Title

Biometric and Psychometric Remote Monitoring and Cardiovascular Risk Biomarkers in Ischemic Heart Disease

Journal

Journal of the American Heart Association, 9(18)

ISSN

2047-9980

Authors

Shufelt, Chrisandra L
Kim, Andy
Joung, Sandy
et al.

Publication Date

2020-09-15

DOI

10.1161/jaha.120.016023

Journal of the American Heart Association

ORIGINAL RESEARCH

Biometric and Psychometric Remote Monitoring and Cardiovascular Risk Biomarkers in Ischemic Heart Disease

Chrisandra L. Shufelt, MD, MS; Andy Kim; Sandy Joung, MS; Lili Barsky, MD; Corey Arnold, PhD; Susan Cheng, MD; Shivani Dhawan, MS; Garth Fuller, MS; William Speier, PhD; Mayra Lopez, MPH; Mitra Mastali, PhD; Kelly Mouapi, PhD; Irene van den Broek, PhD; Janet Wei, MD; Brennan Spiegel, MD, MS*; Jennifer E. Van Eyk, PhD*; C. Noel Bairey-Merz, MD*

BACKGROUND: Patients with stable ischemic heart disease represent a heterogeneous population at variable risk for major adverse cardiac events (MACE). Because MACE typically occurs outside the hospital, we studied whether biometric and psychometric remote patient monitoring are associated with MACE risk biomarkers.

METHODS AND RESULTS: In 198 patients with stable ischemic heart disease (mean age 65±11 years, 60% women), we evaluated baseline measures, including biometric (FitBit 2) and psychometric (acquired via smartphone-administered patient-reported outcomes) remote monitoring, in the PRE-MACE (Prediction, Risk, and Evaluation of Major Adverse Cardiac Events) study. In multivariable adjusted regression analyses, we examined the association of these measures with biomarkers of MACE risk, including NT-proBNP (N-terminal pro-b-type natriuretic peptide), u-hs-cTnI (ultra-high sensitivity cardiac-specific troponin I), and hs-CRP (high-sensitivity C-reactive) protein. Both biometric and psychometric measures were associated with NT-proBNP. Specifically, step count, heart rate, physical activity, global health score, and physical function score were all inversely related, whereas physical limitation score was directly related ($P \leq 0.05$ for all). However, only biometric measures (step count and heart rate) were associated with u-hs-cTnI (inversely related, $P<0.05$), while only the psychometric measures of physical limitation were associated with hs-CRP (directly related, $P \leq 0.05$).

CONCLUSIONS: In stable ischemic heart disease patients, remotely monitored measures were associated with MACE risk biomarkers. Both biometric and psychometric measures were related to NT-proBNP. In contrast, biometric measures were uniquely related to u-hs-cTnI, while psychometric indices were uniquely related to hs-CRP. Further investigation could assess the predictive value of these metrics for MACE in ischemic heart disease.

Key Words: ischemic heart disease ■ major adverse cardiac events ■ precision medicine ■ remote patient monitoring

Patients with stable ischemic heart disease (IHD) represent a heterogeneous population at variable risk for major adverse cardiac events (MACE). While secondary prevention medical therapy with statins, inhibitors of the renin-angiotensin system, and antiplatelet therapies, combined with lifestyle interventions, are effective at reducing MACE, IHD remains the leading cause of mortality in both women and men in this population.[1] Furthermore, adherence to secondary prevention medical regimens decreases over time with a drop from 67% at 1 year to 38% within 5 years.[2]

A precision medicine approach, using multiple timepoints to assess dynamic changes in MACE risk, may offer a more personalized approach to identifying individuals with stable IHD who may require intensified treatment. Biomarkers such as hs-CRP (high sensitivity

Correspondence to: Chrisandra L. Shufelt, MD, MS, 8631 W 3rd St Suite 740, Los Angeles, CA 90048. E-mail: chrisandra.shufelt@cshs.org

Supplementary Materials for this article are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.120.016023

*Dr Spiegel, Dr Van Eyk, and Dr Bairey-Merz are co-senior authors.

For Sources of Funding and Disclosures, see page 8.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- In patients with stable ischemic heart disease, baseline remotely monitored data were associated with serum biomarkers of risk for major adverse cardiac events.
- Biometric measures were uniquely related to serum levels of ultra-high sensitivity cardiac-specific troponin I.
- Self-reported psychometric measures were uniquely related to serum levels of high-sensitivity C-reactive protein, and both biometric and psychometric measures were related to serum levels of N-terminal pro-b-type natriuretic peptide.

What Are the Clinical Implications?

- Remotely monitored biometric and psychometric indices may be of benefit in the prediction of major adverse cardiac events and personalization of treatment, among patients with stable ischemic heart disease.

Nonstandard Abbreviations and Acronyms

hs-CRP	high sensitivity C-reactive protein
IHD	ischemic heart disease
KCCQ	Kansas City Cardiomyopathy Questionnaire
MACE	major adverse cardiac events
NT-proBNP	N-terminal pro-b-type natriuretic peptide
PRE-MACE	Prediction, Risk and Evaluation of Major Adverse Cardiac Events
PROs	patient-reported outcomes
PROMIS	Patient-Reported Outcomes Measurement Information System
RPM	remote patient monitoring
SAQ	Seattle Angina Questionnaire
u-hs-cTnI	ultra-high sensitivity cardiac-specific troponin I

C-reactive protein), NT-pro BNP (N-terminal pro-b-type natriuretic peptide), and u-hs-cTnI (ultra-high sensitivity cardiac-specific troponin I) may provide a better understanding of MACE risk at the individual level. Although higher levels of hs-CRP predict MACE in community population studies, it has large intra-individual variability over time that may not necessarily be attributed to cardiac inflammatory risk.[3] High NT-proBNP and u-hs-cTnI values are predictive of heart failure outcomes, because these biomarkers are directly related to myocardial injury and stress.[4,5]

Because MACE typically occurs outside the confines of a hospital, remote patient monitoring (RPM) using biometric and psychometric indices has the potential to provide a precision medicine approach to monitoring MACE risk among patients with stable IHD. Wearable biosensors that monitor dynamic changes in physiologic and activity parameters, such as heart rate and step counts, may provide clinically useful and timely information about the changing health of patients with stable IHD. In addition to monitoring biometric indices with wearable sensors, smartphones now offer a platform to monitor psychometric indices, such as patient-reported outcomes (PROs), offering another RPM data stream to complement objective physiological and activity metrics. The acceptance and availability of consumer-grade biosensors continues to improve, driven by advancements in technology and reduction in cost.

In this study, we hypothesized that RPM measures, obtained using wearable biosensors and smartphone-based collection of PROs, are associated with the primary outcome of levels of serum cardiovascular MACE risk biomarkers in patients with stable IHD. To our knowledge, this is among the first studies to associate RPM data, including biometric and psychometric parameters, with objective biochemical markers of MACE risk among patients with stable IHD.

METHODS

Recruitment

The PRE-MACE (Prediction, Risk, and Evaluation of Major Adverse Cardiac Events) study is a longitudinal, prospective cohort study design in 200 enrolled patients with stable IHD. Detailed methodology regarding the PRE-MACE study has been previously published.[6] In brief, subjects were recruited from a large, academic hospital-based cardiac rehabilitation center, a tertiary care IHD center and by physician referral. All subjects needed to own or have access to a smartphone or personal computer. Among the 200 subjects with stable IHD, defined as physician-diagnosed, 198 (99%) completed all baseline measures and were included in the current analysis. All subjects provided written informed consent as approved by the Cedars-Sinai institutional review board. The authors declare that all supporting data are available within the article.

Biometric RPM

At the baseline visit, subjects were provided a Fitbit Charge 2 (Fitbit Inc., San Francisco, CA), a wearable device that monitors step counts and heart rate. For

the current analysis, baseline Fitbit data were collected and averaged for the first week. Monitoring was only interrupted by bathing, swimming, or other activities involving water, or while charging the device in its charging cradle.

Psychometric RPM

During the baseline visit, psychometric data were collected using the Patient-Reported Outcomes Measurement Information System (PROMIS), which are validated PROs that measure physical, mental, and social health.[7] The global short form version of PROMIS (PROMIS 4 and 10) was used, which included the following health measures: global health, depression, emotional distress/anxiety, fatigue, physical function, sleep disturbance, and social isolation. Additional disease-targeted PROs included the Kansas City Cardiomyopathy Questionnaire (KCCQ)[8] and the Seattle Angina Questionnaire (SAQ).[9] For both the KCCQ and SAQ, the range of possible subscale scores was 0 to 100, with 100 representing the least burden of symptoms.

Biomarker Monitoring

Cardiovascular MACE risk biomarkers included u-hs-cTnI, NT-proBNP and hs-CRP. On-site serum blood draws for biomarkers occurred at baseline. Biomarkers NT-proBNP and hs-CRP were measured by the Mayo Clinic Immunochemical Core laboratory as previously described.[6] u-hs-cTnI was measured using the Quanterix assay (Quanterix Corporation, Lexington, MA) on the Simoa HD-1 Analyzer, a highly sensitive and fully automated ELISA platform, in duplicate at the Cedars-Sinai Proteomics and Metabolomics Core.[10] Clinically elevated u-hs-cTnI was defined as >5 ng/L,[11] elevated NT-pro-BNP was defined as >300 pg/mL[12] and hs-CRP was elevated when values were >0.3 mg/dL.[13]

Statistical Analysis

For all analyses, we excluded subjects with missing biomarker measures (N=2), leaving N=198 for the main study sample. We used percent frequencies and means±SD to describe categorical and continuous variables, respectively, with the exception of non-normally distributed continuous variables, for which we used medians (25th, 75th percentiles). For non-normally distributed variables, which were all right-skewed, we performed natural log transformation before inclusion in regression analyses. To examine the relation of RPM measures with each of the biomarkers (NT-proBNP, u-hs-cTnI, and hs-CRP), we generated multivariable models of RPM for prediction of log NT-proBNP, log u-hs-cTnI, and log hs-CRP with 95% confidence limits, using multivariable adjusted restricted cubic splines with 3 knots (10th, 50th, and 90th percentiles). All models were adjusted for age, sex, and body mass index (BMI) at baseline. Two-sided *P* values were considered statistically significant after accounting for tests of multiple hypotheses, based on the false discovery rate. We adjusted the *P* values to control the expected proportion of false discoveries (incorrectly rejected null hypotheses). We used the false discovery rate method to account for the multiple hypothesis tests conducted, 1 for each of the biometric and psychometric predictors analyzed in association with each of the 3 biomarker outcomes. This approach was implemented using the Benjamini-Hochberg procedure with a false discovery rate of 0.1. Regression analyses were performed using the *stats* package (v3.5.1) in R v1.1.453 (R foundation, Vienna, Austria) and cubic splines were generated using STATA v13.0 (Stata Corp., College Station, TX). Construction of the model analyses in R and generation of the visual splines in STATA were performed as separate processes. We used R to conduct multivariable adjusted regression analyses as we have done previously for other analyses. We used STATA to generate the spline figures given enhanced functionality of previously established STATA code for visualizing multiple covariate-adjusted splines (ie, a function that is not readily available in R). The modeling approaches for both processes (ie, the covariates selected) were identical for both model analyses in R and splines generation in STATA. All predictors were standardized to a normal distribution with a SD of 1 and a mean of 0. The estimates were also scaled, in order to reflect the change in log of the outcome per 1 SD of each predictor. The estimates reflect the change in log of the outcome per 1 SD difference in each predictor variable.

RESULTS

The group (N=198) mean age was 65±11 years (range 54–76 years) with a mean BMI of 27.2 (range 24.0–31.2), 60% were women, and 28% were non-White. In terms of medical history, 21% of the group had a history of diabetes mellitus and 38% had a history of tobacco abuse. With regard to medication use, 85% of the cohort was taking aspirin, 85% was taking a statin and 65% was taking a β-blocker on enrollment. Overall, 28% of subjects had elevated u-hs-cTnI, 23% had elevated NT-pro-BNP and 28% had elevated hs-CRP. Individual subjects in our study who had elevated levels of all 3 biomarkers (6.0%) were more likely to be men, older in age, and higher in BMI. In the total sample, ln NT-proBNP was strongly correlated with ln u-hs-cTnI (r=0.67, P<0.0001) and only modestly with ln

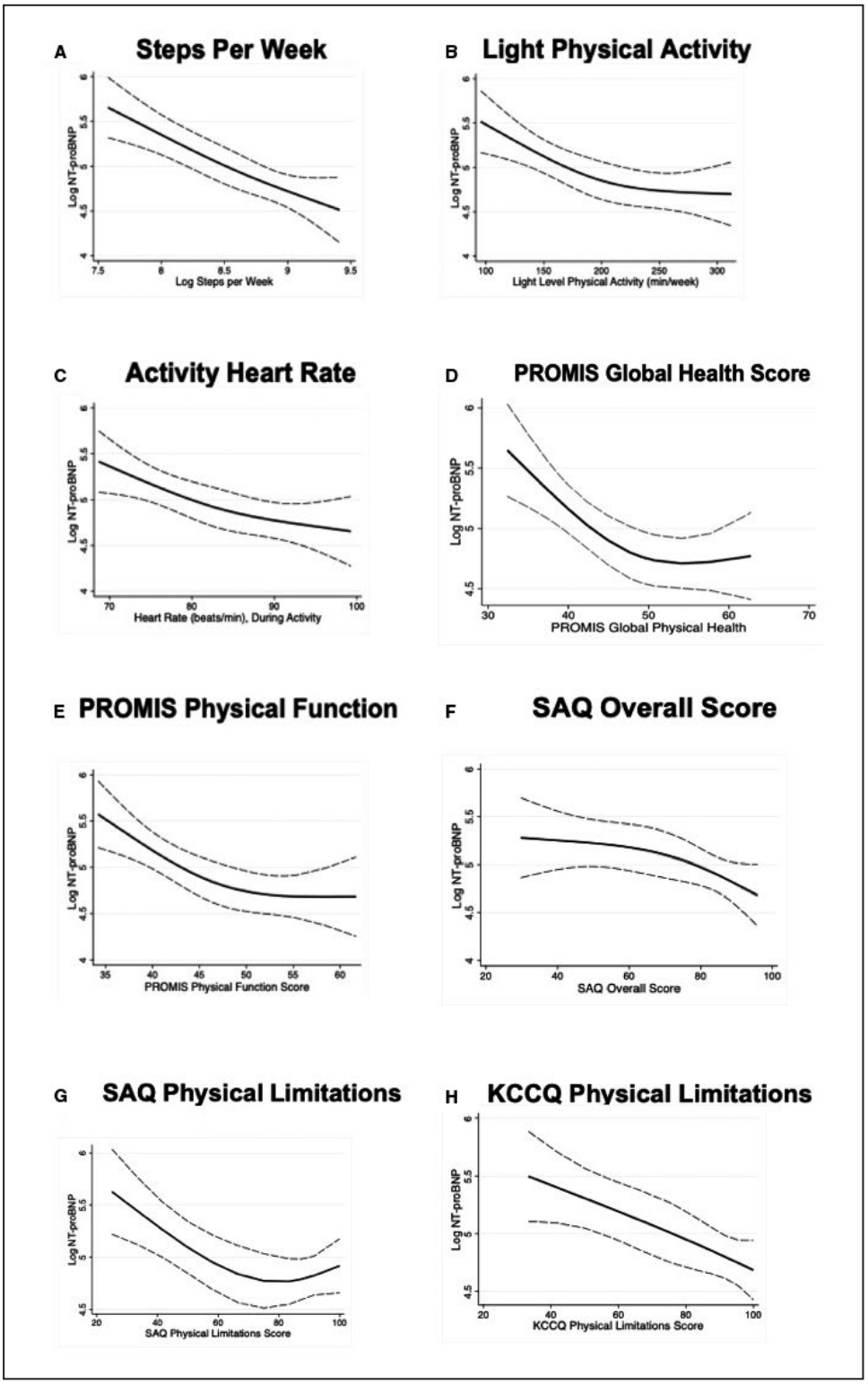

Figure 1. Remote monitoring measures and NT-proBNP.
The multivariable models of steps per week (**A**), light physical activity (**B**), activity heart rate (**C**), Patient-Reported Outcomes Measurement Information System (PROMIS) global health score (**D**), PROMIS physical function score (**E**), Seattle Angina Questionnaire (SAQ) overall score (**F**), SAQ physical limitations score (**G**), and Kansas City Cardiomyopathy Questionnaire (KCCQ) physical limitations score (**H**) for prediction of log NT-proBNP are shown, with 95% confidence limits using multivariable adjusted restricted cubic splines with 3 knots (10th, 50th, and 90th percentiles). All models are adjusted for age, sex, and body mass index. NTproBNP indicates N-terminal pro-b-type natriuretic peptide.

hs-CRP (r=0.17, P=0.016), whereas ln u-hs-cTnI was not significantly correlated with ln hs-CRP (r=0.03, P=0.64). As described in the Methods section, all of these models were adjusted for age, sex, and BMI.

The multivariable models of remote monitoring measures for association with log NT-proBNP, log u-hs-cTnI, and log hs-CRP with 95% confidence limits, using multivariable adjusted linear regression analyses and restricted cubic splines with 3 knots (10th, 50th, and 90th percentiles), are shown in Figures 1 through 3. All models were adjusted for age, sex, and BMI.

Both biometric and psychometric RPM measures were significantly associated with NT-proBNP at baseline (Table 1). There were inverse associations between several biometric measures and NT-proBNP. Specifically, the more steps taken, as well as the greater the amount of light physical activity, the lower the levels of NT-proBNP (Figure 1A and 1B). Additionally, a higher heart rate during activity was associated with a lower NT-proBNP level (Figure 1C). Our evaluation of psychometric RPM measures revealed that higher PROMIS global physical health and physical function scores were associated with lower NT-proBNP (Figure 1D and 1E). Higher SAQ-7 scores, an indication of better overall function, were associated with lower NT-proBNP (Figure 1F). Similarly, the physical limitation subscales for both the SAQ and the KCCQ were inversely related to NT-proBNP (Figure 1G and 1H), indicating that less physical limitation was associated with lower NT-proBNP.

Certain biometric RPM measures were significantly associated with u-hs-cTnI at baseline (Table 1). In particular, a greater number of steps was associated with lower u-hs-cTnI at baseline (Figure 2A). Similarly, higher heart rate, both at rest and with activity at baseline, was significantly associated with lower u-hs-cTnI at baseline (Figure 2B and 2C), a finding that may have possibly been because of the high prevalence of β-blocker use. Interestingly, none of the psychometric RPM measures were associated with u-hs-cTnI at baseline. Conversely, psychometric RPM measures were significantly associated with hs-CRP at baseline, including SAQ and KCCQ (Figure 3A and 3B, Table 1), while none of the biometric RPM measures were related to hs-CRP. Of note, there were no significant age or sex interactions for any biomarker associations examined (data not shown). A summary of the serum biomarker levels, biometric and psychometric data for the cohort is provided in Table S1. The R2 values for each of the tests are displayed in Table S2.

In multivariable regression analyses, the only relationships found to be significantly nonlinear were between ln NT-proBNP and PROMIS Global Physical Health (P=0.028), which appeared to reveal an inflection point around 50, and between ln NT-proBNP and SAQ Physical Limitation score (P=0.041), which appeared to reveal an inflection point around 80 (Figure 1D and 1G, respectively). The corresponding beta coefficients above and below this threshold are reported in Table S3.

DISCUSSION

Our results demonstrate that among stable IHD subjects, baseline biometric and psychometric RPM are associated with cardiovascular MACE risk biomarkers. This is among the first studies, in IHD or otherwise, to evaluate the relationship between RPM parameters and clinically relevant biochemical laboratory markers. Both biometric and psychometric RPM measures were significantly associated with NT-proBNP, a marker of cardiac volume status. While only certain biometric RPM measures were related to u-hs-cTnI, a marker of cardiac damage, only certain psychometric RPM measures were significantly associated with hs-CRP, a marker of cardiac inflammation. These initial findings may have clinical implications. Further investigation to evaluate RPMs for prediction of specific MACE as well as stratify personalized risk in patients with stable IHD is needed.

We found that both step count per week and heart rate had an inverse relationship with NT-proBNP and u-hs-cTnI. These findings support the protective effects of regular exercise for IHD or reflect IHD-related reduced cardiovascular reserve and/or symptom burden that limits physical activity in this cross-sectional analysis.[14] These results may be useful, because step counts are readily accessible on consumer-facing products, such as the Fitbit Charge 2 used in our PRE-MACE study.

To date, research in the area of biometric RPM has shown mixed results with respect to benefit and varies according to the specific cardiovascular population. In patients with heart failure, use of biometric RPM via smartphone and video monitors did not improve heart failure mortality or healthcare utilization.[15] Additionally, in patients after stroke, biometric RPM with ankle accelerometers did not increase time spent walking per day.[16] Other studies have examined biometric RPM in patients with implantable pacemakers or defibrillators. In a randomized clinical trial, wireless RPM providing real-time alerts compared with home monitoring only was found to be safe and effective for reducing hospital visits by 79%.[17] Furthermore, a meta-analysis of 3 studies in patients with defibrillators found the RPM-related absolute total mortality risk was lower by ≈2%.[18] Our data suggest that biometric RPM in stable subjects with IHD are associated with cardiovascular MACE risk biomarkers; these results may be of use in MACE risk prediction and personalized treatment.

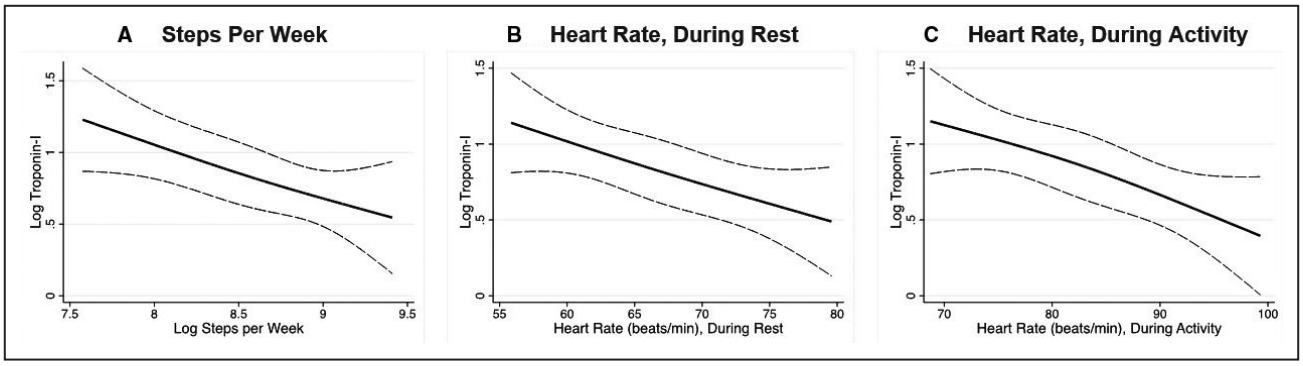

Figure 2. Remote monitoring measures and u-hs-cTnI.
The multivariable models of steps per week (**A**), heart rate during rest (**B**), and heart rate during activity (**C**) for prediction of log troponin I are shown, with 95% confidence limits using multivariable adjusted restricted cubic splines with 3 knots (10th, 50th, and 90th percentiles). All models are adjusted for age, sex, and body mass index. u-hs-cTnI indicates ultra-high sensitivity cardiac-specific troponin I.

The measure of cardiac injury used in this study, u-hs-cTnI, revealed an inverse relationship with resting heart rate. Lower resting heart rate in patients with stable IHD was likely a reflection of beta blockade and/or more limited cardiovascular reserve in our population. Higher heart rates during physical activity, however, had predicted lower levels of u-hs-cTnI, suggesting that achievement of higher heart rates may be a surrogate measure of cardiovascular health.

With regard to psychometric RPM measures, lower global health and physical function scores were associated with higher NT-proBNP, which is clinically associated with higher cardiac volume status. This relationship appears to offer additional insights into both biometric and psychometric RPM domains, because volume overload contributes to reduced physical function because of symptom burden and limited cardiovascular reserve. Both NT-proBNP and hs-CRP exhibited direct relations to SAQ and KCCQ physical limitation subscales. This indicates that higher levels of inflammation and volume status are associated with self-reported physical limitation.

Perhaps as compelling as the relationships we identified were the negative results in this study. A moderate or vigorous level of physical activity, measured as minutes per week, was not associated with any of the cardiovascular MACE risk biomarkers. This appears to support current analyses[19] and guidelines suggesting that less physical activity intensity is needed than previously thought to obtain benefit.[20] Further, PROs for depression, anxiety, fatigue, sleep disturbance or KCCQ quality of life subscale related to any biomarker. Previous studies have found that both depression and anxiety are associated with elevated hs-CRP in community populations.[21,22] Elevated BNP, the precursor hormone to the NT-proBNP that we are analyzing here, has been associated with sleep apnea and sleep disturbances, as well as KCCQ health status.[23,24] Our findings are not consistent with this prior work, and may be underpowered or specific to our stable IHD cohort.

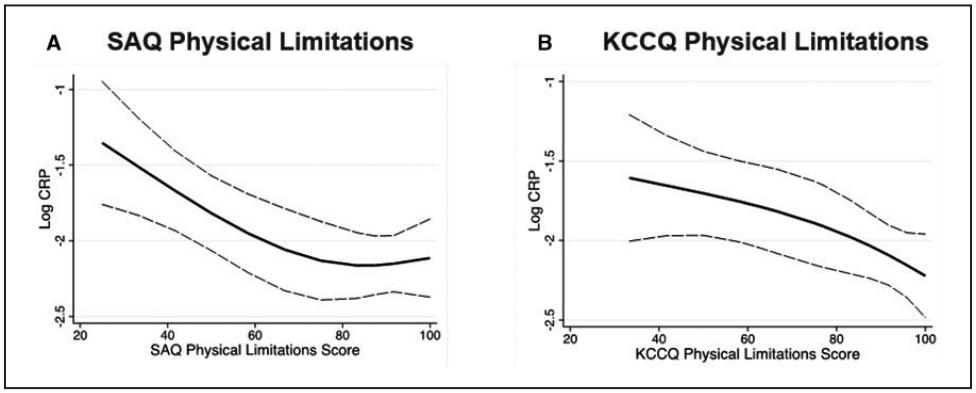

Figure 3. Remote monitoring measures and hs-CRP.
The multivariable models of Seattle Angina Questionnaire (SAQ) physical limitations score (**A**) and Kansas City Cardiomyopathy Questionnaire (KCCQ) physical limitations score (**B**) for prediction of log hs-CRP are shown, with 95% confidence limits using multivariable adjusted restricted cubic splines with 3 knots (10th, 50th, and 90th percentiles). All models are adjusted for age, sex, and body mass index. hs-CRP indicates high sensitivity C-reactive protein.

Table. Multivariable-Adjusted Models of Remote Patient Monitoring Measures With u-hs-cTnI, NT-proBNP, and hs-CRP

Predictors	Outcome: Ln NT-proBNP		Outcome: ln u-hs-cTnI		Outcome: Ln hs-CRP	
	Est. (SE)	*P* Value	Est. (SE)	*P* Value	Est. (SE)	*P* Value
Biometric RPM						
Steps per wk	−0.33 (0.07)	< 0.001*	−0.24 (0.08)	0.008*	−0.09 (0.08)	0.4
Physical activity, min/wk						
Light level	−0.24 (0.07)	0.004*	−0.11 (0.07)	0.25	−0.09 (0.07)	0.38
Moderate/vigorous level	−0.16 (0.08)	0.11	−0.17 (0.08)	0.1	−0.10 (0.09)	0.4
Heart rate, beats/min						
During rest	−0.14 (0.07)	0.1	−0.18 (0.07)	0.03*	0.01 (0.07)	0.92
During activity	−0.21 (0.07)	0.01*	−0.23 (0.07)	0.005*	−0.01 (0.07)	0.9
Psychometric RPM						
PROMIS scores						
Global physical health	−0.26 (0.07)	0.002*	−0.07 (0.07)	0.5	−0.11 (0.07)	0.2
Physical function	−0.27 (0.07)	0.002*	−0.12 (0.07)	0.18	−0.15 (0.07)	0.09
Depression	0.07 (0.07)	0.5	−0.06 (0.07)	0.57	0.04 (0.07)	0.7
Anxiety	0.02 (0.07)	0.88	−0.03 (0.07)	0.8	−0.06 (0.07)	0.53
Fatigue	0.14 (0.07)	0.1	−0.04 (0.07)	0.68	0.09 (0.07)	0.33
Sleep disturbance	0.05 (0.07)	0.65	−0.02 (0.07)	0.88	−0.04 (0.07)	0.68
SAQ scores						
Overall	−0.18 (0.07)	0.05*	−0.02 (0.07)	0.89	−0.08 (0.07)	0.4
Physical limitations	−0.23 (0.07)	0.007*	−0.09 (0.07)	0.38	−0.18 (0.07)	0.02*
KCCQ scores						
Quality of life	−0.16 (0.07)	0.007	−0.06 (0.07)	0.57	0.02 (0.07)	0.87
Physical limitations	−0.23 (0.07)	0.007*	−0.09 (0.07)	0.33	−0.19 (0.07)	0.02*

hs-CRP indicates high sensitivity C-reactive protein; KCCQ, Kansas City Cardiomyopathy Questionnaire; NT-proBNP, N-terminal pro-b-type natriuretic peptide; PROMIS, Patient-Reported Outcomes Measurement Information System; RPM, remote patient monitoring; SAQ, Seattle Angina Questionnaire; and u-hs-cTnI, ultra-high sensitivity cardiac-specific troponin I.

*The findings that are statistically significant ($P \leq 0.05$).

One major strength of the study included a high compliance rate, with <1% with missing baseline data and only 2 subjects dropping out. We have previously reported compliance rates with the wearable sensor in this protocol and found 90% median use in our stable IHD population.[25] Our study also demonstrated feasibility and validation of RPM using several concurrent platforms. The limitations of our study include the observational design that precluded causal inference. There may have also been behavioral influences, such as the awareness of being monitored, and the fact that study subjects already owned a computer or smart phone device, which could have accounted for the higher adherence. Many of our subjects were recruited from a cardiac rehabilitation program and demonstrated a high medication compliance rate of 85%, suggesting above average adherence,[26] which may not reflect a more general stable IHD population.

CONCLUSIONS

In patients with stable IHD, baseline RPMs were associated with cardiovascular MACE risk serum biomarkers. In particular, both biometric and psychometric RPM measures were related to the universal marker of cardiac volume status, NT-proBNP. In contrast, the biometric measures were uniquely associated with u-hs-cTnI, while psychometric indices were uniquely associated with hs-CRP. These findings may have clinical implications and support clinician reinforcement of beneficial health habits among patients. Further investigation is indicated to evaluate RPMs for prediction of change in cardiovascular MACE risk biomarkers, as well as MACE to understand the value of RPM for precision medicine in IHD. Future studies should evaluate these relationships in a larger cohort of patients with stable IHD, with more diverse patterns of adherence and socioeconomic status. Future longitudinal analyses will also assess for prediction of MACE.

ARTICLE INFORMATION

Received January 22, 2020; accepted July 13, 2020.

Affiliations

From the Barbra Streisand Women's Heart Center, Smidt Heart Institute, Cedars-Sinai Medical Center, Los Angeles, CA (C.L.S., A.K., S.J., L.B.,

S.C., S.D., M.M., K.M., I.v.d.B., J.W., J.E.V.E., C.N.B.-M.); Medical Imaging and Informatics Group, University of California, Los Angeles, CA (C.A., W.S., B.S.); Cedars-Sinai Center for Outcomes Research and Education (CS-CORE), Los Angeles, CA (G.F., M.L.); and Advanced Clinical Biosystems Research Institute, Cedars-Sinai Smidt Heart Institute, Cedars-Sinai Medical Center, Los Angeles, CA (M.M., K.M., I.v.d.B., J.E.V.E.).

Acknowledgments

We would like to acknowledge the support by in-kind contribution of our industry partners AliveCor, Beckman Coulter, Cambridge Isotope Laboratories, Neoteryx, SCIEX, Tasso, and Thermo Fisher Scientific.

Sources of Funding

This work was supported by the California State Government: California Initiative to Advance Precision Medicine, San Francisco, California, Cedars-Sinai Precision Health Grants; the National Center for Advancing Translational Sciences Grant UL1TR000124 and UL1TR000064; The Advanced Clinical Biosystems Research Institute, Cedars-Sinai Smidt Heart Institute, Cedars-Sinai Medical Center, Los Angeles, California; The Barbra Streisand Women's Cardiovascular Research and Education Program; Cedars-Sinai Medical Center, Los Angeles, California; Cedars-Sinai Center for Outcomes Research and Education (CS-CORE), Cedars-Sinai Medical Center, Los Angeles, California; The Division of Informatics, Cedars-Sinai Medical Center, Los Angeles, California; the Erika J. Glazer Women's Heart Health Project, Cedars-Sinai Medical Center, Los Angeles, California; The Linda Joy Pollin Women's Heart Health Program, Cedars-Sinai Medical Center, Los Angeles, California; The Sheri and Marc Rapaport Fund for Digital Health Sciences and Precision Health, Cedars-Sinai Medical Center, Los Angeles, California; The Society for Women's Health Research (SWHR), Washington, DC; The National Heart, Lung, and Blood Institute RO1HL111362, R01-HL134168, R01HL131532, R01HL143227, R01HL142983, R01HL141773, R56HL135425, K23HL127262, K23HL125941, and T32HL116273.

Disclosures

Dr Bairey Merz would like to report funding from iRhythm, Abbott Diagnostics, and Sanofi. The remaining authors have no disclosures to report.

Supplementary Materials

Tables S1–S3

REFERENCES

1. Nowbar AN, Gitto M, Howard JP, Francis DP, Al-Lamee R. Mortality from ischemic heart disease. *Circ Cardiovasc Qual Outcomes*. 2019;12:e005375. DOI: 10.1161/CIRCOUTCOMES.118.005375.
2. Pinho-Gomes A-C, Azevedo L, Ahn J-M, Park S-J, Hamza TH, Farkouh ME, Serruys PW, Milojevic M, Kappetein AP, Stone GW, et al. Compliance with guideline-directed medical therapy in contemporary coronary revascularization trials. *J Am Coll Cardiol*. 2018;71:591–602.
3. Bogaty P, Dagenais GR, Joseph L, Boyer L, Leblanc A, Bélisle P, Brophy JM. Time variability of C-reactive protein: implications for clinical risk stratification. *PLoS One*. 2013;8:e60759.
4. Braunwald E. Biomarkers in heart failure. *N Engl J Med*. 2008;358:2148–2159.
5. Kociol RD, Pang PS, Gheorghiade M, Fonarow GC, O'Connor CM, Felker GM. Troponin elevation in heart failure: prevalence, mechanisms, and clinical implications. *J Am Coll Cardiol*. 2010;56:1071–1078.
6. Shufelt C, Dzubur E, Joung S, Fuller G, Mouapi KN, Van Den Broek I, Lopez M, Dhawan S, Arnold CW, Speier W, et al. A protocol integrating remote patient monitoring patient reported outcomes and cardiovascular biomarkers. *NPJ Digit Med*. 2019;2:84.
7. Bevans M, Ross A, Cella D. Patient-Reported Outcomes Measurement Information System (PROMIS): efficient, standardized tools to measure self-reported health and quality of life. *Nurs Outlook*. 2014;62:339–345.
8. Green CP, Porter CB, Bresnahan DR, Spertus JA. Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure. *J Am Coll Cardiol*. 2000;35:1245–1255.
9. Spertus JA, Winder JA, Dewhurst TA, Deyo RA, Prodzinski J, McDonnell M, Fihn SD. Development and evaluation of the Seattle Angina Questionnaire: a new functional status measure for coronary artery disease. *J Am Coll Cardiol*. 1995;25:333.
10. Jarolim P, Patel PP, Conrad MJ, Chang L, Melenovsky V, Wilson DH. Fully automated ultrasensitive digital immunoassay for cardiac troponin I based on single molecule array technology. *Clin Chem*. 2015;61:1283–1291.
11. Fox WR, Diercks DB. Troponin assay use in the emergency department for management of patients with potential acute coronary syndrome: current use and future directions. *Clin Exp Emerg Med*. 2016;3:1–8.
12. Bettencourt PM. Clinical usefulness of B-type natriuretic peptide measurement: present and future perspectives. *Heart*. 2005;91:1489–1494.
13. Mok CC, Birmingham DJ, Ho LY, Hebert LA, Rovin BH. High-sensitivity C-reactive protein, disease activity, and cardiovascular risk factors in systemic lupus erythematosus. *Arthritis Care Res (Hoboken)*. 2013;65:441–447.
14. Bordbar S, Bigi MAB, Aslani A, Rahimi E, Ahmadi N. Effect of endurance and strength exercise on release of brain natriuretic peptide. *J Cardiovasc Dis Res*. 2012;3:22–25.
15. Bashi N, Karunanithi M, Fatehi F, Ding H, Walters D. Remote monitoring of patients with heart failure: an overview of systematic reviews. *J Med Internet Res*. 2017;19:e18.
16. Dorsch AK, Thomas S, Xu X, Kaiser W, Dobkin BH;Investigators S. SIRRACT: an international randomized clinical trial of activity feedback during inpatient stroke rehabilitation enabled by wireless sensing. *Neurorehabil Neural Repair*. 2015;29:407–415.
17. García-Fernández FJ, Osca Asensi J, Romero R, Fernández Lozano I, Larrazabal JM, Martínez Ferrer J, Ortiz R, Pombo M, Tornés FJ, Moradi KM. Safety and efficiency of a common and simplified protocol for pacemaker and defibrillator surveillance based on remote monitoring only: a long-term randomized trial (RM-ALONE). *Eur Heart J*. 2019;40:1837–1846.
18. Hindricks G, Varma N, Kacet S, Lewalter T, Søgaard P, Guédon-Moreau L, Proff J, Gerds TA, Anker SD, Torp-Pedersen C. Daily remote monitoring of implantable cardioverter-defibrillators: insights from the pooled patient-level data from three randomized controlled trials (IN-TIME, ECOST, TRUST). *Eur Heart J*. 2017;38:1749–1755.
19. Piercy KL, Troiano RP. Physical activity guidelines for Americans from the US Department of Health and Human Services. *Circ Cardiovasc Qual Outcomes*. 2018;11:e005263. DOI: 10.1161/CIRCOUTCOMES.118.005263.
20. Piercy KL, Troiano RP, Ballard RM, Carlson SA, Fulton JE, Galuska DA, George SM, Olson RD. The physical activity guidelines for Americans. *JAMA*. 2018;320:2020–2028.
21. Tayefi M, Shafiee M, Kazemi-Bajestani SMR, Esmaeili H, Darroudi S, Khakpouri S, Mohammadi M, Ghaneifar Z, Azarpajouh MR, Moohebati M, et al. Depression and anxiety both associate with serum level of hs-CRP: a gender-stratified analysis in a population-based study. *Psychoneuroendocrinology*. 2017;81:63–69.
22. Deverts DJ, Cohen S, DiLillo VG, Lewis CE, Kiefe C, Whooley M, Matthews KA. Depressive symptoms, race, and circulating C-reactive protein: the Coronary Artery Risk Development in Young Adults (CARDIA) study. *Psychosom Med*. 2010;72:734–741.
23. Ljunggren M, Lindahl B, Theorell-Haglöw J, Lindberg E. Association between obstructive sleep apnea and elevated levels of type B natriuretic peptide in a community-based sample of women. *Sleep*. 2012;35:1521–1527.
24. Luther SA, McCullough PA, Havranek EP, Rumsfeld JS, Jones PG, Heidenreich PA, Peterson ED, Rathore SS, Krumholz HM, Weintraub WS, et al. The relationship between B-type natriuretic peptide and health status in patients with heart failure. *J Card Fail*. 2005;11:414–421.
25. Speier W, Dzubur E, Zide M, Shufelt C, Joung S, Van Eyk JE, Bairey Merz CN, Lopez M, Spiegel B, Arnold C. Evaluating utility and compliance in a patient-based eHealth study using continuous-time heart rate and activity trackers. *J Am Med Inform Assoc*. 2018;25:1386–1391.
26. Korzeniowska-Kubacka I, Bilińska M, Piotrowska D, Wolszakiewicz J, Piotrowicz R. Impact of exercise-based cardiac rehabilitation on attitude to the therapy, aims in life and professional work in patients after myocardial infarction. *Med Pr*. 2019;70:1–7.

SUPPLEMENTAL MATERIAL

Table S1. Cardiovascular Risk Biomarker Levels, Biometric and Psychometric Values.

Cardiovascular Risk Biomarkers	
NT-proBNP (pgram/ml)	126.5 (66, 286.5)
u-hs-cTnI (ng/L)	1.94 (0.98, 5.23)
hs-CRP (mg/dL)]	0.12 (0.05, 0.33)
Biometric RPM	
Steps per week	5726 (4005, 8293)
Physical activity, min/week	
Light level	197 (151, 250)
Moderate/vigorous level	37 (28, 53)
Heart rate, beats/min	
During rest	67±8
During activity	83±10
Psychometric RPM	
PROMIS scores	
Global physical health	47±9
Physical function	45 (40,53)
Depression	49 (41,56)
Anxiety	53 (47,58)
Fatigue	51 (46,57)
Sleep disturbance	51 (44,56)
SAQ-7 scores	
Overall	77 (63,89)
Physical limitation	83 (58,100)
KCCQ scores	
Quality of life	75 (50, 88)
Physical limitation	83 (67, 100)

Values are % frequency for categorical variables, mean±SD for normally distributed continuous variables, median (IQR) for MACE surrogate biomarkers, median (25^{th}, 75^{th} percentile) for non-normally distributed continuous variables. PROMIS, Patient-Reported Outcomes Measurement Information System; SAQ-7, Seattle Angina Questionnaire; KCCQ, Kansas City Cardiomyopathy Questionnaire

Table S2. R2 Values for Each Test.

Term	NT-proBNP_ adjusted_R2	NT-proBNP_ R2	u-hs-cTnI_ adjusted_R2	u-hs-cTnI_ R2	hs-CRP_ adjusted_R2	hs-CRP_R2
Scale(log_steps_week)	0.17	0.19	0.19	0.21	0.16	0.18
Scale(log_ light_physical_activity_week)	0.13	0.15	0.16	0.18	0.16	0.18
Scale(log_moderate_physical_ activity_week)	0.15	0.18	0.28	0.3	0.17	0.2
Scale(resting_heart_rate_week)	0.09	0.11	0.18	0.2	0.17	0.18
Scale(active_heart_rate_week)	0.13	0.14	0.2	0.22	0.16	0.18
Scale(PROMIS_physical_health)	0.13	0.15	0.15	0.17	0.18	0.2
Scale(PROMIS_physical_function)	0.13	0.15	0.17	0.19	0.19	0.2
Scale(PROMIS_depression)	0.07	0.09	0.15	0.17	0.17	0.19
Scale(PROMIS_anxiety)	0.07	0.09	0.15	0.17	0.17	0.19
Scale(PROMIS_fatigue)	0.09	0.11	0.15	0.17	0.18	0.19
Scale(PROMIS_sleep_disturbance)	0.07	0.09	0.15	0.17	0.17	0.19
Scale(SAQ_overall)	0.1	0.12	0.14	0.16	0.17	0.19

Scale(SAQ_physical_limitations)	0.11	0.13	0.15	0.17	0.2	0.22
Scale(KCCQ_quality_of_life)	0.1	0.12	0.15	0.16	0.17	0.19
Scale(KCCQ_physical_limitations)	0.12	0.14	0.15	0.17	0.17	0.18

Table S3. Associations of self-reported outcomes demonstrating non-linear associations with NT-proBNP.

	Outcome: ln NT-proBNP	
	Est. (SE)	**P value**
PROMIS Global Physical Health, for score overall	-0.26 (0.07)	0.002
PROMIS Global Physical Health, if score <50	-0.40 (0.12)	0.001
PROMIS Global Physical Health, if score >=50	0.001 (0.18)	0.99
SAQ Physical Limitation, for score overall	-0.23 (0.07)	0.007
SAQ Physical Limitation, if score <80	-0.44 (0.14)	0.001
SAQ Physical Limitation, if score >=80	0.22 (0.23)	0.35