Do We Really Need So Many Heart Failure Clinicians?

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Friday, June 10th 2022

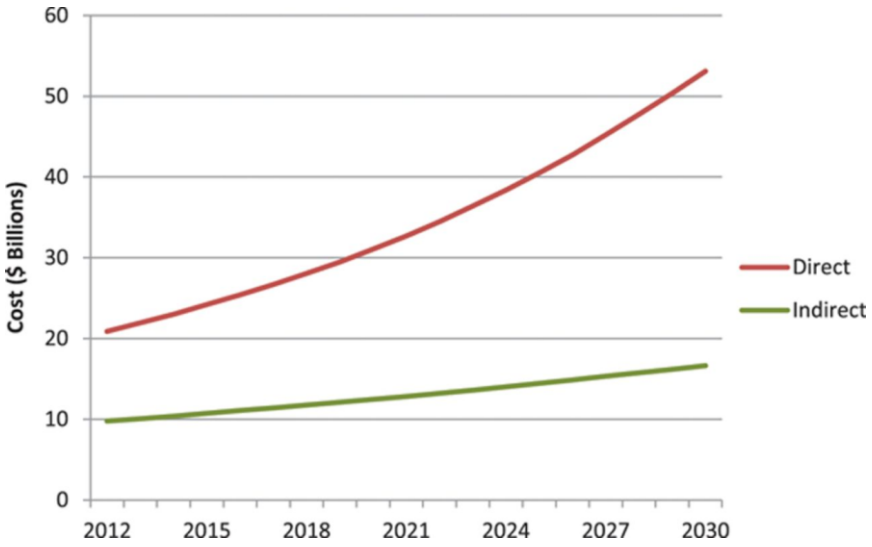
Disclosures

Consultant for Sanofi-Aventis, Amgen, Cytokinetics; Research Funding from Boehringer Ingelheim, AstraZeneca, Cytokinetics, and Relypsa

Heart Failure Clinician

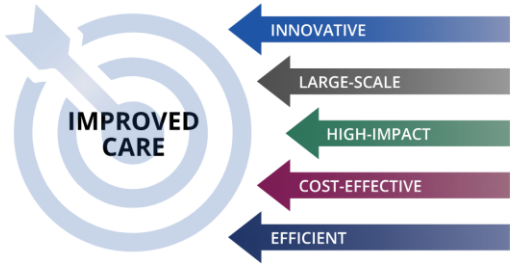
My purpose is to generate discussion, not convince you of a point of view

Why Is This an Important Question?



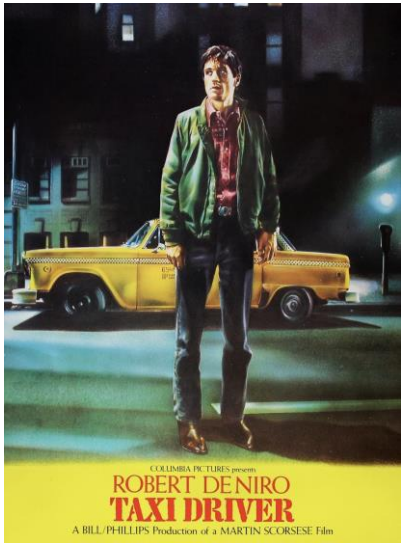
To accomplish this vision, the NIH Pragmatic Trials Collaboratory plans to:

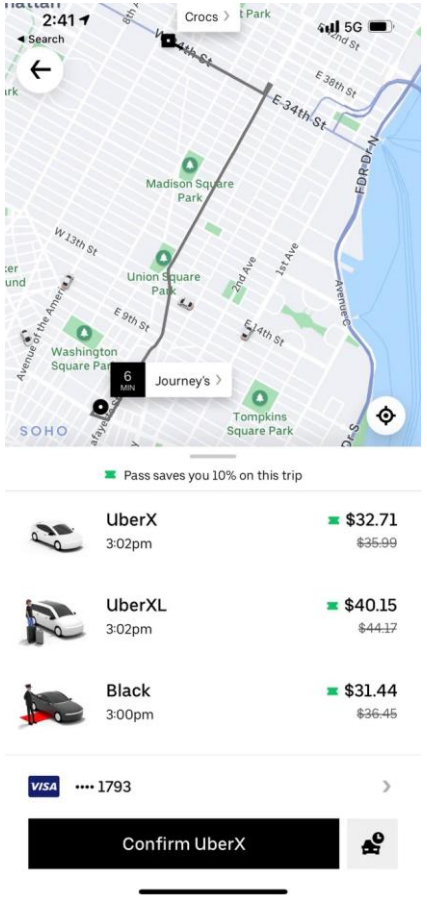
- Create a new infrastructure for collaborative research with healthcare systems partners
- Generate reliable evidence with real-world data
- Improve the cost-effectiveness and efficiency of clinical trials
- Support the conduct of large-scale, high-impact, innovative studies



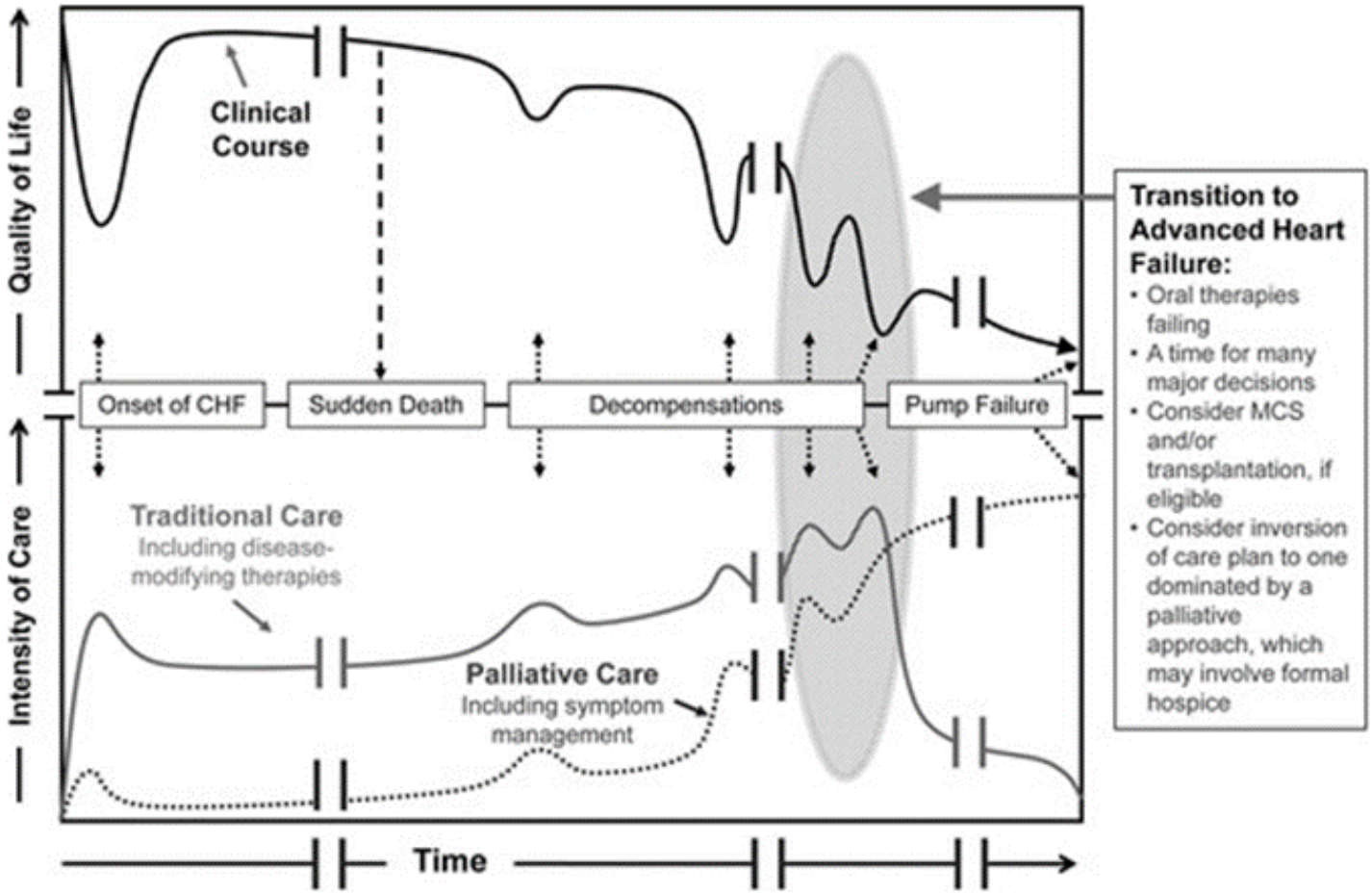
OUR GOAL: Improve care by ensuring healthcare providers and patients have the best clinical evidence on which to base care decisions

Our Role in The Patient Journey



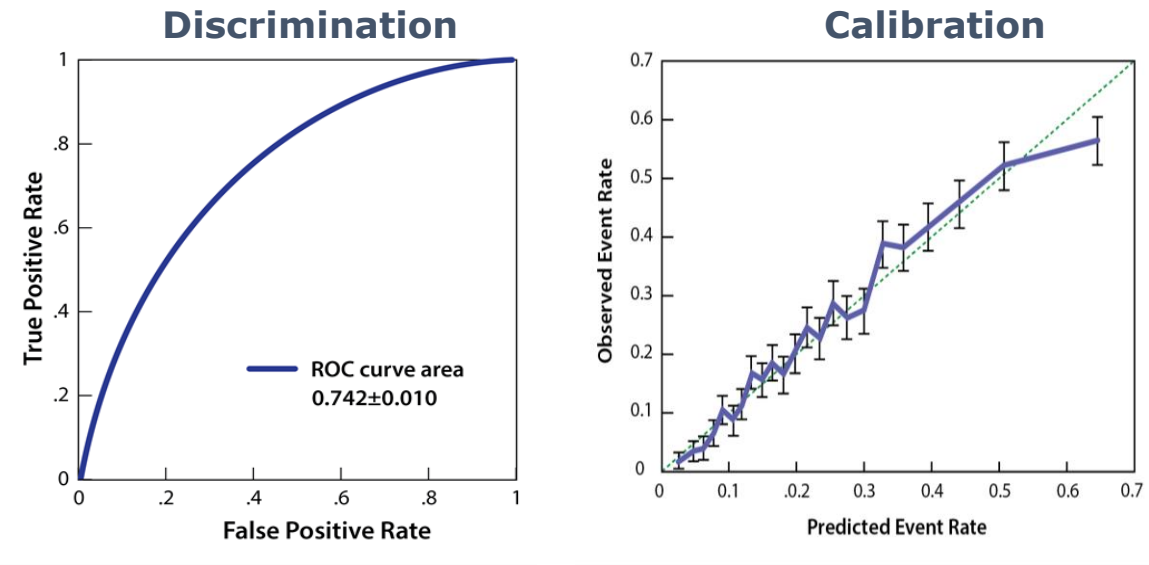


We Can Communicate the Journey



Prognosis in Heart Failure

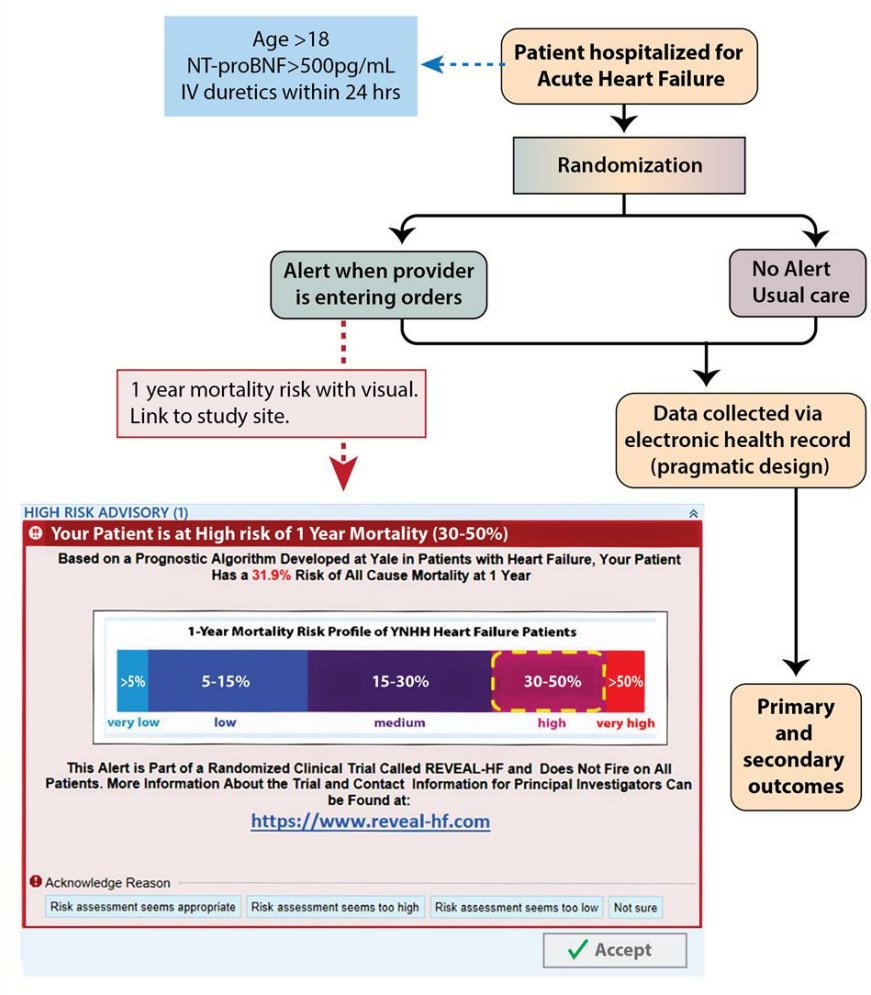
REVeAL-HF Study www.reveal-hf.com



Age, Weight, SBP, RDW, BUN, Monocyte #, Lymphocyte %, BUN/Cr ratio, Troponin, NTproBNP, MCV, ICU admission, Measurement of Arterial pH

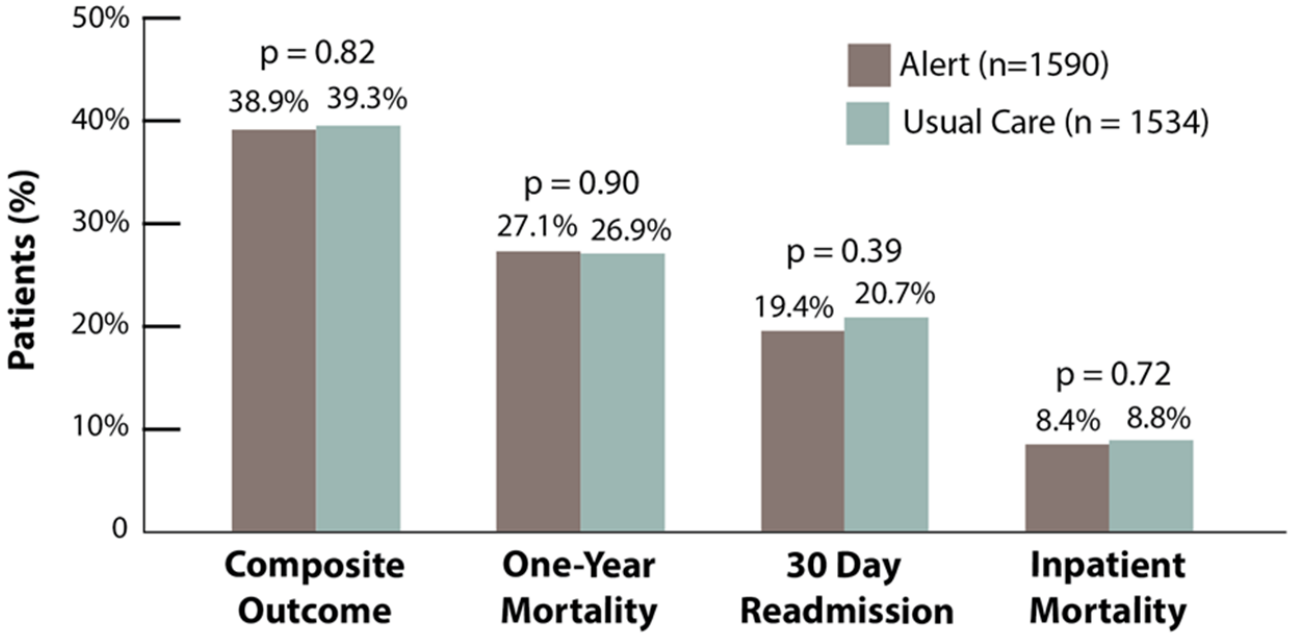
J Am Coll Cardiol HF 2021; 9:409-419

REVeAL-HF Study www.reveal-hf.com



REVeAL-HF

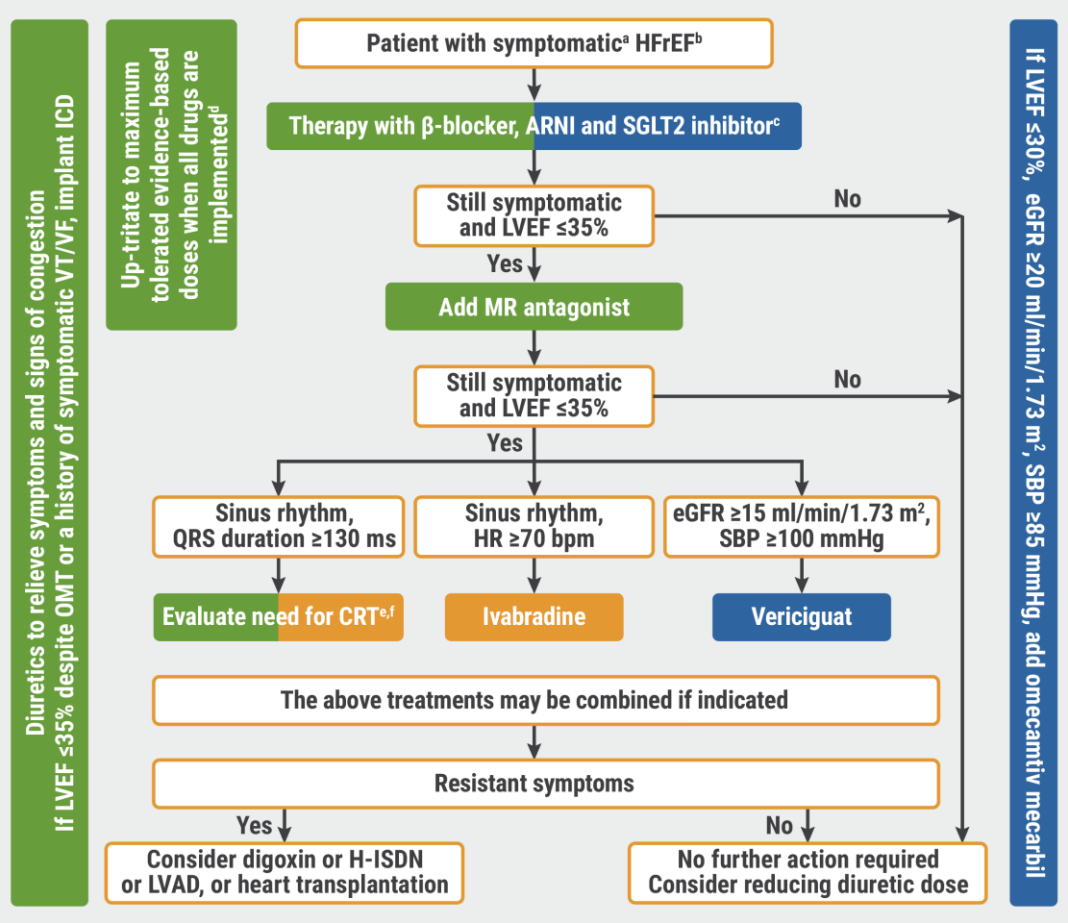
Primary Clinical Endpoints

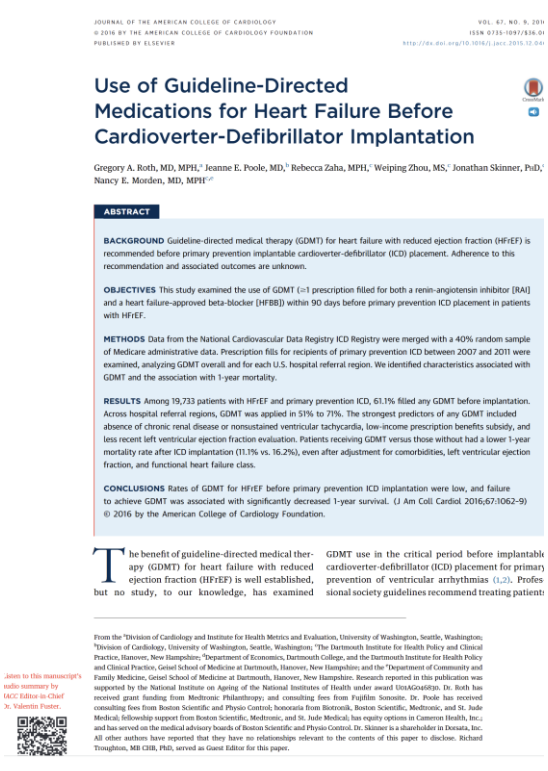


Bedside clinicians may require more **prescriptive decision support**, as these results call into question the hypothesis that **accurate prognostic information alone** will lead to better clinical decision-making and improved outcomes in hospitalized patients with heart failure

Tariq Ahmad et al. LBCT AHA 2021

We Can Ensure Patients Get on the Right Rx





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Use of Guideline-Directed Medications for Heart Failure Before Cardioverter-Defibrillator Implantation

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ABSTRACT

BACKGROUND Guideline-directed medical therapy (GDMT) for heart failure with reduced ejection fraction (HFrEF) is recommended before primary prevention implantable cardioverter-defibrillator (ICD) placement. Adherence to this recommendation and associated outcomes are unknown.

OBJECTIVES This study examined the use of GDMT (≥1 prescription filled for both a renin-angiotensin inhibitor [RAI] and a heart failure-approved beta-blocker [HFBB]) within 90 days before primary prevention ICD placement in patients with HFrEF.

METHODS Data from the National Cardiovascular Data Registry ICD Registry were merged with a 40% random sample of Medicare administrative data. Prescription fills for recipients of primary prevention ICD between 2007 and 2011 were examined, analyzing GDMT overall and for each U.S. hospital referral region. We identified characteristics associated with GDMT and the association with 1-year mortality.

RESULTS Among 19,733 patients with HFrEF and primary prevention ICD, 61.1% filled any GDMT before implantation. Across hospital referral regions, GDMT was applied in 51% to 71%. The strongest predictors of any GDMT included absence of chronic renal disease or nonsustained ventricular tachycardia, low-income prescription benefits subsidy, and less recent left ventricular ejection fraction evaluation. Patients receiving GDMT versus those without had a lower 1-year mortality rate after ICD implantation (11.1% vs. 16.2%), even after adjustment for comorbidities, left ventricular ejection fraction, and functional heart failure class.

CONCLUSIONS Rates of GDMT for HFrEF before primary prevention ICD implantation were low, and failure to achieve GDMT was associated with significantly decreased 1-year survival. (J Am Coll Cardiol 2016;67:1062–9)
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The benefit of guideline-directed medical therapy (GDMT) for heart failure with reduced ejection fraction (HFrEF) is well established, but no study, to our knowledge, has examined GDMT use in the critical period before implantable cardioverter-defibrillator (ICD) placement for primary prevention of ventricular arrhythmias (1,2). Professional society guidelines recommend treating patients

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ORIGINAL INVESTIGATIONS

Titration of Medical Therapy for Heart Failure With Reduced Ejection Fraction

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ABSTRACT

BACKGROUND Guidelines recommend that patients with heart failure with reduced ejection fraction (HFrEF) have medical therapy titrated to target doses derived from clinical trials, as tolerated. The degree to which titration occurs in contemporary U.S. practice is unknown.

OBJECTIVES This study sought to characterize longitudinal titration of HFrEF medical therapy in clinical practice and to identify associated factors and reasons for medication changes.

METHODS Among 2,588 U.S. outpatients with chronic HFrEF in the CHAMP-HF (Change the Management of Patients with Heart Failure) registry with complete medication data and no contraindications to medical therapy, use and dose of angiotensin-converting enzyme inhibitor (ACEI)/angiotensin II receptor blocker (ARB), angiotensin receptor-neprilysin inhibitor (ARNI), beta-blocker, and mineralocorticoid receptor antagonist (MRA) were examined at baseline and at 12-month follow-up.

RESULTS At baseline, 658 (25%), 525 (20%), 287 (11%), and 45 (2%) patients were receiving target doses of MRA, beta-blocker, ACEI/ARB, and ARNI therapy, respectively. At 12 months, proportions of patients with medication initiation or dose increase were 6% for MRA, 10% for beta-blocker, 7% for ACEI/ARB, and 10% for ARNI; corresponding proportions with discontinuation or dose decrease were 4%, 7%, 11%, and 3%, respectively. Over 12 months, <1% of patients were simultaneously treated with target doses of ACEI/ARB/ARNI, beta-blocker, and MRA. In multivariate analysis, across the classes of medications, multiple patient characteristics were associated with a higher likelihood of initiation or dose increase (e.g., previous HF hospitalization, higher blood pressure, lower ejection fraction) and discontinuation or dose decrease (e.g., previous HF hospitalization, impaired quality of life, more severe functional class). Medical reasons were the most common reasons for discontinuations and dose decreases of each therapy, but the relative contributions from patient preference, health team, and systems-based reasons varied by medication.

CONCLUSIONS In this contemporary U.S. registry, most eligible HFrEF patients did not receive target doses of medical therapy at any point during follow-up, and few patients had doses increased over time. Although most patients had no alterations in medical therapy, multiple clinical factors were independently associated with medication changes. Further quality improvement efforts are urgently needed to improve guideline-directed medication titration for HFrEF. (J Am Coll Cardiol 2019;73:2365–83) © 2019 by the American College of Cardiology Foundation.

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VOL. 72, NO. 4, 2018

ORIGINAL INVESTIGATIONS

Medical Therapy for Heart Failure With Reduced Ejection Fraction

The CHAMP-HF Registry

Stephen J. Greene, MD,[a,b] Javed Butler, MD, MPH, MBA,[c] Nancy M. Albert, PhD,[d] Adam D. DeVore, MD, MHS,[a,b] Puza P. Sharma, MBBS, MPH, PhD,[e] Carol I. Duffy, DO,[e] C. Larry Hill, PhD,[e] Kevin McCague, MA,[e] Xiaojuan Mi, PhD,[a] J. Herbert Patterson, PharmD,[f] John A. Spertus, MD, MPH,[g] Laine Thomas, PhD,[e] Fredonia B. Williams, EdD,[f] Adrian F. Hernandez, MD, MHS,[a,b] Gregg C. Fonarow, MD[c]

ABSTRACT

BACKGROUND Guidelines strongly recommend patients with heart failure with reduced ejection fraction (HFrEF) be treated with multiple medications proven to improve clinical outcomes, as tolerated. The degree to which gaps in medication use and dosing persist in contemporary outpatient practice is unclear.

OBJECTIVES This study sought to characterize patterns and factors associated with use and dose of HFrEF medications in current practice.

METHODS The CHAMP-HF (Change the Management of Patients with Heart Failure) registry included outpatients in the United States with chronic HFrEF receiving at least 1 oral medication for management of HF. Patients were characterized by baseline use and dose of angiotensin-converting enzyme inhibitor (ACEI)/angiotensin II receptor blocker (ARB), angiotensin receptor neprilysin inhibitor (ARNI), beta-blocker, and mineralocorticoid receptor antagonist (MRA). Patient-level factors associated with medication use were examined.

RESULTS Overall, 3,518 patients from 150 primary care and cardiology practices were included. Mean age was 66 ± 13 years, 29% were female, and mean EF was 29 ± 8%. Among eligible patients, 27%, 33%, and 67% were not prescribed ACEI/ARB/ARNI, beta-blocker, and MRA therapy, respectively. When medications were prescribed, few patients were receiving target doses of ACEI/ARB (17%), ARNI (14%), and beta-blocker (28%), whereas most patients were receiving target doses of MRA therapy (77%). Among patients eligible for all classes of medication, 1% were simultaneously receiving target doses of ACE/ARB/ARNI, beta-blocker, and MRA. In adjusted models, older age, lower blood pressure, more severe functional class, renal insufficiency, and recent HF hospitalization generally favored lower medication utilization or dose. Social and economic characteristics were not independently associated with medication use or dose.

CONCLUSIONS In this contemporary outpatient HFrEF registry, significant gaps in use and dose of guideline-directed medical therapy remain. Multiple clinical factors were associated with medication use and dose prescribed. Strategies to improve guideline-directed use of HFrEF medications remain urgently needed, and these findings may inform targeted approaches to optimize outpatient medical therapy. (J Am Coll Cardiol 2018;72:351–66)
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Listen to this manuscript's audio summary by JACC Editor-in-Chief Dr. Valentin Fuster.

From the [a]Duke Clinical Research Institute, Durham, North Carolina; [b]Division of Cardiology, Duke University School of Medicine, Durham, North Carolina; [c]Department of Medicine, University of Mississippi, Jackson, Mississippi; [d]Cleveland Clinic Foundation, Cleveland, Ohio; [e]Novartis Pharmaceuticals Corporation, East Hanover, New Jersey; [f]Saheliman School of Pharmacy, University of North Carolina, Chapel Hill, North Carolina; [g]Saint Luke's Mid America Heart Institute and University of Missouri-Kansas City, Kansas City, Missouri; [h]Mended Hearts, Huntsville, Alabama; and the [i]Ahmanson-UCLA Cardiomyopathy Center, University of California-Los Angeles, Los Angeles, California. CHAMP-HF was supported by Novartis Pharmaceuticals. Dr. Greene has received support from U.S. National Institutes of Health (NIH) grant 5T32HL069749-14, Heart Failure Society of America/Emergency Medicine Foundation Acute Heart Failure Young Investigator Award funded by Novartis, and from Novartis. Dr. Butler has received

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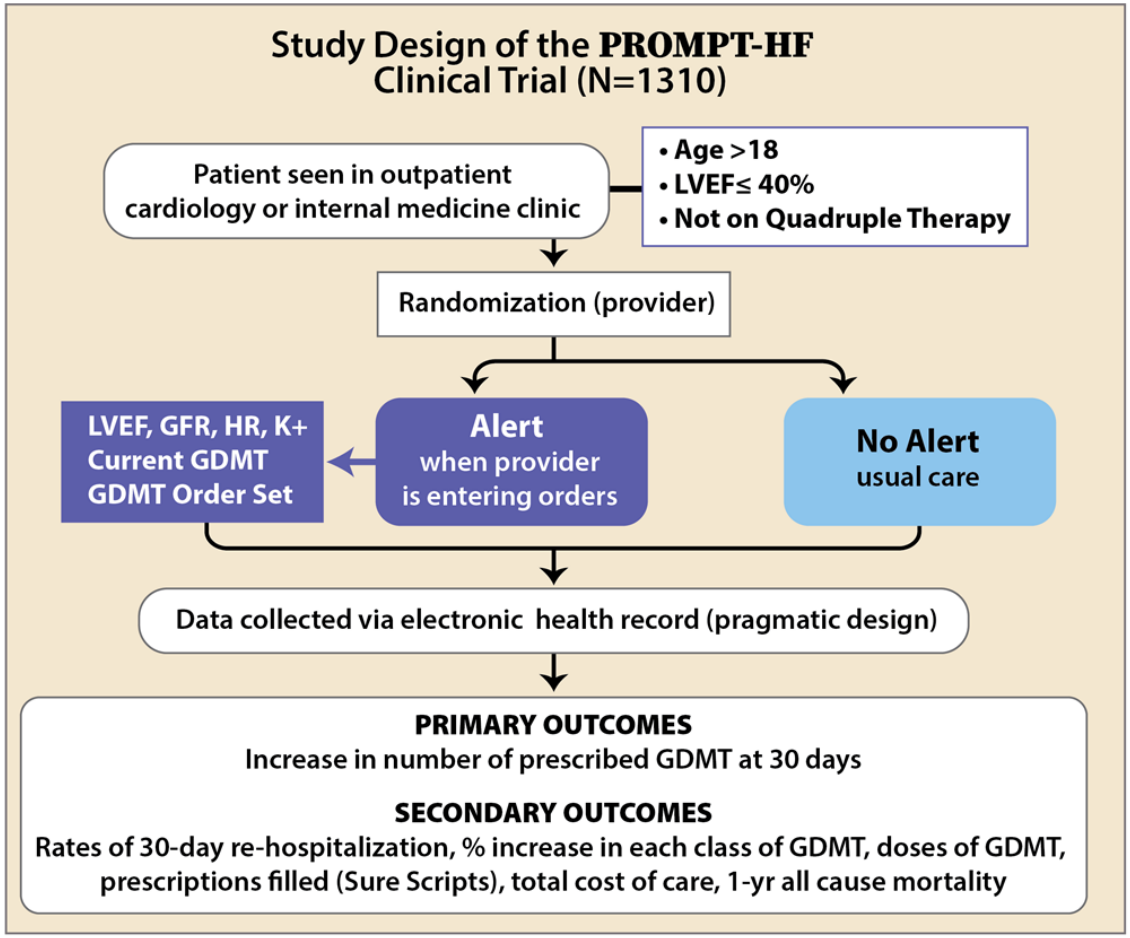
So Far, Things Have Not Looked Good

PROMPT-HF

*PR*agmatic Trial *O*f *M*essaging to *P*roviders about *T*reatment of *H*eart *F*ailure



PROMPT-HF

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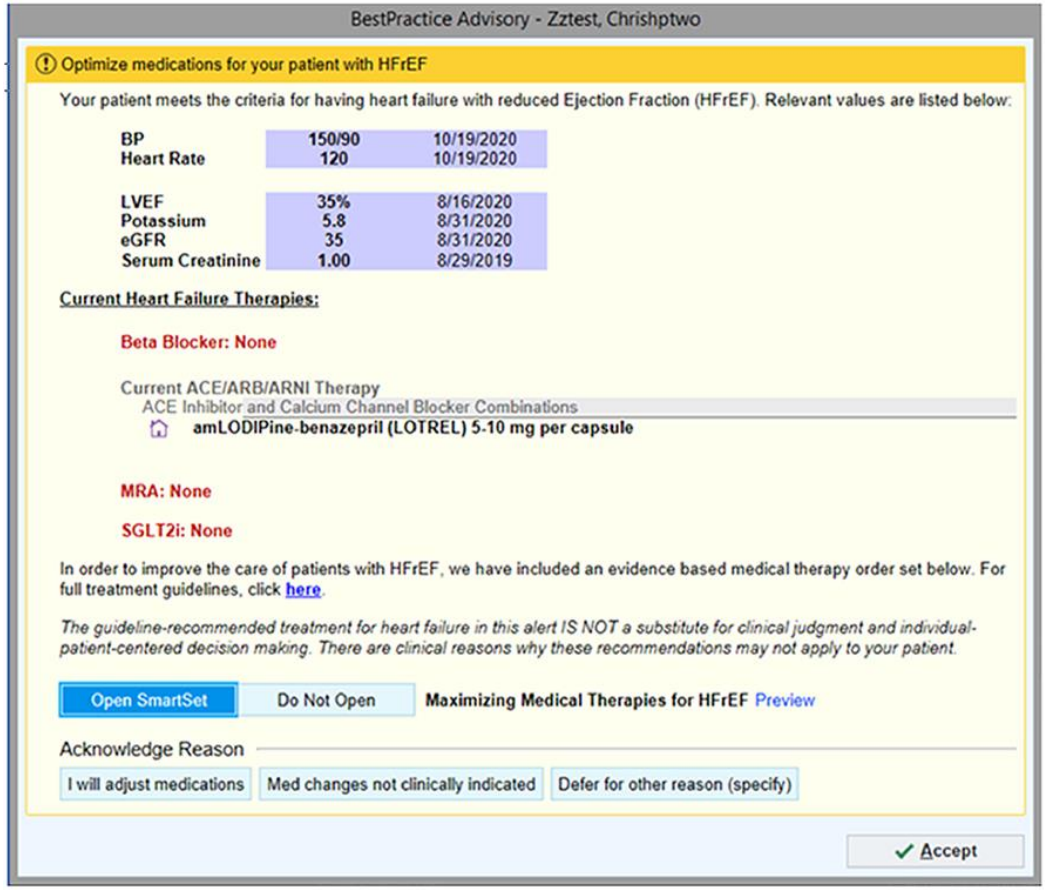

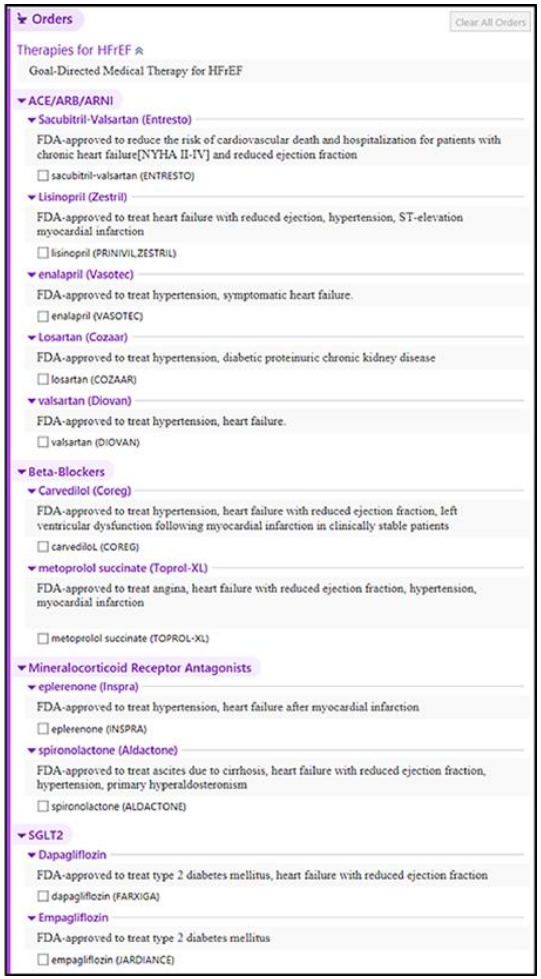

Lama Ghazi et al. AHJ 2021; 9:409-419

Yale SCHOOL OF MEDICINE

PROMPT-HF

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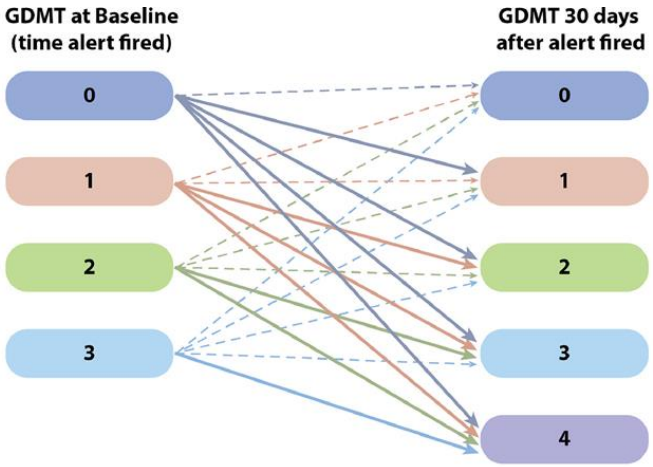
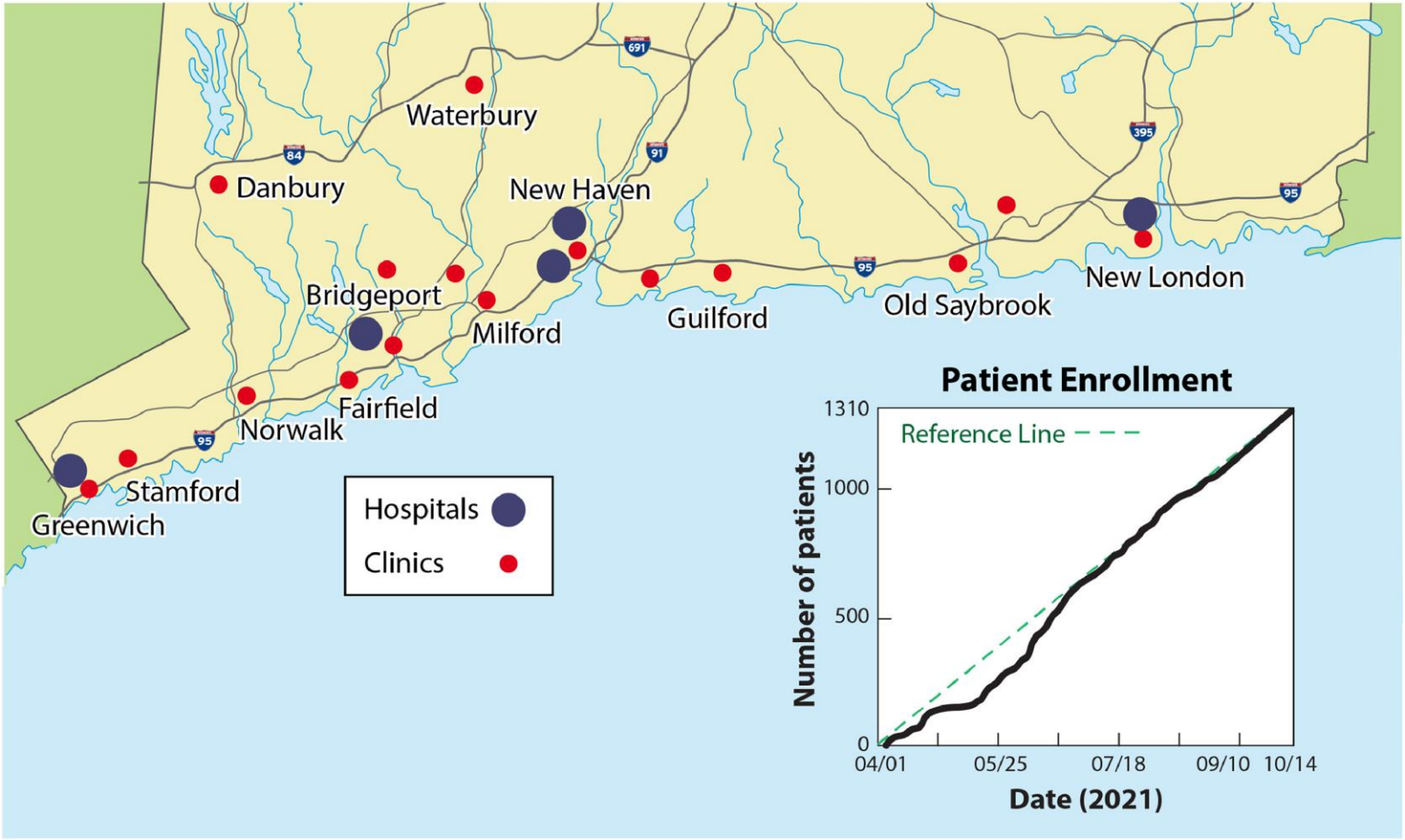


Scenario	Evidence-based medications at randomization	Evidence-based medications 30 days post-randomization	Outcome present (increase evidence-based medications)
1	ACEi + beta blocker	ARB + beta blocker	No
2	ARB + MRA	ARB + SGLT2i	No
3	ACEi	ACEi + SGLT2i + beta blocker	Yes
4	ACEi + MRA	ARNi	No
5	ARB + MRA + SGLT2i	ARB + MRA + SGLT2i + beta blocker	Yes
6	ACEi	ARNi	No

Lama Ghazi et al. AHJ 2021; 9:409-419

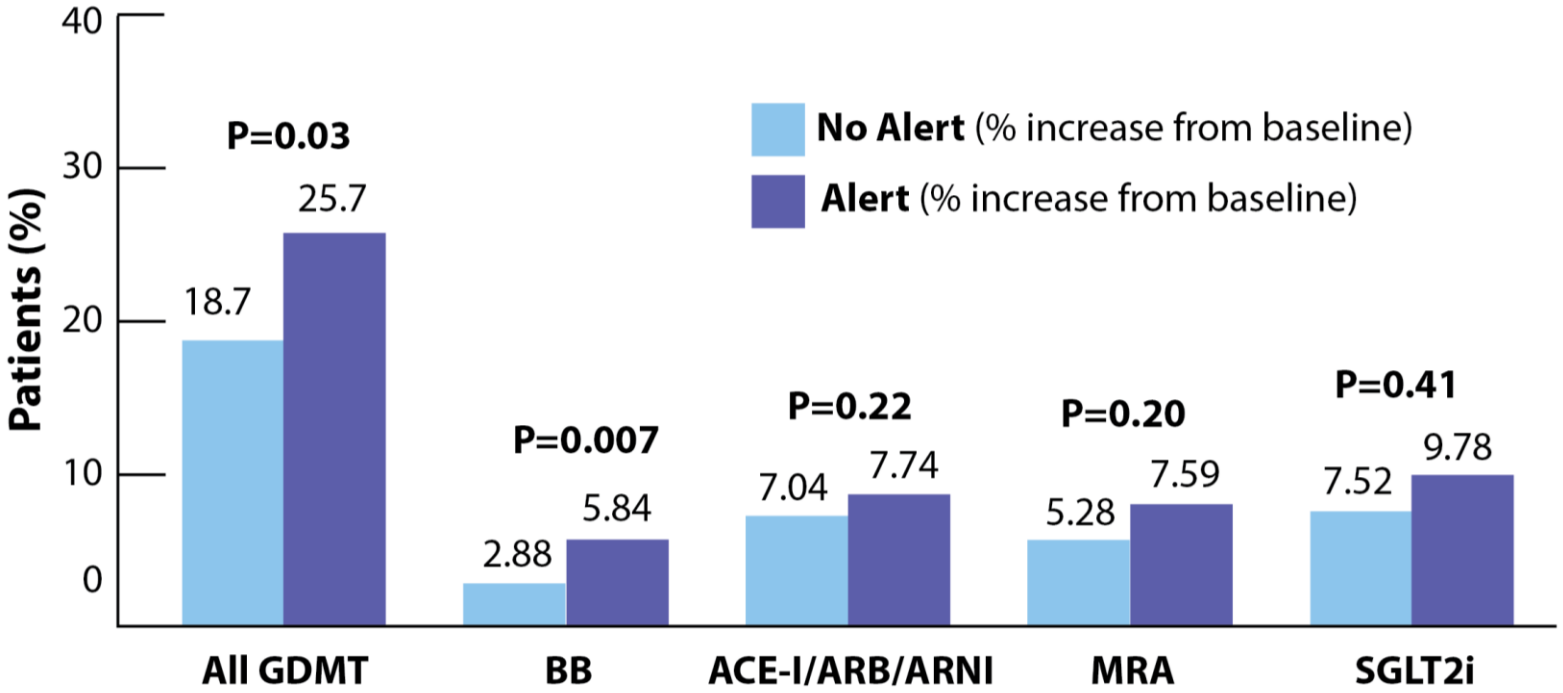
PRagmatic Trial ***O***f ***M***essaging to ***P***roviders about ***T***reatment of ***H***eart ***F***ailure



Lama Ghazi et al. AHJ 2021; 9:409-419

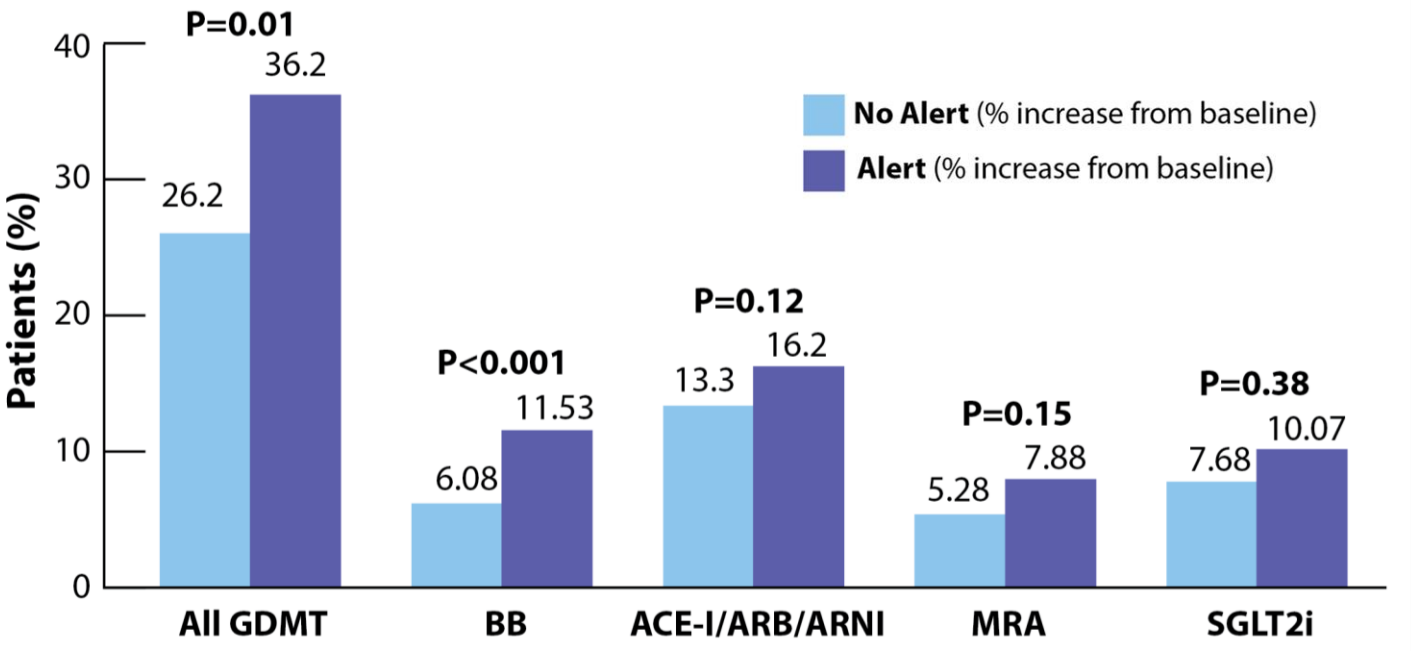
Primary Clinical Endpoint: Additional GDMT Class

RR: 1.41 (1.03, 1.93); P=0.03 | **Number Need to Alert = 14**



Secondary Clinical Endpoint: +GDMT Class/↑Dose

RR: 1.39 (1.08, 1.79); P=0.01	Number Need to Alert= 10



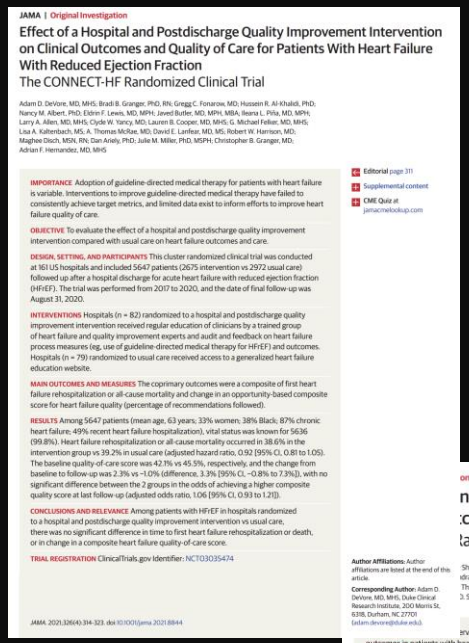
Sun, Apr 3, 8:38 PM

Congrats on PROMPT-HF-- great study. Still a bit humbling that in the intervention arm >70% of patients didn't have GDMT change--- what's your next intervention get to the other 70%?

Expand Current Processes

Create New Paradigms

Expensive, Human Capital-Intensive Interventions Have Not Helped in Heart Failure



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; Brad 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, Maghee Disch, MSN, RN; Dan Ariely, PhD; Julie 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

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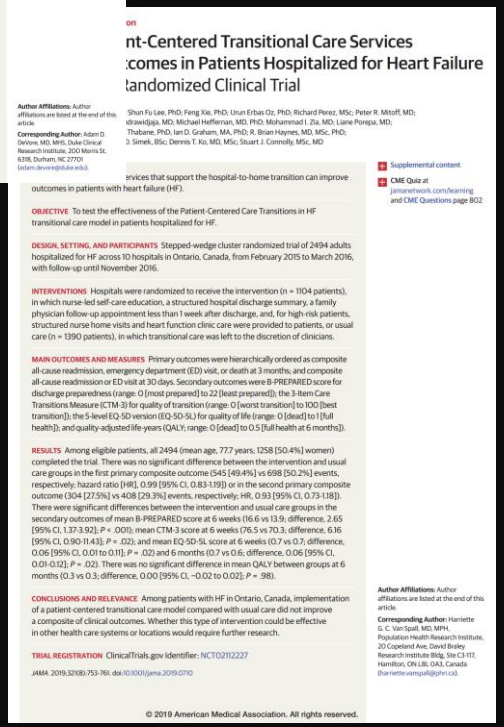
Supplemental content

CME Quiz at jamacmelookup.com

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



...nt-Centered Transitional Care Services ...comes in Patients Hospitalized for Heart Failure ...andomized Clinical Trial

...Shun Fu Lee, PhD; Feng Xie, PhD; Unun Erbas Oz, PhD; Richard Perez, MSc; Peter R. Mitoff, MD; ...drawidjaja, MD; Michael Heffernan, MD, PhD; Mohammad I. Zia, MD; Liane Porepa, MD; ...Thabane, PhD; Ian D. Graham, MA, PhD; R. Brian Haynes, MD, MSc, PhD; ...Simek, BSc; Dennis T. Ko, MD, MSc; Stuart J. Connolly, MSc, MD

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...ervices 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

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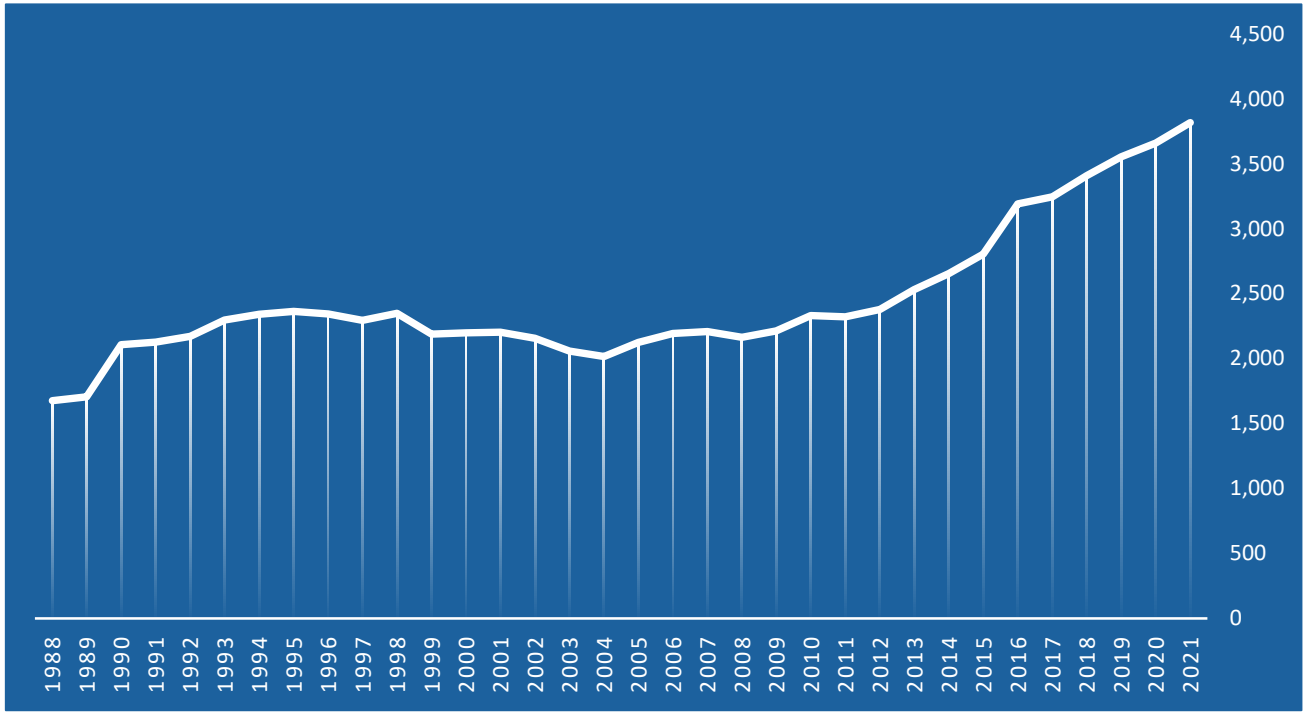
We Are Key to Transplant and LVAD



	Total	
Discipline	All Certificates	Valid Certificates
General Internal Medicine	311,313	208,657
Adolescent Medicine[1]	88	45
Adult Congenital Heart Disease	455	454
Advanced Heart Failure /Transplant Cardiology	1,218	1,212
Cardiovascular Disease	35,594	28,824
Clinical Cardiac Electrophysiology	3,363	2,790
Critical Care Medicine[1]	17,193	12,217
Endocrinology Diabetes and Metabolism	9,543	7,681
Gastroenterology	19,242	16,003
Geriatric Medicine[1]	10,468	4,784
Hematology	12,138	9,226
Hospice and Palliative Medicine[1]	4,752	4,365
Infectious Disease	11,246	9,156
Interventional Cardiology	9,143	6,600
Medical Oncology	18,169	14,723
Nephrology	13,619	11,363
Pulmonary Disease	19,312	15,792
Rheumatology	7,769	6,239
Sleep Medicine[1]	4,223	3,478
Sports Medicine[1]	374	257
Transplant Hepatology[1]	753	649

Upper Limit of Heart Transplants?

State	2021	2001
MA	60	36
CT	83	32
NY	262	151
MI	16	9
NH	10	8
RI	8	5
Total	439	241

JAMA Cardiology | Original Investigation

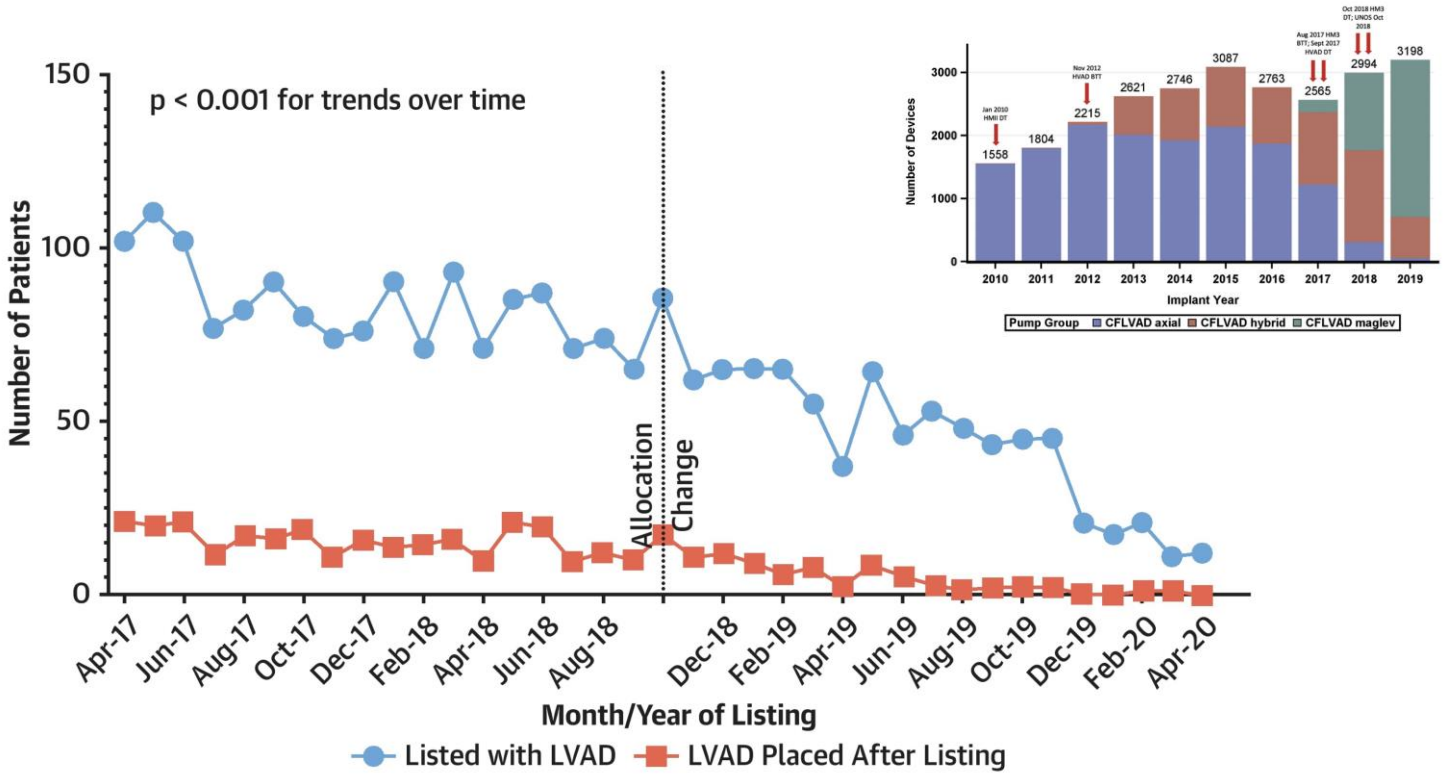
Survival on the Heart Transplant Waiting List

JAMA Network Open

Original Investigation | Cardiology

Evaluation of Case Volumes of a Heart Transplant Program and Short-term Outcomes After Changes in the United Network for Organ Sharing Donor Heart Allocation System

What About LVADs?



Mullan, C.W. et al. J Am Coll Cardiol HF. 2021;9(6):420-9.

We Can Guide Research

Isosorbide Mononitrate in Heart Failure with Preserved Ejection Fraction

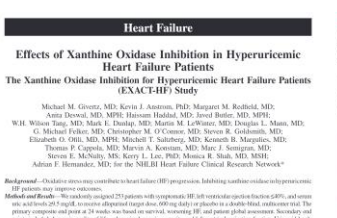
Ultrafiltration in Decompensated Heart Failure with Cardiorenal Syndrome

Effects of Liraglutide on Clinical Stability Among Patients With Advanced Heart Failure and Reduced Ejection Fraction
A Randomized Clinical Trial

Effect of Natriuretic Peptide–Guided Therapy on Hospitalization or Cardiovascular Mortality in High-Risk Patients With Heart Failure and Reduced Ejection Fraction
A Randomized Clinical Trial

Reduction of dietary sodium to less than 100 mmol in heart failure (SODIUM-HF): an international, open-label, randomised, controlled trial

Effect of Oral Iron Repletion on Exercise Capacity in Patients With Heart Failure With Reduced Ejection Fraction and Iron Deficiency
The IRONOUT HF Randomized Clinical Trial



Effects of Xanthine Oxidase Inhibition in Hyperuricemic Heart Failure Patients
The Xanthine Oxidase Inhibition for Hyperuricemic Heart Failure Patients (EXACT-HF) Study

Low-Dose Dopamine or Low-Dose Nesiritide in Acute Heart Failure With Renal Dysfunction
The ROSE Acute Heart Failure Randomized Trial

Effect of a Strategy of Comprehensive Vasodilation vs Usual Care on Mortality and Heart Failure Rehospitalization Among Patients With Acute Heart Failure
The GALACTIC Randomized Clinical Trial

Efficacy and Safety of Spironolactone in Acute Heart Failure
The ATHENA-HF Randomized Clinical Trial

Yale SCHOOL OF MEDICINE

Yet, No One Saw SGLT2i Coming

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

ABSTRACT

BACKGROUND

The effects of empagliflozin, an inhibitor of sodium–glucose cotransporter 2, in addition to standard care, on cardiovascular morbidity and mortality in patients with type 2 diabetes at high cardiovascular risk are not known.

METHODS

We randomly assigned patients to receive 10 mg or 25 mg of empagliflozin or placebo once daily. The primary composite outcome was death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, as analyzed in the pooled empagliflozin group versus the placebo group. The key secondary composite outcome was the primary outcome plus hospitalization for unstable angina.

RESULTS

A total of 7020 patients were treated (median observation time, 3.1 years). The primary outcome occurred in 490 of 4687 patients (10.5%) in the pooled empagliflozin group and in 282 of 2333 patients (12.1%) in the placebo group (hazard ratio in the empagliflozin group, 0.86; 95.02% confidence interval, 0.74 to 0.99; P=0.04 for superiority). There were no significant between-group differences in the rates of myocardial infarction or stroke, but in the empagliflozin group there were significantly lower rates of death from cardiovascular causes (3.7%, vs. 5.9% in the placebo group; 38% relative risk reduction), hospitalization for heart failure (2.7% and 4.1%, respectively; 35% relative risk reduction), and death from any cause (5.7% and 8.3%, respectively; 32% relative risk reduction). There was no significant between-group difference in the key secondary outcome (P=0.08 for superiority). Among patients receiving empagliflozin, there was an increased rate of genital infection but no increase in other adverse events.

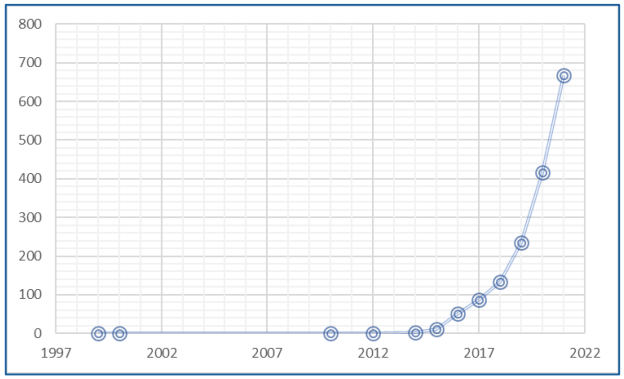
CONCLUSIONS

Patients with type 2 diabetes at high risk for cardiovascular events who received empagliflozin, as compared with placebo, had a lower rate of the primary composite cardiovascular outcome and of death from any cause when the study drug was added to standard care. (Funded by Boehringer Ingelheim and Eli Lilly; EMPA-REG OUTCOME ClinicalTrials.gov number, NCT01131676.)

From the Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital (B.Z.) and the Divisions of Endocrinology (B.Z.) and Cardiology (D.F.), University of Toronto — all in Toronto; the Department of Medicine, Division of Nephrology, Würzburg University Clinic, Würzburg (C.W.), Boehringer Ingelheim Pharma, Biberach (E.B., S.H.), and Boehringer Ingelheim Pharma, Ingelheim (M.M., H.J.W., U.C.B.) — all in Germany; the Biostatistics Center, George Washington University, Rockville, MD (J.M.L.); Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT (T.D.); Boehringer Ingelheim Norway, Asker, Norway (O.E.J.); and the Section of Endocrinology, Yale University School of Medicine, New Haven, CT (S.E.I.). Address reprint requests to Dr. Zinman at Mount Sinai Hospital, 60 Murray St., Suite L5-024, Box 17, Toronto, ONT M5T 3L9, Canada, or at zinman@lunenfeld.ca.

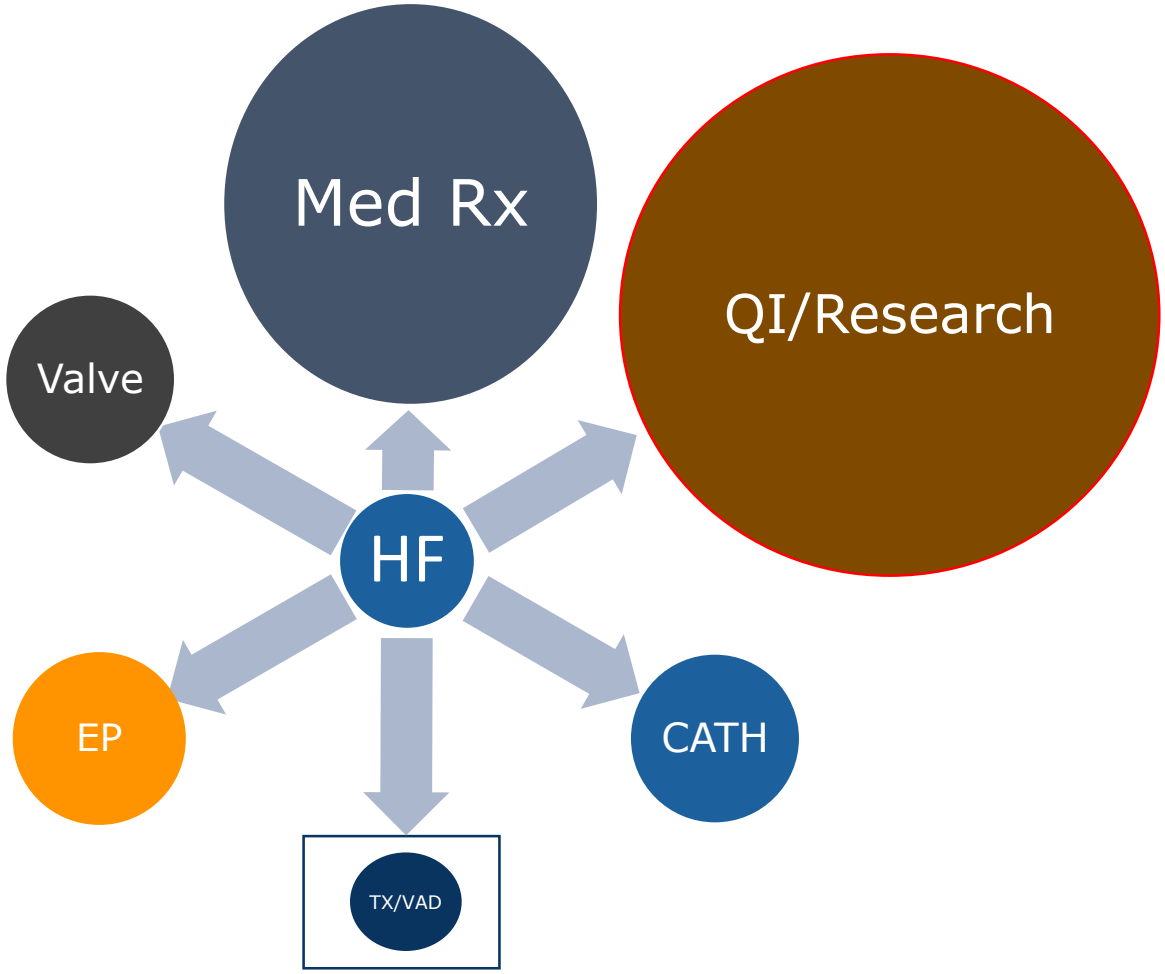
This article was published on September 17, 2015, at NEJM.org.

N Engl J Med 2015;373:2117-28.
DOI: 10.1056/NEJMoa1504720

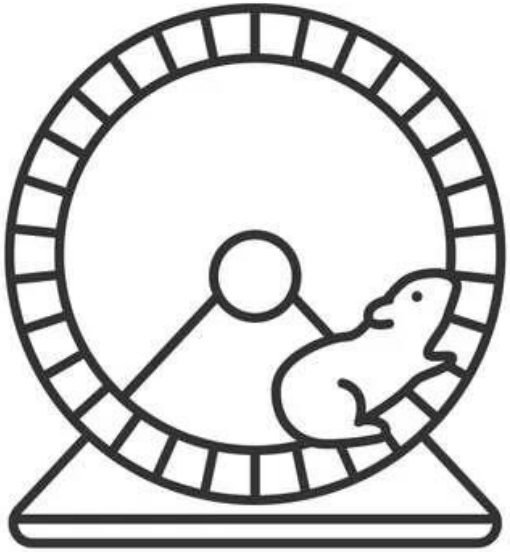


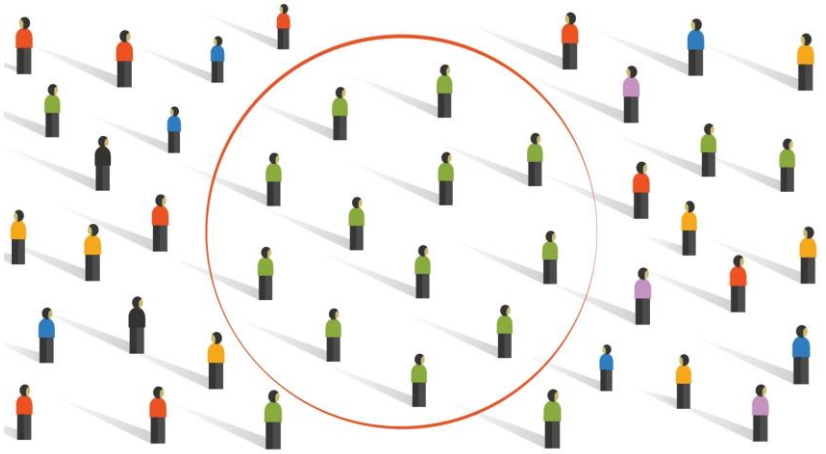
How Can We Improve Things?

Creating the Army We Need

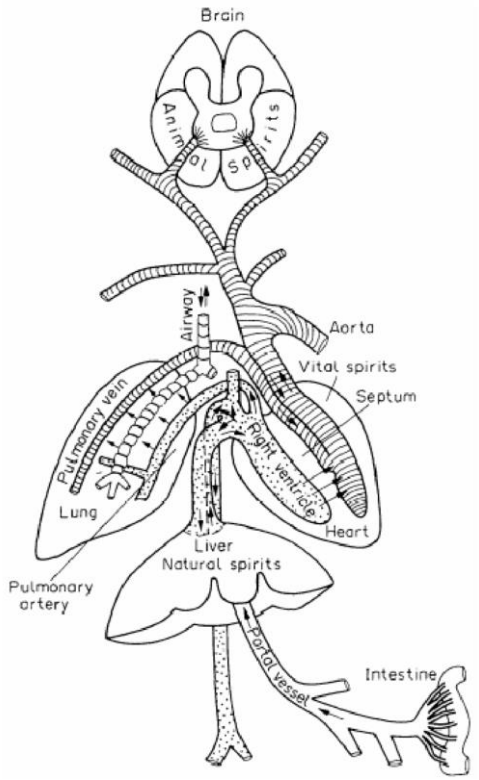


Are We Receptive to Novel Ideas?





We Need to Revisit Our Basic Assumptions



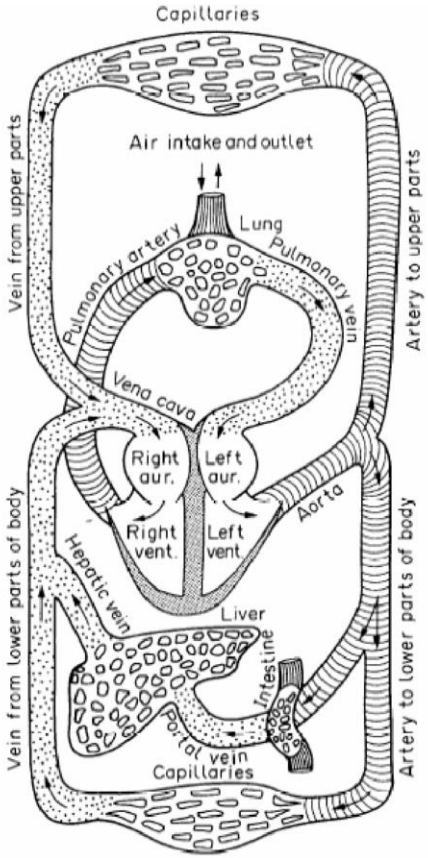
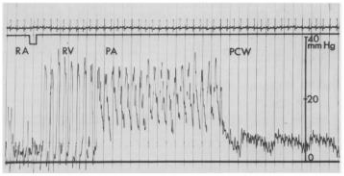


Figure 1.



Continuous Pressure Recording as the Pulmonary-Artery Balloon Catheter Is Passed through the Chambers of the Right Side of the Heart.

Table 1.

Table 1. Normal and Abnormal Intracardiac Pressures.*

Area Tested	Normal Pressure Range (mm Hg)	Conditions in Which Increased	Specific Patterns
RA	0-8	RV failure; PE; COPD; tricuspid-valve abnormality; pericardial tamponade.	TI: giant V wave ("ventricularized" wave form); tamponade: "diastolic plateau," with paradoxical inspiratory rise.
PA	15-30 / 5-12†	Systolic: ↑ resistance: PE; COPD; ↑ flow: VSD; Diastolic: ↑ resistance: PE; COPD; All causes of ↑ PCP.	MI: retrograde V wave; VSD: wide pulse pressure; tamponade: narrow pulse pressure; COPD: marked respiratory fluctuation.
PCP	5-12†	LV failure mitral valve disease tamponade ↓ LV compliance: hypertrophy; infarction.	MI: giant V wave; tamponade: "diastolic plateau," with paradoxical inspiratory rise; COPD: marked respiratory fluctuation.

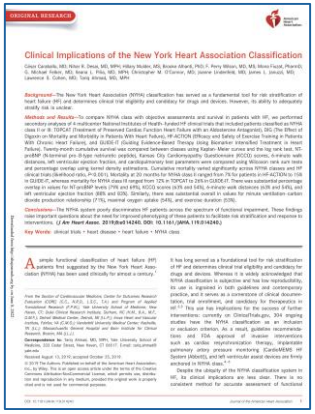
*RA denotes right atrium, PA pulmonary artery, RV right ventricle, PE pulmonary embolism, TI tricuspid insufficiency, MI mitral insufficiency, COPD chronic obstructive pulmonary disease, VSD ventricular septal defect, LV left ventricle, & PCP pulmonary-capillary pressure.

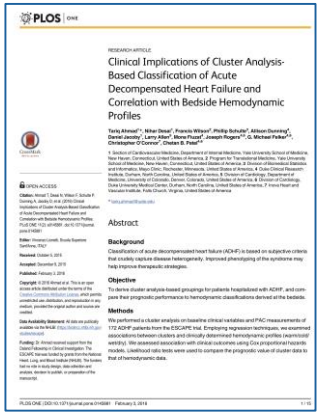
†Although clinical signs of pulmonary congestion begin at approximately 18 mm Hg, the generally accepted upper limit of normal is 12 mm Hg.

Normal and Abnormal Intracardiac Pressures.*

We Need to Revisit Our Basic Assumptions


Machine Learning Methods Improve Prognostication, Identify Clinically Distinct Phenotypes, and Detect Heterogeneity in Response to Therapy in a Large Cohort of Heart Failure Patients


Clinical Implications of the New York Heart Association Classification


Clinical Implications of Cluster Analysis-Based Classification of Acute Decompensated Heart Failure and Correlation with Bedside Hemodynamic Profiles

Currently used descriptors of heart failure—New York Heart Association functional class, left ventricular ejection fraction, and invasive hemodynamics—served important roles when they were first introduced: they allowed for a small degree of granularity in the phenotyping of heart failure when none existed. However, we have come a long way in our understanding of heart failure, and the continued supremacy of these descriptors is now hindering our ability to develop and apply targeted therapies for this syndrome. Unless we update the categorization of heart failure to reflect reality more appropriately, we will remain hamstrung in our efforts to tailor interventions for distinct patient groups, and highly effective therapies will be cast aside because they were tested on too heterogeneous a population.

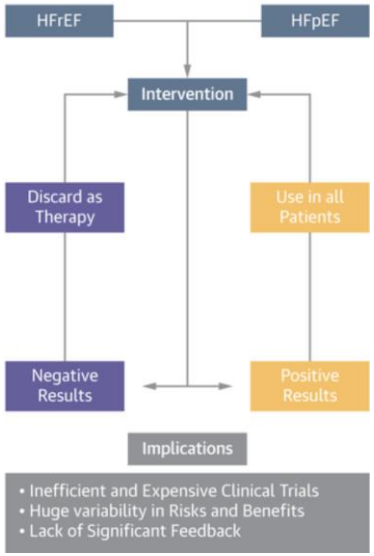
J Am Coll Cardiol HF. 2021 Jul, 9 (7) 528–529

Generating Practice-Based Evidence

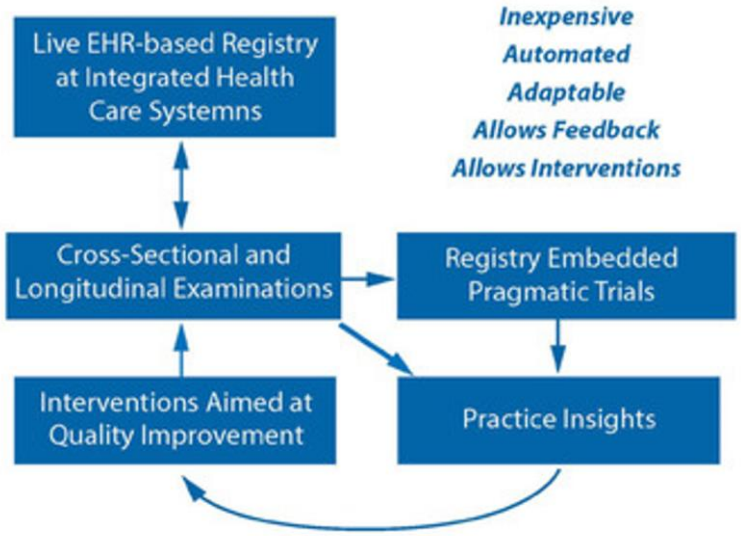
CARDIOVASCULAR PERSPECTIVE

Reimagining Evidence Generation for Heart Failure and the Role of Integrated Health Care Systems

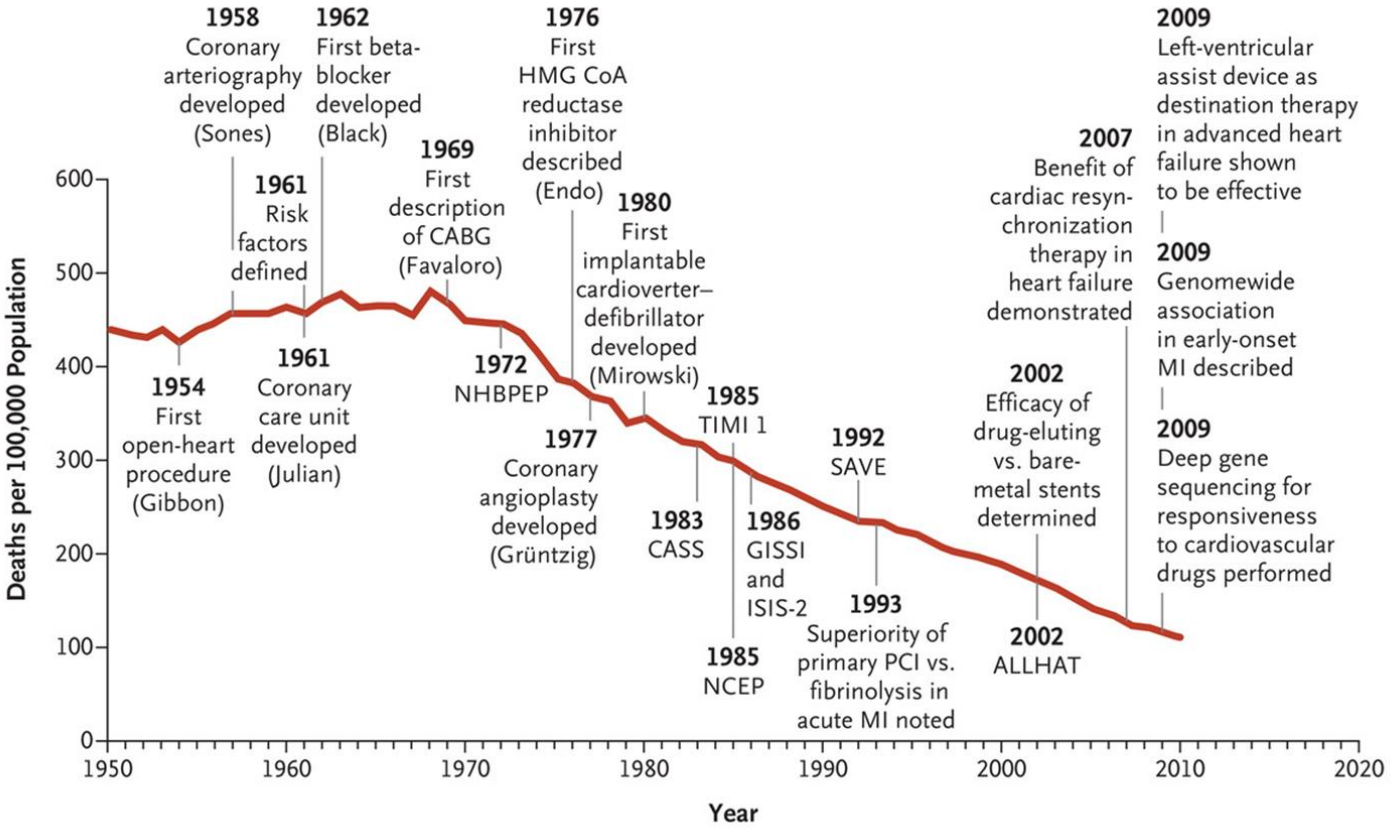
Tariq Ahmad, MD, MPH; Nihar R. Desai, MD, MPH



Expensive
Labor Intensive
Cross Sectional
Not Adaptable
Does not allow Interventions



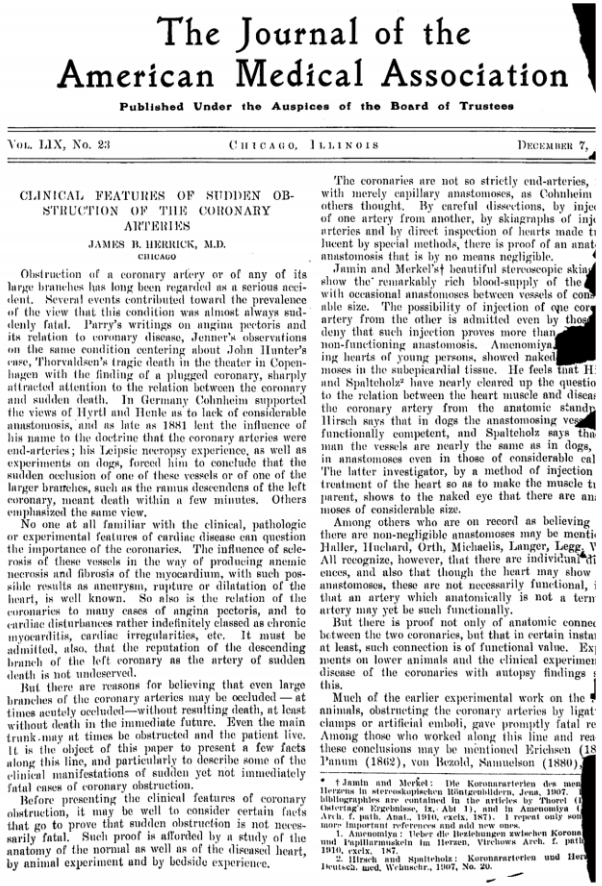
We Have Been Here Before (ACS)



Nabel EG, Braunwald E. N Engl J Med 2012;366:54-63.

What Causes a Heart Attack?

The hope for the damaged myocardium lies in the direction of securing a supply of blood through friendly neighboring vessels so as to restore so far as possible its functional integrity.



The Journal of the American Medical Association

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CLINICAL FEATURES OF SUDDEN OBSTRUCTION OF THE CORONARY ARTERIES

JAMES B. HERRICK, M.D.

CHICAGO

Obstruction of a coronary artery or of any of its large branches has long been regarded as a serious accident. Several events contributed toward the prevalence of the view that this condition was almost always suddenly fatal. Parry's writings on angina pectoris and its relation to coronary disease, Jenner's observations on the same condition centering about John Hunter's case, Thorvaldsen's tragic death in the theater in Copenhagen with the finding of a plugged coronary, sharply attracted attention to the relation between the coronary and sudden death. In Germany Cohnheim supported the views of Hyrtl and Henle as to lack of considerable anastomosis, and as late as 1881 lent the influence of his name to the doctrine that the coronary arteries were end-arteries; his Leipsic necropsy experience, as well as experiments on dogs, forced him to conclude that the sudden occlusion of one of these vessels or of one of the larger branches, such as the ramus descendens of the left coronary, meant death within a few minutes. Others emphasized the same view.

No one at all familiar with the clinical, pathologic or experimental features of cardiac disease can question the importance of the coronaries. The influence of sclerosis of these vessels in the way of producing anemic necrosis and fibrosis of the myocardium, with such possible results as aneurysm, rupture or dilatation of the heart, is well known. So also is the relation of the coronaries to many cases of angina pectoris, and to cardiac disturbances rather indefinitely classed as chronic myocarditis, cardiac irregularities, etc. It must be admitted, also, that the reputation of the descending branch of the left coronary as the artery of sudden death is not undeserved.

But there are reasons for believing that even large branches of the coronary arteries may be occluded — at times acutely occluded—without resulting death, at least without death in the immediate future. Even the main trunk may at times be obstructed and the patient live. It is the object of this paper to present a few facts along this line, and particularly to describe some of the clinical manifestations of sudden yet not immediately fatal cases of coronary obstruction.

Before presenting the clinical features of coronary obstruction, it may be well to consider certain facts that go to prove that sudden obstruction is not necessarily fatal. Such proof is afforded by a study of the anatomy of the normal as well as of the diseased heart, by animal experiment and by bedside experience.

The coronaries are not so strictly end-arteries, with merely capillary anastomoses, as Cohnheim others thought. By careful dissections, by inje of one artery from another, by skiagraphs of inj arteries and by direct inspection of hearts made t lucent by special methods, there is proof of an anat anastomosis that is by no means negligible.

Jamin and Merkel*† beautiful stereoscopic skia show the remarkably rich blood-supply of the with occasional anastomoses between vessels of cons able size. The possibility of injection of one cor artery from the other is admitted even by thos deny that such injection proves more than non-functioning anastomosis. Anemomiya ing hearts of young persons, showed naked moses in the subepicardial tissue. He feels that H and Spaltcholz[2] have nearly cleared up the questio to the relation between the heart muscle and disea the coronary artery from the anatomic stand Hirsch says that in dogs the anastomosing ves functionally competent, and Spaltcholz says tha man the vessels are nearly the same as in dogs, in anastomoses even in those of considerable ca The latter investigator, by a method of injection treatment of the heart so as to make the muscle t parent, shows to the naked eye that there are an moses of considerable size.

Among others who are on record as believing there are non-negligible anastomoses may be menti Haller, Huchard, Orth, Michaelis, Langer, Legg, W All recognize, however, that there are individual di ences, and also that though the heart may show anastomoses, these are not necessarily functional, that an artery which anatomically is not a tern artery may yet be such functionally.

But there is proof not only of anatomic conne between the two coronaries, but that in certain instu at least, such connection is of functional value. Ex ments on lower animals and the clinical experimen disease of the coronaries with autopsy findings this.

Much of the earlier experimental work on the animals, obstructing the coronary arteries by ligat clamps or artificial emboli, gave promptly fatal re Among those who worked along this line and rea these conclusions may be mentioned Erichsen (18 Panum (1862), von Bezold, Samuelson (1880),

* †Jamin and Merkel: Die Koronrarterien des men Herzens in stereoskopischen Röntgenbildern, Jena, 1907. bibliographies are contained in the articles by Thorel Ostertag's Ergebnisse, ix, Abt 1), and in Anemomiya Arch. f. path. Anat., 1910, cxcix, 187). I repeat only son more important references and add new ones.

1. Anemomiya: Ueber die Beziehungen zwischen Koron und Papillarmuskeln im Herzen, Virchows Arch. f. path 1910, cxcix, 187.

2. Hirsch and Spaltholz: Koronrarterien und Herz Deutsch. med. Wchnschr., 1907, No. 20.

The Discovery of Heparin

THE THROMBOPLASTIC ACTION OF CEPHALIN

JAY McLEAN

From the Physiological Laboratory of the Johns Hopkins University

Received for publication, June 15, 1916

In 1912 Howell (1) reported the results of a study of the thromboplastic action of the tissues in which he showed that the active substance is a phosphatid having the general properties of cephalin. The effect of solutions of this phosphatid upon coagulation is very striking and it has been shown that lecithin prepared according to the customary methods is lacking in this property. The identification of the phosphatid rested mainly on its insolubility in cold alcohol and its slight solubility in hot alcohol and the possibility was recognized that the thromboplastic action might be due to some adherent impurity rather than to the phosphatid itself. At the suggestion of Dr. Howell I have undertaken a re-examination of this subject to determine if possible whether the thromboplastic effect may be attributed to an impurity, or is a property of the cephalin itself, and also to determine in how far a similar property is exhibited by other related phosphatids. The phosphatids which have been examined in regard to their thromboplastic action are cephalin, lecithin, sphingomyelin, cuorin and heparphosphatid.

THE METHOD OF TESTING THROMBOPLASTIC ACTIVITY

To determine thromboplastic activity a method was employed which has been in use in this laboratory for some time in connection with other researches on coagulation. The method rests upon the fact that in fresh serum the amount of actual or effective thrombin is small, but the amount of ineffective thrombin is relatively large. This metathrombin may be converted to active thrombin by Morawitz's (2) method of adding alkali with subsequent neutralization. But it can also be activated to effective thrombin by the addition of thromboplastic extracts, especially solutions of cephalin, provided the serum is perfectly fresh. As the serum stands the activating effect of the cephalin becomes less marked and finally disappears entirely after a certain

Discovery of Streptokinase

THE FIBRINOLYTIC ACTIVITY OF HEMOLYTIC STREPTOCOCCI

WILLIAM S. TILLETT

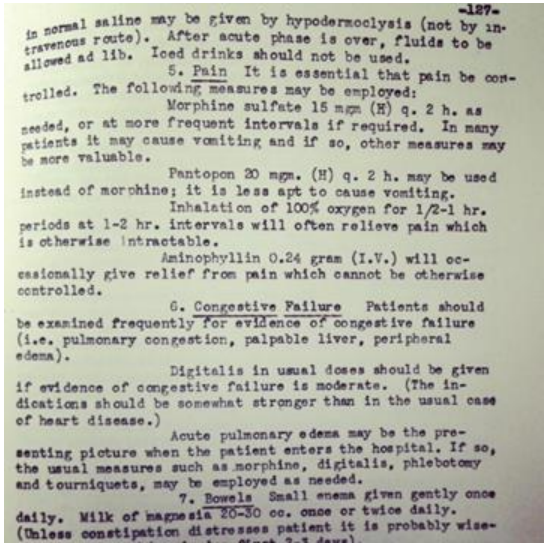
Department of Bacteriology, New York University College of Medicine

Received for publication October 11, 1938

CONTENTS

The fibrinolytic activity of hemolytic streptococci is a term used to designate the capacity of broth cultures of *Streptococcus hemolyticus* of the *beta* type to transform the solid clot of normal human blood into a liquid state. The rapid dissolution of human fibrin by hemolytic streptococci is dependent upon the presence in cultures of an extracellular enzymic substance which is excreted by the living organisms. Reports in the literature evidence the fact that the phenomenon has special characteristics of bacteriological and immunological interest.

The fact that the reaction involves a special kind of bacterial product acting upon a special kind of tissue substrate illustrates the particular qualities of streptococcal fibrinolysis. The process



-127-

in normal saline may be given by hypodermoclysis (not by intravenous route). After acute phase is over, fluids to be allowed ad lib. Iced drinks should not be used.

5. Pain It is essential that pain be controlled. The following measures may be employed:

Morphine sulfate 15 mgm (H) q. 2 h. as needed, or at more frequent intervals if required. In many patients it may cause vomiting and if so, other measures may be more valuable.

Pantopon 20 mgm. (H) q. 2 h. may be used instead of morphine; it is less apt to cause vomiting.

Inhalation of 100% oxygen for 1/2-1 hr. periods at 1-2 hr. intervals will often relieve pain which is otherwise intractable.

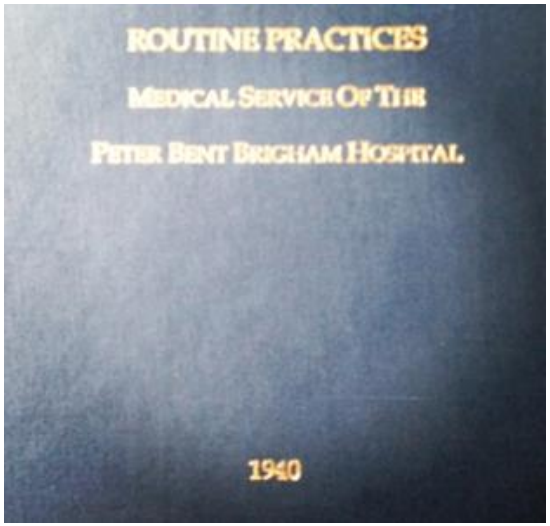
Aminophyllin 0.24 gram (I.V.) will occasionally give relief from pain which cannot be otherwise controlled.

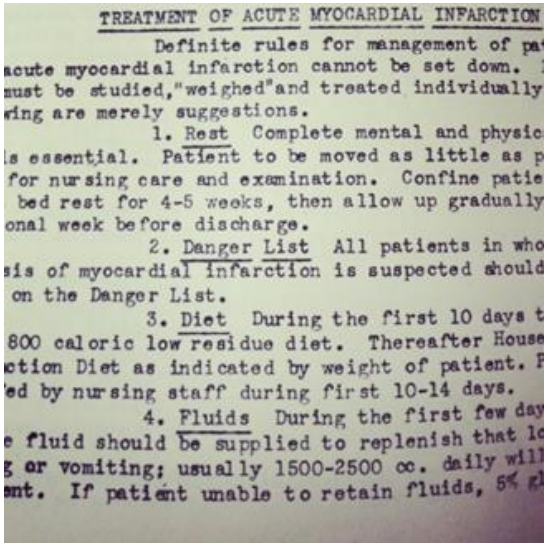
6. Congestive Failure Patients should be examined frequently for evidence of congestive failure (i.e. pulmonary congestion, palpable liver, peripheral edema).

Digitalis in usual doses should be given if evidence of congestive failure is moderate. (The indications should be somewhat stronger than in the usual case of heart disease.)

Acute pulmonary edema may be the presenting picture when the patient enters the hospital. If so, the usual measures such as morphine, digitalis, phlebotomy and tourniquets, may be employed as needed.

7. Bowels Small enema given gently once daily. Milk of magnesia 20-30 cc. once or twice daily. (Unless constipation distresses patient it is probably wise-





TREATMENT OF ACUTE MYOCARDIAL INFARCTION

Definite rules for management of pa
acute myocardial infarction cannot be set down.
must be studied,"weighed"and treated individually
ing are merely suggestions.

1. Rest Complete mental and physic
s essential. Patient to be moved as little as p
for nursing care and examination. Confine patie
bed rest for 4-5 weeks, then allow up gradually
onal week before discharge.

2. Danger List All patients in who
sis of myocardial infarction is suspected should
on the Danger List.

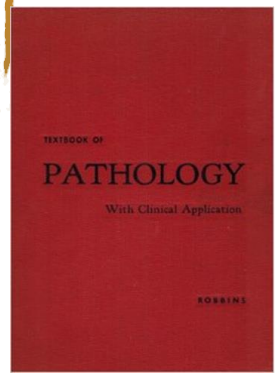
3. Diet During the first 10 days t
800 caloric low residue diet. Thereafter House
ction Diet as indicated by weight of patient.
ed by nursing staff during first 10-14 days.

4. Fluids During the first few day
e fluid should be supplied to replenish that lo
g or vomiting; usually 1500-2500 cc. daily will
nt. If patient unable to retain fluids, 5%

Treatment of AMI 1940s

Progressive Atherosclerosis?

Coronary atherosclerosis is a progressive process; at any stage, factors, as yet unknown, may precipitate either sudden death or patterns of myocardial ischemia or necrosis." AHA 1962



News from the American Heart Association

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PREVALENCE OF TOTAL CORONARY OCCLUSION DURING THE EARLY HOURS OF TRANSMURAL MYOCARDIAL INFARCTION

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Abstract To define the prevalence of total coronary occlusion in the hours after transmural myocardial infarction, we used coronary arteriography to study the degree of coronary obstruction in 322 patients admitted within 24 hours of infarction. Total coronary occlusion was observed in 110 of 126 patients (87 per cent) who were evaluated within four hours of the onset of symptoms; this proportion decreased significantly, to 37 of 57 (65 per cent), when patients were studied 12 to 24 hours after the onset of symptoms. Among 59 patients with angiographic features of coronary thrombosis, the thrombus was retrieved by Fogarty catheter in 52 (88 per cent) but was absent in seven (12 per cent false positive). Among an additional 20 patients without angiographic features of thrombosis, a thrombus was discovered in five (25 per cent false negative). Thus, total coronary occlusion is frequent during the early hours of transmural infarction and decreases in frequency during the initial 24 hours, suggesting that coronary spasm or thrombus formation with subsequent recanalization or both may be important in the evolution of infarction. (N Engl J Med. 1980; 303:897-902.)

THE extent of coronary-artery occlusion during the first few hours of transmural myocardial infarction is poorly understood. Traditionally, reluctance to subject patients to early coronary arteriography has been based on the belief that injection of contrast material into diseased coronary circulation might further injure the ischemic myocardium. Moreover, patients with acute myocardial infarction frequently have unpredictable disorders in cardiac rhythm.

Accordingly, most of our knowledge of the lesions associated with transmural infarction has been derived from autopsy studies. These studies, though helpful, involve a highly selected sample of the population. In addition, the autopsies may have been performed in patients who died suddenly (less than six hours after the onset of symptoms) or in those who died days to weeks after the infarction.[1-5]

Morphologic confirmation of infarction is rarely possible within six hours of the onset of symptoms.[2,3,6] The meaning of pathological findings observed days to weeks after infarction may be obscured by release of coronary spasm, antemortem recanalization of the thrombus, or post-mortem thrombolysis and thrombus retraction from the arterial wall.[3,6,7] The absence of physiologic diastole and the low flow state associated with the failing circulation could both contribute to the formation of a thrombus. Important differences in the methods used to examine the coronary arteries have generated conflicting data.[1-5] The variability in both the methods used and the populations studied in autopsy series is reflected in the reported incidence of thrombosis associated with transmural infarction; this rate has ranged from 21 per cent[2] to 93 per cent.[6]

The frequency of total coronary occlusion in patients hospitalized during the early hours after transmural myocardial infarction remains unknown. Our goal has been to define the prevalence of total coronary occlusion in this group.

METHODS

Patient Population

Between March 1971 and December 1978, we evaluated 322 patients by selective coronary arteriography and ventriculography within 24 hours of onset of symptoms of transmural myocardial infarction. Symptoms and signs included acute chest pain, persistent (more than one hour) ST-segment elevation that progressed to Q waves of at least 0.04 second by standard 12-lead electrocardiography, and elevations in cardiac enzyme (total creatine kinase activity). (The MB fraction of creatine kinase was not available to us until the end of 1973.) This population represents 322 of the 1210 patients (26.6 per cent) who were admitted with early transmural myocardial infarction during the study period. Twenty of the 322 patients were older than 65 years; the average age in this group was 53.6 years (range, 34 to 73 years). Two hundred fifty-eight (80.1

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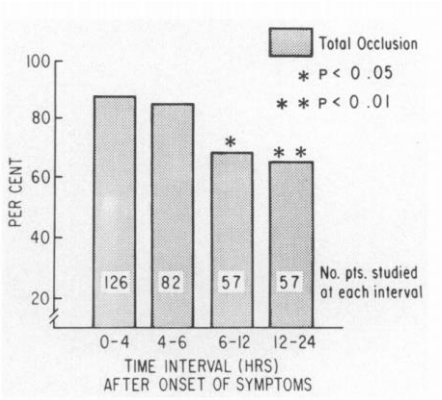

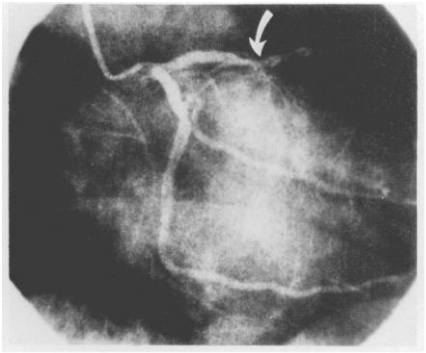

Figure 3. Right-Anterior Oblique Projection of the Left Coronary System in a Patient Judged Negative for Thrombosis.

Ninety per cent obstruction is noted at the point indicated by the arrow. The thrombus was retrieved at surgery and was situated both distal and proximal to the area of stenosis.

Heart Attacks: Acute Thrombosis

The Answer Was Obvious

EFFECTIVENESS OF INTRAVENOUS THROMBOLYTIC TREATMENT IN ACUTE MYOCARDIAL INFARCTION

GRUPPO ITALIANO PER LO STUDIO DELLA STREPTOCHINASI NELL'INFARTO MIOCARDICO (GISSI)*

Summary In an unblinded trial of intravenous streptokinase (SK) in early acute myocardial infarction, 11 806 patients in one hundred and seventy-six coronary care units were enrolled over 17 months. Patients admitted within 12 h after the onset of symptoms and with no contraindications to SK were randomised to receive SK in addition to usual treatment and complete data were obtained in 11 712. At 21 days overall hospital mortality was 10·7% in SK recipients versus 13% in controls, an 18% reduction ($p = 0·0002$, relative risk 0·81). The extent of the beneficial effect appears to be a function of time from onset of pain to SK infusion (relative risks 0·74, 0·80, 0·87, and 1·19 for the 0–3, 3–6, 6–9, and 9–12 h subgroups). SK seems to be a safe drug for routine administration in acute myocardial infarction.

Introduction

THE trial of the Italian Group for the Study of Streptokinase in Myocardial Infarction (Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico, GISSI) was planned in autumn, 1983. At that time there was a growing consensus on the effectiveness of intracoronary streptokinase (SK) in reopening occluded coronary vessels in around 50–60% of treated patients;[1] and analysis of pooled data suggested that intravenous SK, given in various schedules, could reduce overall mortality in patients treated within 24 h from onset of pain.[2] The clinically relevant challenge was therefore to test in a formal prospective trial whether effective and safe thrombolysis could be achieved with intravenous SK under routine conditions in the majority of patients—in contrast to intracoronary thrombolysis which is practicable only in small numbers of cases.[3]

The participation of the majority of the coronary care units (CCUs) grouped in the National Society of Hospital Cardiologists (Associazione Nazionale Medici Cardiologi Ospedalieri, ANMCO) was sought, to ensure recruitment over an acceptable length of time of the large sample needed to test reliably three key issues: Does intravenous SK infusion produce a clinically relevant benefit in terms of reduction of in-hospital and one-year mortality? Is the effect, if any, dependent on the interval from onset of pain to SK treatment? Are the risks associated with the treatment acceptable?

Patients and Methods

The study was planned as a controlled multicentre unblinded trial with central randomisation. Fig 1 summarises the major steps. The only variable distinguishing the treatment group (SK) from the

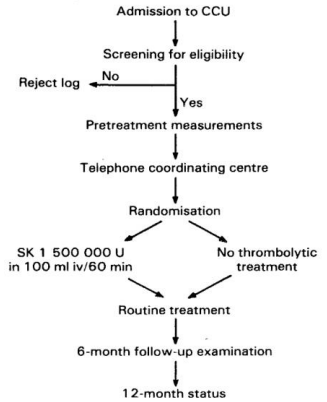

Fig 1—GISSI protocol.

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Do We Really Need So Many Heart Failure Clinicians?

- **HF Doctors are the Marco-Cardiologists of today**
- **Well suited for the move from quantity to value**
- **Training should be modified for current challenges**
- **Impactful research needs input from HF clinicians**
- **Rethinking basic assumptions and better integration of interventions into practice will be key to progress**

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