

The implications of cocaine use and associated behaviors on adverse cardiovascular outcomes among veterans: Insights from the VA Clinical Assessment, Reporting, and Tracking (CART) Program

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Funding information

The study was funded by the US Department of Veterans Affairs. The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs of the US government. The authors are solely responsible for the design and conduct of this study, all study analyses, and drafting and editing the article. All authors have read and agreed to the manuscript as written.

Background: Cocaine use has been associated with adverse cardiovascular outcomes in patients with coronary artery disease (CAD). It is unclear whether this is due to direct effects of cocaine or other factors.

Hypothesis: Cocaine use is associated with worse outcomes in patients undergoing cardiac catheterization

Methods: We used the Veterans Affairs database to identify veterans undergoing coronary catheterization between 2007 and 2014. We analyzed association between cocaine use and 1-year all-cause mortality, myocardial infarction (MI), and cerebrovascular accident (CVA) among veterans with obstructive CAD (N = 122 035). To explore factors contributing to these associations, we sequentially adjusted for cardiac risk factors, risky behaviors, and clinical conditions directly affected by cocaine.

Results: 3082 (2.5%) veterans were cocaine users. Cocaine users were younger (median 58.2 vs 65.3 years; $P < 0.001$), more likely to be African American (58.9% vs 10.6%; $P < 0.001$), and had fewer traditional cardiac risk factors. After adjustment for cardiac risk factors, cocaine was associated with increased risk of mortality (HR: 1.23, 95% CI: 1.08-1.39), MI (HR: 1.40, 95% CI: 1.07-1.83), and CVA (HR: 1.88, 95% CI: 1.38-2.57). With continued adjustment, increased CVA risk remained significantly associated with cocaine use, whereas MI risk was mediated by risky behaviors and mortality was fully explained by conditions directly affected by cocaine.

Conclusions: Cocaine use is associated with adverse cardiac events in veterans with CAD. Contributors to this association are multifaceted and specific to individual cardiovascular outcomes, including associated risky behaviors and direct effects of cocaine. Effective intervention programs to reduce cardiac events in this population will require multiple components addressing these factors.

KEYWORDS

Cardiac Catheterization, Cocaine, Percutaneous Coronary Intervention

1 | INTRODUCTION

Cocaine has been associated with numerous toxic effects on the cardiovascular (CV) system, notably myocardial infarction (MI),

arrhythmias, congestive heart failure (CHF), cerebrovascular accidents (CVA), and sudden cardiac death.^{1,2} Several mechanisms of these effects have been proposed, including increased myocardial oxygen demand, coronary-artery vasoconstriction, enhanced platelet

aggregation, and thrombus formation.³ In addition, cocaine use has been associated with unhealthy lifestyle choices,⁴ comorbid mental and substance-abuse disorders,^{5,6} poor socioeconomic status,⁷ and medication noncompliance⁸—all of which also can lead to adverse CV events.

Currently, it is unclear how these potential mechanisms, individually and in aggregate, contribute to adverse CV outcomes. Better understanding of these mechanisms would help guide more effective prevention and treatment.

To address this gap, we described the association of cocaine use with the 1-year risk of all-cause mortality, MI, and CVA in a Veterans Affairs (VA) population of coronary artery disease (CAD) patients undergoing cardiac catheterization. We then performed sequential, multivariable adjustment to assess the relationships with important confounders such as basic cardiac risk factors, risky behaviors (eg, alcohol and other substance abuse), and conditions directly affected by cocaine (eg, psychological disorders, CHF, and end-stage renal disease). Insights from this analysis would be expected to inform more effective prevention and treatment options in this population.

2 | METHODS

2.1 | Study population source

The VA Clinical Assessment Reporting and Tracking (CART) program is a national quality initiative launched in 2005 focusing on coronary revascularization procedures conducted in all VA cardiac catheterization laboratories.⁹ A key feature of the CART program is a clinical software application designed to collect standardized data on all coronary angiograms and percutaneous coronary interventions (PCI).¹⁰ The software is embedded in the VA electronic health record and allows providers to enter patient and procedural information (preprocedure assessment, coronary angiography, and PCI) as part of routine clinical workflow. The CART software was designed using standardized definitions that conform to the definitions and standards of the American College of Cardiology (ACC) National Cardiovascular Data Registry (NCDR)¹¹ and incorporates features such as pull-down menus and automated clinical report generation to ensure uniformity of data entry by different providers and in different cardiac catheterization laboratories.¹² Participation in CART has been mandatory and universal in all VA cardiac catheterization laboratories since 2009. Quality checks of the data are periodically conducted for completeness and accuracy.¹³ CART data are combined with other VA data sources to create a longitudinal clinical database in support of the quality assessment, quality improvement, and clinical research missions of the CART program.

2.2 | Study population

A total of 218 387 veterans underwent cardiac catheterization during the study period between October 1, 2007, and September 31, 2014. We excluded all veterans without obstructive CAD, defined as 1-, 2-, or 3-vessel/left main obstructive disease by coronary angiography (n = 81 053, 37.1%); those with indeterminate cocaine use (n = 8725, 4.0%);

those missing procedural indication (n = 6537, 3.0%); and those without ≥1 year of administrative follow-up (n = 37, 0.02%) in the VA healthcare system. Our final study cohort consisted of 122 035 veterans.

2.3 | Cocaine use definition

Cocaine use was defined using *International Classification of Diseases, Ninth Revision* (ICD-9) codes for “cocaine abuse” and “cocaine dependence” (305.6x and 304.2x, respectively) associated with any visit to a VA facility in the year prior to cardiac catheterization. ICD-9 codes for “cocaine use in remission” (305.63 or 304.23) were excluded from the study to select for active cocaine users. Veterans were also excluded from the study population if drug use was indicated but no further ICD-9 codes specified the type of drug use.

2.4 | Outcomes

The outcomes of interest were rates of all-cause mortality, rehospitalization for MI, and CVA events during the year following the index angiogram. All-cause mortality was determined by the VA Vital Status file. MI and CVA events were assessed from the VA medical and administrative records, as well as the fee-based data files, using the ICD-9 codes associated with each condition.¹⁴

2.5 | Statistical analysis

We compared baseline demographic and clinical characteristics between veterans with and without cocaine use using χ^2 tests for categorical variables and Mann-Whitney Wilcoxon tests for continuous variables. Cox proportional hazards models were then used to

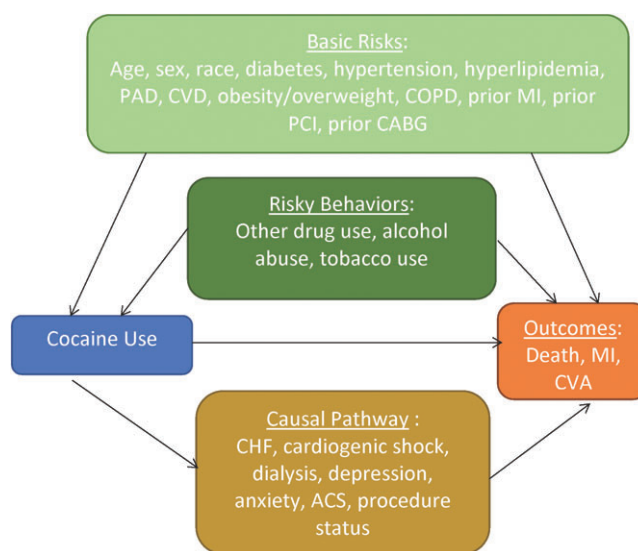


FIGURE 1 DAG of hypothesized confounders and mediators of cocaine use and adverse CV outcomes in veterans with obstructive CAD, based on prior research. Abbreviations: ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; CVA, cerebrovascular accident; CVD, cerebrovascular disease; DAG, directed acyclic graph; MI, myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention

determine the unadjusted associations between cocaine use and 1-year all-cause mortality, MI, and CVA.

To determine the relative impact of cardiac risk factors, risky behaviors, and the physiological effects of cocaine, we modeled the hypothesized relationships using directed acyclic graphs (DAGs; Figure 1).¹⁵ DAGs are graphical representations of relationships between the variables of interest and can assist in constructing models to test these relationships. Both basic cardiac risk factors and risky behaviors were modeled as potential confounders, with effects on both the exposure and the outcome, as shown in Figure 1. Basic risk factors included age, sex, race, diabetes, hypertension, hyperlipidemia, peripheral arterial disease,¹⁶ cerebrovascular disease, obesity/overweight, chronic obstructive pulmonary disease, prior MI, prior PCI, and prior coronary artery bypass grafting. Risky behaviors included alcohol abuse, tobacco use, and other drug use.⁶ It should be emphasized that our differentiation between “basic” risk factors and “risky” behaviors is derived from the aforementioned literature; to address this dichotomy, we analyzed all outcomes as unadjusted and adjusted for basic risks, basic risks and risky behaviors, and basic risks, risky behaviors with the DAG pathway (Figure 2).

Cocaine use may also have physiological effects that affect other major risk factors for adverse cardiac outcomes. Thus, we also examined “causal pathway” factors that may explain the connection between cocaine use and CV outcomes (ie, they are affected by cocaine use and have effects on the outcomes of interest, as shown in Figure 1). The potential “causal pathway” conditions that we examined included CHF, cardiogenic shock, dialysis, depression, anxiety, acute coronary syndrome (ACS) status, and clinical status at the time of the index catheterization (elective, emergent, urgent, or salvage).^{5,6}

The Cox models included a robust estimator of the covariance matrix to account for clustering by site. All tests for statistical significance were evaluated at a significance level of $P < 0.05$. Statistical analyses were performed by the CART Coordinating Center at the Denver VA Medical Center using SAS software, version 9.4 (SAS

Institute Inc., Cary, NC). The study was approved by the Colorado Multiple Institutional Review Board.

3 | RESULTS

3.1 | Baseline patient characteristics

Among all veterans undergoing cardiac catheterization, the prevalence of cocaine use was 3.5%. In our cohort of veterans with obstructive CAD, 3082 (2.5%) had evidence of cocaine use. Cocaine users were younger (median age, 58.2 vs 65.3 years; $P < 0.001$) and more frequently African American (58.9% vs 10.6%; $P < 0.001$; Table 1). There was a lower incidence of traditional cardiac risk factors among cocaine users, including diabetes, hyperlipidemia, peripheral arterial disease, CVA, and obesity ($P < 0.001$ for all). In contrast, psychological comorbidities and substance abuse were substantially higher among cocaine users ($P < 0.001$ for all). Cardiac catheterization was performed more frequently as an emergent (7.5% vs 3.7%) or urgent (35.4% vs 25.6%) procedure, rather than elective (57.1% vs 70.6%), in cocaine users (Table 2). ACS (36.3% vs 25.2%) was noted more frequently as the indication for cardiac catheterization in cocaine users. Cocaine users had lower rates of medical therapy for CAD prior to cardiac catheterization, including the use of β -blockers, nitrates, and statins. The degree of obstructive CAD was less severe in cocaine users than in non-cocaine users.

3.2 | Cocaine use and outcomes

In unadjusted analyses, cocaine use was associated with an increased risk of MI (hazard ratio [HR]: 1.31, 95% confidence interval [CI]: 1.02-1.69) and CVA (HR: 2.00, 95% CI: 1.54-2.61), but a decreased risk of mortality (HR: 0.86, 95% CI: 0.75-0.99; Figure 2). With adjustment for basic cardiac risk factors, cocaine was significantly associated with all 3 outcomes: mortality (HR: 1.23, 95% CI: 1.08-1.39), MI (HR: 1.40, 95% CI: 1.07-1.83), and CVA (HR: 1.88, 95% CI: 1.38-2.57).

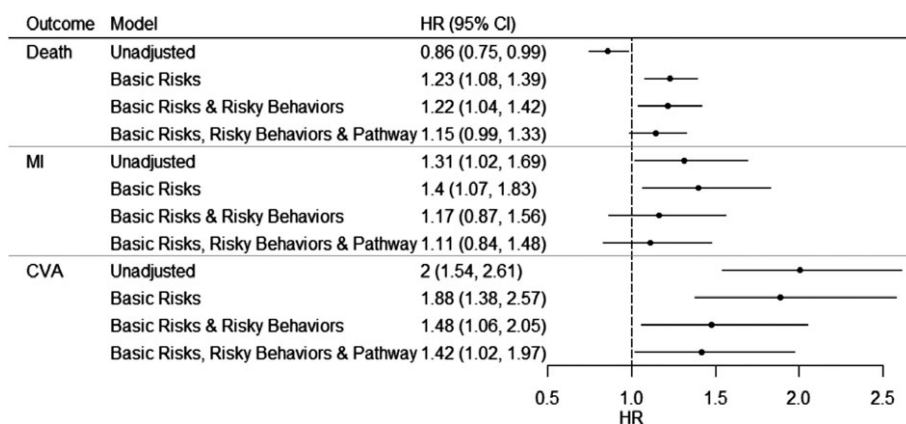


FIGURE 2 Sequential Cox proportional hazard models for death, MI, and CVA in veterans with obstructive CAD by cocaine use. Unadjusted: cocaine. Additional adjustment for basic risks: age, sex, race, DM, HTN, hyperlipidemia, PAD, CVD, obesity/overweight, COPD, prior MI, prior PCI, and prior CABG. Additional adjustment for risky behaviors: alcohol abuse, tobacco use, and other drug use. Additional adjustment for comorbid conditions affected by cocaine use (“causal pathway”): CHF, cardiogenic shock, dialysis, depression, anxiety, ACS, and clinical status (elective, emergent, urgent, or salvage). Abbreviations: ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CHF, congestive heart failure; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; CVD, cerebrovascular disease; DM, diabetes mellitus; HR, hazard ratio; HTN, hypertension; MI, myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention

TABLE 1 Baseline characteristics of veterans with obstructive CAD

	Total, N = 122 035	No Cocaine, n = 118 953	Cocaine, n = 3082	P Value
Demographics				
Age, y, median (IQR)	65.1 (60.9–71.9)	65.3 (61.1–72.2)	58.2 (53.7–62.1)	<0.001
Male sex	98.6	98.6	98.6	0.96
Race				
White	80.8	82	37.2	<0.001
Black	11.8	10.6	58.9	
Other	7.3	7.4	4	
CV risk factors				
DM	49.5	49.7	40.1	<0.001
HTN	90.3	90.3	89.8	0.43
Hyperlipidemia	89.5	89.8	78.1	<0.001
PAD	22.6	22.7	18.1	<0.001
CVD	18.4	18.5	14.5	<0.001
CHF	27.4	27.3	28.8	0.07
COPD	20.9	20.8	23.9	<0.001
Obesity	46.9	47.2	35.3	<0.001
Overweight	35.9	35.9	36.1	0.8
eGFR, mL/min/1.73 m ² , median (IQR)	72.4 (59.6–88.3)	72.2 (59.5–88.0)	80.0 (61.3–98.0)	<0.001
CKD	21	21	20.3	0.39
Dialysis	2.8	2.8	3.3	0.07
Psychological risk factors				
Chronic depression	27	26.4	51.7	<0.001
Anxiety	8.7	8.5	14.3	<0.001
Other substance use				
Tobacco use	61.9	61.3	84.6	<0.001
Alcohol abuse	7.2	6.1	47.3	<0.001
Any illicit drug other than cocaine	4.1	2.8	55.2	<0.001
Cannabis	2.6	1.7	35.1	<0.001
Sedatives	0.3	0.2	5	<0.001
Hallucinogens	0	0	0.6	<0.001
Amphetamines	0.3	0.2	5	<0.001
Opioids	1.4	0.9	21.3	<0.001
Unspecified type of drug use	0.2	0	6.6	<0.001
Prior procedures				
PCI	31	31.1	27.7	<0.0001
MI	36.3	36.3	37.4	0.21
CABG	26.8	27.1	15.1	<0.0001
FRS category				
Low	13.4	13.2	20	<0.0001
Medium	46.6	46.5	49.7	
High	40	40.3	30.3	

Abbreviations: CABG, coronary artery bypass grafting; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; CVD, cerebrovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; FRS, Framingham Risk Score; HTN, hypertension; IQR, interquartile range; MI, myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; SD, standard deviation. Data are presented as percentages (%) unless otherwise noted.

After adjustment for risky behaviors, mortality and CVA remained significantly associated with cocaine use (HR for mortality: 1.22, 95% CI: 1.04–1.42; HR for CVA: 1.48, 95% CI: 1.06–2.05), but MI was no longer significant (HR: 1.17, 95% CI: 0.87–1.56). After adjustment for causal pathway conditions, CVA remained significantly associated with cocaine use (HR: 1.42, 95% CI: 1.02–1.97), but mortality was no longer significant (HR: 1.15, 95% CI: 0.99–1.33).

3.3 | Overall mortality, MI, and stroke

In unadjusted Kaplan-Meier analyses, the overall mortality ($P = 0.024$) and stroke-free survival curves ($P < 0.001$) appear to separate gradually over the 1-year follow-up period. In contrast, the MI-free survival curve appears to separate at 75 days after initial cardiac catheterization and then remain parallel ($P = 0.005$; Figure 3).

TABLE 2 Procedural characteristics of veterans with obstructive CAD

Presentation	Total, N = 122 035	No Cocaine, n = 118 953	Cocaine, n = 3082	P Value
Indication for cardiac catheterization				
ACS	25.5	25.2	36.3	<0.001
Chest pain	44.4	44.4	41.4	
IHD	9.1	9.1	6.4	
Positive functional study	10.7	10.7	7.2	
Cardiomyopathy	3.8	3.8	4.7	
Valvular disease	2.8	2.9	1.2	
Other	3.8	3.8	2.8	
Cardiogenic shock	0.4	0.4	0.8	<0.001
Procedural status				
Elective	70.3	70.6	57.1	<0.001
Emergent	3.8	3.7	7.5	
Urgent	25.9	25.6	35.4	
Salvage	0.1	0.1	0	
Preprocedural stress testing	45	45.2	37.9	<0.001
Results				
Positive	42.1	42.1	42.6	0.83
Negative	2.8	2.8	3.3	
Equivocal	1.8	1.8	1.5	
Dysrhythmia	0	0	0	
Indeterminate	0.4	0.4	0.4	
Unknown	52.9	53	52.1	
Medications at presentation				
β-Blockers	60	60.3	50.4	<0.001
Nitrates	38	38.1	33.1	<0.001
CCBs	23.8	23.8	24.1	0.62
Statins	62.9	63.2	50.6	<0.001
Angiographic findings				
1-vessel obstructive	35.6	35.3	45.8	<0.001
2-vessel obstructive	26.3	26.3	26	
3-vessel/LM obstructive	38.1	38.3	28.2	

Abbreviations: ACS, acute coronary syndrome; CAD, coronary artery disease; CCB, calcium channel blocker; IHD, ischemic heart disease; LM, left main artery. Data are presented as percentages (%).

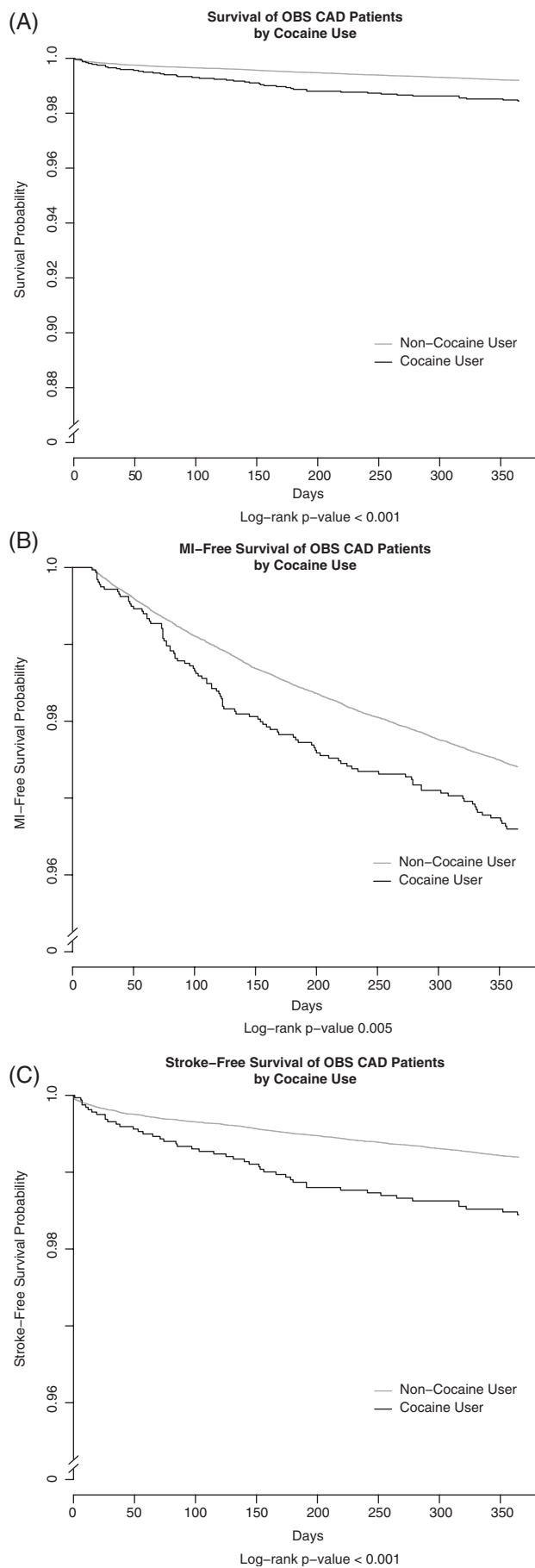
4 | DISCUSSION

In this retrospective observational study of cocaine use among veterans with obstructive CAD undergoing cardiac catheterization, we confirmed the association between cocaine use and adverse CV outcomes and found that the contributors to this association varied by outcomes. Specifically, the association between cocaine and increased mortality risk was no longer apparent after adjustment for “causal pathway” conditions directly affected by cocaine, which included CHF, cardiogenic shock, dialysis, depression, anxiety, ACS, and clinical status at the time of index catheterization. The association with increased risk of MI was no longer apparent after adjustment for risky behaviors associated with cocaine use, which included alcohol abuse, tobacco use, and other drug use. Finally, increased risk of CVA remained significantly associated with cocaine, even after adjustment for basic cardiac risk factors, risky behaviors, and causal pathway conditions.

This study extends our knowledge about the effects of cocaine on adverse CV outcomes. It is the largest study, to our knowledge, of

veterans with CAD undergoing cardiac catheterization, which enables us to more fully explore contributors to this association. It reveals a concerning prevalence of cocaine use (3.5%) among all veterans undergoing catheterization, which is congruent with a recent Congressional report (2013) that estimated a prevalence of substance dependence and abuse of 3% to 5% among all veterans.¹⁷ It also indicates that most of these veterans seek care in the VA healthcare system, because the ACC ACTION Registry–Get With the Guidelines (GWTG) program, which collects information from non-VA hospitals, found that only 0.9% of veterans with acute MI had active cocaine use.¹⁸ Accordingly, it is important for the VA to understand the prevalence of cocaine use and how it contributes to CV outcomes, as this can inform its prevention and management.

A recent National (Nationwide) Inpatient Sample study retrospectively analyzed hospital admissions for chest pain associated with cocaine use.¹⁹ The study investigated an all-comer chest-pain population. In this overall lower-risk population, the observed in-hospital mortality was substantially lower (0.09%) than in our cohort, where



we report 1-year mortality. Additionally, all patients in our study underwent cardiac catheterization, compared with 6.7% in the paper by Singh et al. Comparison with this study is important as it underlines the profound significance in understanding the population being studied. When comparing veteran populations with non-veteran populations, it is important to understand that veterans are mostly male and are considerably older than non-veterans (veteran median age 64 years, vs 44 years for non-veterans). Hence, any characteristics associated with age (such as income, occupation, or disabilities) may be impacted by the age difference. Lastly, individuals who enlist in the US Armed Forces may be selected based on physical or mental abilities, which likely differentiates them from those who elect not to enlist.²⁰

Our study also begins to elucidate how cocaine use contributes to adverse cardiac events. Although multiple physiologic studies have characterized the impact of cocaine on the CV system, our approach also takes into account the variety of behavioral and environmental influences that often impact cocaine users. By characterizing these influences using DAGs and sequentially modeling them in our analyses, we are able to provide some additional insight into real-world influences of cocaine use.

Although there are a variety of ways to model the mediators of adverse effects of cocaine, our selection and grouping of variables was guided by the likely interventions that could mitigate adverse outcomes. For example, risky behaviors, such as tobacco and alcohol use, can often exacerbate cardiac outcomes, both via direct effects of the substances on the CV system and through associated lifestyle factors such as poor diet, decreased exercise, and poor medication adherence. Our analysis demonstrates that these factors were particularly influential in MI rates, and interventions to reduce the harmful effects on these behaviors may be especially beneficial in MI patients. We observed a gradual separation in the overall mortality and stroke-free survival curves over the study period, whereas the myocardial infarction-free survival indicates a stepwise increase in myocardial infarctions 75 days after cardiac catheterization. While a number of biologically plausible mechanisms could be evoked for these observed differences, the cause for the stepwise increase in MIs is uncertain.

Similarly, medical conditions directly impacted by the vasoactive and other properties of cocaine, such as ACS, heart failure, and psychological conditions, were influential in our analysis, most notably in mortality rates. Mitigation strategies suggested by this association, in addition to cocaine cessation, include optimal guideline-suggested therapies for the associated condition and optimal control of risk factors that could lead to these conditions. This is particularly germane for depression and anxiety, which have an inordinately high prevalence among the veteran population.¹⁷ Finally, our study is only 1 additional step in understanding the complex relationship between cocaine and CV disease. The persistent association between cocaine and CVA, even after adjusting for risky behavior and causal pathway variables, underscores the limitations of our current understanding.

FIGURE 3 Unadjusted Kaplan-Meier survival curves for cocaine users vs non-cocaine users. (A) Overall survival, (B) MI-free survival, (C) stroke-free survival. Abbreviations: MI, myocardial infarction

4.1 | Study limitations

Our findings should be interpreted in light of several limitations. First, as an observational study, causation between cocaine use and the outcomes cannot be conclusively determined. Although we constructed a coherent rationale for identifying variables that could be contributing to the association between cocaine and outcomes, no model can completely capture all potential associations and variables. Nonetheless, we collected as many associated confounders and potential mediators as was available in our dataset, and we incorporated them into our modeling to partially mitigate against this limitation. Second, data for our study were collected through the electronic health record and were dependent upon the accuracy and completeness of documentation. In particular, we utilized ICD-9 codes to identify veterans with cocaine use within 1 year of coronary angiography. Thus, we were unable to distinguish between acute and recent cocaine ingestion at the time of outcome occurrence. Although we restricted our analyses to 1 year as a partial offset for this limitation, precise timing of exposure and outcome is not possible. It is also likely that veterans underreport their cocaine use,^{21–23} thus causing some potential misclassification of our exposure. Furthermore, we were only able to determine all-cause mortality, rather than cardiac-specific causes of death. Although our mortality findings have specific implications for this population, future studies with access to cause-specific mortality data should be conducted. Therefore, it should be strongly emphasized that we cannot determine the exact causes or mechanisms of increased overall mortality observed in our cohort. Finally, as indicated previously, our patient population was limited to US veterans, which may not be representative of the general population.

5 | CONCLUSION

Among veterans with CAD undergoing cardiac catheterization, cocaine use was associated with a significant increase in adjusted risk for 1-year mortality, MI, and CVA. Contributors to this association are multifaceted and specific to individual CV outcomes; the toxic effects of cocaine on specific medical conditions augmented the risk of mortality, risky behaviors augmented the risk of MI, and factors unaccounted for in our analysis contributed to the risk of CVA. As a result, effective intervention programs to reduce cardiac events in this population will require multiple components addressing these factors.

Conflicts of interest

The authors declare no potential conflicts of interest.

Author contributions

Study concept and design, AG, MIV, TMM, and MAS. Drafting of the manuscript, AG, TMM, and MIV. Statistical analysis, MAS and AEB. Obtained funding, MIV. All authors were involved in acquisition, analysis, or interpretation of the data; provided critical revision of the manuscript for important intellectual content; and provided administrative, technical, or material support.

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How to cite this article: Gunja A, Stanislawski MA, Barón AE, Maddox TM, Bradley SM, Vidovich MI. The implications of cocaine use and associated behaviors on adverse cardiovascular outcomes among veterans: Insights from the VA Clinical Assessment, Reporting, and Tracking (CART) Program. *Clin Cardiol.* 2018;41:809–816. <https://doi.org/10.1002/clc.22961>