SGLT2i MRi
Hjärt- och njurprotektion

230131

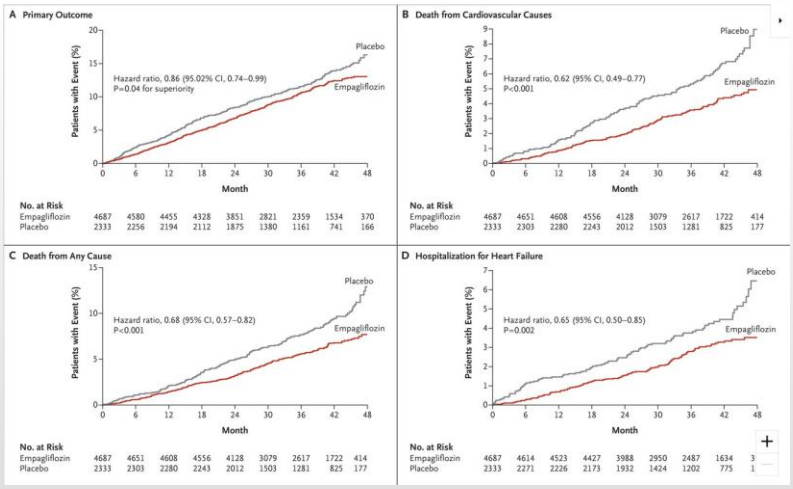
1

SGLT2 mekanism

- Natrium — NHE1, NHE3
- Energiutnyttjande switch — Ketoner metabol
- **Inflammation** — ”Fasta”

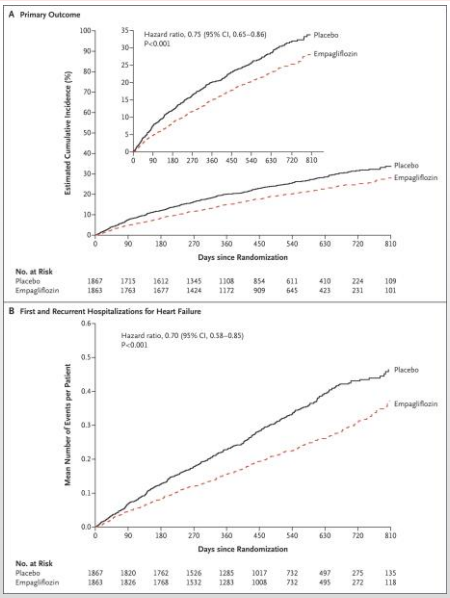
2

EMPAREG 2015



3

EMPEROR HJÄRTSVIKT



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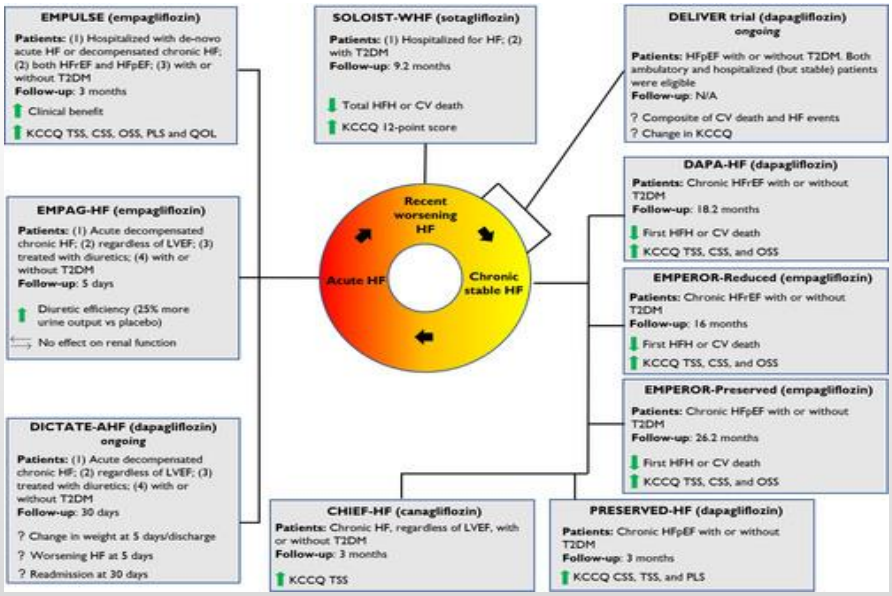
Studiekonkurrens Hjärtsvikt



5

INTRAGLOMERULÄR TRYCKREGLERING

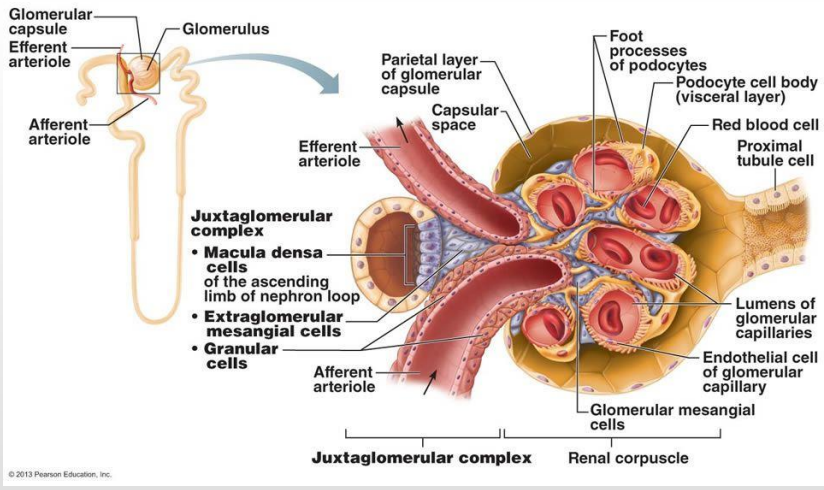
Afferent / efferent

Macula densa

Na

Adenosin

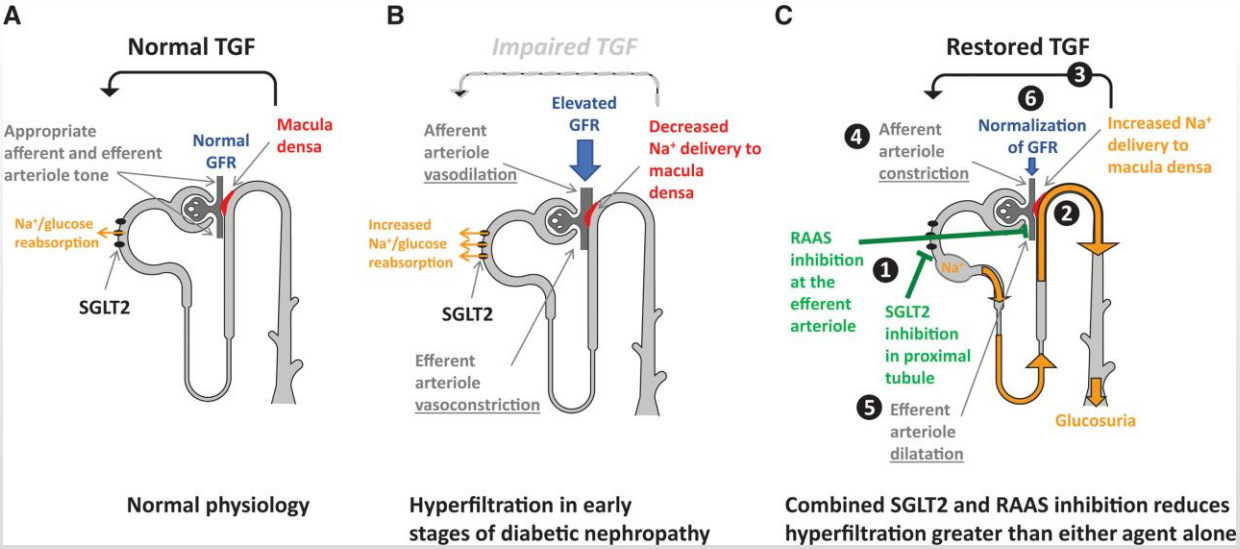
Prostaglandin E



Renin ⟹ *Angiotensin II* ⟹ *Aldosteron*

6

TUBULOGLOMERULÄR FEEDBACK



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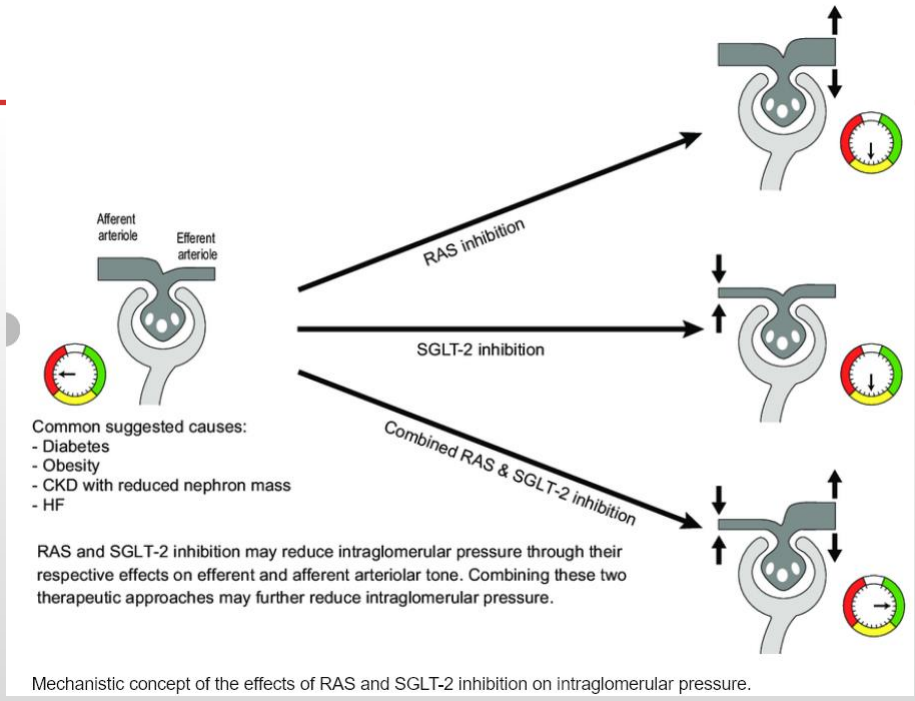
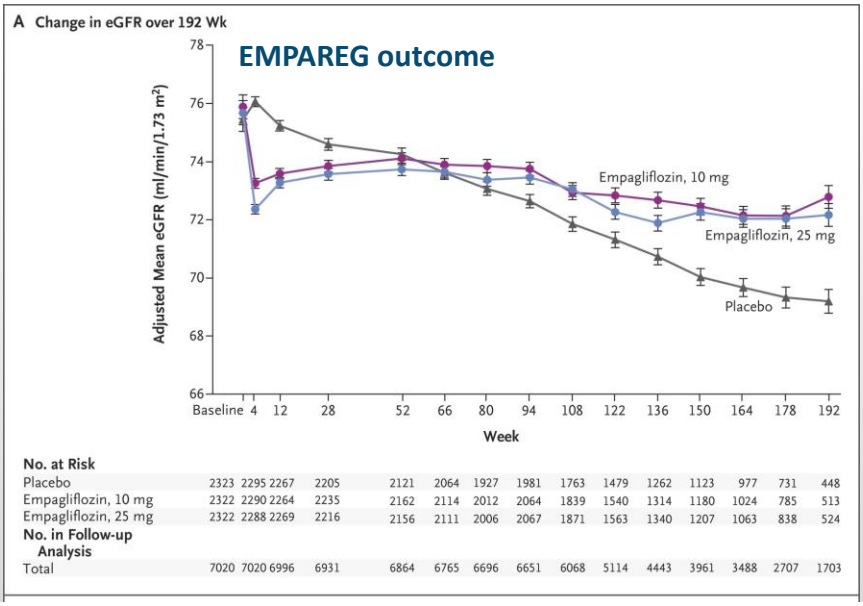


Mechanistic concept of the effects of RAS and SGLT-2 inhibition on intraglomerular pressure.

8

GFR



Parallell med ACEI

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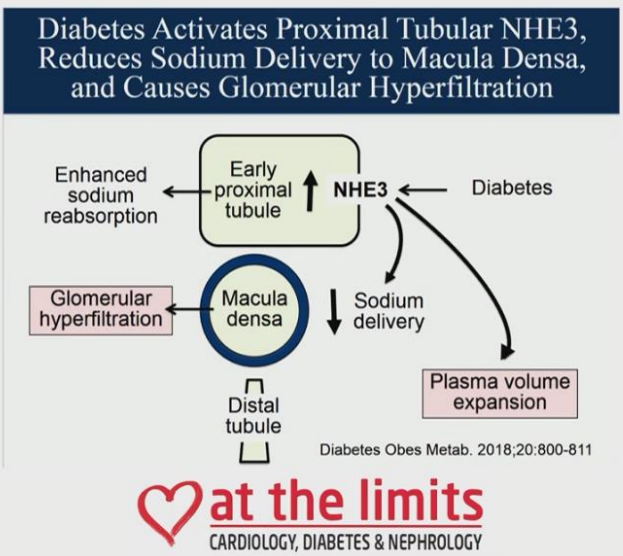
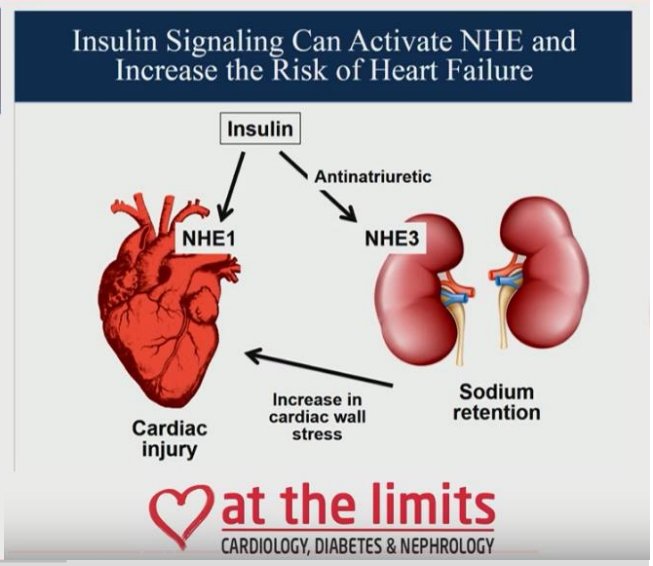
NHE1 / NHE3 Diabetes II Insulin





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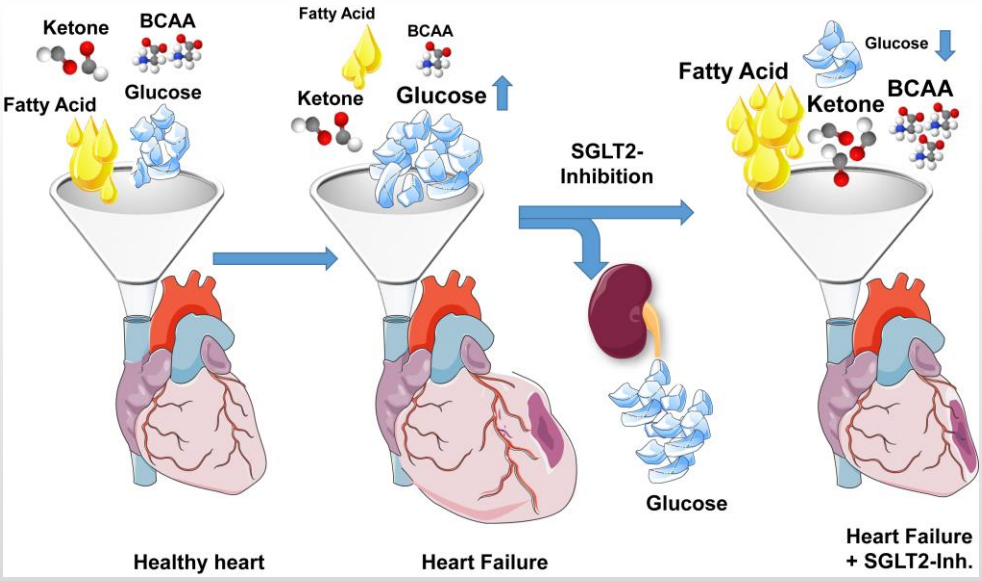
JACC



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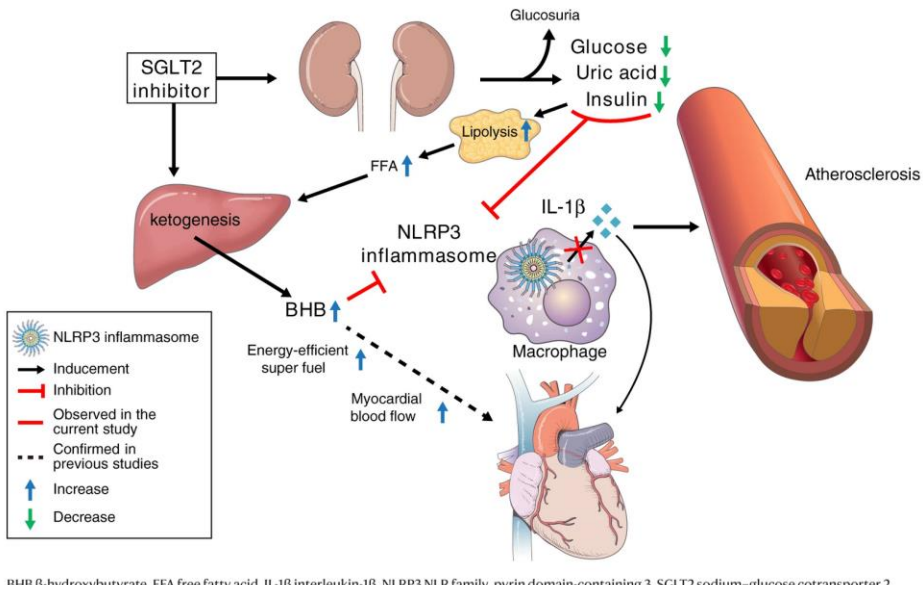
Energiförsörjning

Ketoner

ATP

Fig. 5: Scheme representing the proposed effects of SGLT2 inhibitor on NLRP3 inflammasome activation.

From: SGLT2 inhibition modulates NLRP3 inflammasome activity via ketones and insulin in diabetes with cardiovascular disease



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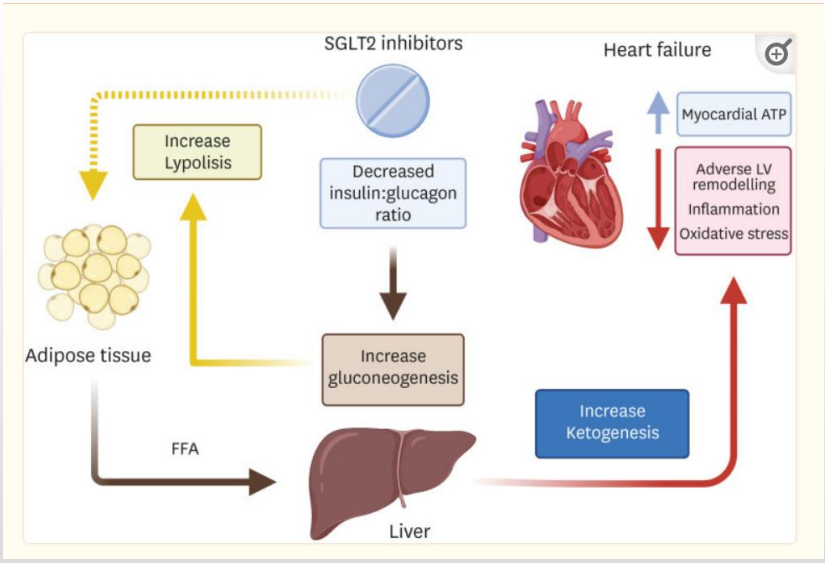
SGLTi



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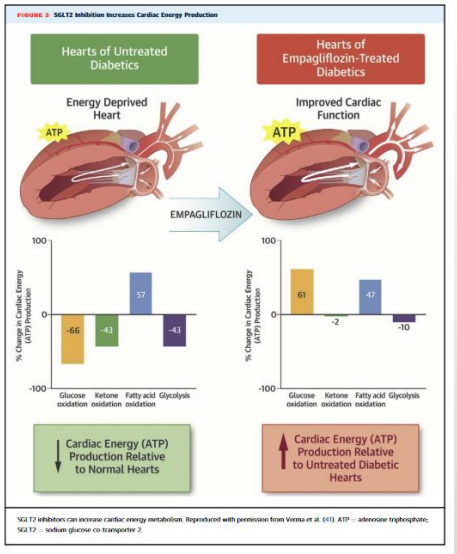
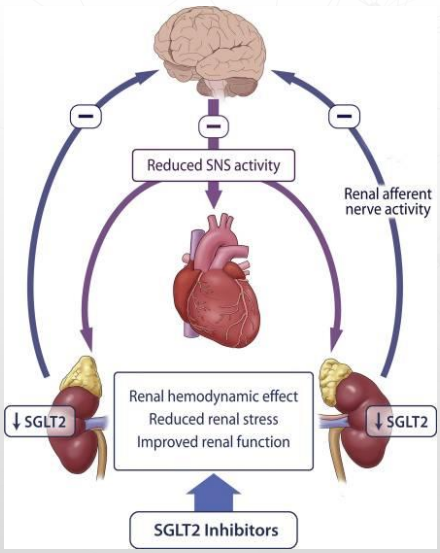
SGLT2i cardiellt energiutnyttjande / SNS

Masterclass





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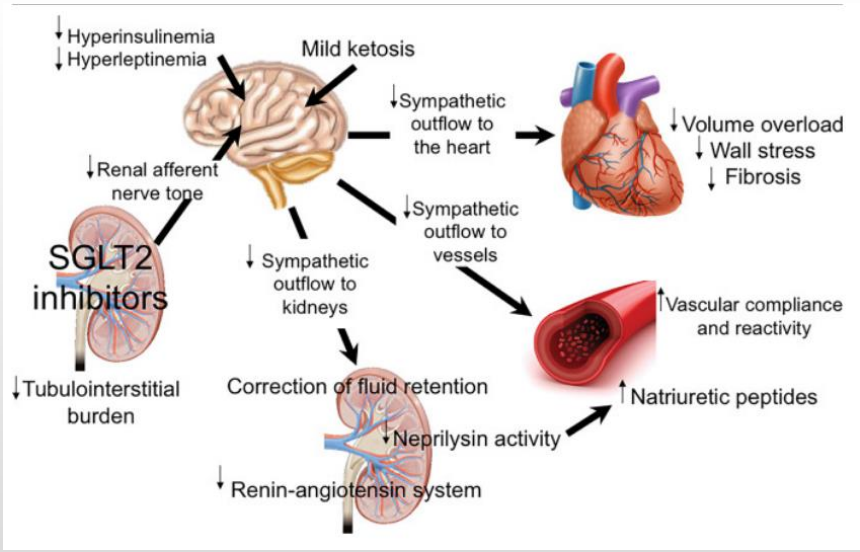
SGLT2 SNS



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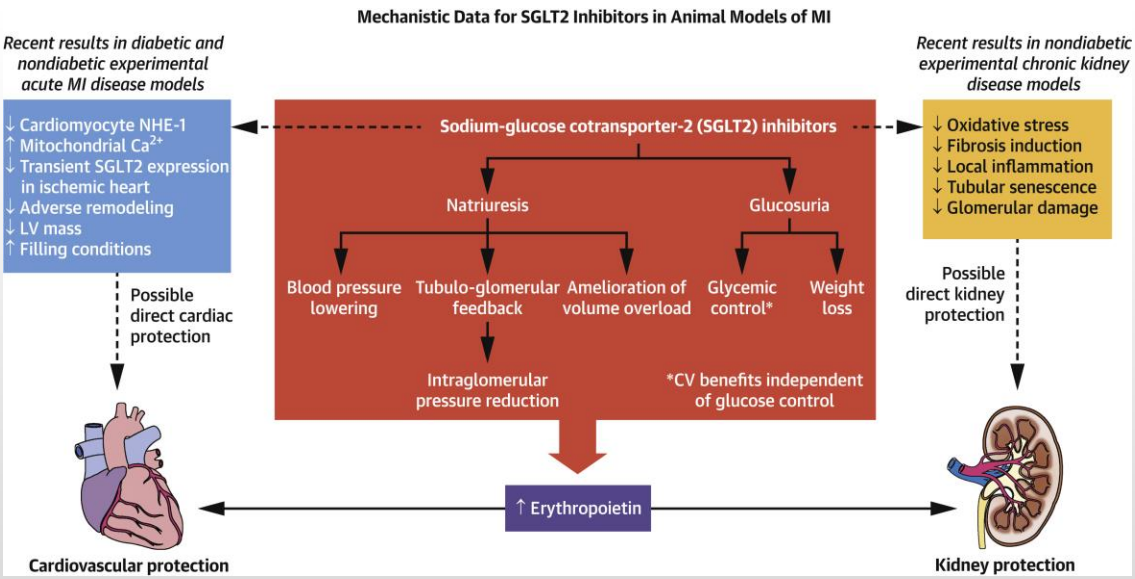
JACC



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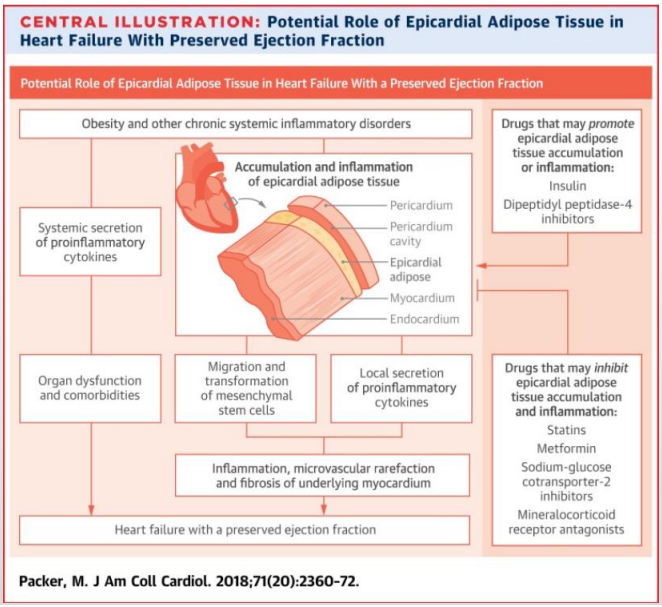
Epikardielt fett HFpEF



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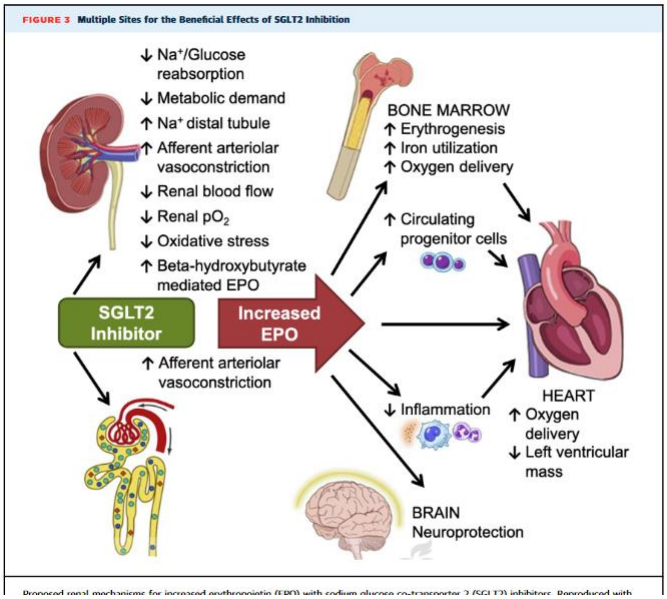

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”House keeping” Mitokondrier SWITCH*

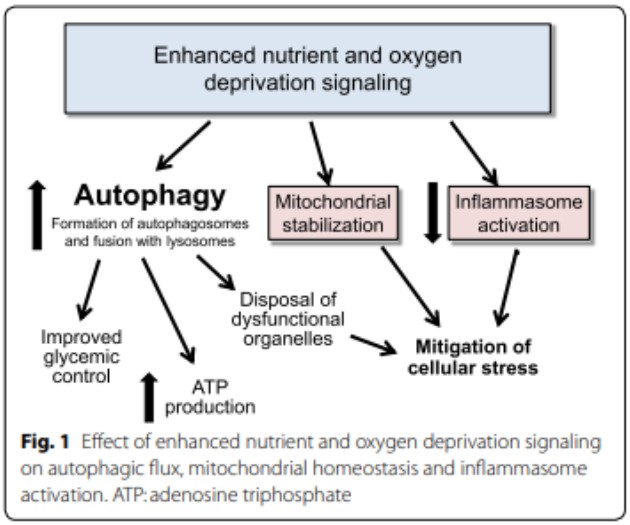

Fig. 1 Effect of enhanced nutrient and oxygen deprivation signaling on autophagic flux, mitochondrial homeostasis and inflammasome activation. ATP: adenosine triphosphate

Nutrient deprivation signaling
vs
Nutrient surplus signaling

-Ketoner

-SGLT2i direkt

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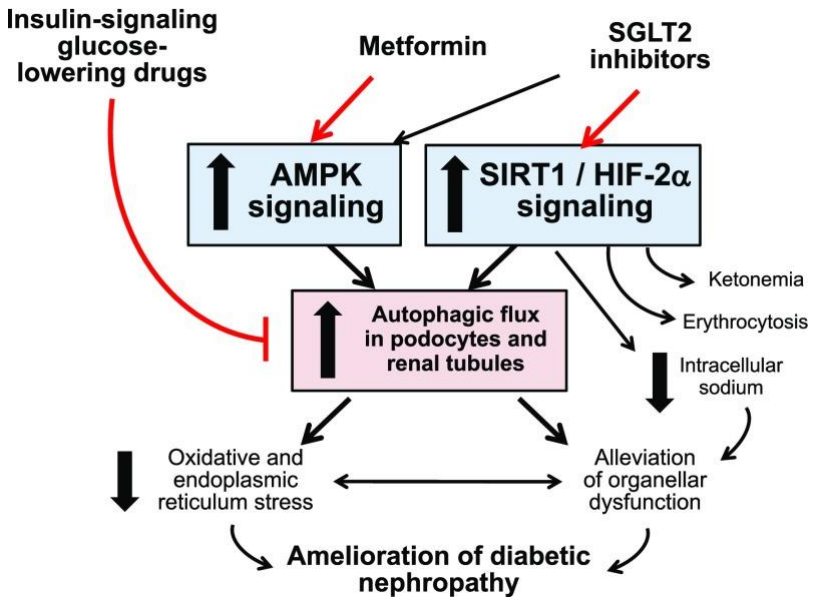

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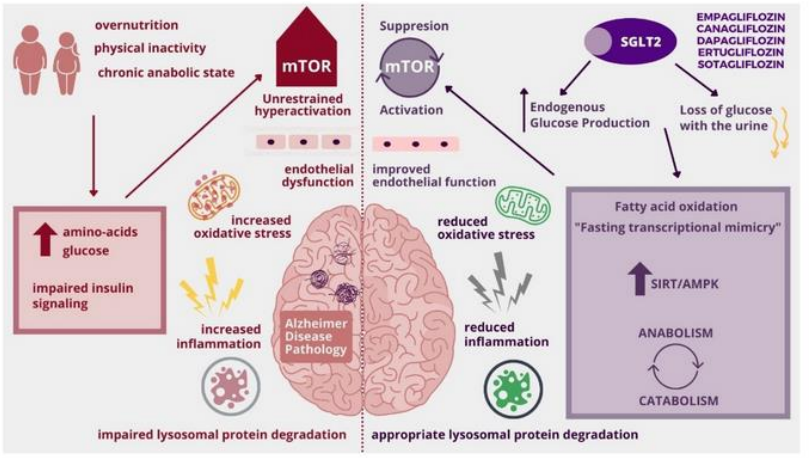
SGLT2i Alzheimer

Fas III Human

Figure 3. Influence of SGLT2 inhibitors on unrestrained activation of mTOR (mechanistic/mammalian target of rapamycin). AMPK-AMP-activated protein kinase, SIRT-Sirtuin.



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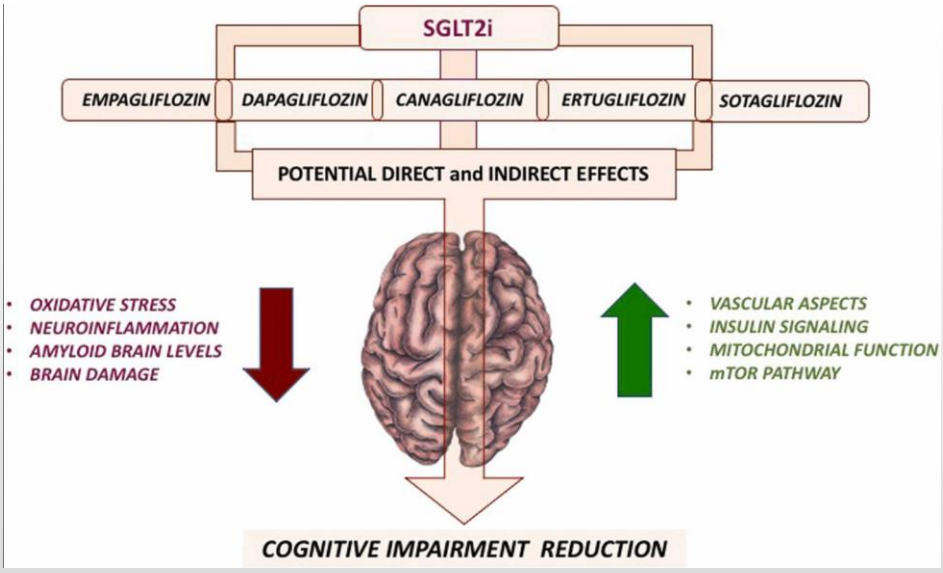
SGLT2i Alzheimer



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SGLT2i Additiv /synergi

+ Metformin
+ GLP-1
+ DPP-4
+ ACEI / ARB
+ MRI *spironolakton / eplerone / finerenon*

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Forxiga = Jardiance* EF 20-60

Väldokumenterat effektiva vid HF*

Snabbt insättande effekt

Oberoende av p-glucos / diabetes

”On top” på RAAS- DPP4-GLP1 + neprilysin inhibition

Njurprotektion

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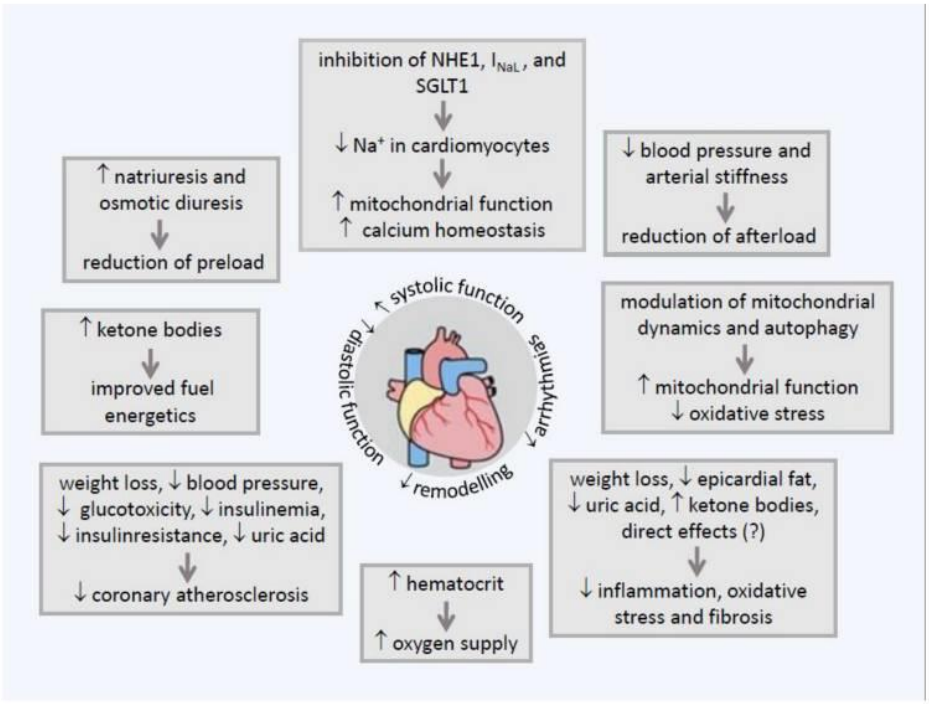
inhibition of NHE1, I_{NaL}, and SGLT1
↓ Na^+ in cardiomyocytes
↑ mitochondrial function
↑ calcium homeostasis
↑ natriuresis and osmotic diuresis
reduction of preload
↓ blood pressure and arterial stiffness
reduction of afterload
↑ ketone bodies
improved fuel energetics
↑ systolic function
↓ diastolic function
↓ arrhythmias
↓ remodelling
modulation of mitochondrial dynamics and autophagy
↑ mitochondrial function
↓ oxidative stress
weight loss, ↓ blood pressure, ↓ glucotoxicity, ↓ insulinemia, ↓ insulinresistance, ↓ uric acid
↓ coronary atherosclerosis
↑ hematocrit
↑ oxygen supply
weight loss, ↓ epicardial fat, ↓ uric acid, ↑ ketone bodies, direct effects (?)
↓ inflammation, oxidative stress and fibrosis

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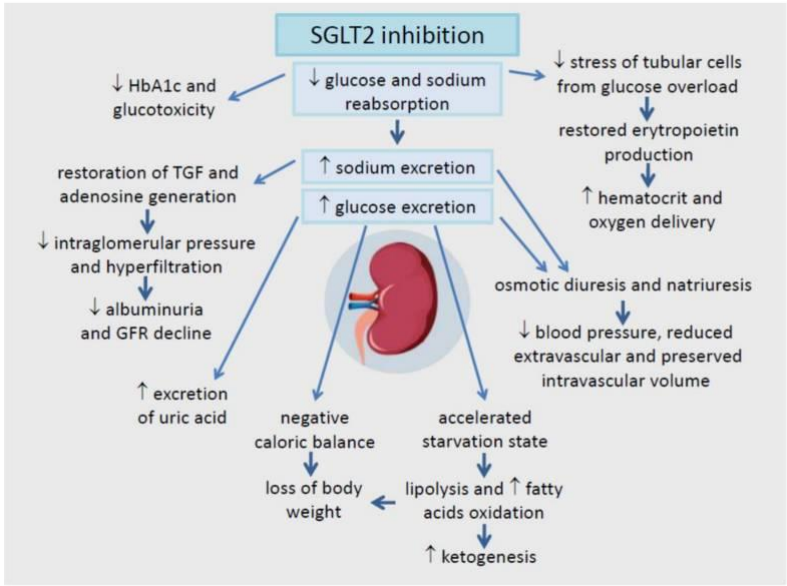
SGLT2 inhibition
↓ glucose and sodium reabsorption
↓ HbA1c and glucotoxicity
↓ stress of tubular cells from glucose overload
restored erytropoietin production
↑ hematocrit and oxygen delivery
↑ sodium excretion
↑ glucose excretion
restoration of TGF and adenosine generation
↓ intraglomerular pressure and hyperfiltration
↓ albuminuria and GFR decline
osmotic diuresis and natriuresis
↓ blood pressure, reduced extravascular and preserved intravascular volume
↑ excretion of uric acid
negative caloric balance
accelerated starvation state
loss of body weight
lipolysis and ↑ fatty acids oxidation
↑ ketogenesis

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Organprotektion och försiktighet i kliniken

- Implementeras tidigt tillsammans med RAAS blockad
- Diabetes II = Icke diabetes d.v.s generellt vid proteinuriska nefropatier
- Undvik undernutrierade multisjuka äldre diabetiker ….. Ketoacidos!!!
- Undvik KAD
- Behandlingsuppehåll på samma sätt som RAAS blockad vid exempelvis gastroenterit
- Vagt diabetes- blodtrycks läkemedel i sig
- Kontraindicerat vid Diabetes I

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Forxiga = Jardiance* EF 20-60

Väldokumenterat effektiva vid HF*

Snabbt insättande effekt

Oberoende av p-glucos / diabetes

”On top” på RAAS- DPP4-GLP1 + neprilysin inhibition

Njurprotektion

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MRAs / MRI

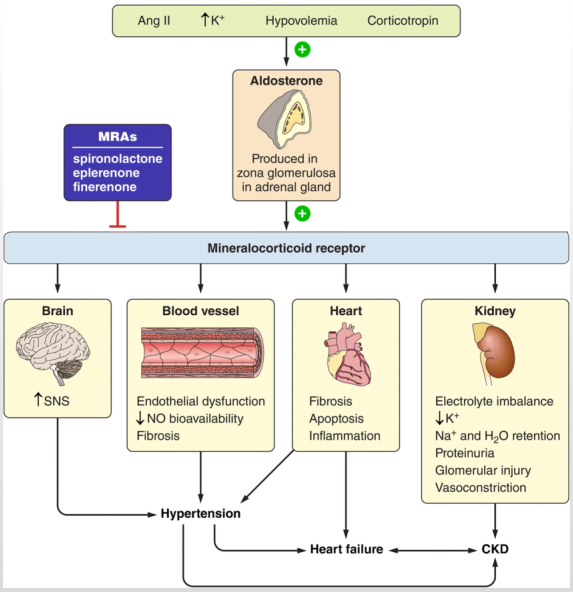

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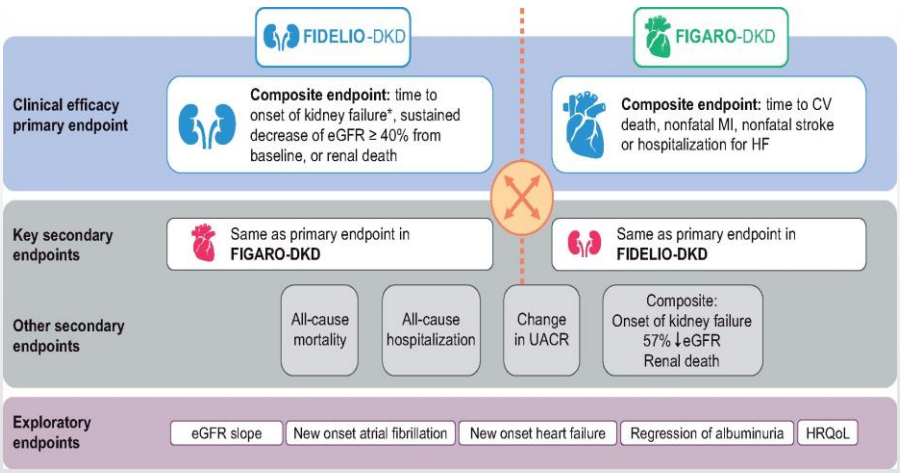
FIGURE 3 FIDELIO-DKD and FIGARO-DKD endpoints. [a]Kidney failure defined as occurrence of ESKD (initiation of ...



Nephrol Dial Transplant, Volume 37, Issue 6, June 2022, Pages 1014–1023, https://doi.org/10.1093/ndt/gfaa294

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MRI Finerenon KERENDIA

- *Fri från steroid endokrina effekter*
- *MR specifik*

Hjärtsvikt studier kommer…..

- *Cardiellt antiinflammatoriska effekter*
- *Mindre hyperkalemi*

- *FASS : Diabetes II +CKD3 - CKD4 + albuminuri* *FIDELIO FIGARO*

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