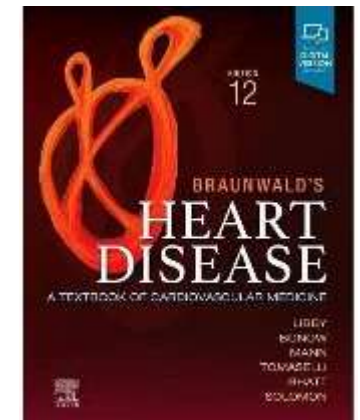




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Sodium-Glucose Co-transporter-2 (SGLT-2) inhibitors: statins of the 21st Century

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Consultant Cardiologist



ESC

European Society
of Cardiology

European Heart Journal (2021) 00, 1–2
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CARDIOPULSE

Braunwald's Corner

SGLT2 inhibitors: the statins of the 21st century

Eugene Braunwald  1,2*



Are they diabetes drugs?

- **GSK settled a fraud case for \$3 billion where CV safety data on Rosiglitazone was not disclosed**
- **0.6%, 6.5 mM/M reduction in HbA1c**
- **Low incidence of hypoglycaemia, effect of glucose lowering is proportional to starting blood glucose**
- **Weight loss up to 3kg (visceral fat reduction)**
- **Effect on glucose reduction diminishes when eGFR < 45**
- **Yes, but not very good at glucose lowering but is safe and associated with weight loss. Much better at CV event reduction¹**

Are they cardiovascular/heart failure drugs?

- **Studies of T2DM with CV risk but not heart failure:**

- Reduction in CV death/MI/stroke and HF Hospitalisation, RRR:

- EMPA REG OUTCOME (2015) 14% and 35% (38% for CV death)
- CANVAS PROGRAM (2017) 14% and 33%
- DECLARE-TIMI 58 (2019)* 17% and 27% *(HHF and CV death)
- VERTIS (2020) Non-inferior and 30%

- **Studies of heart failure:**

- Reduction in CV death and HF hospitalisation in HFrEF:

- DAPA HF (2019) 26% (death any cause 17%, HHF 30%)
- EMPEROR-Reduced (2020) 25% (driven by HHF 31%)

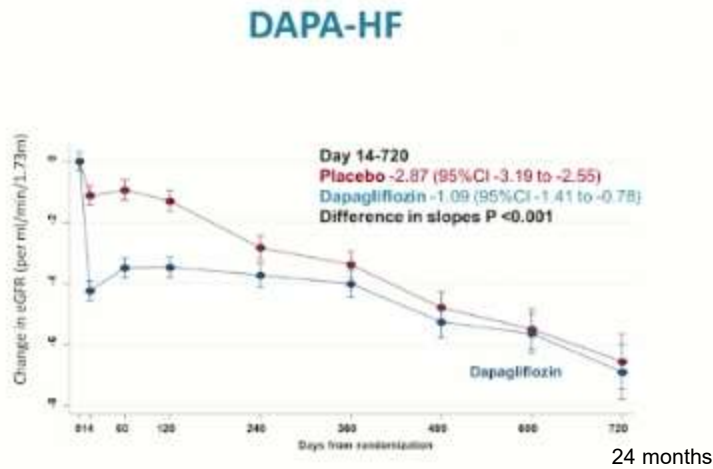
- Reduction in CV death and HF hospitalisation in HFpEF:

- EMPEROR-Preserved (2021) 21% (driven by HHF 29%)

- **Yes, both for prevention of CV death (MI, stroke) and HF and also for treatment for HF (HFrEF more impressively than HFpEF)**

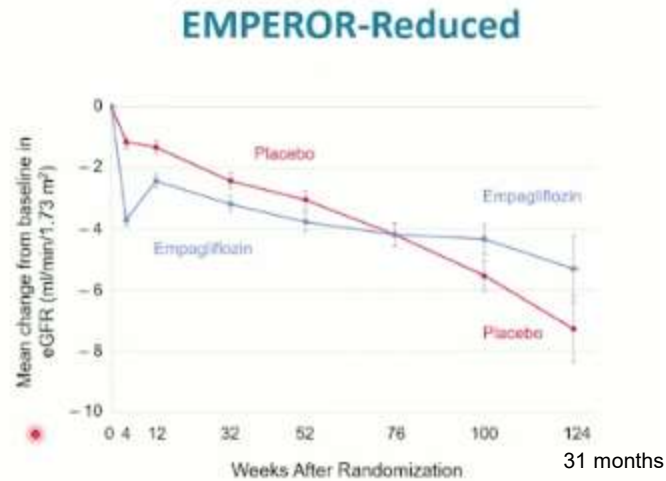
Are they kidney drugs?

SGLT2i slow the rate of decline in eGFR in HFrEF



Difference = 1.78 ml/min/yr

Jhund P et al. *Circulation*. 2020 Oct 12.
doi: 10.1161/CIRCULATIONAHA.120.050391



Difference = 1.73 ml/min/yr

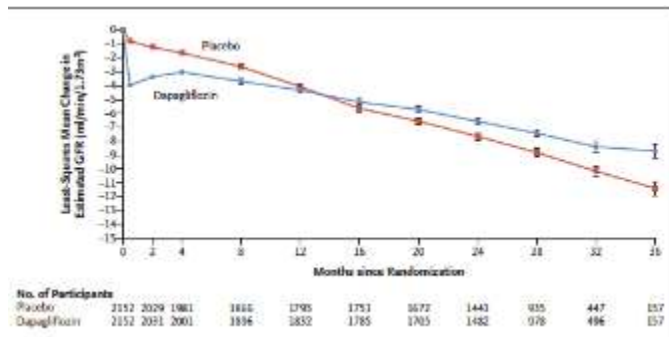
Zannad F et al. *Circulation*. 2020 Oct 23.
doi: 10.1161/CIRCULATIONAHA.120.051685

DAPA-CKD
4,304 proteinuric CKD patients including non-diabetics

Kidney:
eGFR drop 50%
Dialysis (ESKD)
Renal death
RRR 44%

CV:
HHF
CV death
RRR 29%

DAPA-CKD



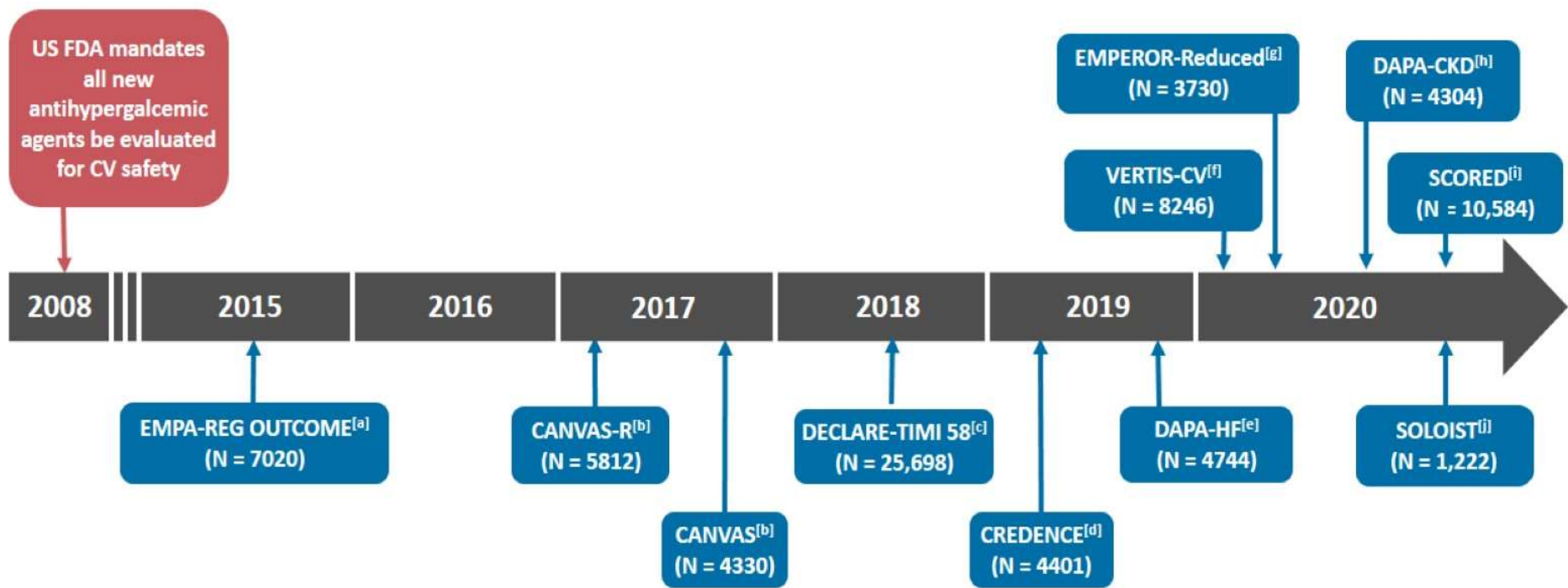
- All cause mortality reduced by **31%**
- Reduces hyperkalaemia by 50%
- **Yes, could be the most significant new CKD treatment in decades since ACE-I but not yet licensed for CKD**

Difference = 1.92 ml/min/yr

Heerspink H et al. *NEJM* 2020 Sept 24.
doi: 10.1056/NEJMoa2024816

SGLT2 Inhibition: A Story of Scientific Replication

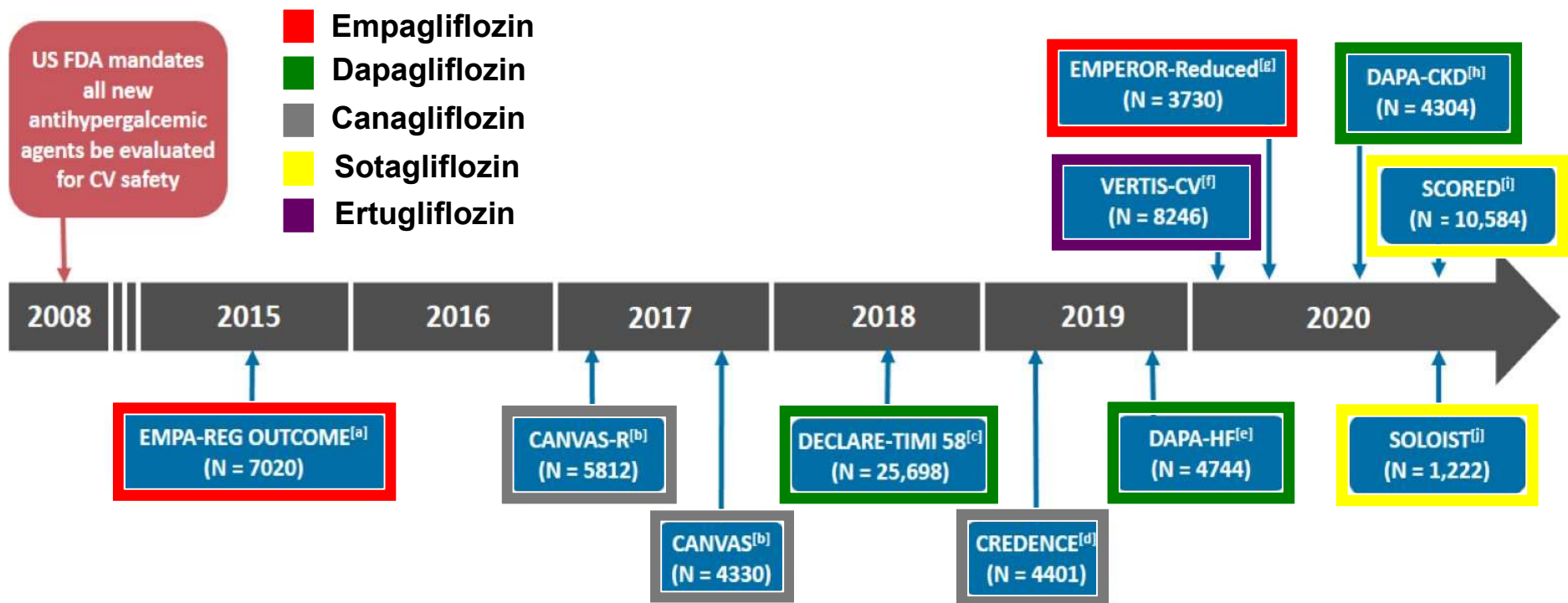
Beneficial Effects of SGLT2 Inhibition Observed in Multiple Patient Populations and Across Multiple RCTs



a. Zinman B, et al. *N Engl J Med.* 2015;373:2117-2128; b. Neal B, et al. *N Engl J Med.* 2017;377:644-657; c. Wiviott SD, et al. *N Engl J Med.* 2019;380:347-357; d. Perkovic V, et al. *N Engl J Med.* 2019;380:2295-2306; e. McMurray JJV, et al. *N Engl J Med.* 2019;381:1995-2008; f. Cannon CP, et al. *N Engl J Med.* 2020;383:1425-1435; g. Packer M, et al. *N Engl J Med.* 2020;383:1413-1424; h. Heerspink HJL, et al. *N Engl J Med.* 2020;383:1436-1446; i. Bhatt DL, Szarek M, Pitt B, et al. *N Engl J Med.* 2020. [Epub ahead of print]; j. Bhatt DL, Szarek M, Steg PG, et al. *N Engl J Med.* 2020. [Epub ahead of print].

SGLT2 Inhibition: A Story of Scientific Replication

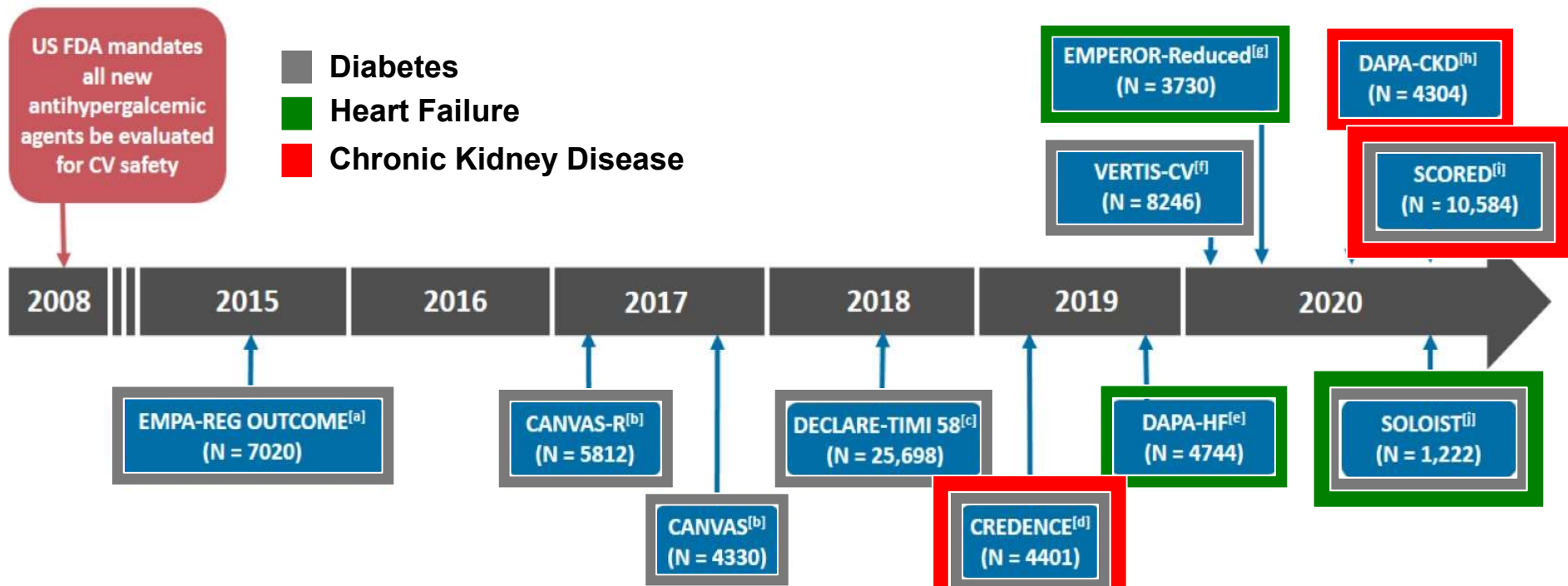
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SGLT2 Inhibition: A Story of Scientific Replication

Beneficial Effects of SGLT2 Inhibition Observed in Multiple Patient Populations and Across Multiple RCTs



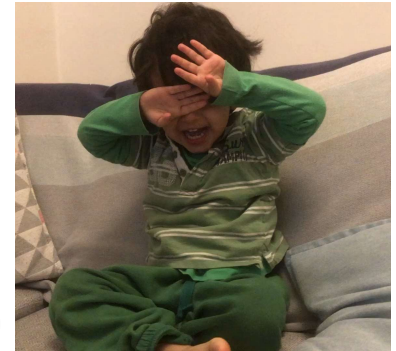
a. Zinman B, et al. *N Engl J Med.* 2015;373:2117-2128; b. Neal B, et al. *N Engl J Med.* 2017;377:644-657; c. Wiviott SD, et al. *N Engl J Med.* 2019;380:347-357; d. Perkovic V, et al. *N Engl J Med.* 2019;380:2295-2306; e. McMurray JJV, et al. *N Engl J Med.* 2019;381:1995-2008; f. Cannon CP, et al. *N Engl J Med.* 2020;383:1425-1435; g. Packer M, et al. *N Engl J Med.* 2020;383:1413-1424; h. Heerspink HJL, et al. *N Engl J Med.* 2020;383:1436-1446; i. Bhatt DL, Szarek M, Pitt B, et al. *N Engl J Med.* 2020. [Epub ahead of print]; j. Bhatt DL, Szarek M, Steg PG, et al. *N Engl J Med.* 2020. [Epub ahead of print].

When could SGLT-2 inhibitors be harmful?

- Type 1 Diabetes (neglected population)
- Diabetics prone to diabetic ketoacidosis (“Type 1.5 Diabetes”)
- “Sick day rules” – sepsis, D&V, severe dehydration, surgery
- In a diabetic patient with well controlled HbA1c on insulin or gliclazide (HbA1c <7%, 53 mM/M), if not reducing insulin (10-20%) or gliclazide (25-50%)
- Very low BP (SBP < 90mmHg) but generally well tolerated

Common concerns

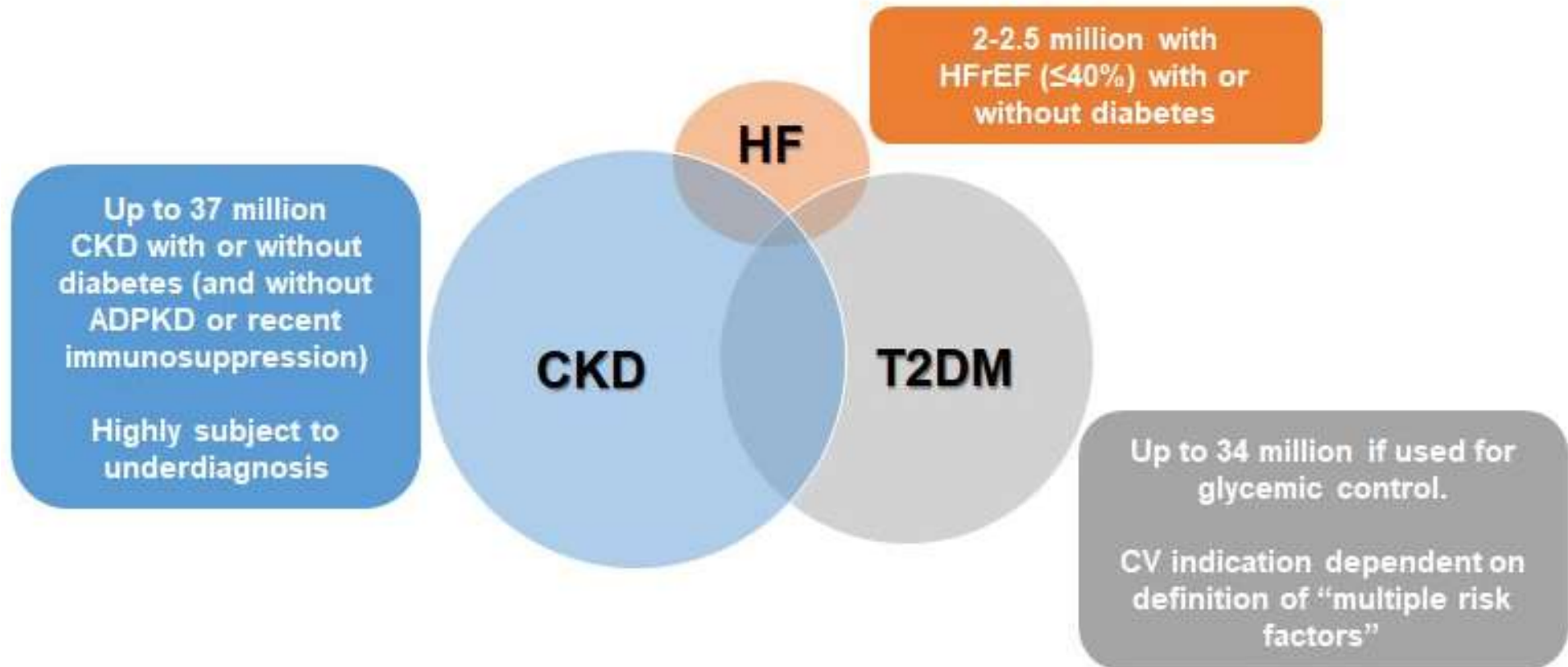
- Chronic kidney disease – data safe to use down to eGFR 20
- Recurrent UTIs – little evidence to suggest increase in bacterial UTI



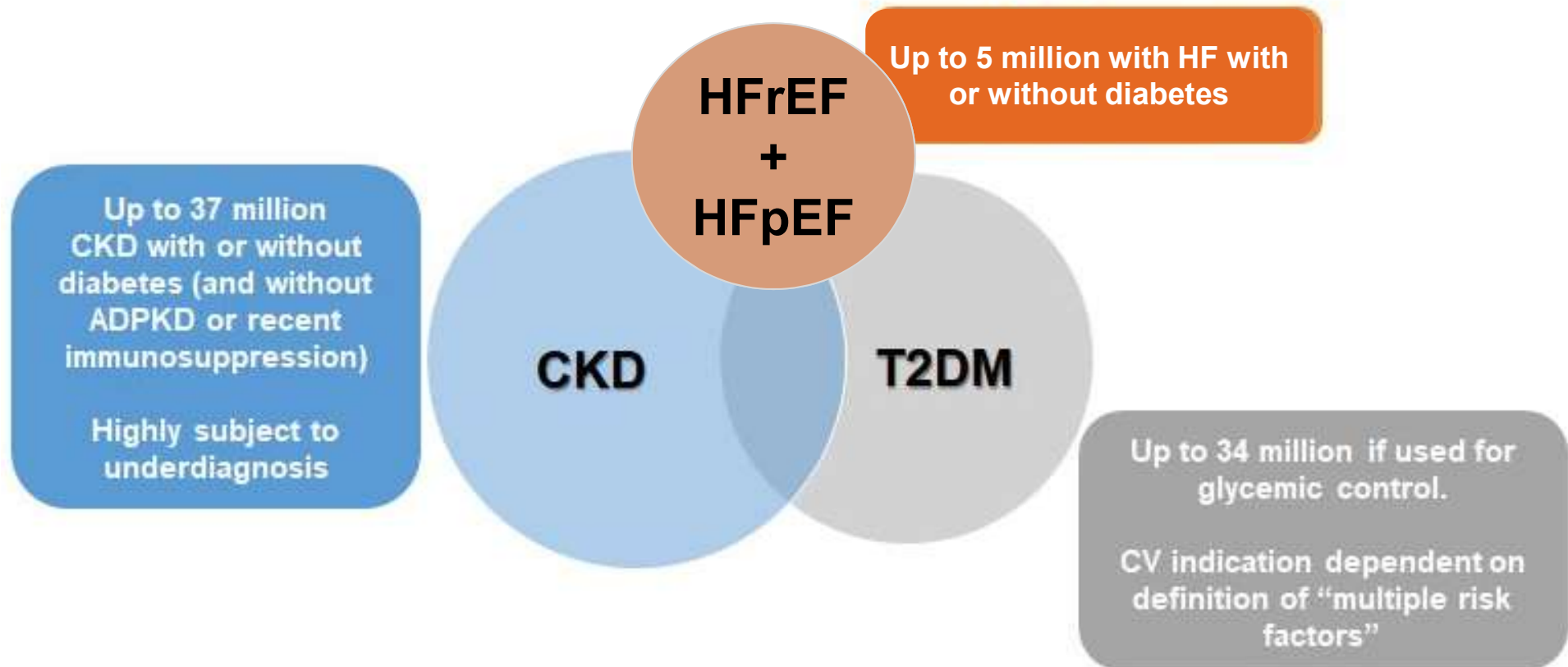
What should patients be told?

- Can cause genital thrush (usually one off rather than recurrent)
- Mild increase in diuresis (1 extra toilet visit)
- Might allow reduction in diuretic dose or lifting of fluid restriction (10%)
- Sick day rules
- If on insulin or gliclazide and well-controlled, monitor CBG more closely after dose reduction
- It can improve your symptoms and quality of life (KCCQ +3.7 @ 3/12)

Estimates of Eligible Populations in the US for Initiation of Dapagliflozin



Estimates of Eligible Populations in the US for Initiation of ~~Dapagliflozin~~ Empagliflozin

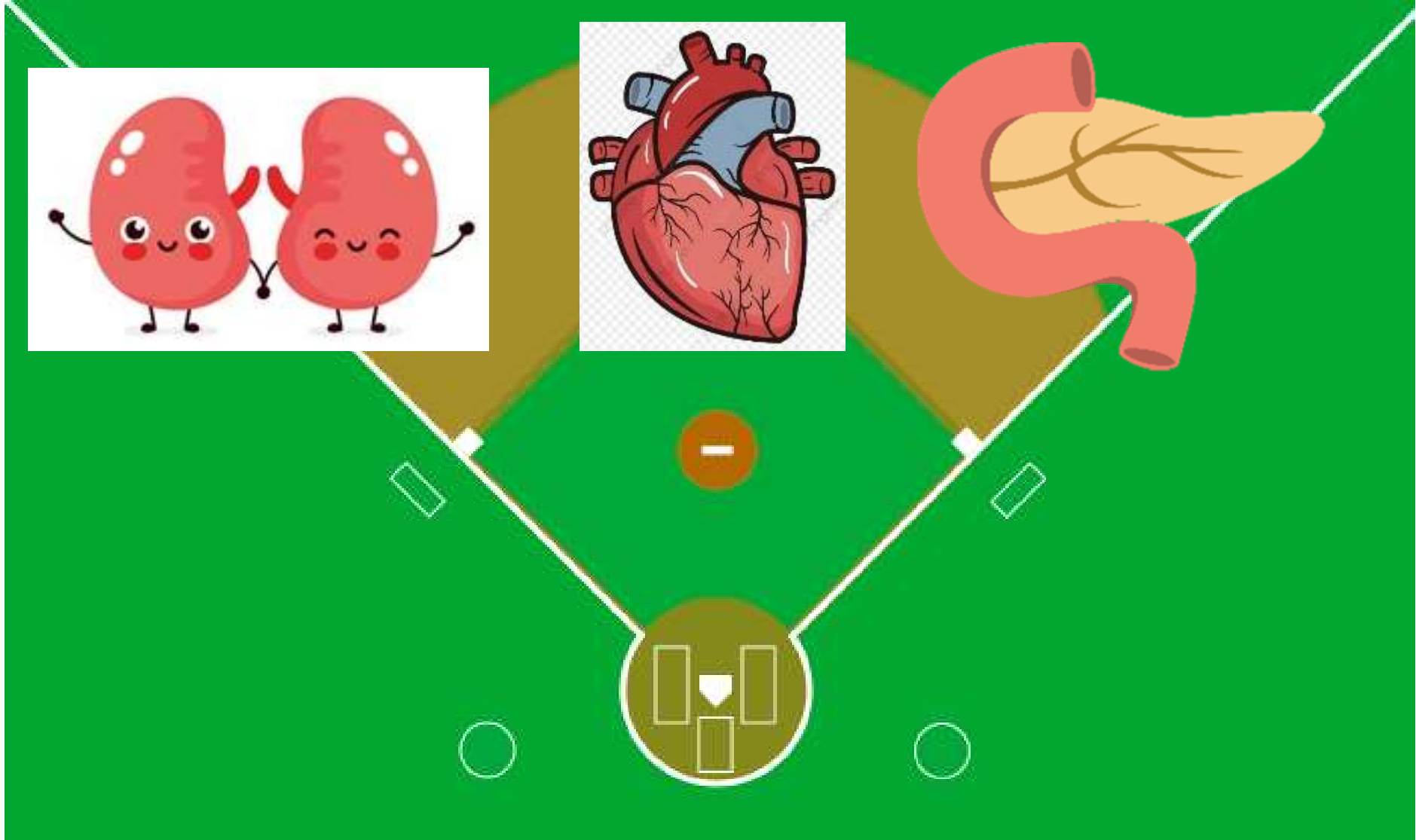
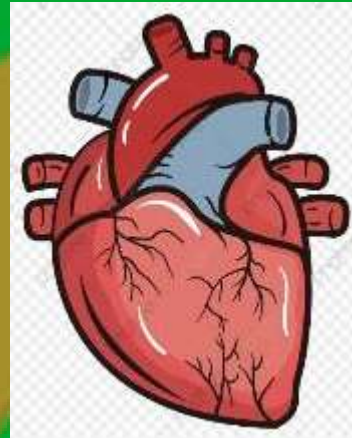
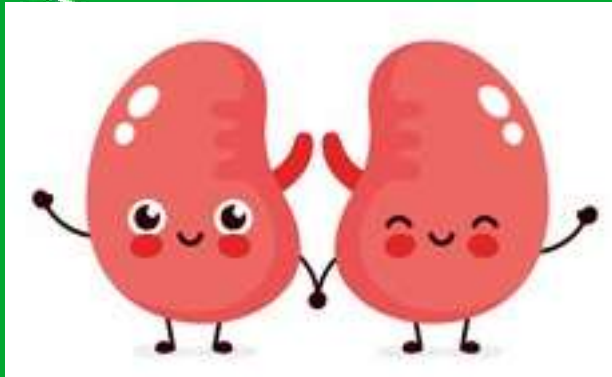




showing
we care

NHS
Guy's and St Thomas'
NHS Foundation Trust

Triple play!



Questions?

- E-mail: andrew.dsilva@gstt.nhs.uk
- Twitter: @AndrewJMDSilva



- Key NICE guideline references:
- Dapagliflozin for HFrEF - <https://www.nice.org.uk/guidance/ta679>
- SGLT-2s for T2DM – Dapagliflozin <https://www.nice.org.uk/guidance/ta288> ,
Empagliflozin <https://www.nice.org.uk/guidance/ta336>
- SGLT-2s for T2DM with CKD (in development) -
<https://www.nice.org.uk/guidance/indevelopment/gid-ng10246/>