

# Drug–Drug Interactions With Novel All Oral Interferon-Free Antiviral Agents in a Large Real-World Cohort

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**Background.** With the approval of direct-acting antivirals (DAAs), the management of drug–drug interactions (DDIs) has become an important challenge while treating individuals with hepatitis C. To date, the potential of causing DDIs for the recently approved DAAs has not been systematically investigated. We aimed to assess the clinical significance of DDI between the regular outpatient medications and DAA therapies in a large real-world cohort.

**Methods.** Overall, 261 hepatitis C virus monoinfected patients who were selected for DAA therapy at 2 intervals between 2011 and 2014 were asked about their regular outpatient medications. The potential for DDIs between all these drugs and sofosbuvir/ribavirin, ledipasvir/sofosbuvir, sofosbuvir/daclatasvir, sofosbuvir/simeprevir, ombitasvir/paritaprevir/ritonavir ± dasabuvir as well as boceprevir and telaprevir triple therapy was assessed using [www.hep-druginteractions.org](http://www.hep-druginteractions.org) and the relevant prescribing information.

**Results.** The 261 patients took a median number of 2 drugs (range 0–15); 20% of patients did not take any medication. Sofosbuvir/ribavirin had the lowest risk to cause a potentially significant DDI (9.6%). In contrast, for ombitasvir/paritaprevir/ritonavir ± dasabuvir potentially significant DDIs could be expected in 66.3% of the patients. Significant DDIs for sofosbuvir/simeprevir would be expected in 31.4%, for sofosbuvir/daclatasvir in 36.8%, and for sofosbuvir/ledipasvir in 40.2%. Proton pump inhibitors, thyroid hormones, and dihydropyridine derivatives were frequently used and presented a risk of interacting with the antiviral regimen.

**Conclusions.** A significant number of patients are at risk for DDIs if treated with the recently approved DAA regimens. A careful evaluation of potential DDI is essential to prevent adverse effects or unnecessary risk of treatment failure.

**Keywords.** hepatitis C virus; direct-acting antiviral agents; drug–drug interactions; cytochrome P450; antiviral therapy.

The effectiveness of treatment for chronic hepatitis C virus (HCV) infection has dramatically improved with the approval of direct-acting antiviral agents (DAAs). In 2011 the first 2 DAAs were approved, the protease inhibitors (PIs) boceprevir (BOC) and telaprevir (TLV). Rates of sustained virological response (SVR) in treatment-naïve genotype 1 patients increased from 40%–50% with pegylated-interferon-alfa (Peg-IFN)/ribavirin (RBV) dual therapy to 70%–80% with Peg-IFN/RBV/PI triple therapy [1]. However, this achievement was accompanied by several challenges associated with these new drugs, in particular, the handling of adverse effects such as severe anemia and toxic skin reactions [2, 3]. One additional encounter was the management of potential drug–drug interactions (DDIs) [4]. Whereas Peg-IFN and RBV have a lower potential for significant interactions, BOC and TLV are both strong inhibitors

and substrates of P-glycoprotein (P-gp) and cytochrome P450 3A4, which are regularly involved in adverse DDIs. Interactions between BOC or TLV and the regular outpatient medications have been reported to affect up to 50% of HCV patients in clinical practice [5].

Over the last 20 months, several new DAAs have been approved. Specific DAA combinations achieve SVR in >90% of patients across all HCV genotypes even without the need for Peg-IFN combination [6, 7]. Due to the high efficacy and good tolerability, Peg-IFN-free DAA combination therapy has already become the new standard of care in the United States and several European countries. The majority of recently approved DAAs are considered to have a reduced impact on cytochrome P450 enzymes and/or P-gp compared with BOC and TLV [8]. However, the actual risk of DDI with these newer DAA regimens and the patients' concomitant medication remains unclear. First, although the potential for DDI may be reduced, all recently approved DAAs show some interaction with either transporters such as P-gp, breast cancer resistance protein or cytochrome P450 enzymes [8]. Second, for the majority of HCV patients, at least 2 different DAAs with different DDI risk profiles need to be combined in order to achieve a reasonable treatment response [6, 7]. In addition, the risk for DDI with regular outpatient medications may increase with the

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number of DAAs included in the antiviral regimen. Third, the number of patients eligible for HCV treatment has increased with the approval of modern DAA combination therapies, allowing treatment even for patients who suffer from several comorbidities or advanced liver disease [9]. However, these patients may also take more drugs and therefore require careful observation and management [10]. Currently, there are no data available regarding the real-world relevance of DDIs in HCV patients while using the new Peg-IFN-free antiviral therapies.

Here, our aim was to assess the clinical significance of DDIs between the patients' regular outpatient medications and currently approved Peg-IFN-free DAA combination therapies in a large real-world cohort of HCV patients.

## PATIENTS AND METHODS

### Study Cohort

A total of 261 HCV monoinfected patients selected for a DAA-containing therapy at the hepatitis outpatient clinic of Hannover Medical School, Germany, were included. The cohort consisted of 2 subcohorts: 115 consecutive patients recruited after the approval of TLV and BOC between June 2011 and November 2011 [5] and 146 consecutive patients recruited after the approval of sofosbuvir (SOF) between January 2014 and September 2014. Patients with coinfections (ie, human immunodeficiency virus or hepatitis B virus), patients who were receiving antiviral treatment during the recruiting period, and patients included in clinical trials were excluded.

### Assessment of Concomitant Medication

Prior to commencing therapy, all patients were routinely asked about all concomitant outpatient medication. Importantly, any kind of over-the-counter medicine and herbal supplements were also assessed. In cases of combination products, each individual active pharmaceutical ingredient was counted separately. In contrast, mixtures of minerals or vitamins as well as herbal supplements were counted as only 1 drug if they contained 4 or more ingredients.

### Assessment of Baseline Parameters

All laboratory tests in this study were determined using standard procedures at Hannover Medical School. HCV genotype was determined before treatment was started. The stage of liver fibrosis was determined by either liver biopsy or, for the majority of cases, by transient elastography. For transient elastography, the following cutoff values were used: F0/F1, <7.1 kPa; F1/F2, ≥7.1 kPa; F2, ≥8.7 kPa; F3, ≥9.5 kPa; F3/F4, ≥12.5 kPa; and definite cirrhosis, ≥14.5 kPa [11]. Patient characteristics are summarized in Table 1.

### Assessment and Classification of Drug-Drug Interactions

DDIs were assessed based on information available at [www.hepdruginteractions.org](http://www.hepdruginteractions.org) and the prescribing information for each drug (as of March 2015). In cases for which no reliable conclusion could be drawn based on the given information, a pharmacology

**Table 1. Baseline Characteristics of the Study Cohort**

Number of Patients	261
Age (mean ± standard deviation)	55 ± 10
Gender (n, %)	
Male	157 (60)
Female	104 (40)
Hepatitis C virus genotype (n, %)	
1a	64 (25)
1b	136 (52)
2	12 (5)
3	41 (16)
4	3 (1)
5	1 (<1)
6	0 (0)
n/a	4 (1)
Fibrosis stage (METAVIR; n, %)	
≤F2	45 (17)
F3/F4	204 (78)
n/a	12 (5)
Patients with decompensated cirrhosis <sup>a</sup> (n, %)	26 (10)
Number of drugs per patient (median, range)	2 (0–15)

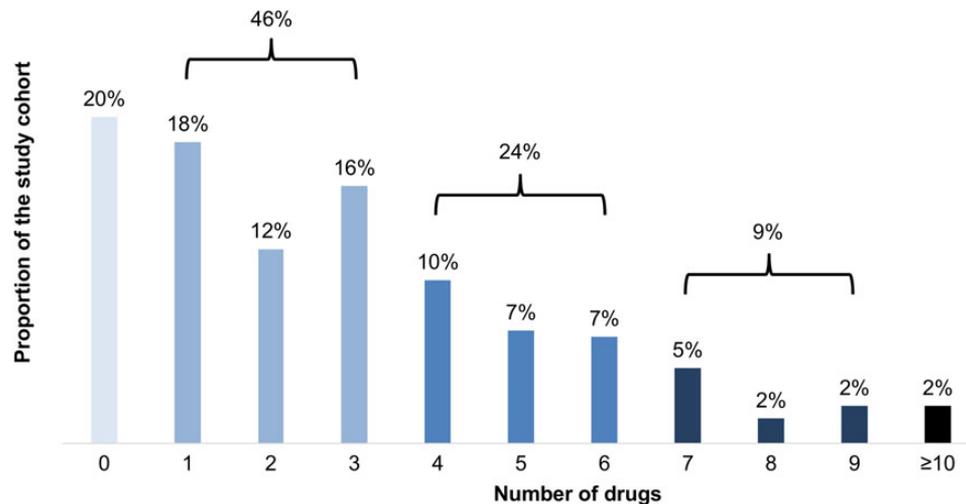
Abbreviation: n/a, not available.

<sup>a</sup> Decompensated cirrhosis defined by Child-Pugh score >6 (class B and C).

expert (F. M., D. B.) was consulted. In contrast to [www.hepdruginteractions.org](http://www.hepdruginteractions.org), safety concerns for a comedication due to hepatic impairment but not due to an interaction with the respective DAA were not considered in this study. DDIs were assessed between the regular outpatient medications and the following Peg-IFN-free HCV therapies (where SMV is simeprevir, DCV is daclatasvir, LDV is ledipasvir, OBV is ombitasvir, PTV is parataprevir, DSV is dasabuvir, and r is ritonavir): SOF/RBV, SOF/SMV ± RBV, SOF/DCV ± RBV, LDV/SOF ± RBV, OBV/PTV/r ± RBV, and OBV/PTV/r/DSV ± RBV. RBV has a very low potential for causing DDIs. There was not a single patient in our cohort in whom RBV would have caused an additional DDI. Therefore, DAA regimens with or without RBV were included together in our analysis, figures, and tables. In addition, DDIs were assessed between the regular outpatient medications and Peg-IFN/RBV/TVR and Peg-IFN/RBV/BOC triple therapy.

DDIs were assigned to 4 risk categories according to the significance of interactions with the DAA as follows: category 0, classification not possible due to lack of information; category 1, no clinically significant interactions expected; category 2, significant interaction possible, may require dose adjustment/closer monitoring; and category 3, coadministration either not recommended or contraindicated. If a patient took more than 1 drug with different risks for an DDI, the highest category was chosen to determine the risk for the patient with a respective treatment regimen.

The regular outpatient medications were sorted into different classes according to the organ or system on which they act based



**Figure 1.** Distribution of the number of drugs in the regular outpatient medications at baseline.

on the anatomical therapeutic chemical classification system proposed by the World Health Organization Collaborating Centre for Drug Statistics Methodology (<http://www.whocc.no>).

Of note, the use of both OBV/PTV/r ± DSV and SMV is off-label in advanced liver disease. However, we decided to evaluate DDIs for these DAAs as recent real-world data for SMV have demonstrated that it can be safely used in these patients [12].

#### Ethics

This study was conducted according to the principles of good clinical practice as well as the Declaration of Helsinki. The local ethics committee of Hannover Medical School approved the anonymous analysis of patient data.

## RESULTS

### Regular Outpatient Medications of the Study Cohort

The regular outpatient medications of the 261 included HCV patients consisted of 188 drugs. The median number of drugs per patient was 2 (range, 0–15). The regular outpatient medication

contained 1–3 drugs in 46% (n = 120 patients), 4–6 drugs in 24% (n = 61), 7–9 drugs in 9% (n = 22), and 10 or more drugs in 2% (n = 6) of patients. In contrast, only 20% (n = 52) did not take any drugs regularly (Figure 1). Importantly, in patients with advanced cirrhosis (Child-Pugh score >6, n = 26), the median number of drugs per patient was doubled in comparison with the overall study cohort, with none of the patients being without a regular outpatient medication (median number of drugs 4; range, 1–14).

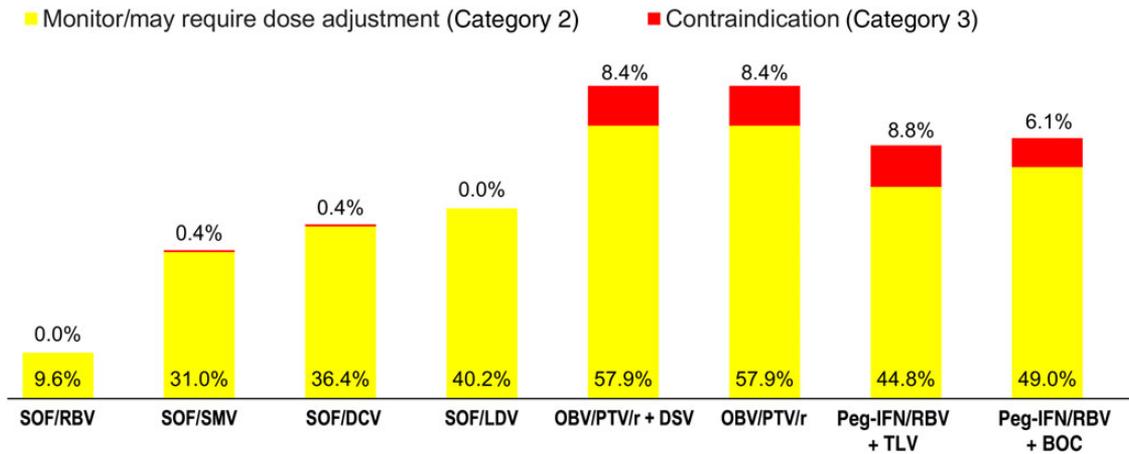
The 4 most frequently used drugs taken by ≥10% of the study population were pantoprazole (49/261, 18.8%), spironolactone (43/261, 16.5%), levothyroxine (43/261, 16.5%), and hydrochlorothiazide (26/261, 10.0%). Table 2 provides an overview of the 10 most common drug classes in the study cohort.

### Frequency of Drug–Drug Interactions Between Analyzed Antiviral Regimens and Regular Outpatient Medications

The risk to cause a potentially clinically significant DDI with the regular outpatient medications varied markedly among the DAA combinations. Overall, SOF/RBV had the lowest

**Table 2.** 10 Most Common Drug Classes on the Regular Outpatient Medication List

Drug Class	3rd Level Anatomical Therapeutic Chemical Classification System Code	Affected Patients (n)	Affected Portion of the Study Cohort (%)
Proton pump inhibitors (ie, pantoprazole)	A02BC	63	24.1
Beta blocking agents, selective (ie, bisoprolol)	C07AB	48	18.4
Aldosterone antagonists (ie, spironolactone)	C03DA	44	16.9
Thyroid hormones (ie, levothyroxine)	H03AA	43	16.5
Angiotensin II antagonists, plain (ie, candesartan)	C09CA	34	13.0
Angiotensin-converting enzyme inhibitors, plain (ie, ramipril)	C09AA	29	11.1
Dihydropyridine derivatives (ie, amlodipine)	C08CA	28	10.7
Thiazides, plain (ie, hydrochlorothiazide)	C03AA	26	10.0
Sulfonamides, plain (ie, torasemide)	C03CA	24	9.2
Beta blocking agents, nonselective (ie, propranolol)	C07AA	21	8.0



**Figure 2.** Proportion of patients with significant drug–drug interactions (DDIs) between their regular outpatient medications and direct-acting antiviral agent (DAA)-containing regimens. The figure shows the proportion of patients for whom a significant DDI between the DAA-including regimens and at least 1 regular outpatient medications could not be excluded. Patients were categorized according to the drug with the highest DDI risk in their outpatient medication list. Patients taking at least 1 drug contraindicated for comedication with the respective DAA regimen (category 3 DDI; dark grey [red in online]); patients with no contraindication but at least 1 drug in their regular outpatient medications that was considered to be manageable by closer monitoring or dose modifications (category 2; grey [yellow in online]). Some patients in the dark grey (red in online) group also took category 2 drugs. Abbreviations: BOC, boceprevir; DCV, daclatasvir; DSV, dasabuvir; LDV, ledipasvir; OBV, ombitasvir; P-IFN, pegylated-interferon-alfa; PTV, paritaprevir; r, ritonavir; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; TLV, telaprevir.

potential for DDI in the study cohort. Only 25 of the 261 patients (9.6%) would have been affected by a DDI requiring either closer monitoring or a dose adjustment (category 2) of at least 1 drug in their regular outpatient medication list. There was more potential for DDIs with the dual DAA combinations LDV/SOF fixed dose, SOF/DCV, and SOF/SMV therapy. With these regimens, category 2 DDIs would be present in 105 (40.2%), 95 (36.4%), and 81 (31.0%) patients, respectively. Importantly, only 1 drug (eslicarbazepine) taken by a single patient (0.4%) was strictly not recommended (category 3) while using SOF/DCV or SOF/SMV. No contraindications were found for SOF/RBV or LDV/SOF in the patients' regular outpatient medications.

For the combination of OBV/PTV/r, we detected category 2 DDIs in 151 (57.9%) and category 3 DDIs in 22 of the 261 patients (8.4%). Interestingly, the addition of DSV did not change the number of patients affected by significant DDIs in our cohort. One patient took 2 drugs that would have been contraindicated for comedication with OBV/PTV/r ± DSV.

For 23 drugs taken by 14.6% of patients (n = 37), insufficient information was found to draw a reliable conclusion regarding the possibility of a DDI with any of the DAA regimens (category 0). This primarily affected herbal and nutritional supplements. One patient regularly took 4 drugs with insufficient information for DDI with HCV DAA. The 3 most common supplements were vitamin D (cholecalciferol), zinc, and ferrous sulfate, affecting 9, 5 and 5, respectively.

Overall, potentially significant DDIs with the regular outpatient medications could be expected (category 2 or 3) in at least 66.3% (n = 173) of this patient cohort treated with OBV/PTV/

r ± DSV but in only 9.6% (n = 25) of patients if SOF/RBV would have been chosen for treatment. Similarly, potentially significant DDIs between the regular outpatient medications and SOF/SMV, SOF/DCV, or LDV/SOF would have been possible in 31.4% (n = 82), 36.8% (n = 96), and 40.2% (n = 105) of patients, respectively. In comparison, if treated with Peg-IFN/RBV and TLV or BOC triple therapy, DDIs would have been seen in 53.6% (n = 140) and 55.2% (n = 144) of patients among the study cohort (Figure 2).

Importantly, patients with advanced cirrhosis were more commonly at risk for significant DDIs. Although none of the patients with advanced cirrhosis had a drug in their regular outpatient medications that was contraindicated with any of the DAA regimens, these patients would be more affected by category 2 DDIs for SOF/RBV (n = 4/26, 15.4%), SOF/SMV (n = 10/26, 38.5%), SOF/DCV (n = 12/26, 46.2%), LDV/SOF (n = 17/26, 65.4%), and OBV/PTV/r ± DSV (n = 24/26, 92.3%).

#### Concomitant Medication Most Frequently Involved in Significant DDIs

The most frequent drug classes involved in significant DDIs (category 2 or 3) varied depending on the DAA regimen. For OBV/PTV/r ± DSV, interactions were most frequently documented with proton pump inhibitors (PPIs; n = 63, 24.1%), thyroid hormones (n = 43, 16.5%), and dihydropyridine derivatives (n = 28, 10.7%). The LDV/SOF fixed combination most often posed a risk for DDIs due to PPIs (n = 63, 24.1%), dihydropyridine derivatives (n = 28, 10.7%), and alpha and beta blocking agents (n = 14, 5.4%). The most commonly expected DDI with SOF/DCV was with thyroid hormones (n = 43, 16.5%), dihydropyridine derivatives (n = 28, 10.7%), and alpha and

Drug	Affected Patients (n; %)	SOF/RBV	SOF/SMV	SOF/DCV	SOF/LDV	OBV/PTV/r+DSV	OBV/PTV/r
pantoprazole	49 (18.8%)	none	none	none	no concomitant intake/ decrease PPI dose	monitor/increase dose of PPI	monitor/increase dose of PPI
levothyroxine	43 (16.5%)	none	none	monitor TSH	none	monitor TSH	monitor TSH
propranolol	21 (8.0%)	none	none	none	none	may increase/monitor	may increase/monitor
bisoprolol	20 (7.7%)	none	none	none	none	monitor and decrease dose	monitor and decrease dose
amlodipine	17 (6.5%)	none	monitor heart rate/BP	increase of DCV/monitor	monitor heart rate/BP	monitor/decrease amlodipine 50%	monitor/decrease amlodipine 50%
torasemide	17 (6.5%)	none	none	none	none	monitor/decrease dose	monitor/decrease dose
carvedilol	14 (5.4%)	monitor	monitor	monitor	monitor	monitor	monitor
omeprazole	12 (4.6%)	none	none	none	no concomitant intake/ decrease dose	monitor/increase dose of PPI	monitor/increase dose of PPI
Prednisolone	7 (2.7%)	none	monitor	none	none	monitor	monitor
lercanidipine	6 (2.3%)	none	monitor heart rate/BP	none	none	contraindication/switch to low dose of amlodipine	contraindication/switch to low dose of amlodipine
simvastatin	6 (2.3%)	none	lowest dose/monitor lipids and CK	lowest dose/monitor lipids and CK	lowest dose/monitor lipids and CK	contraindication/switch to low dose pravastatin or rosuvastatin	contraindication/switch to low dose pravastatin or rosuvastatin
tamsulosin	6 (2.3%)	none	none	none	none	avoid concomitant use	avoid concomitant use
ursodeoxycholic acid	6 (2.3%)	monitor for DAA side effects	monitor for DAA side effects	monitor for DAA side effects	monitor for DAA side effects	none	none
zopiclone	5 (1.9%)	none	reduced elimination/ consider dose reduction	reduced elimination/ consider dose reduction	none	increase, lowest dose possible	increase, lowest dose possible
buprenorphine	4 (1.5%)	none	none	none	increase, monitor for side effects of buprenorphine/ dose reduction	monitor for side effects of buprenorphine/dose reduction	monitor for side effects of buprenorphine/dose reduction
felodipine	3 (1.1%)	none	monitor heart rate/BP	monitor heart rate/BP	monitor heart rate/BP	monitor heart rate/BP, avoid concomitant use	monitor heart rate/BP, avoid concomitant use
phenprocoumon	3 (1.1%)	monitor INR	monitor INR	monitor INR	monitor INR	monitor INR	monitor INR
verapamil	3 (1.1%)	none	monitor	monitor	none	start with lowest dose	start with lowest dose
esomeprazole	2 (0.8%)	none	none	none	no concomitant intake/ decrease dose	monitor/increase dose of PPI	monitor/increase dose of PPI
olmesartan	2 (0.8%)	none	none	monitor heart rate/BP	none	monitor/decrease dose	monitor/decrease dose

**Figure 3.** Drugs most commonly involved in drug–drug interactions (DDIs) and suggested actions per direct-acting antiviral agents (DAAs) regimen. For each DAA regimen, the 5 most frequently used drugs on the outpatient medication list for which significant DDIs were expected were included. Drugs taken by fewer than 2 patients were excluded. Color code as follows: green, category 1, no significant DDI; yellow, category 2, significant DDI possible; and red, category 3, coadministration either not recommended or contraindicated. Abbreviations: BP, blood pressure; CK, creatine kinase; DAA, direct-acting antiviral agent; DCV, daclatasvir; DSV, dasabuvir; INR, international normalized ratio; LDV, ledipasvir; OBV, ombitasvir; PPI, proton pump inhibitor; PTV, parataprevir; r, ritonavir; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; TSH, thyroid-stimulating hormone.

beta blocking agents ( $n = 14$ , 5.4%). For SOF/SMV, the most relevant drug classes, which affected at least 5% of included patients, were dihydropyridine derivatives ( $n = 28$ , 10.7%) and alpha and beta blocking agents ( $n = 14$ , 5.4%). Alpha and beta blocking agents were also the only drug class with a risk for considerable DDIs with SOF/RBV, which were taken by at least 5% of the study population ( $n = 14$ , 5.4%). Drugs most commonly involved in DDIs with recently approved DAA regimens in our study population are listed in Figure 3, which includes suggested actions to avoid DDIs or reduce their impact.

## DISCUSSION

It is well known that DDIs and adverse drug reactions have a significant influence on the risk for hospitalization, morbidity, and mortality [13, 14]. Here, we show in a large real-world cohort that many HCV patients are taking comedications that have the potential to lead to clinically significant DDIs with the recently approved DAAs against HCV.

The occurrence of DDIs is an often-underestimated problem. The 2 main adverse scenarios of DDIs to consider are an increase in plasma levels, potentially leading to adverse events, and a decrease in drug levels that may result in a loss of efficacy. Lower DAA drug levels need to be avoided, in particular, for

HCV NS5A inhibitors. Selection of resistant-associated variants (RAVs) is a concern since NS5A RAVs seem to persist for several years [15] and recent data show that the presence of NS5A RAV is associated with lower chances for retreatment SVR [16]. PPIs, which were taken by almost 25% of our patients, may decrease the exposure of the NS5A inhibitor ledipasvir by more than 50% if taken 2 hours prior to ledipasvir [17]. This DDI can be prevented by a simultaneous intake of both drugs. However, the DDI was assessed with 20 mg omeprazole, and it is not known whether different effects are observed if higher doses of omeprazole or other PPIs are used.

The challenge of DDI management obviously increases with the number of drugs taken by an individual patient. In our cohort, more than one third of the patients took 3 or more drugs, while only 20% took no regular outpatient medications. Most frequently, comedications included drugs that target the cardiovascular system. Of note, chronic HCV infection seems to be linked to a higher incidence of cardiovascular diseases [18, 19], which would be in line with data presented here.

DDI management gained relatively greater attention after the approval of TLV and BOC, due to their marked inhibition of P-gp and CYP3A4 [8]. Several adverse events due to DDIs have been reported, including a case of rhabdomyolysis, which

resulted after coadministration of TLV with simvastatin [20], and a liver transplant patient who suffered from renal failure due to increased serum levels of tacrolimus after starting PI therapy [21]. Recently approved DAAs are generally considered to have a lower potential for interactions through P-gp and CYP3A4, and there is a greater awareness of the importance of managing DDIs. Indeed, the regimen that contains multiple DAAs (OBV/PTV/r ± DSV) and considered to have a higher potential for interactions was safe even in liver transplant recipients [22]. Other data from DDI studies with OBV/PTV/r ± DSV suggest that this regimen can be safely used with many commonly used drugs [23]. However, in the present study, we show that the risk for potentially clinically significant DDIs is still an important issue while using recently approved DAA regimens. Of note, about two thirds of the study population is at potential risk of a significant DDI that would require either close monitoring for side effects or possibly a change in the comedication. Thus, being aware of DDIs while treating HCV patients with the recently approved DAA regimens is as necessary as when using TLV and BOC; in particular, if several DAAs with individual DDI risk profiles are combined.

Excellent tolerability of modern Peg-IFN-free DAA regimens facilitates treatment eligibility. Thus, several patients who had contraindications for Peg-IFN/RBV due to comorbidities as well as patients with advanced liver disease may now receive antiviral therapy [9]. These patients also have the most urgent need for therapy. Importantly, the patients with advanced liver disease have twice the median number of medications in their regular outpatient medications than the regular study cohort and are therefore more affected by DDIs.

Our study has several limitations including the single-center design. All patients were recruited at a tertiary referral center presumably with a higher frequency of complicated and more severe cases. Therefore, the number of drugs taken per patient might have been overestimated. On the other hand, an underreporting of comedications cannot be excluded as evaluation of comedication was dependent on patient reports and letters of referral from physicians. Because patients are free to choose various pharmacies in Germany for different prescriptions, it is not possible to track individual patient's medications by contacting distinct pharmacies. Moreover, the study site is taking part in several clinical trials, and thus a small selection bias cannot be excluded as patients with fewer comedications may have been preferentially included in clinical trials.

Our findings have important clinical implications for the management of DDI during HCV therapy. Drugs most frequently involved in DDIs varied among the different DAA regimens. Thus, no list of drugs that should be avoided or are preferred across all DAA classes can be provided. Instead, a careful individual assessment of a patient's regular medications and a subsequent individual evaluation of potential DDIs are required. Here, Web tools such as [www.hep-druginteractions.org](http://www.hep-druginteractions.org)

may offer a convenient way to handle this time-consuming challenge. Based on our data, close monitoring for early detection of adverse effects might be sufficient for the majority of drugs involved in DDIs with DAAs. However, this may also be challenging, in particular, if more than 1 drug is affected in 1 patient. Indeed, in 2 of our patients, 7 different drugs were identified in the outpatient medications for which potentially significant DDIs were expected. Another important finding was that in a considerable number of patients, the available information was insufficient to exclude a significant DDI. This almost exclusively affected herbal and nutritional supplements, which may simply be withdrawn for the time of HCV therapy. Finally, it cannot be excluded that some DDIs may occur unexpectedly despite a careful evaluation before starting treatment, as demonstrated by the recent US Food and Drug Administration warning against the concomitant use of amiodarone- and SOF-containing DAA regimens due to the occurrence of potentially life-threatening bradycardia [24].

In summary, we show that a significant number of patients are at risk for DDIs when treated with novel HCV DAA regimens, in particular, if several DAAs are used. Although strictly contraindicated comedications seem to be rare, a careful assessment of the patient's regular medication and a comprehensive evaluation of potential DDIs with each DAA used for therapy is essential to prevent adverse effects or unnecessary risks of treatment failure.

## Notes

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**Author contributions.** C. H. z. S., B. M., K. P., and K. D. collected the data. C. H. z. S., B. M., F. M., D. B., and H. W. analyzed and interpreted the data. C. H. z. S., B. M., F. M., M. P. M., M. C., D. B., and H. W. were responsible for the concept and design of the study. C. H. z. S., B. M., and H. W. drafted the manuscript. All authors critically reviewed the manuscript and approved the final version.

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