BIEN AMC

DAPAGLIFLOZIN

26.04.27 내과 신약 세미나

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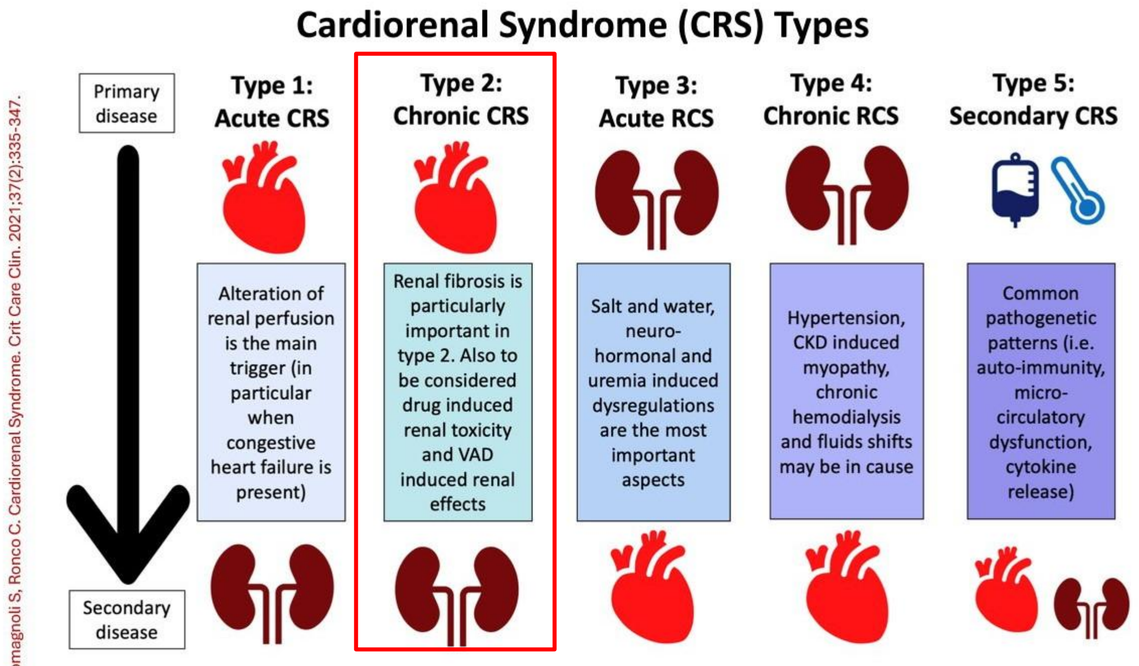
PART 01. Introduction

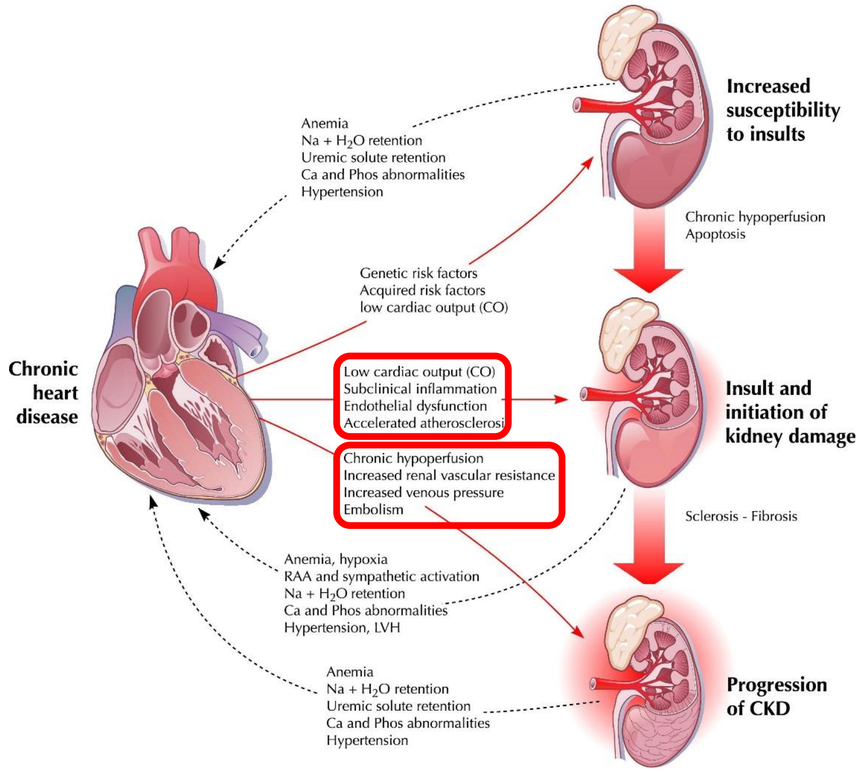
I. CRS (CardioRenal Syndrome)

The Vicious Cycle: Interconnected Pathophysiology of Heart and Kidney



Ricci Z, Romagnoli S, Ronco C. Cardiorenal Syndrome. Crit Care Clin. 2021;37(2):335-347.

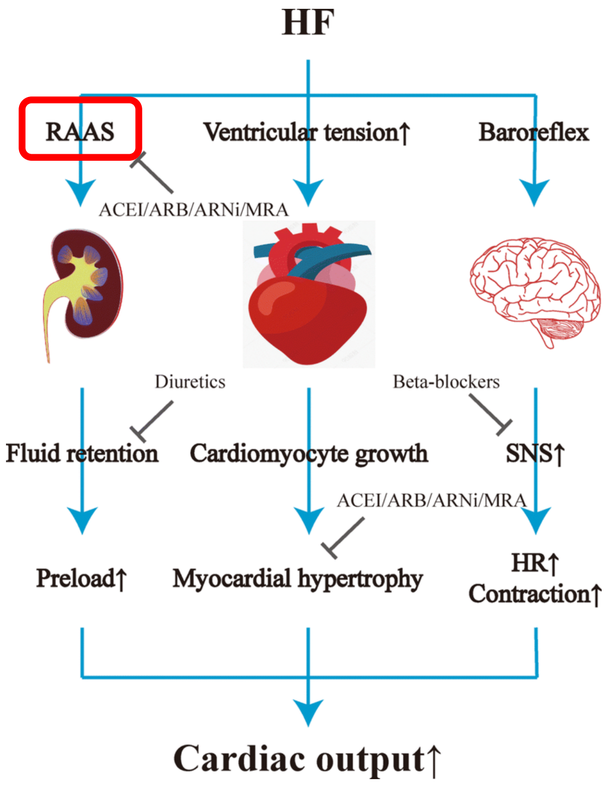
Schematic representation of the five Cardiorenal syndrome (CRS) types according to the organ direction (primary > secondary disease) and the time window (acute or chronic). According to this classification, two CRS (acute and chronic), two renocardiac (acute and chronic) syndromes, and one secondary CRS are depicted.
CKD, chronic kidney disease; RCS, renocardiac syndrome; VAD, ventricular assist device.

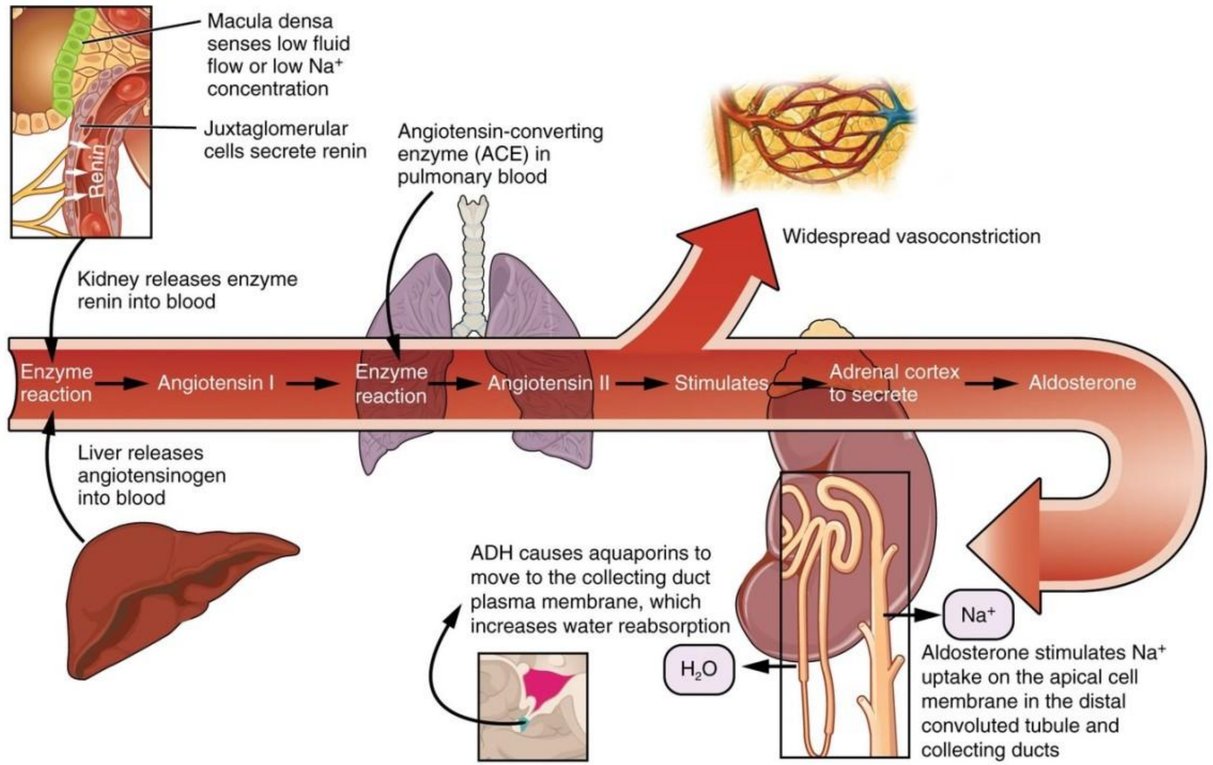


Ronco C, et al. (2008) JACC / Braam B, et al. (2014) Heart Fail Rev.

II. MMVD & RAAS

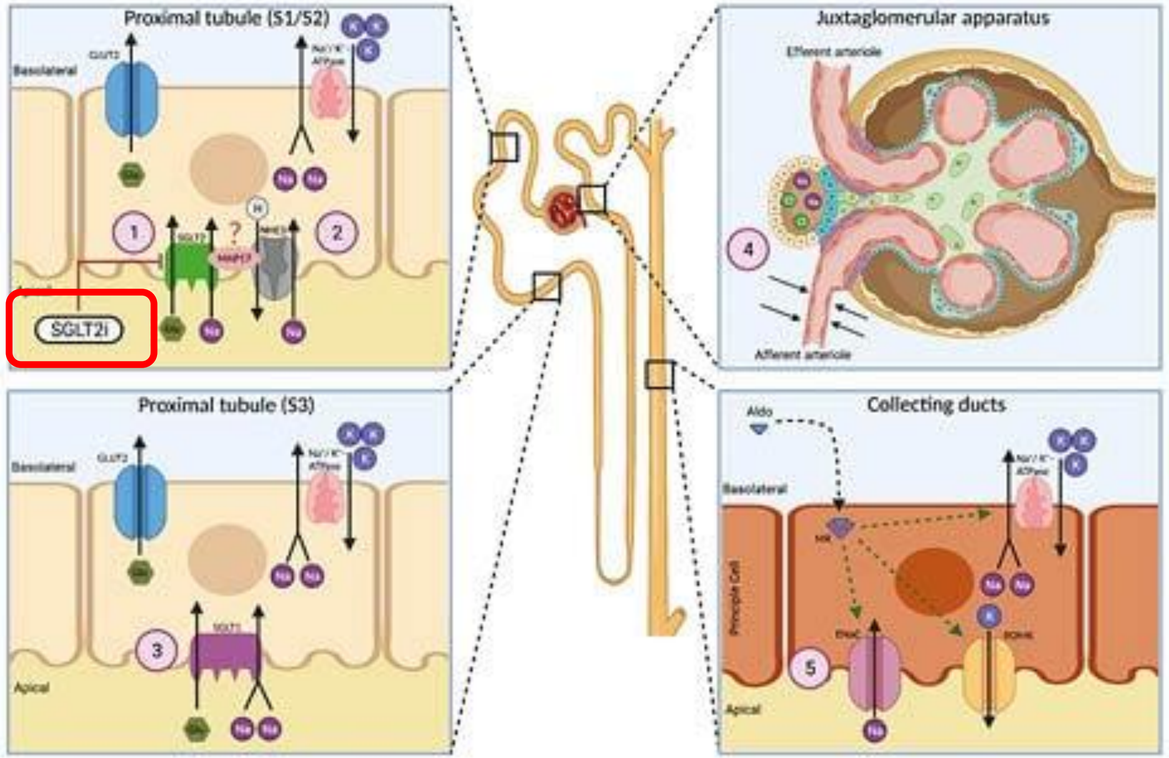
The Vicious Cycle of RAAS: Why MMVD Destroys the Glomerulus



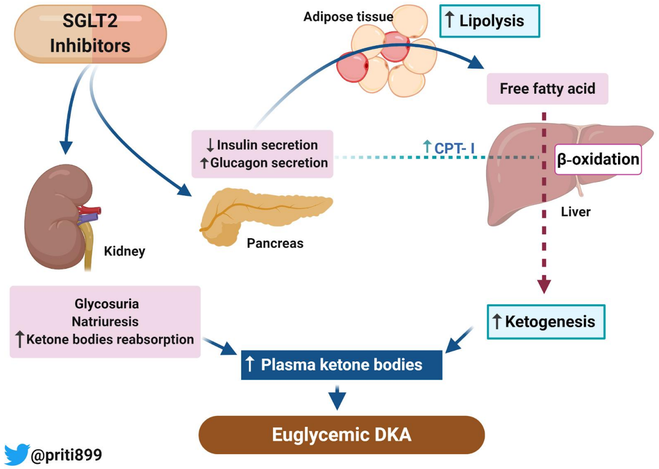


III. Sodium Glucose Linked Transporter 2

Mechanism of Action: Restoring Tubuloglomerular Feedback (TGF)



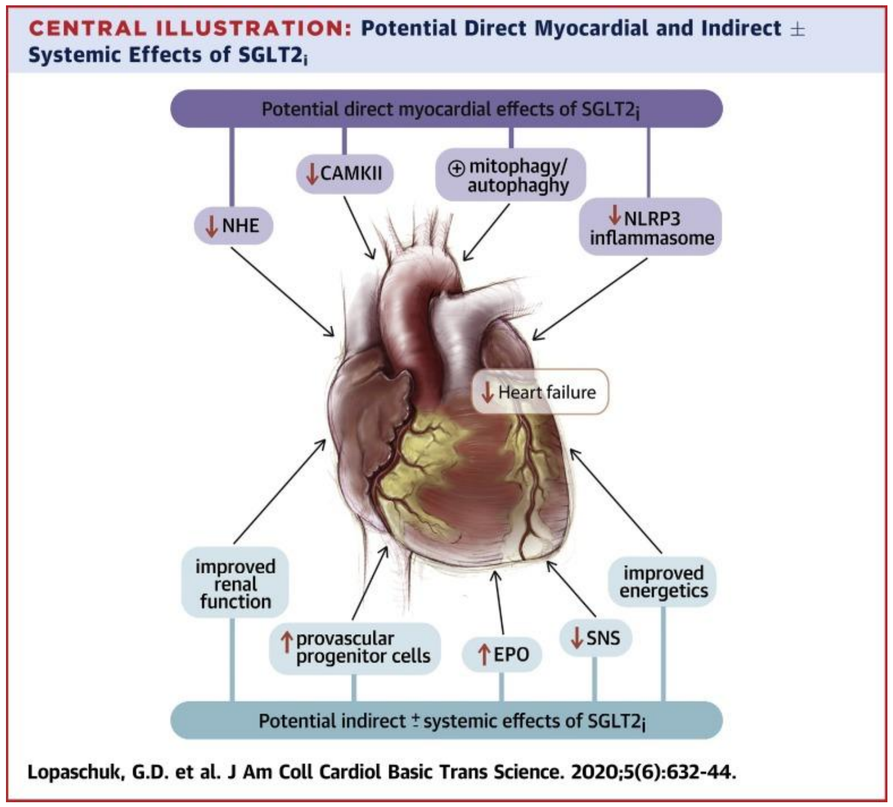
1. Inhibition of SLGT2 results in the loss of glucose as well as sodium
2. Inhibition of SGLT2 results in downregulation of NHE3 through MAP17 which results in sodium loss
3. Increased glucose delivery to the S3 segment of the proximal convoluted tubule will result in increased action of SGLT1 which reabsorbs 2 sodium ions per glucose
4. Increased distal tubular sodium and chloride will cause afferent artiolar vasoconstriction through the tubulo glomerular feedback mechanism. This decreases glomerular filtration and results in less sodium loss
5. Decreased renal purfusion will result in an increase in aldosterone due to activation of RAAS. This results in more sodium reabsorption through ENaC

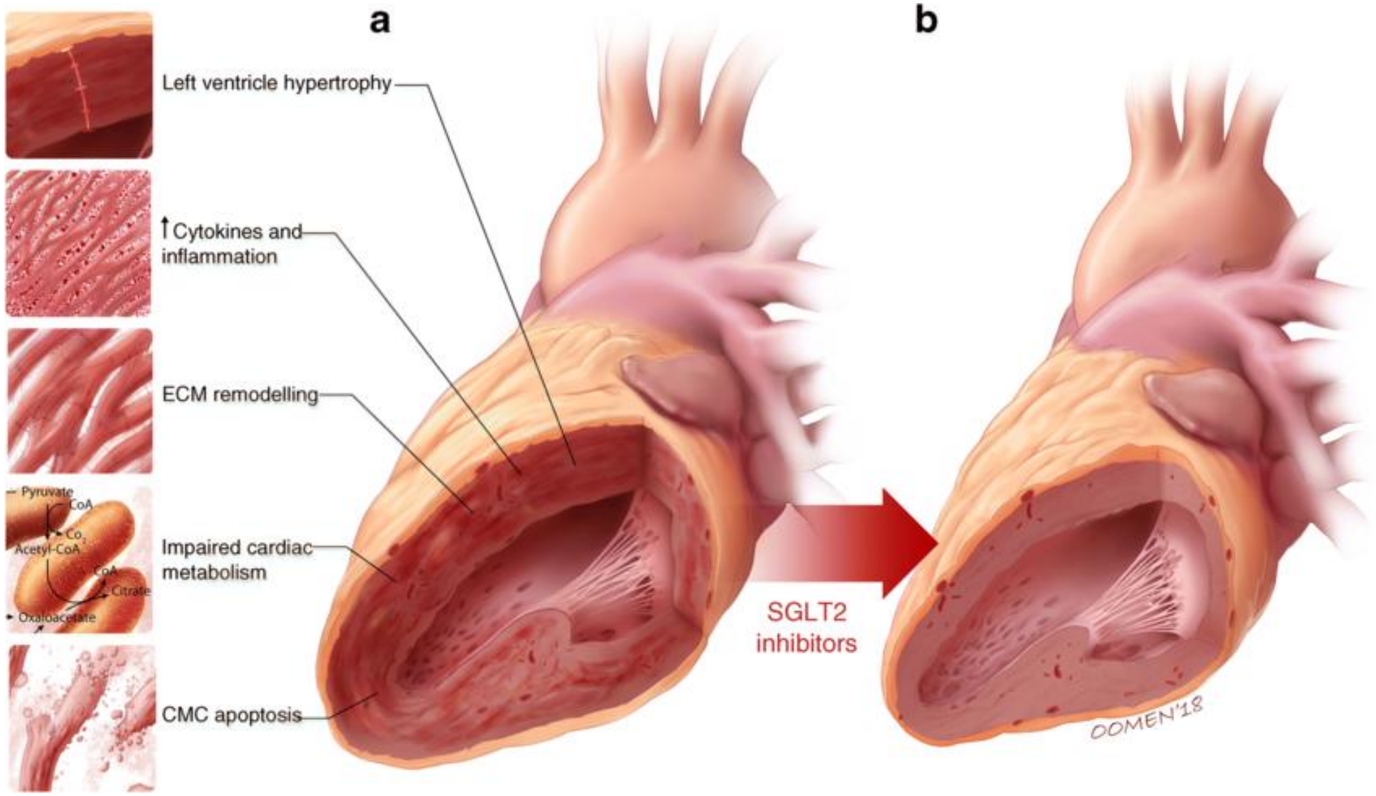


Hanny Sawaf The Renal Effects of SGLT2 Inhibitors

III. Sodium Glucose Linked Transporter 2

Pleiotropic Effects of SGLT2i: Beyond the Renal Mechanism

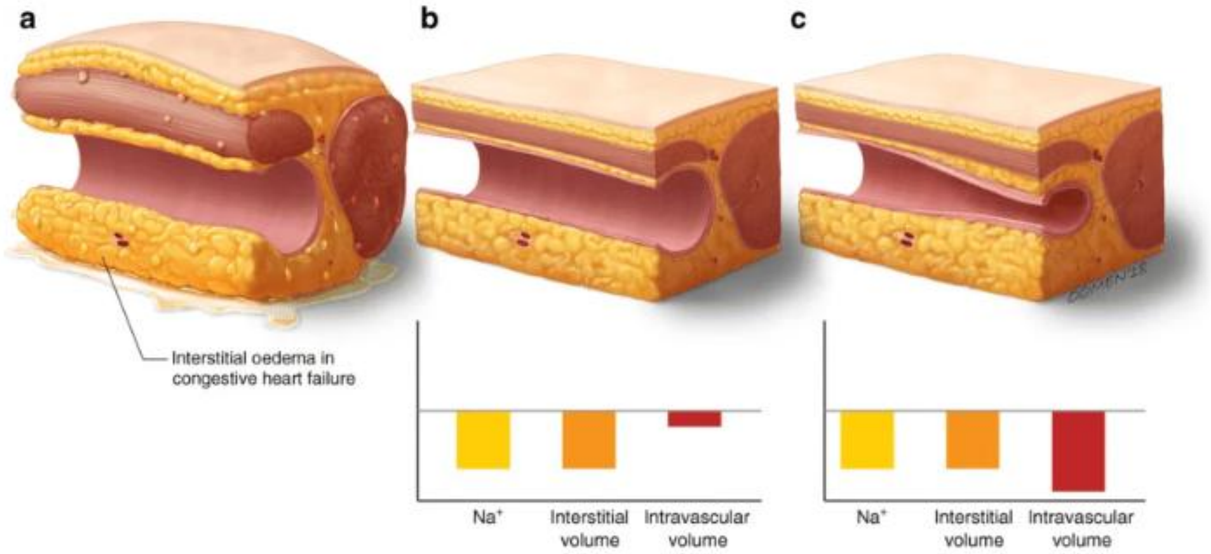




Lopaschuk, G. D., et al. (2020).

III. Sodium Glucose Linked Transporter 2

Why SGLT2i is Kidney-Friendly: Preserving Perfusion while Reducing Edema



SGLT2 inhibitors may differentially regulate the interstitial vs intravascular compartment when compared with loop diuretics. In individuals with congestive heart failure, interstitial oedema is evident (a). SGLT2 inhibitors may selectively reduce interstitial volume with minimal change in blood volume (b) whereas loop diuretics may cause a reduction in both interstitial and intravascular volume (c). It has been postulated that this differential volume regulation by SGLT2 inhibitors (interstitial > intravascular) may limit the aberrant reflex neurohumoral stimulation that occurs in the setting of intravascular depletion. © G. Oomen 2018. This figure is available as part of a downloadable slideset

Hallow KM, et al. (2018).

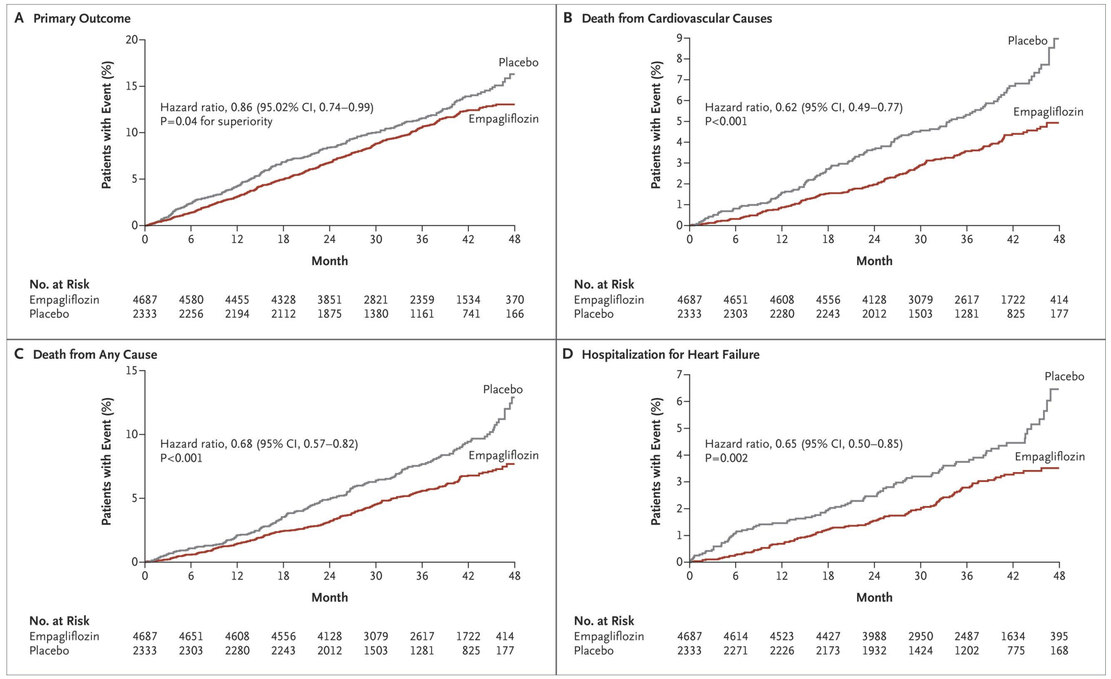
PART 02. Human Medicine

02. HUMAN MEDICINE

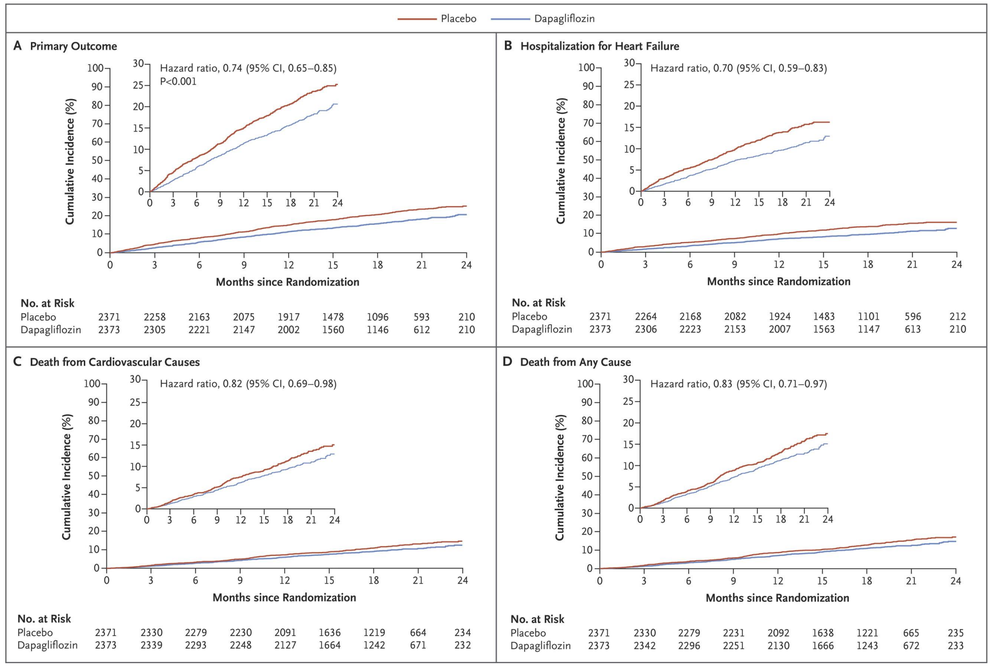
I. Timeline

Evidence-Based Medicine: From Diabetes to Heart Failure

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes



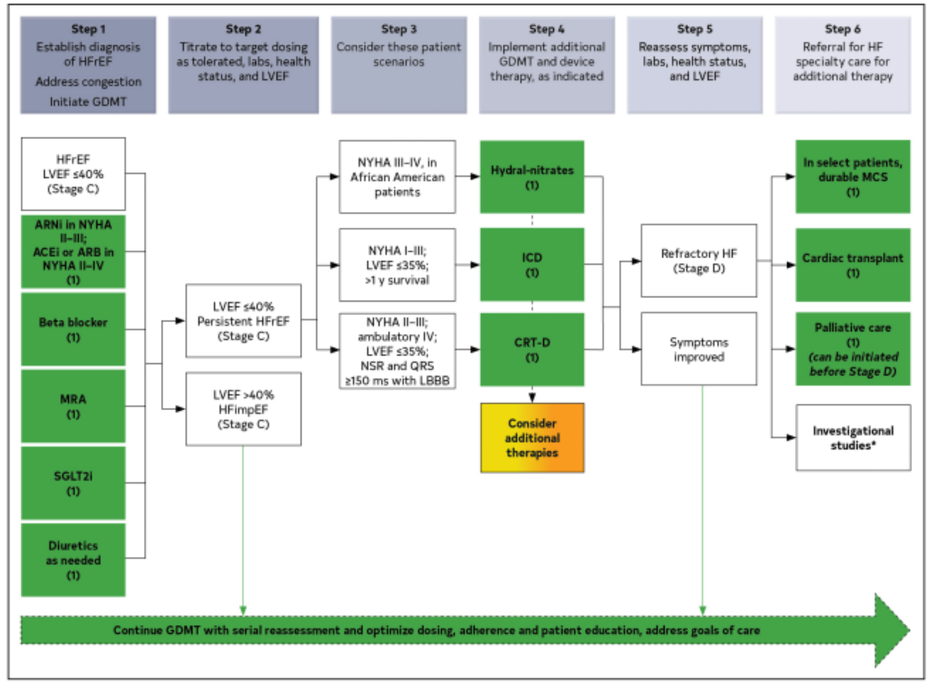
Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction



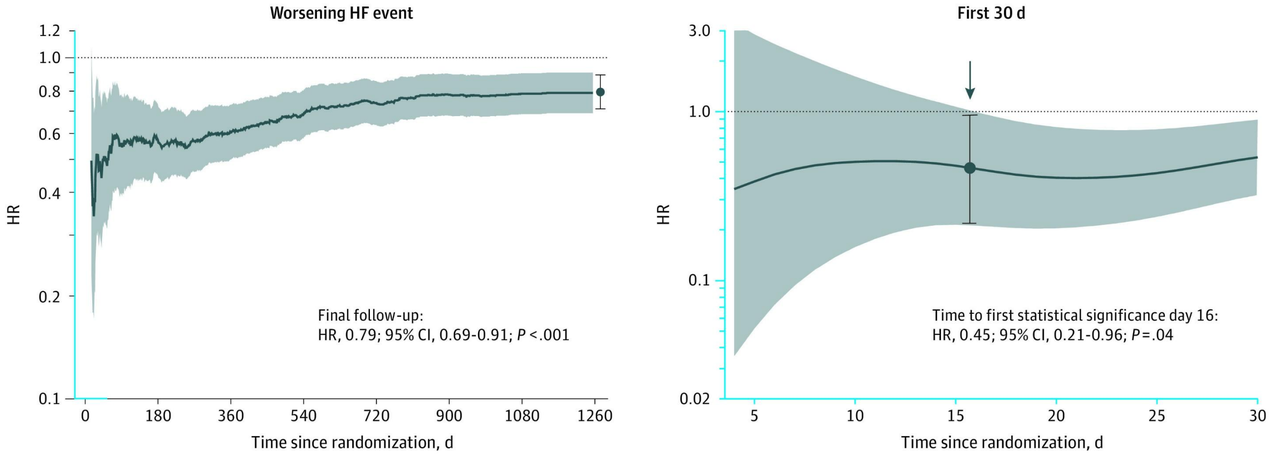
II. SGLT2i, the Earlier the Better?

Rapid Clinical Benefit and Integration into Global Guidelines

2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines



Time to Clinical Benefit of Dapagliflozin in Patients With Heart Failure With Mildly Reduced or Preserved Ejection Fraction: A Prespecified Secondary Analysis of the DELIVER Randomized Clinical Trial

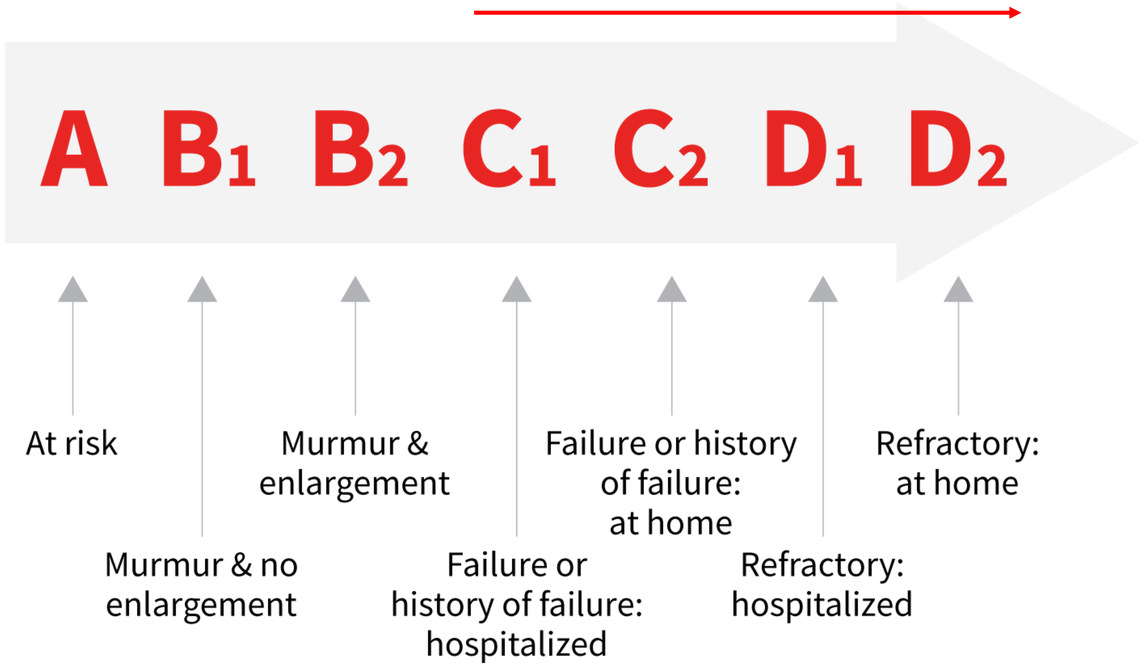


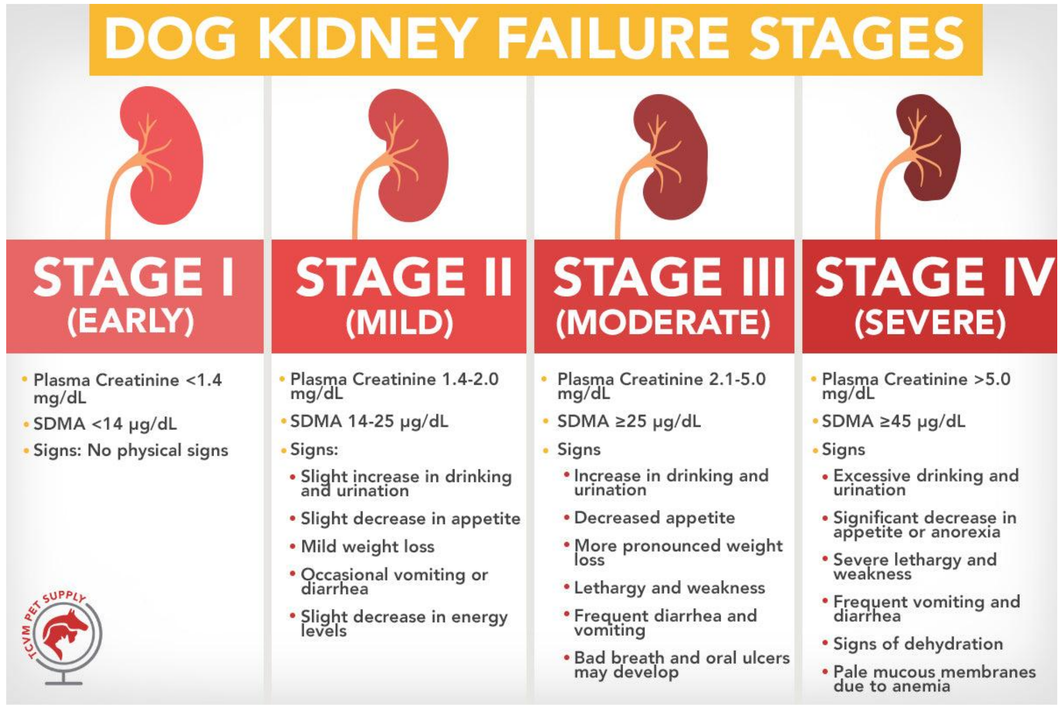
2022 AHA/ACC/HFSA Guideline, Berg D. D. et al. (2021) JAMA Cardiol

PART 03. Veterinary Application

I. The Right Patient

MMVD C, CKD stage 2





II. The Right Dose: 0.5 mg/kg SID

Right SGLT2i for canine MMVD?

Sodium-glucose co-transporter 2 inhibitors: Prospects for canine myxomatous mitral valve disease and finding the "right drug" and the "right dose" for dogs

Mutsuki UMEZAWA[1)], Yoko FUJII[1)], Kensuke ORITO[2)], Ryo YOSHIMOTO[3)]*

In conclusion, dapagliflozin appears to be the "right drug" in dogs, offering an adequate efficacy-safety margin and a balanced excretion pathway. While canagliflozin may also be tolerable in dogs, it may increase the incidence of diarrhea and elicit DDI by inhibiting MDR1 at therapeutic doses. Empagliflozin has a minimal margin between efficacy and nephrotoxicity in dogs. PK/PD studies using the approved formulation of dapagliflozin should be conducted to identify the "right dose" for future studies in dogs. Furthermore, it is important to note that the safety studies were conducted on a limited number of healthy beagle dogs.

II. The Right Dose: 0.5 mg/kg SID

Right Dose?

Pilot study on the effects of dapagliflozin on echocardiographic parameters in dogs with symptomatic myxomatous mitral valve disease

five-month study period. The dose of dapagliflozin (0.31 mg/kg, PO, q24h) was chosen based on our unpublished in-house pharmacokinetic and tolerability study in healthy dogs, which evaluated three dose levels: 0.31, 0.62, and 1.25 mg/kg. While the lowest dose was well tolerated, higher doses resulted in penile edema (1 out of 6 dogs). Therefore, 0.31 mg/kg was selected as the safest effective dose for this pilot study. The

Spillmann T. (2020), Cridge H. et al. (2022) JVIM.

III. Beyond Diuretics

Beyond Diuresis: Clinical Evidence of Cardiac Size Reduction in Dogs

Pilot study on the effects of dapagliflozin on echocardiographic parameters in dogs with symptomatic myxomatous mitral valve disease

Table 2
Effects of dapagliflozin on echocardiographic parameters in dogs with naturally occurring, symptomatic myxomatous mitral valve disease (MMVD) stage C.

Parameters	Time (Day)	Dapagliflozin (n = 5)	Control (n = 7)	P value
LA/Ao	0	2.29(2.08 – 2.79)	2.64(2.23 – 2.77)	0.530
LA/Ao (% change from BL)	28	−17.0(−20.5 – −11.0)	−7.58(−9.01 – −4.33)	0.030
	84	−18.8(−28.5 – −17.8)	−13.5(−15.2 – −10.4)	0.003
	140	−21.8(−22.7 – −18.4)	−17.8 (−20.1 – −12.2)	0.030
LVIDDN	0	1.98(1.71 – 2.03)	1.82(1.80 – 1.98)	1.000
LVIDDN (%; change from BL)	28	−2.53(−11.8 – −1.63)	−2.97(−5.13 – 4.09)	0.755
	84	−6.83(−15.2 – −3.09)	0.00(−1.11 – 11.0)	0.005
	140	−11.5(−16.8 – −4.56)	−1.95(−4.03 – 1.63)	0.048

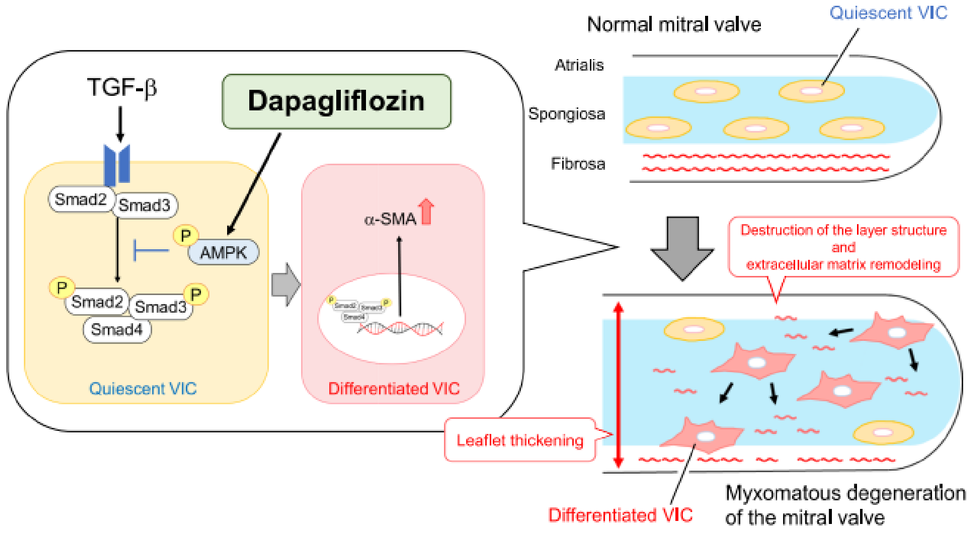


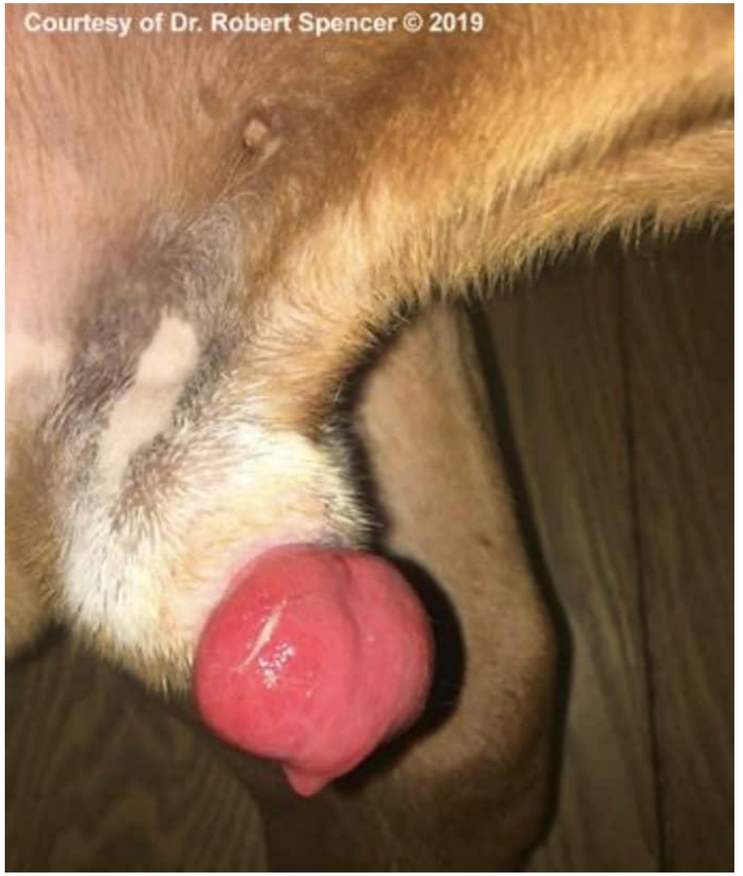
Fig. 6 Summary of the present study results. Activation of AMPK by DAPA suppresses the TGF-β-induced transdifferentiation of quiescent VIC, partly by inhibiting the Smad signaling pathway, thereby alleviating MV leaflet thickening and extracellular matrix remodeling

IV. Troubleshooting

Adverse effect & Hazard issue

SGLT2 inhibitor and side effects

1. VOLUME DEPLETION /DEHYDRATION
2. GENITAL MYCOTIC INFECTION
3. EUGLYCEMIC KETOACIDOSIS
4. BONE FRACTURE



Q&A