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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
- Bisoprolol 10mg OD
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- Euvolaemic, pulse 60 bpm AF, BP 110/85
- Wt 147.3 kg, BMI 39

- K 4.3, Cr 99, eGFR 68

showing we care

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What should you do next?

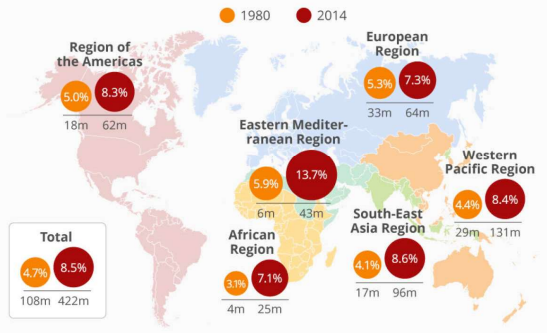
End

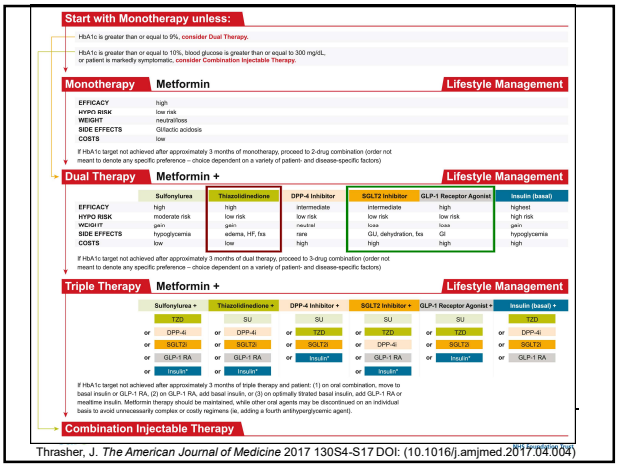
A Sac/Val to 97/103mg BD

B Spironolactone to 50mg OD

C Start Dapagliflozin 10mg OD

D AF ablation





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 glitizones

rosiglitazone

Acute MI
HR 1.8
(0.9-3.6)

- **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**

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

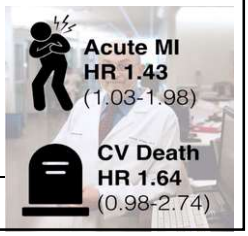
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 14, 2007 VOL. 356 NO. 24

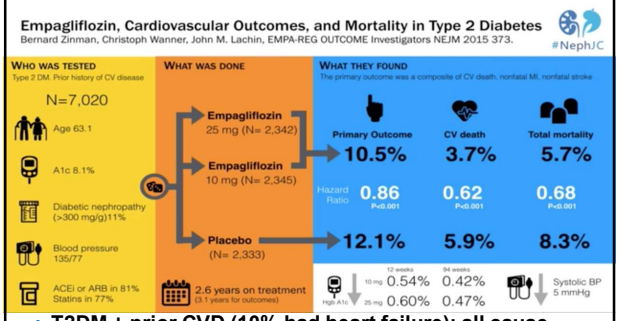
Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

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**

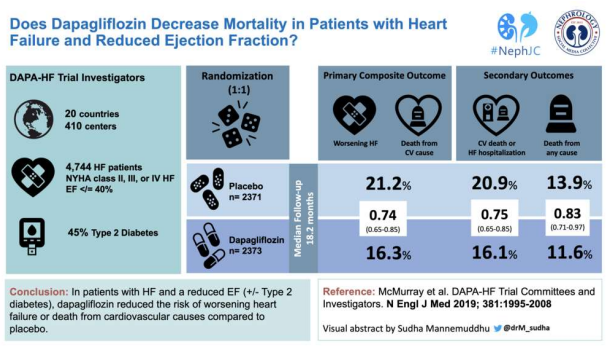


Empagliflozin – EMPA REG OUTCOME



- **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



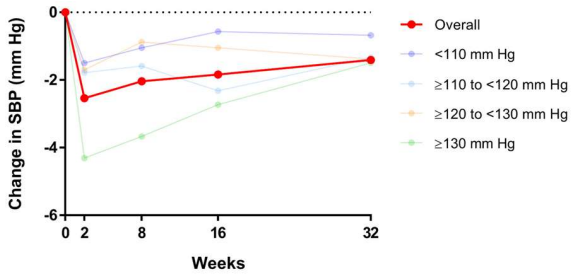
25% reduction in HF hospitalization, typical BP reduction drop in 2-4/1-2 mmHg (S/D)

Safety Outcomes

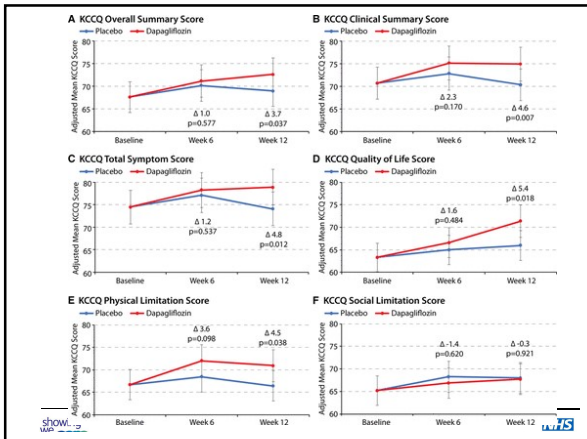
Variable	Dapagliflozin (n=2368)	Placebo (n=2368)	p-value
AE leading to treatment discontinuation, n (%)	111 (4.7)	116 (4.9)	0.79
Adverse Events of Interest, n (%)			
Volume depletion†	178 (7.5)	162 (6.8)	0.40
Renal AE‡	153 (6.5)	170 (7.2)	0.36
Fracture	49 (2.1)	50 (2.1)	1.00
Amputation	13 (0.5)	12 (0.5)	1.00
HbA1c in diabetic patients, %	-0.21	+0.04	<0.001
Major hypoglycaemia‖	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.

Placebo-corrected change in systolic blood pressure with dapagliflozin from baseline to 2 weeks, 2 months, 4 months, and 8 months

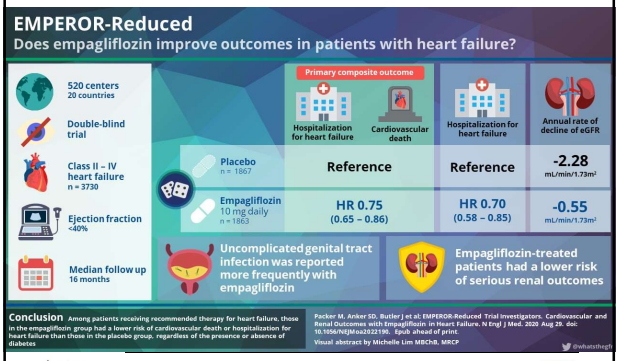


Serenelli *et al* European Heart Journal (2020) 41, 3402–3418, https://doi.org/10.1093/eurheartj/ehaa496



Nassif, M et al. Circulation. 2019;140:1463–1476. DOI: 10.1161/CIRCULATIONAHA.119.042929

Empagliflozin – EMPEROR-Reduced

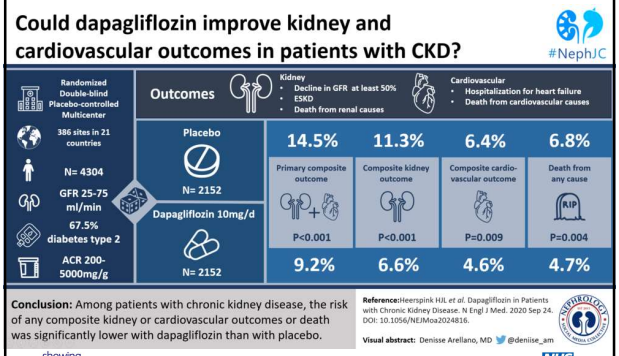


showing we care 30% reduction in HF hospitalization

Dapagliflozin – DAPA CKD

Could dapagliflozin improve kidney and cardiovascular outcomes in patients with CKD?

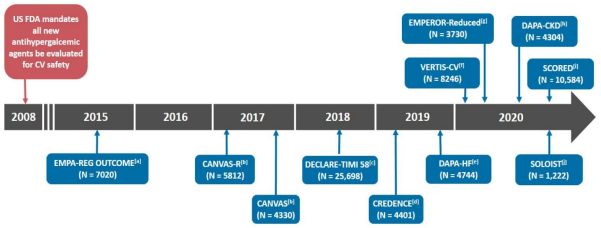
#NephJC



showing we care 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



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].

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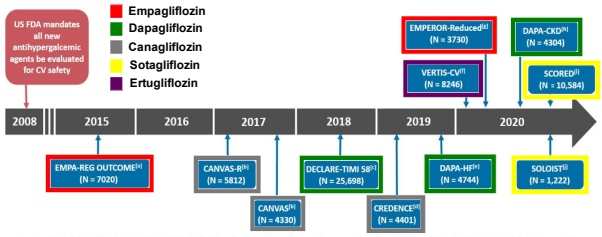

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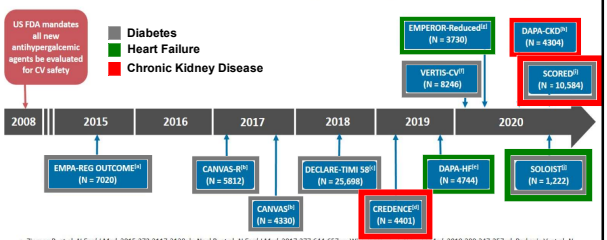

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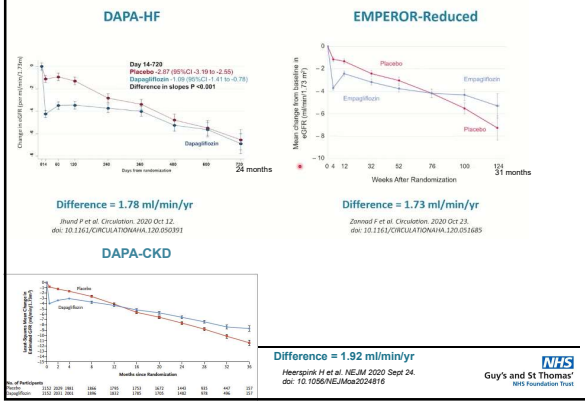
SGLT2i slow the rate of decline in eGFR in HFrEF



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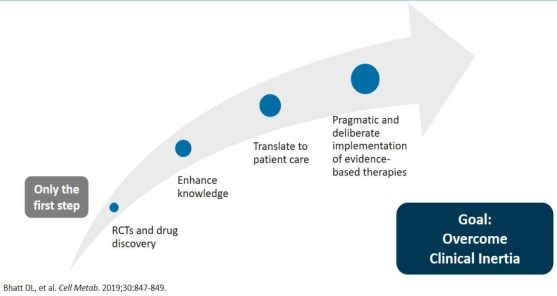
Steps to Improve Outcomes of Patients With HFrEF



Bhatt DL, et al. *Cell Metab*. 2019;30:847-849.

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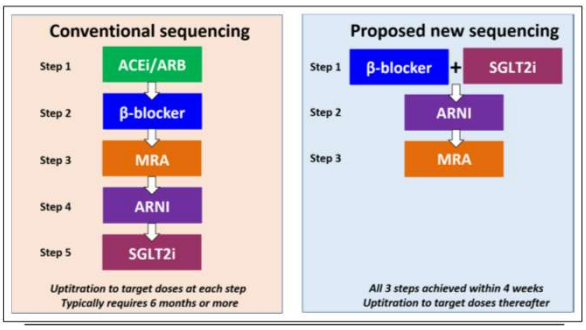
EBM: Evolution or Revolution?

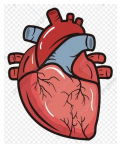


showing

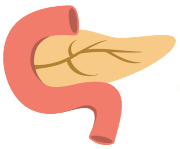
NHS

McMurray et al. Circulation. 2021;143:875–877. DOI: 10.1161/CIRCULATIONAHA.120.052926

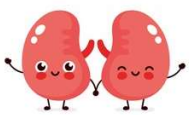
Rare and game-changing: Triple benefits



- 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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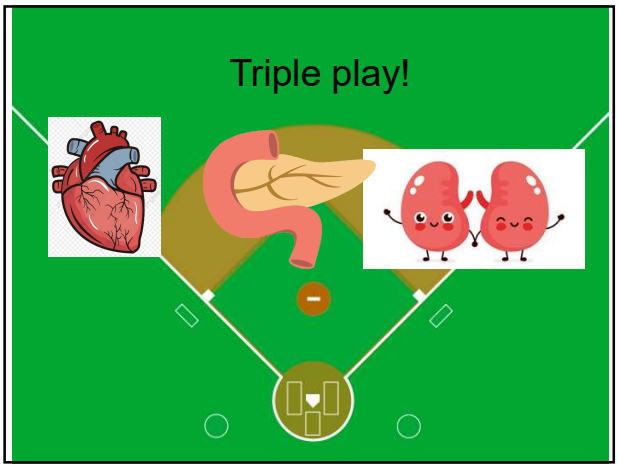


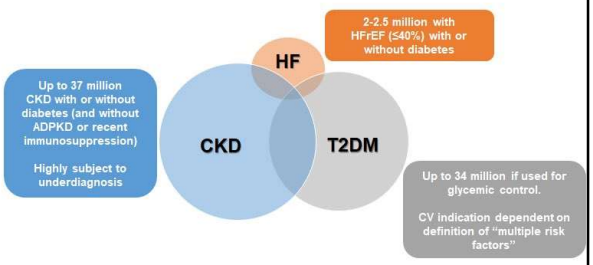
Practical counselling

- 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

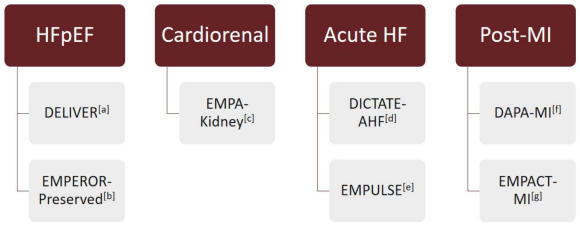
Who shouldn't you start an SGLT2i on?

- 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

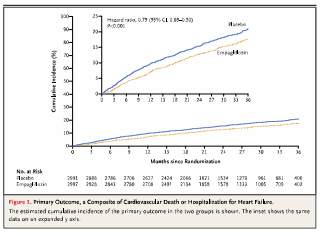


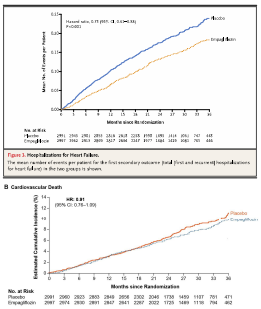
Evaluation of SGLT2 Inhibitors Beyond HFrEF: Ongoing RCTs



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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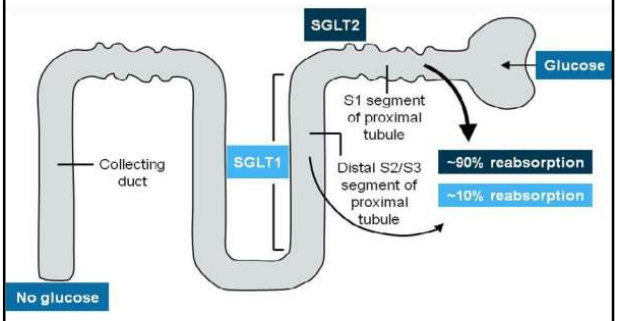
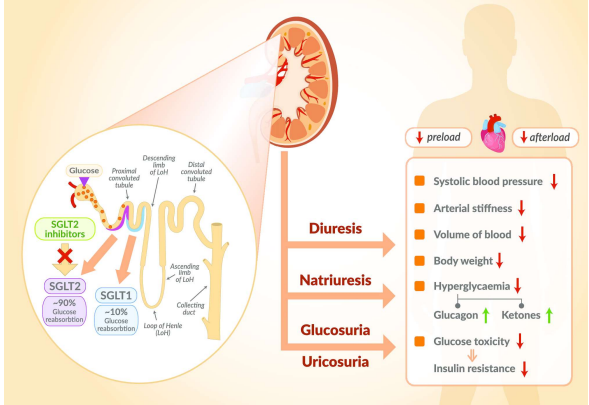
Questions?

• **E-mail:** andrew.dsilva@gstt.nhs.uk





Dutka et al. Heart Failure Reviews (2021) 26:603–622