Effects of Eradication of HCV on Cardiovascular Risk and Preclinical Atherosclerosis in HIV/HCV-Coinfected Patients

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Background: To assess the effects of eradication of hepatitis C virus (HCV) on cardiovascular risk (CVR) and preclinical atherosclerosis in HIV/HCV-coinfected patients.

Setting: Prospective cohort study.

Methods: We assessed serum lipids, 10-year Framingham CVR scores, pulse wave velocity, carotid intima–media thickness, and biomarkers of inflammation and endothelial dysfunction (BMKs) at baseline and 96 weeks (wk) after initiation of anti-HCV therapy (Rx) in HIV/HCV-coinfected patients.

Results: A total of 237 patients were included. Anti-HCV therapy comprised pegylated interferon and ribavirin plus 1 direct-acting antiviral in 55.2%, pegylated interferon and ribavirin in 33.8%, and all-oral direct-acting antiviral in 11.0%. A total of 147 (62.0%) patients achieved sustained viral response (SVR). Median increases in low-density lipoprotein cholesterol in patients with and without SVR were 14 mg/dL and 0 mg/dL ($P = 0.024$), respectively. Increases in CVR categories were found in 26.9% of patients with SVR ($P = 0.005$ vs. baseline) and 8.1% of patients without SVR ($P = 0.433$). This resulted in a significant interaction between SVR and CVR over time ($P < 0.001$). No significant effect of SVR was observed for pulse wave velocity ($P = 0.446$), carotid intima–media thickness ($P = 0.320$), and BMKs of inflammation and endothelial dysfunction.

Conclusions: In coinfected patients, eradication of HCV had no effect on markers of preclinical atherosclerosis and BMKs of inflammation and endothelial dysfunction but was associated with a clinically relevant rise in serum low-density lipoprotein cholesterol. Evaluation of CVR should be an integral part of care after the cure of chronic hepatitis C in patients with HIV.

Key Words: HIV infections/*complications, hepatitis C, antiviral agents/*therapeutic use, coinfection, cardiovascular diseases, vascular stiffness, pulse wave analysis/*methods, carotid intima–media thickness, biomarkers/blood

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INTRODUCTION

Atherosclerosis is a chronic condition that involves a cascade of vascular modifications from intimal thickening and fatty streak to vulnerable and ruptured atherosclerotic plaques.[1] Clinically important manifestations of atherosclerosis include coronary artery disease, stroke, and peripheral artery disease. Well-identified risk factors of atherosclerosis include dyslipidemia, diabetes, cigarette smoking, hypertension, and genetic abnormalities; however, clinical and experimental data support an additional critical role for inflammation in atherosclerosis.[2,3]

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The association between hepatitis C virus (HCV) infection and cardiovascular events is a controversial issue. Some observational studies have identified an association between HCV infection and heart disease events,[4] myocardial infarction,[5] stroke,[6] and peripheral artery disease.[7] However, 3 large studies failed to identify an association between HCV infection and coronary artery disease or myocardial infarction.[8–10] The Department of Veterans Affairs HIV Clinical Case Registry revealed an association between HCV infection and cerebrovascular events in HIV-infected individuals[11]; however, the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study Group found no association between HCV coinfection and the development of myocardial infarction.[12] The Women's Interagency HIV Study, a multicenter prospective cohort study of women with and without HIV infection in the United States, found no association between HCV infection and increased risk of peripheral artery disease.[13] Some meta-analyses have concluded that HCV infection is associated with increased cardiovascular mortality,[14] stroke,[15] and cardiovascular disease.[16] However, other meta-analyses found no association between HCV infection and increased risk of coronary artery disease.[17]

Studies on the subject are generally limited by their retrospective design and the absence of information about relevant cardiovascular risk (CVR) factors such as family history of coronary artery disease, obesity, diet, and exercise habits, as well as critical lifestyle-related factors such as smoking and alcohol and illicit drug use, which are more prevalent among HCV-infected than non–HCV-infected individuals.[18] Understanding the link between HCV and cardiovascular disease and how this relationship is affected by anti-HCV therapy may have significant implications for public health.

In a previous study, we found that sustained viral response (SVR) after anti-HCV therapy in HIV/HCV-coinfected patients was associated with a reduction in the risk of diabetes and renal failure and, unexpectedly, with an increase in the risk of cardiovascular events.[19] This last finding led us to design this study. We aimed to assess the impact of SVR induced by anti-HCV therapy on plasma lipids, CVR scores, pulse wave velocity (PWV), and carotid intima–media thickness (cIMT), all of which are validate surrogates of preclinical atherosclerosis. We also analyzed the impact of SVR on plasma levels of biomarkers of inflammation and endothelial dysfunction in coinfected patients.

METHODS

Design and Patient Selection

Ours was a multicenter prospective study of HIV/HCV-coinfected patients initiating anti-HCV therapy for chronic hepatitis C between February 2012 and February 2016 at 14 centers in Spain. The eligibility criteria included confirmed HIV infection, detectable HCV-RNA, stable antiretroviral therapy or no need for antiretroviral therapy, absence of previous hepatic decompensation, absence of active opportunistic infections, and no active injection drug use. In Spain, this therapy is provided by hospital pharmacies and is covered by the National Health System. The decision to administer anti-HCV therapy and the selection of appropriate treatment regimens was taken by infectious disease physicians at each institution according to national and international guidelines. The study was approved by the ethics committee of Hospital General Universitario Gregorio Marañón. The study was conducted in accordance with the Declaration of Helsinki. All patients provided their written informed consent to participate in the study. All centers were monitored 3 times (after the baseline visit of the last patient, at an intermediate time-point, and after the last patient's last visit) to verify that all the information in the database was consistent with the patient's medical records.

Investigations

Clinical and laboratory variables were collected at baseline, every 4 weeks during anti-HCV treatment, and every 12 weeks after discontinuation of therapy until 96 weeks after the initiation of treatment. All the information was recorded at each institution using a shared database through an online form.

Baseline variables included demographics, height and weight, and systolic and diastolic blood pressure. They also included clinical information associated with HIV, HCV-related liver disease, other comorbid conditions, history of ischemic heart disease in first-degree relatives, previous anti-HCV therapy, whether or not patients were receiving combination antiretroviral therapy (cART) or other medications (including opioid substitution therapy), smoking history, ongoing alcohol intake of more than 50 g/d, and pneumococcal vaccination. Laboratory tests included complete blood counts, coagulation tests, and a comprehensive serum biochemistry profile including quantification of lipids, HIV-1-RNA, and HCV-RNA. We also assessed HCV genotype, hepatitis B surface antigen (HBsAg), and CD4 + and CD8 + T-lymphocyte counts. All blood samples at baseline and follow-up were obtained after fasting.

Liver fibrosis was assessed using transient elastography (FibroScan; Echosens, Paris, France) performed by trained operators. Results were expressed in kilopascals (kPa), with a range of 2.5–75 kPa. We considered 10 acquisitions with a success rate of at least 60% and an interquartile range less than 30% of the median value as representative measurements of liver stiffness. Fasting was not routinely required before the examination. Cirrhosis was defined as a liver stiffness value $\geq$12.5 kPa[20] or by liver biopsy findings. Patients with an undetectable serum HCV-RNA level 12 weeks after discontinuation of therapy were classified as having SVR.

At the follow-up visits, we recorded all cardiovascular events, that is, coronary events, cerebrovascular events, peripheral arterial disease, and congestive heart failure.[19]

Assessment of CVR

Ten-year CVR was assessed at baseline and 96 weeks after the initiation of therapy according to the Framingham equation.[21] We used age and smoking status at baseline to

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calculate CVR during both time-periods (baseline and 96 weeks after initiation of anti-HCV therapy). Ten-year CVR scores were categorized according to the Framingham equation as low risk (<10%), intermediate risk (10%–20%), and high risk (≥20%). Electrocardiogram was performed in all patients at baseline.

Assessment of Preclinical Atherosclerosis

Carotid–femoral PWV measurements were taken at baseline and 96 weeks after the initiation of therapy by trained examiners following well-established recommendations.[22] In brief, measurements were taken in a quiet room with a stable temperature and the patient in the supine position after at least 10 minutes of rest. The validated device SphygmoCor CPV System (AtCor Medical Pty Ltd, West Ryde, New South Wales, Australia) was used to measure pulse wave travel time (t) between the common right carotid and common right femoral arteries. The direct straight distance between the 2 points was measured with a tape, and 80% of this distance was used as pulse wave traveled distance (d). PWV was calculated based on the formula PWV = d/t, and the results were expressed in m/s.

Ultrasound scans to measure cIMT were performed at each center at baseline and 96 weeks after the initiation of therapy by experienced technicians using a standardized protocol.[23] In brief, 12 segments of the right and left carotid arteries were studied (near and far wall segments of the common carotid artery, carotid artery bifurcation, and internal carotid artery). Images were stored in Digital Imaging and Communications in Medicine format and sent to the Cardiac Imaging Laboratory of Hospital General Universitario Gregorio Marañón for analysis. Measurements obtained on digital images using semiautomatic calipers were taken by the same experienced technician, who was blinded to the participant's clinical characteristics. The mean cIMT value (in mm) was calculated for each subject from the 12 measurements at the predefined segments.

Inflammatory Biomarkers

Plasma samples were taken at baseline and 96 weeks after the initiation of therapy and stored frozen in the HIV BioBank of Hospital General Universitario Gregorio Marañón (http://hivhgmbiobank.com). Biomarkers determined in these samples included proinflammatory cytokines such as tumor necrosis factor alpha (TNF α), interleukin 1 beta (IL-1 β), interleukin 6 (IL-6), and interleukin 8 (IL-8), as well as biomarkers of endothelial dysfunction such as soluble intercellular adhesion molecule-1 (sICAM-1) and soluble vascular cell adhesion molecule-1 (sVCAM-1). We selected these plasma biomarkers because they are involved in the pathogenesis of atherosclerosis and have been previously found to be higher in HIV/HCV-coinfected patients than in healthy controls and HIV-monoinfected patients.[24] All biomarkers were measured using the ProcartaPlexTM multiplex immunoassay (ThermoFisher, Waltham, MA) according to the manufacturer's specifications with a Luminex 200 analyzer (Luminex Corporation, Austin, TX). Inflammatory biomarker determinations were performed at Unidad de Infección Viral e Inmunidad, Centro Nacional de Microbiología, Instituto de Salud Carlos III, Majadahonda, Madrid, Spain.

Statistics

The descriptive statistics used were the absolute number and percentage and median and interquartile range. Differences between groups were analyzed using the χ^2 test, *t* test, or Mann–Whitney test, as appropriate. Normality was analyzed using the Kolmogorov–Smirnov test. Linear mixed-models for longitudinal data were used to account for repeated measures of CVR, PWV, cIMT, and serum biomarkers, with SVR and time and their interaction taken as fixed effects, and the patient as a random effect. Least-square means and their standard error (SEM) are reported for these models. In addition, tests for repeated measures (paired *t* test and Wilcoxon test) were used to study changes between baseline and week 96 serum lipids and CVR. IBM SPSS Statistics for Windows, Version 21.0, was used for all calculations. All statistical tests were 2-sided, and a *P* value of <0.05 was considered statistically significant.

RESULTS

The study population comprised 262 patients, of whom 25 were excluded from the analysis because they initiated therapy with statins during the study period. Therefore, the final sample included 237 patients. The only statistically significant difference at baseline between the 25 patients who initiated statins and the 237 who did not was a higher frequency of arterial hypertension among the former [9 (36.0%) vs. 27 (11.4%); $P < 0.05$] (see Table S1, Supplemental Digital Content, http://links.lww.com/QAI/B413).

Patient Characteristics

SVR was recorded in 147 patients (62.0%); the characteristics of these patients, categorized by whether or not they achieved SVR, are shown in Table 1.

Men accounted for 75.9%, the median age was 49.2 years, 27.0% had had previous AIDS-defining conditions, 97.9% were on cART, the median baseline CD4 cell count was 540 cells/mm,^{3} 87.3% had an undetectable HIV viral load, 65.8% were infected with HCV genotype 1, the median HCV-RNA load was 6.3 log10 IU/mL, and 2.5% were HBsAg-positive. Liver cirrhosis was detected in 50.2% of patients, and 12.2% had received previous anti-HCV therapy. Alcohol intake > 50 g/d was reported by 3.0% patients, 68.4% were current smokers, 11.4% had arterial hypertension, 8.4% had diabetes mellitus, and 11.0% had a history of coronary artery disease. Anti-HCV regimens included pegylated interferon (Peg-IFN) plus ribavirin (RBV) in 33.8%, Peg-IFN plus RBV plus a first-generation anti-HCV protease inhibitor (PI) in 49.3%, Peg-IFN plus RBV plus daclatasvir in 5.9%, and sofosbuvir plus RBV in 11.0%. HCV-RNA was the only baseline variable in which significant differences were found between responders and nonresponders (median

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TABLE 1. Baseline Patient Characteristics

Characteristic	SVR (n = 147)	No SVR (n = 90)	Total (N = 237)
Male sex, No. (%)	116 (78.9)	64 (71.1)	180 (75.9)
Age, y, median (IQR) (baseline)	49.1 (45.6–52.5)	49.2 (46.4–52.6)	49.2 (46–52.6)
BMI (n = 226), median (IQR)	24.6 (21.6–27.3)	24.2 (22–26.1)	24.4 (21.7–26.7)
Prior injection drug use, No. (%)	112 (76.2)	72 (80.0)	184 (77.6)
Methadone therapy, No. (%)	18 (12.2)	11 (12.2)	29 (12.2)
CDC disease category C, No. (%)	35 (23.8)	29 (32.2)	64 (27.0)
$CD4^+$, nadir, cells/mm^3, median (IQR)	166 (84–243)	191 (72–263)	171 (84–251)
cART during anti-HCV treatment, No. (%)			
2 nRTI + 1 nnRTI	46 (31.3)	22 (24.4)	68 (28.7)
2 nRTI + 1 INSTI	40 (27.2)	20 (22.2)	60 (25.3)
2 nRTI + 1 bPI	30 (20.4)	19 (21.1)	49 (20.7)
Other regimens	28 (19.0)	27 (30.0)	55 (23.2)
None	3 (2.0)	2 (2.2)	5 (2.1)
$CD4^+$, baseline, cells/mm^3, median (IQR)	518 (377–762)	559 (410–842)	540 (377–802)
Undetectable HIV-RNA load at baseline, No. (%)	131 (89.1)	76 (84.4)	207 (87.3)
Prior anti-HCV therapy, No. (%)	19 (12.9)	10 (11.1)	29 (12.2)
HCV genotype, No. (%)			
1	102 (69.4)	54 (60.0)	156 (65.8)
2	2 (1.4)	2 (2.2)	4 (1.7)
3	22 (15.0)	18 (20.0)	40 (16.9)
4	8 (5.4)	10 (11.1)	18 (7.6)
Other/mixed	12 (8.2)	5 (5.6)	17 (7.2)
Unknown	1 (0.7)	1 (1.1)	2 (0.8)
HCV-RNA, Log_{10} IU/mL, median (IQR)	6.2 (5.7–6.6)*	6.5 (6–7)	6.3 (5.9–6.7)
HBsAg positivity, No. (%)	4 (2.7)	2 (2.2)	6 (2.5)
Liver stiffness (n = 215), kPa, median (IQR)	12.9 (8.6–21.1)	11.9 (8.6–21.3)	12.5 (8.6–21.1)
Liver stiffness >12.5, No. (%)	75 (51)	40 (44.4)	115 (48.5)
Liver cirrhosis, No. (%) (METAVIR 4 or TE >12.5)	79 (53.7)	40 (44.4)	119 (50.2)
Current alcohol intake >50 g/d, No. (%)	5 (3.4)	2 (2.2)	7 (3.0)
Diabetes mellitus, No. (%)	12 (8.2)	8 (8.9)	20 (8.4)
Current smoking, No. (%)	99 (67.3)	63 (70)	162 (68.4)
Arterial hypertension, No. (%)	15 (10.2)	12 (13.3)	27 (11.4)
Coronary artery disease, No. (%)	18 (12.2)	8 (8.9)	26 (11.0)
Anti-HCV therapy, No. (%)			
Peg-IFN + RBV	50 (34.0)	30 (33.3)	80 (33.8)
Peg-IFN + RBV + HCV protease inhibitor	82 (55.8)	35 (38.9)	117 (49.3)
Peg-IFN + RBV + daclatasvir	8 (5.4)	6 (6.7)	14 (5.9)
Sofosbuvir + RBV	7 (4.8)	19 (21.1)	26 (11.0)

*$P < 0.05$ compared with the No SVR group.

IQR, interquartile range; BMI, body mass index; CDC, Centers for Disease Control and Prevention; nRTI, nucleoside reverse transcriptase inhibitor; nnRTI, non-nucleoside reverse transcriptase inhibitor; INSTI, integrase strand transfer inhibitor; bPI, boosted protease inhibitor; HBsAg, hepatitis B surface antigen; Peg-IFN, pegylated interferon alpha; RBV, ribavirin; TE, transient elastography.

value of 6.2 vs. 6.5 Log_{10} IU/mL, respectively, $P < 0.05$). After baseline, changes in cART were made in 40/144 responders (27.7%) and 29/88 nonresponders (32.9%); $P = 0.499$. Therapy was switched to an integrase strand transfer inhibitor–based regimen after baseline in 13 responders (9.0%) and in 9 nonresponders (10.2%); $P = 0.946$. Only 1 cardiovascular event was reported during the 96 weeks of follow-up (acute myocardial infarction at week 73 in a patient from the SVR group). During follow-up, there was 1 incident case of arterial hypertension among patients without SVR compared with 3 among patients with SVR (1.1% vs. 2.0%, $P = 0.590$). There was also 1 incident case of diabetes mellitus among patients without SVR compared with 2 among patients with SVR (1.1% vs. 1.4%, $P = 0.868$).

Serum Lipids

Paired determination of serum lipids at baseline and 96 weeks after the initiation of anti-HCV therapy was available for 227 patients. No statistically significant differences at baseline were found between responders and nonresponders in total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), or high-density lipoprotein cholesterol (HDL-C) (Table 2). The concentration of both TC and LDL-C was significantly higher at 96 weeks than at baseline in responders (median increase of 15 mg/dL in TC and median increase of 14 mg/dL in LDL-C) but remained unchanged in nonresponders. The concentration of HDL-C at 96 weeks remained unchanged in comparison with baseline in both responders

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TABLE 2. Concentration of Serum Lipids At Baseline and 96 Weeks After the Initiation of Anti-HCV Therapy in 227 Patients Categorized According to Whether or Not They Achieved SVR

Variable–median (IQR)	SVR n = 141	Non-SVR n = 86	*P*
TC, mg/dL			
Baseline	164 (137–188)	161 (140–193)	0.666
Week 96	180 (160–200)	167 (143–193)	0.008
Median change	15 (−3; 39)	1 (−25; 18)	0.001
P (repeated measures)	<0.001	0.815	
LDL cholesterol, mg/dL			
Baseline	92 (71–109)	87 (73–105)	0.598
Week 96	104 (89–128)	92 (68–116)	0.004
Median change	14 (−3; 30)	0 (−10; 23)	0.024
P (repeated measures)	<0.001	0.474	
HDL cholesterol, mg/dL			
Baseline	39 (34–54)	46 (39–60)	0.057
Week 96	41 (33–52)	48 (39–57)	0.018
Median change	−1 (−6; 5)	1.5 (−4.5; 8)	0.290
P (repeated measures)	0.375	0.445	

IQR, interquartile range.

and nonresponders (Table 2 and see Figure S1, Supplemental Digital Content, http://links.lww.com/QAI/B413).

Cardiovascular Risk

The CVR score according to the Framingham equation was assessed in 227 patients. The estimated least-square means (SEM) of the CVR score at baseline were 11.0% (0.6%) in responders and 11.1% (0.8%) in nonresponders. At 96 weeks, these values were 13.0% (0.6%) and 10.5% (0.8%), respectively. For CVR, a significant interaction was observed between time and response to treatment ($P < 0.001$) (Fig. 1A).

Figure 2 shows changes in CVR score categories according to the Framingham equation (low, intermediate, and high) for the 227 patients who underwent paired determination of serum lipids at baseline and 96 weeks after initiation of anti-HCV therapy. The Framingham risk score category increased in 26.9% of responders and 8.1% of nonresponders. Likewise, the Framingham risk score category decreased in 9.2% of responders and 13.1% of nonresponders. Finally, the Framingham risk score category remained unchanged in 63.9% of responders and 78.8% of nonresponders.

Pulse Wave Velocity

Carotid–femoral PWV was assessed in 184 patients (Fig. 1B). The estimated least-square mean (SEM) PWV at baseline was 7.06 m/s (0.26) in responders and 7.44 m/s (0.32) in nonresponders. The estimated least-square mean (SEM) PWV at 96 weeks was 7.46 m/s (0.27) in responders and 7.55 m/s (0.33) in nonresponders. No significant effect of SVR was observed on PWV ($P = 0.446$ for the interaction between time and SVR).

Carotid Intima–Media Thickness

cIMT was assessed in 168 patients (Fig. 1C). The least-square mean (SEM) cIMT at baseline was 0.68 mm (0.01) in responders and 0.72 mm (0.02) in nonresponders. The least-square mean (SEM) cIMT at 96 weeks was 0.72 mm (0.02) in responders and 0.73 mm (0.03) in nonresponders. No significant effect of SVR on cIMT was observed ($P = 0.320$ for the interaction).

Plasma Biomarkers

Least-square means (SEM) of plasma concentrations of TNF α (N = 171), IL-1 β (N = 171), IL-6 (N = 171), IL-8 (N = 175), sICAM-1 (N = 177), and sVCAM-1 (N = 177) at baseline and at 96 weeks in both responders and nonresponders are shown in Figure 3 and in Table S2, Supplemental Digital Content, http://links.lww.com/QAI/B413. Decreases in plasma concentrations from baseline to week 96 were observed for IL-6, IL-8, sICAM-1, and sVCAM-1 in both responders and nonresponders, whereas increases in plasma concentration from baseline to week 96

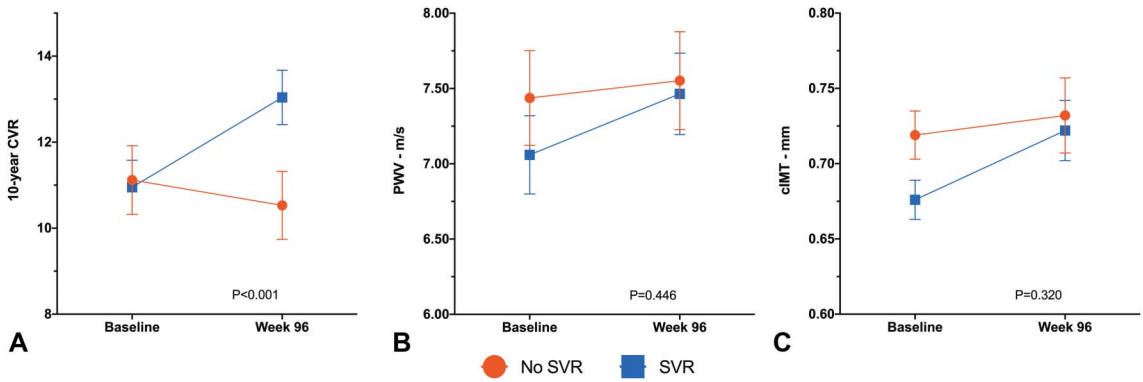

FIGURE 1. Estimated means (SEM) of Framingham 10-year general CVR score (A), carotid–femoral pulse wave velocity (B), and cIMT (C) at baseline and 96 weeks in patients with and without SVR. Linear mixed-models for longitudinal data were used to account for repeated measures with SVR and time as fixed effects and the patient as a random effect. The *P* value refers to the significance of the interaction (ie, the impact of SVR on the time-course of the variable). PWV, carotid–femoral pulse wave velocity.

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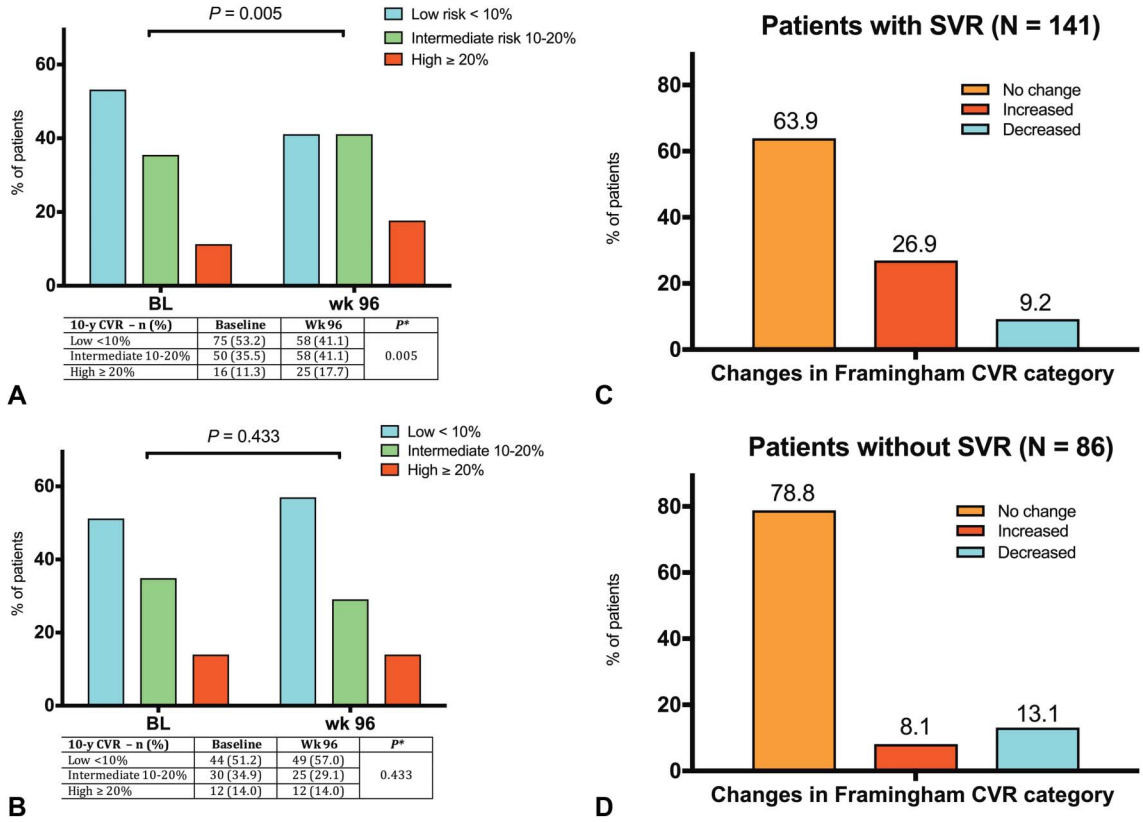

10-y CVR – n (%)	Baseline	Wk 96	P*
Low <10%	75 (53.2)	58 (41.1)	0.005
Intermediate 10-20%	50 (35.5)	58 (41.1)	
High ≥ 20%	16 (11.3)	25 (17.7)	

10-y CVR – n (%)	Baseline	Wk 96	P*
Low <10%	44 (51.2)	49 (57.0)	0.433
Intermediate 10-20%	30 (34.9)	25 (29.1)	
High ≥ 20%	12 (14.0)	12 (14.0)	

FIGURE 2. Distribution of Framingham 10-year general CVR score categories at baseline and 96 weeks in patients with (A) and without (B) SVR. Proportion of patients with changes in Framingham 10-year general CVR score categories from baseline to week 96 in patients with (C) and without (D) SVR. BL, baseline.

were observed for TNF α and IL-1 β. Of note, SVR had not impact on plasma biomarkers ($P > 0.05$ for all biomarkers).

DISCUSSION

In this prospective study, we did not observe a medium-term beneficial effect of eradicating HCV in HIV/HCV-coinfected patients with chronic hepatitis C on arterial stiffness, arterial intimal thickening, and plasmatic concentrations of proinflammatory cytokines and biomarkers of endothelial dysfunction. However, we found an association between SVR and an increase in the Framingham 10-year general CVR that was driven by the rise in serum LDL-C in patients who responded to treatment. Of note, the 10-year CVR in our cohort of coinfected patients at baseline and 96 weeks after initiation of anti-HCV therapy for both responders (11.0% and 13.0%) and nonresponders (11.1% and 10.5%) was higher than the mean 10-year CVR for men and women aged 49 years in Spain (9.2% and 6.2%, respectively).[25]

The rebound of LDL and TC after SVR in patients with chronic HCV infection has been described in retrospective studies[26,27]; however, to the best of our knowledge, ours is the first prospective study to clearly demonstrate that these lipid abnormalities manifest clinically as an increase in CVR.

More than 3 quarters of the study patients underwent determination of carotid–femoral PWV, the gold standard for the measurement of arterial stiffness and a validated surrogate predictor of coronary heart disease and stroke in apparently healthy subjects.[28] Small increases in PWV were found in patients with and without SVR, although no impact of SVR was found on the time-course of changes in PWV. Increased arterial stiffness from baseline to the time of confirmation of SVR was recently reported in HCV-monoinfected patients with advanced fibrosis successfully treated with direct-acting antivirals.[29]

cIMT is a reliable predictor of myocardial infarction and stroke in adults with no history of cardiovascular disease.[30] We also found small increases in cIMT in patients with and without SVR, although no significant impact of SVR on cIMT was observed. A recently published study showed a significant decrease in cIMT after successful direct-acting antiviral-based therapies in a cohort of 182 patients with advanced fibrosis or cirrhosis.[31] However, the control group was a historical cohort of 76 HCV-infected patients with advanced fibrosis or cirrhosis who did not receive antiviral therapy. In addition, the interval between the paired determinations of cIMT after the end of therapy was 36–48 weeks.

Proinflammatory cytokines such as IL-8 and adhesion molecules play a significant role in the development of atherosclerosis.[2] Adhesion molecules also play a key role in the recruitment of leukocytes in acute and chronic liver inflammation.[32,33] Plasma concentrations of IL-6, IL-8, sICAM-1, and sVCAM-1 decreased from baseline to week 96

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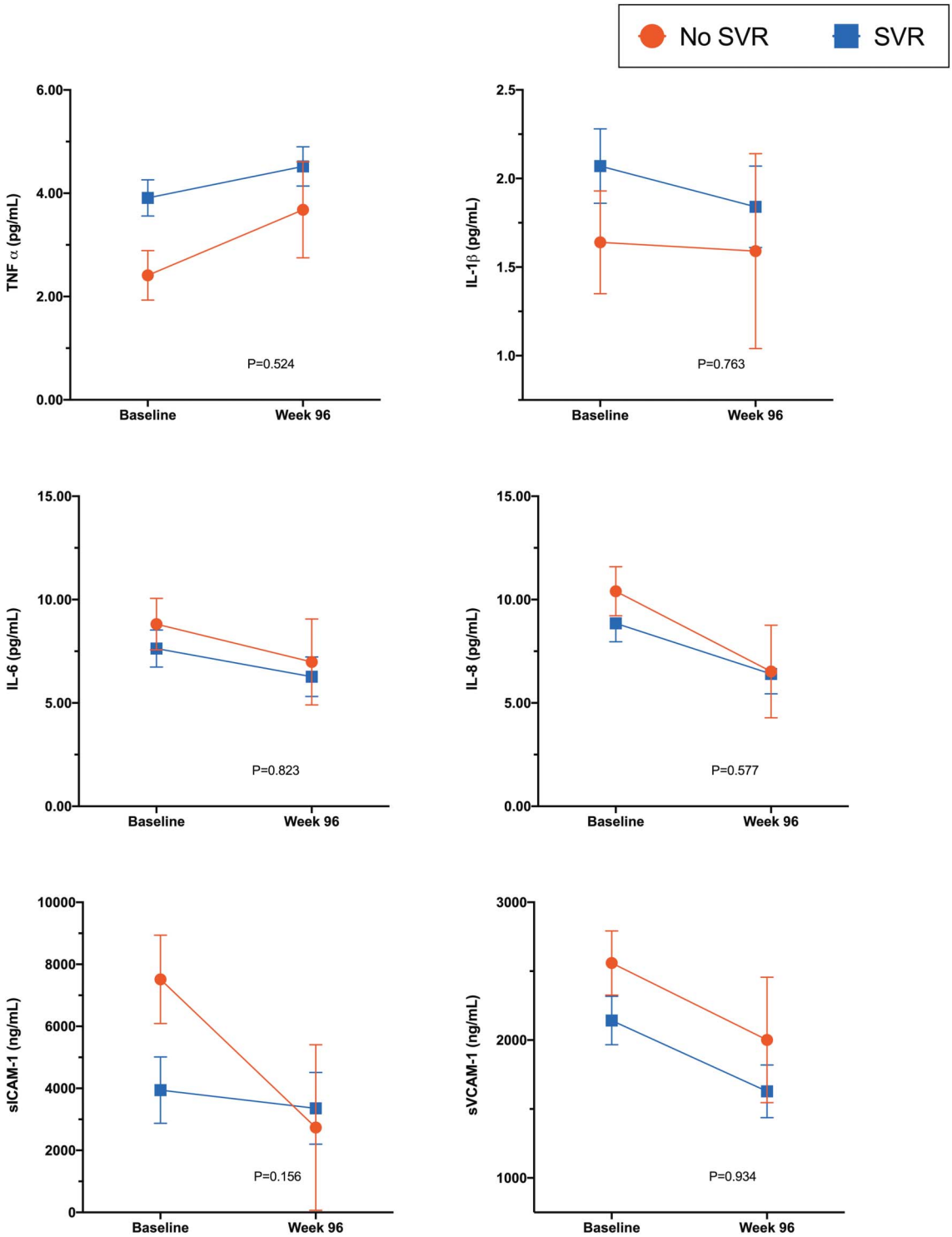

FIGURE 3. Estimated means (SEM) of plasma concentrations of biomarkers at baseline and 96 weeks in patients with and without SVR. Linear mixed-models for longitudinal data were used to account for repeated measures with SVR and time as fixed effects and the patient as a random effect. The *P* value refers to the significance of the interaction (ie, the impact of SVR on the time-course of the variable). TNF α, tumor necrosis factor alpha; IL-1 β, interleukin 1 beta; IL-6, interleukin 6; IL-8, interleukin 8; sICAM-1, soluble intercellular adhesion molecule-1; sVCAM-1, soluble vascular cell adhesion molecule-1.

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in both responders and nonresponders; however, no significant effect of SVR was identified for any of the biomarkers of inflammation or endothelial dysfunction.

Very little is known about the effect of eradication of HCV on cardiovascular clinical outcomes. In our study, one patient with SVR experienced an acute myocardial infarction at week 73, whereas no cardiovascular events were detected during follow-up among patients without SVR. In a retrospective cohort study from Taiwan that included 3113 subjects with a newly detected HCV infection, 208 of whom received interferon-based anti-HCV therapy, an association was found between anti-HCV therapy and a significant reduction in the hazard of stroke during follow-up.[34] As mentioned previously, in a cohort of 1625 HIV/HCV-coinfected patients treated with interferon plus ribavirin followed for a median of 5 years after completion of treatment, the adjusted hazard of cardiovascular events was almost statistically significantly higher in responders than in nonresponders, although the adjusted hazards of mortality, HIV progression, liver-related events, diabetes mellitus, and chronic renal failure were lower in responders than in nonresponders.[19]

Our study was not designed to assess the effect of eradicating HCV on clinical outcomes in patients with cardiovascular disease. In addition, outcomes were assessed in the medium term (96 weeks after the initiation of anti-HCV therapy) and not in the long term. Finally, the relatively small sample may be insufficient to detect significant changes in the effects studied. However, using highly sensitive statistical methods such as repeated-measures mixed-effect linear models, we found high *P* values for the effects of SVR. Thus, although significant changes were observed in much larger cohorts, the clinical impact of these findings seems questionable.

Our study has several strengths, including its prospective design, appropriate independent monitoring, and exclusion of bias due to differences between responders and nonresponders with respect to CVR factors and lifestyle-related factors. Moreover, the effect of eradicating HCV on cardiovascular health was assessed comprehensibly in both responders and nonresponders; this included determination of serum lipids and CVR and assessment of relevant surrogates of preclinical atherosclerosis such as PWV, cIMT, and plasma biomarkers.

In conclusion, the results of this study do not support medium-term beneficial effects of SVR on markers of preclinical atherosclerosis and plasmatic concentrations of proinflammatory and endothelial dysfunction biomarkers in HIV/HCV-coinfected patients. On the contrary, HCV clearance after anti-HCV therapy in this population group is associated with a clinically relevant rise in serum LDL-C. This finding suggests that evaluation of CVR should be an integral part of care after the cure of chronic hepatitis C in patients with HIV.

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