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ORIGINAL RESEARCH

Platelet Reactivity in Hepatitis C Virus–Infected Patients on Dual Antiplatelet Therapy for Acute Coronary Syndrome

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BACKGROUND: Coronary artery disease (CAD) has been recognized as a serious and potentially life-threatening complication of Hepatitis C Virus (HCV) infection. High on-treatment platelet reactivity has been associated with high risk of ischemic events in patients with CAD, but data regarding the association with HCV infection are still lacking. This post hoc analysis aims to assess high on-treatment platelet reactivity, severity of CAD, and long-term outcomes of patients with acute coronary syndrome (ACS) who were infected with HCV.

METHODS AND RESULTS: Patients with ACS who were infected with HCV (n=47) were matched to patients with ACS and without HCV (n=137) for age, sex, diabetes mellitus, hypertension, and renal function. HCV-infected patients with ACS had higher levels of platelet reactivity (ADP_{10}–light transmittance aggregometry, 56±18% versus 44±22% [*P*=0.002]; arachidonic acid–light transmittance aggregometry, 25±21% versus 16±15% [*P*=0.011]) and higher rates of high on-treatment platelet reactivity on clopidogrel and aspirin compared with patients without HCV. Moreover, HCV-infected patients with ACS had higher rates of multivessel disease (53% versus 30%; *P*=0.004) and 3-vessel disease (32% versus 7%; *P*<0.001) compared with patients without HCV. At long-term follow-up, estimated rates of major adverse cardiovascular events (cardiac death, nonfatal myocardial infarction, and ischemia-driven revascularization) were 57% versus 34% (*P*=0.005) in HCV- and non–HCV-infected patients with ACS, respectively. In addition, thrombolysis In Myocardial Infarction (TIMI) major bleeding rates were higher in HCV-infected patients (11% versus 3%; *P*=0.043) compared with noninfected patients. Multivariable analysis demonstrated that HCV infection was an independent predictor of high on-treatment platelet reactivity, severity of CAD, and long-term outcome.

CONCLUSIONS: In this hypothesis-generating study, patients with ACS and HCV infection showed increased on-treatment platelet reactivity, more severe CAD, and worse prognosis compared with patients without HCV.

Key Words: acute coronary syndrome ■ hepatitis C virus ■ high on-treatment platelet reactivity ■ long-term outcome ■ multivessel disease

Hepatitis C Virus (HCV) infection is endemic worldwide and a major health problem. Recent estimates showed an increase in its seroprevalence over the past decade to nearly 3%, corresponding to >185 million infected people worldwide.[1] The virus exerts its action mainly on the liver, with serious, well-known, organ-related complications such as hepatic fibrosis, cirrhosis, and liver cancer. However, numerous extrahepatic manifestations may occur and frequently affect morbidity and mortality of infected patients.[2] Among these, cardiovascular disease, including coronary artery disease (CAD), has been recognized as a serious

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CLINICAL PERSPECTIVE

What Is New?

- Patients with acute coronary syndrome who are infected with Hepatitis C Virus have increased platelet reactivity and higher rates of high on-treatment platelet reactivity on dual antiplatelet therapy, either to aspirin or to clopidogrel, compared with patients with acute coronary syndrome who are not infected with hepatitis C.
- Despite poor response to antiplatelet agents, patients with hepatitis C are at increased risk of major bleeding events during dual antiplatelet therapy.

What Are the Clinical Implications?

- Given their high likelihood of high on-treatment platelet reactivity on clopidogrel and of recurrent events, patients with acute coronary syndrome and hepatitis C might benefit from more potent antiplatelet therapy.
- Concurrent increased bleeding risk requires strict and careful patient follow-up and dual antiplatelet therapy length that is as short as possible.

Nonstandard Abbreviations and Acronyms

ACS	acute coronary syndrome
CAD	coronary artery disease
DAPT	dual antiplatelet therapy
HCV	hepatitis C virus
HTPR	high on-treatment platelet reactivity
LTA	light transmittance aggregometry
MACE	major adverse cardiovascular events
MI	myocardial infarction

and potentially life-threatening complication of HCV infection. The pathogenic relationships between HCV infection, chronic liver disease, and atherosclerosis are still not completely elucidated. It has been hypothesized that HCV promotes atherogenesis and its complications through several direct and indirect mechanisms, including virus colonization and replication within the arterial wall,[3] fatty liver disease and fibrosis, cryoglobulinemia, oxidative stress, and enhanced production of inflammatory cytokines.[4,5] Previous studies suggested the association between HCV infection and increased risk of carotid artery plaques and carotid intima–media thickening independent of other classic risk factors for atherosclerosis[6,7] and with a possible local direct role of the virus in initiating the plaque.[3] The observation that the virus induces production of proatherogenic cytokines[5] and the link between chronic HCV infection and plaque development, growth, and instability support a role for HCV in the development of cerebrovascular disease.

We hypothesized that a potential mechanism for the increased risk of recurrent acute coronary events could be high on-treatment platelet reactivity (HTPR) in patients with HCV. HTPR was shown to be an independent risk factor of major adverse cardiovascular events (MACE) after percutaneous coronary intervention or acute coronary syndrome (ACS).[8]

The aim of the study was to assess platelet reactivity on dual antiplatelet therapy (DAPT), severity of CAD, and long-term outcome of patients with ACS who were infected with HCV.

METHODS

Study Design

The data that support the findings of this study are available from the corresponding author on reasonable request. This study is based on a post-hoc analysis of the Responsiveness to Clopidogrel and Stent-related Events (RECLOSE) 2-ACS study. The RECLOSE 2-ACS study was a prospective single-center cohort study of consecutive patients with ACS undergoing an invasive strategy, in whom platelet reactivity after clopidogrel loading was assessed.[9] All interventions were performed according to current standards, and the type of stent implanted and the use of glycoprotein IIb/IIIa inhibitors were at the discretion of the operators; patients treated by thrombolysis were excluded. All patients were treated with clopidogrel 600-mg loading dose, followed by a 75-mg daily dose on top of aspirin. Platelet reactivity after clopidogrel loading was prospectively assessed by light transmittance aggregometry (LTA) before hospital discharge. For patients receiving both the loading dose of clopidogrel and a glycoprotein IIb/IIIa inhibitor in the catheterization laboratory, blood samples were obtained after 7 days. HTPR on aspirin was defined as platelet aggregation by arachidonic acid 1 mmol/L ≥20% and HTPR on clopidogrel as platelet aggregation by ADP 10 μmol/L ≥70%. The local ethics committee approved the study, and all patients gave informed consent.

Study Population

Of 1789 patients enrolled in the RECLOSE 2-ACS study, 60 were excluded because they were lost to follow-up within 1 year (n=17) or had an indication for chronic anticoagulant therapy (n=43). The remaining 1729 patients were included in this analysis. Overall, 47

patients were infected with HCV. Virological diagnosis of HCV infection is based on assays detecting a specific antibody to HCV.[10] Patients with coinfection with hepatitis B virus and HIV were excluded.

Patients with ACS with and without HCV infection were matched 1:3 based on age, sex, diabetes mellitus, renal function, dyslipidemia, and hypertension.

End Points

The primary study end point was the proportion of patients with HTPR. The secondary end points of this study were a composite of MACE (cardiac death, reinfarction, and ischemia-driven revascularization) at long-term follow-up, TIMI major bleeding, and severity of CAD. Individual components of the composite end point were other secondary end points. Cardiac death includes death resulting from myocardial infarction (MI), sudden cardiac death, death due to heart failure, and death due to cardiac procedures. Nonfatal MI was defined according to the current universal definition of MI.[11] All revascularization events were considered to be ischemia-driven if one of the following conditions was met: (1) a positive functional study corresponding to the area served by the target lesion; (2) ischemic ECG changes at rest in a distribution consistent with the target vessel; (3) typical ischemic symptoms referable to the target lesion; (4) intravascular ultrasound of the target lesion with a minimal lumen area of ≤4 mm^2 for nonleft main lesions or ≤6 mm^2 for left main lesions; and (5) fractional flow reserve of the target lesion ≤0.80 or instantaneous wave-free ratio ≤0.90.

Follow-Up

All patients had scheduled follow-up at 1, 6, and 12 months from the ACS and annually thereafter. All other possible information gathered from hospital readmission charts or by referring physicians, relatives, or municipality vital registries was entered into the prospective database.

Statistical Analysis

Discrete data are expressed as frequencies and continuous data as mean±SD or median and interquartile range, as appropriate. The χ^2 test was used to compare categorical variables. Survival curves were generated with the use of the Kaplan–Meier method, and the difference between groups was assessed by the log-rank test. To address concerns about the potential confounding variables to affect the prognostic performance of the HCV infection, we performed multivariable analysis by binary logistic and Cox proportional hazards models. The variables that were significantly different between the study groups (including HCV as a categorical variable) and those that are known to affect the severity of HTPR and the incidence of MACE were incorporated in the model. The proportional hazards assumption was assessed and satisfied graphically by plotting log (–log) survival curves against log survival time for each predictor category and verifying whether curves were parallel. Model discrimination was assessed with the C statistic and goodness of fit with the Hosmer-Lemeshow test. Binary logistic regression and Cox proportional hazards models were used to test interaction among covariates. Preliminary matching procedures were performed to obtain a covariate-balanced control group. Covariates included in the model are those known to affect platelet reactivity. A propensity score–matched analysis (3:1) was performed because of the expected differences in baseline characteristics between patients with and without HCV infection. We performed nearest neighborhood matching with Mahalanobis distance (0.25-SD distance tolerance caliper). Bias reduction was assessed by comparing the standardized difference for propensity score and the other covariates before and after matching between the 2 groups (a value <10% after matching indicates inconsequential imbalance). $P<0.05$ was considered significant. All tests were 2-sided. Analyses were performed with the SPSS statistical package v21 (IBM Corp).

RESULTS

Patient Population Clinical and Angiographic Characteristics

Baseline clinical characteristics of the whole population are summarized in Table 1. Proper characteristics of HCV-infected patients are summarized in Table S1. As shown in Table 1, after matching, HCV-infected patients with ACS were more likely to have a higher rate of non–ST-segment–elevation MI (72% versus 53% in HCV-positive and HCV-negative patients, respectively; $P=0.017$) and worse left ventricle ejection fraction. Furthermore, after matching, HCV-infected patients with ACS had a higher rates of multivessel coronary disease (53% versus 30% in HCV-positive and HCV-negative patients, respectively; $P=0.004$) and 3-vessel coronary disease (32% versus 7% in HCV-positive and HCV-negative patients, respectively; $P<0.001$) (Table 1). By multivariate analysis, HCV infection was independently associated with 3-vessel disease (odds ratio, 4.1; 95% CI, 2.18–7.77; $P<0.001$) (Table 2) and remained significantly associated with HTPR after propensity score adjustment (C statistic=0.69, $P<0.001$; $P=0.61$ for Hosmer-Lemeshow test). Furthermore, interactions between HCV and covariates were not statistically significant.

Table 1. Baseline Characteristics of Study Patients

	All HCV– (n=1682)	Matched HCV– (n=137)	HCV+ (n=47)	*P* Value*
Age, y, mean±SD	69±11	69±11	71±11	0.767
Age >75 y	638 (38)	67 (49)	20 (43)	0.452
Male sex	1372 (81)	99 (75)	33 (70)	0.788
Obesity	288 (17)	18 (13)	7 (15)	0.762
Hypertension	979 (58)	108 (79)	36 (77)	0.748
Dyslipidemia	769 (45)	65 (47)	25 (53)	0.349
Diabetes mellitus	338 (20)	38 (28)	13 (28)	0.992
Renal failure	174 (10)	15 (11)	5 (11)	0.953
Previous MI	309 (18)	29 (21)	14 (30)	0.228
Previous PCI	257 (15)	21 (15)	12 (25)	0.116
LVEF, mean±SD	49±8	49±8	45±11	0.013
LVEF ≤40%	513 (30)	44 (32)	57 (20)	<0.001
Type of ACS				
STEMI	806 (48)	65 (47)	13 (28)	0.018
NSTEMI/UA	911 (54)	72 (53)	34 (72)	0.017
Treated vessel				
LM	123 (7)	12 (9)	7 (15)	0.425
LAD	903 (53)	74 (54)	32 (68)	0.241
LCx	569 (33)	46 (34)	25 (53)	0.017
RCA	679 (40)	56 (41)	25 (53)	0.425
Multivessel disease	984 (58)	41 (30)	25 (53)	0.004
Three-vessel disease	470 (28)	10 (7)	15 (32)	<0.001
No. of vessels, mean±SD	1.8±0.8	1.8±0.8	1.8±1.1	0.998
No. of stent used, mean±SD	1.8±1.2	1.8±1.2	2.1±1.1	0.485

ACS indicates acute coronary syndrome; HCV, Hepatitis C Virus; LAD, left anterior descending artery; LCx, left circumflex artery; LM, left main; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSTEMI, non–ST-segment–elevation myocardial infarction; PCI, percutaneous coronary intervention; RCA, right coronary artery; STEMI, ST-segment–elevation myocardial Infarction; and UA, unstable angina.

*By HCV (positive) vs matched HCV (negative).

HCV and HTPR on DAPT

Results of the platelet function tests used to evaluate platelet reactivity on aspirin and clopidogrel are presented in Figure 1.

As summarized in Table 3, patients with ACS and HCV had significantly higher arachidonic acid–LTA (25±21% versus 16±15%; *P*=0.011) than patients without HCV (Figure 1A). Accordingly, HTPR in response to aspirin therapy was significantly more frequent in patients with versus without HCV (40% versus 18% in HCV-positive and HCV-negative patients, respectively; *P*=0.002). By multivariate analysis, HCV infection was independently associated with HTPR on aspirin (odds ratio, 2.6; 95% CI, 1.41–4.80; *P*=0.002) (Table 4) and remained significantly associated with HTPR after propensity score adjustment (C statistic=0.63, *P*=0.001; *P*=0.81 for Hosmer-Lemeshow test). Furthermore, interactions between HCV and covariates were not statistically significant.

As with aspirin, patients with ACS and HCV had significantly higher ADP_{10}-LTA (56±18% versus 44±22%; *P*=0.002) than patients without HCV (Figure 1B); the prevalence of HTPR in response to P_2Y_{12} platelet receptor inhibitor was significantly higher in those with versus without HCV (32% and 14% in HCV-positive and HCV-negative patients, respectively; *P*=0.006). By multivariate analysis, HCV infection was independently associated with HTPR on clopidogrel (odds ratio, 2.85; 95% CI, 1.49–5.45; *P*=0.002) (Table 5) and remained significantly associated with HTPR after propensity score adjustment (C

Table 2. Predictors of 3-Vessel Disease

	HR	95% CI	*P* Value
HCV	4.1	2.18–7.77	<0.001
Age >75 y	1.4	1.07–1.71	0.010
Hypertension	1.3	1.02–1.61	0.031
HTPR on clopidogrel	…	…	…
Diabetes mellitus	1.7	1.28–2.16	<0.001
LVEF ≤40	1.6	1.27–2.00	<0.001
Male sex	1.5	1.10–1.96	0.009
CKD	…	…	…
Previous MI	3.0	2.30–3.89	<0.001

CKD indicates chronic kidney disease; HCV, Hepatitis C Virus; HR, hazard ratio; HTPR, high on-treatment platelet reactivity; LVEF, left ventricular ejection fraction; and MI, myocardial infarction.

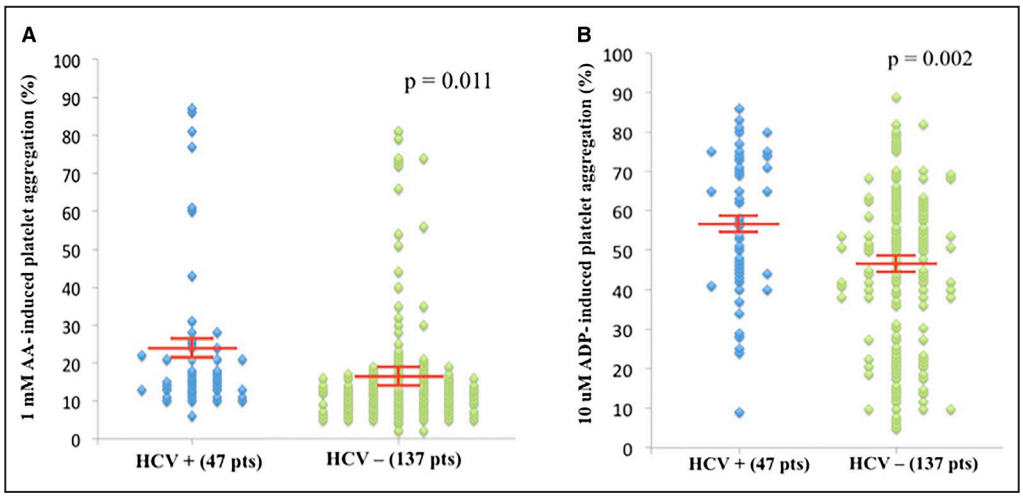

Figure 1. Response to anti-platelet agents in Hepatitis C virus (HCV) and non HCV patients.
A, Platelet reactivity to arachidonic acid (AA). Scattered distribution of 1 mmol/L AA-induced platelet aggregation. **B**, Platelet reactivity to ADP. Scattered distribution of 10 μM ADP-induced platelet aggregation. Blue dots: Hepatitis C Virus (HCV)–positive group; green dots: HCV-negative matched group.

statistic=0.72, *P*=0.001; *P*=0.71 for Hosmer-Lemeshow test). Furthermore, interactions between HCV and covariates were not statistically significant.

HCV and MACE

Follow-up rate was 95%, and median follow-up length was 2.8 years (interquartile range, 2.3–3.7 years). The MACE rate was 57% versus 34% (*P*=0.005) in HCV-infected and noninfected patients with ACS, respectively. Rates of secondary end points are reported in Table 6, and estimated cumulative incidences of MACE are reported in Figure 2.

By multivariable analysis, HCV infection was independently associated with MACE (hazard ratio, 3.1; 95% CI, 1.69–5.63; *P*<0.001) (Table 7) and remained significantly associated with this end point after the assessment of the predictive accuracy of the multivariable analysis with the C statistic and goodness of fit with the Hosmer-Lemeshow test (C statistic=0.63, *P*=0.005; *P*=0.89 for Hosmer-Lemeshow test). Furthermore, interactions between HCV and covariates were not statistically significant.

TIMI major bleeding rates were higher in HCV-infected patients than non–HCV-infected patients (11% versus 3% in HCV-positive and HCV-negative patients, respectively; *P*=0.043). As expected, regardless of infection status, patients with HTPR had higher incidence of MACE (60% versus 36% in patients with versus without HTPR, respectively; *P*=0.014).

DISCUSSION

The main findings of the study are as follows:

1. Patients with ACS who are infected with HCV have increased platelet reactivity and a higher rate of HTPR on DAPT, either to aspirin or to clopidogrel, compared with patients with ACS but without HCV.
2. Patients with ACS who are infected with HCV have more extensive CAD.
3. HCV infection was confirmed to be an independent predictor of MACE in patients with ACS.

Table 3. Platelet Function of Study Patients

	All HCV– (n=1682)	Matched HCV– (n=137)	HCV+ (n=47)	*P* Value*
HTPR on aspirin	339 (20)	25 (18)	19 (40)	0.002
HTPR on clopidogrel	235 (14)	19 (14)	15 (32)	0.006
Dual resistance	145 (9)	11 (8)	11 (23)	0.015
ADP-LTA, mean±SD	44±21	44±22	56±18	0.002
AA-LTA, mean±SD	17±18	16±15	25±21	0.011
DAPT at 2 y	1029 (61)	80 (58)	14 (30)	0.001

AA indicates arachidonic acid; DAPT, dual antiplatelet therapy; HCV, Hepatitis C Virus; HTPR, high on-treatment platelet reactivity; and LTA, light transmittance aggregometry.
*By HCV (positive) vs matched HCV (negative).

Table 4. Predictors of HTPR on Aspirin

	HR	95% CI	*P* Value
HCV	2.6	1.42–4.83	0.002
Age >75	1.8	1.44–2.37	<0.001
Hypertension	…	…	…
Diabetes mellitus	1.6	1.20–2.09	0.001
LVEF ≤40%	…	…	…
Smokers	…	…	…
CKD	…	…	…

CKD indicates chronic kidney disease; HCV, Hepatitis C Virus; HR, hazard ratio; HTPR, high on-treatment platelet reactivity; and LVEF, left ventricular ejection fraction.

4. Despite poor response to antiplatelet agents, patients with HCV are at increased risk of major bleeding events during DAPT.

In this study, we assessed the impact of HCV infection on treatment residual platelet reactivity by matching ACS patients with and without HCV to adjust for potential confounding factors. To our knowledge, for the first time, we were able to demonstrate that patients with ACS and HCV exhibit increased on-treatment platelet reactivity when treated by aspirin but also by clopidogrel, compared with patients with ACS but without HCV.

The odds of patients with HTPR on clopidogrel were increased by almost 3-fold among those with HCV. All results above remained significant after control matching and adjustment for potential confounding factors, clearly demonstrating the robustness and independence of HCV status as a predictor of HTPR.

Several pathophysiologic findings among HCV patients support our results. First, the virus itself is known to affect platelet activity though internalization into platelets.[12,13] In addition, inadequate hepatic conversion of clopidogrel to its active metabolite as a result of liver disease, the chronic inflammatory syndrome, and the higher rate of diabetes mellitus[14] and insulin-resistance[15] in HCV patients are concomitant factors that, negatively, increase platelet function. Furthermore, a multifactorial platelet count decrease (ie, thrombocytopenia) is frequently observed in cirrhotic patients, caused by numerous pathophysiologic modifications, such as decreased liver production of platelet growth factors and peripheral sequestration in hypersplenism due to portal hypertension.[16]

Table 5. Predictors of HTPR on Clopidogrel

	HR	95% CI	*P* Value
HCV	2.8	1.49–5.44	0.002
Age >75	1.7	1.31–2.31	<0.001
Dyslipidemia	1.4	1.10–1.91	0.008
Diabetes mellitus	1.7	1.23–2.23	0.001
LVEF ≤40%	…	…	…
Smokers	…	…	…
CKD	…	…	…

CKD indicates chronic kidney disease; HCV, Hepatitis C Virus; HR, hazard ratio; HTPR, high on-treatment platelet reactivity; and LVEF, left ventricular ejection fraction.

In our study, HCV infection was strongly associated with the severity of CAD, and this association persisted after control matching and adjustment for potential confounding factors. This result confirmed the pathophysiologic thesis in which the virus promotes atherosclerotic cardiovascular disease because of derangements in metabolic pathways and chronic inflammation.[17] Furthermore, HCV-infected patients had a more complex clinical profile characterized by higher probability of non–ST-segment–elevation MI and left ventricular dysfunction.

Patients with ACS and HCV showed an increased risk of MACE, possibly as a consequence of HTPR on DAPT[18] or of increased extension and severity of CAD, as well as more advanced left ventricular dysfunction. Therefore, we confirmed previous findings showing doubled all-cause mortality in HCV-positive versus HCV-negative patients.[19] In infected patients, the reported increased mortality is both liver-related and non–liver-related, the latter being ascribed mainly to cardiovascular disease. Moreover, in our cohort of patients with ACS, HCV-infected patients showed higher risk of both ischemic events (mainly driven by nonfatal MI and revascularizations) and bleeding complications. It is well known that the high bleeding risk in HCV-infected patients is caused by rebalanced hemostasis sustained by low production of both clotting factors, vitamin K deficiency, enhanced synthesis of fibrinolytic factors, or development of esophageal varices and hypersplenism as consequences of portal hypertension.[20]

These findings have some clinical perspectives. First, given the high likelihood of HTPR on clopidogrel and, at the same time, high recurrent event rates, patients with ACS and HCV might benefit from more potent antiplatelet therapy. However, concurrent increased bleeding risk requires strict and careful patient follow-up and DAPT length that is as short as possible. Second, viral eradication by use of increasingly effective antiviral drugs could be associated with an improvement in platelet function and a decrease in cardiovascular risk.[21] However, new direct-acting antiviral agents for the treatment of HCV have numerous drug–drug interactions with platelet P_2Y_{12} inhibitors; therefore, recommendations on the type and length of DAPT in patients with ACS and HCV infection should be made at the individual level after carefully balancing the ischemic and

Table 6. Outcomes of Study Population

	All Cohort HCV– (n=1682)	Matched HCV– (n=137)	HCV+ (n=47)	*P* Value*
MACE	539 (32)	47 (34)	27 (57)	0.005
Cardiovascular death	113 (7)	11 (8)	2 (4)	0.384
Nonfatal MI	43 (3)	4 (3)	15 (32)	<0.001
Ischemia-driven revascularization	445 (26)	37 (27)	20 (42)	0.047
Stent thrombosis	51 (3)	4 (3)	2 (4)	0.631
TIMI major bleeding	37 (2)	4 (3)	5 (11)	0.043

HCV indicates Hepatitis C Virus; MACE, major adverse cardiovascular events; MI, myocardial infarction; and TIMI, thrombolysis in myocardial infarction.
*By log-rank test.

bleeding risks and adequately considering concurrent therapies.

In conclusion, patients with ACS and HCV infection have increased on-treatment platelet reactivity, either to aspirin or to clopidogrel; more severe CAD; and increased adverse clinical events than patients without HCV.

Our study must be evaluated in the light of some limitations. First, this is a nonrandomized single-center study. However, we used propensity score matching to make the patient groups comparable according to the measured confounders. Nevertheless, residual unmeasured confounding cannot be excluded. Wider studies and randomized trials are needed to validate the impact of HCV infection on platelet function and its prognostic role in patients with ACS. Second, because of the limited size of the HCV group, our study was not properly powered for hard clinical end points, and it should be considered only as explorative and hypothesis generating. Third, our patients did not receive the 2 new P_2Y_{12} inhibitors (ie, prasugrel and ticagrelor), which were not available at the time of study enrollment. Consequently, we are not able to speculate about the extent to which these results would be different using the new drugs rather than clopidogrel. Therefore, our results cannot be generalized to patients receiving prasugrel or ticagrelor. However, because of the perceived high bleeding risk and potential drug–drug interactions with the newer antiplatelet agents, patients with HCV frequently receive clopidogrel in association with aspirin. Fourth, platelet reactivity was assessed only by LTA. However, LTA is the most well-established laboratory method for the determination of HTPR,[22] and its results have been strongly associated with an increased incidence of MACE.[8] Fifth, we are not able to analyze the influence of the different HCV genotypes, viral load, and severity of liver disease because of the relatively small size of the HCV-infected group. Finally, HTPR was defined as an ADP_{10}–LTA test >70%, based on the RECLOSE-1 result,[23] although not corresponding to the current standard. Nevertheless, at the time of study planning, the prognostic value of point-of-care assays was still to be defined.[24]

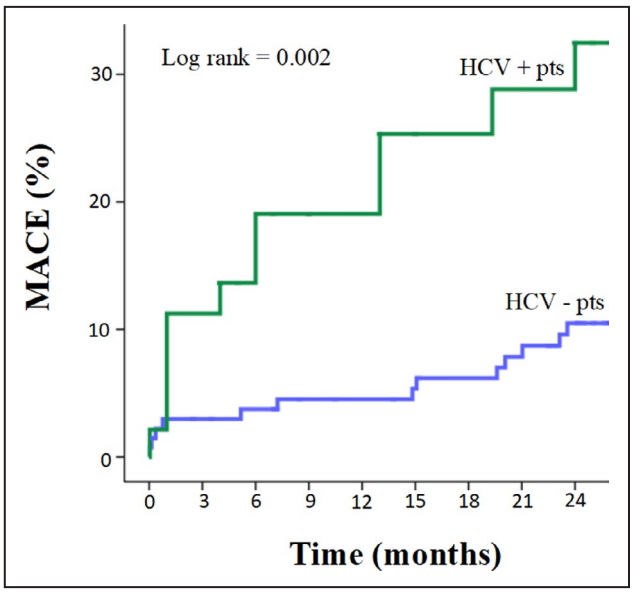

Figure 2. Major adverse cardiovascular events (MACE) cumulative incidence curves at 24-month follow-up.
Green curve: Hepatitis C Virus (HCV)–infected patients. Blue curve: HCV-negative matched patients. MACE, a composite end point of cardiovascular death, nonfatal myocardial infarction, and ischemia-driven revascularization.

Table 7. Predictors of MACE

	HR	95% CI	*P* Value
HCV	3.1	1.69–5.63	<0.001
Age >75 y	…	…	…
Hypertension	…	…	…
HTPR on clopidogrel	…	…	…
Multivessel disease	2.2	1.74–2.70	<0.001
Diabetes mellitus	…	…	…
LVEF ≤40	…	…	…
Male sex	…	…	…
CKD	…	…	…

CKD indicates chronic kidney disease; HCV, Hepatitis C Virus; HR, hazard ratio; HTPR, high on-treatment platelet reactivity; LVEF, left ventricular ejection fraction; and MACE, major adverse cardiovascular events.

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Supplementary Material

Table S1

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SUPPLEMENTAL MATERIAL

Table S1. Proper characteristics of HCV-infected patients.

	HCV + pts **(n= 47)**
Duration of HCV infection, years, mean SD	19 (7)
Cirrhosis, %	4 (8)
Serum Albumin, g/L, mean SD (n.v. 35-50 g/L)	48 (10)
Serum Ferritin, ng/dL, mean SD (n.v. 20-200 mg/dL)	155 (122)
Total Bilirubin, mg/dL, mean SD (n.v. 0.2-1.0 mg/dL)	0.72 (0.29)
Total Cholesterol, mg/dL, mean SD (n.v. 130-200 mg/dL)	153 (40)
Platelet count, x 10^9/L, mean SD (n.v. 140 – 440 x 10^9/L)	205 (97)
Prothrombin time, sec, mean SD (n.v 22-38 sec)	31 (4)
AST, U/L, mean SD (n.v. 15-37 U/L)	43 (40)

ALT, U/L, mean SD (n.v. 12-65 U/L)	44 (29)
GGT, U/L, mean SD (n.v. 5-85 U/L)	59 (50)

HCV, Hepatis C Virus; AST, Aspartate transaminase; ALT, Alanine transaminase; GGT, Gamma-Glutamyl Trans