STUDY PROTOCOL

Study Information

Title	Evaluating Strategies to Improve Guideline Directed Medical Therapy: The **G**DMT **R**esearch **E**ducation & **A**ssist **T**rial for **H**eart **F**ailure **Care (GREAT-HF Care)**
Protocol version identifier	Version 1.0
Date	September 4, 2024
Research objective	The objective of this study is to implement and evaluate a multifaceted, interdisciplinary intervention to improve guideline-directed medical therapies (GDMT) use, reduce mortality, and reduce future heart failure events in patients with HFrEF.
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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACEi	Angiotensin converting enzyme inhibitors
ARB	Angiotensin receptor blockers
ARNI	Angiotensin-neprilysin inhibitors
BPA	Best practice alert
CDS	Clinical decision support
CE	Cost Effectiveness
CKD	Chronic kidney disease
CME	Continuing medical education
CPA	Collaborative practice agreement
EBBB	Evidence-based beta-blockers
ED	Emergency department
EHR	Electronic health records
GDMT	Guideline-directed medical therapies
GHP	Geisinger Health Plan
HF	Heart failure
HFrEF	Heart failure with reduced ejection fraction
ICER	Incremental cost effectiveness ratios
ITT	Intention-to-treat
LVEF	Left ventricular ejection fraction
MTDM	Medication Therapy Disease Management
MRA	Mineralocorticoid receptor antagonists
MRN	Medical record number
OLS	Ordinary least squares
PACDC	Phenomic Data Analytics and Clinical Data Core
PHI	Protected health information
ROI	Return on Investment
SGLT2i	Sodium-glucose cotransporter 2 inhibitors
WTP	Willingness-to-pay

2. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

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3. ABSTRACT

GREAT- HF Care

- Background and Rationale - Heart failure with reduced Ejection Fraction (HFrEF) is associated with high mortality and adverse events (hospitalization or urgent outpatient visits for heart failure (HF)), along with diminished quality of life. Despite convincing data that evidenced-based, guideline-directed medical therapies (GDMT) improve mortality and heart failure-related events, there remains insufficient utilization of these life-saving drugs (evidence-based beta-blockers (EBBB), angiotensin-neprilysin inhibitors (ARNI)/ angiotensin converting enzyme inhibitors (ACEi)/ angiotensin receptor blockers (ARB), mineralocorticoid receptor antagonists (MRA) and sodium-glucose cotransporter 2 inhibitors (SGLT2i)) in patients with HFrEF.

- Objectives - The primary objective of this study is to implement and evaluate a multifaceted, interdisciplinary intervention to improve GDMT use, reduce mortality, and reduce future heart failure events in patients with HFrEF.

- Study Design – We will conduct a cluster-randomized controlled trial at the level of the clinician comparing two multi-faceted interventions to usual care with or without systemic education within a population of patients with HFrEF seen at a Geisinger cardiology clinic who are not on complete GDMT.

- Population - Patients at least 18 years of age with documented HFrEF or Left Ventricular Ejection Fraction (LVEF) < 40 (within two years prior to the triggering visit) who have an outpatient encounter with the Geisinger Cardiology department (office visit or telemedicine). Patients must also not currently be on optimal GDMT according to their electronic health records (EHR), as reflected in use of medications in fewer than four of the recommended classes or in all four classes but not ARNI. And patients must not currently be in hospice or palliative care or allergic to all non-prescribed GDMT. The clinician target population comprises clinicians practicing at one or more Geisinger outpatient cardiology clinics who manage care for patients with HFrEF and include cardiologists (MD/DO), nurse practitioners, and physician assistants.

- Interventions – We will implement the following interventions: 1) focused education through a series of focused in-person or virtual sessions (randomized to receive early or late education); 2) multi-pronged clinical decision support (CDS) inclusive of a patient portal message, an interruptive advisory upon chart entry notifying clinicians to consider GDMT, and a Best Practice Advisory (BPA) that opens a GDMT order set; and 3) the same CDS as #2 but replacing the GDMT order set with a referral to integrated clinical pharmacist co-management.

- Control – Patients seen by clinicians randomized to usual care will be labeled as control patients and receive care as per usual standard practice, which may also include referral to Medication Therapy Disease Management (MTDM).

- Outcomes – The primary outcome will be whether or not improvements in GDMT prescribing occur within 30 days of index date. Additional outcomes will include the primary outcome at 60 and 90 days, GDMT changes at 30, 60 and 90 days, healthcare resource utilization, and total costs of care.

- Data analysis – Analyses are described in detail below. Primary analyses will assess whether outcomes improve between each interventional arm versus control.

4. BACKGROUND AND SIGNIFICANCE

HFrEF is associated with high mortality and events (hospitalization or urgent outpatient visit for HF), along with poorer quality of life.[1] Newer agents (ARNI, SGLT2i) have been demonstrated to improve outcomes in multiple trials[2-4] and are strongly advocated by ACC/AHA Guidelines[1] Despite evidenced-based, guideline-directed medical therapies (GDMT) including evidence-based beta-blockers (EBBB), angiotensin-neprilysin inhibitors (ARNI) /Angiotensin converting enzyme inhibitors (ACEi)/ angiotensin receptor blockers (ARB), mineralocorticoid receptor antagonists (MRA) and sodium-glucose cotransporter 2 inhibitors (SGLT2i), there remains insufficient utilization of these life-saving drugs in patients with HFrEF.[1]

Some background research taught us the following:

- A review of Geisinger data on 7,144 patients with HFrEF from 2018-2021 demonstrated that ~80% of patients were on EBBB; ~50% on ARNI/ACEi/ARB; (3.2-9.7% ARNI), 16-22% on an MRA and 1.3-4.6% on SGLT2i.[5]
- Machine learning algorithms derived from Geisinger data suggest prioritization of patients and closure of treatment gaps will result in lower patient mortality.[6]
- Interviews with 20 Geisinger cardiologists identified "familiarity with newer medications" and "recollection at time of prescribing" as barriers to prescribing GDMT and "assistance by a clinical pharmacist" as a facilitator.[7]

Electronic health record functionality and clinical pharmacy services may help to address underlying barriers that presently exist to GDMT optimization. Although clinical decision support (CDS) and best practice alerts (BPAs) are ubiquitous in the EPIC system and may assist with broad efforts to improve GDMT prescribing, many barriers exist to their effectiveness in practice.

- HF BPAs do not lead to action: A recent analysis identified 454 BPAs fired for HF for 257 unique patients. There were zero actions taken and 66 overrides of the BPA.[8]
- HF BPAs are not comprehensive: Present BPAs firing for HF at Geisinger are limited to single drug recommendations, do not provide sufficient context for adequate decision-making, and do not include newer agents (i.e., ARNI or SGLT2i) with strong evidence for use.
- HF BPAs are not designed with best evidence principles: Alerts can be ineffective due to multiple design factors that affect behavior, such as inappropriate workflow placement, passive alerting, and alert fatigue.[9]

Having identified the problems above, we have investigated solutions to help guide us to improve GDMT prescribing. Solutions include:

- Education and engagement of the clinical staff (physicians, nurse practitioners, physician assistants, clinical pharmacists, nurses).
- Electronic facilitation to overcome clinical inertia.
    - Recent evidence from the PROMPT-HF study suggests a more tailored advisory presented to prescribers increases GDMT.[10]
    - Additional evidence from the BETTER CARE-HF study suggests that alerting informed by evidence-based design principles can substantially increase MRA prescribing in HFrEF.[11]
    - Principles guiding lightweight interventions (behavioral "nudges"), from the fields of psychology and economics—including loss framing, social norms, optimal defaults, and other means of changing choice architecture—can be implemented using tools such as EHR-based CDS to increase the likelihood that clinicians and patients engage more consistently in optimal behaviors.[12,13]
- Embedded pharmacists with established collaborative practice agreements (CPA) enabling medication assessment, initiation, titration, monitoring and management.

5. OBJECTIVE AND HYPOTHESIS

5.1 Objective

The primary objective of this study is to implement and evaluate a multifaceted, interdisciplinary intervention to improve GDMT use, reduce mortality, and reduce future heart failure events in patients with HFrEF.

5.2 Hypothesis

H_0: The implementation of a multifaceted, interdisciplinary intervention will not improve GDMT for patients with HFrEF.

H_{A1}: The implementation of a multifaceted, interdisciplinary intervention incorporating an order set will improve GDMT for patients with HFrEF more than usual care.

H_{A2}: The implementation of a multifaceted, interdisciplinary intervention incorporating a pharmacist referral will improve GDMT for patients with HFrEF more than usual care.

6. STUDY METHODS

6.1 Study Design

This is a cluster randomized study designed to evaluate the effectiveness of interventions aimed at improving GDMT in patients with HFrEF. Clinicians were stratified based on practice specialty, location, and pharmacist referral habits (see details below) and were permuted block randomized to achieve 45%/45%/10% proportional distribution across the following arms respectively: (1) usual care **(Control arm);** (2) multi-pronged CDS inclusive of a patient portal message about GDMT, an interruptive advisory upon chart entry advising clinicians of the need to optimize treatment, and a BPA that links to a GDMT order set

(**CDS-OS arm**); and (3) multi-pronged CDS as in #2 but replacing GDMT order set with referral to integrated clinical pharmacist co-management (**CDS-MTDM arm**). Secondarily, each of the 5 clinical practice sites of roughly equal HFrEF patient loads were assigned to receive either an early or delayed education rollout.

6.2 Randomization details

Permuted blocked randomization was completed once at the beginning of the study.

Randomization was stratified as described below given concerns about imbalances in GDMT prescribing practices across clinics, certain roles, and current MTDM referral practices.

Clinicians were divided into HF specialists and non-HF specialists given differences in practicing patterns and propensity for increased GDMT prescribing patterns among specialists.

Within Non-HF specialists, randomization was stratified on the following variables:

- Role: electrophysiology, interventional, non-invasive
- MTDM referral history: none/0%, 1%-100%
- Primary practice location: Northeast (GCMC, GWV, Orwigsburg), Central (GMC, Shamokin, Lewisburg), and West (GLH, Gray's Woods)

Within HF specialists, randomization was stratified on MTDM referral history. They were NOT stratified on practice location because there was not hypothesized to be a significant difference in practice as a function of location in this group.

We also generated permuted block randomized sequences for allocating any new clinicians who enter the system during the study. The study team collected information about role and primary practice location for any new clinician joining the system monthly. However, all new clinicians were assigned to the 0% MTDM referral history stratum, because new clinicians do not have an MTDM referral history in the system. Based on the pre-randomized sequence generated, the clinician would be assigned to an interventional arm. In generating these sequences, we assumed turnover rates would be equal across strata.

One hundred and fifty-five clinicians (103 current and 52 hypothetical) were randomized into control (45%), CDS-OS (45%) and CDS-MTDM arms (10%).

6.3 Setting

This study is being implemented at Geisinger, an integrated health delivery network in Central and Northeastern Pennsylvania, that serves more than 1 million patients per year. The system includes 10 hospital campuses, a health plan with more than half a million members, two research centers, an addiction treatment center, and the Geisinger Commonwealth School of Medicine. Geisinger’s Cardiology Department includes 35 outpatient clinics with over 120 providers engaged in care delivery.

6.4 Targeted Clinician Inclusion

Clinicians practicing within a Geisinger cardiology clinic and caring for patients with HFrEF were included. These include Cardiologist Physicians (MD, DO), Nurse Practitioners, and Physician Assistants. The lead Principal Investigator on this study was excluded from participation.

6.5 Inclusion Criteria

Patients are included if:

1. Patients are aged 18 years or older

AND

2. Completed visit at included Geisinger cardiology outpatient clinics (office visit or telemedicine)

AND

3. Patients' clinicians are on a list of currently active Geisinger clinicians in outpatient cardiology clinics who can prescribe heart failure medications

AND

4a. Active problem list diagnosis of HFrEF at time of Cardiology clinic encounter,

OR

4b. Left Ventricular Ejection Fraction (LVEF) < 40: most recent to the cardiology clinic encounter within 2 years of the visit.

6.6 Exclusion Criteria

Currently in hospice or palliative care. (ICD 10 code: Z51.5)

Patient has been prescribed medications from all four categories of GDMT, including ARNI specifically.

Patient has a documented allergic reaction to each class of GDMT not presently prescribed.

6.7 Interventions

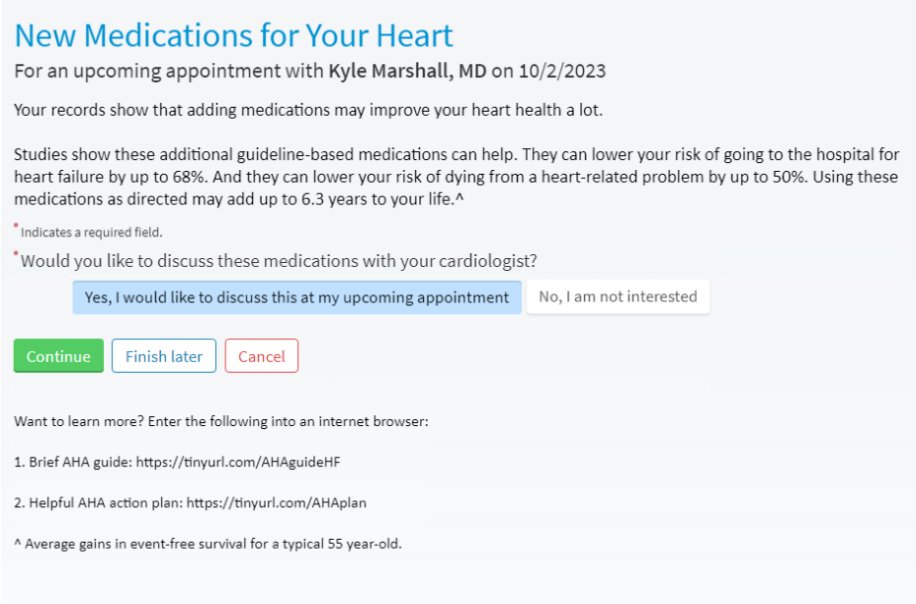
The study includes the following three intervention arms, crossed with the presence or absence of focused education:

1. **Control:** Clinicians in this arm do not receive CDS and instead experience usual care. To index targeted patients, we initiated a BPA during eligible encounters for patients meeting inclusion/exclusion criteria that is not seen by clinicians but is recorded with date and time for the study team. No additional interventions are provided (i.e., no order sets or referral notices), although pharmacist services are available to clinicians that are allocated to this group.

2. **Multiprong CDS with GDMT order set (CDS-OS)**, including:

    a. A patient-facing nudge to improve GDMT prescribing is delivered to patients 14 days prior to their scheduled cardiology encounters. The questionnaire includes a statement about their cardiac mortality risk and a prompt inquiring if the patient would like to discuss GDMT options with their provider. For those without portal access, an in-clinic questionnaire delivered at the time of rooming with the nurse is available. See Figure 1 below.

Figure 1. Patient-facing questionnaire presented through patient portal.



    b. A clinician-facing "Heads-Up" BPA that fires upon initial launch of the encounter in Epic. The BPA notifies the clinician of the patient's diagnosis of HFrEF and encourages assessment of present GDMT. Patient response to the pre-visit questionnaire is provided in alternate color font if completed in the affirmative by the patient. See Figures 2 and 3 below.

Figure 2. Provider-facing EHR alert upon entry into patient chart (without portal information).

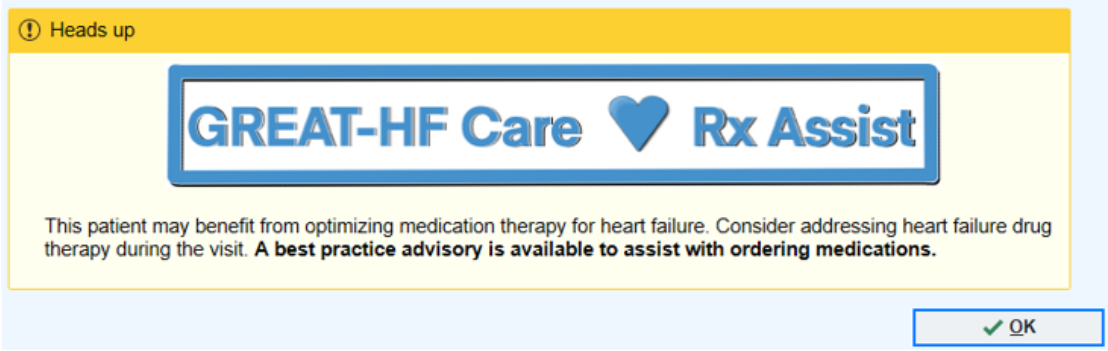
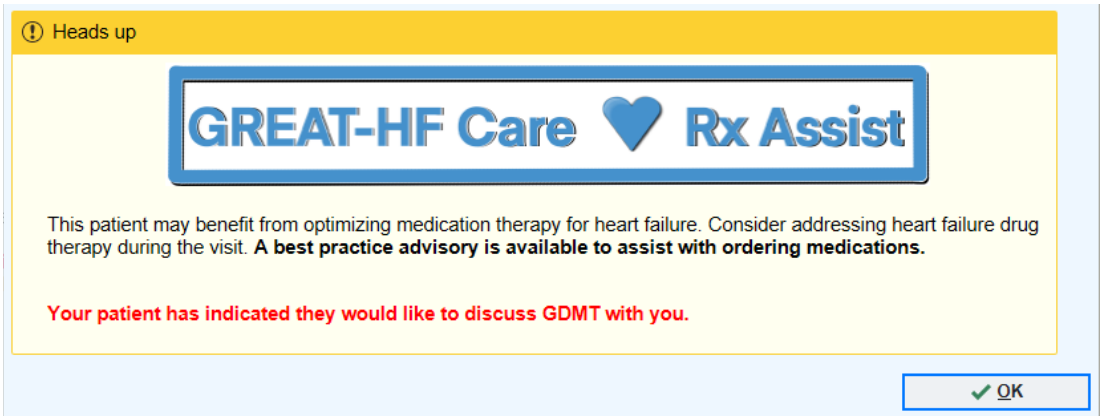
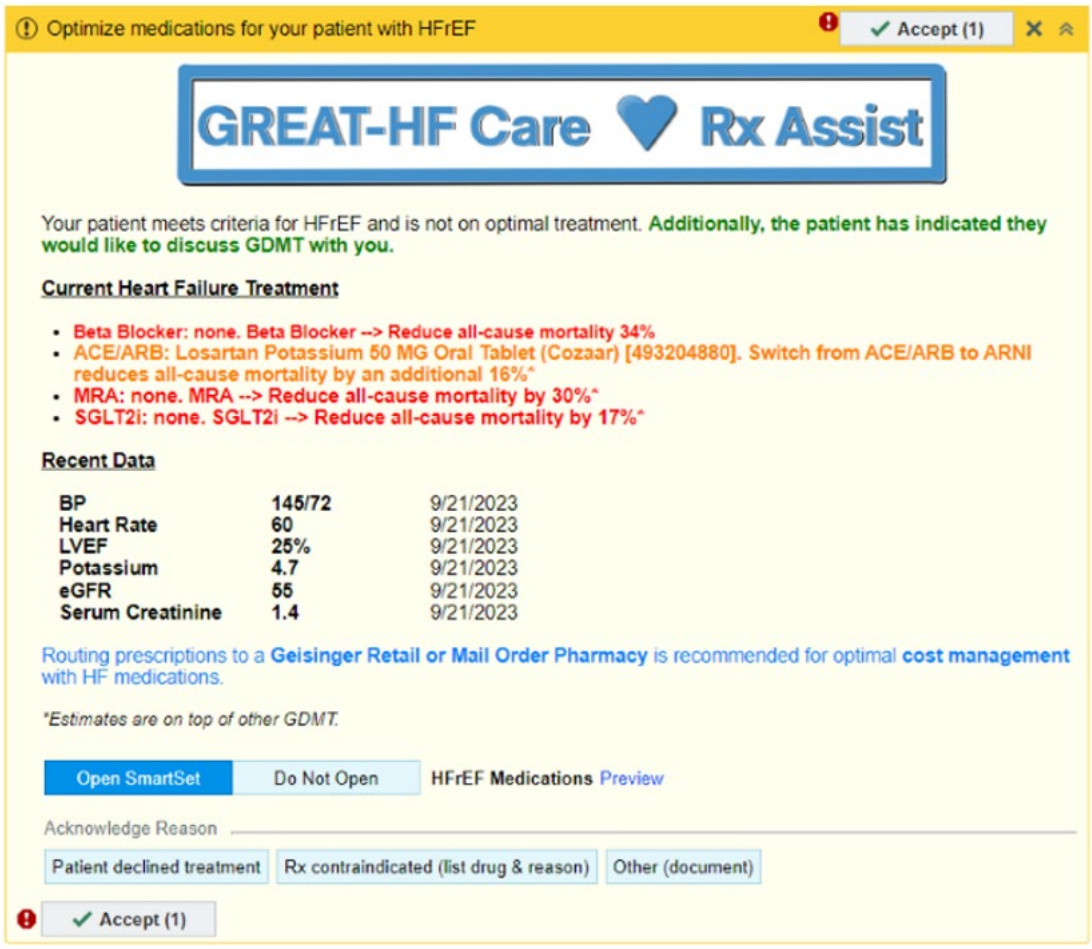


Figure 3. Provider-facing EHR alert upon entry into patient chart (with portal information).



c. A BPA during the encounter that supplies a multitude of relevant heart failure-related metrics (e.g. Left Ventricular Ejection Fraction, heart rate, glomerular filtration rate, etc.) and indicates present use or non-use of GDMT along with the medication information. If a class of GDMT is not active on the EHR medication list, alternative text is conveyed to the provider, in bolded and alternate color font, the mortality reductions expected with drug class initiation, as observed in published studies. The preferred action within the BPA is to open the GDMT order set, which has been informed by prior studies and by behavioral science nudge principles. Classes least likely to be prescribed (i.e., ARNI, SGLT2i, and MRA) are listed before the more commonly prescribed EBBBs. One-click ordering options are available within the order set that link to a medication order if selected. If this option is not selected, the clinician must document their reason for not selecting a GDMT change in the acknowledgement section of the BPA. This section includes one option for patient declining treatment (where a written reason is not required), one for a contraindication to prescription (with required open text response), and an "other" category (with required open text response). See figure 4 below for one example of how a BPA may appear.

Figure 4. Provider-facing EHR alert upon order entry for GDMT prescribing.



3. **Multiprong CDS with referral to pharmacist co-management (CDS-MTDM),** including:

    a. A patient-directed questionnaire administered as above in the multi-prong CDS intervention.

    b. A clinician-facing "Heads-Up" BPA that fires upon initial launch of the encounter in Epic. The BPA notifies the clinician of the patient's diagnosis of HFrEF and encourages referral to pharmacy for co-management. Patient responses to the pre-visit questionnaire are provided in alternate color font if completed as affirmative by the patient. See Figures 5 and 6 below.

Figure 5. Provider-facing EHR alert upon entry into patient chart (without portal information).

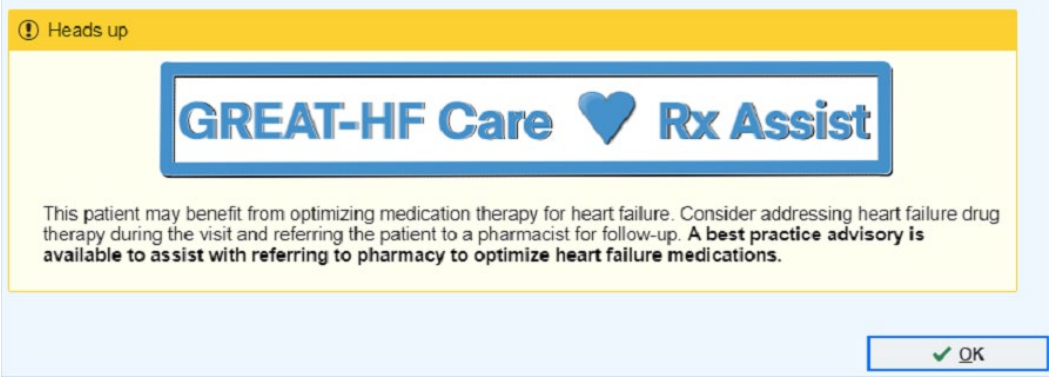
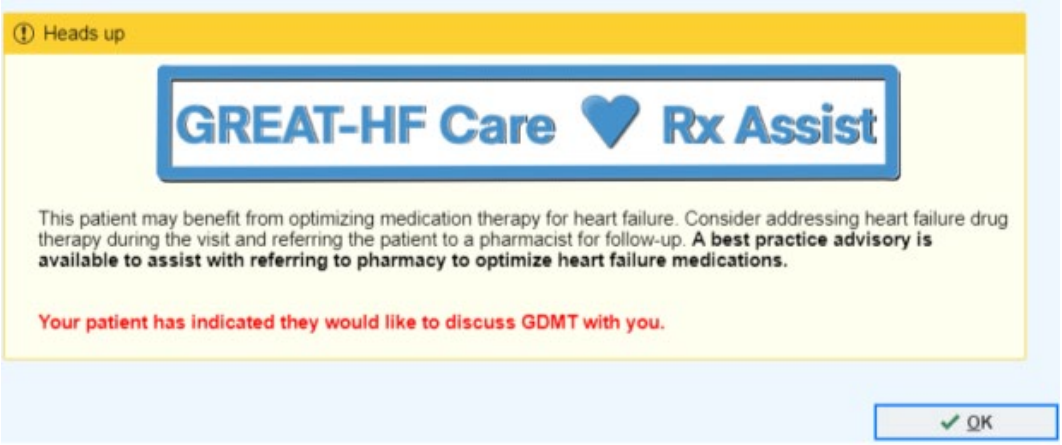
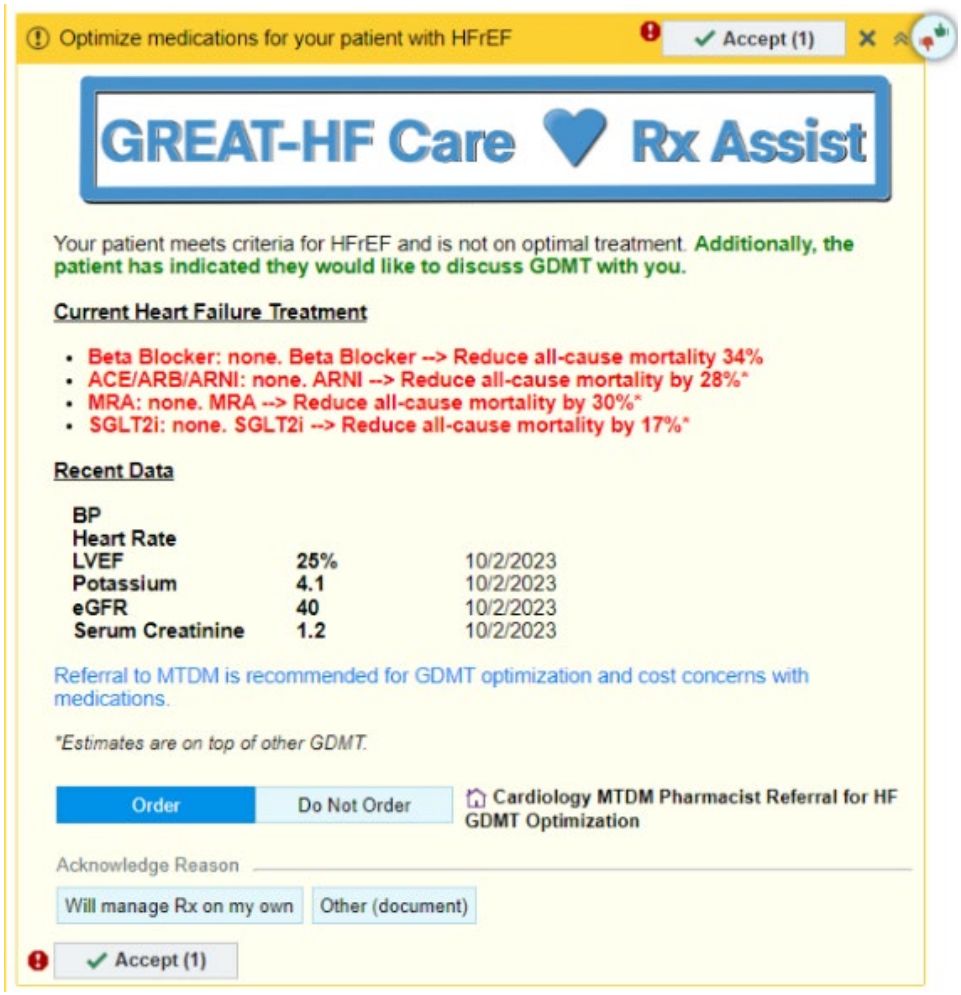


Figure 6. Provider-facing EHR alert upon entry into patient chart (without portal information).



c. A BPA during the encounter that presents information exactly as in the GDMT order set version described above. The preferred action within the BPA is to refer patients to embedded pharmacist co-management, which is already highlighted for the clinician with an urgent referral sent to pharmacy. Pharmacists are expected to schedule patients within 3 days and meet with patients and optimize GDMT through a CPA. If this option is not selected, the clinician must document their reason for not selecting referral in the acknowledgement section of the BPA. This section included one option for patient declining treatment (will manage Rx on their own), and an "other" category (with required open text response). See Figure 7 below.

Figure 7. Provider-facing EHR alert upon order entry for pharmacist referral and co-management.



The main interruptive BPA is located in the Best Practice Advisory section of the patient charts. If no action is taken, the BPA fires at the time of first order or when the clinician tries to close out of the chart. Once an action has been taken, the BPA is suppressed for a period of 30 days for that patient (except for contraindications, which result in a 90-day lockout period), to avoid repetitive firing and resultant alert fatigue. This suppression logic is applicable both to the order set and the referral-specific BPAs. A silent BPA is triggered for clinicians assigned to the no-BPA control arm and for all included clinicians and sites between the time when clinicians are randomized across the interventional and control BPAs and in the 2 months prior, when the initial round of education has been rolled out. This is intended to assist with tracking prescribing behavior accurately.

In the pharmacist co-management arm, pharmacists follow a protocol for managing patients with HFrEF as developed by Cardiology and pharmacy. The procedures are listed in Tables 1 and 2 below.

Table 1. Cardiologist and pharmacist HFrEF treatment intervals and actions.

Week	Visit	Actions Taken
-1	Cardiology Provider	▪ Determination of diagnosis (HFrEF, HFmrEF, HFpEF) o ischemic vs nonischemic ▪ Order additional diagnostic tests / labs ▪ Determination of treatment plan ▪ Initiate GDMT optimization ▪ MTDM referral placed
0	Pharmacist	▪ Educate on disease state / GDMT optimization plan ▪ Care Gap screening and address ▪ Assess for co-morbid conditions o Initiate protocol(s) as needed ▪ GDMT (unless contraindicated) o eBBB, ACEI/ARB/ARNI, MRA, SGLT2i ▪ Assess for contraindications / potentially harmful meds ▪ Assess tolerability and adherence ▪ Assess affordability of medications and assist if needed ▪ Assess labs ▪ Send prescription(s) ▪ Order and schedule labs ▪ Schedule f/u with pharmacist ▪ Ensure physician follow up appt (+/- echo) scheduled
1-2	Pharmacist	▪ Assess tolerability and adherence ▪ Further optimize GDMT ▪ Schedule repeat labs & follow up pharmacist visit ▪ Ensure patient has appointment with physician scheduled ▪ New / worsening HF symptoms – escalate to provider ▪ Significant medication AE – escalate to provider ▪ **Repeat every 1-2 weeks until optimized (target dose or max tolerated)**
12-16	Cardiology Provider	• Clinic visit with exam • Review/order labs, imaging, procedures • Assess HF symptoms • Assess tolerability & adherence • Reclassification (HFrEF, HFimpEF) • Assessment/Plan
2 week post provider visit	Pharmacist	• Review/order labs • Assess tolerability and adherence • Assess Care Gaps for closure • Assess GDMT for targets • Discharge follow-up to physician (if Care Gaps closed and GDMT optimized) • Further optimization of GDMT as needed • **Repeat every 1-2 weeks until optimized (target dose or max tolerated)**

Table 2. GDMT treatment options and monitoring parameters.

CO-MANAGEMENT MEDICATION BOARD			
Medication	**Initial Dose**	**Target Dose**	**Mean Dose in Clinical Trials**
Evidence-based Beta Blocker	**Monitoring:** HR/BP (1-2 wks after increase and prn), fatigue, new HF symptoms		
Bisoprolol	1.25 mg once daily	10 mg once daily	8.6 mg total daily
Carvedilol	3.125 mg twice a day	25-50 mg twice a day	37 mg total daily
Metoprolol succinate	12.5-25 mg once daily	200 mg daily	159 total daily
ACEI /ARB / ARNI	**Monitoring:** BP (1-2 wks after increase and prn), BMP (1-2 wks after increase, every 6 months chronically) dizziness, cough,		
Captopril	6.25 mg 3 times a day	50 mg 3 times a day	122.7 mg total daily
Enalapril	2.5 mg twice a day	10-20 mg twice a day	16.6 mg total daily
Lisinopril	2.5-5 mg once daily	20-40 mg once daily	32.5-35 mg total daily
Candesartan	4-8 mg once daily	32 mg once daily	24 mg total daily
Losartan	25-50 mg once daily	50-150 once daily	129 mg total daily
Valsartan	20-40 mg once daily	160 mg twice daily	254 mg total daily
Sacubitril-valsartan	24/26 mg-49/51 mg twice daily	97/103 mg twice daily	182/193 mg total daily
Mineralocorticoid Receptor Antagonist	**Monitoring:** BP (1-2 wks after increase and prn), BMP (1 wk, 1 mth, after increase, every 6 months chronically) dizziness, gynecomastia (spironolactone)		
Spironolactone	12.5-25 mg once daily	25-50 mg once daily	26 mg total daily
Eplerenone	25 mg once daily	50 mg daily	42.6 mg daily
SGLT2i	**Monitoring:** BMP 2-4 weeks, s/s yeast infection/UTI, pt reported urine output/fluid status, hypoglycemia		
Dapagliflozin	10 mg once daily	10 mg once daily	9.8 mg total daily
Empagliflozin	10 mg once daily	10 mg once daily	(not reported)
Isosorbide DN + hydralazine	**Monitoring:** blood pressure		
Isosorbide DN + hydralazine	20-30 mg + 25-50 mg 3-4 times a day	120 mg + 300 mg in divided doses	(not applicable)
I_f Channel inhibitor	**Monitoring:** heart rate, QTc interval		
Ivabradine	5 mg twice a day	7.5 mg twice a day	12.8 mg total daily
Soluble guanylate cyclase stimulator	**Monitoring:**		
Vericiguat	2.5 mg once daily	10 mg once daily	9.2 mg total daily
Digoxin	0.125-0.25 mg once daily	Based on HR and drug level	(not applicable)

The mechanism to refer patients to MTDM who were eligible was agreed upon by the study team and clinical leadership in advance of intervention implementation. Since individual clinician referral rates to MTDM varied prior to study initiation, those with none or few MTDM referrals were educated on the role of the MTDM pharmacist and referral process. To assist with implementation, feedback on referral rates among eligible patients is provided to pharmacy leadership and clinical pharmacists throughout the study. In some cases, 1:1 discussions with clinicians on referring patients into MTDM care are made to address barriers to placing MTDM referrals within the CDS.

4. **Focused Education:** A series of focused, interactive education sessions were developed by study team members and clinical personnel to educate cardiology clinicians on why, when, and how to prescribe GDMT to patients. The objectives of the sessions are to: address previously identified barriers to GDMT such as clinician knowledge and comfort with use of GDMT, encourage clinician prescribing of GDMT, and improve attention to MTDM to work cohesively to improve GDMT prescribing.

   The target audience for this education program are Cardiology clinicians (physicians (MD, DO) and advanced practitioners (PA, CRNP)) at Geisinger. Three clinics were selected for early education (i.e. before additional CDS and pharmacist referral interventions) and two clinics were reserved for late education (timed to occur after sufficient time has elapsed to assess the impact of the early education on its own). The early education programs were delivered over one month to each clinic with in-person attendance being encouraged.

   Topics delivered in the early education sessions included:

   1. Sacubitril / Valsartan (ARNI) in CHF
   2. SGLT2 inhibitors in CHF
      a. SGLT2i in Cardiovascular Disease & HFrEF
      b. SGLT2i in HFrEF with Diabetes: What the Cardiologist should know
   3. Management of HFrEF and chronic kidney disease (CKD)
   4. Geisinger Pharmacist role in HFrEF

   The early education sessions were delivered live, at each clinic location separately on a given date (either in-person or virtually depending on clinic preference). Participants were encouraged by the lead PI to attend the live sessions if they were being offered at their clinic location. Continuing medical education (CME) credits were provided to attendees where applicable and lunch was provided during the live sessions. Presentations lasted about 30 minutes with a question-and-answer session to follow. An RSVP request was asked of those attending. Those missing their sessions were invited to a virtual session being held to try to increase attendance rates. The virtual sessions were recorded. The same approach will be used for delayed education.

6.8 Outcome Measures

Primary effectiveness outcome: HF GDMT prescription increased (new class added, dose titrated upward on existing medication, or switch to ARNI from ACEi/ARB), within 30 days of index visit.

Secondary effectiveness outcomes:

- HF GDMT prescription increased (new class added, dose titrated upward on existing medication, or switch to ARNI from ACEi/ARB), within 60 and 90 days of index visit.
- Addition of SGLT2i or ARNI (including switch from ACEi/ARB to ARNI), within 30, 60, and 90 days of index visit. This will be analyzed primarily using the entire eligible

sample and secondarily only among those who have not already been prescribed SGLT2i or ARNI prior to the intervention.

Other pre-specified effectiveness outcomes:

- All-cause mortality or emergency visit or hospitalization for heart failure, within 365 days of index visit. This will be assessed as patient death (yes/no), patient with emergency visit with a primary diagnosis of heart failure (yes/no), or admission for inpatient hospitalization with primary diagnosis of heart failure (yes/no).
- Optimal GDMT dosing (at least 50% of target dose) on all classes (with or without ARNI), within 180 days of index visit.
- Increased dosing or initiation for each individual class, within 180 days of index visit.
- Decreased dosing or removal for each individual class, within 180 days of index visit.
- Timing of increases in GDMT over 180 days since index visit.
- Economic outcomes such as (1) return on investment (ROI) and (2) cost effectiveness (CE) of CDS and MTDM interventions compared with standard of care (using modeling approaches specified in the ROI and CE analysis section above).

Implementation Outcomes

- We used the RE-AIM framework to evaluate Reach, Adoption, Implementation and Maintenance for each interventional strategy (effectiveness is measured as noted above). A summary of metrics is in Table 3.

Table 3 Implementation Outcomes

Variable	Reach	Adoption	Implementation	Maintenance
Focused Education	% of providers completing education	% of clinics receiving education	• Feedback received from continuing education forms • Adaptations made from original education plan	Change in GDMT over time post education vs. control
CDS-OS	• % of eligible patients where BPA action taken by provider • % of eligible patients where the BPA SmartSet was opened	% of eligible clinicians participating in the CDS intervention	Acknowledgement response assessment	Changes in %BPA action taken by providers over time.
CDS-MTDM	• % of eligible patients where clinician referred to MTDM • % of eligible patients seen by MTDM	% of eligible pharmacists participating in the MTDM intervention	Fidelity to HFrEF protocol (e.g. % scheduled within 3 days)	Return on Investment of CDS-MTDM

7. STATISTICAL ANALYSIS PLAN

7.1 Power analysis

Data will be collected from 4,300 patients assigned to the clinicians in the study. With CDS-OS and CDS-MTDM (versus control), we expect to have 80% power to detect approximately 5 and 9 percentage-point increases, respectively, in prescribing GDMT within 30 days, at two-tailed $p < .05$ with robust standard errors clustered at the clinician level. With education versus delayed education, we expect to have 80% power to detect an approximately 5.5 percentage-point increase in prescribing GDMT, with robust standard errors clustered at the clinician level. Power analyses were conducted using DeclareDesign.[14]

7.2 Analysis details

Analyses described below represent our planned analyses assuming statistical assumptions are met. If assumptions are not met, we will run alternative tests appropriate for the outcome distribution (e.g., non-parametric tests).

The analyses will be conducted based on the principle of intention-to-treat (ITT). All patients who met the inclusion criteria will be included in the analyses in the arms to which they were assigned. Likewise, all clinicians will be included in analysis in their assigned education arms, regardless of whether they attended their education sessions. Because exposure to pharmacists is dependent upon action by a clinician to refer, we will also conduct a per protocol sensitivity analysis for patients who were consulted to pharmacist care and those patients seen by the pharmacist.

Two-tailed p-values < 0.05 will be used to determine statistical significance in all analyses.

7.2.1 Descriptive statistics

Descriptive statistics will be computed for baseline socioeconomic and demographic characteristics (i.e., sex, age, race, ethnicity, insurance, etc.), including broken out across study arms, with differences compared using the appropriate statistical tests: two-tailed Student's t-tests will be used for continuous data, column proportion z tests or $\chi 2$ for categorical data, and Mann-Whitney for non-normal quantitative data.

7.2.2 Approach for comparisons across intervention arms

CDS analyses: We will test whether each outcome differs as a function of each CDS active arm (CDS-OS and CDS-MTDM) relative to no-CDS control. Regressions will include as covariates education arm and interactions between CDS and education. We will retain both terms if the interaction is significant and retain the main effect if only it is significant. The education variable in CDS analyses will be coded as delayed education (baseline), early education, other (for clinicians who were not in the system early enough to be included in an education arm, to avoid either diluting or biasing the education effects).

As an exploratory analysis, we will compare CDS-MTDM against CDS-OS to see which is most effective.

Additionally, covariates will be added to exploratory versions of the final models as sensitivity analyses, to adjust for measured differences across clinicians, such as role, number of patients seen, and baseline rates of prescribing each of the GDMT classes. We have no *a priori* hypotheses about the moderating effects of these covariates.

Education analyses: We will test whether each outcome differs as a function of early education relative to delayed education. Regressions will include as covariates CDS arm and interactions between CDS and education. We will retain both terms if the interaction is significant and retain the main effect if only it is significant. Assignment to early versus delayed education is not random; therefore, regression analysis comparing education to no-education controls will adjust for as many relevant covariates as possible, including baseline prescribing rates.

In these analyses, we will exclude clinicians who were not present throughout the data collection period, beginning at assignment to early education. That is, we only intend to include clinicians in early and delayed education arms who theoretically could have been exposed to the education and who then had time to treat patients based on what they learned.

7.2.3 Regression Specifications

For all outcomes except timing of GDMT increases and ROI outcomes, ordinary least squares (OLS) regressions will be run[15] with heteroskedasticity-robust standard errors clustered at the clinician level (to account for clustering of patients within clinicians). We will also explore the effect of clustering standard errors at the clinic level.

We will run a survival analysis to assess timing of GDMT increases.

Cost and outcomes estimate for the cost-effectiveness model will be obtained using EHR data, claims data, and literature-based sources. These data will be used to develop a decision tree analytical model with a state transition Markov cohort simulation to compute incremental cost effectiveness ratios (ICER), cost-effectiveness acceptance curves will be generated for all cost-effectiveness measurements. The effects of uncertainties from the model parameters will be evaluated by deterministic and stochastic sensitivity analyses. Following the World Health Organization's guidelines,[16,17] we will define the willingness-to-pay (WTP) threshold as 1 to 3 times the local gross domestic product per capita.[16,18] Interventions with an ICER below the threshold will be considered cost-effective. We will also compare the total dollar amount spent on implementing this program against the cost savings, if any, attributable to the interventions (CDS-OS + CDS-MTDM) to calculate the corresponding ROI.

7.3 Variables

We will explore demographic information, past medical history, clinical procedures, medications, encounters (ambulatory, ED, and hospital), and administrative claims (inclusive of costs of care) among the HF population. Examples of variables of interest include age, sex, BMI, comorbid conditions, medication use, healthcare utilization, and costs of care.

7.4 Data Sources

A data broker in Geisinger's Phenomic Data Analytics and Clinical Data Core (PACDC) will extract EHR data, Geisinger Health Plan (GHP) medical and prescription claims, and patient reported data necessary for the study. Approved study personnel may need to consult individual patient medical records for manual chart review and abstraction if further investigation/validation of the data is needed.

Protected Health Information (PHI) will be limited to medical record numbers (MRNs), dates, GHP insurance numbers, and department and clinician IDs. Approved study personnel conducting the manual chart reviews will be exposed to other elements of PHI, but these elements will not be collected as part of chart abstraction. In addition to PHI, we will also collect data including but not limited to the following:

- Demographics (e.g., age, sex)
- Vitals (e.g., body mass index, blood pressure)
- Encounter and Problem list diagnosis
- Patient-reported data
- Health behaviors (e.g., smoking status)
- Medications (ordered and dispensed)
- Procedures (e.g., surgery)
- Laboratory values
- Utilization of health services (e.g., inpatient, outpatient, emergency room)
- Cost of care
- Social determinants of health data (when available)

7.5 Data Management

Members of the Geisinger approved study team will coordinate with the data broker to pull the necessary data for the study. Members of the Geisinger approved study team who have been trained in chart abstraction will conduct chart reviews as needed. Study data will only be directly accessible to Geisinger approved study team members and stored on password protected computers and/or locked in filing cabinets. Any data shared externally will be de-identified and/or aggregated.

7.6 Record Retention

Records of data generated during the study may be retained indefinitely.

8. PROTECTION OF HUMAN SUBJECTS

Anticipated risk to participants will be minimal. This study will not affect patient care or access to care. While PHI will be requested, it will only be available to approved study team members to limit the risk of breaching confidentiality. All electronic study data will be kept in password-protected locations and any hard copy data will be locked in filing cabinets and only accessible to approved study team members on an as needed basis. Only group-level information without personal identifiers will be included when presenting results or submitting manuscripts for publication. We intend to permanently and securely archive a fully deidentified dataset at a research repository such as Open Science Framework (OSF) in order to be consistent with the best practices for open and reproducible science.

8.1 Patient Information

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

The personal data will be stored at the study site in electronic and/or paper form and will be password-protected and/or secured in a locked filing cabinet to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

9. PLANS FOR DISSEMINATING STUDY RESULTS

We plan to disseminate our findings as abstracts and presentations at national meeting(s) and in peer-reviewed journal(s).

10. PROJECT STATUS

Early education was launched on 8/1/2023 and data collection is ongoing. CDS and MTDM arms launched on 10/9/2023. Outcome data have not yet been extracted or examined as a function of study arms, except in a very limited way for the initial BPA investigation described below.

We removed non-telemedicine telephonic encounters as an inclusion criterion partway into data collection (as of 11/4/2023), based on immediate post-launch investigations of BPAs that were intended to help ensure BPAs were functioning correctly and firing appropriately in terms of patients, clinicians, and encounters. These investigations included chart reviews to examine acknowledgement reasons and prescribing patterns in the referral and order set arms. The results suggested that telephonic encounters were inappropriate occasions in which to expect clinicians to make prescription adjustments, given other pressing reasons for a majority of these calls (e.g., review of lab results, scheduling appointments) and very low rates of prescribing during these encounters. Prescribing rates were not compared between the no-BPA control arm and the CDS arms, and no other outcomes were examined.

Telemedicine telephonic encounters remain a valid inclusion criterion, as those are scheduled appointments appropriate for prescribing.

Within the referral arm only, data on referral rates across clinicians were monitored and chart reviews conducted to better understand where and why referrals to MTDM were not occurring for certain clinicians. These data were used to inform follow-up by MTDM pharmacists and potential escalation by clinical leadership to overcome lack of awareness and educate clinicians on the purpose and appropriate use of the referral. For example, if referral rate to MTDM for a given clinician was below 50% in February 2024, the study PI contacted the clinicians to educate or remind them about the benefits of pharmacy co-management.

Delayed education sessions began in early August 2024. This was anticipated to occur after final data were collected, but enrollment was still incomplete at the time. We will limit our primary education analysis so it only includes encounters before the delayed education sessions began (i.e. the period where the delayed education group had not yet experienced education), so the delayed education encounters can be used as controls. However, follow-up exploratory analyses will include encounters after delayed education so we can examine main effects of delayed education, or interactions between delayed education and ongoing CDS interventions.

11. REFERENCES

1. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: A report of the american college of cardiology/american heart association joint committee on clinical practice guidelines. *Journal of the American College of Cardiology*. 2022;79(17):e263-e421. https://www.ncbi.nlm.nih.gov/pubmed/35379503. doi: 10.1016/j.jacc.2021.12.012.

2. McMurray JJV, Packer M, Desai AS, et al. Angiotensin–Neprilysin inhibition versus enalapril in heart failure. *The New England journal of medicine*. 2014;371(11):993-1004. https://nejm.org/doi/full/10.1056/NEJMoa1409077. doi: 10.1056/NEJMoa1409077.

3. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *The New England journal of medicine*.

2019;381(21):1995-2008. https://nejm.org/doi/full/10.1056/NEJMoa1911303. doi: 10.1056/NEJMoa1911303.

4. Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. *The New England journal of medicine*. 2020;383(15):1413-1424. https://nejm.org/doi/full/10.1056/NEJMoa2022190. doi: 10.1056/NEJMoa2022190.

5. Graham J. Personal communication. prep to research. 2022.

6. Jing L, Ulloa Cerna AE, Good CW, et al. A machine learning approach to management of Heart Failure populations. *JACC. Heart failure*. 2020;8(7):578-587. https://dx.doi.org/10.1016/j.jchf.2020.01.012. doi: 10.1016/j.jchf.2020.01.012.

7. Paterson K, Nguyen M, Pradhan A, Lussier M, Wright E, Voyce S. Understanding barriers and facilitators to prescribing sodium-glucose cotransporter inhibitors (SGLT2i) in patients with heart failure with reduced ejection fraction (HFrEF) . *ACC Submitted Abstract*. 2022.

8. Tavares S. Personal communication.

9. Maddox TM. Clinical decision support in statin Prescription—What we can learn from A negative outcome. *JAMA Cardiology*. 2020;6(1):48-49. http://dx.doi.org/10.1001/jamacardio.2020.4756. doi: 10.1001/jamacardio.2020.4756.

10. Ghazi L, Yamamoto Y, Riello RJ, et al. Electronic alerts to improve Heart Failure therapy in outpatient practice: A Cluster Randomized trial. *Journal of the American College of Cardiology*. 2022;79(22):2203-2213. https://www.ncbi.nlm.nih.gov/pubmed/35385798. doi: 10.1016/j.jacc.2022.03.338.

11. Mukhopadhyay A, Reynolds HR, Phillips LM, et al. Cluster-randomized trial comparing ambulatory decision support tools to improve Heart Failure care. *Journal of the American College of Cardiology*. 2023;81(14):1303-1316. https://dx.doi.org/10.1016/j.jacc.2023.02.005. doi: 10.1016/j.jacc.2023.02.005.

12. Adusumalli S, Aragam G, Patel M. A nudge towards cardiovascular health: Applications of behavioral economics for primary and secondary cardiovascular prevention. *Curr Treat Options Cardio Med*. 2020;22(9). https://link.springer.com/article/10.1007/s11936-020-00824-y. doi: 10.1007/s11936-020-00824-y.

13. Patel MS, Volpp KG, Asch DA. Nudge units to improve the delivery of health care. *The New England journal of medicine*. 2018;378(3):214-216. https://nejm.org/doi/full/10.1056/NEJMp1712984. doi: 10.1056/NEJMp1712984.

14. Blair G, Coppock A, Humphreys M. *Research Design in the Social Sciences: Declaration, Diagnosis, and Redesign.* 2023. Princeton University Press.

15. Gomila R. Logistic or linear? estimating causal effects of experimental treatments on binary outcomes using regression analysis. *Journal of experimental psychology. General*. 2021;150(4):700-709. https://www.ncbi.nlm.nih.gov/pubmed/32969684. doi: 10.1037/xge0000920.

16. Yu DS, Li PW, Li SX, Smith RD, Yue SC, Yan BPY. Effectiveness and cost-effectiveness of an empowerment-based self-care education program on health outcomes among patients with heart failure: A randomized clinical trial. *JAMA network open*.

2022;5(4):e225982. https://www.ncbi.nlm.nih.gov/pubmed/35380643. doi: 10.1001/jamanetworkopen.2022.5982.

17. TAN-TORRES EDEJER T, BALTUSSEN R, ADAM T, et al. *Making choices in health : WHO guide to cost effectiveness analysis.* Genève: OMS; 2003.

18. The World Bank. GDP per capta (current US$) – hong kong SAR, china. https://data.worldbank.org/indicator/NY.GDP.PCAP.CD?locations=HK Web site. Accessed January 9, 2024.