KING'S HEALTH PARTNERS

An Academic Health Sciences Centre for London

Pioneering better health for all

Welcome back - to all special (ist) heart failure team

Sodium–glucose co-transporter 2 (SGLT2) inhibitor

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ESC HF 2021 NICE Local Guidelines

What's new

- **the following are now all 1st Line**

ACE-I/ARNIa / Beta-blocker / MRA / Dapagliflozin/Empagliflozin **'The four pillars'**

And of course

- Loop diuretic for fluid retention if / when required

- **What's out**

Not much

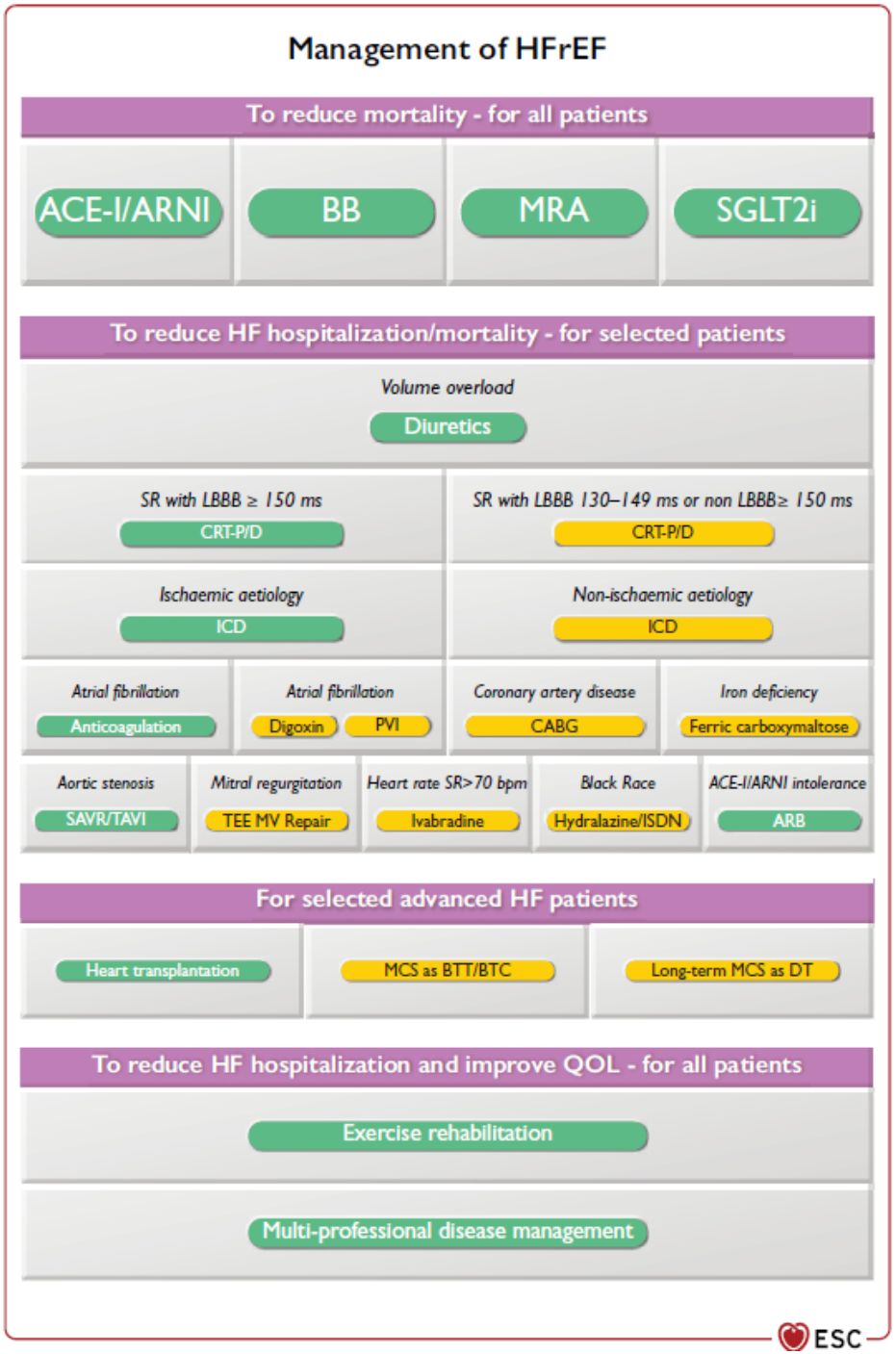
Less evidence for CRT if QRS < 150MS, slightly less emphasis / evidence for ICD in DCM but increased evidence for AF ablation

- **What's the same ?**

Most every things else with increasing emphasis on Cardiac exercise rehab/ palliative care and holistic care gets a few more lines

What about NICE / local guidelines ?

ESC HF 2021



SGLT2 Inhibitors New friend or old foe

1835 Phlorizin – naturally occurring phenol glycoside 1st isolated from the bark of an apple tree

Early animal studies: phlorizin – renal glycosuria, weight loss without hyperglycaemia

1980s – 1999 Studies evolved – work in diabetic – renal vascular

SGLT2i used in Diabetes since 2012

T2DM with CV risk but not HF:	Reduction in CV death/MI/stroke and HHF
2015 EMPA-REG CV outcome study	**14% and 35% (38% for CV death)**
2017 CANVAS CV outcome study	**14% and 33%**
2019 DECLARE-TIMI 58.	**17% and 27% (HHF /CV death)**
2019 DAPA- HF	**26% (death any cause 17%, HHF 30%)**

2019, CREDENCE (CKD) 2020 VERTIS CV,

2020 EMPEROR- Reduced	**25% (driven by HHF 31%)**
2021 EMPEROR-preserved	**21% (driven by HHF 29%)**

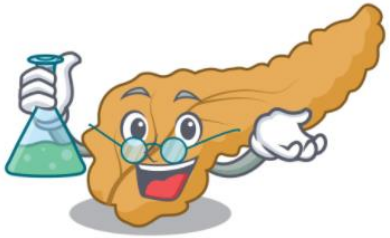
2022 DAPA–CK SOLOIST-WHF, SCORED

NICE approval and local guidelines

•EMPA-REG CV outcome study DECLARE-TIMI 58 CV / HF renal with diabetes .

•NICE approved SGLT2 inhibitors dapagliflozin▼(T.A.679 Feb 2022) and empagliflozin▼ (T.A. 773 Mar 2022) in HFrEF, (≤40%) without diabetes mellitus

•HFpEF - EMPEROR-Preserved SGLT2 inhibitor (empagliflozin) in patients with HFpEF Significantly reduce HF hospitalization, neutral effect on cardiovascular (CV) death (Exciting but not NICEed yet)



Case study 1 Mr DJ, Age 73

Criteria or SGLT2 inhibitor

Echocardiogram reduction in LV function to 31%

IHD with coronary artery bypass -2005

Angiogram 2016: two drug-eluting stents

ICD insertion 2019 post OOHVF arrest

angiogram no obstructive coronary disease

Episodes of VT 2021 with appropriate ICD shocks

Type 2 diabetes

Hypercholesterolaemia

Hypertension

BP 136/86 mmHg

HR 85 BPM

Weight 122 kg

ECG paced with CHB, QRS 190 ms.

LVEF: < 40%

BP: No issues as BP > 95 mmHg
(3-5/2 mmHg drop)

Age: Caution as aged >65

HR : SGLT2I has no effect on HR

Weight: loss up to 3kg (visceral fat reduction)

Renal function / HBA1c

C-reactive Protein				HbA1c (IFCC),		17Nov21 11:19	16Dec21 09:55
Sodium	139		136	HbA1c (DCCT),			↑ 96
Potassium	↑ 5.4		↑ 6.1	Urine Creatinine (Random)			* ↑ 10.9
Creatinine	↑ 163	*	↑ 244	idocrine			
Urea	↑ 21.1		↑ 27.8	Ferritin		↓ 17	
Total Protein	73		↑ 83	Folate			
Albumin	44		50	NT-proBNP.			
Globulin	29	*	33	B12			
Bilirubin (Total)	5		9	Thyroid Stimulating Hormone			
Alkaline Phosphatase	78		83	Free Thyroxine			
Aspartate Transaminase	28		18	ecial investigations			
Gamma-glutamyl Transf...	↑ 69		53	Iron		↓ 11.2	
Uric Acid	↑ 455			Total Iron Binding Capacity.		65	
Estimated GFR	* ↓ 28	*	↓ 17	Transferrin Saturation		↓ 17	

Case study 1 Mr

Current Medications: No allergies /

Sacubitril Valsartan 97/103 mg twice daily

MRA – none yet

Bisoprolol 2.5 mg twice a day

ISMN 60mg once a day

Bumetanide 2 mg + / - 1 – 2 mg per day

Ranolazine 375 mg twice daily

Aspirin 75 mg once a day

Metformin 1 g twice a day

Rosuvastatin 10 mg once a day

Liraglutide as directed

Lansoprazole 30 mg once a day

Gabapentin 600 mg mane, 300 mg midda

Zopiclone 3.75 mg at night

GTN spray prn

No OTC medicines

Medication cessation: Ramipril STOPP

BP: 147/74 mmHg HR 75 BPM

	04Apr22 13:56	04Apr22 13:56
hemistry		
outine chemistry		
Sodium		142
Potassium		⬆ 5.4
Creatinine		72
Urea		5.9
Phosphate	1.07	
Calcium	2.32	
Adjusted Calcium	2.18	
Total Protein		63
Magnesium	⬇ 0.64	
Albumin	47	47
Globulin		⬇ 16
Bilirubin (Total)		10
Alkaline Phosphatase	67	67
Aspartate Transaminase		18
Gamma-glutamyl Transferase		29
HbA1c (IFCC),	⬆ 76	
HbA1c (DCCT),	* ⬆ 9.1	
Estimated GFR		>90
ndocrine		
Ferritin		91
pecial investigations		
Iron		17.3
Total Iron Binding Capacity.		53

ventions to date

igh potassium

ed / reduced diuretics

t

soprolol

mmHg HR 75 BPM

loods with a plan to add Eplerenone. / increase
l

t cardio-renal-diabetic forum the addition of
hibitor (knonw high HbA1c)

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RUST) kch-tr.br-
tedheartfailurenurses@nhs.net

Renal function / HBA1c as follows

Weight: loss up to 3kg (visceral fat reduction)

Case study 2 Mr LW , Age 61

Diagnoses:

HFrEF index LVEF < 30% February 2021 (*LVEF 22.4%)*

Cardiac MRI, 16.02.21: suggest end-stage hype
with AF noted during MRI

No coronary artery calcification on CTPA

Head CT

PAF / sinus rhythm in July 2021

Uncontrolled hypertension

Type 2 diabetes (poorly controlled taking about 2
dose of metformin)

Cushing syndrome, 2015

Erectile dysfunction

2 cans of beer a day, smoker /secondary polycyt

Social History: Ex company director, failing eyesigh
and COVID brought an end to his working life. well-s
family

HR 74 BPM, BP 163/128 mmHg (bag of meds / m

HR 72 bpm, BP 116/82 mmHg (post all medicat

HR 111 bpm, BP 170/103 mmHg (run out of) 01/

HR 70 bpm, BP 119/82mmHg (took some meds)

Weight 72.35 kg Height 178.7 cm BMI kg/m²

ECG SR , QRS 110 ms. (March 2022)

Criteria or SGLT2 inhibitor

LVEF

	3Aug21 14:13	07Oct21 12:18	27Oct21 14:49	02Dec21 11:26	12Jan22 10:00
emistry					
outine chemistry					
C-reactive Protein					
Sodium	138	143	142	141	140
Potassium	4.1	4.7	3.9	4.4	4.4
Creatinine	107	* 117	* 118	* 121	108
Urea	3.5	4.9	7.6	5.8	5.3
Total Protein	62	67	71	69	67
Albumin	40	42	44	45	41
Globulin	22	* 25	* 27	* 24	26
Bilirubin (Total)	18	13	12	15	7
Alkaline Phosphatase	88	82	89	75	103
Aspartate Transaminase	15	14	↓ 8	↓ 9	10
Gamma-glutamyl Transferase	70	↑ 133	↑ 114	↑ 107	↑ 80
Estimated GFR	61	* ↓ 55	* ↓ 55	↓ 53	60
s02					
HBA1c (DCCT)		↑ 15.1			
HBA1c (IFCC)		* ↑ 142			
HbA1c (IFCC),				↑ 75	
HbA1c (DCCT),				* ↑ 9.0	
ndocrine					
Ferritin	114			↑ 483	
NT-proBNP.	↑ 4711				
pecial investigations					
Carboxyhaemoglobin					

Case study 2 Mr LW Age 61

Current Medications: No allergies / **dosette box**

Sacubitril/Valsartan 97/103 mg twice daily

Bisoprolol 10 mg once daily

Eplerenone 50 mg once daily (added 03.08.21 /Spiro s

Furosemide 40 mg once per day - do not add to dosett

Indapamide 2.5 mg once daily

Hydralazine 25mg twice daily (added

Isosorbide mononitrate 30 mg SR once daily (added

Atorvastatin 40 mg once daily at night

Omeprazole 20 mg once daily

Metformin 500 mg x2 twice a day (supported with

Gabapentin 300 three times per day (taking one pe

Vardenafil 20 mg prn (not in dosette

Edoxaban 60 mg once daily

Lantus Insulin and NovoRapid, (on Insulin > five years

Double COVID vaccinated

No OTC medicines

Medication Management Issues: Were in individ most boxes expired or issued in 2019 / 2020 - very help to get medication right.

Drug cessation / Intolerance History: Ramipril st February 2021. Amlodipine, Spironolactone stoppe Indapamide stopped during admission

	3Aug21 14:13	07Oct21 12:18	27Oct21 14:49	02Dec21 11:26	12Jan22 10:00
emistry					
outine chemistry					
C-reactive Protein					
Sodium	138	143	142	141	140
Potassium	4.1	4.7	3.9	4.4	4.4
Creatinine	107	* 117	* 118	* 121	108
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Total Protein	62	67	71	69	67
Albumin	40	42	44	45	41
Globulin	22	* 25	* 27	* 24	26
Bilirubin (Total)	18	13	12	15	7
Alkaline Phosphatase	88	82	89	75	103
Aspartate Transaminase	15	14	↓ 8	↓ 9	10
Gamma-glutamyl Transferase	70	↑ 133	↑ 114	↑ 107	↑ 80
Estimated GFR	61	* ↓ 55	* ↓ 55	↓ 53	60
s02					
HBA1c (DCCT)		↑ 15.1			
HBA1c (IFCC)		* ↑ 142			
HbA1c (IFCC),				↑ 75	
HbA1c (DCCT),				* ↑ 9.0	
docrine					
Ferritin	114			↑ 483	
NT-proBNP.	4711				
ecial investigations					
Carboxyhaemoglobin					

Ms YN Age 74

Current Diagnoses:

Heart failure with reduced ejection fraction: EF of 22%

Ischaemic heart disease

Moderate pulmonary hypertension

Hypertension

High cholesterol

Atrial fibrillation

ICD

Vaginal hysterectomy and left salpingo-oophorectomy and pelvic floor repair 2018

Under Urogynaecology for secondary bladder prolapse Vaginal prolapse – not amendable to conservative measures, under consideration for surgery

Admission to King's College Hospital with gastric outlet obstruction, underwent laparoscopic gastrojejunostomy (August 2021)

Current Medications:

Sacubitril/Valsartan 97/103mg twice daily

Bisoprolol 1.25 mg once a day

Eplerenone 25mg once daily

Frusemide 40 mg on alternative days

Simvastatin 40 mg once a day

Edoxaban 30 mg once a day

Vital signs

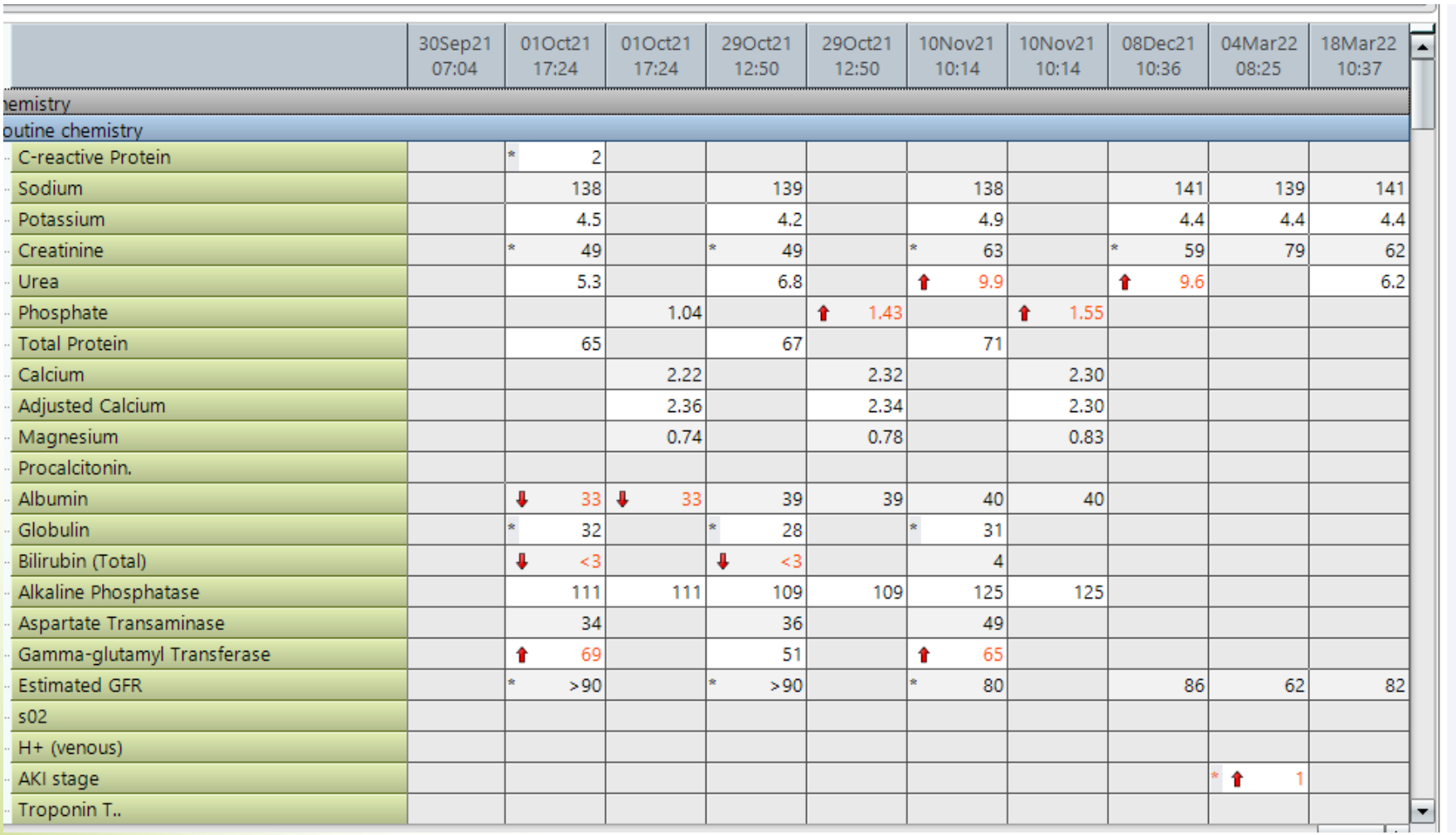
Pulse/Heart Rate min: 82 min

BP mmHg: 100/57 mmHg

Height in cm cm: 146.8 cm

Weight (kg) : 52.55 BMI kg/m^2: 24.4

Ms YN Age 74



	30Sep21 07:04	01Oct21 17:24	01Oct21 17:24	29Oct21 12:50	29Oct21 12:50	10Nov21 10:14	10Nov21 10:14	08Dec21 10:36	04Mar22 08:25	18Mar22 10:37
hemistry										
outine chemistry										
C-reactive Protein		* 2								
Sodium		138		139		138		141	139	141
Potassium		4.5		4.2		4.9		4.4	4.4	4.4
Creatinine		* 49		* 49		* 63		* 59	79	62
Urea		5.3		6.8		↑ 9.9		↑ 9.6		6.2
Phosphate			1.04		↑ 1.43		↑ 1.55			
Total Protein		65		67		71				
Calcium			2.22		2.32		2.30			
Adjusted Calcium			2.36		2.34		2.30			
Magnesium			0.74		0.78		0.83			
Procalcitonin.										
Albumin		↓ 33	↓ 33	39	39	40	40			
Globulin		* 32		* 28		* 31				
Bilirubin (Total)		↓ <3		↓ <3		4				
Alkaline Phosphatase		111	111	109	109	125	125			
Aspartate Transaminase		34		36		49				
Gamma-glutamyl Transferase		↑ 69		51		↑ 65				
Estimated GFR		* >90		* >90		* 80		86	62	82
s02										
H+ (venous)										
AKI stage									* ↑ 1	
Troponin T..										

Issues / concerns Case 3 YN, age 74

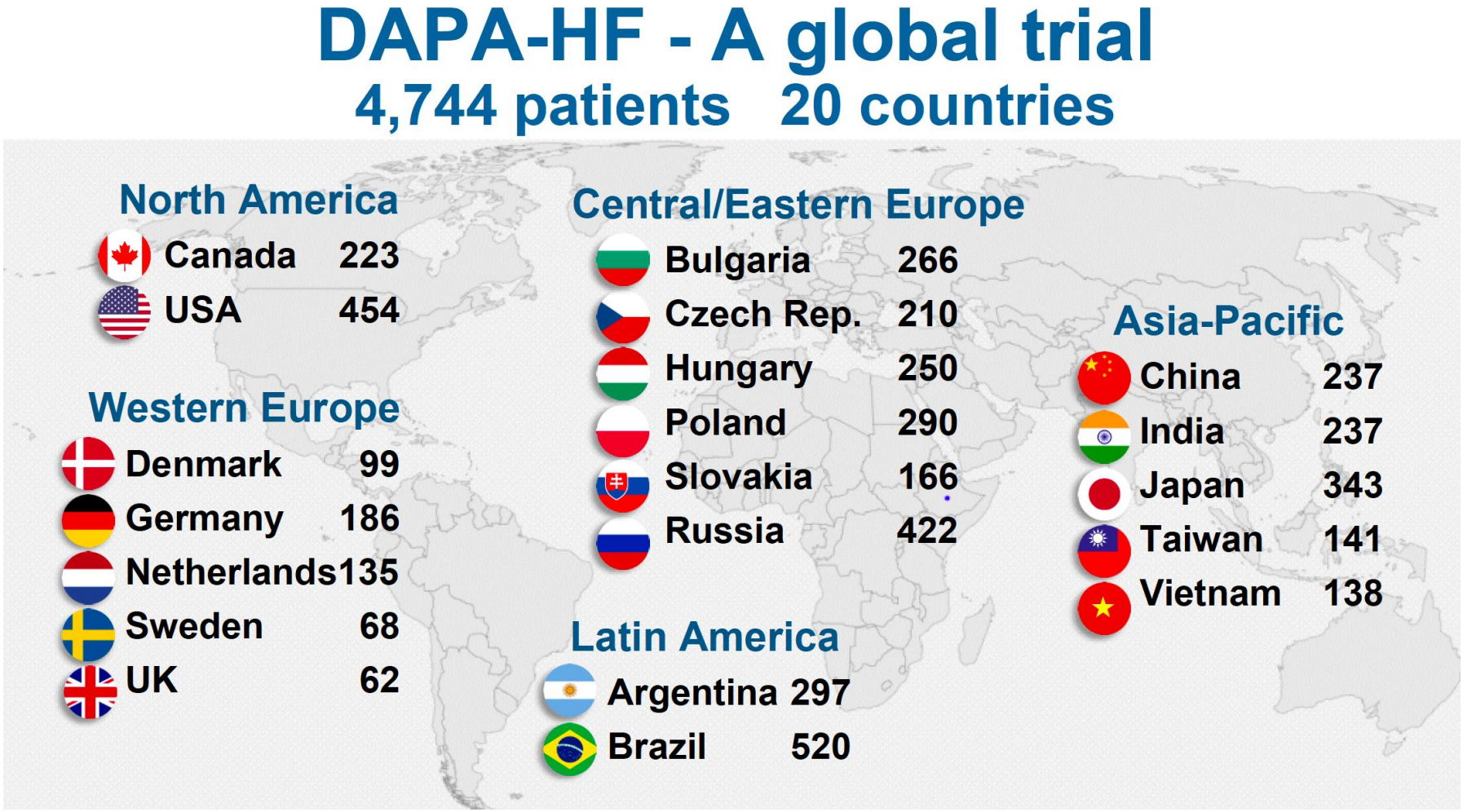
1. Are the bladder / Vaginal prolapse a cause for concern issue! Is there risk for thrush / infection?
2. Should we add an SGLT2 Inhibitor
3. Cautions with lower body weight
4. Cautions with pre operative / fasting procedures

Thank you

Trials in Heart Failure

SGLT2i	Trial name	Primary outcome	N	Results
DAPA	DEFINE-HF[1]	Average reduction of NT-proBNP	250	Feb 2019
DAPA	PRESERVED-HF[2]	Change in NT-proBNP	320	March 2019
DAPA	DAPA-HF[3]	Time to first CV death, hHF or urgent HF visit	4500	Dec 2019
DAPA	DELIVER[4]	Time to first CV death, hHF or urgent HF visit	4700	June 2021
DAPA	DAPACARD[5]	Change in global longitudinal strain of the left ventricle	52	April 2019
EMPA	EMBRACE-HF[6]	Change in pulmonary artery diastolic pressure	60	June 2018
EMPA	EMPEROR-Preserved[7]	Effects on cardiorespiratory fitness	4126	June 2018
EMPA	EMPEROR-Reduced[8]	Time to first CV death or hHF	2850	June 2020
EMPA	EMPERIAL program[9,10]	Change in exercise capacity	300	June 2019
EMPA	EMPA-RESPONSE[11]	Change in dyspnea, diuretic response, length of stay, plasma NT-proBNP	80	Dec 2019
CANA	NCT02920918[12]	Change in aerobic exercise capacity and ventilator efficiency	88	Nov 2018
Sotagliflozin (SOLOIST)	Studies in patients with diabetes who were hospitalized with HF			2020 / 2021

DAPA HF - large world wide study



Safety/adverse events

Patients exposed to at least one dose of study drug	Dapagliflozin (n=2368)	Placebo (n=2368)	p-value
Adverse events (AE) of interest (%)			
Volume depletion[+]	7.5	6.8	0.40
Renal AE[‡]	6.5	7.2	0.36
Fracture	2.1	2.1	1.00
Amputation	0.5	0.5	1.00
Major hypoglycaemia	0.2	0.2	-
Diabetic ketoacidosis	0.1	0.0	-
AE leading to treatment discontinuation (%)	4.7	4.9	0.79
Any serious adverse event (incl. death) (%)	38	42	<0.01

[+] Volume depletion serious AEs in 29 dapagliflozin patients (1.2%) and 40 placebo patients (1.7%), p=0.23

[‡] Renal serious AEs in 38 dapagliflozin patients (1.6%) and 65 placebo patients (2.7%), p=0.009

DAPA HF summary

Dapagliflozin in addition to standard therapy

- **Reduces worsening HF / admissions**
- **Reduced death both CV and all cause death**
- **Substantial risk reduction *(compositive end point of a 26% risk reduction)* in mortality / admissions across all groups including non Type 2 diabetics across a wide range of HBA1c levels**

Tolerated well

- **Fewer adverse events in DAPA group versus Placebo**
- **Improved QOL measured on Kansas City Questionnaire**
- **Benefits seen early after introduction**

DAPA – HF Trial

- **LVEF ≤40%, EGFr >30 , Inc NYHA class `11- IV (11% pts Sac Val)**

EMPEROR –Reduced summary

Empagliflozin in addition to standard therapy

- **Reduces worsening HF / admissions / Reduced CV death**
- **Risk reduction *(compositive end point of a 25% risk reduction)***

Tolerated well

- **Fewer adverse events in EMPEROR-Reduced group v Placebo**
- **Improved QOL measured**
- **Reduced decline in eGFR**

EMPEROR-Reduced HF Trial

- **LVEF ≤40%, EGFr >20 , Inc NYHA class 11- IV**

Recent meta-analysis of the DAPA-HF and EMPEROR-Reduced trials found no heterogeneity in CV mortality. Hence dapagliflozin or empagliflozin are recommended, in addition to OMT with an ACE-I/ARNI, a beta-blocker and an MRA, for patients with HFrEF regardless of diabetes status

Local guidance (SEL)

Dapagliflozin is approved for use in HF in patients without DM.

Empagliflozin

- approved by NICE and may be prescribed by hospital teams but all HF prescribing will be from the hospital
- Aim is for May IMOC approval- it usually takes about 3 months from NICE approval to local guidance and approvals.

SGLT2i in HF are initiated by a HF specialist (doctor, nurse or pharmacist in hospital or community settings) and first month issued but then followed up by primary care. In exceptional circumstances, such as prescriber unavailable, GP may be asked to initiate but they may refuse this request.

The guidance for dapagliflozin in patients with HF and DM is going to IMOC this month for approval.

For Sacubitril Valsartan - formulary change application from amber 3 (shared care) to amber 2 in line with SGLt2is in HF from end of May also..

Dapagliflozin In Heart Failure with Reduced Ejection Fraction (HFrEF) In Patients without Diabetes Mellitus

NHS

April 2021 v7

Dapagliflozin is a sodium glucose co-transporter 2 inhibitor (SGLT2i) traditionally prescribed for diabetes, but this guidance focuses on patients with HFrEF defined by left ventricular ejection fraction (LVEF) ≤40% ***without diabetes mellitus*** *(DM).*

In South London, dapagliflozin is recommended, within its marketing authorisation (unless contra-indicated), as an option for treating symptomatic chronic heart failure with reduced ejection fraction in adults, as an add-on to optimised standard medicines for chronic heart failure (Link: *SEL CHF guidance*):

Patient: with symptomatic HFrEF (NYHA class 2 to 4) and LVEF ≤40% **without diabetes**

↓

Prescribed:
Angiotensin-converting enzyme (ACEI) or angiotensin-2 receptor blocker (ARB) **OR** Sacubitril valsartan
With a beta-blocker (BB)
And, if tolerated, a mineralocorticoid receptor antagonist (MRA)

↓

On the advice of a heart failure specialist and if eGFR ≥ 30ml/min:
Start dapagliflozin 10mg once daily
(5mg daily initial dose if severe hepatic impairment: *see cautions on page 2*)

↓

Monitoring by a healthcare professional: (HF team and/or primary care)

1. **Blood pressure (BP)**: Initiation above systolic blood pressure (SBP) 95mmHg is recommended, especially in patients aged ≥65 years, as dapagliflozin can lead to a reduction in BP- consider also volume depletion/dehydration with diuretic therapy and review of other medications affecting BP. Refer to HF specialist for advice if required.
2. **Renal function**: Record at initiation and at least annually when clinically stable. If eGFR drops to <30ml/min refer to specialist (HF/renal team) but continue therapy unless there is an urgent clinical need to stop. No dose adjustment is required based on renal function but there is limited experience in heart failure patients with severe renal impairment (eGFR <30ml/min).
3. **Patient tolerance/adherence and side effects:** See page 2 for side effects to consider.
4. **Heart failure management plan**- If initiated in hospital, patients will be reviewed by the initiating HF team or referred to the community HF team, to reduce the risk of re-admission. Prescribing of dapagliflozin will transfer to primary care following hospital discharge, but HF teams are available to support and advise as required. Some patients will be initiated on dapagliflozin in outpatient clinics with a follow up in primary care on HF specialist advice (*see roles and responsibilities on page 2*).

Initiation: Evidence from clinical trial data suggests that, when added to optimised medical therapy, dapagliflozin lowers the risk of dying from cardiovascular causes and reduces the likelihood of hospitalisation or urgent outpatient visit due to heart failure. This benefit should be considered for each patient with a discussion concerning the risk of adverse effects, current co-morbidities and contra-indications to this therapy.
The starting dose is 10mg daily (*see cautions*: for severe hepatic impairment prescribe 5mg daily starting dose but this may be increased to 10mg if well tolerated), baseline renal function is required before starting therapy (caution in eGFR <30ml/min) and baseline blood pressure (caution if SBP below 95mmHg for elderly ≥65 years).

Patient information: An information leaflet has been developed for non-diabetics (in draft-*link*), as currently all product information refers to dapagliflozin in diabetics and will cause confusion. It is imperative that the patient does not think that they have diabetes and that their healthcare providers know this is

Dapagliflozin In Heart Failure with Reduced Ejection Fraction (HFrEF) In Patients without Diabetes Mellitus

NHS

April 2021 v7

therapy for HF and not DM. The patient should have clear information concerning the benefits of therapy (improved quality of life and HF symptoms, and reduced risk of hospitalisation for HF) and potential adverse effects, with monitoring requirements for this medication (see below).

Good Prescribing Practice: Ensure the indication for dapagliflozin is added to the prescription eg "for the heart" and that this is added to the dispensing label in pharmacy and the patient's clinical record.

Cautions and contra-indications (full list: *BNF and SPC*)

Contra-indications	Cautions
Pregnancy and breastfeeding	Limited experience in HF indication in severe renal impairment (CrCl <30ml/min)
Hypersensitivity to active substance or excipients	Anti-hypertensive therapy in hypotensive or elderly/frail patients if at risk from BP drop due to dapagliflozin: caution SBP below 95mmHg at initiation
	Lactose intolerance
	Severe hepatic impairment: Childs-Pugh score C, AST/ALT > 3x ULN or Bilirubin > 2x ULN except in Gilbert's: use 5mg initial dose but may increase to 10mg if well tolerated
	Limited experience in NYHA class IV

Interactions (link: Dapagliflozin | Interactions | BNF content published by NICE)
Documented interactions are related to the potential effects of synergistic hypotension with medications that lower blood pressure, and these parameters should be monitored in patients without diabetes.

Monitoring Requirements

1. **Blood pressure:** Due to its mechanism of action, dapagliflozin increases diuresis which may lead to the modest decrease in blood pressure (about 3-5mmHg SBP and 2mmHg DBP) observed in studies.
   - Caution should be exercised in patients for whom a dapagliflozin-induced drop in blood pressure could pose a risk, such as patients on anti-hypertensive therapy with a history of hypotension or elderly/frail patients. Patients who have experienced or are at risk of hypotension and/or dehydration may require additional monitoring if prescribed diuretics- may require diuretic dose reductions.
2. **Intercurrent conditions that may lead to volume depletion** (eg. gastrointestinal illness):
   - Monitoring of volume status (eg. physical examination, blood pressure measurements, laboratory tests including haematocrit and electrolytes, urea) is recommended.
   - Temporary interruption of treatment with dapagliflozin is recommended for patients who develop volume depletion until the depletion is corrected. See[7] Sick day rules in AKI
3. **Renal function:** Monitoring of renal function is recommended as follows:
   - Prior to initiation of dapagliflozin and at least yearly thereafter (eGFR can fall after initiation and if eGFR falls below 30ml/min- consider specialist/renal advice and co-prescribed medications/co-morbidities that may affect eGFR).
   - Seek advice and guidance from a renal specialist if eGFR drop of >10ml/min in a 6 month period or >15ml/min in a 12 month period.
4. **Important side effects that may require cessation of therapy:** for full side effect profile see[2] SPC Forxiga 10mg
   - Mycotic genital infections: common side effect managed with antifungals- usually only at the start of therapy- reassure patient and ensure adequate genital hygiene- if problematic/recurrent, stop*
   - Urinary tract infections (UTIs): due to its mechanism of action, dapagliflozin causes glucose in the urine, if causing significant UTIs such as pyelonephritis or urosepsis, stop therapy*
   - Fournier's gangrene: Necrotising fasciitis of the perineum is rare and therapy should be stopped*
   - Rash: eliminate possible other causes and consider stopping therapy*
   - Angioedema: rare but therapy should be stopped*
   - ***Always discuss stopping therapy with a HF specialist, unless there is an urgent clinical need to stop immediately**

Dapagliflozin In Heart Failure with Reduced Ejection Fraction (HFrEF) In Patients without Diabetes Mellitus

NHS

April 2021 v7

Roles and Responsibilities: Following initiation in hospital at least 2 weeks supply of dapagliflozin will be given to the patient in line with other medications at discharge (unless a medicines compliance aid is required- *local guidance applies*) and a discharge letter sent to primary care with initiation information and monitoring/follow up requirements.
Following initiation in outpatients, the primary care HCP may be asked to prescribe on HF specialist advice, on receipt of initiation information in the clinic letter and specific follow up/monitoring requirements.
When this is initiated in primary care, on the advice of a HF specialist, ensure the indication for therapy is linked to the patient record and ensure a follow up is scheduled either by a primary care healthcare provider (HCP) or with community HF support to check patient adherence/tolerance to therapy and heart failure management (eg. BP, U&Es, fluid balance) within the first month of therapy.

Initiation information to be completed by the prescriber:

- Indication for therapy, including an updated heart failure management/medicines optimisation plan
- Baseline renal function assessment and blood pressure reading
- Details of HF specialist and/or community HF team for follow up/support within the first month (*if required*)

It is recommended that patients are referred to their **local community pharmacy** for the New Medicines Service (NMS) or Discharge Medicines Service (DMS), that will assist understanding of and adherence to therapy, and ensure accurate medicines reconciliation. All **medicines compliance aid patients** must be discussed with their community pharmacy for new initiations to safeguard the patient and reduce the risk of medication errors.

For primary care, continue prescribing dapagliflozin, monitor this therapy and the patient at least annually (*see monitoring and side effects on page 2*). Ensure the patient is supported to adhere to this treatment unless adverse effects necessitate ceasing therapy (discuss with the HF team before stopping any prognostic medicines for heart failure, unless a clear clinical reason to stop immediately). As this is a new indication for an established medicine, report any adverse effects via the MHRA yellow card system.

When to refer from primary to secondary care?
Seek advice and guidance from the initiating team or appropriate specialist team for: renal function decline <30ml/min, patient tolerability issues and frailty concerns, that may lead to cessation of therapy.

This guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer. If dapagliflozin is prescribed for non-approved/unlicensed indications, prescribing responsibility will remain with the initiating clinician/organisation.

References: *accessed 24/3/21*

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2. Forxiga 10 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) accessed 16/3/21 updated 17/2/21
3. McMurray JJV, Solomon SD, Inzucchi SE, *et al.* Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med* 2019; 381: 1995–2008.
4. Dapagliflozin. SPS - Specialist Pharmacy Service. https://www.sps.nhs.uk/medicines/dapagliflozin/
5. Ponikowski P, Voors AA, Anker SD, *et al.* 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failureThe Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016; 37: 2129–200.
6. Heerspink HJL, Stefánsson BV, Correa-Rotter R, *et al.* Dapagliflozin in Patients with Chronic Kidney Disease. *New England Journal of Medicine* 2020; 383: 1436–46.
7. "Sick day rules" in patients at risk of Acute Kidney Injury; 2015; https://www.thinkkidneys.nhs.uk/wp-content/uploads/2015/07/Think-Kidneys-Sick-Day-Rules-160715.pdf#:~:text=Think%20Kidneys%20Programme%20Board%20is%20that%20it%20is,of%20AKI%20based%20on%20an%20individual%20risk%20assessment

Approval date: 2May 2021 Review date: May 2023 **(or sooner if evidence or practice changes)**

Follow-up:

1. Recommend rechecking renal function one month after initiation. Please note

Initiating dapagliflozin 10mg OD for HF in Patients with Type 2 Diabetes Mellitus

	HbA1c		
	<7%	7-10%	>10%
No medications	OK	OK	Diabetic team review
Metformin only	OK	OK	Diabetic team review
etformin + sulphonylurea (or repaglinide)	Stop sulphonylurea (or repaglinide)	Watch for hypoglycaemia	OK
Metformin + GLP1 receptor antagonist	OK	OK	Diabetic team review

Any patient on insulin should have a Diabetic team review *prior* to initiating dapagliflozin

lotes:

- If retinopathy worse than R1 (background retinopathy) ± HbA1c >10% discuss with Diabetic team to avoid decompensation of retinopathy.
- If history of DKA or type 2 diabetes for >10 years and not on insulin discuss with Diabetic team as high risk DKA.
- If BMI less than ..... or cachexia then discuss with Diabetic team as patient will be at high risk of further catabolic state and metabolic decompen
- See contraindications section overleaf.

Draft Dapagliflozin▼ In Heart Failure with Reduced Ejection Fraction (HFrEF) In Patients with Type 2 Diabetes Mellitus

Dapagliflozin for use in heart failure with reduced ejection fraction and type 2 diabetes

When starting dapagliflozin for non-glycaemic reasons, clinicians and patients need to be aware of the risks of hypoglycaemia (hypos), diabetic ketoacidosis (DKA) and acute kidney injury (AKI). Patients should be assessed for suitability of therapy. See page 3 for cautions and contra-indications and follow the flow chart below

Hypos: risk is higher in patients with lower HbA1c levels, those on medication(s) with a higher risk of hypos e.g. sulfonylureas (e.g. gliclazide, glimepiride), repaglinide or insulin, changes to eating patterns or those with a history of hypos

DKA: risk is likely to be higher in those with: a low body mass index, long duration of diabetes, dehydration, previous history of DKA or ketone prone type 2 diabetes, in a catabolic state, acutely unwell, pre and post surgery, pancreatitis, low calorie/carbohydrate intake, or where insulin doses have been reduced too much when starting dapagliflozin therapy

AKI: risk is higher in those with low renal function, acute illness or dehydration

Initiating dapagliflozin for patient with symptomatic HFrEF (NYHA class 2 to 4) and LVEF ≤40% with type 2 diabetes flow chart

Prescribed a maximum tolerated dose of:
Angiotensin-converting enzyme (ACEI) or angiotensin-2 receptor blocker (ARB) OR Sacubitril valsartan
With a beta-blocker (BB)
And, if tolerated, a mineralocorticoid receptor antagonist (MRA)

On a GLP-1 analogue (*e.g. semaglutide, dulaglutide, liraglutide*), gliptin (*e.g. sitagliptin, linagliptin*) or metformin

Start dapagliflozin 10mg daily and follow initiation checklist below

On insulin or a sulfonylurea (e.g. gliclazide, glimepiride) or repaglinide

eGFR >30ml/min to <45ml/min

HbA1c* < 69mmol/mol (<8.5%)

Start dapagliflozin 10mg daily and follow initiation checklist below
Although glucose lowering effects may be modest, consider reducing dose of sulfonylurea, repaglinide or insulin to prevent hypos as synergistic glucose lowering effects may be seen - monitor blood glucose levels closely for hypoglycaemia and seek advice from diabetes team as needed. If considering stopping insulin, discuss with diabetes team first

HbA1c* ≥ 69mmol/mol (<8.5%)

Start dapagliflozin 10mg daily and follow initiation checklist below
Although glucose lowering effects may be modest, monitor blood glucose levels closely for hypoglycaemia and seek advice from diabetes team as needed

eGFR ≥45ml/min

HbA1c* <69mmol/mol (<8.5%)

Contact the diabetes team for advice prior to starting dapagliflozin. If starting dapagliflozin, follow the initiation checklist below

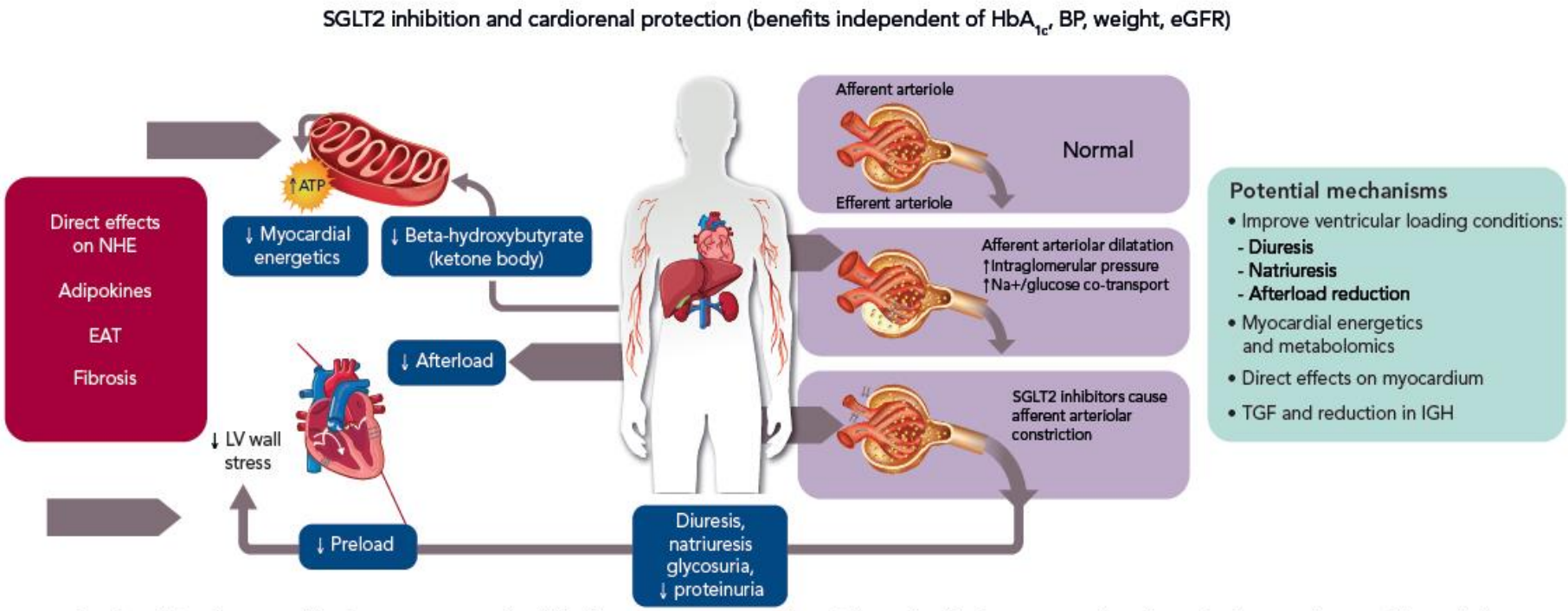
HbA1c* ≥ 69mmol/mol (≥8.5%)

Start dapagliflozin 10mg daily and follow initiation checklist below
Reduction in glucose is very likely. Monitor blood glucose levels closely for hypoglycaemia and seek advice from diabetes team as needed

- If a decision is made to start dapagliflozin (where relevant in conjunction with diabetes and/or heart failure specialists) and if eGFR≥ 30ml/min, follow initiation checklist below. **Dapagliflozin in HFrEF is 'Amber 2' in SEL – initiation and initial supply (first month) by specialist.**
- **Please ensure patient is counselled on hypoglycaemia, as well as sick day rules to prevent DKA and AKI.** For ongoing monitoring requirements, see monitoring requirements table below
- A shared decision to start dapagliflozin follows a discussion of the benefits and risks, current co-morbidities and contra-indications to therapy. The patient should have clear information concerning the benefits (improved quality of life and HF symptoms and reduced risk of hospitalisation for HF) and potential adverse effects and monitoring requirements (see page 3-4).
- If clinical concerns (or unsure) about the management of individual patients, or concerns over risk of hypos, DKA or AKI, heart failure team to seek advice from the diabetes team

**HbA1c in acutely unwell patients may not be reliable e.g. in anaemia, acute kidney injury, acute heart failure. Where acute changes may mean that the HbA1c is not reflective of current glycaemic levels, contact the diabetes team for advice prior to initiating*

Proposed Mechanism of Cardiovascular Benefits



ATP = adenosine triphosphate; BP = blood pressure; EAT = epicardial adipose tissue; eGFR = estimated glomerular filtration rate; IGH = intraglomerular hypertension; LV = left ventricular; NHE = sodium-hydrogen exchanger; SGLT2 = sodium–glucose co-transporter 2; TGF = tubuloglomerular feedback. Source: Verma et al. 2017.[37] Adapted with permission from the American Medical Association.

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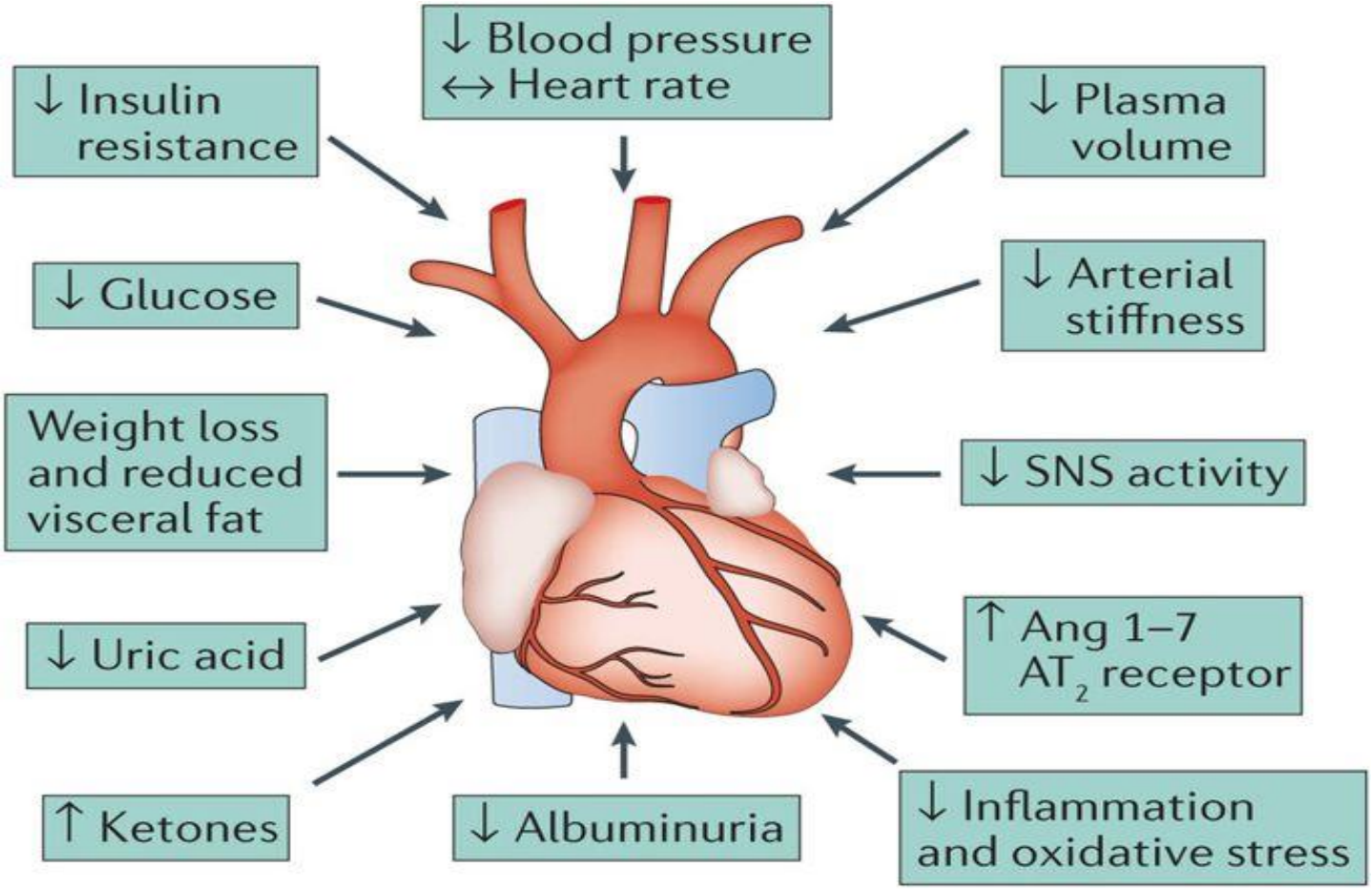
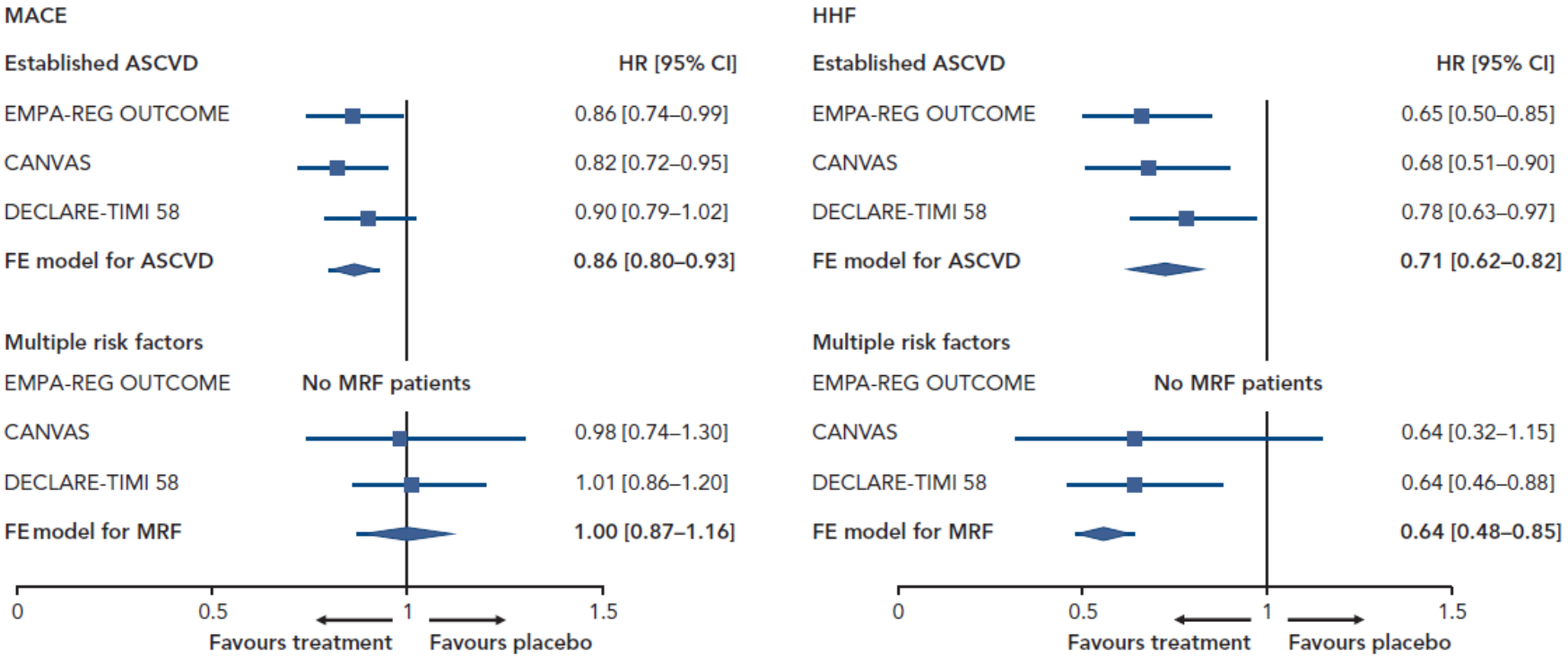
SGLT2 I mode of action



Nature Reviews | Nephrology

Impact of SGLT2 Inhibition on Cardiovascular Disease

Figure 1: Impact of SGLT2 Inhibition on Cardiovascular Disease Endpoints in Patients with Type 2 Diabetes



ASCVD = atherosclerotic cardiovascular disease; CVD = cardiovascular disease; HHF = hospitalisation for heart failure; FE = fixed effects; MACE = major adverse cardiovascular events; MRF = multiple risk factors; SGLT2 = sodium–glucose co-transporter 2; T2D = type 2 diabetes. Source: Zelniker et al. 2019.[12] Reproduced with permission from Elsevier.

Canagliflozin -Invokana

Dapagliflozin - Forxiga

Dapagliflozin -Edistride

Empagliflozin -Jardiance

- Ebymect (Dapagliflozin/metformin
- Synjardy (Empagliflozin / Metformin)
- Vokanamet (Canagliflozin / Metformin)
- Xigduo (Dapagliflozin / Metformin)

– Sotagliflozin (SOLOIST)
– Ertugliflozin (VERTIS CV)

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6 Jan 2022

DR SURGERY
Sent via Docman

HEART FAILURE CLINIC
Clinic Date: 5th January 2022
Typed Date: 6 Jan 2022
OUR REF: CM/al

Dear Doctors,

Current signs and symptoms: Mr was reviewed in the nurse led heart failure clinic at King Harold's way on 5th January 2022. He tells me he feels brilliant and has had an excellent response to the Dapagliflozin to the point where he is wearing shoes for the first time in five years. The oedema has practically resolved. He continues to have a good exercise tolerance and mobilises at a slow pace with a stick for support outside of the house. He denies any chest pain, dizziness, palpitations, breathlessness or PND. I would consider him to be NYHA Class I-II.

Examination: Chest auscultation was clear, he had very minimal pedal and ankle oedema bilaterally, His blood pressure sitting was 151/84mmHg and standing 159/95mmHg. His heart rate was 70bpm. Oxygen saturations were 96% on room air. Weight was 103kg a loss of 1kg.

Heart Failure Management Plan:

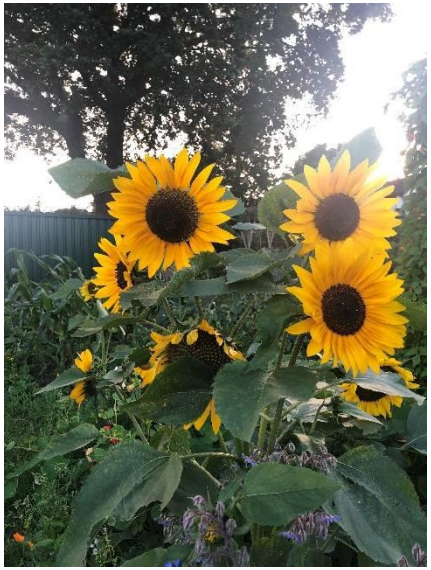
- **GP please could you add the Dapagliflozin 10mg once daily for heart failure to his repeat prescription**. I have issued him with another prescription meanwhile to tide him over. He is on this for heart failure and he has an eGFR 30 or greater and he has responded and feels much better for it.
- I note that his blood pressure has been creeping up and we discussed lifestyle measures in the first instance to try and improve on this. We discussed reducing portion size and stopping desserts apart from occasionally, in the hope that his weight will come down along with his blood pressure.
- I have asked him to aim for a blood pressure of 130/85mmHg and if this is not achievable at home he will give me a call and we will increase his Eplerenone to 50mg purely to improve hypertension control.
- I will review him in three months time.

Yours sincerely

Caroline Mapstone, Heart Failure Specialist Nurse
Community Heart Failure Team

KING'S HEALTH PARTNERS

?



Summary of Heart Failure Outcomes in SGLT2 Inhibitor Clinical Studies

Table 1: Summary of Heart Failure Outcomes in SGLT2 Inhibitor Clinical Studies

Outcome	Meta-analysis of SGLT2 Inhibitors in T2D CVOTs (Empagliflozin, Canagliflozin and Dapagliflozin)[17]		DAPA-HF (Dapagliflozin)[8]	EMPEROR-Reduced (Empagliflozin)[9]
	Overall Population (n=38,723)	History of HF (n=4,543)	HFrEF (n=4,744)	HFrEF (n=3,700)
Relative risk reduction (%)				
HHF	32	31	30	30
HHF and CV death	24	27	26	25
HR				
HHF	0.68 (95% CI [0.60–0.76]; p<0.001)	0.69 (95% CI [0.57–0.83]; p<0.001)	0.70 (95% CI [0.59–0.83]; p<0.001)	0.70 (95% CI [0.58–0.85]; p<0.001)
HHF and CV death	0.76 (95% CI [0.63–0.84]; p<0.001)	0.73 (95% CI [0.63–0.84]; p<0.001)	0.74 (95% CI [0.65–0.85]; p<0.001)	0.75 (95% CI [0.65–0.86]; p<0.001)

CV = cardiovascular; CVOT = cardiovascular outcomes trial; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; HHF = hospitalisation for heart failure; SGLT2 = sodium–glucose co-transporter 2; T2D = type 2 diabetes. Source: Arnott et al. 2020,[17] McMurray et al. 2019[8] and Packer et al. 2020.[9]

Rachel Howatson talked through the draft guidelines for use of SGLT2 inhibitors for HF patients *without diabetes* – attached. Action: Please let Rachel have any comments on the guidelines.

Despite Dapa having Green status for use with patients with diabetes, NICE is recommending that it is Amber for HF patients. A number of concerns were raised regarding delays to initiation due to the lack of prescribers, particularly in SWL. SGLT2i in HF without DM will still have to be amber- as NICE states start on advice of a specialist- however Rachel will propose a formulary change to Amber 1 rating: *Treatment can be initiated in primary care after a recommendation from an appropriate specialist.* It was stressed that these patients would all be followed-up by HF specialists as currently all HFrEF patients. Action: To support this proposal, please send Rachel examples of waiting lists and avoidable hospital admissions as evidence that patients are not receiving appropriate therapies in a timely fashion. Sally-Anne to provide Rachel with details regarding NMPs across South London. Rachel to draft formulary change submission.

There is still no progress on the guidelines for patients with HF *with diabetes*. This is hopefully going to IMOC this month.

A formulary change submission for sacubitril/valsartan going from Amber 2 to Amber 1 is going to IMOC this month – submission attached. This will remove the need for TOC forms.

NT-proBNP reporting – further to the discussion at the last meeting, the attached document has been drafted for use by SWLP reporting. This is in line with wording used across London, although the rest of London will not be using age cut-offs. It was agreed that ng/L would be used throughout. Action: please send any comments to Sue.

PIFU for heart failure – the lead consultant and HFNS should have received an invite to the PIFU event on 19th May. This is an opportunity to get an overview of the recent guidance on PIFU with HF patients, to hear from trusts who have already implemented this and start the process of reaching a Pan-London consensus on how this will work.

North London Priorities – it was agreed in general that SL would align with NL where appropriate. NL were more advanced in terms of engagement with primary care and further forward with digital innovations, such as remote monitoring and the use of apps. Does ORTIS have a role in HF – potentially in the future, initially it is being rolled out across cardiac surgery. It was also identified that PASs sich as EPIC and Cerner could be used to facilitate virtual wards etc. Action: it was suggested that a rep from NL ODN be invited to the next meeting, with a view to looking at HF templates for primary care referrals and management.

Primary Care Engagement – this has proved to be a long standing challenge in terms of identifying GPs to engage with. It was recognised that have Nicola Jones's involvement was extremely beneficial and we need to replicate this in SEL. There is CPIP funding at ODN level to facilitate GP engagement. It was suggested that perhaps a separate meeting should be set-up to engage with primary care at a time which worked for them to explore ways to engage. Action: Alice to raise needs for reps at SEL and SWL level. Members of this group to volunteer to be involved in such a meeting and send through names of potential GPs to approach.