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SGLT2-INHIBITORS AND MECHANISMS OF CARDIOVASCULAR BENEFIT BEYOND GLYCAEMIC CONTROL

Several clinical trials have consistently shown that SGLT2-I have impressive beneficial cardiovascular benefits in patients with and without diabetes and who have heart failure (reduced ejection fraction, EF and preserved EF). The use of SGLT2-I results in an average weight loss (adipose tissue mass) of 1-3kg, a reduction of approximately 1% in the HbA1c and a fall in systolic and diastolic blood pressure of 3-6mmHg and 0-2mmHg, respectively.

The early divergence of the primary cardiac major adverse cardiac events (MACE) endpoint curves in these trials would imply that the benefits are not occurring as a slowing down of the coronary atherosclerotic process. Thus, the clinical data suggests the mechanism(s) must respect the following considerations: 1. Efficacy in the treatment and prevention of heart failure, 2. Rapid onset of benefit, 3. Efficacy independent of glycaemic status, 4. Association with renal protection. Furthermore, the SLGT2 receptors are located in the proximal convoluted tubules of the nephron rather than cardiomyocytes. Inhibition of these receptors prevents reabsorption of filtered glucose at the proximal convoluted tubule resulting in insulin-independent glycosuria. As SGLT2 receptors are not expressed in the heart, the mechanism of the direct cardiac effects has remained unclear. The principal mechanistic benefits supporting SGLT2-I are described below and summarized in Figure 1.

Glomerular afferent arteriolar vasoconstriction

SGLT2-inhibition results in an early hemodynamic effect at the level of the proximal renal tubule. This promotes sodium and water loss and through tubule-glomerular feedback, promoting arteriolar constriction. The ensuing reduction in intra-glomerular pressure leads to renal protection. The improvement in renal function can indirectly improve cardiac function through multiple pathways, including reduced afferent sympathetic NS activity, reduced inflammation and oxidative stress / ROS activation.

Increase in haematocrit

Optimal cardiac function is dependent upon the balance between the preload and afterload of the ventricle. SGLT2-I, through both osmotic diuresis and natriuresis reduce the volume overload, i.e. preload and therefore shift the patient's heart to work on a more optimal part of the Frank-Starling curve. This is especially beneficial in patients with heart failure. Haematocrit could be a surrogate marker for plasma volume and one analysis of the EMPA-REG Outcome trial found that changes in the haematocrit of all the variables explored had the greatest impact on the hazard ratio for cardiovascular health. Empagliflozin significantly increased haematocrit which lends strong evidence to the theory that the cardiovascular benefits of SGLT2-I are mediated through reduced plasma volume and cardiac preload. Compared to oft prescribed loop diuretics (frusemide) and thiazide diuretics (hydrochlorothiazide), which have no proven cardiovascular outcomes benefit in heart failure, SGLT2-I preferentially reduce interstitial fluid volume relative to circulatory volume, which in turn, may reduce neuro-hormonal activation via the renin-angiotensin-aldosterone system.

Improved myocardial energetics and Increased Ketone Body Metabolism

The metabolic demands of cardiomyocytes are exceptionally high and for this to be sustained, the heart is able to recruit several different metabolic substrates to meet it's ATP requirements including fatty acids, glucose, ketone bodies and amino acids. SGLT2-I result in an increase in ketone bodies as an energy source, principally through a "starvation" mechanism by effectively depleting the body of glucose via the urine, raising glucagon levels and a reduction in the excretion of ketone bodies via the kidney. Myocardial ketone metabolism has been shown to have beneficial haemodynamic effects with regards to increased stroke volume, cardiac output and LVFEF in patients with chronic heart failure with reduced ejection fraction (HFrEF). Precise data on the effect of SGLT2-I on myocardial energetics is lacking but this shift in metabolism likely plays an important role.

Improved myocardial ionic homeostasis

Myocardial intracellular sodium (Na+) plays a significant role in the regulation of calcium (Ca2+) cycling, which in turn modulates contractility, oxidative stress and the potential for arrhythmias. In heart failure and diabetes, myocyte intracellular sodium is increased because the Na+/H+ exchanger is upregulated. This in turn, promotes calcium influx into the cytosol, depleting sarcoplasmic reticulum Ca2+ stores, thereby weakening myocardial contraction. In animal models, SGLT2-inhibitors have been shown to lower intra-cellular Na+ and Ca2+ whilst increasing mitochondrial Ca2+ concentrations via direct inhibition of the Na+/H+ exchanger. The finding that the inhibition does not require SGLT2 receptors provides credence to a direct myocardial benefit. However, this putative mechanistic benefit of SGLT2-I is hard to reconcile with the lack of cardio-protective benefit observed in large trials of Na+/H+ exchanger inhibitors.

Conclusion

Consistent and impressive cardio-protective benefits of SGLT2-I commence early with initiation of treatment in patients with heart failure, regardless of diabetic status and despite the absence of SGLT2 receptors in the heart. The mechanisms underpinning their benefit, independent of glycaemic control, is becoming clearer and evidently involves feedback from local haemodynamic consequences at the level of the glomerulus, cardiac loading conditions, a shift towards ketone bodies as the metabolic substrate for both the heart and kidney and also direct intra-myocardial ionic homeostasis.

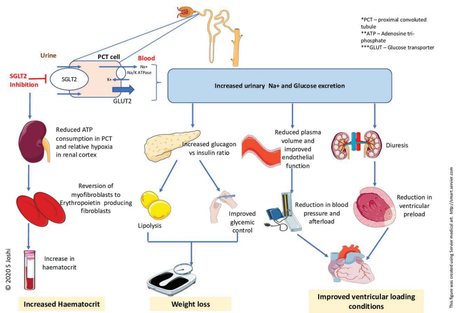

Figure 1, Adapted from Shruti S et al. Heart 2021; 107: 1032-1038

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THE EXPANDING INDICATIONS FOR SGLT2 INHIBITORS

In the last 10 years the treatment of diabetes has had a major shift in focus from glucocentric to CV risk reduction. This shift has been driven by 2 newly available drug categories (GLP-1 agonists and SGLT2 inhibitors) that have been proven to reduce cardiovascular events, something older diabetic agents were never shown to do. Now the SGLT2 inhibitors have moved beyond diabetes and can be used to treat both heart failure and chronic kidney disease in patients with and without diabetes.

Diabetes

The first SGLT2 inhibitor to show CV risk reduction was empagliflozin in the EMPA-REG outcome trial.[1] This was closely followed by the DECLARE TIMI 58 trial for dapagliflozin.[2] These trials cemented the use of SGLT2 inhibitors in patients with diabetes and also demonstrated the drugs potential at reducing the risk of heart failure hospitalization and progression of CKD.

With their trial evidence of cardiovascular risk reduction, SGLT2 inhibitors now feature prominently in the guidelines for diabetes treatment. In the ESC guidelines[3] they are first line therapy in higher risk diabetes patients and in the ADA guidelines they are second line after metformin in diabetes patients with a history of cardiovascular disease or CKD.[4]

Which diabetic patients should get an SGLT2i?

Maybe the question should be who should not get one? SGLT2 inhibitors should be used in most diabetes patients independently of their HbA1c. Perhaps the only patients not to get them are those at lowest risk – younger patients with new onset type 2 diabetes (<10 years) with no other CV risk factors.

Chronic Kidney Disease

CKD is defined as the presence of reduced kidney function ([eGFR] <60 mL/min/1.73 m^2) or kidney damage (urinary albumin excretion of ≥30 mg/day or equivalent).

The Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial enrolled 4304 individuals with eGFR 25 to 75 mL/min/1.73 m2 and urinary albumin to creatinine ratio of 200 to 5000 mg/g.[5] Patients were randomly assigned to dapagliflozin 10 mg daily or placebo. 1/3 did not have diabetes. After a median follow-up of 2.4 years, dapagliflozin reduced all-cause mortality (4.7 versus 6.8 percent), incidence of end stage renal disease (5.1 versus 7.5 percent), and the risk of 50 percent or greater decline in eGFR (5.2 versus 9.3 percent). The benefit was the same in patients with and without diabetes. Hot on its heels is the EMPA-Kidney trial. The results of this are not out yet, but it was stopped early due to clear benefit in CKD.

Which CKD patients should get an SGLT2i?

Given that the only positive trial published so far is DAPA-CKD, then we should consider giving dapagliflozin to patients that fit the inclusion criteria for this trial (see above).

Heart Failure

In the initial diabetes trials with empagliflozin and dapagliflozin it was clear that both drugs reduced heart failure hospitalization in patients with diabetes. Therefore, specific heart failure trials in patients with and without diabetes were set up. In both the DAPA-HF[6] trial and the EMPEROR-reduced[7] trials SGLT2 inhibitors reduced the rate of HF hospitalization and CV death by 25% in patients with reduced ejection fraction, and this was irrespective of diabetes status.

In patients with preserved and mildly reduced ejection fraction, 2 trials were commenced, EMPEROR-preserved[8] (empagliflozin) and DELIVER-HF (dapagliflozin). EMPEROR-Preserved was the first to publish and showed a significant improvement in heart failure hospitalization versus placebo 4.3 v 6%, regardless of diabetic status. DELIVER-HF will publish its results later this year.

The most recent ACC guidelines[9] were updated to cover SGLT2 inhibitor use in patients with heart failure. All patients with symptomatic HFrEF should be given an SGLT2 inhibitor to reduce HF hospitalisaiton and CV death, regardless of diabetes status. In addition they now recommend SGLT2 inhibitors with a class 2a rating in patients with HFmrEF and HFpEF, regardless of diabetes status.

Which heart failure patients should get an SGLT2i?

All patients with symptomatic heart failure should be considered for treatment with an SGLT2i regardless of ejection fraction or diabetes status.

Conclusion

SGLT2 inhibitors are no longer just a "diabetic" drug. They have proven efficacy in heart failure and CKD in patients with and without diabetes. There may be new indications in the future too: we await trial in myocardial infarction; and they also may have potential benefit in prevention of diabetes too.

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2) N Engl J Med 2019; 380:347-357
3) European Heart Journal (2020) 41, 255323
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7) N Engl J Med 2020; 383:1413-1424
8) N Engl J Med 2021; 385:1451-1461
9) Circulation. 2022;145:00–00. DOI: 1161/CIR.0000000000001063

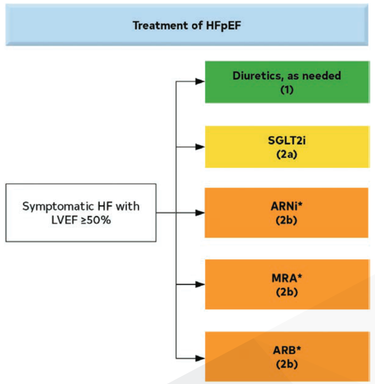

Figure 12, Recommendations for Patients With Preserved LVEF (≥50%)

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THE ROLE OF CARDIAC CT IN CARDIOVASCULAR RISK PREDICTION IN 2022

There are two groups of patients doctors often see in clinic when it comes to assessment for coronary artery disease and cardiovascular risk:

1) patients who present with symptoms such as chest pain or dyspnoea- the doctor needs to assess if the symptoms are due to a cardiovascular cause
2) patients who are asymptomatic but may have cardiovascular risk factors- the doctor needs to risk stratify these patients to determine how aggressively they need to be managed

Historically, evaluation of coronary artery disease (CAD) was guided by functional tests, such as exercise treadmill test, stress echo or myocardial perfusion scan. However, these tests provided limited diagnostic and prognostic information and many patients went on to undergo invasive coronary angiography to confirm the presence or significance of suspected coronary artery disease, which carried associated risks.

Cardiac CT (CCT) imaging has transformed the detection, characterisation and stratification of CAD risk in individuals and has emerged as the preferred non-invasive modality for the assessment of patients with chest pain or for cardiovascular risk assessment. In 2010, the UK's National Institute for Health and Clinical Excellence (NICE) recommended that CCT should be the first line test for people with recent onset chest pain (NICE CG95). The European Society of Cardiology guidelines, published in August 2019, upgraded CCTA to a first-line investigation (level of evidence class 1) for patients with a low to moderate clinical likelihood of CAD. The 2021, US guidelines were modified to reflect the increased utility of CCT, particularly in younger people. [1]

Current status of CCT in cardiovascular diagnosis and risk assessment:
In its simplest form, CCT can quantify the degree of coronary artery calcification by generating the coronary artery calcium score (CACS)- this represents a surrogate marker of the presence and extent of CAD. The higher the CACS, the higher the CV risk. Several large studies with long-term follow-up have confirmed the utility of CACS as a useful risk predictor. The use of CACS can reclassify patients to higher or lower risk categories allowing for a more personalized management of the patient's individual risk. However, the limitations of CACS include its inability to detect soft plaque, limited individual predictive value and the fact that it does not provide any functional data (see Table). Also, major alterations in risk over time are not necessarily reflected in changes in CACS in an individual patient. A clear illustration of this is that statin treatment increases the CACS, despite substantially reducing cardiovascular risk.

In comparison, CT coronary angiography (CCTA), which requires a bolus injection of contrast into a peripheral vein, can identify coronary artery plaque, assess stenosis, infer the presence of ischaemia from functional modelling (using dedicated software to calculate the FFR) and identify plaque features that are associated with high risk of future clinical events. The clinical utility of CCTA and its effectiveness over ischaemia testing has been shown by many large multicentre studies, including PROMISE trial (which studied over 10,000 patients presenting with chest pain)[2] and the SCOT-HEART Study (which tested the clinical impact of early CCTA in 4146 patients with chest pain compared with routine clinical care).[3] However, limitations of CCTA include the inaccuracies in estimation of luminal stenoses if there is high coronary calcification and its inability to detect vulnerable plaque. It is well known that most acute MIs occur secondary to occlusion in vessels with minor coronary plaque disease that erodes or ruptures. In the PROMISE trial, 54% of adverse events occurred in patients without significant stenoses, whereas patients with significant stenoses accounted for only 12% of the population undergoing CCTA. The functional significance of stenoses can be calculated using computational flow dynamic or machine learning techniques to derive the CT-FFR. Some studies have shown that CT-FFR can reduce the need for invasive coronary angiography and intracoronary pressure wire studies [4] although the benefits are currently only modest and the technology increases healthcare cost without clear long term clinical benefit.[5].
Imaging perivascular adipose tissue (PVAT) around the coronary arteries has emerged as a promising technique to image inflammation in the coronary artery wall and may reclassify CV risk of patients, allowing for earlier and more aggressive treatments in higher risk individuals. A recent algorithm has shown how incorporation of fat attenuation index (FAI) analysis in patients undergoing CCTA could improve risk stratification and clinical management pathways.[6].

Conclusion

Cardiac CT imaging, either in the form of the CT calcium score as a screening tool, or CT coronary angiogram to assess for coronary artery stenoses and provide information on plaque characteristics, are now considered first line investigations in the assessment of patients with suspected coronary artery disease or increased CV risk. The pros and cons of these tests are shown in the table. Functional testing (e.g using exercise treadmill test or stress echo) to assess for ischaemia still has a role to play, especially in patients with chest pain, but alone may be insufficient to provide information on overall cardiovascular risk. In most patients, a combination of a functional test and cardiac CT may be the best option to provide a more complete picture to help guide clinical decision making. CT-FFR and measurement of the FAI appear to show promise for the future.

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Cardiac CT parameter	Advantages	Disadvantages
Calcium score	• Simple • Low radiation • Highly reproducible and can be repeated over time • Surrogate marker for total atheroma burden	• Misses soft/ non-calcified plaque • No haemodynamic information • Paradoxical increase with statins • Limited individual predictive value
CT coronary angiogram	• Can quantify degree of stenosis • Provides information on luminal and mural disease • Provides information on plaque characteristics • Improves cardiovascular outcomes	• May overestimate stenosis with calcified lesions • Variable correlation with ischaemia • Does not provide information on vulnerable plaques • Involves contrast injection (risk of allergic reaction) and higher radiation than CT calcium score
CT FFR	• Surrogate marker of functional significance of stenosis detected on CT	• Dedicated software required • Limited cost benefit • No long-term clinical outcome data
Pericoronary fat attenuation index (FAI)	• Identifies inflammation • Allows early prediction of risk (pre-luminal disease)	• Dedicated software required

Table. Advantages and disadvantages of various cardiac CT-derived parameters

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ALL PLAQUES ARE NOT THE SAME – UNDERSTANDING A CAROTID DUPLEX SCAN REPORT

Stroke is one of the major health care problems in the world today. It is the third leading cause of mortality in western countries and the most common cause of mortality of any neurological disorder. Incidence of stroke is 160 per 100,000 population per year; 40 percent of victims require some type of special services and 10 percent require total care. Consequently, stroke rehabilitation places a large drain on national health care resources. A significant proportion of strokes are ischemic in nature, one of the leading causes for which is internal carotid artery (ICA) atherosclerosis. 20-25 percent of all strokes can be attributed directly to carotid bifurcation atherosclerosis.

Atherosclerotic plaques are not static lesions; they undergo dynamic changes in their size and morphological characteristics. These changes manifest themselves as changes in plaque volume and consistency, otherwise known as plaque progression and regression. These, together with adaptive responses of the arterial wall, determine the degree of stenosis in the diseased artery. This degree of stenosis is the measurable clinical finding which, together with timing and nature of symptoms and co-morbidities, correlates with the risk of developing further neurological events.

Over the last 20 years a lot has been learned about the morphological characteristics of an atherosclerotic plaque responsible for plaque progression and instability. The strength of the evidence from the NASCET (North American Symptomatic Carotid Endarterectomy Trial) trial has meant that most clinicians recognise plaque cap ulceration as a risk factor for development of further carotid territory embolic neurological events. Atherosclerotic plaques that are prone to rupture are known to have certain cellular, molecular and structural features. Notably these include an intense inflammatory process within the plaque, angiogenesis, and intra-plaque haemorrhage with gradual thinning of the fibrous cap, subsequent loss of plaque cap integrity and ulceration. Inflammatory activity within the plaque is associated with plaque ulceration and has a role in pathogenesis of intimal damage.

Duplex ultrasound is arguably the most important imaging modality for preoperative assessment of patients with carotid atherosclerotic disease. It is non-invasive, relatively inexpensive and very accurate at identification of significant ICA stenosis. The B-mode ultrasound image is also used to assess morphologic characteristics of an atherosclerotic lesion. It has been known for some time that plaques that are lipid-rich, or have an ulcerated surface or intra-plaque haemorrhage are associated with histologic characteristics of plaque instability, ipsilateral neurological or ocular events.

Stroke risk is thus not just a function of the degree of stenosis (over 70% stenosis is usual the cut-off criterion for intervention), but also unstable plaque structure. At the Harley Street Heart and Vascular Centre, we use the widely accepted Gray-Weale classification of plaque morphology1 in combination with the plaque surface on Duplex ultrasound to indicate the risk of stroke (Table 1). Echogenic plaques are white on ultrasound, fibrous and have low embolic potential and are considered stable. Echolucent plaques are black to dark grey on ultrasound, lipid-rich, inflammatory and prone to cause embolism. Plaques with ulcerated or fissured surfaces, with intra-plaque haemorrhage or thrombus on the surface are also at high risk of causing a stroke.

Understanding the Carotid Duplex Ultrasound report thus is crucial to make medication decisions. Whilst the degree of stenosis is an important factor in assessing the need for intervention, it is the morphology of the plaque that determines both the nature of the best medical therapy – aggressive lipid control, anti-coagulation, anti-platelet or dual anti-platelet therapy – in conjunction with patient age, gender and co-morbidities. This is particularly so as recent metanalyses of carotid intervention trials now make it clear that carotid stenting carries a significantly HIGHER stroke risk than open carotid endarterectomy surgery, particularly in symptomatic carotid disease2, and best medical therapy must remain the mainstay of management.

Plaque morphology type (Gray-Weale classification)	Morphology descriptor (High embolic risk to low risk)	Plaque surface type	Surface descriptor (High embolic risk to low risk)	Embolic stroke risk of morphology and surface combination	Suggested therapy to consider based on patient bleeding risk*
Type 1	Echolucent	Type 5	Thrombus, no ulceration	Imminent stroke	Anti-coagulation
Type 2	Predominantly Echolucent	Type 4	Ulceration + Thrombus	Very high risk	Aspirin + low dose rivaroxaban (COMPASS trial3)
Type 3	Predominantly Echogenic	Type 3	Ulcerated	High risk	Dual anti-platelet therapy
Type 4	Echogenic	Type 2	Irregular	Moderate to low risk	Anti-platelet therapy
		Type 1	Smooth	Low risk	Anti-platelet therapy

Table 1 : Plaque assessment used at the Harley Street Heart and Vascular Centre to assess individual stroke risk on Carotid Duplex Ultrasound (in combination with the degree of ICA stenosis)

**The therapy suggested must take into account the bleeding risks of an individual patient, their co-morbidities and lifestyle and are not prescriptive. In addition intermediate risks exist where the risk-benefit decision should be made by the treating physician – for e.g. Type 1 morphology (high risk) with a Type 5 surface (low risk) may need dual anti-platelet therapy in a low bleeding risk patient and single anti-platelet therapy in an older high bleeding risk patient.*

References:

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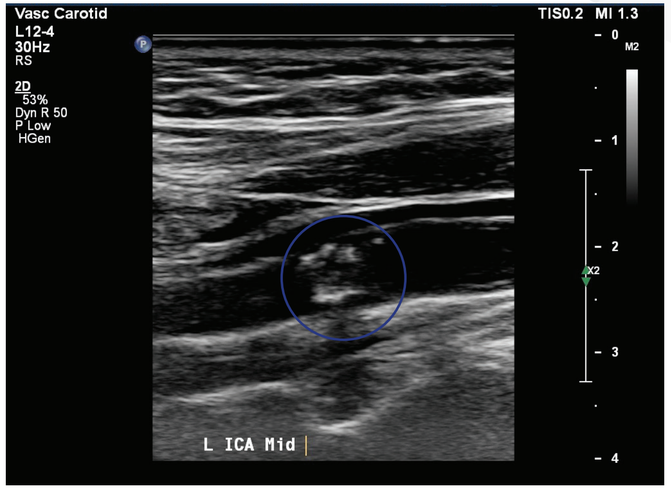
QUIZ



The image shows a left internal carotid artery plaque in a 68 year old male with a history of 3 Transient ischemic attacks in 2 months. The plaque shows Type 2 (predominantly echolucent) morphology, with a Type 2 (irregular) surface, and is causing 80% stenosis in the artery. He has no other major cardiovascular co-morbidities. Recommended treatment options for this patient would be (you may choose more than one option)

a. Aggressive lipid control with statins or evolocumab
b. Aspirin with low dose Rivaroxaban
c. Anti-coagulation with a direct oral anti-coagulant
d. Dual anti-platelet therapy with Aspirin and Clopidogrel
e. Left carotid endarterectomy
f. Left carotid artery stenting

Answer is available on our website:
http://www.harleystreet.sg/quiz - answers/medbulletin-may-2022/

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THE HARLEY STREET
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INTRODUCTION

In this issue of the newsletter we focus on cardiovascular risk stratification. In both primary and secondary prevention, risk stratification is the first step in the treatment pathway. We explore the use of imaging; with CT scanning and carotid ultrasound being used to discriminate risk. Then we take a look at how the SGLT2 inhibitors are evolving into a cv risk reduction tool in multiple disease states. We hope you enjoy the articles, and please get in touch if you have any questions or comments.

From The Harley Street Heart and Vascular Centre

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