Mechanism of action of SGL2is

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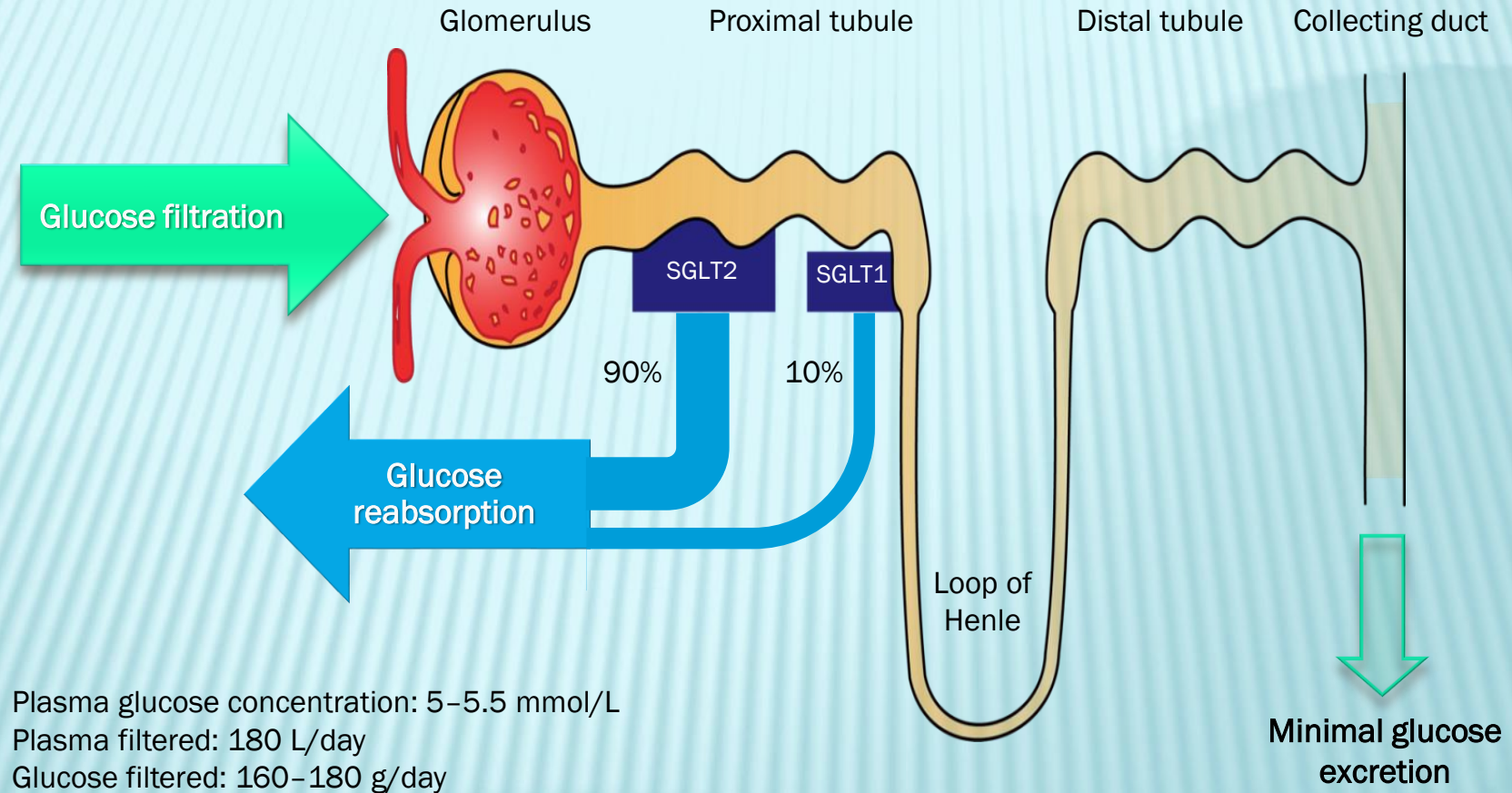
Renal glucose handling in the nephron of the healthy individual



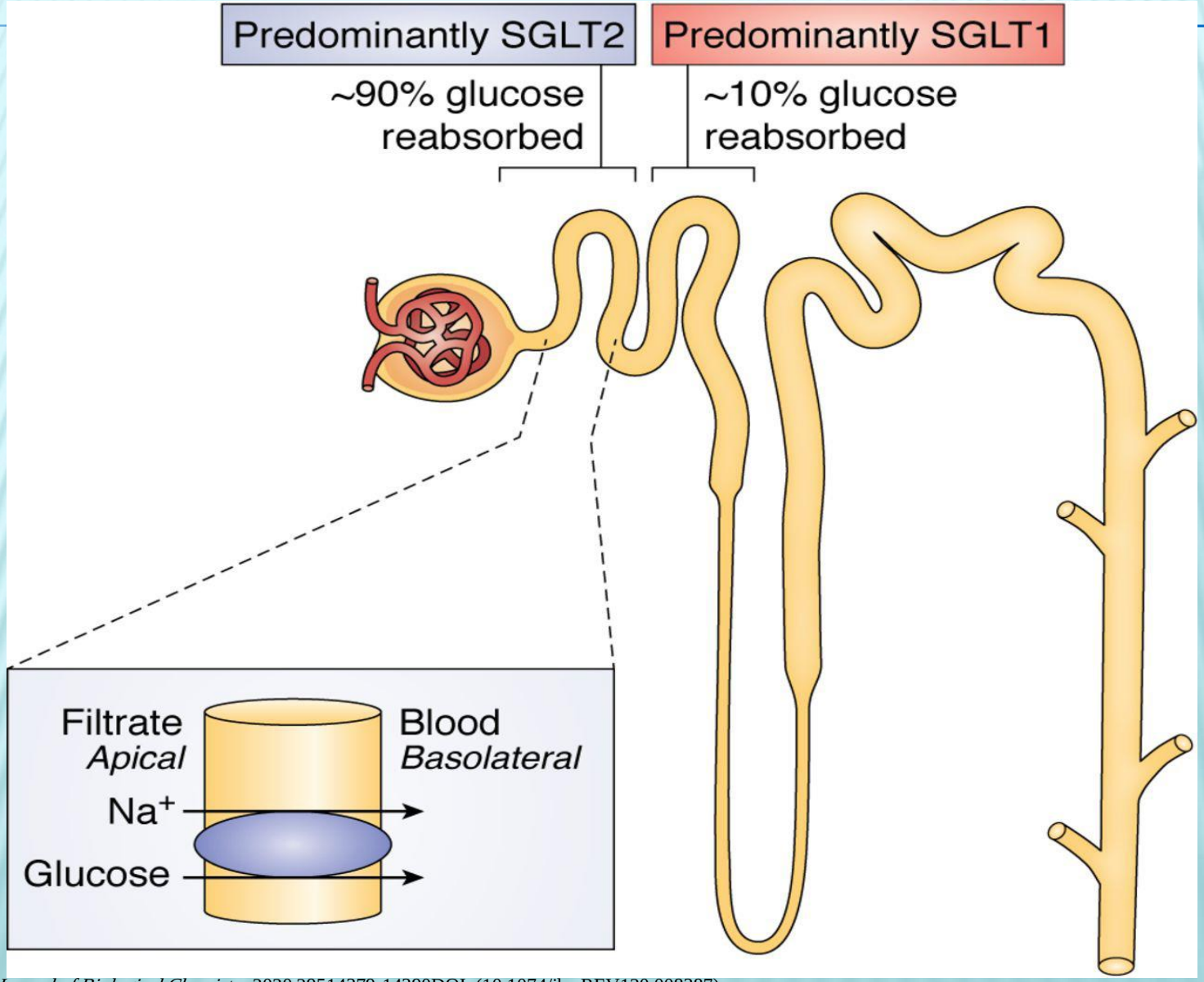
- Plasma glucose concentration: 5–5.5 mmol/L
- Plasma filtered: 180 L/day
- Glucose filtered: 160–180 g/day
- Glucose excreted: Minimal

SGLT: sodium–glucose co-transporter.

Figure adapted from: Bailey CJ. *Trends Pharmacol Sci.* 2011;32:63–71.

Figure 1

Metabolic effects of SGLT2 inhibitors



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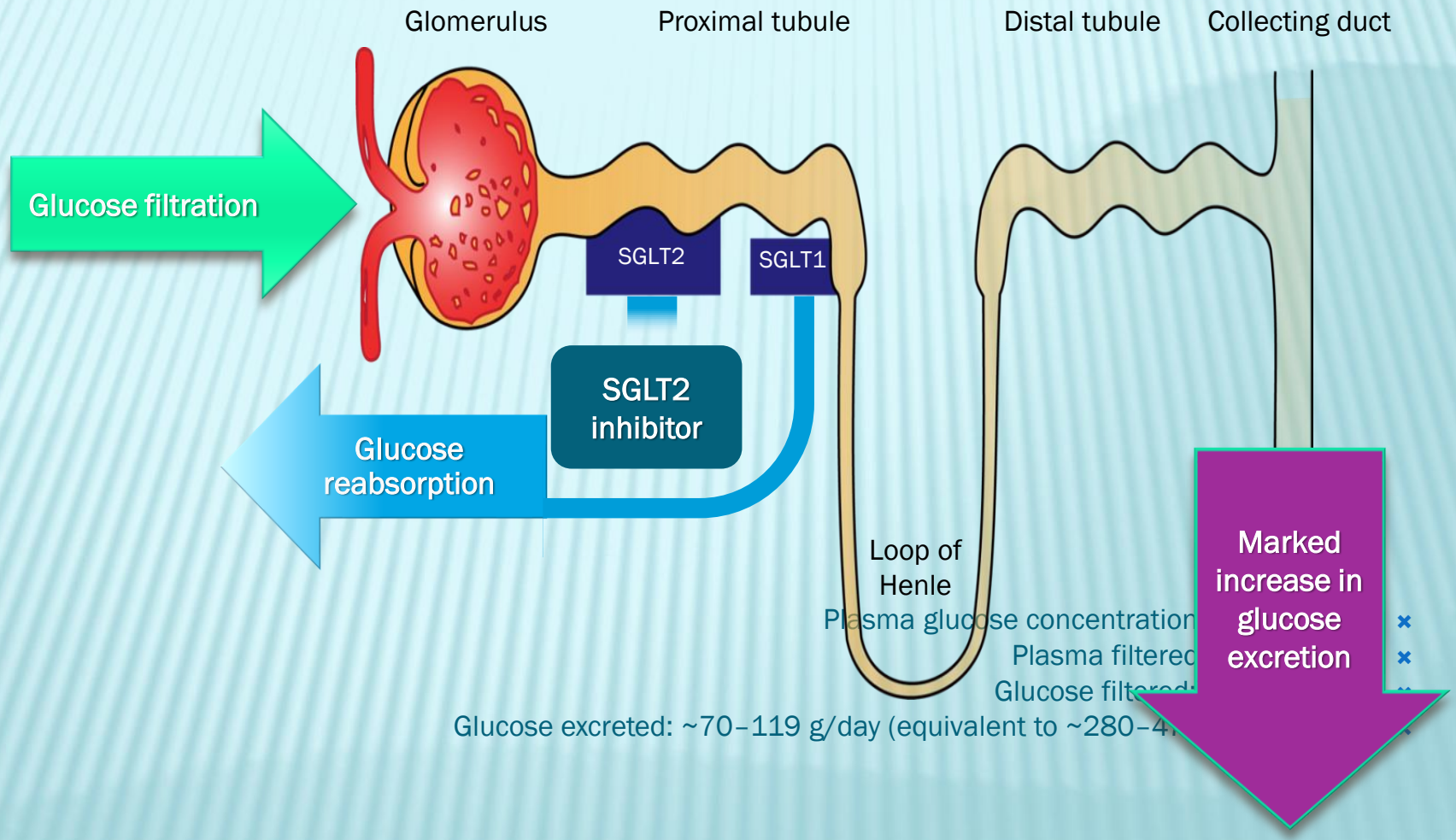
SGLT2 inhibition lowers the elevated renal threshold for glucose in type 2 diabetes[1]



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1. DeFronzo RA *et al. Diabetes Obes Metab.* 2012;14:5–14; 2. Invokana (canagliflozin). Summary of Product Characteristics; 3. Jardiance (empagliflozin). Summary of Product Characteristics; 4. Forxiga (dapagliflozin). Summary of Product Characteristics. All SmPCs available at: https://www.medicines.org.uk/emc/ (accessed April 2018).

Several SGLT2i including

- Canagliflozin
- Dapagliflozin
- Ipragliflozin
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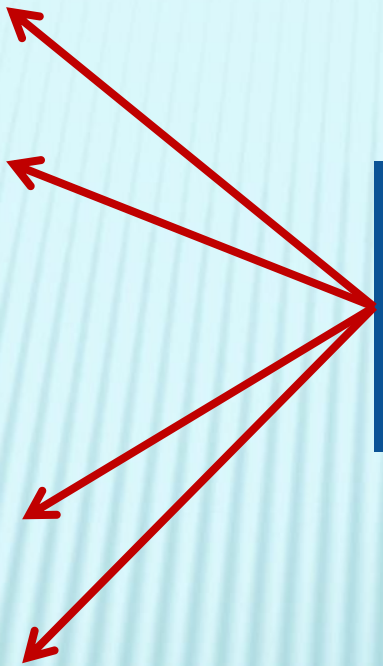


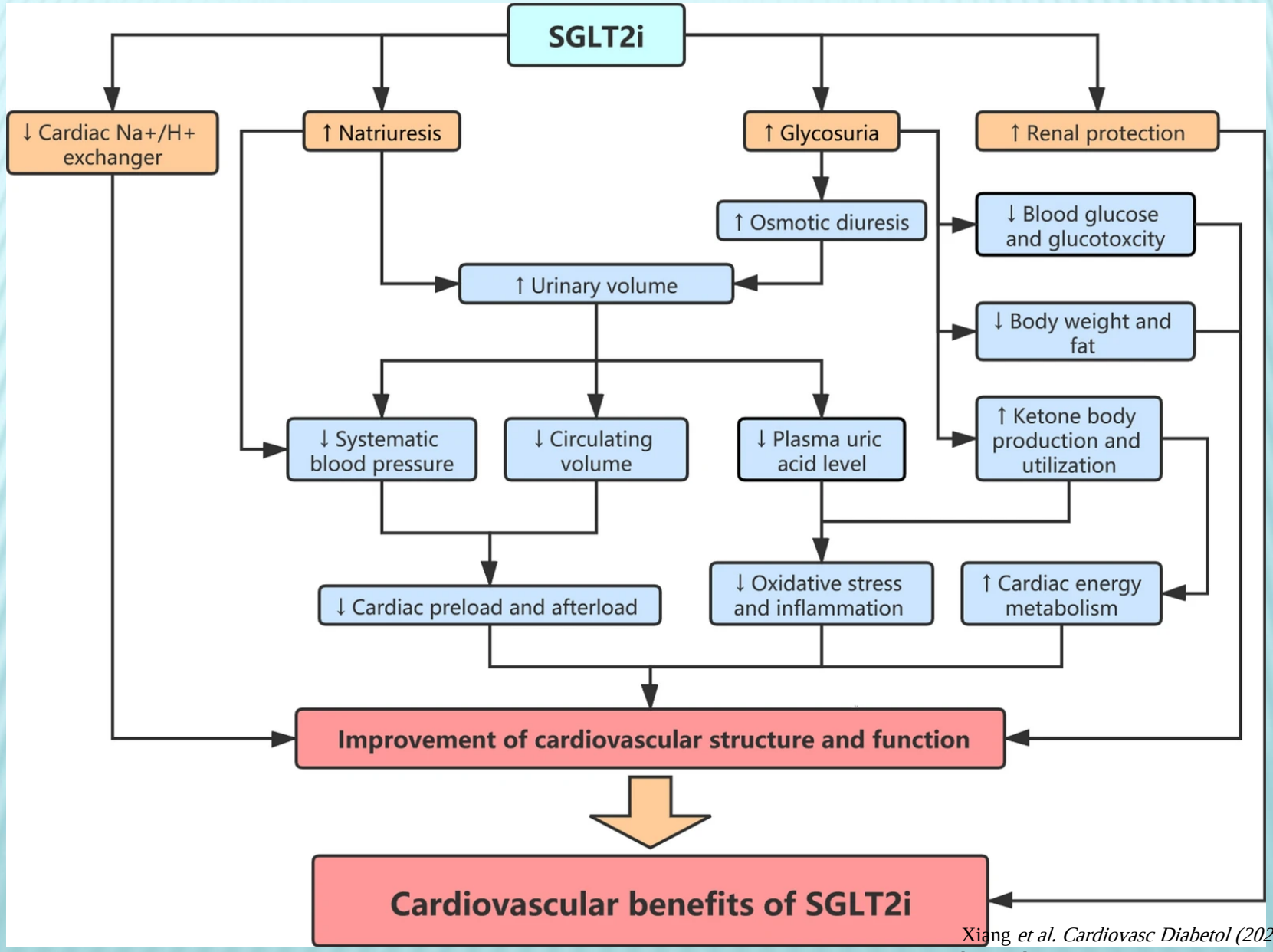
Approved for clinical use in patients with T2DM in several countries.

Pharmacokinetic and clinical parameters of the three currently approved SGLT2 inhibitors

A1c-lowering effects refer to studies in which the SGLT2 inhibitor was given as an add-on to metformin (compared with metformin alone).

Drug	Bioavailability (187)	$t_{1/2}$	Route of excretion	A1c lowering
	%	*h*		%
Canagliflozin	65	10–13 (188)	Urine, feces	0.8–1.0 (189, 190)
Dapagliflozin	78	13 (191)	Urine	0.7–0.8 (192, 193)
Empagliflozin	90	13 (194)	Urine, feces	0.6–0.8 (195, 196)

Cardiovascular benefits of sodium-glucose cotransporter 2 inhibitors in diabetic and nondiabetic patients



Xiang *et al. Cardiovasc Diabetol (2021) 20:78*
https://doi.org/10.1186/s12933-021-01266-x

Two-hit hypothesis for the effect of SGLT2 inhibitors to promote euglycemic ketoacidosis

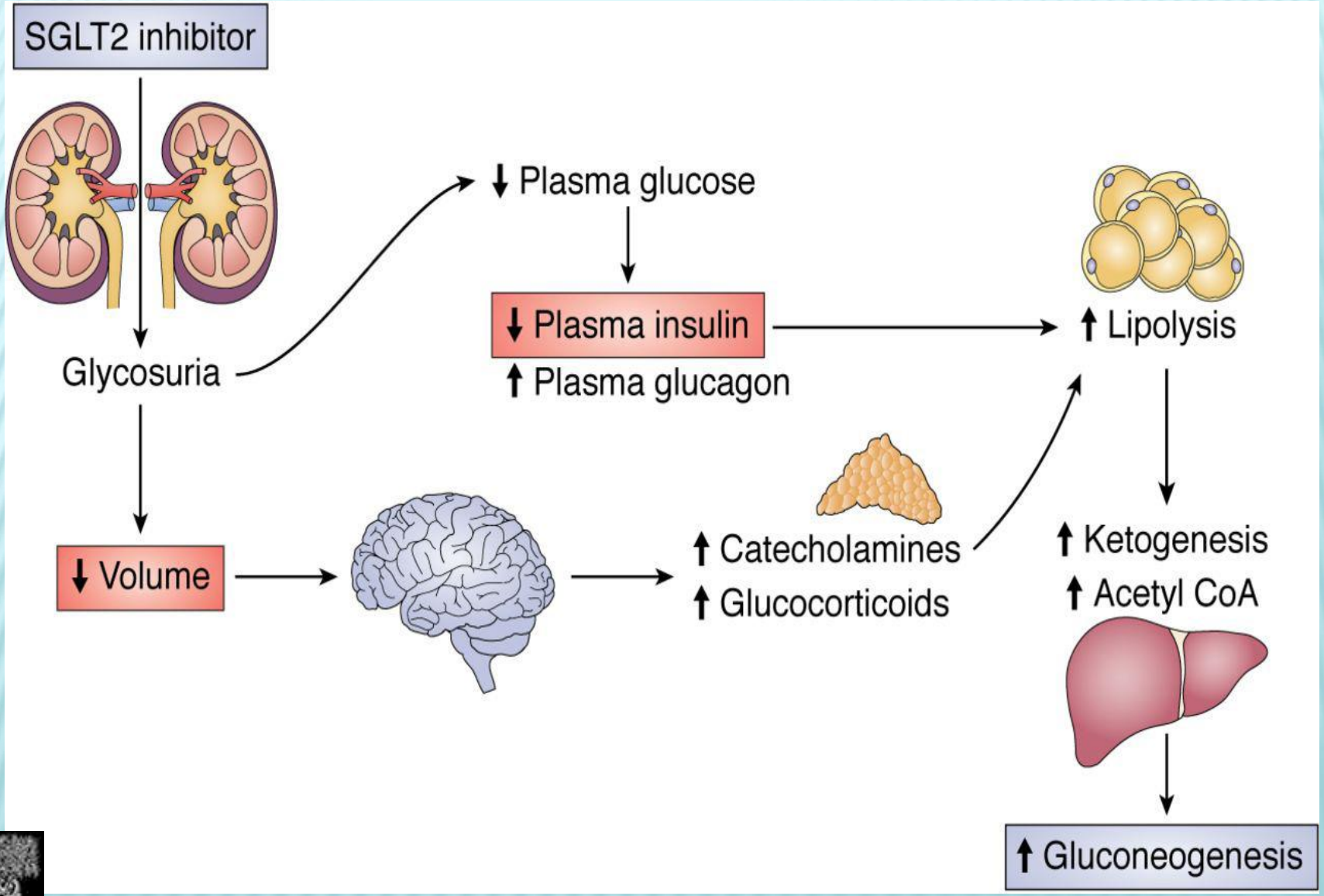


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Figure 3

Proposed mechanisms by which SGLT2 inhibitors may reduce heart failure and improve cardiovascular outcomes.

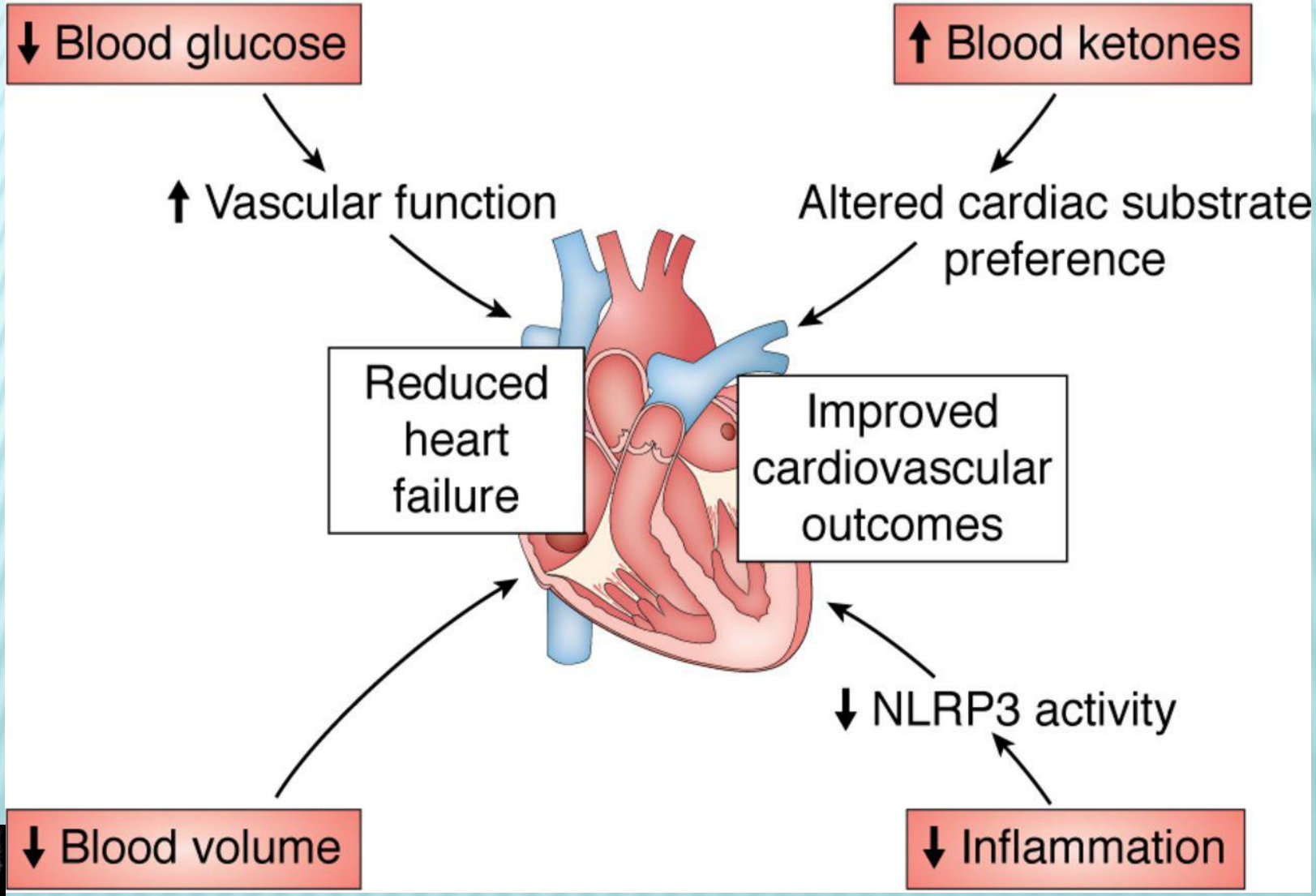

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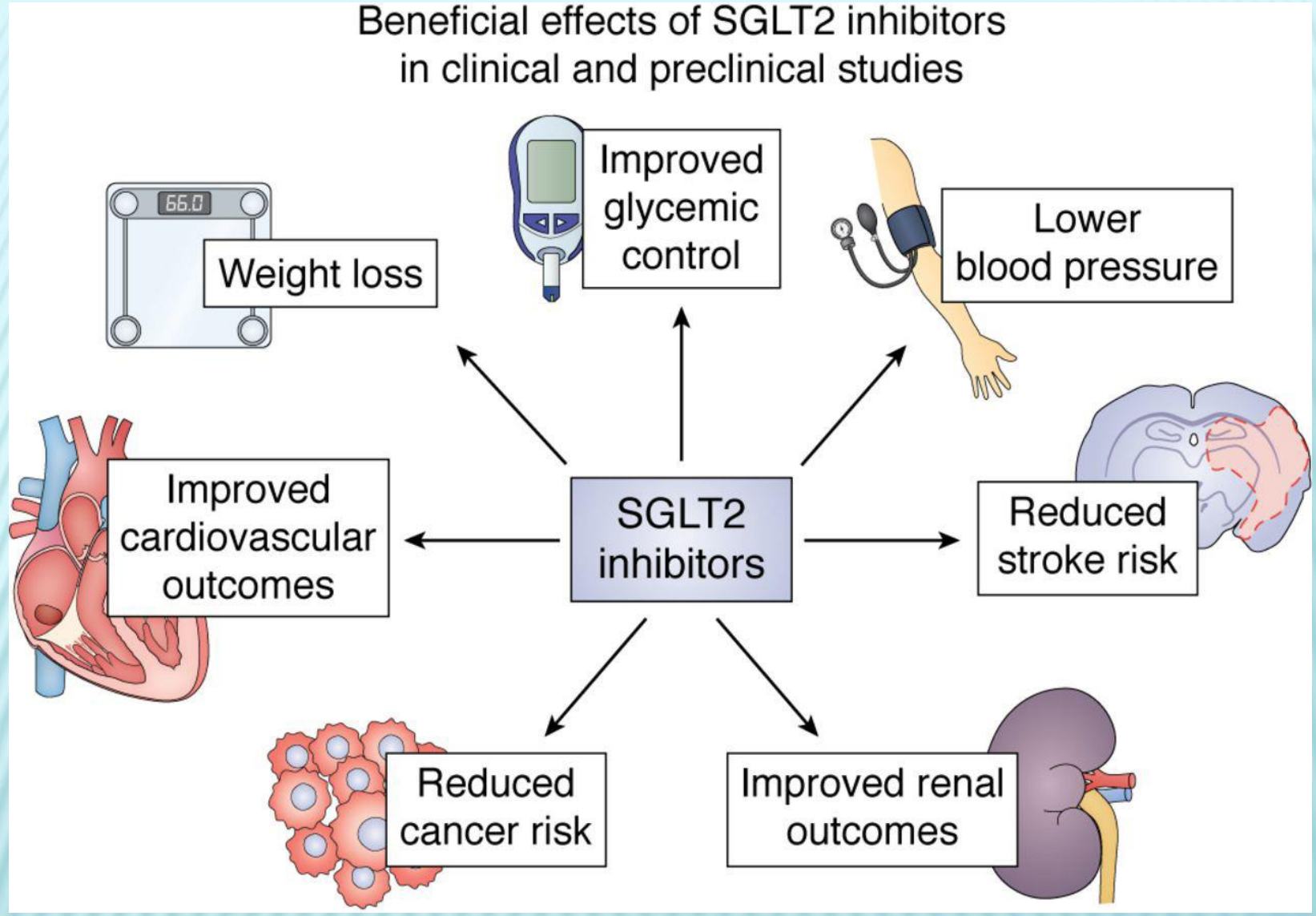
Figure 4



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