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## SGLT-2 inhibitors, diabetes drugs, scandals and serendipity!

**Dr Andrew D'Silva**  
Consultant Cardiologist

### Case

- 57 M, White European
- T2DM – diet controlled, HbA1c 9.2%, 77mM/M
- HFrEF, LVEF 28%, ischaemic aetiology with scars on CMR
- OOH cardiac arrest with secondary prevention ICD March 2021
- AF, Gout, Obesity

- Sacubitril/Valsartan 49/51mg BD
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### What should you do next?

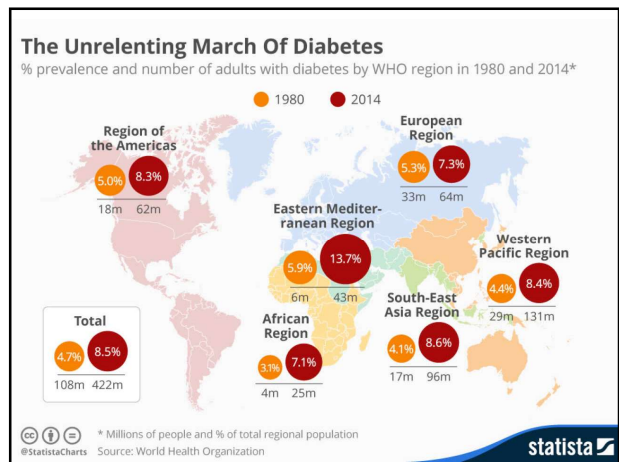
**A** Sac/Val to 97/103mg BD

**B** Spironolactone to 50mg OD

**C** Start Dapagliflozin 10mg OD

**D** AF ablation

End



**Start with Monotherapy unless:**

- HbA1c is greater than or equal to 9%, consider Dual Therapy.
- HbA1c is greater than or equal to 10%, blood glucose is greater than or equal to 300 mg/dL, or patient is markedly symptomatic, consider Combination Injectable Therapy.

Monotherapy	Metformin	Lifestyle Management
EFFICACY	high	
HYPO RISK	low risk	
WEIGHT	neutrals	
SIDE EFFECTS	Gastroic acidosis	
COSTS	low	

If HbA1c target not achieved after approximately 3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference – choice dependent on a variety of patient- and disease-specific factors)

Dual Therapy	Metformin +	Lifestyle Management
EFFICACY	high	
HYPO RISK	intermediate	
WEIGHT	gain	
SIDE EFFECTS	hypoglycaemia	
COSTS	low	

If HbA1c target not achieved after approximately 3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference – choice dependent on a variety of patient- and disease-specific factors)

Triple Therapy	Metformin +	Lifestyle Management
EFFICACY	high	
HYPO RISK	intermediate	
WEIGHT	gain	
SIDE EFFECTS	hypoglycaemia	
COSTS	low	

If HbA1c target not achieved after approximately 3 months of triple therapy and patient: (1) on one combination, move to basal insulin or GLP-1 RA, (2) on GLP-1 RA, add basal insulin, or (3) on optimally titrated basal insulin, add GLP-1 RA or mealtime insulin. Metformin therapy should be maintained, while other oral agents may be discontinued on an individual basis to avoid unnecessary complexity or costs, e.g. adding a fourth antihyperglycaemic agent.

**Combination Injectable Therapy**

Thrasher, J. *The American Journal of Medicine* 2017 130S4-S17 DOI: (10.1016/j.amjmed.2017.04.004)

### 1999-2008 Lessons learned

- 1999 FDA and 2000 EMA approval of Rosiglitazone for diabetes

Fluid retention and heart failure known problems with the glitazones

rosiglitazone

LDL ↑ 18%

Acute MI HR 1.8 (0.9-3.6)

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- EMA demanded prospective trial to prove CV safety as a condition to approval (RECORD – Lancet 2009, 9 years after drug approval)
- 2005 WHO requested a meta-analysis (37 trials) on Rosiglitazone from GSK for CV harm
  - HR 1.29 (0.99 – 1.89)
- 2006 WHO requested meta-analysis (42 trials)
  - HR 1.31 (1.01 – 1.70)
- HELD AS CONFIDENTIAL, FDA and EMA not notified

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### Scandal

- 2004 – GSK taken to court sued for off-label promotion, initially for marketing Paroxetine (Paxil) to children and adolescents without disclosing data on suicide risk. Later included was failure to disclose safety data for Rosiglitazone (Avandia)
- New York Times: Glaxo agrees to pay \$3 billion in fraud settlement
- Had to release all patient level data from all their trials

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The NEW ENGLAND JOURNAL of MEDICINE  
ESTABLISHED IN 1812 JUNE 14, 2007 VOL. 356 NO. 24

Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes  
Steven E. Nissen, M.D., and Kathy Wolski, M.P.H.

- Using GSK's own data
- 2008 FDA (changed position) – All new anti-diabetic drugs need pre-approval and post-approval studies to rule out excess CV risk

Acute MI HR 1.43 (1.03-1.98)  
CV Death HR 1.64 (0.98-2.74)

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### Empagliflozin – EMPA REG OUTCOME

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes  
Bernard Zinman, Christoph Wanner, John M. Lachin, EMPA-REG OUTCOME Investigators NEJM 2015 373. #NephJC

WHO WAS TESTED	WHAT WAS DONE	WHAT THEY FOUND
Type 2 DM. Prior history of CV disease N=7,020 Age 63.1 A1c 8.1% Diabetic nephropathy (>300 mg/g) 11% Blood pressure 135/77 ACEI or ARB in 81% Statins in 77% 2.6 years on treatment (3.1 years for outcomes)	Empagliflozin 25 mg (N= 2,342) Empagliflozin 10 mg (N= 2,345) Placebo (N= 2,333)	Primary Outcome <b>10.5%</b> CV death <b>3.7%</b> Total mortality <b>5.7%</b> Hazard Ratio <b>0.86</b> (P<.001) 0.62 (P<.001) 0.68 (P<.001) 12 weeks: 10 mg 0.54%, 25 mg 0.60% 94 weeks: 0.42%, 0.47% Systolic BP 5 mmHg

- T2DM + prior CVD (10% had heart failure): all cause mortality NNT = 39, CV mortality NNT = 46.
- 35% reduction in HF hospitalization (HF prevention)

### Dapagliflozin - DAPA HF

Does Dapagliflozin Decrease Mortality in Patients with Heart Failure and Reduced Ejection Fraction?

DAPA-HF Trial Investigators	Randomization (1:1)	Primary Composite Outcome	Secondary Outcomes
20 countries 410 centers 4,744 HF patients NYHA class II, III, or IV HF EF <= 40% 45% Type 2 Diabetes	Placebo n= 2371 Dapagliflozin n= 2373 Median follow-up 38.2 months	Worsening HF Death from CV cause CV death or HF hospitalization Death from any cause <b>21.2%</b> <b>0.74</b> (0.65-0.83) <b>16.3%</b>	<b>20.9%</b> <b>0.75</b> (0.65-0.83) <b>16.1%</b> <b>13.9%</b> <b>0.83</b> (0.71-0.97) <b>11.6%</b>

Conclusion: In patients with HF and a reduced EF (+/- Type 2 diabetes), dapagliflozin reduced the risk of worsening heart failure or death from cardiovascular causes compared to placebo.

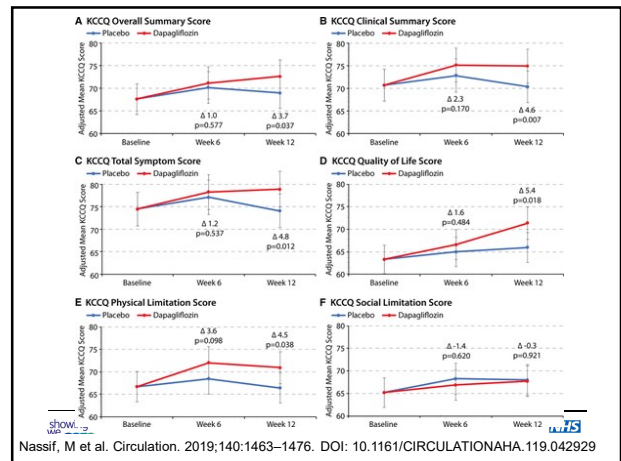
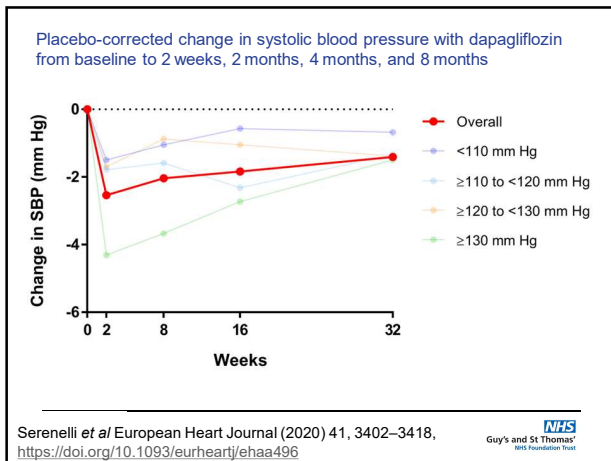
Reference: McMurray et al. DAPA-HF Trial Committees and Investigators. N Engl J Med 2019; 381:1995-2008  
Visual abstract by Sudha Mannemudthu @4M\_sudha

25% reduction in HF hospitalization, typical BP reduction drop in 2.4/1-2 mmHg (S/D)

### Safety Outcomes

Variable	Dapagliflozin (n=2368)	Placebo (n=2368)	p-value
AE leading to treatment discontinuation, n (%)	111 (4.7)	116 (4.9)	0.79
Adverse Events of Interest, n (%)			
Volume depletion†	178 (7.5)	162 (6.8)	0.40
Renal AE‡	153 (6.5)	170 (7.2)	0.36
Fracture	49 (2.1)	50 (2.1)	1.00
Amputation	13 (0.5)	12 (0.5)	1.00
HbA1c in diabetic patients, %	-0.21	+0.04	<0.001
Major hypoglycaemia¹	4 (0.2)	4 (0.2)	-
Diabetic ketoacidosis §	3 (0.1)	0.0	-
Fournier's gangrene	0	1 (<0.1)	-
Systolic blood pressure change, mmHg	-1.92	-0.38	0.002

McMurray JJV et al. N Engl J Med. 2019. <https://doi.org/10.1056/NEJMoa1911303>.



### Empagliflozin – EMPEROR-Reduced

**EMPEROR-Reduced**  
Does empagliflozin improve outcomes in patients with heart failure?

520 centers, 28 countries, Double-blind trial, Class II – IV heart failure (n = 3730), Ejection fraction <40%, Median follow-up 16 months

Primary composite outcome: Hospitalization for heart failure, Cardiovascular death, Hospitalization for heart failure, Annual rate of decline of eGFR

Placebo (n=1867)	Reference	Reference	-2.28 ml/min/1.73m <sup>2</sup>
Empagliflozin 10 mg daily (n=1863)	HR 0.75 (0.65 – 0.86)	HR 0.70 (0.58 – 0.85)	-0.55 ml/min/1.73m <sup>2</sup>

Uncomplicated genital tract infection was reported more frequently with empagliflozin

Empagliflozin-treated patients had a lower risk of serious renal outcomes

Conclusion: Among patients receiving recommended therapy for heart failure, those in the empagliflozin group had a lower risk of cardiovascular death or hospitalization for heart failure than those in the placebo group, regardless of the presence or absence of diabetes

30% reduction in HF hospitalization

### Dapagliflozin – DAPA CKD

**Dapagliflozin – DAPA CKD**  
Could dapagliflozin improve kidney and cardiovascular outcomes in patients with CKD?

Randomized Double-blind Placebo-controlled Multicenter, 386 sites in 21 countries, N=4304, GFR 25-75 ml/min, 67.5% diabetes type 2, ACR 200-500mg/g

Outcomes:

Outcome	Placebo (N=2152)	Dapagliflozin 10mg/d (N=2152)
Primary composite outcome	14.5%	9.2%
Composite kidney outcome	11.3%	6.6%
Composite cardiovascular outcome	6.4%	4.6%
Death from any cause	6.8%	4.7%

Conclusion: Among patients with chronic kidney disease, the risk of any composite kidney or cardiovascular outcomes or death was significantly lower with dapagliflozin than with placebo.

11% had HF at baseline but NYHA class IV excluded, 37% had a history of CV disease

### SGLT2 Inhibition: A Story of Scientific Replication

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

US FDA mandates all new antihyperglycemic agents be evaluated for CV safety

Timeline (2008-2020): EMPA-REG OUTCOME<sup>®</sup> (N=7020), CANVAS-R<sup>®</sup> (N=5812), CANVAS<sup>®</sup> (N=4330), DECLARE-TIMI 58<sup>®</sup> (N=25,698), CREDENCE<sup>®</sup> (N=4401), EMPEROR-Reduced<sup>®</sup> (N=3730), DAPA-CKD<sup>®</sup> (N=4304), VERTIS-CV<sup>®</sup> (N=8246), SCORED<sup>®</sup> (N=10,584), DAPA-HF<sup>®</sup> (N=4744), SOLOIST<sup>®</sup> (N=1,222)

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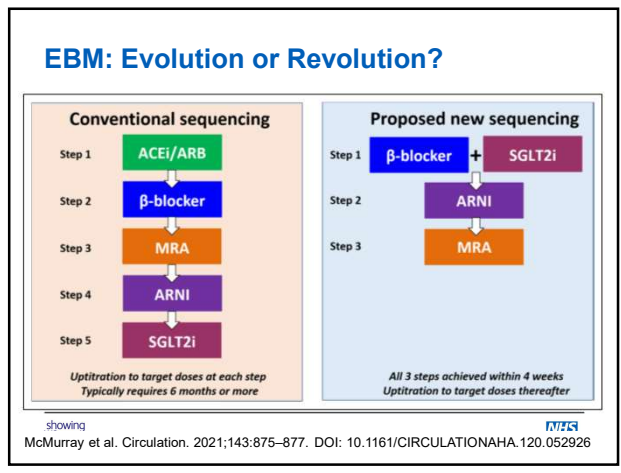
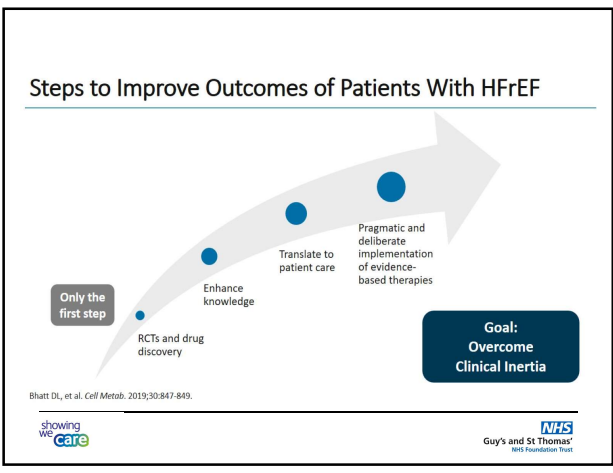
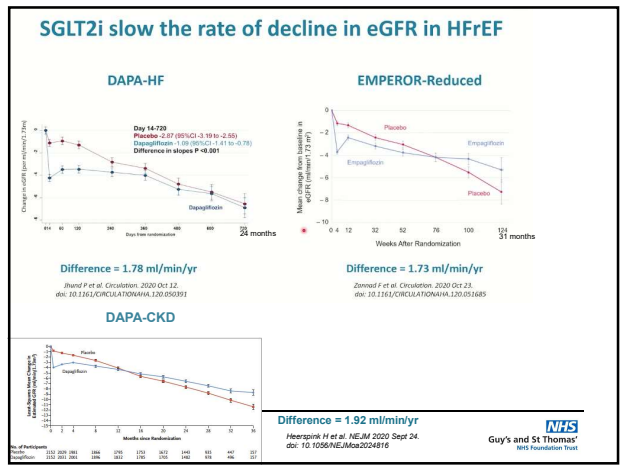
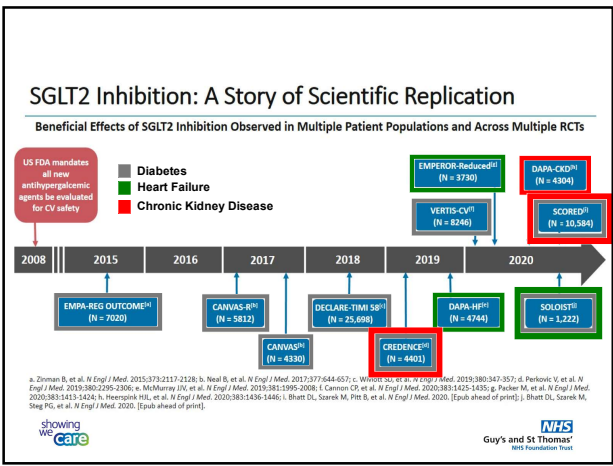
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Legend: Empagliflozin (red), Dapagliflozin (green), Canagliflozin (blue), Sotagliflozin (yellow), Ertugliflozin (purple)

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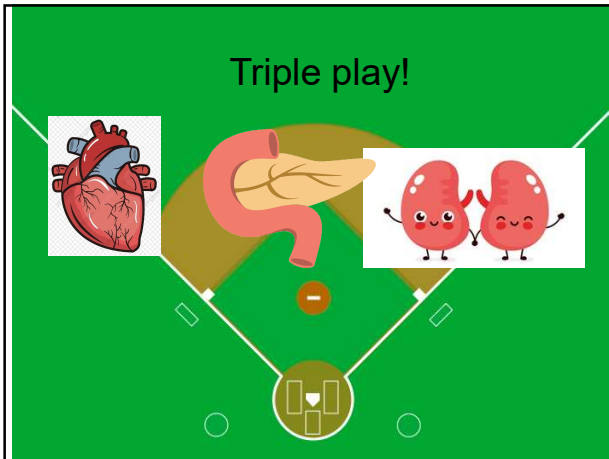


### Rare and game-changing: Triple benefits

- Heart**
  - Reduced CV death
  - Reduced nonfatal MI
  - Reduced nonfatal stroke
  - BP reduction
- Pancreas**
  - 0.4% HbA1c reduction
  - Up to 2kg weight loss
  - Reduces risk of DM in HF by 32%
- Kidneys**
  - Reduces rate of renal decline
  - Reduces dialysis and death from renal causes
  - Reduces hyper-K by 50%

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**Practical counselling**

- Risk of thrush genital infection (usually one off), personal hygiene
- Mild increase in diuresis (1x extra visit)
- Sick day rules – if dehydration/sepsis/vomiting/abdo pain, etc. stop to avoid euglycaemic ketoacidosis
- Check renal function 2-4 weeks after initiating, then 2 months, then 4 monthly
- Volume status assessment reduction of diuretic/fluid restriction (only required in approx. 10%)
- If DM and HbA1c < 7% (< 53 mM/M) then review insulin (reduce 10-20%) and SU dose (reduce 25-50%) and increase CBG monitoring

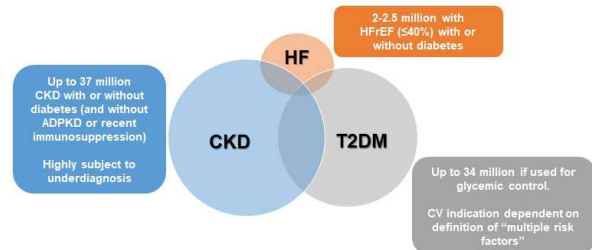


**Who shouldn't you start an SGLT2i on?**

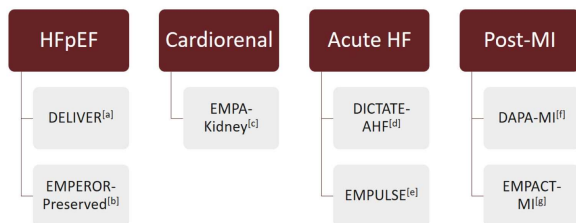
- Type 1 Diabetes. Not licensed, may not be safe with euglycaemic DKA risk
- Caution in diabetic patients with previous severe DKAs
- Symptomatic hypotension and very low BPs
- Severe renal failure. Not licensed for eGFR <30 (but down to 20 may be reasonable for Empagliflozin)



**Estimates of Eligible Populations in the US for Initiation of Dapagliflozin**



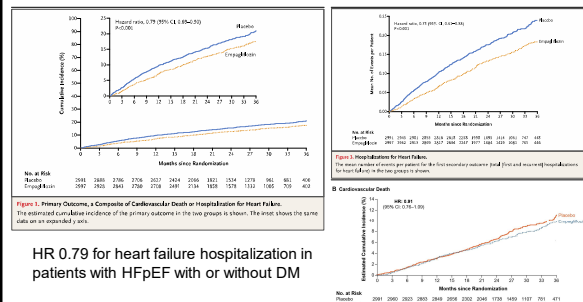
**Evaluation of SGLT2 Inhibitors Beyond HFpEF: Ongoing RCTs**



a. ClinicalTrials.gov. NCT03619213; b. ClinicalTrials.gov. NCT03057951; c. ClinicalTrials.gov. NCT03594110; d. ClinicalTrials.gov. NCT04298229; e. ClinicalTrials.gov. NCT04157751; f. AstraZeneca.com. Phase III DAPA-MI trial; g. ClinicalTrials.gov NCT04509674.



**EMPEROR-Preserved: Empagliflozin**



HR 0.79 for heart failure hospitalization in patients with HFpEF with or without DM



Anker SD, et al. N Engl J Med. 2021



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**Questions?**



• E-mail: [andrew.dsilva@gstt.nhs.uk](mailto:andrew.dsilva@gstt.nhs.uk)

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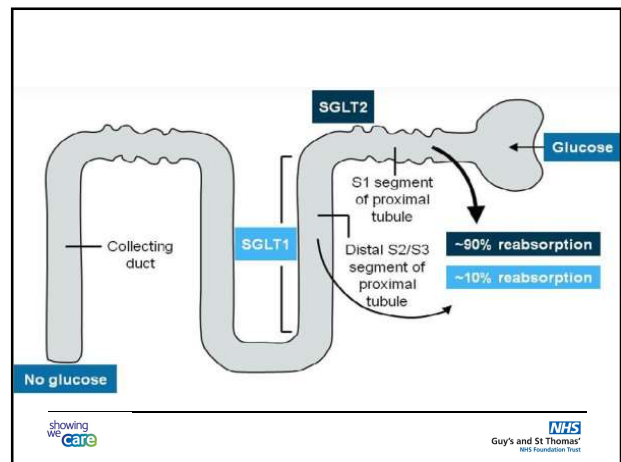


Diagram illustrating the effects of SGLT2 inhibitors. SGLT2 inhibitors block glucose reabsorption in the proximal tubule, leading to diuresis, natriuresis, glucosuria, and uricosuria. This results in a decrease in preload and afterload, leading to a decrease in systolic blood pressure, arterial stiffness, volume of blood, and body weight. It also leads to a decrease in hyperglycaemia, glucose toxicity, and insulin resistance, and an increase in glucagon and ketones.

showing we care      Dutka et al. Heart Failure Reviews (2021) 26:603–622      NHS Guy's and St Thomas' NHS Foundation Trust