
5th HEF CARD
The 5th Indonesian
Symposium on Heart Failure and
Cardiometabolic Disease
Indonesian Working Group
on Heart Failure
and Cardiometabolic Disease
WHFS
World Heart Failure Society
HEART FAILURE SOCIETY
(SINGAPORE)
Heart Failure in Cardio Renal Metabolic Syndrome:
Unraveling the Complexities of a Deadly Triad
Siti Elkana Nauli

Disclosures

- I have received grants, speaker fees or served on advisory boards for Boehringer Ingelheim,Astra Zeneca, Bayer, Menarini, Novartis, Servier, ZPT, Roche, Darya Varia, Otsuka, Pfizer, Merck

OUTLINES

- What do we learn from Cardio-Renal-Metabolic diseases in 2025
- Can we predict the presence of future heart failure in this diseases
- Where do we stand for heart failure prevention in Cardio-Renal-Metabolic diseases (is there any Diseases Modifying Treatment in this field?

APPETIZER

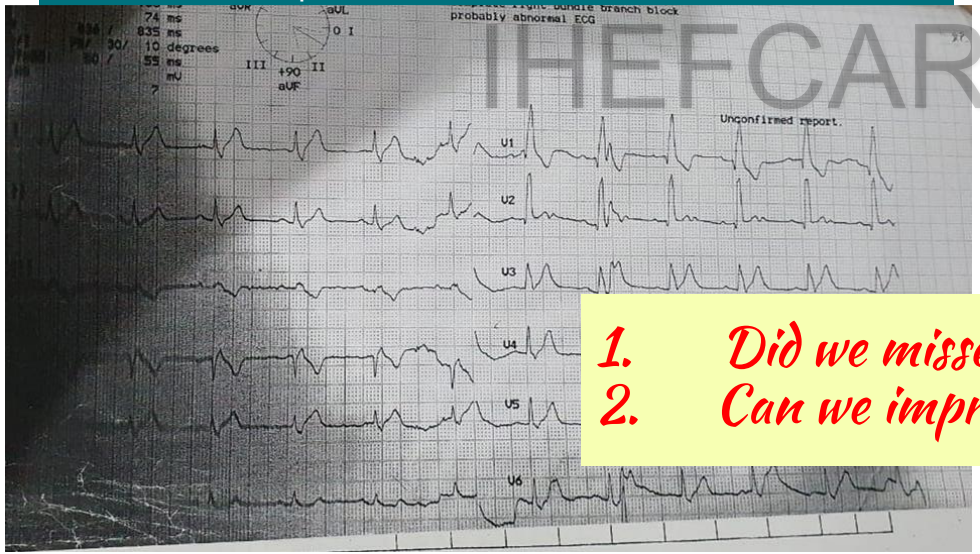
- 52 yo male with long standing T2DM and hypertension (th/amlodipine, glibenklamid)
- NSTEMI in 2019 : no PCI, 40% stenosis in LCx. Loss to follow up

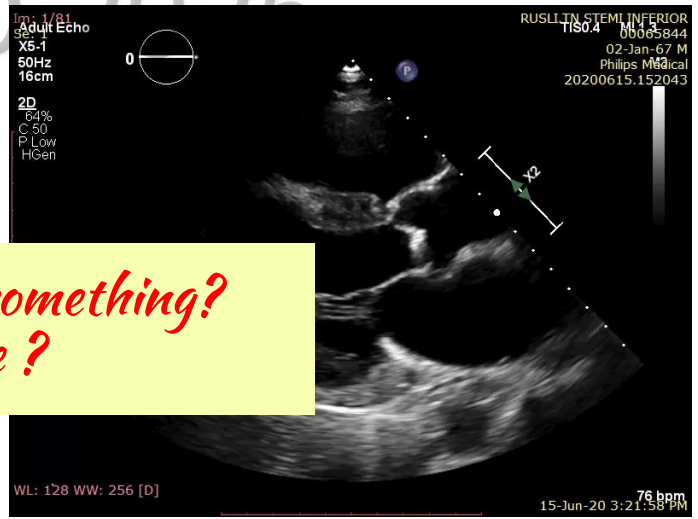
- Typical chest pain with Inferior STEMI, 2nd degree AVB, DKA, AKI
- Already felt hypesthesia
- A1C : 11,9%
- RBG 668 mg/dL, K 5,3/Cr 1.6

JUNE 2024

- LM normal
- LAD normal
- LCx : 50% stenosis in mid
- RCA total occlusion → PCI DES → TIMI 3 flow

→ Develop symptomatic HF 1 day after PCI





1. *Did we missed something?*
2. *Can we improve ?*

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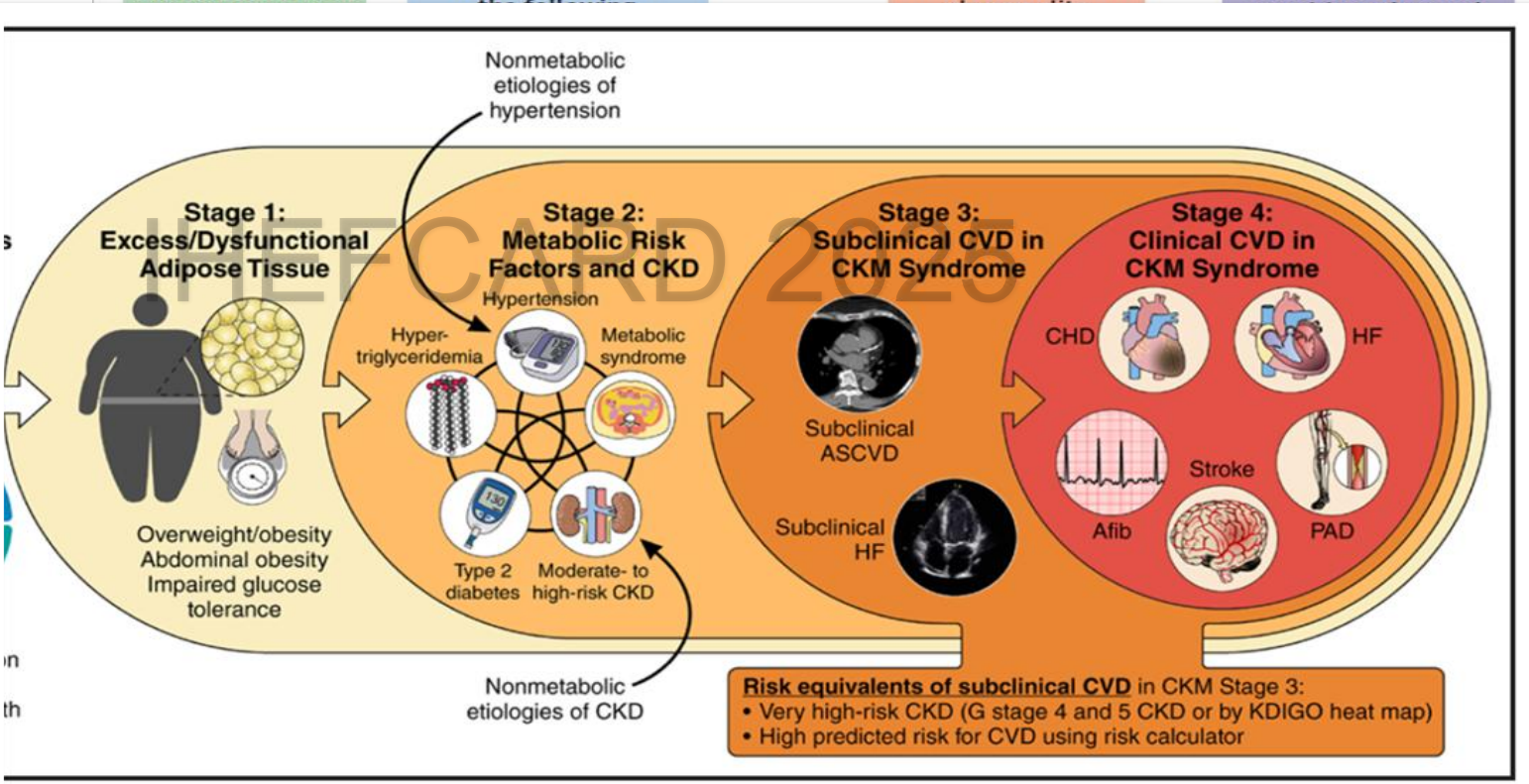
AT-RISK FOR HEART FAILURE (STAGE A)	PRE-HEART FAILURE (STAGE B)	HEART FAILURE (STAGE C)	ADVANCED HEART FAILURE (STAGE D)
Patients at risk for HF but without current or prior symptoms or signs of HF and without structural,	Patients without current or prior symptoms or signs of heart failure but evidence of one of	Patients with current or prior symptoms and/or signs of HF caused by structural and/or functional cardiac	Severe symptoms and/ or signs of HF at rest, recurrent hospitalizations despite GDMT, refractory or intolerant to GDMT

LEARNING H
HEART FAILU
and CKM
develop with
SIMILARITY



HOW DO OUR LIVES goes to HEART FAILURE

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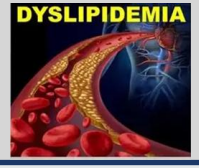
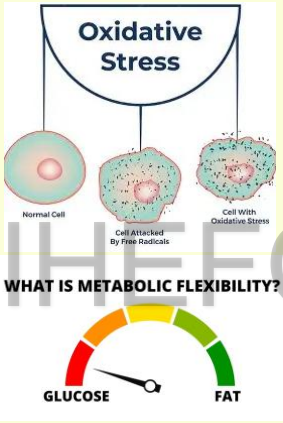
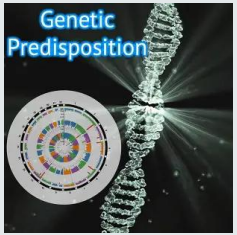
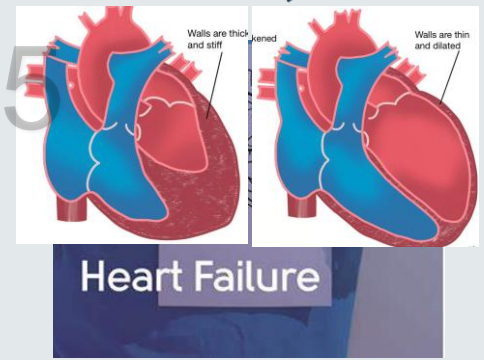
TRADITIONAL RISK FACTORS



ACCELERATED FACTORS

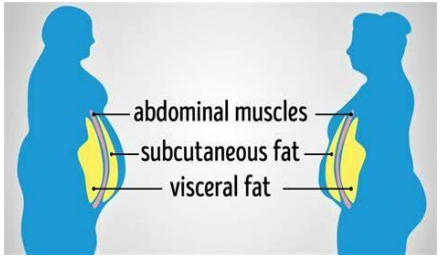






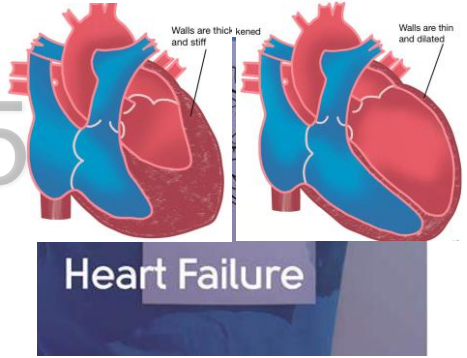
WHEN IT WAS STARTED

METABOLIC INFLEXIBILITY
(inability to rapidly adjust energy substrate utilization)



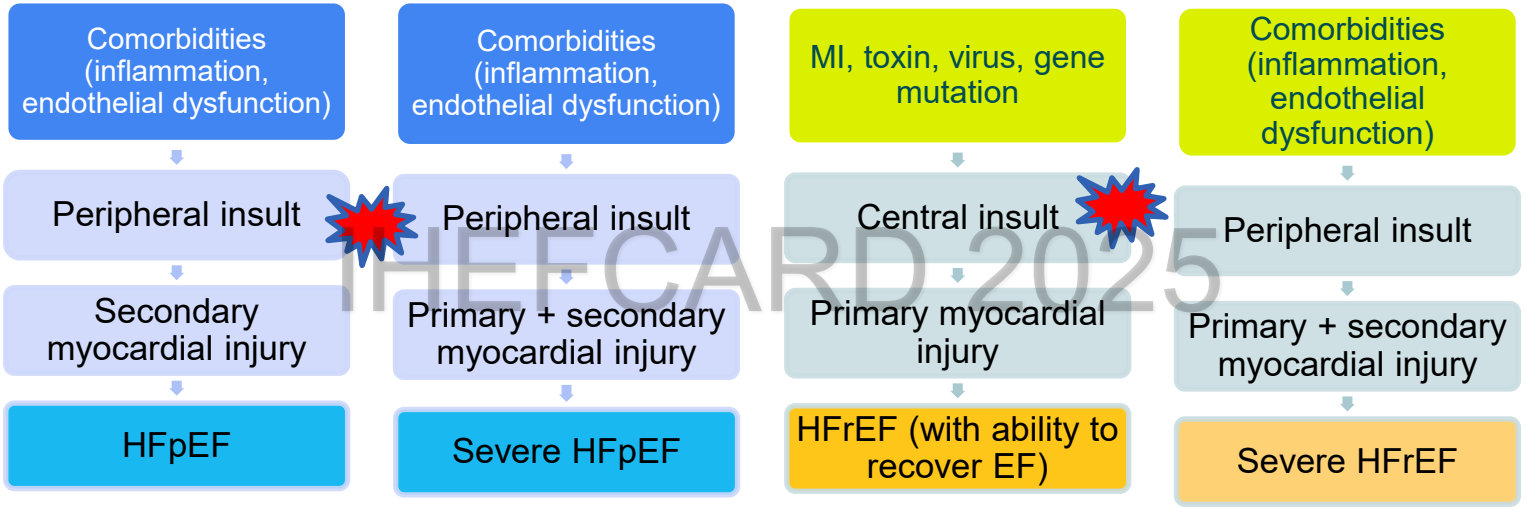
Hemodynamic
Metabolic
Inflammatory
Fibrotic

-proinflammatory products
-pro-oxidative products
-insulin resistance
-fat deposition : epicardium, pericardium



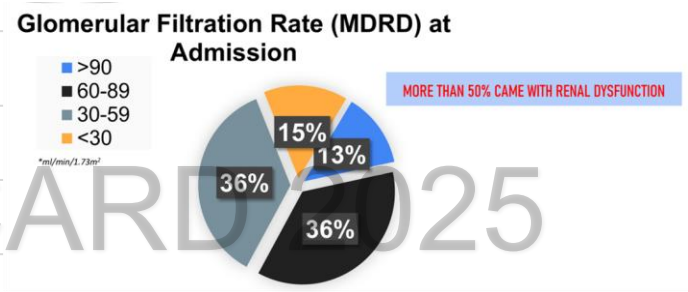
Endothelial dysfunction
Atherogenesis
Thrombosis
Myocardial injury
Fibrosis
Cardiac remodelling
Glomerular hyperfiltartion

LEARNING FROM HF PATHOPHISIOLOGY



- **PUMP DYSFUNCTION**
- **ENERGY UNDERUTILIZATION**
- **VALVULAR DYSFUNCTION**
- **ARRHYTHMIA**
- **THROMBOEMBOLISM**

- **CAD, Hypertension, dan T2DM more common as the etiology of HF**
- **High population attributable risk of hypertension and T2DM for the development of HF**



IF WE TALK ABOUT SYMPTOMATIC HF PROGNOSIS STILL POOR
BIG QUESTION : Can we improve ?

IMMEDIATE PREDICTION : understand the PROGNOSIS

DISEASES MODIFYING THERAPY (drugs)

Structural heart disease:
eg, LVH, chamber enlargement, wall motion abnormality, myocardial tissue abnormality, valvular heart disease

Abnormal cardiac function:
eg, reduced LV or RV ventricular systolic function, evidence of increased filling pressures or abnormal diastolic dysfunction

Elevated natriuretic peptide levels or elevated cardiac troponin levels in the setting of exposure to cardiotoxins

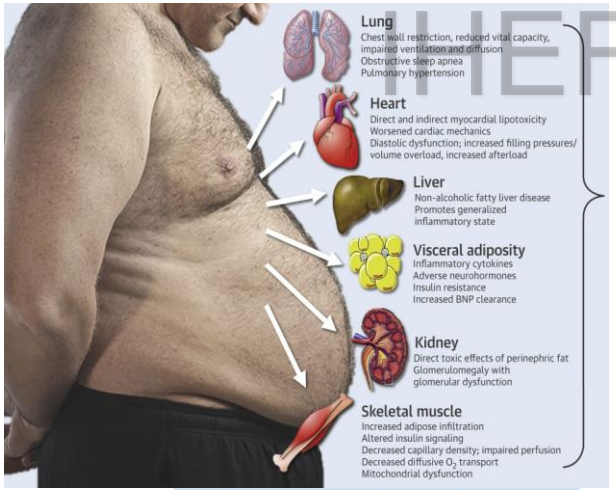
UNRECOGNIZED or SYMPTOMATIC HF = poor outcomes[1–3]

SUBCLINICAL HF
NTproBNP ≥ 300 pg/ml
Hs-Troponin T ≥ 22 ng/l (male) or ≥ 14 ng/l (female)
Hs-Troponin I ≥ 12 ng/l (male) or ≥ 10 ng/l (female)
Echo : LV hypertrophy, chamber enlargement, tissue deformity, diastolic dysfunction

EARLY RECOGNITION+IMMEDIATE PREDICTION

1. Van Riet EES *et al. Eur J Heart Fail.* 2014;16:772; 2. Bottle A *et al. Heart.* 2018;104:600; 3. Butler J *et al. J Am Coll Cardiol*. 2014;2:97; 4. Azad N *et al. J Geriatr Cardiol*. 2014;11:329; 5. Vasan R *et al. JACC Cardiovasc Imaging*. 2018;11:1; 6. Owan TE *et al. N Engl J Med*. 2006;355:251.

IMMEDIATE PREDICTION



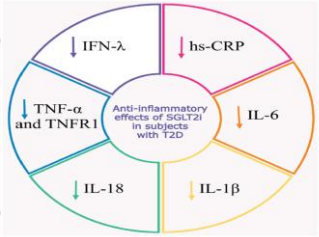
Albuminuria Predicts Risk of Incident HF

- **RENAAL Trial**
  ↑Albuminuria→↑2.7 x risk of incident HF
- **FHS Study**
  ↑Albuminuria→↑1.7 x risk of incident HF
- **MESA Study**
  ↑Albuminuria→↑2.7 x risk of incident HF
- **ARIC Study**
  ↑Albuminuria→↑2.5 x risk of incident HF

Kitzman D, Shah SJ. JACC 2016
Khan MS et al. (J Am Coll Cardiol 2023;81:270–282

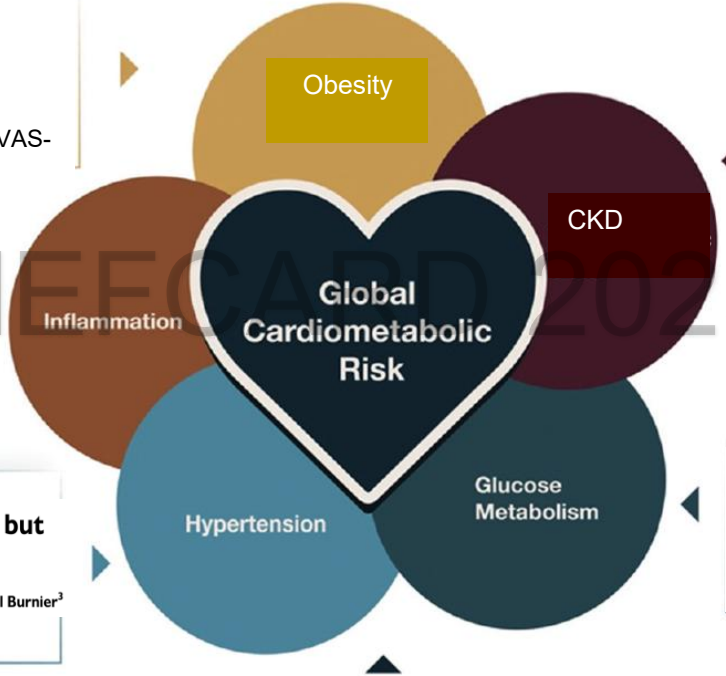
DISEASES MODIFYING THERAPY

GLP1 –RA
(SCALE, STEP, SELECT, SUSTAIN, SURMOUNT)
SGLT-2 inhibitor
(EMPAREG, DECLARE-TIMI 58, CANVAS-VERTIS)



SGLT2 inhibitors: not *for* hypertension but exceedingly useful *in* hypertension

Franz H. Messerli [1,*], Renate Schoenenberger-Berzins[2], and Michel Burnier[3]



SGLT-2 inhibitor
(EMPA-KIDNEY, DAPA-CKD, CREDENCE)
GLP1 –RA (in T2DM)
Non steroidal MRA
(FIDELIO, FIGARO)

SGLT-2 inhibitor
(EMPAREG, DECLARE-TIMI 58, CANVAS-VERTIS)
GLP1 –RA
(SELECT, SURMOUNT, LEADER)

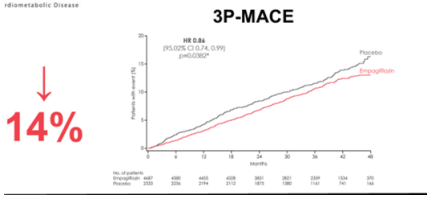
No Cardiometabolic Risk Factors that must be evaluated or treated to achieve an optimal **GLOBAL CARDIOMETABOLIC RESIDUAL RISK REDUCTION**
Tobacco (in any form). Sedentarism / Psicosocial stress/ Muscular strenght/Polution and smoke in home / Low fruits diet

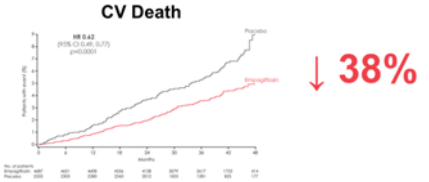
PREVENTION OF HEART FAILURE

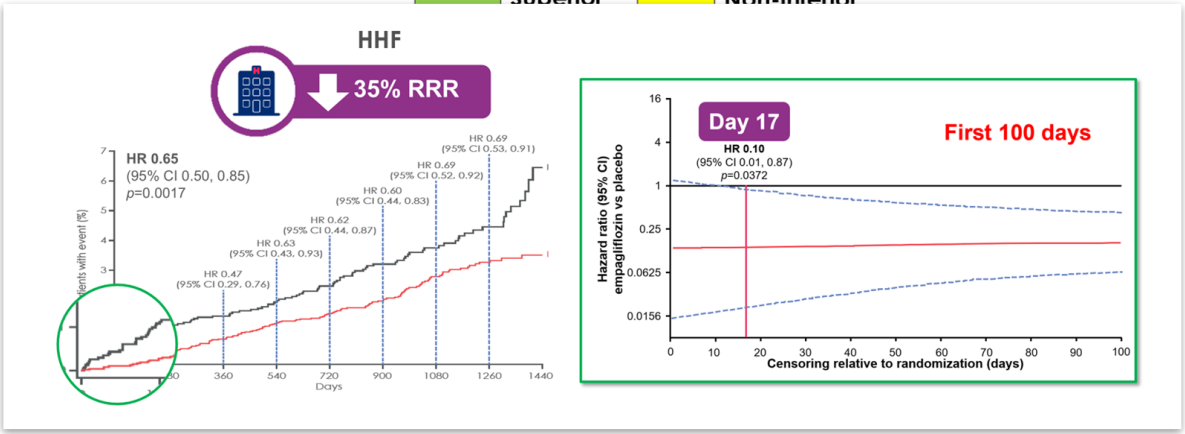
CV Outcomes in SGLT-2 Inhibitors CVOTs

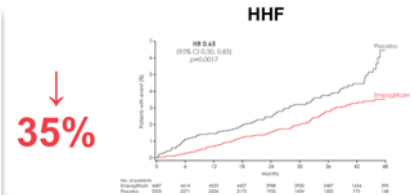
	3P-MACE	CV Death	HHF	All-cause mortality	Renal Endpoints
EMPA-REG Outcome (Empagliflozin)	HR 0.86 (0.74-0.99)	HR 0.62 (0.49-0.77)	HR 0.65 (0.50-0.85)	HR 0.68 (0.57-0.82)	HR 0.61 (0.53-0.70)
CANVAS Program (Canagliflozin)	HR 0.86 (0.75-0.97)	HR 0.87 (0.72-1.06)	HR 0.67 (0.52-0.87)	HR 0.87 (0.74-1.01)	HR 0.60 (0.47-0.77)
DECLARE-TIMI 58 (Dapagliflozin)	HR 0.93 (0.84-1.03)	HR 0.98 (0.82-1.17)	HR 0.73 (0.61-0.88)	HR 0.93 (0.82-1.04)	HR 0.53 (0.43-0.66)
VERTIS CV (Ertugliflozin)	HR 0.97 (0.85-1.11)	HR 0.92 (0.77-1.11)	HR 0.70 (0.54-0.90)	HR 0.93 (0.80-1.08)	HR 0.81 (0.63-1.04)

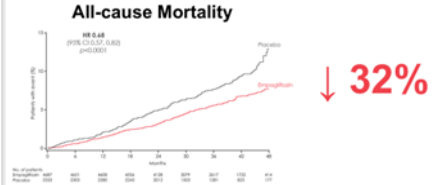
Superior Non-inferior



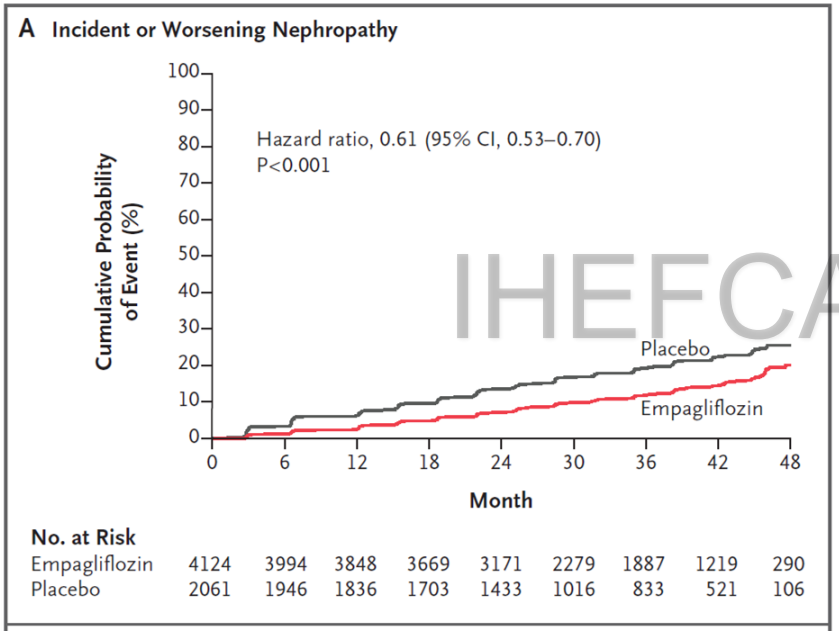


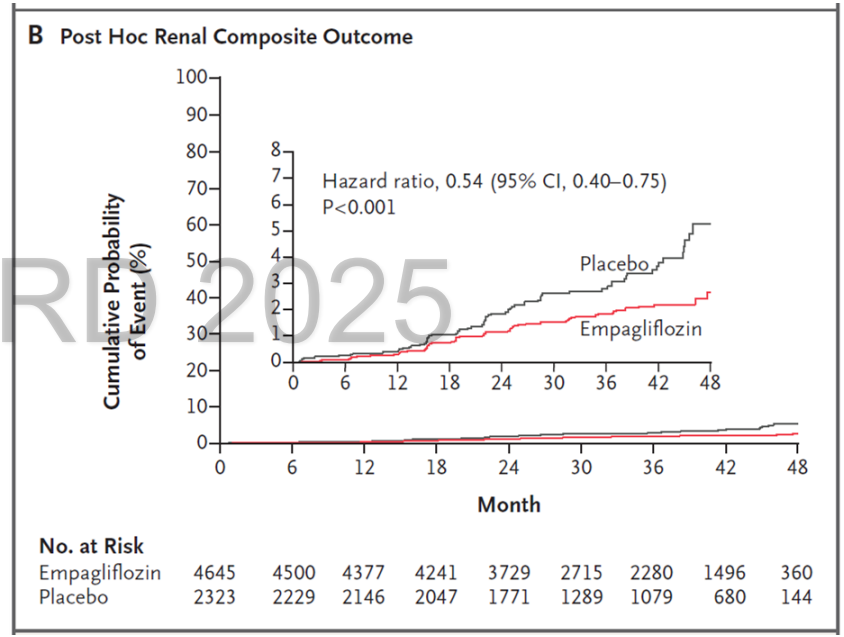






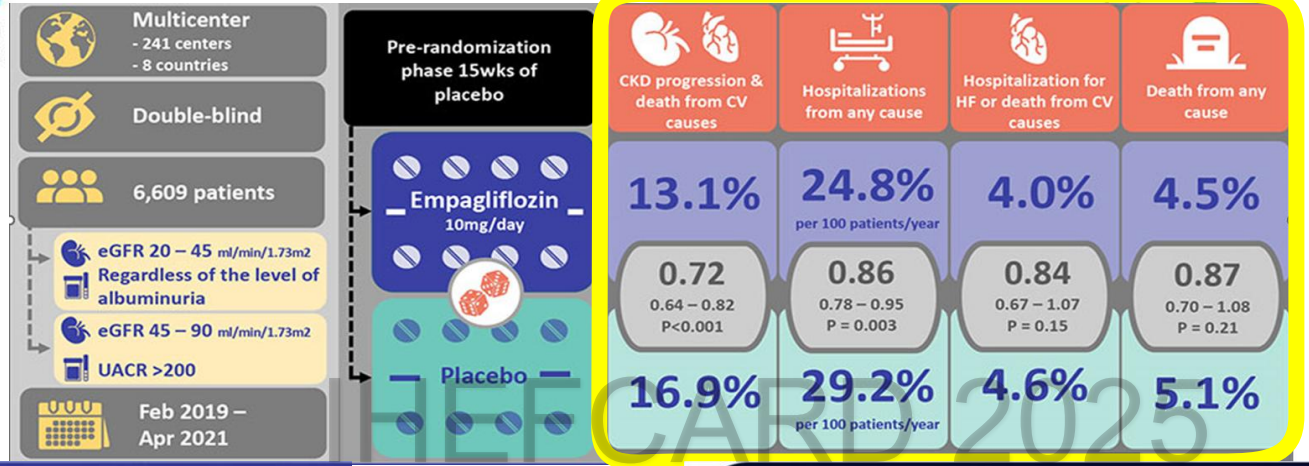
KIDNEY OUTCOMES FROM EMPAREG TRIAL



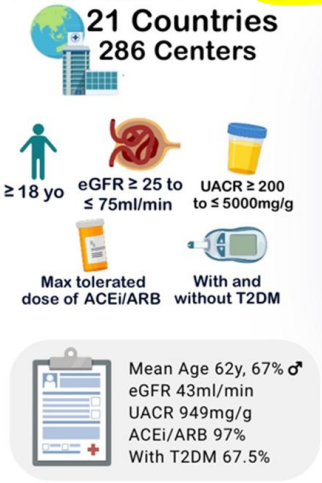


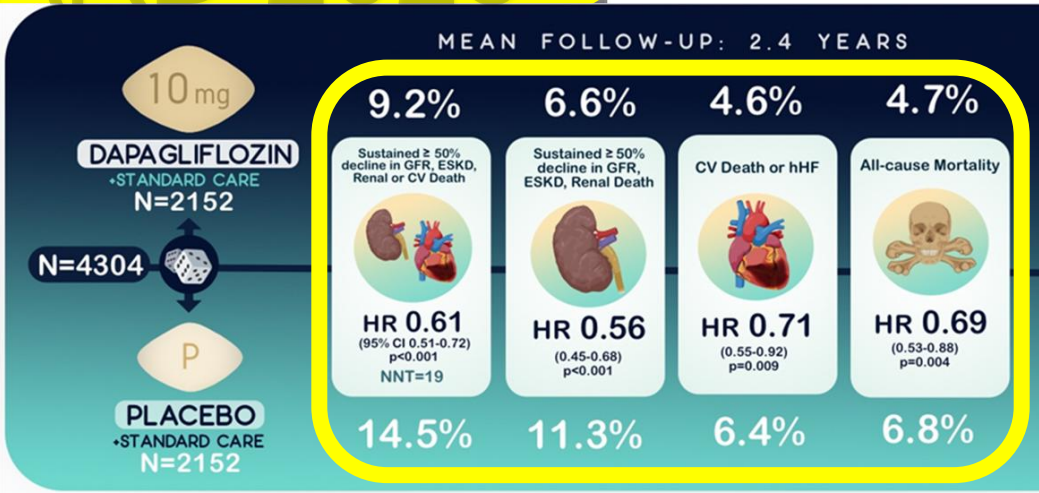
Wanner C, st al. N Engl J Med 2016;375:323-34.

KIDNEY OUTCOMES FROM NON DM TRIAL



Reference: EMPA-KIDNEY Collaborative Group. (2022). Empagliflozin in Patients with Chronic Kidney Disease. *New England Journal of Medicine*.





DAPA-CKD
Heerspink et al (2020). Dapagliflozin in Patients with Chronic Kidney Disease. *New England Journal of Medicine*. September 24,2020
DOI: 10.1056/NEJMoa2024816

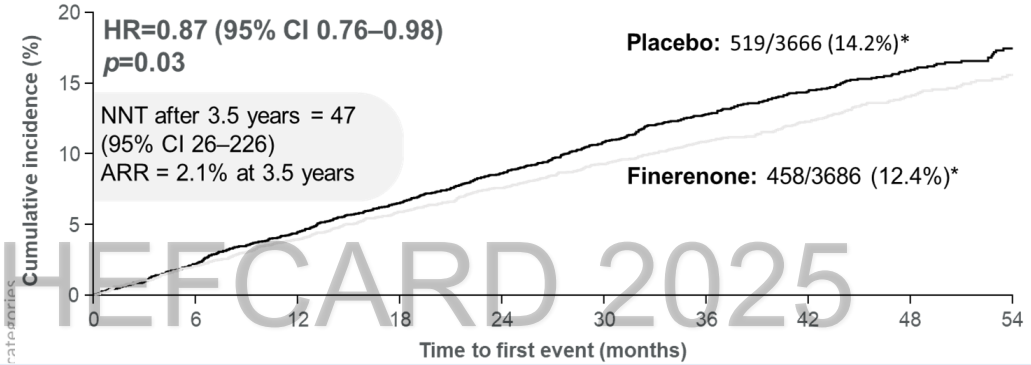
FIGARO-DKD included a broad patient population across early-to-late disease stages of CKD in T2D

Inclusion criteria

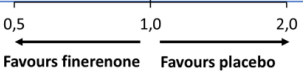
- T2D and CKD, defined as **either:**
  - UACR 30–300 mg/g and eGFR ≥25–≤90 ml/min/1.73 m² **or**
  - UACR ≥300–≤5000 mg/g and eGFR ≥60 ml/min/1.73 m²
- Treated with either an ACEi or an ARB at maximum tolerated dose
- Serum [K⁺] ≤4.8 mmol/l

Key exclusion criteria

- Non-diabetic kidney disease
- Uncontrolled hypertension*
- HbA1c >12%
- **Chronic symptomatic HFrEF#**
- Recent CV event‡
- Dialysis for acute kidney failure
- Kidney transplant

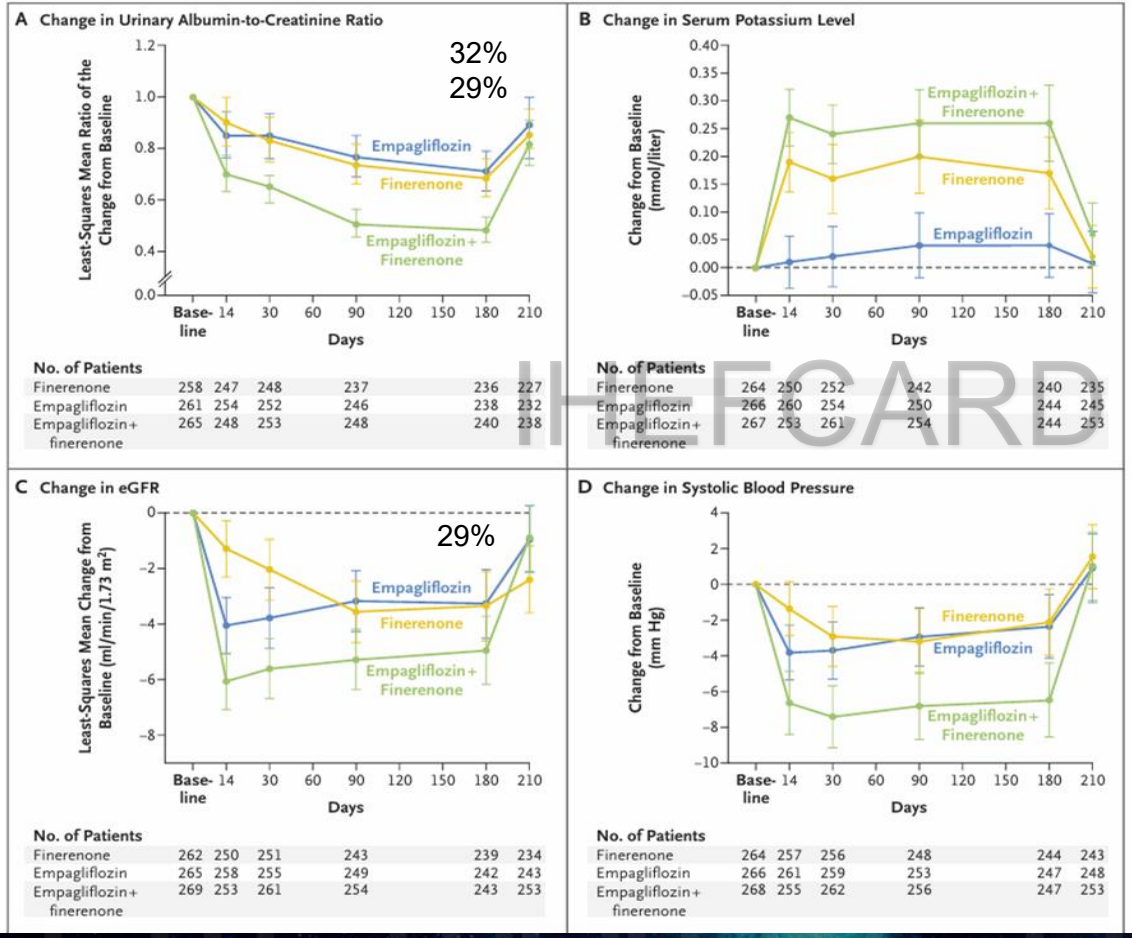


Outcome	Finerenone (n=3686) n (%)	Finerenone (n=3686) n/100 PY	Placebo (n=3666) n (%)	Placebo (n=3666) n/100 PY	HR (95% CI)	p-value
Primary composite CV outcome*	**458 (12.4)**	**3.87**	**519 (14.2)**	**4.45**	**0.87 (0.76–0.98)**	**0.03**
CV death	194 (5.3)	1.56	214 (5.8)	1.74	0.90 (0.74–1.09)	–
Non-fatal MI	103 (2.8)	0.85	102 (2.8)	0.85	0.99 (0.76–1.31)	–
Non-fatal stroke	108 (2.9)	0.89	111 (3.0)	0.92	0.97 (0.74–1.26)	–
Hospitalisation for HF	117 (3.2)	0.96	163 (4.4)	1.36	0.71 (0.56–0.90)	–



Pitt B, et al. **N Engl J Med 2021;385:2252-63.**

PREVENTION OF HEART FAILURE



CONFIDENCE Trial

ORIGINAL ARTICLE

Finerenone with Empagliflozin in Chronic Kidney Disease and Type 2 Diabetes

INCLUSION CRITERIA

-T2DM

-A1C< 11

-GFR 30-90 ml/min/1,73 m2

-UACR 100-5000

Agarwal R, et al. DOI: 10.1056/NEJMoa2410659

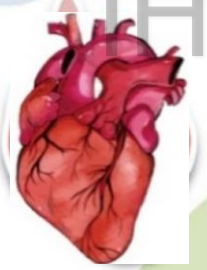
WHEN WE TALK ABOUT SGLT2 inhibitor IN 2025

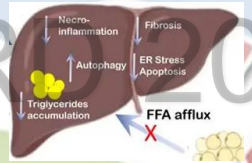
- Reduce oxidative stress
- Enhance contractility
- Normalize mitochondrial function
- Reduce cardiomyopathy
- Reduce coronary microvascular damage

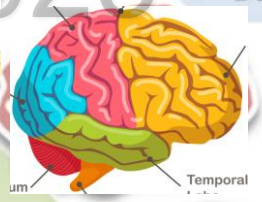
- Reduce albuminuria
- Reduce tubular injuries
- Suppress ROS generation
- Reduce renal interstitial inflammation and fibrosis
- Optimize endothelial function
- Improve mitochondrial function

- Normalize liver enzymes
- Ameliorate fat deposition
- Attenuate fibrosis
- Reduce oxidative stress
- Enhance antioxidant capacities
- Reduce inflammation

- Attenuate cerebral oxidative stress
- Improve cognitive function
- Reduce infarct size
- Improve motor function
- Reduced senile plaque density and amyloid β
- Decrease seizure activity



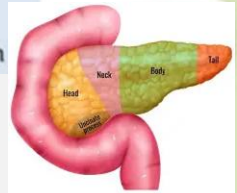


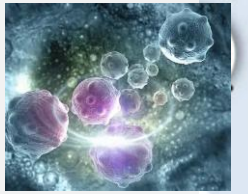


SGLT2 inhibitors

Oxidative Stress

- Better glucose control
- Reduce insulin resistance
- Optimize hemodynamic effects
- Lowering free radical generation
- Enhance antioxidant capacity





- Reduce free radical production
- Inhibit tumor neovascularization
- Attenuate oncogenic inflammation
- Inhibit tumor cell proliferation

TAKE HOME MESSAGES

KEY FOR UNDERSTANDING CARDIO-KIDNEY-METABOLIC SYNDROME :

1. Prevention is MANDATORY despite new technology in HF treatment
2. Know your patient profile (*metabolic-renal-cardiac) :* SCORING system, UACR, biomarker (NTproBNP, Trop), Calsium score provide DISEASES MODIFYING THERAPY : SGLT2-inh, GLP1-RA, NS-MRA, Statin, RAS-inh
3. CVD and kidney diseases are currently treated as separate health conditions should be terminated

WHEN HEART FAILURE DEVELOPED

1. Good sequencing treatment : RAS inh+beta blocker+MRA+SGLT2inh
2. Rapid titration (6 weeks) : STRONG HF Provide early benefit on mortality and HHF
3. Tight monitoring for renal and electrolyte, seek for comorbidities & good decongestion (PUSH AHF, combination) is keys to STRONG HF

WHEN WE TALK ABOUT SGLT-2 inhibitor : Start early in population with T2DM, Albuminuria, CKD, Heart Failure (eGFR ≥ 20ml/min/1.73m2) to get early benefit for CKM connection

Empagliflozin is A DISEASE MODIFYING DRUG improve mortality and heart failure hospitalization outcome in T2DM, CKD; prevent kidney damage progression, with good safety profile and cost effective