The 3rd Indonesia Symposium on Heart Failure and Cardiometabolic Disease 2023

# Breakthrough in HFpEF Management: How Do SGLT2i's Help Patients In Need ?

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# Disclosure

Professor Sindone has indicated that he has a relationship which in the context of this presentation, could be perceived as a real or apparent conflict of interest but does not consider that it will influence his presentation.

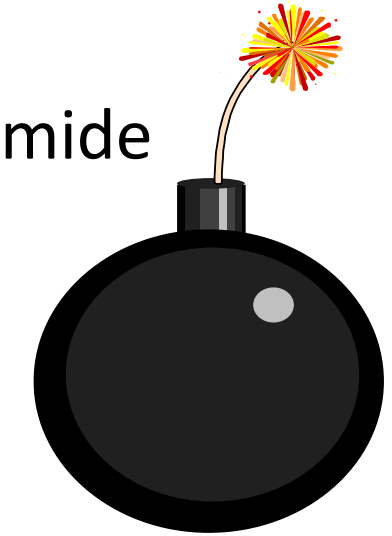


Professor Sindone has received honoraria, speaker fees, consultancy fees, is a member of advisory boards or has appeared on expert panels for: Abbott, Alphapharm, Amgen, Aspen, Astra Zeneca, Bayer, Biotronic, Boehringer Ingelheim, Bristol Myers Squibb, CSL, Edwards, Eli Lilly, Glaxo Smith Kline, HealthEd, Jansen Cilag, Medtronic, Menarini, Merck Sharp and Dohm, Mylan, Novartis, Otsuka, Pfizer, Roche, Sanofi, Servier, St Jude, Vifor

# Aminah

- 63 year old retired nurse
- Says on baseline she is “unable to breathe all the time”
- PHx: Atrial Fibrillation, CVA x 2, HT, OSA- CPAP, obesity
- Medications: apixaban 5mg bd, verapamil SR 180mg mane, frusemide 40mg daily, ramipril 10mg daily, rosuvastatin 10mg mane

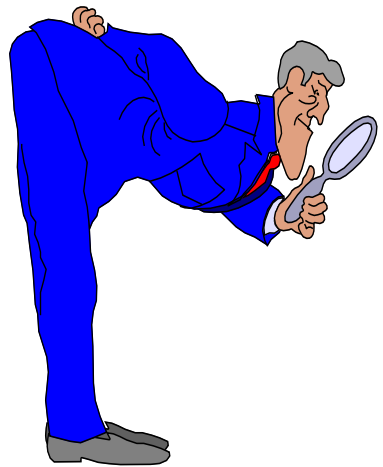




# Emergency Department

- HR 120 AFib, afebrile, BP140/85, Sats 85% RA, weight 104kg
- JVP at earlobe, apex beat normal, HS dual, bibasal crepitations to mid-zones, oedema to mid-shins
- CXR bilateral pleural effusions with upper lobe diversion.
- ECG AF, nil ischaemic changes
- eGFR 38, TSH normal, Troponin normal, NTproBNP 1400
- Imp – rapid atrial fibrillation with heart failure.

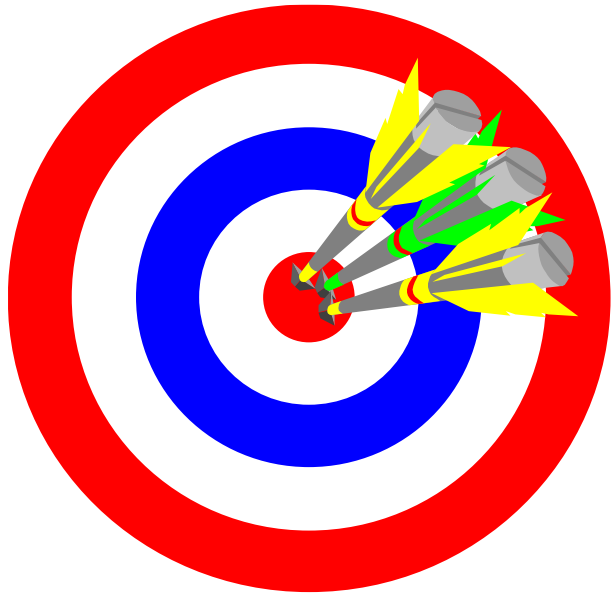




# Initial Management

- 1.5L fluid restriction
- IV furosemide 80mg IV bd
- Spironolactone 12.5mg daily
- Empagliflozin 10mg daily
- Cease verapamil, commence digoxin 62.5mcg mane
- Iron studies: Ferritin 74, Tsat 12%

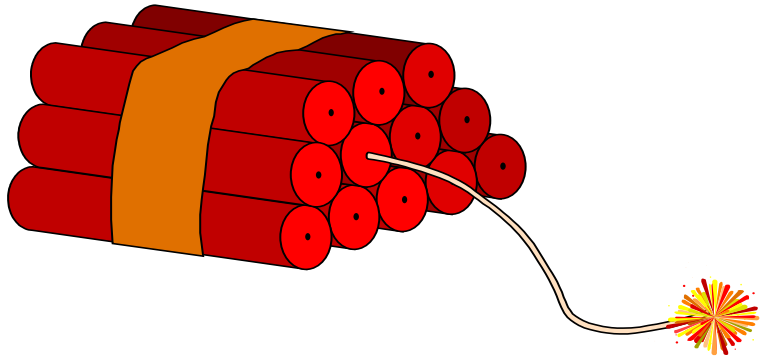




# Echocardiogram

- Normal left ventricular size with concentric remodelling, mild to moderate left ventricular hypertrophy and normal LV ejection fraction
- Diastolic dysfunction with elevated mean left atrial pressure
- Moderate bilateral atrial dilatation
- Satisfactory valve function
- Mild pulmonary hypertension





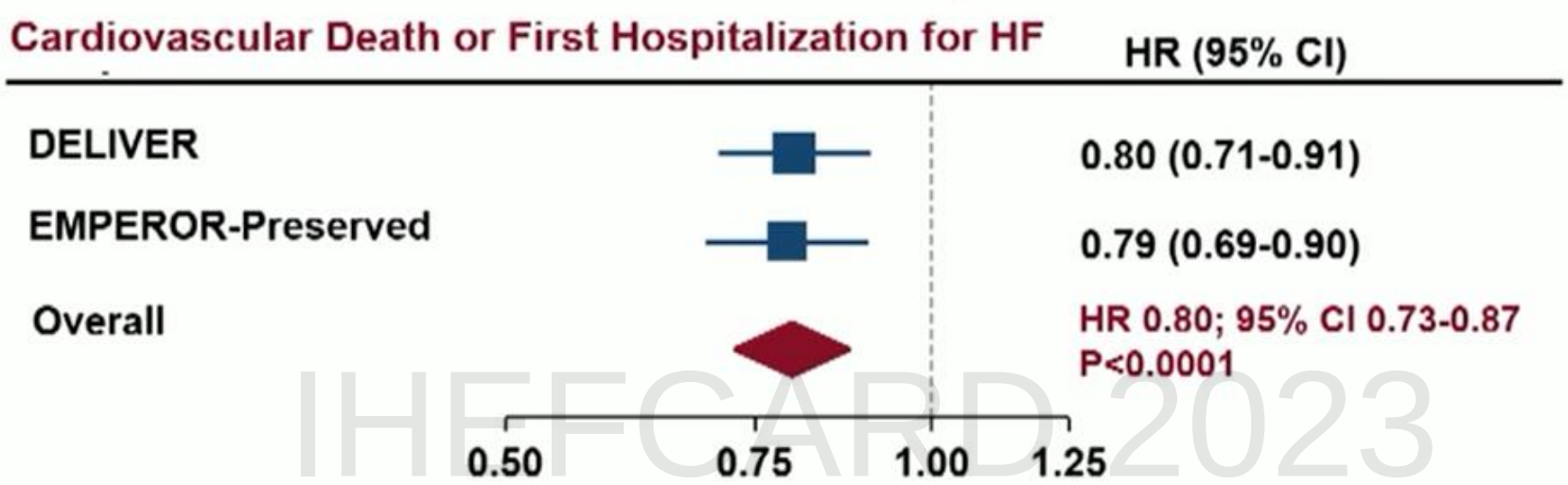
# Progress

- Loses 4kg and is euvolaemic
- BP 110/70, HR 63, weight 100kg
- Discharged on
  - furosemide 40mg daily
  - spironolactone 12.5mg daily
  - empagliflozin 10mg daily
  - bisoprolol 5mg nocte + digoxin 62.5mcg + apixaban 5mg bd
  - rosuvastatin 10mg
  - ramipril 10mg daily
- IV ferric carboxymaltose on discharge
- Feels much better

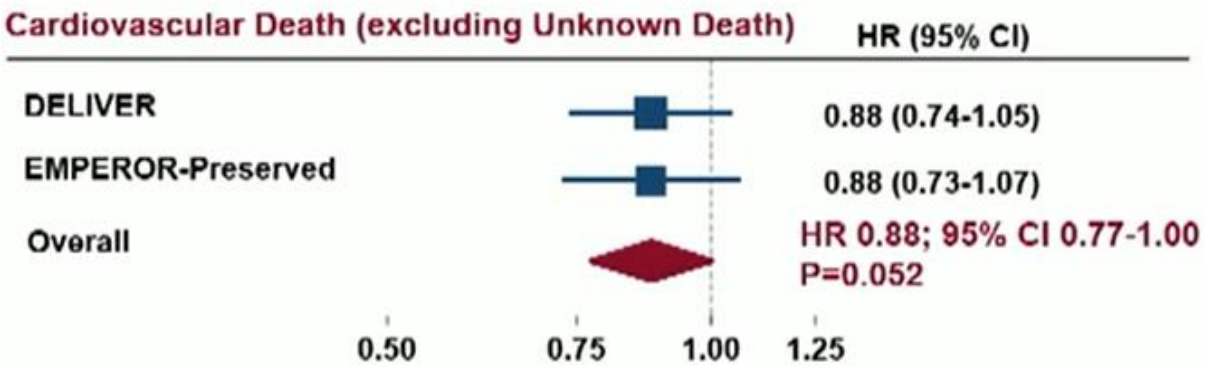


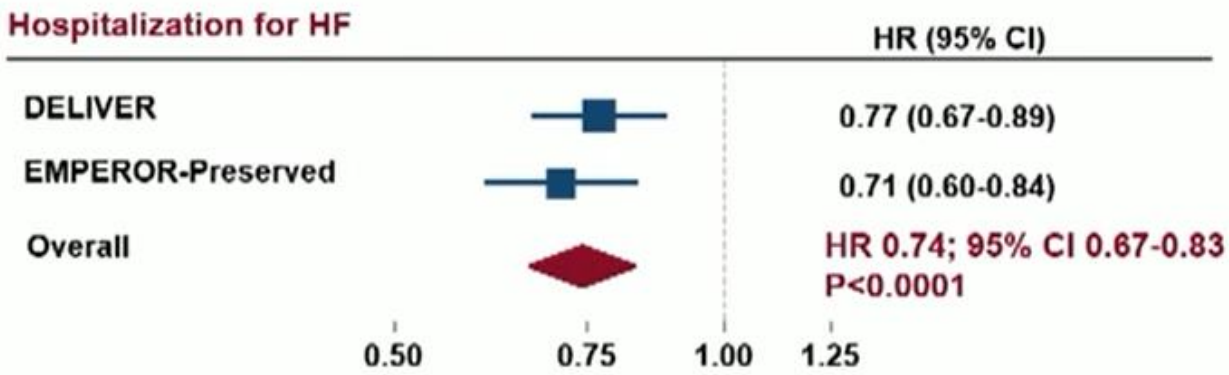
# Benefits of SGLT2 Inhibitors in HFpEF

# DELIVER and EMPEROR Preserved – 20% (13-27%) ↓ in Risk



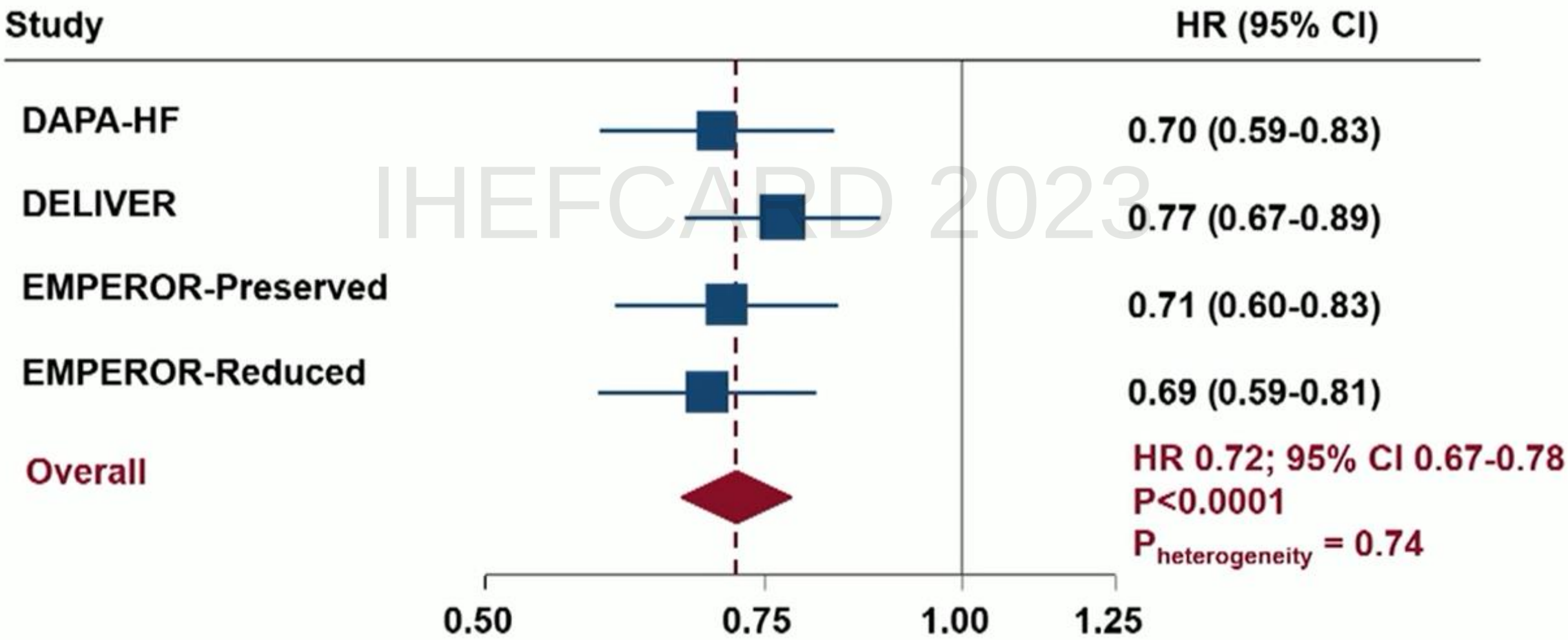


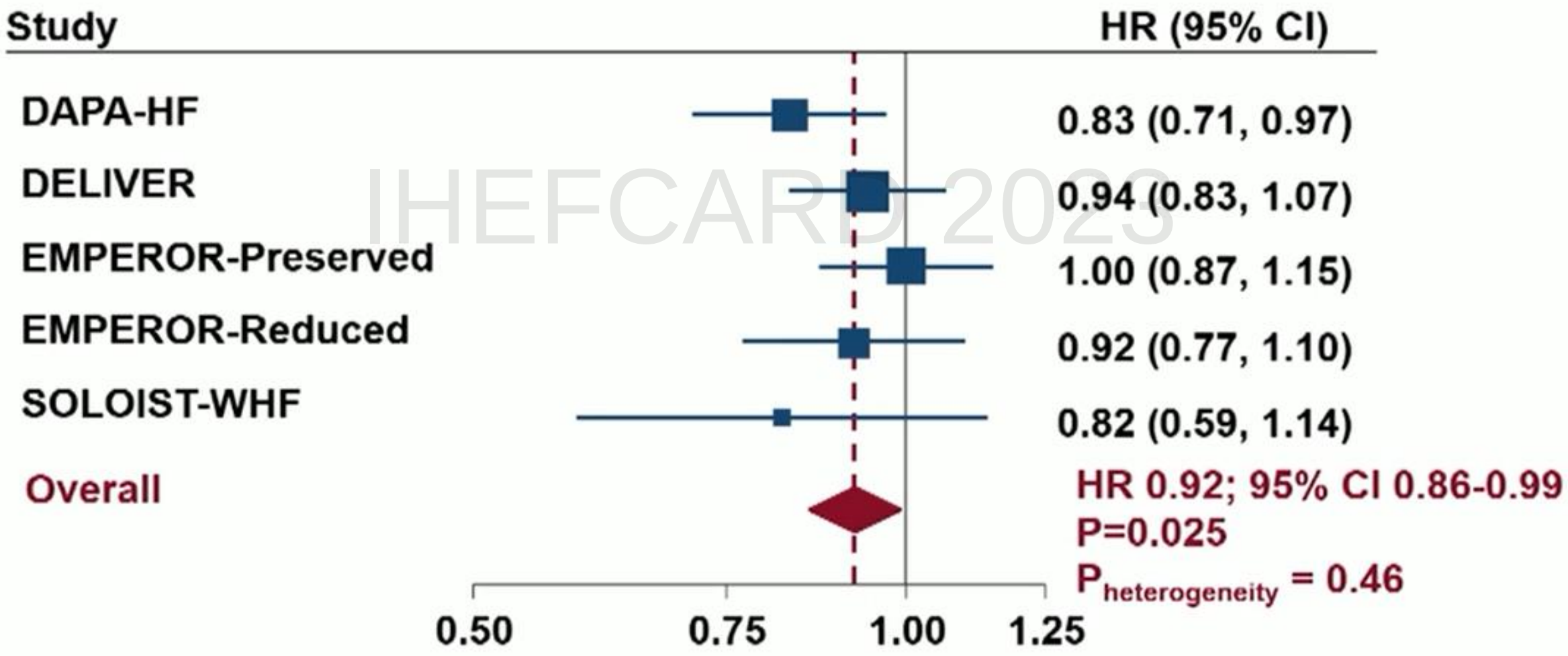




$P_{heterogeneity}$ >0.40 for all endpoints

# Meta-Analysis of 4 Large Trials – 28% (22-33%) ↓ in Risk HHF

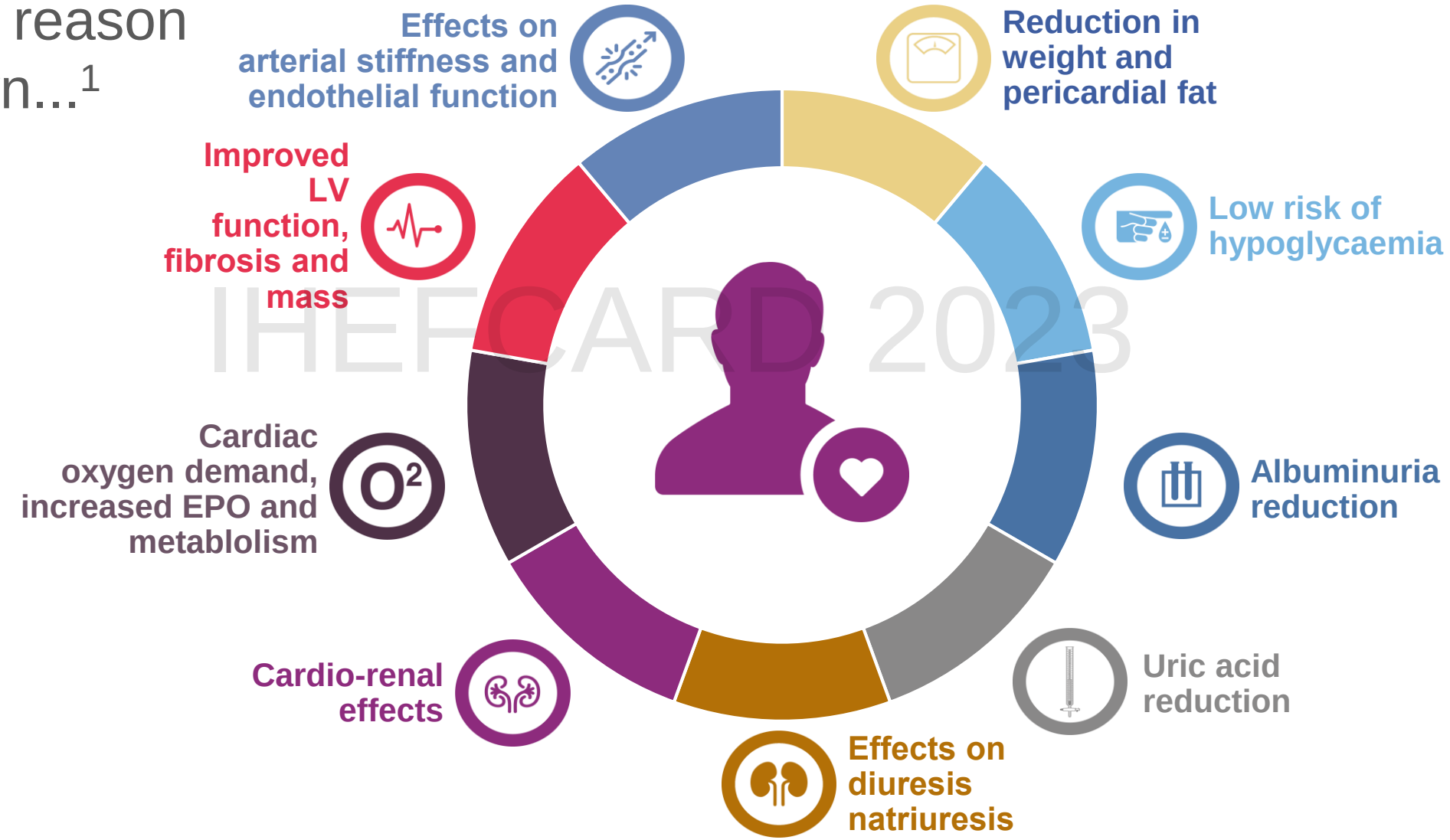


# Meta-Analysis of 5 Large Trials –8% (1-14%) ↓ in Mortality



# These Results Are Not Explained By $HbA_{1c}$ Reduction Alone[1]

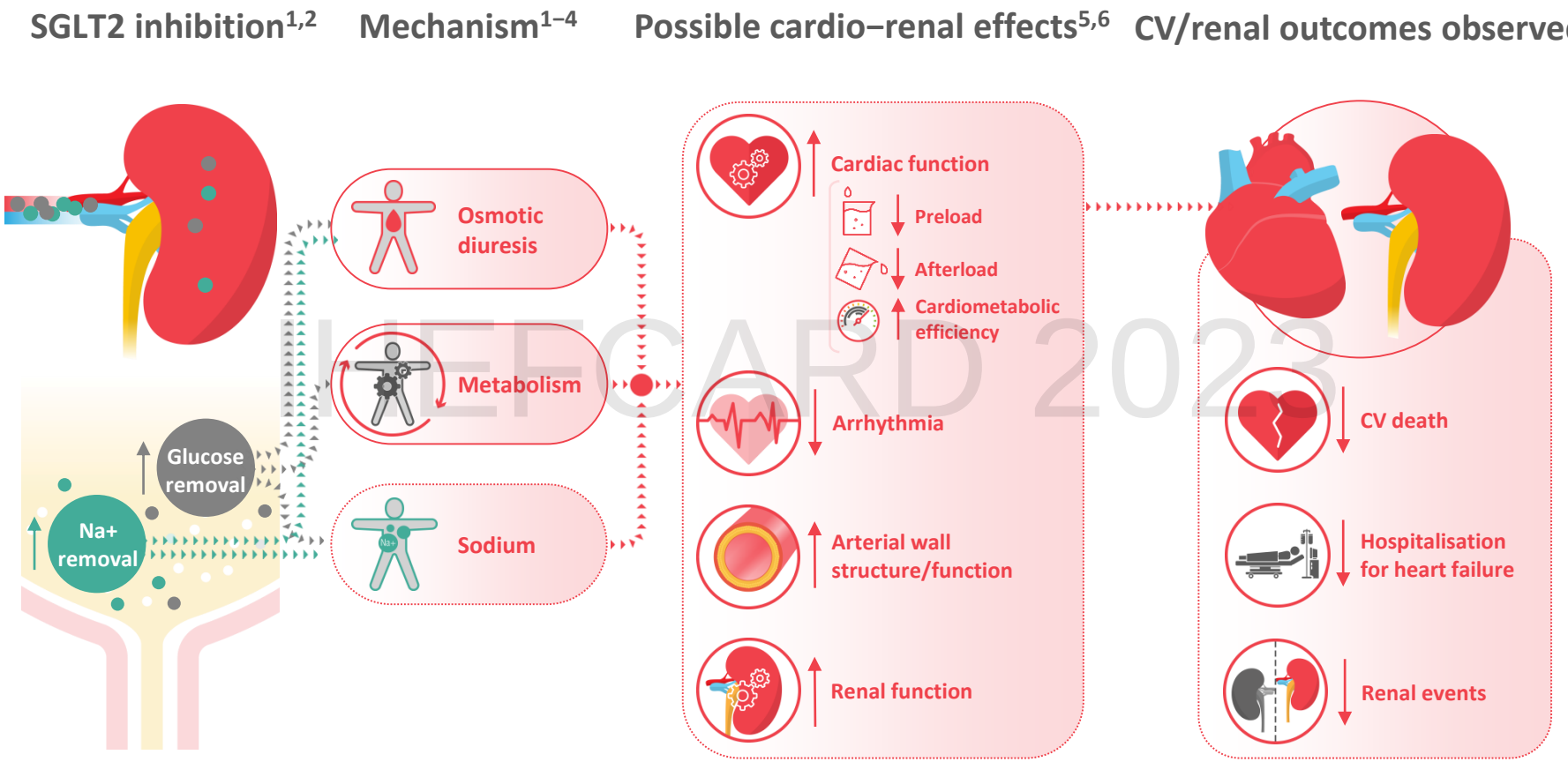
- The exact reason is unknown...[1]






1. Zinman B *et al. N Engl J Med* 2015; 373:2117–28.

# CV and Renal Function Mechanisms of SGLT2 Inhibitors That May Benefit Heart Failure






SGLT2, sodium-glucose co-transporter-2

1. Heise T *et al. Diabetes Obes Metab* 2013;15:613; 2. Heise T *et al. Clin Ther* 2016;38:2265; 3. Ferrannini G *et al. Diabetes Care* 2015;38:1730; 4. Briand F *et al. Diabetes* 2016;65:2032; 5. Heerspink HJ *et al. Circulation* 2016;134:752; 6. Inzucchi S *et al. Diab Vasc Dis Res* 2015;12:90; 7. Zinman B *et al. N Engl J Med* 2015;373:2117; 8. Wanner C *et al. N Engl J Med* 2016;375:323

# Cardio-Renal Effects

# ‘Smart Diuretics’: SGLT2 Inhibitors vs Diuretics I

| Physiological Effect | SGLT2 Inhibitors | Diuretics |
|---|---|---|
| Sodium | ↔ | ↓ |
| Potassium | ↔ | ↓ |
| Magnesium | ↔ | ↓ |
| Uric Acid | ↓ | ↑ |
| LDL cholesterol | ↔ | ↑ |
| Plasma Glucose | ↓ | ↑ |
| Haematocrit | ↑ | ↔ |
| Heart rate | ↓ | ↑ |
| Systolic blood pressure | ↓ | ↓ |
| Intravascular volume | ↓ | ↓ |
| Interstitial volume | ↓ | ↔ |



Rasalam, R…Sindone AP. In press

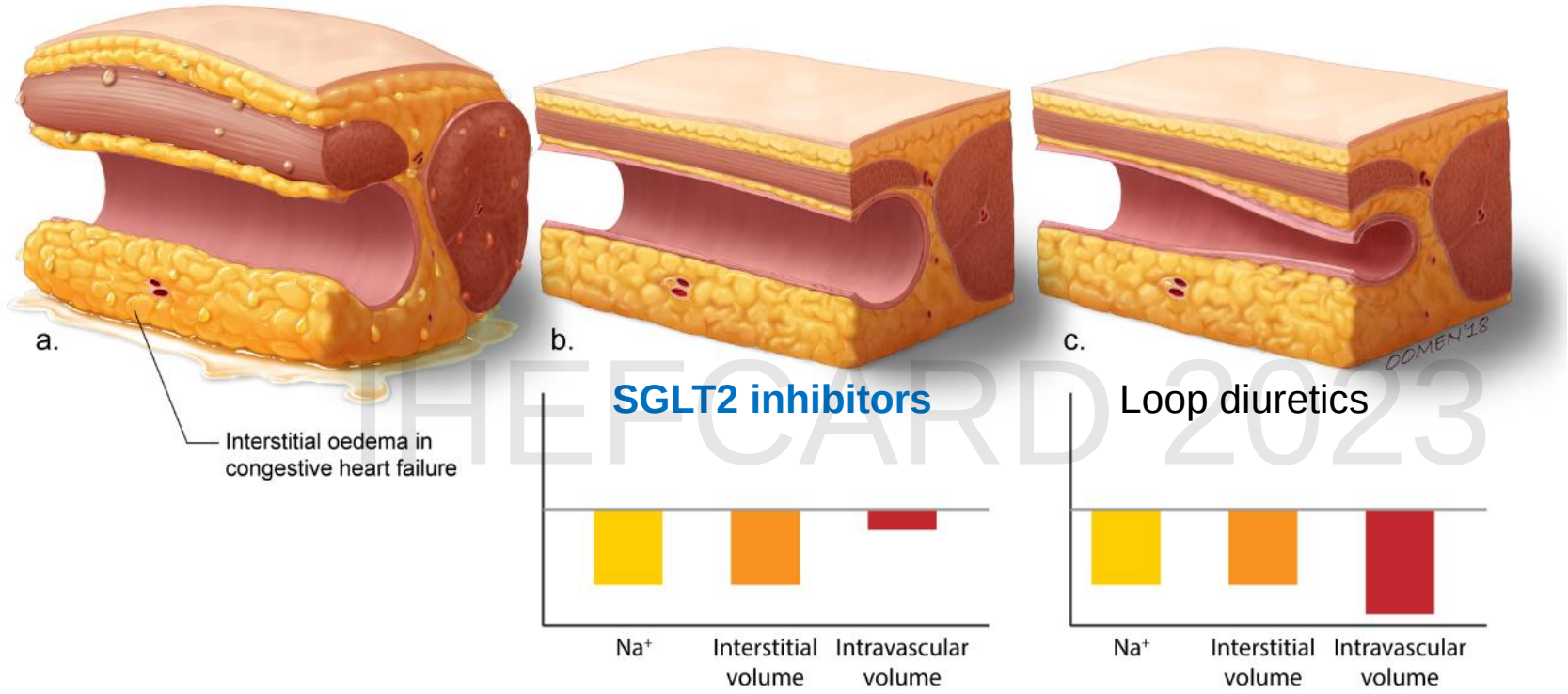
# ‘Smart Diuretics’: SGLT2 Inhibitors vs Diuretics II

| Physiological Effect | SGLT2 Inhibitors | Diuretics |
|---|---|---|
| Myocardial infarction | ↔/↓ | ↔ |
| Stroke | ↔ | ↓ |
| eGFR | ↓ then ↔ | ↓ |
| Intra-Glomerular Pressure | ↓ | ↔ |
| Tubuloglomerular Feedback | ↑ | ↔ |
| Renin / Angiotensin II | ↓ | ↑ |
| Aldosterone | ↓ | ↑ |
| Sympathetic Tone | ↓ | ↑ |
| Arginine Vasopressin | ↔ | ↑ |
| Intravascular volume | ↔ | ↓ |
| Extravascular volume | ↓ | ↔ |



Rasalam, R…Sindone AP. In press

# In Contrast To Loop Diuretics, SGLT2 Inhibitors Reduce Interstitial Volume More So Than Intravascular Volume



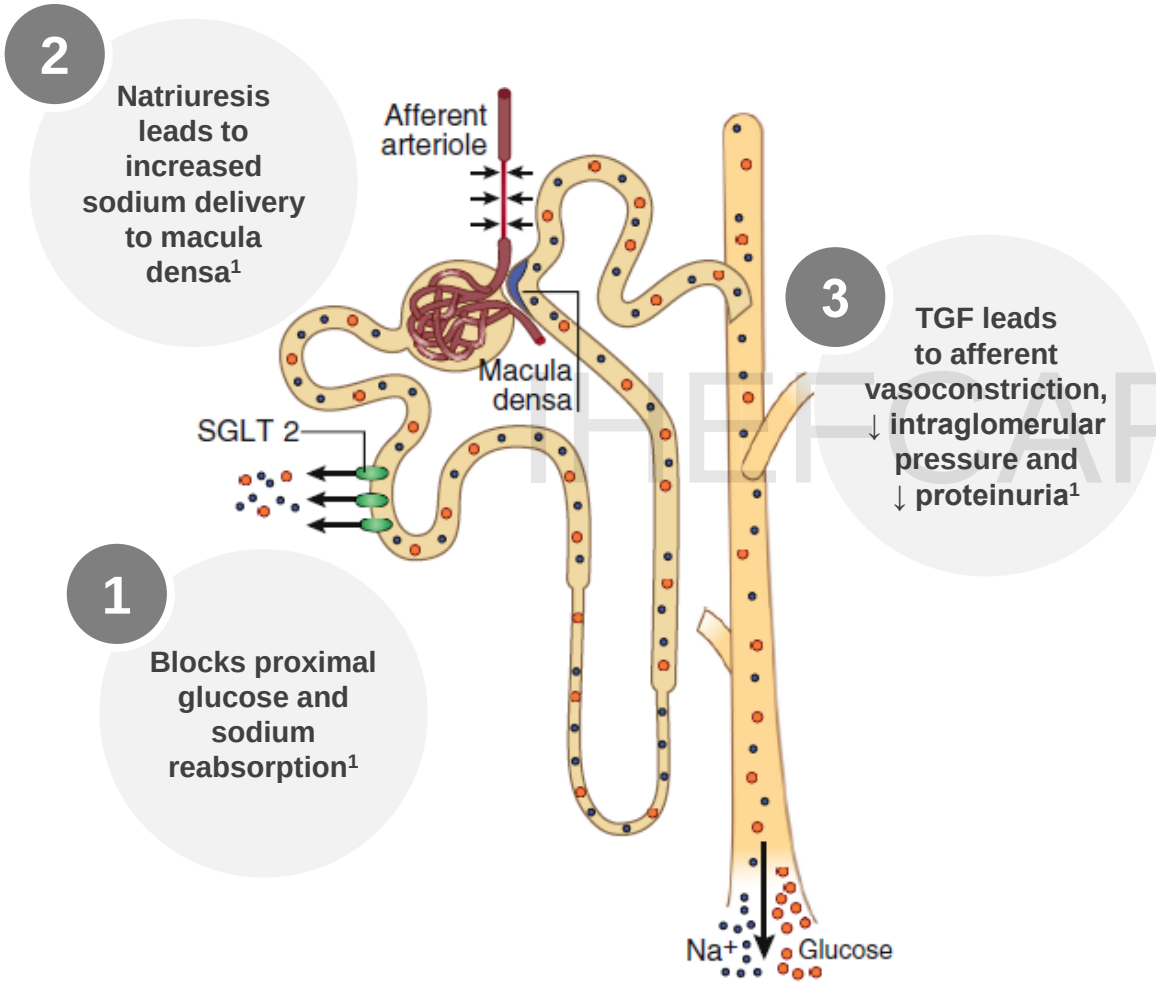



- SGLT2 inhibitors may differentially regulate the interstitial vs intravascular compartment compared with loop diuretics
- Interstitial oedema is evident in patients with congestive heart failure (a)
- SGLT2 inhibitors may selectively reduce interstitial volume with minimal change in blood volume (b) whereas loop diuretics may cause a reduction in both interstitial and intravascular volume (c)
- This differential volume regulation by SGLT2 inhibitors (interstitial > intravascular) may limit the aberrant reflex neurohumoral stimulation that occurs in the setting of intravascular depletion

SGLT2, sodium-glucose cotransporter 2.

Verma S, McMurray JJV. *Diabetologia.* 2018;61:2108-2117.

# SGLT2 Inhibitor–Mediated Inhibition of Sodium Reabsorption in the Proximal Tubule is Renal Protective[1]






**Effects mediated by SGLT2i in the kidney**

## Natriuresis

- ↓blood pressure[1]
- ↓plasma volume[1]
- ↓afterload[3]
- ↓preload[3]
- ↓LV wall stress[3]
- ↓intraglomerular hypertension[1]
- ↓intraglomerular hyperfiltration[1]

## Glucoresis

- ↓HbA1c[1]
- ↓total body fat mass[1]
- ↓plasma uric acid[1]

SGLT2, sodium-glucose cotransporter 2; TGF, tubuloglomerular feedback.

**1.** Rajasekeran H, et al. *Kidney Int.* 2016;89;524-526. **2.** Alicic RZ, et al. *Clin J Am Soc Nephrol.* 2017;12:2032-2045. **3.** Verma S. *JAMA Cardiol.* 2017;(9):939-940.

# Protective effects of SGLT2i on the kidney

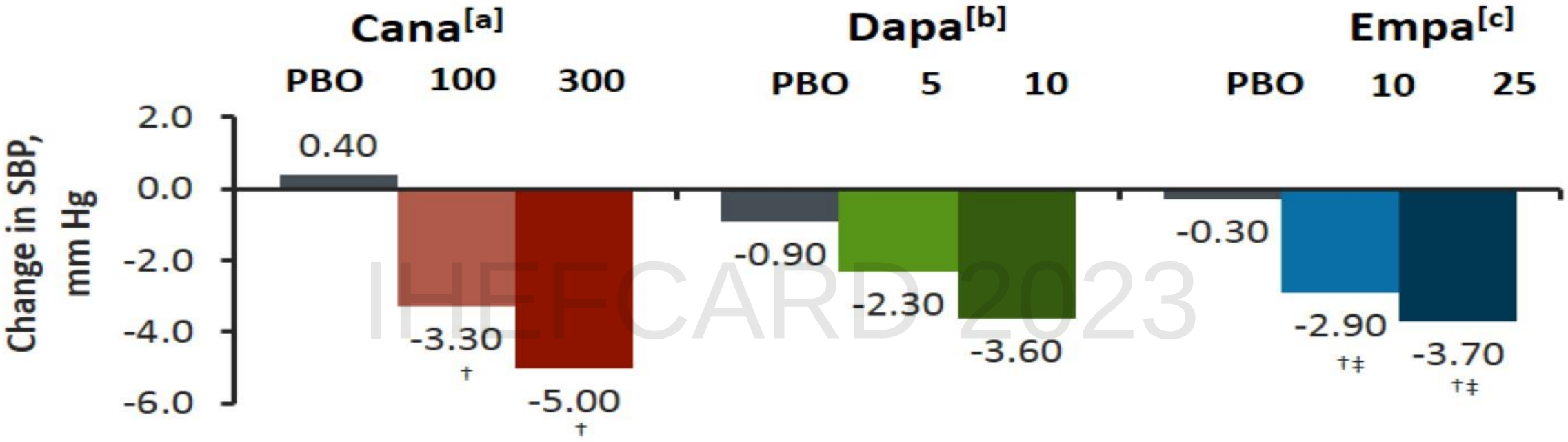
| Action | Mechanism |
|---|---|
| Direct effects | Improve glomerular hyperfiltration |
| | Reduce renal oxygen consumption |
| | Reduce renal inflammatory reactions |
| | Restore the mode of cellular energy metabolism |
| Indirect effects | Improve blood glucose |
| | Improve blood pressure |
| | Decrease uric acid levels |
| | Promote weight loss |
| | Increase the level of glucagon |
| | Reduce the level of insulin |
| | Promote diuresis |



Ni et al. Cardiovasc Diabetol (2020) 19:98

# Haemodynamic Effects

# Systolic Blood Pressure Effects with SGLT2 Inhibitors as Monotherapy






*None of the agents listed are approved for the treatment of hypertension.

†Greater than PBO ($P < .05$).

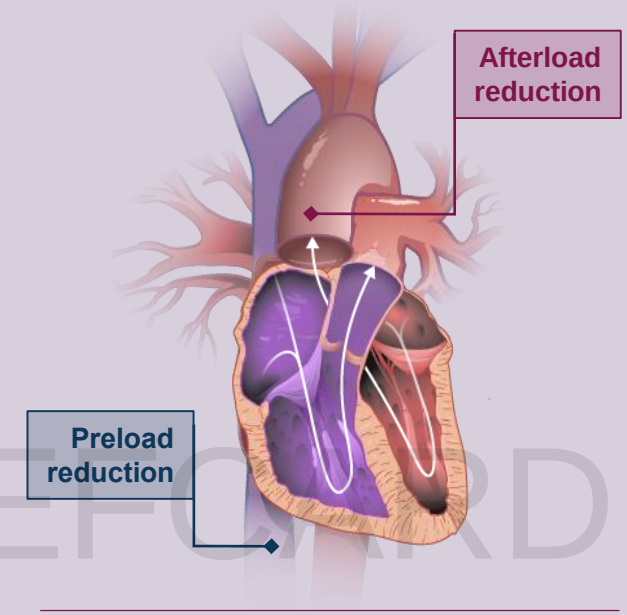
‡Greater than Sita ($P < .05$).

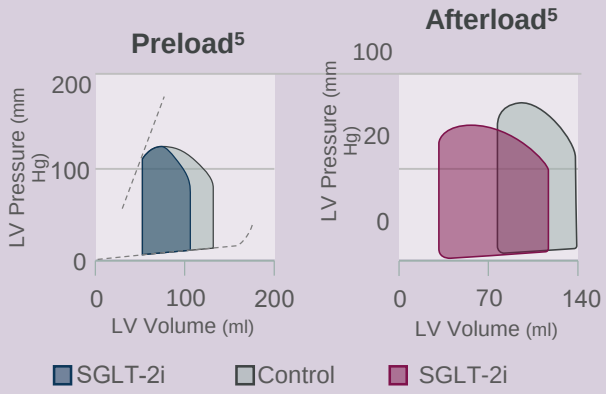
a. Stenlöf K, et al. *Diabetes Obes Metab*. 2013;15:372-382; b. Ferrannini E, et al. *Diabetes Care*. 2010;33:2217-2224; c. Roden M, et al. *Lancet Diabetes Endocrinol*. 2013;1:208-219.

# SGLT-2 Inhibitors Improve Myocardial Loading Conditions[1]

## SGLT-2 INHIBITION

**Reduce Preload/Afterload[1]**
↓Plasma volume
↓Vascular resistance




### Preload reduction

- Natriuresis and osmotic diuresis reduce preload
  (LV filling) and resultant LV wall stress[2]
- This is particularly important in patients with diastolic dysfunction who are sensitive to changes in intravascular volume[1]
  - 46% of patients with T2D have LV diastolic dysfunction[3]

### Afterload reduction[4]

- SGLT-2i have been shown to reduce arterial stiffness and blood pressure, which contribute to reduced afterload



1. Verma S. *JAMA Cardiol*. 2017;2(9):939-940. 2. Verma S, et al. *Diabetologia*. 2018; 61(10):2108-2117. 3. Bouthoorn S, et al. *Diab Vasc Dis Res*. 2018;15(6):477-493. 4. Kalra S. *Cardiol Ther*. 2016;5(2):161-168. 5. Rocha N, et al. *Kidney Int Suppl* (2011). 2018;8(1):8-17.

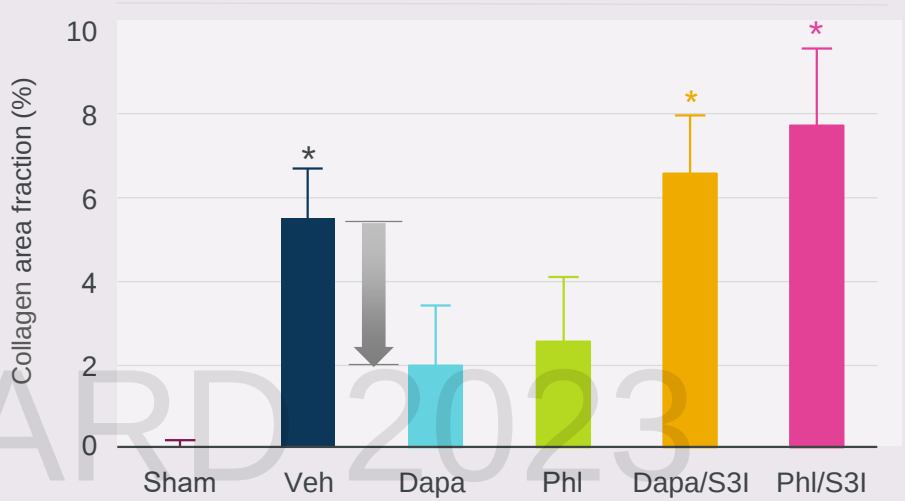
# SGLT-2 Inhibitors May Attenuate the Development of Cardiac Hypertrophy, Fibrosis, and Remodeling

## SGLT-2 INHIBITION

**Reduce Preload/Afterload**
↓Plasma Volume
↓Vascular resistance

**Improved Myocardial Energetics**
↑Fatty acid oxidation
↑Ketone body formation
↓Cardiac NHE1

**Cardiac Remodeling**
↓Inflammation/fibrosis
↓Cardiac wall stress





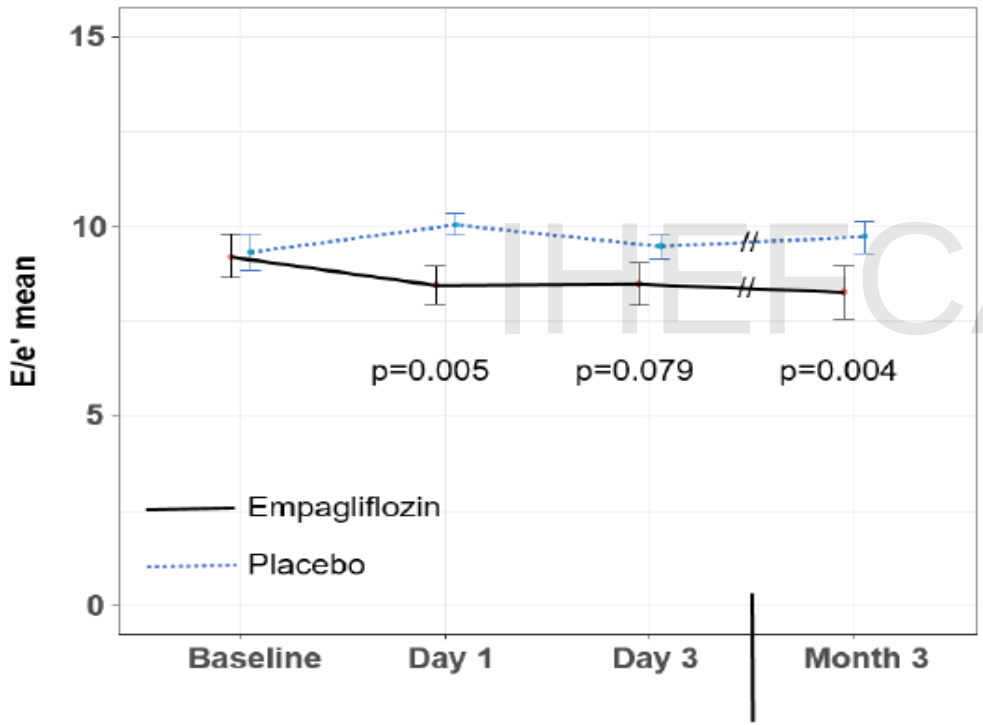

- Cardiac fibrosis is an important contributor to the development of HF by impeding ventricular compliance[1]
- Advanced Glycogen End-products that play a role in diabetes also lead to cardiomyocyte stiffness and myocardial collagen deposition[2]
- Collagen deposition by cardiac fibroblasts, in concert with neurohormonal activation, ultimately cause elevated wall stress, chamber dilatation, contractile dysfunction and HF[3]
- SGLT-2 inhibition has been shown in rodent models and *ex vivo* human studies to exhibit anti-fibrotic effects by inhibiting fibroblast activation and collagen synthesis[4]

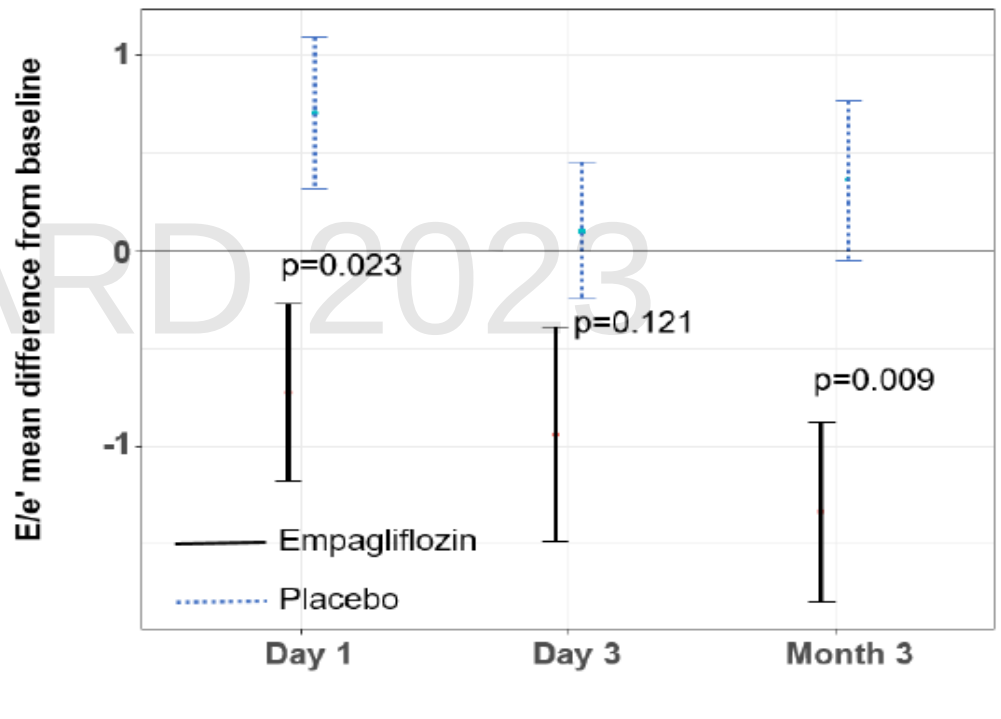
AGE=advanced glycation end products; Phl=phlorizin; S31=S3I-201 (STAT3 inhibitor); Veh=vehicle.

1. Verma S, et al. *Diabetologia*. 2018;61(10):2108-2117. 2. Lehrke M, et al. *Am J Med*. 2017;130(6S):S40-S50. 3. Wilson AJ, et al. *Heart*. 2018;104(4):293-299. 4. Lee TM, et al. *Free Radical Biol Med*. 2017;104:298-310.

# EMPA Hemodynamics

## Echocardiography
## E/e‘

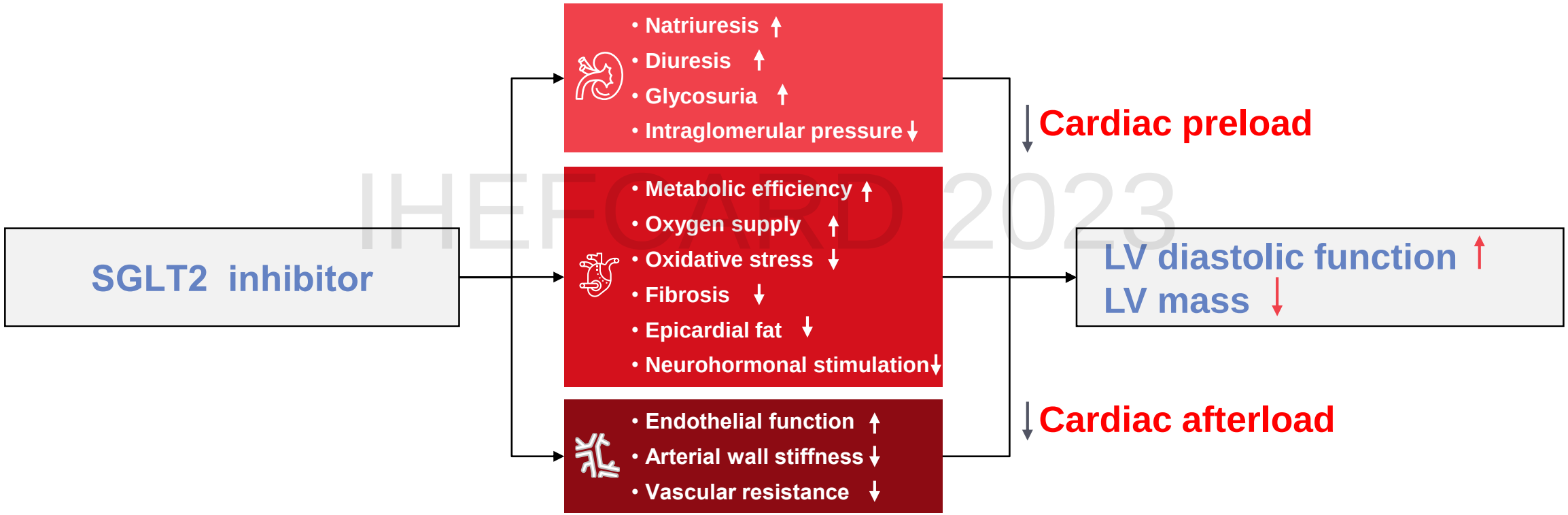





→ Empaglifozin leads to an acute improvement in measures of LV filling pressure

# Potential Mechanisms for Improved Left Ventricular Diastolic Function and Reduced Left Ventricular Mass with SGLT2 Inhibitors[1]



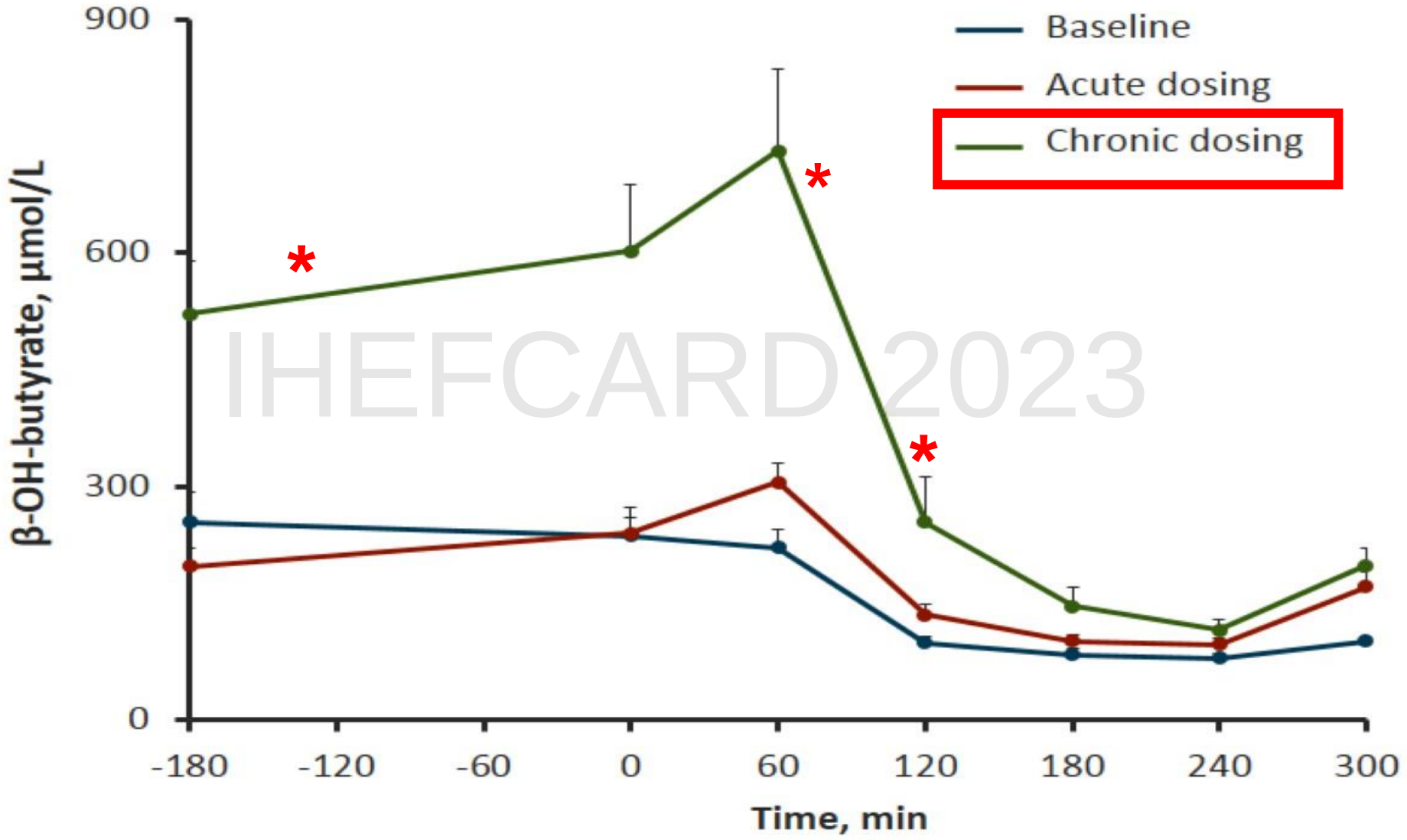



1. Lan N *et al. ESC Heart Fail* 2019;6:927

LV, left ventricular; SGLT2, sodium-glucose co-transporter-2

# Metabolic Effects

# Impact of SGLT2 Inhibitors on Fasting and Post-Prandial Ketonaemia



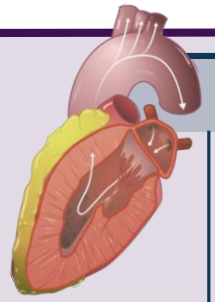



Ferrannini E, et al. *Diabetes*. 2016;65:1190-1195.

# SGLT-2 Inhibitors May Induce a Shift to More Energy Efficient Metabolic Substrates in the Failing Heart[1]

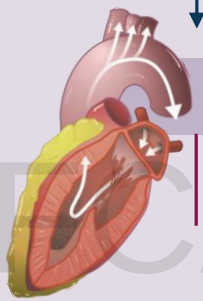
## SGLT-2 INHIBITION

**Improved Myocardial[1] Energetics**
↓ Reliance on fatty acids
↑Ketone body formation
↓Cardiac NHE1



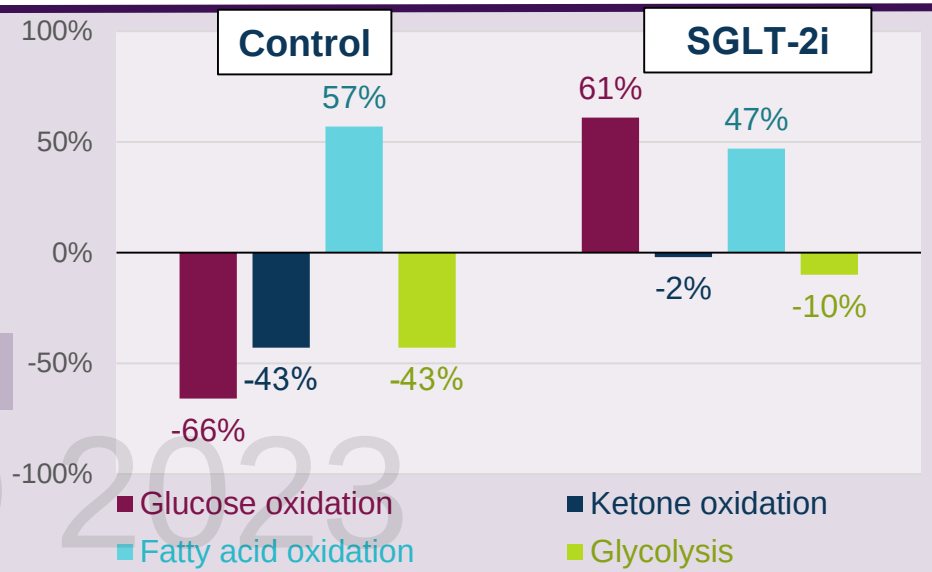
Diabetic Heart

Energy deprived heart



Diabetic Heart Treated With SGLT-2i

Improved cardiac function




- To meet the high metabolic demands of continuous contractility, the heart employs metabolic flexibility to catabolize an array of substrates[2]
- In T2D and/or HF, metabolic flexibility decreases and an overreliance on fatty acid oxidation reduces cardiac efficiency[1,2]
- SGLT-2 inhibition increases the production of ketone bodies, which are a higher energetic and oxygen-efficient fuel than fatty acids[3-5]
- SGLT-2i may reduce the risk for HF by enhancing cardiac efficiency and contractile function through increased metabolism of ketone bodies[6]
  - In pre-clinical models, SGLT-2i increased overall cardiac ATP production by ~30%[3]

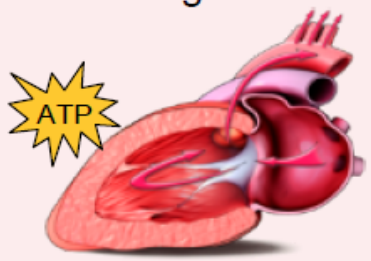


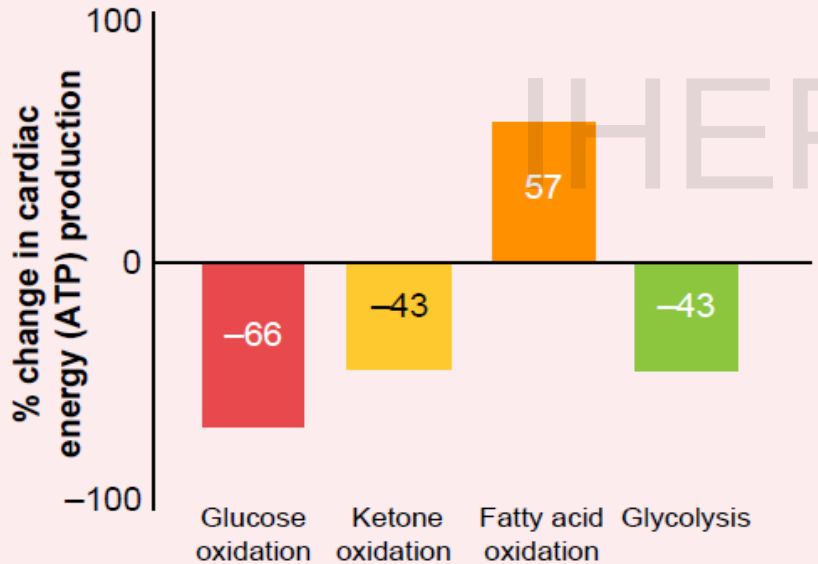
ATP=adenosine triphosphate.

1. Wende AR, et al. *JACC Basic Transl Sci*. 2017;2(3):297-3101. 2. Ferrannini E, et al. *Diabetes Care*. 2016;39(12):1108-1114. 3. Verma S, et al. *JACC Basic Transl Sci*. 2018; 26:575-587.
4. Garcia-Ropero A, et al. *Expert Opin Drug Metab Toxicol*. 2019;15(4):275-285. 5. Tamargo J. *Eur* Cardiol. 2019;14(1):23-32. 6. Bertero E, et al. *Cardiovasc Res.* 2018;114(1):12-18.

## Untreated diabetes hearts

Failing heart



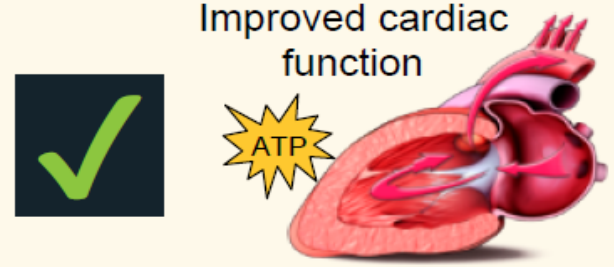



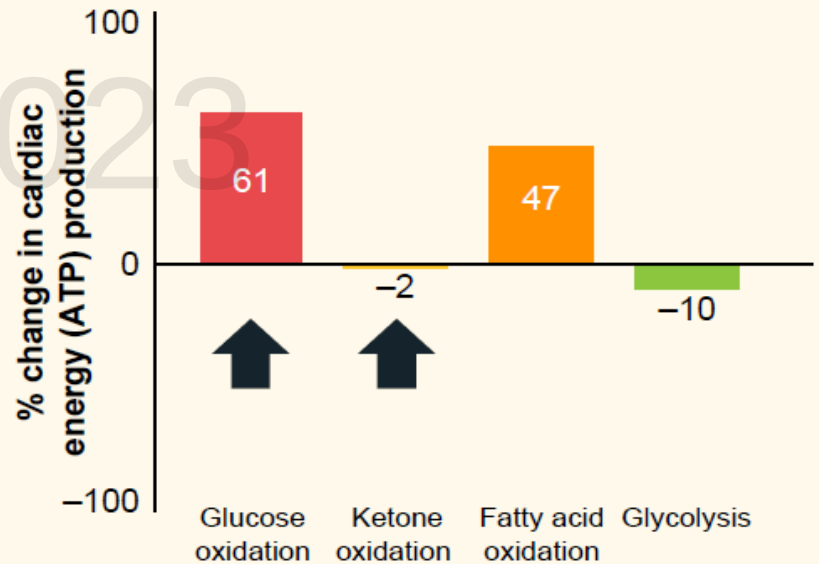

**↓ Cardiac energy (ATP) production relative to normal hearts**

SGLT2 inhibitors

## Diabetes hearts treated with empagliflozin for 4 weeks

Improved cardiac function



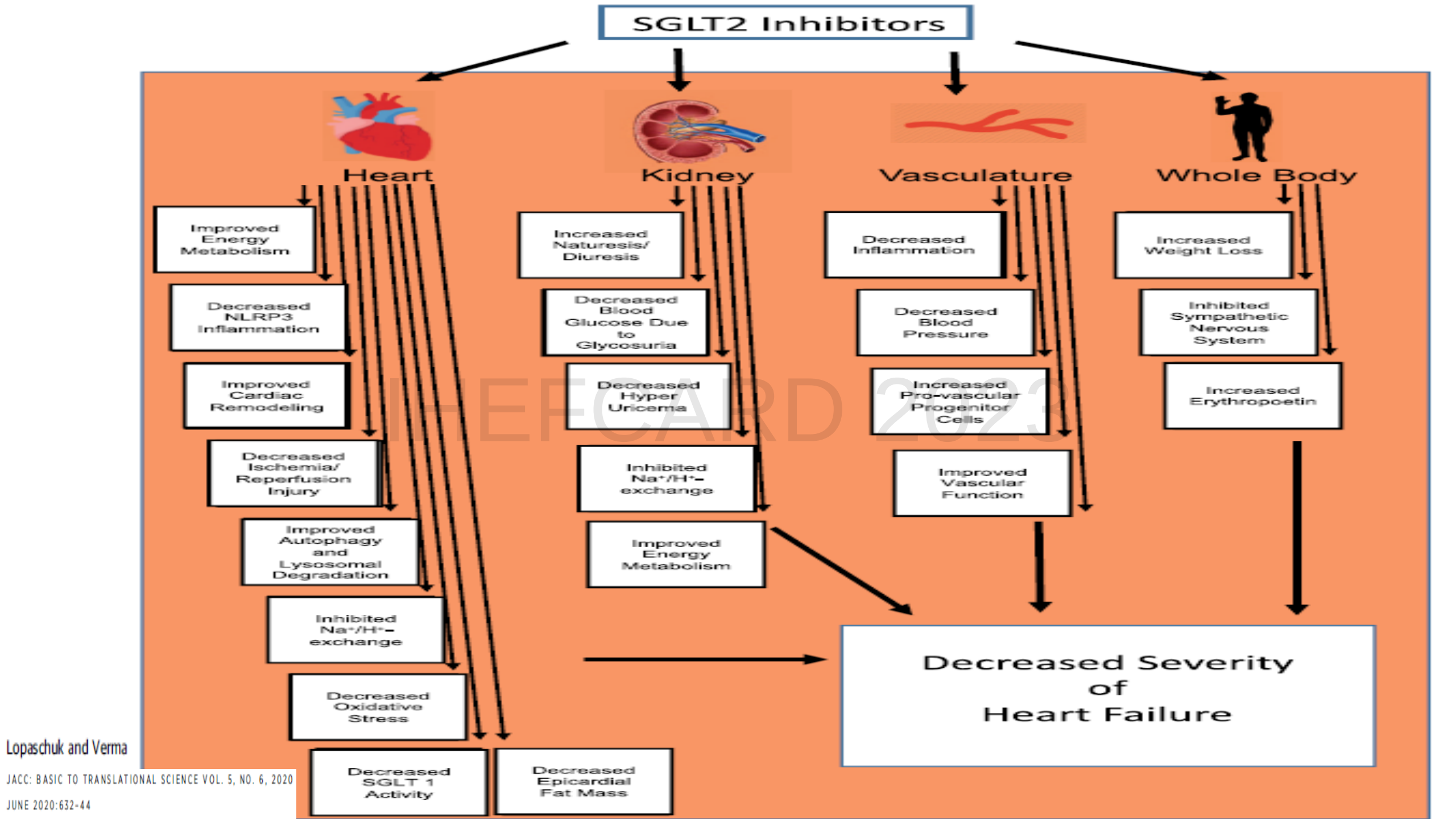

**↑ Cardiac energy (ATP) production relative to untreated hearts**



ATP, adenosine triphosphate

Verma S, et al. *JACC Basic Transl Sci* 2018;3:575–587

# Summation of Effects

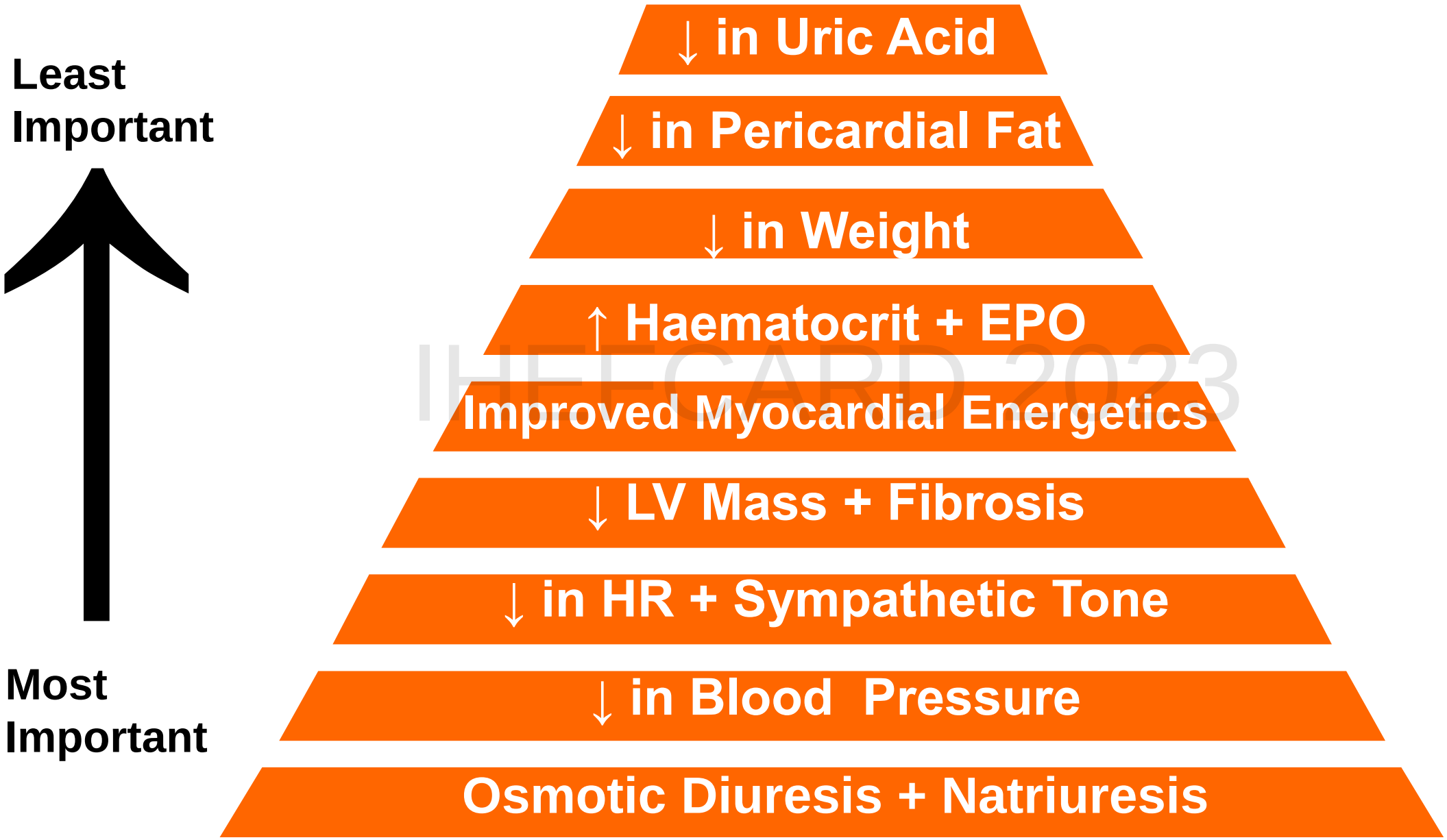



Lopaschuk and Verma

JACC: BASIC TO TRANSLATIONAL SCIENCE VOL. 5, NO. 6, 2020

JUNE 2020:632-44

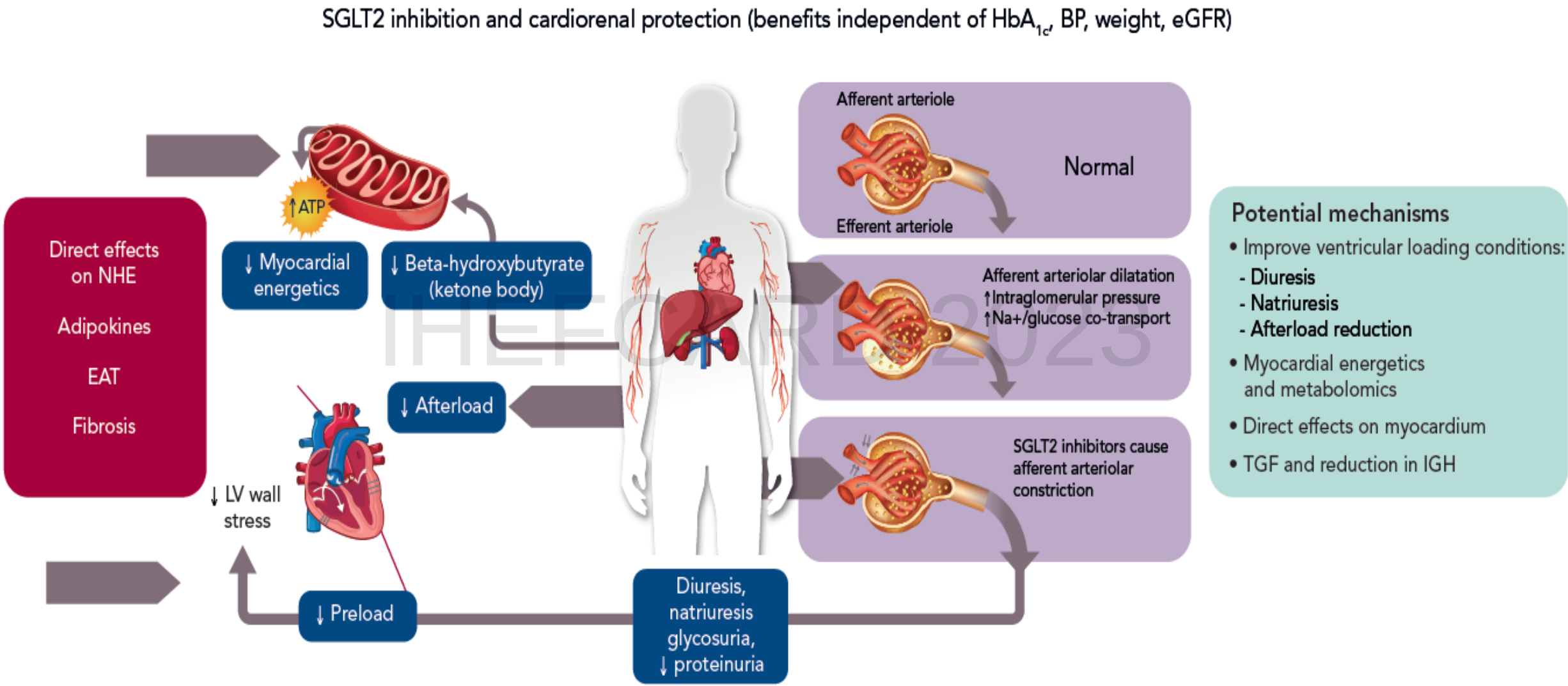
# Hierarchy of Potential Benefits of SGLT-2 Inhibitors in HF






Rasalam, R…Sindone AP 2022. ESC Heart Failure 2021;8:4093–4118

# Figure 3: Proposed Mechanism of Cardiovascular Benefits of SGLT2 Inhibitors




*ATP = adenosine triphosphate; BP = blood pressure; EAT = epicardial adipose tissue; eGFR = estimated glomerular filtration rate; IGH = intraglomerular hypertension; LV = left ventricular; NHE = sodium-hydrogen exchanger; SGLT2 = sodium–glucose co-transporter 2; TGF = tubuloglomerular feedback. Source: Verma et al. 2017.[37] Adapted with permission from the American Medical Association.*

# Thank you