HHS Public Access

Author manuscript

J Acquir Immune Defic Syndr. Author manuscript; available in PMC 2022 March 07.

Published in final edited form as:

J Acquir Immune Defic Syndr. 2021 February 01; 86(2): 208–212. doi:10.1097/QAI.0000000000002534.

Differences in types of myocardial infarctions among people aging with HIV

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Abstract

Background—Type 1 myocardial infarctions (T1MI) result from atherosclerotic plaque instability, rupture and/or erosion. Type 2 MI (T2MI) are secondary to causes such as sepsis and cocaine-induced vasospasm resulting in oxygen demand-supply mismatch and are associated with higher mortality than T1MI. T2MI account for a higher proportion of MI among people living with HIV (PLWH) compared to the general population. We compared MI rates by type among aging PLWH. We hypothesized that increases in MI rates with older age would differ by MI type, and T2MI would be more common than T1MI in younger individuals.

Methods—Potential MIs from six sites were centrally adjudicated using physician notes, ECGs, procedure results, and lab results. Reviewers categorized MIs by type and identified T2MI causes.

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Results were presented in part at the Conference on Retroviruses and Opportunistic Infections in Seattle in March, 2019

We calculated T1MI and T2MI incidence rates. Incidence rate ratios were calculated for T2MI vs. T1MI rates per decade of age.

Results—We included 462 T1MI (52%) and 413 T2MI (48%). T1MI rates increased with older age, although T1MI occurred in all age decades including young adults. T2MI rates were significantly higher than T1MI rates for PLWH under 40. T1MI rates were similar or higher than T2MI rates among those over 40 (significantly higher for those 50–59 and 60–69 years of age).

Conclusions—Rates of T2MI were higher than T1MI until age 40 among PLWH, differing from the general population, but rates of both were high among older PLWH. Given prognostic differences between MI types, these results highlight the importance of differentiating MI types among PLWH.

Keywords

myocardial infarction; type 1 MI; type 2 MI; aging; HIV

Background

There are many unanswered questions regarding myocardial infarction (MI) in people living with HIV (PLWH). The Universal Definition of Myocardial Infarction classifies MIs into 5 types according to the mechanism of myocardial ischemia[1,2]. For example, Type 1 MIs (T1MI) result spontaneously from atherosclerotic plaque instability and type 2 MIs (T2MI) are secondary to causes other than atherosclerotic plaque rupture, including sepsis, hypoxia, and stimulant-induced spasm resulting in increased oxygen demand-supply mismatch. Type 3 MIs are deaths occurring with symptoms suggestive of MI however cardiac biomarkers are not measured. Type 4 and 5 MIs occur in the setting of coronary revascularization procedures.

Different MI types may indicate different prognoses and optimal medical management[3]. In the general population, most MIs were thought to be T1MI; estimates of T2MI incidence vary depending on the population and event ascertainment methods, but most general population studies suggest T2MIs are a minority of MIs[4–12]. In contrast, we previously demonstrated that almost half of MIs among PLWH in care at our clinics across the US are T2MI[13]. We also demonstrated that there are important differences in demographic and clinical characteristics among PLWH with T1MI vs. T2MI[13]. Furthermore, we demonstrated that there are prognostic differences whereby T2MI are associated with higher mortality than T1MI among PLWH[14]; this pattern was also recently shown in the general population, with higher T2MI-associated mortality than T1MI-associated mortality[15]. However, many previous studies have not differentiated MI types limiting the ability to understand MI characteristics and prognosis in PLWH.

General population studies have demonstrated that those with T1M1 are younger than those with T2MI[16,17]. However, little is known about how age might vary by MI type in PLWH. We conducted this study to compare MI incidence rates by type and age among PLWH. We hypothesized that increases in rates with older age would differ by MI type, and that in contrast to the general population, T2MI would be more common in younger individuals

due to the different pattern of causes of T2MI among PLWH than the general population. Additionally, we hypothesized that there would be a measurable rate of T1MI among young adults (<30 years old) PLWH.

Methods

Study setting:

Longitudinal observational cohort study in the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS), a multisite clinical cohort of PLWH receiving HIV care at sites across the United States[18].

Study participants:

PLWH ≥18 years of age receiving HIV care at six CNICS sites after MI adjudication began (inclusion dates varied by site, ~2000–2019). Site locations included Seattle, Birmingham, Chapel Hill, Baltimore, San Diego, and San Francisco. We excluded individuals with information suggesting a previous MI prior to the start of MI surveillance in CNICS to focus analses on first incident MI events only.

Data sources:

The CNICS Data Repository integrates comprehensive clinical data from outpatient and inpatient encounters including information on demographic characteristics, clinical and laboratory data, and medications.

CNICS has an established state-of-the-art approach to MI adjudication[13,19] with MIs categorized by type based on the Universal Myocardial Infarction definition[1,2]. We identified potential MIs in the centralized CNICS data repository using a comprehensive set of MI diagnostic and procedure codes and elevated cardiac biomarker values to optimize ascertainment sensitivity as described previously[13,19]. For each potential MI, sites assembled a de-identified packet that included available provider notes, electrocardiograms, laboratory results, and imaging and procedure results including from cardiac catheterizations. Two physicians with expertise in adjudicating cardiac disorders reviewed each packet, followed by a third reviewer if discrepancies occurred. Reviewers categorized MIs by type, identified causes for T2MI, and also identified PLWH without an MI but with coronary interventions such as a coronary artery bypass graft (CABG) surgery or percutaneous transluminal coronary angioplasty (PTCA). We grouped coronary interventions with T1MI, based on prior work evaluating the similarity of PLWH with adjudicated T1MI and coronary interventions[13]. MI types other than T1MI and T2MI are not discussed further due to the low event numbers (there have been <10 Type 4 and 5 MIs in CNICS to date).

Outcomes:

We examined T1MI and T2MI.

Analyses:

We used Chi-squared and t-tests for categorical and continuous variables, respectively, to assess differences in demographic and clinical characteristics among PLWH with T1MI

or cardiac intervention versus T2MI. By decade of age, we calculated T1MI and T2MI incidence rates and jackknife confidence intervals (CI) per 1,000 person-years of follow-up. Time at risk for MI started at the initial CNICS visit or the site-specific MI surveillance date, whichever was later. Follow-up continued until the earliest of MI, death, last CNICS visit or laboratory plus nine months or administrative censoring date by site. Incidence rate ratios (IRR) and 95% CIs were subsequently calculated to compare rates of T2MI vs. T1MI by decade of age. For PLWH <30 or 70 or older, we combined all individuals due to smaller numbers of PLWH. Analyses were done using STATA version 14.2.

Results

Among 28,741 PLWH, 875 PLWH were adjudicated to have had an MI during a median follow-up of 5.3 years (interquartile range IQR 2.2–9.4). Among those with an MI, 79% were men, the median age was 51 (IQR, 44–57), 50% were African-American, 78% were on antiretroviral therapy (ART), and the current median CD4 cell count was 355 cells/mm^3 (IQR 144–584); current CD4 count was based on measures drawn during care a median of 49 days before the MI (IQR 15–114 days).

Among the 875 MIs, 462 were T1MI (53%) and 413 were T2MI (47%); included as part of T1MI were 122 (14%) events adjudicated not to have met MI criteria, but were PLWH with severe enough atherosclerotic disease that they underwent a coronary intervention such as a PTCA or CABG. A higher proportion of PLWH who had a T1MI were >40 years of age, male, white, on ART, on a statin, and had higher total cholesterol or LDL levels compared with those with a T2MI (Table 1). The median CD4 cell count was higher among those with a T1M1 vs. T2MI (423 vs 253 cells/mm^3, p <0.001).

We examined incidence rates by age and found T1MI occurred in all age decades, including young adults <30, among PLWH. The rates of T1MI increased for each decade of older age (Table 2) with much higher rates among those 70 and older (9.32 T1MI per 1,000 person-years of follow-up). T2MI also occurred in every decade of adult PLWH and rates increased with age among PLWH 40 and older (Table 2).

We compared incidence rates between T1MI and T2MI. T2MI rates were significantly higher than T1MI rates for PLWH <40 (Table 2). In particular, the comparison of T2MI to T1MI rates demonstrated the highest relative difference in those <30 (IRR=10.0, 95% CI 2.43–88.24, p<0.001). Rates of T1MI and T2MI were not significantly different among those 40–49. However, among PLWH 50–59 and 60–69 years of age, T1MI rates were significantly higher (IRR=0.78, 95% CI 0.62–0.97, p=0.02; IRR=0.67, 95% CI 0.45–0.98, p=0.03, respectively).

We also examined causes of T2MI. Sepsis (36%), cocaine or other drug-induced vasospasm (11%), and respiratory failure (10%) were the most frequently identified likely causes of T2MI (Supplement Figure 1). In every decade, more T2MI were associated with sepsis than any other T2MI cause. However, while sepsis was always the most common cause, the proportion of T2MI due to sepsis varied by age, with more T2MI due to sepsis among younger adult PLWH (50% of T2MI among those <30) and older adults (50% of T2MI

among those >60) and a lower percentage among those who were middle aged (27% of T2MI among those 40–49). Demographic characteristics of those with T2MIs due to sepsis resembled those with T2MIs due to other causes, however CD4 counts, particular nadir counts of those with T2MI due to sepsis who were younger than 50 were very low (median 21 cells/mm^3) (Supplemental Table 1).

Discussion

We examined MI types by age in a large, nationally distributed HIV cohort. T2MI were common, comprising half of all MIs observed during follow-up. PLWH with a T1MI were on average older, had a higher CD4 cell count, and were more likely to be on ART than those with a T2MI. We found that both T1MI and T2MI occurred in every age category including young adult PLWH (<30 years of age). T1MI incidence rates increased among adults with each decade of age and T2MI incidence rates increased with each decade over 40, resulting in higher T2MI vs. T1MI rates for PLWH under 40, and higher T1MI vs. T2MI rates among PLWH 50–69. Sepsis was the most common cause of T2MI in every decade, although the proportion due to sepsis varied with age. These results highlight that T1MI and T2MI represent distinct clinical entities that require different approaches to prevention and treatment, as noted in the general population and in our recent investigation of PLWH[3,13–15]. Importantly, T1MI vs. T2MI impact PLWH at different rates across the age spectrum, with implications for prevention and prognosis. This study is the first to report rates of T1MI and T2MI by age among PLWH.

A key finding from our study is that PLWH with a T2MI are on average younger than those with a T1MI. This is in contrast to general population studies where T2MI account for a much smaller proportion of MIs and typically occur in older individuals. For example, a single center study of all patients (not limited to those with HIV) admitted with non-ST-segment-elevation myocardial infarction (NSTEMI) found that 75% were T1MI vs. 25% were T2MI. Furthermore, patients with a T2MI were older (median 73 versus 65 years, $P<0.001$)[17]. A Swedish study characterized ~20,000 hospitalizations with MI and found 7.1% were T2MI. Furthermore, the mean age among those with a T1MI was 71.1 years vs. 75.9 for those with a T2MI[11]. A meta-analysis found that compared to those with T1MI, those with T2MI were older (mean age 74 years for T2MI vs. 70 years for T1MI)[20]. We expect these differences are due, in part, to different causes driving T2MI. For example, among a meta-analysis including a large number of T2MI, the most common cause associated with T2MI was operative stress (20%), followed by sepsis (19%), arrhythmia (19%), heart failure (15%), and anemia (12%)[20]. In contrast, among PLWH we found that sepsis was the most common cause of T2MI, although the percentage varied by decade of age ranging from 27–50% of T2MI.

This study has several strengths and limitations. Strengths include the use of centrally adjudicated MIs differentiated by type, and the use of multiple ascertainment criteria to identify potential events. This is crucial given how poorly prior studies have found diagnoses codes alone work to accurately identify MIs, particularly given inadequacy of diagnosis codes for T2MI[19,21,22]. The large size and comprehensive clinical data are strengths, although the more limited number of women is not. The number of MIs is a limitation.

While >800 MIs allowed us to evaluate T1MI and T2MI separately, T2MI are due to heterogenous causes; a larger number of outcomes are needed to further separate T2MI by cause. Lastly, we focused on first incident MI for each PLWH. While this approach has many advantages, it limits comparisons to some general population studies where those with T2MI are more likely to have had a prior MI.

Conclusions

We found that among PLWH, T1MI occurred in adults of all ages. T2MI accounted for almost half of all MIs and T2MI occurred at a higher rate than T1MI until age 40, differing from what is seen in the general population; rates of both T2MI and T1MI were very high among older PLWH. T2MI were heterogenous with multiple causes, although sepsis was the most common cause across decades. The high proportion of T2MI highlights the importance of including both T1MI and T2MI in studies of PLWH. The age differences, as well as heterogeneous causes, highlights the importance of distinguishing MI types among PLWH. A better understanding of these important comorbidities, who is impacted, when, and why, is needed to further comprehend the underlying mechanisms and successfully intervene to improve long term outcomes for older PLWH as the population in care continues aging.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

We would like to acknowledge all CNICS study participants and personnel for their contributions to this work.

This work was supported by National Institute on Aging at the National Institutes of Health grants R24 AG044325 and R33AG067069. Additional support came from the National Institute of Allergy and Infectious Diseases (NIAID) at the National Institutes of Health [CNICS R24 AI067039, UW CFAR NIAID Grant P30 AI027757; and UAB CFAR grant P30 AI027767]. Additional support came from the National Heart, Lung, and Blood Institute at the National Institutes of Health R01 HL126538.

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Table 1.

Clinical and demographic characteristics of people living with HIV at six sites across the United States by myocardial infarction type

Characteristic	No MI N=27,866 N (%)	T1MI* N=462 N (%)	T2MI N=413 N (%)	P-value^
Age, years median (IQR)	47 (38,55)	52 (46,58)	50 (43,56)	<0.001
Age, years by decade				<0.001
<30	2254 (8)	2 (<1)	20 (5)	
30–39	6101 (22)	30 (6)	47 (11)	
40–49	8187 (29)	152 (33)	134 (32)	
50–59	7816 (28)	189 (41)	147 (36)	
60–69	2935 (11)	68 (15)	45 (11)	
≥70	573 (2)	21 (5)	20 (5)	
Sex				<0.001
Male	22561 (81)	393 (85)	301 (73)	
Race/Ethnicity				<0.001
White	11529 (41)	225 (49)	106 (26)	
African American	11245 (40)	175 (38)	264 (64)	
Hispanic	3605 (13)	45 (10)	34 (8)	
Other/unknown	1487 (5)	17 (4)	9 (2)	
HIV Transmission Risk Factor				<0.001
Heterosexual	7071 (25)	106 (23)	123 (30)	
Men who have sex with men	14427 (52)	239 (52)	127 (31)	
Injection drug use	5018 (18)	97 (21)	147 (36)	
Other/unknown	1350 (5)	20 (4)	16 (4)	
Antiretroviral therapy				<0.001
Yes	22,100 (79)	390 (84)	298 (72)	
CD4 count closest to event (cells/μl)				<0.001
0–200	4480 (16)	92 (20)	170 (41)	
201–350	4107 (15)	82 (18)	75 (18)	
>350	19199 (69)	287 (62)	168 (41)	
Nadir CD4 cell count (cells/μl)				0.06
Median (IQR)	223 (70,390)	150 (41,298)	98 (17,242)	
HIV-1 RNA closest to event (copies/ml)				<0.001
<500	21181 (76)	339 (74)	229 (55)	
500–100,000	4900 (18)	97 (21)	121 (29)	
>100,000	1617 (6)	25 (5)	63 (15)	
Lipid Levels mean (mean, SD)				
Total Cholesterol (mg/dL)	172 (42)	188 (53)	164 (58)	<0.001
HDL (mg/dL)	46 (16)	41 (14)	43 (20)	0.06

Characteristic	No MI N=27,866 N (%)	T1MI* N=462 N (%)	T2MI N=413 N (%)	P-value^
LDL (mg/dL)	98 (34)	108 (41)	86 (39)	<0.001
Triglycerides	156 (132)	213 (183)	192 (223)	0.2
Statin use				<0.001
Yes	5403 (19)	228 (49)	103 (25)	
Blood pressure (mean, SD)				
Systolic (mmHg)	126 (16)	131 (20)	129 (23)	0.2
Diastolic (mmHg)	79 (11)	80 (13)	79 (14)	0.1
Anti-hypertensive medication use				0.3
Yes	10685 (39)	323 (70)	273 (67)	
Diabetes				0.3
Yes	3429 (12)	113 (24)	113 (27)	
Ever smoking				0.3
Yes	10152 (36)	216 (47)	180 (44)	
Body mass index (mean, SD)				<0.001
BMI (kg/m2)	27 (6)	27 (6)	25 (6)	
Risk Score (mean, SD)				0.7
ASCVD (%10 year event risk)	8 (10)	14 (12)	14 (14)	

*T1MI also includes patients with coronary interventions

^Comparing T1MI to T2MI

Demographic and clinical characteristics at time of MI or at end of follow-up

MI: myocardial infarctions; T1MI: type 1 myocardial infarction; T2MI type 2 myocardial infarctions

Table 2.

Rates of Type 1 and Type 2 myocardial infarctions per 1000 person-years of follow-up among people living with HIV at six CNICS sites across the United States

Age category	Rate (CI) Type I MI	Rate (CI) Type 2 MI	IRR (CI)Type 2 vs Type 1 MI, p-value
<30	0.13 (0.03–1.32)	1.31 (0.86–2.11)	10.0 (2.43–88.24), 0.001
30–39	0.71 (0.50–1.03)	1.11 (0.84–1.49)	1.57 (0.97–2.57), 0.05
40–49	2.33 (1.99–2.74)	2.06 (1.74–2.45)	0.88 (0.69–1.12), 0.3
50–59	3.91 (3.40–4.53)	3.04 (2.59–3.59)	0.78 (0.62–0.97), 0.02
60–69	5.13 (4.07–6.56)	3.42 (2.58–4.63)	0.67 (0.45–0.98), 0.03
≥70	9.32 (6.16–14.78)	8.88 (5.80–14.26)	0.95 (0.49–1.85), 0.9

CI: confidence interval; MI: myocardial infarction; IRR: incidence rate ratio