Supplementary Table S1: study inclusion and exclusion criteria

	DIASTOLIC	**LYDIA**	**SEESAW**
Inclusion criteria	Capacity to provide informed consent before any trial-related activities. Age ≥18 and ≤65 years Diagnosis of type 2 diabetes (T2D) before the age of 60 years of age. Established T2D (≥3 months). Body mass index (BMI) >30 kg/m^2 (27 kg/m^2 if South Asian or other black and minority ethnic (BME) populations). HbA1c ≤9% if on triple therapy or ≤10% on diet and exercise or monotherapy or dual therapy. Current glucose-lowering therapy either mono, dual or triple of any combination of metformin, sulphonylurea, DPP-IV inhibitor, GLP-1 therapy or an SGLT2i±diet and exercise. Poorly managed diet controlled diabetes (with HbA1c >6.5%, not currently taking any glucose-lowering therapy, meeting BMI inclusion range). Able to understand English	Capacity to provide informed consent before any trial-related activities Individuals aged 18 - 60 years inclusive Established T2DM BMI ≥ 30 kg/m^2 (≥27 kg/m^2 for South Asians or other BME populations) An HbA1c value of greater than or equal to 6.5% and less than 10% On mono or combination oral therapy (sulphonylurea and/or metformin) for ≥ 3months Able to understand English	Capacity to provide informed consent before any trial-related activities. Male and postmenopausal female participants aged between 30-75 years of age inclusive Type 2 diabetes on diet and lifestyle control or stable dose of metformin only for at least 3 months Stable weight (less than 5% change in body weight in last 3 months) HbA1c 48-86mmol/mol (6.0 - 10%) Estimated glomerular filtration rate (eGFR)≥60ml/min/1.73m^2 BMI ≥ 25kg/m^2 Able and willing to give informed consent Able to understand English

Exclusion criteria	Diabetes duration >12 years. Currently taking more than three glucose-lowering therapies. Weight loss of >5 kg in the preceding 6 months. eGFR <30 mL/min/1.73 m^2. Current therapy with insulin, thiazolidinediones, steroids or atypical antipsychotic medication. Untreated thyroid disease. Known macrovascular disease including coronary artery disease, stroke/ tranisent ischaemic attack (TIA) or peripheral vascular disease. Presence of arrhythmia (including atrial fibrillation, atrial flutter or second or third degree atrioventricular block). Known heart failure or other clinically relevant heart disease. Inability to exercise or undertake a MRP. Absolute contraindication to cardiac magnetic resonance imaging (CMRI).	Type 1 diabetes (identified through C-peptide analysis) Women who are pregnant, breast-feeding or intend to become pregnant or are not using adequate contraceptive methods Suffer from terminal illness eGFR < 30 ml/min/1.73m^2 Impaired liver function (Alanine aminotransferase (ALT)≥2.5 times upper limit of normal) Known to be Hepatitis B antigen or Hepatitis C antibody positive Clinically significant active cardiovascular disease including history of myocardial infarction within the past 6 months and/or heart failure (New York Heart Association (NYHA) class III and IV) at the discretion of the investigator Recurrent major hypoglycaemia as judged by the investigator Known or suspected allergy to the trial products	Patients with Type 1 diabetes Patients on loop diuretics eGFR<60ml/min/1.73m^2 HbA1c >86mmol/mol (10%) or recent hospital admission with diabetic emergency in last 3 months Patients with familial renal glycosuria Patients with recurrent balanitis, vaginal or urinary tract infections Shift workers Patients who have participated in another study of an investigational medicinal product in the last 3 months Active malignancy Serious illness with a life-expectancy of less than 1 year Hypersensitivity to Empagliflozin (Jardiance™) or to any of the excipients Patients with latent autoimmune diabetes in adults (LADA)

	Cardiovascular symptoms (angina and limiting dyspnoea during normal physical activity). Inflammatory condition, for example, connective tissue disorder and rheumatoid arthritis.	Known or suspected thyroid disease Receipt of any investigational drug within four weeks prior to this trial Have severe and enduring mental health problems Are not primarily responsible for their own care Receiving insulin therapy Have taken a thiazolidinedione (TZD) within the last 3 months Absolute contraindications to MRI Any contraindication to Sitagliptin or Liraglutide Have severe irritable bowel disorder Have pancreatitis or a previous history of pancreatitis	Patients with a history of chronic pancreatitis Evidence of conditions that lead to restricted food intake or severe dehydration Patients with a history of excessive alcohol consumption Patients on a severely calorie restricted diet (i.e., ≤800 calories per day)

Supplementary Table S2: Study characteristics stratified by study

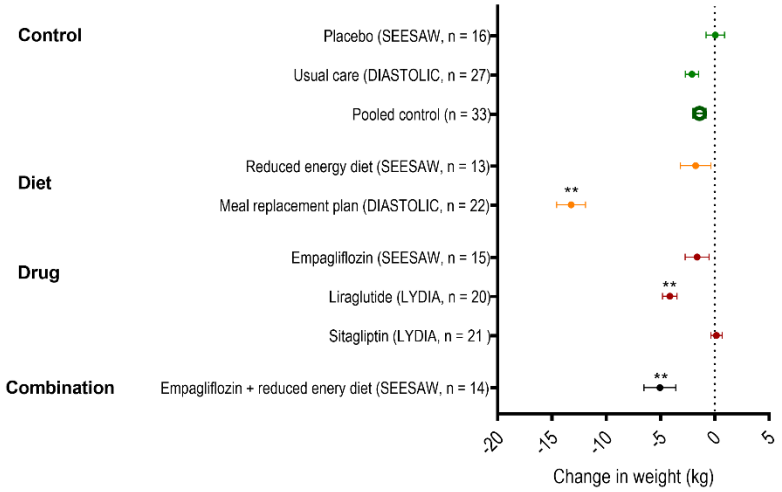
Characteristic	DIASTOLIC (control and meal replacement plan groups, n = 49)	LYDIA (liraglutide and sitagliptin groups, n = 41)	SEESAW (placebo, diet, empaglifozin, empaglifozin plus diet groups, n = 58)
Age (years)	51 (47, 55)	47 (39, 49)	65 (58, 69)
Sex			
Women (%)	20 (41)	20 (49)	21 (36)
Men (%)	29 (59)	21 (51)	36 (64)
Ethnicity			
White (%)	32 (65)	26 (66)	43 (74)
South Asian (%)	12 (25)	15 (34)	9 (16)
Other (%)	5 (10)	0 (0)	6 (10)
Medications			
Metformin (%)	46 (94)	40 (98)	47 (81)
Sulphonylureas (%)	6 (12)	10 (25)	0 (0)
Other (%)	6 (12)	0 (0)	0 (0)
Diabetes duration (years)	4.5 (2.3, 5.6)	3.0 (1.0, 6.5)	7.0 (4.0. 10.0)
BMI (kg/m^2)	35.0 (33.0, 38.1)	33.8 (31.3, 40.0)	31.4 (28.9, 35.3)
HbA1c (mmol/m)	54 (48, 63)	56 (51, 64)	51 (48, 54)
HbA1c (%)	7.1 (6.5, 7.9)	7.3 (6.8, 8.0)	6.8 (6.5, 7.1)
Ambulatory activity (steps/day)	6132 (4588, 7986)	7794 (5738, 9038)	5101 (4005, 7720)
Moderate to vigorous physical activity (mins/day)	23.3 (13.9, 35.6)	24.4 (16.2, 44.4)	17.9 (9.7, 31.3)
Sedentary behaviour (mins/day)	584.0 (852, 945)	536.4 (468.9, 584.0)	576.7 (520.9, 645)
Accelerometer wear time (mins/day)	891.4 (851.7, 944.6)	869.4 (824.5, 921.3)	876.9 (845.6, 907.1)

Data as median (IQR) or number (%)

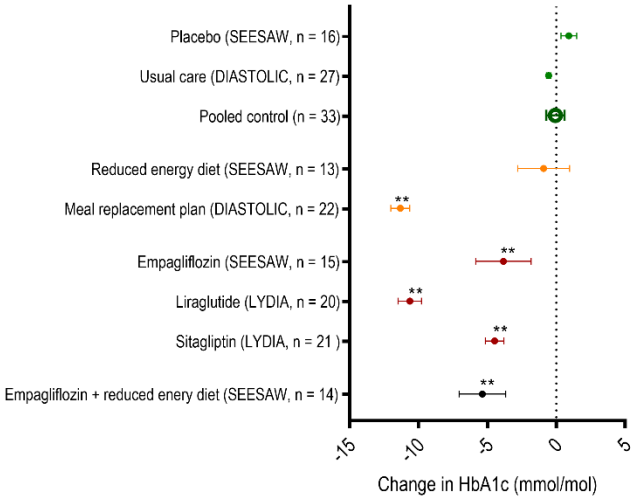
Supplementary Table S3: Study characteristics stratified by inclusion status

Characteristic	**Included (= 148)**	**Excluded (n = 50)**
Age (years)	52 (47, 62)	47 (42, 55)
Sex		
Women (%)	61 (41)	25 (50)
Men (%)	87 (59)	25 (50)
Ethnicity		
White (%)	101 (68)	26 (52)
South Asian (%)	36 (24)	23 (46)
Other (%)	11 (7)	1 (2)
Medications		
Metformin (%)	133 (90)	49 (98)
Sulphonylureas (%)	16 (11)	13 (26)
Other (%)	6 (4)	3 (6)
Diabetes duration (years)	4.7 (2.6, 7.7)	4.0 (2.0, 6.8)
BMI (kg/m^2)	34.0 (31.0, 37.3)	33.1 (31.6, 39.2)
HbA1c (mmol/mol)	53 (48, 59)	56 (51, 64)
HbA1c (%)	7.0 (6.5, 7.5)	7.3 (6.8, 8.0)

Supplementary Figure S1: Change from baseline in weight and HbA1c by control, diet, drug and combination interventions. Data as mean (95% CI)



Adjusted for age, sex, ethnicity,diabetes duration, baseline weight.
* = P<0.05 vs. control, ** = P<0.01 vs. control



Adjusted for age, sex, ethnicity, diabetes duration, baseline BMI, baseline HbA1c
* = P<0.05 vs. control, ** = P<0.01 vs. control

Supplementary Figure S2: Distribution of change values for total physical activity in each analysed group