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TRANSFORM3: Evaluation of Implementation Strategies of Teaching, Technology, and Teams to Optimize Medical Therapy in Cardiovascular

TRANSFORM^3: Evaluation of Implementation Strategies of Teaching, Technology, and Teams to Optimize Medical Therapy in Cardiovascular Disease (T^3)

Study Protocol

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Study Overview

This initiative supports a quality improvement effort evaluating the use of strategies (including technology-based decision support, referral to a virtual GDMT team, and general educational tools/resources for clinicians and patients) to improve use of guideline-directed therapeutics known to lower cardiovascular (CV) events among patients with cardiovascular diseases of heart failure, atrial fibrillation and type 2 diabetes (T2D)/ASCVD with a specific focus on underserved populations and those with a history of health care disparities.

Patient Recruitment

TRANSFORM[3]	**750** **(250 HFrEF, 250 HFpEF, 500 Atrial Fibrillation, 250 T2D/ASVCD)**

Intervention

Patients Randomized – 3 Quality Improvement Arms				
Arm	**Duration**	**Surveys**	**Primary Outcome**	**Secondary Outcome**
Teaching - CardioSmart Resources + Clinician Education	9 months	Patient perception QOL	GDMT baseline to 9 month change in average composite endpoint of receiving the main classes of drugs (50% or higher of target doses for HF) among eligible patients	QOL Individual drug improvements Patient perception Cost/cost effectiveness
Technology - Facilitated Solution (Existing Team)				
Teams - Protocol-Supported Team, (Virtual GDMT Team)				

List of Abbreviations

ACCF	American College of Cardiology Foundation
ACE-I	Angiotensin-converting enzyme inhibitors
ASCVD	Atherosclerotic Cardiovascular Disease
ARB	Angiotensin II receptor blockers
CV	Cardiovascular
CVD	Cardiovascular Disease
CVRiD	CV Risk in Diabetes
DCR	Diabetes Collaborative Registry
EHR	Electronic Health Record
ESRD	End Stage Renal Disease
ECDP	Expert Consensus Decision Pathway
GDMT	Guideline Directed Medical Therapy
GLP1-RA	Glucagon-like peptide-1 receptor agonists
GPP	Good Pharmacoepidemiology Practice
HF	Heart Failure
LVEF	Left Ventricle Ejection Fraction
SGLT-2I	Sodium glucose cotransporter-2 inhibitors
SI	System Integration
SIM CVRiD	Success in Managing CV Risk in Diabetes
T2D	Type 2 Diabetes
VAD	Ventricular Assist Device

Rationale and Background

TRANSFORM^3 is a Quality Improvement initiative conducted in parallel to the current TRANSFORM CVRiD study and aligned with its goals of using a real-world population study to enable the American College of Cardiology Foundation ("ACCF") to better identify impactful ways to improve guideline directed medical therapy for patients. TRANSFORM^3 is focused on improving GDMT use in underserved patients and patients with a history of health care disparities who have one or more of the following: heart failure, atrial fibrillation, and ASCVD/Type 2 diabetes.

There is a significant disconnect between increasing availability of effective and safe therapeutics that significantly reduce CV event risk in patients with Heart Failure, T2D and ASCVD, and Atrial Fibrillation—and clear guideline recommendations endorsing these therapies—but very low adoption in clinical practice with the majority of eligible patients that are most likely to benefit from these therapies not receiving them. A high proportion of patients have more than one of these conditions further reducing the chances of receiving optimal guideline directed medical therapy and avoiding the CV events they are designed to prevent.

Heart Failure (HF)

HF is the cardiovascular epidemic of the 21st century, affecting millions of patients worldwide. It is the #1 diagnosis leading to hospitalization among Medicare beneficiaries. In addition to being increasingly prevalent, HF has a poor outlook after initial diagnosis and is associated with poor quality of life (QOL) in affected patients; this not only leads to burden on patients, family and other caregivers, but also on the healthcare system.

Although clinical practice guidelines clearly articulate optimal GDMT for care of patients with HF, implementation of GDMT into the management of such patients has proven to be suboptimal, with most patients under-treated relative to goal therapy.

To evaluate contemporary status of GDMT delivery for HFrEF, the recent Change the Management of Patients with Heart Failure (CHAMP-HF) registry included 3518 patients from 150 primary care and cardiology practices (1,2). The mean age of this cohort was 66 ± 13 years, 29% were female, and mean EF was 29 ± 8%, thus representing a very characteristic population of patients with HFrEF. In CHAMP-HF, the investigators found 27%, 33%, and 67% of eligible patients were not prescribed angiotensin converting enzyme inhibitor (ACEI)/angiotensin II receptor blocker (ARB)/angiotensin receptor/neprilysin inhibitor (ARNI), beta-blocker, and mineralocorticoid receptor antagonist (MRA) therapy, respectively. Furthermore, when medications were prescribed, few patients were receiving target doses of ACEI/ARB (17%), ARNI (14%), and beta-blocker (28%); most patients were receiving target doses of MRA therapy (77%). Most notably, among patients eligible for all classes of medication, only 1% were simultaneously receiving target doses of renin-angiotensin system inhibitors (RASi; ACE/ARB/ARNI), beta-blocker, and MRA. Remarkably, little improvement in GDMT was noted over a 6 to 12-month period and (importantly) no use of the newest HFrEF GDMT, sodium glucose cotransporter-2 inhibitors (SGLT2i) was reported.

In HFpEF, the MRA spironolactone could be considered for use based on the TOPCAT trial (America's region). Similarly, the ARBs (based on CHARM-Preserved and I-Preserve) appear to modestly lower HF events in patients with HFpEF. The US FDA has expanded labelling for ARNI to all patients with chronic HF noting that patients with an LVEF below normal are most likely to benefit. This regulatory labelling change was based on the PARAGON-HF trial which showed modest clinical benefits of this therapy when studied against valsartan. The SGLT2i empagliflozin was shown to be beneficial in reducing HF events or cardiovascular death among patients with HF with mildly reduced or preserved EF.

Atrial Fibrillation (AF)

AF, the most common arrhythmia in adults, is a top priority for the TRANSFORM[3] program. The estimated risk of developing atrial fibrillation over a lifetime is 1 in 4, and a diagnosis of atrial fibrillation confers a 5-fold increase in ischemic stroke risk.

Anticoagulation reduces the risk of stroke by 60-70%, which is a benefit that outweighs the risk of bleeding for the majority of patients. The American College of Cardiology (ACC), American Heart Association (AHA), and Heart Rhythm Society (HRS) recommend the use of the CHA2DS2-VASc score to estimate stroke risk and to start an anticoagulant in anyone with a score greater than or equal to 2 in men and greater than or equal to 3 in women. The proportion of patients at elevated stroke risk based on the CHA2DS2-VASc score who receive oral anticoagulation (OAC) therapy is a performance metric used by cardiovascular societies and the Joint Commission to assess the quality of cardiovascular care being delivered. Despite the clear benefits of oral anticoagulation for stroke prophylaxis of atrial fibrillation, only 50-60% of eligible patients receive an anticoagulation prescription.

Type 2 Diabetes Mellitus (T2D)

Over 34 million Americans have T2D and >7 million have established cardiovascular disease. T2D is associated with diminished life expectancy (by up to 6-7 years for an average 60-year-old patient).

Patients with T2D have traditionally been managed with diet/lifestyle optimization, glycemic control, other risk factor control (including of blood pressure, weight, and smoking cessation), statin therapy, and renin-angiotensin-system inhibitors (in select patients). The SGLT2i and the GLP-1RA are 2 classes of antihyperglycemic therapies that have demonstrated clinically important improvements in cardiovascular, kidney, and mortality outcomes among high-risk patients with T2D. Despite their availability and a strong evidentiary base, their uptake in clinical practice remains suboptimal. Even with expanding insurance coverage and accruing clinical practice guideline support (across specialties), recent national data have suggested that only ~10-15% of eligible patients are on 1 of these risk reduction therapies. Innovative strategies are needed to promote optimal care practices among high-risk patients living with T2D.

We designed the TRANSFORM[3] as a US-based multi-center trial with the goal of defining optimal implementation strategies to integrate GDMT across disease states, especially in underserved populations or those with health care disparities historically. The study was designed specifically to capture patients across broad integrated health systems encountering multiple

clinician types. All quality improvement initiatives will be remotely deployed directly to clinicians caring for eligible patients by trained Study Managers.

The lack of effective implementation is in part related to therapeutic inertia and lack of effective clinical care models that promote and incentivize adoption of guideline-directed medical therapies (GDMT). Furthermore, while treatment changes are often exclusively made during clinician encounters, this study attempts to evaluate strategies that target the large time periods spent outside of defined ambulatory care encounters. Clinicians may have multiple competing priorities during these short clinic visits and allowing for sufficient time needed to effectively optimize medical therapies may be challenging within the time-constrained context of such a visit. We will seek to investigate a range of currently available clinician-facing implementation strategies (including patient/clinician education, technology-based support, and facilitated referral to a team [specifically virtual GDMT nurse/pharmacy] to determine the potential of various implementation approaches to rethink the 20-minute office visit more broadly and improve use of GDMT among patients with one or more high-risk cardiovascular conditions.

Study Design

TRANSFORM^3 will enroll patients, especially those in underserved populations and those with health care disparities historically, to address guideline directed medical therapy in one or more of the following disease states: HF, ASCVD/diabetes, and AF.

The study will address the following key objectives among patients with Heart Failure Atrial Fibrillation, and/or T2D and ASCVD:

1. Evaluate strategies to improve adoption of evidence-based CV-risk reduction and disease management therapies for HF, AF, and T2D/ASCVD.

The research objectives of this study are outlined below:

Multi-faceted Implementation Study: In this quality improvement initiative, we will test 3 currently available quality improvement strategies designed to improve implementation of the guideline-concordant care for patients with Heart Failure, Atrial Fibrillation, and/or T2D and ASCVD. Across select participating health systems, participants with Heart Failure, Atrial Fibrillation, and/or T2D and ASCVD, will be randomized to 1 of 3 implementation strategies:

a. **Teaching Based Improvement**: Clinician and Patient Education alone;
b. **Technology-Facilitated Improvement**: Technology Guided Care to provide suggestions for care optimization + Education; or
c. **Team Based Improvement**: Referral to a third party virtual GDMT team contracted by study partner Biofourmis for care optimization utilizing the same technology based standardized suggestions + Education.

Key goals of the study will be to:

- Evaluate uptake or intensification of guideline-concordant cardiovascular risk lowering therapies

- Understand guideline consistent comprehensive care for patients with co-related cardiovascular conditions, especially in underserved populations or those with health disparities historically
- Understand barriers and drivers to optimal care

Population:
750 total with comorbidity overlap (250 HFrEF, 250 HFpEF, 500 AF, 250 T2D/ASVD)

Inclusion criteria:

1. Age ≥18 years
2. Personal access to a computer and/or smartphone for app download
3. Heart Failure (reduced and preserved ejection fraction) AND/OR
4. Atrial Fibrillation with CHA2DS2-VASc score greater than or equal to 2 in men and greater than or equal to 3 in women AND/OR
5. T2D and ASCVD, defined as follows:
    a. Known CAD, prior ACS, or coronary artery revascularization
    b. Prior TIA/stroke or known carotid or intracerebral atherosclerosis
    c. Prior PAD including requiring revascularization

Exclusion criteria:

- All patients
    - Current or anticipated participation in an interventional clinical trial of a drug/device
    - Currently receiving comfort care or enrolled in hospice
    - Life expectancy <1 year
    - Pregnancy or active breastfeeding
    - Current or anticipated participation in an interventional clinical trial (other than TRANSFORM[3] GDMT)
    - Patients without a clinical encounter within three years of study start date
- Heart Failure patients:
    - History of or plan for heart transplantation or left ventricular assist device
    - Palliative chronic inotropic therapy
    - NYHA Class 4 heart failure
- Atrial Fibrillation patients:
    - Current prescription for OAC
    - Reversible cause of atrial fibrillation, such as post-cardiothoracic surgery or thyrotoxicosis
    - History of ischemic stroke in prior 7 days
    - Transient ischemic attack in prior 3 days
    - Platelet count <70,000/ml
    - Hemoglobin concentration <8g/dl
    - History of or condition associated with increased bleeding risk, such as hemophilia
    - History of mechanical valve replacement
    - Major surgical procedure or trauma within 14 days
    - Clinically significant gastrointestinal bleeding within 8 weeks

        - History of intracranial, intraocular, spinal, or atraumatic intra-articular bleeding

    - T2D/ASCVD patients with or without HF or AF:
        - Current prescription for SGLT2i and GLP-1RA
        - Current or planned hemodialysis
        - Decompensated end stage liver disease
        - Type 1 diabetes
        - Prior diabetic ketoacidosis
        - Gestational diabetes
        - History of pancreatitis or pancreatic cancer

Data Sources

This is a prospective implementation trial in which patients in 4-6 large health systems will be randomized to various quality improvement strategies to optimize cardiovascular guideline directed medical therapy.

In all arms clinician choice will not be restricted and care recommendations will not be mandated. All interventions are clinician-facing, already available in current care, and promote best practice / guideline recommended care. All clinicians will be informed at the start of the study about the various quality improvement interventions from which they can "opt out". All patients will be requested to provide informed consent to allow for data acquisition and follow-up. Data over 9 months in the 3 quality improvement groups will be mapped to pre-specified data fields, a data extractor (external vendor or study site) will extract the EHR data and may be used to supplement data recorded in the Biofourmis patient management platform. Adverse events (should they occur) will be captured at the clinical site level. Patients reporting adverse events will address these with their providing physician. There is no Data Safety Monitoring Board for this study.

Data Analysis

At study completion, a data set across study visits will be provided to the contracted analytic center using a analytic plan developed by the study team.

Research Question, Objectives & Aims

The goal of this implementation trial is to evaluate several clinician and patient-facing implementation strategies to increase adherence to guideline recommended care and to increase prescription of evidence-based therapies proven to reduce the risk of cardiovascular outcomes in patients, HF, AF and T2D/ASCVD.

Patients will be randomized to 1 of 3 implementation strategies conducted over 9 months: 1) clinician and patient education; 2) technology + clinician and patient education +; 3) referral to

third party virtual team (GDMT team) contracted by Biofourmis+ clinician and patient education. Patients will be followed for 9-months to evaluate for changes in the % of patients who ever receive new CV risk reduction therapies by type of strategy. We hypothesize that care of patients with HF, AF, and T2D/ASCVD, including underserved populations and those with health care disparities historically, can be effectively and safely optimized with support outside traditional ambulatory care encounters.

Primary Objective

The primary objective of this multi-faceted implementation trial is to determine the impact, if any, of use of teaching, technology or facilitated referral to a dedicated third party team (virtual GDMT) contracted by Biofourmis on:

TRANSFORM³: GDMT baseline enrollment to 9 month change in prescription of the main classes of drugs (receiving 50% or higher of target doses for HF patients) for the relevant disease states among eligible patients

Subanalysis for each disease state:

T2D/ASCVD:

a. the proportion of treatment-naïve patients who are newly prescribed a SGLT2i and/or GLP-1RA over 9-months

b. Rate of medication persistence: % of patients on a SGLT2i and/or GLP-1RA at baseline who remained on a SGLT2i and/or GLP-1RA during the study period

HFrEF: For those with HFrEF, baseline to 9 months change in average composite endpoint of at least 50% target dose achievement for the main classes of drugs (RASi/beta blockers/MRA/SGLT2i) among eligible patients.

a. Goal doses will be based on the 2020 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment (4).

b. To calculate this composite:

i. Numerator = receiving ARNI/ACEI/ARB at 50% or higher of target dose + receiving evidence-based beta blocker at 50% or higher of target dose + receiving MRA at 50% or higher of target dose + receiving SGLT2i at 50% or higher of target dose.

ii. Denominator = eligible to receive ARNI/ACEI/ARB, eligible to receive evidence-based beta blocker, and eligible to receive MRA, and eligible to receive SGLT2i.

iii. Using this approach, each patient may contribute to the numerator or be in the denominator 1, 2, 3 or 4 times, depending on meeting criteria and if eligible in that domain. An advantage of this composite approach is that it allows for a holistic view of all classes of drugs considered and allows for assessment not only of up-titration but also down-titration as well.

c. Rate of medication persistence: % of patients on medications at baseline who remained on medications during the study period

Page Break

HFpEF:
For those with HFpEF, baseline to 9 months change in average composite endpoint of target dose achievement for the main classes of drugs (RASi/MRA/SGLT2i) among eligible patients.

a. Goal doses will be based on the 2020 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment (4) and 2022 Heart Failure Guidelines.
b. Calculation similar to the above for HFpEF using the three relevant classes
c. Rate of medication persistence: % of patients on medications at baseline who remained on medications during the study period

AF: Total proportion of eligible patients with an OAC prescription at baseline and 9 months

a. Rate of OAC initiation: % of patients not on OAC at baseline who were started on OAC during the study period
b. Rate of OAC persistence: % of patients on OAC at baseline or who started OAC thereafter who remained on OAC during the study period

All outcomes data will be stratified by the following subgroups: age, race, sex, socioeconomic status, English vs non-English speaking.

Secondary Objective

TRANSFORM[3]:

1. Difference in patient reported outcome scores specifically;

a) Difference in patient reported outcomes on Morisky Medication Adherence Scale (MMAS-4) from baseline, 3 and at 9 months
b) Difference in patient reported outcomes on Patient Activation Measure® (PAM) from baseline, 3 and at 9 months
c) Difference in patient-reported outcome/KCCQ-12 scores from baseline to 9 months (applicable to HFrEF and HFpEF study cohorts only)

By Disease State:

T2D/ASCVD:

1. greater use of guideline-directed cardioprotective therapies
2. improved metabolic parameters (body weight, BMI, HbA1c, systolic BP, lipid levels)
3. lower total daily insulin dose (among patients on any insulin at baseline)
4. Proportion of eligible patients with visits with an opportunity to discuss GDMT during the study period

HFrEF:

1. Relative change in actual achieved doses of individual classes of pivotal therapies (RASi/beta blocker/ MRA/SGLT2i).
2. Relative change in achievement of target doses (yes/no) of pivotal therapies (RASi/beta blocker/MRA/SGLT2i).

3. Proportion of eligible patients with visits with an opportunity to discuss GDMT during the study period

HFpEF

1. Relative change in actual achieved doses of individual classes of pivotal therapies (RASi/MRA/SGLT2i).
2. Relative change in achievement of target doses (yes/no) of pivotal therapies (RASi/ /MRA/SGLT2i).
3. Proportion of eligible patients with visits with an opportunity to discuss GDMT during the study period

AF:

1. Proportion of eligible patients with visits with an opportunity to discuss OAC during the study period

Implementation Efficacy Measures:

- We will assess engagement with the technology and referral completion rates by patients
- Short questionnaires (PAM, MMAS-4, KCCQ-12, CardioSmart E-Diary) will be completed at baseline by patient participants to determine any patient factors that may modify the responses to each of the intervention arms (centered around baseline perception of care optimization, perceived cardiovascular risk, willingness to take new therapy, clinician trust / therapeutic relationship). See appendix.

Research Methods

All eligible patients (see detailed inclusion/exclusion criteria above) with HF, AF and/or with T2D/ASCVD, who are not currently treated on optimal GDMT will be identified across all health systems.

All eligible patients will be randomized to 1 of the 3 implementation approaches and remain under the randomized strategy for the remainder of the study (following intention-to-treat principles). Even if the patient changes PCP or cardiologist (expected low frequency), patients will continue to receive the care under the arm in which they were randomized to. The interventions will be clinician-facing and we chose to select PCP and cardiologists as the target for quality improvement for several reasons: 1) PCPs represent a large cohort of clinicians across health systems, serving as the entry of care and access point for specialty referrals; 2) Patients are unlikely to change PCPs and cardiologist during the short-term duration of the study; 3) Most or all patients are assigned a PCP in a health system thus allowing for clear clinician attribution; 4) PCPs and cardiologists may have sufficient exposure and comfort with prescription of these risk reduction therapies to allow successful intervention to action. If patients leave the health system entirely, then the participant will be censored as lost to follow-up.

Randomization Scheme: Patients will be randomized 1:1:1 to the 3 quality improvement strategies using a standardized randomization software within the Biofourmis platform. To ensure adequate power, enrollment will only end when all three arms have met their individual targets for

patient accrual in both disease categories and representation of underserved populations and those with health care disparities historically across sites. Enrollment of patients with comorbidities will be accomplished through prospective patient identification of patients eligible by disease state and focus populations.

A) **Clinician and Patient Education:** This implementation strategy will support engaging the patients with their existing clinicians using a CardioSmart materials to guide treatment expectations. Clinicians also will receive education on the latest medications for CV risk management. There is no "placebo" arm.

B) **Technology + Education:** This implementation strategy will leverage technology to apply "audit and feedback" of prior care to inform recommendations for future care. These suggestions will encompass the domains of GDMT medications based on eligibility and potential opportunity for an SGLT2i, GLP-1RA, ACEi/ARB, antiplatelet or antithrombotic therapy, and statin therapy, beta blocker, RASi, MRA and DOAC or warfarin. The incorporation of technology for opportunities for GDMT will be utilized to identify tailored opportunities for each CV medication based on guideline recommendations. Clinicians will be presented individual patient-specific recommendation(s) for further optimization of GDMT approximately every two weeks.

   Specifically, an EHR data extractor or data entry form will process data to Biofourmis, where a dashboard will be created. This dashboard will include a) lists of eligible patients for the study and b) an update on opportunities for further medication optimization. The latter information will be based on guideline-directed medical targets as articulated in the ACC clinical policy. Guidance regarding post-initiation monitoring strategies will be additionally included. A patient facing tool will be connected to the dashboard for patient education, surveying, medication adherence, patient reported outcomes, and patient recorded data.

C) **Referral Support + Education:** Each site will have referral access to a virtual GDMT team (TRANSFORM^3). Primary care physicians or cardiologists caring for patients randomized to this intervention strategy will receive notification of the referral. All patients randomized to this group will be considered in this group whether or not the referral to the virtual GDMT team is completed. Care in this group will be supported by the same technology as arm B with the same standardized opportunities for improvement. The virtual GDMT team will have access to data entered into the Biofourmis platform from the EHR and/or supplemented by standard patient interviews. The virtual team will follow an every two week medication review schedule for possible adjustments until GDMT optimization has been completed.

In order to standardize education about best practices surrounding GDMT directed care (to establish a cognitive baseline), educational materials will include a "suite of tools" shared with all clinicians.

Quality Improvement strategies and resources for all arms will include:

- Population Identification & Reporting

- Quality Ambassadors
- Communications
- Education

Mixed Methods Evaluation of Implementation Outcomes

We will conduct secondary analyses to understand patient-level (age, sex, race, insurance, etc.), clinician/health system-level (academic/non-academic, urban/rural setting, etc.), and intervention-level (timing of delivery of prompt, etc.) predictors of "success" (prescription of an evidence-based CV risk reduction therapy) by each implementation approach where applicable.

In addition, clinicians engaging with any of the implementation interventions, we will assess use of the technology and referral completion rates to the virtual GDMT team. Specifically, we will attempt to track the following elements:

1. Time from referral order to first appointment in GDMT team
2. Attendance rate GDMT team appointment (patient leakage)
3. Timing from message to new appointments/new messages from provider to patient, which helps determine if this inter-visit time is actually a 'semi-hot' state.

We will collect data and assess relative timelines of intervention, clinic visits, and timing of medication prescriptions. This would help us understand if changes in prescription are clustered around the time of the intervention (even in the absence of a scheduled visit) or if visits are scheduled after intervention to discuss therapeutic changes.

Short questionnaires will also be completed by patient participants (See Appendix).

Treatment of Patients

All care decisions will be left to the treating clinician, and no care recommendations will be mandated. We will leverage the Biofourmis platform to manage patients and provide referral to a virtual GDMT team.

Site based procedures and Study Managers:

A) **Patient-Level Randomization Stratified by Study Site:** The unit of allocation will be the patient. However, to ensure balance of participants and account for any large baseline variation in care practices across health systems, the analysis will be stratified by study site.
B) **Study Manager:** In quality improvement arm A, Study Managers may facilitate access of CardioSmart materials to the patient. In quality improvement arm B, Study Managers will enroll patients in technology guided care using standardized language. In study arm C, Study Managers will create e-referrals to the virtual GDMT team.
C) **Qualitative Surveys:** The sites will participate with the quality ambassadors in any surveys, including the qualitative survey, and provide regular feedback to the ambassadors for any challenges and/or best practices discovered. In addition, patient participants will

complete a brief baseline assessment of perceptions around care quality, cardiovascular risk, willingness to take another therapy, and therapeutic relationships.

Rationale for Selection Criteria

The study was designed to identify patients at risk for cardiovascular events who meet eligibility criteria for treatment optimization for GDMT. The exclusion criteria are employed to minimize potential risks of individuals and reduce the number of patients who may be intolerant or ineligible for therapy.

Withdrawal criteria

All PCPs and cardiologists (target clinicians for the quality improvement initiative) will receive a correspondence prior to the start of the study describing the initiative. Any clinician who does not wish to receive the quality improvement communication will be allowed to opt-out such that all patients under their direct care will not be eligible for the study. At any time during the study, clinicians may decide to similarly opt-out. All patients who have already been randomized prior to clinician withdrawal will be analyzed in the originally randomized arm (intention-to-treat approach).

Risk/Benefit Assessment

As study procedures reflect CV medication management via guideline recommendations supported by the clinical judgment of the managing physician, there is no envisioned procedural risk to patients through involvement in the study. No testing, time, risk, or procedures beyond those required for routine care will be imposed. The primary risk associated with this project is the potential for a breach of patient confidentiality. The ACCF has established a robust plan for ensuring appropriate and commercially reasonable physical, technical, and administrative safeguards are in place to mitigate such risks as described in the Quality Control section of this protocol.

Data Sources

Data sources will be EMR, other data in the technology solution, electronic informed consent forms and patient survey questionnaires administered by the Biofourmis patient app.

Statistical Methods

The final Statistical Analysis Plan (SAP) will be finalized prior to the study completion.

Patient-Level Randomization to 3 Quality Improvement Initiative: Simple (traditional) randomization minimizes variation in clinical profiles of patients included in each arm. While cluster randomization at the clinician level may limit the potential for contamination bias (chance that clinicians caring for patients randomized to one implementation approach may influence the care of another patient on their panel), the number of eligible patients under each individual clinician's care is anticipated to be small.

Power Estimates: In this 3-arm trial, stratified by study site, we estimated the sample size of patients needed to show a difference between the quality improvement arms.

Current estimates of use of either SGLT2i or GLP-1RA among eligible patients is 15%%. Assuming an alpha of 0.05, we would require 121 patients in each of the 3 arms to show 80% power to detect at least an absolute difference of 15% between education alone and the education + decision support arms and a 15% between education alone and the education + decision support + facilitated referral group. Assuming a 20-25% loss to follow-up rate, 750 patients would be required.

Current estimates of optimal GDMT prescription and titration for HFrEF are 2%. The differences for each arm are expected to be greater than the SGLT2i or GLP-1RA classes.

Given the evolving evidence for HFpEF, there are no established rates for GDMT.

Current estimates of optimal use of anticoagulation medication for AF is 60-65%. The study does not anticipate reaching power for this disease state.

The primary comparison will be between the education alone arm (1) and the education + decision support + referral group (3). Secondary analyses will compare education alone (1) with the education + decision support group (2). The study will be powered for both primary and secondary comparisons for T2D/ASCVD and HF (HFrEF and HFpEF combined).

Rates of Primary Endpoint Over 9 months			**Estimated Number of Patients in Each of 3 Arms**			
Education Alone (1)	**Education +Decision Support (2)**	**Education+Decision+Referral Support (3)**	**80% power**		**90% power**	
			1 vs 2	**1 vs 3**	**1 vs 2**	**1 vs 3**
0.05	0.075	0.1	1471	435	1969	582
0.1	0.15	0.2	686	199	918	266
0.125	0.1875	0.25	529	152	708	203
0.15	**0.3**	**0.3**	**424**	**121**	**568**	**161**

Quality Control

TRANSFORM[3] collaborators have established a robust plan for ensuring appropriate and commercially reasonable physical, technical, and administrative safeguards are in place to maintain the integrity of study data stored and used.

All study data shall be maintained on secure servers with appropriate safeguards in place. The ACCF project team will periodically review all activities involving Protected Health Information to ensure that such safeguards including standard operating procedures are being followed. The

partners shall also communicate to all study personnel the procedure for notifying the ACCF of any breach of confidentiality and immediate mitigation standards that need to be followed.

ACCF shall limit access to Protected Health Information, and to equipment, systems, networks, applications and media that contain, transmit, process or store Protected Health Information ("Equipment, Systems and Media"), to those employees of ACCF who need to access the Protected Health Information for purposes of performing ACCF's obligations to Covered Entities ("Participants") who are in a contractual relationship with the ACCF. ACCF shall implement discretionary access controls designed to permit each user access to Equipment, Systems and Media, which are specifically necessary to accomplish only assigned tasks on behalf of study participants. ACCF shall strictly control physical and electronic access to Equipment, Systems and Media in the following manner:

Physical access

a. All Protected Health Information, and all Equipment, Systems and Media must be stored in a secure facility or secure area within ACCF's facilities which has separate physical controls to limit access, such as locks or physical tokens ("Secured Areas").
b. ACCF shall limit access to Secured Areas to those of its employees or agents who have a legitimate business need to access the secure area, and after ACCF has made an administrative determination of the employee's trustworthiness. Such determination of trustworthiness may include: checking references, checking education and employment history, and searches of public records.
c. Access to Secured Areas by individuals other than those who have been authorized to access Secured Areas shall only be permitted if there is a legitimate business need, and only if such access is continuously monitored by an employee who has been authorized.
d. Secured Areas must be monitored 24 hours per day, 7 days per week, either by employees or agents of ACCF by video surveillance, or by intrusion detection systems.

Electronic access

a. Each user who has access to Equipment, Systems and Media ("User") must have a unique identifier.
b. Users must be authenticated by one of the following methods: unique token or unique password. ACCF shall prohibit generic user accounts and shall implement inactivity time-outs, where technically feasible, for User devices that access study data.

Wireless Devices

Encryption of wireless network data transmission and authentication of wireless devices containing study data ACCF's network is required.

Transmission of Protected Health Information

Protected Health Information may only be transmitted off ACCF's premises to approved parties, Electronic Protected Health Information may only be transmitted via encrypted and authenticated channels, such as VPN, encrypted FTP, SSL or HTTPS.

External Access

Internet
If any Equipment, Systems or Media have Internet connectivity, users must be advised that their unique identifier and authentication tool (e.g. password) must not be shared with others. Where password authentication is employed to authenticate Users, ACCF access and communication to or from the Internet must occur through an actively managed Internet firewall service.

Remote access
If any employees or agents of ACCF have remote access to Protected Health Information, or to Equipment, Systems and Media, from offsite locations, ACCF shall adopt systems and procedures to secure such connections and transmissions. At a minimum, ACCF must ensure the following: 1) dial-up access will occur through a technical security service such as Remote Authentication Dial-In User Service (RADIUS); 2) access via the Internet will be controlled via secure technologies to include authentication and encryption. Acceptable technologies include firewalls and virtual private network services; and 3) ACCF shall require users who access Protected Health Information via personally owned devices and remote access services to take responsibility for the integrity and security of their systems and employ anti-virus software and apply operating system service packs as they are released. Protected Health Information may not be stored on personally owned devices.

Software Controls
Virus Protection
ACCF shall employ virus protection on systems or networks that store, process, access or transmit Protected Health Information, and such protection systems must include real-time or periodic scans.

Service Packs and Security Patches
ACCF shall apply operating system service packs and security patches to systems or networks that store, process, access or transmit Protected Health Information as soon as practicable after they are released.

Audit
ACCF shall implement technical features or controls to record security-relevant activity. ACCF periodically reviews activity logs, investigates and resolves incidents where unauthorized access and attempts are identified. ACCF shall maintain audit logs.

Violations
ACCF shall have a process in place for employees to report instances of violations of privacy and security policies and procedures to the appropriate ACCF personnel.

Transportation and Transmission of Protected Health Information
Protected Health Information, and Equipment, Systems and Media may not be transported off of ACCF's premises unless such Protected Health Information is encrypted.

Disposal of files or media which contain Protected Health Information.

If ACCF is required to destroy files or media containing Protected Health Information pursuant to the Business Associate Agreement, such destruction shall be performed in the following manner:

Magnetic Media
Magnetic Media such as tapes, diskettes, hard drives, must be purged of all information such that the data is no longer reasonably retrievable from the media. Degaussing is an acceptable method of purging information from magnetic media.

Non-Magnetic Media
Non-magnetic media such as hard copies, CDs or DVDs must be physically destroyed such that the data is no longer reasonably retrievable from the media. Acceptable methods of physical destruction include shredding.

TRANSFORM[3] participating collaborators shall employ comparable safeguards that store, process, access or transmit Protected Health Information with real-time protection. No printed materials will be generated as part of this study.

Informed Consent

In all arms, clinician choice will not be restricted and care recommendations will not be mandated. These quality improvement initiatives are all clinician-facing to promote best practice / guideline recommended care and supported by a linked patient application, to support data collection and clinician engagement. All study arms can be considered standard of care, and no investigation intervention or therapy is being provided. All PCPs and cardiologists will receive a correspondence prior to the start of the study describing the initiative. Any clinician who does not wish to receive the quality improvement communication will be allowed to opt-out such that all patients under their direct care will not be eligible for the study. At any time during the study, clinicians may decide to similarly opt-out.

Eligible patients will be enrolled via paper consent or electronically utilizing software services provided by Biofourmis.

Consent materials will be provided with sufficient time for the patient to consider their participation in the study. All consent materials will be in the patients' native language and will describe the quality improvement nature of the study and that data collection of therapies will be tracked.

If the patient agrees to participation in the study via paper, the informed consent and signature will be stored at the study site and/or the Biofourmis platform.

If the patient agrees to participation in the study electronically, their informed consent will be recorded through e-consent processes with signature stored at Biofourmis with a copy to the study site. At any time, patients may withdraw consent. In such a circumstance, patients will be analyzed per intent to treat. Only those patients capable of giving informed consent will be enrolled in the study.

There are no costs or compensation to the patient for participation in the TRANSFORM³ study.

References

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Lloyd-Jones DM, Huffman MD, Karmali KN, et al. Estimating Longitudinal Risks and Benefits From Cardiovascular Preventive Therapies Among Medicare Patients: The Million Hearts Longitudinal ASCVD Risk Assessment Tool: A Special Report From the American Heart Association and American College of Cardiology [published correction appears in Circulation. 2017 Mar 28;135(13):e824-e825]. *Circulation*. 2017;135(13):e793-e813. doi:10.1161/CIR.0000000000000467

APPENDIX

PDF/Printable Materials

Heart Failure
Action Plans
Your Action Plan for Heart Failure With Preserved Ejection Fraction (HFpEF)
Your Action Plan for Heart Failure With Reduced Ejection Fraction (HFrEF)

Worksheets
Heart Failure: Making the Most of Your Follow-Up Visits
Your Heart Failure Daily Tracker
Your Heart Failure Checklist

Quick Tips
Quick Tips Sheet: Daily Weight Check
Quick Tips Sheet: Minding Your Emotional Health
Quick Tips: Exercise and Your Heart
Quick Tips: Heart Failure Medications
Quick Tips: Limiting Salt
Quick Tips: Heart Failure Signs and Symptoms
Quick Tips: Triggers and What To Do

More Resources
Heart Failure, The Basics
Heart Failure: Questions to Ask
Heart Failure: Frequently Asked Questions
Heart Failure: What Your Treatment Plan Might Include
Heart Failure: Caregivers

Action Plan
- Your Action Plan for Managing Atrial Fibrillation

Worksheets
- AFib Medication List
- 10 Steps You Can Take to Manage Atrial Fibrillation
- Keeping Track of Symptoms and How AFib Affects Your Life
- AFib Symptom Diary

Action Plan
- Your Action Plan for Managing Diabetes and Protecting Your Heart

Worksheets
- Diabetes and Heart Disease: What You Need to Know:
- 10 Steps to Lower Your Chance of Diabetes-Related Heart Problems:
- My Medication List:

Patient Survey Questions

CardioSmart E-Diary
Source: Cardiosmart.org

1. Here is how I would describe I feel today
    a) A good day with heart failure
    b) A bad day with heart failure
    c) My worst day with heart failure
2. On a scale from 0 to 10, my stress or anxiety level is (0-10)
3. On a scale from 0 to 10, how sad or depressed have I been feeling? (0-10)
4. Generally, how am I coping with my [heart disease] diagnosis?
    a) Very poorly
    b) Poorly
    c) Ok
    d) Pretty well
    e) Very well, all things considered
5. Overall, describe the stage you are at in living with [heart disease]
    a) Acceptance
    b) Denial
    c) Anger
    d) Depressed

Morisky Medication Adherence Scale (MMAS-4) (Yes/No)
Source: 1569058438 (768×1024) (scribdassets.com)

1. Do you ever forget to take your medicine?
2. Are you careless at times about taking your medicine?
3. Sometimes, if you feel worse when you take your medicine, do you stop taking it?
4. When you feel better, do you sometimes stop taking your medicine?

Page Break

Patient Activation Measure (PAM)
Source: https://www.insigniahealth.com/research/research-licenses
(Disagree Strongly, Disagree, Agree, Agree Strongly)

1. When all is said and done, I am the person who is responsible for taking care of my health
2. Taking an active role in my own health care is the most important thing that affects my health
3. I am confident I can help prevent or reduce problems associated with my health
4. I know what each of my prescribed medications do
5. I am confident that I can tell whether I need to go to the doctor or whether I can take care of a health problem myself
6. I am confident that I can tell a doctor concerns I have even when he or she does not ask
7. I am confident that I can follow through on medical treatments I may need to do at home
8. I understand my health problems and what causes them
9. I know what treatments are available for my health problems
10. I have been able to maintain (keep up with) lifestyle changes, like eating right or exercising
11. I know how to prevent problems with my health

12. I am confident I can figure out solutions when new problems arise with my health
13. I am confident that I can maintain lifestyle changes, like eating right and exercising even during times of stress

Kansas City Cardiomyopathy Questionnaire (KCCQ-12

KCCQ-Questionnaire-12.pdf