

HAEMODYNAMIC EFFECTS OF SGLT-2 INHIBITORS

Supplementary table 1: Search string

Database	Date	Search	Search strings	No. of hits
PubMed	18 <sup>th</sup> of September	#1	<b>Heart failure</b> ("heart failure"[MeSH Terms] OR ("heart"[All Fields] AND "failure"[All Fields]) OR "heart failure"[All Fields])	316,488
PubMed	18 <sup>th</sup> of September	#2	<b>SGLT-2 inhibitor</b> ("sodium glucose transporter 2 inhibitors"[Pharmacological Action] OR "sodium glucose transporter 2 inhibitors"[MeSH Terms] OR "sodium glucose transporter 2 inhibitors"[All Fields] OR "sglt 2 inhibitor"[All Fields])	7,938
PubMed	18 <sup>th</sup> of September	#3	<b>(((Pulmonary capillary wedge pressure) OR (Pulmonary artery pressure)) OR (Hemodynamic)) OR (Cardiac output)) OR (Blood pressure)) OR (Cardiac remodeling)</b> ("pulmonary wedge pressure"[MeSH Terms] OR ("pulmonary"[All Fields] AND "wedge"[All Fields] AND "pressure"[All Fields]) OR "pulmonary wedge pressure"[All Fields] OR ("pulmonary"[All Fields] AND "capillary"[All Fields] AND "wedge"[All Fields] AND "pressure"[All Fields]) OR "pulmonary capillary wedge pressure"[All Fields] OR (("pulmonary artery"[MeSH Terms] OR ("pulmonary"[All Fields] AND "artery"[All Fields]) OR "pulmonary artery"[All Fields]) AND ("pressure"[MeSH Terms] OR "pressure"[All Fields] OR "pressures"[All Fields] OR "pressure s"[All Fields] OR "pressurisation"[All Fields] OR "pressurised"[All Fields] OR "pressuriser"[All Fields] OR "pressurization"[All Fields] OR "pressurizations"[All Fields] OR "pressurize"[All Fields] OR "pressurized"[All Fields] OR "pressurizer"[All Fields] OR "pressurizes"[All Fields] OR "pressurizing"[All Fields])) OR ("haemodynamic"[All Fields] OR "hemodynamics"[MeSH Terms] OR "hemodynamics"[All Fields] OR "hemodynamic"[All Fields] OR "haemodynamical"[All Fields] OR "haemodynamically"[All Fields] OR "haemodynamics"[All	1,171,594

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			Fields] OR "hemodynamical"[All Fields] OR "hemodynamically"[All Fields]) OR ("cardiac output"[MeSH Terms] OR ("cardiac"[All Fields] AND "output"[All Fields]) OR "cardiac output"[All Fields]) OR ("blood pressure"[MeSH Terms] OR ("blood"[All Fields] AND "pressure"[All Fields]) OR "blood pressure"[All Fields] OR "blood pressure determination"[MeSH Terms] OR ("blood"[All Fields] AND "pressure"[All Fields] AND "determination"[All Fields]) OR "blood pressure determination"[All Fields] OR ("blood"[All Fields] AND "pressure"[All Fields]) OR "blood pressure"[All Fields] OR "arterial pressure"[MeSH Terms] OR ("arterial"[All Fields] AND "pressure"[All Fields]) OR "arterial pressure"[All Fields] OR ("blood"[All Fields] AND "pressure"[All Fields])) OR (("cardiacs"[All Fields] OR "heart"[MeSH Terms] OR "heart"[All Fields] OR "cardiac"[All Fields]) AND ("remodel"[All Fields] OR "remodelation"[All Fields] OR "remodeled"[All Fields] OR "remodeler"[All Fields] OR "remodelers"[All Fields] OR "remodeling"[All Fields] OR "remodelings"[All Fields] OR "remodelled"[All Fields] OR "remodeller"[All Fields] OR "remodellers"[All Fields] OR "remodelling"[All Fields] OR "remodellings"[All Fields] OR "remodels"[All Fields]))))	
PubMed	18 <sup>th</sup> of September	#4	#1 AND #2 AND #3	955

# HAEMODYNAMIC EFFECTS OF SGLT-2 INHIBITORS

Supplementary table 2: Effect of SGLT-2 inhibitors on SBP and DBP in HFpEF patients

Studies	SBP	DBP	NYHA	No. of treated patients	Dose	Duration
<b>Observational</b>						
Soga et al [1]*	(→)	N/A	I (94%)	58	5 mg dapagliflozin OD	6 months
Sakai et al [2]	(↓)	(↓)	< III	184	10-25 mg empagliflozin, 2,5-5 mg luseogliflozin, or 20 mg tofogliflozin OD	12 weeks
<b>Randomized controlled trials</b>						
EMPEROR-Preserved [3]	↓	N/A	II-IV	2997 (5988)	10 mg empagliflozin OD	Median of 26.2 months
DELIVER trial [4]	↓	N/A	≥II	3131 (6263)	10 mg dapagliflozin OD	Median of 2.3 years
MUSCAT-HF [5]	↓	N/A	II-III	83 (173)	2.5 mg luseogliflozin OD	12 weeks
CANONICAL-HF [6]	→	→	II-III	42 (82)	100 mg canagliflozin OD	24 weeks
PRESERVED-HF [7]	→	N/A	II-IV	162 (324)	10 mg dapagliflozin OD	12 weeks
EMBRACE-HF [8]**	→	N/A	II-III	33 (65)	10 mg empagliflozin OD	12 weeks
EXCEED [9]	→	→	I-II	36 (68)	Ipragliflozin (Dose: unspecified)	24 weeks
CANDLE [10]***	→	N/A	I-III	113 (233)	100 mg canagliflozin OD	24 weeks

↓: for between group (vs. placebo or other treatment intervention)  $p < 0.05$

(↓): for within group (vs. baseline)  $p < 0.05$

(x): total no. of patients

\*: 69% had HFpEF and 31% had either HFmrEF or HFrEF

\*\* : 31 (48%) of patients had HFrEF and (32) 52% had HFpEF with no shown subgroup analysis regarding SBP

\*\*\*: 71% had HFpEF and 29% had either HFmrEF or HFrEF

SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; NYHA: New York Heart Association.

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Supplementary table 3: Effect of SGLT-2 inhibitors on cardiac remodelling in HFrEF patients

Studies	LVESV/ LVESVI	LVEDV/ LVEDVI	LVM/ LVMI	LAV/ LAVI	LVEF	GLS	NYHA	No. of treated patients	Dose	Duration	Method of measurement
<b>Exploratory post hoc analysis</b>											
Omar et al [11]	↓	↓	↓	↓	→	→	I-III	95 (190)	10 mg empagliflozin OD	12 weeks	Echocardiography
<b>Observational</b>											
GLISCAR study [12]	→	→	→	→	↑	↑	II-IV	31	10 mg empagliflozin OD	6 months	Echocardiography
<b>Retrospective</b>											
Hwang et al [13]	N/A	↓	↓*	N/A	↑	↑	≥II	74 (304)	Dapagliflozin or empagliflozin	Median of 10 months	Echocardiography
Camci et al [14]	(↓)	(↓)	N/A	N/A	(↑)	N/A	≥II	168	Unspecified SGLT-2 inhibitor	6 months	Echocardiography
<b>Randomized controlled trials</b>											
SUGAR-DM- HF [15]	↓	↓	→	→	→	→	II-III	52 (105)	10 mg empagliflozin OD	36 weeks	Cardiac magnetic resonance
EMPA-VISION [16]	N/A	→	↓	N/A	→	→	II-III	17 (36)	10 mg empagliflozin OD	12 weeks	Cardiac magnetic resonance
EMPA- TROPISM [17]	↓	↓	↓	N/A	↑	N/A	II-III	42 (84)	10 mg empagliflozin OD	6 months	Cardiac magnetic resonance
REFORM [18]	→	→	→	→	→	N/A	I-II	28 (56)	10 mg dapagliflozin OD	1 year	Cardiac magnetic resonance
DAPA-VO2 [19]	→	→	N/A	→	→	N/A	II-IV	90	10 mg dapagliflozin OD	3 months	Echocardiography
CANA-HF [20]	↑	→	N/A	N/A	↑	N/A	II-III	17 (36)	100 mg canagliflozin OD	12 weeks	Echocardiography
CANDLE-Trial [10]	N/A	N/A	N/A	N/A	→	N/A	I-III	113 (233)**	100 mg canagliflozin OD	24 weeks	Echocardiography

↓: for between group (vs. placebo or other treatment intervention)  $p < 0.05$

(↓): for within group (vs. baseline)  $p < 0.05$

\*: Assumed HFrEF value despite lack of subgroup analysis due to improvement pattern in the other variables observed in this trial

\*\* : 25 HFrEF patients treated with canagliflozin with LVEF-measurements

LVESV(I): left ventricular end-systolic volume (index); LVEDV: left ventricular end-diastolic volume (index); LVM: left ventricular mass; LAV: left atrial volume (index); LVEF: left ventricular ejection fraction; GLS: global longitudinal strain; NYHA: New York Heart Association.

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Supplementary Table 4: Effect of SGLT-2 inhibitors on cardiac remodelling in HFpEF patients

Studies	LVESV/ LVESVI	LVEDV/ LVEDVI	LVM/ LVMI	LAV/ LAVI	LVEF	GLS	NYHA	No. of patients	Dose	Duration	Method of measurement
<b>Observational</b>											
Soga et al [1]	(→)	(→)	(↓)	(↓)	(↑)	N/A	I (94%)	58	5 mg dapagliflozin OD	6 months	Echocardiography
Tanaka et al [21]*					(↑)						
Oka et al[22]	N/A	N/A	N/A	N/A	N/A	↑	N/A	35 (55)	10 mg empagliflozin OD	12 months	Echocardiography
<b>Retrospective</b>											
Hwang et al [13]	N/A	↓	N/A	N/A	→	→	≥II	74 (304)	Dapagliflozin or empagliflozin	Median of 10 months	Echocardiography
<b>Randomized controlled trials</b>											
EXCEED [9]	→	→	→	→	→	N/A	I-II	36 (68)	Ipragliflozin	24 weeks	Echocardiography
EMPA-VISION [16]**	N/A	→	→	N/A	→	→	II-IV	18 (36)	10 mg empagliflozin OD	12 weeks	Cardiac magnetic resonance
MUSCAT-HF [5]	N/A	N/A	→	→	→	N/A	II-III	83 (173)	2.5 mg luseogliflozin OD	12 weeks	Echocardiography
CANONICAL- HF [6]	N/A	N/A	N/A	N/A	→	N/A	II-III	42 (82)	100 mg canagliflozin OD	24 weeks	Echocardiography
CANDLE-Trial [10]	N/A	N/A	N/A	N/A	→	N/A	I-III	113 (233)***	100 mg canagliflozin OD	24 weeks	Echocardiography

↓: for between group (vs. placebo or other treatment intervention)  $p < 0.05$

(↓): for within group (vs. baseline)  $p < 0.05$

\*: same data as Soga et al – contributes with LV-GLS analysis

\*\* : 5 patients treated with SGLT-2i and 7 patients treated with placebo were excluded after randomization

\*\*\*: 68 HFpEF patients treated with canagliflozin with LVEF-measurements

LVESV(I): left ventricular end-systolic volume (index); LVEDV: left ventricular end-diastolic volume (index); LVM: left ventricular mass; LAV: left atrial volume (index); LVEF: left ventricular ejection fraction; GLS: global longitudinal strain; NYHA: New York Heart Association.

## References:

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