the investigators (coded according to the Medical Dictionary for Regulatory Activities [MedDRA] version 18.0) and clinical laboratory tests.
- Safety topics of interest included:
  - confirmed hypoglycemic AEs (plasma glucose ≤3.9 mmol/L and/or requiring assistance)
  - events consistent with UTI, genital infection, and volume depletion
  - bone fractures
  - cancer
  - decreased renal function
  - diabetic ketoacidosis
  - hepatic injury
  - acute pancreatitis
  - amputations.*

*As lower limb amputations were not usually captured in AE reports, the frequency of lower limb amputations was assessed based on a manual review of the pooled safety data and AE narratives.
AE, adverse event; UTI, urinary tract infection.

Participant disposition and exposure

- In total, 4203, 4221 and 4196 participants were treated with placebo, empagliflozin 10 mg and empagliflozin 25 mg, respectively.
- Total exposure was 7369, 7782, and 7754 patient-years in the placebo, empagliflozin 10 mg, and empagliflozin 25 mg groups, respectively.

Demographics and baseline characteristics (1/3)

	Placebo (N=4203)	Empagliflozin 10 mg (N=4221)	Empagliflozin 25 mg (N=4196)
Male	2700 (64.2)	2731 (64.7)	2745 (65.4)
Age, years	60.6 ± 9.7	60.7 ± 9.5	60.6 ± 9.7
Race			
White	2765 (65.8)	2811 (66.6)	2787 (66.4)
Asian	1219 (29.0)	1209 (28.6)	1198 (28.6)
Black/African-American	183 (4.4)	171 (4.1)	174 (4.1)
Other*	36 (0.9)	29 (0.7)	35 (0.8)
Missing	0	1 (<0.1)	2 (<0.1)
Region			
Europe	1656 (39.4)	1662 (39.4)	1652 (39.4)
Asia	1124 (26.7)	1122 (26.6)	1111 (26.5)
North America (plus Australia and New Zealand)	857 (20.4)	868 (20.6)	859 (20.5)
Latin America	450 (10.7)	452 (10.7)	456 (10.9)
Africa/Middle East	116 (2.8)	117 (2.8)	118 (2.8)

Data are n (%) or mean ± SD in participants who received ≥1 dose of study drug.
*American Indian/Alaska Native/Hawaiian/Pacific Islander.

Demographics and baseline characteristics (2/3)

	Placebo (N=4203)	Empagliflozin 10 mg (N=4221)	Empagliflozin 25 mg (N=4196)
Time since diagnosis of T2DM			
≤1 year	227 (5.4)	252 (6.0)	256 (6.1)
>1 to 5 years	922 (21.9)	858 (20.3)	860 (20.5)
>5 years	3039 (72.3)	3096 (73.3)	3064 (73.0)
Missing	15 (0.4)	15 (0.4)	16 (0.4)
Number of background glucose-lowering medications			
0	525 (12.5)	523 (12.4)	524 (12.5)
1	1212 (28.8)	1221 (28.9)	1175 (28.0)
2	1880 (44.7)	1862 (44.1)	1900 (45.3)
Other	586 (13.9)	615 (14.6)	597 (14.2)

Data are n (%) in participants who received ≥1 dose of study drug.

Demographics and baseline characteristics (3/3)

	Placebo (N=4203)	Empagliflozin 10 mg (N=4221)	Empagliflozin 25 mg (N=4196)
Weight, kg*	85.5 ± 19.6	85.3 ± 19.5	85.8 ± 19.6
Body mass index, kg/m^2†	30.4 ± 5.4	30.4 ± 5.5	30.5 ± 5.5
HbA1c, %‡	8.06 ± 0.83	8.05 ± 0.84	8.04 ± 0.83
FPG, mmol/L§	8.55 ± 2.31	8.54 ± 2.33	8.52 ± 2.30
SBP, mmHg¶	134.3 ± 16.6	133.9 ± 16.2	134.1 ± 16.5
DBP, mmHg¶	77.9 ± 9.7	77.8 ± 9.6	77.8 ± 9.4
eGFR, mL/min/1.73m^2‖	79.1 ± 21.0	79.3 ± 21.5	79.2 ± 21.6
eGFR			
≥90 mL/min/1.73m^2	1172 (27.9)	1204 (28.5)	1233 (29.4)
60 to <90 mL/min/1.73m^2	2298 (54.7)	2285 (54.1)	2216 (52.8)
30 to <60 mL/min/1.73m^2	726 (17.3)	722 (17.1)	728 (17.3)
<30 mL/min/1.73m^2	7 (0.2)	9 (0.2)	16 (0.4)
Missing	0	1 (<0.1)	3 (0.1)

Data are n (%) or mean ± SD in participants who received ≥1 dose of study drug.
*Placebo n=4182; empagliflozin 10 mg n=4201; empagliflozin 25 mg n=4177.
†Placebo n=4182; empagliflozin 10 mg n=4201; empagliflozin 25 mg n=4177.
‡Placebo n=4203; empagliflozin 10 mg n=4219; empagliflozin 25 mg n=4195.
§Placebo n=4176; empagliflozin 10 mg n=4194; empagliflozin 25 mg n=4180.
¶Placebo n=4145; empagliflozin 10 mg n=4165; empagliflozin 25 mg n=4142.
‖Placebo n=4203; empagliflozin 10 mg n=4220; empagliflozin 25 mg n=4193.
FPG, fasting plasma glucose; SBP, systolic blood pressure; DBP, diastolic blood pressure;
eGFR, estimated glomerular filtration rate by Modification of Diet in Renal Disease (MDRD) equation.

Adverse events (1/2)

	Placebo (N=4203)		Empagliflozin 10 mg (N=4221)		Empagliflozin 25 mg (N=4196)	
	n (%)	Rate/100 patient-yrs	n (%)	Rate/100 patient-yrs	n (%)	Rate/100 patient-yrs
≥1 AE	3449 (82.1)	195.4	3401 (80.6)	167.2	3383 (80.6)	163.6
≥1 drug-related AE*	921 (21.9)	14.9	1144 (27.1)	18.6	1117 (26.6)	18.1
≥1 AE leading to discontinuation	540 (12.8)	7.6	490 (11.6)	6.5	484 (11.5)	6.4
≥1 severe AE†	718 (17.1)	10.8	634 (15.0)	8.9	682 (16.3)	9.6
≥1 serious AE‡	1150 (27.4)	19.2	1020 (24.2)	15.5	1052 (25.1)	16.5
Fatal AE	122 (2.9)	1.6	100 (2.4)	1.3	83 (2.0)	1.1

Data from participants treated with ≥1 dose of study drug.
*In opinion of investigator.
†AE that is incapacitating or causing inability to work or to perform usual activities.
‡AE that results in death, is immediately life-threatening, results in persistent or significant disability/incapacity, requires or prolongs patient hospitalization, is a congenital anomaly/birth defect, or is deemed serious for any other reason.
AE, adverse event.

Adverse events (2/2)

	Placebo (N=4203)		Empagliflozin 10 mg (N=4221)		Empagliflozin 25 mg (N=4196)	
	n (%)	Rate/100 patient-yrs	n (%)	Rate/100 patient-yrs	n (%)	Rate/100 patient-yrs
AEs with frequency of ≥5% in any group (by MedDRA preferred term)						
Hypoglycemia	956 (22.7)	16.1	977 (23.1)	15.9	952 (22.7)	15.5
Hyperglycemia	709 (16.9)	11.0	346 (8.2)	4.7	306 (7.3)	4.1
UTI	523 (12.4)	7.7	528 (12.5)	7.4	510 (12.2)	7.2
Nasopharyngitis	424 (10.1)	6.1	417 (9.9)	5.7	408 (9.7)	5.6
URTI	292 (6.9)	4.2	285 (6.8)	3.8	288 (6.9)	3.9
Hypertension	291 (6.9)	4.1	205 (4.9)	2.7	218 (5.2)	2.9
Back pain	238 (5.7)	3.3	232 (5.5)	3.1	253 (6.0)	3.4
Dizziness	208 (4.9)	2.9	246 (5.8)	3.3	250 (6.0)	3.4
Diarrhea	247 (5.9)	3.5	219 (5.2)	2.9	212 (5.1)	2.8
Bronchitis	221 (5.3)	3.1	185 (4.4)	2.4	163 (3.9)	2.1
Influenza	219 (5.2)	3.1	173 (4.1)	2.3	199 (4.7)	2.6
Arthralgia	196 (4.7)	2.7	180 (4.3)	2.4	213 (5.1)	2.8

Data from participants treated with ≥1 dose of study drug.
AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; UTI, urinary tract infection; URTI, upper respiratory tract infection.

Confirmed hypoglycemic adverse events* by glucose-lowering medication used at baseline

	Placebo			Empagliflozin 10 mg			Empagliflozin 25 mg		
	n/N	%	Rate/100 patient-yrs	n/N	%	Rate/100 patient-yrs	n/N	%	Rate/100 patient-yrs
Insulin use†									
No	230/2595	8.9	5.9	240/2612	9.2	5.9	251/2607	9.6	6.1
Yes	676/1608	42.0	31.7	683/1609	42.4	32.1	659/1589	41.5	31.4
Sulfonylurea use†									
No	595/2781	21.4	16.9	575/2801	20.5	15.4	571/2748	20.8	15.7
Yes	311/1422	21.9	12.3	348/1420	24.5	14.0	339/1448	23.4	13.0
Metformin use†									
No	257/1275	20.2	17.3	251/1259	19.9	15.5	220/1255	17.5	13.5
Yes	649/2928	22.2	14.2	672/2962	22.7	14.6	690/2941	23.5	14.9
Metformin alone use									
No	885/3607	24.5	17.1	903/3583	25.2	17.4	889/3594	24.7	16.8
Yes	21/596	3.5	2.4	20/638	3.1	1.9	21/602	3.5	2.2

Data from participants treated with ≥1 dose of study drug.
*Plasma glucose ≤3.9 mmol/L and/or requiring assistance.
†With or without other glucose-lowering medication.

Adverse events of special interest (1/7)

	Placebo (N=4203)			Empagliflozin 10 mg (N=4221)			Empagliflozin 25 mg (N=4196)		
	n or n/N	%	Rate/100 patient-yrs	n or n/N	%	Rate/100 patient-yrs	n or n/N	%	Rate/100 patient-yrs
Events consistent with UTI*	629	15.0	9.5	639	15.1	9.2	607	14.5	8.7
Sex									
Male	193/2700	7.1	4.0	217/2731	7.9	4.3	206/2745	7.5	4.0
Female	436/1503	29.0	23.9	422/1490	28.3	21.7	401/1451	27.6	21.8
Age									
<50 years	75/531	14.1	12.4	59/533	11.1	7.9	64/544	11.8	8.8
50 to <65 years	281/2206	12.7	7.9	299/2176	13.7	8.3	257/2154	11.9	7.1
65 to <75 years	208/1184	17.6	10.5	204/1235	16.5	9.4	222/1213	18.3	10.2
≥75 years	65/282	23.0	13.0	77/277	27.8	16.8	64/285	22.5	13.6

Data from participants treated with ≥1 dose of study drug.
*Based on 79 MedDRA preferred terms; 25 were reported, of which urinary tract infection, asymptomatic bacteriuria and cystitis were the most frequent.
UTI, urinary tract infection; MedDRA, Medical Dictionary for Regulatory Activities.

Adverse events of special interest (2/7)

	Placebo (N=4203)			Empagliflozin 10 mg (N=4221)			Empagliflozin 25 mg (N=4196)		
	n or n/N	%	Rate/100 patient-yrs	n or n/N	%	Rate/100 patient-yrs	n or n/N	%	Rate/100 patient-yrs
Events consistent with genital infection*	67	1.6	0.9	259	6.1	3.5	251	6.0	3.4
Sex									
Male	33/2700	1.2	0.7	135/2731	4.9	2.6	107/2745	3.9	2.0
Female	34/1503	2.3	1.5	124/1490	8.3	5.2	144/1451	9.9	6.6
Age									
<50 years	14/531	2.6	2.1	44/533	8.3	5.8	37/544	6.8	4.8
50 to <65 years	29/2206	1.3	0.8	135/2176	6.2	3.5	129/2154	6.0	3.4
65 to <75 years	20/1184	1.7	0.9	63/1235	5.1	2.6	70/1213	5.8	2.9
≥75 years	4/282	1.4	0.7	17/277	6.1	3.2	15/285	5.3	2.8

Data from participants treated with ≥1 dose of study drug.
*Based on 88 MedDRA preferred terms; 31 were reported, of which balanoposthitis, vulvovaginal mycotic infection and vulvovaginal candidiasis were the most frequent.
MedDRA, Medical Dictionary for Regulatory Activities.

Adverse events of special interest (3/7)

	Placebo (N=4203)			Empagliflozin 10 mg (N=4221)			Empagliflozin 25 mg (N=4196)		
	n or n/N	%	Rate/100 patient-yrs	n or n/N	%	Rate/100 patient-yrs	n or n/N	%	Rate/100 patient-yrs
Events consistent with volume depletion*	126	3.0	1.7	138	3.3	1.8	142	3.4	1.9
Age									
<50 years	5/531	0.9	0.7	5/533	0.9	0.6	10/544	1.8	1.3
50 to <65 years	48/2206	2.2	1.2	48/2176	2.2	1.2	53/2154	2.5	1.4
65 to <75 years	60/1184	5.1	2.8	68/1235	5.5	2.9	63/1213	5.2	2.6
≥75 years	13/282	4.6	2.3	17/277	6.1	3.2	16/285	5.6	3.0
Diuretic use at baseline									
Yes	74/1419	5.2	2.7	76/1451	5.2	2.6	80/1429	5.6	2.8
No	52/2784	1.9	1.1	62/2770	2.2	1.3	62/2767	2.2	1.3
Loop diuretic use at baseline									
Yes	31/424	7.3	3.5	41/400	10.3	5.0	40/433	9.2	4.4
No	95/3779	2.5	1.5	97/3821	2.5	1.4	102/3763	2.7	1.5

Data from participants treated with ≥1 dose of study drug.
*Based on 8 MedDRA preferred terms; 6 were reported, of which hypotension, syncope and dehydration were the most frequent.
MedDRA, Medical Dictionary for Regulatory Activities.

Adverse events of special interest (4/7)

	Placebo (N=4203)			Empagliflozin 10 mg (N=4221)			Empagliflozin 25 mg (N=4196)		
	n or n/N	%	Rate/100 patient-yrs	n or n/N	%	Rate/100 patient-yrs	n or n/N	%	Rate/100 patient-yrs
Bone fractures*	123	2.9	1.7	119	2.8	1.6	105	2.5	1.4
eGFR at baseline									
≥90 mL/min/1.73m²	15/1172	1.3	0.8	27/1204	2.2	1.4	23/1233	1.9	1.1
60 to <90 mL/min/1.73m²	70/2298	3.0	1.8	57/2285	2.5	1.4	53/2216	2.4	1.3
45 to <60 mL/min/1.73m²	30/529	5.7	2.8	23/530	4.3	2.0	21/531	4.0	1.8
30 to <45 mL/min/1.73m²	7/197	3.6	1.6	12/192	6.3	3.0	8/197	4.1	1.9
<30 mL/min/1.73m²	1/7	14.3	7.9	0/9	0	0	0/16	0	0

Data from participants treated with ≥1 dose of study drug.
*Based on 62 MedDRA preferred terms; 41 were reported, of which foot fracture, rib fracture and ankle fracture were the most frequent.
eGFR, estimated glomerular filtration rate by Modification of Diet in Renal Disease (MDRD) equation; MedDRA, Medical Dictionary for Regulatory Activities.

Adverse events of special interest (5/7)

	Placebo (N=4203)			Empagliflozin 10 mg (N=4221)			Empagliflozin 25 mg (N=4196)		
	n or n/N	%	Rate/100 patient-yrs	n or n/N	%	Rate/100 patient-yrs	n or n/N	%	Rate/100 patient-yrs
Cancer events*	95	2.3	1.3	121	2.9	1.6	119	2.8	1.5
With onset ≥6 months from start of treatment/ participants with exposure ≥6 months	76/3159	2.4	1.4	103/3270	3.1	1.8	86/3203	2.7	1.5
Bladder cancer†	2	0.1	0.0	4	0.1	0.1	7	0.2	0.1
Renal cancer‡	5	0.2	0.1	4	0.1	0.1	3	0.1	0.1
Brest cancer§	4	0.1	0.1	3	0.1	0.1	3	0.1	0.1
Melanoma¶	2	<0.1	<0.1	4	0.1	0.1	3	0.1	0.1
Lung cancer‖	7	0.2	0.1	11	0.3	0.2	9	0.3	0.2

Data from participants treated with ≥1 dose of study drug.
*Based on 2 sub-SMQs.
†Based on reported preferred terms: bladder cancer/bladder transitional cell carcinoma/transitional cell carcinoma.
‡Based on MedDRA high level term, reported preferred terms: renal cancer metastatic/renal cell carcinoma/renal cell carcinoma stage I/renal cell carcinoma stage II/clear cell renal cell carcinoma.
§Based on MedDRA high level term, reported preferred terms: breast cancer/invasive ductal breast carcinoma/intraductal proliferative breast carcinoma.
¶Based on MedDRA high level term, reported preferred terms: malignant melanoma/malignant melanoma in situ/metastatic malignant melanoma.
‖Based on MedDRA high level terms, reported preferred terms: lung neoplasm malignant//bronchial carcinoma/lung cancer metastatic/lung adenocarcinoma/squamous cell carcinoma of lung/large cell lung cancer/lung squamous cell carcinoma stage III/non-small cell lung cancer.
MedDRA, Medical Dictionary for Regulatory Activities; SMQ, standardized MedDRA query.

Adverse events of special interest (6/7)

	Placebo (N=4203)			Empagliflozin 10 mg (N=4221)			Empagliflozin 25 mg (N=4196)		
	n or n/N	%	Rate/100 patient-yrs	n or n/N	%	Rate/100 patient-yrs	n or n/N	%	Rate/100 patient-yrs
Events consistent with decreased renal function*	159	3.8	2.2	137	3.2	1.8	141	3.4	1.8
eGFR at baseline*									
≥90 mL/min/1.73m²	13/1172	1.1	0.7	9/1204	0.7	0.5	10/1233	0.8	0.5
60 to <90 mL/min/1.73m²	56/2298	2.4	1.4	56/2285	2.5	1.4	53/2216	2.4	1.3
45 to <60 mL/min/1.73m²	55/529	10.4	5.2	45/530	8.5	4.0	42/531	7.9	3.7
30 to <45 mL/min/1.73m²	32/197	16.2	7.9	24/192	12.5	6.2	34/197	17.3	8.9
<30 mL/min/1.73m²	3/7	42.9	37.7	3/9	33.3	21.4	2/16	12.5	7.6
Acute kidney injury†	38	0.9	0.5	28	0.7	0.4	24	0.6	0.3

Data from participants treated with ≥1 dose of study drug.
*Based on narrow SMQ acute renal failure.
†Based on MedDRA preferred term.
eGFR, estimated glomerular filtration rate by Modification of Diet in Renal Disease (MDRD) equation; SMQ, standardized MedDRA query; MedDRA, Medical Dictionary for Regulatory Activities.

Adverse events of special interest (7/7)

	Placebo (N=4203)			Empagliflozin 10 mg (N=4221)			Empagliflozin 25 mg (N=4196)		
	n or n/N	%	Rate/100 patient-yrs	n or n/N	%	Rate/100 patient-yrs	n or n/N	%	Rate/100 patient-yrs
Hepatic injury*	151	3.6	2.1	106	2.5	1.4	127	3.0	1.7
Acute pancreatitis†	4	0.1	0.1	1	<0.1	<0.1	4	0.1	0.1
Diabetic ketoacidosis‡	5	0.1	0.1	5	0.1	0.1	1	<0.1	<0.1
Venous thromboembolic events§	23	0.5	0.3	11	0.3	0.1	26	0.6	0.3
Lower limb amputations	46	1.1	-	46	1.1	-	48	1.1	-
Events potentially related to lower limb amputations									
Peripheral artery obstructive disease events	96	2.3	-	98	2.3	-	112	2.7	-
Diabetic foot-related events	109	2.6	-	94	2.2	-	106	2.5	-
Relevant infection events	74	1.8	-	79	1.9	-	80	1.9	-
Wound events	57	1.4	-	64	1.5	-	63	1.5	-

Data from participants treated with ≥1 dose of study drug.
*Based on 4 narrow sub-SMQs.
†Based on MedDRA preferred term.
‡Based on 3 MedDRA preferred terms.
§Based on 1 narrow SMQ.
SMQ, standardized MedDRA query; MedDRA, Medical Dictionary for Regulatory Activities.

Laboratory results (1/3)

	Placebo			Empagliflozin 10 mg			Empagliflozin 25 mg		
	n	Baseline	Change from baseline*	n	Baseline	Change from baseline*	n	Baseline	Change from baseline*
Hematocrit, %	4043	41.7 ± 5.3	0.5 ± 4.2	4078	41.8 ± 5.3	4.1 ± 4.9	4030	41.9 ± 5.4	4.3 ± 4.7
Hemoglobin, g/L	4053	136 ± 14	-1 ± 10	4089	137 ± 14	8 ± 12	4041	137 ± 14	8 ± 12
Uric acid, µmol/L	4047	322 ± 134	-1 ± 101	4095	316 ± 131	-31 ± 100	4042	318 ± 131	-34 ± 102
Serum creatinine, µmol/L	4104	86 ± 19	4 ± 18	4136	86 ± 19	3 ± 15	4101	86 ± 19	3 ± 14
eGFR, mL/min/1.73m^2	4101	79.1 ± 21.0	-2.7 ± 12.8	4133	79.3 ± 21.5	-1.7 ± 12.9	4099	79.2 ± 21.6	-1.9 ± 13.2
Aspartate aminotransferase, U/L	4102	15 ± 13	-0 ± 19	4136	15 ± 11	-1 ± 15	4099	15 ± 11	-1 ± 36
Alanine aminotransferase, U/L	4104	20 ± 15	-1 ± 25	4136	20 ± 14	-2 ± 16	4099	20 ± 14	-2 ± 33
Alkaline phosphatase, U/L	4104	66 ± 31	3 ± 27	4136	67 ± 32	1 ± 27	4099	67 ± 33	1 ± 23
Total bilirubin, µmol/L	4052	8.9 ± 3.3	-0.0 ± 2.5	4096	8.8 ± 3.0	0.2 ± 3.2	4044	9.0 ± 3.1	0.1 ± 4.9

Data are mean ± SD in participants who received ≥1 dose of study drug and had laboratory values available at baseline and on treatment. Data are normalized to a standard reference range, except for eGFR.
*Change from baseline at last value on treatment.
eGFR, estimated glomerular filtration rate by Modification of Diet in Renal Disease (MDRD) equation.

Laboratory results (2/3)

	Placebo			Empagliflozin 10 mg			Empagliflozin 25 mg		
	n	Baseline	Change from baseline*	n	Baseline	Change from baseline*	n	Baseline	Change from baseline*
25-hydroxy vitamin D, nmol/L†	291	75.4 ± 35.7	2.6 ± 40.0	307	77.9 ± 33.7	5.7 ± 35.2	307	77.0 ± 34.6	9.1 ± 43.1
Urinary N-telopeptide (NTx)/creatinine ratio (nM/mM Cre)†	280	41 ± 24	-2 ± 17	295	40 ± 20	3 ± 19	290	40 ± 21	6 ± 27
Parathyroid hormone, pmol/L†	285	4.2 ± 1.8	-0.3 ± 1.4	308	4.2 ± 1.7	-0.0 ± 1.3	307	4.4 ± 5.2	-0.3 ± 4.6
Electrolytes									
Sodium, mmol/L	4047	141 ± 2	-0 ± 2	4095	141 ± 2	0 ± 2	4041	141 ± 2	0 ± 2
Potassium, mmol/L	4045	4.2 ± 0.3	0.0 ± 0.3	4094	4.2 ± 0.3	-0.0 ± 0.3	4041	4.2 ± 0.3	-0.0 ± 0.3
Calcium, mmol/L	4047	2.4 ± 0.1	-0.0 ± 0.1	4095	2.4 ± 0.1	-0.0 ± 0.1	4042	2.4 ± 0.1	-0.0 ± 0.1
Magnesium, mmol/L	4031	0.9 ± 0.1	-0.0 ± 0.1	4079	0.9 ± 0.1	0.0 ± 0.1	4026	0.9 ± 0.1	0.1 ± 0.1
Phosphate, mmol/L	4030	1.2 ± 0.1	0.0 ± 0.1	4079	1.2 ± 0.1	0.0 ± 0.1	4026	1.2 ± 0.1	0.0 ± 0.1
Bicarbonate , mmol/L	4023	24.8 ± 2.8	-0.5 ± 3.0	4066	24.8 ± 2.8	-0.9 ± 3.0	4021	24.8 ± 2.8	-0.9 ± 3.0

Data are mean ± SD in participants who received ≥1 dose of study drug and had laboratory values available at baseline and on treatment. Data are normalized to a standard reference range.
*Change from baseline at last value on treatment.
†Urinary N-telopeptide/creatinine ratio, 25-hydroxy vitamin D and parathyroid hormone levels were only recorded in two monotherapy trials.[1,2]
1. Roden M, et al. Lancet Diabetes Endocrinol 2013;1:208–19. 2. Kadowaki T, et al. Adv Ther 2014;31:621–38.

Laboratory results (3/3)

	Placebo			Empagliflozin 10 mg			Empagliflozin 25 mg		
	n	Baseline	Change from baseline*	n	Baseline	Change from baseline*	n	Baseline	Change from baseline*
Total cholesterol, mmol/L	4014	4.4 ± 1.1	0.1 ± 1.0	4035	4.4 ± 1.2	0.2 ± 1.0	3997	4.5 ± 1.1	0.2 ± 1.0
HDL-cholesterol, mmol/L	4015	1.2 ± 0.3	0.0 ± 0.2	4034	1.2 ± 0.3	0.0 ± 0.2	3997	1.2 ± 0.3	0.1 ± 0.2
LDL-cholesterol, mmol/L	3986	2.4 ± 1.0	0.1 ± 0.8	3993	2.4 ± 1.0	0.1 ± 0.8	3967	2.4 ± 0.9	0.1 ± 0.8
LDL/HDL cholesterol ratio	3986	2.1 ± 1.0	0.1 ± 1.0	3993	2.1 ± 0.9	0.0 ± 0.8	3967	2.1 ± 1.0	0.0 ± 0.8
Triglycerides, mmol/L	4014	1.9 ± 1.3	0.1 ± 1.5	4035	1.9 ± 1.6	0.0 ± 1.4	3997	1.9 ± 1.5	0.1 ± 1.5
Apolipoprotein A-I, g/L	3609	1.26 ± 0.06	0.00 ± 0.04	3627	1.26 ± 0.06	0.01 ± 0.04	3616	1.26 ± 0.06	0.01 ± 0.05
Apolipoprotein B, g/L	3609	0.95 ± 0.52	0.08 ± 0.43	3627	0.95 ± 0.53	0.10 ± 0.44	3617	0.96 ± 0.52	0.11 ± 0.42

Data are mean ± SD in participants who received ≥1 dose of study drug and had laboratory values available at baseline and on treatment. Data are normalized to a standard reference range, except for lipids.
*Change from baseline at last value on treatment.
HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Elevations in liver enzymes and bilirubin

	Placebo (N=4203)	Empagliflozin 10 mg (N=4221)	Empagliflozin 25 mg (N=4196)
ALT and/or AST ≥3 x ULN	59 (1.4)	41 (1.0)	38 (0.9)
ALT and/or AST ≥5 x ULN	9 (0.2)	17 (0.4)	21 (0.5)
ALT and/or AST ≥3 x ULN with bilirubin ≥2 x ULN	2 (<0.1)	5 (0.1)	5 (0.1)

Data are n (%) in participants who received ≥1 dose of study drug.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal.

Urine ketone levels: worst recorded measurement on treatment

	Placebo (N=3645)	Empagliflozin 10 mg (N=3682)	Empagliflozin 25 mg (N=3636)
Negative	2973 (81.6)	2822 (76.6)	2757 (75.8)
Trace	511 (14.0)	535 (14.5)	508 (14.0)
1+	144 (4.0)	256 (7.0)	291 (8.0)
2+	15 (0.4)	58 (1.6)	73 (2.0)
3+	2 (0.1)	11 (0.3)	7 (0.2)

Data are n (%) in participants who received ≥1 dose of study drug and had ketone values available at baseline and on treatment.

Summary

- In this analysis of pooled safety data based on >15,000 patient-years' exposure to empagliflozin in placebo-controlled trials, empagliflozin 10 mg and 25 mg were well tolerated in patients with T2DM.
- Empagliflozin was not associated with a higher rate of hypoglycemic events compared with placebo, except in participants on background sulfonylurea.
- The incidence of adverse events consistent with volume depletion was similar between empagliflozin and placebo, except for a higher incidence with empagliflozin in participants aged ≥75 years and in participants receiving loop diuretics at baseline.
- Genital infections, but not urinary tract infections, were more frequent in participants treated with empagliflozin than placebo.
- **The incidences of bone fractures, cancer events, renal adverse events, venous thromboembolic events, hepatic injury, acute pancreatitis, lower limb amputations and diabetic ketoacidosis were not increased with empagliflozin versus placebo.**

Empagliflozin in T2D: summary

T2D is an increasingly prevalent and complex disease that worsens over time

- Patients with T2D are at increased risk of mortality and macrovascular and microvascular complications, despite standard of care therapy

Empagliflozin is a selective SGLT2 inhibitor that provides effective glycaemic control, with the additional benefits of weight loss and blood pressure reduction

- SGLT2 inhibition blocks glucose re-uptake in the proximal renal tubule, leading to urinary excretion of glucose irrespective of β-cell function or insulin resistance

In the EMPA-REG OUTCOME® trial, empagliflozin reduced CV and renal risk in patients with T2D and established CV disease

The CV benefits of empagliflozin are recognised by major clinical guidelines

Empagliflozin is the only oral glucose-lowering therapy to be approved by the FDA to reduce CV mortality risk in patients with T2D and established CV disease

CV, cardiovascular; SGLT2, sodium-glucose co-transporter-2; T2D, type 2 diabetes

Supplementary material

Frequency of participants with lower limb amputation in EMPA-REG OUTCOME® (1/5)

	Placebo		Empagliflozin 10 mg		Empagliflozin 25 mg	
	n/N	%	n/N	%	n/N	%
Lower limb amputation	43/2333	1.8	42/2345	1.8	46/2342	2.0
Sex						
Male	38/1680	2.3	30/1653	1.8	36/1683	2.1
Female	5/653	0.8	12/692	1.7	10/659	1.5
Age						
<65 years	24/1297	1.9	27/1300	2.1	28/1296	2.2
≥65 years	19/1036	1.8	15/1045	1.4	18/1046	1.7
eGFR at baseline						
≥90 mL/min/1.73m²	9/488	1.8	8/519	1.5	9/531	1.7
60 to <90 mL/min/1.73m²	15/1238	1.2	16/1221	1.3	19/1202	1.6
45 to <60 mL/min/1.73m²	13/418	3.1	13/420	3.1	11/411	2.7
30 to <45 mL/min/1.73m²	6/183	3.3	4/178	2.2	6/182	3.3
<30 mL/min/1.73m²	0/6	0	1/7	14.3	1/14	7.1

Data from participants who received ≥1 dose of study drug.

Frequency of participants with lower limb amputation in EMPA-REG OUTCOME® (2/5)

	Placebo		Empagliflozin 10 mg		Empagliflozin 25 mg	
	n/N	%	n/N	%	n/N	%
Lower limb amputation	43/2333	1.8	42/2345	1.8	46/2342	2.0
Diuretics at baseline						
No	23/1345	1.7	17/1309	1.3	23/1331	1.7
Yes	20/988	2.0	25/1036	2.4	23/1011	2.3
Loop diuretics at baseline						
No	33/1969	1.7	31/2002	1.5	33/1960	1.7
Yes	10/364	2.7	11/343	3.2	13/382	3.4
Metformin at baseline						
No	18/599	3.0	11/616	1.8	18/612	2.9
Yes	25/1734	1.4	31/1729	1.8	28/1730	1.6
Insulin at baseline						
No	8/1198	0.7	11/1213	0.9	8/1222	0.7
Yes	35/1135	3.1	31/1132	2.7	38/1120	3.4
Sulfonylurea at baseline						
No	30/1341	2.2	29/1360	2.1	33/1313	2.5
Yes	13/992	1.3	13/985	1.3	13/1029	1.3

Data from participants who received ≥1 dose of study drug.

Frequency of participants with lower limb amputation in EMPA-REG OUTCOME® (3/5)

	Placebo		Empagliflozin 10 mg		Empagliflozin 25 mg	
	n/N	%	n/N	%	n/N	%
Lower limb amputation	43/2333	1.8	42/2345	1.8	46/2342	2.0
History of stroke						
No	33/1779	1.9	33/1810	1.8	39/1793	2.2
Yes	10/553	1.8	9/535	1.7	7/549	1.3
History of CAD						
No	15/570	2.6	15/563	2.7	21/579	3.6
Yes	28/1763	1.6	27/1782	1.5	25/1763	1.4
History of myocardial infarction						
No	24/1250	1.9	23/1238	1.9	26/1259	2.1
Yes	19/1083	1.8	19/1107	1.7	20/1083	1.8
History of CABG						
No	29/1770	1.6	30/1751	1.7	31/1761	1.8
Yes	14/563	2.5	12/594	2.0	15/581	2.6
History of multi-vessel CAD						
No	25/1233	2.0	27/1267	2.1	32/1241	2.6
Yes	18/1100	1.6	15/1078	1.4	14/1101	1.3

Data from participants who received ≥1 dose of study drug.
CAD, coronary artery disease; CABG, coronary artery bypass graft.

Frequency of participants with lower limb amputation in EMPA-REG OUTCOME® (4/5)

	Placebo		Empagliflozin 10 mg		Empagliflozin 25 mg	
	n/N	%	n/N	%	n/N	%
Lower limb amputation	43/2333	1.8	42/2345	1.8	46/2342	2.0
History of single vessel CAD						
No	39/2094	1.9	41/2087	2.0	43/2102	2.0
Yes	4/238	1.7	1/258	0.4	3/240	1.3
History of peripheral artery disease						
No	13/1853	0.7	21/1880	1.1	13/1824	0.7
Yes	30/479	6.3	21/465	4.5	33/517	6.4
History of diabetic retinopathy						
No	25/1810	1.4	26/1824	1.4	29/1840	1.6
Yes	18/523	3.4	16/521	3.1	17/502	3.4
History of diabetic nephropathy						
No	31/1866	1.7	31/1901	1.6	35/1882	1.9
Yes	12/467	2.6	11/444	2.5	11/460	2.4

Data from participants who received ≥1 dose of study drug.
CAD, coronary artery disease.

Frequency of participants with lower limb amputation in EMPA-REG OUTCOME® (5/5)

	Placebo		Empagliflozin 10 mg		Empagliflozin 25 mg	
	n/N	%	n/N	%	n/N	%
Lower limb amputation	43/2333	1.8	42/2345	1.8	46/2342	2.0
History of diabetic neuropathy						
No	20/1606	1.2	15/1610	0.9	18/1607	1.1
Yes	23/727	3.2	27/735	3.7	28/735	3.8
History of diabetic foot						
No	20/2188	0.9	24/2218	1.1	26/2206	1.2
Yes	23/145	15.9	18/127	14.2	20/136	14.7
History of cerebrovascular disease						
No	30/1726	1.7	32/1766	1.8	39/1739	2.2
Yes	13/607	2.1	10/579	1.7	7/603	1.2
History of hypertension						
No	4/180	2.2	3/211	1.4	3/210	1.4
Yes	39/2153	1.8	39/2134	1.8	43/2132	2.0

Data from participants who received ≥1 dose of study drug.