Interventions for Optimizing Guideline Directed Medical Therapy for Heart Failure

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Disclosures: Consulting for Abbott, Amgen, AstraZeneca, Bayer, Cytokinetics, Janssen, Medtronic, Merck, Novartis, and Pfizer

Heart Failure Background

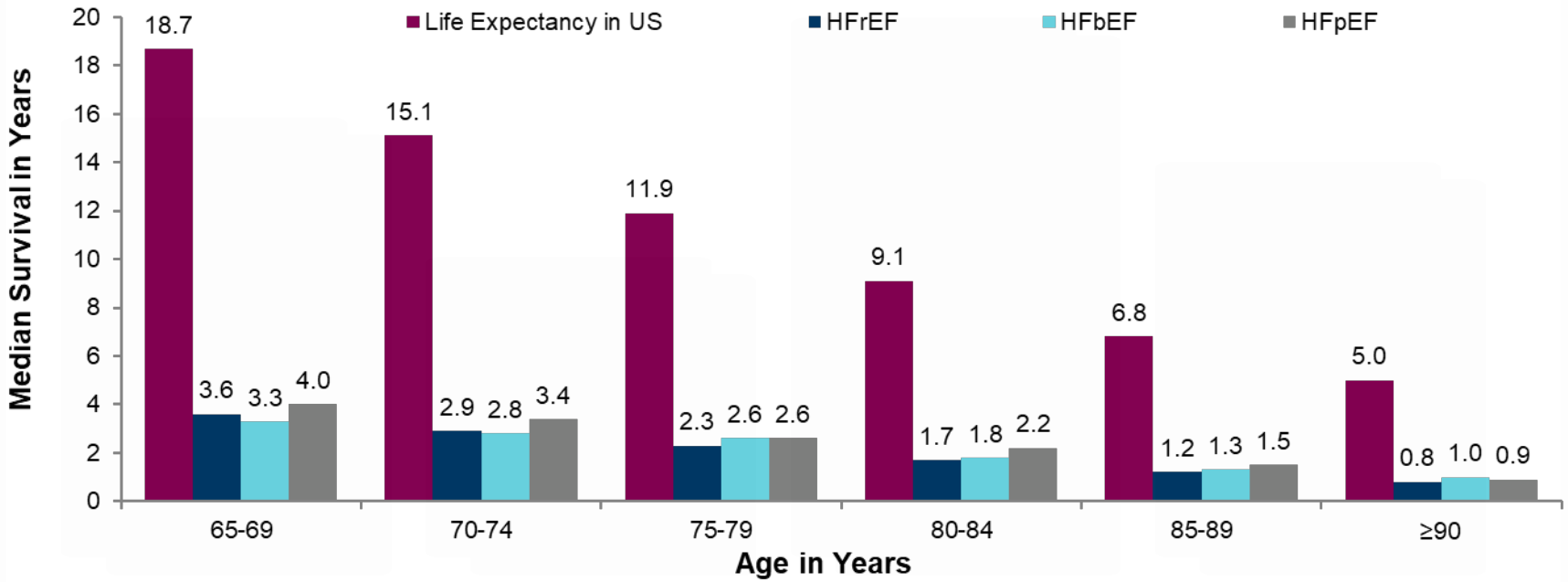
Population Group	Prevalence	Incidence	Mortality	Hospital Discharges	Cost
Total population	6,700,000	1,000,000	421,938 (50% at 5 years)	1,111,500 (3 million secondary)	$30.7 billion

- Heart failure (HF) is a major public health problem resulting in substantial morbidity, mortality, and healthcare expenditures in the US and globally
- Despite treatment advances large number of eligible patients are not receiving one or more evidence-based, guideline-recommended HF therapies
- Greater therapeutic urgency needed

American Heart Association. *2024 Heart and Stroke Statistical Update.* Dallas, Tex: American Heart Association; 2024, Circulation in Press

Outcomes for Heart Failure Compared with the General US Population

Median Survival Stratified by Age



Across various age groups, median survival is substantially greater in the general US population compared with patients with HF across the EF spectrum. Data from GWTG-HF linked to CMS and the National Vital Statistics Report 2004.

Shah KS..Fonarow GC. *J Am Coll Cardiol.* 2017;70(20):2476-2486.

Evidence-Based HFrEF Therapies

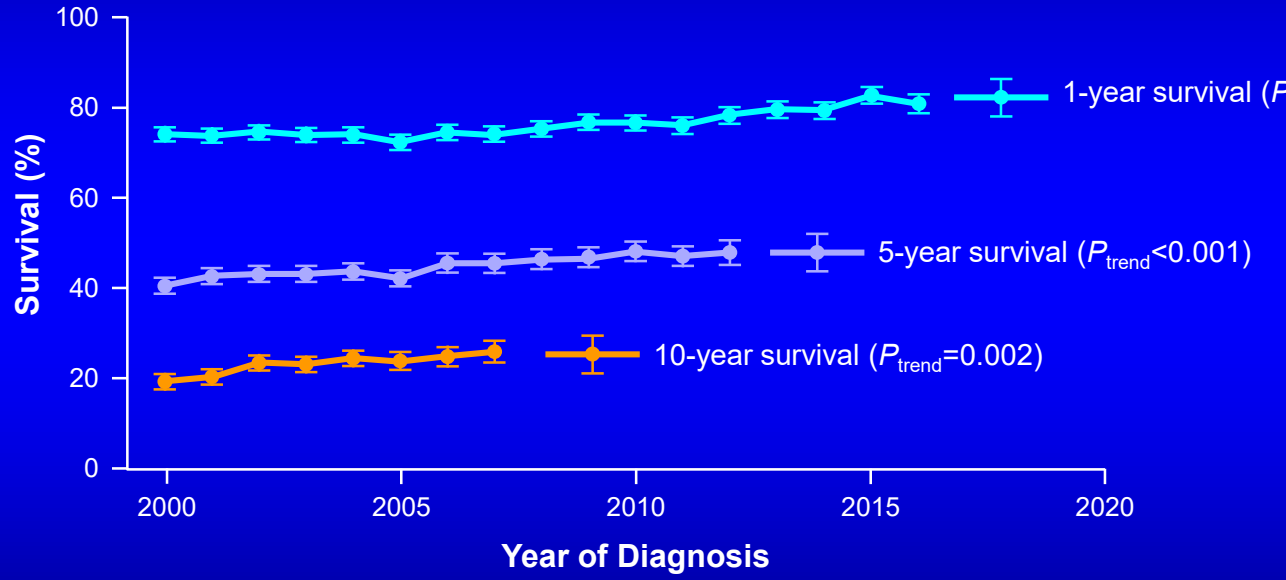
Guideline Recommended Therapy	Relative Risk Reduction in Mortality	Number Needed to Treat for Mortality	NNT for Mortality (standardized to 36 months)	Relative Risk Reduction in HF Hospitalizations
ACEI/ARB	17%	22 over 42 months	26	31%
ARNI*	16%	36 over 27 months	27	21%
Beta-blocker	34%	28 over 12 months	9	41%
Aldosterone Antagonist	30%	9 over 24 months	6	35%
SGLT2 Inhibitor	17%	43 over 18 months	22	30%
Hydralazine/Nitrate**	43%	25 over 10 months	7	33%
CRT	36%	12 over 24 months	8	52%
ICD	23%	14 over 60 months	23	NA

Updated from Fonarow GC, et al. Am Heart J 2011;161:1024-1030.

* Incremental to ACEI/ARB ** Self Identified African Americans

Mortality Among Patients Diagnosed with HF is High

Survival Rates for People With New Onset HF by Year of Diagnosis



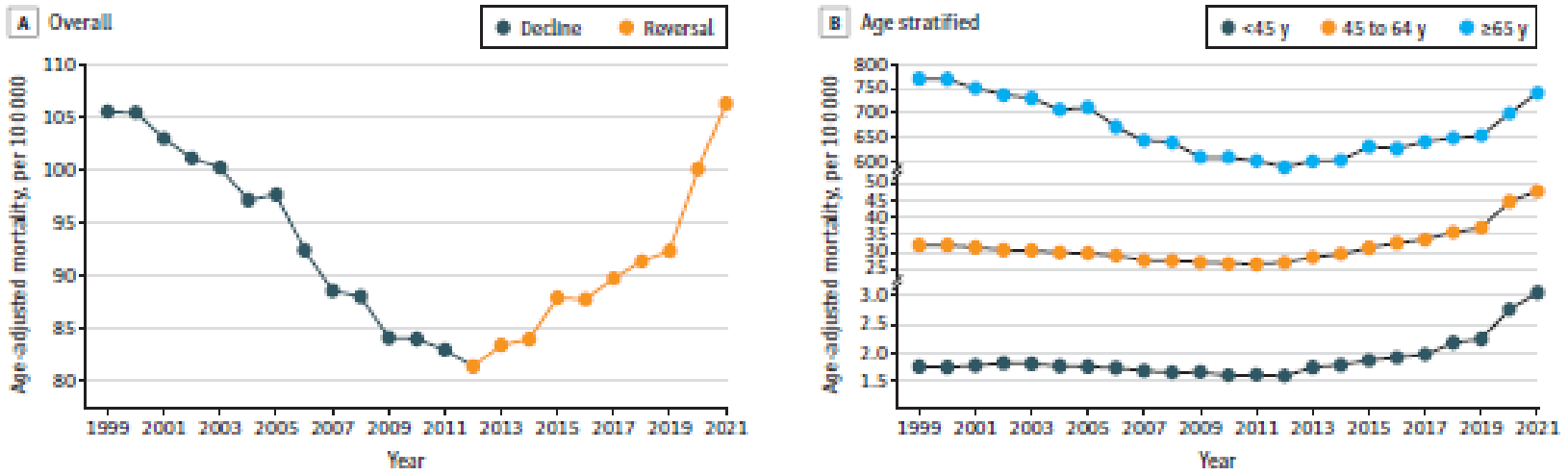
Despite the availability of therapies with established efficacy in HFrEF, morbidity and mortality rates remain high[2]

Primary care data in the United Kingdom for 55,959 patients aged 45 years and older with a new diagnosis of HF and 278,679 age- and sex-matched controls.

1. Taylor CJ et al. *BMJ.* 2019;364:l223. doi:10.1136/bmj.l223; 2. Yancy CW et al. *J Am Coll Cardiol.* 2018;71(2):201-230.

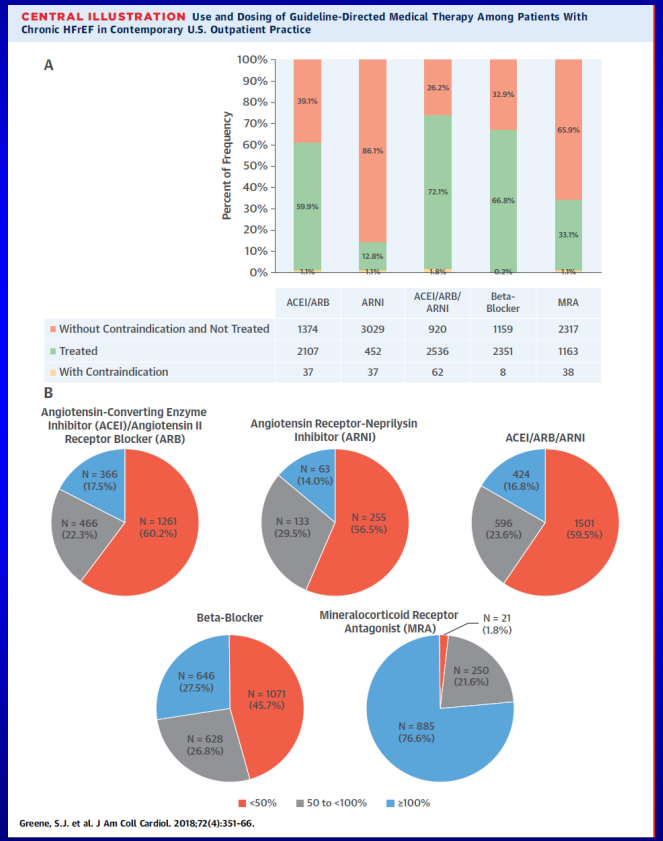
Reversals in the Decline of Heart Failure Mortality in the US, 1999 to 2021

Figure. Temporal Trends in Heart Failure-Related Mortality in the US, 1999 to 2021



JAMA Cardiol. 2024 Jun 1;9(6):585-589.

Use and Dosing of GDMT for HFrEF in the US CHAMP-HF Registry 2016-2018



Most receiving ACEI/ARB and BB

ARNI use 13% in eligible patients
MRA use 33% in eligible patients

When medications were prescribed, few patients were receiving target doses of ACEI/ARB (17%), ARNI (14%), and beta-blocker (28%).

Among patients eligible for all classes of medication, 1% were simultaneously receiving target doses of ACE/ARB/ARNI, beta-blocker, and MRA.

3,518 patients from 150 primary care and cardiology practices

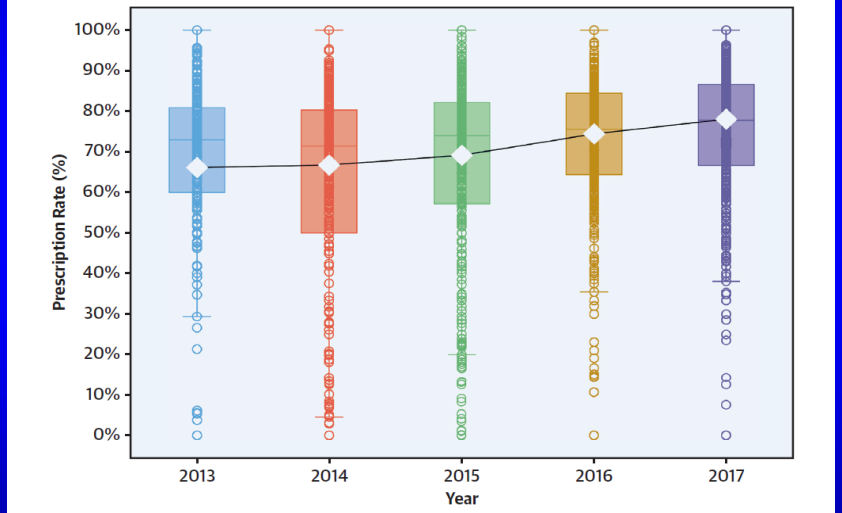
Greene SC, Fonarow, GC. JACC 2018:72(4)351-366

Use of Medical Therapy for HFrEF in the US ACC PINNACLE Registry 2013-2017

Information on 6,040,996 HF patient visits, cared for by 8,853 clinicians in 724 US practices

ACEI or ARB

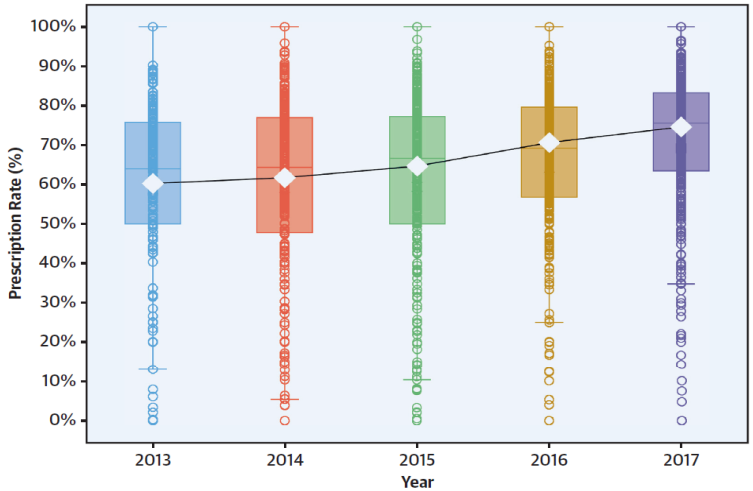
FIGURE 5 Patient Rates and Practice Variation of ACEI, ARB, or ARNI in Patients With HF, Stratified by Year



ACEI/ARB/ARNI	2013 (N = 496,950)	2014 (N = 644,463)	2015 (N = 732,865)	2016 (N = 830,452)	2017 (N = 843,347)	P-value for trend
Patient rates (numerator/eligible denominator)	66.1% (91,883/139,015)	66.8% (119,382/178,835)	69.2% (132,148/191,052)	74.5% (155,117/208,345)	78.0% (166,866/213,855)	<0.001
Practice variation (median, IQR)	73.0% (60.0%, 80.9%)	71.4% (50.0%, 80.3%)	73.9% (57.1%, 82.1%)	75.6% (64.4%, 84.5%)	77.8% (66.7%, 86.6%)	<0.001

Beta Blocker

FIGURE 4 Patient Rates and Practice Variation of Guideline-Indicated BBs (Carvedilol, Metoprolol Succinate, or Bisoprolol) in Patients With HF, Stratified By Year



Guideline-indicated beta-blockers	2013 (N = 496,950)	2014 (N = 644,463)	2015 (N = 732,865)	2016 (N = 830,452)	2017 (N = 843,347)	P-value for trend
Patient rates (numerator/eligible denominator)	60.2% (83,869/139,203)	61.7% (110,696/179,273)	64.7% (123,702/191,261)	70.6% (147,239/208,521)	74.6% (159,518/213,872)	<0.001
Practice variation (median, IQR)	63.9% (50.0%, 75.8%)	64.3% (47.7%, 76.9%)	66.7% (50.0%, 77.2%)	69.3% (56.7%, 79.6%)	75.6% (63.4%, 83.3%)	<0.001

Maddox TM, et al J Am Coll Cardiol 2020;75:93–112.

Use of ARNI <10% Use of MRA <25%

Globally HFrEF Patients are Not Receiving Optimal GDMT

REPORT-HF: Prospective study of patients hospitalized for acute HFrEF across 44 countries

	Total (N=18 102)	Central and South America (n=2525)	Eastern Europe (n=2761)	Eastern Mediterranean region and Africa (n=2172)	North America (n=1565)	Southeast Asia (n=2292)	Western Europe (n=3489)	Western Pacific (n=3298)	p value*
(Continued from previous page)									
Medication at 6-month follow-up									
ACEi or ARB†	9189 (59%)	1272 (61%)	1704 (69%)	1140 (63%)	712 (53%)	876 (44%)	1923 (64%)	1562 (55%)	<0·0001
β blocker†	10 437 (67%)	1400 (67%)	1883 (76%)	1222 (68%)	1057 (78%)	925 (47%)	2330 (78%)	1620 (57%)	<0·0001
Diuretics†	11 176 (67%)	1345 (65%)	1923 (78%)	1376 (63%)	1078 (80%)	1326 (67%)	2516 (84%)	1614 (57%)	<0·0001
MRA†	6608 (43%)	9539 (45%)	1289 (52%)	573 (32%)	469 (35%)	528 (27%)	1411 (47%)	1399 (50%)	<0·0001

37% of patients at discharge and 34% at 6 months were on three medication classes (ACEI/ARB/ARNI, beta-blocker, MRA)[1]

Rates of patients receiving GDMT were lower in lower- and middle-income countries vs high-income countries (19 vs. 41% at discharge; 15 vs. 37% at 6 months)[1,2]

REPORT-HF: an observational, prospective, global cohort study (n=18,553) with patients prospectively enrolled across 358 sites from 44 countries on six continents aiming to assess international variations in clinical practice patterns and outcomes for patients with acute heart failure. The first patient was enrolled in July 23, 2014, and last patient March 2017.

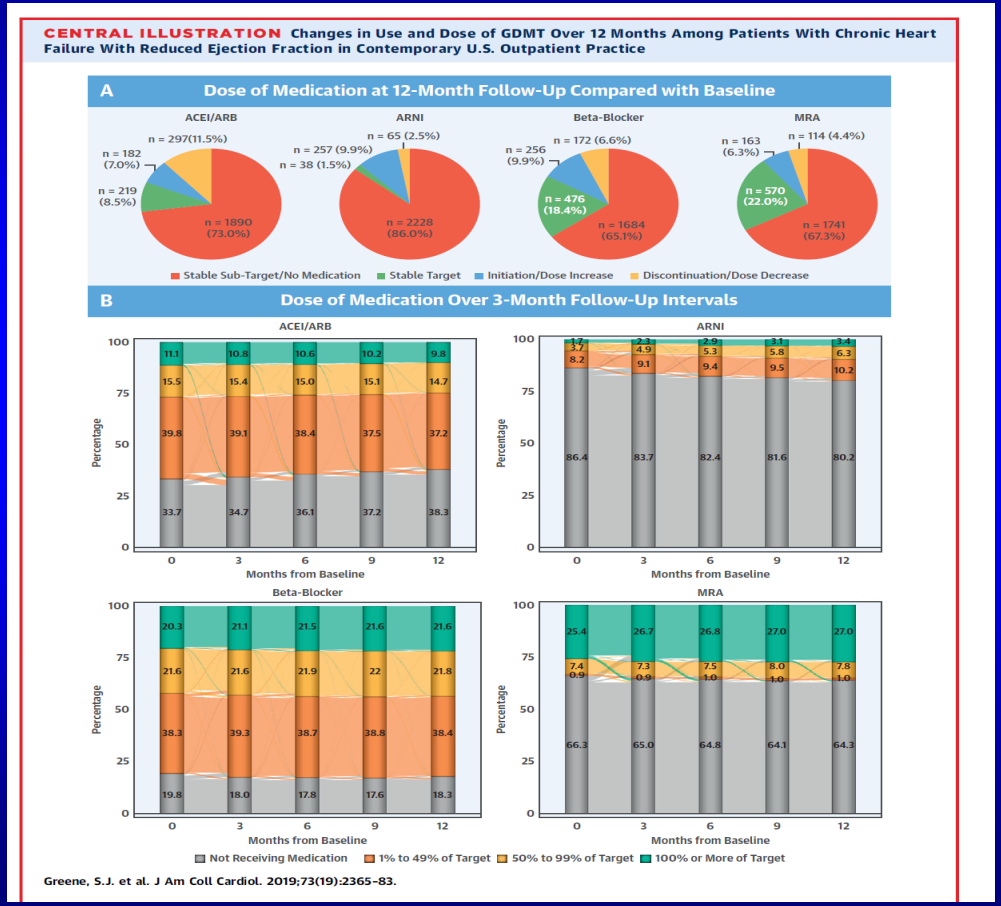
References: 1. Tromp J et al. Eur Heart J 2022; 43: 2224-2234. **2.** Tromp J et al. Lancet Glob Health 2020; 8: e411-e422.

Reasons for Underutilization of Evidence-Based Therapies

- Gaps in knowledge and awareness
- Lack of systems
- Therapeutic inertia and insufficient urgency
- RCTs study patient populations perceived as too narrow in scope
- Uncertainty regarding “effectiveness”
- Concerns about side effects
- Questions regarding: drug/device safety
- Bias (age, sex, race/ethnicity, socioeconomic)
- Concerns about access, costs, and value
- Misalignment in financial incentives

Fonarow, GC et al. Circulation. 2010;122:585–596

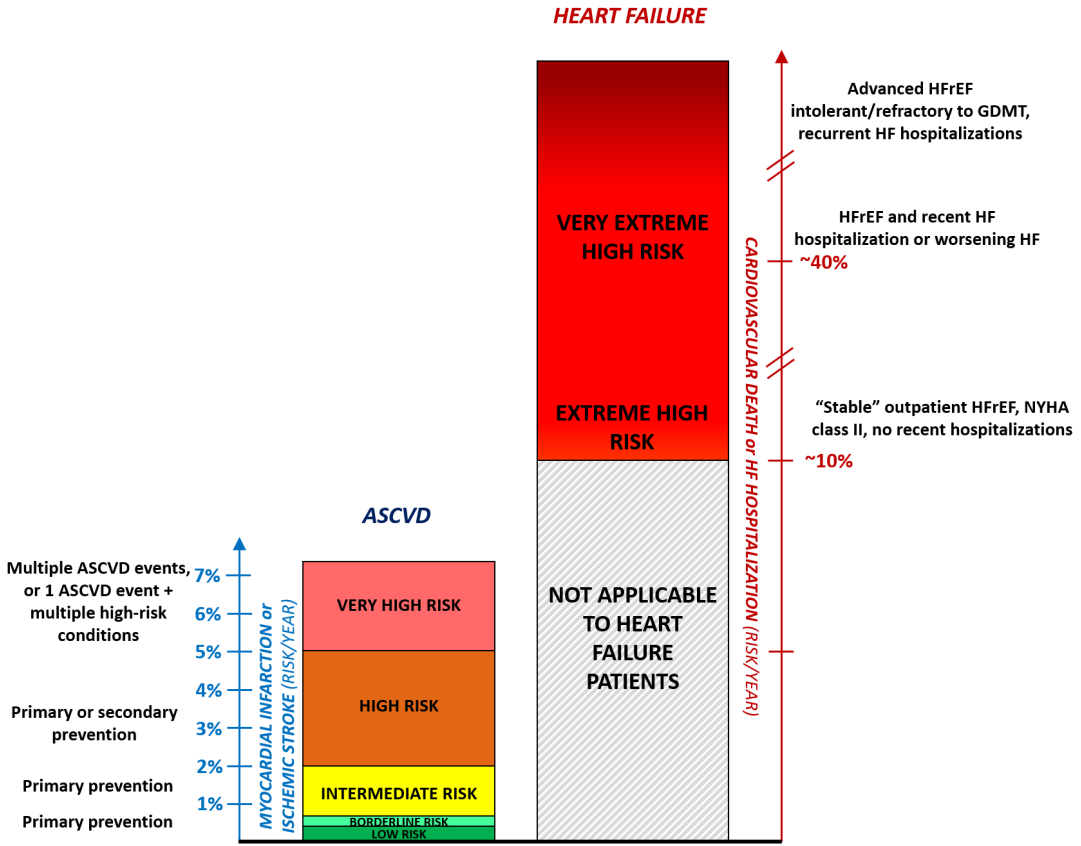
Longitudinal Use/Dosing of GDMT for HFrEF: CHAMP HF Registry
Therapeutic Inertia



Most patients with HFrEF, despite the absence of documented contraindications or intolerance, had no improvement in the use or dosing of GDMT during or after each and every visit that occurred during 12 months of outpatient follow-up

2588 patients from 150 primary care and cardiology practices

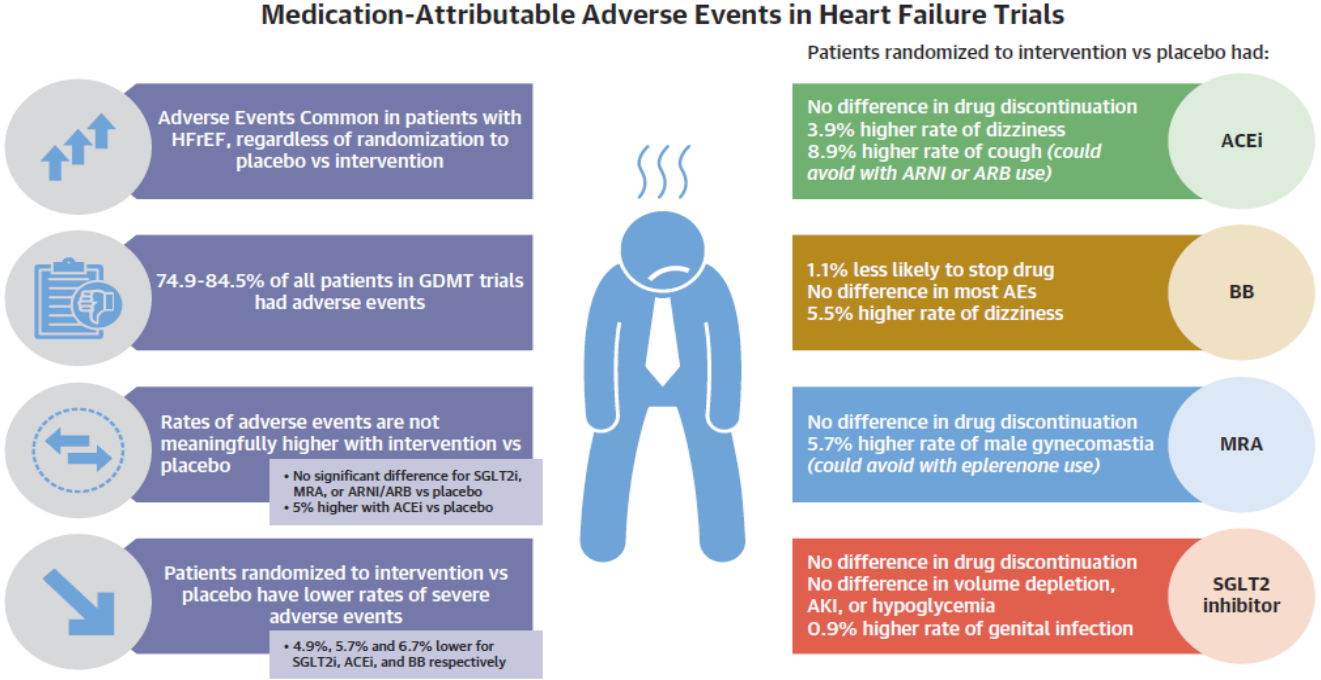
Contextualizing Risk Among Patients with Heart Failure



"The current generalized lack of therapeutic urgency translates to an unfortunate cycle whereby clinical risk is underappreciated, medication changes are deferred, time is lavished, and patients die or require hospitalizations without receiving therapies proven to prevent these events"

Greene SJ, Butler J, Fonarow GC. Contextualizing risk among patients with heart failure. *JAMA. 2021* doi:10.1001/jama.2021.20739

CENTRAL ILLUSTRATION Medication-Attributable AEs in Heart Failure Trials



Harrington J, et al. J Am Coll Cardiol HF. 2023;■(■):■-■.

ACE = angiotensin-converting enzyme; AE = adverse event; AKI = acute kidney injury; BB = beta-blocker; GDMT = guideline-directed medical therapy; HFrEF = heart failure with reduced ejection fraction; mineralocorticoid receptor antagonist; SGLT2 = sodium-glucose cotransporter 2.

JACC Heart Fail. 2023 Apr;11(4):425-436

What is the Effect of Adding One GDMT to Another in HFrEF?

- Subtractive 1 + 1 = 0.5
- Redundant 1 + 1 = 1.0
- Partially Additive 1 + 1 = 1.5
- Fully Additive 1 + 1 = 2.0
- Synergistic 1 + 1 = 2.5

Greene, Butler, Fonarow. *JAMA Cardiology* 2021 doi:10.1001/jamacardio.2021.0496.

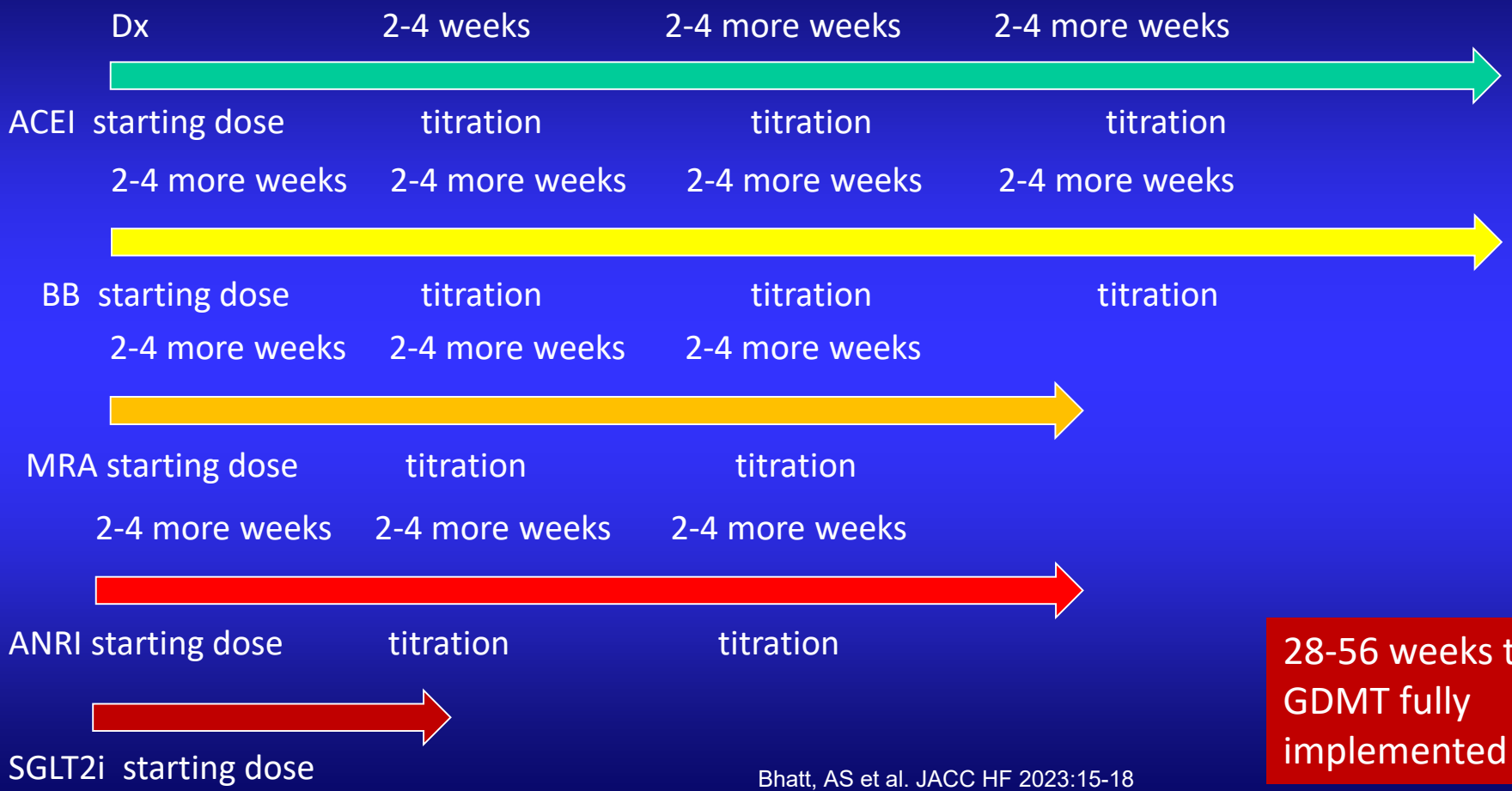
Cumulative Impact of Evidence-Based Heart Failure with Reduced EF Medical Therapies

	Relative-risk	2 yr Mortality
None	- -	35%
ACEI or ARB	↓ 23%	27%
Beta Blocker	↓ 35%	18%
Aldosterone Ant	↓ 30%	13%
ARNI (replacing ACEI/ARB)	↓ 16%	10.9%
SGLT2 inhibitor	↓ 17%	9.1%

Cumulative risk reduction if all evidence-based medical therapies are used:
Relative risk reduction 74.0%, Absolute risk reduction: 25.9%, NNT = 3.9

Updated from Fonarow GC, et al. Am Heart J 2011;161:1024-1030 and Lancet 2008;372:1195-1196.

Sequencing of GDMT: Serial Strategy



28-56 weeks till GDMT fully implemented

Bhatt, AS et al. JACC HF 2023:15-18

GDMT: Simultaneous/Rapid Sequence Strategy

Quadruple Foundational Guideline Directed Medical Therapy from Day 1

Hospitalized or outpatient

Day 1	Day 7-14	Day 14-28	Day 21-42	Beyond
ARNI	…	(Titrate, as tolerated)	Titrate, as tolerated	• Maintenance / further optimization of foundational therapies • Consideration of EP device therapies/TEER • Consideration of add-on therapies or advanced therapies, if refractory • Manage comorbidities
BB	Titrate, as tolerated	Titrate, as tolerated	Titrate, as tolerated	
MRA	…	Titrate, as tolerated	…	
SGLT2i	…	…	…	

Low starting doses
Prioritize beta-blocker titration

Benefits of each Rx demonstrated within 30 days of initiation
Cumulative benefits within 30 days (>75% relative risk reduction)

Focus on complete set of GDMT being implemented

Greene, Butler, Fonarow. *JAMA Cardiology* 2021 doi:10.1001/jamacardio.2021.0496.

Benefits of Simultaneous or Rapid Initiation of ARNi, BB, MRA, and SGLT2i for HFrEF Are Multifaceted

Benefits of Initiating ARNi+BB+MRA+SGLT2i as First-line Treatment for HFrEF Versus Drawn-out Historical Sequencing

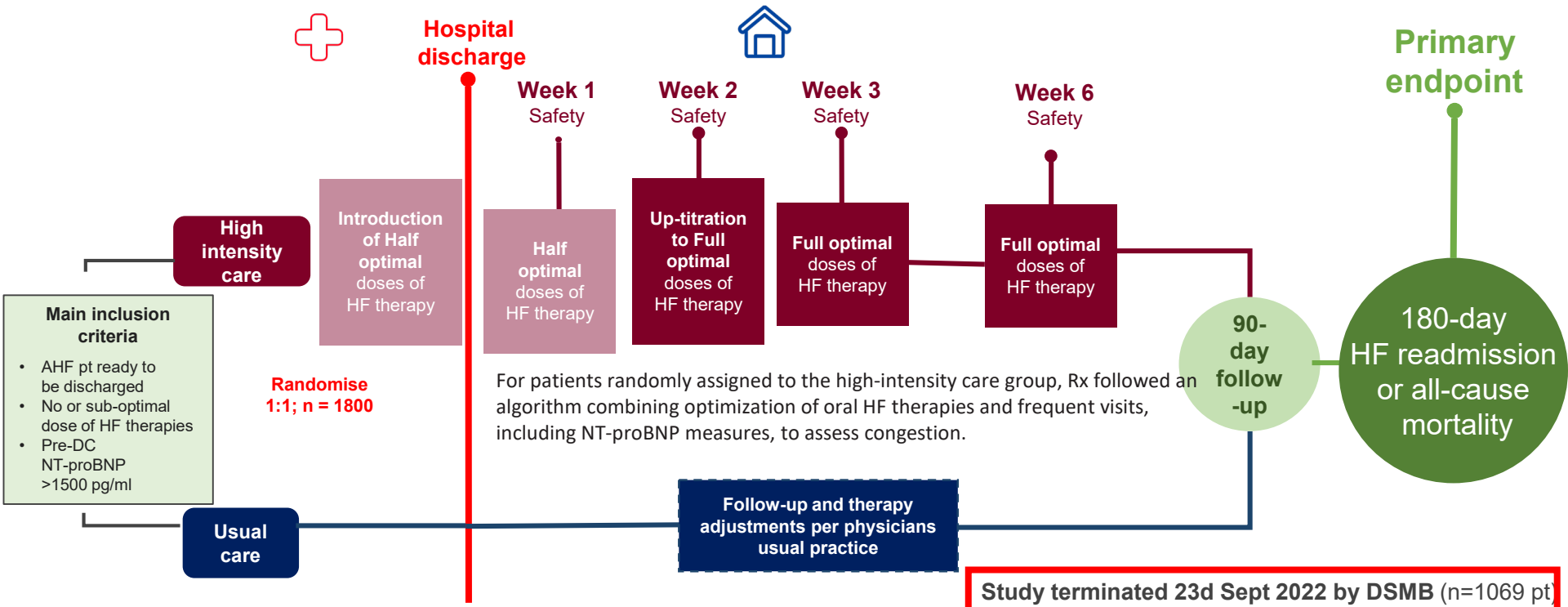
- Rapid improvement in health status (within 1 to 8 weeks)[1,*]
- Rapid improvement in LVEF (within 12 weeks)[2]
- Rapid reduction in HF hospitalizations (within 2 to 4 weeks)*
- Rapid reduction in HF rehospitalizations (within 2 to 4 weeks)[3]
- Rapid reduction in mortality (within 2 to 4 weeks)*
- Improved use, adherence, persistence, overcoming inertia[4,*]

ARNi, angiotensin receptor-neprilysin inhibitor; BB, beta-blocker; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction;
MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium-glucose cotransporter-2 inhibitor.

1. Khariton Y, et al. *JACC Heart Fail*. 2019;7:933-941. 2. Desai AS, et al. *JAMA*. 2019. doi:10.1001/jama.2019.12843. 3. Morrow DA, et al. *Circulation*. 2019;139:2285-2288.
4. Bhatt AS, et al. *Eur J Heart Fail*. 2020;22:313-314.

STRONG-HF Study Design

STRONG-HF
CONTEMPORARY POST-DISCHARGE MANAGEMENT IN HEART-FAILURE



Study terminated 23d Sept 2022 by DSMB (n=1069 pt)
- larger than expected difference in primary endpoint
- unethical to keep patients in usual care

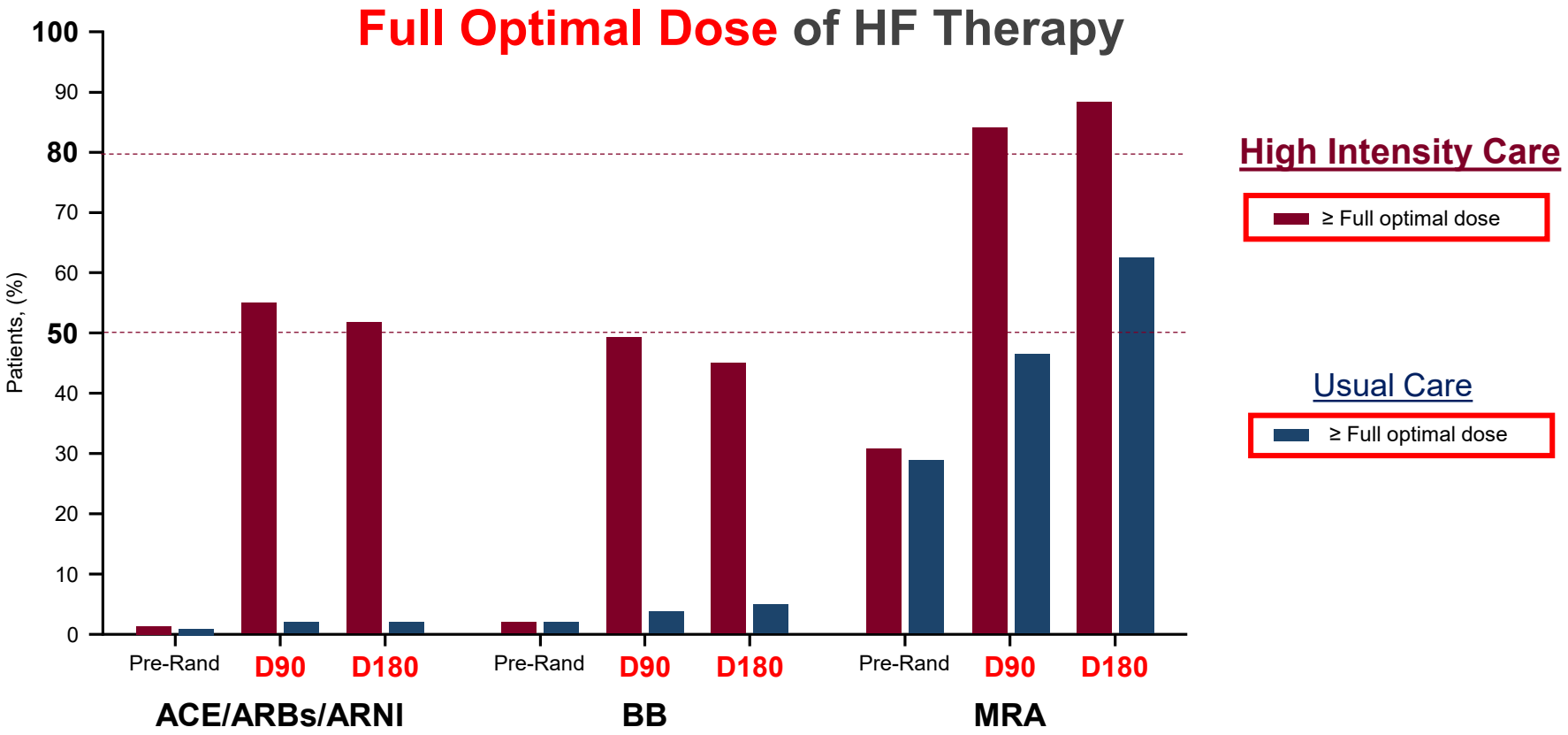
HF therapy: combining ACEi/ARB/ARNi & BB & MRA

Safety = clinical exam & biology (NT-proBNP, K, Creat, hemoglobin)

ACEi, angiotensin converting enzyme inhibitors; AHF, acute heart failure; ARB, angiotensin receptor blockers; BB, beta blockers; HF, heart failure; MRA, mineralcorticoid receptor antagonists; NT-proBNP, N-terminal pro B-type natriuretic peptide

STRONG-HF
CONTEMPORARY POST-DISCHARGE MANAGEMENT IN HEART-FAILURE

Oral HF Therapies Prescribed in High Intensity vs Usual Care



ACEi, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; ARNi, angiotensin receptor-neprilysin inhibitors; BB, beta blockers; MRA, mineralocorticoid receptor antagonists; Pre-Rand, pre-randomization

STRONG-HF
CONTEMPORARY POST-DISCHARGE MANAGEMENT IN HEART-FAILURE

Vital Signs and Symptoms of HF

Improvement in hemodynamics, Day 90

Parameter	Adjusted Treatment Effect (95% CI)	P-value
Heart rate, bpm	-5.8 (-7.3, -4.3)*	<0.0001
Systolic blood pressure, mmHg	-5.4 (-7.2, -3.5)*	<0.0001
Potassium, mmol/L	0.15 (0.09, 0.21)*	<0.0001
eGFR, mL/min/1.73m^2	-0.35 (-2.22, 1.52)*	0.71

Improvement in the parameters of congestion at Day 90

Parameter	Adjusted Treatment Effect (95% CI)	P-value
Weight, kg	-1.36 (-1.91, 0.80)*	<0.0001
Respiratory Rate, breaths/min	-0.4 (-0.7, -0.1)*	0.0028
Peripheral edema, grade	1.30 (1.17, 1.44) †	0.0002
Jugular venous pressure, cm	1.13 (1.05, 1.21) †	0.015
NYHA, class	1.36 (1.22, 1.53)†	<0.0001
NT-proBNP, pg/mL*	0.77 (0.67, 0.89)‡	0.0003

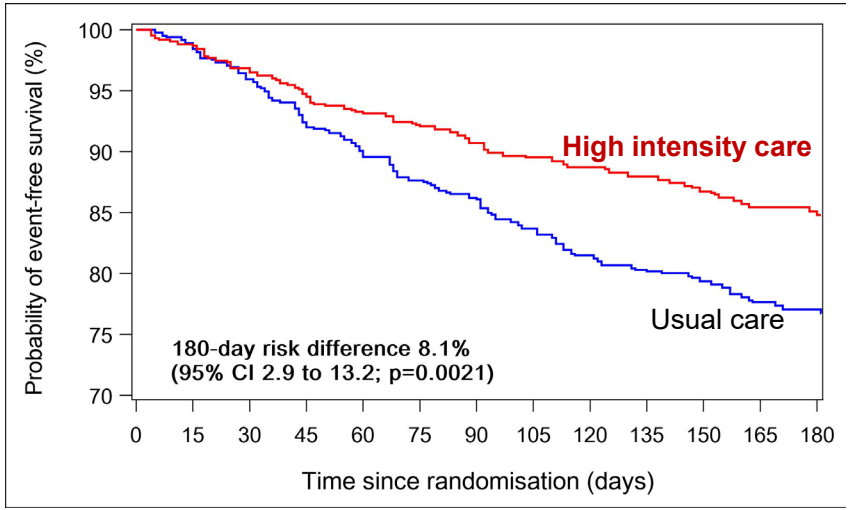
* Least squares mean difference (95% CI) based on an ANCOVA model with fixed terms for treatment, LVEF (<=40/>40), geographical region, and baseline value
† Mann-Whitney odds stratified by LVEF (<=40/>40), geographical region, and baseline value; p-value from van Elteren's test. A Mann-Whitney odds value of >1.0 favors high-intensity care.
‡ Treatment effect represents the ratio of the adjusted geometric mean ratios in the two treatment groups adjusted for the specific covariates. Adjusted geometric mean ratio within each treatment group is the ratio of the post-baseline value over the baseline value from an ANCOVA model with fixed terms for treatment, LVEF<=40/>40, region and baseline log-transformed NT-proBNP value.

CI, confidence interval; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association

STRONG–HF
CONTEMPORARY POST-DISCHARGE MANAGEMENT IN HEART-FAILURE

Primary endpoint:

180-Day Readmission for HF or All-Cause Death



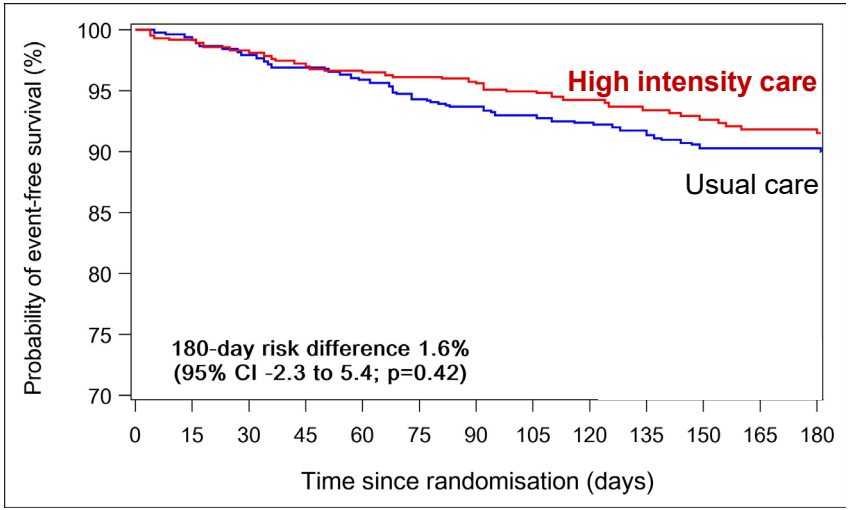
Risk Ratio 0.66 [95% CI 0.50–0.86]

Secondary endpoints:

Change from Baseline to Day 90 in EQ-5D VAS

High Intensity	Usual Care	Treatment effect	P value
10.7 (0.9)	7.2 (0.9)	3.5 (1.7 to 5.2)	< 0.0001

180-Day All-Cause Death



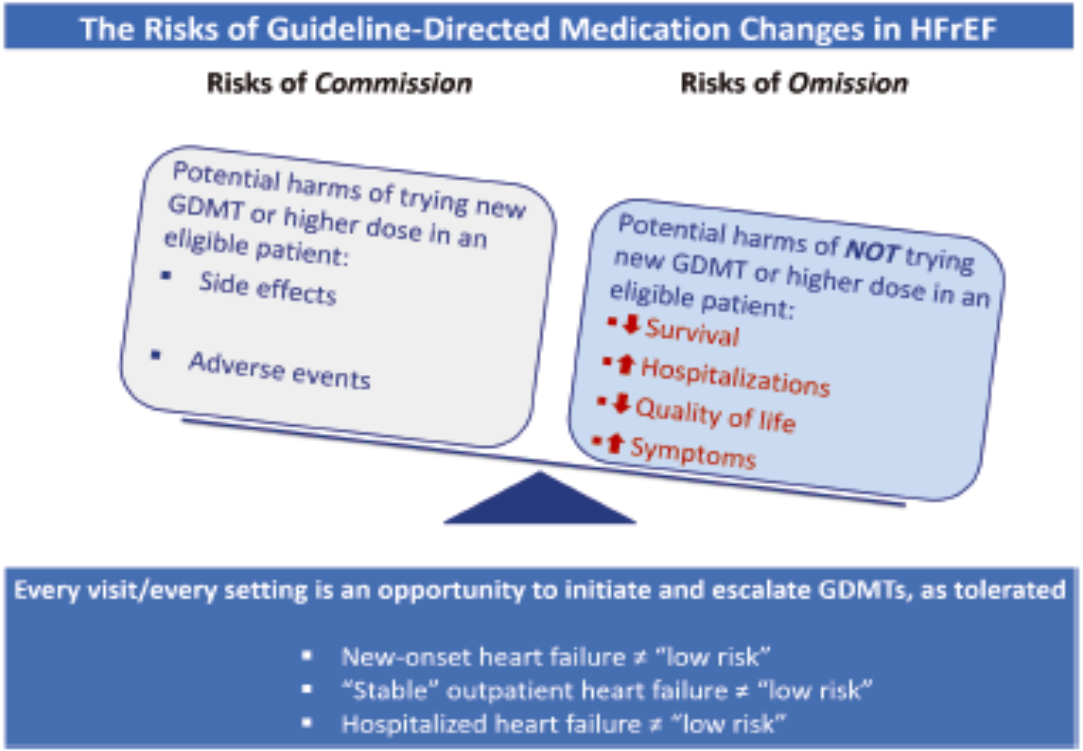


Figure 1 Weighing the risks of heart failure medication changes. In conversations between clinicians and patients regarding medication changes, risks of side effects and adverse events are often discussed. However, for making informed decisions, it is also critical to consider the 'risks of not trying' the medication change, which include increased risk of death, hospitalization, and worsening quality of life. GDMT, guideline-directed medical therapy. Adapted from Greene and DeVore.[7]

Greene SJ and Fonarow GC. European Journal of Heart Failure (2021) **23**, 1343–1345

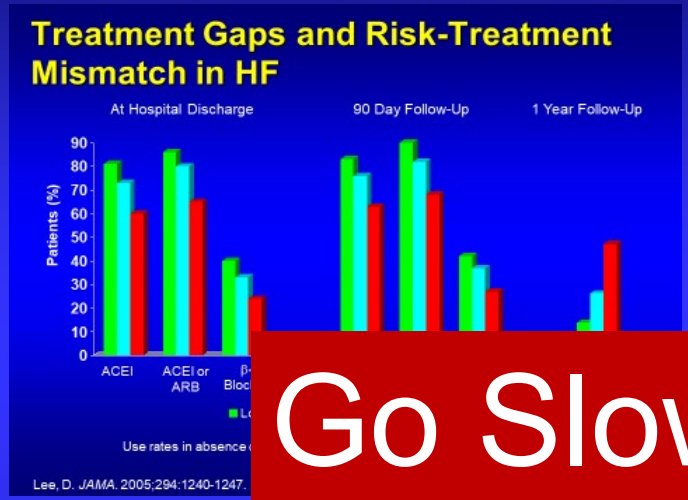
Cumulative Clinical Benefits of GDMT for HFrEF

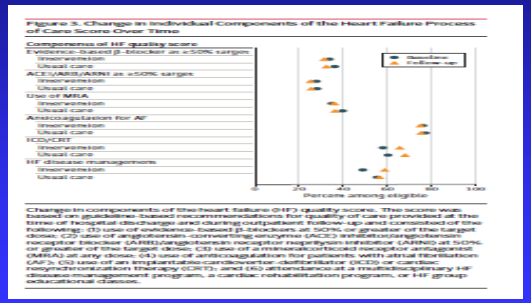
CDMMT	Relative Risk Reduction in Mortality	Absolute 2-year Mortality Rate	Relative Risk Reduction in HF Hospitalisations	Absolute 2-year HF Hospitalisation Rate
None	NA	35%	NA	39%
ACEI or ARB	17%	29%	31%	27%
ARNI*	16%	24%	21%	21%
β-blocker	35%	16%	41%	13%
MRA	30%	11%	35%	8%
SGLT2i	17%	9%	30%	6%
Cumulative	**74% RRR**	**26% ARR**	**85% RRR**	**33% ARR**

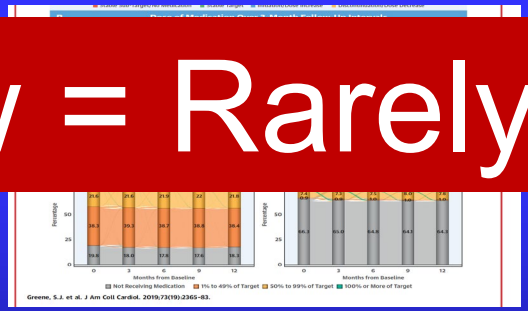
**Replacing ACEI/ARB. ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARR = absolute risk reduction; ARNI = angiotensin receptor-neprilysin inhibitor; CDMMT = comprehensive disease-modifying medical therapy; HF = heart failure; MRA = mineralocorticoid receptor antagonist; RRR = relative risk reduction; SGLT2 = sodium glucose cotransporter 2 inhibitor. Source: Fonarow et al. 2021.*[37,39]

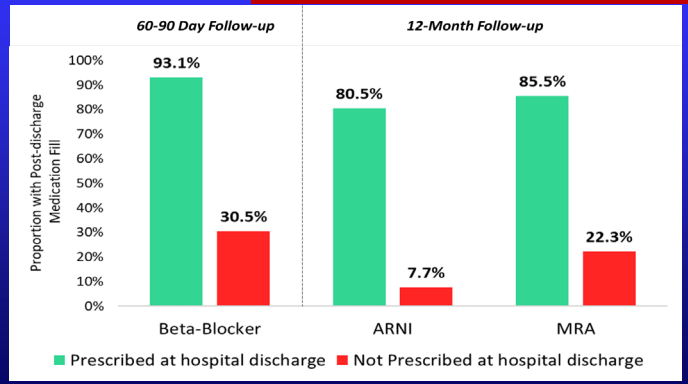
Brownell NK, Ziaeian B, Fonarow GC.Card Fail Rev. 2021 Nov 26;7:e18. doi: 10.15420/cfr.2021.18.

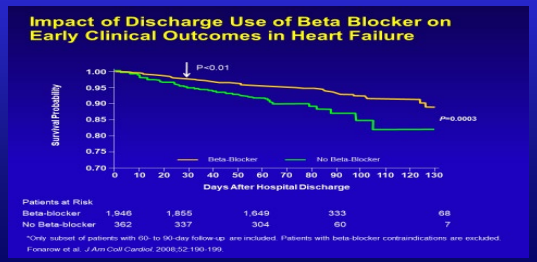
In-Hospital Initiation of GDMT vs Post-Discharge Initiation at Clinician Discretion











Go Slow = Rarely Initiate

In-Hospital Initiation

More likely to be treated

More likely to tolerate

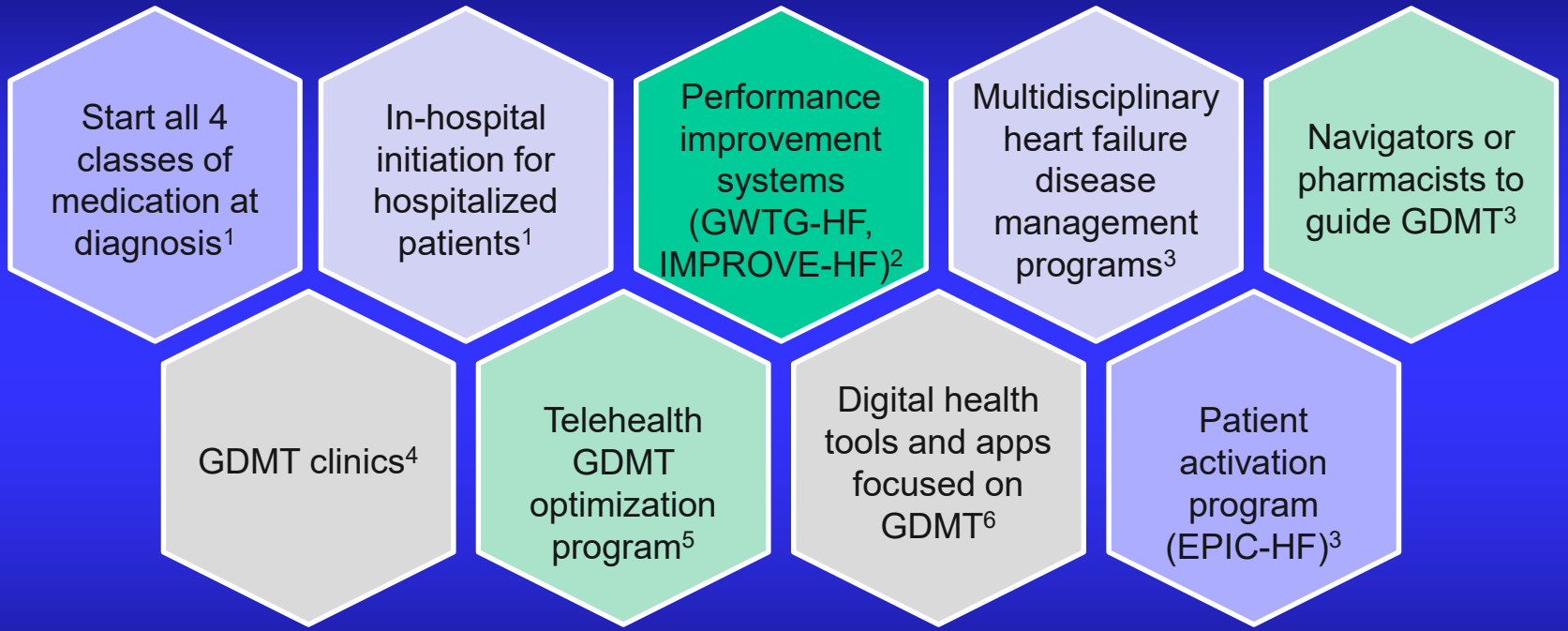
More likely to persist

More likely to feel better

More likely to be home

More likely to survive

Strategies to Help Facilitate GDMT Initiation



1. Greene SJ, et al. *JAMA Cardiol.* 2021. doi:10.1001/jamacardio.2021.0496. 2. Fonarow GC. *Circ J*. 2011;75:1783-1790. 3. Allen LA, et al. *Circulation.* 2021;143:427-437. 4. Balakumaran K, et al. *Int J Cardiol Heart Vasc.* 2019;22:1-5. 5. Thibodeau JT, et al. *Circulation.* 2020;142:1507-1509. 6. Kao DP, et al. *JACC Heart Fail*. 2020;8:223-233.

Clinical Review & Education

JAMA Cardiology | Review

Interventions for Optimization of Guideline-Directed Medical Therapy
A Systematic Review

Amber B. Tang, MD; Nicholas K. Brownell, MD; Jacob S. Roberts, MD; Amier Haidar, MD, MPH; Antonia Osuna-Garcia, MLIS; David J. Cho, MD; Pooya Bokhoor, MD; Gregg C. Fonarow, MD

IMPORTANCE Implementation of guideline-directed medical therapy (GDMT) in real-world practice remains suboptimal. It is unclear which interventions are most effective at addressing current barriers to GDMT in patients with heart failure with reduced ejection fraction (HFrEF).

OBJECTIVE To perform a systematic review to identify which types of system-level initiatives are most effective at improving GDMT use among patients with HFrEF.

EVIDENCE REVIEW PubMed, Embase, Cochrane, CINAHL, and Web of Science databases were queried from January 2010 to November 2023 for randomized clinical trials that implemented a quality improvement intervention with GDMT use as a primary or secondary outcome. References from related review articles were also included for screening. Quality of studies and bias assessment were graded based on the Cochrane Risk of Bias tool and Oxford Centre for Evidence-Based Medicine.

FINDINGS Twenty-eight randomized clinical trials were included with an aggregate sample size of 19 840 patients. Studies were broadly categorized as interdisciplinary interventions (n = 15), clinician education (n = 5), electronic health record initiatives (n = 6), or patient education (n = 2). Overall, interdisciplinary titration clinics were associated with significant increases in the proportion of patients on target doses of GDMT with a 10% to 60% and 2% to 53% greater proportion of patients on target doses of β-blockers and renin-angiotensin-aldosterone system inhibitors, respectively, in intervention groups compared with usual care. Other interventions, such as audits, clinician and patient education, or electronic health record alerts, were also associated with some improvements in GDMT utilization, though these findings were inconsistent across studies.

CONCLUSIONS AND RELEVANCE This review summarizes interventions aimed at optimization of GDMT in clinical practice. Initiatives that used interdisciplinary teams, largely comprised of nurses and pharmacists, most consistently led to improvements in GDMT. Additional large, randomized studies are necessary to better understand other types of interventions, as well as their long-term efficacy and sustainability.

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Supplemental content

CME at jamacmelookup.com

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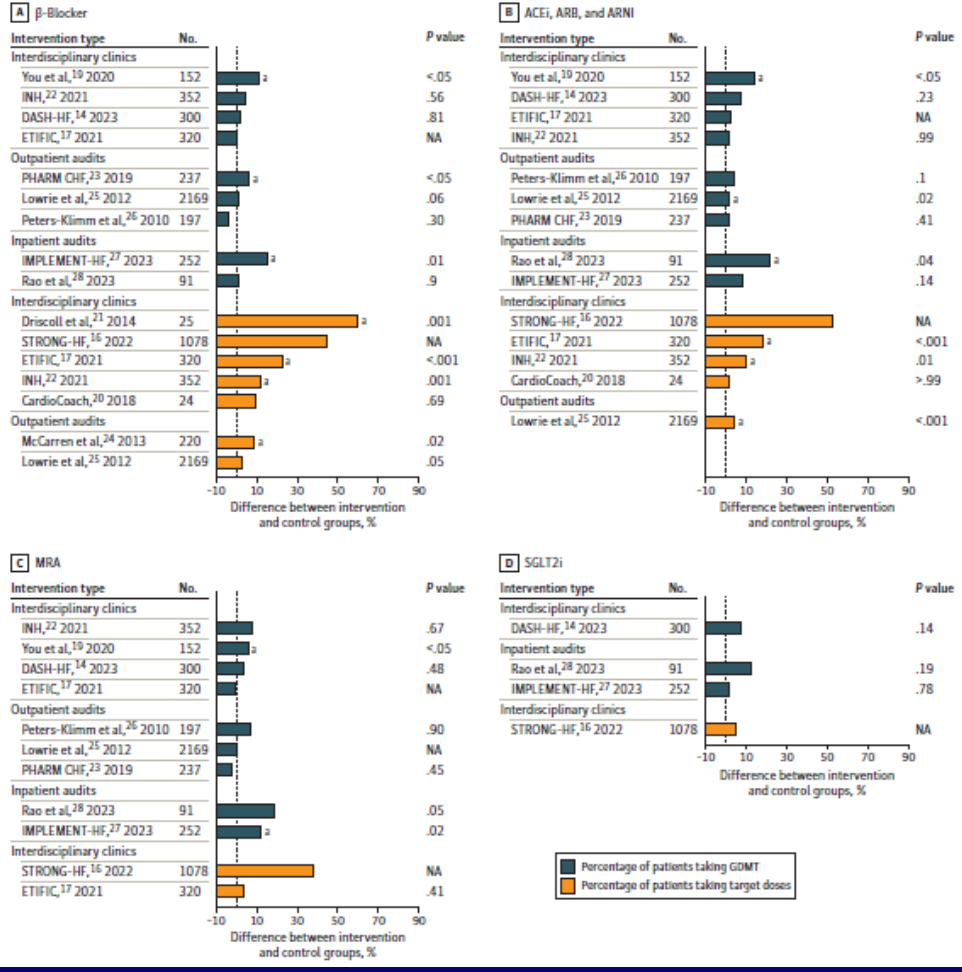
28 randomized clinical trials were included with an aggregate sample size of 19,840 patients.

Studies were broadly categorized as interdisciplinary interventions (n = 15), clinician education (n = 5), electronic health record initiatives (n = 6), or patient education (n = 2).

Figure 1. Interdisciplinary Interventions



Use and Titration of GDMT for HFrEF: Therapeutic Inertia from Discharge to 12 Months

JAMA | Original Investigation

Effect of a Hospital and Postdischarge Quality Improvement Intervention on Clinical Outcomes and Quality of Care for Patients With Heart Failure With Reduced Ejection Fraction

The CONNECT-HF Randomized Clinical Trial

Adam D. DeVore, MD, MHS; Bradi B. Granger, PhD, RN; Gregg C. Fonarow, MD; Hussein R. Al-Khalidi, PhD; Nancy M. Albert, PhD; Eldrin F. Lewis, MD, MPH; Javed Butler, MD, MPH, MBA; Ileana L. Piña, MD, MPH; Larry A. Allen, MD, MHS; Clyde W. Yancy, MD; Lauren B. Cooper, MD, MHS; G. Michael Felker, MD, MHS; Lisa A. Kaltenbach, MS; A. Thomas McRae, MD; David E. Lanfear, MD, MS; Robert W. Harrison, MD; Maghoe Disch, MSN, RN; Dan Ariely, PhD; Julia M. Miller, PhD, MSPH; Christopher B. Granger, MD; Adrian F. Hernandez, MD, MHS

IMPORTANCE Adoption of guideline-directed medical therapy for patients with heart failure is variable. Interventions to improve guideline-directed medical therapy have failed to consistently achieve target metrics, and limited data exist to inform efforts to improve heart failure quality of care.

OBJECTIVE To evaluate the effect of a hospital and postdischarge quality improvement intervention compared with usual care on heart failure outcomes and care.

DESIGN, SETTING, AND PARTICIPANTS This cluster randomized clinical trial was conducted at 161 US hospitals and included 5647 patients (2675 intervention vs 2972 usual care) followed up after a hospital discharge for acute heart failure with reduced ejection fraction (HFrEF). The trial was performed from 2017 to 2020, and the date of final follow-up was August 31, 2020.

INTERVENTIONS Hospitals (n = 82) randomized to a hospital and postdischarge quality improvement intervention received regular education of clinicians by a trained group of heart failure and quality improvement experts and audit and feedback on heart failure process measures (eg, use of guideline-directed medical therapy for HFrEF) and outcomes. Hospitals (n = 79) randomized to usual care received access to a generalized heart failure education website.

MAIN OUTCOMES AND MEASURES The coprimary outcomes were a composite of first heart failure rehospitalization or all-cause mortality and change in an opportunity-based composite score for heart failure quality (percentage of recommendations followed).

RESULTS Among 5647 patients (mean age, 63 years; 33% women; 38% Black; 87% chronic heart failure; 49% recent heart failure hospitalization), vital status was known for 5636 (99.8%). Heart failure rehospitalization or all-cause mortality occurred in 38.6% in the intervention group vs 39.2% in usual care (adjusted hazard ratio, 0.92 [95% CI, 0.81 to 1.05]). The baseline quality-of-care score was 42.1% vs 45.5%, respectively, and the change from baseline to follow-up was 2.3% vs −1.0% (difference, 3.3% [95% CI, −0.8% to 7.3%]), with no significant difference between the 2 groups in the odds of achieving a higher composite quality score at last follow-up (adjusted odds ratio, 1.06 [95% CI, 0.93 to 1.21]).

CONCLUSIONS AND RELEVANCE Among patients with HFrEF in hospitals randomized to a hospital and postdischarge quality improvement intervention vs usual care, there was no significant difference in time to first heart failure rehospitalization or death, or in change in a composite heart failure quality-of-care score.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT03035474

Editorial page 311
Supplemental content
CME Quiz at jamacmelookup.com

Author Affiliations: Author affiliations are listed at the end of this article.

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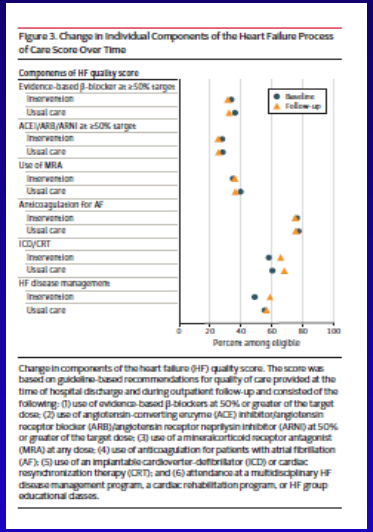
JAMA. 2021;326(4):314-323. doi:10.1001/jama.2021.8844



CONNECT-HF

From time of hospital discharge to 12 months of outpatient follow-up among 161 participating sites:

Median change in use and dosing of GDMT in absence of contraindications or intolerance was ZERO

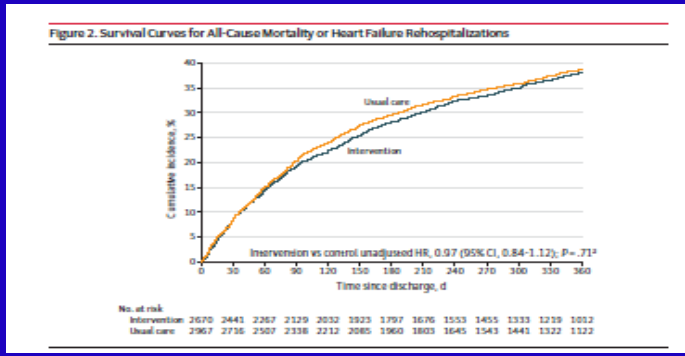
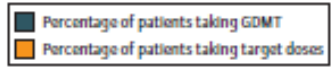
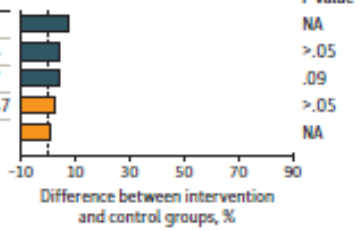


Figure 2. Clinician Education



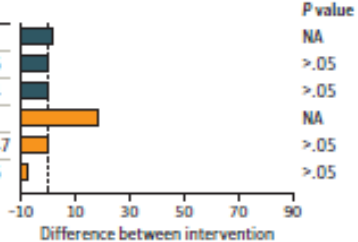
A β-Blocker

Clinical education	No.	P value
van Riet et al,[31] 2016	17	NA
Valk et al,[30] 2020	204	>.05
Sanchez et al,[33] 2010	627	.09
CONNECT-HF,[29] 2021	5647	>.05
van Riet et al,[31] 2016	17	NA



B ACEi, ARB, and ARNI

Clinical education	No.	P value
van Riet et al,[31] 2016	17	NA
Pina et al,[32] 2012	216	>.05
Valk et al,[30] 2020	204	>.05
van Riet et al,[31] 2016	17	NA
CONNECT-HF,[29] 2021	5647	>.05
Pina et al,[32] 2012	216	>.05



C MRA

Clinical education	No.	P value
CONNECT-HF,[29] 2021	5647	<.05
Valk et al,[30] 2020	204	>.05
van Riet et al,[31] 2016	17	NA

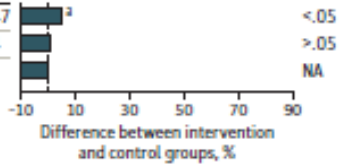
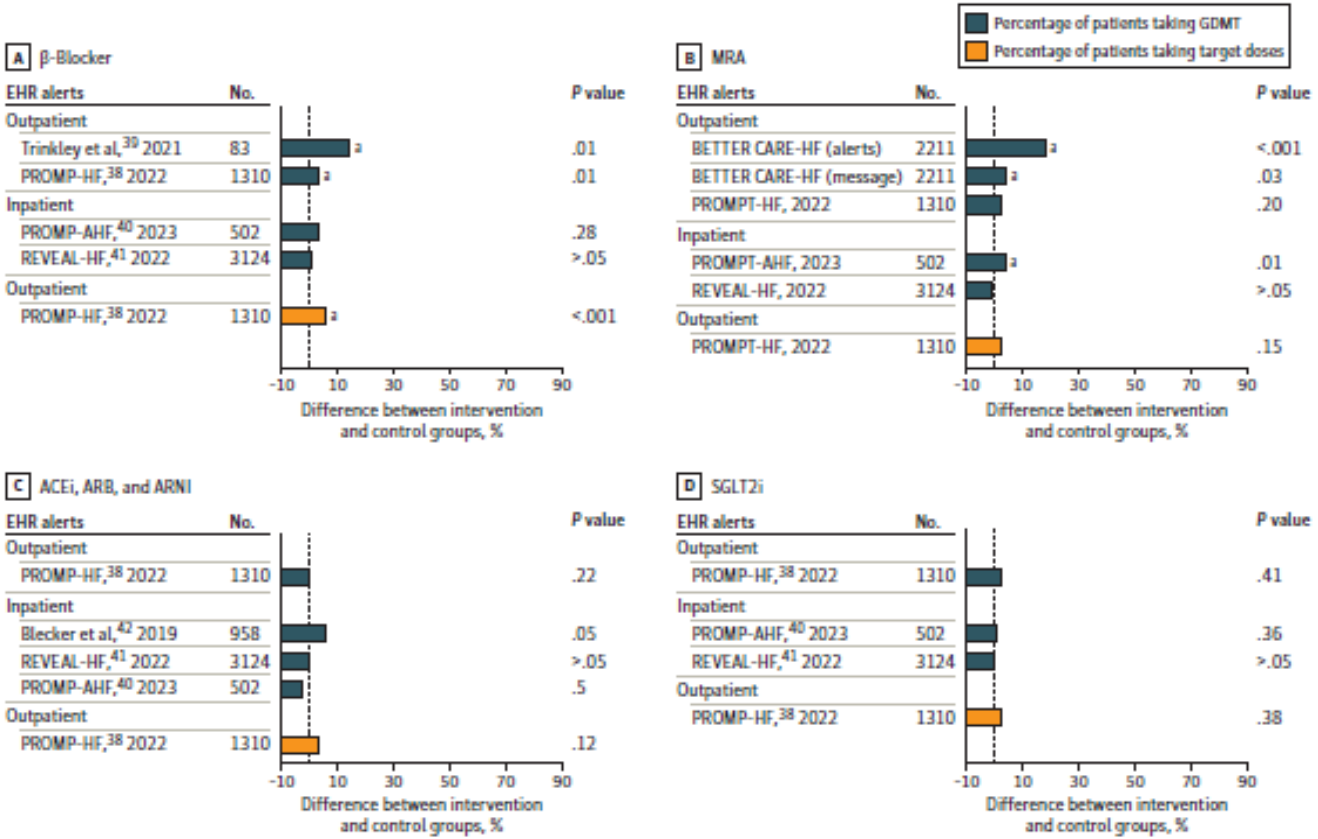


Figure 3. Electronic Health Record (EHR) Alerts



Electronic Health Record Nudges for GDMT Initiation: PROMPT-HF

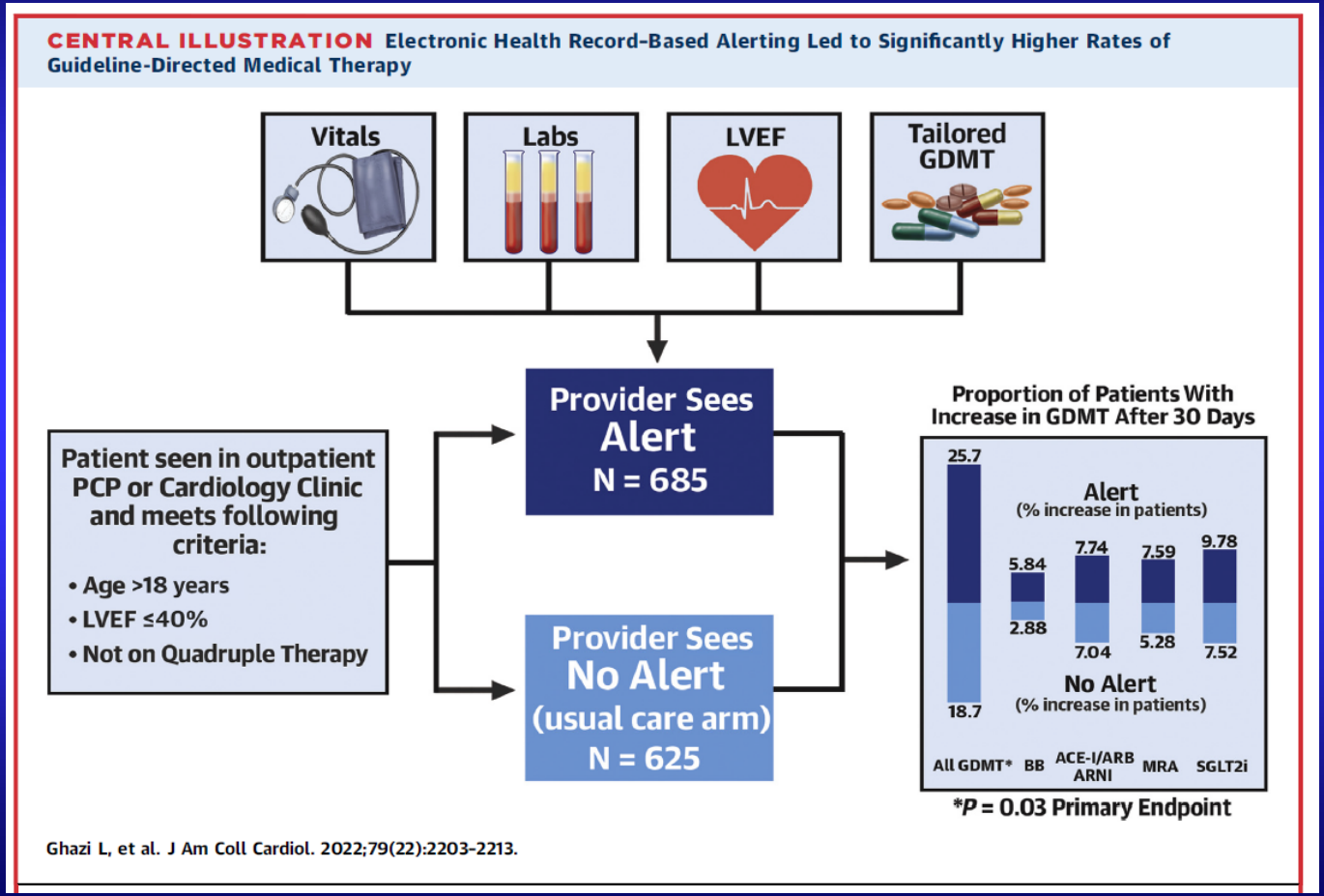


Figure 4. Patient Education

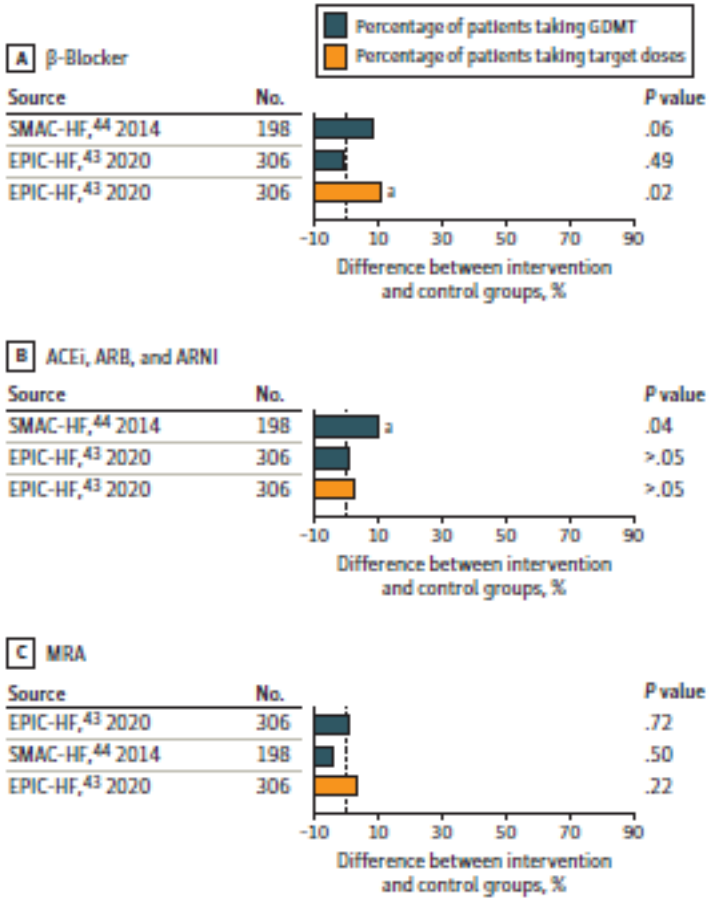
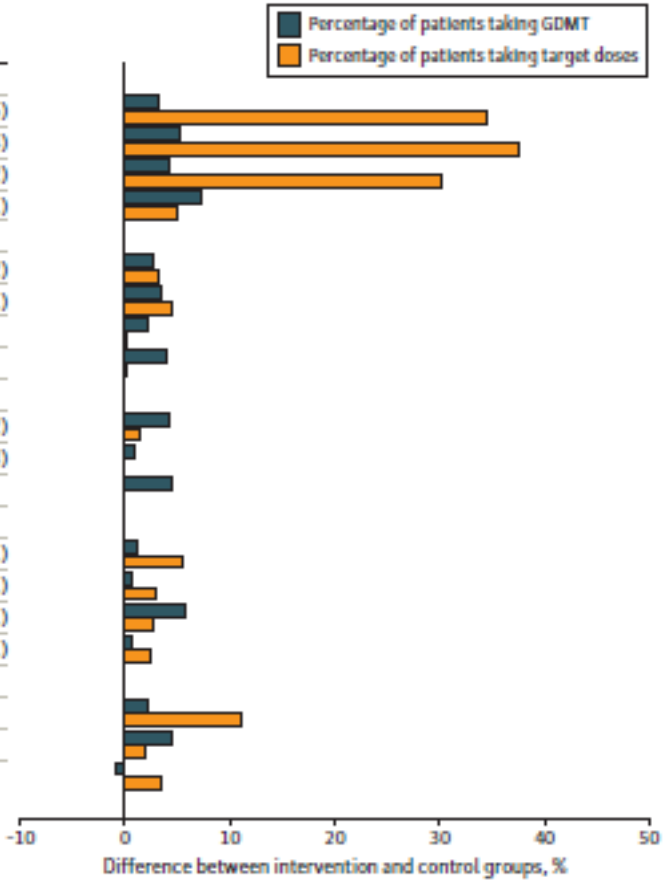


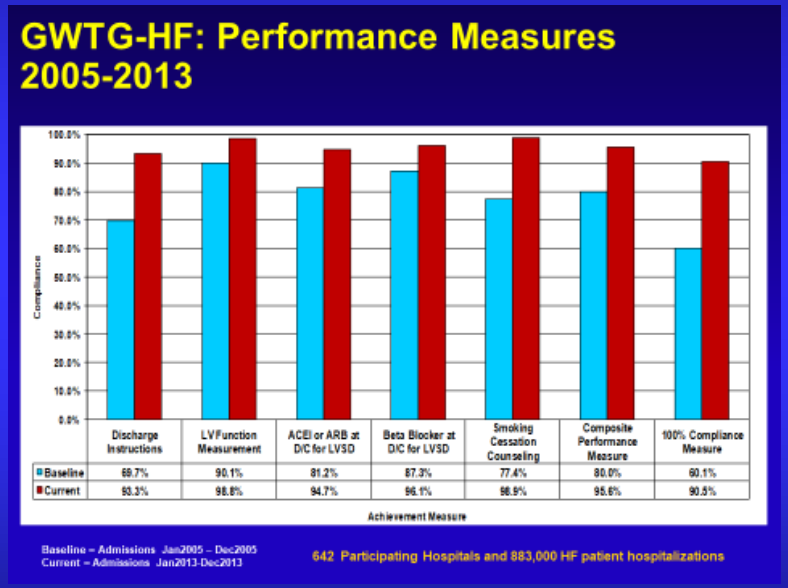
Figure 5. Guideline-Directed Medical Therapy (GDMT) Utilization and Target Dosing

Intervention type	Total No. (No. of studies) Utilization	Dosing
Interdisciplinary clinics		
β-Blocker	1124 (4)	1799 (5)
ACEi, ARB, and ARNI	1124 (4)	1774 (4)
MRA	1124 (4)	1398 (2)
SGLT2i	300 (1)	1078 (1)
Interdisciplinary audits		
β-Blocker	2946 (5)	2389 (2)
ACEi, ARB, and ARNI	2946 (5)	2169 (1)
MRA	2946 (5)	
SGLT2i	343 (2)	
Clinician education		
β-Blocker	848 (3)	5664 (2)
ACEi, ARB, and ARNI	437 (3)	5880 (3)
MRA	5868 (3)	
EHR alerts		
β-Blocker	5019 (4)	1310 (1)
ACEi, ARB, and ARNI	5894 (4)	1310 (1)
MRA	7147 (4)	1310 (1)
SGLT2i	4936 (3)	1310 (1)
Patient education		
β-Blocker	504 (2)	306 (1)
ACEi, ARB, and ARNI	504 (2)	306 (1)
MRA	504 (2)	306 (1)

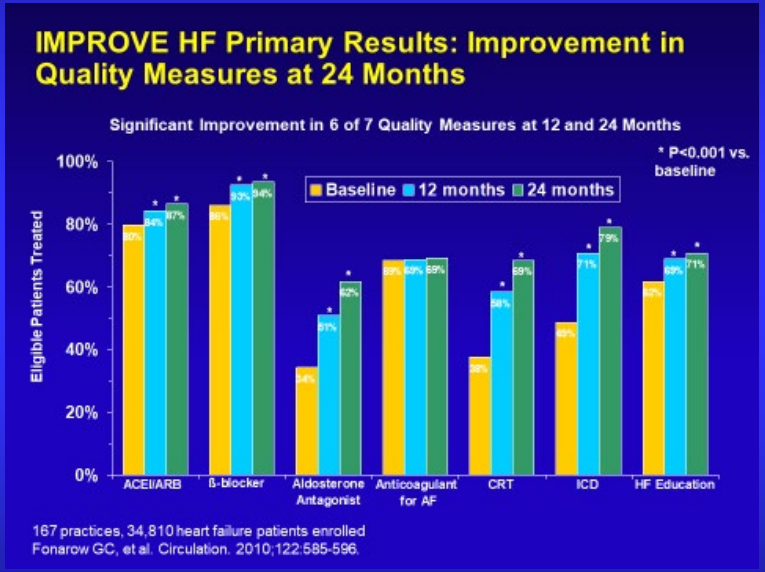


Performance Improvement Systems to Facilitate GDMT Initiation

GWTG-HF: Hospital Setting



IMPROVE-HF: Outpatient Setting



642 Participating Hospitals and 883,000 HF patient hospitalizations

167 practices, 34,810 heart failure patients enrolled
Fonarow GC, et al. Circulation. 2010;122:585-596.

JAMA | Original Investigation

Effect of Patient-Centered Transitional Care Services on Clinical Outcomes in Patients Hospitalized for Heart Failure
The PACT-HF Randomized Clinical Trial

Harriette G. C. Van Spall, MD, MPH; Shun Fu Lee, PhD; Feng Xie, PhD; Urun Erbas Oz, PhD; Richard Perez, MSc; Peter R. Mitoff, MD; Manish Maingi, MD; Michael C. Tjandrawidjaja, MD; Michael Heffernan, MD, PhD; Mohammad I. Zia, MD; Liane Porepa, MD; Mohamed Panju, MSc, MD; Lehana Thabane, PhD; Ian D. Graham, MA, PhD; R. Brian Haynes, MD, MSc, PhD; Dilys Haughton, BScN, MHSc; Kim D. Simek, BSc; Dennis T. Ko, MD, MSc; Stuart J. Connolly, MSc, MD

IMPORTANCE Health care services that support the hospital-to-home transition can improve outcomes in patients with heart failure (HF).

OBJECTIVE To test the effectiveness of the Patient-Centered Care Transitions in HF transitional care model in patients hospitalized for HF.

DESIGN, SETTING, AND PARTICIPANTS Stepped-wedge cluster randomized trial of 2494 adults hospitalized for HF across 10 hospitals in Ontario, Canada, from February 2015 to March 2016, with follow-up until November 2016.

INTERVENTIONS Hospitals were randomized to receive the intervention (n = 1104 patients), in which nurse-led self-care education, a structured hospital discharge summary, a family physician follow-up appointment less than 1 week after discharge, and, for high-risk patients, structured nurse home visits and heart function clinic care were provided to patients, or usual care (n = 1390 patients), in which transitional care was left to the discretion of clinicians.

MAIN OUTCOMES AND MEASURES Primary outcomes were hierarchically ordered as composite all-cause readmission, emergency department (ED) visit, or death at 3 months; and composite all-cause readmission or ED visit at 30 days. Secondary outcomes were B-PREPARED score for discharge preparedness (range: 0 [most prepared] to 22 [least prepared]); the 3-Item Care Transitions Measure (CTM-3) for quality of transition (range: 0 [worst transition] to 100 [best transition]); the 5-level EQ-5D version (EQ-5D-5L) for quality of life (range: 0 [dead] to 1 [full health]); and quality-adjusted life-years (QALY; range: 0 [dead] to 0.5 [full health at 6 months]).

RESULTS Among eligible patients, all 2494 (mean age, 77.7 years; 1258 [50.4%] women) completed the trial. There was no significant difference between the intervention and usual care groups in the first primary composite outcome (545 [49.4%] vs 698 [50.2%] events, respectively; hazard ratio [HR], 0.99 [95% CI, 0.83-1.19]) or in the second primary composite outcome (304 [27.5%] vs 408 [29.3%] events, respectively; HR, 0.93 [95% CI, 0.73-1.18]). There were significant differences between the intervention and usual care groups in the secondary outcomes of mean B-PREPARED score at 6 weeks (16.6 vs 13.9; difference, 2.65 [95% CI, 1.37-3.92]; $P < .001$); mean CTM-3 score at 6 weeks (76.5 vs 70.3; difference, 6.16 [95% CI, 0.90-11.43]; $P = .02$); and mean EQ-5D-5L score at 6 weeks (0.7 vs 0.7; difference, 0.06 [95% CI, 0.01 to 0.11]; $P = .02$) and 6 months (0.7 vs 0.6; difference, 0.06 [95% CI, 0.01-0.12]; $P = .02$). There was no significant difference in mean QALY between groups at 6 months (0.3 vs 0.3; difference, 0.00 [95% CI, −0.02 to 0.02]; $P = .98$).

CONCLUSIONS AND RELEVANCE Among patients with HF in Ontario, Canada, implementation of a patient-centered transitional care model compared with usual care did not improve a composite of clinical outcomes. Whether this type of intervention could be effective in other health care systems or locations would require further research.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT02112227

JAMA. 2019;321(8):753-761. doi:10.1001/jama.2019.0710

Supplemental content

CME Quiz at jamanetwork.com/learning and CME Questions page 802

Author Affiliations: Author affiliations are listed at the end of this article.

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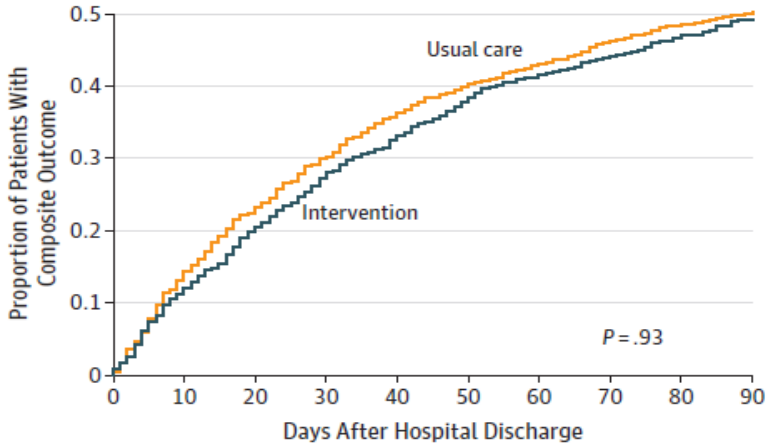
Figure 2. Time to First Composite Readmission, Emergency Department Visit, or Death at 3 Months in the Intervention and Usual Care Groups



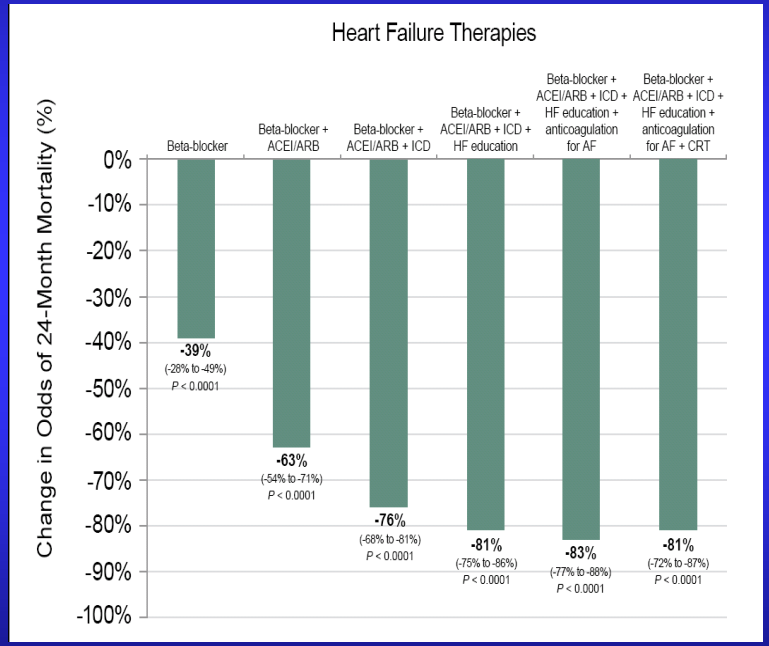
Patients at risk										
Intervention	1104	979	884	804	745	686	649	619	589	560
Usual care	1390	1206	1077	973	892	834	795	750	718	695

Outcomes are measured relative to the date of hospital discharge following index hospitalization for heart failure, with patients analyzed in their allocated treatment group. Median (interquartile range) days of follow-up was 90 (81-90) for the intervention group and 90 (76-90) for the usual care group.

Improved Adherence to HF Guidelines Translates to Improved Clinical Outcomes in Real World Patients

Each 10% improvement in ACC/AHA heart failure guideline recommended composite care was associated with a 13% lower odds of 24-month mortality (adjusted OR 0.87; 95% CI, 0.84 to 0.90; *P<0.0001)*

ACC/AHA Guideline Directed Therapy for Heart Failure Improves Outcomes



Fonarow GC, et al. *Circulation*. 2011;123:1601-1610.

Fonarow GC et al J Am Heart Assoc 2012;1:16-26

Interventions for Optimization of Guideline-Directed Medical Therapy A Systematic Review

In this review summarizing interventions aimed at optimization of GDMT in clinical practice:

Initiatives that used interdisciplinary teams, largely comprised of nurses and pharmacists, most consistently led to improvements in GDMT

Clinician education, electronic health record initiative, or patient education interventions results in no or modest improvements in GDMT

Additional large, randomized studies are necessary to better understand other types of interventions, as well as their long-term efficacy and sustainability

JAMA Cardiol. 2024;9(4):397-404. doi:10.1001/jamacardio.2023.5627

Challenges to Implement a Heart Failure Performance Improvement System

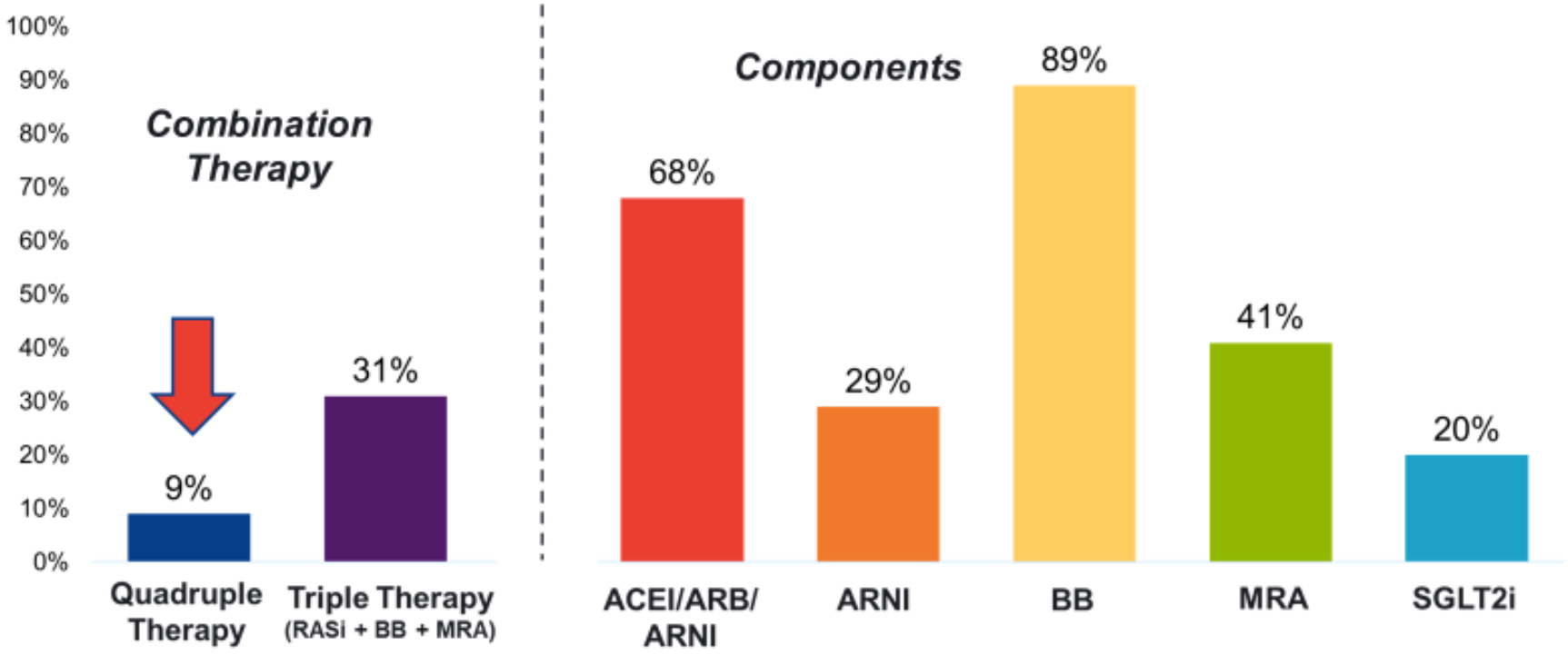
- This will not work in my practice or hospital
- The physicians will not agree to this
- We cannot get a consensus
- The managed care organization will not pay for it
- Patients do not want to be on a lot of medications
- There is not enough time
- It will cost too much
- It may not be safe to start β-blocker medications in heart failure patients
- CRT and ICD don't work
- This will benefit the competition
- The administration will not pay for it
- What about the liability?
- It will take too much time
- All my patients are too complex for this
- The patients should all be followed by someone else
- It is too hard to get things through the practice committee
- The physicians do not like cookbook medicine
- We do not have anyone to do this

Key Elements to Quality Improvement: Why Do Some Programs Succeed?

- Access to current and accurate data on treatment and outcomes
- Have stated goals
- Administrative support
- Support among clinicians
- Use of care maps and pathways
- Use of data to provide feedback

Bradley. *JAMA.* 2001;285:2604-2611.

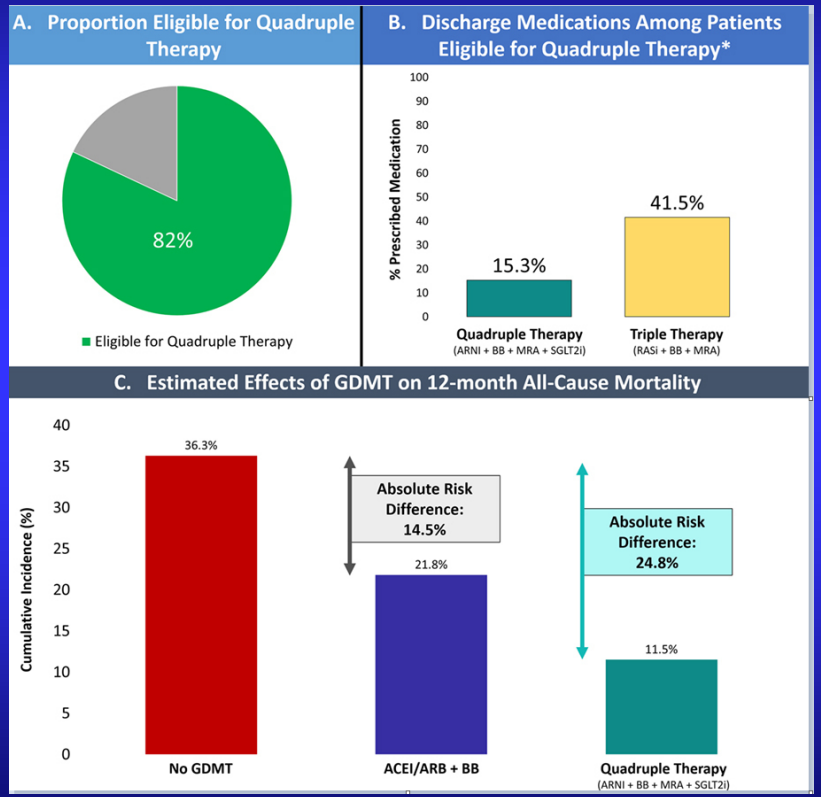
GDMT for HFrEF in the US (2021-2022)*



*population with eGFR >20 mL/min/1.73m^2, no type 1 diabetes

Pierce JB...Greene SJ. *JAMA Cardiol* 2023

Eligibility and Projected Benefits of Rapid Initiation of Quadruple Medical Therapy for Newly Diagnosed Heart Failure



"Applying the relative risk reductions in clinical trials, complete implementation of quadruple therapy by time of discharge was projected to yield absolute risk reductions in 12-month mortality of 10.4% (number-needed-to-treat [NNT]=10) compared with ACEI/ARB and beta-blocker, and 24.8% (NNT=4) compared with no GDMT."

Green S, Fonarow GC. J Am Coll Cardiol HF. Mar 25, 2024. Epublished DOI: 10.1016/j.jchf.2024.03.001

Journal of Cardiac Failure Vol. 29 No. 5 2023

Editor's Comment

Time to Quadruple Guideline-Directed Medical Therapy as a Key Performance Measure for Heart Failure

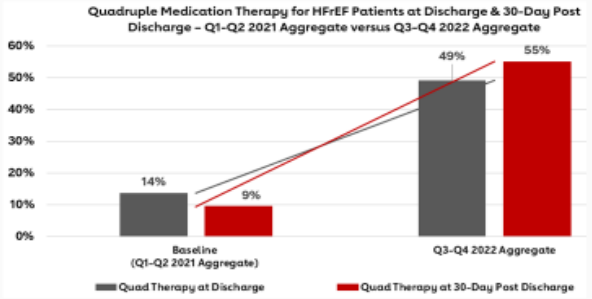
IZZA SHAHID, MBBS,[1] GREGG C. FONAROW, MD,[2] AND STEPHEN J. GREENE, MD[3,4]

Houston, TX; Los Angeles, CA; and Durham, NC

AHA's IMPLEMENT-HF Focus on Quadruple GDMT

Results

- Data from 78 initiative sites of 9,102 HFrEF patient hospitalization episodes (median age 68, 33% females, median LVEF 26%) demonstrated that prescribing Q-GDMT at discharge increased from 14% at baseline to 49% for Q3-Q4 2022 **(+35%, p value <0.001)**
- 30-day post discharge data from 55 initiative sites of 2,894 HFrEF patient hospitalization episodes (median age 68, 30% females, median LVEF 27%) demonstrated an increase from 9% at baseline to 55% for Q3-Q4 2022 **(+46%, p value <0.001)**



	Baseline (Q1 & Q2 2021 Aggregate)		Q3 & Q4 2022 Aggregate		P Value
	Numerator	Denominator	Numerator	Denominator	
Discharge Q-GDMT for HFrEF Patients	549	4030	2018	4112	<0.001
30-Day Q-GDMT for HFrEF Patients	100	1064	879	1593	<0.001

ESC Congress 2023
Amsterdam & Online

The American Heart Association's National Heart Failure Initiative, IMPLEMENT-HF, is made possible with funding by founding sponsor, Novartis and national sponsor, Boehringer Ingelheim and in-kind support from Amgen.

Circulation: Heart Failure

ORIGINAL ARTICLE

Economic Modeling Analysis of an Intensive GDMT Optimization Program in Hospitalized Heart Failure Patients

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BACKGROUND: The STRONG-HF trial demonstrated substantial reductions in the composite of mortality and morbidity over 6 months among hospitalized patients with heart failure (HF) who were randomized to intensive guideline-directed medical therapy (GDMT) optimization compared with usual care. Whether an intensive GDMT optimization program would be cost-effective for patients with HF with reduced ejection fraction is unknown.

METHODS: Using a 2-state Markov model, we evaluated the effect of an intensive GDMT optimization program on hospitalized patients with HF with reduced ejection fraction. Two population models were created to simulate this intervention, a clinical trial model, based on the participants in the STRONG-HF trial, and a real-world model, based on the Get With The Guidelines–HF registry of patients admitted with worsening HF. We then modeled the effect of a 6-month intensive triple therapy GDMT optimization program comprised of cardiologists, clinical pharmacists, and registered nurses. Hazard ratios from the intervention arm of the STRONG-HF trial were applied to both population models to simulate clinical and financial outcomes of an intensive GDMT optimization program from a US health care sector perspective with a lifetime time horizon. Optimal quadruple GDMT use was also modeled.

RESULTS: An intensive GDMT optimization program was extremely cost-effective with incremental cost-effectiveness ratios <$10 000 per quality-adjusted life-year in both models. Optimal quadruple GDMT implementation resulted in the most gains in life-years with incremental cost-effectiveness ratios of $60 000 and $54 000 in the clinical trial and real-world models, respectively.

CONCLUSIONS: An intensive GDMT optimization program for patients hospitalized with HF with reduced ejection fraction would be cost-effective and result in substantial gains in clinical outcomes, especially with the use of optimal quadruple GDMT. Clinicians, payers, and policymakers should prioritize the creation of such programs.

"An intensive GDMT optimization program for patients hospitalized with HFrEF would be cost-effective and result in substantial gains in clinical outcomes, especially with the use of optimal quadruple GDMT"

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Estimating lifetime benefits of comprehensive disease-modifying pharmacological therapies in patients with heart failure with reduced ejection fraction: a comparative analysis of three randomised controlled trials

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	EMPHASIS-HF[6] (n=2737)	PARADIGM-HF[9] (n=8399)	DAPA-HF[8] (n=4744)
Comparison	Eplerenone *vs* placebo	Sacubitril-valsartan *vs* enalapril	Dapagliflozin *vs* placebo
Enrolment period	2006–10	2009–12	2017–18
Median follow-up, months	21 (10–33)	27 (19–36)	18 (13–21)
Age, years	69 (8)	64 (11)	66 (11)
Sex			
Men	2127 (78%)	6567 (78%)	3635 (77%)
Women	610 (22%)	1832 (22%)	1109 (23%)
Systolic blood pressure, mm Hg	124 (17)	121 (15)	122 (16)
Heart rate, beats per min	72 (13)	72 (12)	72 (12)
Left ventricular ejection fraction, %	26 (5)	30 (6)	31 (7)
New York Heart Association class			
1	0	389 (5%)	0
2	2737 (100%)	5919 (70%)	3203 (68%)
3	0	2018 (24%)	1498 (32%)
4	0	60 (1%)	43 (1%)
Atrial fibrillation	844 (31%)	3091 (37%)	1818 (38%)
Diabetes	859 (31%)	2907 (35%)	1983 (42%)
Previous hospital admission for heart failure	1440 (53%)	5274 (63%)	2251 (47%)
Diuretics	2326 (85%)	6738 (80%)	4008 (84%)
ACE inhibitor, ARB, or ARNI*	2557 (93%)	8379 (100%)	4442 (94%)
β blocker	2374 (87%)	7811 (93%)	4558 (96%)
Mineralocorticoid receptor antagonist	..	4671 (56%)	3370 (71%)

Data are n (%) or mean (SD) unless otherwise stated. ACE inhibitor=angiotensin-converting enzyme inhibitor. ARB=angiotensin receptor blocker. ARNI=angiotensin receptor-neprilysin inhibitor. *DAPA-HF is the only trial that enrolled patients on background ARNIs (n=508).

Table: Baseline patient characteristics and background medical therapy

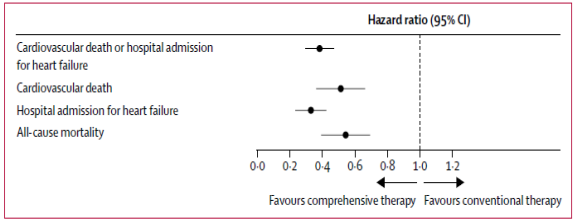


Figure 1: Estimation of relative treatment effects of comprehensive disease-modifying pharmacological therapy on key cardiovascular events

Compared to ACEI/ARB+BB:
Comprehensive Rx including ARNI+BB+MRA+SGLT2i

HR 0.38 CV Death/HF Hospitalization

HR 0.50 CV Death

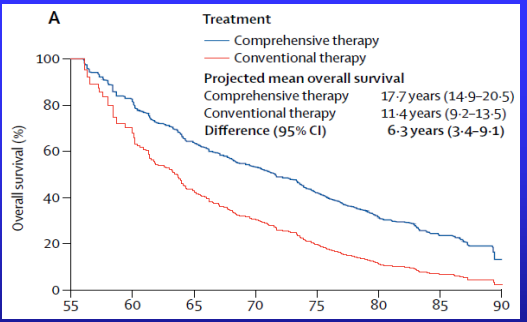
HR 0.32 HF Hospitalization

HR 0.53 Mortality

Compared to ACEI/ARB + BB:

1. Switch to ARNI
2. Start MRA
3. Start SGLT2i

Survival free from All Cause Mortality



Extend Your HFrEF Patient's Life by 6.3 Years

Lancet 2020; 396: 121–28

Change in Mortality in the Past 20 Years in Chronic Heart Failure Clinical Trials vs Clinical Practice

Outcome of Placebo Arms of Randomized Controlled HFrEF Clinical Trials

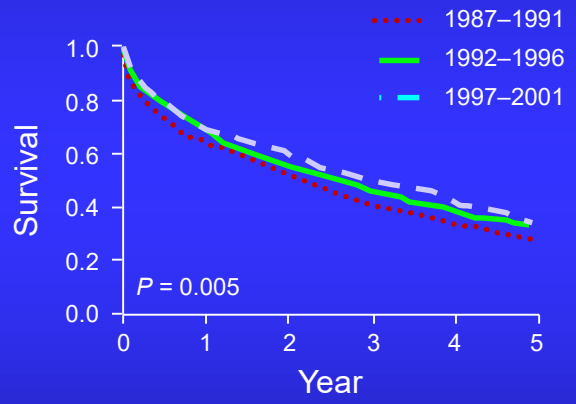
Time Frame	# of Trials	NYHA Class	Cardiac HR	Non-Cardiac HR	Total Mortality HR
1991-1995	13	2.4	33.1	0.82	10.3
1996-2000	15	2.6	20.7	1.27	7.2
2001-2005	23	2.4	14.2	0.99	5.1
2006-2010	18	2.5	9.9	1.04	3.8

Over the past 20 years, overall mortality rates for HF patients have decreased by 63%, while cardiac mortality in HF trials has decreased by almost 70%

Bryg RJ et al. J Card Fail 2011;116:s91

Outcomes in Community Practice

Patient with Reduced Ejection Fraction



No. at Risk

1987–1991	819	525	424	336	274	220
1992–1996	857	594	481	395	331	273
1997–2001	748	520	447	319	210	114

Owan TE, et al. *N Engl J Med.* 2006;355:251-259.

Cumulative Impact of Evidence-Based HFrEF Medical Therapies on All Cause Mortality

	Relative Risk	2 Year Mortality
None	- -	35.0%
ARNI (vs imputed placebo)	↓ 28%	25.2%
Beta Blocker	↓ 35%	16.4%
Aldosterone Ant	↓ 30%	11.5%
SGLT2 inhibitor	↓ 17%	9.5%

Cumulative risk reduction in mortality if all evidence-based medical therapies are used:
Relative risk reduction 72.9%, Absolute risk reduction: 25.5%, NNT = 4

Updated from Fonarow GC, et al. Am Heart J 2011;161:1024-1030 and Lancet 2008;372:1195-1196.

Potential Impact of Optimal Implementation of Evidence-Based HFrEF Therapies on Mortality

Guideline Recommended Therapy	HF Patient Population Eligible for Treatment, n*	Current HF Population Eligible and Untreated, n (%)	Potential Lives Saved per Year	Potential Lives Saved per Year (Sensitivity Range*)
ARNI (replacing ACEI/ARB)	2,287,296	2,287,296 (100)	28,484	(18,230-41,017)
Beta-blocker	2,512,560	361,809 (14.4)	12,922	(6616-22,329)
Aldosterone Antagonist	603,014	385,326 (63.9)	21,407	(10,960-36,991)
SGLT2 Inhibitor	2,132,800	2,132,800 (100)	34,125	(21,840-49,140)
Total	-	-	96,938	(57,646-149,477)

Updated from Fonarow GC, et al. Am Heart J 2011;161:1024-1030. and JAMA Cardiology 2016;1(6)714-717 and JAMA Cardiology 2020;5(8)948-951

HFrEF GDMT Implementation

- The benefits of HFrEF medications are additive/incremental
- The optimal approach is to utilize each medication shown to reduce mortality in combination, so long as not contraindicated/not tolerated, and start all without delay
- A serial or selective approach leads to delays and HF hospitalizations / deaths which could have been prevented with earlier use of GDMT
- ARNI+BB+MRA+ SGLT2i each provide high economic and clinical value
- Implementation of GDMT needs to improve in all clinical settings
- Need for further implementation science innovation and testing