The renal and vascular effects of combined SGLT2 and angiotensin converting enzyme inhibition

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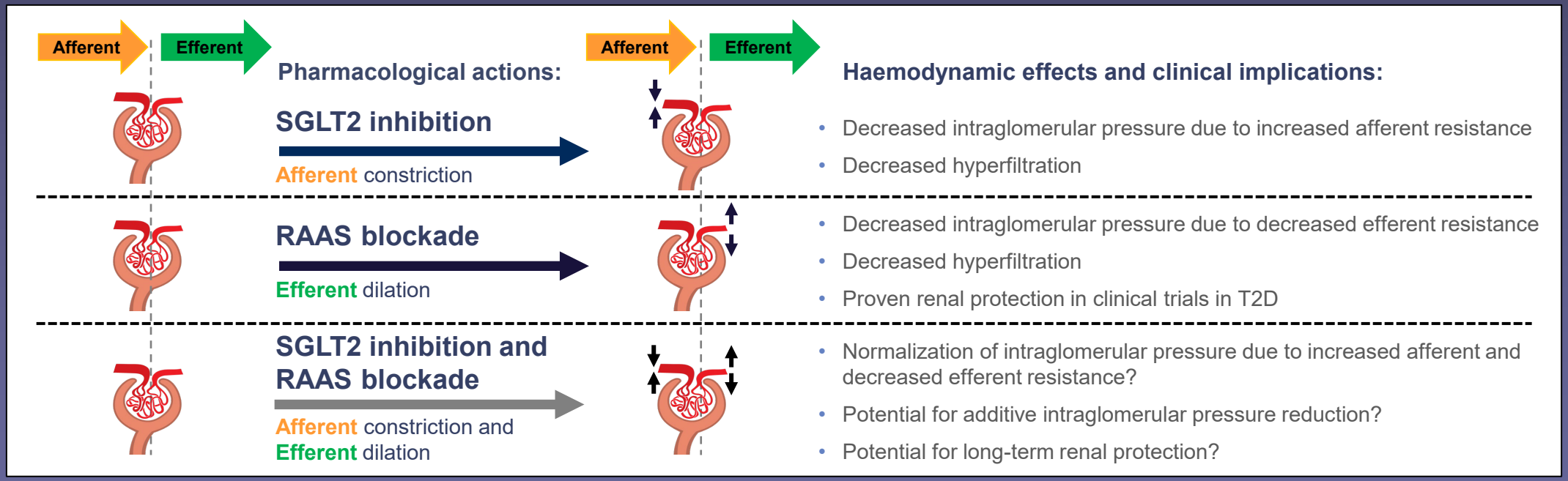
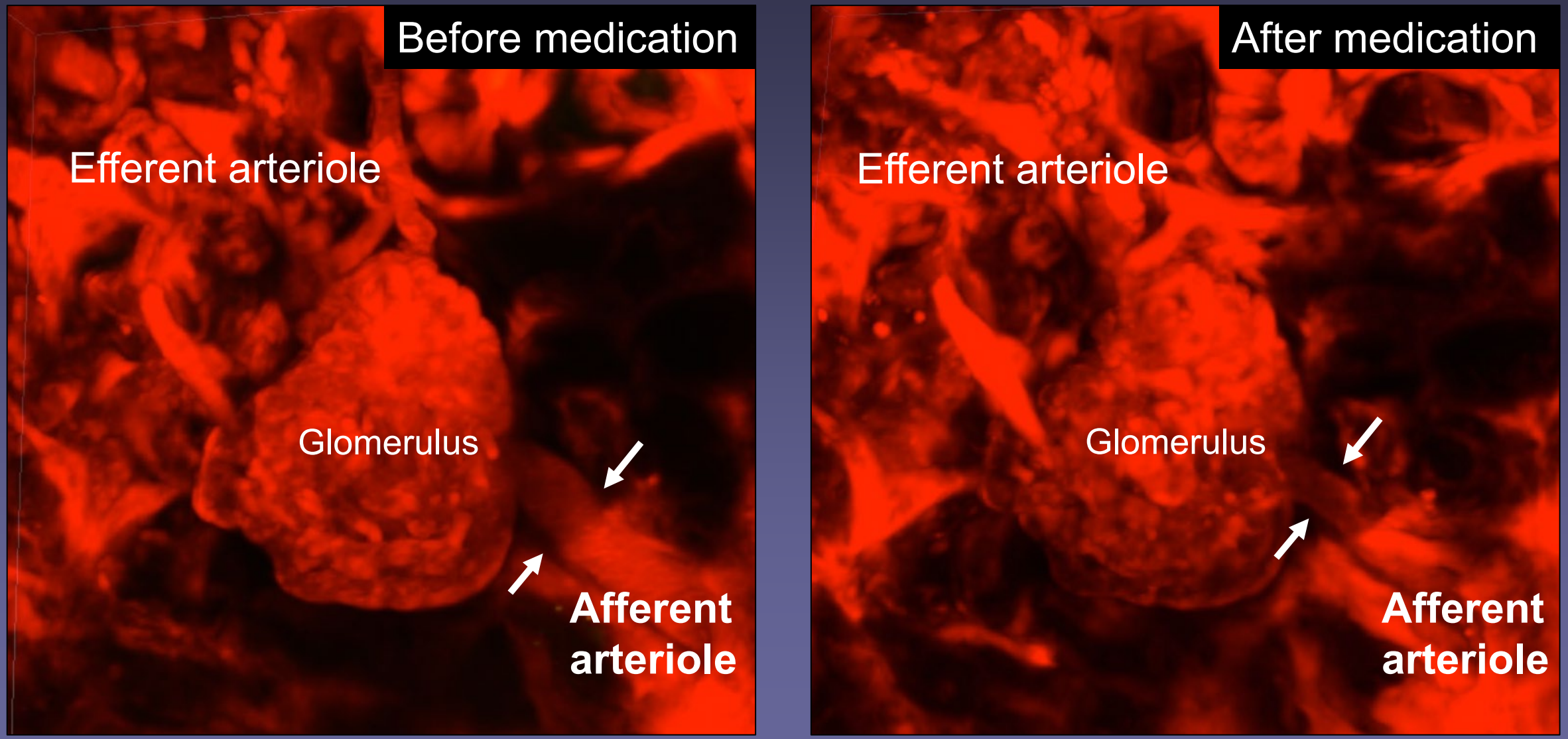
Background

- SGLT2 inhibitors reduce cardiorenal risk in T2D[1-3]
- SGLT2 inhibitors reduce HbA1c, systolic BP, and body weight in patients with T2D and uncomplicated T1D[4-6]
- Both SGLT2 inhibitors and RAAS inhibitors decrease intraglomerular pressure in patients with T1D and hyperfiltration[7,8]



1. McGuire DK, *et al. JAMA Cardiol* 2021;6:148–58. 2. Perkovic V, *et al. N Engl J Med* 2019;380:2295–306. 3. Heerspink HJL, *et al. N Engl J Med* 2020;383:1436–46. 4. Musso G, *et al. Ann Med* 2012;44:375–93. 5. Ferrannini E, *et al. Nat Rev Endocrinol* 2012;8:495–502. 6. Mudaliar S, *et al. Diabetes Care* 2012;35:2198–200. 7. Škrtić M, *et al. Diabetologia* 2014;57:2599–602. 8. Van Bommel ELM, *et al. Kidney Int* 2020;97:202–212. Figure adapted from Škrtić M, *et al. Diabetologia* 2014;57:2599–602.
BP, blood pressure; HbA1c, glycated hemoglobin; RAAS, renin-angiotensin-aldosterone system; SGLT2, sodium-glucose co-transporter-2; T1D, type 1 diabetes; T2D, type 2 diabetes.

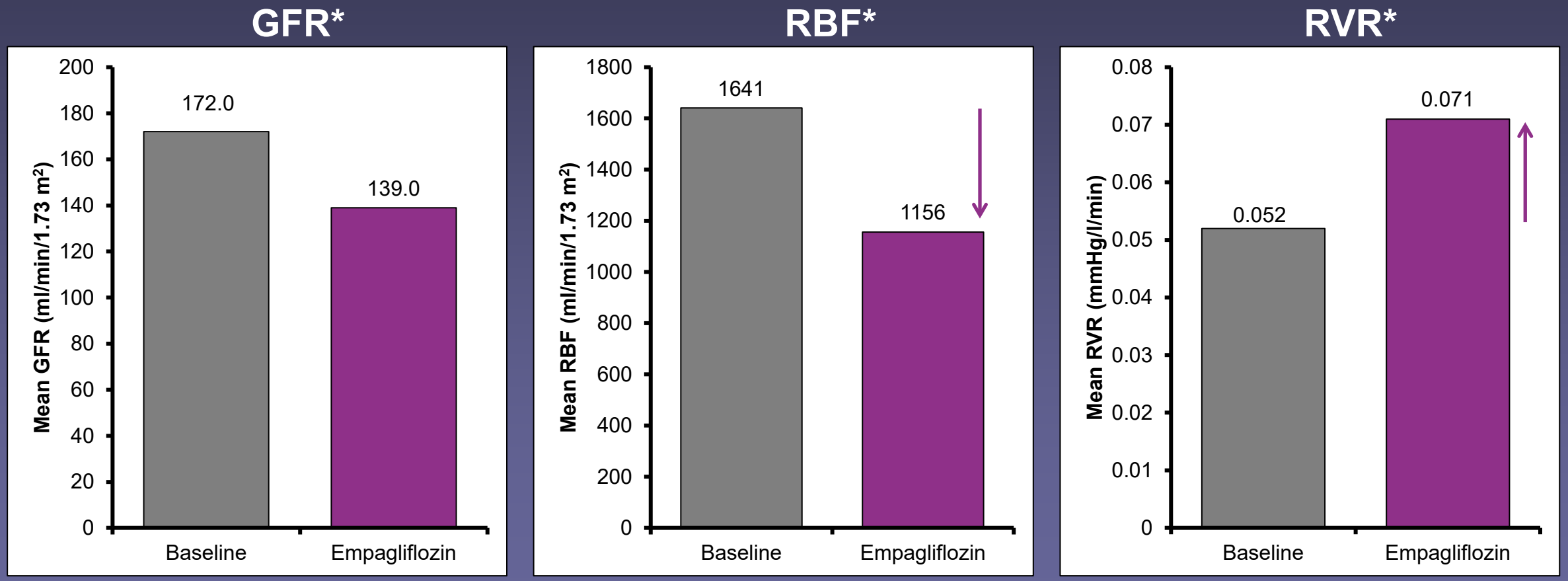
Background: *in vivo* imaging of afferent arteriole change before and after treatment with empagliflozin



Kidokoro K, Cherney DZI, Bozovic A, Nagasu H, Satoh M, Kanda E, Sasaki T, Kashihara N. Evaluation of Glomerular Hemodynamic Function by Empagliflozin in Diabetic Mice Using In Vivo Imaging. *Circulation* 2019;140:303–315. https://doi.org/10.1161/CIRCULATIONAHA.118.037418. Red indicates BSA-Alexa594. BSA, bovine serum albumin.

Background: reduced hyperfiltration is mediated by effects on renal blood flow and vascular resistance in T1D

- In a 2014 study, empagliflozin 25 mg reduced RBF and increased RVR after 8 weeks of treatment, consistent with afferent arteriole vasoconstriction[1]



*p<0.01

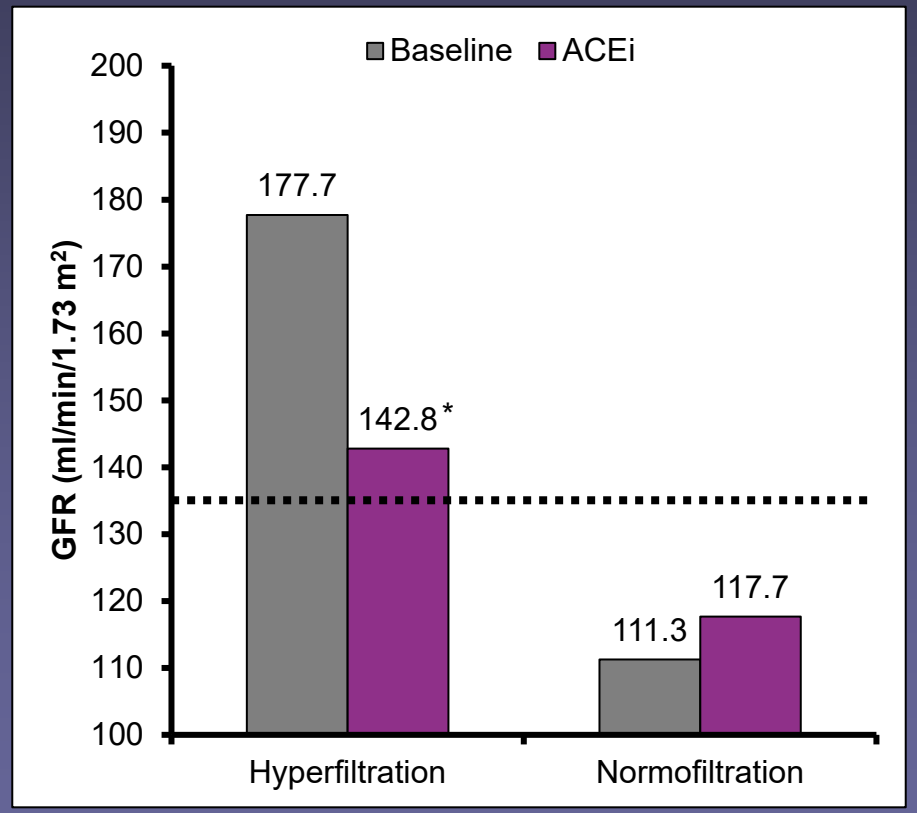
Patients with type 1 diabetes and hyperfiltration at baseline. GFR, RBV, and RVR recorded in euglycemic state.

1. Cherney D, *et al. Circulation* 2014;129:587–97. Figure adapted from Cherney D, *et al. Circulation* 2014;129:587–97.

GFR, glomerular filtration rate; RBF, renal blood flow; RVR, renal vascular resistance; T1D, type 1 diabetes.

Background: efferent mediators of hyperfiltration ACEi in patients with T1D

- In a previous study, patients with hyperfiltration experienced a significant reduction in GFR, whereas patients with normofiltration experienced no significant change after 21 days of ACEi treatment[1]



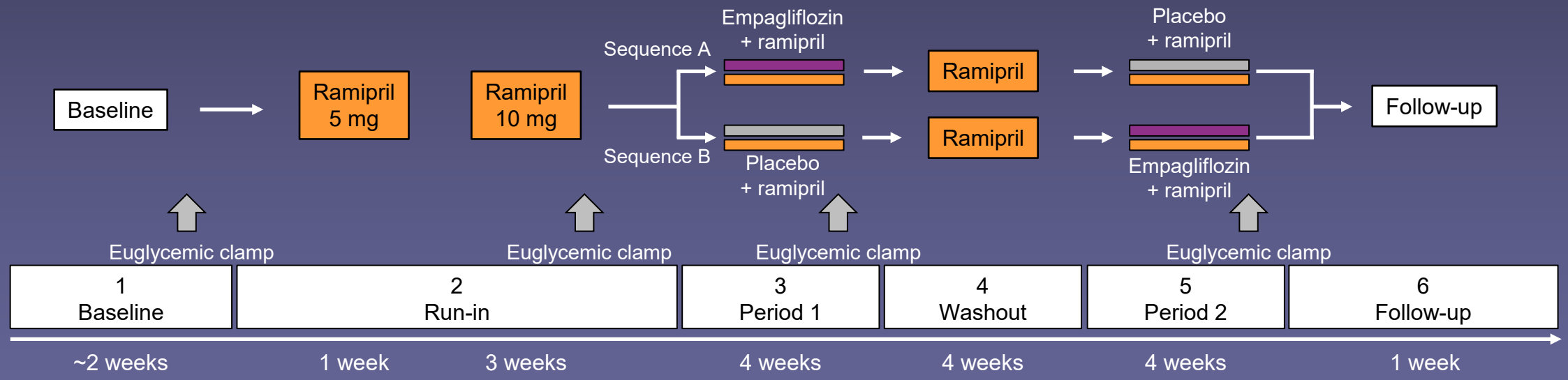
*p<0.05 versus baseline and versus normofiltration. Patients with T1D. GFR recorded in euglycemic state.
Figure developed based from data in Sochett EB, *et al*. *J Am Soc Nephrol* 2006;17:1703–9.

1. Sochett EB, *et al*. *J Am Soc Nephrol* 2006;17:1703–9.

ACEi, angiotensin converting enzyme inhibitor; GFR, glomerular filtration rate; T1D, type 1 diabetes.

The BETWEEN study

- The aim of the study was to investigate the kidney and cardiovascular effects of combined treatment with an SGLT2 inhibitor (empagliflozin 25 mg once daily) and an ACEi (ramipril 10 mg once daily or maximum tolerated dose) for 4 weeks in patients at risk of kidney hyperfiltration
- The BETWEEN study (NCT02632747) was a single-center, prospective, double-blind, randomized, placebo-controlled, cross-over study, comprised of 6 sequential phases:



- Participants with T1D or T2D or non-diabetic obesity (BMI ≥30 kg/m^2), aged ≥18 years with HbA1c 6.5%–11.0% for those with T1D or T2D, estimated GFR ≥60 ml/min/1.73 m², and BP >90/60 mmHg and ≤140/90 mmHg were eligible for inclusion in the study

ACEi, angiotensin converting enzyme inhibitor; BMI, body mass index; BP, blood pressure; GFR, glomerular filtration rate; HbA1c, glycated hemoglobin; SGLT2, sodium-glucose co-transporter-2; T1D, type 1 diabetes; T2D, type 2 diabetes.

Outcomes and statistical methods

- Primary outcome: effect of empagliflozin-ramipril treatment on GFR versus placebo-ramipril treatment
- At the end of each study phase, under clamped euglycemia (4-6 mmol/l), we measured:
  - Inulin (GFR) and para-aminohippurate clearances
  - Tubular sodium handling
  - Ambulatory BP
  - Arterial stiffness
  - Heart rate variability
  - Non-invasive cardiac output monitoring
  - Plasma and urine biochemistry
- A MMRM model was used to assess treatment differences using a random effect for patient, fixed effects for the class variables treatment and period, and a fixed effect for the continuous variable randomization baseline of the endpoint
- Due to the low recruitment of patients with hyperfiltration, study recruitment was stopped and data from available patients were analyzed in an exploratory manner

BP, blood pressure; GFR, glomerular filtration rate; MMRM, Mixed-Effects Model for Repeated Measures.

Results: baseline characteristics

	FAS (N=30)
	Baseline
Male, n (%)	13 (43.3)
Age, years	26.7±4.5
Diabetes duration, years	16.0±7.0
Smoking status: never smoked, n (%)	24 (80.0)
	Run-in
Continuous subcutaneous insulin infusion, n (%)	20 (67.7)
Multiple daily injections, n (%)	10 (33.3)
Insulin pump total daily dose, IU	44.0±18.5
Basal, IU	31.9±13.9
Bolus, IU	31.4±13.4
Weight, kg	77.2±16.6
Waist circumference, cm	94.0±13.9
BMI, kg/m^2	26.3±4.5
SBP, mmHg	109±9
DBP, mmHg	68±5
HR, bpm	72±14
eGFR, $ml/min/1.73\ m^2$	121±12

Data presented as mean ± SD unless otherwise stated. Only patients with T1D were enrolled. One patient was not included in the FAS due to not having a baseline GFR measurement. RIS and FAS had similar baseline characteristics. BMI, body mass index; bpm; beats per minute; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FAS, full analysis set; HR, heart rate; IU, international unit; RIS, run-in set; SBP, systolic blood pressure; SD, standard deviation; T1D, type 1 diabetes.

Results: sodium handling and kidney hemodynamic responses to empagliflozin compared to placebo in T1D

- Ramipril treatment for 4 weeks during the run-in period significantly decreased RVR, SBP, DBP and MAP

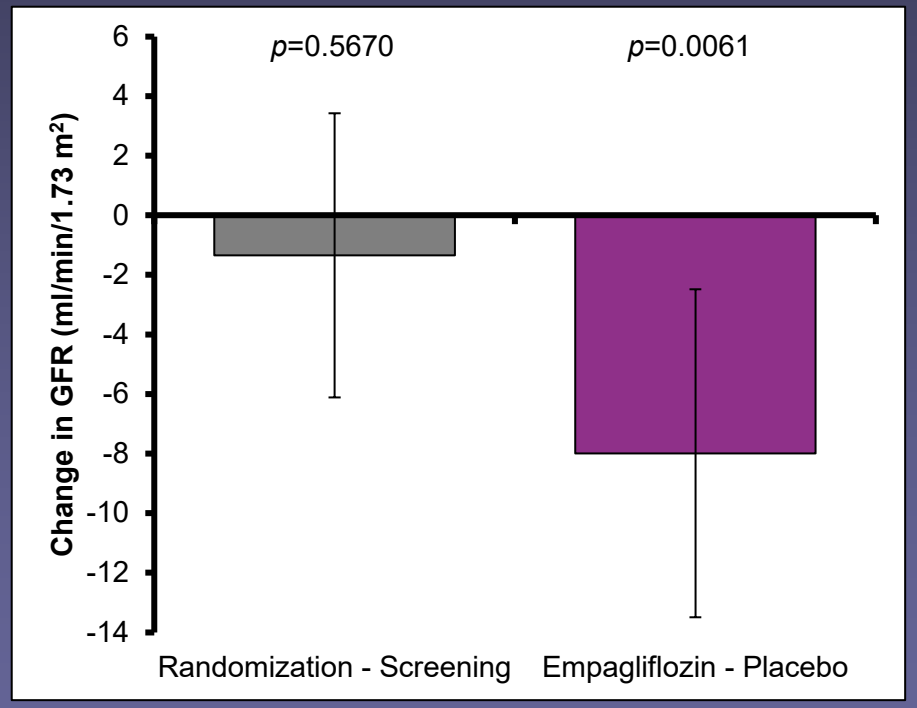
	Baseline (N=31) Mean ± SD	Run-in Ramipril (N=30) Mean ± SD	Placebo* (N=30) Mean ± SE	Empagliflozin* (N=30) Mean ± SE	*P*-value Placebo versus empagliflozin
Kidney hemodynamic function					
GFR, ml/min/1.73 m^2	116±14	115±12	118±3	110±3	0.0061
ERPF, ml/min/1.73 m^2	650±116	691±151	680±18	651±18	0.240
Filtration fraction	0.182±0.029	0.173±0.035	0.181±0.007	0.174±0.007	0.408
RBF, ml/min/1.73 m^2	1049±196	1112±229	1094±30	1062±30	0.455
RVR, mmHg/l/min	0.079±0.017	0.071±0.016**	0.072±0.002	0.072±0.002	0.975
Blood pressure and heart rate					
HR, bpm	73±15	72±14	76±1	73±1	0.130
SBP, mmHg	112±12	108±11**	109±1	105±1	0.0112
DBP, mmHg	69±8	66±7**	67±1	64±1	0.0032
MAP, mmHg	83±9	80±8**	81±1	77±1	0.0022

*Corrected for randomization after the run-in period. ***P*<0.05 versus baseline.
BMI, body mass index; bpm; beats per minute; DBP, diastolic blood pressure; ERPF, effective renal plasma flow; GFR, glomerular filtration rate; HR, heart rate; MAP, mean arterial pressure; RBF, renal blood flow; RVR, renal vascular resistance; SBP, systolic blood pressure; SD, standard deviation; SE, standard error; T1D, type 1 diabetes.

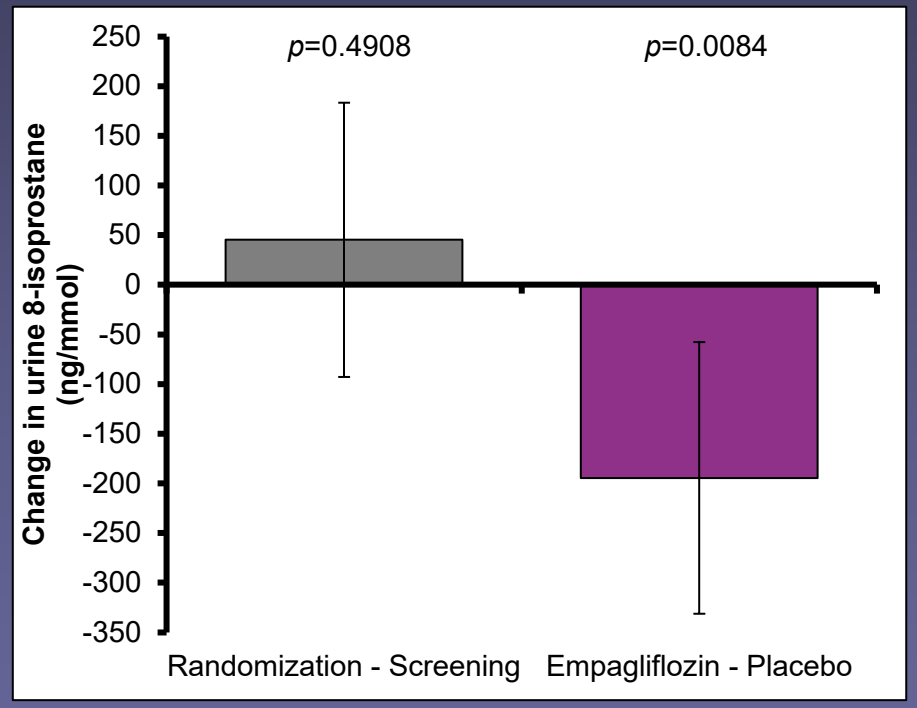
Results: effect of empagliflozin-ramipril treatment on kidney function and urine biochemistry

- Empagliflozin-ramipril treatment for 4 weeks during the run-in period resulted in an 8 ml/min/1.73 m^2 decrease in GFR, and lower urinary 8-isoprostane relative to placebo-ramipril treatment

GFR*



Urine 8-isoprostane†



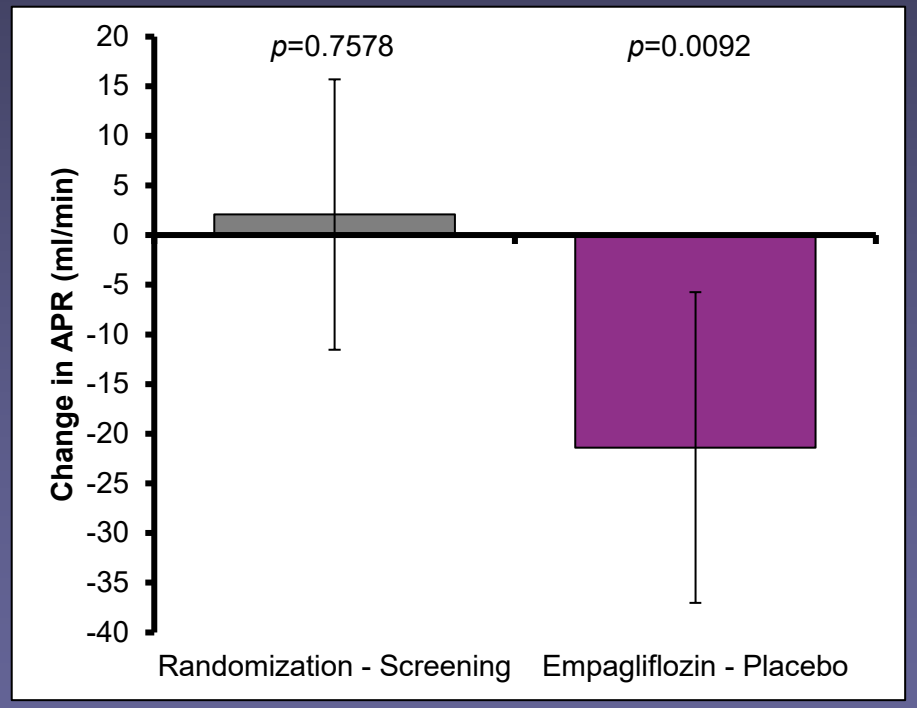
- No significant changes in other renal hemodynamic function parameters

Changes during screening subtracted from randomization and placebo subtracted from empagliflozin in patients with baseline T1D, and in response to ramipril treatment following addition of empagliflozin or placebo. *Estimated under steady state conditions of infusing inulin. †Corrected for urinary creatinine at the time of collection; plasma 8-isoprostane changes were not significant. GFR, glomerular filtration rate; T1D, type 1 diabetes.

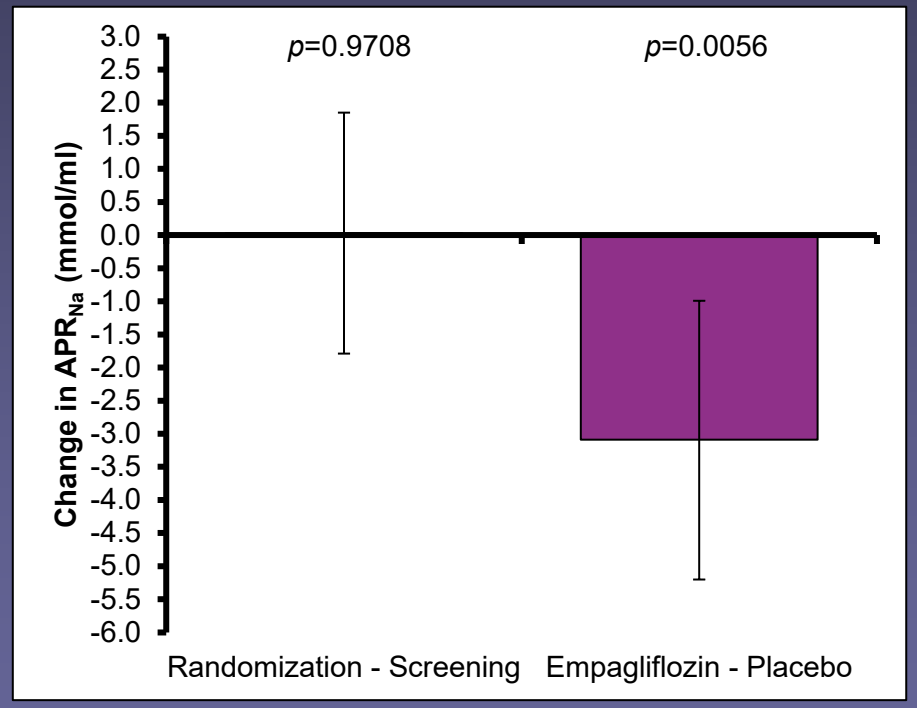
Results: effect of empagliflozin-ramipril treatment on kidney function and sodium handling

- Empagliflozin-ramipril treatment for 4 weeks during the run-in period increased FE_{Na+} and FE_{Li+} ($p<0.05$), and lowered APR and APR_{Na} relative to placebo-ramipril treatment

APR*



APR_{Na}†

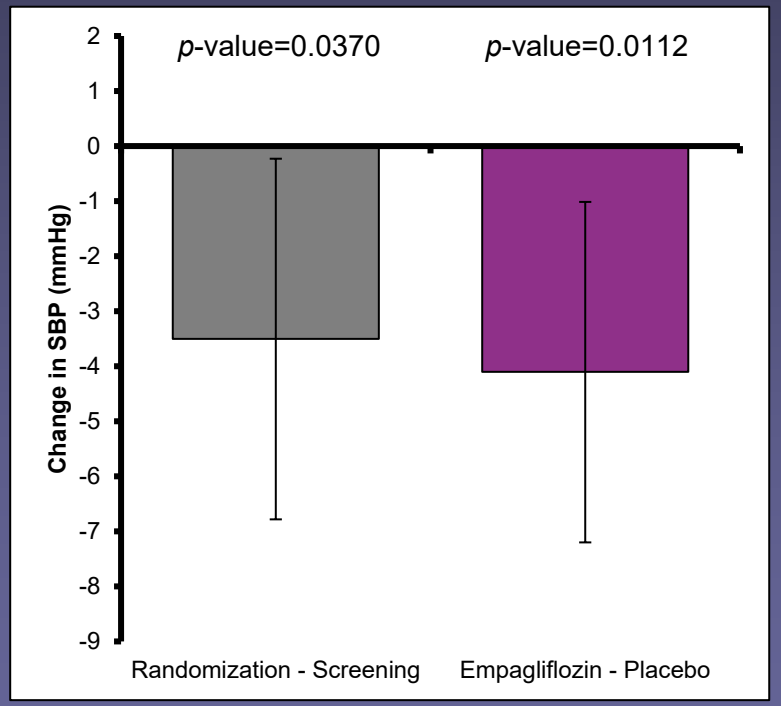


Change at screening and randomization, and placebo and empagliflozin in patients with T1D at baseline, and in response to ramipril treatment following addition of empagliflozin or placebo.
*GFR – C_{Li}. †Plasma Na x APR.
APR, absolute proximal fluid reabsorption rate; APR_{Na}, absolute proximal sodium reabsorption rate; C_{li}, lithium clearance; FE_{Li+}, fractional excretion of lithium; FE_{Na+}, fractional excretion of sodium; GFR, glomerular filtration rate; T1D, type 1 diabetes.

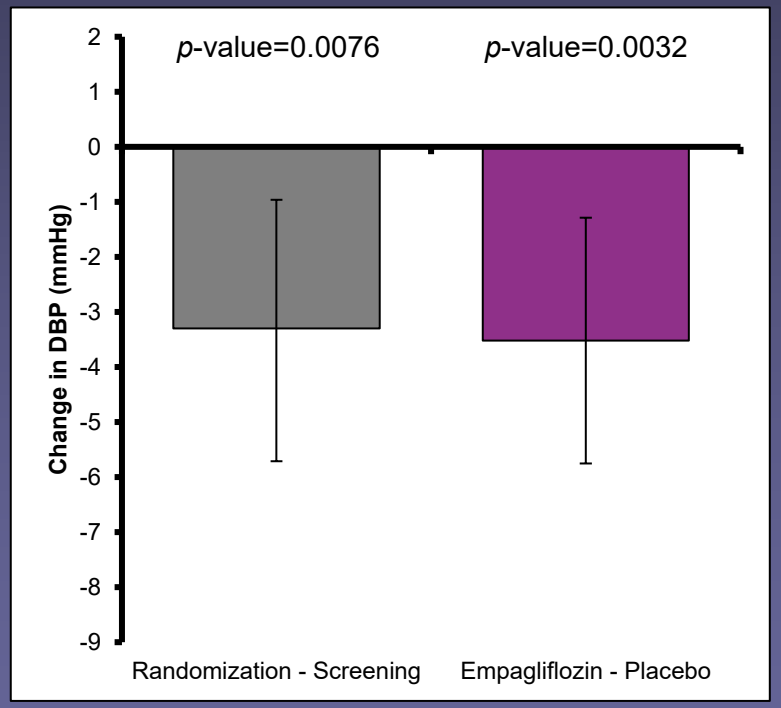
Results: effect of empagliflozin-ramipril treatment on cardiovascular hemodynamic parameters

- Empagliflozin-ramipril treatment for 4 weeks during the run-in period resulted in additive BP lowering effects and a lower TPR relative to placebo-ramipril treatment

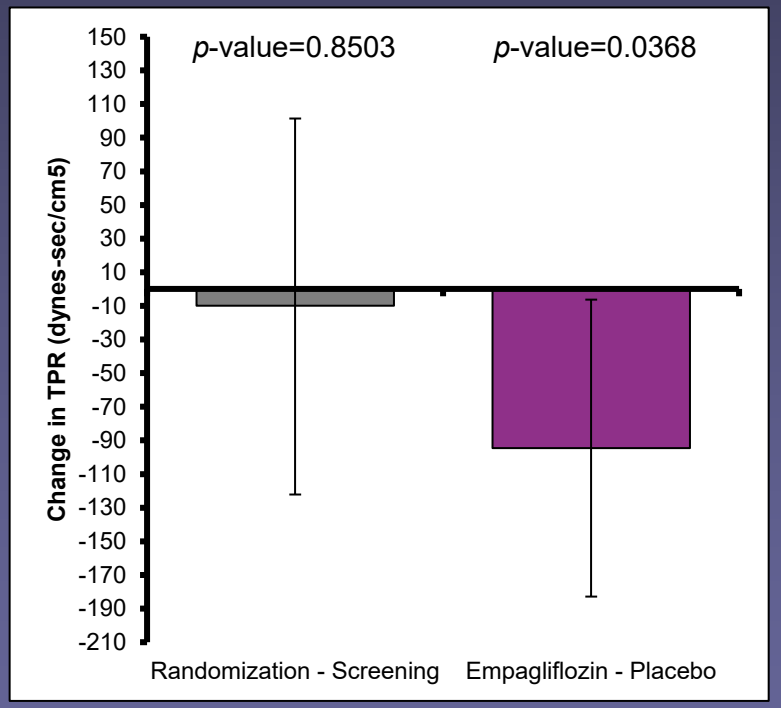
SBP*



DBP*



TPR†



- No changes in ambulatory blood pressure, heart rate variability, arterial stiffness

Change at screening and randomization, and placebo and empagliflozin in patients with T1D at baseline, and in response to ramipril treatment following addition of empagliflozin or placebo.
*Measured by an automated sphygmomanometer over the right brachial artery throughout the physiologic assessment study days.
†Non-invasive cardiac output monitoring measurements were performed for 10 minutes and in duplicate, the mean of the measurements are reported.
BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure; T1D, type 1 diabetes mellitus; TPR, total peripheral resistance.

Conclusions

- SGLT2 inhibitor added to ACEi background treatment resulted in an expected acute GFR ‘dip’, suppression of oxidative stress, and declines in BP and TPR in T1D
- Our results are consistent with a protective physiological profile, with lowering of intraglomerular pressure and related cardiorenal risk when adding an SGLT2 inhibitor to conservative therapy
- The mechanism of GFR lowering in this setting might differ compared to hyperfiltration, but still consistent with acute hemodynamic effect

ACEi, angiotensin converting enzyme inhibitor; BP, blood pressure; GFR, glomerular filtration rate; SGLT2, sodium-glucose co-transporter-2; T1D, type 1 diabetes; TPR, total peripheral resistance.

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