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Research into the effect Of SGLT2 inhibition on left ventricular remodelling in patients with heart failure and diabetes mellitus (REFORM) trial rationale and design

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Abstract

Background: Heart failure (HF) and diabetes (DM) are a lethal combination. The current armamentarium of anti-diabetic agents has been shown to be less efficacious and sometimes even harmful in diabetic patients with concomitant cardiovascular disease, especially HF. Sodium glucose linked co-transporter type 2 (SGLT2) inhibitors are a new class of anti-diabetic agent that has shown potentially beneficial cardiovascular effects such as pre-load and after load reduction through osmotic diuresis, blood pressure reduction, reduced arterial stiffness and weight loss. This has been supported by the recently published EMPA-REG trial which showed a striking 38 and 35 % reduction in cardiovascular death and HF hospitalisation respectively.

Methods: The REFORM trial is a novel, phase IV randomised, double blind, placebo controlled clinical trial that has been ongoing since March 2015. It is designed specifically to test the safety and efficacy of the SLGT2 inhibitor, dapagliflozin, on diabetic patients with known HF. We utilise cardiac-MRI, cardio-pulmonary exercise testing, body composition analysis and other tests to quantify the cardiovascular and systemic effects of dapagliflozin 10 mg once daily against standard of care over a 1 year observation period. The primary outcome is to detect the change in left ventricular (LV) end systolic and LV end diastolic volumes. The secondary outcome measures include LV ejection fraction, LV mass index, exercise tolerance, fluid status, quality of life measures and others.

Conclusions: This trial will be able to determine if SGLT2 inhibitor therapy produces potentially beneficial effects in patients with DM and HF, thereby replacing current medications as the drug of choice when treating patients with both DM and HF.

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Keywords: Heart failure, Diabetes, SGLT2 inhibitor, Mechanistic trial, Cardiac MRI, Cardiopulmonary exercise testing

Background

Heart failure (HF) is a growing global pandemic with a 14 % increase in prevalence from 1990 to a staggering 41 million patients worldwide in 2010 [1]. With improving acute cardiovascular outcomes and longer life expectancy, this number will rise further. HF is already one of

the leading causes of hospitalisation in elderly patients [2]. This translates to a burgeoning financial burden on the healthcare system; costing $39.2 billion in the US alone in 2010 [3].

HF is associated with numerous co-morbidities that can contribute to the progression of the disease and may alter the response to therapy [4]. One important co-morbidity of HF is diabetes mellitus (DM). In population based studies and in HF trials, the prevalence of type 2 DM among patients with symptomatic HF is estimated to

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Singh *et al. Cardiovasc Diabetol* (2016) 15:97

Page 2 of 11

be between 12 and 49 % [5, 6]. Among all patients hospitalized for HF, it has been reported that up to 40 % have type 2 DM [7, 8]. This association can be lethal since DM has consistently been shown to be an independent predictor of increased morbidity and mortality in patients with HF; [9] patients with DM and HF have a median survival of 4 years [10]. However, treating patients with these concomitant diseases can be challenging.

Treating heart failure and diabetes

In the treatment of DM, EASD/ADA guidelines recommend tailoring therapeutic approaches to individual needs and/or risks [11]. For most patients, metformin is the first choice anti-diabetic drug in type 2 DM including those with HF. In 2010, investigators reported potential benefits of metformin therapy in HF in DM in the Scottish population [12], a finding that has since been confirmed by others [13, 14]. However, metformin alone is often not enough to keep glycaemia under control and there frequently is a need for a second line anti-diabetic drug in patients with HF and DM. However, the choices for patients with concomitant HF are very limited; sulphonylureas (SU) are agents that are commonly prescribed in DM but are associated with weight gain and hypoglycaemia which are detrimental in heart failure [15, 16]. Moreover, there remain concerns that SUs may increase all-cause and CV-mortality [17], although this link is not fully established. Glitazones are contra-indicated in New York Heart Association functional class (NYHA) III or IV HF, while their role in milder degrees of HF remain somewhat controversial with a few observational studies indicating increased HF hospitalisation [18]. More recent agents such as DPPIV inhibitors have also failed to show cardiovascular benefit; TECOS showed sitagliptin had a neutral effect on cardiovascular outcomes [19]. Similarly EXAMINE revealed alogliptin had no effect on major adverse CV events (MACE) among diabetic patients with recent ACS [20]. While SAVOR-TIMI-53 revealed that saxagliptin increased HF hospitalisations [21]. Therefore, we can conclude that second line therapeutic options in DM and HF are very limited and there is a critical need for agents that will both improve glycaemic control as well as HF outcomes.

Sodium glucose linked co-transporter 2 (SLGT2) inhibitors and the heart

SGLT2 inhibitors employ a novel mechanism to lower blood glucose by preventing the reabsorption of glucose in the renal tubules. There are currently 3 agents that have been licenced for clinical use; dapagliflozin, empagliflozin and canagliflozin. By competitively blocking the SGLT2 receptors in the proximal convoluted tubules (PCT), SGLT2 inhibitors prevent the reabsorption of filtered sodium and glucose, resulting in glycosuria and

natriuresis [22, 23] (Fig. 1). This novel mechanism of action means SGLT2 inhibitors function independently of insulin levels, pancreatic function and degree of insulin resistance. Accordingly, this class of drug is expected to continue to maintain its potency as beta cell function deteriorate along with disease progression—a key feature that is not seen in other oral anti-diabetic drug classes [24]. Another distinctive feature of SGLT2 inhibitors is its low hypoglycaemic risk. By limiting its activity to urinary glucose excretion, SGLT2 inhibitors do not stimulate insulin release [25] or interfere with the physiologic response to hypoglycaemia [26].
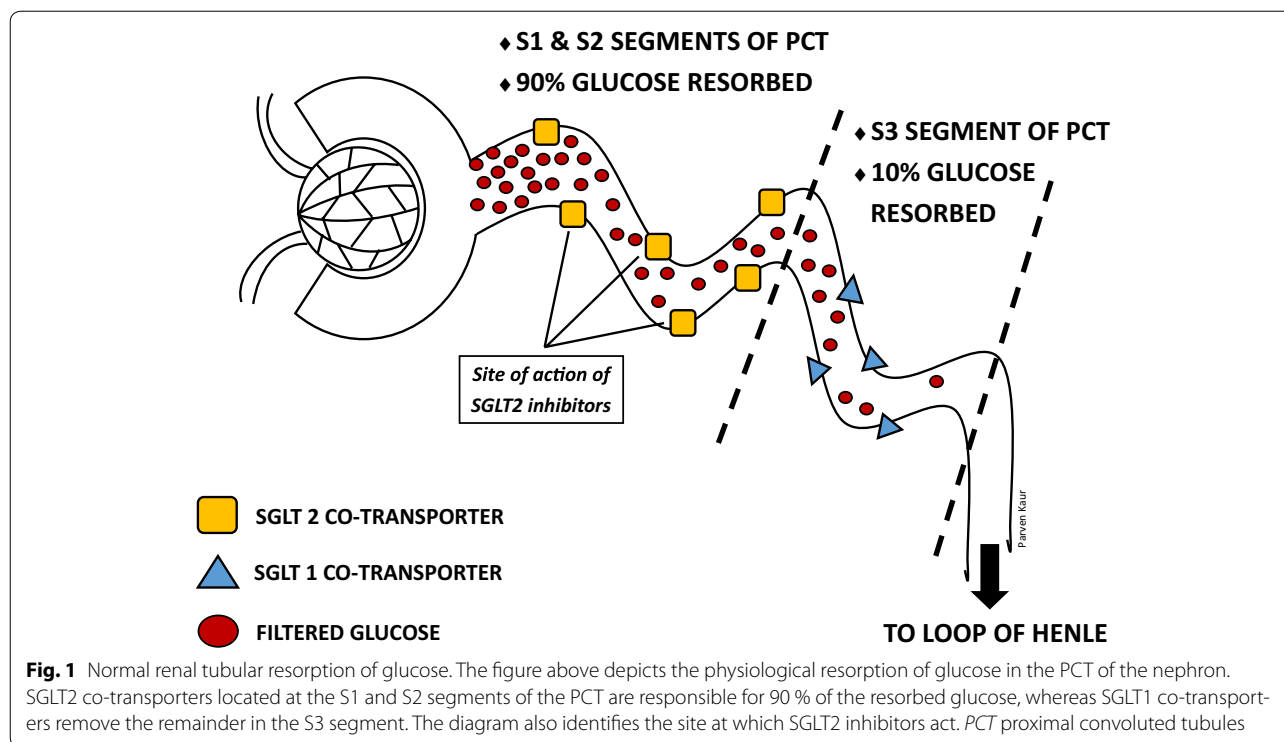
The additional natriuretic effect (and resultant osmotic diuresis) of SGLT2 inhibitors could potentially be beneficial in patients with cardiovascular disease, especially those with HF, thereby distinguishing SGLT2-inhibitors from all the other oral anti-diabetic agents. Indeed SGLT2-ihibitors have been shown to have a number of positive cardiovascular effects on top of their glycaemic effects. This class of drug has been shown to lower blood pressure (by 7–10 mmHg) [27, 28], reduce arterial stiffness [29], reduce urinary microalbuminuria [30] (a marker of CV risk) and reduce triglycerides and increase HDL and LDL cholesterol (without altering HDL/LDL ratios) [24].

Recently, the EMPA-REG Outcomes trial had demonstrated a remarkable reduction in CV mortality and HF hospitalisations, by 38 and 35 % respectively, among patients with high CV risk who were treated with empagliflozin [31]. Further analysis of the data suggested that this benefit was consistent in patients with or without HF at baseline [32]. However, it is important to note that EMPA-REG Outcomes studied a broad range of CV risk patients and only 10 % had HF at baseline, thus raising the possibility the outcomes seen in this group be due to chance. Nevertheless, such striking results warrants further inquiry. Interestingly, separation of the event curves in EMPA-REG outcomes were seen very early—within 3 months—leading some to speculate that the osmotic diuresis effect of SGLT2-inhibitors was responsible for this, as its effect other mechanisms such as LV remodelling and atherosclerosis would have taken longer to manifest. However, there has yet to be a mechanistic trial to test this hypothesis. As we specify below, the REFORM Trial will rigorously test the mechanisms behind the potential cardiovascular benefits of the SGLT2-inhibitor, dapagliflozin, specifically in the diabetic heart failure population.

Methods
Study design

The REFORM trial is a randomised, double blinded, placebo controlled single-centre study conducted in NHS tayside, Scotland to compare the SGLT2 inhibitor,

Singh *et al. Cardiovasc Diabetol* (2016) 15:97

Page 3 of 11

Fig. 1 Normal renal tubular resorption of glucose. The figure above depicts the physiological resorption of glucose in the PCT of the nephron. SGLT2 co-transporters located at the S1 and S2 segments of the PCT are responsible for 90 % of the resorbed glucose, whereas SGLT1 co-transporters remove the remainder in the S3 segment. The diagram also identifies the site at which SGLT2 inhibitors act. *PCT* proximal convoluted tubules

dapagliflozin 10 mg to placebo (standard of care). A recruitment window of 1.5 years has been set between March 2015 and August 2016. Participants will be enrolled in this trial for a period of between 12 to 13 months, (Fig. 2) therefore the overall trial end date will be August 2017.
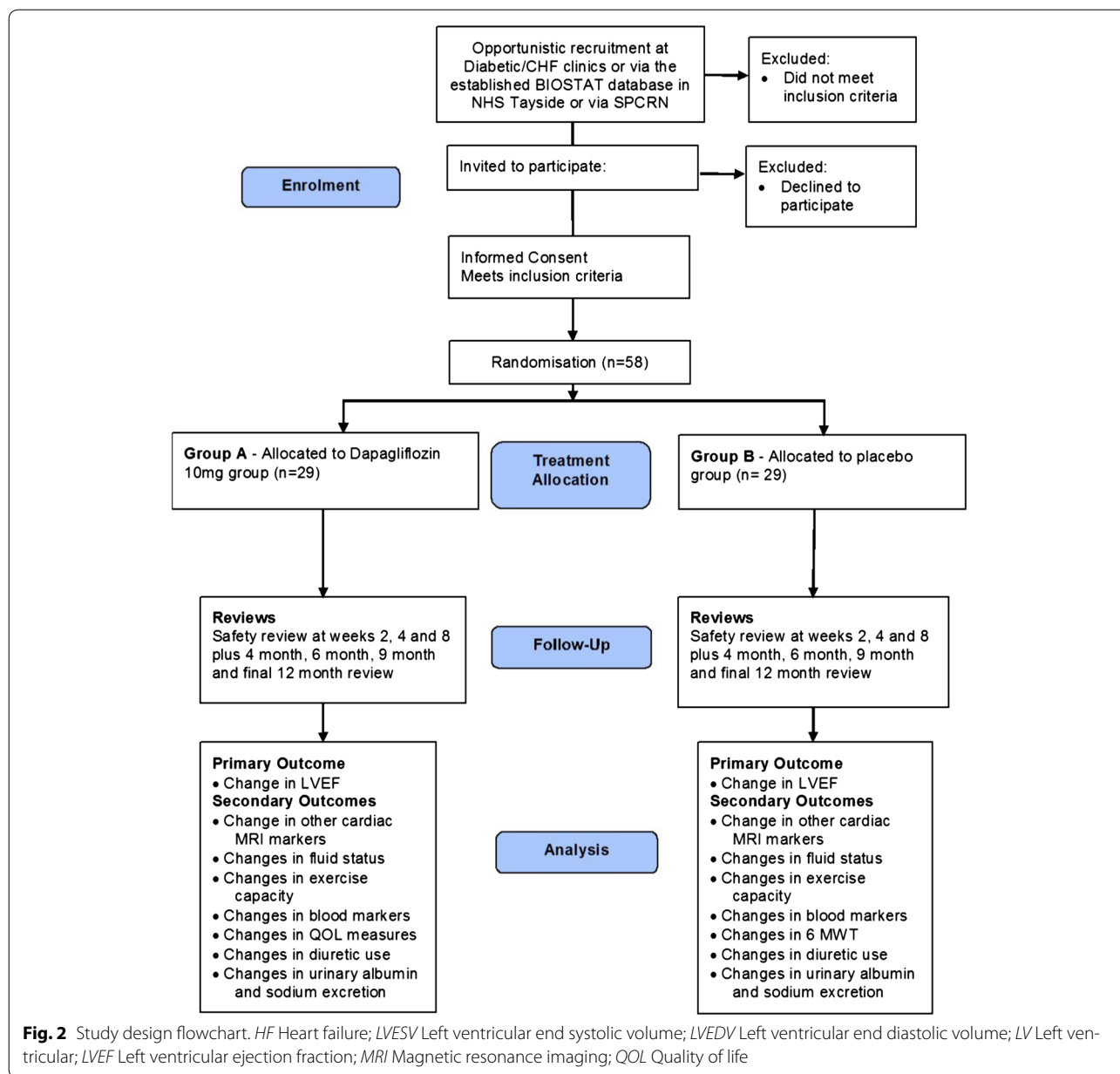
At the screening visit an initial medical history and clinical examination will be performed following informed consent. Participants will have bloods taken for safety analysis and vital signs recorded to confirm eligibility prior to enrolment. Should the participant meet the inclusion criteria and have no exclusions identified they will return for a cardiac magnetic resonance imaging (MRI) scan at the Clinical Research Centre, Ninewells Hospital, Dundee, within 4 weeks of the planned baseline (randomization) visit. At the randomization visit participants will complete a 6 min walk test, quality of life measures, vital signs, body composition analysis (BCA) and cardio-pulmonary exercise test (CPEX) measurements taken. During this visit, participants will also be randomly assigned to either Dapagliflozin 10 mg or matching placebo. The first dose will be administered at this visit and participants will be educated on the symptoms of hypoglycaemia and given a written action plan on how to manage it in the event it occurs. Patients on insulin will have their total daily dose reduced by 10 % and given a 2-week glucose monitoring chart with written instructions to self-manage their insulin doses. This will be reviewed by the research team at the next visit.

Participants will return 2 weeks later for a short safety visit where they will have safety and BNP bloods, insulin dose (if applicable), adverse events and vital signs monitored. This will be followed by 2 more visits on months 2 and 6 with the same agenda. Three telephone visits are planned in the study schedule, at week 4, months 4 and 9. These calls will enable the research team to follow up on changes in concomitant medications, adverse events and to remind the participant of study drug compliance. Participants will continue with all their usual medications, these remain unchanged throughout unless clinically indicated. If any titration of a participant's other medications (i.e. anti-diabetic agents or diuretic agents) is indicated these changes will be done, in consultation with their general practitioners (GP), and the changes recorded for analysis later.

At the end of the 1 year study period, participants will return for a repeat assessment of the 6 min walk test, quality of life measures, BCA, CPEX and cardiac MRI. These values will be compared to their baseline tests to determine if any significant change has occurred with each of the two arms of the study populations. (See Table 1 for an overview of all visits scheduled for the trial).

Study population

We will employ a two-pronged recruitment process. Firstly, we will identify potential patients from the local

Singh *et al. Cardiovasc Diabetol* (2016) 15:97

Page 4 of 11

Fig. 2 Study design flowchart. *HF* Heart failure; *LVESV* Left ventricular end systolic volume; *LVEDV* Left ventricular end diastolic volume; *LV* Left ventricular; *LVEF* Left ventricular ejection fraction; *MRI* Magnetic resonance imaging; *QOL* Quality of life

tayside pool of the systems biology study to tailored treatment in chronic heart failure (BIOSTAT) database consisting of around 1800 patients with HF who have previously consented to be approached for future research. We will also identify patients from the Scottish Primary Care Research Network (SPCRN), SHARE The Scottish Health Research Register, Generation Scotland Database, Scottish Diabetes Research Network and Wellcome Study Database. Secondly, we will also allow opportunistic recruitment from the various cardiovascular and HF clinics as well as from the cardiac rehabilitation program conducted in Ninewells Hospital. All these sources

should provide a sufficient pool of diabetic HF patients to be recruited into the trial.

Eligibility
All potential participants who meet the following inclusion and exclusion criteria will be eligible for the trial:
    Inclusion criteria:

- Aged 18–75 years were previously diagnosed with type 2 DM.
- Diagnosed with NYHA functional I–III HF with prior echocardiographic evidence of left ventricular

Singh *et al. Cardiovasc Diabetol* (2016) 15:97

Page 5 of 11

Table 1 Overview of all visits and tests scheduled for participants of the REFORM Trial

Visit	Visit 1 screening — Up to 4 weeks pre visit 2	Visit 2 baseline/ randomisation — Day 0	Visit 3 — 2 week (±3 days)	Visit 4 tele call — 4 week (±3 days)	Visit 5 — Month 2 (±1 week)	Visit 6 tele call — Month 4 (±1 week)	Visit 7 — Month 6 (±1 week)	Visit 8 tele call — Month 9 (±1 week)	Visit 9 final visit — Month 12 (±2 weeks)	Early discontinuation visit[b] — As required
Informed consent	X									
Check inclusion/exclusion criteria	X									
Medical history and family history	X									
Clinical examination	X									
Demographics	X									
Vital signs	X	X	X		X		X		X	X
Safety blood tests and BNP	X^A	X^A	X^B		X^A		X^A		X^A	X^A
Research bloods		X							X	X
Genetic blood sample (if consented)		X								
MRI[a]		X							X	X
Bioelectrical composition analysis		X	X		X		X		X	X
Cardiopulmonary exercise testing		X							X	X
6 min walk test		X							X	X
QoL questionnaires		X							X	X
Dispense study medication		X	X		X		X			
Adverse event assessment		X	X	X	X	X	X	X	X	X
Record or review concomitant meds	X	X	X	X	X	X	X	X	X	X

Safety blood tests = X^A = U&Es, LFTs, FBC, glucose, HB A1C, BNP: X^B = U&Es, LFTs, FBC, glucose, BNP only

[a] Screening MRI to be done only if echo criteria fulfilled. Note MRI can be done (± 2 weeks of scheduled visits 2 and 9 date)

[b] Early discontinuation visit: all tests to be done only where participant agrees

[c] Urine pregnancy testing on females of childbearing potential or who do not abstain from sex or use effective contraception

Singh *et al. Cardiovasc Diabetol* (2016) 15:97

Page 6 of 11

systolic dysfunction (LVSD) (ejection fraction <45 % or subjective assessment of LV dysfunction that is mild or worse).

- On furosemide 80 mg daily or less, or equivalent loop diuretic.
- Have stable HF symptoms for at least 3 months prior to consent.
- On stable therapy for HF for at least 3 months prior to consent.
- Have not been hospitalised for HF for at least 3 months prior to consent.

Exclusion criteria:

- Severe hepatic disease.
- Renal disease defined as CKD stage 3b or worse (i.e. eGFR <45 ml/min).
- Systolic BP <95 mmHg at screening visit.
- Screening HbA1c <6.0 %.
- Unable to walk or to perform cardio pulmonary exercise testing or 6MWT.
- Malignancy (receiving active treatment) or other life threatening diseases.
- Pregnant or lactating women.
- Any contraindication to MRI (e.g. claustrophobia, metal implants, penetrative eye injury or exposure to metal fragments in eye requiring medical attention).
- Patients who have participated in any other clinical trial of an investigational medicinal product within the previous 30 days.
- Patients who are unable to give informed consent.
- Any other reason considered by a study physician to be inappropriate for inclusion.

Randomisation and treatment allocation

After successful screening for eligibility and safety, participants will be randomised to either dapagliflozin 10 mg or matching placebo (microcrystalline cellulose Ph Eur overencapsulated in a hard gelatine capsule shell) in a double blind fashion. The double blind medication (dapagliflozin or placebo) will be prepared, packaged and labelled by our onsite clinical trials pharmaceutical manufacturer. Randomisation will be carried out by our dedicated clinical trials pharmacy using block randomisation. They will use a validated randomisation program and will securely backup both the randomisation seed and the randomisation allocation and have it available in the onsite 24-h emergency unblinding facility.

Once randomised, the participant will continue taking the trial medication once daily for 1 year, if tolerated. Compliance will be checked and documented, by the dispensing pharmacy, using tablet counts at each visit. If non-compliant, they will be encouraged to become compliant. If study drug needs to be stopped due to intolerance or adverse events, they will remain in the study in order to do an "intention to treat" analysis.

Study outcomes

Primary outcomes

The primary outcome is to determine if dapagliflozin induces a change in LV end systolic volume (ESV) or LV end diastolic volume (EDV) in patients with DM associated HF when compared to placebo.

Secondary outcomes

- To determine if there is a change in LV mass, LV ejection fraction (EF), right ventricular (RV) EDV, RV ESV, RV EF, atrial dimensions and volumes, and LV remodelling index (RI) (LV mass/LVEDV) with dapagliflozin in DM associated HF compared with placebo.
- To determine if there is a change in BCA as a measure of fluid status with dapagliflozin in DM associated HF compared with placebo.
- To determine if dapagliflozin can improve exercise tolerance in DM patients with HF as measured by pre and post 6 min walk test and CPEX.
- To determine if there are patient reported improvements in quality of life with dapagliflozin compared to placebo as measured by the Minnesota Living with Heart Failure Questionnaire and SF-36 questionnaire.
- To determine the effect of dapagliflozin on BNP, markers of inflammation and oxidative stress (IL-6, F2-isoprostane, HS-CRP and Oxidised LDL).
- To determine if dapagliflozin use results in any change in diuretic dose among patients with DM and HF.
- To determine if dapagliflozin reduces microalbuminuria in patients with DM and HF.
- To determine if dapagliflozin increases natriuresis in patients with DM and HF.
- To assess the safety of dapagliflozin in DM associated HF.

Sample size and power calculations

Improvements in LV volumes have stood out as a marker that most strongly correlates with the impact of a drug/device therapy on improving heart failure survival [33]. Grothues et al. [34] suggests that a 10 mL change in LV EDV and LV ESV is clinically significant. In a population of HF patients the SD for the mean difference of LV EDV and LV ESV has been demonstrated to be 7.6 and 7.4 respectively [34]. Therefore, to detect a 10 mL change in EDV and ESV (primary endpoint) with 90 % power and α error (p value) of 0.05, a sample size of 13 and 12 respectively is required per arm.

Singh *et al. Cardiovasc Diabetol* (2016) 15:97

Page 7 of 11

LV mass is also an important determinant of survival in patients with HF [33] and a 10 g reduction in LV mass has been shown to be clinically meaningful [34]. It was also determined that the SD for 10 g mean change in LV mass in the HF population is 9.6 using cardiac MRI, implying 20 patients are required per arm [34].

The change in LV EF which best discriminated between drugs with positive and neutral effects on mortality was 3 % [35]. This is also the figure recommended by Grothues as the LV EF change which should be used to power studies [34]. Furthermore, Kramer et al. demonstrated a 3 % change in LV EF was associated with a 20 % improvement in mortality [35]. Our previous MRI experience have shown an in-house and published SD of the change in LV EF within individuals over time as 3.75 % for both active and placebo therapies [36]. Therefore in order to have 80 % power at $p < 0.05$ to detect a ≥3 % change in LV EF in a parallel group study, 26 patients per group are needed.

As this is a discovery trial, we aim to ensure the trial is adequately powered to detect all the clinically relevant markers of LV remodelling (LV ejection function, mass and volume). Therefore 52 patients will be recruited (26 patients per arm) to provide at least 80 % power (α error 0.05) to detect clinically significant changes in LV EDV, LV ESV, LV mass and LV EF.

Cardiac MRI protocol

Baseline and repeat CMRI examinations in screening (±2 weeks before randomisation) and after the final 12 month (±2 weeks) visit will be performed on a 3T Magnetom scanners (Siemens, Erlangen, Germany) using body array cardiac and spine matrix radiofrequency coils. Analysis will be performed offline (Argus Software, Siemens) by a single blinded observer for the assessment of atrial and ventricular volumes and dimensions, EF, ventricular mass and LV remodelling index. This single observer will analyse all the scans.

The reproducibility of all parameters using MRI will be derived for this observer. A test–retest intra-observer coefficient of variation of 2.0 % is usual in this department's past MRI studies. Should the scanner become unavailable for a prolonged period of time during the study an alternative scanner will be used. MRI methods will be adapted as appropriate to ensure optimal study results can be obtained
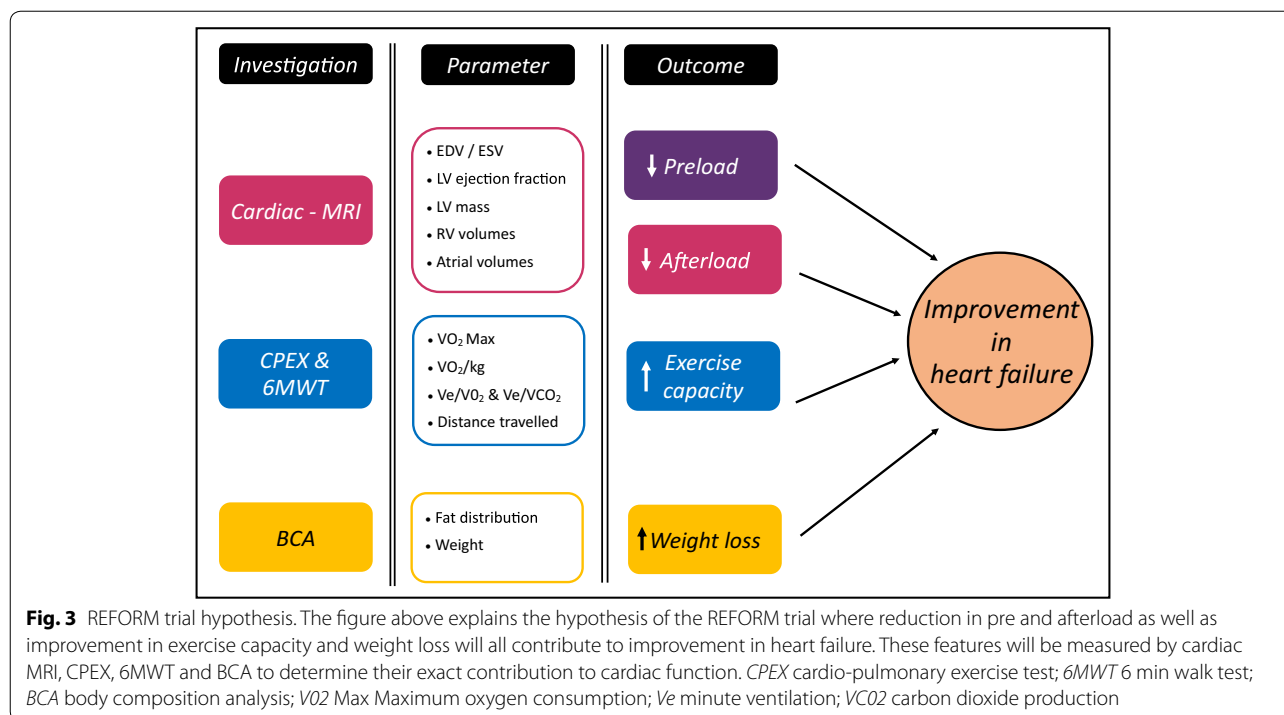
Discussion

In this study we propose that there may be unique features of SGLT2 inhibitors that result in a number of haemodynamic and metabolic effects that can ultimately improve survival of patients with HF and DM (Fig. 3).

The primary haemodynamic effect of SGLT2 inhibitors is osmotic diuresis. Approximately 375 ml of extra urine per day is produced in diabetic patients treated with dapagliflozin [24]. Empagliflozin has also been shown to modestly increase urinary volumes among patients with type 1 DM and hyperfiltrating kidneys [37]. The key question is whether or not SGLT2 inhibitors will maintain their diuretic properties in HF patients who are already on loop diuretic therapy and have impaired renal function. A recent meta-analysis of 5 clinical trials showed dapagliflozin 10 mg produced clinically meaningful reductions in HbA1c, weight and systolic BP in HF patients over a 1 year follow up period [38]. Additionally, SGLT2 inhibitors also reduce blood pressure by reducing arterial stiffness [29], and indirectly, as a result of increased diuresis [39, 40]. These effects on intravascular volume and blood pressure will result in reduced preload and afterload respectively, thereby facilitating the positive remodelling of the heart [41, 42].

This effect of SGLT2 inhibitors on positive LV remodelling will have major implications on morbidity and mortality in patients with DM and HF. Indeed, a drug's effect on LV remodelling is the best surrogate marker of its efficacy and its impact on hard outcomes like survival and disease progression. A consensus paper by Cohn et al. [43] recommends new drug treatment in HF be assessed by their effect on LV remodelling. To emphasise this, Kramer et al. [35] performed a meta-analysis of 30 mortality trials (involving 25 drugs or device interventions) and 88 remodelling studies and showed excellent correlations between effects on LV remodelling and its impact on mortality. Indeed pre-clinical work has shown that SGLT2 inhibitors are capable of reducing LV mass and volume in a rat model with progressive HF [44]. Accordingly, we have selected cardiac MRI measurements of LV EDV and LV ESV as the primary outcome measures for the REFORM Trial. Other measures of LV remodelling such as LV mass and LVEF are key secondary outcome measures. By ensuring the trial is adequately powered for all three facets of LV remodelling we will, for the first time in humans, determine if treatment with an SGLT2 inhibitor be able to induce positive LV remodelling in diabetic patients with HF.

The metabolic effects of SGLT2 inhibitors include weight loss and reduced insulin resistance. Weight loss addresses a universal problem in the HF population; poor effort tolerance, which establishes a vicious cycle that propagates DM and HF. A patient's weight is a major determinant of their effort tolerance, and physical activity has repeatedly been shown to benefit patients with HF [45–47]. A 24 week study comparing dapagliflozin to placebo showed 2.5–3.5 kg weight reduction as

Singh *et al. Cardiovasc Diabetol* (2016) 15:97

Page 8 of 11

Fig. 3 REFORM trial hypothesis. The figure above explains the hypothesis of the REFORM trial where reduction in pre and afterload as well as improvement in exercise capacity and weight loss will all contribute to improvement in heart failure. These features will be measured by cardiac MRI, CPEX, 6MWT and BCA to determine their exact contribution to cardiac function. *CPEX* cardio-pulmonary exercise test; *6MWT* 6 min walk test; *BCA* body composition analysis; *V02* Max Maximum oxygen consumption; *Ve* minute ventilation; *VC02* carbon dioxide production

a result of the caloric loss produced by the glycosuria, thus potentially improving overall effort tolerance [48]. Besides weight, the degree of insulin resistance (IR) has also been demonstrated to be inversely related to exercise capacity and directly related to disease severity and clinical outcomes; Doehner et al. had demonstrated that lower insulin sensitivity was associated with significantly lower peak oxygen consumption and LV EF. They also showed reduced insulin sensitivity was an independent predictor of mortality in patients with HF [49]. The relationship between IR and exercise capacity has also been demonstrated in apparently healthy individuals and in diabetic patients [50–52]. The mechanisms for this has yet to be defined, however one possible mechanism could be explained by the endothelial dysfunction caused by the blunting of insulin-induced endothelial nitric oxide synthase (eNOS) as a result of IR. This in turn leads to impaired muscle and cardiac blood flow and glucose transport resulting in reduced exercise capacity [53]. Improving insulin sensitivity has been shown to improve exercise capacity in diabetic individuals with HF [54, 55]. Studies utilising insulin sensitizers such as thiozolidinediones have shown improving insulin sensitivities increases exercise capacity [56]. There is yet to be similar work done around SGLT2 inhibitors, however ZDF rats treated with dapagliflozin [25] and empagliflozin [57] have shown improving insulin sensitivity in treated populations. Also, a randomized double blind placebo controlled trial using dapagliflozin also showed improved

insulin sensitivity during hyperinsulinaemic euglycaemic clamping in T2DM patients [58]. By causing weight loss and improving insulin sensitivity, SGLT2 inhibitors could significantly increase the effort tolerance of patients with HF, thereby reducing morbidity and mortality.

The EMPA-REG Outcomes trial revealed potentially beneficial effects of empagliflozin among patients with HF, however it is unknown if these effects are seen throughout the SGLT2 inhibitor class. Other cardiovascular outcome trials such as DECLARE-TIMI 58 (NCT: 01730534) for dapagliflozin and CANVAS (NCT: 01032629) for canagliflozin will reveal whether or not the cardioprotective effects of SGLT2-inhibitor therapy is seen across this drug class. As described above, this study will be able to provide insights into the mechanism of the positive cardiovascular effects conferred by SGLT2 inhibitor therapy and may also help underpin future outcome trials in HF patients involving this drug class.

Limitations
Firstly this is a relatively small, single centre trial. The use of cardiac MRI has allowed the power of the trial to be preserved despite the small number of participants. However, some differences observed may still be the result of chance and is therefore a limitation of this study. Secondly heart failure is a dynamic disease, as a patient's intravascular volume changes, their loop diuretic requirement may fluctuate. This may necessitate dose adjustments during the trial which could confound

Singh *et al. Cardiovasc Diabetol* (2016) 15:97

Page 9 of 11

the final outcome. However, every measure is taken to ensure blinding of the investigators is maintained and uniformity in the dose adjustments made.

Conclusions

HF and DM remain major clinical problems that are associated with increased mortality and morbidity. Therapeutic options to optimize glycaemic control in DM and HF are limited, and only metformin appears to have beneficial effects on CV outcomes. SGLT2 inhibitors could potentially improve LV remodelling and exercise capacity in these patients, thus offering an important new approach to HF management in DM. If they improve exercise capacity and LV remodelling in HF by reducing both preload and afterload, a strong case could be made for a larger trial specifically in HF patients with DM to test if SGLT2 inhibitors really do have a mortality benefit in this unique patient group. Of course these drugs might, conceivably, alter fluid status in HF without altering LV remodelling. We therefore, also need safety data on what (if anything) they do to fluid status in HF patients. If they behave like glitazones, they could increase fluid retention (and by doing so exacerbate HF). On the other hand, since they produce diuresis, they are more likely to have the opposite effect. Only by studying this, will we know the answer. There is currently no data on combining SGLT2 inhibitors and diuretics which is why this combination is not recommended at this point in time. This study will, with careful monitoring, begin to address this combination, and for the reasons given above, it is likely to be more beneficial than harmful in patients with HF. If this study shows that SGLT2 inhibitors have the dual effect of being a diuretic and favourably remodelling the LV in HF patients, then they would stand head and shoulders above other potential second line anti-diabetics for use in HF patients.

Abbreviations

BCA: body composition analysis; BNP: brain naturetic peptide; BP: blood pressure; CPEX: cardio pulmonary exercise testing; CrCl: creatinine clearance; CRF: case report form; DM: diabetes mellitus; DPPIV: dipeptidyl peptidase inhibitor; EASD: European Association for the Study of Diabetes; EDV: end diastolic volume; EF: ejection fraction; EFSD: European Foundation for the Study of Diabetes; eGFR: estimated glomerular filtration rate; ESV: end systolic volume; FBC: full blood count; GP: general practitioner; HBA1c: glycated haemoglobin; HF: heart failure; IMP: investigational medicinal product; LFT: liver function test; LV: left ventricular; LVEDV: left ventricular end diastolic volume; LVEF: left ventricular ejection fraction; LVESV: left ventricular end systolic volume; LVSD: left ventricular systolic dysfunction; LVH: left ventricular hypertrophy; LVRI: left ventricular remodelling index; MHRA: Medicine and Healthcare products Regulatory Agency; MHFQ: the Minnesota living with heart failure questionnaire; MRI: magnetic resonance imaging; NHS: National Health Service; NYHA: New York Heart Association; QOL: quality of life; RV: right ventricle; RVEDV: right ventricular end diastolic volume; RVEF: right ventricular ejection factor; RVESV: right ventricular end systolic volume; SD: standard deviation; SF-36: short form-36; SGLT2: sodium-glucose co-transporter-2; SPCRN: Scottish Primary Care Research Network; SPSS: statistical package for the social sciences;

T2DM: type 2 diabetes mellitus; U&Es: urea & electrolytes; ZDF: Zucker diabetic fatty; 6MWT: 6 minute walk test.

References
1. Forouzanfar MH, Moran A, Phillips D, Mensah G, Ezzati M, Naghavi M, Murray CJL. Prevalence of heart failure by cause in 21 regions: global burden of diseases, injuries and risk factors-2010 Study. J Am Coll of Cardiol. 2013; 61(10_S).
2. Jessup M, Brozena S. Heart failure. N Engl J Med. 2003;348:2007–18.
3. Members WG, Lloyd-Jones D, Adams RJ, Brown TM, Carnethon M, Dai S, Simone GD, Ferguson TB, Ford E, Furie K, et al. Heart disease and stroke statistics—2010 update. Circulation. 2010;121:e46–215.
4. Chong VH, Singh J, Parry H, Saunders J, Chowdhury F, Mancini DM, Lang CC. Management of non-cardiac comorbidities in chronic heart failure. Cardiovasc Ther. 2015.
5. MacDonald MR, Petrie MC, Hawkins NM, Petrie JR, Fisher M, McKelvie R, Aguilar D, Krum H, McMurray JJ. Diabetes, left ventricular systolic dysfunction, and chronic heart failure. Eur Heart J. 2008;29:1224–40.
6. Kristensen SL, Preiss D, Jhund PS, Squire I, Cardoso JS, Merkely B, Martinez F, Starling RC, Desai AS, Lefkowitz MP, et al. Risk related to pre-diabetes mellitus and diabetes mellitus in heart failure with reduced ejection fraction: insights from prospective comparison of arni with acei to determine impact on global mortality and morbidity in heart failure trial. Circ Heart Fail. 2016;9:e002560.
7. Deswal A, Petersen NJ, Souchek J, Ashton CM, Wray NP. Impact of race on health care utilization and outcomes in veterans with congestive heart failure. J Am Coll Cardiol. 2004;43:778–84.
8. Rathore SS, Foody JM, Wang Y, et al. Race, quality of care, and outcomes of elderly patients hospitalized with heart failure. JAMA. 2003;289:2517.
9. Murcia AM, Hennekens CH, Lamas GA, Jimenez-Navarro M, Rouleau JL, Flaker GC, Goldman S, Skali H, Braunwald E, Pfeffer MA. Impact of diabetes on mortality in patients with myocardial infarction and left ventricular dysfunction. Arch Intern Med. 2004;164:2273–9.
10. Cubbon RM, Adams B, Rajwani A, Mercer BN, Patel PA, Gherardi G, Gale CP, Batin PD, Ajjan R, Kearney L, et al. Diabetes mellitus is associated with adverse prognosis in chronic heart failure of ischaemic and non-ischaemic aetiology. Diab Vasc Dis Res. 2013;10:330–6.
11. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, Peters AL, Tsapas A, Wender R, Matthews DR. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2012;35:1364–79.

Singh *et al. Cardiovasc Diabetol* (2016) 15:97

Page 10 of 11

12. Evans JM, Doney AS, AlZadjali MA, Ogston SA, Petrie JR, Morris AD, Struthers AD, Wong AK, Lang CC. Effect of Metformin on mortality in patients with heart failure and type 2 diabetes mellitus. Am J Cardiol. 2010;106:1006–10.

13. Andersson C, Olesen JB, Hansen PR, Weeke P, Norgaard ML, Jorgensen CH, Lange T, Abildstrom SZ, Schramm TK, Vaag A, et al. Metformin treatment is associated with a low risk of mortality in diabetic patients with heart failure: a retrospective nationwide cohort study. Diabetologia. 2010;53:2546–53.

14. Elder DH, Singh JS, Levin D, Donnelly LA, Choy AM, George J, Struthers AD, Doney AS, Lang CC. Mean HbA1c and mortality in diabetic individuals with heart failure: a population cohort study. Eur J Heart Fail. 2016;18:94–102.

15. Aquilante CL. Sulfonylurea pharmacogenomics in Type 2 diabetes: the influence of drug target and diabetes risk polymorphisms. Expert Rev Cardiovasc Ther. 2010;8:359–72.

16. Tzoulaki I, Molokhia M, Curcin V, Little MP, Millett CJ, Ng A, Hughes RI, Khunti K, Wilkins MR, Majeed A, Elliott P. Risk of cardiovascular disease and all cause mortality among patients with type 2 diabetes prescribed oral antidiabetes drugs: retrospective cohort study using UK general practice research database. BMJ. 2009;339:b4731.

17. Forst T, Hanefeld M, Jacob S, Moeser G, Schwenk G, Pfutzner A, Haupt A. Association of sulphonylurea treatment with all-cause and cardiovascular mortality: a systematic review and meta-analysis of observational studies. Diab Vasc Dis Res. 2013;10:302–14.

18. Eurich DT, McAlister FA, Blackburn DF, Majumdar SR, Tsuyuki RT, Varney J, Johnson JA. Benefits and harms of antidiabetic agents in patients with diabetes and heart failure: systematic review. BMJ. 2007;335:497.

19. Green JB, Bethel MA, Armstrong PW, Buse JB, Engel SS, Garg J, Josse R, Kaufman KD, Koglin J, Korn S, et al. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2015;373:232–42.

20. White WB, Cannon CP, Heller SR, Nissen SE, Bergenstal RM, Bakris GL, Perez AT, Fleck PR, Mehta CR, Kupfer S, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med. 2013;369:1327–35.

21. Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, Ohman P, Frederich R, Wiviott SD, Hoffman EB, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med. 2013;369:1317–26.

22. Shubrook JH, Bokaie BB, Adkins SE. Empagliflozin in the treatment of type 2 diabetes: evidence to date. Drug Des Devel Ther. 2015;9:5793–803.

23. Kalra S. Sodium glucose Co-transporter-2 (SGLT2) inhibitors: a review of their basic and clinical pharmacology. Diabetes Ther. 2014;5:355–66.

24. Nauck MA. Update on developments with SGLT2 inhibitors in the management of type 2 diabetes. Drug Des Devel Ther. 2014;8:1335–80.

25. Han S, Hagan DL, Taylor JR, Xin L, Meng W, Biller SA, Wetterau JR, Washburn WN, Whaley JM. Dapagliflozin, a selective SGLT2 inhibitor, improves glucose homeostasis in normal and diabetic rats. Diabetes. 2008;57:1723–9.

26. McCrimmon RJ, Evans ML, Jacob RJ, Fan X, Zhu Y, Shulman GI, Sherwin RS. AICAR and phlorizin reverse the hypoglycemia-specific defect in glucagon secretion in the diabetic BB rat. Am J Physiol Endocrinol Metab. 2002;283:E1076–83.

27. Oliva RV, Bakris GL. Blood pressure effects of sodium-glucose co-transport 2 (SGLT2) inhibitors. J Am Soc Hypertens. 2014;8:330–9.

28. Majewski C, Bakris GL. Blood pressure reduction: an added benefit of sodium-glucose cotransporter 2 inhibitors in patients with type 2 diabetes. Diabetes Care. 2015;38:429–30.

29. Cherney DZ, Perkins BA, Soleymanlou N, Har R, Fagan N, Johansen OE, Woerle HJ, von Eynatten M, Broedl UC. The effect of empagliflozin on arterial stiffness and heart rate variability in subjects with uncomplicated type 1 diabetes mellitus. Cardiovasc Diabetol. 2014;13:28.

30. Cherney DVEM, Lund S, Kaspers S, Crowe S, Woerle HJ, Hach T. Sodium glucose cotransporter 2 (SGLT2) inhibition with empagliflozin (EMPA) reduces microalbuminuria in patients with type 2 diabetes (T2D) [abstract]. Diabetes. 2014;63((suppl 1)):1125.

31. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015;373:2117–28.

32. Fitchett D, Zinman B, Wanner C, Lachin JM, Hantel S, Salsali A, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE. Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME(R) trial. Eur Heart J. 2016.

33. Konstam MA, Kramer DG, Patel AR, Maron MS, Udelson JE. Left ventricular remodeling in heart failure: current concepts in clinical significance and assessment. JACC Cardiovasc Imaging. 2011;4:98–108.

34. Grothues F, Smith GC, Moon JC, Bellenger NG, Collins P, Klein HU, Pennell DJ. Comparison of interstudy reproducibility of cardiovascular magnetic resonance with two-dimensional echocardiography in normal subjects and in patients with heart failure or left ventricular hypertrophy. Am J Cardiol. 2002;90:29–34.

35. Kramer DG, Trikalinos TA, Kent DM, Antonopoulos GV, Konstam MA, Udelson JE. Quantitative evaluation of drug or device effects on ventricular remodeling as predictors of therapeutic effects on mortality in patients with heart failure and reduced ejection fraction: a meta-analytic approach. J Am Coll Cardiol. 2010;56:392–406.

36. Rekhraj S, Gandy SJ, Szwejkowski BR, Nadir MA, Noman A, Houston JG, Lang CC, George J, Struthers AD. High-dose allopurinol reduces left ventricular mass in patients with ischemic heart disease. J Am Coll Cardiol. 2013;61:926–32.

37. Cherney DZI, Perkins BA, Soleymanlou N, Maione M, Lai V, Lee A, Fagan NM, Woerle HJ, Johansen OE, Broedl UC, von Eynatten M. Renal hemodynamic effect of sodium-glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus. Circulation. 2014;129:587–97.

38. Kosiborod M, Gause-Nilsson I, Sonesson C, Johnsson2 E. Efficacy and safety of dapagliflozin in patients with type 2 diabetes mellitus and concomitant heart failure. European Assoc For The Study of Diabetes Annual Meeting (abstract); 2015.

39. Weber MA, Mansfield TA, Cain VA, Iqbal N, Parikh S, Ptaszynska A. Blood pressure and glycaemic effects of dapagliflozin versus placebo in patients with type 2 diabetes on combination antihypertensive therapy: a randomised, double-blind, placebo-controlled, phase 3 study. Lancet Diabetes Endocrinol. 2015.

40. Tikkanen I, Narko K, Zeller C, Green A, Salsali A, Broedl UC, Woerle HJ. Empagliflozin reduces blood pressure in patients with type 2 diabetes and hypertension. Diabetes Care. 2015;38:420–8.

41. Devereux RB, Roman MJ. Left ventricular hypertrophy in hypertension: stimuli, patterns, and consequences. Hypertens Res. 1999;22:1–9.

42. Devereux RB, Palmieri V, Liu JE, Wachtell K, Bella JN, Boman K, Gerdts E, Nieminen MS, Papademetriou V, Dahlof B. Progressive hypertrophy regression with sustained pressure reduction in hypertension: the Losartan intervention for endpoint reduction study. J Hypertens. 2002;20:1445–50.

43. Cohn JN, Ferrari R, Sharpe N. Cardiac remodeling—concepts and clinical implications: a consensus paper from an international forum on cardiac remodeling. J Am Coll Cardiol. 2000;35:569–82.

44. Younis FMHK, Mayoux EW, et al. Effect of prophylactic treatment with empagliflozin on cardiac function and diabetes in CRDH rats. Diabetes. 2014;63((suppl. 1)):A273 **(P1056)**.

45. Conraads VM, Spruit MA, Braunschweig F, Cowie MR, Tavazzi L, Borggrefe M, Hill MR, Jacobs S, Gerritse B, van Veldhuisen DJ. Physical activity measured with implanted devices predicts patient outcome in chronic heart failure. Circ Heart Fail. 2014;7:279–87.

46. O'Connor CM, Whellan DJ, Lee KL, Keteyian SJ, Cooper LS, Ellis SJ, Leifer ES, Kraus WE, Kitzman DW, Blumenthal JA, et al. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. JAMA. 2009;301:1439–50.

47. Taylor RS, Sagar VA, Davies EJ, Briscoe S, Coats AJ, Dalal H, Lough F, Rees K, Singh S. Exercise-based rehabilitation for heart failure. Cochrane Database Syst Rev. 2014;4:Cd003331.

48. Bolinder J, Ljunggren Ö, Kullberg J, Johansson L, Wilding J, Langkilde AM, Sugg J, Parikh S. Effects of dapagliflozin on body weight, total fat mass, and regional adipose tissue distribution in patients with type 2 diabetes mellitus with inadequate glycemic control on metformin. J Clin Endocrinol Metab. 2011;97:1020–31.

49. Doehner W, Rauchhaus M, Ponikowski P, Godsland IF, von Haehling S, Okonko DO, Leyva F, Proudler AJ, Coats AJ, Anker SD. Impaired insulin sensitivity as an independent risk factor for mortality in patients with stable chronic heart failure. J Am Coll Cardiol. 2005;46:1019–26.

50. Kriska AM, Hanley AJ, Harris SB, Zinman B. Physical activity, physical fitness, and insulin and glucose concentrations in an isolated Native Canadian population experiencing rapid lifestyle change. Diabetes Care. 2001;24:1787–92.

51. Kasa-Vubu JZ, Lee CC, Rosenthal A, Singer K, Halter JB. Cardiovascular fitness and exercise as determinants of insulin resistance in postpubertal adolescent females. J Clin Endocrinol Metab. 2005;90:849–54.

Singh *et al. Cardiovasc Diabetol* (2016) 15:97

Page 11 of 11

52. Seibæk M, Vestergaard H, Burchardt H, Sloth C, Torp-Pedersen C, Nielsen SL, Hildebrandt P, Pedersen O. Insulin resistance and maximal oxygen uptake. Clin Cardiol. 2003;26:515–20.

53. Hsueh WA, Lyon CJ, Quinones MJ. Insulin resistance and the endothelium. Am J Med. 2004;117:109–17.

54. Wong AK, Symon R, AlZadjali MA, Ang DS, Ogston S, Choy A, Petrie JR, Struthers AD, Lang CC. The effect of metformin on insulin resistance and exercise parameters in patients with heart failure. Eur J Heart Fail. 2012;14:1303–10.

55. Brandenburg SL, Reusch JE, Bauer TA, Jeffers BW, Hiatt WR, Regensteiner JG. Effects of exercise training on oxygen uptake kinetic responses in women with type 2 diabetes. Diabetes Care. 1999;22:1640–6.

56. Regensteiner JG, Bauer TA, Reusch JE. Rosiglitazone improves exercise capacity in individuals with type 2 diabetes. Diabetes Care. 2005;28:2877–83.

57. Thomas L, Grempler R, Eckhardt M, Himmelsbach F, Sauer A, Klein T, Eickelmann P, Mark M. Long-term treatment with empagliflozin, a novel, potent and selective SGLT-2 inhibitor, improves glycaemic control and features of metabolic syndrome in diabetic rats. Diabetes Obes Metab. 2012;14:94–6.

58. Mudaliar S, Henry RR, Boden G, Smith S, Chalamandaris AG, Duchesne D, Iqbal N, List J. Changes in insulin sensitivity and insulin secretion with the sodium glucose cotransporter 2 inhibitor dapagliflozin. Diabetes Technol Ther. 2014;16:137–44.