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Impact of Direct-Acting Antiviral Treatment for Hepatitis C on Cardiovascular Diseases and Extrahepatic Cancers

Short title: Extrahepatic Impact of DAAs for HCV

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Abbreviations

ACD, cardiac arrhythmias and conduction disorders; ACS, acute coronary syndrome; ALD, affection longue durée (long-term illness); ALT, alanine aminotransferase; AST, aspartate aminotransferase; ATC, anatomical therapeutic chemical classification System; BMI, body mass index; CHC, chronic hepatitis C; CI, confidence interval; CNAM, Caisse Nationale de l'Assurance Maladie (French National Health Insurance Fund); CNIL, Commission Nationale de l'Informatique et des Libertés (French Data Protection Authority); Cox-PH, Cox proportional-hazards; Cox-TVC, Cox's time-varying covariate; DAA, direct-acting antiviral; EASL, European Association for the Study of the Liver; GLS, global longitudinal strain; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; ICD-10, International Classification of Diseases, 10th Revision; IPW, inverse probability weighting; IR, incidence rate; MACE, major cardiovascular events; MSM, marginal structural model; NSAIDs, non-steroidal anti-inflammatory drugs; PAD, peripheral arterial disease; PE, acute pulmonary embolism; PMSI, programme de médicalisation des systèmes d'information (French hospital-discharge database system); PY, person-year; SNDS, Système National des Données de Santé (French administrative health insurance database); SVR, sustained virologic response; ULN, upper limit of normal; WHO, World Health Organization

Abstract

Purpose: The impact of direct-acting antivirals (DAAs) on extrahepatic complications in chronic hepatitis C (CHC) patients remains poorly described. We estimated the association of DAAs with cardiovascular events and extrahepatic cancers.

Methods: The prospective ANRS CO22 HEPATHER cohort was enriched with individual data until December 2018 from the French Health Insurance Database (SNDS). CHC patients were enrolled between August 2012 and December 2015 in 32 French hepatology centers. A total of 8148 CHC adults were selected. Cardiovascular events (stroke, acute coronary syndrome, pulmonary embolism, heart failure, arrhythmias and conduction disorders [ACD], peripheral arterial disease [PAD]) and extrahepatic solid cancers were derived from the SNDS. Associations between DAAs and extrahepatic events were estimated using marginal structural models, with adjustments for clinical confounders.

Results: Analyses of 12 905 person-years of no DAA exposure and 22 326 person-years following DAA exposure showed a decreased risk of PAD after DAA exposure (hazard ratio [HR], 0.54; 95% CI, 0.33 to 0.89), a beneficial effect of DAAs on overall cardiovascular outcomes in patients with advanced fibrosis (aHR, 0.58; 95% CI, 0.42 to 0.79), and an increased risk of ACD (hazard ratio [HR], 1.46; 95% CI, 1.04 to 2.04), predominant after the first year following DAA initiation. There was no association between DAAs and extrahepatic cancer risk (HR, 1.23; 95% CI, 0.50 to 3.03).

Conclusions: DAAs were not associated with extrahepatic cancer development or reduction. They were associated with a decreased risk of PAD and an increased risk of ACD, supporting long-term cardiac monitoring after DAA therapy.

Keywords: Oral direct antiviral agents; Hepatitis C virus; Extrahepatic manifestations; Adverse events; SNDS

Key Points:

- Little is known about the association of direct-acting antiviral (DAA) with extrahepatic manifestations in patients with chronic hepatitis C virus.
- In a prospective cohort study that included 8148 patients with data enrichment using national health administrative databases, DAAs were significantly associated with a reduced risk of peripheral arterial disease.
- Additionally, DAAs were associated with a reduced risk of overall cardiovascular events in patients with advanced fibrosis.
- Treatment with DAAs was associated with a progressive increased risk of arrhythmias and conduction disorders.
- In patients with chronic HCV, long-term cardiac monitoring after DAA therapy may be warranted.

Plain Language Summary

Little is known about the association of direct-acting antiviral with extrahepatic manifestations, originating or occurring outside the liver, in patients with chronic hepatitis C virus, particularly cardiovascular events and extrahepatic cancers. We estimated the association of direct-acting antivirals with cardiovascular events and extrahepatic cancers in a cohort study with data enrichment using French national health administrative databases (SNDS). Cardiovascular events and extrahepatic solid cancers were derived from the SNDS. Analyses of 8148 patients enrolled between August 2012 and December 2015 in 32 French hepatology centers showed a decreased risk of peripheral arterial disease after direct-acting antiviral exposure, a beneficial effect of direct-acting antivirals on overall cardiovascular outcomes in patients with advanced liver fibrosis, and an increased risk of arrhythmias and conduction disorders, predominant after the first year following direct-acting antiviral exposure initiation. Treatment with direct-acting antivirals exposure was not associated with extrahepatic cancer development or reduction. Long-term cardiac monitoring after direct-acting antiviral therapy may be warranted in patients with chronic hepatitis C virus.

Purpose

The introduction of direct-acting antiviral (DAA) agents has reduced the development of hepatocellular carcinoma (HCC) and all-cause mortality in chronic hepatitis C (CHC) patients.^{1,2} Consequently, universal access to DAAs was implemented in August 2017 in France, following a priority access policy adopted in December 2013 restricting DAAs to patients with advanced liver disease and high-risk populations.³

It is now well established that HCV-induced immune dysregulation and persistent inflammation explain the occurrence of several extrahepatic manifestations.⁴⁻⁶ In particular, HCV infection is recognized as a risk factor for the development of several cardiovascular diseases.⁷⁻⁹ Similarly, the effect of HCV-induced inflammation on the blood coagulation process may lead to an increased risk of venous thromboembolism.^{10,11} In addition, HCV promotes carcinogenesis and leads to an increased risk of several extrahepatic cancers.¹²

Although causality is established between HCV and non-Hodgkin lymphoma, a causal link is still debated for other cancers, with the exception of intrahepatic cholangiocarcinoma.¹³

Several retrospective studies have evaluated the impact of HCV clearance on the risk of extrahepatic manifestations,¹⁴⁻¹⁶ but long-term follow-up data are lacking,¹⁵⁻¹⁷ although this impact remains of major public-health interest.^{18,19} In addition, few data are available regarding the impact of DAAs on extrahepatic risk.

Our main objective was to estimate the impact of DAAs on extrahepatic complications in CHC patients using data from the French HEPATHER cohort completed by anonymized individual data collected from the French National Health Insurance System (SNDS).²⁰

Methods

Study design and data sources

Data from patients in the HEPATHER cohort linked with those in the SNDS,²⁰ were used to investigate the occurrence of extrahepatic events. This cohort included 20 353 patients with a hepatitis B virus (HBV) or HCV infection from 32 French expert hepatology centers.²

Clinical characteristics at study entry and spontaneous reports for events were collected on specific data forms (e.g., initiation of DAA therapy, death).

The French administrative health insurance database (Système National des Données de Santé – SNDS) covers approximately 99% of the French population.²⁰ It contains data on ambulatory healthcare reimbursement, including drugs dispensed, laboratory tests, and medical procedures performed. It includes data from the French hospital discharge database system (PMSI) covering discharge diagnoses that have been coded according to the International Classification of Diseases, 10th Revision (ICD-10),²¹ and medical procedures performed during the hospitalizations. It also contains information on costly major or long-term illness (ALD). Based on the availability of SNDS data, we defined the end of follow-up on December 31, 2018. We obtained informed consent from each patient before inclusion and a specific consent for the linkage with the SNDS. The protocol was carried out in accordance with the Declaration of Helsinki and the French law on biomedical research and was approved by the appropriate research ethics committee (Comité de Protection des Personnes Ile de France 3), the French National Agency for Medicines and Health Products (ANSM), and the French Data Protection Authority (CNIL).

Participants

CHC patients included between August 6, 2012, and December 31, 2015, were assessed for eligibility. We selected DAA-naïve CHC patients who agreed for the linkage of the cohort data with the SNDS. We excluded patients with a history of HBV, decompensated cirrhosis,

and HCC. The linkage process employed both deterministic and probabilistic approaches. The deterministic record linkage procedure was based on a unique patient identity code (NIR). In case of failure of the deterministic approach, the probabilistic linkage procedure was performed. This latter approach included the following identifiers for matching: gender, date of birth, place of residence, dates of medical visits and geographic and legal identifiers of the corresponding health facilities. The deterministic linkage is intended to be error-free. A deterministic record linkage procedure was used for 7639 (93.8%) patients and a probabilistic approach was performed for the remaining 509 (6.2%) patients.

Exposure

The decision to initiate DAA therapy was guided by the European Association for the Study of the Liver (EASL) and French Association for Study of the Liver (AFEF) guidelines.²²

DAA exposure was defined as the period between the initiation of DAAs and death, the incident event of interest, or December 31, 2018, whichever came first. Exposure status was modeled as a time-dependent covariate.

Outcomes measures

eTable 1 shows the ICD-10 codes used to identify the main events of interest in the SNDS.

We analyzed the occurrence of six cardiovascular events: acute stroke, acute coronary syndrome (ACS), acute pulmonary embolism (PE), acute heart failure, cardiac arrhythmias and conduction disorders (ACD), and peripheral arterial disease (PAD). We also examined rates of hospitalization and extrahepatic solid cancers for the following sites: colorectal, bladder, prostate, kidney, lung, pancreas, thyroid, head and neck, and breast. Acute stroke, ACS, PE, acute heart failure, and PAD were classified as major cardiovascular events (MACE). Patients with evidence of prior occurrence of the events of interest between January 2012, and study entry, were excluded.

Procedures and covariates measurement

The demographic, clinical and biological characteristics were extracted from the HEPATHER cohort data. Details on clinical, biological and liver fibrosis procedures have been previously reported.² Additionally, we explored the SNDS to identify exposure to NSAIDs (non-steroidal anti-inflammatory drugs including aspirin), amiodarone, statin, antihypertensive drugs, and medications for dyslipidemia, and diabetes (eTable 2).

Statistical methods

The number of patients for whom consent was obtained determined our final sample size. To predict the probability of DAA exposure, a propensity score was computed. Inverse probability treatment weights (IPW)^{23,24} using the propensity score were then calculated at each time point during the follow-up. Marginal structural models (MSM)²⁵ were used to handle for time-varying confounders and exposures and address confounding by indication.²⁶ The stabilized weight assigned to each observation was proportional to the inverse of the probability of treatment after controlling for clinical and biological confounders, medications, and frequency of physician visits. More details on IPW estimation are included in the supplementary material (eFigure 1).

Because early cancer, detected before sustained virologic response (SVR) achievement, is likely to be unrelated to DAA exposure; we shifted the DAA exposure period by one year to analyze the risk of extrahepatic cancers in our adjusted models.

Additionally, we used an extension of the Cox model that accounts for continuous time-dependent coefficients for DAA exposure.²⁷ We then illustrated the dynamics of the hazard ratio over time using a log(time) interaction with the DAA exposure status assuming the potential time-varying effect of DAAs.²⁸

The impact of HCV clearance on the occurrence of extrahepatic events was also explored by comparing patients having achieved SVR to patients without HCV clearance 12 weeks after the end of the first DAA treatment.

Death was treated as a censoring event and cause-specific hazard ratios were estimated in all our models.²⁹ Age, frequency of visits to medical specialists and time since HCV diagnosis were handled numerically. Other numerical variables were categorized according to conventional clinical cut points.

To correct for a potential detection bias³⁰ that might arise from unequal surveillance before and after DAA therapy, we adjusted our analyses for frequency of visits to medical specialists, which was also used as a proxy for residual confounders related to general illness.³¹ This proxy was considered as an additional mean to exclude reverse causality, along with the exclusion of patients with a prior history of cardiac disease or cancer to prevent confounding due to pre-existing diseases. Potential confounders were selected on their known involvement in the occurrence of extrahepatic events.

We considered missing data as missing at random and inserted a missing category indicator for the identified variables in analyses. No participants were excluded because of missing data. To address missing data related to major clinical comorbidities, we explored medication use indicated for these comorbidities in the SNDS. Since we explored patient data via the SNDS, we addressed any potential follow-up loss and informative censoring. Data was analyzed using R version 4.1.0 (R Core Team). All *P* values were obtained in bilateral tests and *P* values below 0.05 were considered statistically significant.

Results

Participants

Overall, 8148 patients (53.6% male, median age, 56.7 years) were eligible for the study and were analyzed (Figure 1). Of these, 7037 patients started DAAs (eTable 3) by the end of December 2018 (22 326 person-years of observation following DAA exposure). A total of 1111 patients remained untreated in December 2018, due in part to the implementation of universal access in late 2017. Median follow-up was 4.29 years (IQR 3.78-4.97) and 4.51 years (IQR 3.80-5.28) in patients with and without DAA exposure, respectively. Compared with patients not treated during the study (Table 1), patients who started DAAs were older by 2.1 years ($P < .001$). They had more advanced liver fibrosis ($P < .001$), more diabetes ($p = 0.02$), and were infected with HCV for a longer period ($P = .03$). Other clinical characteristics including arterial hypertension and history of cardiovascular events were similar between both groups. The frequencies of visits to medical specialists were 1.50 (IQR 0.71-3.16) and 2.01 (IQR 1.00-3.58) per year in patients without DAA exposure and after DAA exposure, respectively.

Impact of DAAs on extrahepatic complications

The incidence of clinical outcomes is reported in Table 2 and eTable 4. DAA exposure was associated with a decreased risk of peripheral arterial events (aHR, 0.54; 95% CI, 0.33 to 0.89). In patients with advanced fibrosis (eTable 5), besides a beneficial effect of DAAs on PAD (aHR, 0.36; 95% CI, 0.17 to 0.13) and heart failure (aHR, 0.47; 95% CI, 0.27 to 0.81), a positive effect on overall cardiovascular outcomes (aHR, 0.58; 95% CI, 0.42 to 0.79) and MACE (aHR, 0.50; 95% CI, 0.36 to 0.71) was observed. We identified a higher risk of ACD after DAA exposure (aHR, 1.46; 95% CI, 1.04 to 2.04) after accounting for confounders (Table 3). Interestingly, risk of ACD was primarily associated with exposure to Sofosbuvir-based DAA regimens (eTable 6). History of MACE, age and obesity were independent

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predictive factors for developing ACD in patients treated with Sofosbuvir-based regimens (eTable 7). The median time between DAA exposure and the occurrence of ACD was 1.86 (IQR 0.94-3.11) years. Atrial fibrillation, atrial flutter, and complete atrioventricular block together accounted for 65% of incident ACD (eTable 8). The occurrence of ACD following DAA exposure was concomitant with the dispensing of antithrombotic and antiarrhythmic medications in 75% of cases (eTable 9). We observed a time-varying association between DAA exposure and the occurrence of ACD, and this association appeared to be stronger after the first year of treatment while being maintained over time (Figure 2, eFigure 2 and 3). For instance, the adjusted HRs for the occurrence of ACD were 1.32 (95% CI, 0.93 to 1.86), 1.55 (95% CI, 1.09 to 2.18), and 1.73 (95% CI, 1.23 to 2.45) at 1, 2 and 3 years of follow-up, respectively (eTable 10). We found no interaction between DAAs and both fibrosis stage ($P = .85$) and amiodarone use ($P = .86$) in the occurrence of ACD after testing a joint effect of these variables. Indeed, in patients with advanced fibrosis (eTable 5), no significant association was found between ACD and DAAs (aHR, 1.02; 95% CI, 0.57 to 1.84). There was no association between DAA exposure and organ-specific cancers. Furthermore, DAA exposure was associated with a significant decrease in rates of hospitalization (eTable 11). Similar results were obtained for all extrahepatic outcomes in the subset of individuals linked to the SNDS with the deterministic approach only (eTable 12).

Overall, 6419 out of 6706 patients (95.7%) with known SVR status achieved SVR: as shown in eTable 13, HCV clearance was not associated with extrahepatic cancer development (aHR, 0.74; 95% CI, 0.37 to 1.45) and cardiovascular events (aHR, 0.99; 95% CI, 0.56 to 1.76).

Discussion

We showed that DAAs were associated with a decreased risk of peripheral arterial events in all CHC patients, and a reduced risk of PAD, heart failure, and overall cardiovascular outcomes in patients with advanced fibrosis. In contrast, DAA exposure was associated with an increase in ACD. DAAs were not associated with extrahepatic cancer development or reduction.

We found a decreased risk of peripheral arterial events, MACE, and overall cardiovascular events after DAA exposure in patients with advanced fibrosis and cirrhosis. This has been previously reported in patients with Child class A cirrhosis included in the ANRS CO22 CirViR cohort,³² as well as in US veteran patients who had a decreased risk of cardiovascular events after DAAs.³³ In another study suggesting a decrease in the risk of cardiovascular events after HCV clearance by DAAs, regardless of the degree of fibrosis, the diseases defining cardiovascular events were limited to ischemic heart disease and ischemic cerebral stroke.¹⁴ It is known that liver fibrosis increases risk for atherosclerosis,^{9,34} which in itself is associated with chronic inflammation related to HCV infection.¹³ In a nationwide cohort study, HCV infection was independently associated with a higher risk of developing PAD.¹⁷ Furthermore, it has been shown that DAA-induced viral suppression improves the carotid intima-media thickness,¹⁵ probably by limiting chronic inflammation. Nevertheless, DAAs did not affect the composite cardiovascular outcome in all CHC patients. Because our study was designed to generate new hypotheses regarding the extrahepatic impact of DAAs in CHC patients, further investigations in other populations are needed to validate our results and confirm the beneficial effect of DAAs on PAD. The lack of association between DAAs and overall cardiovascular outcomes in all CHC patients, regardless of fibrosis stage, was in part explained by the less pronounced effect of DAAs on inflammation in patients with mild

fibrosis and by the divergent effect of DAAs on the components of the composite cardiovascular end point, as the effect was beneficial for PAD and harmful for ACD. After DAA exposure, CHC patients remained at risk for the late development of ACD, particularly atrial fibrillation and flutter, with more than 75% of patients receiving antithrombotic and antiarrhythmic medication shortly after the diagnosis of ACD. Although the increased risk of ACD was predominant after Sofosbuvir-based regimens, a potential association with also Sofosbuvir-free regimens cannot be completely ruled out due to the limited number of patients treated with Sofosbuvir-free regimens. In a retrospective cohort study using administrative health records, DAA exposure was associated with lower rates of arrhythmias.³⁵ This finding may in part be explained by the assumption used to analyze safety signals. In that study, patients were indeed followed up to only six months after DAA therapy. Since potential cardiotoxicity cannot be totally excluded over this short follow-up period, we explored the short- as well as long-term outcomes after starting DAA therapy. Moreover, since several studies reported ACD after DAA therapy,^{36–39} we investigated both arrhythmias of focal origin and blocks using a wider range of diagnosis codes to correctly identify ACD.⁴⁰

Several studies support potential DAA-related cardiotoxicity explaining the development of ACD.^{41,42} A potential change in cardiac energy generation observed in vitro may be involved.^{43,44} In addition, a hypothesis involving a potential action of DAA mediated by nerve fibers of the sinoatrial node influencing cardiac electrical activity has also been put forward.⁴⁵ Interestingly, the potential toxicity of DAAs was investigated following a study with a non-structural 5B inhibitor (BMS-986094) that resulted in the death of a patient from rapidly progressive heart failure.⁴⁴ The authors observed diffuse ventricular cell elongation and thinning, myocyte damage with interstitial fibrosis in the index case and reported cardiotoxic changes associated with the nucleotide analog polymerase inhibitor, suggesting a

toxic cardiomyopathy. In addition, a study suggested a deterioration in cardiac function measured by global longitudinal strain (GLS) after sofosbuvir-based regimens.⁴⁶ It illustrated the negative cardiac impact of the DAAs on cardiovascular functions and supported a potential mechanism of cardiac toxicity. The deterioration of the GLS continued after the end of the DAA therapy and was suggestive of chronic cardiotoxicity. It is, therefore, possible to speculate that a potential toxic cardiomyopathy could explain the development of ACD late after DAA exposure.

We did not detect an association between DAAs and the occurrence of extrahepatic solid cancers. This result agrees with findings already reported in previous studies. In a retrospective cohort study in 33 808 HCV-infected patients, no difference was observed between those exposed and not exposed to DAAs in the occurrence of extrahepatic cancers.³⁵ In the CirViR cohort study, there was no association between SVR achievement and the occurrence of extrahepatic cancer after a median follow-up of 58.2 months.³²

Strengths and limitations

The main strength of our study lies in the large number of included patients for whom long-term follow-up data were obtained by a comprehensive analysis of the SNDS. Furthermore, due to the study design, a wide range of extrahepatic outcomes not routinely collected in studies in CHC patients were analyzed. Finally, we ensured to account for numerous potential confounders and a potential detection bias by estimating frequency of physician visits before and after DAA exposure.

Our study has some limitations. First, due to the observational nature of the study, a causal effect of DAAs cannot be confirmed. Second, we cannot fully rule out potential misclassification of events due to coding errors. Nevertheless, we identified diseases using validated available algorithms,^{40,47} recommended by the French National Health Insurance Fund (CNAM), to properly investigate claims data for clinical purposes. Furthermore, any

bias due to misclassification would not be differential. To prevent spurious association, a sensitivity analysis including only cohort data linked to the SNDS by the deterministic approach was performed. Due to legal restrictions, a retrospective medical chart review of ACD cases was not feasible. Consequently, we detailed the types of ACD and associated medication use to detect clinically significant ACD. Third, a potential type 1 error cannot be excluded as we explored multiple extrahepatic outcomes. Lastly, the strength of several associations was limited since some analyses were restricted by the number of incident events. Therefore, we used composite variables to increase the statistical power of our analyses.⁴⁸

Conclusions

Treatment with DAAs was associated with cardiovascular benefits, including a decreased risk of peripheral arterial events in all CHC patients and a reduced risk of overall cardiovascular events in patients with advanced fibrosis. In contrast, our results suggest, for the first time, a prolonged increase in the risk of ACD after DAA exposure. Given the potential cardiotoxicity of DAAs, diligent cardiac monitoring should be considered in patients at risk for cardiac events to minimize the risk for the late development of ACD.

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Ethics Statement: The protocol was carried out in accordance with the Declaration of Helsinki and the French law on biomedical research and was approved by the appropriate research ethics committee (Comité de Protection des Personnes Ile de France 3), the French National Agency for Medicines and Health Products (ANSM), and the French Data Protection Authority (CNIL).

Conflict of Interest Disclosures: FC reports grants from INSERM-ANRS, during the conduct of the study; personal fees from Sanofi, outside the submitted work. HF reports personal fees and invitations for medical meetings from Gilead, AbbVie, Bristol-Myers Squibb, MSD and Janssen, outside the submitted work. PN has received honoraria from and/or consults for Astra-Zeneca, Bayer, Bristol-Myers Squibb, Eisai, Ipsen, and Roche, outside the submitted work. MB reports grants and personal fees from AbbVie and Gilead, outside the submitted work, and personal fees from MSD, Janssen, Boehringer Ingelheim, Intercept and Bristol-Myers Squibb, outside the submitted work. DL has served as a speaker/advisor for AbbVie, Gilead Sciences and Merck Sharp & Dohme. SP has received consulting and lecturing fees from Janssen, Gilead, MSD, Abbvie, Biotest, Shinogui, Viiv and grants from Bristol-Myers Squibb, Gilead, Roche and MSD without relation to this manuscript. HF reports personal fees and invitations for medical meeting from Gilead, Abbvie, BMS, MSD, Janssen, MSD outside this work. LL, NL, CD, JB, CL-N, FT, AD, CC, and GH have nothing to disclose.

Data Availability Statement: Due to the nature of this research based on the French administrative health care database, data that support the findings of this study are not available due to ethical and legal restrictions.

Author Contributions: LL and FC had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: LL and FC. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: LL and FC. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: LL and FC. All authors approved the final version of the submission.

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Figure legends:

Figure 1. Flowchart Showing the Disposition of Patients Included in the Study

Abbreviation: CHC, chronic hepatitis C; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; DAA, direct-acting antiviral; SNDS, French administrative health insurance database

^a One patient may have more than one exclusion criteria.

Figure 2. Hazard Ratios Associated With DAAs for the Occurrence of Arrhythmias and Conduction Disorders Over Time

Abbreviation: Cox-PH, Cox proportional hazards; Cox-TVC, Cox's time varying covariate model; DAA, direct-acting antiviral; IPW MSM, inverse probability-weighted marginal structural model.

The curves represent estimates of cause-specific adjusted hazard ratios associated with DAA exposure in chronic HCV-infected patients for the occurrence of arrhythmias and conduction disorders over time. The Cox-TVC model (solid curve) and the Cox-PH model (dotted line) were adjusted for age, gender, body mass index, fibrosis stage, alcohol and tobacco consumption, frequency of visits to medical specialists and amiodarone use. For the IPW fitted marginal structural model (dashed line), the weight assigned to each observation is proportional to the inverse of the probability of treatment (IPTW) received after controlling for the following confounders: age, gender, geographical origin, body mass index, fibrosis stage, alcohol and tobacco consumption, HCV genotype, time since HCV diagnosis, hypertension, diabetes, use of amiodarone, antihypertensive drugs, medications for dyslipidemia and diabetes, biological variables (albumin, AST, ALT, hemoglobin, prothrombin time, platelet count) and frequency of visits to medical specialists. The TVC-Cox model (Cox models with time-varying coefficients) was computed after including a time-varying coefficient with a parametric time function for the risk associated with DAA

exposure. The grey shade area represents the 95% confidence interval for the time-varying hazard ratio.

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Tables with captions

Table 1. Characteristics of Patients Included in the Study (n=8148)^a

	Not exposed to DAA (n=1111)	Exposed to DAA (n=7037)
Age, median (IQR), years	54.1 (48.0, 63.3)	56.2 (50.3, 64.1)
Gender (%)		
Male	578/1111 (52)	3793/7037 (54)
Female	533/1111 (48)	3244/7037 (46)
BMI (%), kg/m ²		
< 18.5	52/1103 (5)	210/7002 (3)
≥ 18.5 to < 24.9	603/1103 (55)	3569/7002 (51)
≥ 25 to < 30	322/1103 (29)	2294/7002 (33)
≥ 30	126/1103 (11)	929/7002 (13)
Geographical origin (%)		
France and Europe	832/1111 (75)	5558/7037 (79)
Asia	28/1111 (3)	152/7037 (2)
Africa	194/1111 (18)	1010/7037 (14)
Other	57/1111 (5)	317/7037 (5)
History of excessive alcohol intake ^b (%)	316/1111 (28)	1935/7035 (28)
History of tobacco consumption (%)	710/1110 (64)	4491/7020 (64)
HCV genotype (%)		
1	647/1082 (60)	4715/6974 (68)
2	109/1082 (10)	423/6974 (6)
3	145/1082 (13)	825/6974 (12)
4	149/1082 (14)	845/6974 (12)
5, 6 or 7	32/1082 (3.0)	166/6974 (2)
Time since HCV diagnosis (years)	13.6 [6.3-19.5]	14.5 [6.9-20.0]
Missing data	34	169
Fibrosis scoring (%)		
F0, F1 or F2	719/991 (73)	3210/6524 (49)
F3	92/991 (9)	1015/6524 (16)
F4	180/991 (18)	2299/6524 (35)
Diabetes (%)	102/1111 (9)	819/7037 (12)
Arterial hypertension (%)	291/1109 (26)	1997/7031 (28)
Dyslipidemia (%)	101/1110 (9.1%)	610/7027 (8.7%)
History of cardiovascular events (%)		
Major cardiovascular events ^c	27/1111 (2.4)	160/7037 (2.3)
Arrhythmias and conduction disorders	26/1111 (2.3)	130/7037 (1.8)
Anemia (%)	115/961 (12)	528/6341 (8)
Albumin ≤ 3 g/dL (%)	10/829 (1)	70/5988 (1)
Prothrombin time ≤ 70% (%)	43/917 (5)	300/6256 (5)
Platelet count < 100 × 10 ³ /μL (%)	40/1025 (4)	499/6701 (7)
AST > 5 ULN (%)	19/1042 (2)	205/6774 (3)
ALT > 5 ULN (%)	28/1079 (3)	341/6930 (5)
Use of medications (%)		
Indicated for arterial hypertension	340/1111 (31)	2246/7037 (32)
Indicated for dyslipidemia	101/1111 (9)	542/7037 (8)
Indicated for diabetes	83/1111 (8)	680/7037 (10)
Amiodarone	18/1111 (2)	37/7037 (1)
NSAIDs (including aspirin)	45/1111 (4)	275/7037 (4)

Abbreviation: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body

mass index; DAA, direct-acting antiviral; HCV, Hepatitis C virus; NSAIDs, non-steroidal

anti-inflammatory drugs; ULN, upper limit of normal.

^a Data are presented as median (25th percentile-75th percentile) and counts (%) for continuous and categorical variables, respectively. We provided denominators for variables with missing data. ^b Excessive Daily alcohol intake is defined as at least 15 alcoholic drinks (150 g) per week for a woman or 22 alcoholic drinks (220 g) per week for a man, or at least six consecutive alcoholic drinks (60 g) on at least one occasion per week. ^c MACE included acute stroke, acute coronary syndrome, pulmonary embolism, acute heart failure, and peripheral arterial disease.

SI conversion factors: To convert platelet count to $\times 10^9/L$, multiply values by 1; To convert albumin to g/L, multiply values by 10.

Table 2. Incidence Rates of Cardiovascular Events and Solid Extrahepatic Cancers^a

	No DAA exposure		Post-DAA exposure	
	n per PY	IR ^b (95% CI)	n per PY	IR ^b (95% CI)
Cardiovascular events				
Acute stroke	26/12 825	2.03 (1.32, 2.97)	62/22 099	2.80 (2.15, 3.60)
Acute coronary syndrome	28/12 814	2.19 (1.45, 3.16)	60/22 112	2.71 (2.07, 3.49)
Acute pulmonary embolism	4/12 894	0.31 (0.08, 0.79)	17/22 272	0.76 (0.44, 1.22)
Acute heart failure	35/12 820	2.73 (1.90, 3.80)	76/22 074	3.44 (2.71, 4.31)
Arrhythmias/conduction disorders	50/12 618	3.96 (2.94, 5.22)	141/21 625	6.52 (5.48, 7.69)
Peripheral arterial disease	33/12 777	2.58 (1.77, 3.63)	36/21 988	1.64 (1.15, 2.27)
MACE ^c	113/12 533	9.02 (7.43, 10.84)	222/21 310	10.42 (9.09, 11.88)
Any cardiovascular event	146/12 286	11.88 (10.04, 13.97)	309/20 768	14.88 (13.27, 16.63)
Extrahepatic solid cancers				
Colorectal cancer	17/12 806	1.33 (0.77, 2.13)	35/22 117	1.58 (1.10, 2.20)
Bladder cancer	4/12 865	0.31 (0.08, 0.80)	14/22 215	0.63 (0.34, 1.06)
Prostate cancer ^d	19/5959	3.19 (1.92, 4.98)	27/12 444	2.17 (1.43, 3.16)
Kidney cancer	7/12 857	0.54 (0.22, 1.12)	8/22 242	0.36 (0.16, 0.71)
Lung cancer	20/12 825	1.56 (0.95, 2.41)	41/22 172	1.85 (1.33, 2.51)
Pancreatic cancer	11/12 891	0.85 (0.43, 1.53)	24/22 260	1.08 (0.69, 1.60)
Thyroid cancer	5/12 853	0.39 (0.13, 0.91)	6/22 223	0.27 (0.10, 0.59)
Head and neck cancer	5/12 866	0.39 (0.13, 0.91)	18/22 220	0.81 (0.48, 1.28)
Breast cancer	28/12 585	2.22 (1.48, 3.22)	31/21 803	1.42 (0.97, 2.02)
Any cancer	109/12 110	9.00 (7.39, 10.5)	190/20 820	9.12 (7.87, 10.5)

Abbreviation: CI, confidence interval; DAA, direct-acting antiviral; IR, incidence rate;

MACE, major cardiovascular events; n, number of events; PY, person-year.

^a For all the analyses, patients with a history of the endpoint of interest were excluded. ^b

Crude incidence rates per 1000 person-years. ^c MACE included acute stroke, acute coronary syndrome, pulmonary embolism, acute heart failure, and peripheral arterial disease. ^d In male patients only.

Table 3. Adjusted Hazard Ratios of Incident Cardiovascular Events and Extrahepatic Cancers Associated With DAA Exposure

Outcomes ^a	IPW MSM ^b	
	HR (95% CI)	P Value ^c
Cardiovascular events		
Acute stroke	1.30 (0.82, 2.08)	.27
Acute coronary syndrome	1.00 (0.63, 1.60)	.99
Acute pulmonary embolism	2.10 (0.64, 6.85)	.22
Acute heart failure	1.15 (0.74, 1.78)	.53
Arrhythmias and conduction disorders	1.46 (1.04, 2.04)	.03
Peripheral arterial disease	0.54 (0.33, 0.89)	.02
MACE ^d	1.03 (0.81, 1.31)	.82
Any cardiovascular event	1.10 (0.90, 1.36)	.36
Extrahepatic solid cancers^e		
Colorectal cancer	0.44 (0.14, 1.39)	.16
Bladder cancer	0.78 (0.22, 2.80)	.70
Prostate cancer ^f	0.72 (0.18, 2.93)	.65
Kidney cancer	0.83 (0.17, 4.01)	.81
Lung cancer	1.09 (0.30, 3.99)	.90
Pancreatic cancer	0.38 (0.08, 1.78)	.22
Thyroid cancer	0.16 (0.02, 1.06)	.06
Head and neck cancer	2.71 (0.78, 9.41)	.12
Breast cancer	0.52 (0.18, 1.53)	.24
Any cancer	1.23 (0.50, 3.03)	.66

Abbreviation: CI, confidence interval; DAA, direct-acting antiviral; HR, hazard ratio; IPW

MSM, inverse probability-weighted marginal structural model; MACE, major cardiovascular events.

^a For all the analyses, patients with a history of the endpoint of interest were excluded. ^b For the marginal structural model (MSM), the weight assigned to each observation is proportional to the inverse of the probability of treatment (IPTW) after controlling for the following confounders: age, gender, geographical origin, body mass index, fibrosis stage, alcohol, tobacco consumption, HCV genotype, time since HCV diagnosis, hypertension, diabetes, biological variables (albumin, AST, ALT, hemoglobin, prothrombin time, platelet count), antihypertensive drugs, medications for dyslipidemia and diabetes (for all cardiac events), amiodarone use (for the occurrence of cardiac arrhythmia and conduction disorders), NSAIDs medications (for the occurrence of colorectal and prostate cancers), and use of statins (for the occurrence of prostate cancers). ^c Adjusted p-values controlling the false discovery rate (FDR) were all not significant. ^d MACE included acute stroke, ACS, PE, acute heart failure,

and PAD. ^e DAA exposure period was lagged by one year to analyze the risk of extrahepatic cancers. ^f In male patients only.

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12 065 CHC patients recruited in the HEPATHER cohort assessed for eligibility

- 2273 excluded from the linkage
- 2004 lack of consent
 - 179 linkage not successful
 - 90 discrepancy on the date of birth, gender or data source with the SNDS

1644 ineligible patients^a

- 829 history of decompensated cirrhosis
- 555 history of HCC
- 288 ongoing DAA therapy
- 267 liver transplant recipients
- 171 included after 12/31/2015
- 77 HBV coinfection
- 66 eligibility criteria missing

8148 eligible CHC patients included from August 2012 to December 2015 with data available for analysis (35 231 person-years)

12 905 person-years of no DAA exposure (n = 7081)

22 326 person-years following DAA exposure (n = 7037)

Incident cardiovascular events:

- 50 arrhythmias and conduction disorders
- 35 acute heart failure
- 26 acute stroke
- 28 acute coronary syndrome
- 33 peripheral arterial disease
- 4 acute embolism

Incident extrahepatic cancer cases:

- 20 lung
- 17 colon and rectum
- 28 breast
- 19 prostate
- 11 pancreas
- 4 bladder
- 5 head and neck
- 7 kidney
- 5 thyroid

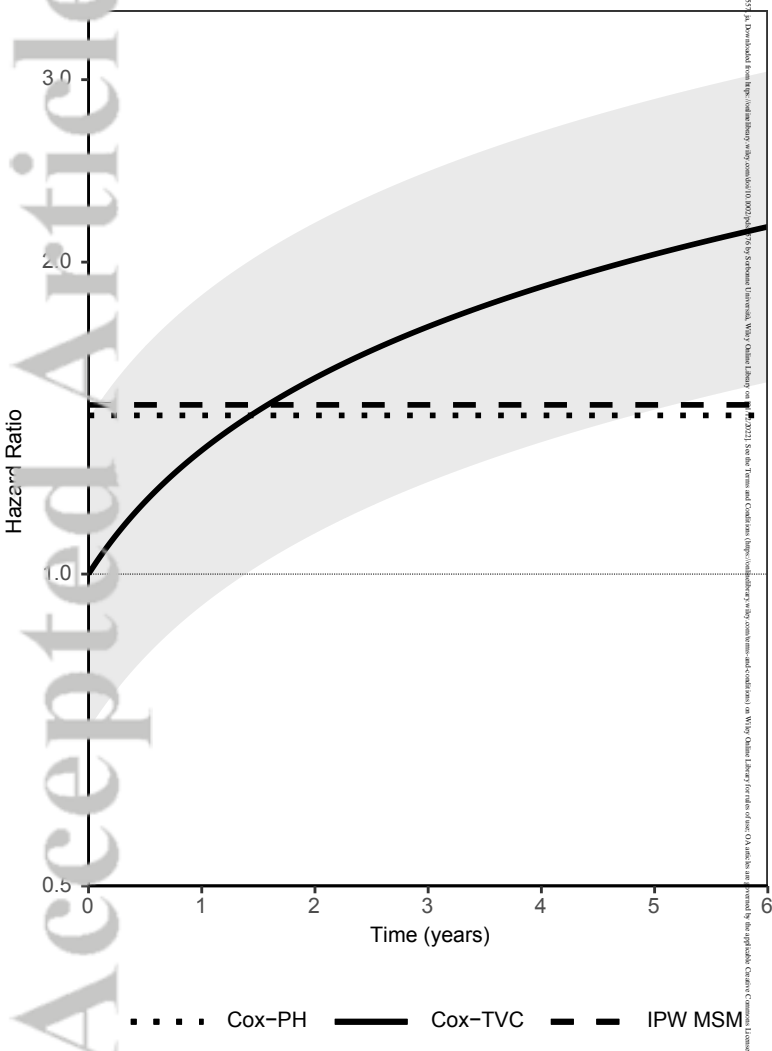
Incident cardiovascular events:

- 141 arrhythmias and conduction disorders
- 76 acute heart failure
- 62 acute stroke
- 60 acute coronary syndrome
- 36 peripheral arterial disease
- 17 acute embolism

Incident extrahepatic cancer cases:

- 41 lung
- 35 colon and rectum
- 31 breast
- 27 prostate
- 24 pancreas
- 14 bladder
- 18 head and neck
- 8 kidney
- 6 thyroid

Arrhythmias and Conduction Disorders



..... Cox-PH ——— Cox-TVC - · - · IPW MSM