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Sofosbuvir and risk of estimated glomerular filtration rate decline or end-stage renal disease in patients with renal impairment

Mark Sulkowski[1] | Laura E. Telep[2] | Massimo Colombo[3] | Francois Durand[4] | K. Rajender Reddy[5] | Eric Lawitz[6] | Marc Bourlière[7,8] | Nelson Cheinquer[2] | Stacey Scherbakovsky[2] | Liyun Ni[2] | Lindsey Force[2] | Heribert Ramroth[2] | Anuj Gaggar[2] | Anand P. Chokkalingam[2] | Meghan E. Sise[9]

[1]Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

[2]Gilead Sciences, Inc., Foster City, California, USA

[3]M Colombo Liver Center, San Raffaele Hospital, Milan, Italy

[4]Hôpital Beaujon, University Paris Diderot, Clichy, France

[5]Department of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA

[6]Texas Liver Institute, University of Texas Health Science Center, San Antonio, Texas, USA

[7]Hépato-Gastro-Entérologie, Hôpital Saint Joseph, Marseille, France

[8]INSERM 1252, IRD, Sciences Economiques & Sociales de la Santé & Traitement de l'Information Médicale, Aix-Marseille University, Marseille, France

[9]Massachusetts General Hospital, Boston, Massachusetts, USA

Correspondence
Meghan E. Sise, MD, MS, Department of Medicine, Division of Nephrology, Massachusetts General Hospital, Boston, Massachusetts, USA.
Email: msise@partners.org

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Summary

Background: Sofosbuvir, a prodrug nucleoside inhibitor of hepatitis C virus, has a predominant circulating metabolite that is renally eliminated. Whether sofosbuvir is associated with chronic kidney disease (CKD) progression is not well understood.

Methods: We performed a retrospective analysis of patients with estimated glomerular filtration rate (eGFR) 30–89 mL/min/1.73 m^2 treated with sofosbuvir in 76 Phase 2/3 registrational trials. We evaluated eGFR at each study visit. Separately, we performed a retrospective analysis of an administrative claims database (IQVIA PharMetrics Plus™) to compare the risk of incident end-stage renal disease (ESRD) associated with the use of sofosbuvir or non-sofosbuvir regimens among patients with CKD using propensity score methods. Exposure, CKD status and outcomes were determined using diagnosis and medication claim codes. Cox proportional hazards methods were used to estimate ESRD risk.

Results: Among 4642 trial participants with baseline stage 2 CKD (eGFR 60–89 ml/min/1.73 m^2) and 682 trial participants with stage 3 CKD (eGFR 30–59 ml/min/1.73 m^2) mean (SD) eGFR improved from baseline to 4 weeks post-treatment (+0.7 [9.3] and +2.6 [8.8] ml/min/1.73 m^2, respectively; $p < 0.001$ each). In the second analysis, among 2042 patients with CKD receiving sofosbuvir-based regimens compared to 431 receiving non-sofosbuvir-based regimens, after adjusting for baseline covariates and weighting based on treatment propensity scores, there was no significant difference in risk of ESRD (adjusted HR = 0.85, 95% CI: 0.51–1.42).

Conclusions: Clinical trial participants with CKD did not experience worsening eGFR during sofosbuvir-based treatment, and sofosbuvir was not associated with an increased risk of ESRD in patients with CKD in a nationally-representative administrative claims database.

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1 | INTRODUCTION

Globally, approximately 70 million persons have chronic infection with hepatitis C virus (HCV),[1] which can lead to advanced liver disease, hepatocellular carcinoma or death.[2,3] Chronic HCV infection is both independently associated with the development of chronic kidney disease (CKD), and is more prevalent in patients with CKD than in the general population.[4-7] In patients with CKD, chronic HCV infection can accelerate the decline of kidney function and increase the risk of end-stage renal disease (ESRD).[8-11] Fortunately, successful treatment of HCV can slow CKD progression,[11,12] and in patients with diabetes, it can improve both kidney and cardiovascular outcomes.[13]

Sofosbuvir (SOF), a prodrug inhibitor of the HCV NS5B polymerase, is a component of several direct-acting antiviral (DAA) treatment regimens because of its antiviral potency, low risk of resistance and favourable safety profile. GS-331007, SOF's predominant circulating metabolite, is renally eliminated[14] and accumulates in patients with severe CKD (estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73 m^2) or ESRD.[15] Because of this, HCV patients with severe CKD or ESRD were excluded from pre-approval clinical trials of SOF-containing treatments, and SOF was not initially approved for use in HCV-infected patients with severe CKD or ESRD. However, on the basis of two recent post-marketing clinical trials in patients with ESRD,[16,17] SOF-containing treatments are now approved by the Food and Drug Administration (FDA) for use in patients with severe CKD and ESRD.[18-20] Because of the potential concerns that SOF-based regimens may have adverse effects on kidney function particularly in patients with CKD,[21,22] we evaluated the impact of SOF on eGFR and risk of progression to ESRD in HCV-infected patients with CKD using a two-pronged approach: (1) an integrated analysis of all patients with eGFR 30 to <90 ml/min/1.73 m^2 who received SOF in 76 clinical trials to characterise longitudinal changes in eGFR and treatment-emergent adverse kidney and urinary events, and (2) an investigation of patients with CKD treated in clinical practice using real-world, nationally-representative administrative claims database to characterise the incidence rate and relative risk of ESRD with SOF vs non-SOF-based DAA regimens.

2 | MATERIALS AND METHODS

2.1 | Analysis of pooled clinical trial data

At the time of this analysis, 82 phase 2 or 3 clinical trials of SOF/ribavirin, ledipasvir/SOF (LDV/SOF), SOF/velpatasvir (SOF/VEL) or SOF/VEL/voxilaprevir (SOF/VEL/VOX) had been completed. Six trials were excluded as they focused on paediatric patients (four trials) or patients with ESRD (two trials). Prospectively collected kidney function and safety data from all available data from the remaining 76 trials (Table S1) were integrated and assessed retrospectively. The primary results of these individual studies, including both efficacy and overall safety, are reported elsewhere (see references in Table S1); the current analysis is focused only on changes in eGFR and kidney and urinary adverse events. Patients exposed to active treatment (LDV/SOF, SOF/VEL, or SOF/VEL/VOX with or without ribavirin) were included; at baseline (treatment initiation) all were 18 years of age or older. Baseline eGFR was calculated using the Cockcroft-Gault method as per the trial protocols.[23] Baseline kidney impairment was categorized as mild eGFR impairment (stage 2 CKD) if eGFR was ≥60 ml/min/1.73 m^2 but <90 ml/min/1.73 m^2, or moderate (stage 3 CKD) if eGFR was ≥30 ml/min/1.73 m^2 but <60 ml/min/1.73 m^2. Patients with normal kidney function (eGFR ≥ 90 ml/min/1.73 m^2) and those with severe kidney impairment or ESRD (eGFR <30 ml/min/1.73 m^2) at baseline were not included in this analysis. Baseline liver function was categorized as compensated liver disease (including no cirrhosis and compensated cirrhosis) or decompensated liver disease. eGFR was assessed at baseline; on-treatment weeks 1, 2, 4, 8 and 12; on-treatment week 24 with 24-week regimens; and at post-treatment week 4. Differences in a trend of eGFR over time between CKD subgroups were assessed using mixed models with repeated measures. In addition, we evaluated the frequency of large fluctuations in eGFR (≥10 ml/min/1.73 m^2) through post-treatment week 4 that could signal clinically significant changes in kidney function. We summarised the risk of treatment-related adverse events (AEs) within the "Renal and Urinary Disorders" system organ class (Medical Dictionary for Regulatory Activities version 22.0) from baseline through post-treatment week 4.[24] Analyses of eGFR over time and treatment-related AEs were stratified by degree of baseline kidney and liver impairment (decompensated vs. compensated liver disease). Each of the individual clinical trials in this pooled analysis were overseen by institutional review boards, and all patients provided written informed consent.

2.2 | Administrative claims analysis

The retrospective, observational, cohort analysis included patients within the IQVIA PharMetrics Plus™ database, an administrative claims database with integrated enrolment, medical and pharmacy coverage of more than 150 million patient-lives from January 1, 2006, through March 30, 2019. All claims data were de-identified, and therefore this analysis was not subject to institutional review board oversight.

Patients included in this analysis were ≥18 of age with claims indicating HCV treatment with a DAA and presence of CKD prior to treatment initiation based upon International Classification of Diseases 9th and 10th Revision, Clinical Modification (ICD-9-CM and ICD-10-CM) diagnosis codes and Generic Product Identifier medication dispensing codes. DAA treatment regimens had to be interferon-free and included any SOF-containing therapy and any regimen containing glecaprevir/pibrentasvir, elbasvir/grazoprevir, ombitasvir/paritaprevir/ritonavir or ombitasvir/paritaprevir/ritonavir with dasabuvir. Regimens with boceprevir or telaprevir were not included. Patients were required to have at least 1 year of database enrolment prior to their index HCV medication claim. Severity of CKD was determined by claimed ICD codes for early-stage CKD (stage 1–2, eGFR ≥60 ml/min/1.73 m^2), stage 3

CKD (eGFR 30 to <60 ml/min/1.73 m^2), and advanced CKD (stage 4–5, eGFR <30 ml/min/1.73 m^2) or unspecified CKD (Table S2). Exclusion criteria included simultaneous exposure to both SOF- and non-SOF-containing DAA regimens, kidney transplant prior to initiation of DAA therapy, ESRD or dialysis claims prior to initiating DAAs for HCV, or interferon dispensing claims up to 30 days prior to or after initiating DAA treatment.

The primary outcome was ESRD, which was defined as having at least one claim for ESRD or dialysis (Supplementary Table 3) within an observation period beginning on the date of the most recent initiation of DAA treatment and ending at the first of any of the following: a claim for ESRD or dialysis, a claim for kidney transplant, insurance enrolment discontinuation or last date of follow-up in the dataset (March 30, 2019).

Descriptive statistics were used to summarise baseline characteristics between patients treated with or without SOF. Absolute (unadjusted) rates of ESRD per 100 person-years (PY) were calculated with exact 95% Poisson confidence intervals (CIs) for patients treated with or without SOF. After adjustment for baseline covariates and weighting based on treatment propensity scores, Cox proportional hazards methods were used to calculate hazard ratios (HRs) estimating ESRD risk associated with SOF-containing vs SOF-free DAA regimens. Baseline covariates significant at $p < 0.10$ were retained in the model.

3 | RESULTS

3.1 | Analysis 1: Kidney function and adverse events in pooled clinical trial data

We identified 4642 patients with mild eGFR reduction/stage 2 CKD (eGFR 60 to <90 ml/min/1.73 m^2) and 682 patients with stage 3 CKD (eGFR 30 to <60 ml/min/1.73 m^2) at baseline. Among patients with mild and moderate CKD respectively, the mean ages were 58 and 64 years, 48% and 45% were male, 66% and 62% were White, 8% and 7% were Black, and 24% and 30% were Asian (Table 1). Overall, 1055 (19.8%) had compensated cirrhosis and 431 (8.1%) had decompensated cirrhosis.

At baseline, mean eGFR was 77.4 and 51.6 ml/min/1.73 m^2 among patients with mild and moderate CKD, respectively (Table 2). The majority of patients across all studies had eGFR collected at baseline and weeks 1, 2, 4, 8 and 12 and post-treatment week 4; 4550 (85%) of patients with baseline eGFR had a post-treatment week 4 eGFR assessment. Mean eGFR remained stable during exposure to SOF-based treatment and for 4 weeks post-treatment within each group, regardless of baseline CKD stage and liver function (Figure 1). There was no significant difference in eGFR trends over time between patients with mild vs moderate CKD ($p = 0.13$), regardless of baseline liver function. Relative to baseline, there was no evidence of lower GFR at end of treatment (Table 2). By the end of post-treatment follow-up week 4, mean eGFR levels were not markedly different from baseline; patients with moderate and mild CKD experienced a slight but significant increase from baseline in mean eGFR (mean (SD): +0.7 (9.3) ml/min/1.73 m^2 and +2.6 (8.8) ml/min/1.73 m^2 increase, respectively; p-value <0.0001 each, Table 2). These findings were similar for patients with or without decompensated liver disease (Table 2, Figure 1).

To evaluate large fluctuations in eGFR (≥10 ml/min/1.73 m^2) that could signal a clinically significant change in kidney function, eGFR levels were examined from baseline through follow-up week 4. Large fluctuations were common, affecting 2927 (63%) patients with mild CKD (eGFR 60 to <90 ml/min/1.73 m^2) and the 303 (44%) patients with moderate CKD (eGFR 30–59 ml/min/1.73 m^2). In both groups, proportions with large declines were exceeded by

TABLE 1 Baseline demographic and clinical characteristics, clinical trials

	Total		Patients without cirrhosis or with compensated cirrhosis		Patients with decompensated cirrhosis	
	Mild CKD eGFR 60 to <90 (*n* = 4642)	Moderate CKD eGFR 30 to <60 (*n* = 682)	Mild CKD eGFR 60 to <90 (*n* = 4348)	Moderate CKD eGFR 30 to <60 (*n* = 545)	Mild CKD eGFR 60 to <90 (*n* = 294)	Moderate CKD eGFR 30 to <60 (*n* = 137)
Mean age, year (SD)	58 (8.8)	63 (8.9)	58 (8.9)	64 (9.2)	60 (6.9)	62 (7.8)
Male, *n* (%)	2275 (49.0)	316 (46.3)	2103 (48.4)	244 (44.8)	172 (58.5)	72 (52.6)
Race, *n* (%)						
White	3101 (66.8)	445 (65.2)	2872 (66.1)	339 (62.2)	229 (77.9)	106 (77.4)
Black	386 (8.3)	48 (7.0)	366 (8.4)	37 (6.8)	20 (6.8)	11 (8.0)
Asian	1085 (23.4)	181 (26.5)	1046 (24.1)	162 (29.7)	39 (13.3)	19 (13.9)
Mean BMI, kg/m^2 (SD)	24.4 (4.04)	24.7 (4.77)	24.1 (3.72)	24.1 (4.31)	28.4 (5.91)	27.2 (5.61)
Mean HCV RNA, log_{10} IU/ml (SD)	6.3 (0.72)	6.2 (0.71)	6.3 (0.72)	6.3 (0.69)	6.0 (0.64)	5.9 (0.71)
Treatment experienced, *n* (%)	1863 (40.1)	348 (51.0)	1671 (38.4)	262 (48.1)	192 (65.3)	86 (62.8)
Cirrhosis, *n* (%)	1211 (26.1)	275 (40.3)	917 (21.1)	138 (25.3)	294 (100)	137 (100)
Mean ALT, U/L (SD)	71 (64.3)	63 (53.4)	71 (65.6)	62 (55.6)	65 (39.2)	66 (43.6)

TABLE 2 Estimated glomerular filtration rate (eGFR) during sofosbuvir exposure, by baseline renal and hepatic function, clinical trials

	Total		Patients without cirrhosis or with compensated cirrhosis		Patients with decompensated cirrhosis	
eGFR, mean, ml/min/1.73 m^2 (SD)	Mild CKD eGFR 60 to <90 (n = 4642)	Moderate CKD eGFR 30 to <60 (n = 682)	Mild CKD eGFR 60 to <90 (n = 4348)	Moderate CKD eGFR 30 to <60 (n = 545)	Mild CKD eGFR 60 to <90 (n = 294)	Moderate CKD eGFR 30 to <60 (n = 137)
Baseline	77.4 (8.3)	51.6 (6.8)	77.6 (8.3)	51.9 (6.8)	74.5 (8.4)	50.2 (6.8)
End of treatment	78.1 (12.2)	53.4 (11.0)	78.4 (12.0)	53.8 (10.9)	74.3 (14.9)	51.8 (11.1)
Post-treatment week 4	78.1 (12.0)	54.3 (10.7)	78.2 (11.7)	54.3 (10.5)	76.8 (15.6)	54.4 (11.6)
Difference, end of treatment—baseline	+0.7 (9.5)*	+1.7 (8.6)*	+0.8 (9.3)*	+1.8 (8.3)*	−0.2 (12.6)	+1.3 (9.9)
Difference, post-treatment week 4—end of treatment	−0.1 (8.4)	+0.9 (7.2)***	−0.2 (8.2)	+0.5 (7.1)	+2.5 (11.3)***	+2.6 (7.5)**
Difference, post-treatment week 4—baseline	+0.7 (9.3)*	+2.6 (8.8)*	+0.6 (9.0)**	+2.3 (8.4)*	+2.3 (13.6)***	+3.9 (10.2)**

*p < 0.0001.; **p < 0.001.; ***p < 0.05.

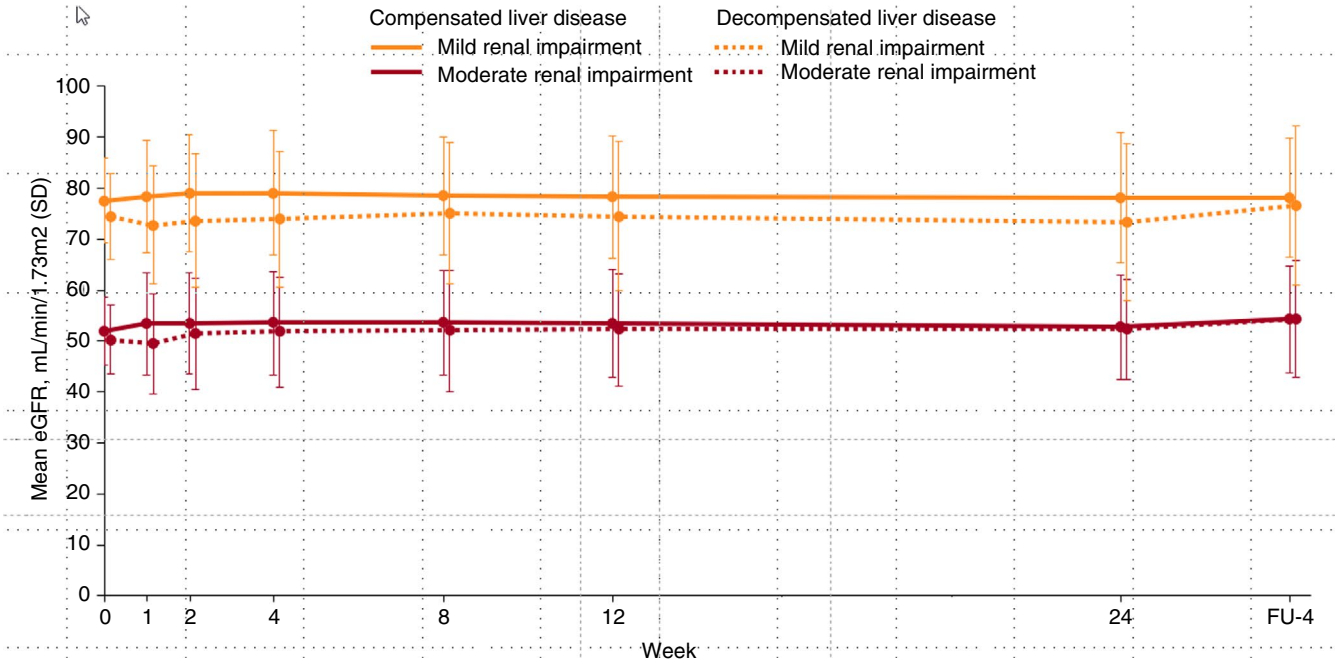

FIGURE 1 Mean estimated glomerular filtration rate (eGFR) over time during and after sofosbuvir treatment among patients with mild and moderate chronic kidney disease. Mean eGFR over time during SOF treatment and through post-treatment follow-up week 4, among 4642 and 682 patients with mild (eGFR 60 to <90) and moderate CKD (eGFR 30 to <60). Error bars indicate standard deviations

the proportions with large improvements: 1105 declines (38%) vs 1584 improvements (54%) among patients with mild CKD, and 95 declines (31%) vs 188 improvements (62%) among patients with moderate CKD.

Among patients with mild, stage 2 CKD at baseline, the proportion experiencing treatment-related kidney or urinary disorder AEs were low, occurring in 33 patients (0.8%) with compensated liver disease, and none in patients with decompensated liver disease. Among patients with stage 3 CKD at baseline, the proportions experiencing treatment-related kidney or urinary disorder AEs were 0.4% (n = 8) in patients with compensated liver disease, and 0.7% (n = 1) in patients with decompensated liver disease. Ribavirin, which is often dose-reduced in patients with impaired kidney function to reduce the risk of haemolytic anaemia,[25] was co-administered to 2693 (51%) of patients in this study. Ribavirin use did not appear to affect changes in eGFR (Table S4).

3.2 | Administrative claims analysis

From the IQVIA PharMetrics Plus™ administrative claims database, we identified 2473 patients with HCV infection and CKD who were treated with a DAA regimen. Of these, 2042 received a SOF-containing DAA regimen and 431 received a SOF-free DAA regimen (Table 3). The two cohorts were similar in terms of age, sex, percentage of having been prescribed a diabetes medication, and presence of arrhythmia or essential hypertension. Compared with the group who received SOF, the group that did not receive SOF had higher percentages of patients with Stage 4–5 CKD (16% vs 6%), a prior acute kidney injury claim (41% vs 33%), coronary atherosclerosis (29% vs 26%), and a prescription for calcium channel blockers (55% vs 44%). Both mean (323 vs 589) and median (249 vs 484) follow-up days of person-time were shorter in the SOF-free group vs the SOF-treated group.

Overall, among the 2473 patients with HCV infection and CKD treated with a DAA, the observed incidence rate of ESRD was 3.81 (95% CI, 3.20–4.49) per 100 PY (Table 4). Incidence rates were highest among person with Stage 4–5 CKD (eGFR <30 ml/min/1.73 m^2) (19.49 per 100 PY).

Without accounting for differences in baseline characteristics, the unadjusted observed incidence rate of ESRD was higher in the cohort that did not receive SOF compared with the cohort that did receive SOF (7.34 vs 3.40 per 100 PY) (Table 5). After adjusting for baseline covariates and weighting based on treatment propensity scores, the risk of incident ESRD was similar for patients treated with and without SOF-containing DAA regimens (adjusted HR = 0.85, 95% CI: 0.51–1.42). Among patients with Stage 4–5 CKD, the unadjusted rate of incident ESRD was greater among patients receiving a SOF-free regimen vs a SOF-containing regimen (32.66 per 100 PY [95% CI 19.35–51.61] vs 15.11 per 100 PY [95% CI 9.78–22.31]). After adjustment for baseline covariates and weighting based on treatment propensity scores, the risk associated with SOF-containing vs SOF-free DAAs was not significantly different (adjusted HR = 0.83, 95% CI: 0.35–2.02).

4 | DISCUSSION

The results presented in this two-pronged study provide compelling support to growing evidence of the kidney safety of SOF, both in terms of during-treatment impact on eGFR and the risk of long-term progression to ESRD in patients with CKD. Our pooled analysis of the entire Phase 2 and 3 SOF clinical development programme included 76 clinical trials with 5324 patients and is the largest to date to examine the impact of SOF on kidney function. We found that among patients with mild to moderate CKD (eGFR 30 to <90 ml/min/1.73 m^2), mean eGFR remained stable throughout SOF treatment. On average, patients with stage 3 CKD (eGFR 30 to <60 ml/min/1.73 m^2) experienced a small, statistically significant improvement in kidney function during therapy. Results were similar when we stratified our analysis by compensated vs decompensated liver disease (Table 2, Figure 1). The findings were similar across different patient sub-populations defined by baseline kidney function, baseline liver function and concomitant use of ribavirin. Taken together, these observations indicate an overall trend towards slightly improved kidney function in CKD patients during treatment with SOF. In addition, rates of kidney and urinary AEs were very low (<1% of trial participants). While the pooled analysis of clinical trials supports the kidney safety of SOF in patients with mild and moderate CKD during and immediately after treatment, the administrative claims analysis supports the longer-term safety of SOF in patients with baseline CKD. As expected, increasing severity of CKD corresponded with higher risk of subsequent ESRD; however this analysis demonstrated no increased risk of progression to ESRD among patients with CKD treated with SOF vs non-SOF-containing DAA regimens.

In the absence of curative treatment, patients with chronic HCV infection and kidney disease have an increased risk of progression to ESRD.[8-11] SOF is the backbone for several HCV treatment regimens that are important antiviral options for patients with HCV infection worldwide. SOF-containing regimens were initially approved for patients with eGFR ≥30 ml/min/1.73 m^2, but have subsequently gained approval for the treatment of patients with all levels of kidney function, including ESRD requiring dialysis. Yet, a shortage of available data, and the kidney elimination of the SOF metabolite GS-331007, has led to concern regarding its potential effects on kidney function, which in turn has led to concern about the use of SOF-based regimens in patients with CKD.[21,22] An early pooled analysis from HCV-TARGET identified higher incidence of kidney AEs and anaemia in patients with eGFR <45 ml/min/1.73 m^2 as compared to patients with eGFR ≥45 ml/min/1.73 m^2.[22,26-28] However, in this paper, as expected, the group with eGFR <45 ml/min/1.73 m^2 had a significantly higher comorbidity burden compared to those with eGFR ≥45 ml/min/1.73 m^2; for example, the rate of decompensated cirrhosis was substantially higher (73% vs 24%), thus making it likely that there were other reasons why this group had higher rates of kidney AEs and anaemia. The results of our above analyses are consistent with a recent study that demonstrated that patients with CKD who received DAAs experiencing a significant improvement in kidney function decline.[12]

Multiple recent studies have evaluated changes in eGFR over time in "real-world" data. A retrospective study by D'Ambrosio et al evaluated serial laboratory data from 3264 patients receiving DAAs (~80% were SOF-containing). They found a slight decline in eGFR during treatment in patients with eGFR ≥60 ml/min/1.73 m^2, but improvement in eGFR in the 334 patients with eGFR <60 ml/min/1.73 m^2. It is unclear whether or not these small declines in eGFR in the normal range of eGFR are clinically meaningful; there was no difference between SOF- and non-SOF-containing regimens.[29] A prospective study by Liu and colleagues enrolled patients with compensated liver disease undergoing SOF-based (N = 308) and non-SOF-based (N = 173) DAA therapy for HCV and prospectively followed eGFR during 12-week therapy and for 24 weeks post-DAAs, and found that there was a slight reduction in eGFR during SOF therapy with

TABLE 3 Patient baseline characteristics patients with CKD receiving DAA therapy included in the administrative claims analysis

	Direct-acting antiviral treatment		Unweighted		Weighted		
	With sofosbuvir ($n = 2042$)	Without sofosbuvir ($n = 431$)	With SOF	Without SOF	With SOF	Without SOF	SMD
Age, years, mean (SD)			59.3 (7.5)	59.5 (8.8)	59.3 (7.5)	58.9 (9.0)	0.05
	(*n*)	(*n*)	(%)	(%)	(%)	(%)	
Years of age, *n* (%)							
18–34	27	14	1.3	3.3	1.4	3.8	NA
35–44	59	11	2.9	2.6	2.9	3.4	NA
45–54	295	64	14.5	14.9	14.4	15.7	NA
55–64	1300	241	63.7	55.9	63.4	55.2	NA
65–74	331	89	16.2	20.7	16.5	19.8	NA
≥75	30	12	1.5	2.8	1.5	2.2	NA
Sex, *n* (%)							
Male	1424	293	69.7	68.0	69.8	67.7	0.04
Female	618	138	30.3	32.0	30.2	32.3	–
CKD stage, *n* (%)							
Unspecified or Stage 1–2	1223	202	59.9	46.9	57.6	56.2	0.03
Stage 3	696	161	34.1	37.4	34.7	36.3	0.03
Stage 4–5	123	68	6.0	15.8	7.7	7.4	0.01
Comorbidities,[a] *n* (%)							
Prior AKI claim	666	175	32.6	40.6	34.0	35.1	0.02
Arrhythmia	659	145	32.3	33.6	32.4	35.2	0.06
Essential hypertension	1818	377	89.0	87.5	89.2	86.1	0.09
Coronary atherosclerosis	522	125	25.6	29.0	26.3	27.4	0.03
Liver necrosis	60	5	2.9	1.2	2.8	1.3	0.10
Hepatic encephalopathy	193	18	9.5	4.2	8.5	8.3	0.01
Anaemia	1093	216	53.5	50.1	52.8	53.1	0.01
Prescriptions,[a] *n* (%)							
Calcium channel blockers	900	235	44.1	54.5	45.7	44.8	0.02
Diabetes medication	880	196	43.1	45.5	42.8	44.7	0.04
Follow-up, days of person time							
Median (Q1, Q3)	484 (220, 869)	249 (105, 423)					NA

Note: Baseline characteristics are shown before and after matching. A standardised mean difference (SMD) is a measure of distance between two group means in terms of a variables and is a conventional metric used to evaluate the quality of a match. By convention, a standardised mean difference of less than 0.1 is considered a well-balanced covariate.

Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; HCV, hepatitis C virus; SD, standard deviation; SMD, standardised mean difference.

[a]Variables considered for adjustment in the model included age group; sex; CKD stage; US region; year of direct-acting antiviral treatment; prior diagnoses of chronic obstructive pulmonary disease; lung disease due to external agents; substance abuse; smoking; alcohol use; liver and non-liver cancer; cirrhosis/fibrosis; diabetes; nutritional and other forms of anaemia; arrhythmia; congestive heart failure; essential hypertension; overweight/obesity; autoimmune disease; hyperlipidaemia; myocardial infarction; angina; coronary atherosclerosis; stroke; hepatitis B virus; mental/personality disorders; convulsions; alcoholic fatty liver disease; alcoholic hepatitis; alcoholic liver damage; non-alcoholic liver disease; biliary cirrhosis; hyperbilirubinemia; elevated serum enzymes; portal hypertension; end-stage liver disease; thrombocytopenia; acute kidney injury; acute glomerulonephritis; prior liver transplant; prior acute glomerulonephritis; prior receipt of radiology or chemotherapy procedures; and prior filled prescriptions of direct-acting antivirals, interferon, HIV antiretroviral therapy, antihypertensives, antihyperlipidaemics, immunomodulators, calcium channel blockers, beta-blockers, antidiabetics, aspirin and statins.

TABLE 4 End-stage renal disease or dialysis claims among chronic kidney disease patients treated with direct-acting antivirals for hepatitis C, administrative claims analysis

DAA-treated HCV patients	Events (*n*)	Patients (*n*)	Time at Risk (person-years)	Unadjusted rate of ESRD/dialysis, per 100 person-years	
				Rate	95% CI
Any CKD stage	140	2473	3676	3.81	3.20–4.49
CKD stage					
Stage 1–2 or unspecified stage	33	1425	2245	1.47	1.01–2.06
Stage 3	64	857	1211	5.29	4.07–6.75
Stage 4–5	43	191	221	19.49	14.11–26.26

Abbreviations: CKD, chronic kidney disease; CI, confidence interval; DAA, direct-acting antiviral; ESRD, end-stage renal disease.

TABLE 5 Association of direct-acting antiviral treatment with end-stage renal disease administrative claims analysis

	Events (*n*)	Patients (*n*)	Time at risk (person-years)	Unadjusted rate of ESRD/dialysis (per 100 person-years)		Adjusted and Propensity-Score-Weighted HR	
				Rate	95% CI	HR	95% CI
Any CKD							
Without sofosbuvir	28	431	382	7.34	4.88–10.61	1.00	—
With sofosbuvir	112	2042	3295	3.40	2.80–4.09	0.85	0.51–1.42
CKD stage							
Stage 3							
Without sofosbuvir	8	161	138	5.78	2.49–11.39	1.00	—
With sofosbuvir	56	696	1072	5.22	3.95–6.78	0.91	0.41–2.01
Stage 4–5							
Without sofosbuvir	18	68	55	32.66	19.35–51.61	1.00	—
With sofosbuvir	25	123	165	15.11	9.78–22.31	0.83	0.35–2.02

Note: Results are stratified by CKD stage where counts of events were ≥5 with sofosbuvir and without sofosbuvir.
Abbreviations: CI, confidence interval; ESRD, end-stage renal disease; HR, hazard ratio.

improvement after therapy.[30] The estimated reduction in eGFR (0.33 ml/min/month) attributed to SOF was small and unlikely to be clinically relevant in this population where >85% of the cohort had Stage 1 or 2 CKD, as this study enrolled only a limited number of patients with stage 3 CKD (N = 58 total). Furthermore, it was reassuring that among SOF-treated patients, eGFR was numerically higher at SVR24 than at baseline. Finally, because ribavirin use was used almost exclusively with SOF-based regimens (51/56 patients), it is not possible to assess the potential impact of ribavirin on these results.[30] In a multicentre, retrospective study, Okubo and colleagues followed 706 patients with stage 1, 2 or 3, CKD and found that administration of ledipasvir and sofosbuvir did not affect serial eGFR levels in patients with CKD stage 3 (N = 132 patients) and that severe adverse events were rare (3%) in patients with stage 3 CKD.[31] Butt and colleagues examined a large cohort of HCV-infected Veterans and demographically matched HCV uninfected controls (ERCHIVES) to evaluate the risk of worsening kidney function, defined as a decline in eGFR >30 ml/min/1.73 m^2 from baseline, and found a statistically significantly lower risk associated with SOF-containing vs non-SOF-containing regimens.[32] Finally, recent studies that have confirmed the kidney safety of coadministration of SOF with tenofovir-based treatments in HIV/HCV co-infected patients further corroborate this study's findings.[33,34]

Our results complement recent findings of clinical trials evaluating LDV/SOF and SOF/VEL in patients with ESRD which concluded these regimens were safe and effective and led to an expanded FDA label for SOF-containing regimens in patients with all levels of kidney function in 2019,[16,17] and data demonstrating that the GS-331007 metabolite is efficiently removed by haemodialysis (53% extraction ratio) resulting in markedly reduced exposure after dialysis.[35] A systematic review and meta-analysis of 21 retrospective studies in which HCV patients with eGFR <30 ml/min/1.73 m^2 received SOF-based therapy also demonstrated low rates of severe AEs; in the four studies reporting kidney function before and after

SOF-based treatment, eGFR remained stable after treatment.[36] Liu and colleagues conducted a multi-centre "real-world" study of 191 patients with CKD stage 4 or 5 receiving SOF/VEL +/− ribavirin that confirmed that this combination is safe and effective with no severe adverse events attributed to therapy.[37]

Our study has several limitations. In the pooled clinical trial data of SOF-exposed patients, there is no control group of patients treated with SOF-free DAAs for comparison. This prevents a direct comparison of eGFR between SOF-based vs SOF-free regimens, and therefore the relative impact of SOF on kidney function vs improvement of kidney function caused by HCV clearance cannot be distinguished. However, the findings of the complementary administrative claims analysis demonstrating no increased risk of ESRD between SOF-based vs SOF-free DAA regimens provide strong evidence that kidney function improvements caused by HCV clearance are not somehow masking a potential detrimental effect of SOF. In addition, the pooled clinical trial data includes patients treated for 8, 12 and 24 weeks of SOF-based therapy, though the majority were treated for 12 weeks. Although the integrated dataset does not permit stratification by duration of treatment, examination of eGFR at 8, 12 and 24 weeks does not demonstrate a decline in eGFR over time, and indeed by 4 weeks after treatment completion, eGFR levels improved overall. Furthermore, although patients were followed closely, with 85% of patients having available creatinine measurement data at the end of follow-up, the duration of follow-up was limited to 4 weeks after treatment completion, thus limiting our ability to determine long-term effect of SOF on eGFR. Baseline characteristics for patients with vs. without available creatinine measurements at the end of follow-up were not markedly different (Table S5). Additionally, clinical trial participants are often highly selected and thus findings may not be generalizable; however, our findings mirror those in a smaller, real-world cohorts of patients with CKD.[12,38] Among the group with mild eGFR reduction (eGFR ≥60 ml/min/1.73 m^2 but <90 ml/min/1.73 m^2) we were unable to determine which patients actually met criteria for CKD stage 2 given lack of available urinalysis. Additionally, we could not diagnose stage 1 CKD in patients with normal eGFR >90 ml/min/1.73 m^2 due to lack of urinalysis data. Similarly, we grouped patients into kidney function groups based on a single baseline creatinine measurement, which may have led to some misclassification. Though our findings were similar across different patient sub-populations defined by baseline kidney function, baseline liver function and concomitant use of ribavirin, our integrated trial database lacked diabetes and hypertension status and we were unable to stratify the results by these important covariates. In our claims analysis, on average, SOF-treated patients had longer follow-up than patients treated with non-SOF-containing regimens. The differential follow-up is the result of the early approval of SOF-based DAAs in late 2013 (SOF plus ribavirin with or without interferon) and 2014 (LDV/SOF) whereas the non-SOF-based treatments in the analysis were generally not available until 2015 or later. To account for potential differences caused by the differential follow-up time, we applied time-to-event methods for our analysis. The lack of mortality data in the claims database prevented correction for death as a competing risk. In addition, the IQVIA PharMetrics Plus™ dataset does not capture race and ethnicity, preventing characterisation and adjustment for these variables. Another potential limitation of the claims analysis was those entry criteria and outcomes were defined by claimed diagnostic codes and not creatinine measurements. Staging information was lacking for 41% of patients with CKD, although among those for whom it was available, differences in rates of ESRD or dialysis were consistent with the identified severity of CKD stage. Patients without a specified CKD stage had a lower rate of reported ESRD compared to those with a specified CKD stage, suggesting these patients had, on average, less severe CKD. Because of the limitations in diagnostic coding for CKD stages, we were unable to evaluate the risk of SOF-based therapy on changes in CKD severity stages; therefore we focused on the patient-important outcome of development of ESRD. Finally, given the differences in baseline demographic and disease characteristics between the SOF-treated and non-SOF treated patients in the claims database, there is a possibility of channelling bias in that patients with a concern of progression to ESRD or dialysis may have been less likely to be prescribed SOF. The potential of this effect was mitigated by adjustment for baseline covariates and application of propensity score methods, specifically inverse probability of treatment weighting. These approaches balance demographic factors and baseline health conditions that could contribute to inherent differences in risk of ESRD in patients treated with SOF vs non-SOF DAAs.

In conclusion, in this two-pronged analysis of patients treated in both clinical trials and in clinical practice, we found that among all patients in the entire Phase 2 and 3 clinical programmes of SOF-based DAA therapies who had mild to moderate kidney impairment, eGFR levels remained stable throughout SOF treatment, and that in real-world claims data, there was no difference in risk of ESRD in HCV-infected CKD patients treated with SOF- vs non-SOF-containing DAA regimens. These results provide strong support for the kidney safety of SOF and support its use in this at-risk population.

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CONFLICTS OF INTEREST

Author: Conflicts of Interest (*Research grants*, *advisory boards*, *speaker*, *consultant*, *other [please specify] OR none*). Mark Sulkowski: Ad hoc advisory board: Gilead, Abbvie, Arbutus, Assembly Bio; ImmunoCore, Biomarin. Research (paid to JHU): Gilead, AbbVie, Assembly, Arbutus. DSMB: Gilead. Massimo Colombo: Ad hoc Advisory Board: Merck, Roche, Novartis, Bayer, BMS, Gilead, Tibotec, Vertex, Janssen Cilag, Achillion, Lundbeck, GSK, GenSpera, AbbVie, Alfa Wasserman, Intercept, Target HCC, COST, IDMC Exelixis. Speaking and Teaching: Tibotec, Roche, Novartis, Bayer, BMS, Gilead, Vertex, Merck, Janssen, AbbVie. Francois Durand: None. K. Rajender Reddy: Ad hoc Advisory Board: Mallinckrodt, Gilead, Merck. Research grants (paid to the

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AUTHOR CONTRIBUTIONS

L.E. Telep, A.P. Chokkalingam and M.E. Sise contributed to the conception and design of the study. M. Sulkowski, M. Colombo, F. Durand, K.R. Reddy, E. Lawitz and M. Bourlière contributed to the collection of data. All authors contributed to the interpretation of data and drafting or revision of the manuscript. All authors approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

Gilead shares anonymized Individual Patient Data (IPD) from clinical trials upon request or as required by law and/or regulation with qualified external researchers. Approval of such requests is at Gileads discretion and is dependent on the nature of the request, the merit of the research proposed, the availability of the data, and the intended use of the data. Data requests should be sent to datarequest@gilead.com. PharMetrics Plus administrative claims data are available to the public via subscription from IQVIA.

ORCID

Mark Sulkowski https://orcid.org/0000-0002-2145-6352
Anand P. Chokkalingam https://orcid.org/0000-0001-5200-3033
Meghan E. Sise https://orcid.org/0000-0002-4327-9713

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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