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Circulation

RESEARCH LETTER

Kidney Hemodynamic Effects of Angiotensin Receptor Blockade, Sodium-Glucose Cotransporter-2 Inhibition Alone, and Their Combination: A Crossover Randomized Trial in People With Type 2 Diabetes

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Renin-angiotensin system (RAS) inhibitors and sodium-glucose cotransporter-2 (SGLT2) inhibitors improve kidney outcomes in people with type 2 diabetes.[1] Lowering of glomerular pressure, clinically characterized by an acute estimated glomerular filtration rate (eGFR) decline, contributes to the kidney-protective properties of these drugs.[2] In all trials studying their kidney effects, SGLT2 inhibitors were introduced on top of standard of care, including RAS inhibition. The effect of the combination of these drugs on kidney hemodynamic function remains unstudied. Therefore, we investigated the effects of monotherapy and combination therapy with the SGLT2 inhibitor empagliflozin and the RAS inhibitor losartan on kidney hemodynamic function, particularly, measured GFR (mGFR), in individuals with type 2 diabetes.

We conducted a phase 4, monocenter, randomized, double-blind, comparator-controlled, 4-armed, crossover mechanistic study. The study was approved by our institutional review committee, and participants provided informed consent. Data are available on reasonable request. We included 24 overweight or obese individuals with type 2 diabetes (age, 66±6 years; hemoglobin A1c, 7.4±0.9%) treated with metformin (100%) and/or sulfonylurea (46%). Systolic blood pressure was 145±16 mm Hg. Hypertension (58%) was regulated by α- or β-blockers. Participants were randomized to a 1-week treatment with 10 mg of empagliflozin once daily, 50 mg of losartan once daily, empagliflozin+losartan once daily, and matching placebo, with 4-week washout periods between each treatment period (Figure [A]). Primary end points were fasting mGFR and effective renal plasma flow. mGFR and were determined by iohexol and para-aminohippurate clearances, respectively. A linear mixed-model analysis was used to compare outcome measures between treatment sequences.

All treatments reduced mGFR compared with placebo (107 mL/min [SD, 20 mL/min]): empagliflozin by 7.2 mL/min (95% CI, −13.9 to −0.6), losartan by 7.5 mL/min (95% CI, −14.1 to −0.9), and empagliflozin+losartan by 10.9 mL/min (95% CI, −17.5 to −4.3; Figure [B]). Compared with empagliflozin, empagliflozin+losartan reduced GFR by 3.7 mL/min (95% CI, −13.7 to 6.4), whereas compared with losartan, empagliflozin+losartan reduced GFR by 3.4 mL/min (95% CI, −13.5 to 6.6). Effective renal plasma flow (placebo, 624 mL/min [SD, 158 mL/min]) was not changed by any treatment (Figure [C]), whereas renal vascular resistance tended to decline (Figure [D]). Both preglomerular (Figure [E]) and postglomerular (Figure [F])

Key Words: angiotensin receptor blocker ■ diabetic kidney disease ■ sodium glucose cotransporter-2 inhibitor ■ type 2 diabetes mellitus

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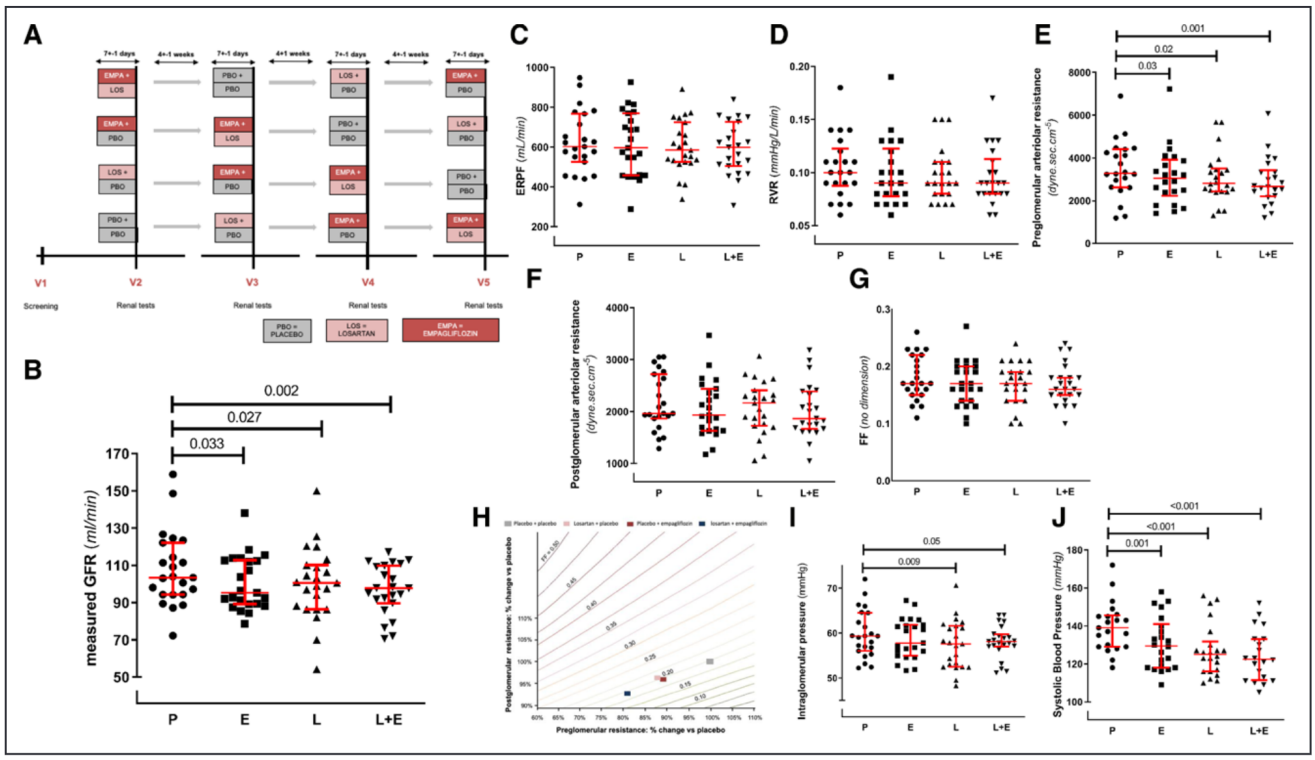

Figure. Kidney hemodynamic effects of empagliflozin and losartan in the RECOLAR study.
A, A crossover study design was used for the present trial. The washout period was 4 weeks between treatments. **B** through **I**, Treatment-induced changes in kidney hemodynamic function. **B**, Measured glomerular filtration rate (GFR). **C**, Effective renal plasma flow (ERPF). **D**, Renal vascular resistance (RVR). **E**, Preglomerular resistance. **F**, Postglomerular resistance. **G**, Filtration fraction (FF). **H**, Adapted plot based on calculations in the article by Carmines et al,[3] which related changes in preglomerular and postglomerular resistance to FF. Placebo-placebo treatment was used as reference with values set at 100%. **I**, Estimated intraglomerular pressure. **J**, Systolic blood pressure. Data represent mean with SEM. Statistical analyses carried out by linear mixed model, which included a random intercept for the subject, taking into account the dependency of the observations within one subject and included treatment order as a factor to exclude carryover effects. Significant findings compared with placebo are indicated. Statistically significant mean differences of treatments compared with placebo are indicated with brackets. E indicates empagliflozin; L, losartan; and P, placebo.

reductions in arteriolar resistance were noted, with filtration fraction kept constant (Figure [G and H]).

We demonstrate that, compared with placebo, RAS and SGLT2 inhibition combination therapy induced a numerically greater reduction in mGFR and estimated glomerular pressure (Figure [I]) than either treatment alone. The study was not powered to compare the monotherapy arms with the combination therapy arm; however, we could observe clinically relevant mGFR reductions of 3 to 4 mL/min between these conditions. An interesting point is that both drugs showed similar kidney hemodynamic effects that contribute to mGFR and glomerular pressure reductions.

Losartan monotherapy reduced mGFR and estimated glomerular pressure without increasing renal vascular resistance. Estimated preglomerular and postglomerular resistances were reduced, supporting vasoconstrictive actions of angiotensin II on both preglomerular and postglomerular vessels. Because postglomerular arterioles have smaller diameters than preglomerular arterioles, the hemodynamic impact in response to angiotensin II of these arterioles is larger compared with the preglomerular arterioles, according to the equation of Hagen-Poiseulle[4] and as proposed in the nomogram by Carmines et al,[3] in which smaller changes in efferent arteriolar resistance have larger kidney hemodynamic effects. This effect explains the observed overall reduction in mGFR with constant filtration fraction (Figure [G and H]). The reduction in systolic blood pressure may also contribute to the observed kidney hemodynamic profile (Figure [J]).

Empagliflozin induced a similar kidney hemodynamic profile. In contrast to stimulating afferent vasoconstriction in hyperfiltering individuals with type 1 diabetes, SGLT2 inhibition induces an overall vasodilative response in people with type 2 diabetes.[5] SGLT2 inhibitors activate tubuloglomerular feedback secondary to increased distal sodium and chloride uptake, triggering the macula densa to secrete adenosine, inducing vasodilatory endothelial responses in people with type 2 diabetes. In addition, SGLT2 inhibitors are known to cause systemic and intrakidney RAS activation. It has been suggested that an SGLT2 inhibitor–induced increase in angiotensin II could activate the nonclassic RAS pathways independent of simultaneous RAS inhibition. This nonclassic pathway generally opposes the classic RAS pathway and is considered to induce general vasodilation.

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These different mechanisms of action, that is, direct endothelial effects related to angiotensin II receptor blockade of RAS inhibitors and tubular-mediated endothelial effects of SGLT2 inhibitors, lead to additive effects when used in combination, although, as stated, we had insufficient power to reach statistical significance for these differences.

Our study is limited by its short duration, although hemodynamic effects with both agents occur very rapidly and remain stable over time. In addition, we included mostly White men with preserved kidney function, therefore limiting generalizability. Furthermore, we could only estimate glomerular pressure and resistance with the Gomez formulas.

In conclusion, we show that the SGLT2 inhibitor empagliflozin, combined with the RAS blocker losartan, has additional beneficial kidney hemodynamic effects compared with either drug alone in people with type 2 diabetes. These data support the combined use of these agents to reduce the kidney disease burden in this population.

ARTICLE INFORMATION

Registration: URL: https://www.clinicaltrials.gov; Unique identifier: NCT04238702.

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Disclosures

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