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In-Depth Mechanism of SGLT2 Inhibitor

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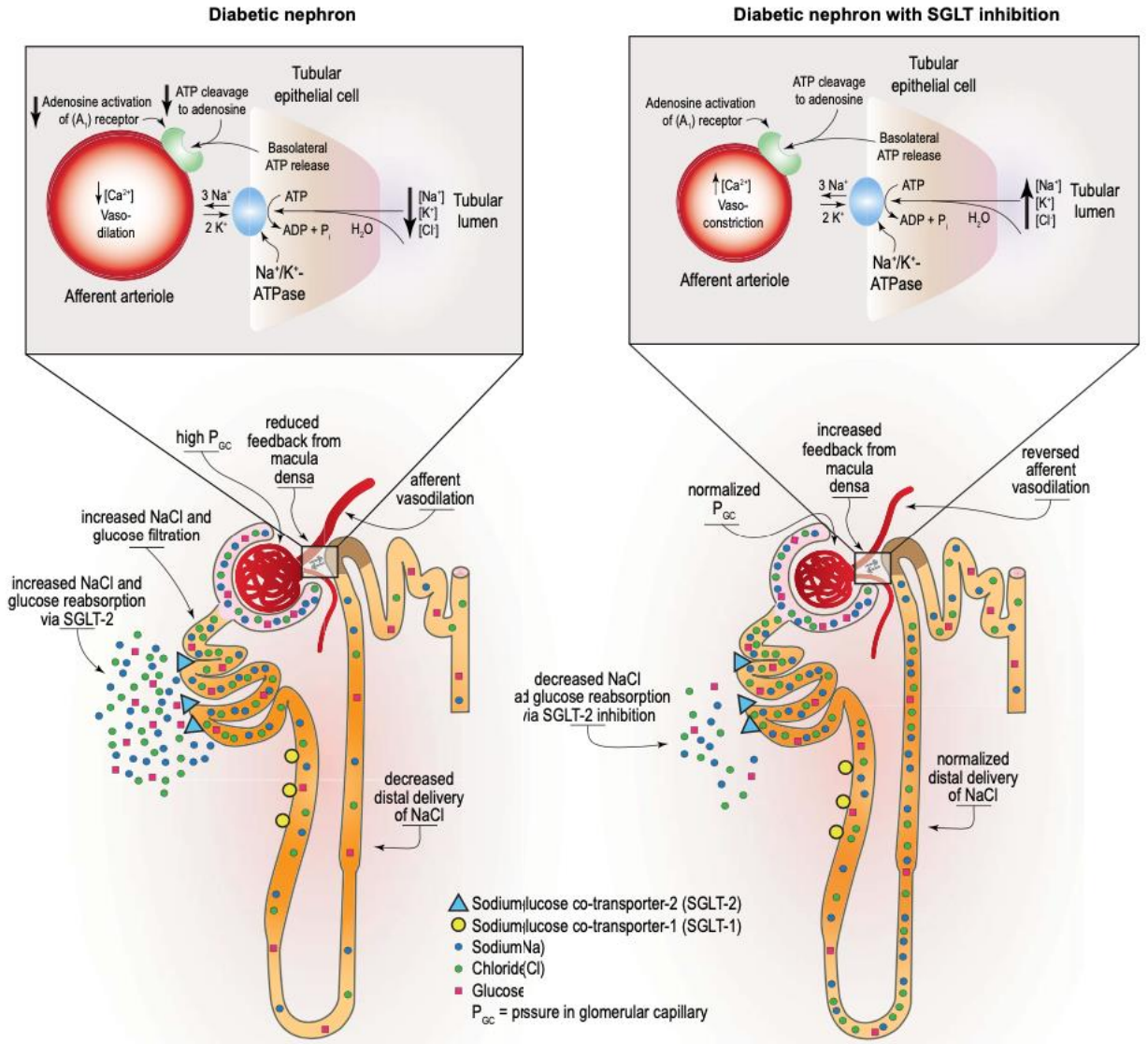
SGLT2-INHIBITORS

- Sodium–glucose co-transporters (SGLTs) are the newest drugs

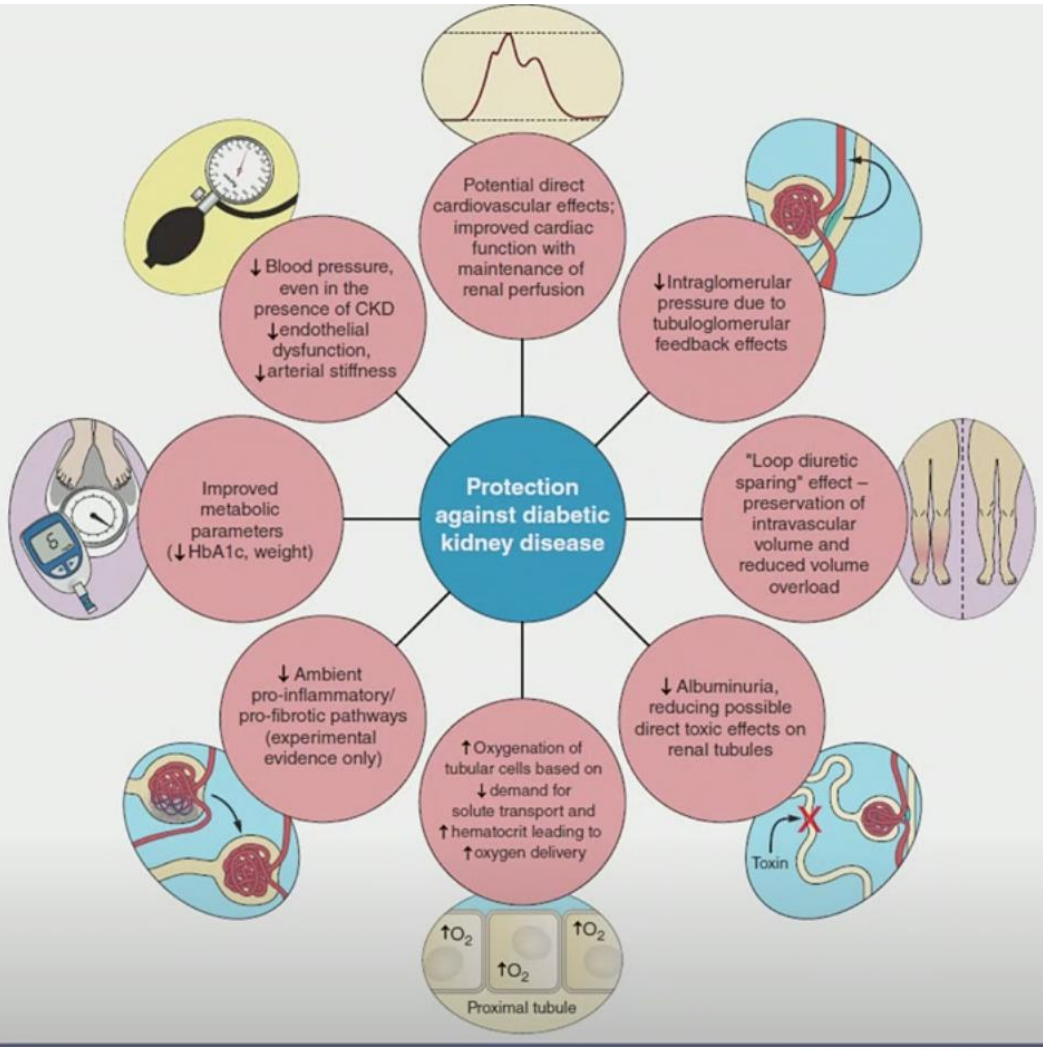
- MOA is by blocking the glucose reabsorption in the kidney, inhibitors of the sodium-glucose cotransporter 2 (SGLT2) increase the urinary glucose excretion



Tuttle KR, et al, DOI: 10.1053/j.ajkd.2020.08.003

Figure 1. Sodium/glucose cotransporter 2 (SGLT-2) inhibition and glomerular hemodynamics in diabetes. Abbreviations: ADP, adenosine diphosphate; ATP, adenosine triphosphate; P, phosphate. Reproduced from Alicic et al[18] with permission of the copyright holder; original graphic © 2018 by the National Kidney Foundation.

Proposed renal protective pathways with SGLT2 inhibitors



Heerpsink//Cherney. Kidney Int 2018

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Kidney Blood Press Res 2019;44:449–456

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Table 1. Cardio-renal protective mechanisms of SGLT2 inhibitors

1	Hemodynamic factors (natriuretic effects) Reduction in BP Modulation of TGF Improvement of salt sensitivity Improvement of sympathetic nerve hyperactivity
2	Metabolic factors (glycosuric effects) Plasma glucose-lowering Improvement of insulin sensitivity Less glucose toxicity Reduction in body weight UA-lowering TG and small dense LDL-C-lowering
3	Miscellaneous potential factors Improvement of erythropoiesis and reduced oxidative stress Inhibition of the NHE in heart and kidney Restoration of energy efficiency in myocardial utilization by switching Glucose to the more energy efficient metabolites, KB, FFA and BCAA

UA, uric acid; TG, triglyceride; LDL-C, LDL-cholesterol; NHE, Na-H exchanger; KB, ketone bodies; FFA, free fatty acid; BCAA, branched chain amino acid; BP, blood pressure; TGF, tubulo-glomerular feedback; SGLT2, sodium-glucose cotransporter 2.

Conclusions

- Diabetes is the leading cause of CKD worldwide, with high risks for kidney failure, ASCVD, HF, and premature mortality.
- SGLT2 inhibitors were developed as T2D therapies with a novel glucose-lowering mechanism. Insulin independent mechanism of action allows use in early and late stages of diabetes
- The large RCTs of SGLT2 inhibitors showed cardiorenal protection. SGLT2 inhibitors should be used when possible by people with T2DM to reduce risks for CKD and CVD.
- SGLT2 inhibitors beyond glucose lowering effects are weight loss, antihypertension and serum uric acid reduction.
- Current evidence does not suggest an increased risk of harm with SGLT2 inhibitors as a class over placebo or active comparators with respect to AKI, DKA, UTI or fracture.