The importance of measuring substance use: A Mendelian randomization of chronic Hepatitis C and myocardial infarction

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Chronic hepatitis C virus (HCV), common in people living with HIV (PLWH), is associated with cardiovascular disease such as myocardial infarction (MI). The two most frequently occurring types of MI are atheroembolic Type 1 (T1MI) and oxygen supply-demand mismatch Type 2 (T2MI). Our recent study in PLWH found that chronic infection with HCV was associated with T2MI, particularly T2MI attributed to sepsis, but not T1MI. We hypothesize that this relationship is confounded by sociobehavioral factors, such as injection drug use, and accompanying risk of sepsis. We used Mendelian randomization (MR) to estimate the causal effect of chronic HCV infection on T2MI (n events = 143) in 6,116 PLWH in the CFAR Network of Integrated Clinical Systems (CNICS), a multi-center clinical cohort of PLWH. T2MI events were ascertained by centralized adjudication. Genotyping of four candidate variants with known association to HCV clearance in diverse populations was via the Illumina Multiethnic Global Array. MR estimates on the basis of each variant were combined via meta-analysis. Variants were associated with 17 to 32% higher odds of chronic HCV infection. Findings do not support a causal relationship between chronic HCV and T2MI (ratio of odds ratios (ORR): 0.78, 95% CI: 0.33, 1.83) or the subset of T2MI attributed to sepsis (ORR 1.13, 95% CI: 0.54, 2.36). This suggests that factors other than HCV infection, such as substance use, may explain the observed association between chronic HCV infection and T2MI, highlighting the importance of comprehensive longitudinal substance use assessments in clinical cohorts of PLWH.