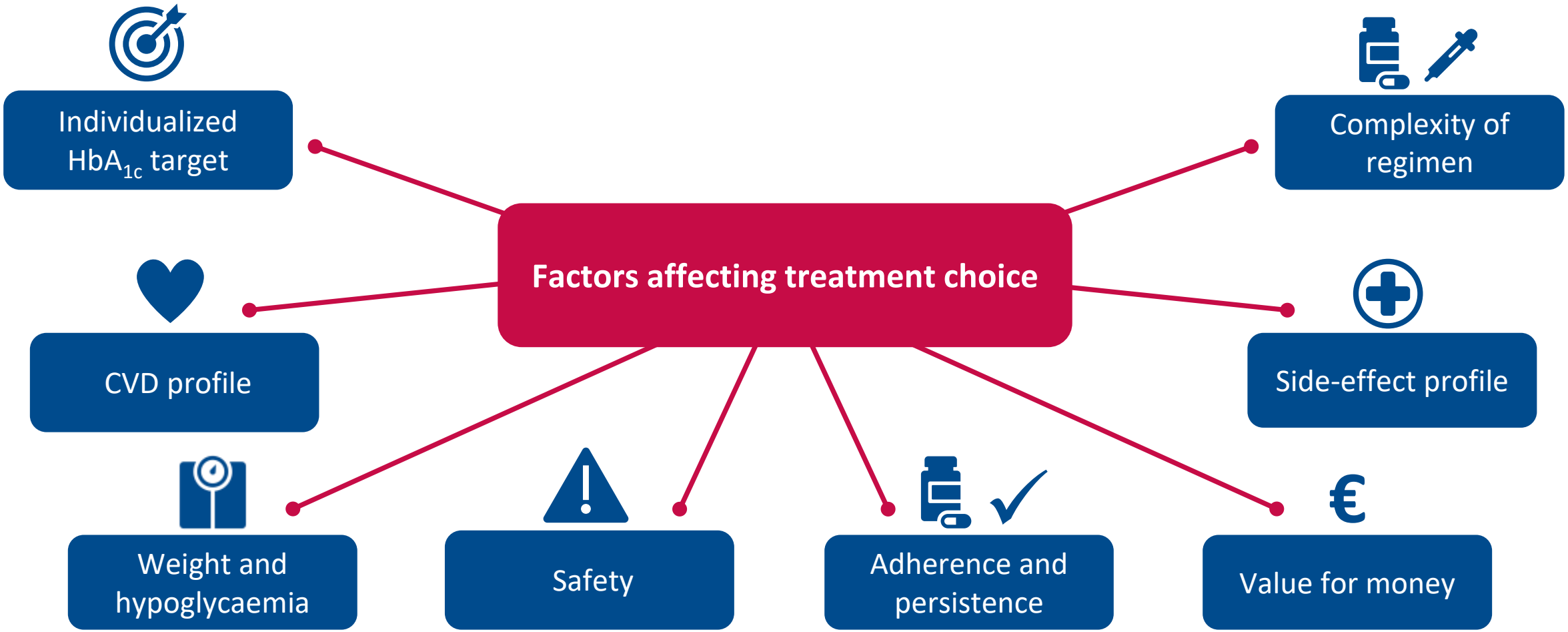
The cost of heart failure in people with type 2 diabetes

Marc Evans

Disclosures

- I have received honoraria and research awards from Astra Zeneca, Novonordisk, Takeda, Novartis, MSD, NAPP

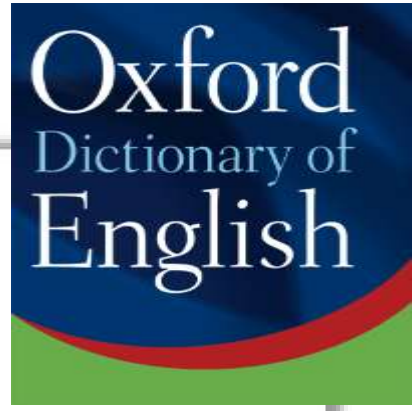
Factors to consider when choosing an anti-hyperglycaemic therapy



CKD, chronic kidney disease; CVD, cardiovascular disease

1. Davies MJ *et al. Diabetologia* 2018;41:2669–701

What is value?



value

1. the worth of something compared to the price paid or asked for it

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

What Is Value in Health Care?

Michael E. Porter, Ph.D.

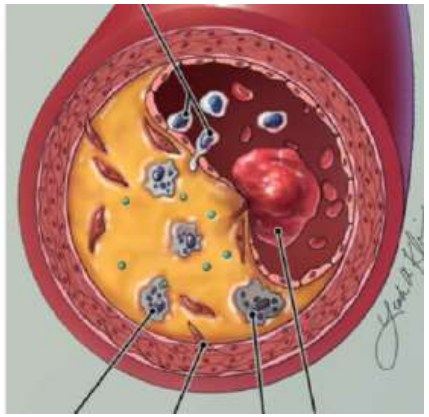
N Engl J Med 2010; 363:2477-2481 | December 23, 2010 | DOI: 10.1056/NEJMp1011024

Outcomes, the numerator of the value equation, are inherently condition-specific and multidimensional. For any medical condition, no single outcome captures the results of care. Cost, the equation's denominator, refers to the total costs of the full cycle of care for the patient's medical condition, not the cost of individual services. To reduce cost, the best approach is often to spend more on some services to reduce the need for others.

Mechanisms of CV disease in diabetes[1,2]

Diabetes-related factors
- Hyperglycaemia
- Advanced glycosylated end products
- Oxidative stress

Obesity-related factors
- Inflammatory cytokines
- Adipokines
- Insulin resistance
- Oxidative stress



Hypertension/ haemodynamic-related factors
- Metabolic demand
- Oxidation
- Tissue ischaemia
- Endothelial dysfunction

Dyslipidaemia
- Oxidative stress
- Elevated LDL-cholesterol
- Adducted lipoproteins

CV, cardiovascular; LDL, low-density lipoprotein

1. Low Wang CC *et al. Circulation* 2016;133:2459–502; 2. England BR *et al. BMJ*;316:k1036

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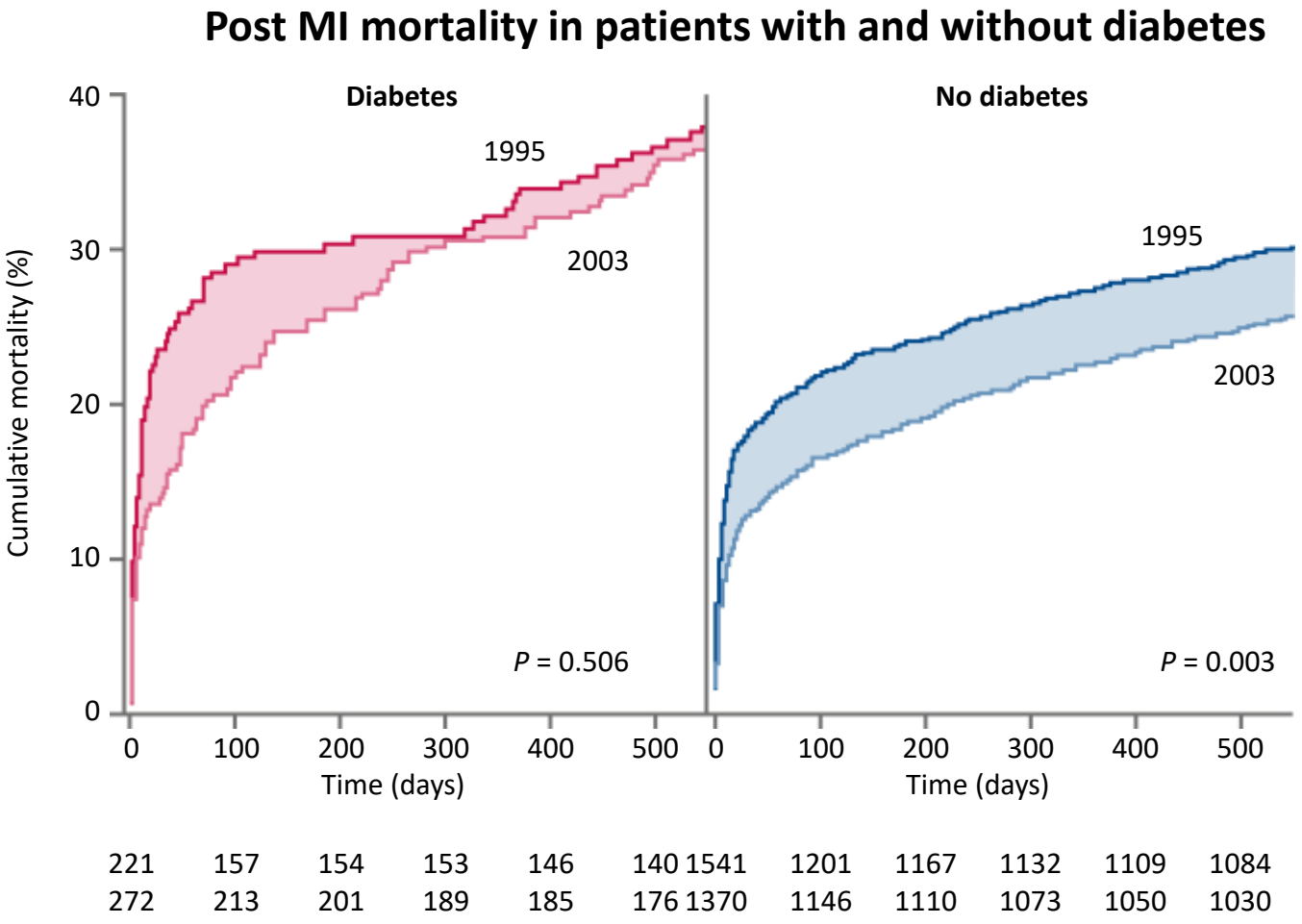
Long-term outcomes after acute myocardial infarction are worse in patients with diabetes than in those without[1]



Reductions in early mortality in all patients with acute MI were not sustained over the long term in those with diabetes

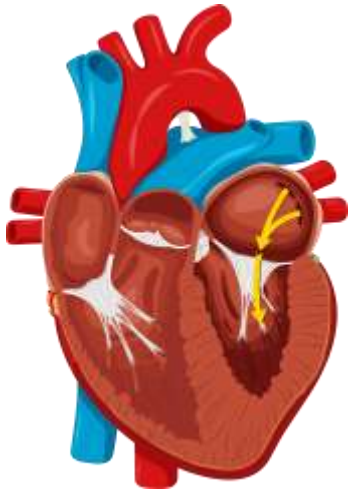
Highlighted areas in Kaplan–Meier curves represent survival improvement within each group between 1995 and 2003
CI, confidence interval; MI, myocardial infarction

1. Cubbon RM *et al. Eur Heart J* 2007;376:540–5

Cardiac remodelling is a feature of T2D

Hyperglycaemia, insulin resistance, obesity[1]

- Inflammatory cytokine release from adipose tissue[1]
- Increased oxidative stress[1]
- Mitochondrial dysfunction[1]
- Altered substrate utilization: FFAs used instead of glucose[1]



- Cardiac fibrosis that may reduce myocardial compliance[2]
- Left ventricular hypertrophy[1]

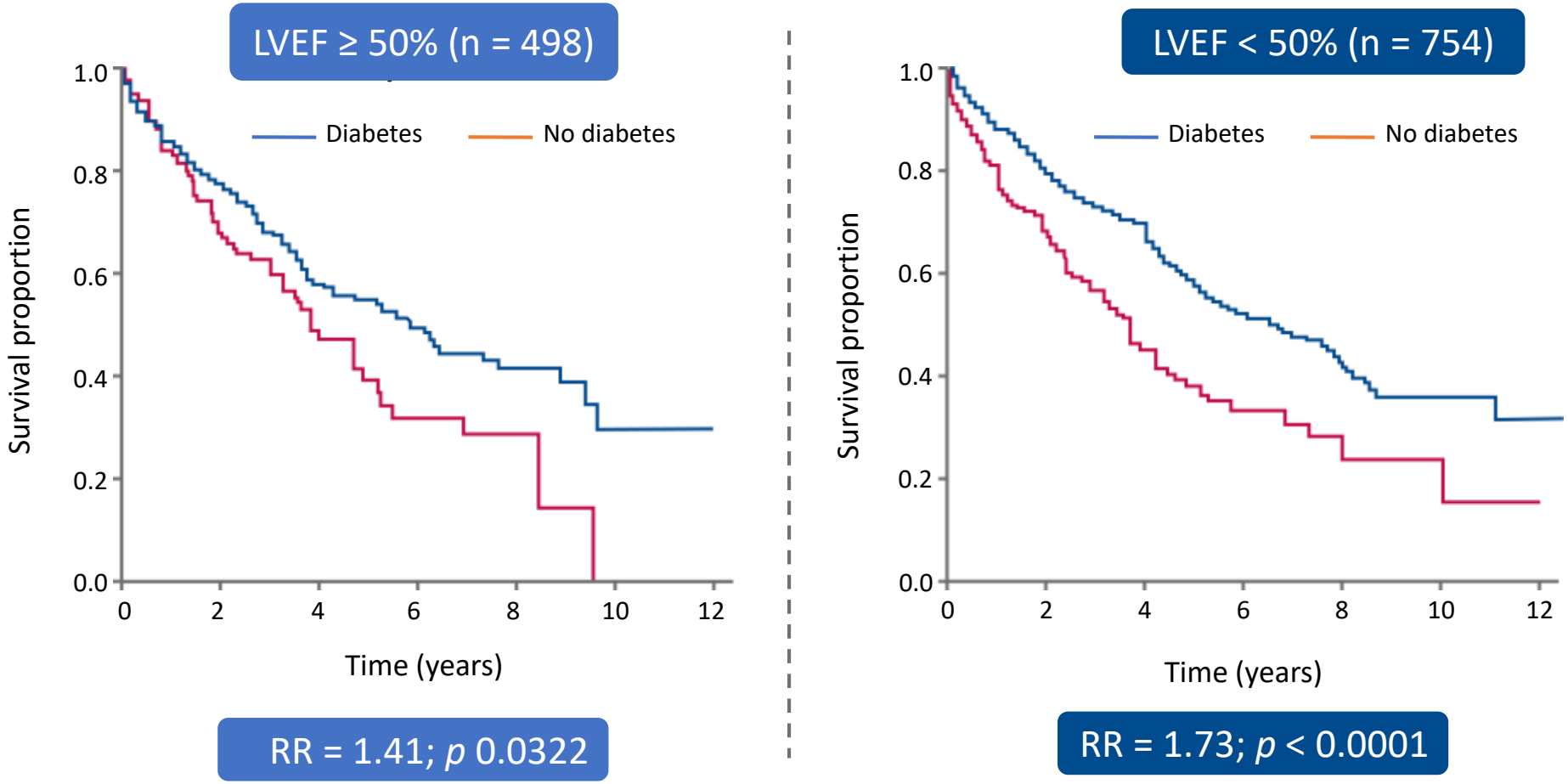
Heart failure

FFA, free fatty acid

1. Boudina S *et al. Rev Endocr Metab Disord* 2010;11:31–9; 2. Russo I *et al. J Mol Cell Cardiol* 2016;90:84–93

Diabetes worsens heart failure prognosis[1]

Poorer HF survival in patients with diabetes than in those without diabetes



HF, heart failure; LVEF, left ventricular ejection fraction; RR, relative risk

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

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Hyperglycaemia and haemodynamic effects lead to structural changes in the kidney

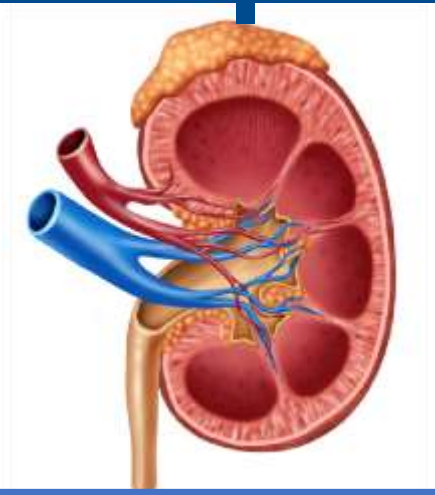
Inflammation[1]

Renin–angiotensin system activation[1]

Oxidative stress[1]

Thickening of arteriole wall[2]

Mesangial cell hypertrophy[2]



Efferent arteriolar occlusion[1]

Basement membrane thickening[2]

Glomerular hypertension, hyperfiltration, albuminuria, reduced eGFR[2]

eGFR, estimated glomerular filtration rate

1. Toth-Manikowski S *et al. J Diabetes Res* 2015;2015:697010; 2. Reidy K *et al. J Clin Invest* 2014;124:2333–40

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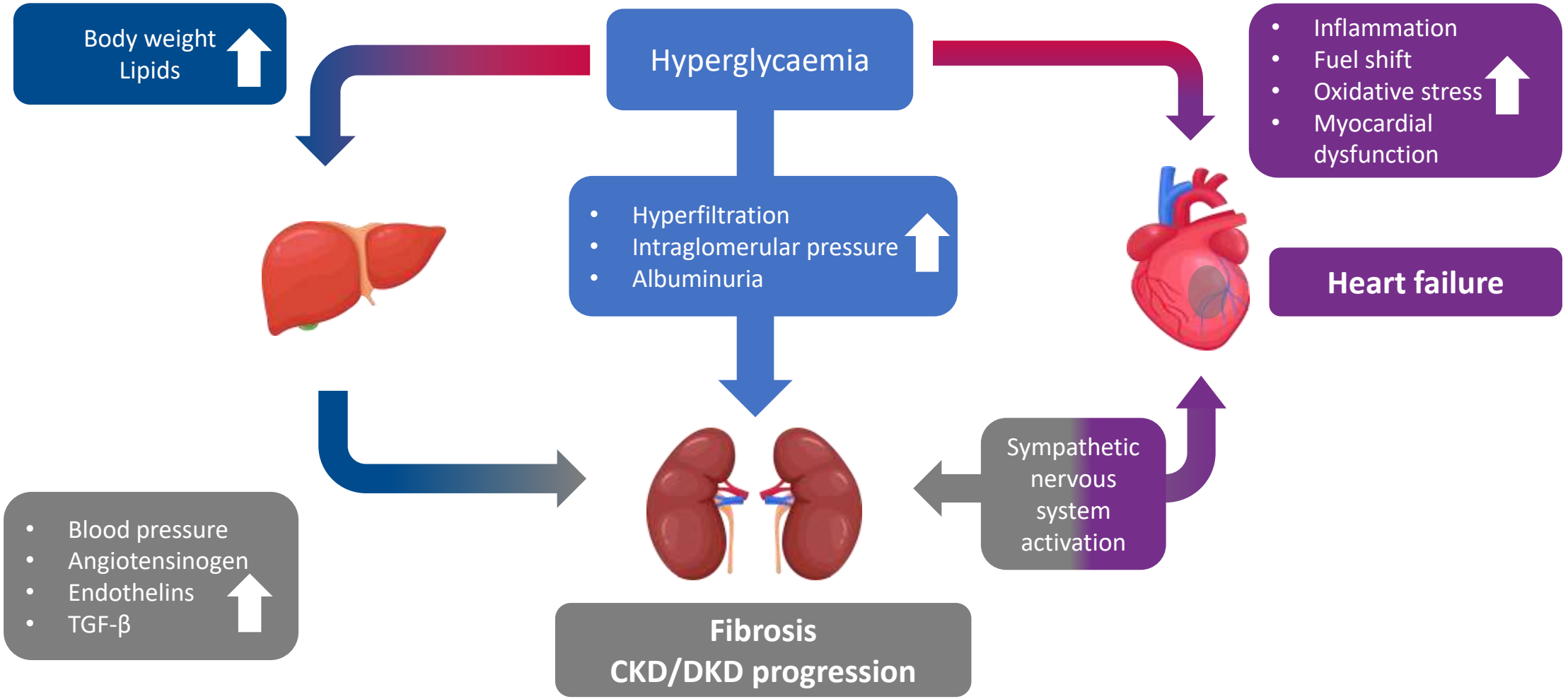
CV damage, heart failure and kidney failure are intrinsically linked[1,2]



CKD, chronic kidney disease; CV, cardiovascular; DKD, diabetic kidney disease; TGF-β, transforming growth factor β

1. Bongartz L *et al. Eur Heart J* 2005;26:11; 2. Wanner C *et al. Diabetologia* 2018;61:2134–9

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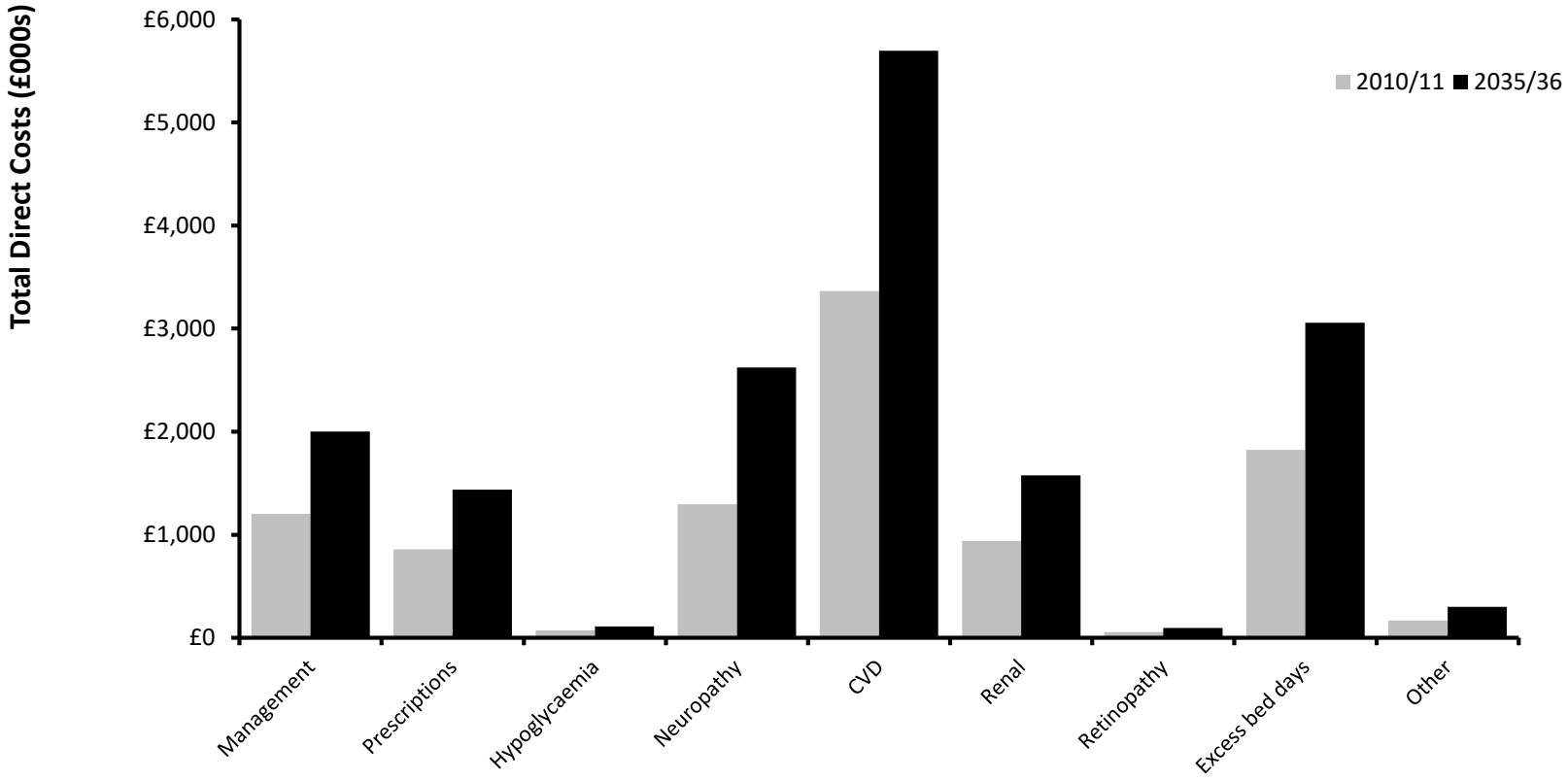
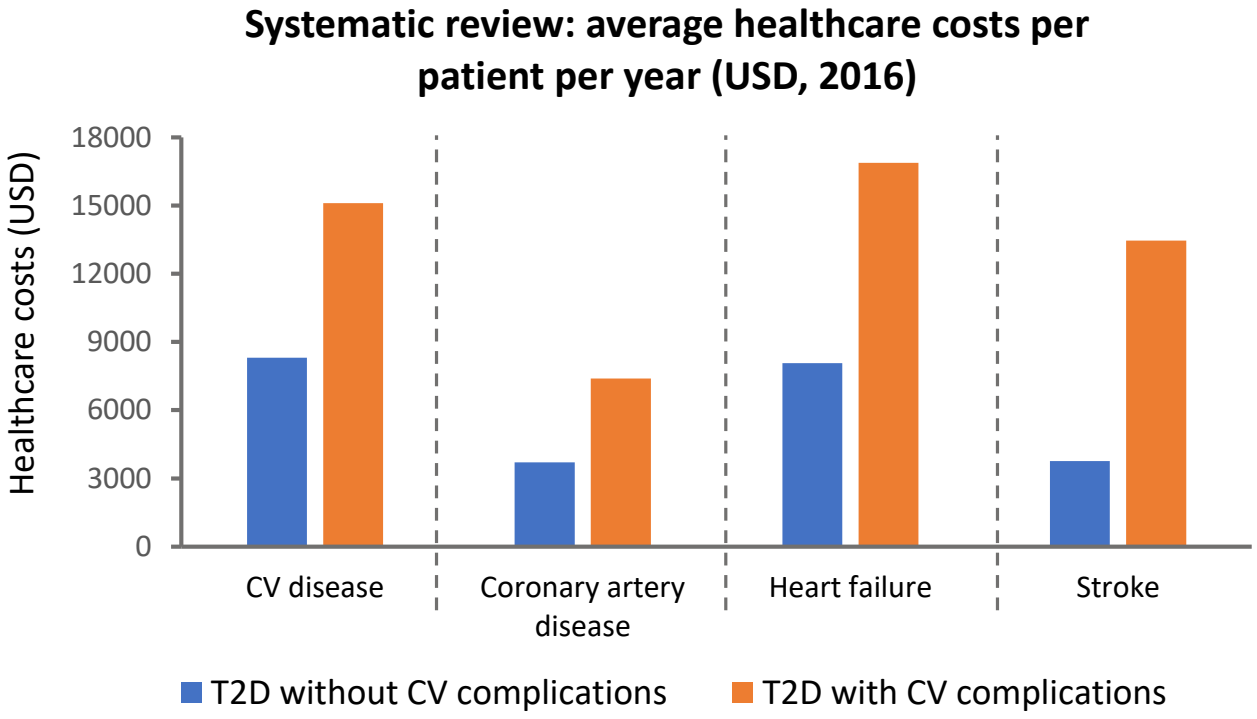
Cost drivers in diabetes

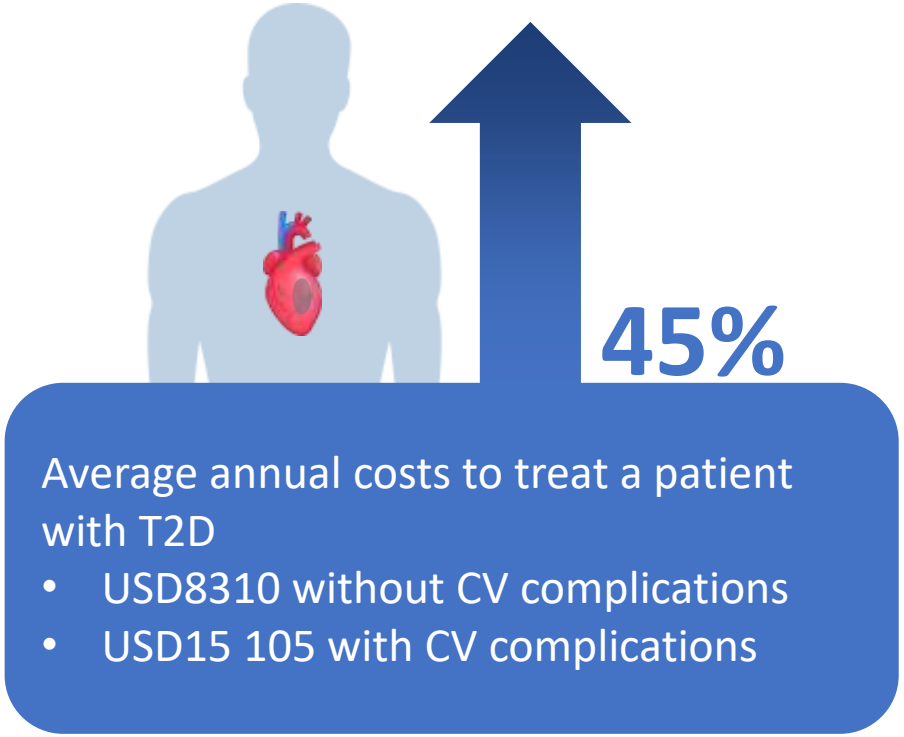
- Overall cost of diabetes in UK in 2010/11: £23.7bn
- £9.8bn related to direct costs; £13.9bn indirect costs



Hex et al. *Diabetic Medicine* 2012;29:855–62.

CV disease contributes 20–49% of total direct costs of treating T2D globally[1]



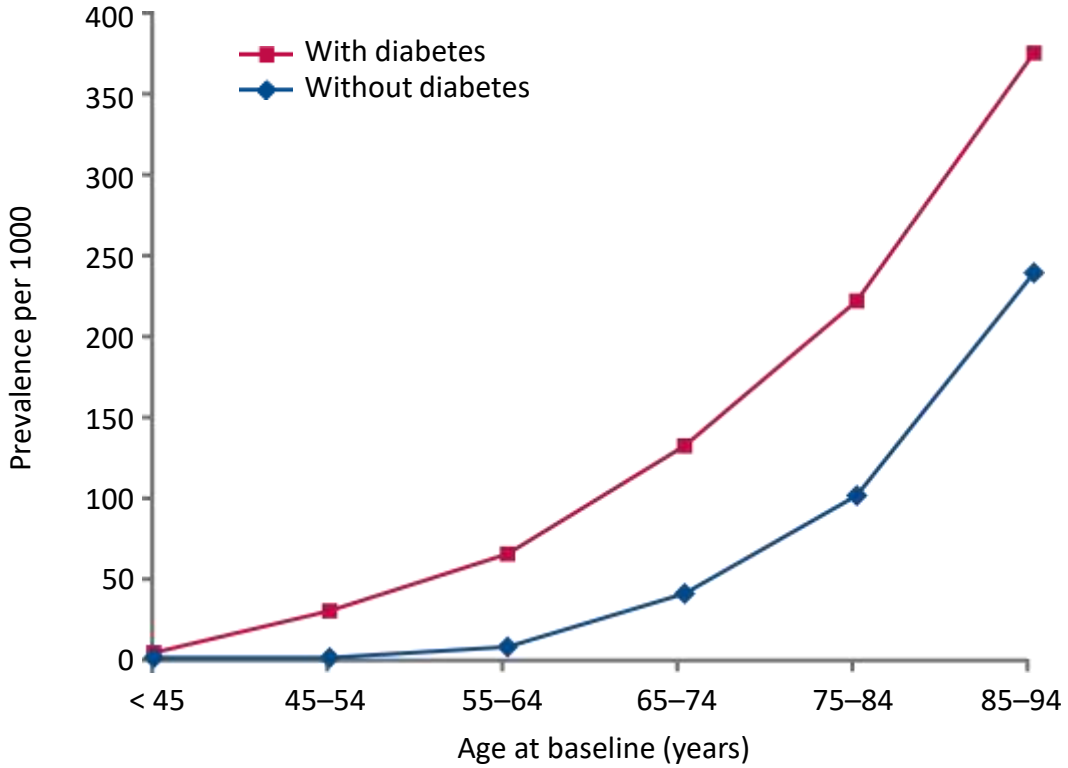


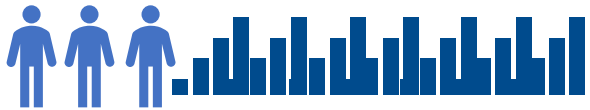
CV, cardiovascular; USD, US dollar

1. Einarson TR *et al. Value Health* 2018;21:881–90

Diabetes and heart failure often go hand in hand

Age-associated prevalence of heart failure in individuals with and without diabetes[1]



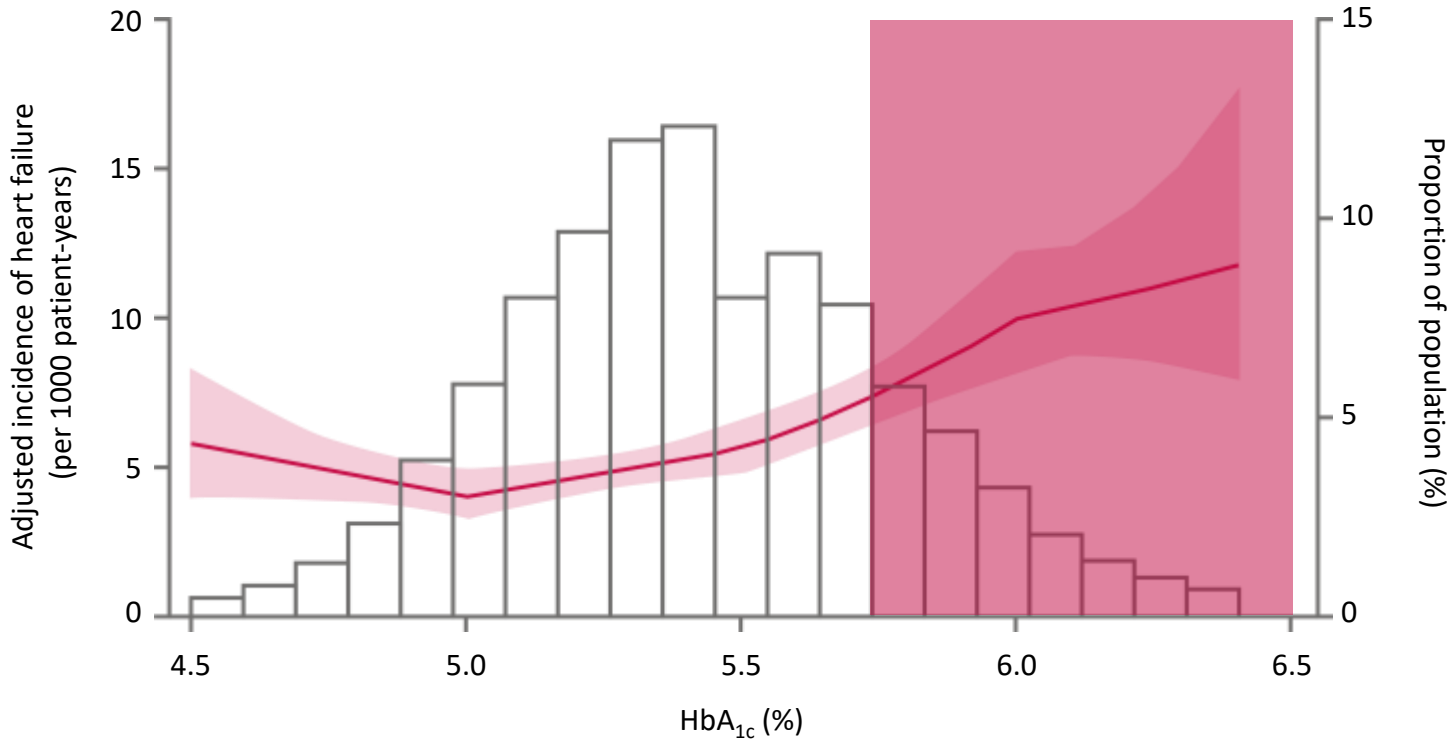


10–30% of patients with T2D also have heart failure[2]

Approximately 30% of all patients with heart failure also have T2D[2]

1. Gilbert RE *et al. Lancet* 2015;385:2107–17; 2. Seferovic PM *et al. Eur J Heart Failure* 2018;20:853–72

An increase in heart failure risk is observed in patients with pre-diabetes[1]

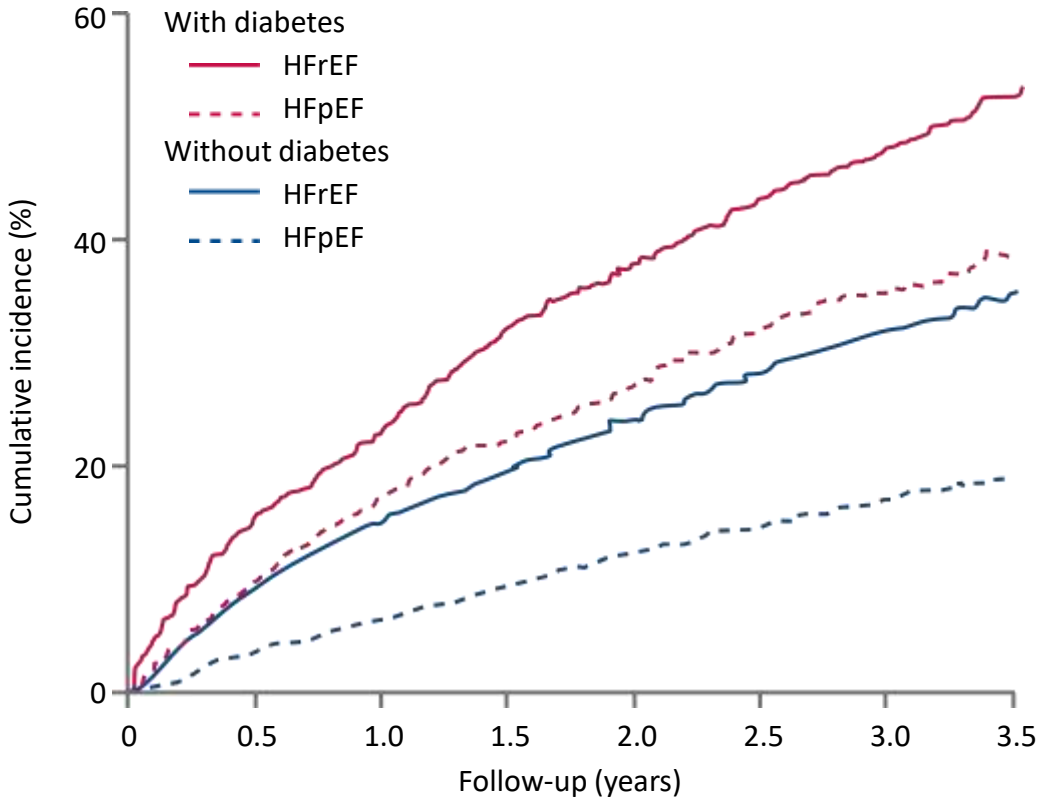


Risk of heart failure begins to rise steeply in patients with pre-diabetes (HbA_{1c} < 5.7%)

1. Matsushita K *et al. Diabetes* 2010;59:2020–6

Heart failure prognosis is worse in patients with diabetes than in patients without diabetes[1]

CV death or hospitalization due to heart failure in patients with diabetes stratified by ejection fraction category



Heart failure with **reduced** ejection fraction
HR 1.60
95% CI 1.44–1.77
$p < 0.0001$

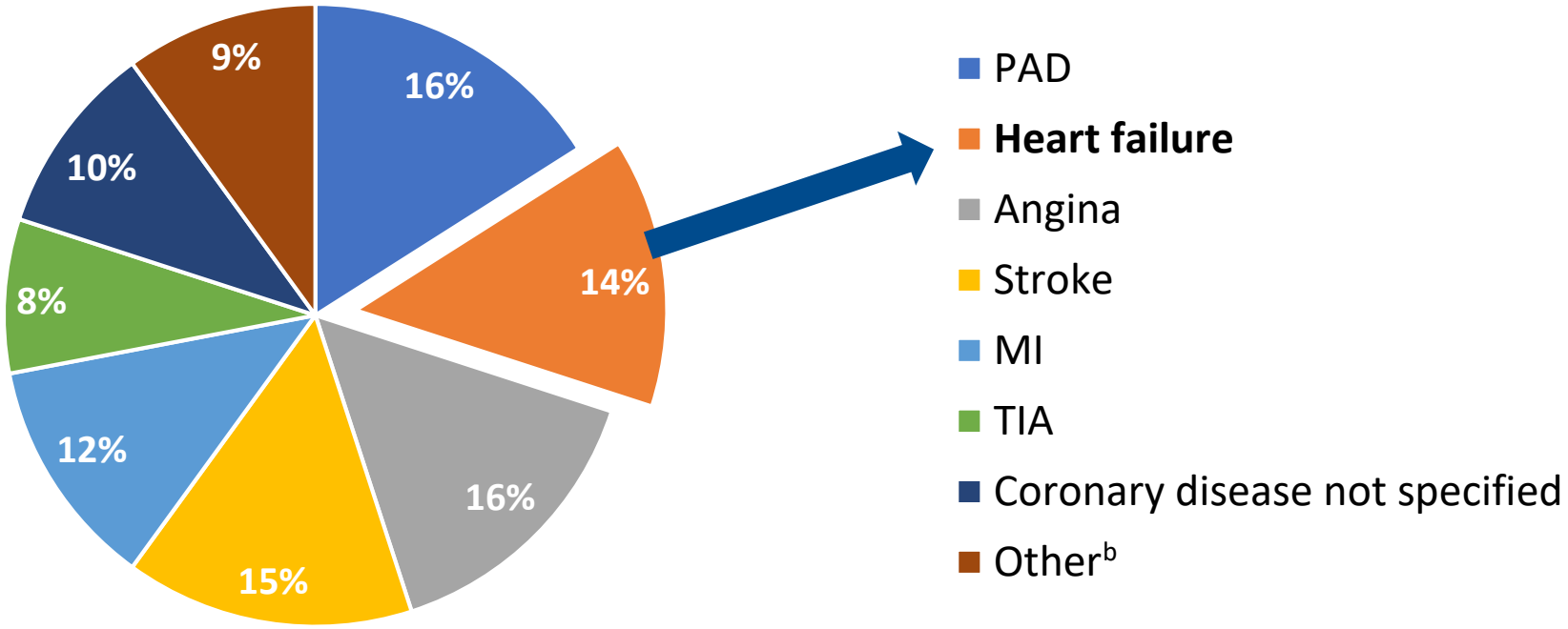
Heart failure with **preserved** ejection fraction
HR 2.0
95% CI 1.70–2.36
$p < 0.0001$

CI, confidence interval; CV, cardiovascular; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio

1. MacDonald MR *et al. Eur Heart J* 2008;29:1377

Heart failure is an under-recognized complication of T2D

Distribution of initial presentation of CV disease in patients with T2D[a,1]

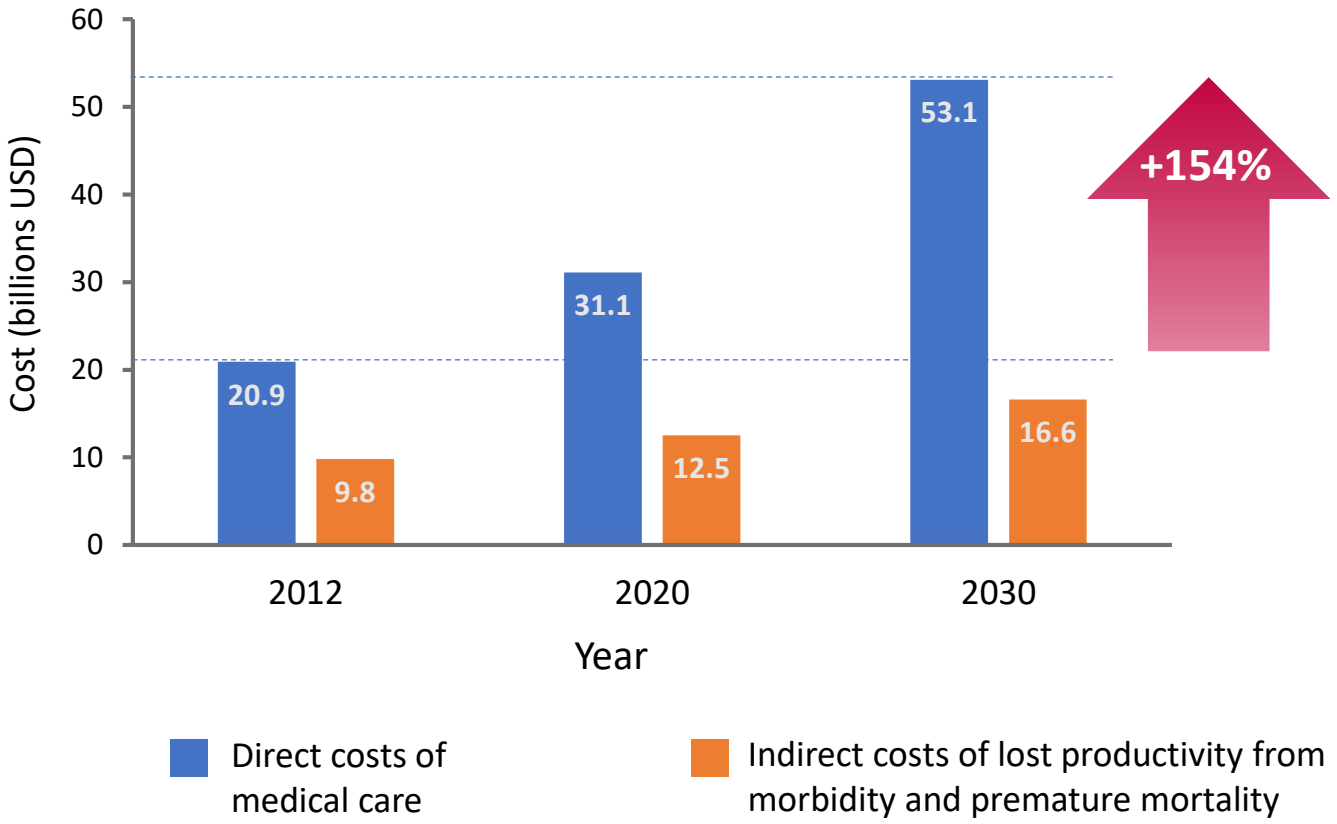


[a]N = 6137 events; [b]Unheralded CV death, abdominal aortic aneurysm, intercranial haemorrhage, subarachnoid haemorrhage, arrhythmia or sudden CV death

CV, cardiovascular; HFpEF, heart failure with preserved ejection fraction; MI, myocardial infarction; PAD, peripheral artery disease; TIA, transient ischaemic attack

1. Shah AD *et al. Lancet Diabetes Endocrinol* 2015;3:105–13; 2. Altara R *et al. Front Endocrinol* 2017;8:160

The cost of treating heart failure is expected to rise over the coming decades[1]



By 2030, **one in every 33** people in the USA is projected to have heart failure

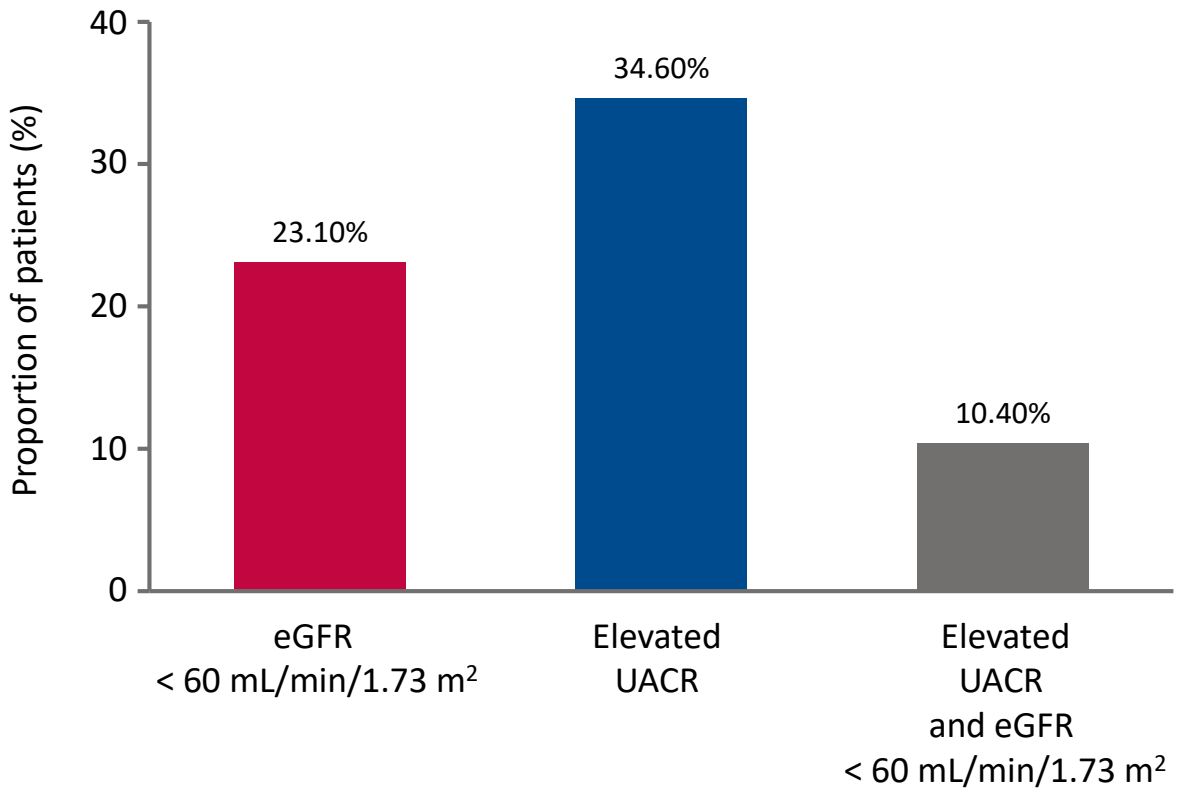
The total direct and indirect costs of treating heart failure are expected to rise to ~ **USD70 billion** by 2030

USD, US dollar

1. Heidenreich PA *et al. Circ Heart Fail* 2013;6:606–19

Kidney disease is one of the most common complications of T2D

Prevalence of CKD in patients with T2D in a primary care setting[1]



N = 3893[1]
Primary care setting in Australia
Elevated UACR defined as
≥ 2.5 mg/mmol for men or
≥ 3.5 mg/mmol for women

In the UK, USA and Australia, incidence of ESRD is broadly stable[2]

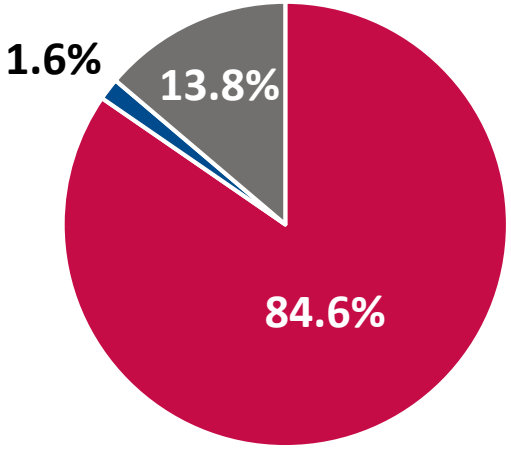
In Asia, incidence of ESRD is increasing[2]

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; UACR, urine albumin:creatinine ratio

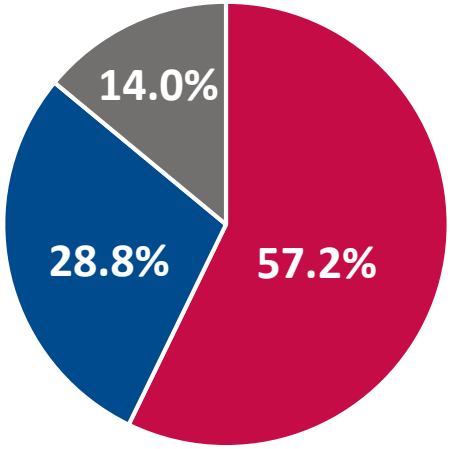
1. Thomas MC *et al. Med J Aust* 2006;185:140–4; 2. Harding JL *et al. Diabetologia* 2019;62:3–19

Most patients with moderate-to-severe CKD in England are managed in primary care[1]

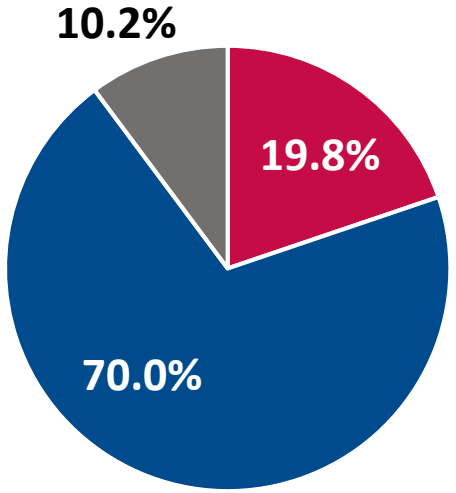
Patients with stage 3 CKD
(eGFR 30–60 mL/min/1.73 m^2)



Patients with stage 4 CKD
(eGFR 15–29 mL/min/1.73 m^2)



Patients with stage 5 CKD
(eGFR < 15 mL/min/1.73 m^2)



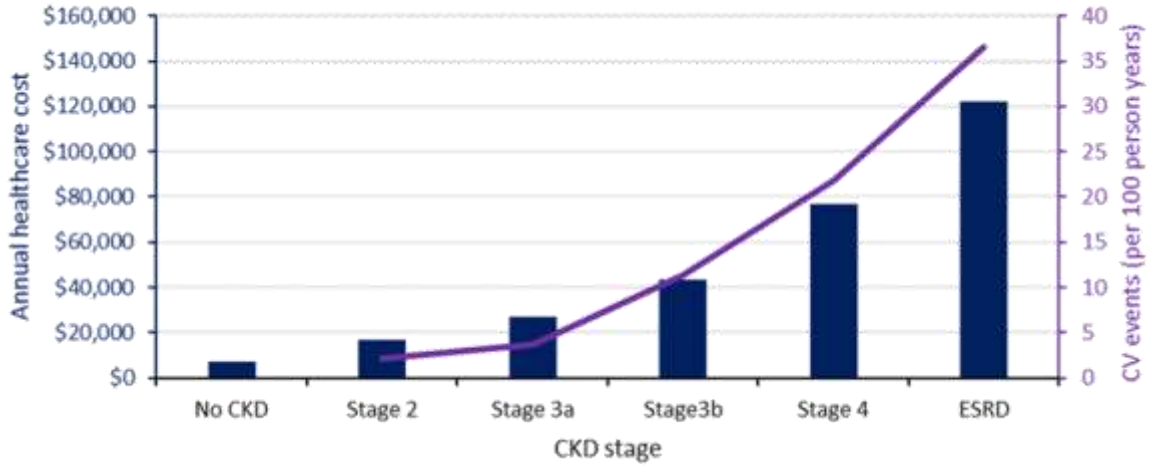
Managed in primary care
Managed by nephrologist
Managed in secondary care

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate

1. Personal communication. Data from NHS England

Kidney function and cost

- Risk of adverse outcomes increases with CKD progression
- Delaying CKD progression will result in fewer adverse events, lower disease management and monitoring costs, and therefore increased capacity

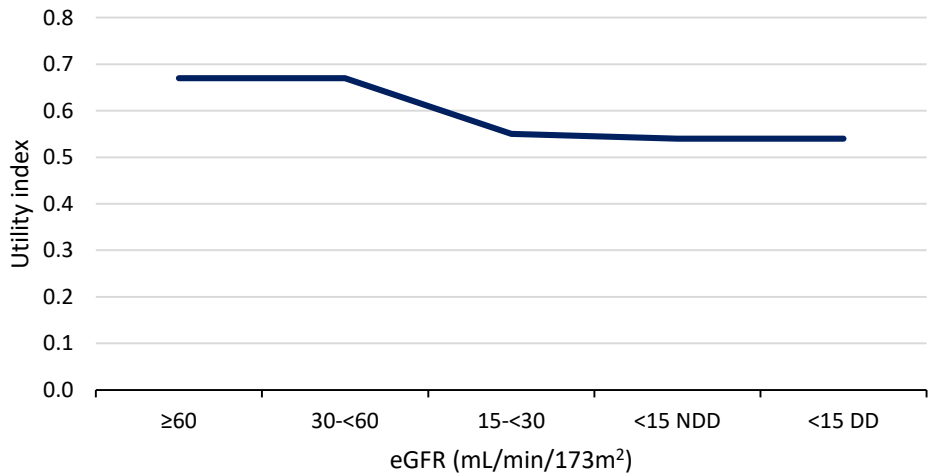


CKD: chronic kidney disease; ESRD: end-stage renal disease; MACE: major adverse cardiac event

Go et al. N Engl J Med (2004) 351:1296-305
Golestaneh et al. Am J Managed Care (2017) 23(10 Suppl):S163-S172

Quality of life and kidney function

- Measures of HRQoL are reduced in patients with renal impairment
- Patients with late stage CKD (4 onwards) experience large reductions in HRQoL
- Reduced incidence of MACE and mortality also improve HRQoL and life expectancy respectively



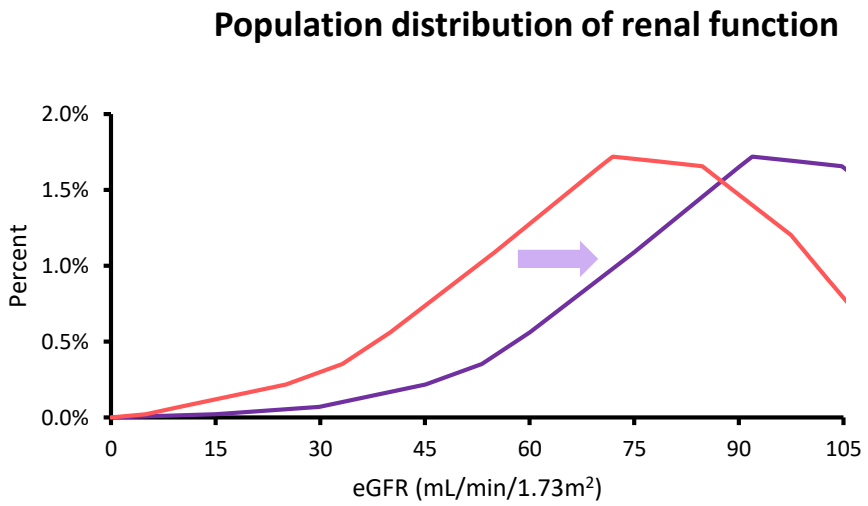
CKD: chronic kidney disease; DD: dialysis dependent; ESRD: end-stage renal disease; HRQoL: health related quality of life; NDD: non-dialysis dependent

Gorodetskaya et al. Kidney Int. 2005 Dec;68(6):2801-8
Go et al. N Engl J Med 2004; 351:1296-1305

The value of improving renal function

Policies that support earlier diagnosis and management of CKD at a population level may result in reduced disease burden

- Attenuating CKD progression
- Reductions in incidence of MACE and end-stage renal disease

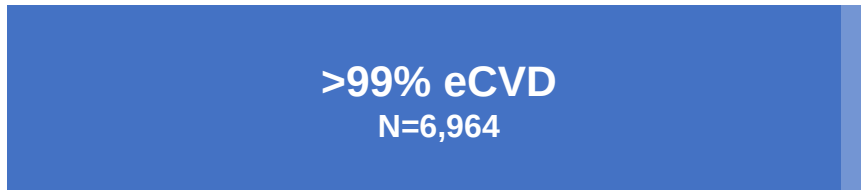


CKD: chronic kidney disease; MACE: major adverse cardiac event

DECLARE has the largest proportion and numbers of T2D patients at low CV risk among the SGLT-2i CV outcomes studies to date

In the T2D patient population, most patients do not have established CV disease[1]

EMPA-REG OUTCOME[2]



(N=7,020)

Placebo event rate
43.9/1000 pt-yrs

CANVAS[3]

(N=10,142)

Placebo event rate
31.5/1000 pt-yrs

DECLARE[4,5]

(N=17,160)

Placebo event rate
24.2/1000 pt-yrs

	DECLARE	CANVAS	EMPA-REG
eGFR, mean (mL/min/1.73m^2)	**85.2**	76.5	74.1
Micro-/macro-albuminuria (%)	**30.2**	30.2	40.6

CV, cardiovascular; eCVD, established CV disease; SGLT-2i, sodium glucose co-transporter 2 inhibitor; T2D, type 2 diabetes

1. Einarson TR, et al. *Cardiovasc Diabetol* 2018;17:83; 2. Zinman B, et al. *N Engl J Med* 2015;373:2117–2128; 3. Neal B, et al. *N Engl J Med* 2017;377:644–657;
4. Raz I, et al. *Diabetes Obes Metab* 2018;20:1102–1110 5. Wiviott SD et al. Online ahead of print. N Engl J Med. 2018

Modifiable risk factors were addressed in patients with T2D in SGLT2i CV outcomes trials

Management of modifiable risk factors in SGLT2i CV outcomes trial populations[1–5]

Statin use ranged from 75–81% of patients across CVOTs[1–4a]

Anti-thrombotic use ranged from 61–90% of patients across CVOTs[1–4a]

RAS-inhibitor use ranged from 80–81% of patients across CVOTs[1–4a]

β-blocker use ranged from 53–69% of patients across CVOTs[1–4a]

Diuretic use ranged from 41–45% of patients across CVOTs[1–4a]

Total cholesterol[1,2,4,5,b]

Range: 4.2–4.4 mmol/L

Blood pressure[1–4,a]

Systolic range: 133–137
Diastolic range: 77–78

Obesity (BMI)[1–4,a]

30.7–32.0 kg/m²

HbA_{1c}[1–4,a]

8.1–8.3%
(65–67 mmol/mol)

[a]Average of placebo-group populations from CANVAS Program, DECLARE-TIMI 58, EMPA-REG OUTCOME and overall population for VERTIS CV, CV outcomes trials [b]Average of placebo-group populations from CANVAS Program, EMPA-REG Outcome and overall population for DECLARE-TIMI 58 and VERTIS CV. BMI; BMI, body mass index; CV, cardiovascular, RAS, renin–angiotensin system

1. Zinman B *et al. N Engl J Med* 2015;373:2117–28; 2. Neal B *et al. N Engl J Med* 2017;377:644–57; 3. Wiviott SD *et al. N Engl J Med* 2019;380:347–57; 4. Cannon CP *et al. Am Heart J* 2018;206:11–23; 5. Raz I *et al. Diabetes Obes Metab* 2018;20:1102–10.

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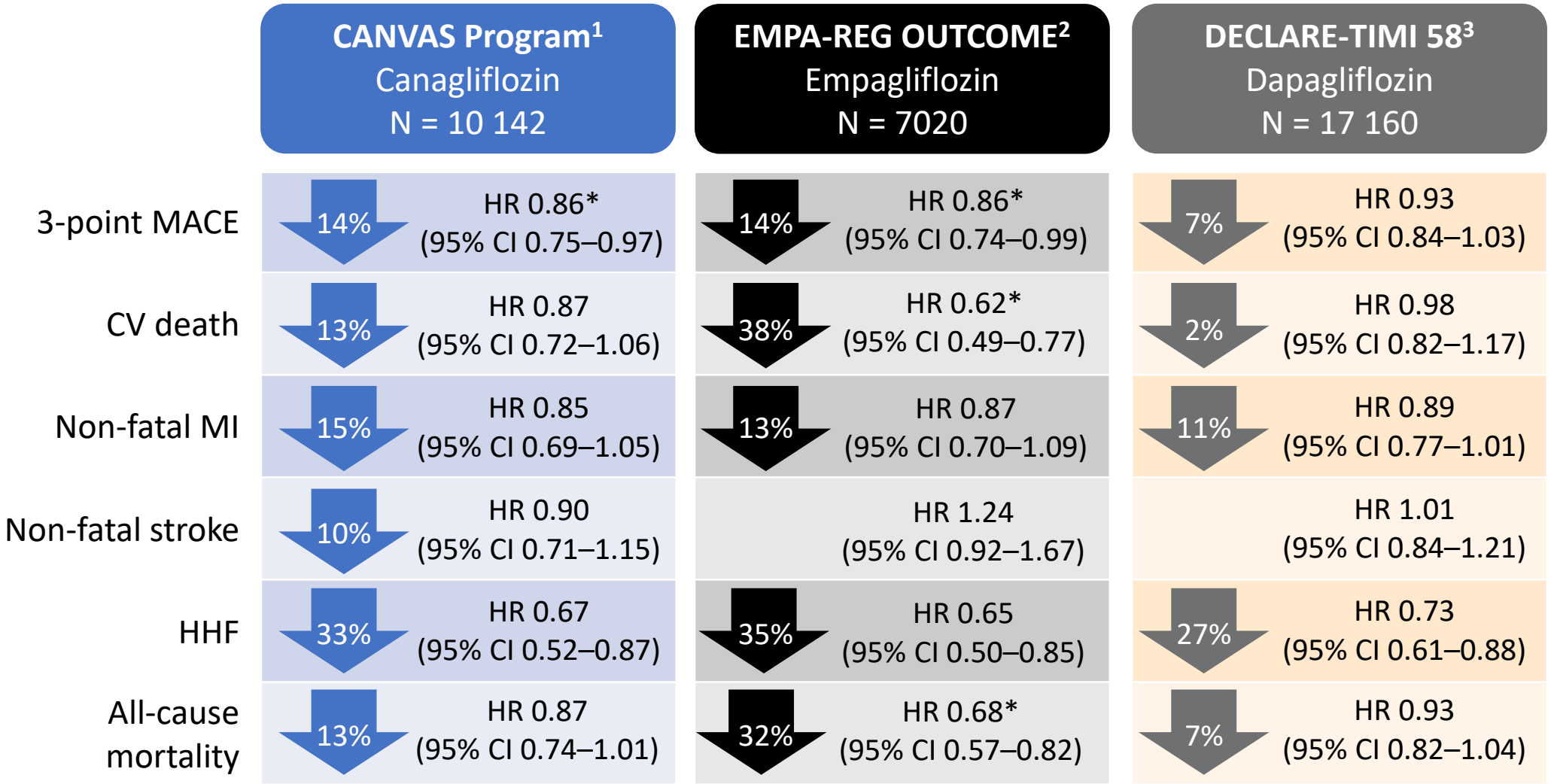
CV outcomes in SGLT2i CV outcomes trials



**p* < 0.05 for superiority versus placebo. CI, confidence interval; CV, cardiovascular; HHF, hospitalization for heart failure; HR, hazard ratio; MACE, major adverse cardiovascular events; MI, myocardial infarction

1. Neal B *et al. N Engl J Med* 2017;377:644–57; 2. Zinman B *et al. Stroke* 2017;48:1218–25; 3. Wiviott SD *et al. N Engl J Med* 2019;380:347–57

ADA/EASD 2018 consensus for glucose-lowering medication in T2D

The ADA/EASD report is a consensus statement and should not be used as guidance

FIRST-LINE THERAPY IS METFORMIN AND COMPREHENSIVE LIFESTYLE (INCLUDING WEIGHT MANAGEMENT AND PHYSICAL ACTIVITY)
IF HbA_{1c} ABOVE TARGET PROCEED AS BELOW

To avoid clinical inertia reassess and modify treatment regularly (3–6 months)

Established ASCVD or CKD

ASCVD predominates

GLP-1RA with proven CVD benefit* **EITHER /OR** SGLT-2i with proven CVD benefit*, if eGFR adequate†

If HbA_{1c} above target

If further intensification is required or patient is now unable to tolerate GLP-1RA and/or SGLT-2i, choose agents demonstrating CV safety:

- Consider adding the other class (GLP-1RA and/or SGLT-2i) with proven CVD benefit
- DPP-4i if not on GLP-1RA
- Basal insulin§
- TZD¶
- SU||

HF OR CKD predominates

PREFERABLY

SGLT-2i with evidence of reducing HF and/or CKD progression in CVOT if eGFR adequate‡

OR

If SGLT-2i not tolerated or contraindicated or if eGFR less than adequate† add GLP-1RA with proven CV benefit*

If HbA_{1c} above target

- Avoid TZD in the setting of HF

Choose agents demonstrating CV safety:

- Consider adding the other class with proven CVD benefit*
- DPP-4i (not saxagliptin) in the setting of HF (if not on GLP-1RA)
- Basal insulin§
- SU||

NO

Without established ASCVD or CKD

Compelling need to minimise hypoglycaemia

DPP-4i	GLP-1RA	SGLT-2i†	TZD
If HbA_{1c} above target			
SGLT-2i† **OR** TZD	SGLT-2i† **OR** TZD	GLP-1RA **OR** DPP-4i **OR** TZD	SGLT-2i† **OR** DPP-4i **OR** GLP-1RA

If HbA_{1c} above target

Continue with addition of other agents as outlined above

If HbA_{1c} above target

Consider the addition of SU|| **OR** basal insulin:

- Choose later generation SU with lower risk of hypoglycaemia
- Consider basal insulin with lower risk of hypoglycaemia#

Compelling need to minimise weight gain or promote weight loss

GLP-1RA with good efficacy for weight loss** **EITHER /OR** SGLT-2i†

If HbA_{1c} above target

SGLT-2i† | GLP-1RA with good efficacy for weight loss**

If HbA_{1c} above target

If triple therapy required or SGLT-2i and/or GLP-1RA not tolerated or contraindicated use regimen with lowest risk of weight gain

PREFERABLY

DPP-4i (if not on GLP-1RA) based on weight neutrality

If DPP-4i not tolerated or contraindicated or patient already on GLP-1RA cautious addition of:

• SU|| • TZD¶ • Basal insulin

Cost is a major issue††‡‡

SU|| | TZD‡‡

If HbA_{1c} above target

TZD‡‡ | SU||

If HbA_{1c} above target

- **Insulin therapy** basal insulin with lowest acquisition cost

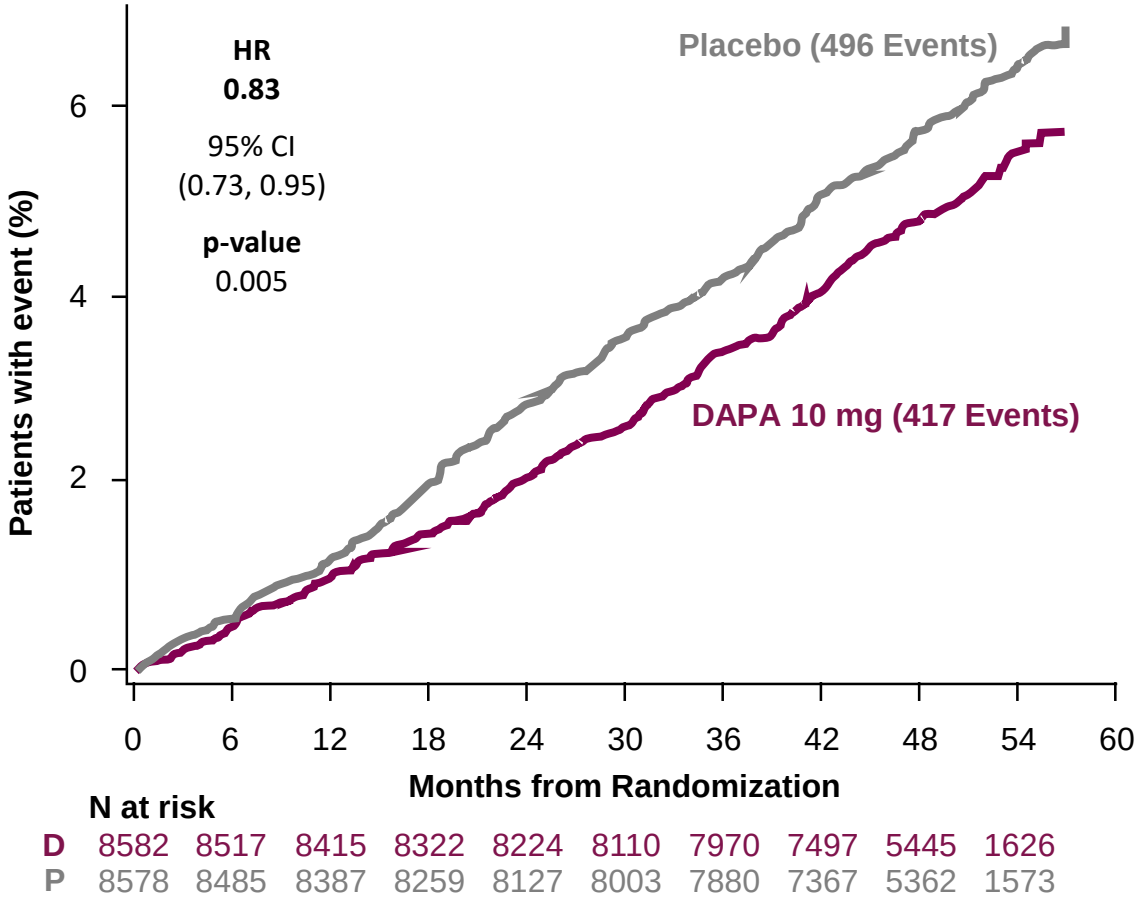
OR

- Consider DPP-4i **OR** SGLT-2i with lowest acquisition cost‡‡

*Proven CVD benefit means it has label indication of reducing CVD events. For SGLT-2i evidence modestly stronger for empagliflozin>canagliflozin; †Be aware that SGLT-2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use; ‡Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVOTs; §Degludec or U100 glargine have demonstrated CVD safety; ¶Low dose may be better tolerated though less well studied for CVD effects; ||Choose later generation SU with lower risk of hypoglycaemia; #Degludec / glargine U300<glargine U100 / detemir<NPH insulin; ††If no specific comorbidities (i.e. no established CVD, low risk of hypoglycaemia and lower priority to avoid weight gain or no weight-related comorbidities); ‡‡Consider country- and region-specific cost of drugs. In some countries, TZDs relatively more expensive and DPP-4i relatively cheaper

In this low CV risk population, dapagliflozin patients had a significant reduction of hHF/CV death events and fewer MACE events and compared to placebo

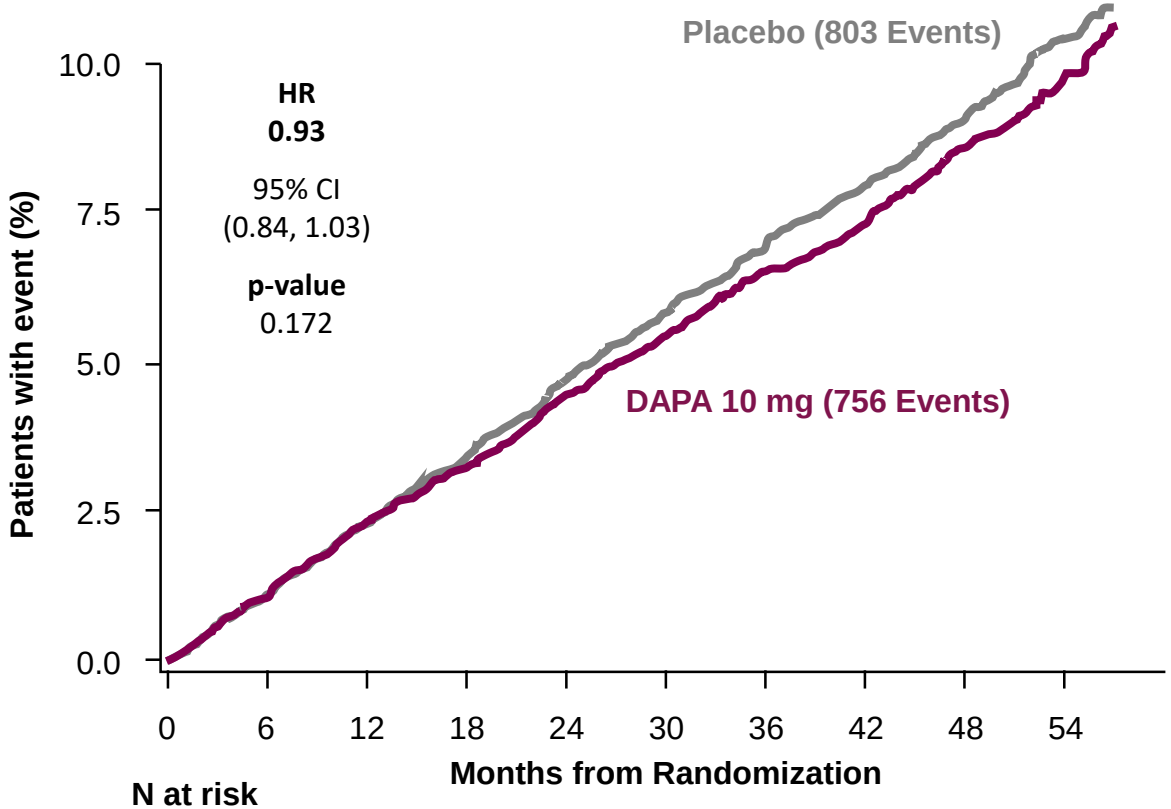
hHF/CVD



N at risk

D	8582	8517	8415	8322	8224	8110	7970	7497	5445	1626
P	8578	8485	8387	8259	8127	8003	7880	7367	5362	1573

MACE



N at risk

D	8582	8466	8303	8166	8017	7873	7708	7237	5225	1548
P	8578	8433	8281	8129	7969	7805	7649	7137	5158	1501

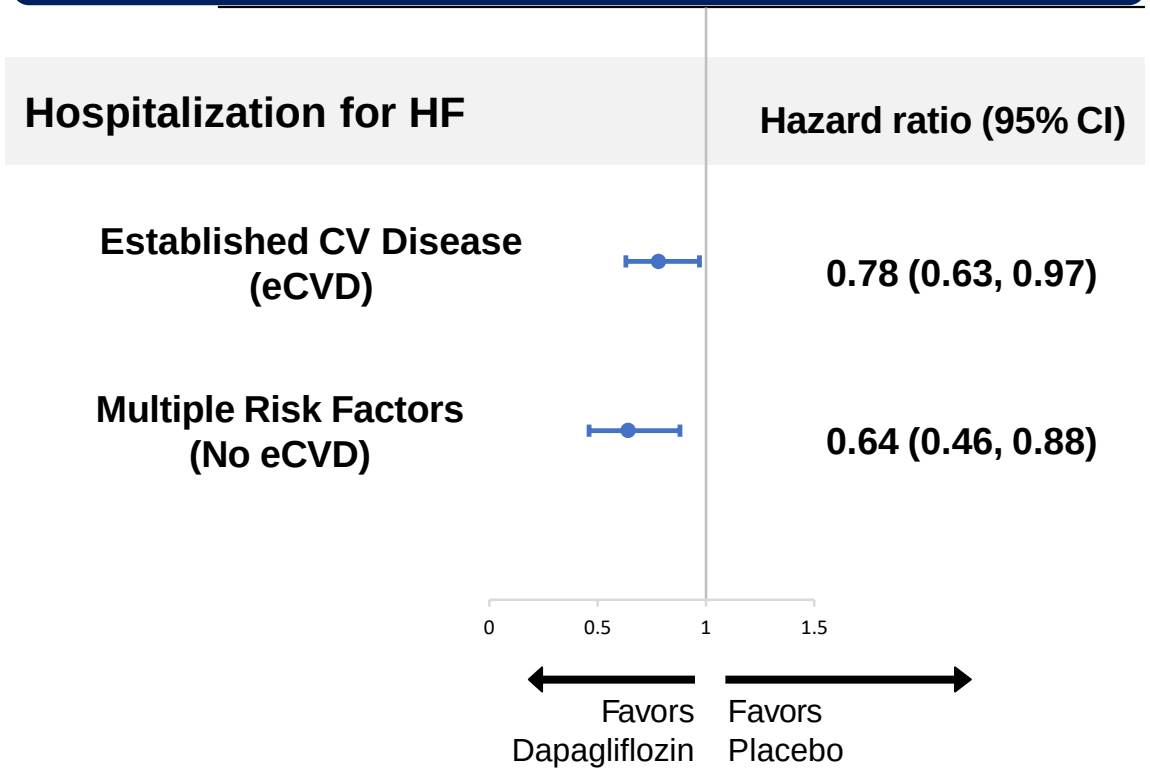
N at risk is the number of subjects at risk at the beginning of the period. 2-sided p-value is displayed; HR, CI, and p-value are from cox proportional hazard model.

CV, cardiovascular; Dapa, dapagliflozin; hHF, hospitalization for heart failure; MACE, major adverse cardiac event

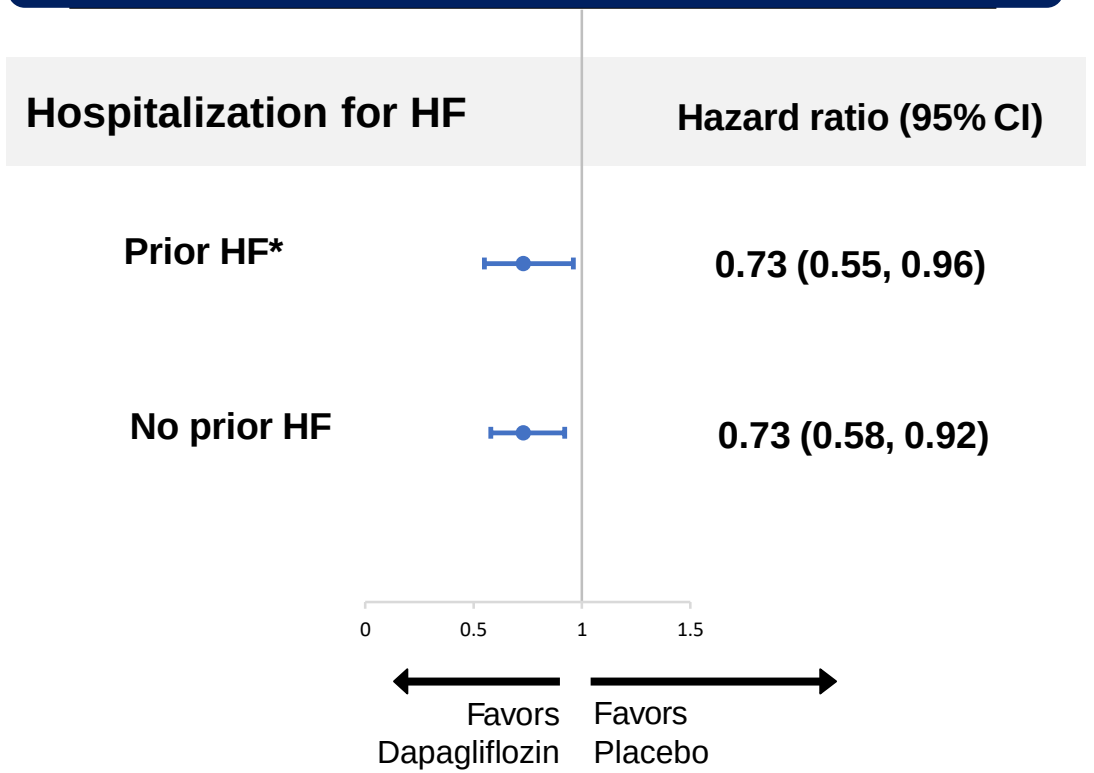
Wiviott SD et al. Online ahead of print. *N Engl J Med*. 2018;

Dapagliflozin prevents hHF consistently across a broad range of T2D patients regardless of history of eCVD or HF

hHF by presence/absence of eCVD



hHF by presence/absence of previous HF



***10% of patients in DECLARE had prior HF**

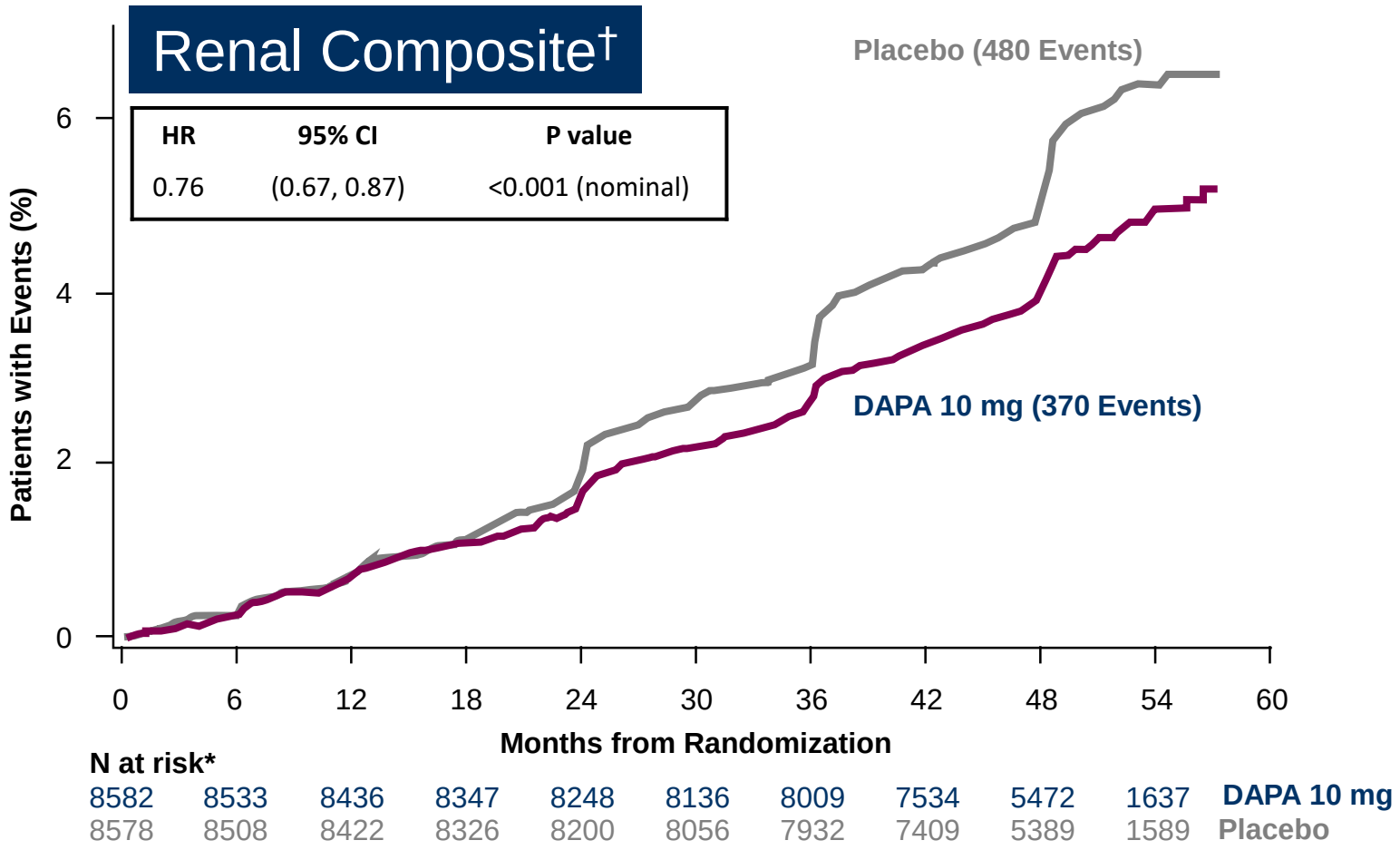
CV, cardiovascular; eCVD, established CV disease; HF, heart failure; hHF, hospitalized heart failure; SGLT-2i, SGLT co-transporter 2 inhibitor; T2D, type 2 diabetes

Wiviott SD et al. Online ahead of print. *N Engl J Med*. 2018

Dapagliflozin slowed renal disease progression in T2D patients with relatively good baseline renal function

The patients in the DECLARE[1,2] trial had better baseline renal function than the EMPA-REG OUTCOME[3] or CANVAS[4] trials

	DECLARE	CANVAS	EMPA-REG
eGFR, mean (mL/min/1.73m^2)	**85.2**	76.5	74.1
Micro-/macro-albumin-uria (%)	**30.2**	30.2	40.6



†Renal composite endpoint defined as sustained confirmed eGFR decrease ≥ 40% to eGFR < 60 ml/min/1.73m^2 using CKD-EPI equation and/or ESRD (dialysis ≥ 90 days or kidney transplantation, sustained confirmed eGFR < 15 ml/min/1.73m^2) and/or renal or CV death (pre-specified secondary outcome)

CV, cardiovascular; CKD, chronic kidney disease; Dapa, dapagliflozin; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease

1. Raz I, et al. *Diabetes Obes Metab* 2018;20:1102–1110; 2. Wiviott SD et al. Online ahead of print. *N Engl J Med*. 2018; ; 3. Zinman B, et al. *N Engl J Med* 2015;373:2117–2128; 4. Neal B, et al. *N Engl J Med* 2017;377:644–657

Heart failure is expensive!

- Heart failure hospitalization accounts for –

1 Million hospital bed days

2% of all NHS inpatient bed days

Costs around £2bn (2% of the total NHS budget)

- 81,400 Emergency admissions annually
- Commonest cause for admission in people > 65 years of age
- A GP will typically make **10 NEW** heart failure diagnoses annually and look after around 30 patients with heart failure
- Heart failure drug costs £150 M per year

https://www.nice.org.uk/guidance/ng106/resources/resource-impact-report-pdf-6537494413

Estimating the economic implications of the DECLARE TIMI 58 data

Type 2 diabetes economic estimates -

- Mean HHF LOS – 10 days [1]
- HHF event cost - £3,153.56 [2]
- HHF maintenance costs (6 months only) - £1308.72 [2]
- ESRD cost of care (6 months only) - £18931.06 [3,4]

DECLARE TIMI 58 includes a cohort of people with type 2 diabetes estimated to represent 59 % (range 49 – 73%) in Europe and 39.8% in other settings [5,6]

1. NHS Digital. Hospital Admitted Patient Care Activity, 2017-18.
2. Alva et al. Diabet Med. 2015 Apr;32(4):459-66
3. Lamping et al. Lancet. 2000;356(9241):1543-50.
4. NICE. Type 2 diabetes in adults: management (NG28).
5. Birkeland et al. Diabetes Obes Metab. 2019;21:968–974.
6. Wittbrodt et al. Am J Manag Care. 2018;24:S138-S145

Estimating the economic implications of the DECLARE TIMI 58 data

- Dapagliflozin treatment vs placebo over 4 years per 1,000 patients results in [1] –

8.9 fewer predicted HHF events

1.5 fewer ESRD events

- Dapagliflozin treatment vs placebo over a life time per 1,000 patients results in [1] –

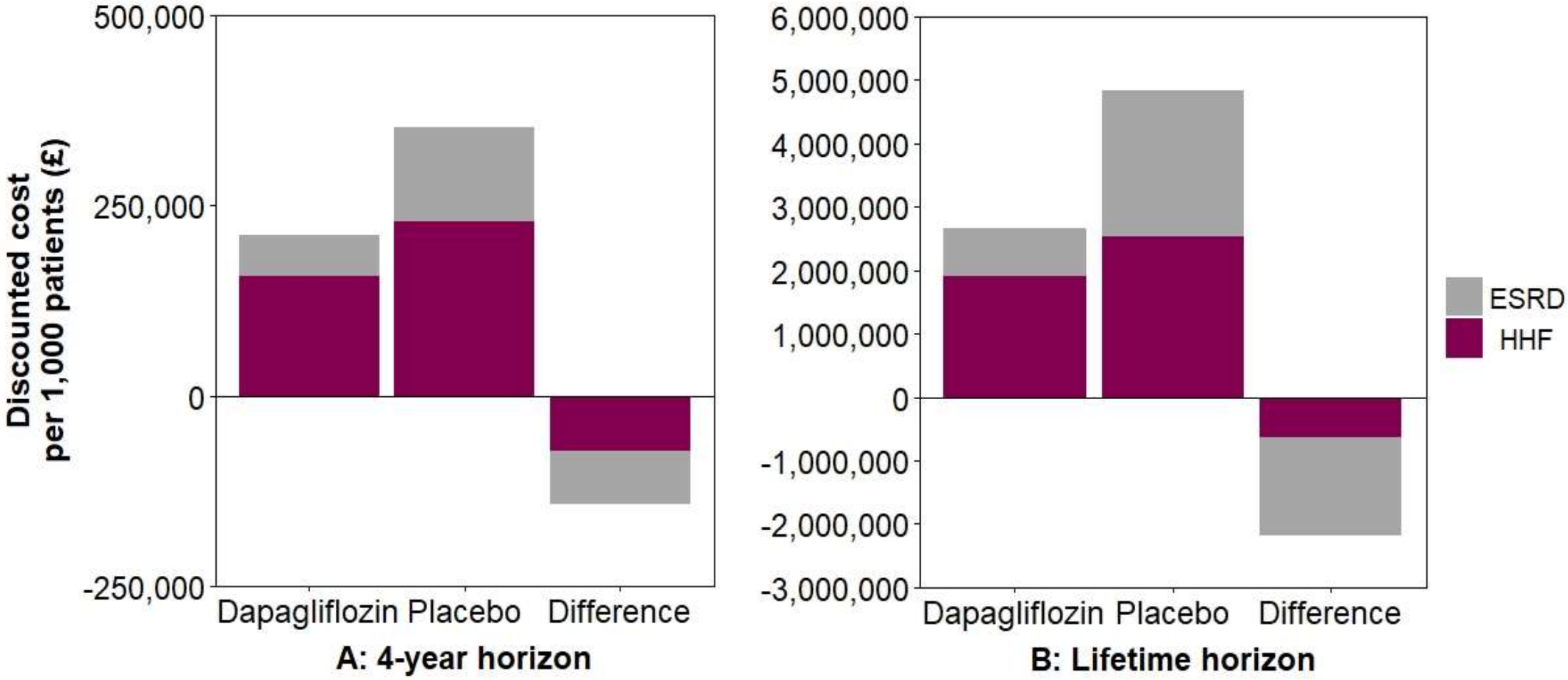
39.5 fewer predicted HHF events

7.2 fewer predicted ESRD events

- As a result of fewer HHF events, a 27% reduction in total HHF-related LOS predicted for dapagliflozin-treated patients compared to placebo, corresponding to the avoidance of 89 inpatient days over 4 years and 395 inpatient days over a lifetime, per 1,000 patient [1]
- Due to reduced incidence of ESRD, estimated time receiving renal replacement therapy more than halved with dapagliflozin compared to placebo: 1.5 versus 3.6 years per 1,000 patients at 4 years and 32.3 versus 100.7 years per 1,000 patients over a lifetime [1].

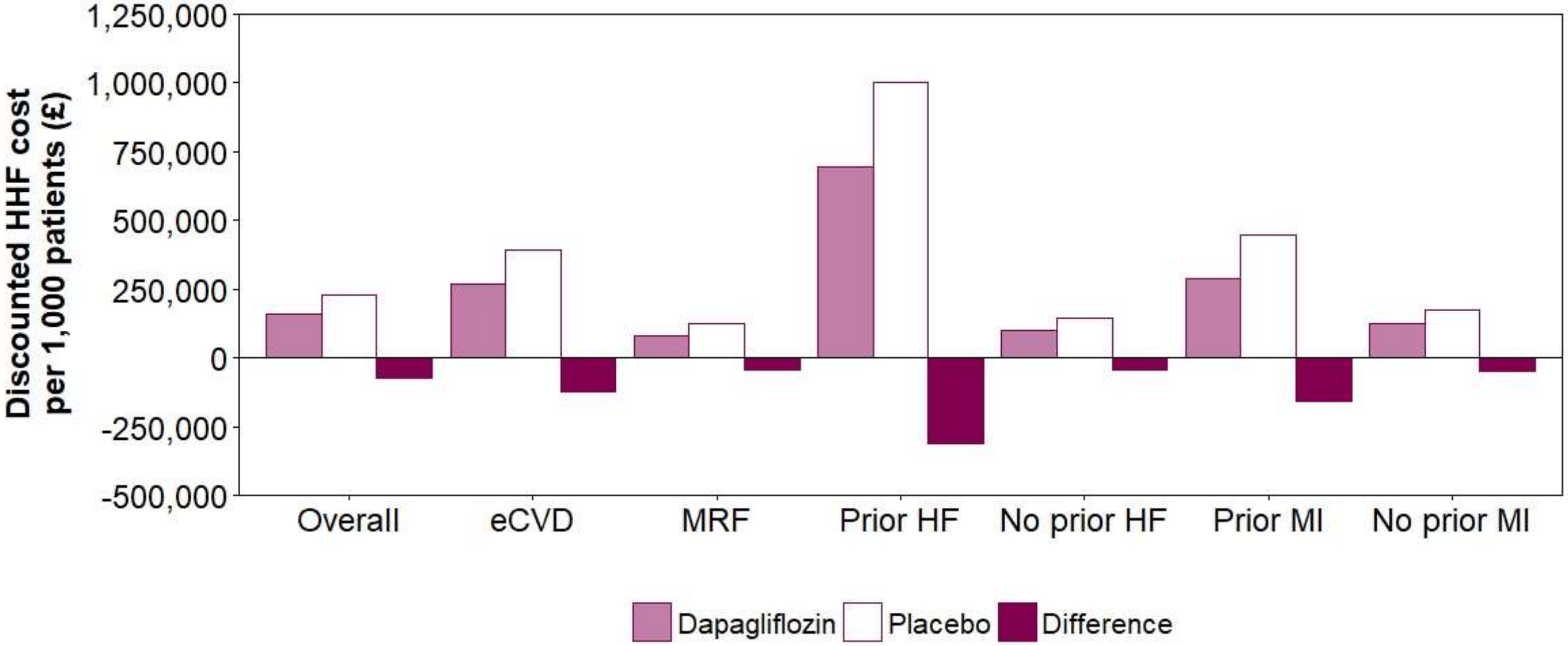
1. *McEwan P816, 55th EASD Annual Meeting, Barcelona, 16-20 September 2019*

Heart failure and kidney disease potential cost savings with Dapagliflozin



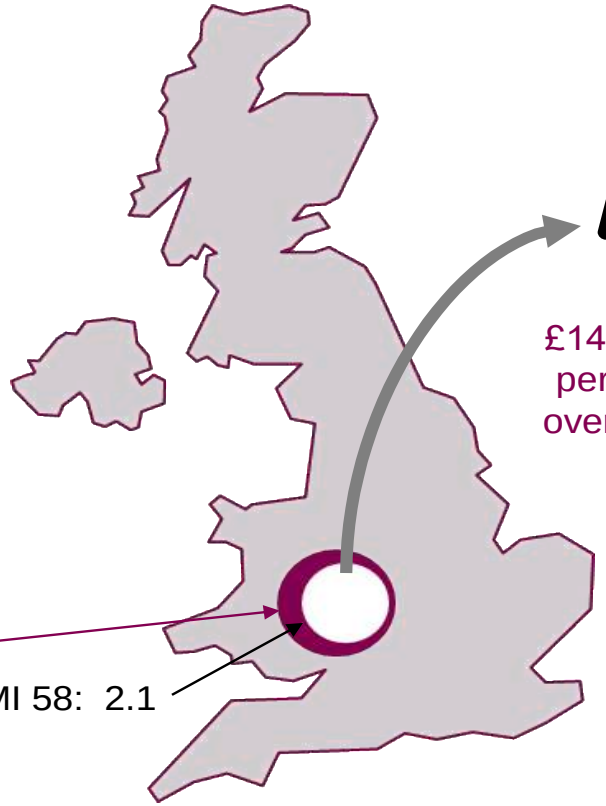
1. *McEwan P816, 55th EASD Annual Meeting, Barcelona, 16-20 September 2019*

Heart failure cost implications by population



1. *McEwan P816, 55th EASD Annual Meeting, Barcelona, 16-20 September 2019*

National cost implications of dapaglflozin over 4 years



Numbers of people (millions):
- People with T2DM: 3.6
- Represented by DECLARE-TIMI 58: 2.1

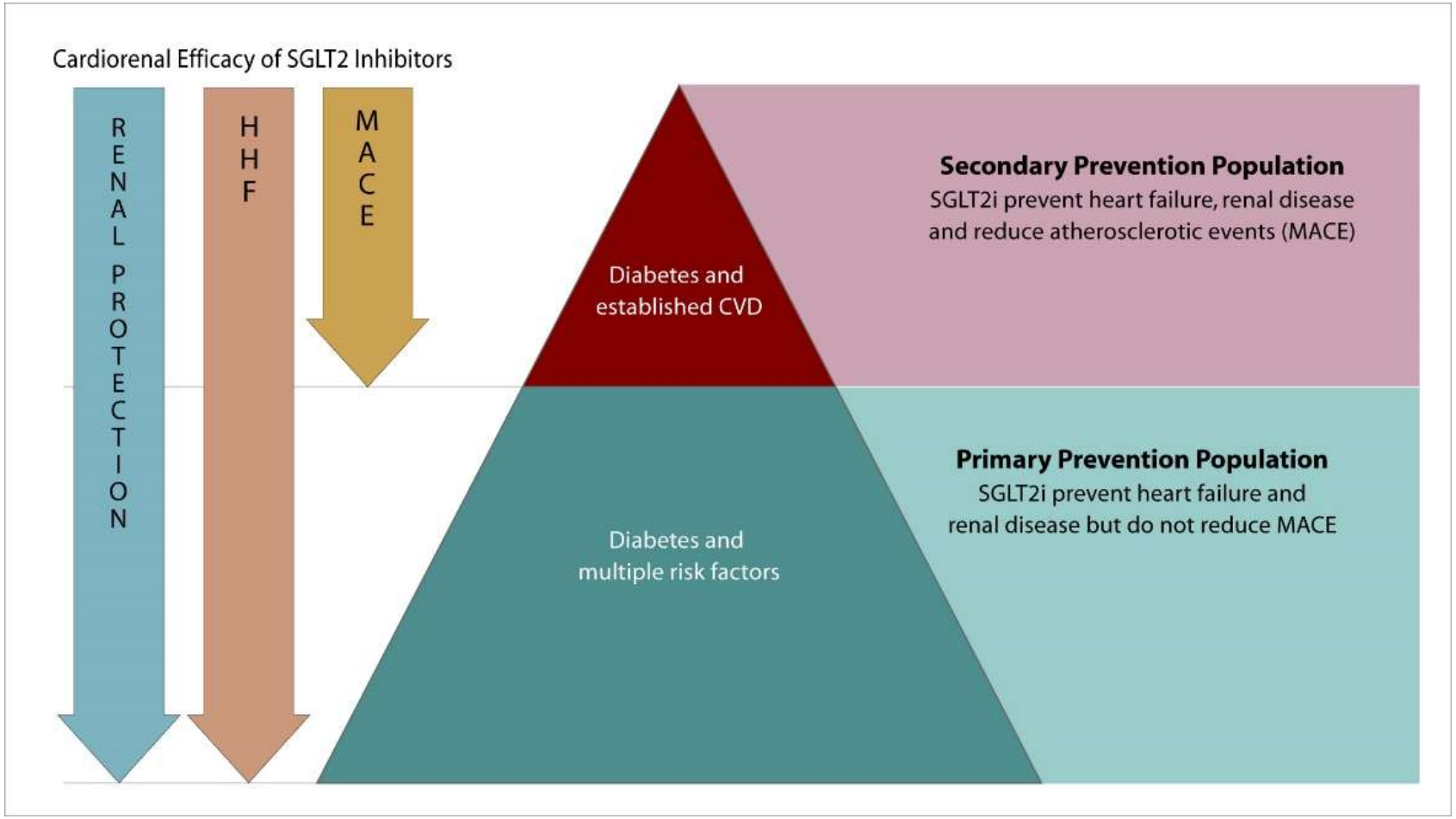
£142 saving per person over 4 years

Avoidance of healthcare resource use and cost savings:

0.2 million inpatient days 4,230 years' RRT provision
£298 million **avoided over 4 years**

1. *McEwan P816, 55th EASD Annual Meeting, Barcelona, 16-20 September 2019*

Conclusion



These data with dapagliflozin from **DECLARE- TIMI 58 extend the benefit of SGLT2i to a broader population of patients** for primary and secondary prevention

Verma S, Jüni P, Mazer CD, The Lancet 2018

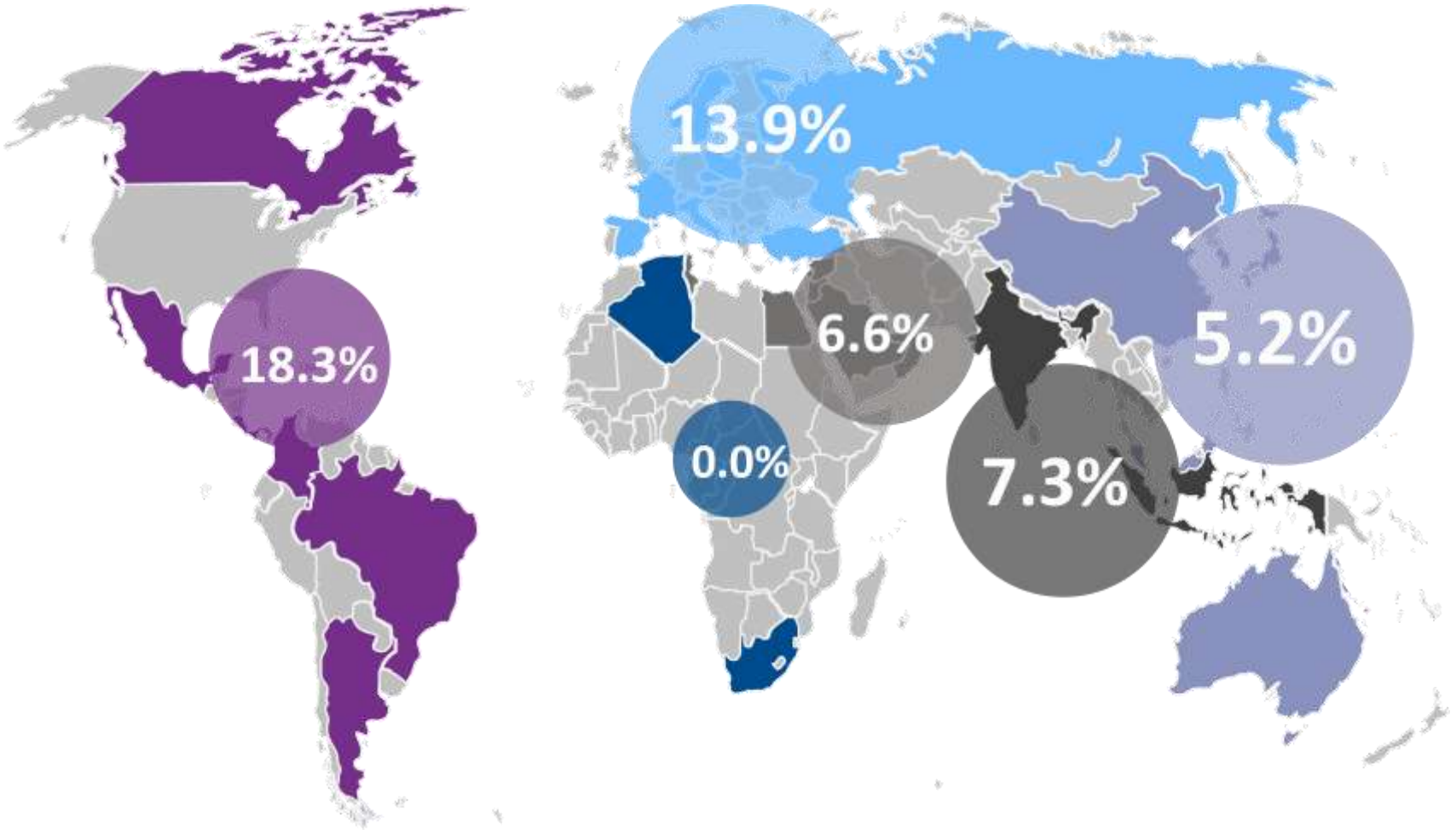
Summary

- Heart failure represents a significant clinical and economic burden in people with type 2 diabetes
- Significant heart failure outcome benefits seen with SGLT-2 inhib itors in a broad patient population
- Translating into clinical, quality of life and economic gains

CV, cardiovascular; HbA1c, glycated haemoglobin; hHF, hospitalized heart failure; MACE, major cardiovascular disease; SGLT-2, sodium-glucose co-transporter 2; T2D, type 2 diabetes

1. Zinman B, et al. N Engl J Med 2015;373:2117–2128; 2. Neal B, et al. N Engl J Med 2017;377:644–657 3. Wiviott SD et al. Online ahead of print. N Engl J Med. 2018.

Clinical use of SGLT2is is increasing but remains limited (DISCOVER)[1]



Uptake of SGLT2is as a second-line therapy at baseline or as a later-line therapy (during the first year of follow-up) was greatest in the Americas between December 2014 and June 2016[1]

1. Kosiborod M *et al*. Poster presented at the 78th Scientific Sessions of the American Diabetes Association. 2018