



Empowering hospitalists.
Transforming patient care.

Heart Failure Implementation Science and Best Clinical Practices

Rapid Clinical Updates



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Heart Failure Implementation Science and Best Clinical Practices

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Disclosures

Lily Ackermann has no relevant financial or advisory relationships with corporate organizations related to this activity.

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Disclosures

Ebrahim Barkoudah discloses the following relevant financial or advisory relationships:

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- *Editor-in-Chief Journal of Clinical Outcomes Management*

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Dr. Ankheet Bhatt has no relevant financial or advisory relationships with corporate organizations related to this activity.

A blurred photograph of a hospital hallway. In the center, a woman in a white lab coat and a man in blue scrubs are looking at a tablet together. Other people in white coats and scrubs are walking in the background, creating a sense of a busy medical environment. The lighting is bright and natural, coming from large windows in the background.

QUESTIONS

Question 1

For patients hospitalized with acute heart failure on GDMT (beta blocker, ACEi/ARNi, SGLT2i, MRA) with an increased creatinine on admission, it is best to practice to

- A. Stop all GDMT (beta blocker, ACEi/ARNi, SGLT2i, MRA) until outpatient cardiology visit**
- B. Continue only the beta blocker until outpatient cardiology follow up, stop ACEi/ARNi, SGLT2i, MRA**
- C. Prior to discharge restart all GDMT (beta blocker ACEi, SGLT2i, MRA, ARNi) when the patient is stable**
- D. Restart the beta blocker and MRA when the patient is stable prior to discharge**

Question 2

With a new diagnosis of HFrEF or acute HFrEF exacerbation, the goal timeline to be on GDMT quadruple therapy (beta blocker, ARNi/ACEi, SGLT2i, MRA) is

A. Within 4 to 6 weeks

B. Within six months

C. Within one year

D. No clear timeline, it depends on the patient's ability to tolerate each medication as they are added

Implementation Science and Clinical Trials in Heart Failure

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Associate Physician, Kaiser Permanente San Francisco Medical Center

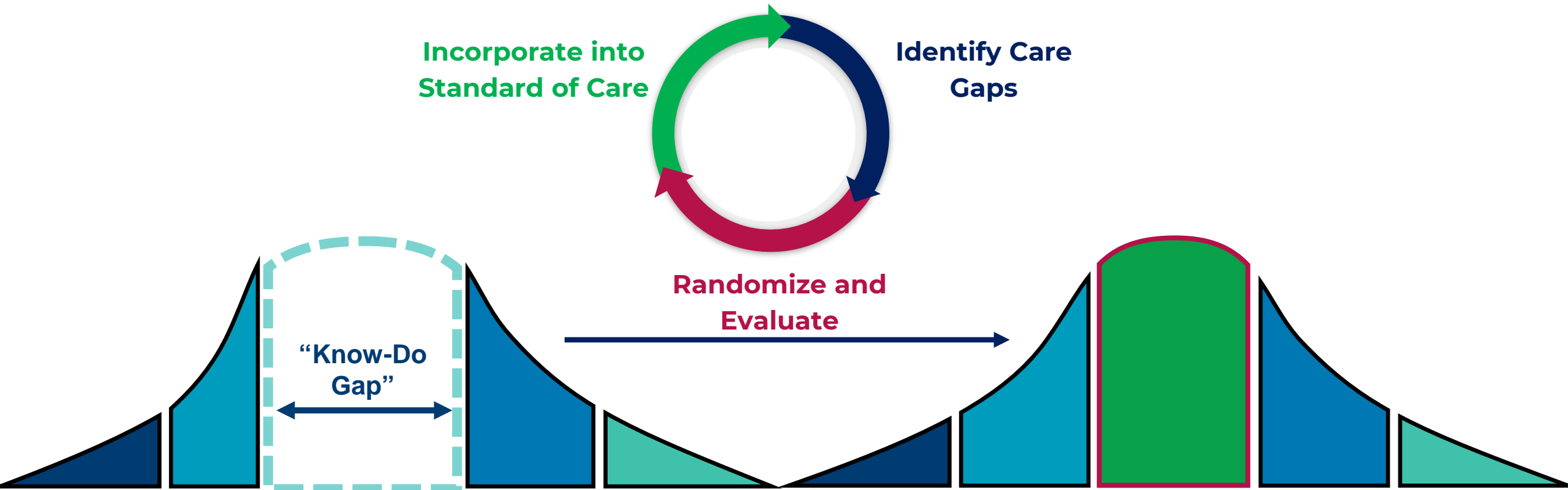
Research Scientist, KPNC Division of Research

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Implementation Science

“...the scientific study of methods and strategies that facilitate the uptake of evidence-based practice and research into regular use by practitioners and policymakers.”



The Case for Implementation Research in Heart Failure



The stakes are high!!

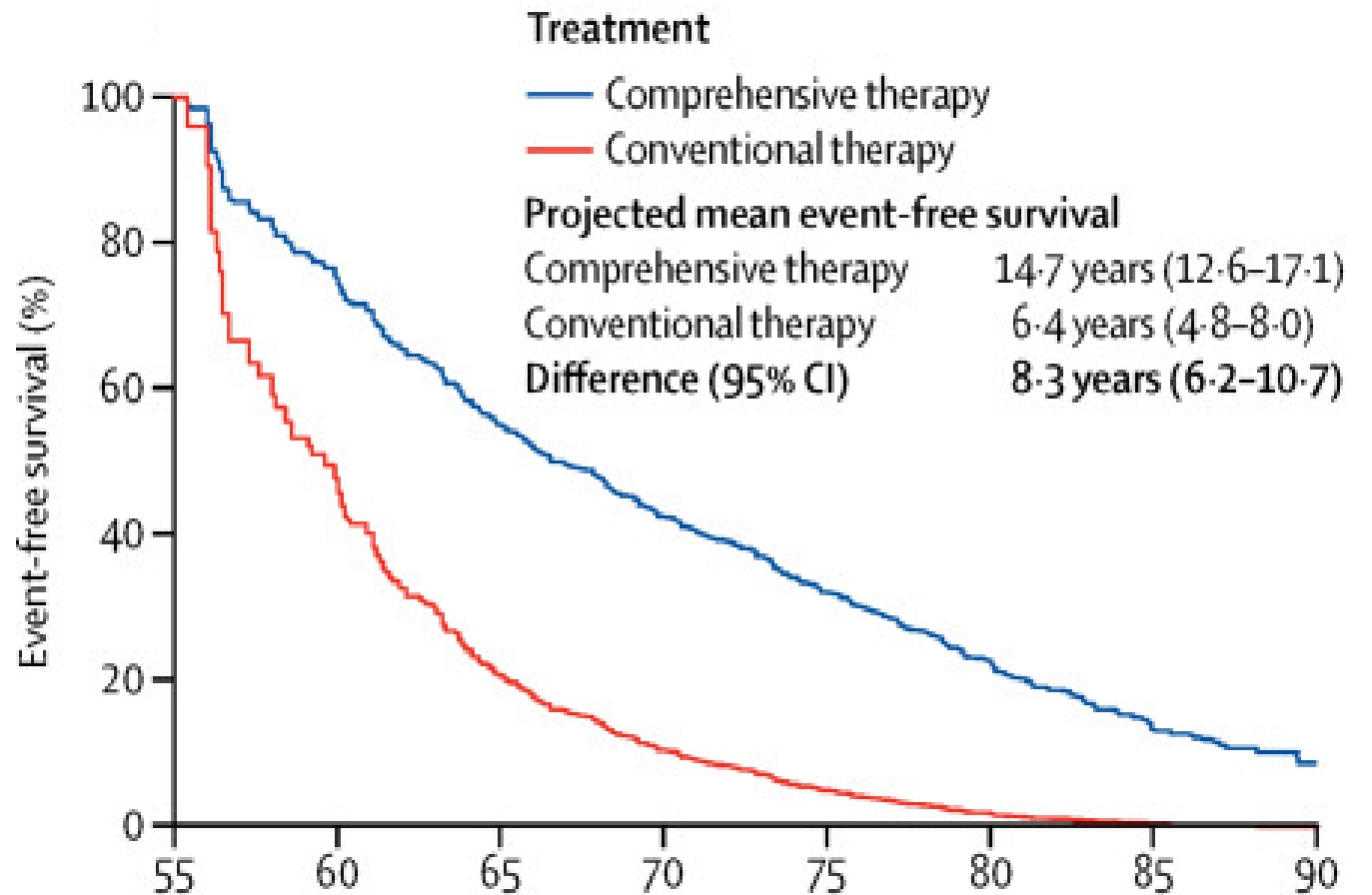
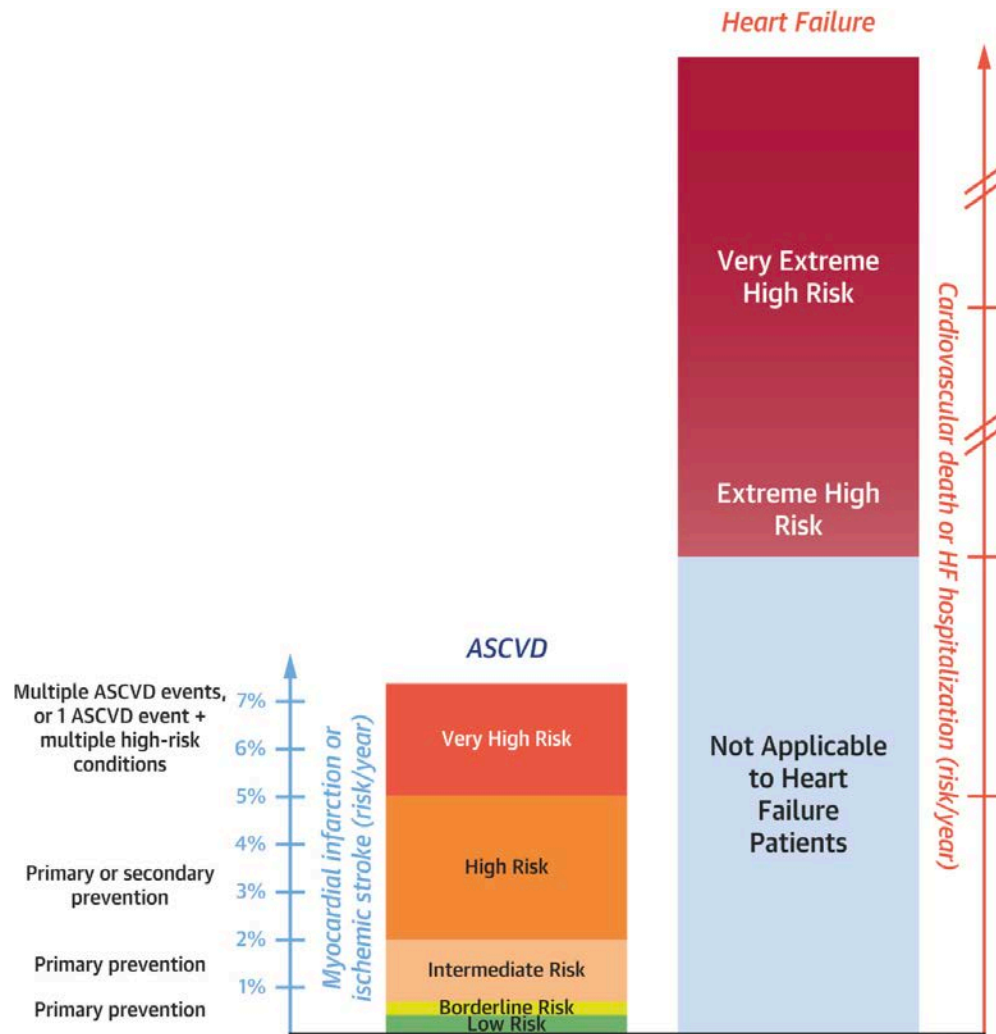
Risk is increasingly modifiable & successful implementation interventions may be transferrable to adjacent diseases.



Incomplete implementation limits population level risk reductions.



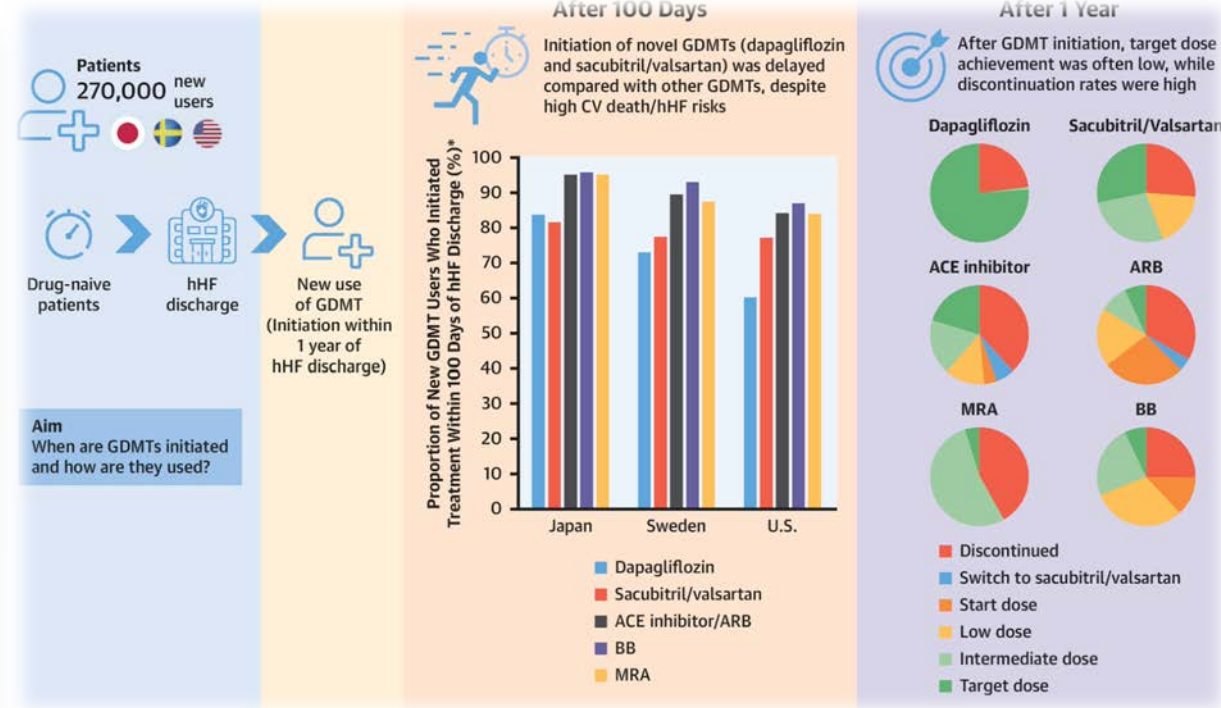
The Case for Implementation Research in Heart Failure



How are we doing?

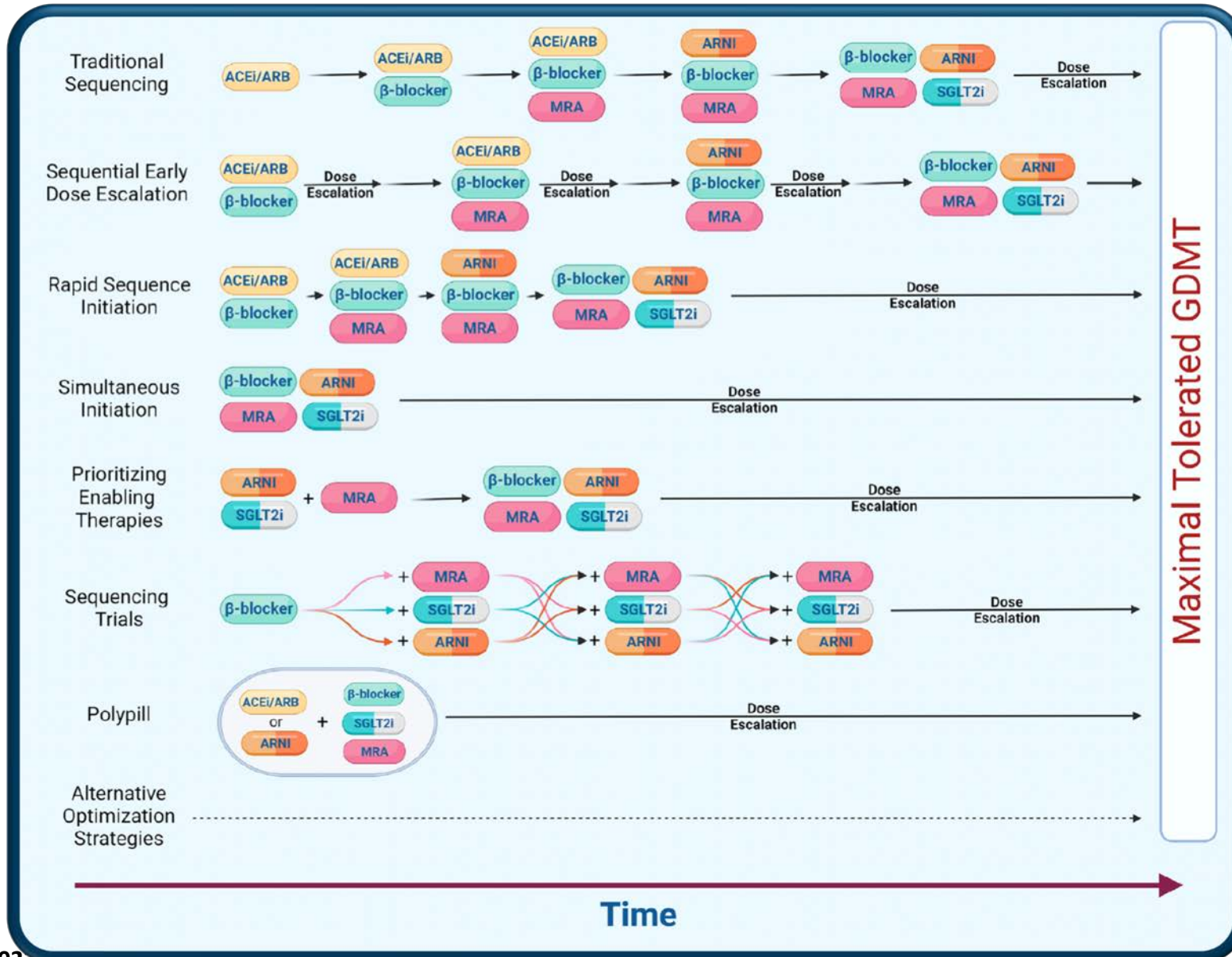


	ACEI/ARB	ARNI	ACEI/ARB/ARNI	Beta-Blocker	MRA
Without Contraindication and Not Treated	1374	3029	920	1159	2317
Treated	2107	452	2536	2351	1163
With Contraindication	37	37	62	8	38

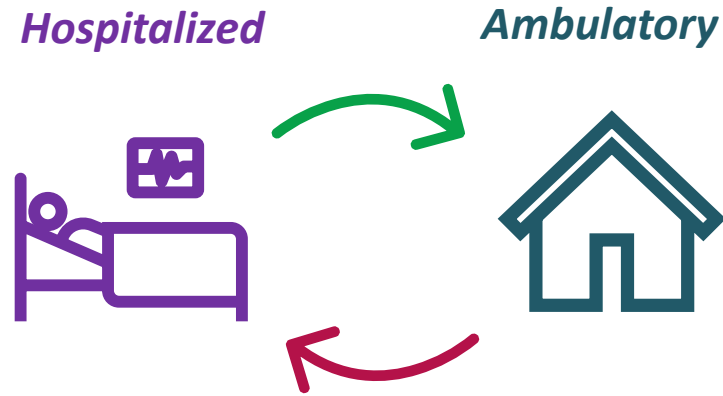
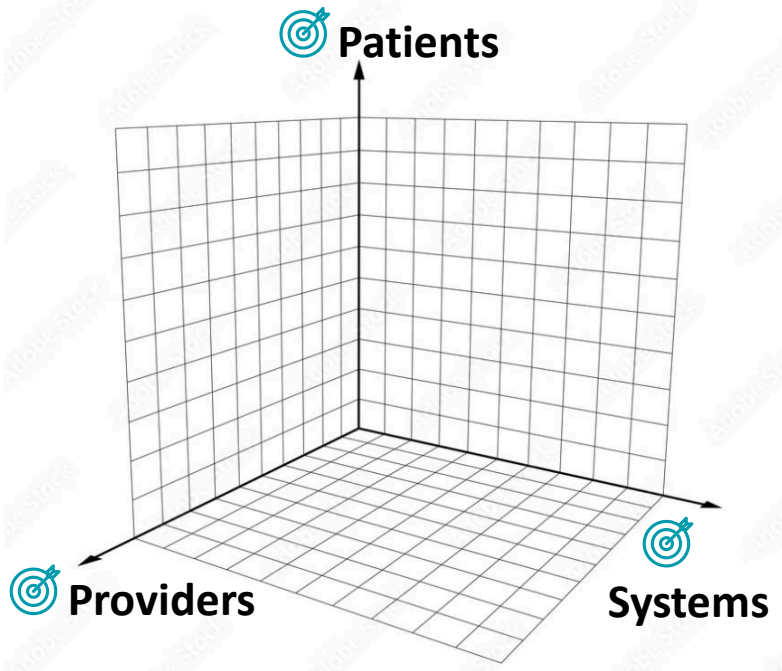


<5% of patients are on optimal guideline recommended HF therapy

Implementation Science in Cardiometabolic Care



Implementation Science Frameworks



*Stronger Intervention
Less Scalability*

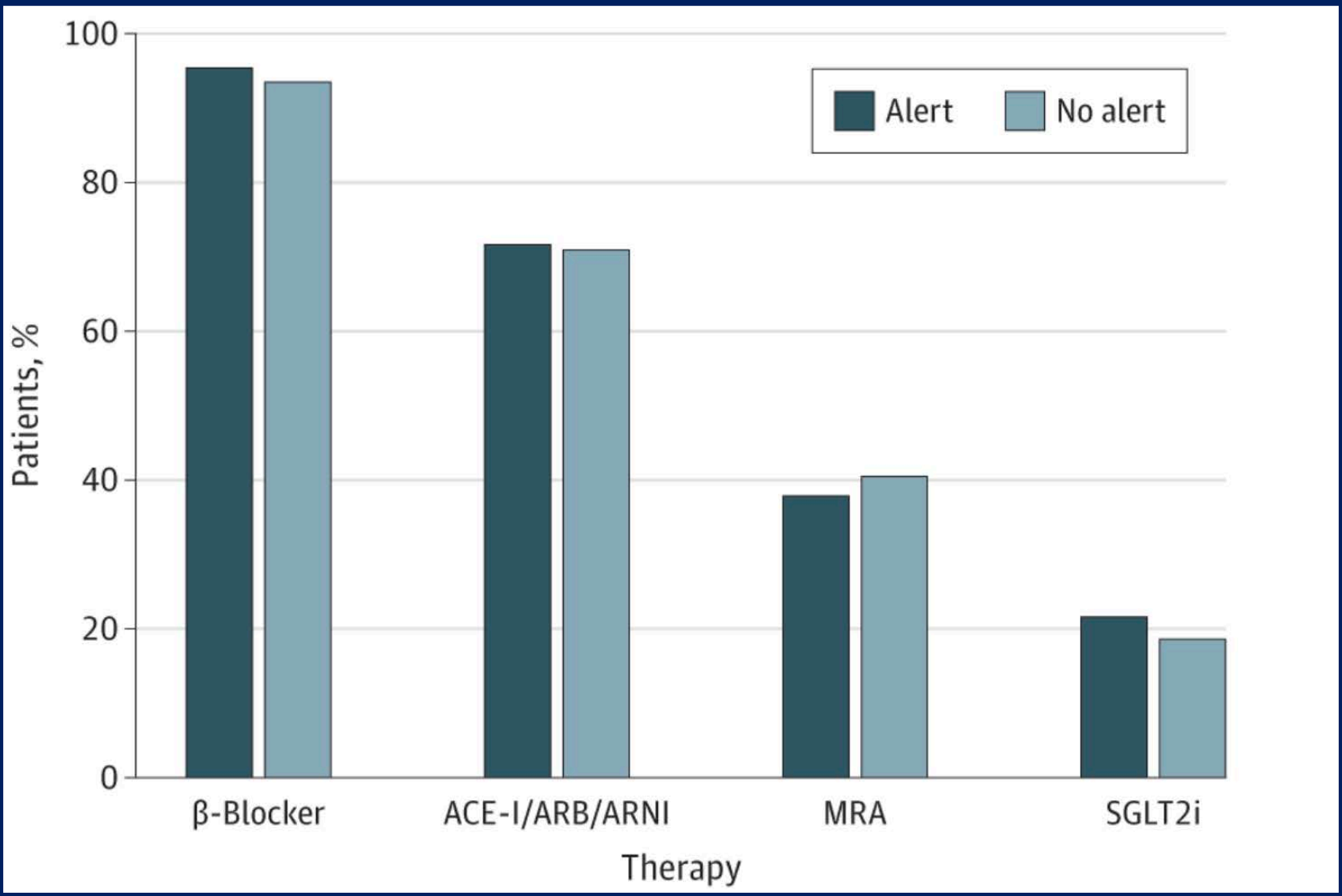


*Weaker Intervention
Greater Scalability*

REVEAL-HF: Risk Based Audit & Feedback

POPULATION
1540 Men, 1584 Women
Adults ≥18 y hospital admission for heart failure
Median age, 77

SETTINGS / LOCATIONS
Yale New Haven Hospital
Yale Medicine Health Services
Yale University School of Medicine



Comparison of outcomes between the alert intervention group and the control group of participants with the usual care. The alert group had a significantly lower rate of readmission or 1-year mortality.

Participants with outcome

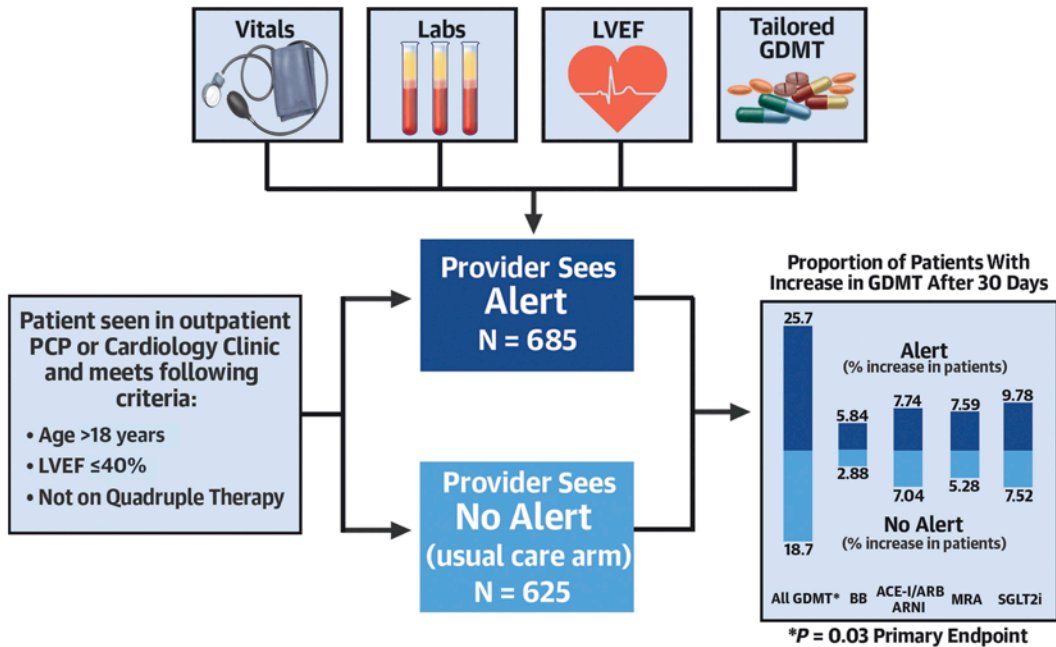
Usual care

39.3%

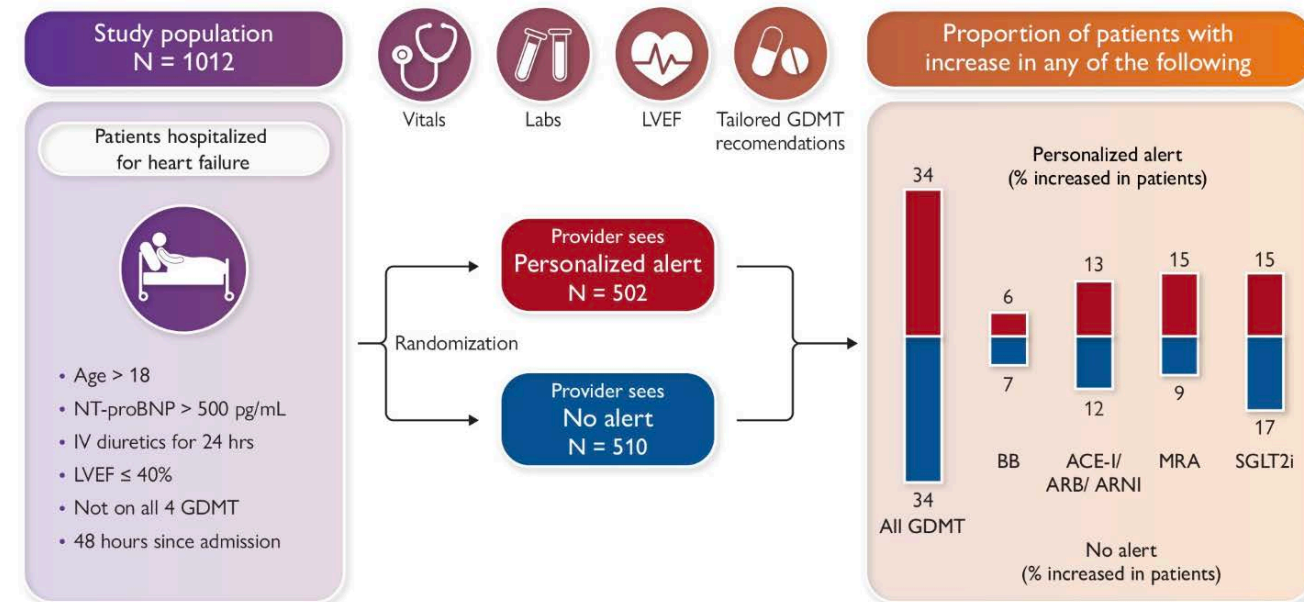
603 of 1534 Participants

PROMPT-HF/AHF: Best Practice Alerts

PROMPT-HF: Outpatient

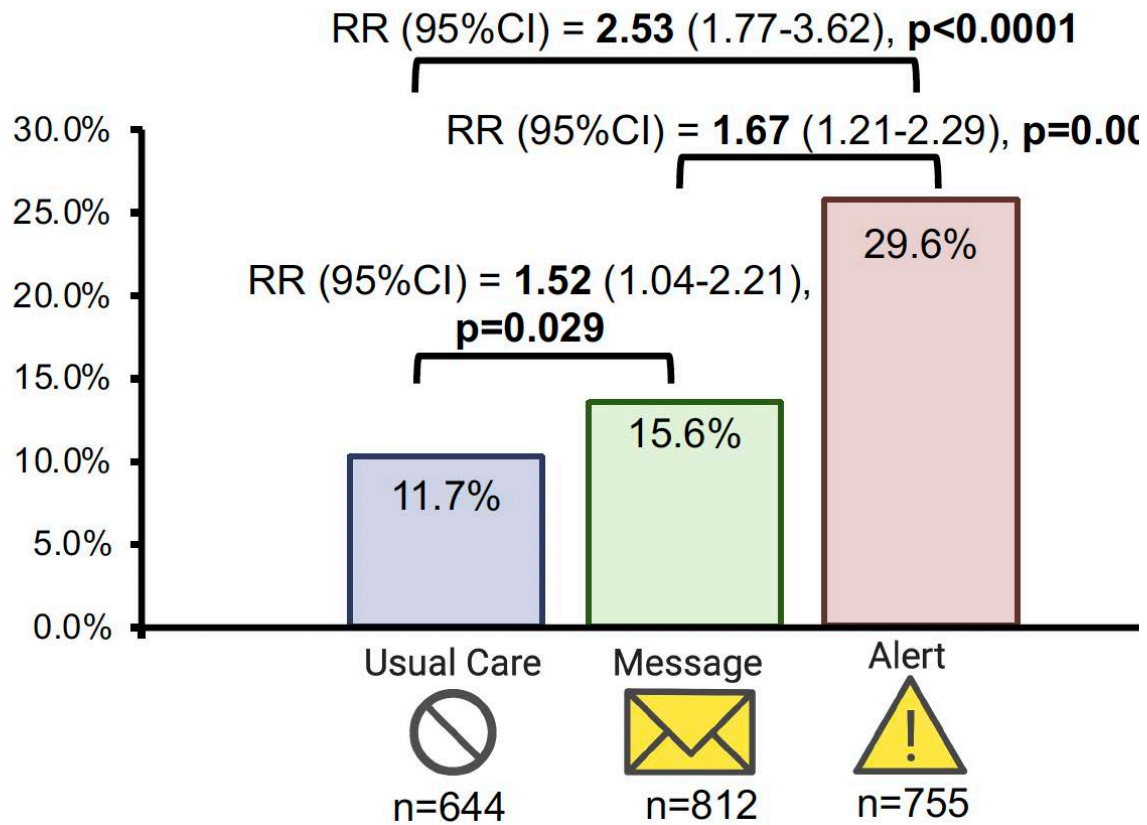


PROMPT-AHF: Hospitalized

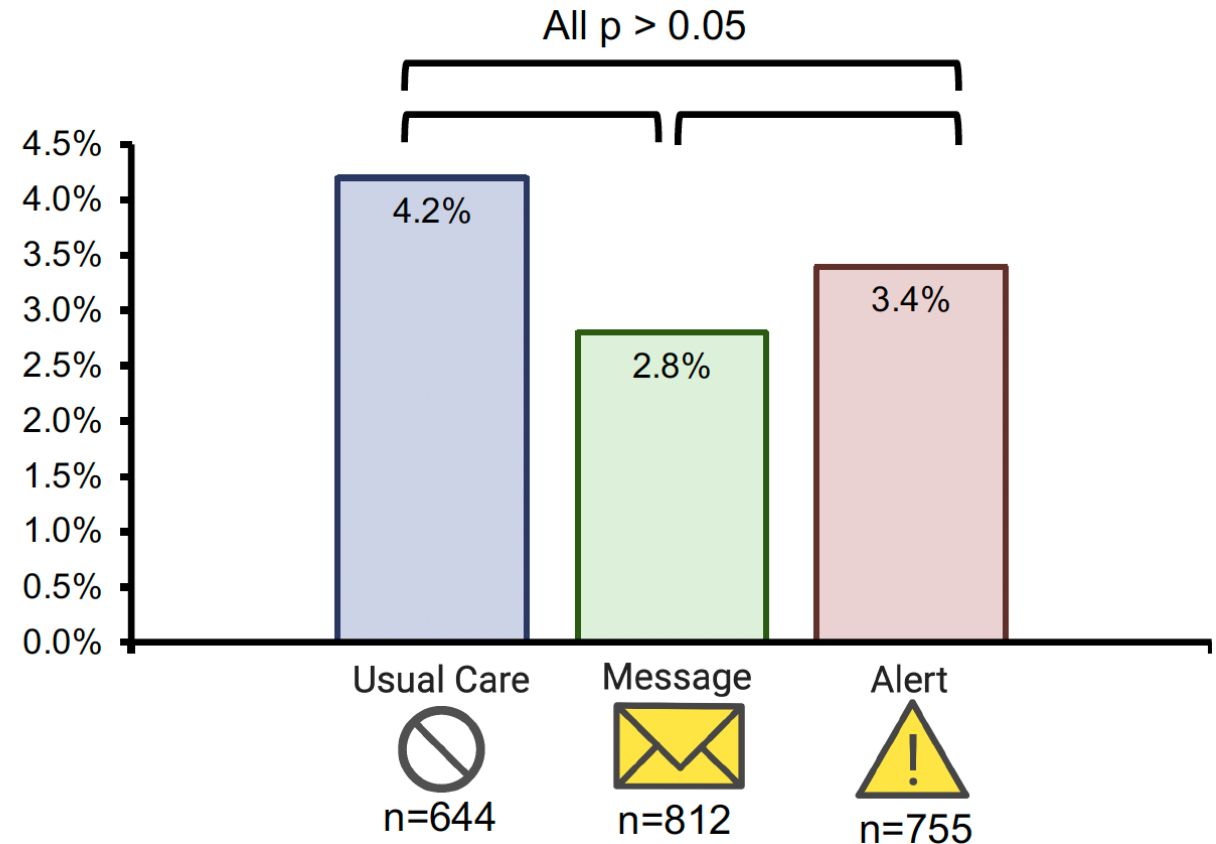


BETTER-CARE-HF: Targeted MRA Alerts

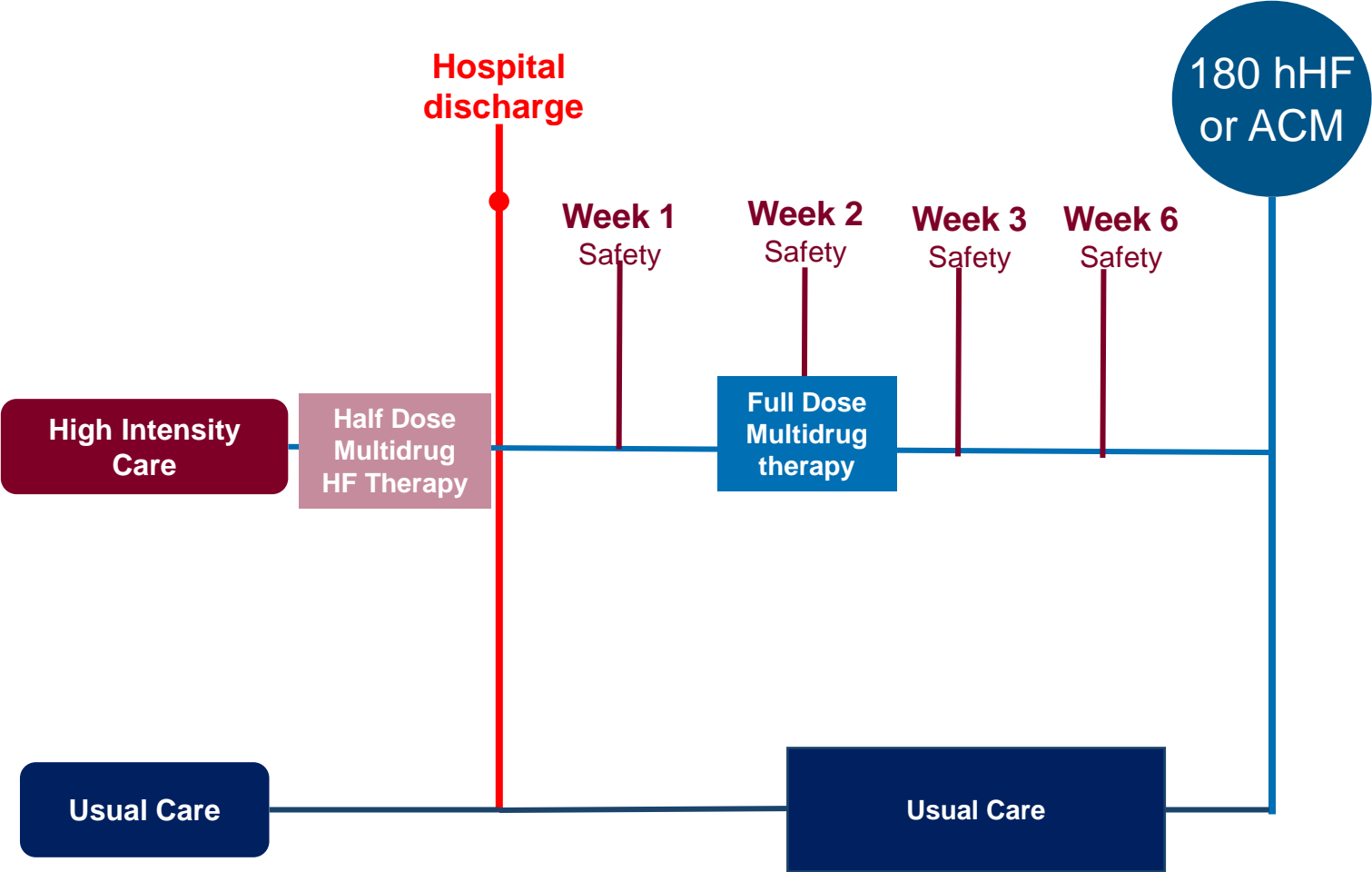
1^o Outcome: MRA Rx



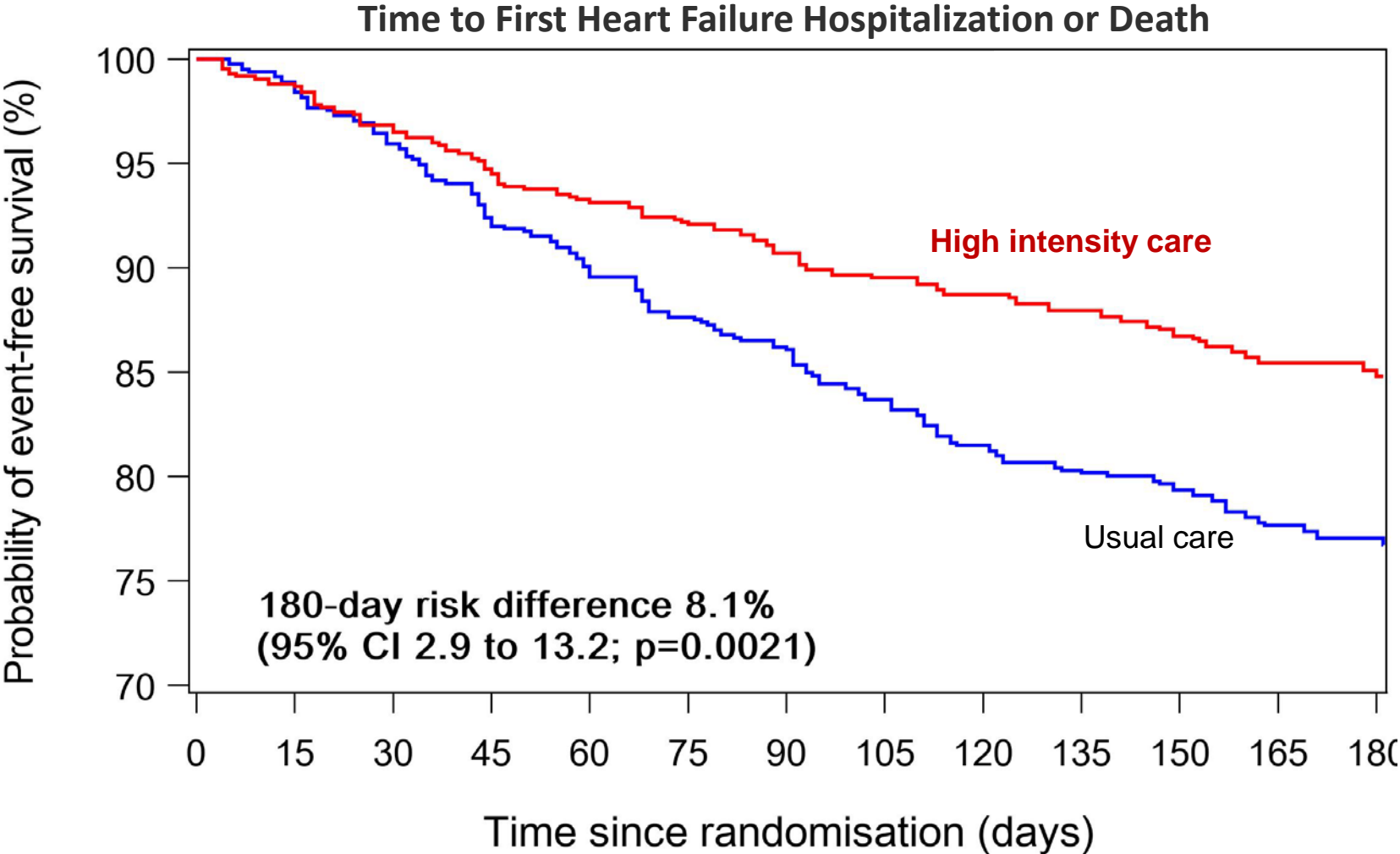
2^o Outcome: BB/RASi Rx



STRONG-HF: Protocolized Care

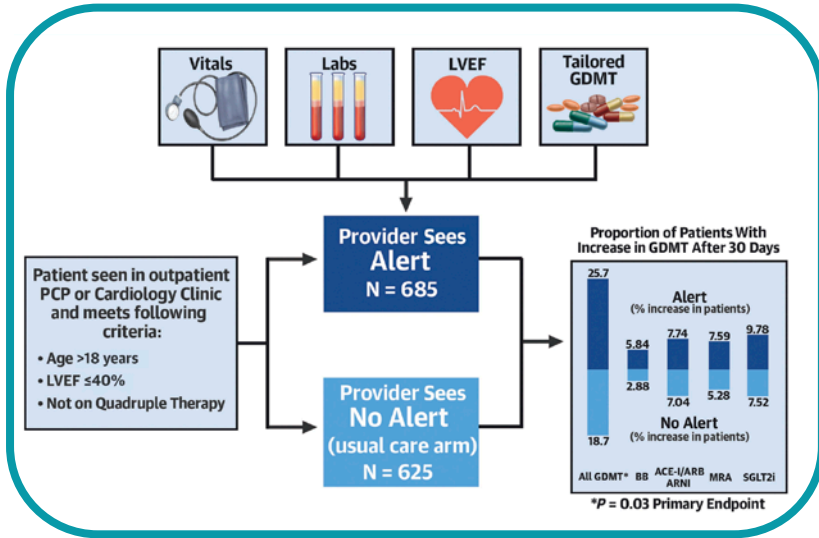


STRONG-HF: Protocolized Care

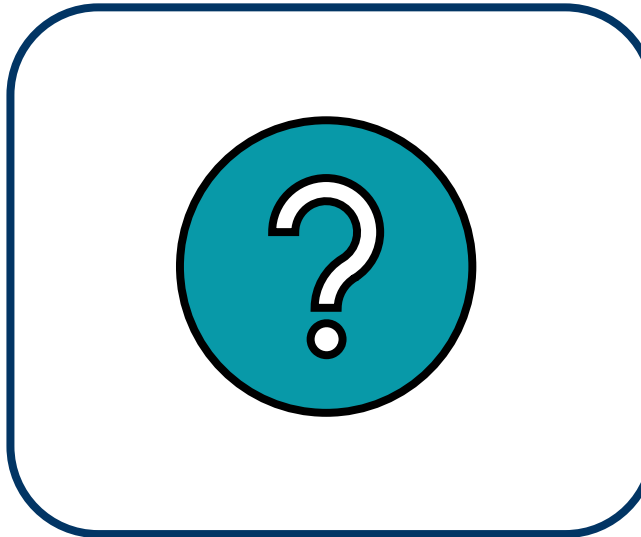


Finding Middle Ground in Implementation Science

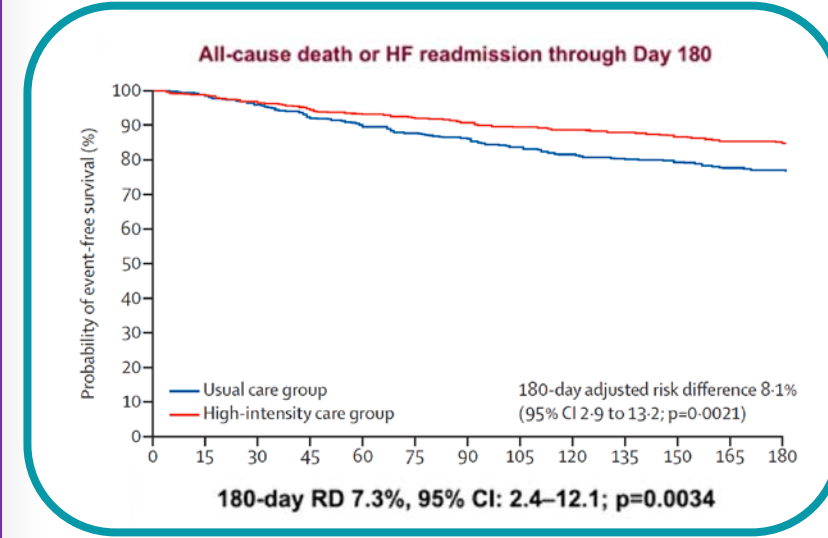
EHR-Based Clinical Decision Support



Highly Scalable
Modest Effect Size; ?Alert Fatigue



Protocolized care

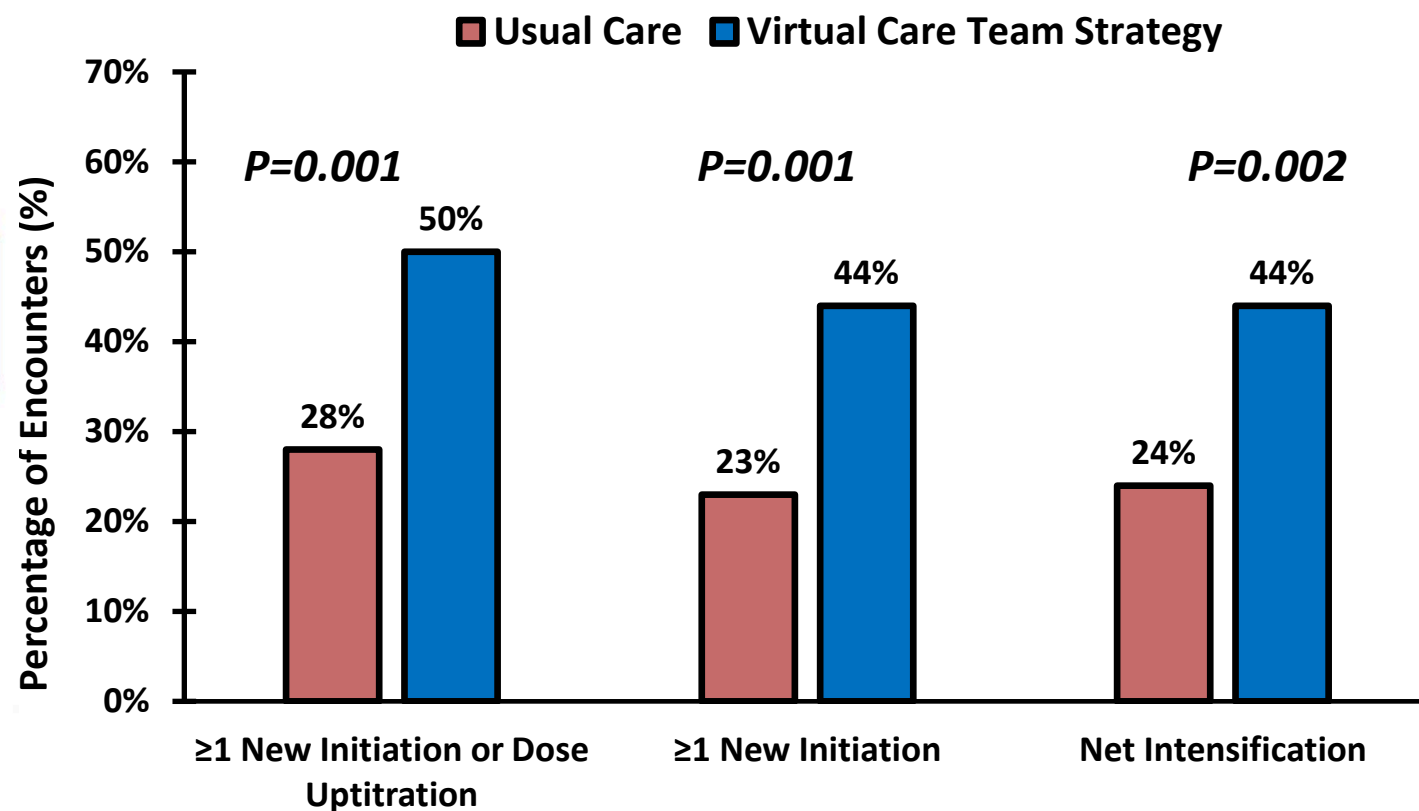
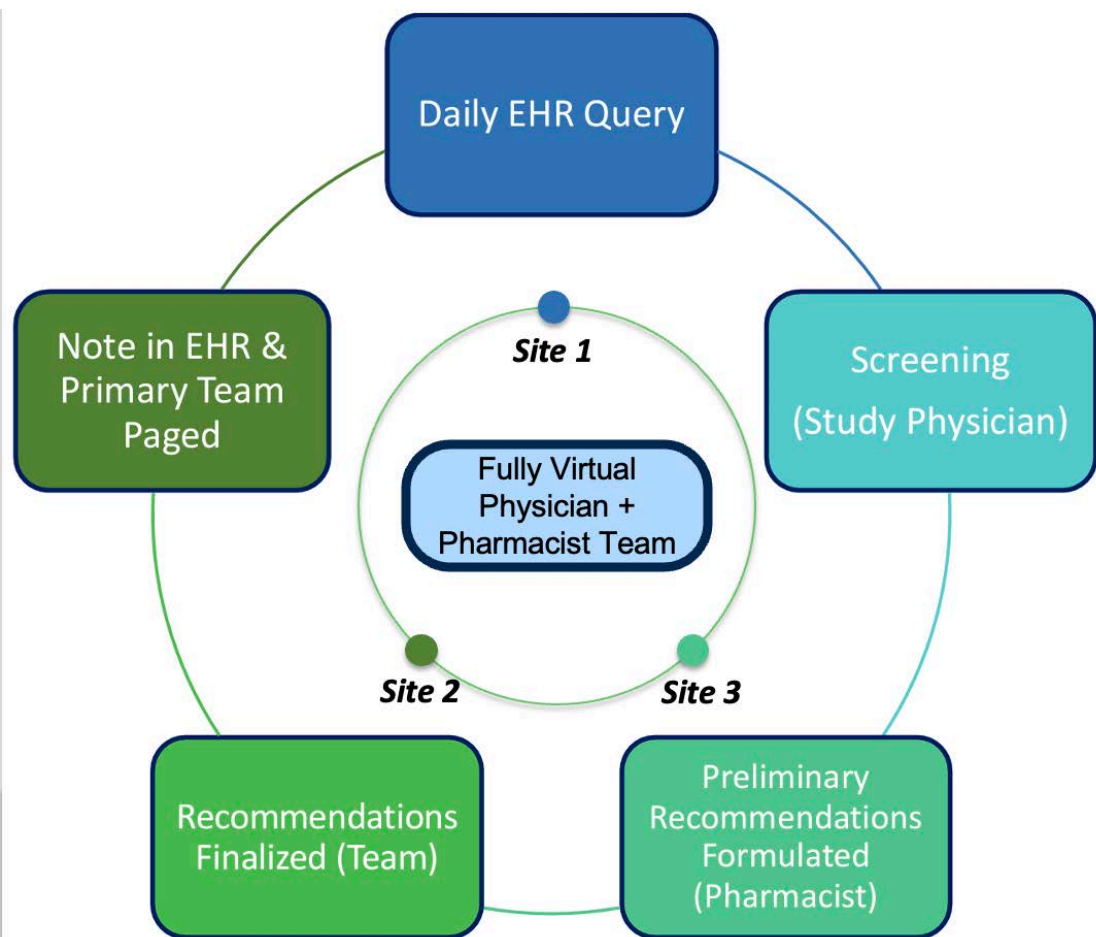


Resource Intensive
Large Effect Size

Hospitalization = Opportunity for GDMT Optimization

- Targets **high-risk** patients in a **well-resourced** setting
- Addresses potential reasons for poor outpatient GDMT optimization (time, reinforcement, education)
- Allows for frequent **hemodynamic** and symptom **monitoring**
- Can include patients hospitalized **for and with** HFrEF
- Potential for **virtual nudging strategies** to allow for scale across integrated health systems.

IMPLEMENT-HF: Virtual Care Teams

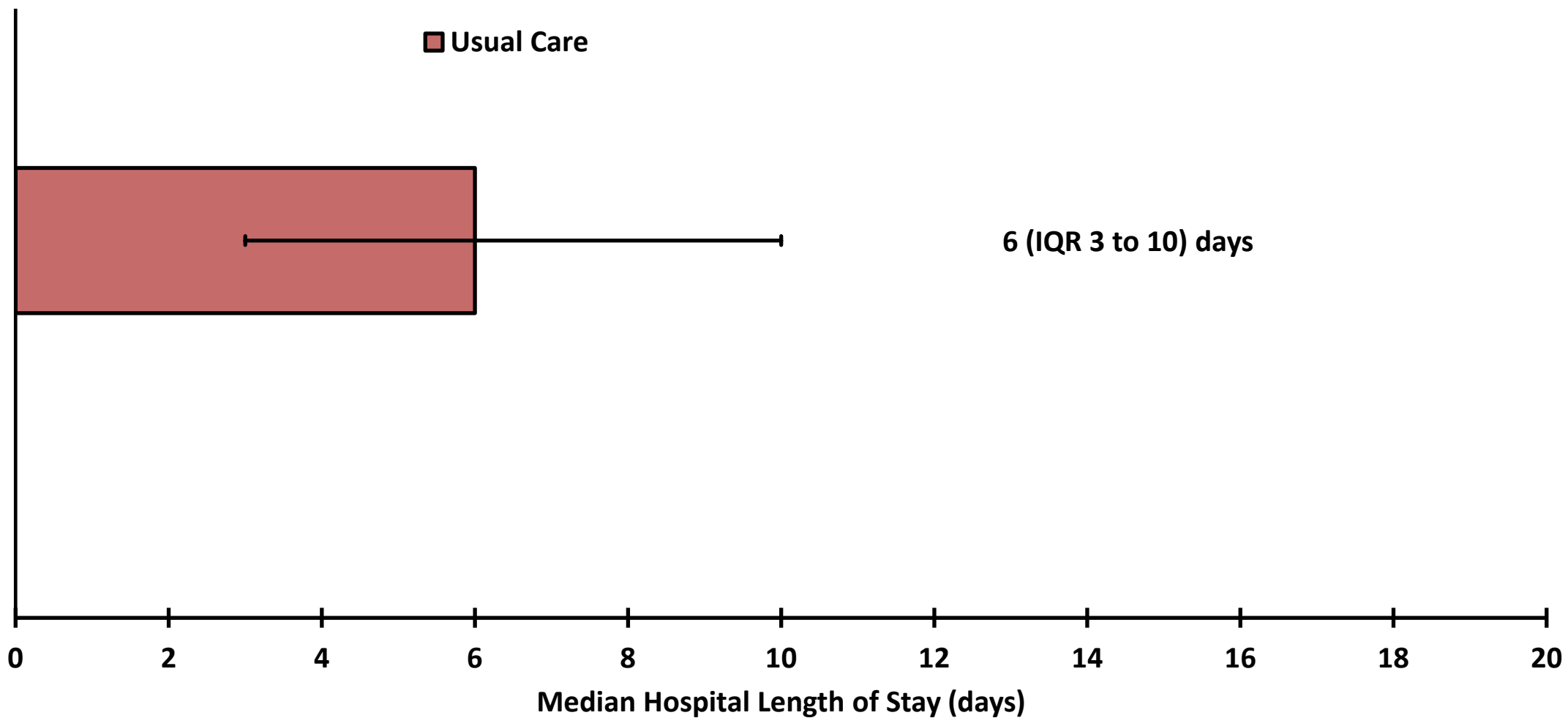


Number Needed to Intervene: ~5 Encounters

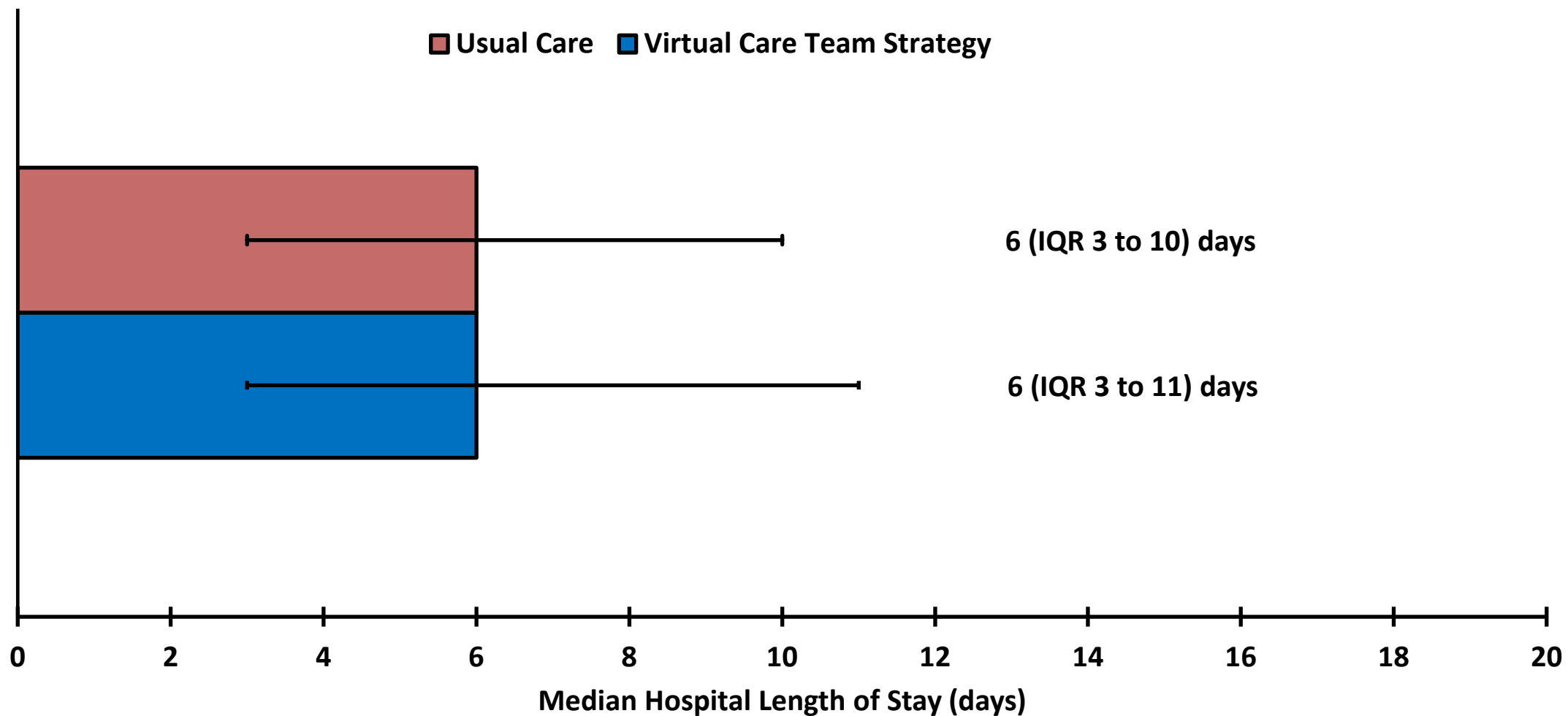
In-Hospital Adverse Events (CEC Adjudicated)

	Virtual Care Team Strategy n=107	Usual Care n=145	P-Value
Any Adverse Event	23 (21.5%)	40 (27.6%)	0.30
Hypotension	12 (11.2%)	24 (16.6%)	0.28
Hyperkalemia	8 (7.5 %)	18 (12.4%)	0.22
Acute kidney injury	5 (4.7%)	3 (2.1%)	0.29
Bradycardia	0 (0.0 %)	0 (0.0 %)	--
In Hospital Death	1 (0.9 %)	2 (1.4 %)	--

Hospital Length of Stay



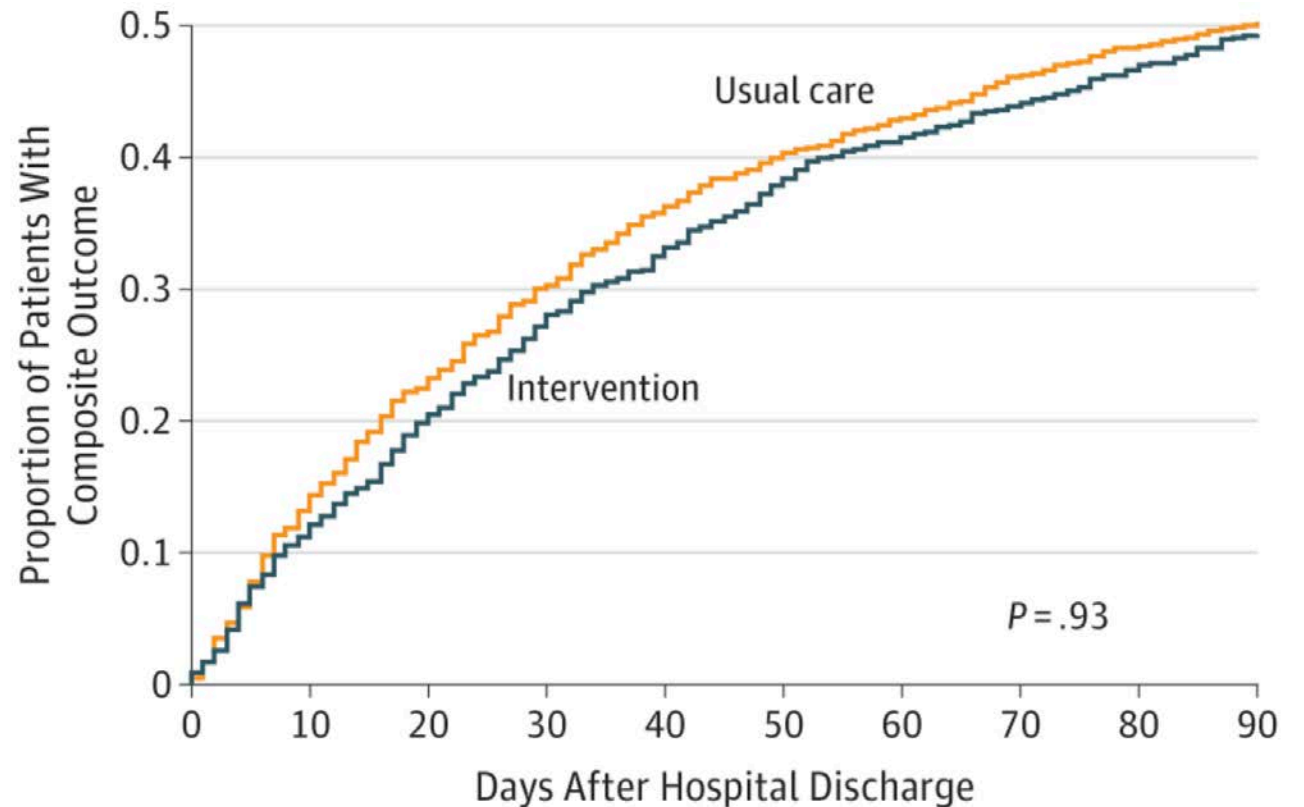
Hospital Length of Stay



PACT-HF: Multifaceted Transitional Care

- 🎯 Nurse-Driven Education
- 🎯 Structured Discharge Summary
- 🎯 Timely Physician Follow-up
- 🎯 Nurse Home Visits
- 🎯 Heart Function Clinic Referral


Time to First Composite Readmission, Emergency Department Visit, or Death



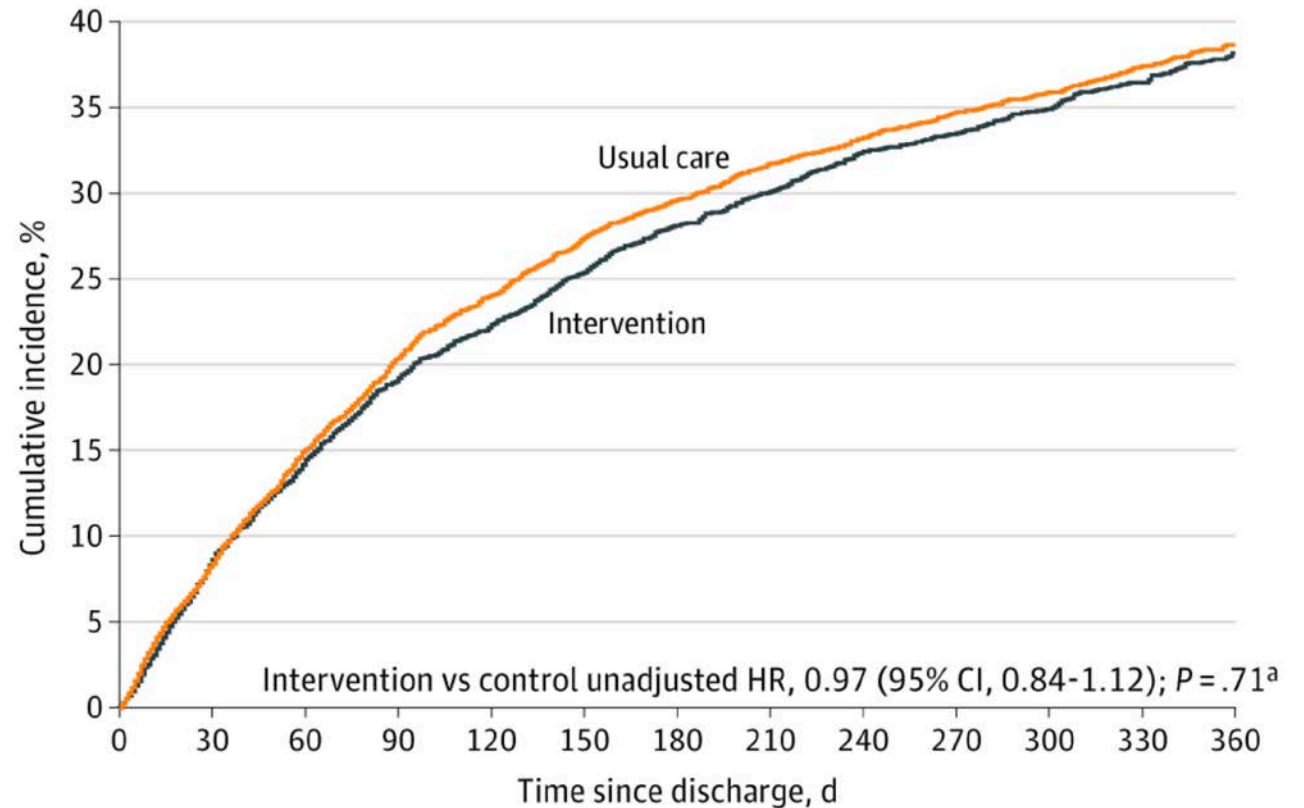
CONNECT-HF: Multifaceted Transitional Care

 HF Expert Delivered Education

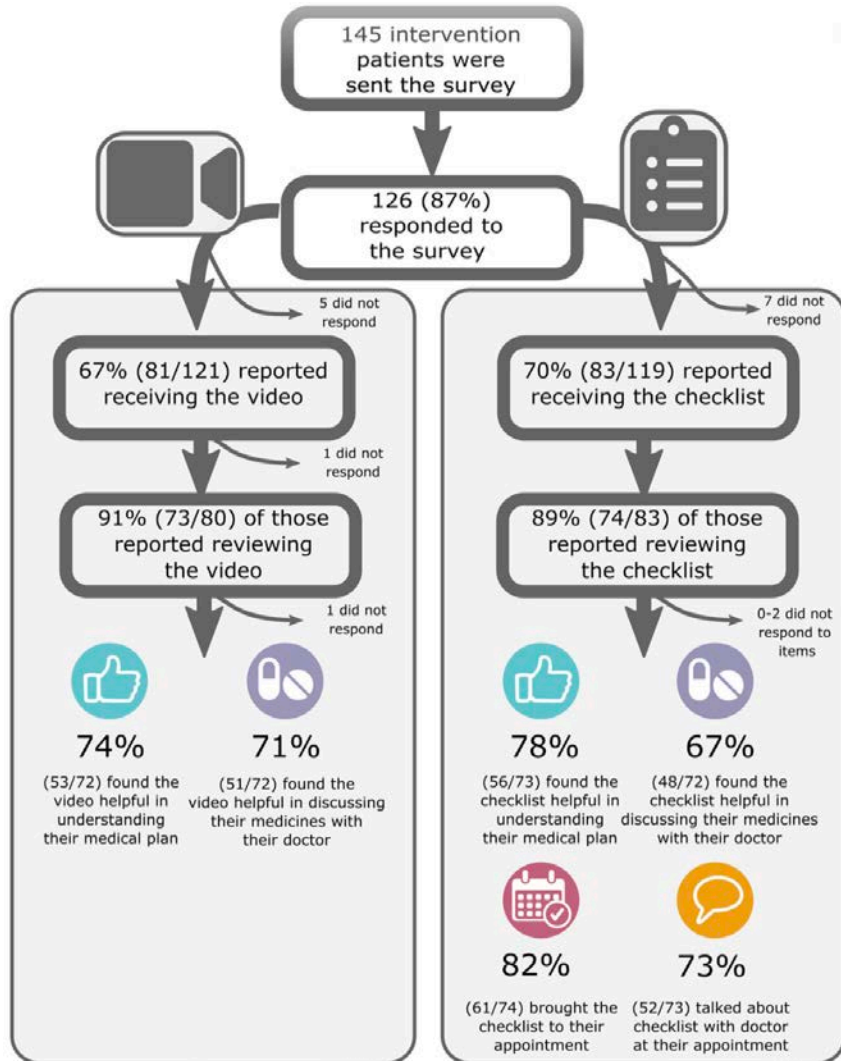
 Site-Level Gap Analysis

 Ongoing Site-Level
Audit & Feedback

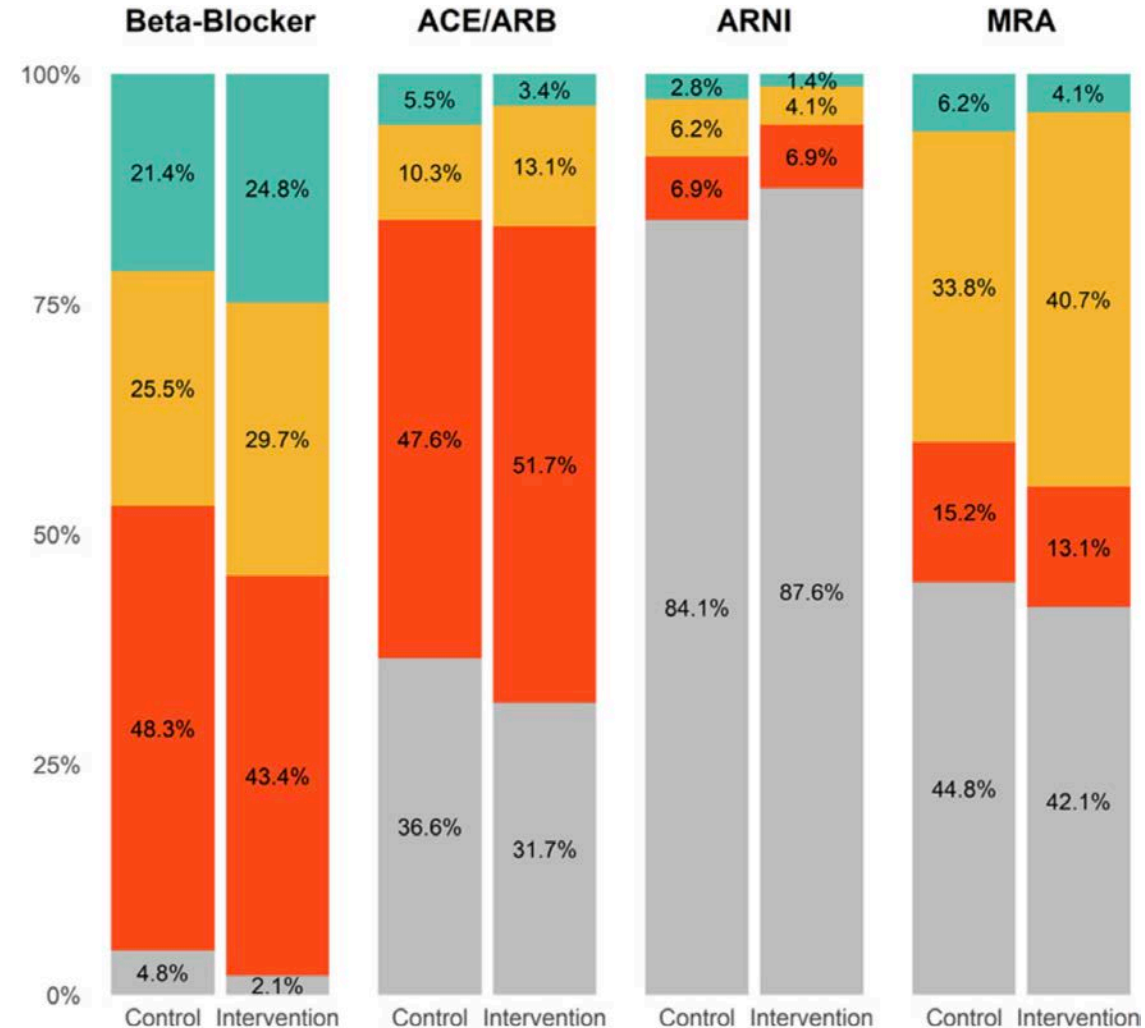
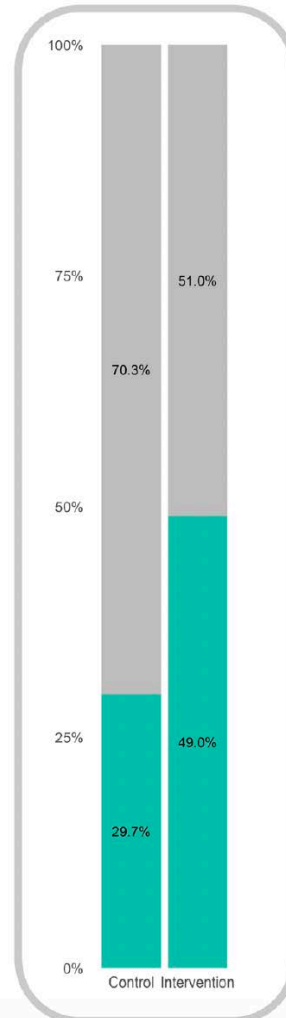
Time to First Heart Failure Hospitalization or Death



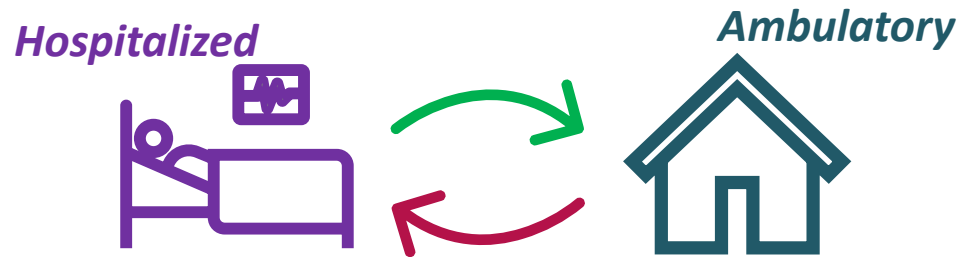
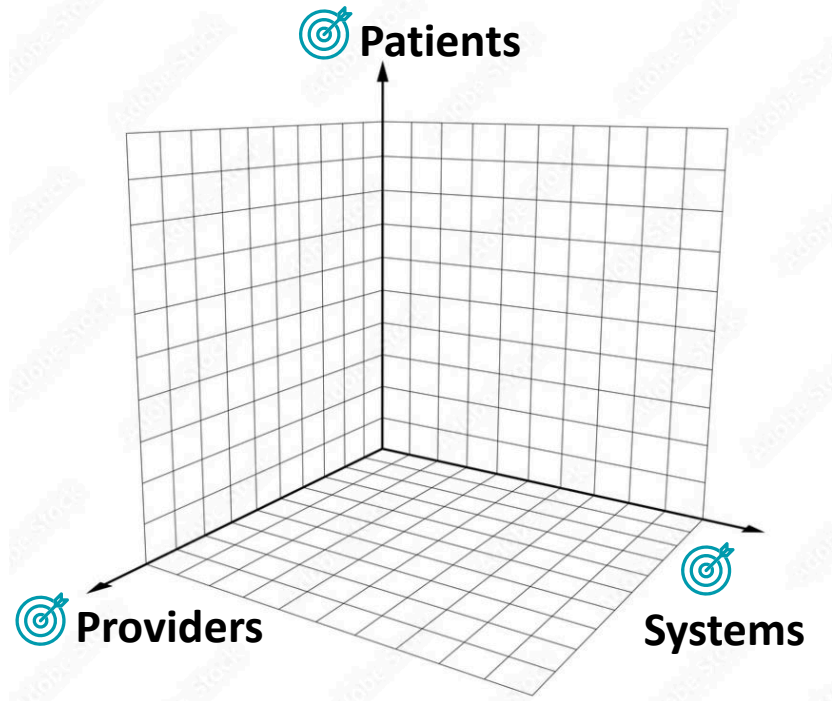
EPIC-HF: Patient Directed Activation



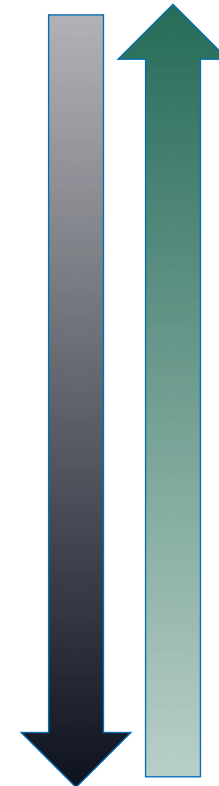
Primary outcome:
Initiation or intensification
of GDMT



Implementation Science in HF: A Look Toward the Future

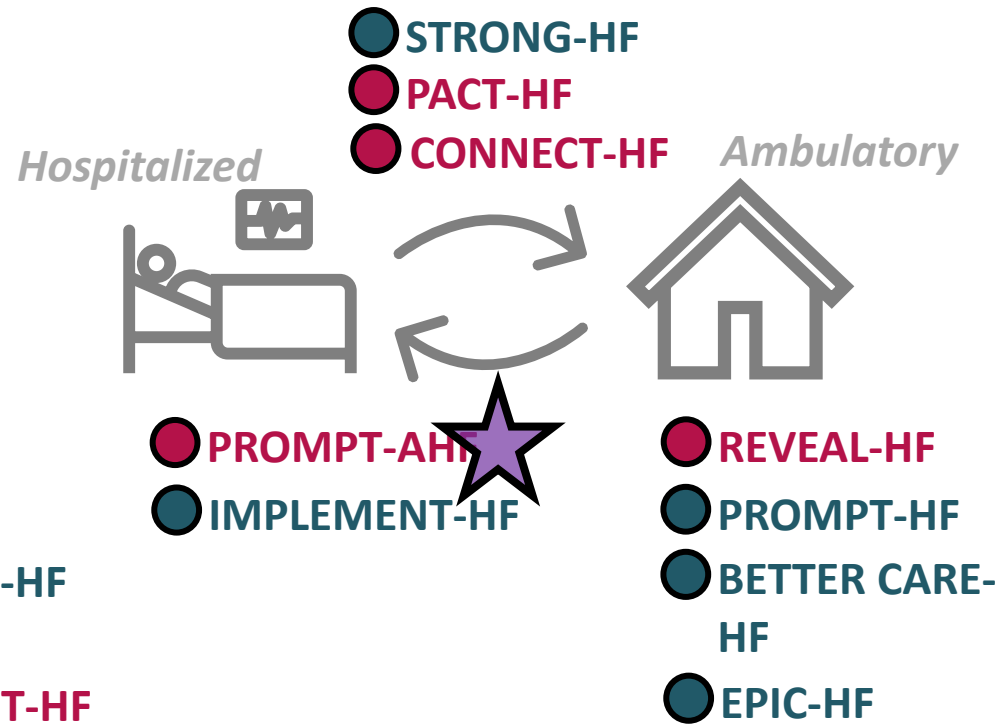
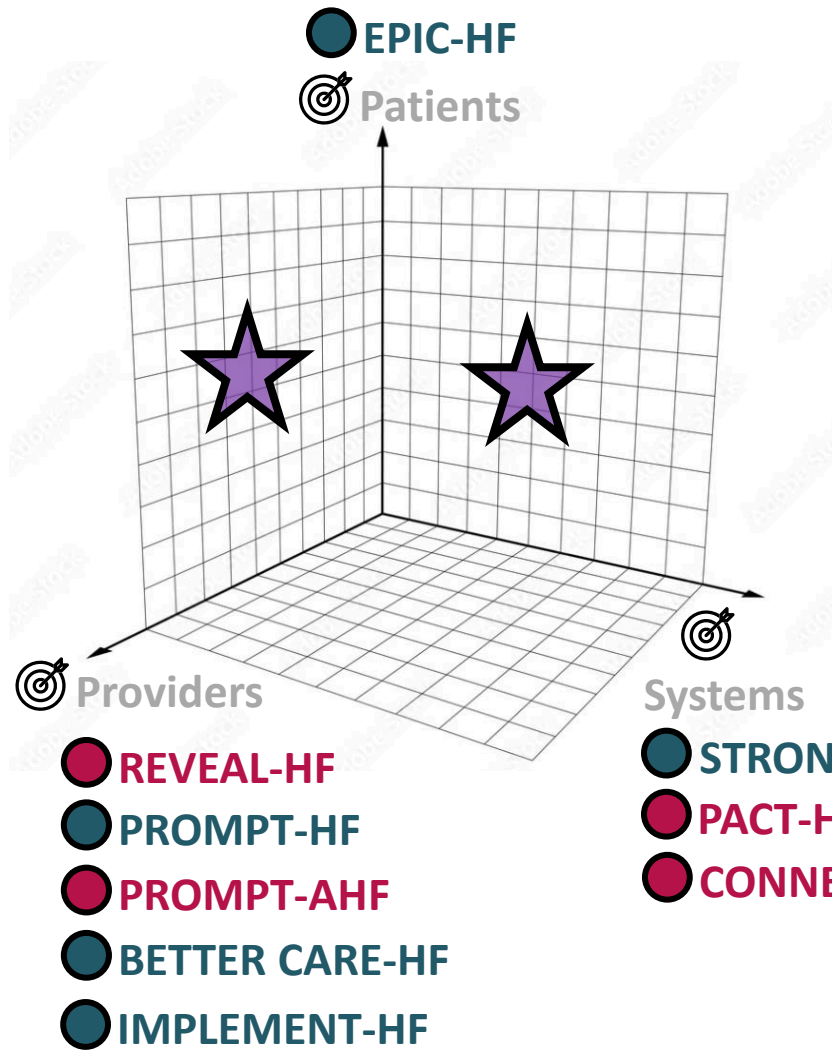


*Stronger Intervention
Less Scalability*

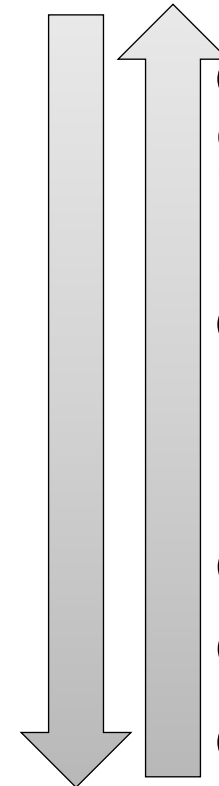


*Weaker Intervention
Greater Scalability*

Implementation Science in HF: A Look Toward the Future



*Stronger Intervention
Less Scalability*

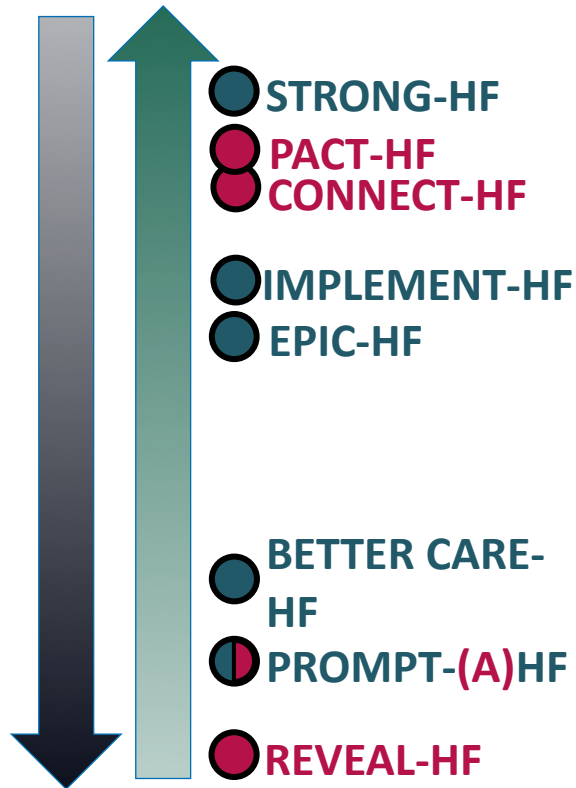


*Weaker Intervention
Greater Scalability*

- STRONG-HF
- PACT-HF
- CONNECT-HF
- IMPLEMENT-HF
- EPIC-HF
- BETTER CARE-HF
- PROMPT-(A)HF
- REVEAL-HF

Precision Implementation Science?

Stronger Intervention
Less Scalability



Weaker Intervention
Greater Scalability

- 🎯 **Prior Clinician Performance**
- 🎯 Rural vs. Urban Populations
- 🎯 Risk-Based Implementation
- 🎯 Comorbidity Based Implementation
- 🎯 Expansion Across the CKM Spectrum

Thank You

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Implementation of Heart Failure GDMT In Patients with Impaired Renal Function: Dips, Declines and Deteriorations

Safia Chatur, MD

**Cardiologist, Massachusetts General Hospital (Incoming)
Clinical Instructor, Harvard Medical School (Incoming)**



Patients with CKD Face Increased Clinical Risks



Persistent albuminuria categories Description and range		
A1	A2	A3
Normal to mildly increased	Moderately increased	Severely increased
<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol

GFR categories (ml/min/1.73 m ²) Description and range	GFR (ml/min/1.73 m ²)		Risk Category		
	Description	Range	A1	A2	A3
G1	Normal or high	≥90	Low	Low	Low
G2	Mildly decreased	60–89	Low	Moderate	Moderate
G3a	Mildly to moderately decreased	45–59	Moderate	Moderate	High
G3b	Moderately to severely decreased	30–44	Moderate	High	High
G4	Severely decreased	15–29	High	High	Very High
G5	Kidney failure	<15	Very High	Very High	Very High

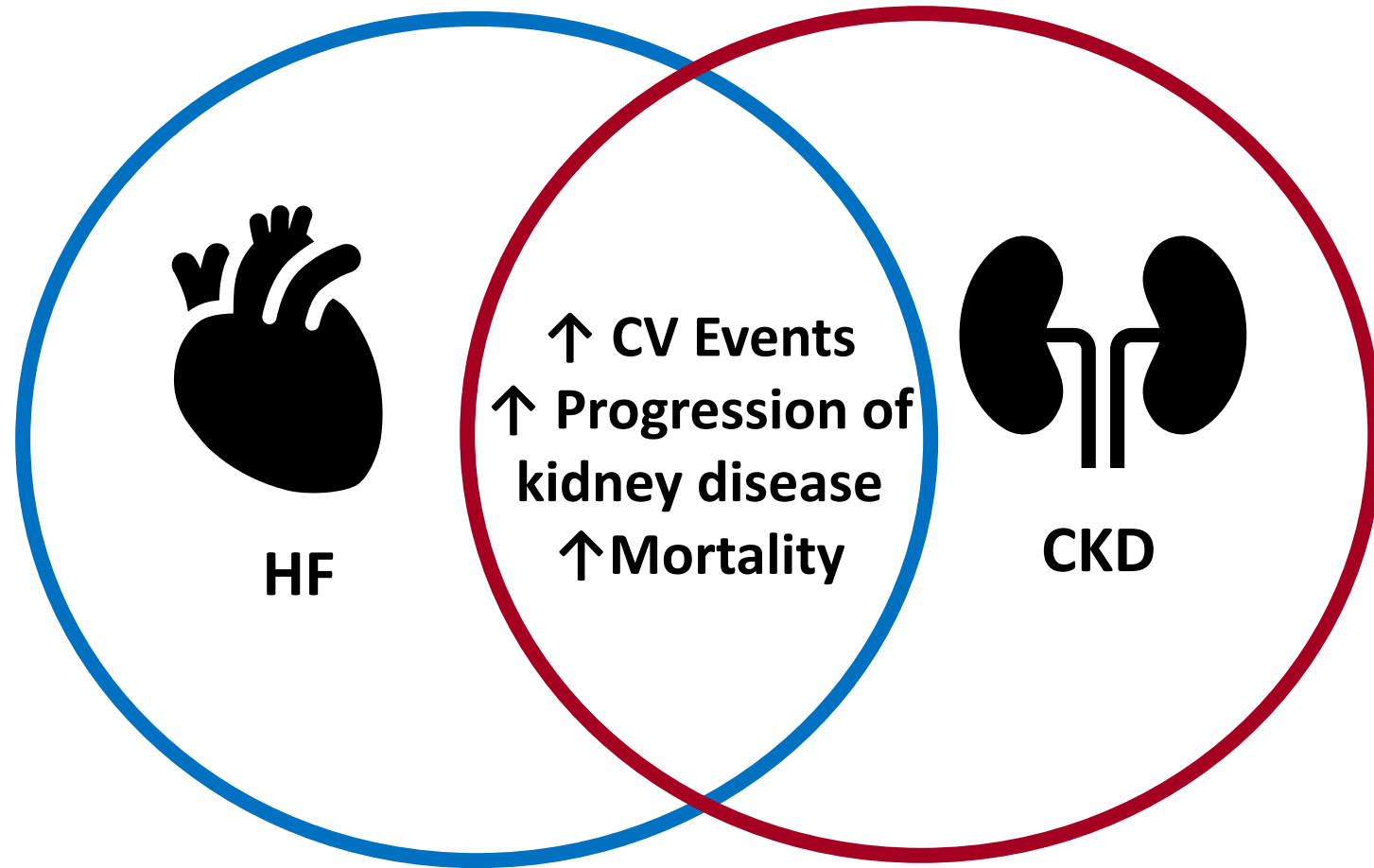
↑ CV mortality
 ↑ All-Cause mortality
 ↑ Kidney Events

Distribution of KDIGO Risk In PARADIGM-HF

eGFR(ml/min/1.73m ²)	UACR (mg/g)	UACR (mg/g)		
		A1	A2	A3
		<30	30-300	>300
G1	≥90	5.3%	1.6%	0.6%
G2	60-89	36.4%	10.4%	2.3%
G3a	45-59	19.9%	6.8%	1.1%
G3b	30-44	9.9%	4.5%	0.7%
G4	15-29	0.3%	0.1%	0.1%
G5	<15	0	0	0

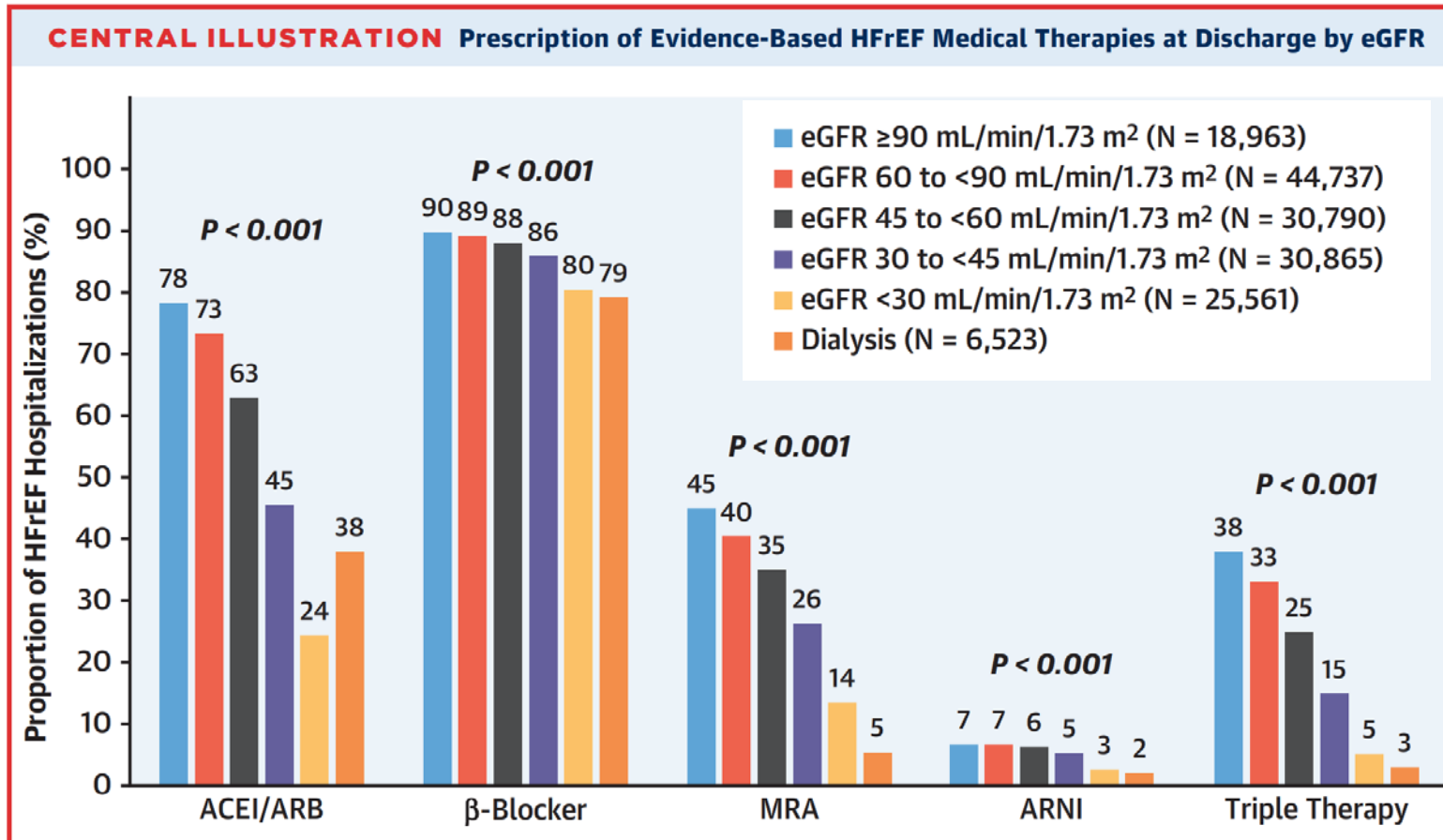
KDIGO Risk Categories		
Low Risk (n=797)	Moderate Risk (n=609)	High/Very High Risk (n=504)
42%	32%	26%

Comorbid Intersection of HF and CKD



↑ clinical risk and ↑ rates of premature drug discontinuation

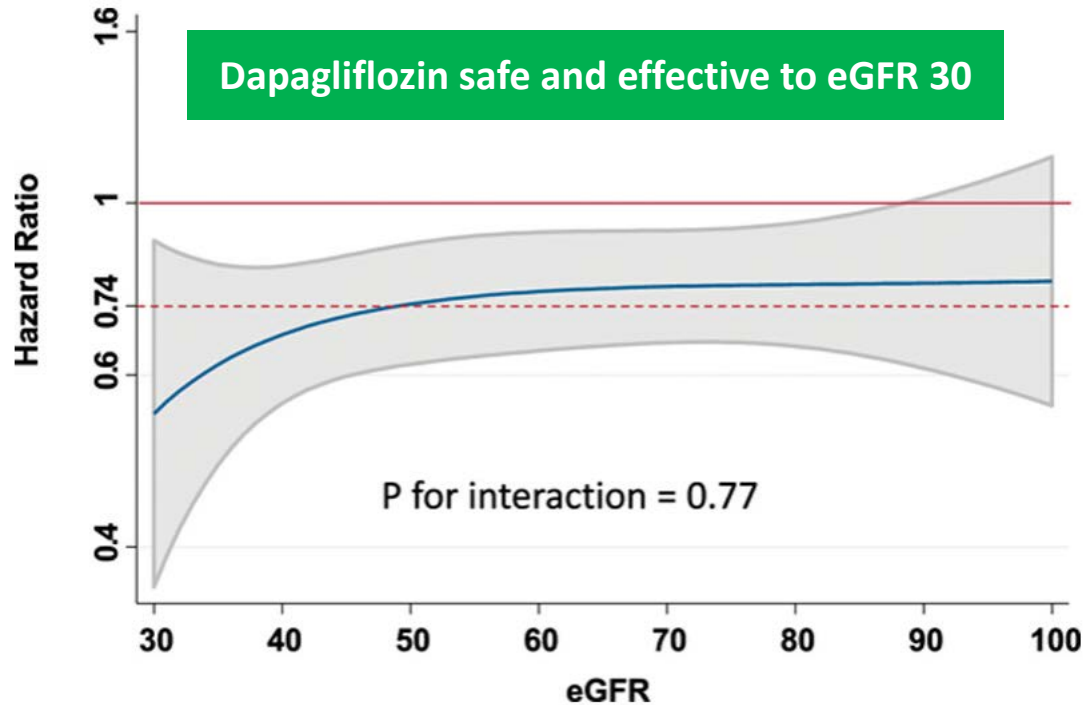
Prescription of HF GDMT at Discharge By eGFR



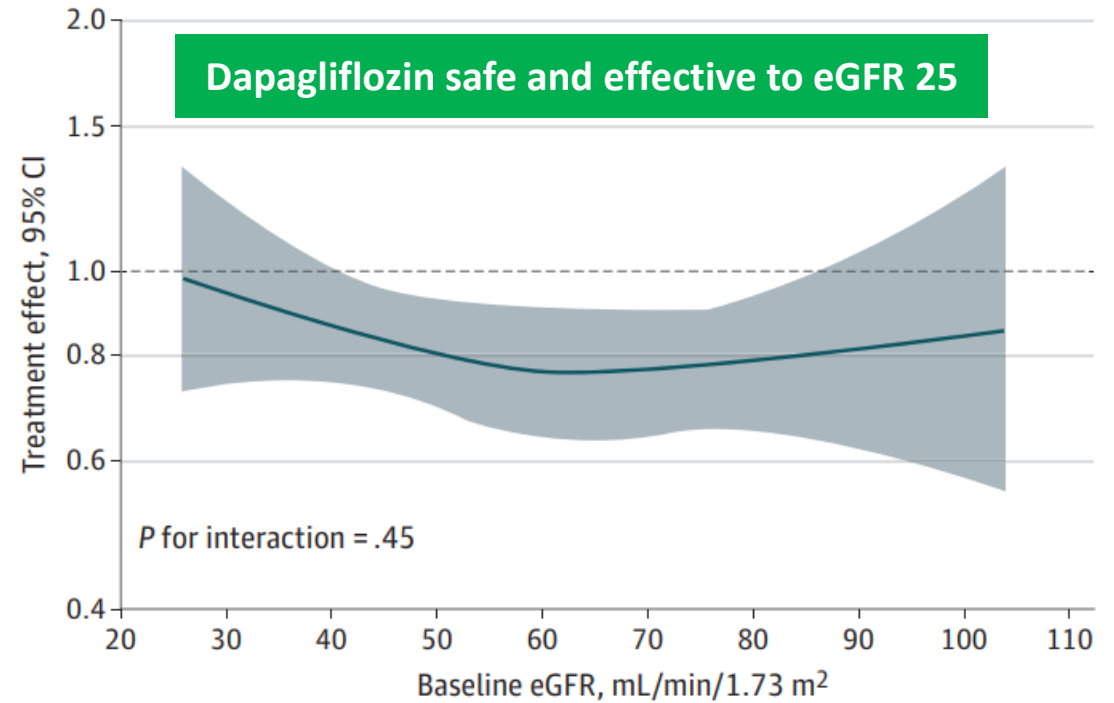
- Graded decrease in prescription rates for *all components of HF GDMT* across **lower eGFR categories**

SGLT2i Exhibits Broad Safety and Efficacy Across Spectrum of Kidney Function

DAPA-HF



DELIVER

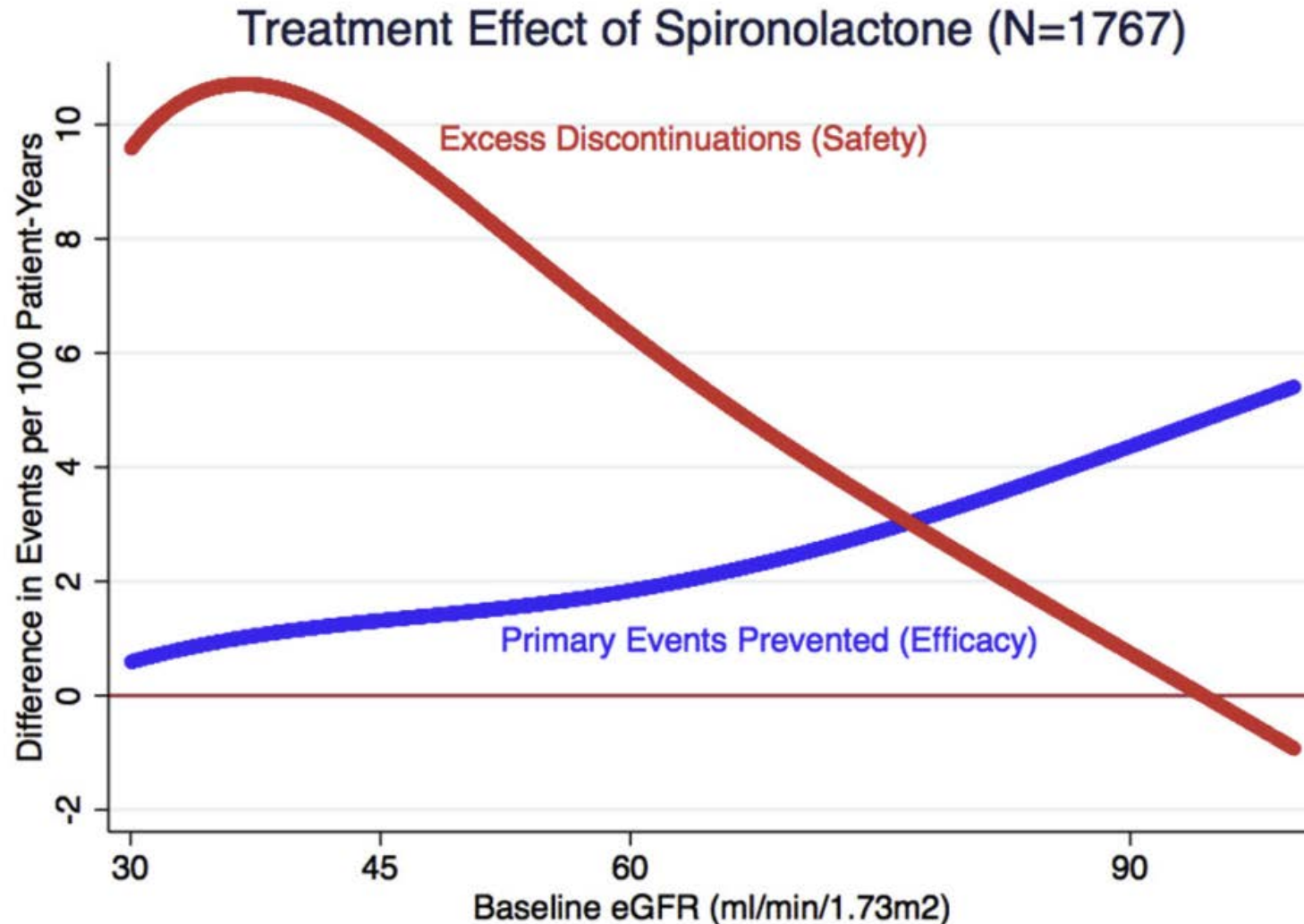


ARNI Exhibits Consistent Safety and Efficacy Irrespective of Baseline CKD

TABLE 2 Effect of Sacubitril/Valsartan on Renal and Cardiovascular Endpoints Stratified by Baseline CKD Status

	All Patients (N = 8,399)				CKD (n = 2,745) (eGFR < 60 ml/min/1.73 m ²)			No CKD (n = 5,654) (eGFR ≥ 60 ml/min/1.73 m ²)			
	Sacubitril/ Valsartan (n = 4,187)	Enalapril (n = 4,212)	HR (95% CI)	p Value	Sacubitril/ Valsartan (n = 1,333)	Enalapril (n = 1,412)	HR (95% CI)	Sacubitril/ Valsartan (n = 2,854)	Enalapril (n = 2,800)	HR (95% CI)	p Value Interaction
Cardiovascular endpoints											
CV death or HF hospitalization*	914 (22)	1,117 (27)	0.80 (0.73-0.87)	<0.001	358 (27)	465 (33)	0.79 (0.69-0.90)	556 (19)	652 (23)	0.81 (0.73-0.91)	0.70
CV death	558 (13)	693 (17)	0.80 (0.71-0.89)	<0.001	211 (16)	291 (21)	0.76 (0.63-0.90)	347 (12)	402 (14)	0.84 (0.72-0.96)	0.39
HF hospitalization	537 (13)	658 (16)	0.79 (0.71-0.89)	<0.001	223 (17)	288 (20)	0.79 (0.67-0.95)	314 (11)	370 (13)	0.81 (0.70-0.94)	0.83
All-cause mortality	711 (17)	835 (20)	0.84 (0.76-0.93)	<0.001	269 (20)	354 (25)	0.79 (0.68-0.93)	442 (15)	481 (17)	0.89 (0.78-1.01)	0.27

sMRA: Balance of Safety and Efficacy Across eGFR



- Consistent efficacy across eGFR categories: Pinteraction=0.13
- Increased absolute risk of permanent drug discontinuation in lower eGFR categories Pinteraction=0.003

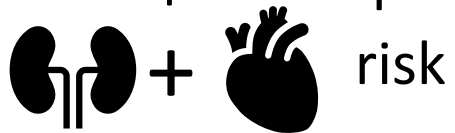
Risk Predication in CKD



2024 Clinical Practice Guidelines

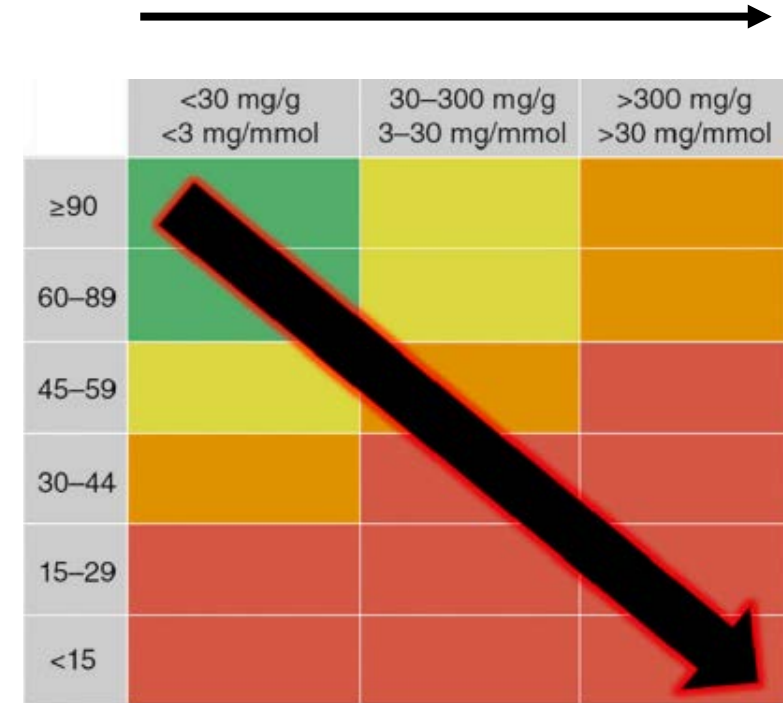
- Strongly recommends the use of externally validated risk stratification tools for clinical decision making

- ↓ eGFR and ↑ UACR predict adverse



eGFR

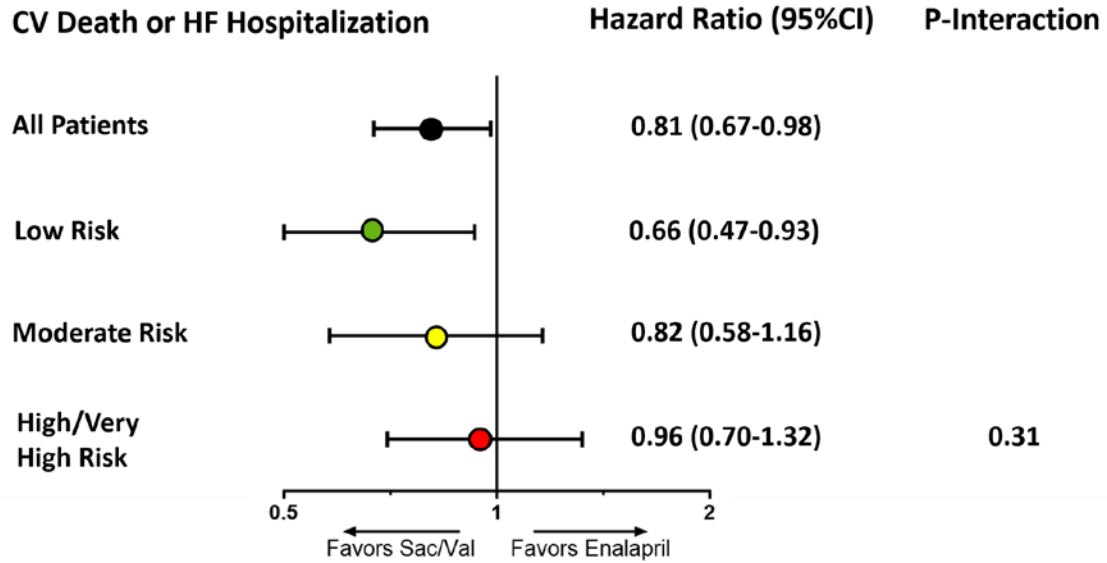
UACR



Both **eGFR** and **UACR** represent *different* axes of **CKD** risk and are **independently and incrementally prognostic**

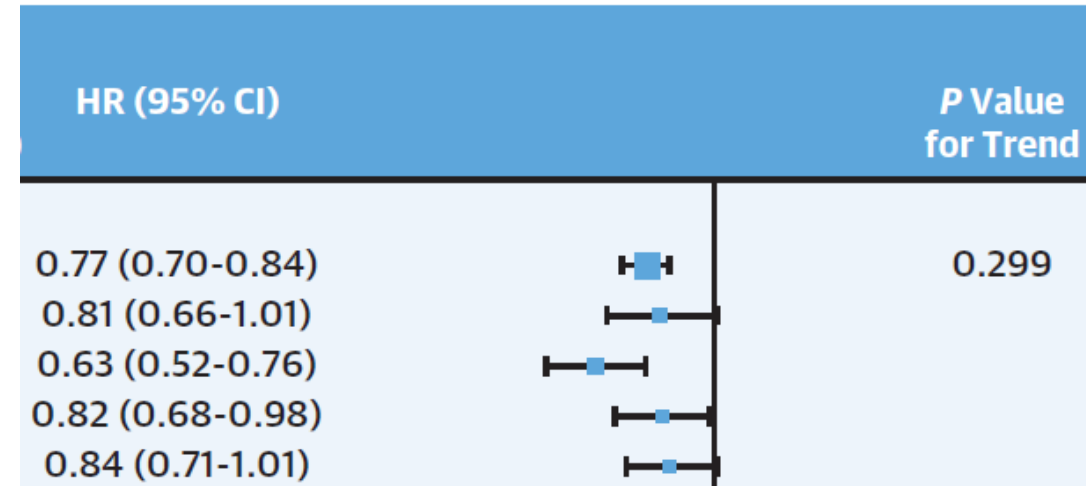
Treatment Effects Across KDIGO Risk Categories

Sacubitril/Valsartan: PARADIGM-HF



Chatur S et al; JACC(2024)

Empagliflozin: EMPEROR Program



Butler J et al; JACC(2023)

Initiation of HF GDMT According to Baseline CKD Status

Table 4 Initiation of heart failure drugs in relation to baseline chronic kidney disease status

Drug	Evidence across GFR strata according to baseline eGFR enrolment criteria				Acute drop GFR	Impact on GFR slope in HF trial	CKD treatment interaction	Treatment effect with CKD
	ESKD	15–30	30–60	>60				
ACE-I/ARB	Moderate evidence if dialysis, weak evidence if not on dialysis				Yes	No (beneficial effect of around 1–2 ml/min/1.73 m ² per year in CKD trials)	No	Relative benefit: ~ Absolute benefit: ↑
Beta-blockers					No	No	Yes (potentially but some conflicting results)	Relative benefit: ~ Absolute benefit: ↑
MRA					Yes	No	No	Relative benefit: ~ Absolute benefit: ↑
ARNI					Yes	Yes (around 0.5 ml/min/1.73 m ² per year)	No	Relative benefit: ~ Absolute benefit: ↑
SGLT2-i		>20			Yes	Yes (around 1–2 ml/min/1.73 m ² per year)	No	Relative benefit: ~ Absolute benefit: ↑
Ivabradine					No	No	No	Relative benefit: ~ Absolute benefit: ↑
Vericiguat					No	No	No	Relative benefit: ~ Absolute benefit: ↑
Omecamtiv mecarbil					No	No	No	Relative benefit: ~ Absolute benefit: ↑

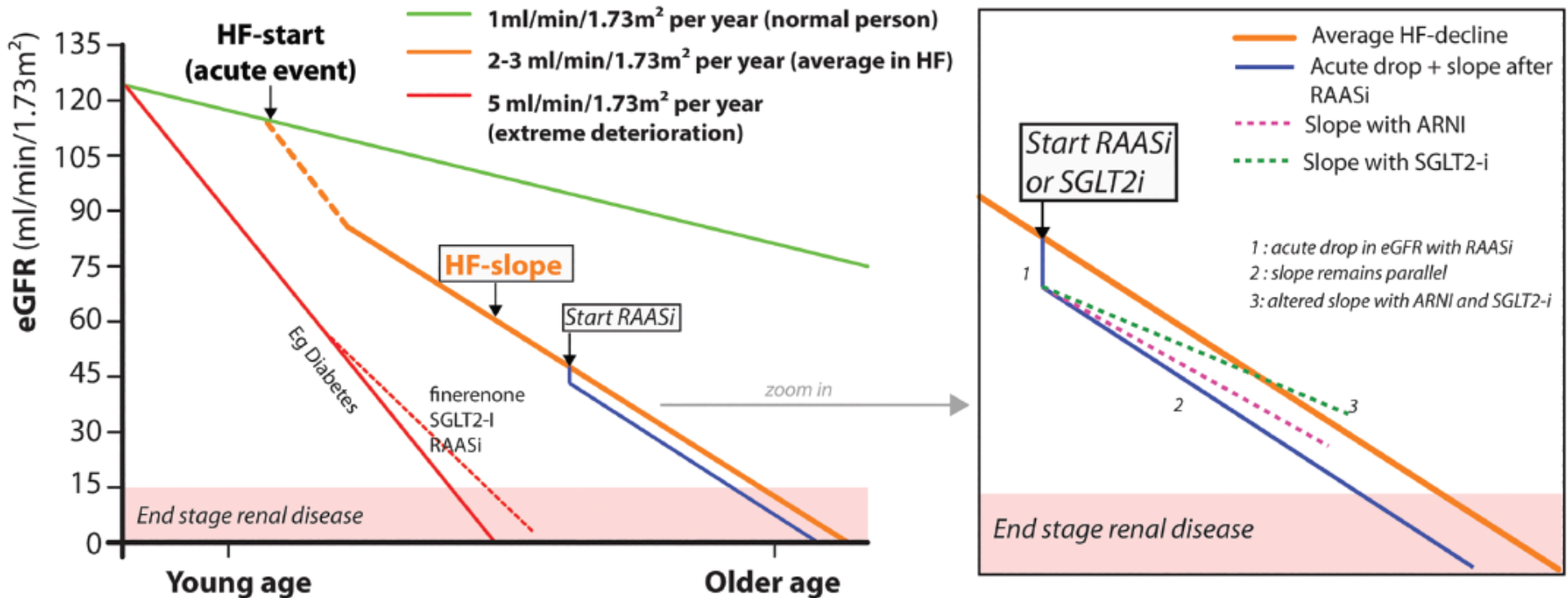
A decrease in eGFR over time does not automatically mean RAASi/SGLT2-i need to be downtitrated or discontinued

Dark green, strong evidence; light green, moderate evidence; red, not advised; light grey, no data. ACE-I, angiotensin-converting enzyme inhibitor; ABR, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; CKD, chronic kidney disease (eGFR <60 ml/min/1.73 m²); eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HF, heart failure; MRA, mineralocorticoid receptor antagonist; RAASi, renin–angiotensin–aldosterone system inhibitor; SGLT2-i, sodium–glucose cotransporter 2 inhibitor.

Renal Outcomes with ARNI and SGLT2i in HF

Trial	N	Design	ESKD events	≥40% / 50% ↓ in eGFR	Effect on renal endpoint
Angiotensin receptor–neprilysin inhibitors					
PARADIGM-HF	8442	Sac/val vs. enalapril	Sac/val: 8 (0.2%) Enalapril: 16 (0.4%)	Sac/val: 32 (0.8%) Enalapril: 41 (1.0%)	HR 0.63 (95% CI 0.42–0.95) for ESKD+ ≥50% eGFR decline (post hoc)
PARAGON-HF	4822	Sac/val vs. valsartan	Sac/val: 7 (0.3%) Valsartan: 12 (0.5%)	Sac/val: 27 (1.1%) Valsartan: 60 (2.5%)	HR 0.50 (95% CI 0.33–0.77) for ESKD+ ≥50% eGFR decline or renal death
Sodium–glucose cotransporter 2 inhibitors					
DAPA-HF	4744	Dapagliflozin vs. placebo	Dapagliflozin: 16 (0.7%) Placebo: 16 (0.7%)	Dapa: 14 (0.6%) Placebo: 23 (1.0%)	HR 0.71 (95% CI 0.44–1.16) for ESKD+ ≥50% eGFR decline or renal death
DELIVER	6262	Dapagliflozin vs. placebo	Dapagliflozin: 14 (0.4%) Placebo: 20 (0.6%)	Dapa: 74 (2.4%) Placebo: 68 (2.2%)	HR 1.08 (95% CI 0.79-1.49) Rate of eGFR decline: group difference 1.4 mL/min/year
EMPEROR-Reduced	3730	Empagliflozin vs. placebo	No breakdown ESKD vs. 40% eGFR drop Empagliflozin: 30 (1.6%), placebo: 58 (3.1%)		Rate of eGFR decline: group difference 1.7 ml/min/year
EMPEROR-Preserved	5988	Empagliflozin vs. placebo	No breakdown ESKD vs. 40% eGFR drop Empagliflozin: 108 (3.6%), Placebo: 112 (3.7%)		Rate of eGFR decline: group difference 1.4 ml/min/year

ARNI and SGLT2i Attenuate eGFR Decline

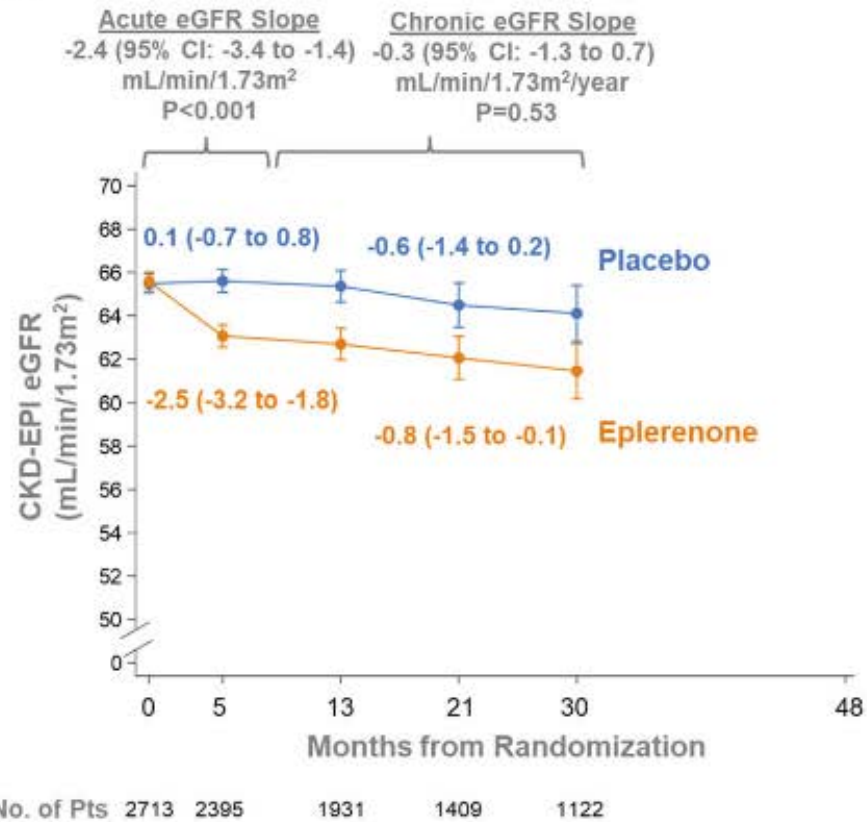


Key messages

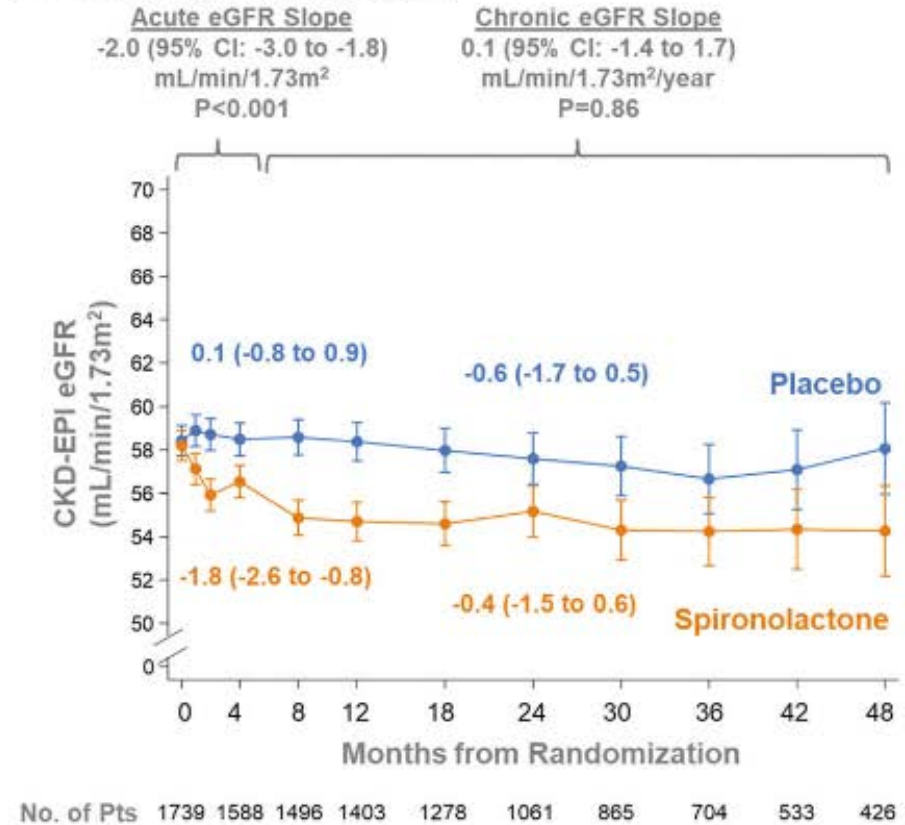
1. Acute drop in GFR with RAASi, ARNI and SGLT2-i does not diminishes treatment effect
2. A reduction in slope deterioration in HF rEF with ARNI and SGLT2-i is associated with reduced hard renal endpoints

MRA Does not Modify Long-Term eGFR Trajectory

A EMPHASIS-HF



B TOPCAT (Americas Region)

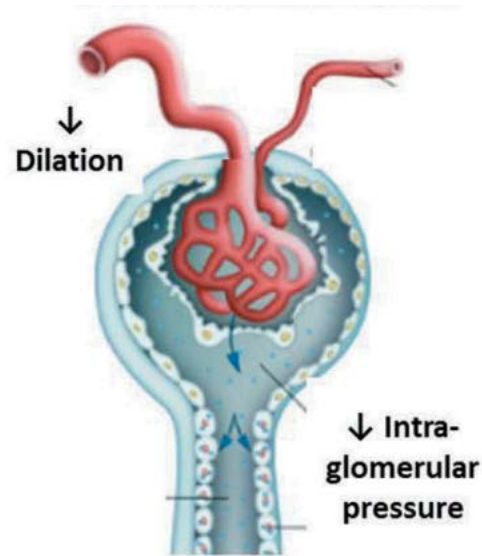


Variable Renal Responses to Established and Newer HF Therapies: Early “eGFR Dip”

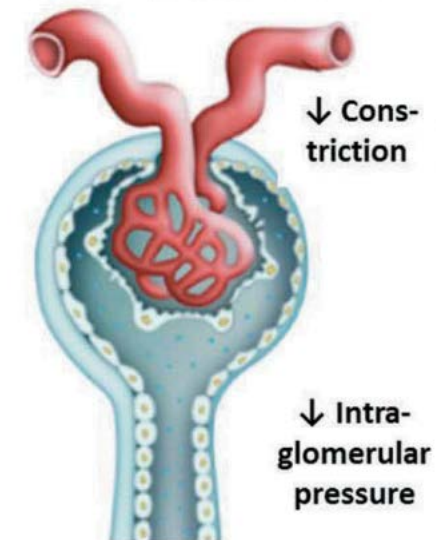
Evaluation of kidney function throughout the heart failure trajectory – a position statement from the Heart Failure Association of the European Society of Cardiology

Expert consensus statements suggest that moderate decline in eGFR of up to **15-20%** may be expected on treatment initiation

SGLT2 Inhibition

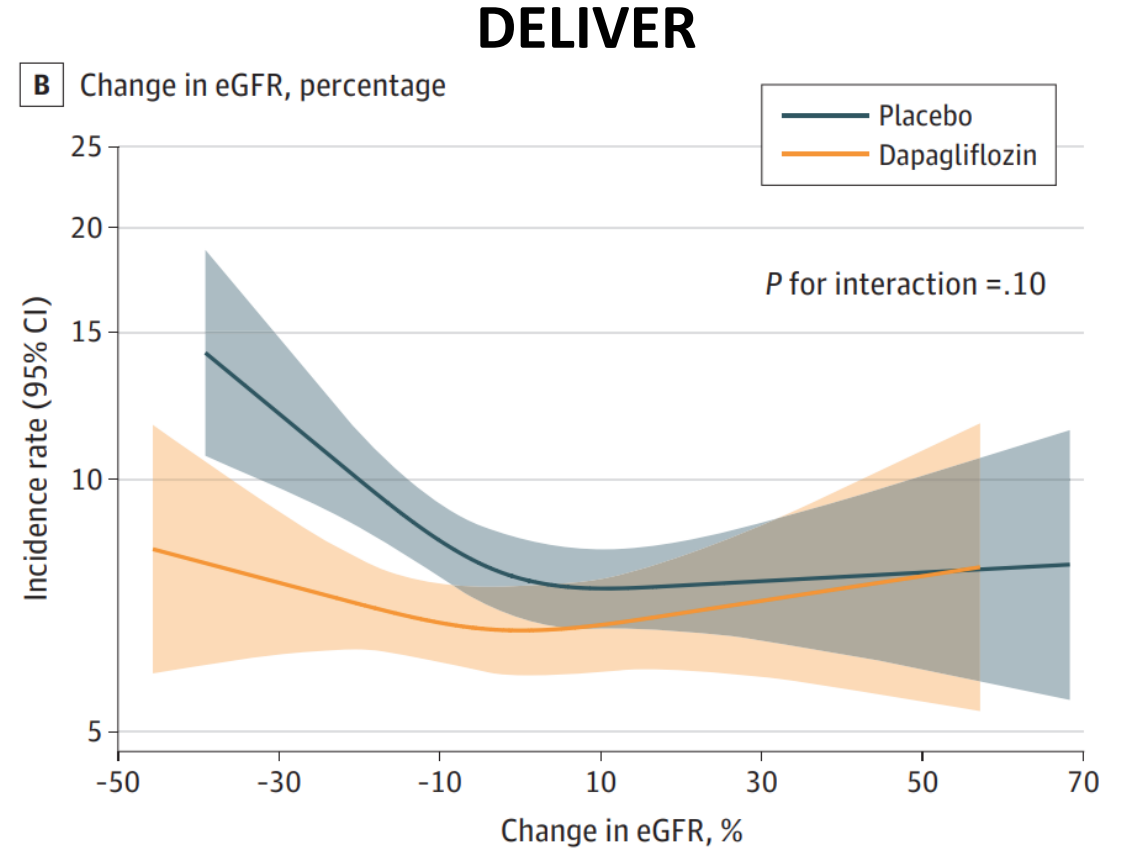
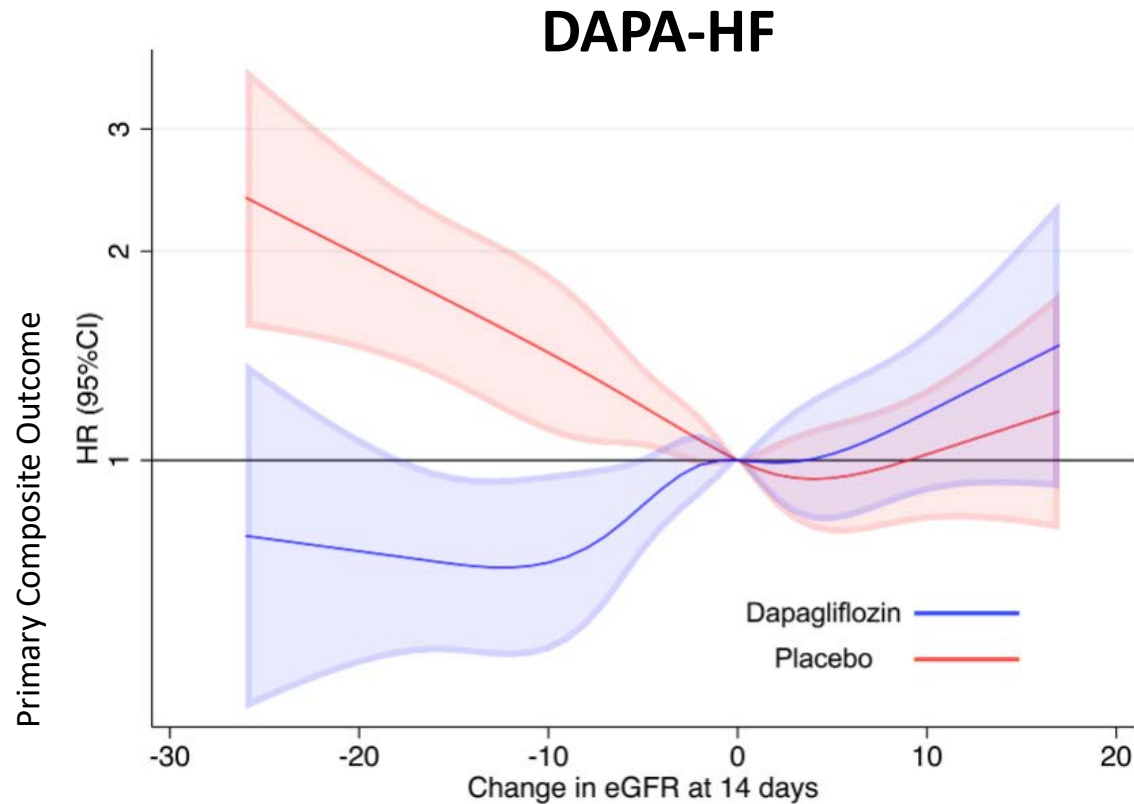


RAS/Neprilysin Inhibition



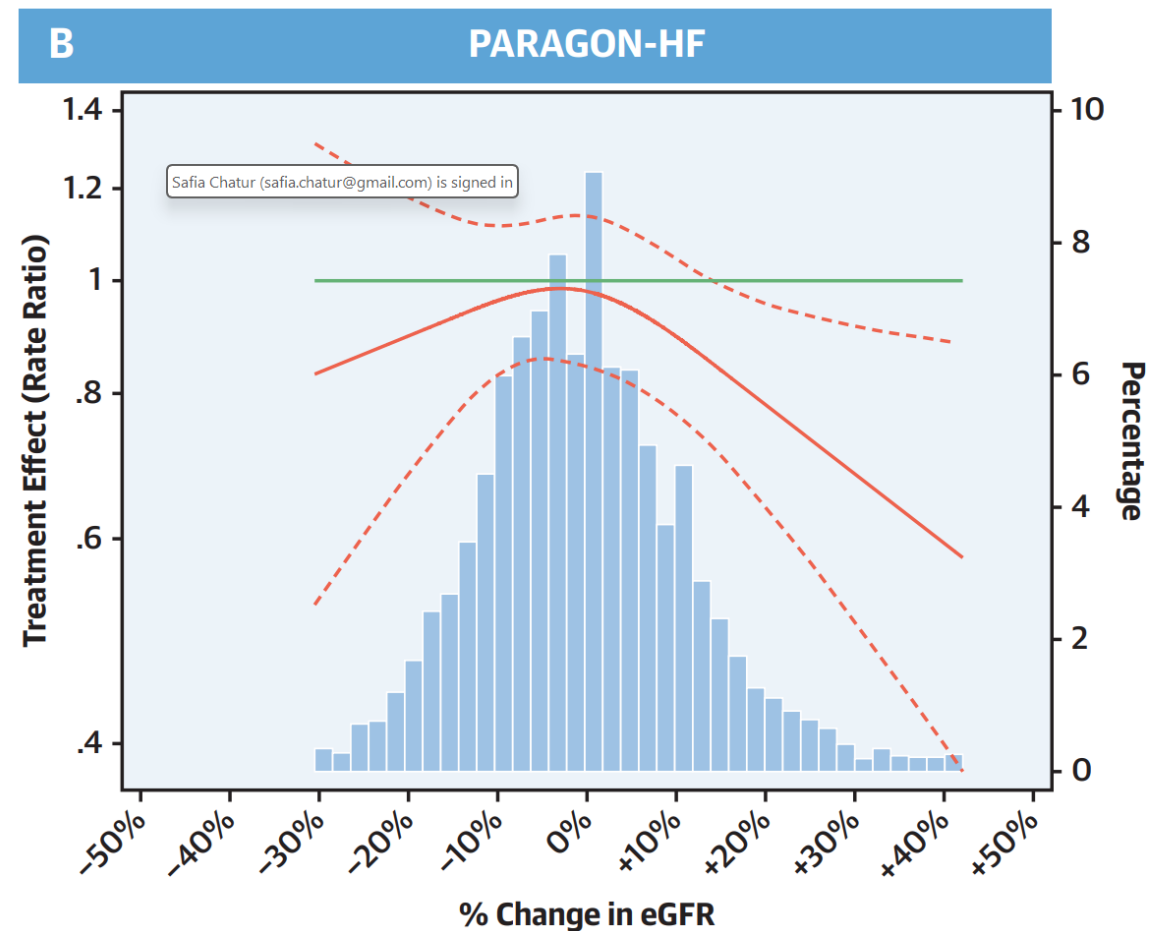
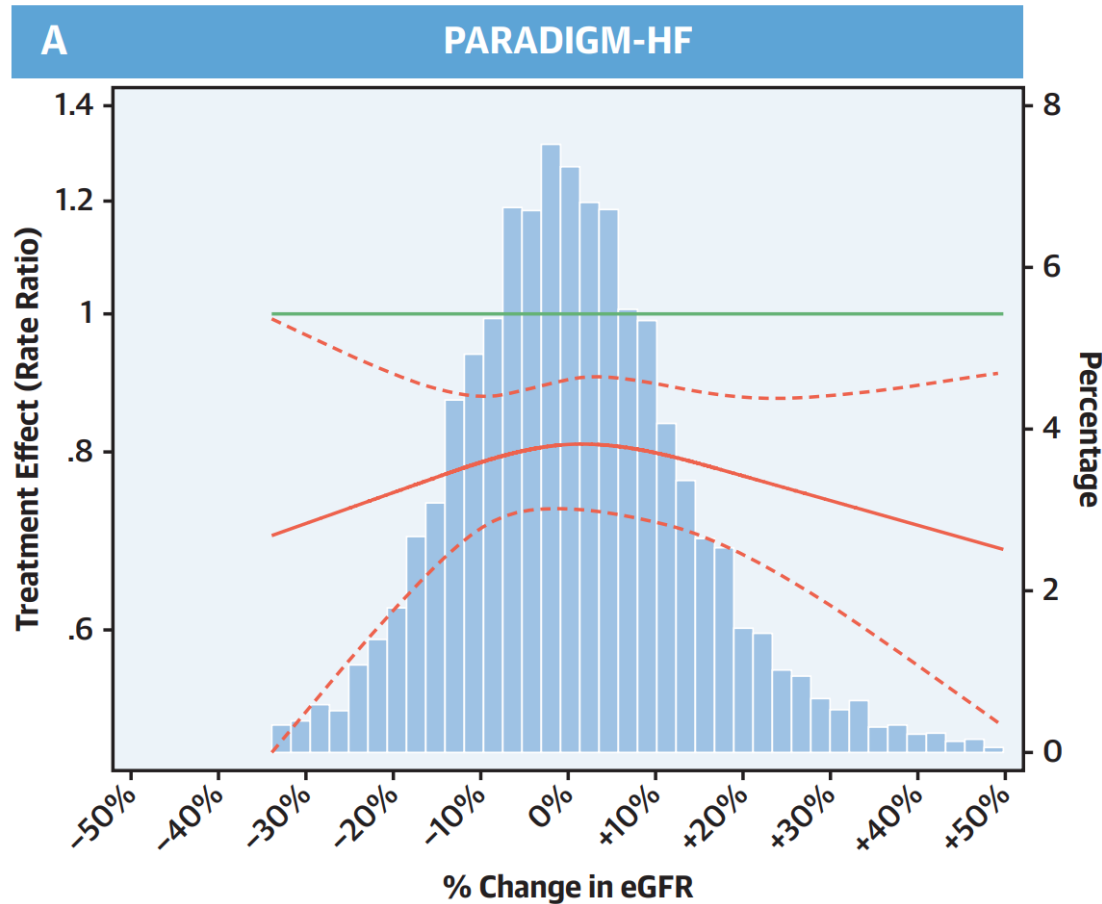
Early eGFR 'dip' on Treatment Initiation: SGLT2i

NOT adversely prognostic



Consistent treatment effects across a wide range of post-initiation eGFR declines

Early eGFR 'dip' on Treatment Initiation: ARNI



Consistent treatment effects across wide range of post initiation eGFR declines

Patients with More Advanced CKD?



			Persistent albuminuria categories		
			Description and range		
			A1	A2	A3
			<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
GFR categories (ml/min/1.73 m ²) Description and range	G1	≥90			
	G2	60–89			
	G3a	45–59			
	G3b	30–44			
	G4	15–29			
	G5	<15			

Trial	eGFR Threshold ml/min/1.73m ²
DAPA-HF	<30
DELIVER	<25
PARADIGM-HF	<30
PARAGON-HF	<25
EMPHASIS	<30
RALES	<30

Current US FDA/Expert Consensus Guidance

SGLT2i

US FDA Labelling

- Does not recommend initiation of dapagliflozin in patients with eGFR<25; however, can be continued to reduce CV and kidney risk.



2021 ESC Guidelines

- SGLT2i *contraindicated* in patients with baseline **eGFR< 20**

ARNI

US FDA Labelling

- Does *NOT identify* threshold **renal function precluding initiation or continuation** of sacubitril/valsartan
- Dose reduction of sacubitril/valsartan with eGFR< 30 mL/min/1.73 m²



2021 ESC Guidelines

- Sacubitril/valsartan *contraindicated* in patients with baseline **eGFR< 30** and should be *discontinued* if **eGFR falls below 30**

sMRA

US FDA Labelling

- Does not recommend initiation of dapagliflozin in patients with eGFR<30

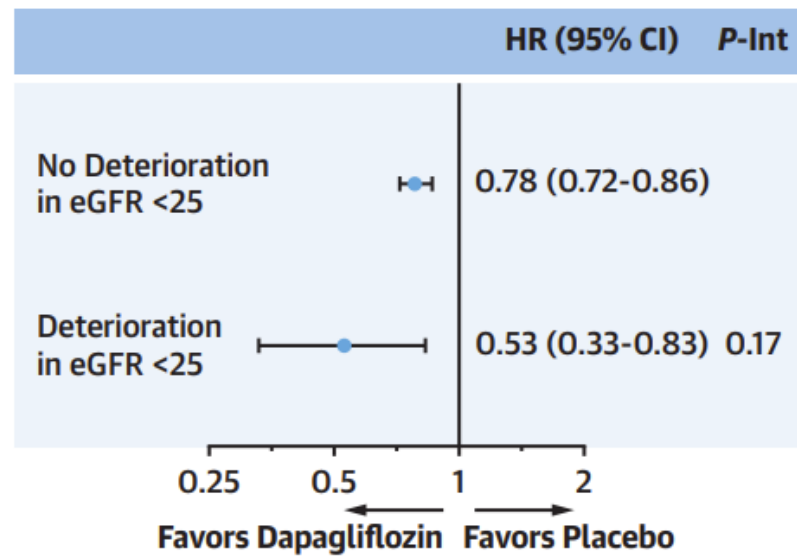


2021 ESC Guidelines

- MRA *contraindicated* in patients with baseline **eGFR< 30**. Halve dose and monitor if eGFR drops to <30; discontinue immediately if eGFR drops to <20

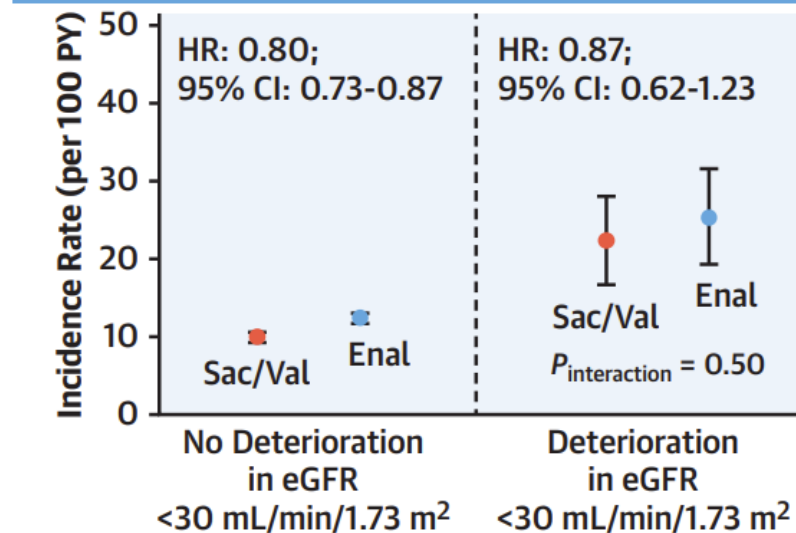
Benefit-to-Risk Ratio May Favor Continuation of Therapy with eGFR Decline < Threshold for Trial Inclusion

Dapagliflozin Reduced CV Death or Worsening HF Irrespective of Deterioration in eGFR <25 mL/min/1.73 m²



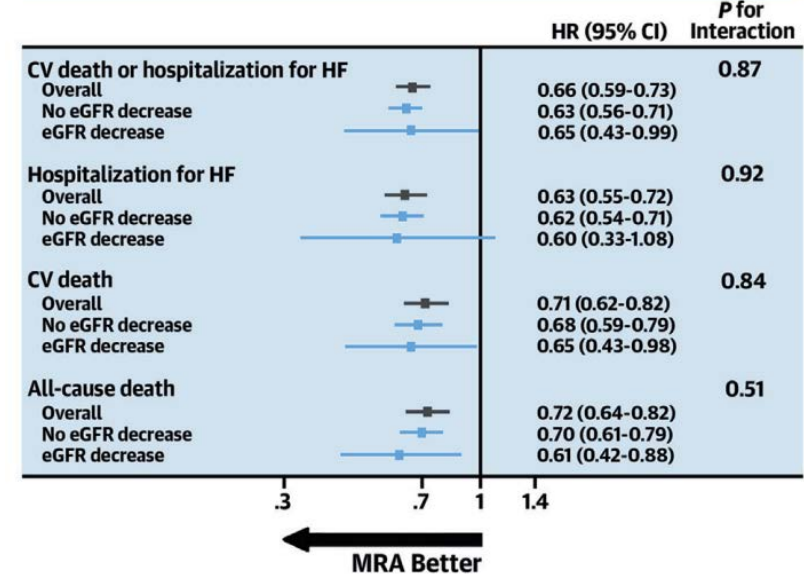
Chatur S et al; JACC(2023)

First HF Hospitalization or CV Death
PARADIGM-HF



Chatur S et al; JACC-HF(2024)

Effects of MRA Compared to Placebo According to Decrease in eGFR to <30 mL/min/1.73 m²



Matsumoto S et al; JACC(2024)

Ongoing Clinical Trials Will Help To Fill The Knowledge Gap in Advanced CKD

SGLT2i

- RENAL LIFECYCLE Trial
- SDHF

ARNI

- ESARHD-HF
- The Effect of Sacubitril/Valsartan on CV Events in Maintenance Dialysis Patients: A Prospective Cohort Study

Further Randomized evidence is required to better understand the safety and efficacy of components of HF GDMT in patients with HF and advanced CKD



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Transforming patient care.

Q & A