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The best treatment options for type 2 diabetes in 2020

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The Physician's Prayer – Sir Robert Hutchison (1871-1960):
'Good Lord, deliver us from inability to let well alone; from too much zeal for the new and contempt for what is old; from putting knowledge before wisdom, science before art and cleverness before common sense; from treating patients as cases and from making the cure of the disease more grievous than the endurance of the same.'

This report was made possible by an unrestricted educational grant from Boehringer Ingelheim. *The content of the report is independent of the sponsor.*

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SC-ZA-00289

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Introduction

New evidence is emerging on the ability of sodium-glucose co-transporter 2 (SGLT-2) inhibitors to save eyesight,[1] kidney, heart and even liver function in the patient with type 2 diabetes mellitus (T2DM).[2]

The EMPA-REG OUTCOME trial examined the effects of empagliflozin on cardiovascular morbidity and mortality in T2DM patients at high cardiovascular risk, and was the first study to demonstrate that use of an SGLT-2 inhibitor is associated with a significant reduction in the risk of three-point major adverse cardiovascular events (MACE) - a composite of cardiovascular death, non-fatal myocardial infarction (MI) or non-fatal stroke. The reduction in MACE, 14% versus placebo, was driven primarily by a 38% reduction in the risk of cardiovascular death.[3] Empagliflozin also reduced the risk of microvascular outcomes (a pre-specified composite of time to first initiation of retinal photocoagulation, vitreous haemorrhage, diabetes-related blindness or incident/worsening nephropathy) by 38% versus placebo, driven mainly by a reduction in kidney outcomes.

In examining current evidence on the protective benefits of SGLT-2 inhibitor therapy, Professor Chilton emphasised the important role of the endocrinologist and diabetologist in the treatment of T2DM and the reduction of associated long-term complications. "Cardiologists may initiate SGLT-2 inhibitor treatment, but the ongoing care of the patient will return to diabetes-focused general practitioners, physicians or endocrinologists and their multidisciplinary teams," Professor Chilton noted.

LEARNING OBJECTIVES

You will learn:

- To critically examine the evidence for new antidiabetic medicines in different diabetic populations
- To not simply treat patients as 'guideline cases', but to evaluate and treat each patient holistically
- To not be over-zealous, but to treat patients appropriately, so that those who will really benefit from new medications get them.

Protecting vision

Concerns about an increased risk of retinopathy in T2DM patients treated with glucagon-like peptide 1 receptor agonists (GLP-1 RAs) arose from the SUSTAIN-6 trial, which compared semaglutide to placebo for cardiovascular outcomes.[4] Also taking into account the non-significant increase in retinopathy events associated with the GLP-1 RA liraglutide, this prompted further analyses of the retinopathy data from the EMPA-REG OUTCOME trial.

Post-hoc analysis of pre-specified retinopathy-related complications was performed after week 12 in two sub-groups of EMPA-REG OUTCOME; those who achieved a reduction in HbA_{1c} of ≥1% or <1%. There were no differences in retinopathy-related complications between these subgroups; there were also no differences in patients treated with either 10mg or 25mg empagliflozin. Cox regression analysis was performed on the combined subgroups to reflect a cumulative incidence of retinopathy outcomes - a composite of initiation of retinal photocoagulation, vitreous haemorrhage, diabetes-related blindness, or administration of intravitreal agents (Table 1, Figure 1).

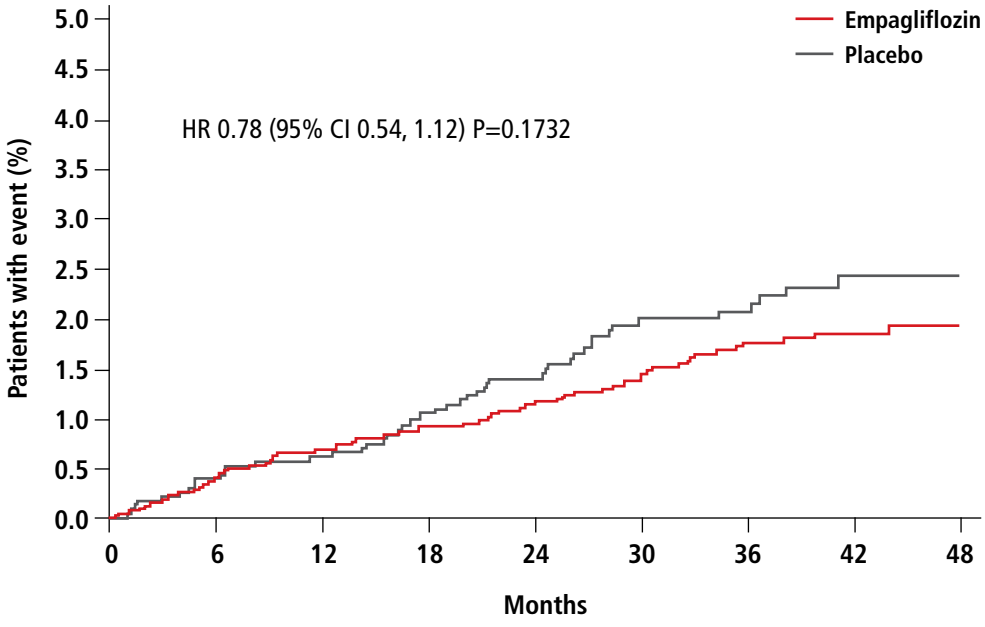
This is a very important beneficial outcome for patients as saving vision is critical to the quality of life of T2DM patients.

Endocrinology is, in my view, a research opportunity for cardiology

Table 1. Retinopathy outcomes in EMPA-REG OUTCOME[1]

	Empagliflozin	Placebo
Composite retinopathy	5.6*	7.3*
Initiation of retinal photocoagulation	3.0	4.4
Vitreous haemorrhage	2.2	2.4
Administration of intravitreal agents	0.7	1.0

*per 1 000 patient-years



Number of patients

Placebo	2 332	2 283	2 240	2 179	1 939	1 431	1 218	784	172
Empagliflozin	4 686	4 608	4 520	4 433	3 999	2 949	2 499	1 639	396

Figure 1. EMPA-REG OUTCOME: Cumulative incidence of a composite of retinopathy outcomes

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Saving the nephron

It may be that as the macula shrinks because of an action of SGLT-2 inhibitors on receptors at the back of the eye, you are able to save vision

Results of the EMPA-REG OUTCOME trial suggested that SGLT-2 inhibition could improve renal outcomes in T2DM. However, as relatively few patients reached end-stage kidney disease and the trial cohort was generally at low risk for kidney failure, some uncertainty remained. The Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE)[5] trial was designed to examine the effects of SGLT-2 inhibition in patients with T2DM and albuminuric chronic kidney disease.

All patients in CREDENCE had an eGFR of between 30 and <90ml/min/1.73m^2 and albuminuria with a urine albumin-to-creatinine ratio (UACR) >300-500mg/g. All patients were stable on standard angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker treatment. The trial was stopped early (median 2.62 years) as the renal benefits emerged in the canagliflozin-treated group. The final results showed that the canagliflozin-treated patients had a lower risk of the primary composite outcome of end-stage kidney disease, doubling of serum creatinine level, or death from renal or cardiovascular causes (Table 2).

The post-CREDENCE era reinforces the position of SGLT-2 inhibitors as drugs providing renal protection, in addition to their anti-glycaemic effects.[6]

Table 2. CREDENCE trial

	Canagliflozin	Placebo	Canagliflozin	Placebo	Hazard ratio (95% CI)	P-value
	No./total no.		Events/1 000 patient-yr			
Efficacy						
Primary composite outcome	245/2202	340/2199	43.2	61.2	0.70 (0.59-0.82)	0.00001
Doubling of serum creatinine	118/2202	188/2199	20.7	33.8	0.60 (0.48-0.76)	<0.001
End-stage kidney disease	116/2202	165/2199	20.4	29.4	0.68 (0.54-0.86)	0.002
Cardiovascular death	110/2202	140/2199	19.0	24.4	0.78 (0.61-1.00)	0.05
Secondary outcomes						
Cardiovascular death or hospitalisation for heart failure (HF)	179/2202	253/2199	31.5	45.4	0.69 (0.57-0.83)	<0.001
Cardiovascular death, myocardial infarction, or stroke	217/2202	269/2199	38.7	48.7	0.80 (0.67-0.95)	0.01
Hospitalisation for HF	89/2202	141/2199	15.7	25.3	0.61 (0.47-0.80)	<0.001
End-stage kidney disease, doubling of serum creatinine, or renal death	153/2202	224/2199	27.0	40.4	0.66 (0.53-0.81)	<0.001

Saving the liver

Non-alcoholic fatty liver disease (NAFLD) often co-exists with T2DM. In the presence of T2DM, NAFLD progresses more rapidly to non-alcoholic steatohepatitis (NASH), liver fibrosis and cirrhosis. The presence of NASH increases the risk of MI three-fold. Preventing progression to NASH is a focus of antidiabetic drugs, as NASH is also associated with insulin resistance. Currently, pioglitazone is the only diabetes drug that has a registered indication for treatment of NAFLD. This is set to change as data on the benefit of SGLT-2 inhibitors in NAFLD emerge.

In animal model studies, SGLT-2 inhibitors have been shown to reduce accumulation of fatty tissue in the liver, as well as liver fibrosis.[7] While studies in humans are scarce, the recent E-LIFT trial of 10mg empagliflozin treatment over 20 weeks in T2DM patients with NAFLD showed reduced liver fat and improved alanine transaminase (ALT) levels in empagliflozin-treated patients, compared to those on standard treatment without empagliflozin (Figure 2).[8]

It is in this context that the EMPA-REG OUTCOME trial changed the world of clinical cardiology practice for the first time

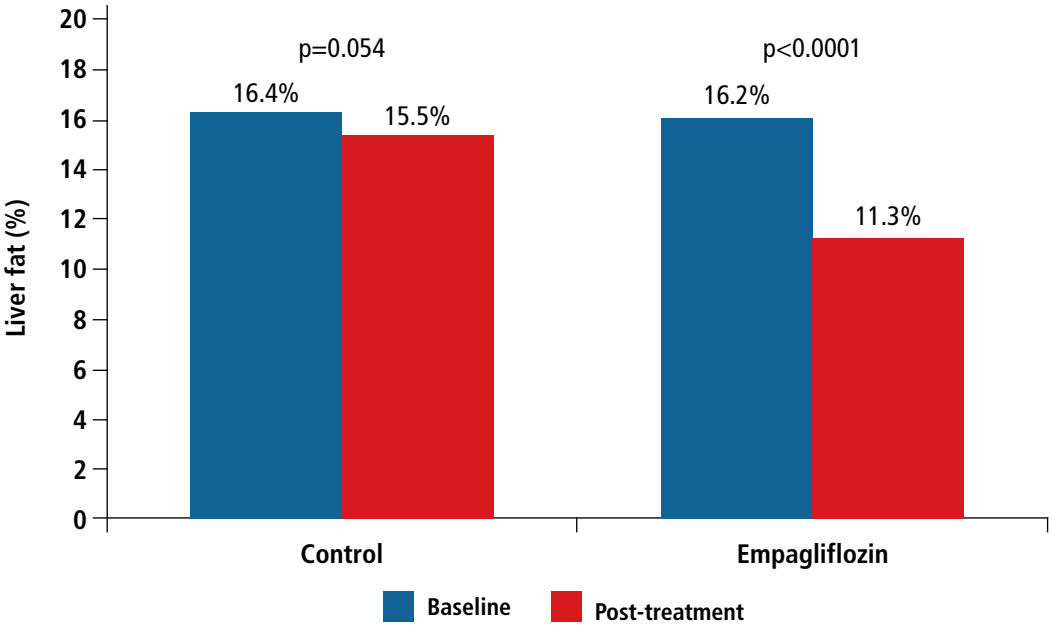

Figure 2. E-LIFT: Baseline and post-treatment changes in liver fat

Saving the heart

Importantly, 99% of the patients included in the EMPA-REG OUTCOME trial had pre-existing cardiovascular disease, a pattern that other SGLT-2 inhibitor trials seek to emulate. In this very high-risk group, the addition of empagliflozin to standard treatment was associated with a relative risk reduction (RRR) of 38% for death from cardiovascular causes, a 35% RRR for hospitalisation for HF and a 32% RRR for death from any cause, compared to standard treatment without empagliflozin (Figure 3).[3] It is in this context that the EMPA-REG OUTCOME trial changed the world of clinical cardiology practice for the first time.[9]

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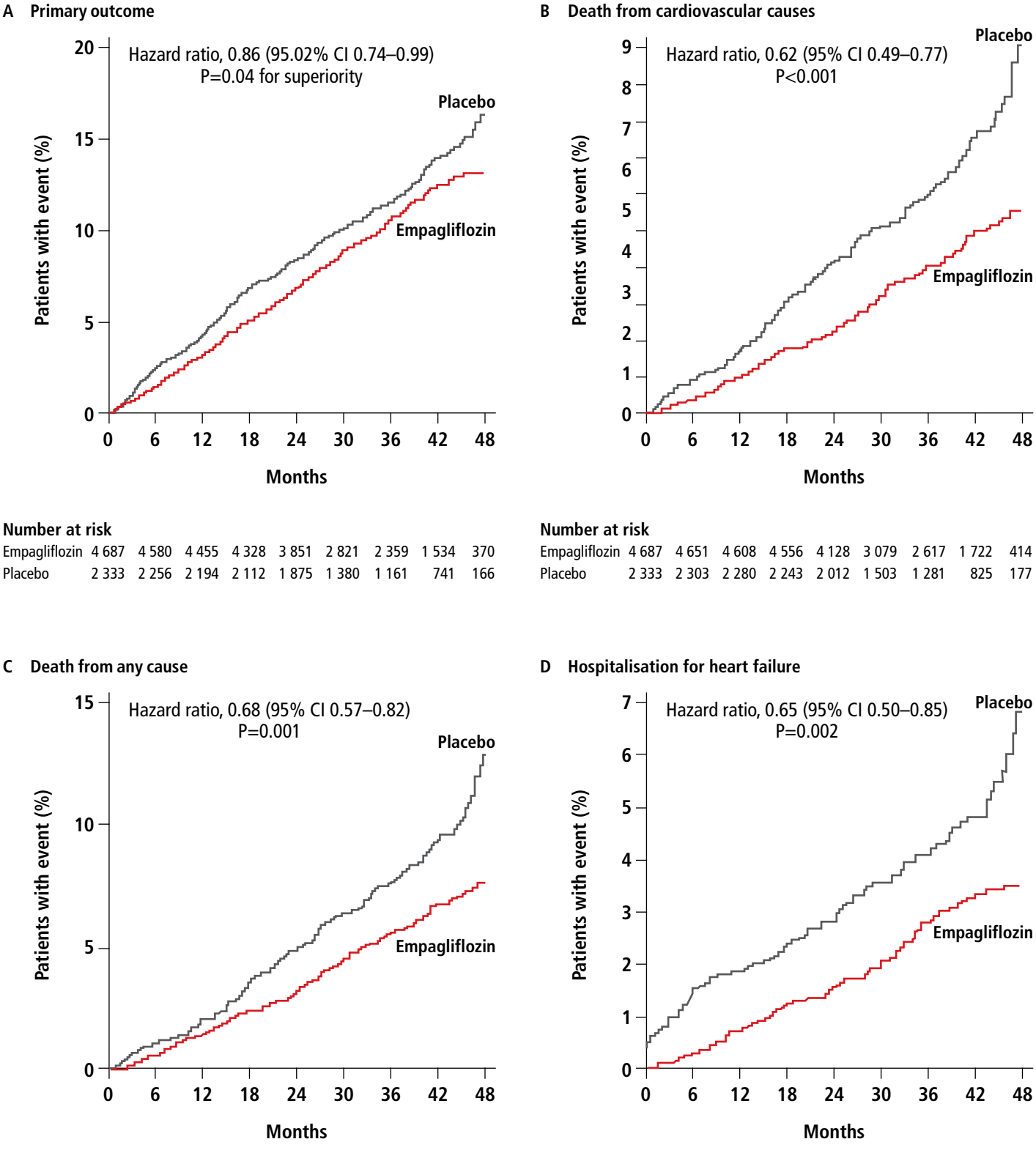

Figure 3. EMPA-REG OUTCOME: Cardiovascular outcomes and all-cause mortality[3]

What do we expect to see in the future?

All agents in the SGLT-2 class are probably going to show benefit in HF

The most surprising finding of the EMPA-REG OUTCOME trial was that the HF benefit was seen early, within three days of administering empagliflozin (Figure 4).[10] This benefit was seen in patients with or without diabetes, although Professor Chilton pointed out that most patients would have certainly been insulin-resistant and '*en route* to a diagnosis of diabetes'. "All agents in the SGLT-2 class are probably going to show benefit in HF," Professor Chilton noted.

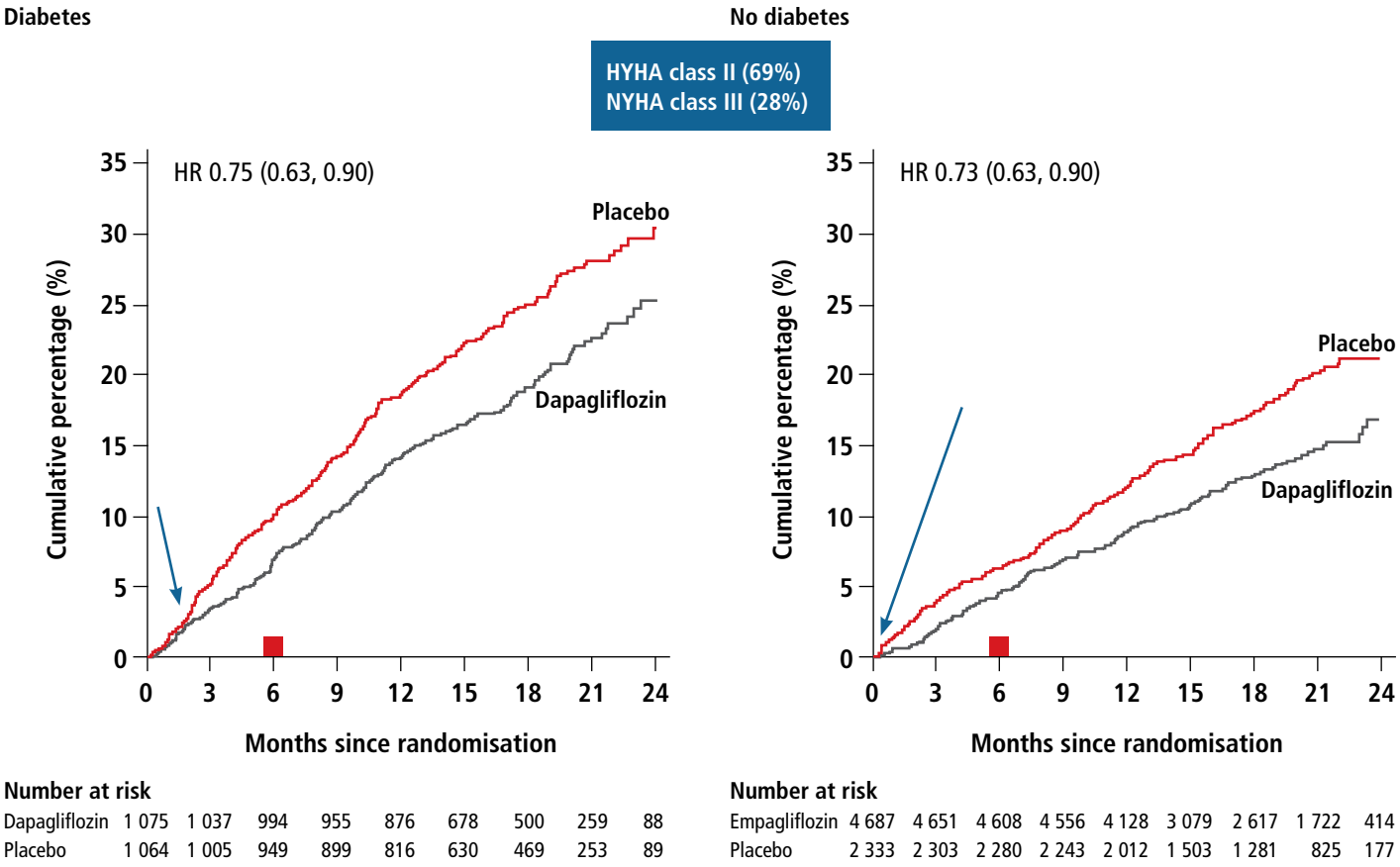

Figure 4. EMPA-REG OUTCOME's primary composite outcome – cardiovascular death/HF hospitalisation/urgent HF visit

A new era in heart failure treatment is likely to emerge as trials with SGLT-2 inhibitors announce results in 2020 and 2021

It is important to note that the angiotensin-neprilysin benefit for HF observed in the PARADIGM-HF trial only occurred later, at about 180 days after treatment initiation.[10] Angiotensin-neprilysin has totally different mechanisms of action from SGLT-2 inhibitors; with several mechanisms of action likely to be involved in the HF benefit of SGLT-2 inhibitors (Figure 5).[11] The benefits of dapagliflozin seen in HF patients without diabetes participating in the DAPA-HF trial[12] will likely increase the number of studies investigating the potential mechanisms of action (Figure 6).

In Professor Chilton's experience, "When giving SGLT-2 inhibitors to HF patients, the medication is very well tolerated and patients feel the benefit sooner."

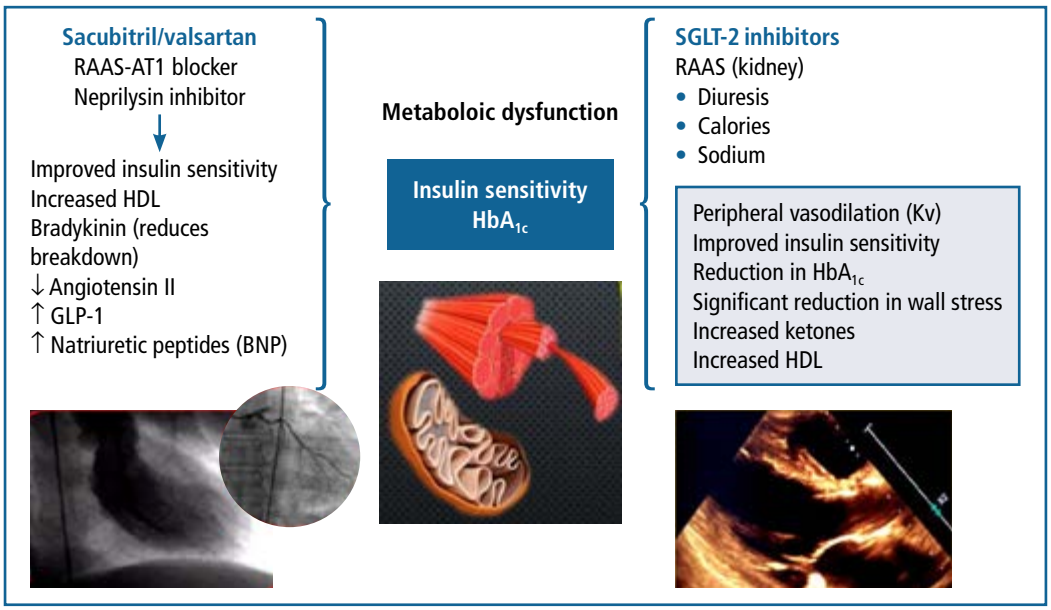

Figure 5. Translational biology of heart failure drugs

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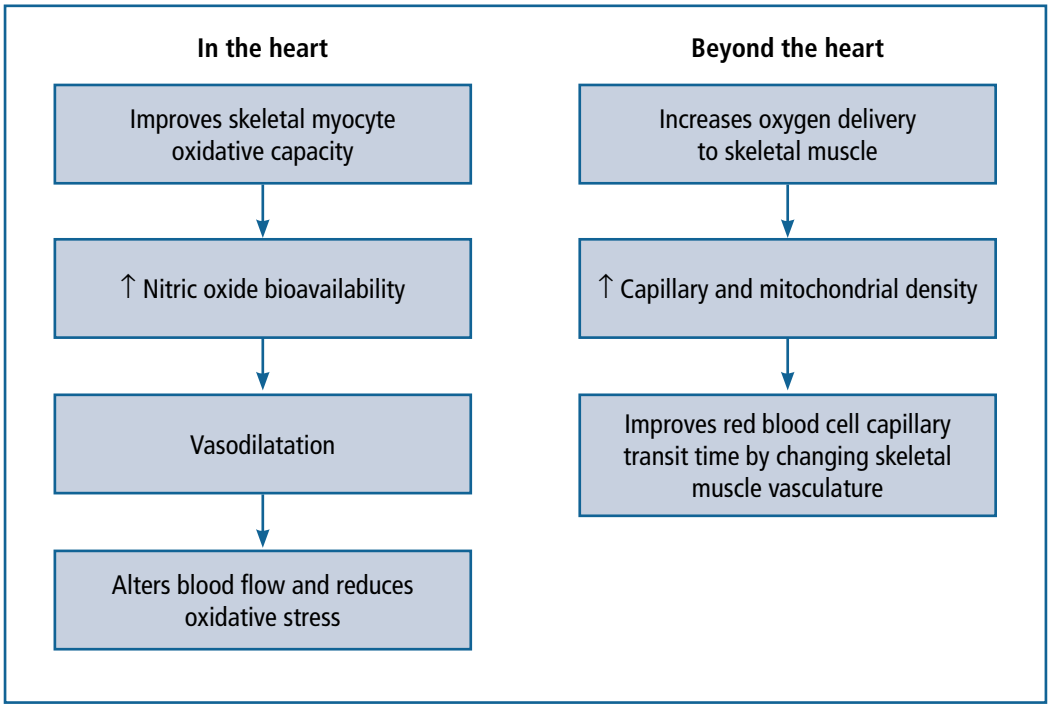

Figure 6. Summary of SGLT-2 inhibition actions at a cellular level

Does cardiology intervention reduce MACE long term in patients with diabetes?

The initial FREEDOM trial[13] found that in patients with diabetes and multivessel disease, coronary artery bypass grafting (CABG) was associated with better clinical outcomes than percutaneous coronary intervention (PCI) with drug-eluting stents. These procedures reduced death rates and rates of MI, but were associated with a higher rate of stroke. Subsequent evaluation of the long-term outcome of patients on insulin therapy and non-insulin therapy showed a higher five-year percentage rate of death, MI and stroke in insulin-treated patients.[14]

This mortality and event rate is indicative of the limitations of current intervention strategies, and places an important emphasis on novel antidiabetic agents, such as empagliflozin, which can reduce cardiovascular mortality, as well as on preventative strategies such as weight loss and modification of the other risk factors found, in the INTERHEART trial, to account for 90% of MIs.[15]

KEY LEARNINGS

- The long-term care of T2DM patients will remain with diabetes-focused general practitioners, physicians and endocrinologists to achieve maximum benefit
- Retinopathy outcomes in EMPA-REG OUTCOME emphasise the important role of SGLT-2 inhibitors in saving vision
- Results from CREDENCE demonstrate renal protection using SGLT-2 inhibitors in T2DM patients with impaired kidney function
- SGLT-2 inhibitors reduce fibrosis and the accumulation of fatty tissue in the liver of T2DM patients; this is important as NASH contributes greatly to the risk of MI
- HF benefits emerge early after initiation of SGLT-2 inhibitor therapy, heralding a new era in HF treatment.

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