

Chronic obstructive pulmonary disease and the risk for myocardial infarction by type in people with HIV

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Objectives: The relationship between chronic obstructive pulmonary disease (COPD) and cardiovascular disease in people with HIV (PWH) is incompletely understood. We determined whether COPD is associated with risk of myocardial infarction (MI) among PWH, and if this differs for type 1 (T1MI) and type 2 (T2MI).

Design: We utilized data from five sites in the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) cohort, a multisite observational study.

Methods: Our primary outcome was an adjudicated MI, classified as T1MI or T2MI. We defined COPD based on a validated algorithm requiring COPD diagnosis codes and at least 90-day continuous supply of inhalers. We conducted time-to-event analyses to first MI and used multivariable Cox proportional hazards models to measure associations between COPD and MI.

Results: Among 12 046 PWH, 945 had COPD. Overall, 309 PWH had an MI: 58% had T1MI ($N=178$) and 42% T2MI ($N=131$). In adjusted models, COPD was associated with a significantly increased risk of all MI [adjusted hazard ratio (aHR) 2.68 (95% confidence interval (CI) 1.99–3.60)] even after including self-reported smoking [aHR 2.40 (95% CI 1.76–3.26)]. COPD was also associated with significantly increased risk of T1MI and T2MI individually, and with sepsis and non-sepsis causes of T2MI. Associations were generally minimally changed adjusting for substance use.

Conclusion: COPD is associated with a substantially increased risk for MI, including both T1MI and T2MI, among PWH. Given the association with both T1MI and T2MI, diverse mechanistic pathways are involved. Future strategies to decrease risk of T1MI and T2MI in PWH who have COPD are needed.

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Introduction

Survival has improved among people with HIV (PWH) since the introduction of potent antiretroviral therapy (ART). As a result, PWH are experiencing a growing burden of comorbid diseases that are linked with both aging and HIV infection. In particular, PWH have an increased risk of cardiovascular disease (CVD) including myocardial infarction (MI) [1]. PWH are also at increased risk for both infectious as well as noninfectious pulmonary diseases, such as pneumonia and chronic obstructive pulmonary disease (COPD) compared to HIV-uninfected persons [2–4].

In HIV-uninfected persons, an association between both stable and acute pulmonary disease with increased risk of CVD has been demonstrated [5–7]. In a meta-analysis, individuals with COPD had a 2.5-fold increased odds of being diagnosed with CVD [6], and an estimated 1.4–3.5-fold higher risk of MI [8,9]. COPD exacerbations also increase risk of MI and other CVD events particularly in the 30-days after exacerbation, but rates can remain elevated for a year [10]. Likewise, community acquired pneumonia is associated with increased risk of MI and other CVD events such as arrhythmias and congestive heart failure [11,12].

However, the relationship between pulmonary disease and CVD in PWH is less well established. COPD has been associated with preclinical markers of CVD in PWH. In one study, greater severity of emphysema on chest CT scan correlated with greater coronary artery calcification scores, adjusting for Framingham risk and other factors [13]. In another study, a decreased lung diffusing capacity was associated with increased coronary artery calcification and with mortality when both were present [14]. Community acquired pneumonia has been associated with a similar increase in the adjusted risk of CVD events in PWH as in uninfected persons [15]. No studies, however, have investigated the association of COPD with risk and different types of MI events in a cohort of PWH.

Therefore, we sought to determine whether COPD is associated with an increased risk of MI among PWH, and if the association differs by type of MI. The Universal Definition of MIs classifies MIs into several types, including type 1 (T1MI, atherothrombotic coronary plaque rupture) and type 2 (T2MI, supply-demand mismatch as with sepsis or vasospasm from drug use such as cocaine) [16]. We have previously shown that almost half of MIs among PWH are T2MI, a larger

proportion than in the general population [17]. Understanding whether and which types of MIs may be associated with COPD in PWH is important for targeting potential mechanistic pathways, tailoring patient management and improving outcomes. We hypothesized that COPD would be associated with increased MI risk among PWH, both T1MI given data from uninfected patients but also T2MI given the association of COPD with increased risk for pneumonia and respiratory failure that may be particularly relevant for PWH. An earlier version of this analysis was previously presented as an abstract [18].

Methods

Study design and participants

We conducted a retrospective observational study using data collected in the Centers for AIDS Research (CFAR) Network of Integrated Clinical Systems (CNICS), a large multisite collaboration of eight clinical care sites delivering care to PWH across the United States [19]. All adults (18 years or older) receiving HIV care at CNICS sites are eligible to be enrolled into the CNICS cohort. CNICS is approved by institutional review boards at all participating sites.

We included participants from five CNICS sites with centrally adjudicated MI events available at the time of these analyses. Inclusion dates varied by site based on ongoing MI adjudication completion, from ~2006–2018. CNICS participants were included if they were enrolled in clinical care at a CNICS site for at least 6 months and completed at least one patient reported measures and outcomes (PROs) during the period of active MI adjudication. PROs are completed every ~4–6 months as part of routine clinical care visits.

Data collection

The CNICS data repository captures longitudinal data from the CNICS cohort. Comprehensive clinical data are collected through electronic medical records and other institutional data systems including patient demographic characteristics, diagnoses, prescribed medications, and laboratory results. Diagnoses include COPD; prescribed medication data include COPD inhalers, statins, medications used to treat diabetes and hypertension, and others. The CNICS data repository integrates data from the CNICS clinical assessment of PROs. PWH use touch screen tablets to complete the clinical assessment at the time of routine clinic appointments approximately every

6 months using web-based survey software developed specifically for collecting PROs [20–22]. CNICS data undergo rigorous quality assessment, are harmonized in a central repository, and are updated on a quarterly basis [19].

Outcome

Our primary outcome was a centrally adjudicated MI. Potential events were identified retrospectively in the CNICS data repository by MI clinical diagnoses, cardiac biomarkers, and procedures. De-identified packets of primary data including physician notes, electrocardiograms, results of relevant diagnostic tests such as cardiac catheterization, and other information were centrally adjudicated by two reviewers (three if discrepancies) to ascertain MI as previously described, and also to categorize by type and cause of T2MI [17,23,24]. MIs were categorized as probable or definite and by MI type. These analyses focus on T1MI and T2MI as other MI types (types 3, 4 and 5 MI) were rare. As part of central adjudication of the primary data, reviewers identified causes of T2MI, with the most common being MIs attributed to sepsis and cocaine-induced vasospasm [23].

Primary exposure

Our primary exposure was COPD. We defined verified COPD based on an algorithm previously validated against spirometry with a c -statistic of 0.734 [95% confidence interval (CI) 0.675–0.792], requiring COPD International Classification of Disease (ICD) diagnosis codes and an at least 90-day continuous supply of COPD short-acting (short-acting beta-agonist or muscarinic antagonists) or long-acting controller inhaler medications (long-acting beta-agonist, long-acting muscarinic antagonist, or inhaled corticosteroid) [25]. PWH were determined to have verified COPD if criteria were fulfilled at baseline or if the diagnosis was made during the follow-up period prior to MI.

Covariates and confounders

Dyslipidemia was defined as lipid abnormalities severe enough to require lipid-lowering medications, specifically HMG Co-A reductase inhibitors (statins). Kidney function was assessed with estimated glomerular filtration rate (eGFR) [26]. Hepatitis C virus (HCV) status was based on positive lab values (e.g. the presence of positive antibody, genotype, or viral load); treatment of HCV was rare during most of the study period. Diabetes was based on any of the following: hemoglobin A1c ≥ 6.5 or use of a diabetes-specific medication such as insulin or use of a diabetes-related medication not exclusively used to treat diabetes (e.g. biguanides) in the setting of also having a diabetes diagnosis [27].

Smoking, drug and alcohol use were all measured using data from the CNICS clinical assessment of PROs. Cigarette use was categorized as current, former, or never used and among those with current or former use, pack-years were also calculated. AUDIT-C scores for current

alcohol consumption measured over the prior year were calculated by summing scores for each item question [28]. We used a modified version of the Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST) [29] to operationally define use of four individual drug classes (marijuana, cocaine/crack, methamphetamines/crystal, and illicit opioids/heroin) and categorized use as current (past 3 months), former, or never.

Analysis

Our primary objective was to determine the association between COPD and risk of MI overall, and risk of MI stratified as T1MI vs. T2MI among PWH. Characteristics of PWH who had COPD (either at baseline or during follow-up) were first compared to those without COPD using t -tests for continuous variables and chi-squared tests for categorical variables. We then conducted time to event analyses to first MI with time-updated COPD diagnosis. Baseline index date was defined as whichever was latest, the date that participants had been enrolled in CNICS for 6 months or more, the start of MI surveillance (that varied slightly by site based on when they were able to completely capture key primary data such as electrocardiograms), or the first complete PRO. Participants were followed until first MI, with censoring at time of death, last engagement in care + 9 months, or administrative censoring.

Cox proportional hazards models were used to measure the association between COPD and all MIs overall; T1MI; T2MI; and among T2MI, those due to sepsis/bacteremia vs. cocaine/illicit drug use and other causes. All models were adjusted for: age, sex, race/ethnicity, site, HIV viral load, nadir CD4⁺ cell count, diabetes, hypertension, eGFR <30, HCV, and statin use. HIV viral load and nadir CD4⁺ were time-varying. In addition, we constructed several other models adjusting sequentially for additional potential confounders. In a second model, we included adjustment for smoking (never, former, or current); a third model included adjustment for smoking pack-years, and a fourth model included adjustment for smoking pack-years, alcohol (AUDIT-C score), methamphetamine, marijuana, illicit opioid/heroin, and cocaine/crack use (never, former, or current). Lastly, we conducted several sensitivity analyses to assess the robustness of the results, namely excluding those with HCV, current or former substance use, and HIV viral loads above 400 copies/ml; as the number of events was low (<50) when assessing the association with different causes of T2MI, we present the association of COPD with overall MIs, T1MI and T2MI in these restricted analyses.

Results

Patient characteristics by chronic obstructive pulmonary disease diagnosis

In total, 12 046 PWH were included after exclusion of 749 who were lost to follow-up in their first 6 months

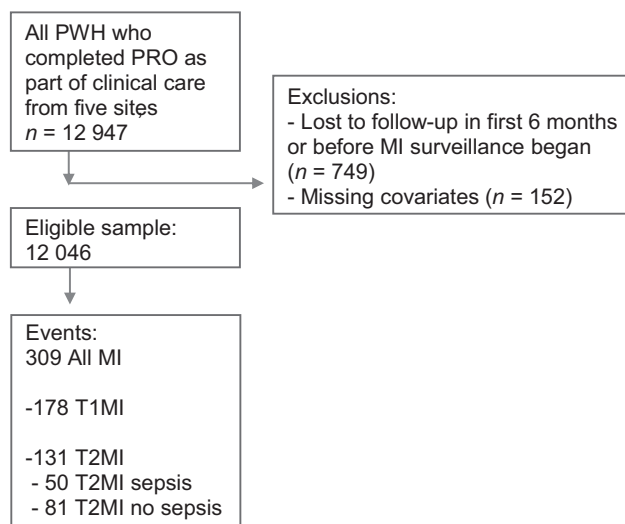


Fig. 1. Inclusion/exclusion criteria of people with HIV in routine clinical care from five sites across the United States. MI, myocardial infarction; PRO, patient reported outcome; PWH, people with HIV; T1MI, T2MI, type 1 or type 2 MI.

after initial CNICS visit or before MI surveillance began and 152 with incomplete covariate information (Fig. 1). There were 945 PWH who met our definition of COPD either at baseline or during follow-up prior to MI event. Those who had COPD diagnosed at baseline or during follow-up were significantly older, more likely to be female, to have increased comorbidities, substance use and to smoke (Table 1). There was no difference in proportion with an HIV viral load above 400 copies by COPD status and nearly all patients (95–98%) were on ART; PWH who had COPD were more likely to have a lower nadir CD4⁺ cell count than those without COPD.

Incidence of myocardial infarction

Median time between index date and end of follow-up was 4.2 years, and time between COPD diagnosis and MI event was on average 5.0 years. Over follow-up, there were 309 PWH who had an MI. More than half were classified as T1MI: T1MI *N* = 178 (58%) and T2MI *N* = 131 (42%).

Association of chronic obstructive pulmonary disease with myocardial infarction risk

Of the 309 MIs, 61 occurred in the 945 PWH with COPD diagnosed at baseline or during follow-up. The unadjusted incidence rate for all MI was nearly four-fold higher in PWH with COPD compared to without COPD (17.7 vs. 4.7 per 1000 person-years, respectively, Table 2). When stratified by MI type, unadjusted incidence rates were higher for both T1MI as well as T2MI in those who had COPD.

In adjusted Cox proportional hazards models (Table 3), COPD was associated with a significantly increased risk

of all MI [adjusted hazard ratio (aHR) 2.68 (95% CI 1.99–3.60)] even after adding smoking status [aHR 2.40 (95% CI 1.76–3.26)] with nearly equivalent results after adjusting for smoking pack-years. The association between COPD and T1MI and T2MI was also statistically significant, for both sepsis and non-sepsis causes of T2MI. These associations remained significant in sequential models adjusting for smoking pack-years and for substance use for T1MI as well as T2MI due to sepsis and due to non-sepsis causes (Table 3). In sensitivity analyses (Table 4), associations were overall generally similar or larger especially with T2MI. The exception was the association of COPD with T1MI; the hazard ratio was elevated but no longer statistically significant [aHR 1.82 (95% CI 0.87–3.81)] when restricted to those without HCV and no current or former substance use.

Chronic obstructive pulmonary disease medication prescription

We assessed the proportion of PWH prescribed COPD medications at the time of verified COPD, prior to MI, and at last visit before censoring in those who did not have MI. By definition, 100% of patients had at least 90 days of short or long-acting inhalers at time of verified COPD. At the time of MI or censoring, the proportion on any inhalers was lower but similar in those prior to T1MI, T2MI or last visit before censoring (79, 96 and 80%, respectively).

Discussion

In these analyses of a cohort of PWH from five sites across the United States, we found that COPD is associated with an independently increased risk for MI among PWH. The risk was increased for T1MI as well as T2MI. The associations were strong, with hazard ratios indicating approximately 2.5–3-fold higher risk associated with COPD for T1MI and T2MI in PWH, even after adjusting for demographic characteristics, HIV disease control, smoking, substance use, and other typical MI risk factors including age and comorbidities. Results were also robust in sensitivity analyses that excluded several confounders. These data support that COPD is not merely a marker of shared risk factors for T1MI and T2MI but is a risk factor of its own for MI among PWH.

Prior studies of HIV-uninfected patients have demonstrated an association between COPD and both T1MI and T2MI risk [30,31]. However, among PWH studies have not reported on COPD and risk for T1MI and T2MI within the same cohort, and further examined risk for different causes of T2MI. This is the first study to our knowledge to investigate and demonstrate an increased risk of T1MI and T2MI in PWH and COPD; to assess differences in risk for T1MI vs. T2MI in the

Table 1. Baseline characteristics of people with HIV in routine clinical care from five sites across the United States categorized by COPD status (N = 12 046)^a.

Characteristic	No COPD (n = 11 101) n (%)	COPD at baseline (n = 488) n (%)	COPD during follow-up (n = 457) n (%)	P-value [#]
Age, median (IQR), years	43 (34–51)	53 (48–59)	49 (44–55)	<0.001
Female	1934 (17)	163 (33)	111 (24)	<0.001
Race/ethnicity				<0.001
White	4743 (43)	226 (46)	241 (53)	
African American	4200 (38)	240 (49)	169 (37)	
Hispanic	1641 (15)	14 (3)	40 (9)	
Other/unknown	517 (5)	8 (2)	7 (2)	
Site				<0.001
University of Washington	2027 (18)	93 (19)	70 (15)	
Johns Hopkins University	742 (7)	146 (30)	44 (10)	
University of Alabama, Birmingham	3253 (29)	94 (19)	105 (23)	
University of California, San Diego	3799 (34)	106 (22)	198 (43)	
University of North Carolina	1280 (12)	49 (10)	40 (9)	
Viral load >400 copies/ml	2188 (20)	75 (15)	95 (21)	0.2
Nadir CD4 ⁺ , median (IQR) (cells/mm ³)	256 (97–430)	145 (44–274)	206 (63–370)	<0.001
ART use	10507 (95)	477 (98)	436 (95)	0.009
Diabetes	938 (8)	81 (17)	55 (12)	<0.001
Treated hypertension	2742 (25)	226 (46)	142 (31)	<0.001
Statin use	1886 (17)	164 (34)	120 (26)	<0.001
Hepatitis C	1525 (14)	185 (38)	136 (30)	<0.001
eGFR <30	145 (1)	15 (3)	8 (2)	0.005
AUDIT-C score, median (IQR) [#]	1 (0–4)	0 (0–3)	1 (0–3)	<0.001
Methamphetamine use				<0.001
Never	7741 (70)	331 (68)	276 (60)	
Former	2424 (22)	122 (25)	153 (33)	
Current	936 (8)	35 (7)	28 (6)	
Cocaine use				<0.001
Never	6491 (58)	192 (39)	176 (39)	
Former	3854 (35)	237 (49)	223 (49)	
Current	756 (7)	59 (12)	58 (13)	
Illicit opioid use				<0.001
Never	9485 (85)	354 (73)	361 (79)	
Former	1311 (12)	107 (22)	74 (16)	
Current	305 (3)	27 (6)	22 (5)	
Marijuana use				0.004
Never	4018 (36)	155 (32)	138 (30)	
Former	3727 (34)	182 (37)	174 (38)	
Current	3356 (30)	151 (31)	145 (32)	
Smoking status				<0.001
Never	4634 (42)	66 (14)	54 (12)	
Former	2552 (23)	108 (22)	89 (19)	
Current	3915 (35)	314 (64)	314 (69)	
Smoking pack-years, median (IQR) [#]	1 (0–6)	5 (3–16)	10 (5–16)	<0.001

COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate.

^aNumbers presented as n (%) for binary and categorical variables or median (interquartile range (IQR)) for continuous variables.

[#]P-value compares no COPD group to any COPD (both at baseline and during follow-up). Continuous variables were compared using t-tests, categorical variables were compared using chi-square tests.

Table 2. Unadjusted incidence rates of MIs by type and causes of type 2 MI by COPD status.

	Rate (95% CI) per 1000 PY No COPD	Rate (95% CI) per 1000 PY COPD
All MI	4.7 (4.2,5.3)	17.7 (13.8,22.8)
Type 1 MI	2.7 (2.3,3.2)	9.9 (7.1,13.8)
Type 2 MI	2.0 (1.6,2.4)	7.8 (5.4,11.4)
Type 2 MI due to sepsis	0.7 (0.5,1.0)	3.2 (1.8,5.8)
Type 2 MI due to all non-sepsis causes	1.2 (1.0,1.6)	4.7 (2.8,7.6)

COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; PY, pack-years.

same cohort; and to examine the association between COPD and different causes of T2MI. Despite the higher prevalence of MI among PWH, the magnitude of MI risk associated with COPD among PWH was generally similar as in published rates from uninfected populations, although possibly the link between COPD and risk of T2MI due to sepsis may be greater in our cohort [6,8,9]. This may be driven by an elevated risk of pneumonia in PWH, which is further increased by COPD, independent of HIV disease control [32]. Co-occurring substance use and enhanced susceptibility to adverse effects of cigarette smoking may additionally increase risk.

Table 3. Risk of MI associated with COPD in unadjusted and adjusted Cox regression models.

	Unadjusted	Adjusted ^a	Adjusted with smoking status ^b	Adjusted with smoking pack-years ^c	Adjusted with smoking pack-years and SU ^d
All MI	3.72 (2.80–4.92)	2.68 (1.99–3.60)	2.40 (1.76–3.26)	2.41 (1.78–3.28)	2.46 (1.80–3.35)
Type 1 MI	3.58 (2.46–5.21)	2.67 (1.81–3.95)	2.23 (1.49–3.34)	2.23 (1.48–3.35)	2.21 (1.47–3.33)
Type 2 MI	3.90 (2.55–5.97)	2.67 (1.70–4.20)	2.61 (1.63–4.19)	2.67 (1.67–4.28)	2.81 (1.75–4.51)
Type 2 MI due to sepsis/ bacteremia	4.31 (2.20–8.45)	2.61 (1.26–5.40)	2.98 (1.38–6.40)	2.75 (1.30–5.81)	3.27 (1.55–6.90)
Type 2 MI due to non-sepsis causes	3.66 (2.11–6.34)	2.73 (1.53–4.87)	2.42 (1.32–4.41)	2.63 (1.43–4.81)	2.57 (1.39–4.73)

^aAdjusted for age, sex, race/ethnicity, HIV viral load, nadir CD4⁺ cell count, diabetes, treated hypertension, statin use, eGFR <30, hepatitis C, and study site.

^bAlso includes adjustment for smoking status.

^cAlso includes adjustment for smoking pack-years.

^dAlso includes adjustment for smoking pack-years, and substance use (AUDIT-C score; marijuana, methamphetamine, cocaine and illicit opioid use (never, former, or current)).

COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; SU, substance use.

Multiple mechanisms may account for the association of COPD with MI risk in PWH, and different factors are likely to be important for T1MI vs. T2MI (Fig. 2). These include hypoxia, COPD severity, acute exacerbations of disease and the increased risk for pneumonia among patients with COPD. Additionally, endothelial dysfunction, immune activation and inflammation that can be elevated in those with COPD may all confer risk for MI in PWH. Understanding which of these factors is contributing will be important to inform tailored strategies to decrease MI risk in this population.

We postulate that pulmonary infection and inflammation – namely pneumonia and COPD exacerbation – are key mediators of the association between COPD and MI risk. Optimizing COPD treatment may be a modifiable factor that could influence risk for both pneumonia and exacerbations among PWH. Under-use of long acting bronchodilators among PWH with COPD is common and could confer a greater risk for COPD exacerbation

Table 4. Sensitivity analyses for risk of MI associated with COPD in adjusted Cox regression models in those without HCV, substance use, or detectable viral load at baseline.

	Those without HCV N = 10 200	Those without HCV and no current or former SU N = 5537	Those with HIV VL ≤400 at baseline N = 9688
All MI	2.57 (1.76–3.74)	2.76 (1.60–4.78)	2.88 (2.05–4.04)
Type 1 MI	2.46 (1.54–3.92)	1.82 (0.87–3.81)	2.56 (1.64–4.01)
Type 2 MI	2.73 (1.44–5.19)	5.48 (2.42–12.39)	3.41 (2.02–5.75)

All models are adjusted for age, sex, race/ethnicity, nadir CD4⁺ cell count, diabetes, treated hypertension, statin use, eGFR <30, study site, and smoking pack-years. Where patients with these risk factors are not excluded, models are also adjusted for HCV, substance use (AUDIT-C score; marijuana, methamphetamine, cocaine and illicit opioid use (never, former, or current)), and detectable HIV viral load. COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; SU, substance use.

[33]. On the other hand, inhaled corticosteroids are frequently used as a controller inhaler among PWH with COPD [33]. Use of inhaled corticosteroids among patients with COPD can increase risk of pneumonia, which in turn can increase MI risk [15]. We found that the majority of patients remained on inhaler therapy through follow-up; however, we did not have prospective data on patient-reported disease control and COPD exacerbations to assess appropriateness of COPD treatment. Additional investigations should seek to understand the role of COPD treatment and strategies to optimize the management of COPD in PWH to decrease risk for complications that include MI.

Our study has several strengths and limitations. We used a large, nationwide sample with diversity in race/ethnicity, sex, clinical characteristics, and geographic distribution. However, results do not necessarily generalize to PWH not in clinical care or not aware of their HIV diagnosis. Our primary outcome was an MI, which have all been adjudicated centrally and classified by type. Although we did not have pulmonary function testing data to verify diagnoses and to assess severity of COPD, we used a validated definition based on data from the electronic medical record to determine the presence of COPD [25]. We have previously found that requiring both components (diagnoses and 90 days of inhalers) greatly increased the specificity and accuracy of the approach as diagnosis codes alone are inaccurate and short-term use of inhalers for other reasons is common [25]. In addition, we were able to adjust analyses for patient self-reported smoking status, pack-years of smoking and substance use to control for potential confounders.

In conclusion, we found that COPD is associated with approximately 2.5–3-fold higher risk for T1MI and T2MI among PWH. These results highlight the substantial risk of MI in PWH who have COPD, and have significant implications given the morbidity and mortality associated with MI, especially T2MI that has

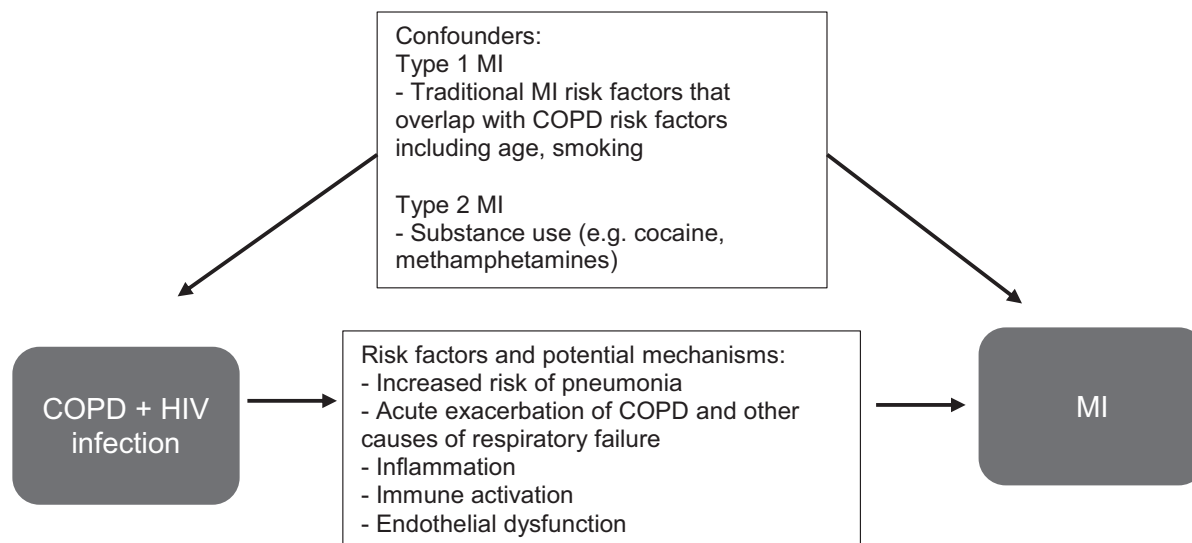


Fig. 2. Potential factors in the association of COPD with MI. COPD, chronic obstructive pulmonary disease; MI, myocardial infarction.

been found to have mortality rates that are higher in both PWH and uninfected persons compared to T1MI [31,34]. Given the association with both T1MI and T2MI, diverse potential mechanistic pathways are likely involved. Further investigation is required to understand mechanisms for this association and to implement tailored preventive and therapeutic strategies in order to improve patient outcomes.

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Conflicts of interest

E.R.C. reports unrestricted research funds paid to University of California regents from Gilead and Merck for unrelated research topics and serving on the advisory board for Gilead and Theratechnologies on unrelated

medical subjects. J.C.K. reports serving on the advisory board for the American Board of Internal Medicine on the Infectious Diseases Specialty Board. M.S.S. reports serving on the Board for the I-SPY COVID ICU treatment study, and on the Board of the International Antiviral Society USA. For the remaining authors none were declared.

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