Utilizing mobile technologies to improve physical activity and medication adherence in patients with heart failure and diabetes mellitus: Rationale and design of the TARGET-HF-DM Trial

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Heart failure (HF) and diabetes mellitus (DM) are major public health issues that place significant burden on patients and health care systems. Patients with both HF and DM are at higher risk of adverse cardiovascular and HF outcomes than those with either disease in isolation. Different antihyperglycemic medications (even within the same medication class) have conflicting results of benefit or harm in patients with established and incident HF. Recent data highlight the importance of a renewed focus on optimal pharmacotherapy for this population with DM and HF (or at risk for HF). Both HF and DM require major lifestyle modification for optimal management, in terms of both optimizing health behaviors (eg, physical activity, diet) and adherence to complex medical and self-care regimens. Mobile health (mHealth) technologies (eg, apps, wearables) are widely available in the community and may play a role in optimizing the health status of patients; however, there is limited and conflicting information on whether such technologies are actually beneficial in at-risk populations. In this article, we summarize current strategies, including mobile health interventions, to improve physical activity levels, drug adherence, and outcomes in patients with DM, HF, or both and describe the design and rationale for the Technologies to improve drug Adherence and Reinforce Guideline based Exercise Targets in patients with heart Failure and Diabetes Mellitus trial, which is designed to test the efficacy of using mHealth technology to improve health behaviors and outcomes in this high-risk population. (Am Heart J 2019;211:22-33.)

Heart failure (HF) currently affects >6.5 million Americans, is a major source of morbidity and mortality, and is a significant driver of health care resource utilization.[1] The burden of comorbid conditions is increasingly recognized as a major modifier of HF hospitalization risk,[1,2] response to therapy, and outcomes in patients with HF. Type 2 diabetes mellitus (T2DM) is a comorbid condition of particular interest in HF given the large and increasing data on the risk associated with HF among patients with T2DM, as well as the development of T2DM therapies that have been shown to potentially modulate HF risk.[3]

Management of HF and DM requires complex pharmacologic management as well as ongoing behavioral changes and self-care (eg, dietary modification, sodium restriction, monitoring of weight and blood glucose). Complex medical regimens are often associated with poor adherence in patients with HF and T2DM, and poor adherence is associated with adverse clinical outcomes.[4-7] Similarly, adherence to recommendations regarding lifestyle modification such as increased physical activity is often limited despite the favorable effects of these changes in patients with both HF and T2DM[5-9].

Although interventions to improve health behaviors in patients with HF, T2DM, or both have generally been resource-intensive and have delivered inconsistent results, the rise of mobile consumer-oriented technology

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ClinicalTrials.gov Identifier: NCT02918175.
Submitted January 25, 2019; accepted January 25, 2019.

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0002-8703

https://doi.org/10.1016/j.ahj.2019.01.007

("mHealth") focused on health and health behaviors creates opportunities to deploy personalized, scalable health interventions in at-risk populations.[10] In this article, we review prior data on physical activity and medication adherence in HF and DM, including approaches to using mHealth interventions to modify these behaviors, and describe the rationale and design of the Technologies to improve drug Adherence and Reinforce Guideline based Exercise Targets in patients with Heart Failure and Diabetes Mellitus (TARGET-HF-DM) trial. TARGET-HF-DM is funded through the American Heart Association (AHA) Strategically Focused Research Network in Heart Failure. This funding initiative by the AHA targets priority research areas (such as HF) and funds 3-5 research centers nationally for 4 years of funding focused on basic, clinical, and population science as well as research training.

The HF and diabetes interaction

In the United States, HF affects >5 million adults and costs >$30 billion.[11] By 2030, >8 million people in the United States (1 in every 33) will have HF, with total costs exceeding an estimated $70 billion. The problem for DM is worse, as >29 million adults in the United States are currently affected.[11] Furthermore, 1 in 3 individuals is projected to develop T2DM by 2050, resulting in total costs of $336 billion.[11,12] T2DM is a known independent risk factor for HF, conferring a 2.5 times higher risk for developing HF.[13-15] After HF onset, T2DM increases the risk of cardiovascular death by 38%, all-cause mortality by 40%, and hospitalization by 33%.[16] The REACH registry (an international outpatient registry focused on high cardiovascular risk patients) demonstrated that patients with HF with T2DM are at marked risk of cardiovascular death (adjusted hazard ratio [HR], 2.45; 95% CI, 2.17-2.77; $P < .001$) and HF hospitalization (adjusted odds ratio [OR], 4.72; 95% CI, 4.22-5.29; $P < .001$).[16]

Physical activity in patients with HF and diabetes

In a recent call to action, the AHA emphasized that physical inactivity is a major public health burden and contributes to a significant amount of morbidity and mortality.[9] Exertional intolerance is a fundamental component of chronic HF morbidity. The Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) study demonstrated modest reductions in the cardiovascular outcome (mortality and hospitalizations) with exercise training compared to control group in patients with HF.[17] Furthermore, the exercise training arm, compared to placebo, had significant improvements in quality of life and depression scores. These data led to formal recommendations in the AHA guidelines for exercise training in chronic HF and approval of cardiac rehabilitation services by the Centers for Medicare and Medicaid Services. Exercise training and cardiac rehabilitation now carry class I and IIA recommendations, respectively, in HF guidelines.[18,19]

In patients with T2DM, observational studies have shown that higher daily step counts are associated with lower HbA1c values and reduced waist circumference and body mass index.[20] In one study, a 1000-steps/d increase in patients with T2DM was associated with reductions in blood pressure.[21] In another study of a pedometer-based activity intervention, an increase to >4000 steps/d was found to be the threshold for a positive impact on HbA1c. However, recent reviews on physical activity monitoring in patients with T2DM demonstrated an overall paucity of robust data on glucose metabolism markers and physical activity.[22] HF patients with DM have substantially worse baseline functional status and quality of life compared to similar patients without DM[23]. Randomized evaluation exploring strategies to increase physical activity in patients with HF and DM is needed to support evidence-based clinical decision making.

Medication adherence in HF and diabetes

Medication adherence is a second keystone for improving health outcomes in patients with HF and DM.[51–53] Research in recent years has led to treatment guidelines that reduce complications and improve outcomes in T2DM and HF populations.[11,18,19,24-34] However, in addition to slow adoption of these guidelines by providers and health systems, patient adherence to evidence-based medications recommended in guidelines has been poor. Poor medication adherence leads to errors, adverse events, and death.[4-7] The inability to correctly manage prescribed medications, including inadequate dosing and administration, low health literacy, untimely medication access, and lack of understanding of instructions, is a growing burden to the health system. This contributes to repeated illness exacerbation, acute hospital admissions, and frequent clinic encounters. Challenges with adherence to complex medical regimens have been described in both HF and DM[4-7]. Nonadherence is a multidimensional problem that involves social and financial factors, health care delivery complexities, medication-specific factors, disease-related factors, and factors specific to individual patients.[4,6,7]

Interventions to improve medication adherence in patients with chronic diseases have addressed these barriers through a variety of approaches including mHealth,[10] community pharmacists, and peer coaching. Yet the rate of adherence in larger, population-based studies remains low. Therefore, new interventions are needed to move beyond these known barriers and facilitate adherence with complex medication regimens, thus improving guideline optimization for patients with DM.

Challenges in improving physical activity and medication adherence

Improving medication management begins with an accurate exchange of information between the health care provider and the patient. However, regardless of the language, the overall literacy level for FDA medication information is poor.[4] Similar challenges arise when studies have attempted to improve physical activity.[9] Skill-building is a missing feature in most medication education and physical activity programs. Skill-building requires discussion, practice, and debriefing and is not readily learned using didactic, text-based tools such as brochures, medication flyers, or simply handing over a discharge prescription. The utilization of mHealth may facilitate skill building and development to improve physical activity and adherence to medications.[10]

There are several studies evaluating the role of strategies to increase exercise, improve medication adherence, and improve glycemic control in patients with HF and T2DM. However, studies were small (n = 23 to 223),[35-45] used heterogeneous methods, and had conflicting outcomes (Table I). Two nurse-led education/lifestyle interventions studies improved patient reported activity and disease specific knowledge but not quality of life. One study[36] demonstrated an improvement in 6-minute walk test, but although drug adherence was a part of the education provided to patients, this outcome was not specifically measured. One exercise program improved functional capacity[38] whereas the other did not improve measures of endothelial function[39]. Of the 6 studies (all exercise based) in patients with DM and subclinical left ventricular dysfunction, 3 of the studies demonstrated improvements in echocardiographic- derived diastolic parameters,[40,41] whereas 3 did not.[41,43,44] These data suggest a need for a robust evaluation of behavioral interventions to improve measures of outcomes in patients with HF and DM. Potentially, mHealth interventions may provide a novel avenue to implement behavioral interventions to increase exercise and drug adherence in patients with HF and T2DM.

Role of mobile technologies to improve chronic disease management

In recent years, interest has grown in assessing cumulative physical activity via emerging wearable technology (collectively termed *mHealth*).[10,46-48] Furthermore, capturing physical activity through wearable activity monitors via "actigraphy" (ie, noninvasive monitoring of rest/activity cycles) has gained acceptance among health care professionals and clinical trialists through availability of devices using accelerometers to measure activity and rest.[49,50] The increased availability and use of consumer oriented devices to measure physical activity provide an opportunity to both measure and impact daily physical activity in at-risk populations (such as those with both HF and T2DM) through targeted interventions.

The ubiquity of mHealth technologies introduces substantial opportunities to improve health outcomes in at-risk populations. mHealth potentially allows for highly scalable, patient-centered interventions with real-time feedback. The Tobacco, Exercise, and Diet Messages (TEXT-ME) trial demonstrated that a lifestyle-focused text messaging program improved lipid control and other cardiovascular disease risk factors including blood pressure and body mass index.[54] A meta-analysis of mobile health interventions demonstrated an improvement in drug adherence across a spectrum of cardiovascular diseases.[55] However, the Innovative Approaches to Diet, Exercise and Activity (IDEA) trial demonstrated a potential increase in weight associated with the use of a wearable technology.[56] These conflicting results highlight the need for more randomized studies before mobile technologies can be widely recommended for health purposes. The need for rigorous study of these technologies using robust methods in representative populations is the topic of a recent AHA Scientific Statement on the consumer use of mHealth technologies for cardiovascular prevention.[57]

Design of the TARGET-HF-DM trial

In light of the challenges and unmet needs described above, we designed the TARGET-HF-DM trial as part of the AHA Strategically Focused Research Network in Heart Failure. The overall objective of the TARGET-HF-DM trial is to test a personalized mHealth intervention designed to increase physical activity and improve medication adherence in a randomized controlled trial of population with concomitant HF and DM. The study will leverage consumer technology as both an intervention and a tool for data collection. The underlying hypothesis is that the proposed intervention can favorably impact specific health behaviors (physical activity and medication adherence) and physiologic measures of disease status (NT-proBNP and HbA1c) for both HF and DM.

An overview of the study design is shown in Figure 1. The TARGET-HF-DM trial is a multicenter randomized controlled clinical trial in eligible subjects with HF (regardless of EF) and DM. Activity levels (measured by a wearable step counter), self-reported quality of life (Kansas City Cardiomyopathy Questionnaire [KCCQ]), medication adherence (assessed by prescription refill rate and a validated questionnaire), and relevant clinical measures (including baseline demographics, socioeconomic variables, comorbidity history, and currently prescribed medications) will be collected from all study subjects. The intervention has 2 parts—(1) personalized feedback about physical activity from a wearable mHealth device and (2) access to a medication adherence training tool (Duke Pillbox). This intervention will be

Table I. Selected trials to improve activity, optimize medication adherence, and improve measures of cardiac dysfunction in patients with diabetes mellitus and HF

Trial	Patient population	Intervention	Primary outcome	Result
Patients with HF and diabetes mellitus				
Randomized clinical trial of an integrated self-care intervention for persons with heart failure and diabetes: quality of life and physical functioning outcomes (2015).[36]	N = 134 Hospitalization for HF in past 3 m, NYHA 2-4. Patients with 1st diagnosis of HF were excluded. Enrolled from 4 tertiary care hospitals.	Heart failure-Diabetes Mellitus (HF-DM) tool kit provided by a trained nurse which provided reading material regarding HF and DM care (medication use, physical activity, goal setting, and symptom monitoring) followed by a home visit by the research nurse. Follow-up in clinic after 2 wk and telephone follow-up at 1, 2, and 4 m. Final follow-up at 6 m.	Changes in (1) QOL using the EuroQol 5 dimension tool (2) 6-min walk test, (3) physical activity via the Community Healthy Activities Model Program for Seniors (CHAMPS) questionnaire	(1) The intervention group improved in QOL scores at 3 m (0.75 intervention vs 0.69 control; $P = .001$) with retention of improvements at 6 m, (2) improved 6MWT in intervention group distance (924 ft to 952 ft; $P = .03$), whereas the control group declined (834 ft to 775 ft; $P = .01$). The intervention group increased self-reported activity between baseline and 6 m (50% to 74.5% intervention vs 48.4% to 59.6% control; $P = .01$).
A pilot test of an integrated self-care intervention for persons with heart failure and concomitant diabetes. (2012)[37]	N = 71 Patients hospitalized with HF with DM and reduced LV function.	Two 30- to 45-min educational sessions (symptom monitoring, medication use, self-care in HF and DM strategies) prior to hospital discharge. A telephone call 48-72 h postdischarge and a clinic visit follow-up 2-4 wk later with reinforcement of self-care behavior.	Changes in the following surveys at 30 and 90 d postdischarge: (1) Atlanta HF-Knowledge Test (AHFKT), (2) Michigan Diabetes Knowledge Test, (3) self-care confidence scale of the Self-Care in Heart Failure (SCHFI), (4) Perceived Diabetes Self-Management Scale (PDSMS), (5) Minnesota Living with Heart Failure (MLWHF) questionnaire	Improvement in all surveys assessing knowledge of HF and DM (78.0% to 81.7% in intervention vs 81% to 80.8% control; $P = .0$). No improvement in QOL.
Aquatic exercise is effective in improving exercise performance in patients with heart failure and type 2 diabetes mellitus (2012)[38]	N = 24 Stable HF patients with, NYHA 2-3, EF <50%, and age >55.	Randomized to usual care or a 45-min session in a heated pool, 3 times a week over an 8-wk period	Changes in exercise capacity (peak V02)	Significant improvement in exercise capacity (+2.1 intervention vs. −0.9 control; $P = .001$)
Effect of an exercise training program on endothelial dysfunction in diabetic and nondiabetic patients with severe chronic heart failure (2006)[39]	N = 42. Chronic HF patients (EF< 30%) and insulin-dependent DM (n = 20) or non-DM patients (n = 22).	All patients participated in a 4-wk exercise program consisting of ergometer and muscle training.	Change in the endothelium-dependent and endothelium-independent vasodilatory capacity before and after exercise.	No significant change in the endothelium-dependent and endothelium-independent vasodilatory capacity in patients with or without DM.
Patients with diabetes mellitus and asymptomatic preclinical HF				
High-intensity interval exercise effectively improves cardiac function in patients with type 2 diabetes mellitus and diastolic dysfunction (2014)[40]	N = 83 Stable outpatients with type 2 DM and diastolic dysfunction (e' < 8 cm/s) but no history of cardiovascular disease.	Compare the effect of high-intensity interval exercise (HIIE 4 4-min interval, 90% to 95% maximal heart rate, 40 min/bout, 3/wk) to moderate-intensity exercise according to current guidelines (MIE; 10 min/bout, 210 min/wk)	Peak early diastolic tissue Doppler velocity (e' cm/s) after 12 wk of exercise intervention.	High-intensity exercise improved primary outcome (7.0 to 8.8 cm/s HIIE vs 7.1 to 7.6 cm/s MIE; $P < .0001$ difference).
A 6-month exercise intervention in subclinical diabetic heart	N = 49. Stable outpatients with type	Divided (nonrandomized) into usual care or intensive	Co-primary end point of treadmill	VO_2(peak) increased by 11% during the exercise

(continued on next page)

Table I (*continued*)

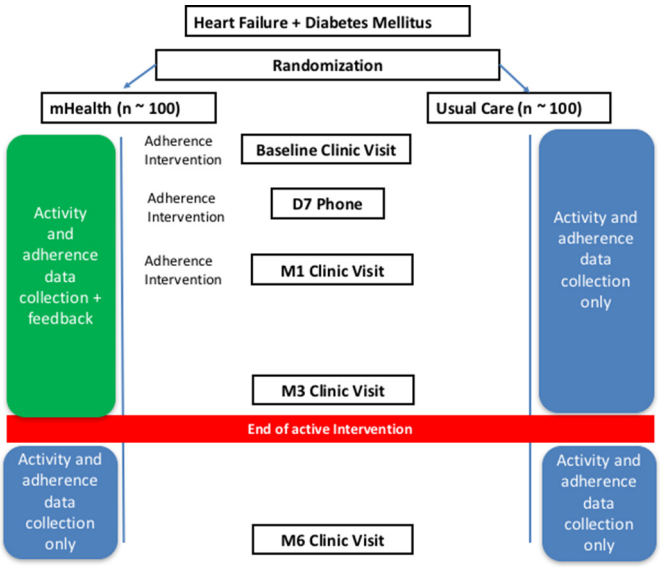
Trial	Patient population	Intervention	Primary outcome	Result
disease: Effects on exercise capacity, autonomic and myocardial function (2014)[41]	2 DM and early diastolic tissue Doppler velocity >1 SD below the age-based mean	exercise intervention (up to 75 min twice weekly, comprising 20-40 min of aerobic exercise and 6-12 resistance exercises) and home-based prescription)	VO_2(peak) and 5-min heart rate variability.	intervention (P = .001 vs. −1% in controls), but heart rate variability did not change (P = .23).
Soccer training improves cardiac function in men with type 2 diabetes (2013)[42]	N = 21. Men with no history of heart disease recruited from an outpatient DM clinic in Denmark.	Randomized to usual care or a soccer training group that trained 1 h twice a week or a control group with no change in lifestyle for 24 wk.	Measurements of blood pressure, changes in comprehensive transthoracic echocardiography measurements, maximal oxygen consumption (V O2max) and 12 and 24 wk.	Decrease in systolic blood pressure in soccer group versus control group (138 to 129 mm Hg intervention vs 126 to 129 mm Hg control; P = .001), change in mitral inflow velocity (0.9 to 1.1 vs 1.2 to 1.1; P < .001 difference); significant improvement in VO2 in soccer group (V02 30 to 34 mL/min/kg soccer group vs 27.5 to 28 mL/min/kg; P < .001 difference).
Application of an exercise intervention on the evolution of diastolic dysfunction in patients with diabetes mellitus: efficacy and effectiveness (2011)[43]	N = 223 Stable outpatients with a history of type 2 DM. 50% with diastolic dysfunction at baseline.	Randomized to usual care or a supervised exercise-based lifestyle intervention (initial gym-based program for 4 wk followed by telephone-guided supervision 2 wk for 3 m then monthly for 3 y)	Changes in the prevalence and evolution of diastolic dysfunction at 3 y compared to baseline.	No difference between the prevalence of diastolic dysfunction was seen between intervention and control (P = .10).
Exercise training does not improve myocardial diastolic tissue velocities in type 2 diabetes (2007)[44]	N = 48 Stable outpatients with type 2 DM and no prior history of cardiovascular disease.	Randomized to usual care or intensive exercise group which involved aerobic exercise to 75% maximal O2 consumption and resistance training 4 times a week for 1 y	Diastolic parameters on echocardiography.	No change in diastolic parameters on echocardiography.
Normalization of diastolic dysfunction in type 2 diabetics after exercise training (2007)[45]	N = 23 Stable outpatients with type 2 DM and varying degrees of diastolic dysfunction	Randomized into usual care or a 3-m aerobic exercise program (3 times per week)	Changes in exercise capacity (V02 max) and indices of left v entricular diastolic dysfunction before and after 3 m	Normalization of echocardiography measures of diastolic dysfunction (45% normalization intervention vs no change in control P < .0001) and improvement in V02 max (28.6 to 32 mL/min/kg vs

compared to usual care. The Duke Pillbox is a Web-based application designed for both inpatient and ambulatory care settings to deliver skill-based education about medications and medication management.[58] The application allows the clinician to assess medication-associated readmission risk, health literacy, patient-perceived medication adverse effects, medication burden on quality of life, and the likelihood for medication nonadherence using a series of validated patient-reported outcomes surveys. The patient fills a "virtual" pillbox with prescribed medications by selecting pictures of the correct drug and dose and "dragging" the pills into the pillbox and placing them in the correct day and time slot. The patient demonstration is scored for accuracy, level of understanding of the regimen, and skill level to select, organize, and manage pills each day. A total of approximately 200 eligible subjects will be randomized in a 1:1 ratio to either usual care with the mHealth (intervention group) or usual care alone (control group). Given the nature of the study intervention, the study will be unblinded. The study will involve 3 months of active intervention followed by an additional 3 months of data collection for a total study duration of 6 months. Pill count and prescription refill rate will be assessed by study coordinators at each of the study subject visits.

Study population

Details of the inclusion and exclusion criteria are shown in Table II. To be applicable to the most

Figure 1



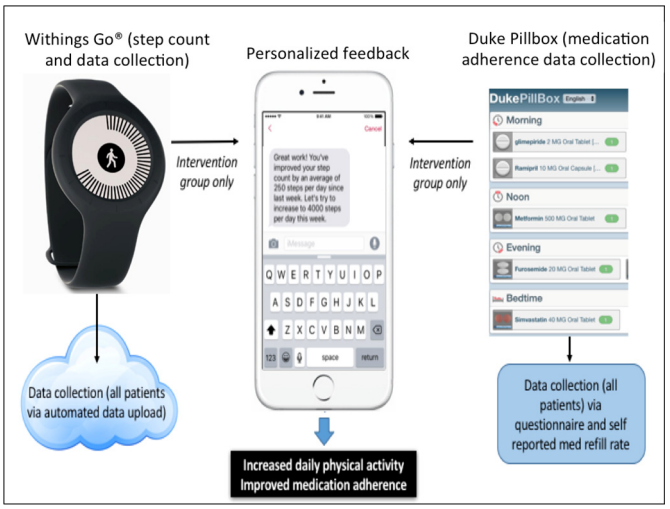
Outline of TARGET-HF-DM trial.*mhealth*, mobile health; *M*, month.

Table II. Inclusion-exclusion criteria for the TARGET-HF-DM trial

Inclusion criteria
• ≥18 y of age
• Chronic HF, NYHA class II-IV, with ongoing treatment with medications for HF for at least 1 m prior to enrollment
• Prior diabetes mellitus diagnosis, with ongoing treatment with antidiabetes medications for at least 1 m prior to enrollment
• Adequate clinical stability in the judgment of the investigator to allow participation in study assessments and the intervention
• Independent with basic activities of daily living, including the ability to ambulate independently
• No plan for revascularization (cardiac or peripheral), outpatient continuous intravenous inotrope administration, cardiac transplant or ventricular assist device implantation, or other cardiac surgery within 6 m of randomization
• Access to a compatible smartphone (either iOS or Android)
• Signed informed consent
Exclusion criteria
• Acute myocardial infarction within prior 4 wk
• Already actively participating in formal, facility-based cardiac rehabilitation
• Severe stenotic valvular disease (eg, severe aortic stenosis)
• Terminal illness other than HF with life expectancy <6 m
• Impairment from stroke, injury, or other medical disorder that precludes participation in the intervention
• Inability or unwillingness to comply with the study requirements

generalizable population, the study was designed to be broadly inclusive. Specifically, it includes patients with symptomatic HF regardless of ejection fraction (ie, both HF with reduced ejection fraction and HF with preserved ejection fraction are included). Patients with HF will have New York Heart Association (NYHA) class II-IV, with ongoing treatment with medications for HF for at least 1 month prior to enrollment. History of DM will be defined as a patient or medical chart report diagnosis with ongoing treatment with antidiabetes medications for at least 1 month prior to enrollment. Patients will be recruited from 5 HF centers in the United States. The Duke Clinical Research Institute is the clinical and data coordinating center for the TARGET-HF-DM trial. Subjects will be enrolled in the outpatient setting. Patient recruitment will use screening of clinical encounters and automated screening of electronic medical records. Recruitment began August 2, 2017, and the trial completion is anticipated in 2020.

Figure 2



Schematic of mobile health intervention in TARGET-HF-DM trial.

Interventions

The mHealth intervention involves the iterative assessment of the target behavior (whether physical activity or medication adherence) accompanied by personalized performance feedback. The intervention will collect data on physical activity (daily step count as measured by the Withings Go) and medication adherence (as assessed by the medication adherence instrument as well as refill rate and pill count) and iteratively feed this information back to the patient via personalized text messages. These messages will include both summary of performance (feedback) as well as setting of specific goals for the upcoming time period (typically 1 week). Data flow will be 1 way in control subjects (data collection only without feedback) and bidirectional in intervention subjects (data collection plus personalized feedback). The mHealth intervention is summarized in Figure 2. The medication adherence intervention will involve an electronic tool (Duke Pillbox) that delivers skill-based teaching about medication management and provides ongoing monitoring of medication use for all pills, patches, pens, and vials. The Pillbox tool can be accessed via the Web or on mobile devices. The Pillbox tool will be used in the intervention arm only. The feedback for physical activity is provided through the application daily. The entire mHealth prompting will occur through the patient facing digital application. The feedback prompts are automated and will be sent to the patients on a daily basis based on level of physical activity to motivate participants to incrementally improve daily step count and also try to get closer to the 10,000/d step goal (Table III). Study sites were able to ascertain comfort with using smartphone to screen and enroll patients who would be willing to comply with the study requirements (Table II). Participants were required to have their own personal smartphone.

Endpoints and statistical considerations

The primary end point will be change in mean weekly step count from baseline through 3 months. Based on available data regarding daily step counts in subjects with HF and diabetes mellitus, we estimate a mean baseline daily step count of 3000 ± 1500 steps/d. In this scenario, the planned sample size of 200 subjects will provide an estimated 90% power to detect a 25% difference and 80% power to detect a 20% difference in the primary outcome between treatment groups. Similar differences in have been seen in other trials that have aimed to improve physical activity (Table I). Other end points of interest will include change in medication adherence, change in quality of life (as assessed by the KCCQ), and change in relevant physiologic measure of disease status (NT-proBNP, HbA1c). Additionally, the study will continue to collect data through 6 months of follow-up to assess the persistence ("stickiness") of any observed treatment effects beyond the 3-month active mHealth intervention. Exploratory subgroups of interest will include HF with reduced ejection fraction versus HF with preserved ejection fraction, age, and insurance status.

Standard summary statistics will be presented including the mean, SD, minimum, median, 25th and 75th percentile, and maximum for continuous variables and the number and frequency of subjects in each category for nominal variables. Statistical tests with a P value $< .05$ will be considered statistically significant, unless otherwise stated. Analyses will be performed using SAS version 9.4 or higher (SAS Institute, Inc, Cary, NC). All analyses will be based on intention to treat, with subjects analyzed in the group to which they were randomized.

The statistical method for the primary hypothesis test will be a 2-sample t test, as well as the 95% confidence interval

Table III. Examples of personalized feedback based on step count change during the 3-month intervention period

Changes in step count	Example of feedback
Improvement	
Increased step count/goal met	Great work! You've improved your step count since last week. Your goal for this week is 2000 steps per day.
Stable	
No increase or very small increase of <250 (goal not met)	Keep up the good work! Your goal for this week is to keep trying to walk 2000 steps per day.
Reduction	
Decrease from prior week; goal not met.	You've taken fewer steps this week. Hopefully you are feeling ok and are ready to step things up! Your goal for this week is 2000 steps per day.

(CI) for the treatment difference associated with the 2-sample *t* test. The Kolmogorov-Smirnov test will be used to determine if the continuous distributions are normally distributed. If the test for normality is not met, the Wilcoxon rank sum nonparametric test will be used instead.

We anticipate that there will be some days with missing data due to either technical issues with data capture or failure of patient to wear the wearable. For the purposes of the primary analysis, days with less than 4 hours of data from the wearable will be excluded from the analysis. Because missing data may not be random (ie, subjects may be less likely to wear the activity tracker or upload data on days where they are less well), we will analyze the end points with data as collected (with zeros for days with no data) as a sensitivity analysis to supplement the primary results. Patterns of missing and/or erroneous data will be evaluated prior to unblinding the treatment groups to confirm that the prespecified plan for how to treat missing data is adequate for purposes of the study. There are no current planned adjustments for multiple comparisons or imputation of missing data.

All participants (regardless of study arm) will complete baseline, 3-month, and 6-month assessments of self-reported adherence using the medication adherence instrument developed by Voils et al.[59] Additional measures of adherence will be obtained from patient self-reported fill and refill medication records. This will be quantified as proportion of days covered, which will equal of days that all HF and diabetes drugs were available (filled) divided by the days in the follow-up period. Following the 3-month intervention period, subjects in the intervention arm will no longer receive adherence feedback. At 6 months, the medication adherence questionnaire will be completed again by all subjects. Patient study follow-up and measurement of biomarkers will be conducted in the intervals as shown in Figure 3.

Discussion

The TARGET-HF-DM trial will be one of the first studies that will evaluate the role of a completely digital intervention to improve physical activity and drug adherence in patients with HF and DM. Given the significant morbidity associated with coexisting HF and DM, in addition to the significant burden of disease of these 2 conditions in the United States and globally, there is an urgent need for pragmatic, scalable, and low-cost interventions that may improve health behaviors such as physical activity and drug adherence. Prior studies conducted in health populations provide further evidence for the use of digital strategies to improve physical activity. The MyHeart Counts study randomized 2,783 participants to 4 different e-coaching interventions across a 4-week period.[60] The e-coaching intervention was personalized based on baseline physical activity and daily activity level. The study demonstrated a significant increase in the primary outcome of daily step count by 189-250 steps. The MyHeart Counts randomized trial demonstrates the feasibility of conducting a short-term digital intervention to improve physical activity. Our study extends from these findings to evaluate the role of a digital strategy to improve physical activity in a patient population with more advanced disease (ie, with both established DM and HF). Furthermore, we will be delivering the impact over a longer time frame (3 months) and evaluating whether persistence of the intervention is maintained until 6 months from randomization. The MyHeart Count study also demonstrated the utilization of personalized feedback, which we will be implementing in our study design. These features will significantly improve our understanding of the role of digital health interventions in patient with DM and HF. In addition, our prompting to increase physical activity and improve adherence with medication using the Duke Pill box is structured on prior literature outlining strategies aimed at reporting and modifying behavioral changes.[61]

Limitations

Our study aims to leverage a pragmatic intervention with minimal in-person or health care team directed intervention. Potential limitations include the nonadherence or nonuse of the wearable device to ascertain the

Figure 3

Schedule of Assessments					
All Subjects	Baseline	D7	1 mo.	3 mos.	6 mos.
Clinic visit	x		x	x	x
Physical exam	x		x	x	x
CV and DM meds	x		x	x	x
Phone visit		x			
NTproBNP and HbA1c (local lab)	x			x	x
Plasma for metabolomics	x			x	
Interval clinical events			x	x	x
KCCQ	x			x	x
Step count upload (daily)*					
Adherence questionnaire	x		x	x	x
Self-reported medication fill and refill assessment for prior 4 week period	x		x	x	x
Intervention group only					
Activity-driven feedback (via text)*					
Adherence intervention (F2F)	x		x		
Step counts will be uploaded via regular syncing of the wearable to its associated app and transfer to Validic. Feedback via text message (SMS) will be sent weekly as described in the text.					

Schedule of follow-up.*F2F*, face to face; *CV*, cardiovascular; *D7*, day 7.

step counts. However, if there is an absence of data from a study participant arising on our server system, automatic flags will be triggered to conduct follow-up to ascertain the reason for an absence of data. We are aiming to ensure a pragmatic and broadly applicable study, so patients with both reduced and preserved ejection fraction are eligible to enroll. In addition, patients with a history of either type 1 or type 2 DM may also enroll. Our study is limited to participants with a smartphone and hence may not be generalizable to the entire HF population; however, the penetration of mobile devices now exceeds 80% across socioeconomic categories in the United States.[10] Furthermore, our study is not powered to assess clinical outcomes. However, up to 80% of people in the United States are physically inactive,[62] and physical inactivity is associated with up to 5.3 million premature deaths per year worldwide.[63] Modestly improving physical activity, such as through increased walking, may have the potential to significantly reduce the burden of premature death and cardiovascular comorbidities.[62,63] The TARGET-HF-DM trial will aim to ascertain whether technologically driven intervention can significantly improve physical activity and whether this improvement is sustained over time. Our study follow-up includes a phone call at 1 week and in-person visit at 1 month before the final study visit at 3 months. Although the schedule may not be reflective of the general practice, such a follow-up schedule is often seen for higher-risk patients in HF clinics. Furthermore, the use of simplified inclusion and exclusion criteria will increase the generalizability of this trial.

Conclusion

Both HF and diabetes mellitus are major public health issues that place significant burden on health care systems. Strategies to promote increased physical activity and improved drug adherence are needed. Using mobile health technologies represents an attractive option to improve health behaviors and outcomes given the widespread use of these technologies. The TARGET-HF-DM trial aims to evaluate the hypothesis that a mobile health intervention can improve measures of physical activity in patients with diabetes and HF. If this mobile health intervention demonstrates utility in improving physical activity, a larger adequately powered trial evaluating the benefit to clinical outcomes would be warranted. Given the conflicting reports of outcomes associated with the use of mobile technologies, randomized clinical data will be critically important before widespread utilization of mobile technologies can be recommended.

Funding

The TARGET-HF-DM study is funded by the AHA Strategically Focused Research Network in Heart Failure (AHA-16SFRN30180010) with additional funding from the Duke Clinical Research Institute.

Disclosures

A. S. reports research grant support from the AHA Strategically Focused Research Network–Heart Failure (16SFRN30180010), Alberta Innovates Health Solution Clinician Scientist fellowship, and the European Society of Cardiology Young Investigator research grant and has received research support from Roche Diagnostics, Takeda, BMS-Pfizer, and the Canadian Cardiovascular Society Bayer Vascular award. Z. E. reports an advisory role (modest) with Pattern Health Technologies. G. M. F. reports research funding from the NIH, AHA, Merck, and Amgen, as well as consulting from Novartis, Amgen, Cytokinetics, BMS, Medtronic, Innolife, Abbott, Roche Diagnostics, SC Pharma, Cardionomic, and Sphingotec. There are no other conflicts to disclose.

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