CHFS & JACC HF Plenary Session

Heart - Kidney Interactions:
Convergence of Mechanisms of Disease, Therapeutics, and Care Pathways

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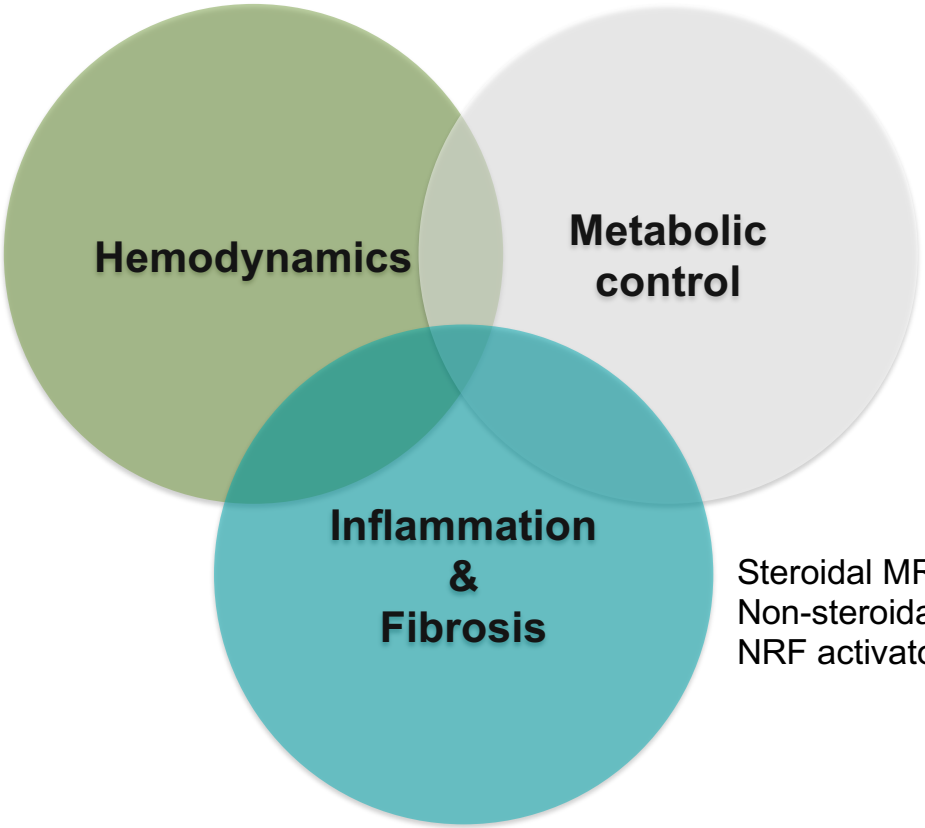
Disclosures: Amgen, American Regent, AstraZeneca, Baxter Healthcare, Bayer AG, Boehringer Ingelheim, Cytokinetics, Impulse Dynamics, Galmed, Lexicon Pharmaceuticals, Novartis, Occlutech, Pharmacosmos, Relypsa, Roche Diagnostics, and Sanofi

#1) Intersecting Mechanistic Pathways for CV and Kidney Disease Progression

ACE inhibitors
ARBs

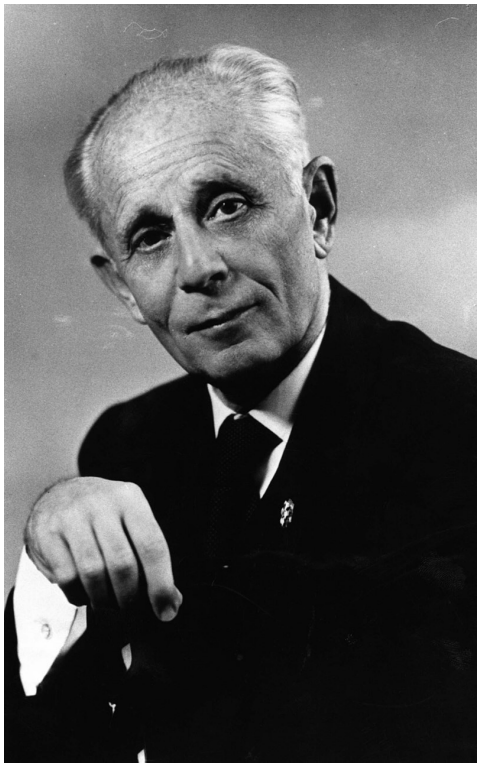


SGLT2 inhibitors
(among other mechanisms)

Steroidal MRA: spironolactone, epleronone
Non-steroidal MRA: finerenone, esaxerenone
NRF activators: bardoxolone

- Kolkhof P, et al. *Mol Cell Endocrinol*. 2012;350:310–317; Kolkhof P, et al. *J Endocrinol*. 2017;234:T125-T140.

MR Overactivation as a Central Driver of Inflammation and Fibrosis in the Heart and Kidneys



Hans Selye, 1907-1982,
Born Vienna, Austria-Hungary
Source: Wikipedia

MALIGNANT HYPERTENSION
PRODUCED BY TREATMENT WITH
DESOXYCORTICOSTERONE ACETATE
AND SODIUM CHLORIDE*

By Hans Selye, M.D., Ph.D., D.Sc., F.R.S.C.,
C. E. Hall,† M.Sc. and E. M. Rowley, B.Sc.

Montreal

- Selye H, et al. *Can Med Assoc J*. 1943;49:88-92.

#2) CKD is a Powerful Driver of HF Events, and Vice Versa

UACR Top Predictor of HF Events in TRS-HFDM HF Risk Prediction Model

Table 2. TRS-HF_{DM} in the Derivation Cohort (Table view)

Risk Indicator	Adjusted HR (95% CI)	*P* Value	Points
Prior heart failure	4.22 (3.18–5.59)	<0.001	2
Atrial fibrillation	2.26 (1.62–3.14)	<0.001	1
Coronary artery disease	2.06 (1.45–2.93)	<0.001	1
eGFR <60 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$	1.85 (1.40–2.46)	<0.001	1
Urine albumin-to-creatinine ratio			
>300 mg/g	4.50 (3.18–6.36)	<0.001	2
30–300 mg/g	2.08 (1.50–2.87)	<0.001	1

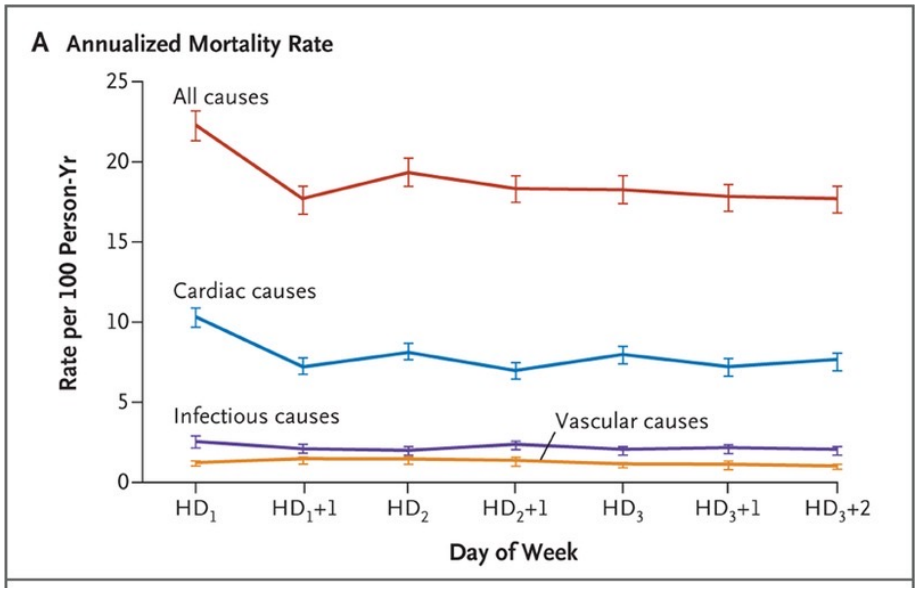
- Berg DD et al. Circ 2019

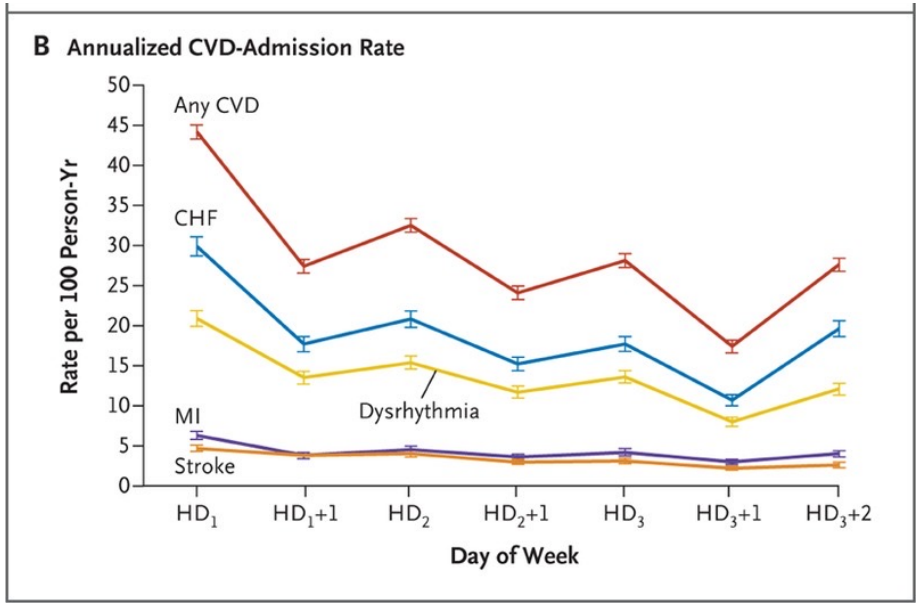
Longer Interdialytic Interval in ESKD Linked with Excess HF Events

ORIGINAL ARTICLE

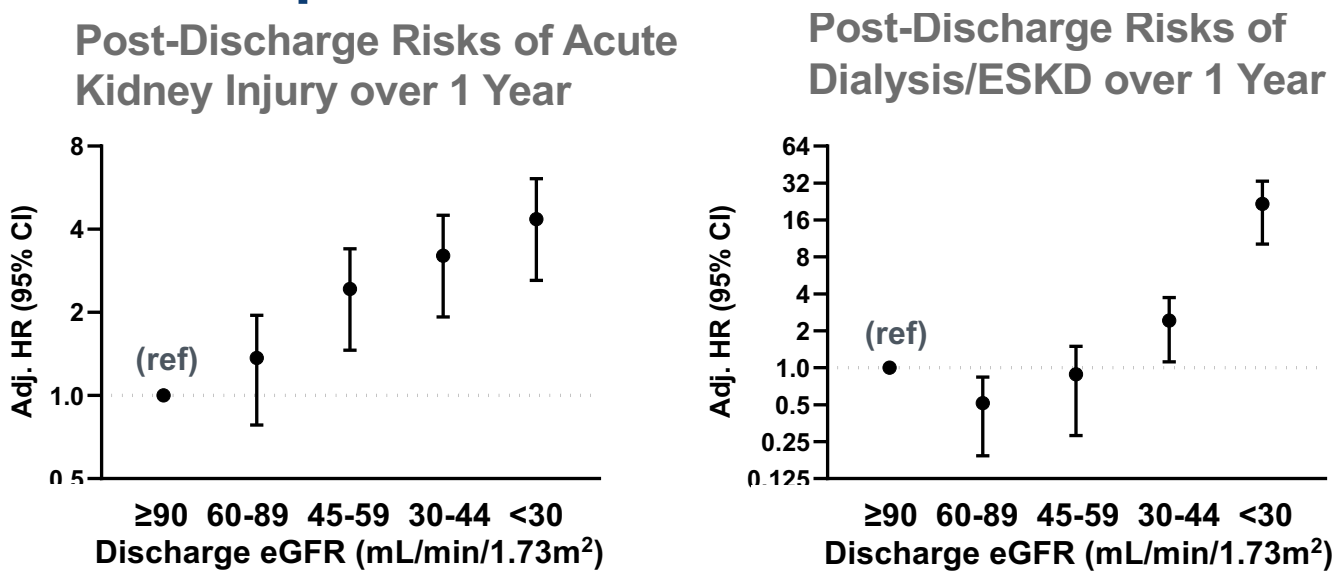
Long Interdialytic Interval and Mortality among Patients Receiving Hemodialysis

Robert N. Foley, M.B., David T. Gilbertson, Ph.D., Thomas Murray, M.S., and Allan J. Collins, M.D.





Post-Discharge Risks of AKI and Dialysis after Hospitalization for HF

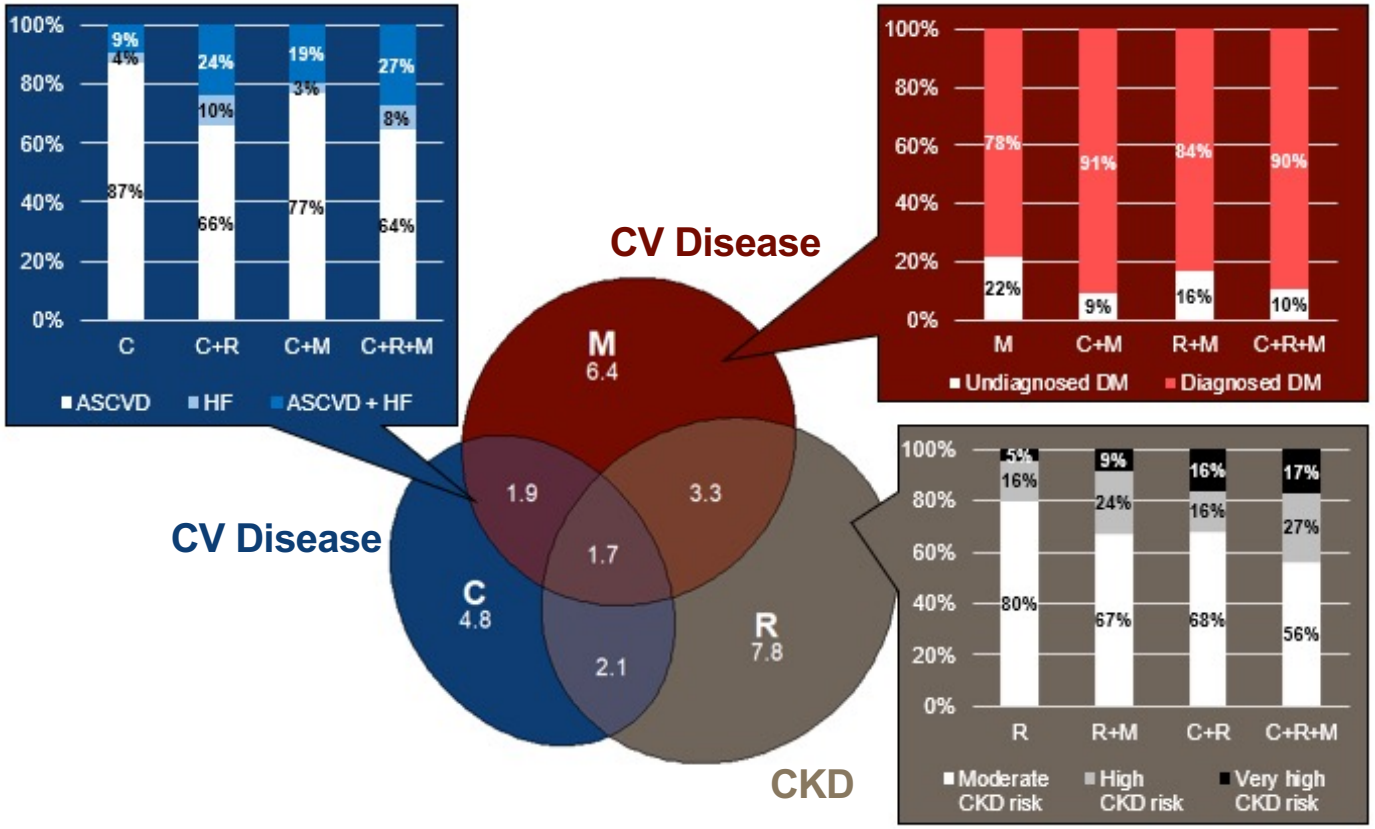


By 1-year, 7% of patients had been readmitted for AKI and 5% for dialysis/ESKD

Lower discharge eGFR (per 10 mL/min/1.73 m^2 decrease) was independently associated with increased readmission for AKI (adjusted HR 1.20[1.15-1.25]) and progression to dialysis/ESKD (adjusted HR 2.22 [1.93-2.55])

Vaduganathan M et al. In Development

#3) Frequent Overlap of Cardio-Renal-Metabolic Conditions



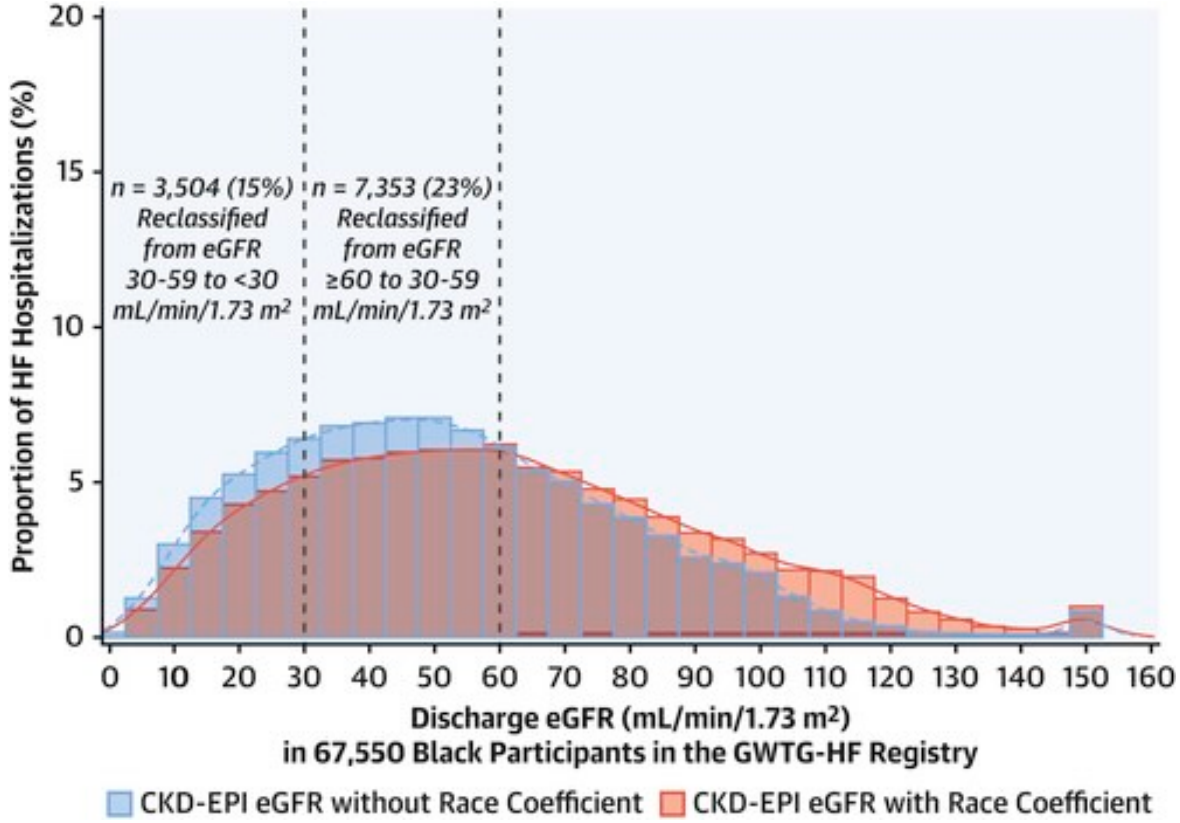
NHANES Data (2015-2020)

<u>Age <65 years</u>
CKD+T2D is the most frequent dyad in younger and middle-aged individuals

<u>Age ≥65 years</u>
CKD+CVD is most common in older people.

- Ostrominski JW et al. In Development

New Race-Free eGFR Calculators Expand Prevalence of CKD in Black Individuals

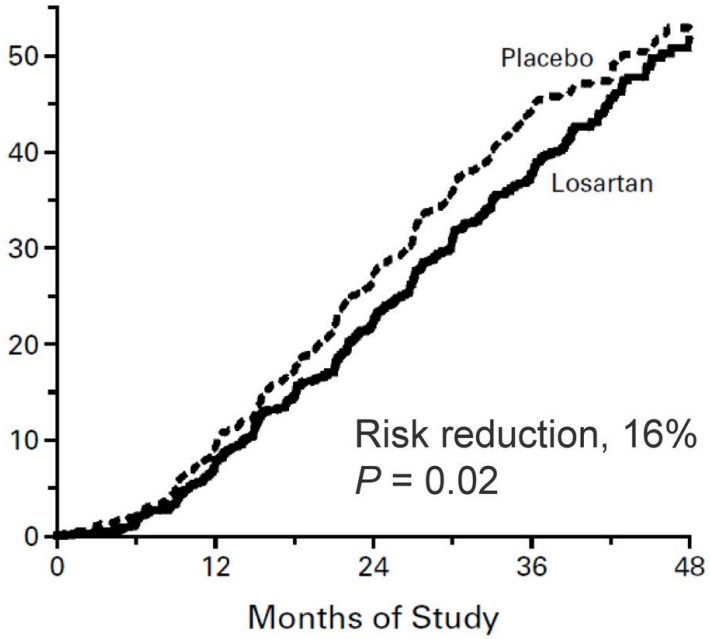


- Patel RB et al. JACC 2021

#4) Therapies to Treat One Disease Prevent New Diagnosis of the Other

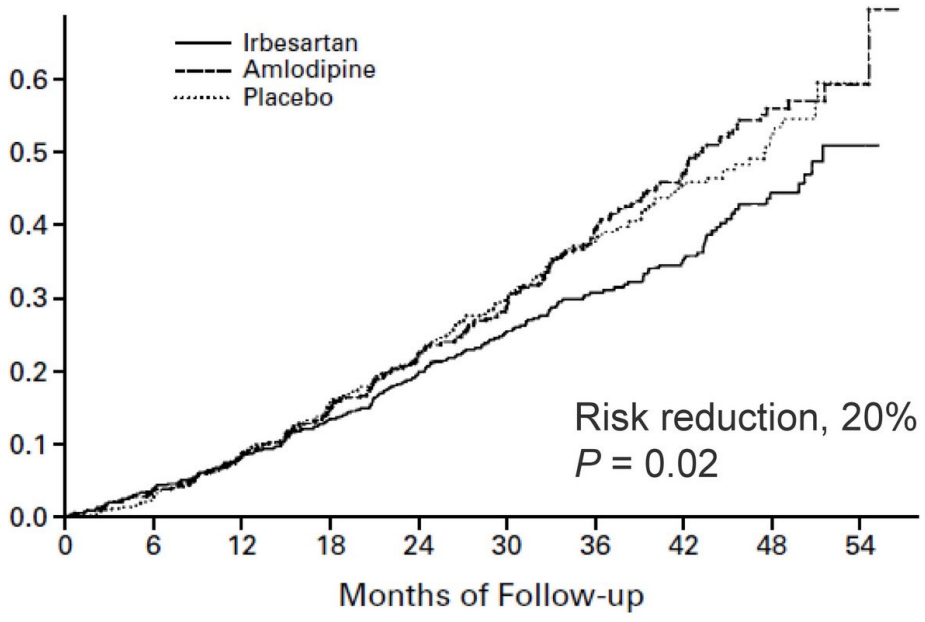
Doubling of serum creatinine, ESKD, or death

RENAAL



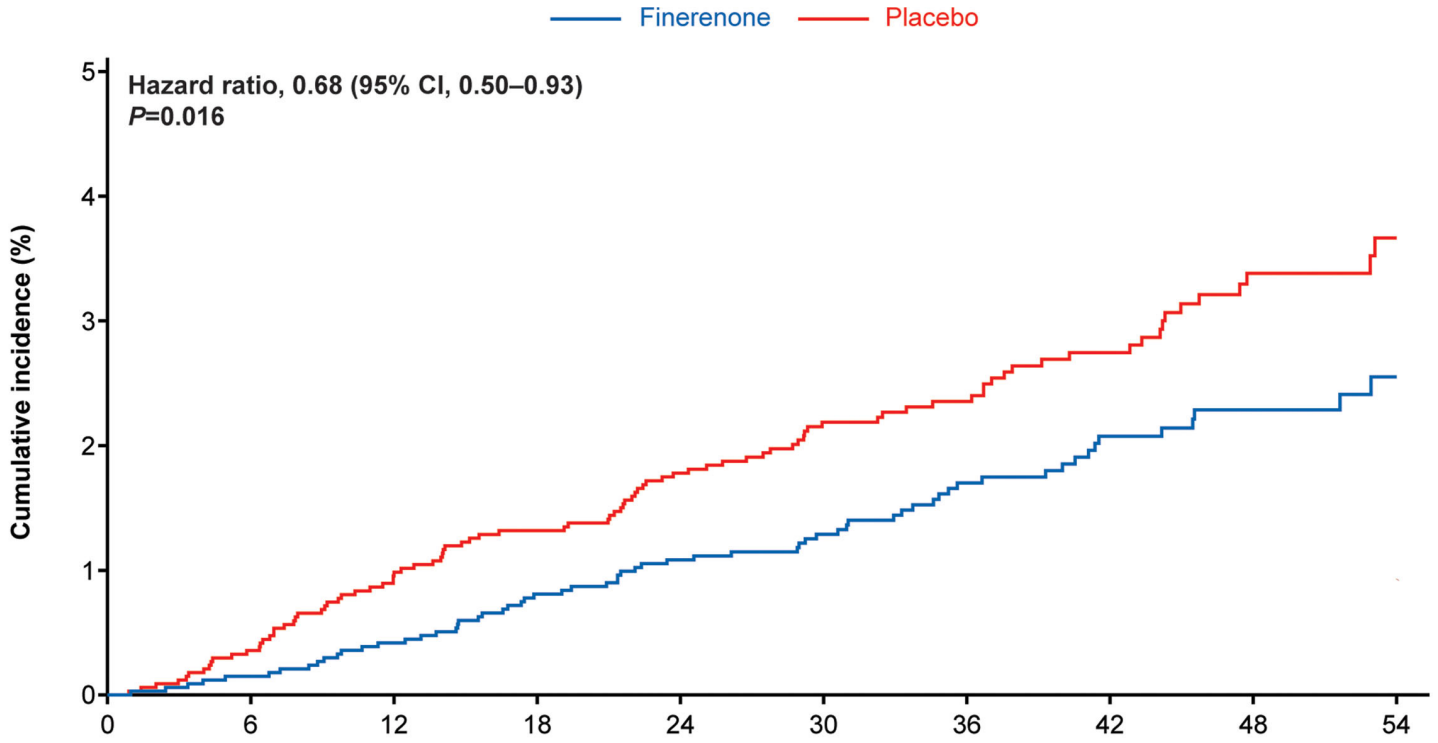
Brenner B, et al. *N Engl J Med*. 2001;345(12):861-869.

IDNT



Lewis EJ, et al. *N Eng J Med*. 2001;345(12):851-860.

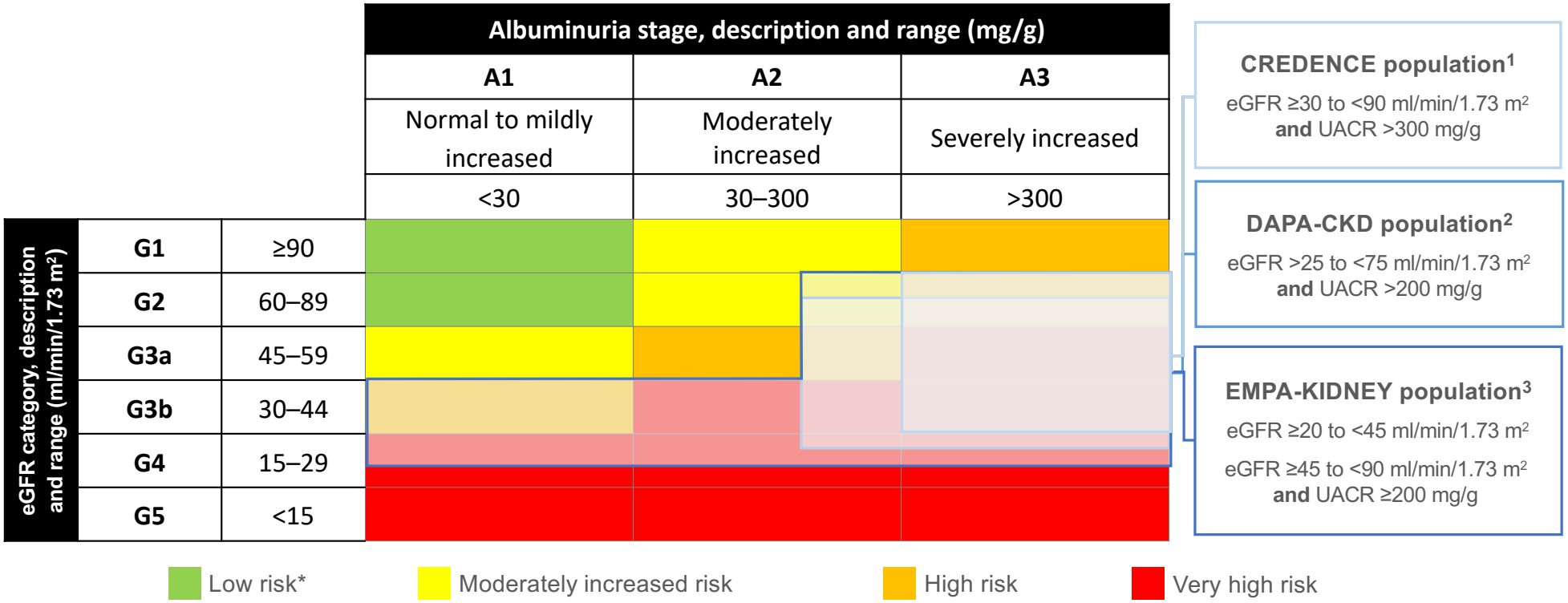
Non-Steroidal MRA Finerenone Reduces Incident HF in Diabetic Kidney Disease



No. at risk										
Finerenone	3396	3367	3323	3274	3195	2710	2168	1705	1091	608
Placebo	3385	3351	3294	3236	3154	2694	2131	1674	1091	606

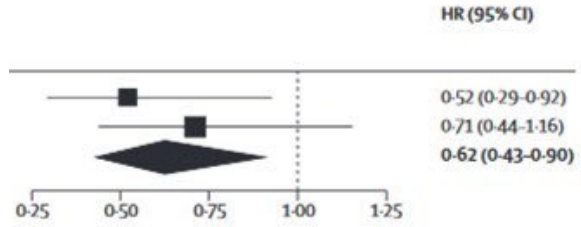
Filippatos G et al. Circ 2022

SGLT2i Reduce HF Risk across the Spectrum of CKD



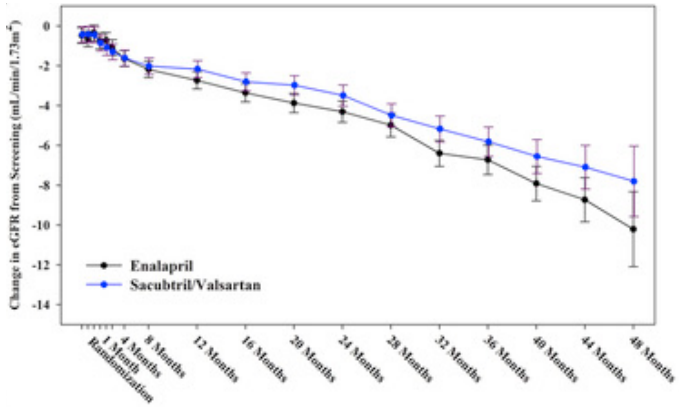
Adapted from Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. *Kidney Int Suppl* 2013;3:1
*If no other markers of kidney disease, no CKD
CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; UACR, urine albumin-to-creatinine ratio
1. Jardine MJ *et al. Am J Nephrol* 2017;46:462; 2. ClinicalTrials.gov. NCT03036150 (accessed April 2019); 3. ClinicalTrials.gov. NCT03594110 (accessed April 2019)

Newer HF Therapies Slow Kidney Disease Progression



38% ↓ Kidney Outcomes with SGLT2i

(Zannad F et al. *Lancet* 2020)



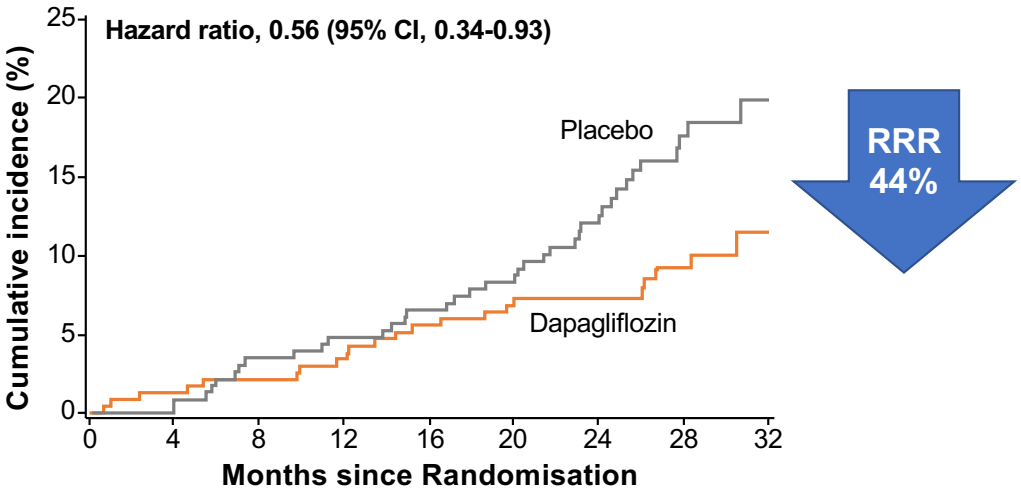
Slower eGFR Decline with ARNI

(Damman K et al. *JACC HF* 2018)

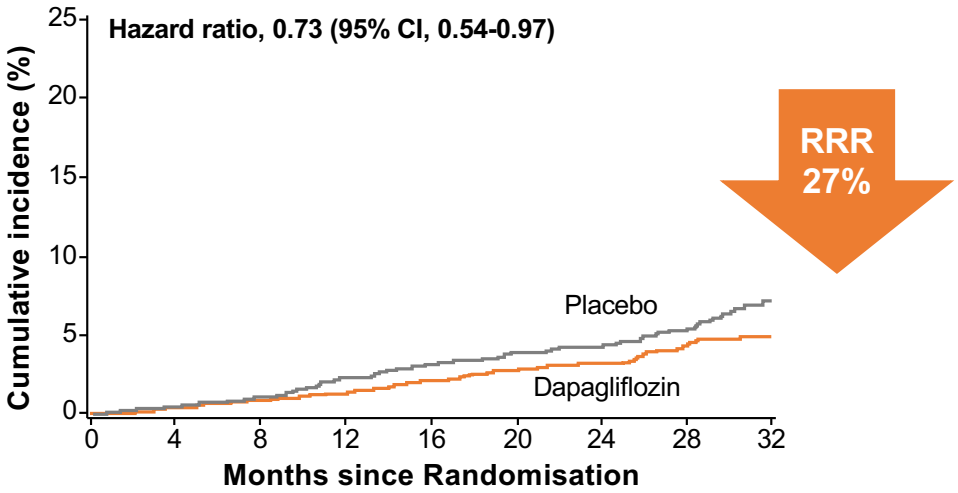
Recent therapies in HF have been shown to slow kidney disease progression

DAPA-CKD: dapagliflozin reduced the risk of all-cause mortality in patients with both CKD and HF

Patients with CKD and HF



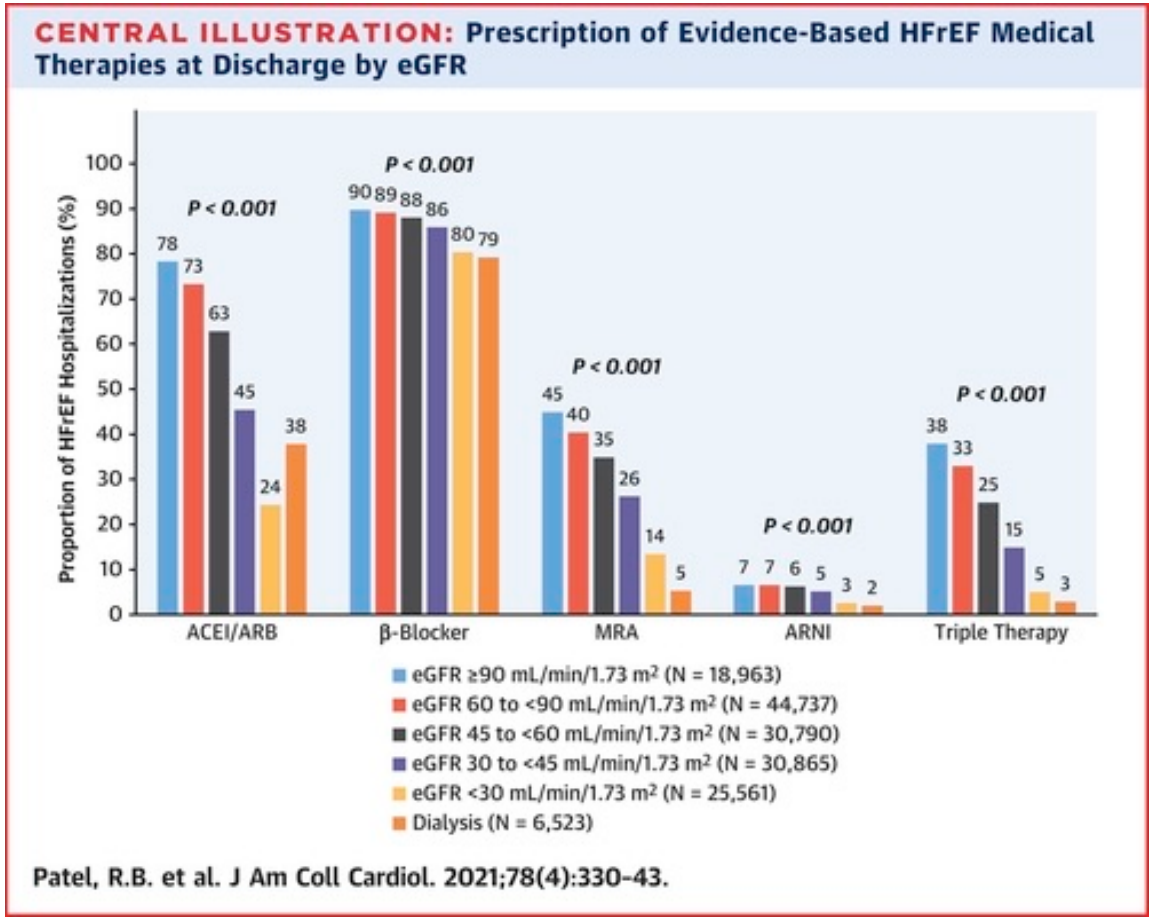
Patients with CKD and no HF



CI, confidence interval; CKD, chronic kidney disease HF; heart failure; HR, hazard ratio; RRR, relative risk reduction

McMurray J et al. *JACC Heart Fail* 2021,9:807–820

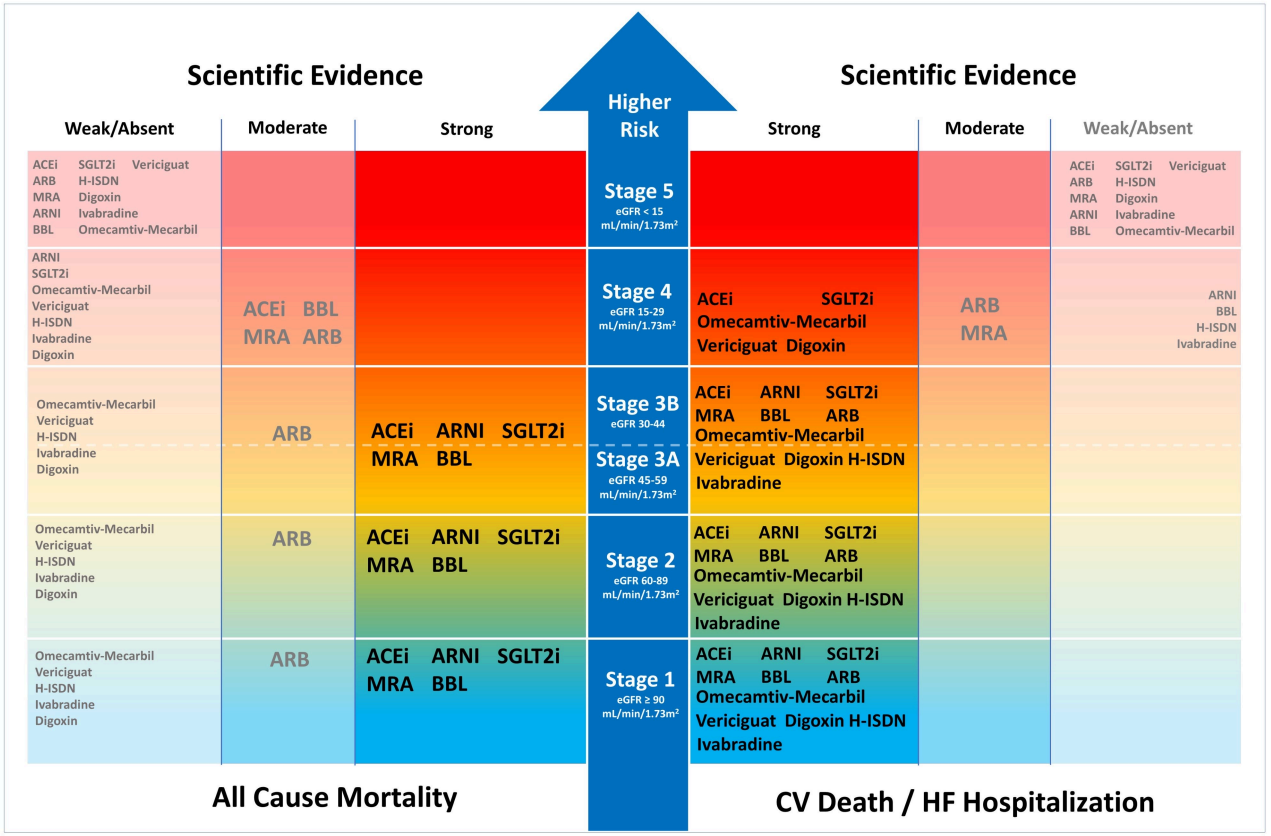
The Risk-Treatment Paradox in HF&CKD



Patel, R.B. et al. J Am Coll Cardiol. 2021;78(4):330-43.

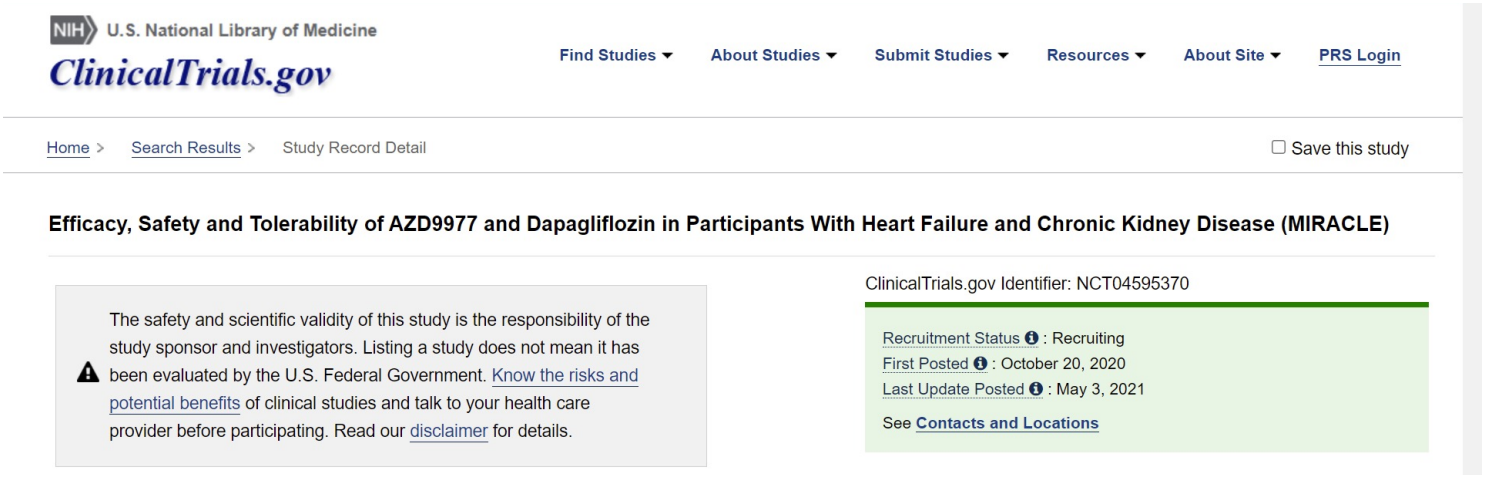
Patients with comorbid HF & CKD face high risks of in-hospital mortality, but are less likely to be treated with evidence-based medical therapies

Limited Evidence-Based Strategies Available to Attenuate Risk in HF and Advanced CKD



Beldhuis I et al. Circ 2022

Dedicated Trials of HF + CKD Overlap: MIRACLE



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Save this study

Efficacy, Safety and Tolerability of AZD9977 and Dapagliflozin in Participants With Heart Failure and Chronic Kidney Disease (MIRACLE)

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT04595370

Recruitment Status : Recruiting
First Posted : October 20, 2020
Last Update Posted : May 3, 2021

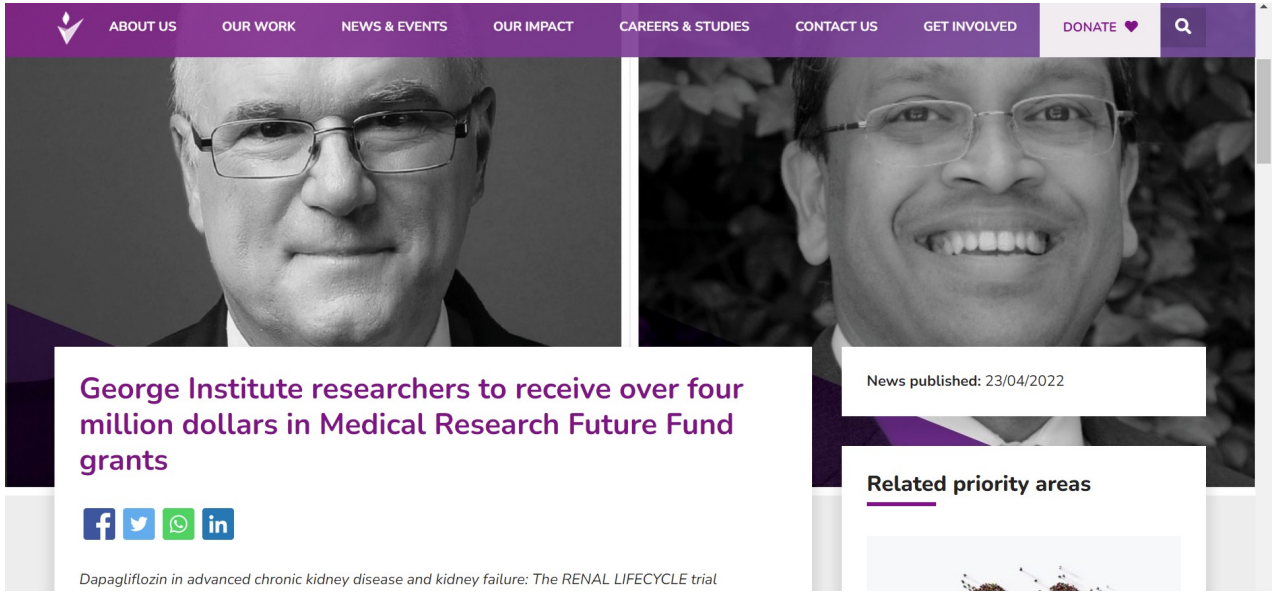
See Contacts and Locations

n=500; follow-up over 12 weeks

- **AZD9977 Dose A + dapagliflozin 10 mg**
- **AZD9977 Dose B + dapagliflozin 10 mg**
- **AZD9977 Dose C + dapagliflozin 10 mg**
- **Dapagliflozin 10 mg**

SGLT2i Being Studied in Advanced CKD or Kidney Failure: The RENAL LIFECYCLE Trial

- **Global, investigator-initiated randomized trial**
- **n=1,750**
- **Primary outcome: Death, HF, or Kidney Failure**



#5) New Care Pathways in Cardio-Renal-Metabolic Care: Combination Medical Therapy

CKD

"Triple Therapy"

- ACEi/ARB
- *Non-Steroidal* MRA
- SGLT-2 Inhibitor
- Endothelin receptor antagonist
- GLP-1RA

HFrEF & HFmrEF

"Quadruple Therapy"

- β-blocker
- ACEi/ARB/ARNI
- *Steroidal* MRA
- SGLT-2 Inhibitor

#5) New Care Pathways in Cardio-Renal-Metabolic Care: Combination Medical Therapy

Circulation: Cardiovascular Quality and Outcomes
Volume 13, Issue 11, November 2020
https://doi.org/10.1161/CIRCOUTCOMES.120.007264

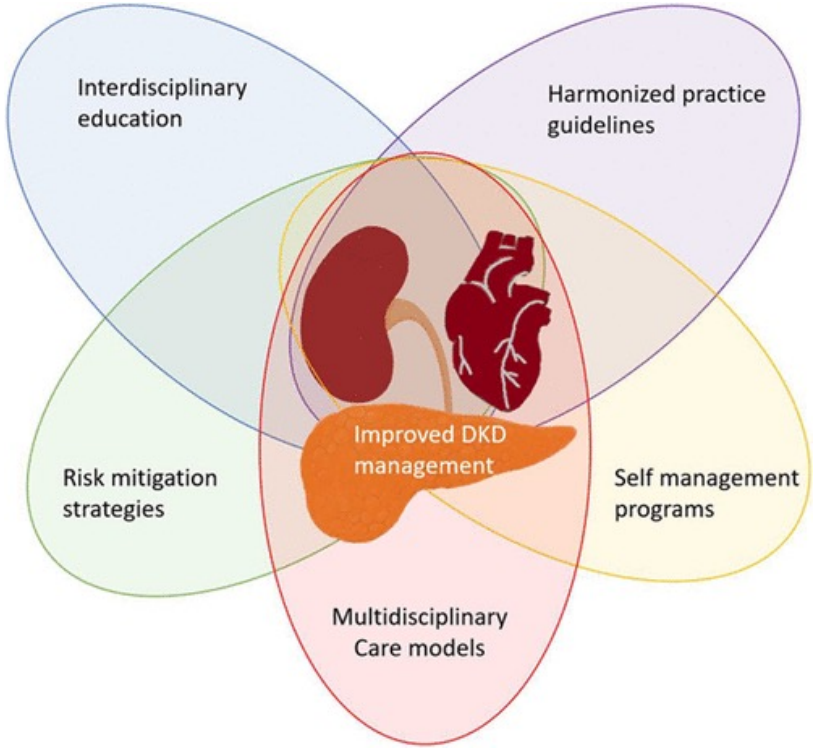
American Heart Association.

CARDIOVASCULAR PERSPECTIVE

Cardio-Renal-Metabolic Care Models

Toward Achieving Effective Interdisciplinary Care

Janani Rangaswami, MD , Katherine Tuttle, MD, and Muthiah Vaduganathan, MD, MPH



Heart - Kidney Interactions
Presented by Muthu Vaduganathan

- HF and CKD share common mechanistic pathways for CV and kidney disease progression
- Worsening disease status of one condition forecasts heightened risk of exacerbation of the other
- HF and CKD are highly overlapping in clinical practice
- Common therapies have been shown to be efficacious in the management of many patients with HF and CKD
- Current evidence base and care strategies are limited for those with advanced CKD (but that is changing!)