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Authors

Riley, Elise D
Kazi, Dhruv S
Coffin, Phillip O
et al.

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Impact of multiple substance use on circulating ST2, a biomarker of adverse cardiac remodeling, in women

Elise D. Riley, PhD[a,*], **Dhruv S. Kazi, MD, MSc, MS**[b,j], **Phillip O. Coffin, MD**[a,c], **Eric Vittinghoff, PhD**[d], **Amanda N. Wade, MPH, BSN, RN**[e], **Tommaso C. Bulfone, MS**[f], **Kara L. Lynch, PhD**[g], **Zahra Atai, MHS, BSN**[h], **Alan H.B. Wu, PhD**[i]

[a]University of California, San Francisco, School of Medicine, Department of Medicine, Division of HIV, Infectious Diseases and Global Medicine, San Francisco, California, USA.

[b]Richard A. and Susan F. Smith Center for Outcomes Research in Cardiology, Beth Israel Deaconess Medical Center, Boston, MA and Harvard Medical School, Boston, Massachusetts, USA

[c]San Francisco Department of Public Health, San Francisco, California, USA

[d]University of California, San Francisco, School of Medicine, Department of Epidemiology and Biostatistics, San Francisco, California, USA

[e]University of California, San Francisco, School of Medicine, Department of Medicine, Division of HIV, Infectious Diseases and Global Medicine, San Francisco, California, USA.

[f]University of California, San Francisco, School of Medicine, Department of Medicine, Division of HIV, Infectious Diseases and Global Medicine, San Francisco, California, USA.

[g]University of California, San Francisco, School of Medicine, Department of Laboratory Medicine, San Francisco, California, USA.

[h]University of California, San Francisco, School of Medicine, Department of Medicine, Division of HIV, Infectious Diseases and Global Medicine, San Francisco, California, USA.

[i]University of California, San Francisco, School of Medicine, Department of Laboratory Medicine, San Francisco, California, USA.

[j]Department of Medicine, Harvard Medical School, Boston, Massachusetts, USA.

Abstract

CONTEXT: Cardiovascular disease (CVD) and heart failure (HF) are major causes of mortality in low-income populations and differ by sex. Risk assessment that incorporates cardiac biomarkers is common. However, research evaluating the utility of biomarkers rarely includes controlled substances, which may influence biomarker levels and thus influence CVD risk assessment.

[*]Corresponding author: Elise D. Riley, 1001 Potrero Ave., UCSF Mailbox 0874, San Francisco, CA 94143-0874, U.S.A.; Tel: +1 (415) 206-4983; elise.riley@ucsf.edu.

Disclosure Statement

The authors report there are no competing interests to declare.

MATERIALS AND METHODS: We identified the effects of multiple substances on soluble "suppression of tumorigenicity 2" (sST2), a biomarker of adverse cardiac remodeling, in 245 low-income women. Adjusting for CVD risk factors, we examined associations between substance use and sST2 over six monthly visits.

RESULTS: Median age was 53 years and 74% of participants were ethnic minority women. An sST2 level>35 ng/mL (suggesting cardiac remodeling) during ≥1 study visit was observed in 44% of participants. In adjusted analysis, higher sST2 levels were significantly and positively associated with the presence of cocaine (Adjusted Linear Effect [ALE]:1.10; 95% CI:1.03-1.19), alcohol (ALE:1.10; 95% CI:1.04-1.17), heroin (ALE:1.25; 95% CI:1.10-1.43), and the interaction between heroin and fentanyl use.

CONCLUSION: Results suggest that the use of multiple substances influences the level of sST2, a biomarker often used to evaluate cardiovascular risk. Incorporating substance use alongside cardiac biomarkers may improve CVD risk assessment in vulnerable women.

Keywords

ST2; substance use; cardiac remodeling; women

1. Introduction

More than 5 million people in the United States are living with heart failure (HF) (Go et al., 2014). Beyond the commonly studied effects of alcohol and tobacco on cardiovascular health, numerous substances have been linked to the development of cardiovascular disease (CVD) and HF, including additional controlled substances like cocaine, methamphetamine, and heroin (Havakuk et al., 2017, Nishimura et al., 2020), which are rarely accounted for in large-scale studies or trials (Mladenka et al., 2018). In addition, the adverse effects of substance use may be more pronounced in vulnerable populations because of a higher co-morbidity burden that may augment cardiovascular risk (Snow et al., 2019).

2. Clinical Significance

While studies powered to detect differences in cardiovascular outcomes are ideal, their large sample size and long follow-up often make them impractical, particularly when studying vulnerable populations. However, the utility of biomarkers in providing a surrogate for cardiovascular dysfunction in health care settings and research is well established (Sabatine et al., 2002), particularly to aid HF diagnosis in women (Sobhani et al., 2018). The specificity for assessing women's risk is notable. Women have higher rates of CVD (Appelman et al., 2015) and HF (Campbell et al., 2012) than men, and worse event-free survival following HF with preserved ejection fraction (Kao et al., 2015). Reasons for this are multifactorial, including the underdiagnosis and under-treatment of women (Bairey Merz, 2014) due to such factors as presenting with 'atypical' symptoms (Dey et al., 2009).

Soluble "Suppression of tumorigenicity 2" (sST2) is a circulating marker of cardiac stress and remodeling. Serum sST2 concentrations are correlated with structural and functional cardiac changes (Shah et al., 2009); they are an independent predictor of HF and death (Boisot et al., 2008), and recommended as one component of multi-component approaches

for stratifying cardiovascular risk (Yancy et al., 2013). While some studies show superior risk stratification performance of sST2 when compared to natriuretic peptides (Villacorta and Maisel, 2016), potential influences of additional factors like substance use, which may confound or modify sST2 levels, have received less attention. Concern over such oversights may be warranted because metabolic disturbances are associated controlled substances such as methamphetamine (Kim et al., 2020, Wang et al., 2021), and may have unrecognized influence on biomarkers used to stratify CVD risk. One of the few studies to consider the use of controlled substances in relation to sST2 levels reported a significant cross-sectional correlation between serum concentrations of benzoylecgonine, a major cocaine metabolite, and sST2 in remnant hospital samples (van Wijk et al., 2017). Whether associations observed over time and adjusted for the effects of other substance use (i.e., polysubstance use), as well as cardiovascular risk factors, is unknown.

We conducted a study to determine associations between the use of multiple substances and sST2 over six monthly visits in unsheltered and unstably housed women, a vulnerable population with disproportionately high rates of substance use.

3. Materials and Methods

3.1 Study design

We collected data from 245 women (Figure 1) between June 2016 and January 2019 to examine the influences of multiple substance use on cardiac dysfunction, as measured by sST2 biomarkers. Data came from ‘Polysubstance Use and Health Outcomes Evaluation,’ (PULSE) a prospective study of women living in San Francisco, California, U.S.A. Inclusion criteria were female sex at birth, age ≥ 18 years and a history of housing instability (i.e., slept in public or a homeless shelter, or stayed with a series of associates because there was no other place to sleep [‘couch-surfed’]).

3.2 Study Participant Recruitment

Based on previously developed methods (Burnam and Koegel, 1988), trained study team members recruited a probability sample of San Francisco unhoused and unstably housed women from shelters, free meal programs, single room occupancy (SRO) hotels and street encampments. Women living with HIV were also recruited from the Zuckerberg San Francisco General Hospital HIV clinic (‘Ward 86’), the largest provider of HIV care to Medicaid patients in San Francisco, and from provider/participant referrals.

HIV testing was conducted at screening, and women living with HIV were oversampled to accomplish HIV-related aims reported elsewhere. CVD status at enrollment was unknown. We obtained informed consent from all study participants and each participant was reimbursed $40 for each study interview. Study procedures reported here were approved by the Institutional Review Board at the University of California, San Francisco.

3.3 Data Collection

Participants completed monthly study visits for six months, consisting of an interview, blood draw, biomarker assessment, urine collection and vital sign assessment. Questionnaires and study procedures were pilot tested to ensure appropriateness for the target population.

3.4 Dependent Outcome Measures

We used serum samples to evaluate the level of sST2 (Critical Diagnostics Presage® ST2 enzyme-linked immunosorbent assay [ELISA] cut-point for adverse cardiac remodeling >35 ng/mL).

3.5 Independent Exposure Measures

Primary study exposures were toxicology-confirmed substance use and the use of prescribed pharmaceutical drugs influencing cardiovascular health. We tested hydrolyzed urine samples using a qualitative liquid chromatography-high resolution mass spectrometry (LC-HRMS) method. Data acquisition and generation of mass spectra took place using an SCIEX 5600 TripleTOF® LC-HRMS system. We used HRMS full scan mode with information-dependent acquisition of HRMS product ion spectra, which were searched against a mass spectral library for positive identification of each substance. This methodology has proven sensitive and specific for the detection of these compounds in urine (Thoren et al., 2016). To increase cannabis test sensitivity, we conducted separate urine tetrahydrocannabinol (THC) screening, which uses a liquid chromatography tandem mass spectrometry (LC-MS/MS) method to detect THC—COOH (>0.5 ng/mL) and THC-COOH-glucuronide (2.5 ng/mL) (Benowitz et al., 2019a). A full list of substances and pharmaceutical drugs is shown in Table 1, including cotinine (>10 pg/ml, a marker of smoking (Benowitz et al., 2019b)), ethyl glucuronide (a marker for alcohol), cocaine, methamphetamine, opioids, beta blockers, calcium channel blockers and statins.

We considered six groups of exposure variables. Demographic variables (group 1) included age and race. Substance use (group 2), included controlled substances, the drug adulterant, levamisole, and metabolites, which are detailed in Table 1. Chronic health conditions (group 3) included HIV infection, hepatitis C infection, diabetes, prior myocardial infarction (MI) and prior stroke. Commonly used pharmaceutical drugs related to CVD (group 4) are detailed in Table 1. Current health status (group 5) included body mass index (BMI), systolic blood pressure, diastolic blood pressure, total cholesterol (Cholesterol_2, Siemens ADVIA® Chemistry XPT), HDL cholesterol (Direct HDL cholesterol, Siemens ADVIA® Chemistry XPT), triglycerides (Triglycerides_2, Siemens ADVIA® Chemistry XPT), calculated LDL cholesterol (Friedewald equation), and high sensitivity C-reactive protein (CardioPhase™ hsCRP, Siemens ADVIA® Chemistry XPT). Group 6 included left ventricular mass (LV mass) and left ventricular ejection fraction (LVEF). To obtain group 6 measures, a 2D transthoracic echocardiogram was performed on each participant. Left ventricular end-diastolic and end-systolic volumes and left ventricular ejection fraction (LVEF) were assessed using the modified Simpson's rule.(Hsue et al., 2010) LV Mass was calculated as follows: 0.8 X {1.04 ([LVEDD + IVSd +PWd]^3 − [LVEDD]^3)} + 0.6 g; where LVEDD= LV end-diastolic dimension (mm), IVSd= Interventricular septal thickness at

end-diastole (mm), PWd= Posterior wall thickness at end-diastole (mm), and 1.04=Specific gravity of the myocardium (g/cm^3) (Lang et al., 2005).

3.6 Analysis

We log-transformed biomarker outcomes and used linear mixed models to determine effects over time between substance use and sST2 measured at each study visit.

To clearly delineate effects, a series of models sequentially added variables from each of the five exposure variable groups. At each step, backward deletion was used to remove variables in the most recently added group with p-values>0.1. Variable significance within adjusted models was considered at the $p<0.05$ level. Finally, we used separate analyses to estimate associations between substance use combinations and outcomes. Analyses were done using Stata Version 15.0 (Stata Corp., College Station, TX).

4. Results

Study participants completed a median of 5 study visits each, resulting in 1,051 study visits total. The median participant age was 53 years and 74% were ethnic minority women (Table 2). Median BMI was 27.9 (“overweight”) (Sahakyan et al., 2015) and 15% of participants had previously been diagnosed with diabetes. Due to oversampling of women living with HIV, the prevalence of HIV was 31% and the prevalence of hepatitis C infection was 32%. Prior physician-diagnosed MI and stroke were reported by 8.2% and 11.5% of participants, respectively. At baseline, 76% of participants had hypertension (i.e., systolic >120 mm Hg or diastolic>80 mm Hg) (Table 2).

The prevalence of toxicology-confirmed substances at baseline and at one or more study visit respectively included glucuronide/alcohol (29% and 48%); cotinine/nicotine (69% and 80%); cannabis (51% and 68%); cocaine (53% and 66%); cocaethylene, a metabolite formed when cocaine and alcohol are co-ingested (Jones, 2019) (17% and 28%); methamphetamine (29% and 43%); heroin (2% and 8%); and additional opioids (22% and 36%). Almost 4 in 5 participants (77%) had evidence of polysubstance use at one or more study visits. The prevalence of toxicology-confirmed pharmaceutical drugs at one or more study visits included methadone (20%), benzodiazepines (11%), hypertensive agents (5%), and beta blockers (8%) (Table 1).

Median sST2 level was 26.8 ng/mL (IQR: 20.7-37.0). An sST2 level exceeding 35 ng/mL, which signaled cardiac remodeling, was observed in 109 participants (44%) at any study visit. Table 3 shows that, using measures across six study visits, cocaine (Adjusted Linear Effect [ALE]:1.10; 95% CI:1.03-1.19), levamisole (ALE:0.91; 95% CI:0.86-0.97), heroin (ALE:1.25; 95% CI:1.10-1.43), and alcohol (ALE:1.10; 95% CI:1.04-1.17) were all significantly associated with higher levels of sST2 (Table 3; Model 2). Magnitudes of association did not diminish substantially, even after adjusting for other significant factors, including HIV (Model 3), naloxone, lidocaine (Table 3; Model 4), systolic blood pressure, diastolic blood pressure and C-reactive protein (Table 3; Model 5). While tobacco use was common in this population, nicotine/cotinine did not reach levels of significance. Left

ventricular mass and left ventricular ejection fraction were not significantly associated with sST2 (Table 3; Model 6).

Additional models considering combined substance use effects on sST2 compared to effects from individual drugs suggested that the combined effects of heroin and fentanyl on sST2 levels were larger than expected based on their independent effects (interaction p=0.04). No other between-substance interactions were observed.

Additional models were also considered in a subset of the population for whom electronic health records (EHRs) were available (n=114) in order to account for HF diagnoses (n=16 [14%]). When EHR-identified HF was included in adjusted analysis, results were similar to the main analysis, with the magnitude of association between sST2 and substance use being slightly stronger for cocaine (ALE: 1.12; 95% CI:1.01, 1.25) and alcohol (ALE: 1.11; 95% CI:1.03, 1.19), but weaker for heroin (ALE: 1.16; 95% CI:0.97, 1.38). Similarly, when participants with EHR-identified HF were removed from this subsample (n=102), differences in adjusted results were negligible.

5. Discussion

In this community-recruited sample of unhoused and unstably housed women without known CVD at the time of enrollment, two-in-five participants had biomarker evidence of adverse cardiac remodeling (sST2>35 ng/mL). In adjusted analysis, cocaine use, alcohol use, and the interactive effect of heroin and fentanyl use were significantly associated with sST2 level, even after accounting for other CVD risk factors and a prior diagnosis of HF. These results are consistent with prior cross-sectional research showing significant correlation between serum concentrations of benzoylecgonine, a major cocaine metabolite, and sST2 in remnant hospital samples (van Wijk et al., 2017). They extend prior findings through longitudinal analyses that adjust for the use of other substances and cardiovascular risk factors. Results are also consistent with prior research in this population showing that high-sensitivity cardiac troponin (hs-cTnI) is associated with cocaethylene, a metabolite of cocaine and alcohol co-use (Riley et al., 2020). Taken together, the existing evidence suggests that risk assessment strategies incorporating biomarkers, including sST2, will be influenced by multiple substances. More specifically, in an era where sST2 is emerging as a valuable prognostic factor, which significantly improves the accuracy of predicting heart failure (Lotierzo et al., 2020) and cardiovascular mortality (Zagidullin et al., 2020, Miftode et al., 2021) by using multiple biomarkers instead of a single biomarker, incorporating substance use alongside cardiac biomarkers may improve CVD risk assessment in vulnerable women.

Substance use was significantly associated with sST2 levels, but several traditional CVD risk factors were not. These results may suggest the dominant effect of substance use compared to many traditional risk factors on heart failure. In this case, adapting risk assessment tools for populations with high proportions of people who use controlled substances may be warranted. However, on the other hand, results may suggest that cocaine and alcohol modify conditions other than HF that are also signaled by sST2, such as inflammation (Charafeddine et al., 2021) and liver disease (Sun et al., 2019). Yet another possibility is

that cocaine and alcohol influence the biomarker itself and not the conditions it signals. Future studies are needed to clarify the effects observed here. Either way, results suggest that cocaine and alcohol are influencing sST2 levels and thus influencing CVD risk assessment strategies that include sST2.

In addition to single drug effects, secondary analyses suggest differential effects from drug combinations. In particular, we found interactive effects from two opioids, heroin and fentanyl (i.e., higher levels of sST2 in the presence of both substances than would be expected from the combination of their individual effects). While combined effects of heroin and fentanyl have not been previously studied in conjunction with sST2, findings are consistent with research reporting that heroin and other opiates are associated with worse cardiovascular outcomes, including arrhythmias, non-cardiac pulmonary edema, reduced cardiac output and additional myocardial damage (Frishman et al., 2003). These findings raise the possibility that the combination of these two opioids may exacerbate CVD progression. However, as stated above, limitations with data used here may alternatively suggest that the combination of heroin and fentanyl influence conditions other than HF, which are also signaled by sST2, or may influence the biomarker itself. Results reported here regarding interactive effects should be replicated in additional diverse samples, but they provide initial evidence to suggest notable sST2 differences in the presence of polysubstance use.

This study has several potential limitations. First, the number of variables and comparisons made were large while the sample was modest. However, estimates were notably consistent between models and substance use variables retained statistical significance in adjusted models, suggesting robust associations that were not impacted by the number of variables. This assessment to rule out substantive bias, and our decision to retain originally planned predictor variables, resulted in a model that is realistic in the context of polysubstance use and not subject to unmeasured confounding. In addition, the over-enrollment of women living with HIV had the potential to bias results; however, HIV status was not associated with sST2 suggesting minimal influence in this population.

Study strengths included a community-based sample which naturally facilitated the inclusion of complex conditions disproportionately common in low-income populations (e.g., polysubstance use). The fact that data were longitudinal was another strength, allowing for the consideration of varying substance use over time. In addition, prior studies examining substances have typically relied on self-reported measures. In this study, both substance use and pharmaceutical drug use were toxicology-confirmed. Finally, the sample population was composed entirely of women, which allowed for the estimation of women-specific results compared with prior studies, which have predominantly enrolled men and assumed similar risks across the sexes.

6. Conclusion

Cocaine use, alcohol use, and the interaction between heroin and fentanyl use are associated with elevated levels of sST2, a marker of adverse cardiac remodeling, in low-income women. Recommendations for using sST2 to improve cardiovascular risk stratification

(Yancy et al., 2013) may be improved when risk assessment also incorporates the use of multiple controlled substances.

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Data Availability Statement

Due to the sensitive nature of substance use in a small sample, data are not publicly available due to privacy concerns. However, deidentified data sets accompanied by agreements for data use are available upon request from the corresponding author.

References

Appelman Y, Van Rijn BB, Ten Haaf ME, Boersma E & Peters SA, 2015. Sex differences in cardiovascular risk factors and disease prevention. Atherosclerosis, 241, 211–8. [PubMed: 25670232]

Bairey Merz CN, 2014. Sex, death, and the diagnosis gap. Circulation, 130, 740–2. [PubMed: 25052404]

Benowitz N, Nardone N, St Helen G, Addo N, Jacob P 3rd, Liakoni E, Jain S, Hooshfar S & Lynch K, 2019a. Quantitative biochemical screening for marijuana use and concordance with tobacco use in urban adolescents. Drug Alcohol Depend, 205, 107583 [Epub ahead of print]. [PubMed: 31600618]

Benowitz NL, Bernert JT, Foulds J, Hecht SS, Jacob P, Jarvis MJ, Joseph A, Oncken C & Piper ME, 2019b. Biochemical Verification of Tobacco Use and Abstinence: 2019 Update. Nicotine Tob Res.

Boisot S, Beede J, Isakson S, Chiu A, Clopton P, Januzzi J, Maisel AS & Fitzgerald RL, 2008. Serial sampling of ST2 predicts 90-day mortality following destabilized heart failure. J Card Fail, 14, 732–8. [PubMed: 18995177]

Burnam MA & Koegel P, 1988. Methodology for obtaining a representative sample of homeless persons: the Los Angeles Skid Row Study. Evaluation Review, 12, 117–152.

Campbell RT, Jhund PS, Castagno D, Hawkins NM, Petrie MC & Mcmurray JJ, 2012. What have we learned about patients with heart failure and preserved ejection fraction from DIG-PEF, CHARM-preserved, and I-PRESERVE? J Am Coll Cardiol, 60, 2349–56. [PubMed: 23141494]

Charafeddine K, Zakka P, Bou Dargham B, Abdulhai F, Zakka K, Zouein FA & Refaat M, 2021. Potential Biomarkers in Atrial Fibrillation: Insight Into Their Clinical Significance. J Cardiovasc Pharmacol, 78, 184–191. [PubMed: 34173807]

Dey S, Flather MD, Devlin G, Brieger D, Gurfinkel EP, Steg PG, Fitzgerald G, Jackson EA, Eagle KA & Global Registry of Acute Coronary Events, I., 2009. Sex-related differences in the presentation, treatment and outcomes among patients with acute coronary syndromes: the Global Registry of Acute Coronary Events. Heart, 95, 20–6. [PubMed: 18463200]

Frishman WH, Del Vecchio A, Sanal S & Ismail A, 2003. Cardiovascular manifestations of substance abuse: part 2: alcohol, amphetamines, heroin, cannabis, and caffeine. Heart Dis, 5, 253–71. [PubMed: 12877759]

Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, Dai S, Ford ES, Fox CS, Franco S, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Huffman MD, Judd SE, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Mackey RH, Magid DJ, Marcus GM, Marelli A, Matchar DB, Mcguire DK, Mohler ER 3rd, Moy CS, Mussolino ME, Neumar RW, Nichol G, Pandey DK, Paynter NP, Reeves MJ, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Wong ND, Woo D, Turner MB, American Heart Association Statistics, C. & Stroke Statistics, S., 2014. Heart disease and stroke statistics--2014 update: a report from the American Heart Association. Circulation, 129, e28–e292. [PubMed: 24352519]

Havakuk O, Rezkalla SH & Kloner RA, 2017. The Cardiovascular Effects of Cocaine. J Am Coll Cardiol, 70, 101–113. [PubMed: 28662796]

Hsue PY, Hunt PW, Ho JE, Farah HH, Schnell A, Hoh R, Martin JN, Deeks SG & Bolger AF, 2010. Impact of HIV infection on diastolic function and left ventricular mass. Circ Heart Fail, 3, 132–9. [PubMed: 19933410]

Jones AW, 2019. Forensic Drug Profile: Cocaethylene. J Anal Toxicol, 43, 155–160. [PubMed: 30796807]

Kao DP, Lewsey JD, Anand IS, Massie BM, Zile MR, Carson PE, Mckelvie RS, Komajda M, Mcmurray JJ & Lindenfeld J, 2015. Characterization of subgroups of heart failure patients with preserved ejection fraction with possible implications for prognosis and treatment response. Eur J Heart Fail, 17, 925–35. [PubMed: 26250359]

Kim S, Jang WJ, Yu H, Kim J, Lee SK, Jeong CH & Lee S, 2020. Revealing Metabolic Perturbation Following Heavy Methamphetamine Abuse by Human Hair Metabolomics and Network Analysis. Int J Mol Sci, 21.

Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ, Chamber Quantification Writing, G., American Society of Echocardiography's, G., Standards, C. & European Association Of, E., 2005. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr, 18, 1440–63. [PubMed: 16376782]

Lotierzo M, Dupuy AM, Kalmanovich E, Roubille F & Cristol JP, 2020. sST2 as a value-added biomarker in heart failure. Clin Chim Acta, 501, 120–130. [PubMed: 31678574]

Miftode RS, Constantinescu D, Cianga CM, Petris AO, Timpau AS, Crisan A, Costache Ii, Mitu O, Anton-Paduraru DT, Miftode IL, Pavel-Tanasa M, Cianga P & Serban IL, 2021. A Novel Paradigm Based on ST2 and Its Contribution towards a Multimarker Approach in the Diagnosis and Prognosis of Heart Failure: A Prospective Study during the Pandemic Storm. Life (Basel), 11.

Mladenka P, Applova L, Patocka J, Costa VM, Remiao F, Pourova J, Mladenka A, Karlickova J, Jahodar L, Voprsalova M, Varner KJ, Sterba M, Tox, O.E.R., Researchers, C.H.K. & Collaborators, 2018. Comprehensive review of cardiovascular toxicity of drugs and related agents. Med Res Rev, 38, 1332–1403. [PubMed: 29315692]

Nishimura M, Bhatia H, Ma J, Dickson SD, Alshawabkeh L, Adler E, Maisel A, Criqui MH, Greenberg B & Thomas IC, 2020. The Impact of Substance Abuse on Heart Failure Hospitalizations. Am J Med, 133, 207–213 e1. [PubMed: 31369724]

Riley ED, Vittinghoff E, Wu AHB, Coffin PO, Hsue PY, Kazi DS, Wade A, Braun C & Lynch KL, 2020. Impact of polysubstance use on high-sensitivity cardiac troponin I over time in homeless and unstably housed women. Drug Alcohol Depend, 217, 108252. [PubMed: 32919207]

Sabatine MS, Morrow DA, De Lemos JA, Gibson CM, Murphy SA, Rifai N, Mccabe C, Antman EM, Cannon CP & Braunwald E, 2002. Multimarker approach to risk stratification in non-ST elevation acute coronary syndromes: simultaneous assessment of troponin I, C-reactive protein, and B-type natriuretic peptide. Circulation, 105, 1760–3. [PubMed: 11956114]

Sahakyan KR, Somers VK, Rodriguez-Escudero JP, Hodge DO, Carter RE, Sochor O, Coutinho T, Jensen MD, Roger VL, Singh P & Lopez-Jimenez F, 2015. Normal-Weight Central Obesity: Implications for Total and Cardiovascular Mortality. Ann Intern Med, 163, 827–35. [PubMed: 26551006]

Shah RV, Chen-Tournoux AA, Picard MH, Van Kimmenade RR & Januzzi JL, 2009. Serum levels of the interleukin-1 receptor family member ST2, cardiac structure and function, and long-term mortality in patients with acute dyspnea. Circ Heart Fail, 2, 311–9. [PubMed: 19808354]

Snow SC, Fonarow GC, Ladapo JA, Washington DL, Hoggatt KJ & Ziaeian B, 2019. National Rate of Tobacco and Substance Use Disorders Among Hospitalized Heart Failure Patients. Am J Med, 132, 478–488 e4. [PubMed: 30562497]

Sobhani K, Nieves Castro DK, Fu Q, Gottlieb RA, Van Eyk JE & Noel Bairey Merz C, 2018. Sex differences in ischemic heart disease and heart failure biomarkers. Biol Sex Differ, 9, 43. [PubMed: 30223899]

Sun Z, Chang B, Huang A, Hao S, Gao M, Sun Y, Shi M, Jin L, Zhang W, Zhao J, Teng G, Han L, Tian H, Liang Q, Zhang JY & Zou Z, 2019. Plasma levels of soluble ST2, but not IL-33, correlate with the severity of alcoholic liver disease. J Cell Mol Med, 23, 887–897. [PubMed: 30478965]

Thoren KL, Colby JM, Shugarts SB, Wu AH & Lynch KL, 2016. Comparison of Information-Dependent Acquisition on a Tandem Quadrupole TOF vs a Triple Quadrupole Linear Ion Trap Mass Spectrometer for Broad-Spectrum Drug Screening. Clin Chem, 62, 170–8. [PubMed: 26453698]

Van Wijk XMR, Vittinghoff E, Wu AHB, Lynch KL & Riley ED, 2017. Cocaine use is associated with a higher prevalence of elevated ST2 concentrations. Clin Biochem, 50, 791–793. [PubMed: 28442257]

Villacorta H & Maisel AS, 2016. Soluble ST2 Testing: A Promising Biomarker in the Management of Heart Failure. Arq Bras Cardiol, 106, 145–52. [PubMed: 26761075]

Wang T, Xu C, Xu S, Gao L, Blazenovic I, Ji J, Wang J & Sun X, 2021. Untargeted metabolomics analysis by gas chromatography/time-of-flight mass spectrometry of human serum from methamphetamine abusers. Addict Biol, 26, e13062. [PubMed: 34114299]

Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr., Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, Mcbride PE, Mcmurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL, American College of Cardiology, F. & American Heart Association Task Force on Practice, G., 2013. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol, 62, e147–239. [PubMed: 23747642]

Zagidullin N, Motloch LJ, Gareeva D, Hamitova A, Lakman I, Krioni I, Popov D, Zulkarneev R, Paar V, Kopp K, Jirak P, Ishmetov V, Hoppe UC, Tulbaev E & Pavlov V, 2020. Combining Novel Biomarkers for Risk Stratification of Two-Year Cardiovascular Mortality in Patients with ST-Elevation Myocardial Infarction. J Clin Med, 9.

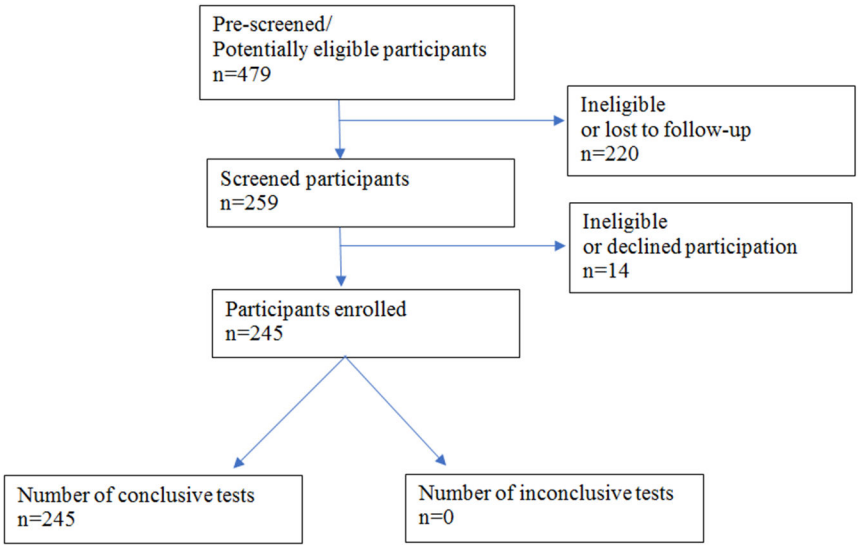

Figure 1.
Participant Flow Diagram

Table 1.

Substances Assessed

Drug or Drug Class	Individual Drugs and Drug Metabolites
Cocaine	Benzoylecgonine, Cocaine, Ecgonine methyl ester, Norcocaine
	Cocaethylene
Amphetamines	Methamphetamine, methamphetamine, MDMA
Antiarrhythmic	Lidocaine
Opioid antagonist	Methadone, EDDP buprenorphine, Norbuprenorphine
Heroin	6-Monoacetylmorphine, Heroin
Opioids	6-Monoacetylmorphine, Heroin, Morphine, Codeine, Hydrocodone, Hydromorphone, Dihydrocodeine, Glucuronide, Codeine Glucuronide, Oxycodone, Oxymorphone
Fentanyl	Fentanyl, Norfentanyl
Naloxone	Naloxone
Benzodiazepines	Clonazepam, Diazepam, Lorazepam, Nordazepam, Temazepam, Oxazepam, Alprazolam alpha-hycroxyalprazolam, Flurazepam, 2-Hydroxyethylflurazepam, Desalkylflurazepam, Flunitrazepam, 7-Aminoflunitrazepam, N-Desmethylflunitrazepam, Midazolam, 7-Aminonitrazepam, Etizolam
Alcohol	Ethyl Glucuronide
Cannabis (THC)	Tetrahydrocannabinol (THC) −COOH and THC—COOH glucuronide
Nicotine	Cotinine, Nicotine
Beta Blockers	Metoprolol, Atenolol, Carvedilol, Labetalol
Calcium Channel Blockers	Amlodipine, Diltiazem, Verapamil
Diuretic	Furosemide, Hydrochlorothiazide
Nitrate	Isosorbide mononitrate
Antihypertensive Agents	Clonidine, Lisinopril, Losartan
Statins	Atorvastatin, Pravastatin, Simvastatin
Vasodilator	Sildenafil
Blood thinner	Coumadin
Analgesic	Acetaminophen

Table 2.

Baseline Characteristics of Study Participants (N=245)

Study Characteristic	Median (IQR) or Proportion (%)
Demographic	
Age (years)	Median=53.4 (45.7-59.5)
Race/Ethnicity	
White	64 (26.1%)
Black/African American	92 (37.6%)
Latina	37 (15.1%)
Multiracial	29 (11.8%)
Other	23 (9.4%)
Post-menopausal [c]	154 (63.1%)
Substance Use	
Cotinine/Nicotine [e]	169 (69.0%)
Cocaine/Benzoylecgonine [e]	129 (52.7)%
Cannabis (THC) [e]	125 (51%)
Levamisole [e]	83 (33.9%)
Methamphetamine [e]	71 (29.0%)
Alcohol (as determined by ethyl glucuronide) [e]	71 (29.0%)
Opioids other than heroin [e]	55 (22.4%)
Cocaethylene [e]	42 (17.1%)
Heroin/ Monoacetylmorphine-6 [e]	5 (2.0%)
Fentanyl/Norfentanyl [e]	6 (2.4%)
History of Chronic Health Conditions	
Diabetes [f]	37 (15.2%)
Prior myocardial infarction [f]	20 (8.2%)
Prior stroke [f]	28 (11.5%)
HIV-positive [g]	77 (31.4%)
HCV-positive [f]	78 (32.0%)
Pharmaceutical Drug Use	
Acetaminophen [e]	64 (26.1%)
Methadone [e]	53 (21.6%)
Lidocaine [e]	38 (15.5%)
Benzodiazepine [e]	21 (8.6%)

Study Characteristic	Median (IQR) or Proportion (%)
Beta blocker [e]	14 (5.7%)
Antihypertensive [e]	11 (4.5%)
Calcium channel blocker [e]	10 (4.1%)
Buprenorphine/Norbuprenorphine [e]	1 (0.4%)
Statin [e]	0 (0.0%)
Naloxone [e]	0 (0.0%)
Current Health Status	
Body Mass Index (BMI)	Median=27.9 (23.2-34.0)
Systolic Blood Pressure	Median=129.0 (115.0-145.0)
Diastolic Blood Pressure	Median=85.0 (77.0-93.5)
Hypertension	
No hypertension	58 (23.5%)
Elevated blood pressure (systolic ≥120 mm Hg or diastolic ≥80 mm Hg)	12 (4.9%)
Stage 1 hypertension (systolic ≥130 mm Hg or diastolic ≥80 mm Hg)	70 (28.3%)
Stage 2 hypertension (systolic ≥140 mm Hg or diastolic ≥90 mm Hg)	102 (41.3%)
Hypertensive crisis (systolic ≥180 mm Hg or diastolic ≥120 mm Hg)	5 (2.0%)
LDL cholesterol (mg/dL)	Median=93.0 (77.0-117.0)
HDL cholesterol (mg/dL)	Median=61.0 (47.0-73.0)
High-sensitivity C-Reactive Protein (hsCRP) (mg/L)	Median=3.1 (0.9-8.9)
High-sensitivity Troponin I (ng/L)	Median=2.0 (1.0-3.0)
Left Ventricular Mass Index (g/m^2)	Median= 86.8 (72.9-100)
Left Ventricular Ejection Fraction	Median= 63% (58%-68%)

[c] >1 year since last menstrual period

[e] Positive toxicology results

[f] Self-reported

[g] ELISA test results

Table 3.

Associations between Study Factors and sST2 Level (ng/mL) Across Six Study Visits (N=245; 1,051 study visits total)

	Unadjusted Effects [a] **(95% CI)**	**Model 1 Adjusted Effects (95% CI) Demographic**	**Model 2 Adjusted Effects (95% CI) Substance Use**	**Model 3 Adjusted Effects (95% CI) History of Chronic Health Conditions**	**Model 4 Adjusted Effects (95% CI) Pharmaceutical Drug Use**	**Model 5 Adjusted Effects (95% CI) Current Health Status /Cardiovascular Risks**	**Model 6 Adjusted Effects (95% CI) Cardiac Structure/ function**
Age (years)	1.00 (0.95-1.06)	1.01 (0.95, 1.06)					
Race/Ethnicity							
White	(Ref)						
Black/African American	1.17 (1.02-1.34)	1.17 (1.00-1.35)					
Latina	1.11 (0.93-1.33)	1.11 (0.93, 1.33)					
Multiracial	1.15 (0.95-1.40)	1.14 (0.94, 1.39)					
Other	1.21 (0.98-1.50)	1.21 (0.98, 1.49)					
Cocaine/Benzoylecgonine [e]	1.07 (1.01-1.14) **		1.10 (1.03-1.18) **	1.10 (1.03-1.18) **	1.09 (1.02-1.17) **	1.08 (1.00-1.15) **	1.09 (1.01, 1.18) **
Cocaethylene [e]	1.05 (0.99-1.12)		1.04 (0.97-1.12)				
Levamisole [e]	0.97 (0.92-1.03)		0.91 (0.86-0.97) **	0.92 (0.87-0.98) **	0.92 (0.86-0.97) **	0.92 (0.87-0.97) **	0.90 (0.85, 0.96) **
Methamphetamine [e]	1.01 (0.95-1.07)		0.99 (0.88-1.11)				
Heroin/Mono-acetylmorphine-6 [e]	1.22 (1.08-1.38) **		1.25 (1.09-1.42) **	1.26 (1.10-1.43) **	1.24 (1.09-1.41) **	1.22 (1.07-1.39) **	1.25 (1.08, 1.44) **
Fentanyl/Norfentanyl [e]	1.08 (0.96-1.21)		1.03 (0.91-1.17)				
Additional opioids [e]	1.02 (0.96-1.09)		1.01 (0.95-1.08)				
Alcohol (as determined by ethyl glucuronide) [e]	1.09 (1.03-1.15) **		1.10 (1.04-1.17) **	1.12 (1.06-1.18) **	1.12 (1.05-1.18) **	1.12 (1.06-1.19) **	1.13 (1.06, 1.20) **
Cannabis (THC) [e]			1.03 (0.97-1.09)				
Cotinine/Nicotine [e]	0.97 (0.91-1.03)		0.96 (0.87-1.07)				
Diabetes [f]	0.98 (0.88-1.09)			1.01 (0.90-1.12)			
Prior myocardial infarction [f]	0.98 (0.94-1.03)			0.99 (0.94-1.04)			

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	Unadjusted Effects [a] (95% CI)	Model 1 Adjusted Effects (95% CI) Demographic	Model 2 Adjusted Effects (95% CI) Substance Use	Model 3 Adjusted Effects (95% CI) History of Chronic Health Conditions	Model 4 Adjusted Effects (95% CI) Pharmaceutical Drug Use	Model 5 Adjusted Effects (95% CI) Current Health Status /Cardiovascular Risks	Model 6 Adjusted Effects (95% CI) Cardiac Structure/ function
Prior stroke [f]	1.00 (0.97-1.03)			1.00 (0.97-1.03)			
HIV-positive [g]	1.16 (1.03-1.31) **			1.18 (1.05-1.33) **	1.18 (1.05-1.33) **	1.19 (1.06-1.34) **	1.18 (1.03, 1.35) **
HCV-positive [f]	1.04 (0.95-1.12)			1.01 (0.92-1.09)			
Benzodiazepine [e]	1.02 (0.94-1.11)				1.01 (0.93-1.10)		
Beta blocker [e]	1.05 (0.94-1.16)				1.07 (0.96-1.20)		
Calcium channel blocker [e]	0.99 (0.88-1.10)				0.98 (0.87-1.09)		
Antihypertensive [e]	1.07 (0.95-1.19)				1.11 (0.98-1.24)	1.10 (0.98-1.24)	1.14 (1.00, 1.29) **
Statin [e]	1.02 (0.85-1.23)				1.11 (0.80-1.17)		
Acetaminophen [e]	0.98 (0.94-1.03)				0.99 (0.95-1.04)		
Naloxone [e]	1.87 (1.02-3.40) **				2.17 (1.12-4.18) **	2.12 (1.10-4.08) **	2.71 (1.35, 5.43) **
Methadone [e]	1.00 (0.92-1.09)				0.98 (0.90-1.07)		
Buprenorphine/Norbuprenorphine [e]	0.92 (0.73-1.16)				0.78 (0.60-1.00)	0.78 (0.61-1.01)	0.61 (0.45, 0.83) **
Lidocaine [e]	1.12 (1.06-1.18) **				1.11 (1.05-1.18) **	1.10 (1.04-1.16) **	1.10 (1.03, 1.17) **
Body Mass Index (BMI)	1.00 (0.99-1.00)					1.00 (0.99-1.00)	
Systolic Blood Pressure	1.01 (1.00-1.02)					1.03 (1.01-1.04) **	1.03 (1.02, 1.05) **
Diastolic Blood Pressure	0.99 (0.98-1.01)					0.97 (0.95-0.99) **	0.96 (0.94, 0.99) **
LDL cholesterol (mg/dL)	1.00 (0.99-1.01)					1.00 (0.99-1.01)	
HDL cholesterol (mg/dL)	1.01 (0.99-1.03)					1.01 (0.99-1.03)	
High-sensitivity C-reactive Protein (hsCRP) (mg/L)	1.02 (1.01-1.04) **					1.02 (1.01-1.04) **	1.02 (1.01, 1.04) **
LV mass (per 10 g/m^2)							1.00 (0.98, 1.01)
LVEF (per 10 units)							0.98 (0.89, 1.08)

** p<0.05

[a] Adjusted for visit only

[e] Positive toxicology results

[f] Self-reported

[g] ELISA test results