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

Factors affecting treatment choice

- Individualized HbA$_{1c}$ target
- Complexity of regimen
- CVD profile
- Side-effect profile
- Weight and hypoglycaemia
- Safety
- Adherence and persistence
- Value for money

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
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\textsuperscript{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
\textsuperscript{1} Low Wang CC et al. Circulation 2016;133:2459–502; \textsuperscript{2} England BR et al. BMJ;316:k1036
Long-term outcomes after acute myocardial infarction are worse in patients with diabetes than in those without\textsuperscript{1}

Highlighted areas in Kaplan–Meier curves represent survival improvement within each group between 1995 and 2003.

CI, confidence interval; MI, myocardial infarction

\textsuperscript{1} Cubbon RM \textit{et al.} Eur Heart J 2007;376:540–5
Cardiac remodelling is a feature of T2D

- Hyperglycaemia, insulin resistance, obesity
  - Inflammatory cytokine release from adipose tissue
  - Increased oxidative stress
  - Mitochondrial dysfunction
  - Altered substrate utilization: FFAs used instead of glucose

- Cardiac fibrosis that may reduce myocardial compliance
- Left ventricular hypertrophy

Heart failure

FFA, free fatty acid
Diabetes worsens heart failure prognosis

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

LVEF ≥ 50% (n = 498)

LVEF < 50% (n = 754)

Survival proportion

Time (years)

RR = 1.41; p 0.0322

RR = 1.73; p < 0.0001

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

1. Varela-Roman A et al. Eur J Heart Failure 2005;7:859
Hyperglycaemia and haemodynamic effects lead to structural changes in the kidney

- Inflammation
- Renin–angiotensin system activation
- Oxidative stress

- Thickening of arteriole wall
- Efferent arteriolar occlusion
- Mesangial cell hypertrophy
- Basement membrane thickening

Glomerular hypertension, hyperfiltration, albuminuria, reduced eGFR

eGFR, estimated glomerular filtration rate
CV damage, heart failure and kidney failure are intrinsically linked\textsuperscript{1,2}

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

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

CV disease contributes 20–49% of total direct costs of treating T2D globally\(^1\)

**Systematic review: average healthcare costs per patient per year (USD, 2016)**

- **CV disease**
  - T2D without CV complications: USD8310
  - T2D with CV complications: USD15,105

- **Coronary artery disease**: USD8310 and USD15,105

- **Heart failure**: USD8310 and USD15,105

- **Stroke**: USD8310 and USD15,105

---

CV, cardiovascular; USD, US dollar

Diabetes and heart failure often go hand in hand

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


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

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

Item code: MINT/MINVK-18035 Date of preparation: Jan 2019
An increase in heart failure risk is observed in patients with pre-diabetes\textsuperscript{1}

\textsuperscript{1}Matsushita K \textit{et al.} \textit{Diabetes} 2010;59:2020–6

Risk of heart failure begins to rise steeply in patients with pre-diabetes (HbA$_{1c}$ < 5.7%)
Heart failure prognosis is worse in patients with diabetes than in patients without diabetes\textsuperscript{1}.

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

\begin{itemize}
  \item Heart failure with \textbf{reduced} ejection fraction
    \begin{itemize}
      \item HR 1.60
      \item 95\% CI 1.44–1.77
      \item \( p < 0.0001 \)
    \end{itemize}
  \item Heart failure with \textbf{preserved} ejection fraction
    \begin{itemize}
      \item HR 2.0
      \item 95\% CI 1.70–2.36
      \item \( p < 0.0001 \)
    \end{itemize}
\end{itemize}

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

Heart failure is an under-recognized complication of T2D

Distribution of initial presentation of CV disease in patients with T2D\textsuperscript{a,1}

- Heart failure: 14%
- PAD: 16%
- Angina: 16%
- Stroke: 8%
- MI: 12%
- TIA: 10%
- Coronary disease not specified: 15%
- Other\textsuperscript{b}: 9%

\textsuperscript{a}N = 6137 events; \textsuperscript{b}Unheralded CV death, abdominal aortic aneurysm, intercranial haemorrhage, subarachnoid haemorrhage, arrhythmia or sudden CV death

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

The cost of treating heart failure is expected to rise over the coming decades\textsuperscript{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 \textasciitilde USD70 billion by 2030.

USD, US dollar
Kidney disease is one of the most common complications of T2D

Prevalence of CKD in patients with T2D in a primary care setting\(^1\)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Proportion of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR &lt; 60 mL/min/1.73 m(^2)</td>
<td>23.10%</td>
</tr>
<tr>
<td>Elevated UACR</td>
<td>34.60%</td>
</tr>
<tr>
<td>Elevated UACR and eGFR &lt; 60 mL/min/1.73 m(^2)</td>
<td>10.40%</td>
</tr>
</tbody>
</table>

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


In the UK, USA and Australia, incidence of ESRD is broadly stable\(^2\)

In Asia, incidence of ESRD is increasing\(^2\)

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

Item code: MiNT/MINVK-18037 Date of preparation: Jan 2019
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\(^2\))
- Managed in primary care: 84.6%
- Managed by nephrologist: 13.8%
- Managed in secondary care: 1.6%

**Patients with stage 4 CKD** (eGFR 15–29 mL/min/1.73 m\(^2\))
- Managed in primary care: 57.2%
- Managed by nephrologist: 28.8%
- Managed in secondary care: 14.0%

**Patients with stage 5 CKD** (eGFR < 15 mL/min/1.73 m\(^2\))
- Managed in primary care: 70.0%
- Managed by nephrologist: 19.8%
- Managed in secondary care: 10.2%

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

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
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

<table>
<thead>
<tr>
<th>Study</th>
<th>eCVD Event Rate</th>
<th>MRF Event Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EMPA-REG OUTCOME</strong></td>
<td>N=6,964</td>
<td>N=3,486</td>
</tr>
<tr>
<td>DECLARE</td>
<td>&gt;99%</td>
<td>~34.4%</td>
</tr>
<tr>
<td>Placebo event rate</td>
<td>43.9/1000 pt-yrs</td>
<td>31.5/1000 pt-yrs</td>
</tr>
<tr>
<td>CANVAS</td>
<td>~65.6%</td>
<td>~34.4%</td>
</tr>
<tr>
<td>DECLARE</td>
<td>~40.6%</td>
<td>~59.4%</td>
</tr>
<tr>
<td>Placebo event rate</td>
<td>43.9/1000 pt-yrs</td>
<td>24.2/1000 pt-yrs</td>
</tr>
</tbody>
</table>

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

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

Statin use ranged from 75–81% of patients across CVOTs

Anti-thrombotic use ranged from 61–90% of patients across CVOTs

RAS-inhibitor use ranged from 80–81% of patients across CVOTs

β-blocker use ranged from 53–69% of patients across CVOTs

Diuretic use ranged from 41–45% of patients across CVOTs

**Total cholesterol**
- Range: 4.2–4.4 mmol/L

**Blood pressure**
- Systolic range: 133–137
- Diastolic range: 77–78

**Obesity (BMI)**
- 30.7–32.0 kg/m²

**HbA₁c**
- 8.1–8.3% (65–67 mmol/mol)

---

CV outcomes in SGLT2i CV outcomes trials

### CANVAS Program\(^1\)
**Canagliflozin**  
N = 10,142

<table>
<thead>
<tr>
<th>Event</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-point MACE</td>
<td>0.86* (0.75–0.97)</td>
</tr>
<tr>
<td>CV death</td>
<td>0.87 (0.72–1.06)</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>0.85 (0.69–1.05)</td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td>0.90 (0.71–1.15)</td>
</tr>
<tr>
<td>HHF</td>
<td>0.67 (0.52–0.87)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>0.87 (0.74–1.01)</td>
</tr>
</tbody>
</table>

### EMPA-REG OUTCOME\(^2\)
**Empagliflozin**  
N = 7020

<table>
<thead>
<tr>
<th>Event</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-point MACE</td>
<td>0.86* (0.74–0.99)</td>
</tr>
<tr>
<td>CV death</td>
<td>0.62* (0.49–0.77)</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>0.87 (0.70–1.09)</td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td>1.24 (0.92–1.67)</td>
</tr>
<tr>
<td>HHF</td>
<td>0.65 (0.50–0.85)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>0.68* (0.57–0.82)</td>
</tr>
</tbody>
</table>

### DECLARE-TIMI 58\(^3\)
**Dapagliflozin**  
N = 17,160

<table>
<thead>
<tr>
<th>Event</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-point MACE</td>
<td>0.93 (0.84–1.03)</td>
</tr>
<tr>
<td>CV death</td>
<td>0.98 (0.82–1.17)</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>0.89 (0.77–1.01)</td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td>1.01 (0.84–1.21)</td>
</tr>
<tr>
<td>HHF</td>
<td>0.73 (0.61–0.88)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>0.93 (0.82–1.04)</td>
</tr>
</tbody>
</table>

*\(p < 0.05\) 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

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 HbA1c ABOVE TARGET PROCEED AS BELOW

Established ASCVD or CKD

- If further intensification is required or patient is now unable to tolerate GLP-1RA or SGLT-2i, choose agents demonstrating CV safety:
  - Consider adding the other class (GLP-1RA and/or SGLT-2i) with proven CV benefit
  - DPP-4 if not on GLP-1RA
  - Basal insulin
  - TZD
  - SU

- Avoid TZD in the setting of HF
- Choose agents demonstrating CV safety:
  - Consider adding the other class with proven CV benefit
  - DPP-4 (not saxagliptin) in the setting of HF (if not on GLP-1RA)
  - Basal insulin
  - SU

- If HbA1c above target
  - Consider basal insulin with lower risk of hypoglycaemia
  - 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

Without established ASCVD or CKD

- Compelling need to minimise hypoglycaemia
  - DPP-4
  - GLP-1RA
  - SGLT-2i
  - TZD

- Compelling need to minimise weight gain or promote weight loss
  - GLP-1RA with good efficacy for weight loss
  - Either OR SGLT-2i

- Cost is a major issue
  - TZD
  - SU

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

*Proven CV benefit means it has label indication of reducing CVD events. For SGLT-2i evidence modestly stronger for empagliflozin/canagliflozin; 1Be aware that SGLT-2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use; 2Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVOTs; 3Degludec or U100 glargine have demonstrated CV safety; 4Low dose may be better tolerated though less well studied for CVD effects; 5Choose later generation SU with lower risk of hypoglycaemia; 6Degludec / glargine U300<glargine U100 / detemir=NPH insulin; 7If no specific comorbidities (i.e. no established CVD, low risk of hypoglycaemia and lower priority to avoid weight gain or no weight-related comorbidities); 8Consider 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.

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.

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

**hHF by presence/absence of eCVD**

<table>
<thead>
<tr>
<th>Hospitalization for HF</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Established CV Disease (eCVD)</td>
<td>0.78 (0.63, 0.97)</td>
</tr>
<tr>
<td>Multiple Risk Factors (No eCVD)</td>
<td>0.64 (0.46, 0.88)</td>
</tr>
</tbody>
</table>

**hHF by presence/absence of previous HF**

<table>
<thead>
<tr>
<th>Hospitalization for HF</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior HF*</td>
<td>0.73 (0.55, 0.96)</td>
</tr>
<tr>
<td>No prior HF</td>
<td>0.73 (0.58, 0.92)</td>
</tr>
</tbody>
</table>

*10% of patients in DECLARE had prior HF
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

<table>
<thead>
<tr>
<th></th>
<th>DECLARE</th>
<th>CANVAS</th>
<th>EMPA-REG</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR, mean (mL/min/1.73m(^2))</td>
<td>85.2</td>
<td>76.5</td>
<td>74.1</td>
</tr>
<tr>
<td>Micro-/macro-albuminuria (%)</td>
<td>30.2</td>
<td>30.2</td>
<td>40.6</td>
</tr>
</tbody>
</table>

\(^{†}\)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

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

Estimating the economic implications of the DECLARE TIMI 58 data

**Type 2 diabetes economic estimates -**

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

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

---

4. NICE. Type 2 diabetes in adults: management (NG28).
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 lifetime 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 dapagliflozin over 4 years

Avoidance of healthcare resource use and cost savings:
- £142 saving per person over 4 years
- 0.2 million inpatient days
- 4,230 years' RRT provision
- £298 million avoided over 4 years

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

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.
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 inhibitors in a broad patient population

• Translating into clinical, quality of life and economic gains
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 2016¹