

**Substance Use Disorder and Acute Myocardial Infarction Readmissions After Heart Failure
Hospitalization: A Nationwide Analysis of U.S. Hospitalizations**

Kyle E. Thurmann, MS¹

ORCID: 0009-0005-8939-6252

Austin A. Charles, BS¹

ORCID: 0009-0003-9018-3196

Peter L. Ernst, BS¹

ORCID: 0009-0008-6065-1389

Trisha G. Mukherjee, BS¹

ORCID: 0009-0008-3246-0788

Paul T. Kang, MS, MPH¹

ORCID: 0000-0002-6857-2932

Michael D. White, MD^{1,2}

ORCID: 0009-0000-0451-4998

¹School of Medicine,
Creighton University
Phoenix, Arizona, USA

²Department of Cardiology
Valleywise Health Medical Center
Phoenix, Arizona, USA

Correspondence: Kyle E. Thurmann, MS. Creighton University School of Medicine. 3100 N Central Ave,
Phoenix, AZ 85012

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review & editing. Trisha G. Mukherjee: Writing-review & editing. Paul T. Kang: Methodology, Formal
analysis, Validation, Writing-review & editing. Michael D. White: Conceptualization, Supervision, Project
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ABSTRACT

Background

Prior work identified substance use disorder (SUD) as the only psychiatric comorbidity independently associated with increased cardiovascular (CV) readmission risk after heart failure (HF) hospitalization. This study aims to characterize the clinical profile of index HF hospitalizations with co-occurring SUD; identify the CV diagnoses associated with the greatest risk of readmission; and compare short- and long-term readmission patterns.

Methods

We conducted a retrospective cohort study using the 2016-2022 Nationwide Readmissions Database and included adults hospitalized for index HF with and without SUD. The primary outcomes were the CV diagnoses associated with the greatest risk of readmission at 30 days and 1 year. A secondary, substance-specific analysis stratifying SUD into individual substance categories was performed to assess their associations with myocardial infarction (MI) readmission.

Results

Among 14,535,581 weighted index HF hospitalizations in the 30-day analytic cohort, acute MI had the highest SUD-associated hazard of CV-specific readmission (aHR 1.09, $p < .001$). In 1-year analyses restricted to January-June index discharges (weighted $N = 7,336,360$), MI yielded an increased significant SUD-associated hazard (aHR 1.13, $p < .001$). Substance-specific analyses showed that cannabis had the highest MI readmission hazards (30 days: aHR 1.17; 1 year: aHR 1.22; both $p < .001$).

Conclusion

Acute MI was the CV diagnosis most strongly associated with readmission among HF index hospitalizations with co-occurring SUD. The strongest MI readmission associations were observed for cannabis and stimulant use, with cocaine showing additional longer-term association. These findings support consideration of integrated CV and addiction-focused care pathways to address ischemic risk in this high-risk population.

KEYWORDS: Heart Failure, Substance-Related Disorders, Myocardial Infarction, Patient Readmission, Cannabis

INTRODUCTION

In the United States, the total annual cost of heart failure (HF) care is projected to approach \$70 billion by 2030, a notable increase from \$31 billion in 2012.¹ Hospitalizations account for roughly half of all direct HF-related medical expenditures, and patients readmitted within 30 days incur costs of thousands of dollars more than those not readmitted, representing a substantial incremental financial burden.^{1,2} Substance use disorders (SUDs) affect approximately 10% of adults (around 25 million people) in the United States with high rates of polysubstance involvement, as more than 70% of those with a drug use disorder also meet criteria for alcohol use disorder and over 40% have another illicit drug use disorder.³ During the COVID-19 era, drug-overdose mortality in the United States reached historic levels, with 107,941 deaths recorded in 2022, an age-adjusted rate of 32.6 deaths per 100,000, which underscores the growing public health impact of substance use.^{4,5}

SUDs, notably involving alcohol, opioids, stimulants, and cocaine, are consistently linked to heightened cardiovascular (CV) risk and mortality, with national data showing that between 1999 and 2019, CV mortality involving substance use more than doubled, driven by the largest absolute contribution from alcohol and the fastest growth from stimulants.⁶ Unfortunately, fewer than 10% of these at-risk patients receive specialty treatment in a given year for SUD.³

HF-related outcomes among younger adults have shown concerning reversals in prior progress. National data have demonstrated that hospitalization rates in adults aged 18-45 declined through 2012 before increasing thereafter, and HF-related CV mortality has followed a similar pattern, declining from 1999 to 2012, then rising through 2017, disproportionately affecting Black adults and those from lower-income communities.⁷ Methamphetamine-associated HF hospitalizations increased from 547 in 2002 to 6,625 in 2014, a more than 12-fold (+1111%) rise nationally and disproportionately affecting younger patients and those who were socioeconomically disadvantaged, with 59.4% insured by Medicaid and 12.0% uninsured.⁸ These trends highlight the urgent need to identify modifiable drivers of early and recurrent HF readmission.

Building on our prior nationwide analysis showing SUD as the only psychiatric comorbidity independently associated with higher CV-specific readmission hazard after HF hospitalization, the present study delineates which CV diagnoses confer the greatest risk of readmission at 30 days and 1 year.⁹ Specifically, the objectives of this study are as follows: (1) comprehensively describe the demographic and clinical characteristics of index HF hospitalizations with co-occurring SUD, (2) identify the CV conditions independently associated with the greatest risk of readmission, and (3) compare short-term (30-day) versus long-term (1-year) readmission trends to highlight differences in timing and diagnosis-specific burden. Given prior evidence linking substance use with sympathetic activation, vasospasm, and prothrombotic states, we hypothesized that acute MI would be the CV diagnosis most strongly associated with CV-specific readmission following HF hospitalization.¹⁰

METHODS

Data Source

We performed a retrospective cohort study using the 2016-2022 Nationwide Readmissions Database (NRD), a component of the Healthcare Cost and Utilization Project (HCUP) that captures all-payer inpatient discharges from 30 states in the United States, representing approximately 60% of national hospitalizations.¹¹ Each annual NRD file is independent; therefore, 1-year readmissions were assessed within the same calendar year.

Study Population

Adults (≥ 18 years) hospitalized with a principal diagnosis of HF were identified using International Classification of Diseases, 10th Revision (ICD-10) codes I50.0-I50.9. The index hospitalization was defined as the first qualifying HF admission per patient per calendar year using the NRD patient linkage variable (NRD_VisitLink), ensuring one index HF hospitalization per person-year. Because each annual NRD file is independent, patients could contribute a new index hospitalization in a subsequent calendar year; 1-year readmissions were therefore assessed within the same calendar year. We included patients with and without co-occurring SUD (F10-F19), encompassing alcohol, opioids, stimulants, cannabis, sedatives, and other psychoactive substances. Nicotine-related diagnoses (F17.x) were not included in the SUD exposure definition. The NRD does not reliably capture granular smoking characteristics (e.g., current vs former use, pack-years), and F17.x coding incompletely reflects true tobacco exposure; therefore, tobacco was addressed as a potential source of residual confounding rather than as part of the primary SUD exposure.

A total of 36,838,617 weighted eligible index HF hospitalizations were identified (Figure 1). Sequential exclusions were then applied to define the analytic cohort, including in-hospital death, discharges with DISPUNIFORM not equal to "Routine," and elective admissions, yielding a final 30-day analytic cohort of 14,535,581 weighted index HF hospitalizations. For 1-year outcomes, the NRD calendar-year structure limits follow-up beyond December 31 of the index year; therefore, index discharges were restricted to January-June of each year to maximize within-year follow-up, yielding a final 1-year analytic cohort of 7,336,360 weighted index HF hospitalizations. Readmissions flagged as planned by HCUP were excluded from outcome ascertainment. Study size was determined by the full available national sample of eligible index HF hospitalizations in the 2016-2022 NRD.

Covariates

Covariates included patient demographics (age, sex, primary payer, and ZIP code-based income quartile), hospital-level characteristics (bed size, location, and teaching status), admission timing

(weekend vs. weekday), discharge disposition, and comorbidity burden measured by the Charlson Comorbidity Index.¹²

Primary Outcome Measures

The primary outcome was the first unplanned CV-specific readmission within 30 days or 1 year following discharge from the index HF hospitalization. CV-specific readmissions were identified using the principal diagnosis field of the readmission record and classified by ICD-10 codes. For each diagnostic category, only the first qualifying CV-specific readmission was counted. Intervening non-CV readmissions did not censor follow-up and were not counted as outcome events. Because outcomes were defined as diagnosis-specific first cardiovascular readmissions identified using the principal diagnosis field, rather than all-cause readmissions or any-diagnosis events, absolute readmission percentages are lower than commonly reported all-cause HF readmission rates. For the 1-year outcomes, only index admissions between January and June for each year were included to maximize the follow-up times for each index admission.

CV-specific readmissions included hospitalizations for HF or pulmonary edema (I50.0-I50.9, J81.0-J81.1), acute myocardial infarction (I21.0-I21.9), arrhythmias or conduction disorders (I47.0-I49.9), stroke or transient ischemic attack (I60.0-I63.9, G45.9), hypertension or hypertensive crisis (HTN; I10-I16), pulmonary circulation disorders (I26.0-I27.9), and venous thromboembolism (I82.0-I82.9). Each CV-specific endpoint was defined a priori as a diagnosis group using inclusive ICD-10 code ranges applied to the principal diagnosis field; readmissions were assigned to a single group based on that principal diagnosis.

Secondary Outcome Measures

Secondary analyses compared individual substance categories and the risk of acute MI-specific readmission at 30 days and 1 year. Specific SUDs were identified using ICD-10 codes F10.10-F19.99, including alcohol (F10.10-F10.99), opioid (F11.10-F11.99), cannabis (F12.10-F12.99), sedative/hypnotic/anxiolytic (F13.10-F13.99), cocaine (F14.10-F14.99), other stimulant use such as amphetamine or methamphetamine (F15.10-F15.99), hallucinogen (F16.10-F16.99), inhalant (F18.10-F18.99), and other or multiple SUDs (F19.10-F19.99). Each substance category was evaluated independently to identify associations with 30-day and 1-year acute MI-specific readmissions, assessing substance-specific contributions to MI risk within the HF population.

Substance use disorder categories were not treated as mutually exclusive. Each substance category was evaluated independently as a binary exposure (presence vs absence), such that the comparator group for a given substance could include patients with other co-occurring substance use disorders. This approach reflects the high prevalence of polysubstance use in real-world heart failure populations; therefore,

observed associations should be interpreted as substance-associated rather than substance-isolated effects.

Statistical Analysis

Survey-weighted estimates were calculated using HCUP-provided discharge weights. Demographic characteristics were summarized as means and standard errors (SEs) for continuous variables, and weighted proportions with SEs for categorical variables between discharges with no SUD and with SUD. Cox proportional hazards models were constructed to estimate adjusted hazard ratios (aHRs) with 95% confidence intervals (CIs) for each CV-specific diagnosis, adjusting for all covariates. For substance-specific analyses of acute myocardial infarction readmission, models used the same covariate set as the primary analyses. Time zero was defined as discharge from the index heart failure hospitalization. Statistical significance was set at $p \leq .001$ to minimize the risk of type I error given the large sample size. Because the NRD contains de-identified administrative data, selection bias was minimized through inclusion of all eligible hospitalizations meeting prespecified criteria, and misclassification bias was mitigated through use of validated ICD-10 coding definitions. Missing data for demographic and hospital variables were $<1\%$ and handled through complete case analysis consistent with HCUP recommendations. Because the NRD does not capture out-of-hospital mortality, formal competing-risk models for death could not be implemented; therefore, hazard ratios reflect cause-specific associations with CV readmission rather than cumulative incidence.

Software and Ethics Compliance

All analyses were performed using Stata SE 18 (StataCorp, 2023). The study adhered to the HCUP Data Use Agreement. The Creighton University Biomedical Institutional Review Board determined that this study did not constitute research involving human subjects as defined by 45 CFR 46.102 (Submission No. **2005432-01**; determination: **Not Human Subjects Research [NHSR]**); therefore, IRB review and approval were not required.

RESULTS

Baseline Characteristics

Among 14,535,581 weighted index HF hospitalizations, 24.4% had co-occurring SUD. Index HF hospitalizations with co-occurring SUD involved younger individuals (59.1 vs 69.4 years) and less often female (35.1% vs 46.8%; both $p < .001$). They were disproportionately in the lowest income quartile (43.4% vs 32.7%) and were more frequently covered by Medicaid (28.4% vs 9.69%) or self-pay (6.16% vs 2.12%; all $p < .001$). Discharge against medical advice was over fivefold higher in SUD than non-SUD hospitalizations (4.82% vs 0.92%, $p < .001$). Differences were statistically significant across all baseline demographic, socioeconomic, hospital, comorbidity, and discharge disposition variables (Table 1; all $p < .001$).

30-Day Cardiovascular Readmissions

Within 30 days, MI conferred the largest CV-specific readmission hazard (aHR 1.09; 95% CI 1.06-1.12; $p<.001$), with corresponding rates of 0.45% in SUD vs 0.39% in non-SUD. Arrhythmias or conduction disorders (aHR 0.81; 95% CI 0.79-0.83; $p<.001$), pulmonary circulation disorders (aHR 0.66; 95% CI 0.61-0.73; $p<.001$), and stroke or TIA (aHR 0.93; 95% CI 0.90-0.96; $p<.001$) were associated with a lower readmission hazard among SUD hospitalizations. Non-significant 30-day hazards were detected for Heart Failure/Pulmonary Edema (aHR 1.01; 95% CI 0.99-1.03; $p=0.24$) and hypertension or hypertensive crisis (aHR 0.99; 95% CI 0.98-1.01; $p=0.37$). All results, including those not demonstrating statistical significance, are presented in Table 2 and illustrated in Figure 2.

1-Year Cardiovascular Readmissions

Among 7,336,360 eligible patients, findings persisted at 1 year. MI remained the diagnosis with the greatest SUD-associated hazard (aHR 1.13; 95% CI 1.10-1.15; $p<.001$; unadjusted 1.37% vs 1.24%). HTN (aHR 1.02; 95% CI 1.01-1.03; $p<.001$; 12.1% vs 10.8%) showed a modest but significantly elevated readmission hazard during the 1-year readmission. Stroke/TIA showed a modest elevation (aHR 1.03; 95% CI 1.00-1.06; $p=0.038$), which did not meet the prespecified $p\leq.001$ threshold. Arrhythmias or conduction disorders (aHR 0.83; 95% CI 0.82-0.85; $p<.001$) and pulmonary circulation disorders (aHR 0.66; 95% CI 0.61-0.71; $p<.001$) were associated with a lower readmission hazard in SUD hospitalizations. Venous thromboembolism (aHR 0.92; 95% CI 0.85-0.99; $p=0.039$) did not meet the prespecified significance threshold. All results, including those not demonstrating statistical significance, are presented in Table 2 and illustrated in Figure 3.

Substance-Specific Associations of Acute Myocardial Infarction Readmission

Among patients with HF and co-occurring SUD, alcohol use was most prevalent (21.8%), followed by cannabis (8.47%), other stimulant use including amphetamines and methamphetamine (8.32%), cocaine (7.75%), and opioids (7.31%). Less frequent substances were sedative (0.80%), multiple substance (2.76%), hallucinogen (0.14%), and inhalant (0.02%) use disorders.

At 30 days, cannabis (aHR 1.17; 95% CI 1.08-1.27; $p<.001$) and other stimulant use (aHR 1.17; 95% CI 1.09-1.26; $p<.001$) were associated with increased readmission hazard of acute MI readmission, while alcohol (aHR 0.68; 95% CI 0.64-0.73; $p<.001$) and opioid use (aHR 0.67; 95% CI 0.61-0.73; $p<.001$) were associated with lower readmission hazard due to MI. All results, including those not demonstrating statistical significance, are presented in Table 3.

At 1 year, cannabis (aHR 1.22; 95% CI 1.15-1.31; $p<.001$), other stimulant (aHR 1.21; 95% CI 1.14-1.28; $p<.001$), and cocaine use (aHR 1.16; 95% CI 1.09-1.24; $p<.001$) were associated with higher MI readmission hazard, whereas alcohol (aHR 0.73; 95% CI 0.69-0.77; $p<.001$) and opioid use (aHR 0.75;

95% CI 0.68-0.81; $p < .001$) demonstrated a lower readmission hazard. Hallucinogen, inhalant, sedative, and multiple SUDs were not significantly associated with MI readmissions. All results, including those not demonstrating statistical significance, are presented in Table 3.

DISCUSSION

Primary Findings: Risk vs. Frequency

Hazard ratios reflect relative differences in event rates over follow-up and should be interpreted alongside absolute readmission proportions and absolute differences to convey real-world clinical impact.

MI showed the largest SUD-associated relative aHR for CV readmission at both 30 days (aHR 1.09) and 1 year (aHR 1.13), corresponding to a 9% and 13% increased risk, respectively. This consistent, diagnosis-specific association suggests that MI may represent an important target for risk mitigation strategies in index HF hospitalizations with co-occurring SUD.

Importantly, the absolute proportion of MI-specific readmissions was small despite the consistent relative association. At 30 days, MI readmission occurred in 0.45% of SUD-associated index HF hospitalizations versus 0.39% in non-SUD hospitalizations (absolute difference 0.06%). At 1 year, MI readmission occurred in 1.37% versus 1.24% (absolute difference 0.13%). Thus, MI represents a lower-frequency outcome with the strongest relative SUD-associated signal, whereas diagnoses such as HTN account for substantially higher absolute readmission volume.

HTN produced the greatest absolute number of CV readmissions, but its SUD-associated effect size was small (aHR 0.99 at 30 days; 1.02 at 1 year). HTN therefore reflects high event volume with limited SUD specificity. HF or pulmonary edema showed point estimates slightly above 1.0, but these associations were not statistically significant at either 30 days or 1 year. Accordingly, we center the mechanistic discussion on MI while also emphasizing the importance of routine blood pressure (BP) optimization in post-discharge care.

Demographic and Social Determinants of Risk

The observed demographic differences, including patients with SUD being younger, more likely to be male, and disproportionately socioeconomically disadvantaged, mirror patterns seen in other HF and SUD research.^{7,8} These patients were more frequently in the lowest income quartiles, had higher rates of Medicaid or self-pay status, and were less often discharged to designated centers or with home health services. Such disparities reflect a population with limited access to longitudinal care, fragmented insurance coverage, and greater social instability, all of which likely contribute to barriers in medication adherence, timely follow-up, and engagement in secondary prevention. Moreover, the markedly higher proportion of discharge against medical advice among patients with SUD further underscores the

challenges of sustained care engagement in this group. Collectively, these social and structural determinants exacerbate vulnerability in the critical post-discharge window, amplifying the risk of preventable readmissions and adverse outcomes.

Substance-Specific Associations with MI Readmission and Potential Mechanisms

Substance-specific analyses demonstrated that cannabis and other stimulant use (including amphetamine/methamphetamine) were each associated with higher hazards of acute MI readmission at 30 days (cannabis aHR 1.17; other stimulants aHR 1.17; both $p < .001$) and at 1 year (cannabis aHR 1.22; other stimulants aHR 1.21; both $p < .001$). Cocaine use was not associated with a higher hazard of MI readmission at 30 days (aHR 1.00, $p = 0.97$) but was associated with higher MI readmission hazard at 1 year (aHR 1.16, $p < .001$).

Stimulants represent potent cardiovascular stressors, with multiple agents converging on sympathetic activation and coronary vasoconstriction/vasospasm that can precipitate ischemia and infarction in susceptible patients.¹³ In parallel, catecholamine surges can promote a transient prothrombotic milieu through platelet activation and coagulation pathway stimulation, which may further increase acute coronary event risk.¹⁴

Cocaine is strongly linked to acute sympathetic stimulation via norepinephrine reuptake blockade, producing coronary vasoconstriction/vasospasm and an abrupt increase in myocardial oxygen demand while simultaneously reducing oxygen supply, predisposing to infarction even without significant coronary stenosis.¹³

Other stimulants, including methamphetamine, are associated with sustained sympathetic activation and coronary vasoconstriction, and chronic exposure is linked to vascular inflammation, endothelial activation, and adverse cardiac remodeling that may increase ischemic vulnerability.¹⁵ MDMA has also been associated with acute tachycardia, HTN, hyperthermia, and metabolic stress that can increase myocardial oxygen demand and contribute to ischemic risk.¹⁶

Cannabis has been associated with endothelial dysfunction and platelet activation, including mechanistic evidence that Δ^9 -tetrahydrocannabinol can upregulate platelet activation markers and promote oxidative stress-mediated endothelial injury in ways that may favor thrombosis and ischemia.¹⁷⁻¹⁹

In addition to mechanistic reports, population-level analyses have described dose-response relationships between cannabis use frequency and increased odds of MI and stroke, including analyses attempting to account for tobacco exposure.²⁰ Because HF is characterized by impaired coronary flow reserve, endothelial dysfunction, microvascular disease, and heightened wall stress, these exposures may plausibly reduce ischemic reserve and lower the threshold for recurrent ischemia after discharge, although these mechanisms should be interpreted as biologic plausibility rather than causal inference

within administrative data, given potential confounding from co-occurring tobacco use and other unmeasured behaviors.²¹

Conversely, alcohol and opioid use disorders were associated with lower cause-specific hazards of MI readmission at 30 days and 1 year. These inverse associations should not be interpreted as cardioprotective effects. Given the observational design and the use of administrative coding, the findings may reflect residual confounding (including tobacco exposure and other unmeasured behaviors), differential clinical pathways, competing events (e.g., death or non-cardiovascular readmission), or variability in diagnosis coding that influences whether MI is recorded as the principal diagnosis on readmission. Accordingly, these results are best interpreted as substance-associated patterns of MI readmission rather than evidence of biological protection.

Mechanistic Convergence in Index HF Hospitalizations with Co-Occurring SUD

While plausible biological mechanisms may explain the elevated MI readmission hazards observed for stimulants and cannabis, mechanistic discussion should be interpreted in the context of administrative data limitations and does not establish causality. HF features, including impaired coronary flow reserve, endothelial dysfunction, microvascular disease, and heightened wall stress, lower the threshold for ischemia when demand rises or vasospasm occurs. Endothelial dysfunction in HF reflects impaired vasoreactivity and a proinflammatory, prothrombotic vascular milieu that can reduce ischemic reserve.²¹ Superimposing stimulant surges or cannabis-related vasospasm onto this vulnerable baseline may further reduce ischemic reserve. While such mechanisms are biologically plausible, the NRD cannot determine active vs remote exposure, severity or route of use, timing relative to readmission, MI subtype (Type 1 vs Type 2), post-discharge treatment initiation, or out-of-hospital mortality. Accordingly, these findings should be interpreted as associations within an administrative dataset rather than evidence of substance-specific causation.

Clinical Implications

Our findings highlight potential areas for integrated strategies that address both CV and addiction-related risks in index HF hospitalizations with co-occurring SUD. Heightened attention to conventional ischemic risk reduction strategies may be considered in patients with co-occurring SUD, given the observed associations in this cohort.^{13,15,22,23} Equally critical is pairing cardiac care with addiction services, as psychosocial interventions such as contingency management, motivational interviewing, and cognitive behavioral therapy reduce dropout and increase abstinence among psychostimulant users, with contingency management showing the most consistent benefit.²⁴ Linking such interventions to HF transitional care may be an area for further study to determine whether integrated models can improve adherence and CV outcomes. In parallel, structured BP optimization remains important given the high-volume hypertension burden, while MI-focused risk assessment and secondary prevention strategies may

warrant consideration in patients with co-occurring SUD, particularly among those with cannabis or stimulant use disorders who demonstrated higher observed cause-specific hazards of MI readmission in this analysis.

For patients with cannabis use disorder, we recommend documenting current use patterns (frequency and route), counseling on potential ischemic risk, and prioritizing linkage to cessation support and behavioral treatment as part of HF transitional care. For patients with stimulant use disorders (including methamphetamine/amphetamine and cocaine), these findings support early post-discharge follow-up with explicit reassessment of ongoing stimulant exposure, proactive referral to addiction medicine or behavioral health, and integration of evidence-based psychosocial interventions (e.g., contingency management and cognitive behavioral therapy) alongside cardiovascular care. In these higher-risk subgroups, clinicians may also consider a lower threshold for reinforcing MI secondary prevention and adherence supports during the early post-discharge period.

Given the marked increase in self-reported daily or near-daily cannabis use over recent decades and the higher MI readmission hazards observed among index HF hospitalizations with cannabis use disorder in this analysis, assessment of cannabis use history should be considered during CV risk assessment in patients hospitalized with HF.²⁵

Study Limitations

Administrative ICD-10 coding cannot distinguish active versus former use, severity, route, or timing of substance exposure, and polysubstance use is inconsistently captured; because substance categories were not mutually exclusive, residual confounding by co-occurring substances (including tobacco) may influence observed associations. Tobacco exposure is a key confounder for myocardial infarction risk. Because the NRD lacks detailed smoking variables (e.g., pack-years, current vs former use) and nicotine dependence coding (F17.x) incompletely captures true tobacco exposure, residual confounding by tobacco use cannot be excluded and may partially contribute to observed MI readmission associations, particularly in cannabis and stimulant subgroups. In addition, observed inverse associations for alcohol or opioid use disorders may reflect selection effects, competing events, or residual confounding rather than true reductions in ischemic risk. The NRD observes readmissions only within the same calendar year and participating states; patients who die after discharge, relocate, or are readmitted across state lines may be missed, which could underestimate longer-term events.

Competing events represent an important consideration in this analysis. The NRD does not capture out-of-hospital mortality, precluding formal competing-risk modeling for death. In addition, non-cardiovascular readmissions were not treated as competing events but rather allowed to occur without censoring. As a result, the reported hazard ratios reflect cause-specific associations with CV readmission among patients

remaining at risk and should not be interpreted as cumulative incidence. If mortality or non-CV readmission differs systematically by SUD status, effect estimates may be biased in uncertain directions.

Because outcomes were defined as diagnosis-specific first CV readmissions using the principal diagnosis field, rather than all-cause or any-diagnosis events, absolute readmission percentages are lower than those reported in all-cause HF readmission studies. We lacked granular clinical data (ejection fraction, ischemia burden, troponin or angiography findings, medication adherence) and toxicology results, so the temporal relationship between substance exposure and readmission could not be established. Process-of-care measures (addiction-medicine consults, initiation of medications for opioid or alcohol use disorder, contingency management, or referral completion) were unavailable, limiting adjustment for treatment effects that might mitigate risk. Differential coding practices for both MI and substance use across hospitals and states may bias effect estimates in uncertain directions. We did not differentiate Type 1 from Type 2 MI, which may have distinct pathophysiology in the context of substance use and HF. Finally, unmeasured social determinants (housing instability, transportation, caregiver support) may contribute to readmission risk but were not available in this dataset.

Future Directions

Building on these findings, future studies should move beyond association toward mechanistic precision. Prospective cohorts with integrated toxicology, biomarker, and imaging data could clarify substance-specific contributions to coronary spasm, microvascular dysfunction, and thrombosis in the vulnerable HF population. Within cannabis use, further stratification by mode of administration (e.g., smoked, vaporized, edible, or concentrated products) is warranted, as route-specific pharmacokinetics and cardiometabolic effects may confer differing levels of CV risk. Randomized and pragmatic trials should evaluate targeted interventions, such as calcium-channel blockers or nitrates for vasospasm-prone patients, stimulant cessation programs, and opioid-sparing analgesia protocols that preserve antiplatelet efficacy. Parallel implementation science work is needed to test models of addiction-informed HF care, integrating cardiology and psychiatry to improve adherence to secondary prevention. Finally, linkage of administrative data with longitudinal registries would enable competing-risk analyses and track longer-term outcomes. Together, these efforts can identify modifiable mechanistic pathways and translate them into precision strategies to reduce MI readmission risk in index HF hospitalizations with co-occurring SUD.

Conclusion

In this nationally representative cohort of patients hospitalized for HF, co-occurring SUD was associated with a significantly higher risk of selected CV-specific readmissions, with acute MI emerging as the CV diagnosis with the strongest relative association with readmission at both 30 days and 1 year. In substance-specific analyses, the strongest associations with MI readmission were observed for cannabis and other stimulant use at both 30 days and 1 year, with cocaine additionally associated with higher MI

readmission hazard at 1 year. Patients with SUD were younger, predominantly male, and disproportionately socioeconomically disadvantaged, reflecting a distinct and highly vulnerable phenotype. These findings highlight an urgent need for integrated models of CV and addiction care that emphasize early post-discharge follow-up, rigorous secondary prevention, and strategies to address structural barriers to adherence. Targeted interventions aimed at mitigating ischemic risk represent a critical opportunity to reduce preventable readmissions and improve long-term outcomes. Future work should advance from descriptive association to mechanistic and interventional precision, with the goal of translating these insights into tailored strategies that can close the gap in care for this at-risk population.

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FIGURES

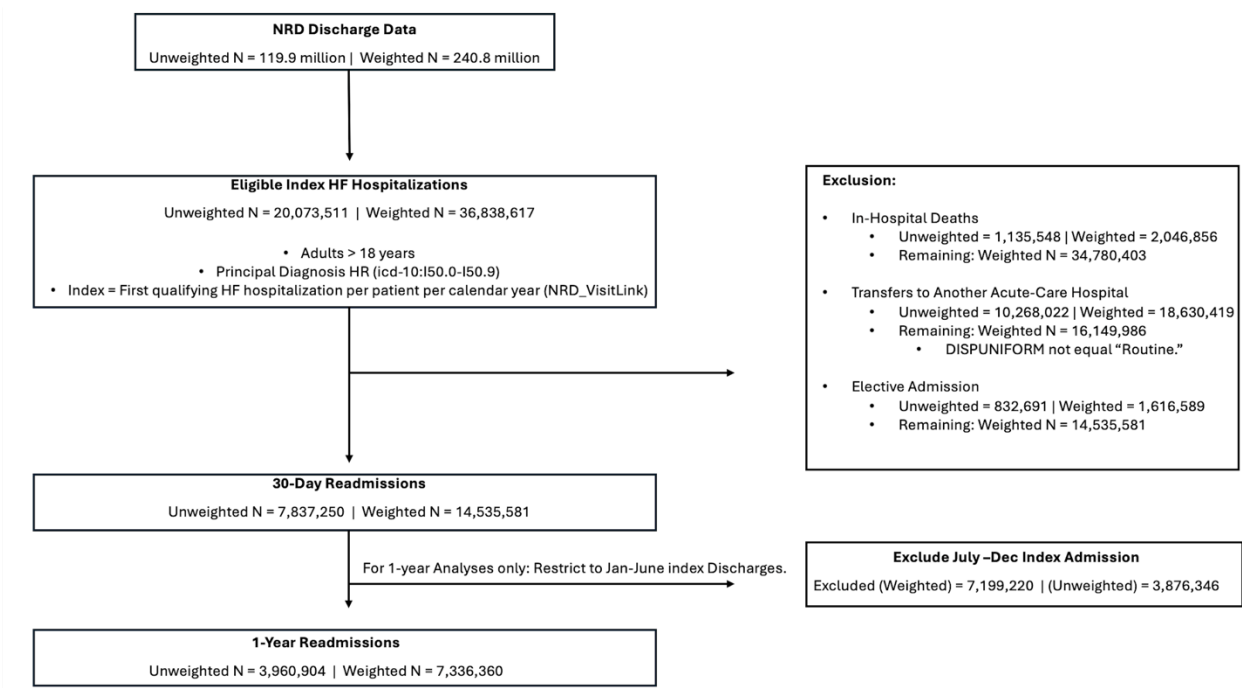


Figure 1: Cohort Selection Flow Diagram and Analytic Sample Sizes (NRD 2016-2022)

Flow diagram showing construction of the index heart failure (HF) cohort from the Nationwide Readmissions Database (NRD), 2016-2022. Eligible index HF hospitalizations included adults ≥ 18 years with a principal diagnosis of HF (ICD-10: I50.0-I50.9), defining the index as the first qualifying HF hospitalization per patient per calendar year using NRD_VisitLink (unweighted N = 20,073,511; weighted N = 36,838,617). Exclusions were applied sequentially: in-hospital deaths (excluded unweighted n = 1,135,548; weighted n = 2,046,856), discharges with DISPUNIFORM not equal to "Routine" (excluded unweighted n = 10,268,022; weighted n = 18,630,419), and elective admissions (excluded unweighted n = 832,691; weighted n = 1,616,589), yielding the final 30-day analytic cohort (unweighted N = 7,837,250; weighted N = 14,535,581). For 1-year analyses, index discharges were restricted to January-June to maximize within-year follow-up, excluding July-December index admissions (excluded unweighted n = 3,876,346; weighted n = 7,199,220) and yielding the final 1-year analytic cohort (unweighted N = 3,960,904; weighted N = 7,336,360).

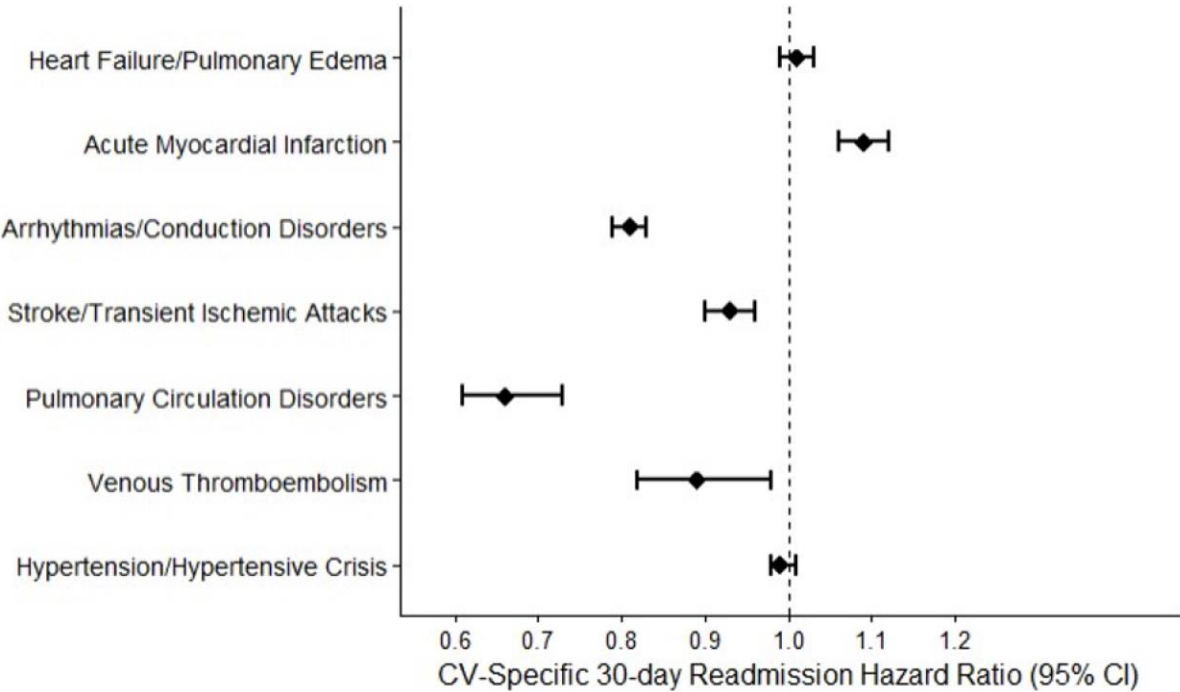


Figure 2: Adjusted Hazard Ratios for 30-Day Cardiovascular-Specific Readmissions by Diagnosis

Forest plot showing adjusted hazard ratios with 95% confidence intervals for cardiovascular-specific readmissions within 30 days among heart failure patients with substance use disorder. Myocardial infarction showed the highest adjusted hazard of diagnosis-specific readmission in patients with substance use disorder (aHR 1.09, 95% CI 1.06-1.12, $p < .001$). Conversely, the risk of readmission due to stroke/TIA, arrhythmias/conduction disorders, and pulmonary circulation disorders was lower among patients with SUD. Models were adjusted for demographic, clinical, and hospital-level covariates.

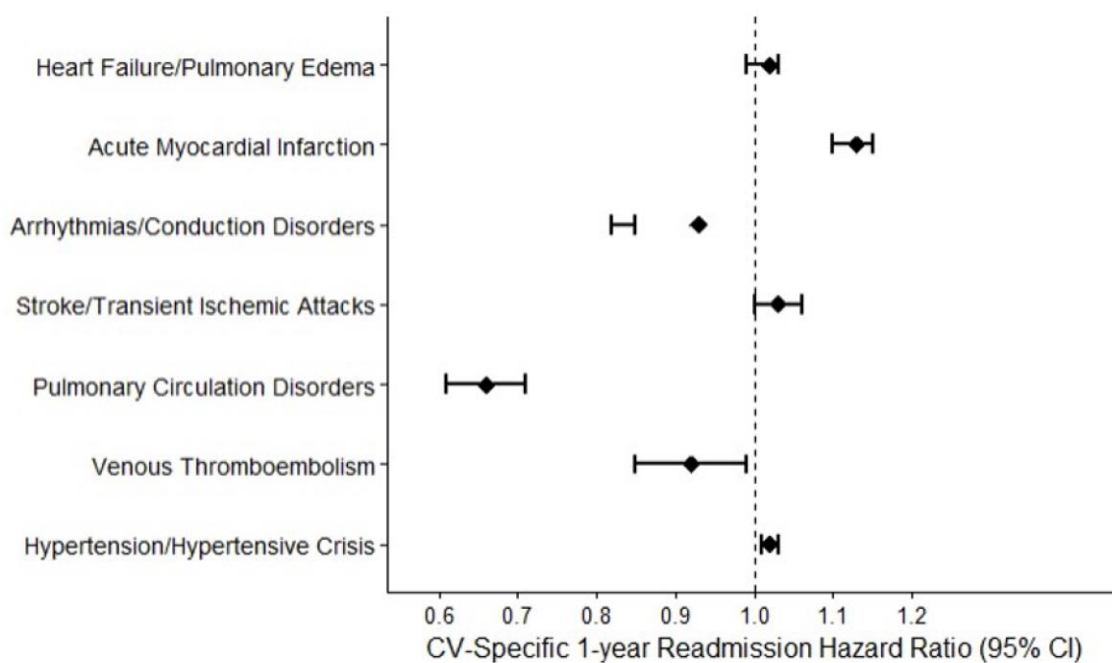


Figure 3: Adjusted Hazard Ratios for 1-Year Cardiovascular-Specific Readmissions by Diagnosis

Forest plot showing adjusted hazard ratios with 95% confidence intervals for cardiovascular-specific readmissions within 1 year among heart failure patients with substance use disorder. Myocardial infarction remained the leading diagnosis with the highest adjusted readmission hazard of diagnosis-specific readmission in patients with SUD (aHR 1.13, 95% CI 1.10-1.15, $p < .001$), with additional modest readmission hazard elevation for hypertension or hypertensive crisis (aHR 1.02, 95% CI 1.01-1.03, $p < .001$). Stroke or TIA showed a positive trend but did not meet statistical significance (aHR 1.03, 95% CI 1.00-1.06, $p = 0.038$). Models were adjusted for demographic, clinical, and hospital-level covariates.

Demographics (Weighted N = 14,535,581)	No Substance Use Disorder (75.6%)	Substance Use Disorder (24.4%)	p-value
Age, years (mean, SE)	69.4 (0.006)	59.1 (0.009)	< .001
Sex, Female (% , SE)	46.8 (0.022)	35.1 (0.037)	< .001
Income Quartile (% , SE)			< .001
1	32.7 (0.02)	43.4 (0.038)	
2	28.0 (0.019)	27.5 (0.035)	
3	23.2 (0.018)	19.1 (0.03)	
4	16.1 (0.015)	10.1 (0.022)	
Primary Payer (% , SE)			< .001
Medicare	71.9 (0.019)	47.0 (0.039)	
Medicaid	9.69 (0.013)	28.4 (0.035)	
Private	13.9 (0.015)	14.5 (0.028)	
Self-Pay	2.12 (0.006)	6.16 (0.019)	
Other	2.50 (0.007)	3.85 (0.015)	
Weekend Admission (% , SE)	23.8 (0.019)	24.8 (0.034)	< .001
Patient Location (% , SE)			< .001
Urban	81.5 (0.015)	80.2 (0.03)	
Rural	18.5 (0.015)	19.8 (0.03)	
Hospital Location (% , SE)			< .001
Urban/Non-Teaching	20.1 (0.008)	19.5 (0.026)	
Urban/Teaching	69.8 (0.010)	70.7 (0.03)	
Rural	10.1 (0.007)	9.79 (0.021)	
Hospital Bed size (% , SE)			< .001
Small	18.3 (0.009)	17.4 (0.026)	
Medium	26.8 (0.01)	27.0 (0.03)	
Large	54.9 (0.012)	55.6 (0.034)	
Charlson Comorbidity Index (% , SE)			< .001
0–1	9.45 (0.013)	9.56 (0.023)	
2	20.2 (0.018)	23.0 (0.033)	
≥3	70.4 (0.02)	67.4 (0.037)	
Disposition at Discharge (% , SE)			< .001
Home	42.6 (0.01)	58.0 (0.03)	
Short Term Facility	1.19 (0.003)	1.23 (0.007)	
Designated Center	27.9 (0.01)	16.2 (0.02)	
Home Healthcare	27.2 (0.01)	19.7 (0.02)	
Against Medical Advice	0.92 (0.003)	4.82 (0.01)	

Table 1: Baseline Demographic and Clinical Characteristics of Heart Failure Patients With and Without Substance Use Disorder.

Comparison of weighted patient characteristics among adults hospitalized for index heart failure in the 30-day analytic cohort (weighted N = 14,535,581), stratified by the presence of substance use disorder. Patients with substance use disorder were younger, more often male, more frequently in the lowest income quartile, and had higher rates of Medicaid or self-pay status. They were also more likely to be admitted on weekends, leave against medical advice, and less likely to be discharged to designated centers or home health care. Differences were significant across all listed variables ($p < .001$). Abbreviation: SE = standard error.

CV-Specific Outcomes	No Substance Use Disorder (75.6%)	Substance Use Disorder (24.4%)	aHR (95% CI)	p-value
<u>30-day Readmission</u> <u>(Weighted N = 14,535,581)</u>	% (SE)	% (SE)		
Heart Failure/Pulmonary Edema	0.80 (0.004)	1.06 (0.008)	1.01 (0.99, 1.03)	0.24
Acute Myocardial Infarction	0.39 (0.002)	0.45 (0.005)	1.09 (1.06, 1.12)	< .001
Arrhythmias/Conduction Disorders	0.78 (0.004)	0.67 (0.006)	0.81 (0.79, 0.83)	< .001
Stroke/Transient Ischemic Attacks	0.31 (0.002)	0.29 (0.004)	0.93 (0.90, 0.96)	< .001
Pulmonary Circulation Disorders	0.042 (0.0009)	0.038 (0.002)	0.66 (0.61, 0.73)	< .001
Venous Thromboembolism	0.043 (0.0009)	0.047 (0.002)	0.89 (0.82, 0.98)	0.012
Hypertension/Hypertensive Crisis	3.92 (0.008)	4.68 (0.016)	0.99 (0.98, 1.01)	0.37
	No Substance Use Disorder (75.7%)	Substance Use Disorder (24.3%)	aHR (95% CI)	p-value
<u>1-year Readmission</u> <u>(Weighted N = 7,336,360)</u>	% (SE)	% (SE)		
Heart Failure/Pulmonary Edema	2.32 (0.009)	2.74 (0.018)	1.02 (0.99, 1.03)	0.08
Acute Myocardial Infarction	1.24 (0.007)	1.37 (0.012)	1.13 (1.10, 1.15)	< .001
Arrhythmias/Conduction Disorders	2.21 (0.009)	1.79 (0.015)	0.83 (0.82, 0.85)	< .001
Stroke/Transient Ischemic Attacks	0.99 (0.006)	0.95 (0.011)	1.03 (1.00, 1.06)	0.038
Pulmonary Circulation Disorders	0.12 (0.002)	0.10 (0.004)	0.66 (0.61, 0.71)	< .001
Venous Thromboembolism	0.11 (0.002)	0.11 (0.004)	0.92 (0.85, 0.99)	0.039
Hypertension/Hypertensive Crisis	10.8 (0.019)	12.1 (0.036)	1.02 (1.01, 1.03)	< .001

Table 2: Cardiovascular-Specific Readmission Outcomes in Heart Failure Patients With and Without Substance Use Disorder.

Rates of cardiovascular-specific readmissions at 30 days and 1 year following index heart failure hospitalization, stratified by substance use disorder. Acute myocardial infarction had the highest adjusted hazard (largest relative association) of diagnosis-specific readmission in SUD patients at both 30 days (aHR 1.09, 95% CI 1.06-1.12; $p < .001$) and 1 year (aHR 1.13, 95% CI 1.10-1.15; $p < .001$). Associations meeting the prespecified significance threshold ($p \leq 0.001$) included lower hazards of arrhythmias/conduction disorders and pulmonary circulation disorders at both time points, lower hazards of stroke/TIA at 30 days, and a modestly higher hazard of hypertension/hypertensive crisis at 1 year. Models were adjusted for demographic, clinical, and hospital-level covariates. Statistical significance was prespecified as $p \leq 0.001$.

Abbreviations: aHR = adjusted hazard ratio; CI = confidence interval; CV = cardiovascular; HF = heart failure; SE = standard error; SUD = substance use disorder; TIA = transient ischemic attack.

Substances	30-Day Acute MI Specific Readmission (Weighted N = 14,535,581)			1-year Acute MI Specific Readmission (Weighted N = 7,336,360)		
	% (SE)	aHR (95% CI)	p-value	% (SE)	aHR (95% CI)	p-value
Alcohol						
No	0.41 (0.002)	REF		1.29 (0.006)	REF	
Yes	0.29 (0.009)	0.68 (0.64, 0.73)	< 0.001	0.90 (0.022)	0.73 (0.69, 0.77)	< .001
Opioids						
No	0.40 (0.002)	REF		1.27 (0.006)	REF	
Yes	0.33 (0.015)	0.67 (0.61, 0.73)	< 0.001	0.95 (0.038)	0.75 (0.68, 0.81)	< .001
Cannabis						
No	0.40 (0.002)	REF		1.27 (0.006)	REF	
Yes	0.47 (0.017)	1.17 (1.08, 1.27)	< 0.001	1.44 (0.045)	1.22 (1.15, 1.31)	< .001
Sedative						
No	0.40 (0.002)	REF		1.27 (0.006)	REF	
Yes	0.29 (0.045)	0.69 (0.50, 0.94)	< 0.001	1.15 (0.13)	0.97 (0.78, 1.21)	0.81
Cocaine						
No	0.39 (0.002)	REF		1.27 (0.006)	REF	
Yes	0.54 (0.02)	1.00 (0.93, 1.08)	0.97	1.51 (0.048)	1.16 (1.09, 1.24)	< .001
Other Stimulants						
No	0.40 (0.002)	REF		1.27 (0.006)	REF	
Yes	0.51 (0.017)	1.17 (1.09, 1.26)	< 0.001	1.45 (0.041)	1.21 (1.14, 1.28)	< .001
Hallucinogens						
No	0.40 (0.002)	REF		1.27 (0.006)	REF	
Yes	0.46 (0.14)	0.96 (0.52, 1.76)	0.89	1.24 (0.35)	0.97 (0.56, 1.69)	0.94
Inhalants						
No	0.40 (0.002)	REF		1.27 (0.006)	REF	
Yes	0.75 (0.44)	1.71 (0.53, 5.49)	0.37	1.45 (0.84)	0.98 (0.30, 3.17)	0.98
Multiple Substances						
No	0.40 (0.002)	REF		1.27 (0.006)	REF	
Yes	0.49 (0.032)	1.03 (0.91, 1.17)	0.62	1.27 (0.072)	1.07 (0.96, 1.20)	0.24

578

579 **Table 3:** Substance-Specific Rates and Risk of Acute Myocardial Infarction Readmissions at 30 Days and
580 1 Year

581 Rates of acute myocardial infarction-specific readmissions at 30 days and 1 year following index heart
582 failure hospitalization, stratified by individual substance use disorder categories. Cannabis and other
583 stimulant use disorders were associated with the highest adjusted readmission hazard of myocardial
584 infarction readmission at both 30 days (aHR 1.17, 95% CI 1.08-1.27; and aHR 1.17, 95% CI 1.09-1.26,
585 respectively) and 1 year (aHR 1.22, 95% CI 1.15-1.31; and aHR 1.21, 95% CI 1.14-1.28, respectively).
586 Models were adjusted for demographic, clinical, and hospital-level covariates. Statistical significance was
587 prespecified as $p \leq 0.001$.
588 Abbreviations: aHR = adjusted hazard ratio, MI = myocardial infarction, REF = reference group, SE =
589 standard error, CI = confidence interval.