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INFECTIOUS DISEASES | RESEARCH ARTICLE

# Prescription and efficacy of daclatasvir and sofosbuvir ± ribavirin for hepatitis C infection, including patient-reported outcomes, in routine practice in three European countries: The CMPASS-EU cohort study

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**Abstract: Prescription and efficacy of daclatasvir and sofosbuvir ± ribavirin, including patient-reported outcomes, in routine practice in three European countries: the CMPASS-EU cohort study. Objectives**: To identify patient characteristics associated with routine prescription of daclatasvir (DCV) in chronic hepatitis C virus (HCV) infection and evaluate effectiveness, safety and quality-of-life (QoL) changes for DCV-based regimens. **Methods**: A prospective, observational cohort study in Germany, Belgium and the Netherlands collected baseline data from all patients initiating a new HCV regimen, with 12-month follow-up of DCV-based treatments. Baseline predictors of prescription, longitudinal efficacy, and patient-reported QoL outcomes (EQ-5D, EQ-VAS and SF-36 global physical/mental health) on DCV were assessed. **Results**: Of 914 patients analyzed, 470 were prescribed DCV

## ABOUT THE AUTHOR

The authors represent a multidisciplinary team of experts in clinical hepatology, epidemiology, health economics and outcomes research, and biostatistics, drawn from academia, clinical practice and industry. The group have authored this manuscript on behalf of the many investigators who carried out this study of real-world hepatitis C treatment in Germany, Belgium and the Netherlands.

## PUBLIC INTEREST STATEMENT

Hepatitis C is a chronic, debilitating liver infection estimated by the WHO to kill almost 400,000 people annually. Hepatitis C may be cured by a course of antiviral drugs, such as the combination of daclatasvir (DCV) and sofosbuvir (SOF) with or without ribavirin (RBV). This combination is widely approved and its generic availability in many lower and middle income countries has greatly improved treatment access. In this paper, the antiviral efficacy and quality-of-life benefits of DCV+SOF(±RBV) treatment for hepatitis C were assessed in observational data reflecting its routine use in three European countries. Very high rates (≥96%) of post-treatment sustained virologic response were seen in the primary analysis, irrespective of liver cirrhosis, coinfection with HIV, or illicit drug use. Furthermore, significant improvements in patient-reported quality-of-life were reported across patient subgroups. These data represent real-world outcomes relevant to clinicians and patients where DCV and SOF are therapeutic options for hepatitis C.

(469 with sofosbuvir [SOF] ± ribavirin [RBV]) and 444 non-DCV regimens. A high proportion prescribed DCV were cirrhotic (36%) and/or illicit drug users (IDU; 24%). Multivariate predictors of DCV treatment included genotype 3 infection (odds ratio 85.9 [95% confidence interval 43.5–170]), age ≥65 years (2.0 [1.2–3.3]), and cirrhosis (3.3 [2.0–5.3]). Sustained virologic response on DCV+SOF±RBV (observed) was 96–100% across subgroups of IDU, HIV co-infection, HCV genotype and cirrhosis status. Statistically significant improvements in all QoL outcomes were observed over 12 months of DCV+SOF±RBV irrespective of RBV use or cirrhosis status, but IDU had no change in SF-36 global mental health although other outcomes improved. **Conclusions**: In this cohort, DCV+SOF±RBV was efficacious for HCV treatment across a range of subgroups and associated with QoL improvements.

**Subjects: Gastroenterology; Hepatology; Infectious Diseases; ClinicalPharmacology & Therapeutics**

**Keywords: hepatitis C; daclatasvir; sofosbuvir; ribavirin; real-world; quality-of-life; efficacy; safety; cirrhosis; HIV coinfection**

## 1. Introduction

Despite recent advances in treatment, chronic hepatitis C virus (HCV) infection remains a major public health problem. An estimated 184 million people are chronically infected with HCV (Mohd Hanafiah, Groeger, Flaxman, & Wiersma, 2013) and, over a period of 20–30 years, 10–20% will develop cirrhosis and 1–5% hepatocellular carcinoma (European Association for the Study of the Liver, 2014).

Prevalence estimates in Europe are highly variable, ranging 25-fold across countries between 0.13% and 3.26% (Blachier, Leleu, Peck-Radosavljevic, Valla, & Roudot-Thoraval, 2013). Overall, however, more than 35,000 new cases of HCV infection were reported across the European Union in 2014, an increase of 29% since 2006. These figures may underestimate the true prevalence, as sources may under-represent high-risk groups, such as intravenous drug users and the prison population (Cornberg et al., 2011).

Prior to 2011, pegylated interferon alpha (IFN) combined with ribavirin (RBV) was the cornerstone of HCV therapy despite a high adverse event (AE) burden and an HCV genotype (GT)-dependent cure rate of only 50–75%. Discontinuations and dose reductions for AEs may have contributed to observations of lower effectiveness for IFN+RBV in the real world compared with clinical trials (Kramer, Kanwal, Richardson, Mei, & El-Serag, 2012; Yood et al., 2011). Moreover, contraindications for IFN—such as severe depression, decompensated cirrhosis and severe cardiovascular disease—restricted treatment uptake (Lauer & Walker, 2001).

Since the advent of direct-acting antiviral agents (DAAs), treatment options, cure rates and safety profiles have improved. One such DAA is daclatasvir (DCV), a pan-genotypic inhibitor of the multifunctional HCV NS5A protein (Gao et al., 2010). In phase III trials, the once-daily oral combination of DCV and sofosbuvir (SOF) for 12 or 16 weeks, with or without RBV, was well tolerated and achieved rates of sustained virologic response 12 weeks post-treatment (SVR12), exceeding 90% in patients regarded as being hard-to-treat, including those with compensated cirrhosis, HIV/HCV coinfection, HCV GT-3 infection and HCV recurrence after liver transplant (Leroy et al., 2016; Poordad et al., 2016; Wyles et al., 2015). Similarly high SVR12 rates were reported among difficult-to-treat patients in several real-world European compassionate use cohorts following longer treatment (24 weeks) with DCV+SOF±RBV (Hezode et al., 2017; Lacombe et al., 2017; Welzel et al., 2016).

Real-world studies are increasingly recognized as an important complement to clinical trials, being better able to assess the effectiveness of a therapy for its broader indication than the

efficacy and safety data obtained from a selected trial population. However, while real-world studies have added crucial information to our understanding of DCV effectiveness, certain gaps remain, including the factors influencing its routine prescription and its impact in populations outside of clinical trials and compassionate use programs.

We report herein the results of an observational cohort study intended to identify the patient characteristics associated with routine prescription of DCV-based regimens in three European countries, and to evaluate the effectiveness, safety and quality-of-life (QoL) changes associated with such regimens in the patients for whom they were prescribed.

## 2. Patients and methods

### *2.1. Study design*

CMPASS-EU was a prospective, observational, multicenter, cohort study in three European countries (Germany, Belgium and the Netherlands), with both cross-sectional and longitudinal components (ClinicalTrials.gov Identifier: NCT02368522). Cross-sectional baseline data were collected at time of initiation of any new HCV regimen, with longitudinal follow-up at 3, 6, 9 and 12 months post-initiation for only those patients prescribed a DCV-containing regimen.

Regimen choice was entirely at the discretion of the treating physician and was unrelated to study inclusion. No-study-specific procedures or visits were required, and data were assessed at routine clinical visits for each participating site. The study enrolled newly initiated patients to avoid selection bias, maximize the completeness of baseline data collection and allow assessment of on-treatment QoL changes via patient-reported outcome (PRO) instruments.

### *2.2. Patients and treatment*

CMPASS-EU enrolled adults ≥18 years of age with chronic HCV infection (any GT). The only exclusion criterion was participation in an interventional HCV clinical trial or early access program. Patients were enrolled at 54 sites across the three countries (Belgium: 14; Germany: 34; the Netherlands: 6), and informed consent was obtained from all patients entering the study. The protocol, amendments, and patient informed consent received appropriate approval by the Institutional Review Board/Ethics Committee prior to initiation of study at each site. Treatment regimen and duration was at investigator discretion, in accordance with drug availability, reimbursement and usage guidelines in each participating country.

### *2.3. Study objectives and assessments*

The study had two primary objectives: to quantify the effectiveness of daclatasvir-containing regimens in real-life clinical care, as measured by SVR12, and to describe and compare the demographic and clinical characteristics of patients initiating a new HCV treatment regimen, identifying those characteristics associated with the initiation of DCV-containing, versus non-DCV, regimens.

Secondary objectives included the appraisal of safety of DCV-containing regimens in real-life clinical care, SVR12 by key subgroups, and the effect of DCV-containing treatments on health-related QoL.

All assessments were conducted at individual centers based on standard local practice and recommendations in the study protocol. SVR12 and SVR24 were defined as a documented HCV RNA level below the lower assay limit of quantification on or after week 12 or 24, respectively, following the end of treatment. Patients completed the EuroQol 5D (EQ-5D) survey of generic health status, including the EQ Visual Analog Scale (EQ-VAS), and also completed the Short-Form 36 (SF-36) instrument at baseline and at months 3, 6, 9 and 12.

### *2.4. Statistical methods*

#### *2.4.1. General*

Normality was assessed for relevant quantitative data using the Shapiro-Wilk test, and between-group comparisons performed using analysis of variance (normal data) or the Kruskal-Wallace test (non-normal). Non-ordered qualitative data were compared using Chi-square, or Fisher's exact test for small numbers. Ordered criteria and scores were compared between groups by Kruskal Wallace. Statistical analyses were performed using SAS V9.4 (SAS Institute, Inc., Cary, NC, USA).

#### *2.4.2. Factors associated with initiation of DCV-based regimens*

The 43 categorical and continuous variables assessed for their predictive association with the choice of treatment are shown in Supplementary Table 1. All analyzed variables, plus the outcome of regimen choice, were included in a Multivariate Imputation by Chained Equations algorithm, and 20 imputed datasets were produced from 10 cycles. Bivariate analyses were performed between each variable and the outcome. For each analysis, the model was constructed on each of the 20 imputed samples and the results aggregated to obtain the final estimator. Clinically relevant criteria significant at the 0.20 level were retained and assessed for collinearity using the Cramer's V statistic. A descending stepwise procedure was then used to select criteria significant at the 0.05 level using a logistic regression approach on each of the 20 samples, among criteria proposed from the previous step. Two-by-two interactions of the variables retained in the model at the previous step were studied and the model with interactions constructed on each of the 20 imputed samples. The results of these 20 models were then aggregated to obtain the final estimator. The final model was constructed on each of the 20 imputed samples and results aggregated to yield final aggregated adjusted odds ratios with 95% confidence intervals (95% CI) and adjusted *p*-values.

#### *2.4.3. Effectiveness analysis*

SVR12 (primary endpoint) and SVR24 were assessed in all patients receiving a DCV-based regimen. The primary analysis for the primary endpoint was as-observed, in which patients without data at the analysis visit were excluded. Two sensitivity analyses were also undertaken: 'sensitivity analysis 1' treated discontinuations for death and/or AEs as failures but missing data at SVR12 were excluded unless the patient achieved SVR24; 'sensitivity analysis 2' treated all patients with missing SVR12 data as failures unless they achieved SVR24.

#### *2.4.4. Patient-reported outcomes*

Changes from baseline in patient-reported outcome measures were estimated using a mixed model for repeated measurements (MMRM) on non-transformed data, with baseline value and visit as fixed covariates. Changes were expressed as least-squares means and associated 95% CIs.

## 3. Results

### *3.1. Baseline demographic and disease characteristics*

Overall, 914 patients were enrolled and analyzed (Belgium: 246; Germany: 350; Netherlands: 70), comprising 444 prescribed regimens without DCV (63, 350, and 31, respectively), and 470 prescribed DCV-containing regimens (183, 248, and 39, respectively). Five enrolled patients (Germany 4; Netherlands: 1) were not analyzed due to no new HCV regimen being documented as initiated. Of the 470 analyzed patients prescribed DCV, all but one received DCV with SOF either with ($N$ = 174) or without ($N$ = 295) concomitant RBV. A single patient initiated DCV+SOF+RBV with simeprevir.

Baseline characteristics of enrolled patients are presented in Table 1. Overall, there were distinct differences in the baseline characteristics of those prescribed DCV compared with those who were not. The DCV group had higher mean serum alanine aminotransferase, and a higher proportion of patients under 65, males, patients with cirrhosis, prior failures on IFN-free regimens containing SOF

**Table 1. Demographic and disease characteristics**

| Parameter | Non-DCV-based regimen (*N* = 444) | DCV-based regimen (*N* = 470) | *p** |
|---|---|---|---|
| Age, median (range) years | 53 (19–82) | 50 (19–88) | <0.001 |
| Age ≥65 years, *n* (%) | 86 (19.4) | 59 (12.6) | 0.005 |
| Female, *n* (%) | 174 (39.2) | 149 (31.7) | 0.018 |
| BMI, median (range) kg/m$^2$ | 25.2 (15.0–50.5) | 24.5 (15.8–47.0) | 0.092 |
| Cirrhosis, *n* (%)†<br>Compensated<br>Decompensated | 119 (26.8)<br>114 (95.8)<br>5 (4.2) | 167 (35.5)<br>154 (92.8)<br>12 (7.2) | 0.005 |
| FIB-4 score, median (IQR) | 1.91 (1.22–3.62) | 2.16 (1.19–3.99) | 0.117 |
| Hepatocellular carcinoma, *n* (%) | 11 (2.5) | 5 (1.1) | 0.135 |
| HIV co-infected, *n* (%) | 60 (15.2) | 36 (8.5) | 0.002 |
| HCV GT, *n* (%)<br>1<br>1a<br>1b<br>2<br>3<br>4<br>Other‡<br>Missing | <br>362 (81.7)<br>170 (38.4)<br>184 (41.5)<br>21 (4.7)<br>11 (2.5)<br>43 (9.7)<br>6 (1.4)<br>1 (<1) | <br>123 (26.2)<br>62 (13.2)<br>56 (11.9)<br>11 (2.3)<br>324 (69.1)<br>11 (2.3)<br>0<br>1 (<1) | <br><0.001<br><0.001<br><0.001<br>0.069<br><0.001<br><0.001 |
| HCV RNA, median (range) $\log_{10}$ IU/mL | 6.06 (2.70–7.52) | 5.96 (2.22–7.66) | 0.113 |
| Treatment experienced, *n* (%)§<br>IFN-free with SOF<br>IFN-free with PI<br>IFN-free with NS5A<br>Other | <br>174 (39.5)<br>7 (4.0)<br>3 (1.7)<br>5 (2.9)<br>159 (91.4) | <br>174 (37.2)<br>22 (12.6)<br>12 (6.9)<br>0 (0)<br>140 (80.5) | <br>0.496<br>0.005<br>0.031<br>0.062 |
| ALT, median (IQR) IU/L | 64.5 (42–100) | 75.0 (48–121) | 0.001 |
| Platelets, median, (IQR) per µL | 185 (125–240) | 181 (123–230) | 0.342 |
| Hemoglobin, mean (SD) g/dL | 16.16 (16.0) | 14.70 (6.5) | 0.519 |
| Abnormal creatinine, *n* (%) | 56 (13.8) | 53 (12.6) | 0.611 |
| Alcohol use, *n* (%)<br>Previous<br>Current | <br>122 (34.0)<br>118 (32.9) | <br>166 (39.9)<br>150 (36.1) | <br>0.018 |
| Illicit drug use, *n* (%) | 54 (12.2) | 113 (24.0) | <0.001 |
| Comorbidity, *n* (%)<br>Severe hypertension<br>Hypercholesterolemia<br>Depression<br>Diabetes<br>Renal insufficiency<br>Thyroid disease | <br>99 (22.3)<br>22 (5.0)<br>72 (16.2)<br>58 (13.1)<br>21 (4.7)<br>50 (11.3) | <br>37 (7.9)<br>19 (4.0)<br>86 (18.3)<br>47 (10.0)<br>15 (3.2)<br>33 (7.0) | <br><0.001<br>0.526<br>0.431<br>0.177<br>0.240<br>0.029 |

**p*-values are for overall non-DVC-based regimens versus DCV-based regimens. †Percentage is of patients with cirrhosis; ‡Includes HCV GTs 5 or 6 (*n* = 2), or other (*n* = 4); §Percentage is of patients with ≥1 previous line of therapy (*n* = 174 for both non-DCV-based and DCV-based regimens).

Unless otherwise specified above, percentages refer to those with available data in the relevant treatment group. Missing data (non-DCV -based regimen/DVC-based regimen): BMI 17/21; cirrhosis stage (comp. or decomp.) 0/1; FIB-4 44/34; HIV/HCV co-infected 48/45; HCV RNA 15/21; Treatment experience 4/2; ALT 8/11; platelets 11/16; hemoglobin 11/17; abnormal creatinine 39/48; alcohol use 85/54.

ALT, alanine aminotransferase; BMI, body mass index; DCV, daclatasvir; FIB-4, Fibrosis-4; GT, genotype; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IFN, interferon; IQR, interquartile range; PI, protease inhibitor; SD, standard deviation; SOF, sofosbuvir.

or HCV protease inhibitor, patients infected with GT-3, patients with a current or prior history of alcohol use, and illicit drug users (IDUs; defined as being on opioid substitution therapy [OST] or a current user of injection drugs). Of note, of those patients who provided data on recreational drug use, 48% (371/777) reported no prior use, 43% (335/777) reported previous use only, and 9% (71/777) reported being current users. Of those 335 with a prior history of drug use, 41% of those who provided data (131/320) were receiving OST. The non-DCV group contained a higher proportion of patients with HIV co-infection and patients infected with GTs other than GT-3.

The proportions of patients with non-HCV comorbidities were generally similar between groups for most conditions; however, fewer patients with severe hypertension or thyroid disease received DCV.

### *3.2. Factors associated with initiation of DCV-based regimens*

The largest independent predictor of DCV use in this study was GT-3 infection, and older age (65 years or over), cirrhosis/fibrosis, and clinically significant abnormalities in platelet levels were also predictive. By contrast, patients with severe hypertension or GT-1b infection were more likely to have been prescribed a non-DCV regimen (Figure 1).

Notably, 55% of IDUs overall, and 80% of drug users prescribed DCV, were GT-3 infected. This association may help explain why illicit drug use was not an independent predictor of DCV prescription, despite a significantly higher representation of IDU patients in the DCV treatment group. In addition, the treatment imbalance among hypertensive patients likely represents an age difference between those with HCV GT-3 (mostly DCV treated) and those with GT-1b (mostly non-DCV). For GT-3 infection, the mean age was 47.3 years, with 5% aged 65 or over; for GT-1b infection, the mean age was 65.6 years, with 50% aged 65 or over. Notably, the mean age of all patients in the study with severe hypertension (59.7 years) was significantly higher than those without it (50.6 years; $p < 0.001$), and significantly more of these hypertensive patients were aged ≥65 years (39% versus 12%; $p < 0.001$).

There were no differences between the types of non-DCV regimens received by those with versus without severe hypertension, and no relevant differences in clinical or disease characteristics

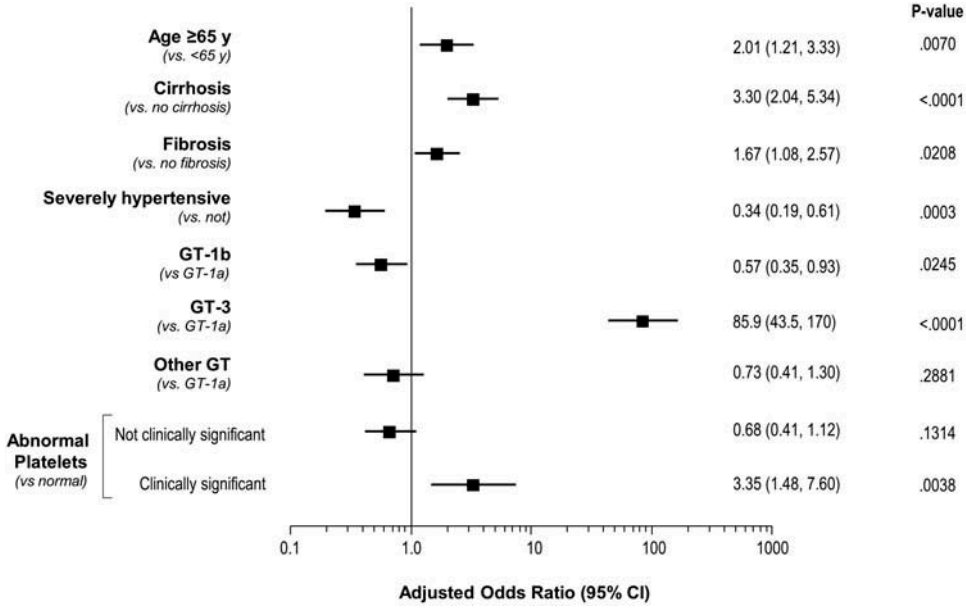


**Figure 1. Factors associated with initiation of DCV-based regimen. DCV, daclatasvir; GT, genotype.**

between those with hypertension starting DCV or non-DCV treatment. For both normotensive and hypertensive patients, the most common non-DCV combination was ledipasvir + SOF (with or without RBV), which accounted for 61–62% of non-DCV prescriptions. Dasabuvir, ombitasvir and ritonavir-boosted paritaprevir (with or without RBV) accounted for a further 22–24% in each group, and SOF+RBV for 6–7%.

### *3.3. DCV initiation by cirrhosis status and HCV genotype*

Table 2 shows DCV initiation by cirrhosis status and HCV GT. The majority of patients without cirrhosis received DCV+SOF for 12 weeks without RBV irrespective of GT, while the majority of those with cirrhosis received DCV+SOF with RBV for 12 weeks (GT-1) or 24 weeks (GT-3).

### *3.4. Real-world effectiveness of DCV-based treatment*

DCV-based treatment resulted in high rates of SVR12 across GTs. SVR12 was achieved in 98% (413/420) overall, 100% (53/53) for HCV GT-1b, and 99% (281/285) for GT-3. Both sensitivity analyses were consistent with the primary as-observed data: 91–97% overall SVR12, 95–98% for GT-1b, and 90–97% for GT-3 (Table 3).

Although the number of observed virologic failures was small (7/420), when compared with those without virologic failure (413/420), those with failure were more often male (86% with failure [6/7] versus 68% without failure [280/413]), treatment experienced (57% [4/7] versus 38% [157/413]), or had baseline viral loads ≥6 million IU/mL (29% [2/7] versus 13% [50/393]). Although cirrhosis did not appear to be associated with SVR12, those with virologic failure tended to have lower median platelet counts ($126.5 \times 10^9$/L [interquartile range (IQR): 57,167] versus $181.0 \times 10^9$/L [IQR: 123,228]) and higher median Fibrosis-4 (FIB-4) scores (3.45 [IQR: 2.82, 5.54] versus 2.15 [IQR: 1.19, 3.94]).

Since both regimen and treatment duration were at physician discretion, it is not possible to explore the contribution to SVR12 outcome of either RBV use or treatment duration. In addition to the treatment imbalances associated with cirrhosis, patients without cirrhosis were mostly treated for 12 weeks but were more likely to have received RBV for this time if they were GT-1 infected; 28% of all GT-1a non-cirrhotic patients and 33% of GT-1b, versus 6% of GT-3, received DCV+SOF +RBV for 12 weeks. Similarly, a higher proportion of treatment-experienced patients received DCV +SOF with RBV for either 12 or 24 weeks (25% and 27%, respectively) than those who were HCV treatment naïve (12% and 10%, respectively). However, since SVR12 rates were similar regardless of duration or the inclusion of RBV (Supplementary Figure 1), it appeared that treatment individualization by prescribing physicians was managed effectively. Overall, observed SVR12 for DCV +SOF with or without RBV was 97 and 99%, respectively, for 12 weeks of treatment, and 97 and 100%, respectively, for 24 weeks. Observed SVR24 rates were similar to the SVR12 data: 97 and 98%, respectively, for 12 weeks of treatment with or without RBV, 94 and 100%, respectively, for 24 weeks.

### *3.5. Real-world effectiveness of DCV-based regimens by subgroup*

Rates of SVR12 remained consistently high across all key subgroups, including cirrhotic status (99% and 100% for compensated and decompensated, respectively), HIV co-infection (97%) and IDUs (99%; Table 3). Among patients with cirrhosis, observed SVR12 was 100% in both GT-1a (17/17) and GT-1b infection (40/40), and 99% (80/81) for GT-3. SVR12 rates by sensitivity analysis 1 (death/discontinuation due to AE = failure) in patients with cirrhosis were 100% (17/17) for GT-1a infection, 98% (40/41) for GT-1b, and 95% (80/84) for GT-3, whereas for sensitivity analysis 2 (all missing = failure), rates were 89% (17/19), 98% (40/41) and 90% (80/89), respectively.

### *3.6. Patient-reported outcomes*

MMRM-estimated changes from baseline in EQ-5D total score, EQ-VAS and SF-36 global physical and mental health scores over time for patients receiving DCV+SOF, according to concomitant RBV use, are shown in Figure 2. For all four measures, patients who received RBV took longer to achieve

**Table 2. Initiation of DCV-based treatment by HCV GT and cirrhosis status**

| | DCV+SOF 12 weeks | DCV+SOF 24 weeks | DCV+SOF+RBV 12 weeks | DCV+SOF+RBV 24 weeks | With other duration |
|---|---|---|---|---|---|
| Overall, *N* = 470, (%) | 257 (54.7) | 26 (5.5) | 81 (17.2) | 78 (16.6) | 27 (5.7) |
| Cirrhosis (%) | | | | | |
| Compensated, *n* = 154 | 10 (6.5) | 15 (9.7) | 47 (30.5) | 68 (44.2) | 13 (8.4) |
| Decompensated, *n* = 12 | 1 (8.3) | 4 (33.3) | 4 (33.3) | 1 (8.3) | 2 (16.7) |
| GT-1a (%) | | | | | |
| Overall, *n* = 62 | 26 (41.9) | 2 (3.2) | 24 (38.7) | 7 (11.3) | 3 (4.8) |
| No cirrhosis, *n* = 39 | 24 (61.5) | 0 | 11 (28.2) | 3 (7.7) | 1 (2.6) |
| Cirrhosis, *n* = 23 | 2 (8.7) | 2 (8.7) | 13 (56.5) | 4 (17.4) | 2 (8.7) |
| GT-1b (%) | | | | | |
| Overall, *n* = 56 | 12 (21.4) | 10 (17.9) | 27 (48.2) | 5 (8.9) | 2 (3.6) |
| No cirrhosis, *n* = 15 | 9 (60.0) | 0 | 5 (33.3) | 1 (6.7) | 0 |
| Cirrhosis, *n* = 41 | 3 (7.3) | 10 (24.4) | 22 (53.7) | 4 (9.8) | 2 (4.9) |
| GT-3 (%) | | | | | |
| Overall, *n* = 324 | 205 (63.3) | 13 (4.0) | 24 (7.4) | 59 (18.2) | 22 (6.8) |
| No cirrhosis, *n* = 234 | 201 (85.9) | 5 (2.1) | 13 (5.6) | 4 (1.7) | 11 (4.7) |
| Cirrhosis, *n* = 90 | 4 (4.4) | 8 (8.9) | 11 (12.2) | 55 (61.1) | 11 (12.2) |
| GT other (%) | | | | | |
| Overall, *n* = 27 | 13 (48.1) | 1 (3.7) | 6 (22.2) | 7 (25.9) | 0 |
| No cirrhosis, *n* = 14 | 11 (78.6) | 1 (7.1) | 1 (7.1) | 1 (7.1) | 0 |
| Cirrhosis, *n* = 13 | 2 (15.4) | 0 | 5 (38.5) | 6 (46.2) | 0 |

DCV, daclatasvir; GT, genotype; HCV, hepatitis C virus; RBV, ribavirin; SOF, sofosbuvir.



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**Table 3. SVR12 for DCV-based treatment by HCV GT and key subgroup**

| ***n* (%), [95% CI]** | **Primary analysis (as observed) *N* = 420** | **Sensitivity analysis 1 *N* = 426** | **Sensitivity analysis 2 *N* = 452** |
|---|---|---|---|
| SVR12 overall | 413 (98.3) [96.6; 99.3] | 413 (96.9) [94.8; 98.4] | 413 (91.4) [88.4; 93.8] |
| Non-SVR12 | 7 (1.7) [0.7; 3.4] | 13 (3.1) [1.6; 5.2] | 39 (8.6) [6.2; 11.6] |
| GT-1a; *n* = 62 | 53/55 (96.4) [87.5; 99.6] | 53/56 (94.6) [85.1; 98.9] | 53/58 (91.4) [81.0; 97.1] |
| GT-1b, *n* = 56 | 53/53 (100) [93.3; 100] | 53/54 (98.1) [90.1; 100] | 53/56 (94.6) [85.1; 98.9] |
| GT-3, *n* = 324 | 281/285 (98.6) [96.5; 99.6] | 281/289 (97.2) [94.6; 98.8] | 281/311 (90.4) [86.5; 93.4] |
| Other GTs, *n* = 27 | 25/26 (96.2) [80.4; 99.9] | 25/26 (96.2) [80.4; 99.9] | 25/26 (96.2) [80.4; 99.9] |
| Compensated cirrhosis, *n* = 154 | 141/143 (98.6) [95.0; 99.8] | 141/146 (96.6) [92.2; 98.9] | 141/150 (94.0) [88.9; 97.2] |
| Decompensated cirrhosis, *n* = 12 | 6/6 (100) [54.1; 100] | 6/7 (85.7) [42.1; 99.6] | 6/10 (60.0) [26.2; 87.8] |
| Treatment naïve, *n* = 264 | 256/259 (98.8) [96.7; 99.8] | 256/262 (97.7) [95.1; 99.2] | 256/280 (91.4) [87.5; 94.4] |
| Treatment experienced, *n* = 174 | 157/161 (97.5) [93.8; 99.3] | 157/164 (95.7) [91.4; 98.3] | 157/170 (92.4) [87.3; 95.9] |
| HCV RNA ≥6 M IU/mL, *n* = 61 | 50/52 (96.2) [86.8; 99.5] | 50/52 (96.2) [86.8; 99.5] | 50/57 (87.7) [76.3; 94.9] |
| Illicit drug users, *n* = 113 | 94/95 (98.9) [94.3; 100] | 94/96 (97.9) [92.7; 99.7] | 94/104 (90.4) [83.0; 95.3] |
| HIV co-infection, *n* = 36 | 34/35 (97.1) [85.1; 99.9] | 34/36 (94.4) [81.3; 99.3] | 34/36 (94.4) [81.3; 99.3] |

DCV, daclatasvir; GT, genotype; HCV, hepatitis C virus; HIV, human immunodeficiency virus; SVR12, sustained virologic response at 12 weeks post-treatment.

significant improvements from baseline than those who did not, but subsequently had numerically greater improvements at month 12.

The majority of patients with cirrhosis who received DCV-based regimens also received RBV (Table 2). The pattern of changes from baseline in these four PROs for those with versus without cirrhosis (Supplementary Figure 2) was therefore similar to that observed according to RBV use (Figure 2).

IDU patients had statistically significant improvements in the EQ-5D total, EQ-VAS and SF-36 global physical health scores at most time points that were broadly comparable to those for non-IDU patients. However, the IDU patient group showed no significant improvement in SF-36 global mental health score at any time point, compared with significant and numerically greater improvements in the non-IDU group at all time points after month 3 (Supplementary Figure 3).

### *3.7. Safety*

A summary of the AEs reported during the follow-up period is presented in Supplementary Table 2. Overall, 42% (199/470) of patients initiating a DCV-based regimen reported at least one AE, and in 20% (94/470) of patients, these events were considered related to DCV. The frequency of AEs leading to discontinuation was low (0.6% [3/470]). The frequency of hepatic AEs was 3% (14/470), with none judged as related to DCV. There were five deaths during the study, representing 1% of the follow-up cohort. None were considered related to treatment by the treating physician.

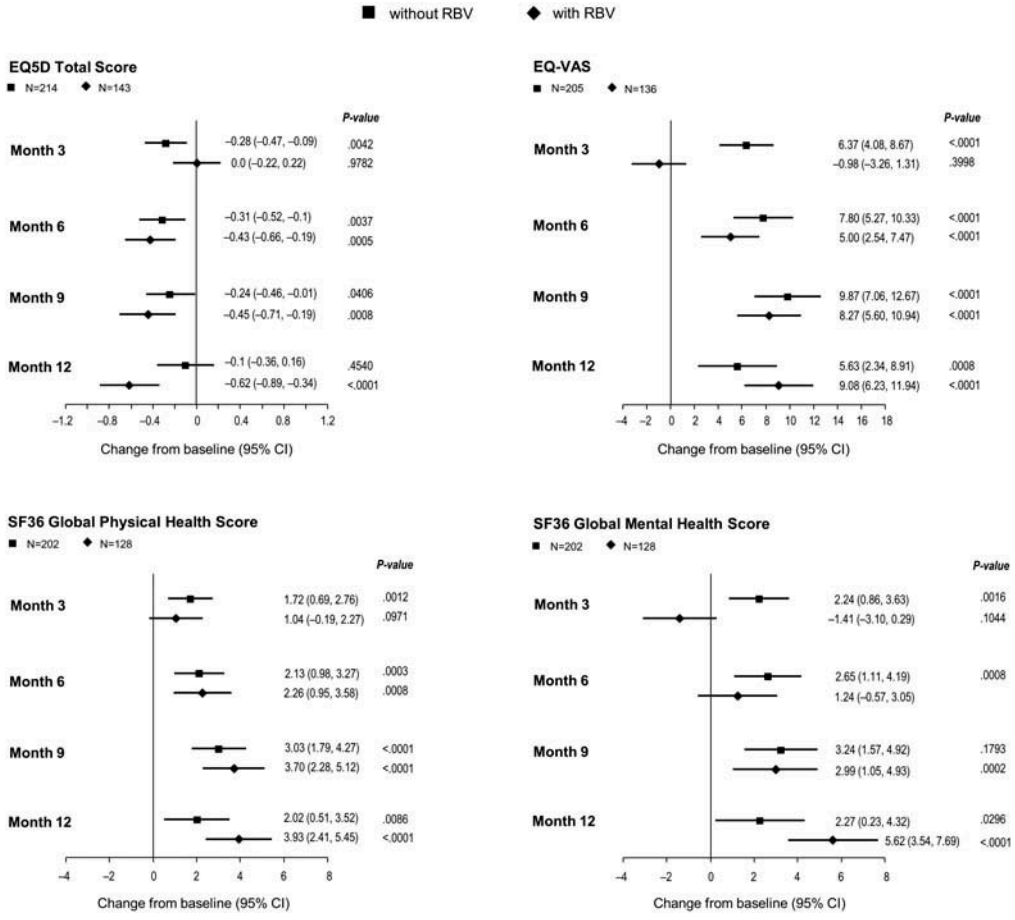


**Figure 2. Patient-reported outcomes among patients who received DCV+SOF with or without RBV. Least-squares means from mixed models for repeated measurements, adjusted on baseline value. DCV, daclatasvir; EQ-5D, EuroQol 5D; EQ-VAS, EQ Visual Analog Scale; RBV, ribavirin; SF-36, Short-Form 36; SOF, sofosbuvir.**

The most frequent AEs (≥5%) reported during the follow-up period were fatigue (9%) and headache (8%). Hematologic AEs were experienced by 7% (35/470) overall; 3% (9/296) of those receiving DCV+SOF, and 15% (26/174) receiving DCV+SOF+RBV. Of these, 1% (4/296) and 11% (19/174), respectively, were related to anemia.

Overall, 7% (35/470) of patients used concomitant medications with the potential to have interactions with DCV. Seven of these underwent DCV dose adjustments, of whom six received DCV at 30 mg/day due to concomitant use of antimycotics ($n$ = 1), bisoprolol ($n$ = 1) or pharmacokinetically boosted antiretrovirals ($n$ = 4), and one received DCV 90 mg/day due to concomitant use of efavirenz. Six patients required dose modification of the concomitant medication (amlodipine [$n$ = 2], atorvastatin [$n$ = 1], diltiazem [$n$ = 1], pravastatin [$n$ = 1], simvastatin [$n$ = 1]). No dose adjustment was required for any patients receiving methadone OST.

## 4. Discussion

In this study of real-world prescription and outcomes, HCV-infected patients initiating DCV+SOF ±RBV were younger, GT-3 infected, and have more clinically advanced liver disease than those initiating other regimens. Those prescribed DCV also included a higher proportion of previous treatment failures on all-oral regimens containing SOF or HCV protease inhibitors, and a higher proportion of IDUs. In part, these differences reflect a combination of preferential DCV prescription to GT-3-infected patients—due to its known high clinical activity against GT-3 (Hezode et al., 2017; Leroy et al., 2016; Nelson et al., 2015) compared with the lesser GT-3 activity of the ledipasvir-, dasabuvir- and simeprevir-containing regimens that comprised almost 90% of the non-DCV group (Cheng et al., 2016; Kati et al., 2015; Moreno et al., 2012)—and underlying differences in the

characteristics of GT-3 versus GT-1-infected patients. In addition, a highly significant contribution to the demography of treatment will have been attributable to differences in reimbursement and practice guidelines between the three participating countries.

In the Netherlands, there were no reimbursement restrictions over the course of the study on any of the regimens used or the disease stage of the patients. However, in Belgium, reimbursement for any direct-acting HCV antiviral was restricted to those with F3 or F4 liver fibrosis and liver transplant patients, and only DCV and SOF were reimbursed for GT-3 infection. Finally, in Germany, there were no restrictions on fibrosis, but reimbursement decisions are largely driven by cost, and many non-GT-3 patients will have been prescribed (or switched to) the fixed-dose coformulation of ledipasvir and sofosbuvir following its EMA registration in December 2014, shortly after the registration of DCV.

Numerically, the high SVR12 rates reported from this present study, particularly for the sensitivity analyses which imputed treatment failures not directly observed in follow-up, are consistent with data from other real-world studies whose primary analyses were based on imputed failure (Hezode et al., 2017; Lacombe et al., 2017; Rockstroh et al., 2017; Welzel et al., 2016). These previous studies—unlike the patient population in CMPASS-EU who were routinely prescribed DCV in normal practice—were undertaken in early access programs for patients treated with DCV+SOF ±RBV on compassionate grounds ahead of local DCV market authorization, due to highly advanced disease with no alternative options. Thus, while neither the patient populations nor the analysis methodologies are directly comparable, the consistency of the high response rates between these various real-world studies of DCV+SOF±RBV is of note. The high and comparable SVR12 rates seen across various subgroups of demography and disease state in CMPASS-EU are also consistent with subgroup data for DCV+SOF±RBV from both real-world cohorts (Hezode et al., 2017; Lacombe et al., 2017; Rockstroh et al., 2017; Welzel et al., 2016) and the various ALLY clinical trials of this combination (Nelson et al., 2015; Wyles et al., 2015; Leroy et al., 2016; Poordad et al., 2016).

There is a relative paucity of data on the efficacy of HCV regimens in active or recent drug users, given their exclusion from many randomized efficacy trials. Thus, the finding that DCV-based regimens remain effective in this group is relevant. Observed SVR12 rates were 99% in IDU patients and, even at the most stringent of the sensitivity analyses, the response rate in this group was 90%. These findings are consistent with a 94% SVR12 rate in 103 patients with HCV GT-1–4 infection and recent injection drug use (59% on OST) who received the pan-genotypic NS5A inhibitor velpatasvir with SOF for 12 weeks in the open-label SIMPLIFY study (Grebely et al., 2018). They are also consistent with data for 301 OST patients receiving elbasvir and grazoprevir in the randomized C-EDGE CO-STAR study (SVR12 90–92%) (Dore et al., 2016), as well as with subanalyses of OST patients receiving velpatasvir + SOF in the phase III ASTRAL trials (SVR12 96%; $n$ = 51) (Grebely et al., 2016a) or ledipasvir and SOF in the phase III ION studies (SVR12 94%; $n$ = 70) (Grebely et al., 2016b).

The SVR12 rate was also maintained in those with HIV co-infection (97% observed; 94% in sensitivity analyses), which is consistent with the >90% SVR12 rates reported for DCV+SOF±RBV in real-world early access cohorts of HIV/HCV co-infected patients (Lacombe et al., 2017; Rockstroh et al., 2017), which included a significant proportion of patients on OST (Rockstroh et al., 2017).

GT-3-infected patients with cirrhosis received more intensive treatment over a longer period than those without. Eighty-four percent of patients with GT-3 infection (76/90) received DCV+SOF with RBV, of whom 72% were treated for 24 weeks. By contrast, 92% of GT-3 patients without cirrhosis (216/234) received DCV+SOF without RBV, and nearly all of them (93%; 201/216) were treated for 12 weeks. These results contrast with GT-1 infection, where RBV use was similarly associated with cirrhosis but most patients (81% GT-1a; 70% GT-1b) received 12 weeks of treatment irrespective of cirrhosis status. Despite this treatment difference, SVR12 rates in GT-3-infected patients were very similar with or without cirrhosis. Overall, observed SVR12 was 99% in the primary analysis irrespective of cirrhosis; in sensitivity analysis 1, 95% of patients with

cirrhosis and 98% without achieved SVR12, while in sensitivity analysis 2, SVR12 rates were 90% with and 91% without cirrhosis. These rates are slightly higher than GT-3 data for DCV+SOF±RBV in cirrhosis from the French ATU compassionate-use program (Hezode et al., 2017), consistent with the less clinically advanced nature of the CMPASS-EU patient group.

Significant improvements in EQ-5D, EQ-VAS and SF-36 outcome measures were typically observable by month 3 among those receiving DCV+SOF without RBV. In contrast, those who received RBV with DCV+SOF included a higher proportion of cirrhotic patients, and approximately equal proportions received 12 weeks (47%) or 24 weeks (45%). Improvements in patient-reported outcomes in this more clinically advanced group were not statistically significant at month 3, but became so thereafter and subsequently matched or exceeded improvements in the non-RBV group by 1 year. It is notable that, in contrast to patients who had not used illicit drugs, no statistically significant improvement in SF-36 social or mental outcomes were observed in the IDU group, despite generally similar improvements in physical health outcomes. There were no significant changes in either the SF-36 emotional role or mental health scales in the IDU group, and early improvements in the social functioning scale subsequently returned to baseline by month 12. By contrast, sustained significant improvements in all three scales occurred by month 6 in the non-IDU group. This lack of improvement in mental health among IDU patients likely reflects situational differences from the non-IDU group. Of note, most IDU patients receiving DCV (67% of 111 with data) were unemployed, mostly due to disability or HCV infection (80% of 35 with data), whereas a smaller proportion of non-IDU patients were unemployed (52% of 349 with data), of whom 51% (of 128 with data) had retired and only 49% were unemployed for reasons of disability or HCV infection.

There were no unexpected safety findings; the AE profile was similar to that reported in other DCV+SOF±RBV clinical studies (Leroy et al., 2016; Nelson et al., 2015) and real-world cohorts (Lacombe et al., 2017; Rockstroh et al., 2017). Fatigue and headache were the most frequent AEs (≥5% of patients). Drug–drug interactions were uncommon and manageable, and few patients required dosing adjustments for either DCV or concomitant medications.

In summary, these results confirm the effectiveness and tolerability of DCV+SOF±RBV for the treatment of HCV in the real-world setting, including subgroups of patients with cirrhosis, HCV/HIV co-infection, and illicit drug use or OST. In addition to virologic efficacy, treatment was associated with statistically significant improvements in health-related QoL measures over a period of 1 year on- and off-treatment, particularly in patients with cirrhosis. Since the completion of this study, the original branded version of daclatasvir is no longer marketed in the European Union, but remains available in a number of other regions, including China, Australia, and Japan. Additionally, generic daclatasvir is now widely used in many lower and middle income countries worldwide *via* the Medicines Patent Pool, as the DCV+SOF combination remains an integral part of World Health Organization Treatment Guidelines (World Health Organization, 2018a; World Health Organization, 2018b; Simmons, Cooke, & Miraldo, 2019). Thus it is anticipated that observational data from our study, accruing as they do from real-world clinical experience, will be of value beyond the geography of their origin and prove of interest to physicians where daclatasvir treatment remains a therapeutic option.

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**Supplementary material**
Supplemental data for this article can be accessed here.

**Data availability statement**
Bristol-Myers Squibb policy on data sharing may be found at https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html.

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