A Randomized Controlled Trial of Mobile Health Intervention in Heart Failure and Diabetes: Lessons Learned

G. Michael Felker, MD, MHS, FACC, FAHA, FHFSA
Professor of Medicine
Vice Chief of Cardiology for Clinical Research
Division of Cardiology
Duke Clinical Research Institute

Disclosures

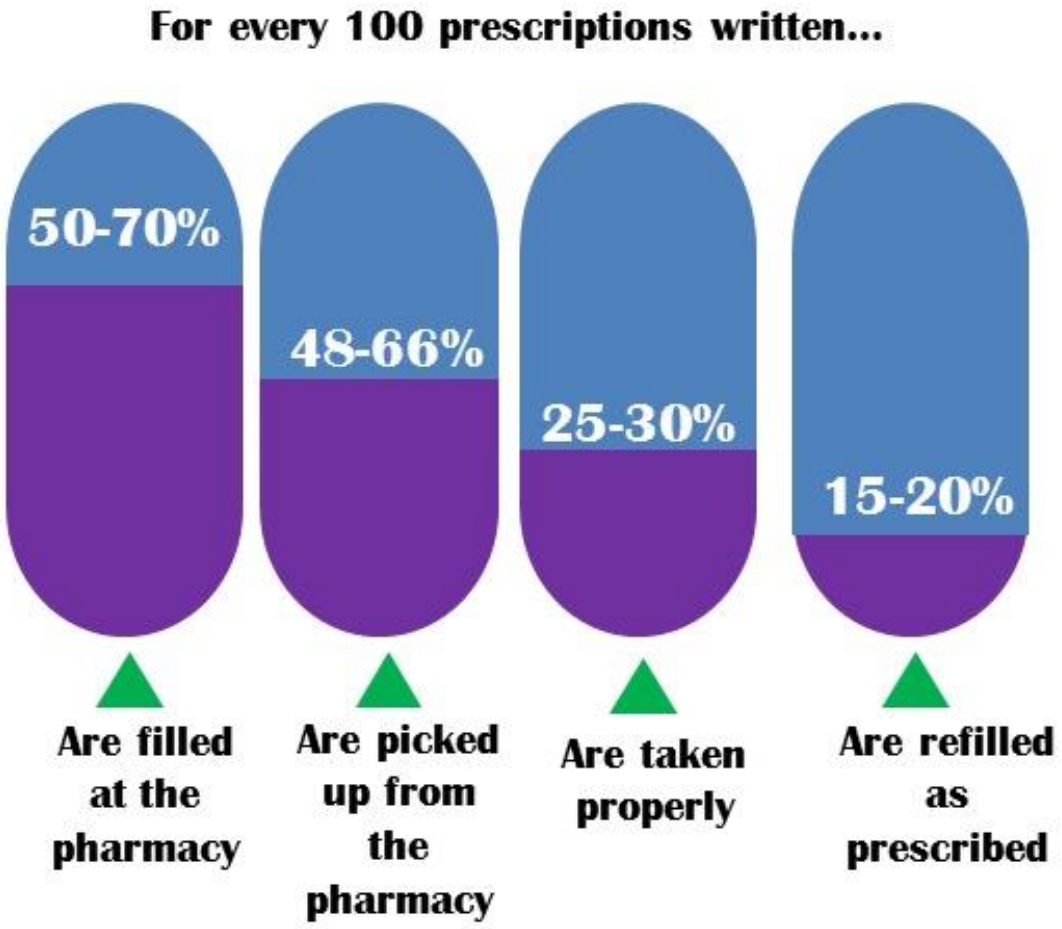
- ***Employment:*** Duke University
- ***Grant Support:*** NHLBI, American Heart Association, Novartis, Amgen, Merck, BMS, Bayer, Cytokinetics
- ***Consulting:*** Novartis, Amgen, Medtronic, BMS, Cytokinetics, Abbott, Myovant, Cardionomic, Innolife, Reprieve, Boehringer Ingelheim, Astra Zeneca
- **Endpoint Adjudication Committees/DSMBs:** Amgen, Merck, Medtronic, EBR Systems, V-Wave, LifaNova, Rocket Pharma, Siemens

Key Healthy Lifestyle Behaviors: AHA Essential 8

- Healthy diet
- Regular exercise
- Control blood sugar
- Healthy weight
- Manage lipids
- Control blood pressure
- No smoking
- Regular and adequate sleep

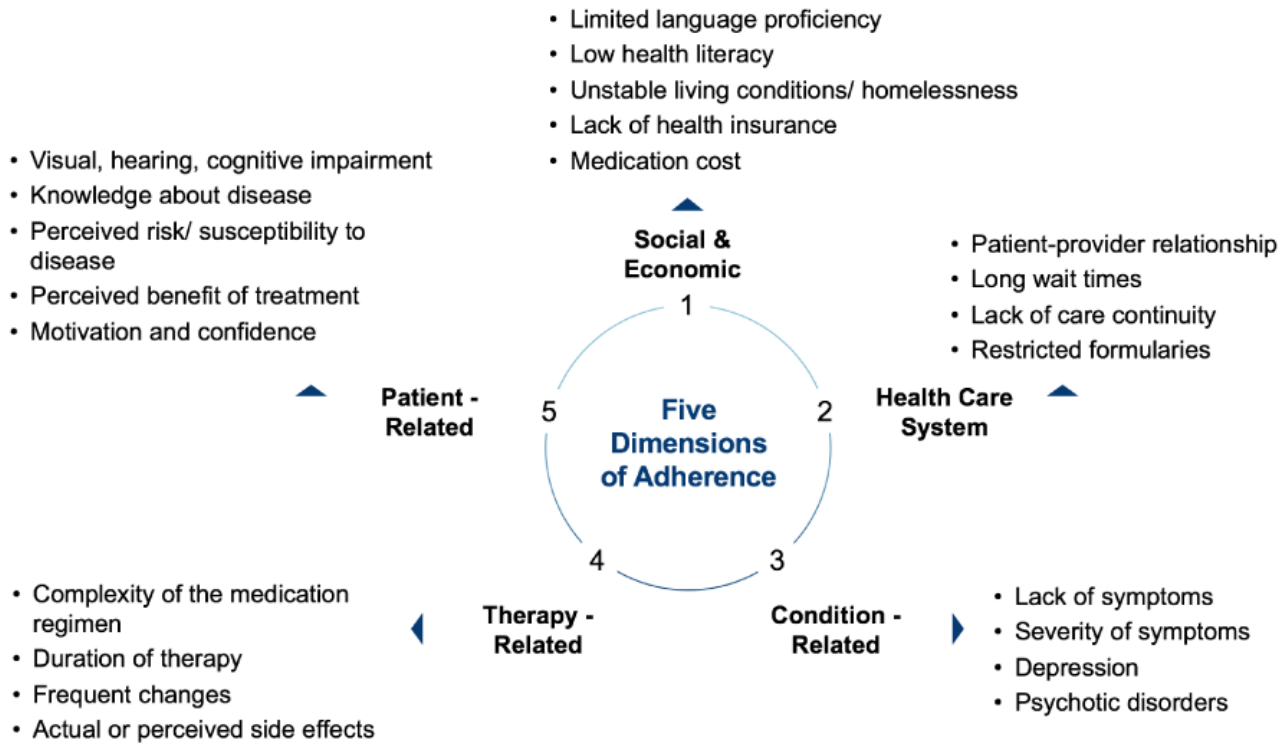
Lifestyle Modification is Difficult

Medication Adherence as a Barrier to Effectiveness



Complexity of Medication Non-Adherence

Diagram Outlining the Factors Related to Non-Adherence.



Source: Sabaté, Eduardo. Adherence to long-term therapies: evidence for action. World Health Organization, 2003.

How Can We Better Facilitate Health Behaviors in Patients with Chronic Diseases?

Can We Leverage Technology?

Original Investigation

Effect of Lifestyle-Focused Text Messaging on Risk Factor Modification in Patients With Coronary Heart Disease
A Randomized Clinical Trial

Clara K. Chow, MBBS, PhD; Julie Redfern, PhD; Graham S. Hillis, MBChB, PhD; Jay Thakkar, MBBS; Karla Santo, MBBS; Maree L. Hackett, PhD; Stephen Jan, PhD; Nicholas Graves, PhD; Laura de Keizer, BSc (Nutr); Tony Barry, BSc; Severine Bompoint, BSc (Stats); Sandrine Stepien, MBiostat; Robyn Whittaker, MPH; Anthony Rodgers, MBChB, PhD; Aravinda Thiagalingam, MBChB, PhD

Parameter	Mean (95% CI)		Mean Difference (95% CI)	*P* Value
	Intervention	Control		
LDL-C, mg/dL	79 (76 to 82)	84 (81 to 87)	−5 (−9 to 0)	.04
Systolic blood pressure, mm Hg	128.2 (126.7 to 129.8)	135.8 (134.3 to 137.3)	−7.6 (−9.8 to −5.4)	<.001
BMI	29.0 (28.8 to 29.3)	30.3 (30.1 to 30.5)	−1.3 (−1.6 to −0.9)	<.001
Physical activity, MET min/wk	932 (825 to 1039)	587 (482 to 692)	345 (195 to 495)	<.001
Smoking, No./total (%)	88/339 (26.0)	152/354 (42.9)	RR, 0.61 (0.48 to 0.76)	<.001

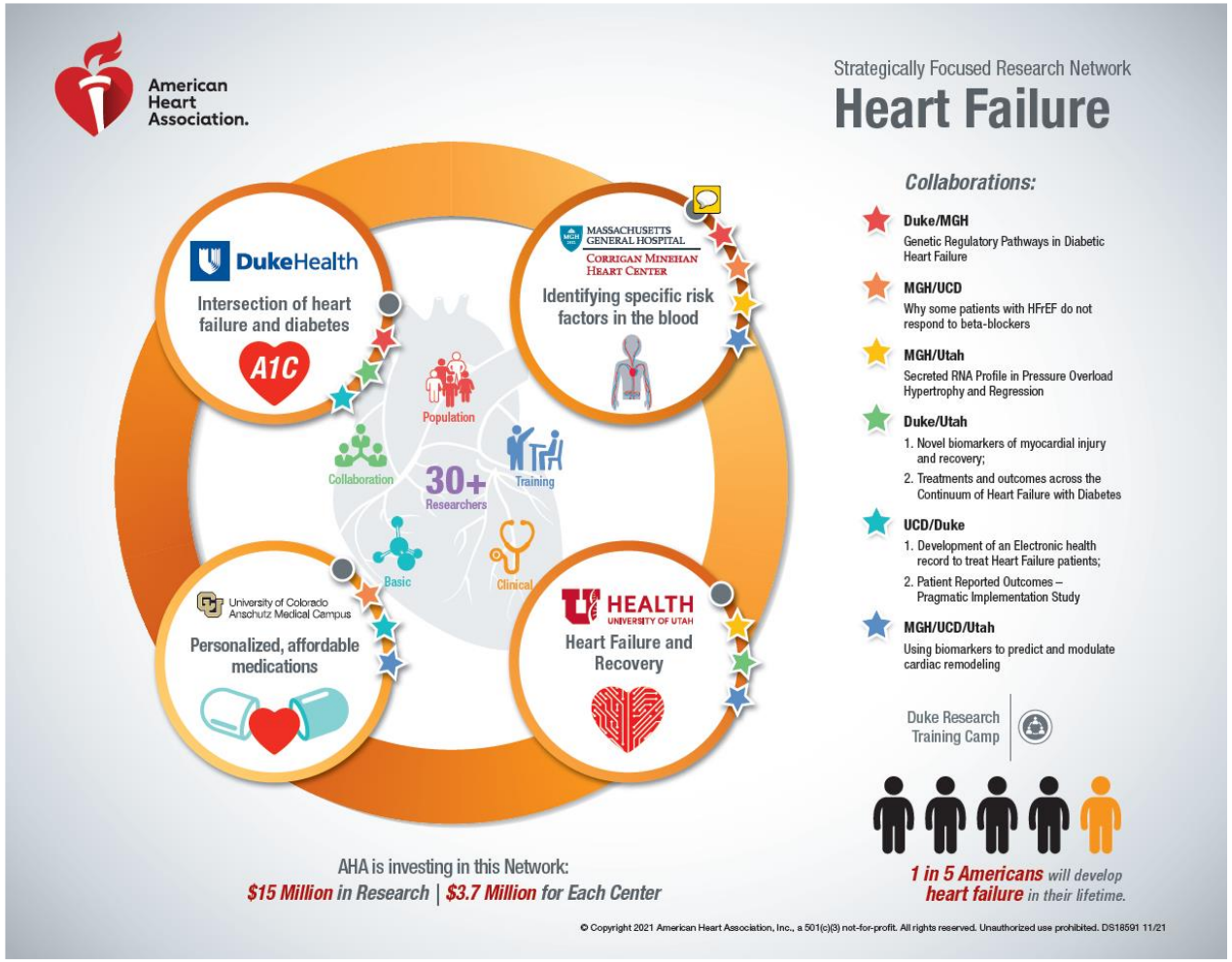
JAMA | Original Investigation

Effect of Wearable Technology Combined With a Lifestyle Intervention on Long-term Weight Loss
The IDEA Randomized Clinical Trial

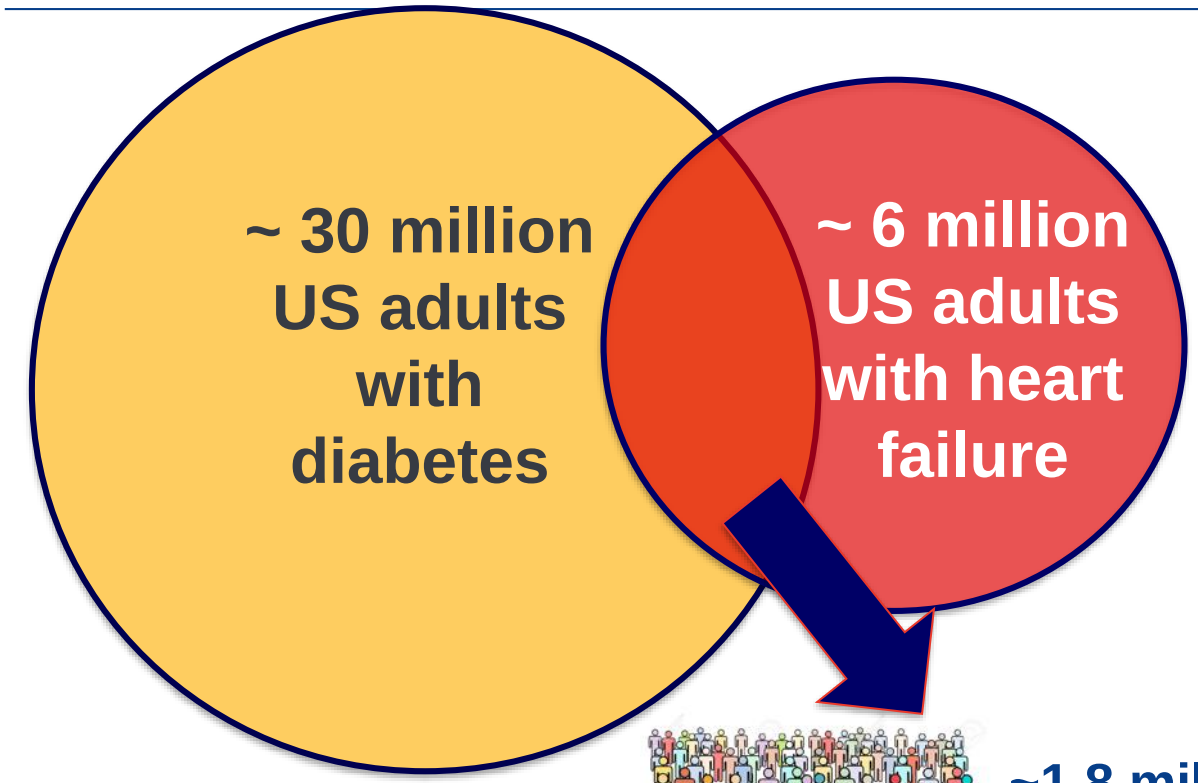
John M. Jakicic, PhD; Kelliann K. Davis, PhD; Renee J. Rogers, PhD; Wendy C. King, PhD; Marsha D. Marcus, PhD; Diane Helsel, PhD, RD; Amy D. Rickman, PhD, RD, LDN; Abdus S. Wahed, PhD; Steven H. Belle, PhD

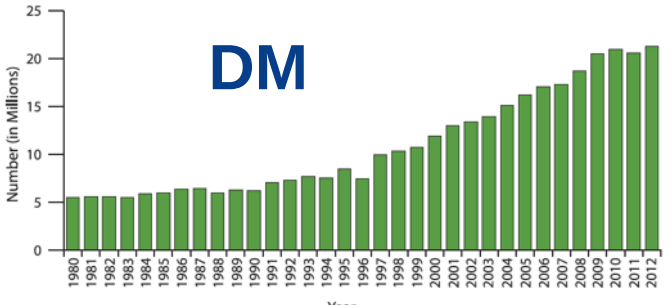
	Standard Intervention	Enhanced Intervention
Weight, mean (95% CI), kg		
Baseline	95.2 (93.0-97.3)	96.3 (94.2-98.5)
24 mo	89.3 (87.1-91.5)	92.8 (90.6-95.0)
Estimated weight loss, mean (95% CI), kg	5.9 (5.0-6.8)	3.5 (2.6-4.5)

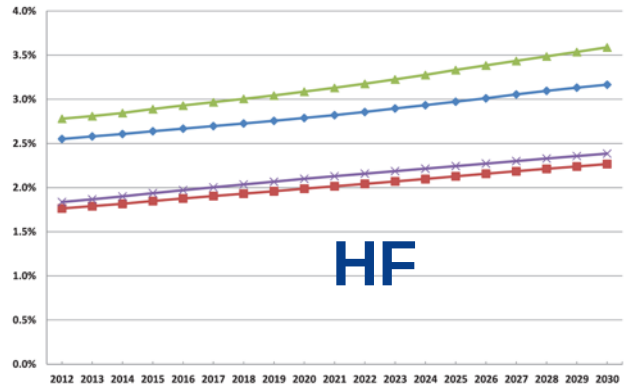
AHA Strategically Focused Research Networks in Heart Failure



Heart Failure and Diabetes







~1.8 million Americans with both HF and DM

- Common risk factors
- Overlapping mechanisms
- Poor outcomes
- Bi-directional response to HF therapies

TARGET-HF-DM:

The Technologies to improve drug Adherence and Reinforce Guideline based Exercise Targets in patients with Heart Failure and Diabetes Mellitus

Background and Objectives

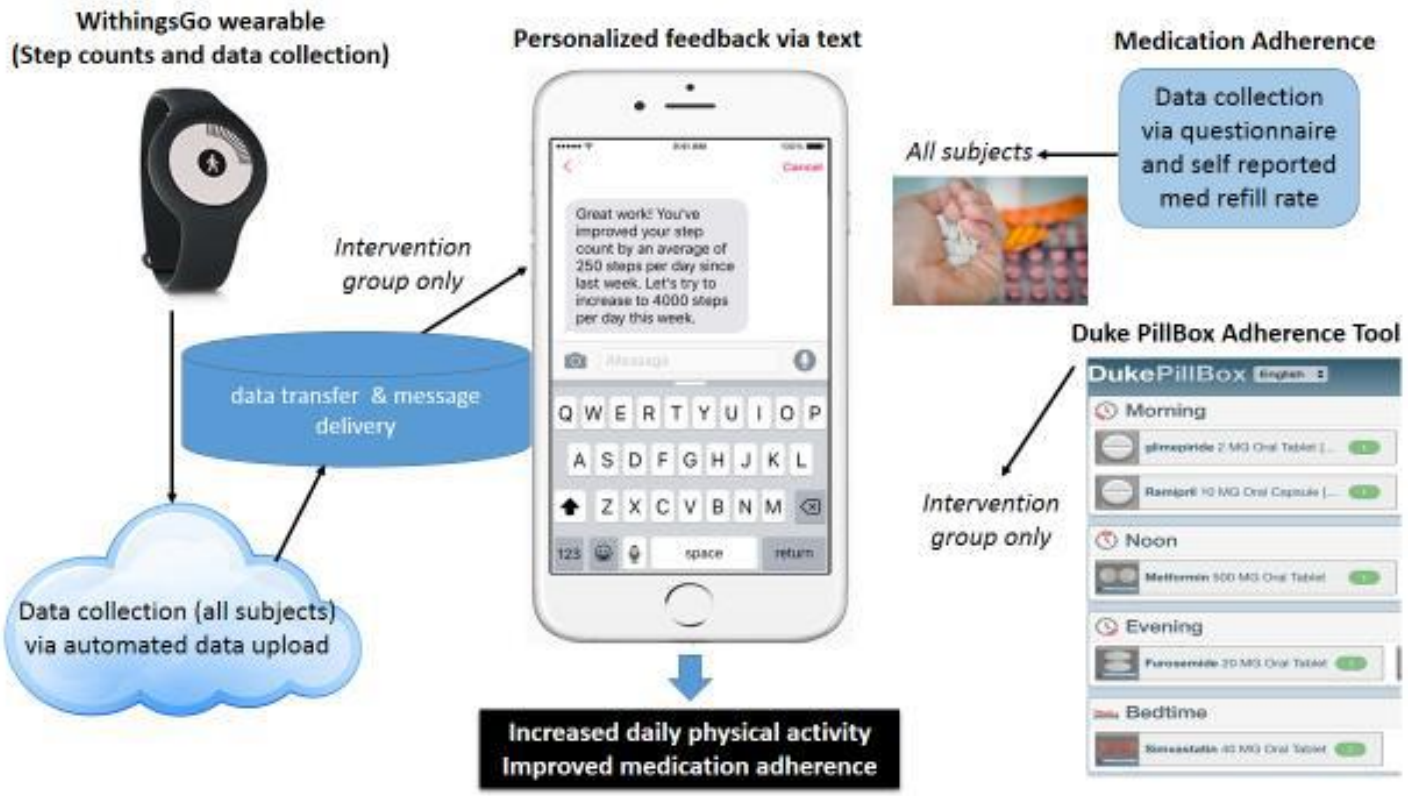
- Regular physical activity is essential to optimal cardiovascular health
  - Improves outcomes and quality of life in heart failure
  - Improves glycemic control and reduces complications in diabetes
- The health impact of behavioral recommendations such as regular exercise is limited by poor long-term adherence
- Digital health interventions (mHealth) provide novel platforms to improve health behaviors but have not been rigorously tested in patients with chronic diseases
- The TARGET-HF-DM study was designed to test the efficacy of a mobile health intervention in patients with both HF and DM on
  - Physical activity
  - Medication adherence

Design: Patients

- TARGET-HF-DM was a ***pragmatic multi-center randomized controlled trial*** at 6 clinical sites in the United States
- ***Broad Entry Criteria***:
  - Both symptomatic heart failure (regardless of EF) and diabetes (requiring medical treatment)
  - Not participating in formal supervised exercise program (such as cardiac rehabilitation)
  - No significant non-cardiac impairments to physical activity
  - Smartphone able to support SMS text messaging

TARGET-HF Overview

- 1:1 randomization to mHealth intervention or usual care
- Intervention for 3 months with additional 3 months of data collection after intervention stopped

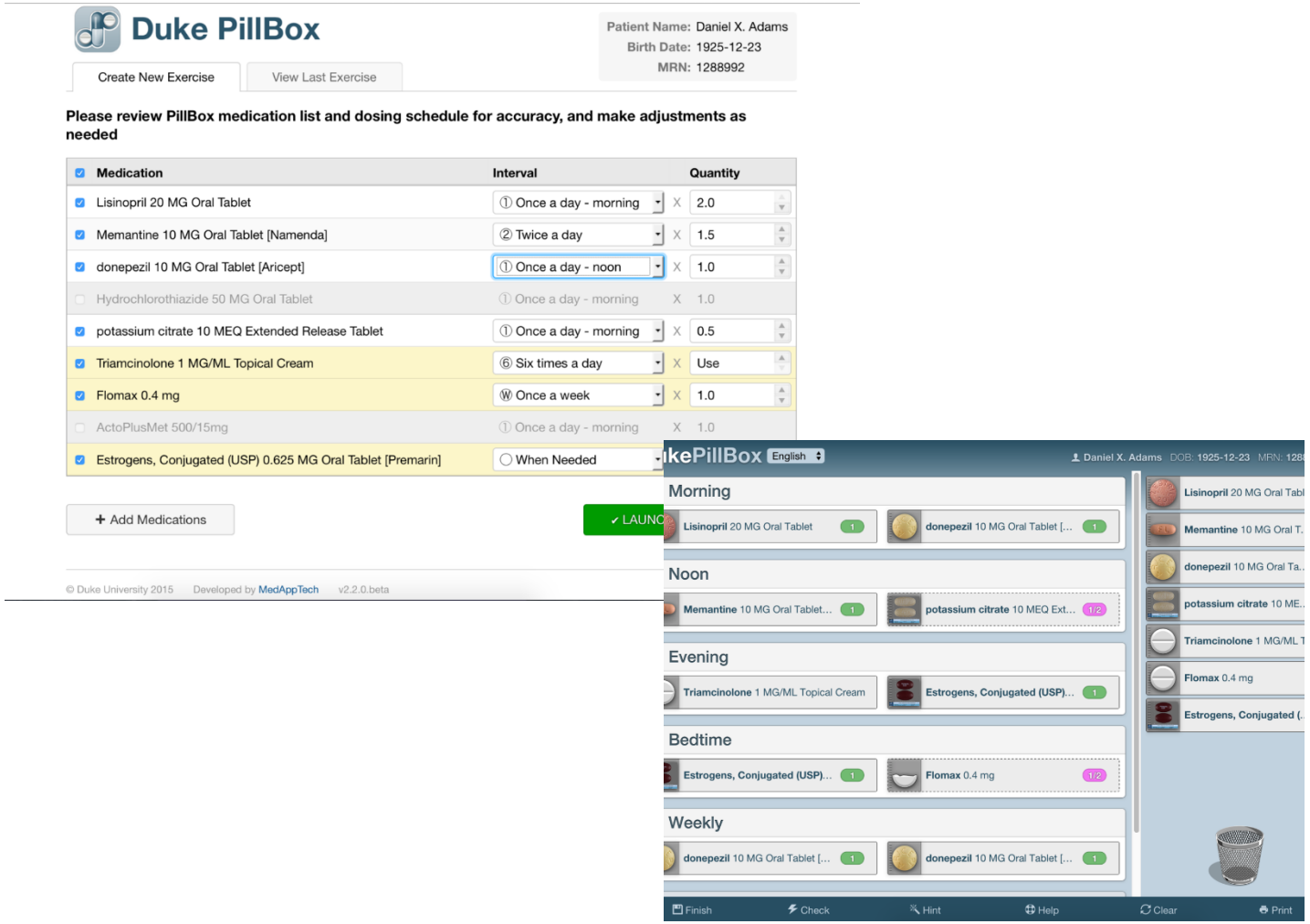


Design: Physical Activity Intervention

- Both groups received step counter and weekly text reminder to wear it
- mHealth group received feedback and incremental personalized activity goals (based on prior week's activity) sent by text 3 times weekly
- 3 months of active intervention followed by 3 months of additional data collection

Design: Adherence Intervention

- Teaching session using D-3 Pillbox online at baseline and 1 month in intervention group only
- Skills management and literacy appropriate indications for each pill/injection/patch with teach back method
- Adherence quantified by Voils Adherence Questionnaire



Sharma, A. et al. Am Heart J 2019

Design: Endpoints

- ***Primary Endpoint:***
  - Change in mean daily step counts from baseline to 3 months
- ***Secondary Endpoints:***
  - Change in medication adherence (Voils adherence questionnaire) from baseline to 3 months
  - Change in HRQOL (KCCQ OSS) from baseline to 3 months
  - Change in NT-proBNP from baseline to 3 months
  - Change in Hemoglobin A1C from baseline to 3 months
- ***Exploratory Endpoints:***
  - Change in mean daily step counts baseline to 6 months (“stickiness”)
  - Change in metabolomic profiling from baseline to 3 months

Design: Statistical Approach

- Changes over time assessed using generalized linear regression model adjusted for baseline measures
- To account for missing or non-physiologic step count data, the primary analysis was limited to patients who had
  - Non-missing data at both baseline and month 3
  - Data were considered non-missing if at least 2 days of data/week were available and within defined physiologic range (200-20,000 steps)

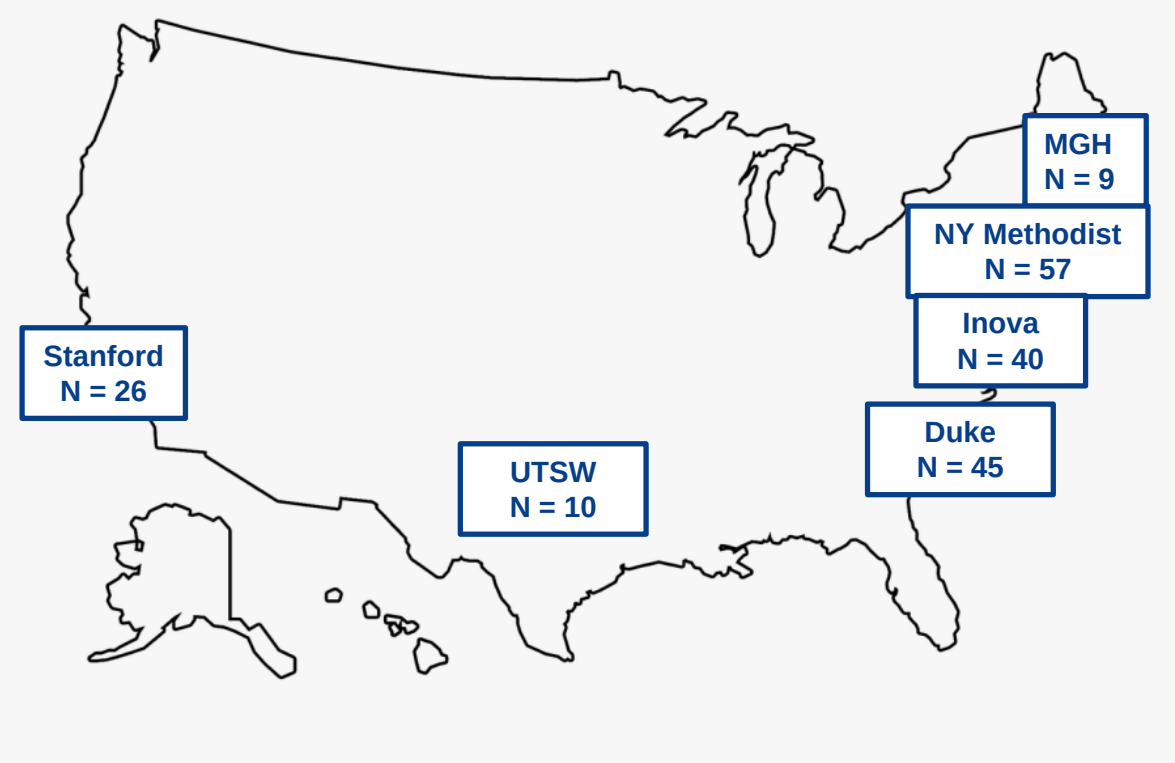
Results: Patient Population

- 35% Women
- 47% African-American
- 10% Hispanic
- Age 59 years

- HFrEF (EF ≤ 40%) = 66%
- NYHA class II = 80%

- Diabetes = 100%
- Atrial Fib = 33%
- NT-proBNP = 1309 pg/mL

N =187



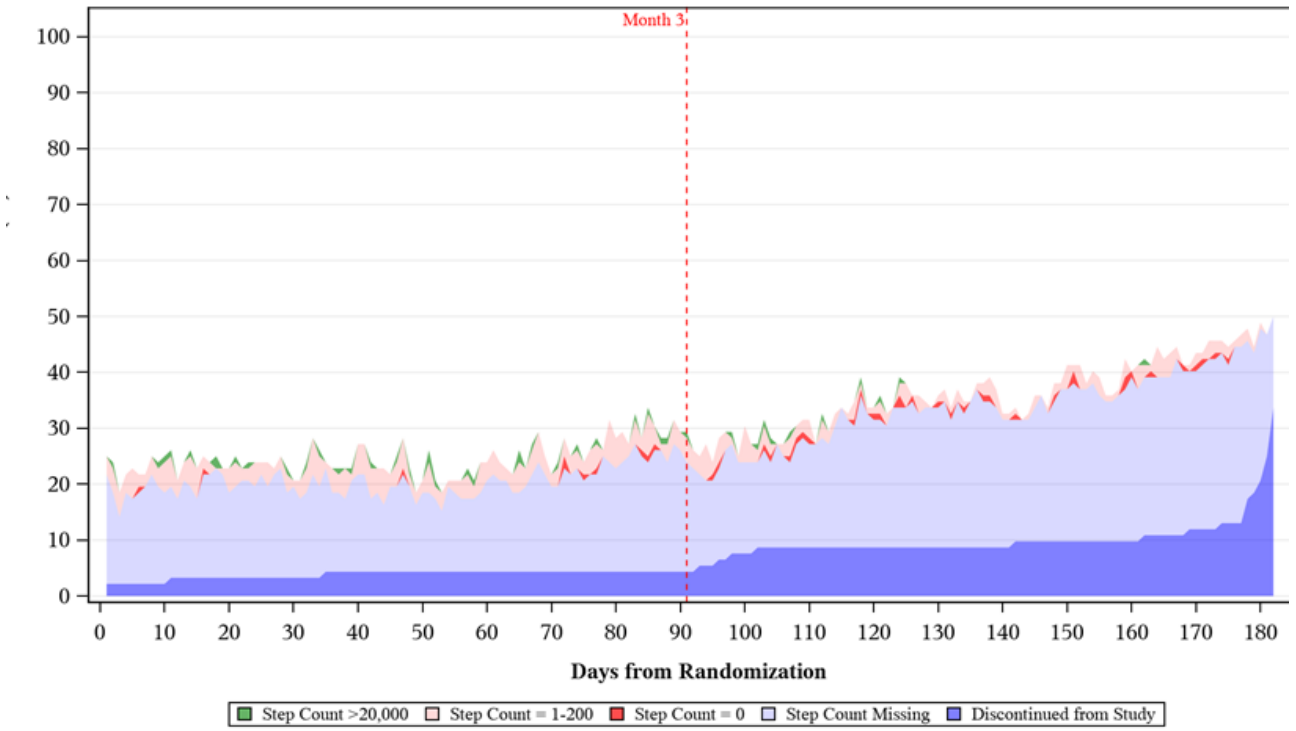
Enrollment halted before planned sample size of 200 due to COVID-19 Pandemic

Results: Baseline Therapies

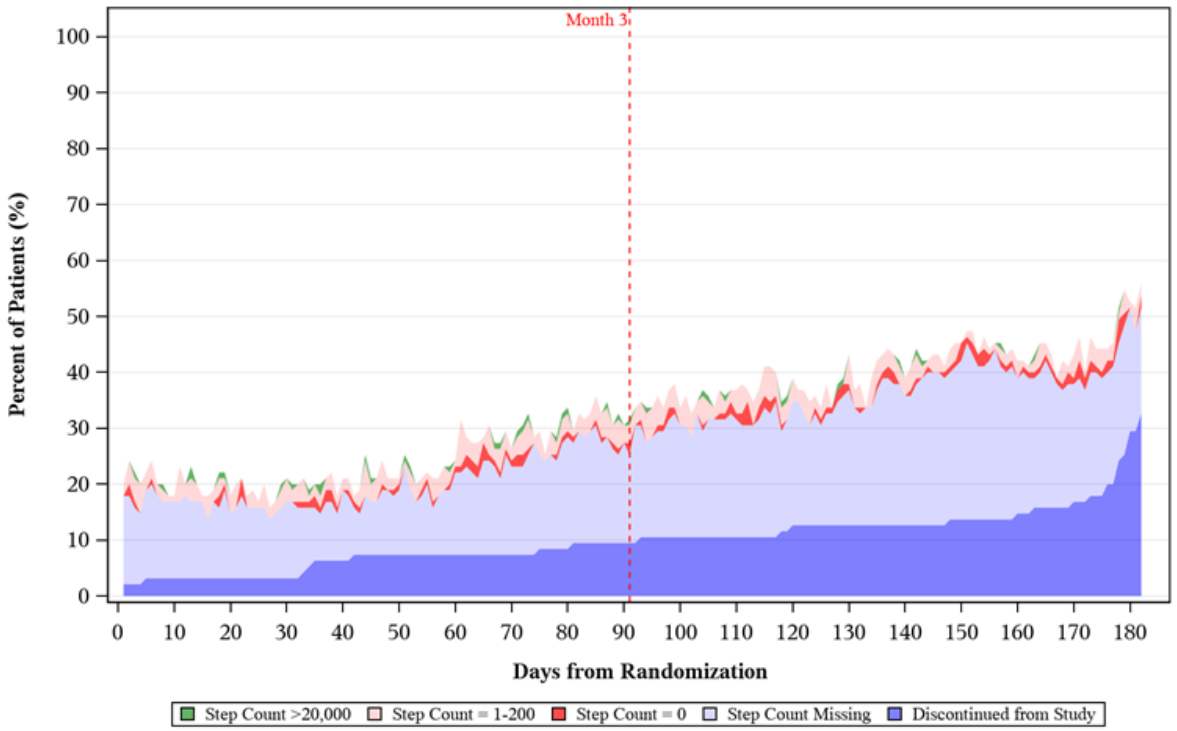
	mHealth (N=92)	Usual Care (N=95)	Total (N=187)
ACE/ARB (n, %)	53 (58%)	56 (60%)	109 (59%)
ARNi (n, %)	24 (26%)	29 (31%)	53 (29%)
Beta-blocker (n, %)	80 (87%)	86 (93%)	166 (90%)
MRA (n, %)	48 (52%)	45 (48%)	93 (50%)
ICD (n, %)	45 (49%)	50 (54%)	95 (51%)
Insulin (n, %)	44 (48%)	55 (59%)	99 (54%)
Biguanidines (n, %)	49 (53%)	38 (41%)	87 (47%)
Sulfonylureas (n, %)	28 (30%)	19 (20%)	47 (25%)
SGLT2i (n, %)	6 (7%)	7 (8%)	13 (7%)

Results: Missing Step Count Data Over Time

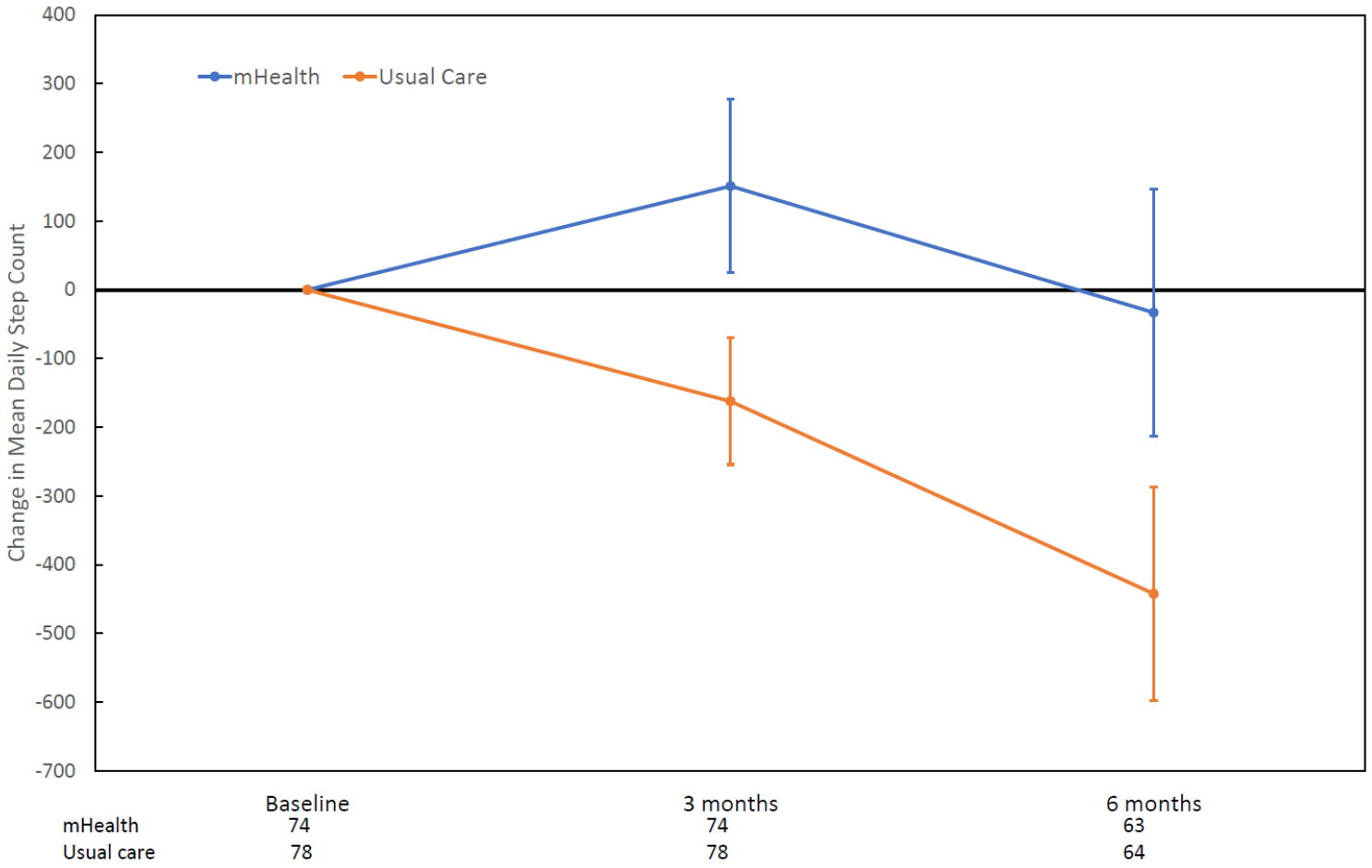
mHealth



Usual Care



Primary Endpoint: Daily Step Counts

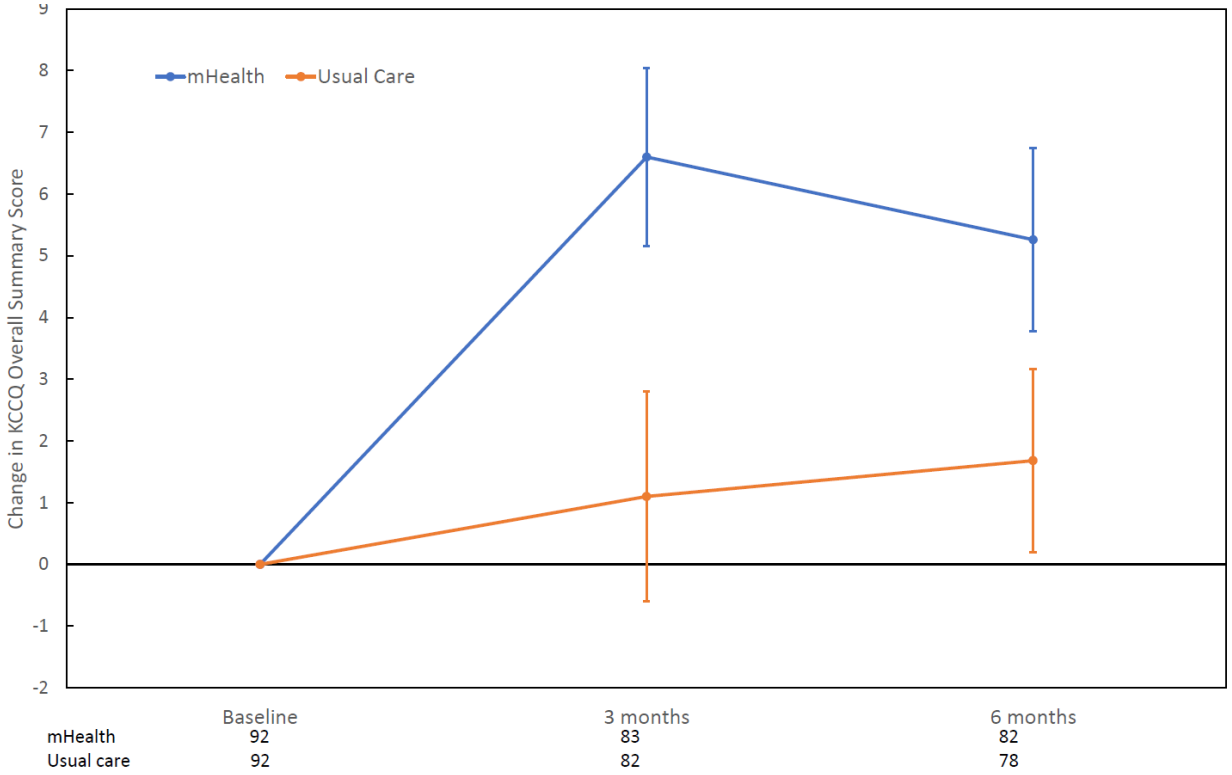


Change in daily step count baseline to month 3:

between group difference of 313 steps/day

95% CI 8, 619
p = 0.04

Quality of Life: KCCQ Overall Summary Score



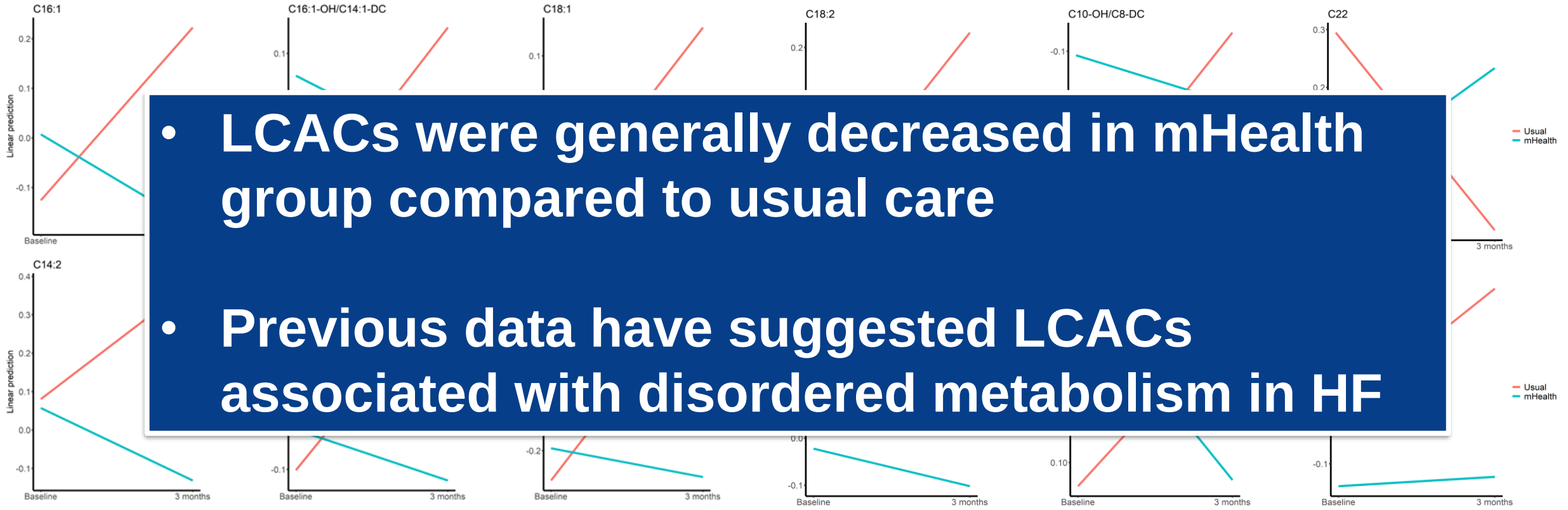
Between group difference 5.5 pts
95% CI 1.4 - 9.6
p = 0.009

Felker, GM et al J Cardiac Failure 2022

Summary of Key Outcome Measures

	mHealth	Usual Care	Treatment difference (95% CI)	P value
Δ mean daily step count (steps/day)	151	-162	313 (8, 619)	0.04
Δ Med. Adherence (Voils)	-0.08	-0.15	0.07 (-0.12, 0.26)	0.47
Δ in KCCQ OSS	6.6	1.1	5.5 (1.4, 9.6)	0.009
Δ mean NT-proBNP (pg/mL)	-41 pg/mL	24 pg/mL	-65 pg/mL	0.20
Δ HbA1c (%)	0.13 %	-0.02 %	0.15 %	0.44

Metabolomic Profiling: Long Chain Acetyl Carnitines (LCACs)



- LCACs were generally decreased in mHealth group compared to usual care
- Previous data have suggested LCACs associated with disordered metabolism in HF

N = 110

Strengths and Limitations

Strengths

- Multi-center
- High enrollment of under-represented populations
- Pragmatic design using consumer facubg technology
- Concordance between step counts, QOL, and metabolic signals

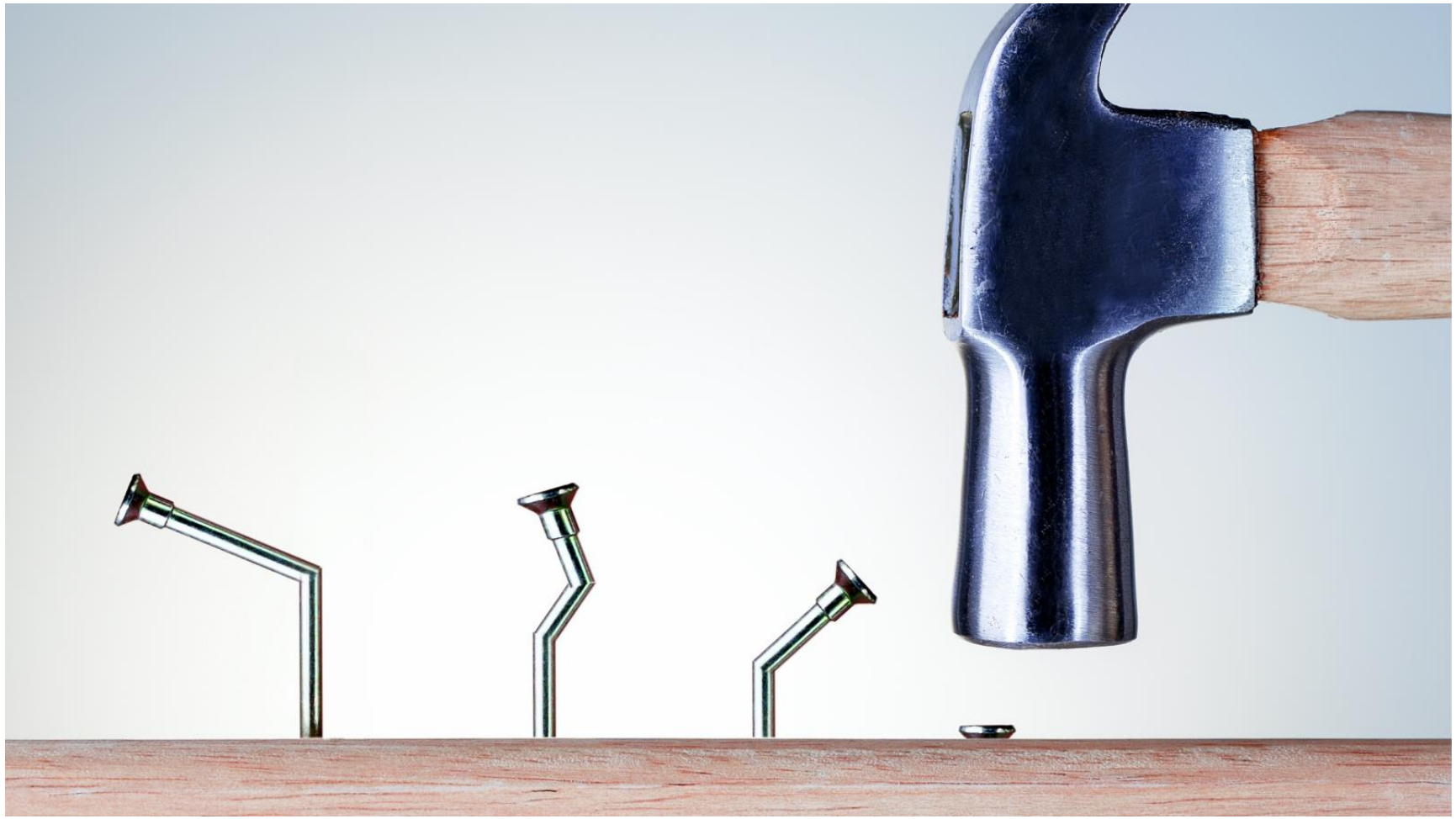
Limitations

- Modest sample size
- Unblinded
- Missing step count data (although generally similar to other mHealth studies)
- Limited follow-up duration

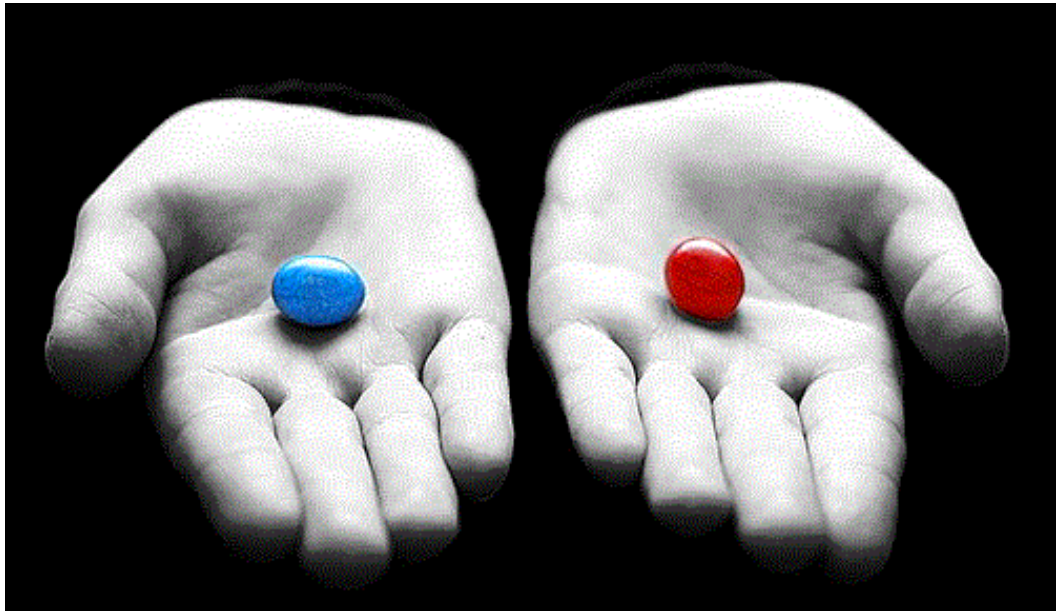
Conclusions

- In a patients with both heart failure and diabetes, a 3-month mHealth intervention significantly improved
  - Daily volitional physical activity as measured by step counts
  - Health related quality of life as measured by KCCQ
  - Metabolomic profiles of peripheral blood
- Treatment effects persisted beyond the active intervention period with some attenuation
- Adherence to medical therapy was not measurably different between arms
- These data have potentially important implications for more effective lifestyle interventions in patients with heart failure and diabetes

Some Lessons Learned



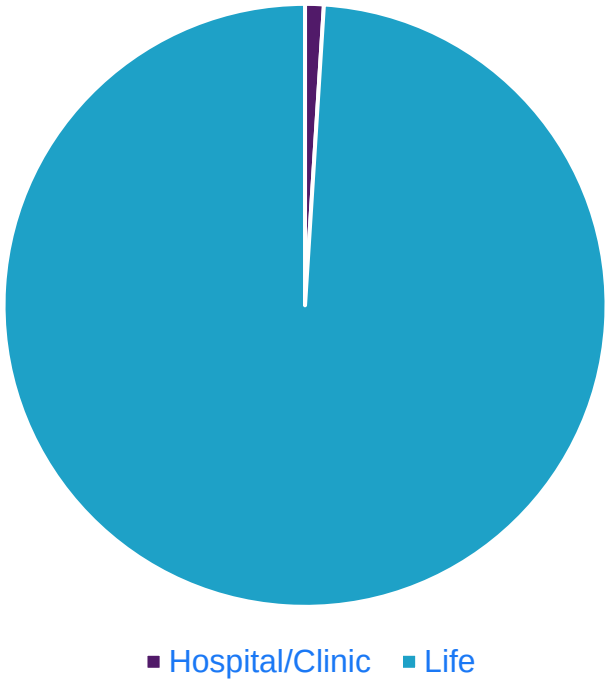
Lifestyle vs. Pharmacologic Interventions



Challenges of Lifestyle and Strategy Trials

- Compliance/engagement challenges lead to varying “dose” of intervention
- Unequal ascertainment of outcomes—patients in control group may be less engaged and more likely to discontinue follow up
- Intervention may interact with human behavior (both participant and clinician) in complex ways
- Lack of blinding leads to strong “placebo” effects

Mortality and Clinical Events are not the whole story!



What is Actigraphy?

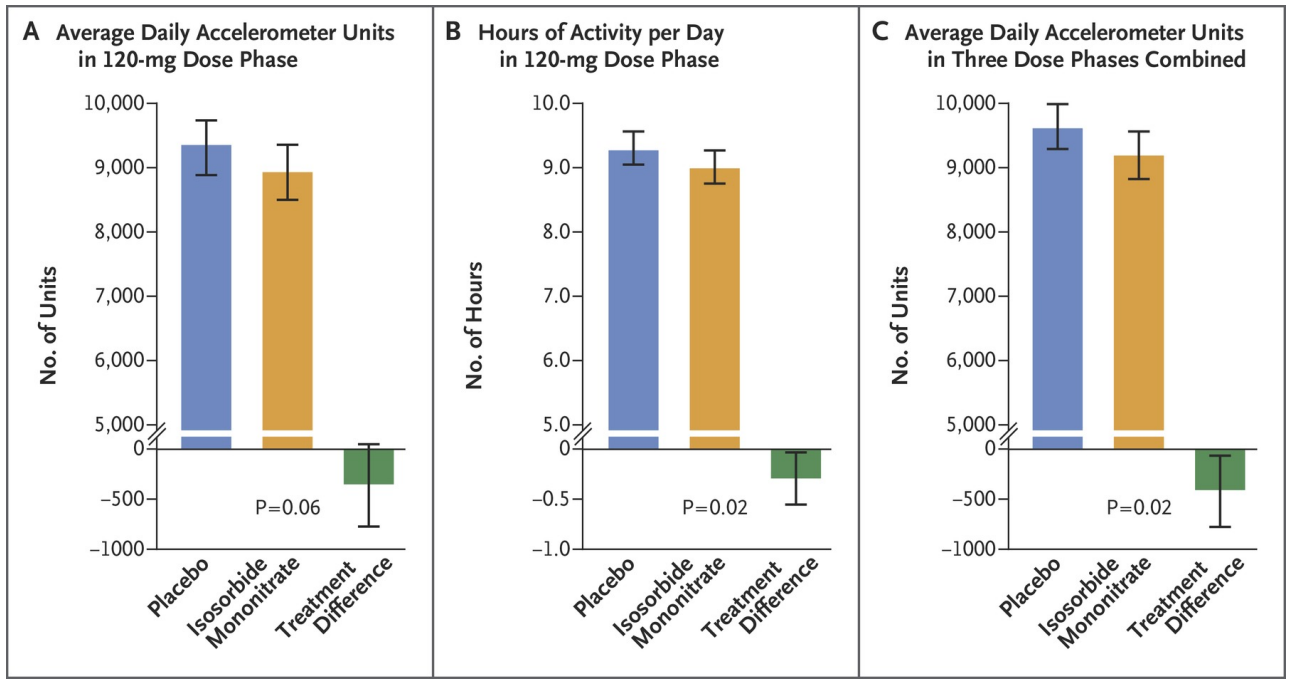
- Assessment of volitional physical activity using wearable technology
- Relies on an accelerometer (at minimum) to measure physical activity
  - Piezoelectic
  - Piezoresistance
  - Capacitive

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Isosorbide Mononitrate in Heart Failure with Preserved Ejection Fraction

Margaret M. Redfield, M.D., Kevin J. Anstrom, Ph.D., James A. Levine, M.D., Gabe A. Koepp, M.H.A., Barry A. Borlaug, M.D., Horng H. Chen, M.D., Martin M. LeWinter, M.D., Susan M. Joseph, M.D., Sanjiv J. Shah, M.D., Marc J. Semigran, M.D., G. Michael Felker, M.D., Robert T. Cole, M.D., Gordon R. Reeves, M.D., Ryan J. Tedford, M.D., W.H. Wilson Tang, M.D., Steven E. McNulty, M.S., Eric J. Velazquez, M.D., Monica R. Shah, M.D., and Eugene Braunwald, M.D., for the NHLBI Heart Failure Clinical Research Network



Functional Capacity in Heart Failure

- 6-minute walk test
- Gait speed
- 2-meter hall walk test
- Cardiopulmonary exercise test
- Actigraphy (**volitional**)

Actigraphy vs. 6MWT vs. CPET

- **Actigraphy**
  - Measures daily volitional activity
  - Influenced by habits, motivation, weather, etc.
  - Missing data common
- **6-minute walk test**
  - Measures sub-maximal activity
  - Influenced by other co-mordibities (arthritis, lung dz, frailty, etc)
  - Doesn’t provide information on what is limiting functional capacity
- **Cardio-pulmonary exercise testing**
  - Measures maximal and sub-maximal activity
  - Quantifies effort
  - Provides insight into source of limitation

Operational Challenges with Actigraphy in TARGET-HFDM

- Commercial Step Counter vs. Research Grade Actigraphy
  - Consumer facing commercial device vs. fit for purpose research device
  - Open ecosystem vs. closed research ecosystem
  - Dependent on different phone app platforms (Apple/Android)
  - User issues with set up/installation/maintenance


Software Update
iOS 12.2 will begin installing in
5 seconds.
Install Now
Later

Commercial Step Tracker Challenges

- October 2015: Planned study with Microsoft Band device/donate by company
- Oct 2016: Microsoft discontinued band device/no further back-end support

Microsoft pulls Band listings from its Store; admits no Band 3 this year

Microsoft officials say there are no plans to introduce a new Microsoft Band fitness device this year and that it has sold through the existing Band 2 inventory.

By Mary Jo Foley for All About Microsoft | October 3, 2016 -- 17:24 GMT (10:24 PDT) | Topic: Mobility

- Nov 2016: Replaced with Withings Go™ device using internal support

- June 2017: Withings sells digital health business to Nokia, rebranded as Nokia Go, changes backend software

mobihealthnews PROVIDER PAYER PHARMA CONSUMER INVESTOR Search

Withings cofounder buys back digital health business from Nokia

By **Laura Lovett** | May 31, 2018

SHARE Share 264

It's official — Eric Carreel, cofounder of French health tech company Withings, has bought back Nokia's digital health division two years after it was sold to the Finnish tech giant. Carreel plans to relaunch the Withings brand by the end of 2018, according to a statement.

"I am delighted to start working again with the brilliant teams that made the brand such a great success," Carreel said in a statement. "We have an exciting challenge ahead of us as we continue to push the boundaries of connected health."

Withings was orginally founded in 2008 and became popular for its smartphone-connected weight scales, blood pressure cuffs, activity trackers, and thermometers.

- Trackers no longer actively sold
- Purchased enough to complete study on ebay and Amazon

Challenges of Retaining “Digital Academic” Investigators

Started study with 5 site PIs all focused on integration of digital technologies into clinical care

Within period of study conduct, 4 had left academic medicine to go into tech industry

Conclusions

- Small, pragmatic studies with modest funding can provide insights into optimizing care for complex conditions like HF and DM
- Optimizing medication adherence remains an unsolved challenge
- Technology may help facilitate improved health behaviors but persistent barriers/gaps/challenges in both research and implementation

Thank you!