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A Systematic Review of Direct-Acting Antivirals for Hepatitis C in Advanced CKD

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Introduction: Direct-acting antivirals (DAAs) have improved treatment of hepatitis C virus (HCV) infection in patients with chronic kidney disease (CKD). To facilitate the 2022 update of the Kidney Disease: Improving Global Outcomes (KDIGO) guideline for CKD patients with HCV, we systematically reviewed DAA regimens in patients with CKD stages G4 and G5 nondialysis (G4–G5ND), CKD stage G5 on dialysis (G5D), and kidney transplant recipients (KTRs).

Methods: We conducted a systematic review by searching PubMed, Embase, Cochrane, CINAHL, and ClinicalTrials.gov through February 1, 2022, and conferences from 2019 to 2021. Studies of HCV-infected patients with CKD G4–G5ND, G5D, and KTRs treated with specified DAA regimens were included. Outcomes included death at 6 months or later, sustained virologic response at 12 weeks (SVR12), serious adverse events (SAEs) attributed to DAA, and treatment discontinuation because of adverse events. Maximum likelihood meta-analyses were determined; certainty of evidence was assessed per GRADE (Grading of Recommendations Assessment, Development, and Evaluation).

Results: We identified 106 eligible studies (22 reported on CKD G4–G5ND, 69 on CKD G5D, and 29 on KTRs). In each population, the majority of DAA regimens achieved SVR12 $\geq$ 93%. We found generally low quality of evidence of low risk of SAEs (mostly 0%, up to 2.9%) and low risk of discontinuation because of adverse events (mostly 0%−5%). Across 3 unadjusted observational studies in KTRs, the risk of death after DAA treatment was substantially lower than without treatment (summary odds ratio, 0.16; 95% CI, 0.04–0.61).

Conclusion: Combination DAA regimens are safe and highly effective in patients with advanced CKD, on dialysis, and with kidney transplants.

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Since the 2018 update of the KDIGO guideline on the management of HCV in CKD,[1] there has been a large volume of new evidence to support use of DAA regimens for patients with CKD. To enable the 2022 KDIGO update[2] and its determinations of recommended regimens, a systematic review of each regimen's effectiveness and safety was needed.

HCV infection is associated with more rapid progression of CKD.[3,4] Transmission of HCV within dialysis units result in high prevalence rates of HCV in patients undergoing dialysis and following kidney transplantation.[5] The development of DAA regimens with high SVR12 has changed the approach to HCV in all CKD populations, including stages G4–G5ND (nondialysis), patients treated with dialysis (G5D), and KTRs.

DAA regimens studied in people with low glomerular filtration rate (GFR) include agents that undergo hepatic clearance, primarily the combinations of NS5A and NS3/4A inhibitors elbasvir (EBR)/grazoprevir (GZR), and glecaprevir (GLE)/pibrentasvir (PIB).[1,6] These regimens achieved SVR12 rates of 94% and 98%, respectively, by intention-to-treat analysis.[7-9] An additional regimen eliminated through hepatic metabolism is the combination of paritaprevir, ritonavir, and ombitasvir with or without dasabuvir (PrO ± D), which resulted in SVR12 rates of 95% in patients with

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CKD G4 to G5 and G5D.[10] The NS5B inhibitor sofosbuvir (SOF) is an important part of multiple DAA regimens in patients without CKD; however, because it is renally metabolized, concerns persisted about its cardiac or kidney toxicity in patients with CKD because of elevated levels of SOF and its metabolite GS-331007.[11] The US Food and Drug Administration and European Medicines Agency ultimately approved the use of SOF for patients with CKD G4–G5ND and dialysis after further studies demonstrated safety and efficacy, adding to available treatment options.

The choice of regimen may be impacted by CKD stage, HCV genotype, hepatic function, prior HCV treatment, concomitant medications, as well as local availability and cost of different DAA regimens. Regimens active against all HCV genotypes (pangenotypic) include SOF-based regimens, most commonly SOF coadministrated with the NS5A inhibitors, daclatasvir (DCV), and velpatasvir (VEL), and also GLE/PIB. SOF coadministered with ledipasvir (LDV) is approved for genotypes 1, 4, 5, and 6 and SOF/simeprevir (SIM) for genotypes 1 and 4. Combination GZR/EBR is active against HCV genotypes 1a, 1b, and 4. Other regimens still used in some settings include combination DCV and asunaprevir (ASV), used primarily in Japan for genotype 1b, and PrO ± D for HCV genotypes 1a, 1b, and 4.

To support the 2022 update of the KDIGO guideline on the management of HCV in CKD,[2] we conducted a systematic review with meta-analysis of benefit and safety outcomes of all available DAA regimens specifically in patients with CKD G4–G5ND, on dialysis, and among KTRs.

METHODS

We conducted this systematic review based on standard KDIGO and Agency for Healthcare Research and Quality methods,[2,12] in accordance with the Preferred Items for Reporting in Systematic Reviews and Meta-Analyses.[13]

We updated previous searches conducted for the prior KDIGO HCV guidelines from 2008 and 2018.[1,14] We conducted literature searches on Medline (via PubMed), Embase, the Cochrane Register of Clinical Trials, the Cochrane Database of Systematic Reviews, CINAHL, and ClinicalTrials.gov, restricted to January 1, 2016 through February 1, 2022. For older studies, we rescreened the reference lists from the 2008 and 2018 KDIGO guidelines. We manually screened conference presentations from 2019 to 2021 meetings for 5 major international nephrology and hepatology annual meetings (American Association for the Study of Liver Diseases, American Society of Nephrology, Asian Pacific Association for the Study of the Liver, European Association for the Study of the Liver, European Renal Association–European Dialysis and Transplant Association). KDIGO guideline Work Group members were also asked to suggest additional studies to be screened.

Electronic literature searches included terms for kidney disease, transplantation, and function; HCV; and DAAs (Supplementary Materials). The search also included terms for other topics, including donor-positive to recipient-negative transplantation, glomerulonephritis, cryoglobulinemia, and their treatments. All identified citations were independently double-screened by a team of 3 researchers using Abstrackr (http://abstrackr.cebm.brown.edu). Conflicts were resolved by group discussion. All potentially relevant studies were rescreened in full text in duplicate.

We included studies of adults with CKD G4 or greater, including KTRs, who were treated for HCV infection with any DAA, alone or in combination. Studies had to specify the DAA regimens and had to report data specifically for patients with either CKD G4–5ND, CKD G5D, or who were KTRs. With the exception of comparisons between DAA treatment and no treatment, studies that combined data for various DAA regimens or for various categories of CKD stages, for which we could not parse out results, were excluded. We allowed up to 10% of each analyzed sample to have received a different DAA regimen or to be in a different CKD stage. We excluded cohorts that included >10% of patients with a viral coinfection with HBV and/or HIV. For DAA regimens, we allowed combinations with and without ribavirin. For PrO ± D, we also allowed combinations with or without dasabuvir. We required at least 10 patients per analyzed group.

Based on discussions with the guideline Work Group, we included the following critical outcomes as appropriate for specific CKD populations: all-cause death (with at least 1 year follow-up), allograft loss, and kidney failure; the following outcomes of high importance: SVR12, SAEs ascribed to DAAs, and discontinuation because of any adverse event, change in CKD category (or related outcomes; except that kidney failure was critical), quality of life, and allograft estimated GFR (eGFR); and following outcomes of moderate importance: delayed graft function, acute rejection, and eGFR (in CKD G4–G5ND patients).

Each study was extracted and assessed for methodological quality by 1 of 3 methodologists into a customized form in the Systematic Review Data Repository-Plus (srdrplus.ahrq.gov/public_data?id=1139&type=project). Each extraction was reviewed and confirmed by at least 1 other experienced methodologist. Disagreements were resolved by discussion among the team. For methodological quality, we considered

completeness of data (related to dropouts and other missing data); the likelihood of selective reporting; whether data were reported sufficiently to allow intention-to-treat analyses; whether study eligibility was based on factors after the start of DAA treatment (such as viremia at end of treatment); and whether there was clear and consistent reporting overall, of study eligibility criteria, of treatments (including dose and duration), outcomes, and adverse events. These features were based on elements in the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool,[15] the Cochrane Risk of Bias tool,[16] and the National Heart, Lung, and Blood Institute tool.[17]

Where appropriate, we conducted restricted maximum likelihood meta-analyses in OpenMetaAnalyst (http://www.cebm.brown.edu/openmeta) of double arcsine transformed proportions. When all or almost all studies had zero events, or meta-analysis produced summary estimates inconsistent with the primary studies, we simply pooled data across studies and calculated exact confidence intervals.

For each outcome and for each DAA regimen, we graded the quality of evidence based on a modification of the Agency for Healthcare Research and Quality and GRADE approaches.[18,19] For each strength of evidence assessment, we considered the number of studies, the number of analyzed patients, the methodological quality of the studies, the consistency across studies, sparseness of data, and imprecision of estimates. We compiled an overall determination of the balance of benefits and harms across outcomes and a quality of the overall evidence, considering the predetermined importance of each outcome.

RESULTS

The electronic literature searches yielded 2730 citations; an additional 76 records were considered from other sources, mostly from conference proceedings (Supplementary Figure 1). After full-text screening, we found 106 eligible studies (Supplementary Tables for study-level findings).

The large majority of studies were retrospective descriptions of patients who had been treated with a specific DAA regimen. The evaluated regimens were generally consistent with those recommended by the American Association for the Study of Liver Disease and Infectious Diseases Society of America joint guideline.[20] Most studies adequately described the DAA regimens and patient characteristics. All but one study reported intention-to-treat analyses. Many studies did not clearly report adverse events. Across 131 cohorts of patients for whom SVR12 was reported ($N = 6375$), SAEs ascribed to DAAs were reported in only 90 cohorts ($N = 2919$, 46%) and discontinuations because of adverse events were reported in only 99 cohorts ($N = 3196$, 50%). Therefore, summarized risks of adverse events suffer from reporting bias and are likely overestimates. A single randomized trial, Hepatitis C: Study to Understand Renal Failure's Effect on Responses (C-SURFER),[7] which evaluated GZR/EBR, was excluded from this study because it did not report data separately for patients with CKD G4–G5ND and CKD G5D. The trial was included in the 2018 KDIGO HCV guideline[1] and was consistent with our findings for both the CKD G4–G5ND and CKD G5D populations.

CKD G4–G5ND

We found 22 studies that reported on specific DAA regimens in patients with CKD G4–G5ND (eGFR <30 ml/min per 1.73 m^2, not on dialysis).[9,21-41] The studies evaluated the following: DCV/ASV (1 study, $N = 10$), GLE/PIB (4 studies, $N = 149$), GZR/EBR (5 studies, $N = 857$), PrO±D (5 studies, $N = 153$), SOF (2 studies, $N = 41$), SOF/DCV (4 studies, $N = 571$), SOF/LDV (2 studies, $N = 43$), SOF/SIM (1 study, $N = 41$), and SOF/VEL (2 studies, $N = 99$). Conclusions pertaining to DAA treatment in patients in CKD G4–G5ND are summarized in Table 1.

No study reported on risk of long-term (≥1 year) death. Across 19 studies, there was high quality of evidence that GLE/PIB, GZR/EBR, and SOF/DCV achieve SVR12 of about 97% to 99%, low quality of evidence that SOF/VEL achieves an SVR12 of about 96%, and very low quality of evidence that DSV/ASV and SOF/LDV achieve SVR12 of 100%, and for SOF/SIM 92%. In contrast, there is low quality of evidence that PrO ± D achieves an SVR12 of only about 89% and very low quality of evidence that SOF (± ribavirin) achieves an SVR12 of only about 72%. Quality of evidence was downgraded primarily because of inconsistency in estimates of SVR12 across studies, imprecision in estimates, and sparseness of studies.

For adverse events, there is low quality of evidence (mainly because of risk of reporting bias and imprecision) for risk of SAEs and discontinuations because of adverse events for all regimens. Among 22 cohorts with 1897 patients for whom SVR12 was reported, SAEs were reported among only 13 cohorts with 344 patients (18% of all participants) and discontinuations because of adverse events among only 12 cohorts with 317 patients (17%). However, with all regimens, almost no SAEs were reported. With SOF-based regimens, 0 of 210 patients (0%; 95% CI, 0–3.7) had SAEs. Discontinuations because of adverse events were also rare. Excluding 1 study for which this outcome was atypically high with SOF monotherapy (20% in 40 patients),[32] in 6 other cohorts, 0 of 163 patients (0%; 95%, CI 0–4.7) on SOF-based regimens discontinued DAAs because of adverse

Table 1. Evidence profile regarding DAA treatment in patients with CKD G4–G5ND

								Summary of findings		
Outcome	Regimen[a]	No. of studies[b]	Total N of patients on treatment	Methodological quality of studies	Consistency across studies	Directness of the evidence	Other considerations	Quality of evidence for outcome	Description of findings	Importance of outcome
Death, ~6–12 mo	Any	0							ND	Critical
SVR12	DCV/ASV	1	10	No limitations	N/A	Direct	Sparse	Very low	100% (52, 100)	High
	GLE/PIB	3	132	No limitations	Consistent	Direct	None	High	98.5% (94.1, 99.6)	
	GZR/EBR	5	857	No limitations	Consistent	Direct	None	High	96.7% (95.4, 97.8)	
	PrO ± D	3	103	No limitations	Inconsistent	Direct	Imprecise	Low	89.4% (75.7, 97.8)	
	SOF	2	41	No limitations	Inconsistent	Direct	Imprecise	Very Low	71.7% (29.1, 98.6)	
	SOF/DCV	4	571	No limitations	Consistent	Direct	None	High	97.1% (95.7, 98.3)	
	SOF/LDV	2	43	No limitations	Consistent	Direct	Imprecise	Very Low	100% (84, 100)	
	SOF/SIM	1	41	No limitations	N/A	Direct	Sparse	Very Low	92.7% (79.6, 97.6)	
	SOF/VEL	2	99	No limitations	Consistent	Direct	Imprecise	Low	96.0% (89.7, 98.5)	
Serious AE because of DAA	DCV/ASV	0							ND	
	GLE/PIB	2	67	Some limitations[c]	Consistent	Direct	Imprecise	Very Low	0% (0, 11)	
	GZR/EBR	1	14	Serious limitations[d]	N/A	Direct	Sparse	Very Low	0% (0, 39)	
	PrO±D	2	53	Serious limitations[e]	Consistent	Direct	Imprecise	Very Low	0% (0, 13)	
	SOF	3	41	No limitations	Consistent	Direct	Imprecise	Very Low	0% (0, 17)	
	SOF/DCV	2	52	Serious limitations[e]	Consistent	Direct	Imprecise	Very Low	0% (0, 14)	
	SOF/LDV	2	43	No limitations	Consistent	Direct	Imprecise	Very Low	0% (0, 16)	
	SOF/SIM	0							ND	
	SOF/VEL	1	74	No limitations	N/A	Direct	Sparse	Very Low	0% (0, 10)	
Discontinued because of AE	DCV/ASV	0							ND	
	GLE/PIB	2	67	Some limitations[c]	Consistent	Direct	Imprecise	Very Low	3.0% (0.7, 11)	
	GZR/EBR	1	14	Serious limitations[d]	N/A	Direct	Sparse	Very Low	0% (0, 39)	
	PrO±D	2	53	Serious limitations[e]	Consistent	Direct	Imprecise	Very Low	0% (0, 13)	
	SOF	2	41	No limitations	Inconsistent	Direct	Imprecise	Very Low	11% (1.2, 28)	
	SOF/DCV	2	25	Serious limitations[e]	Consistent	Direct	Imprecise	Very Low	0% (0, 25)	
	SOF/LDV	2	43	No limitations	Consistent	Direct	Imprecise	Very Low	0% (0, 16)	
	SOF/SIM	0							ND	
	SOF/VEL	1	74	No limitations	N/A	Direct	Sparse	Very Low	0% (0, 10)	

Rare, but insufficient evidence. No evidence of differences among regimens.	High
Rare, but insufficient evidence. No evidence of differences among regimens.	High

AE, adverse events; ASV, asunaprevir; DAA, direct-acting antivirals, DCV, daclatasvir; EBR, elbasvir; GFR, glomerular filtration rate; GLE, glecaprevir; GZR, grazoprevir; LDV, ledipasvir; N/A, not applicable; ND, no data; NS, nonsignificant; PIB, pibrentasvir; PrO ± D, paritaprevir/ritonavir/ombitasvir ± dasabuvir; SIM, simeprevir; SOF, sofosbuvir; SVR12, sustained virologic response at 12 weeks posttreatment; VEL, velpatasvir.

[a]Notation of inclusion of ribavirin omitted from this table. The outcome change in CKD category had sparse evidence from 2 studies providing very low quality of evidence for GLE/PIB and PrO ± D; the outcome estimated glomerular filtration rate had sparse or imprecise evidence from 1 to 2 studies per regimen providing very low quality of evidence for PrO ± D, SOF monotherapy, SOF/DCV, SOF/LDV, and SOF/VEL. These 2 outcomes are omitted from the table.

[b]Single groups, mostly retrospective.

[c]Reporting bias (larger study did not report outcome).

[d]Reporting bias (many studies did not report outcome).

[e]Reporting bias (study with majority of patients did not report outcome).

Balance of potential benefits and harms: DAAs yield very high rates of SVR12 with rare adverse events (although evidence on adverse events is sparse). Some regimens may have poorer SVR12, but there are no randomized or other comparisons of DAA regimens in comparable patients.

Quality of overall evidence: high (for DAAs in general).

events. Including the outlier study, in total 2.0% (95% CI, 0.7–5.1) discontinued DAAs. DAA discontinuations was also uncommon for other DAA regimens and other outcomes were rarely reported (Table 1).

CKD G5D

We found 69 studies pertaining to patients on dialysis. Across 3817 patients, only 35 were on peritoneal dialysis.[9,22-24,26,29-31,34,37-39,42-98] The studies evaluated the following: DCV/ASV (9 studies, $N = 341$), GLE/PIB (12 studies, $N = 608$), GZR/EBR (11 studies, $N = 966$), PrO ± D (16 studies, $N = 599$), SOF (3 studies, $N = 123$), SOF/DCV (9 studies, $N = 571$), SOF/LDV (7 studies, $N = 220$), SOF/SIM (1 study, $N = 12$), and SOF/VEL (8 studies, $N = 629$). Conclusions about DAA treatment in patients on dialysis (CKD G5D) are summarized in Table 2.

Based on 1 or 2 small studies of each DAA regimen, there is very low quality of evidence of low risk of death at about 9 to 12 months of follow-up, but estimates were highly imprecise and suffer from reporting bias and are thus likely overestimates.

There is high quality of evidence that SOF/VEL achieves an SVR12 of about 93%, moderate quality of evidence that GLE/PIB, GZR/EBR, PrO ± D, SOF/DCV, and SOF/LDV all achieve SVR12 rates of about 94% to 97%, and low quality of evidence that DCV/ASV and SOF achieve SVR12 of about 94% and 92%,

Table 2. Evidence profile regarding DAA treatment in patients with CKD G5D

								Summary of findings			
Outcome	Regimen[a]	No. of studies[b]	Total N of patients on treatment	Methodological quality of studies	Consistency across studies	Directness of the evidence	Other considerations	Quality of evidence for outcome	Description of findings		Importance of outcome
Death, ~6–12 mo	DCV/ASV	0									
	GLE/PIB	2	109	Serious limitations[c]	Consistent	Direct	Imprecise	Very low	0.9% (0.1, 6.2)	Reported death rates low (0.9–6.4%) but very sparse, imprecise estimates. Reporting bias likely inflating estimates. No reported deaths related to DAA or HCV.	Critical
	GZR/EBR	0									
	PrO ± D	2	60	Serious limitations[c]	N/A	Direct	Sparse	Very low	1.7% (0.2, 11)		
	SOF	0									
	SOF/DCV	1	31	Serious limitations[c]	N/A	Direct	Sparse	Very low	6.4% (1.6, 22)		
	SOF/LDV	0									
	SOF/SIM	0									
	SOF/VEL	1	59	Serious limitations[c]	N/A	Direct	Sparse	Very low	3.4% (0.8, 13)	No evidence of differences among regimens.	
SVR12	DCV/ASV	9	341	Some limitations[d]	Some inconsistency	Direct	None	Low	93.6% (89.5, 96.8)	Very high SVR12 for all treatments. Mostly ≥94%. No direct evidence of differences among regimens.	High
	GLE/PIB	11	529	Some limitations[d]	Consistent	Direct	None	Moderate	96.9% (95.1, 98.3)		
	GZR/EBR	11	962	Some limitations[d]	Consistent	Direct	None	Moderate	96.5% (94.9, 97.8)		
	PrO±D	16	582	Some limitations[d]	Consistent	Direct	None	Moderate	96.8% (95.2, 98.1)		
	SOF	3	123	No limitations	Inconsistent	Direct	None	Low	91.9% (74.5, 99.8)		
	SOF/DCV	8	278	No limitations	Some inconsistency	Direct	None	Moderate	93.7% (88.9, 97.2)		
	SOF/LDV	7	220	Some limitations[d]	Consistent	Direct	None	Moderate	95.9% (92.8, 98.1)		
	SOF/SIM	1	12	No limitations	N/A	Direct	Sparse	Very Low	83.3% (52.3, 95.8)		
	SOF/VEL	8	629	No limitations	Consistent	Direct	None	High	93.0% (93.0, 97.3)		
Serious AE because of DAA	DCV/ASV	8	274	Some limitations[e]	Consistent	Direct	None	Moderate	0.4% (0.1, 2.5)	Rare. No evidence of differences among regimens.	High
	GLE/PIB	9	435	Some limitations[e]	Consistent	Direct	None	Moderate	0.5% (0.1, 1.8)		
	GZR/EBR	6	163	Serious limitations[c]	Consistent	Direct	Incomplete reporting	Low	0.6% (0.1, 4.2)		
	PrO±D	13	406	Some limitations[e]	Consistent	Direct	None	Moderate	0.2% (0.03, 1.7)		
	SOF	2	63	Serious limitations[f]	Consistent	Direct	Imprecise	Very Low	0% (0, 11.5)		
	SOF/DCV	4	112	Serious limitations[c]	Consistent	Direct	Imprecise	Very Low	0% (0, 6.8)		
	SOF/LDV	6	208	No limitations	Consistent	Direct	Some imprecision	Moderate	0% (0, 3.7)		
	SOF/SIM	1	12	No limitations	N/A	Direct	Sparse	Very Low	0% (0, 43)		
	SOF/VEL	6	408	No limitations	Consistent	Direct	None	High	0% (0, 1.9)		
Discontinued because of AE	DCV/ASV	9	341	No limitations	Consistent	Direct	None	High	3.8% (2.0, 6.0)	Rare. Mostly because of minor AE. No evidence of differences among regimens.	High
	GLE/PIB	8	352	Some limitations[e]	Consistent	Direct	None	Moderate	1.6% (0.6, 3.1)		
	GZR/EBR	6	166	Serious limitations[c]	Consistent	Direct	Incomplete reporting	Low	2.5% (0.7, 5.4)		
	PrO ± D	14	446	Some limitations[e]	Consistent	Direct	None	Moderate	1.8% (0.8, 3.3)		
	SOF	3	123	No limitations	Consistent	Direct	Imprecise	Very Low	0% (0, 6.2)		
	SOF/DCV	8	247	No limitations	Consistent	Direct	None	High	0.4% (0.1, 2.8)		
	SOF/LDV	7	220	No limitations	Consistent	Direct	Some imprecision	Low	0% (0, 3.5)		
	SOF/SIM	1	12	No limitations	N/A	Direct	Sparse	Very Low	0% (0, 43)		
	SOF/VEL	6	407	Serious limitations[f]	Consistent	Direct	Some imprecision	Low	0% (0, 3.2)		

AE, adverse events; ASV, asunaprevir; DAA, direct-acting antivirals; DCV, daclatasvir; EBR, elbasvir; GLE, glecaprevir; Gt, genotype; GZR, grazoprevir; HCV, hepatitis C virus; LDV, ledipasvir; N/A, not applicable; PIB, pibrentasvir; PrO ± D, paritaprevir/ritonavir/ombitasvir ± dasabuvir; SIM, simeprevir; SOF, sofosbuvir; SVR12, sustained virologic response at 12 weeks after end of treatment; VEL, velpatasvir.

[a]Notation of inclusion of ribavirin omitted from this table. The outcome quality of life had sparse evidence from 2 studies providing very low quality of evidence for GLE/PIB and SOF/DCV; it is omitted from this table.

[b]Single groups, mostly retrospective.

[c]Reporting bias (many studies did not report outcome).

[d]Per protocol, analyses with missing data, and/or unclear analyses.

[e]Reporting bias (larger study did not report outcome).

[f]Reporting bias (study with majority of patients did not report outcome).

Balance of potential benefits and harms: DAAs yield very high rates of SVR12 with low rates of discontinuation because of adverse events or serious adverse events attributable to DAAs. Some regimens may have poorer SVR12, but there are no randomized or other comparisons of DAA regimens in comparable patients.

Quality of overall evidence: high (for DAAs in general).

respectively. There is very low quality of evidence that SOF/SIM achieves an SVR12 of only about 83%.

SAEs ascribed to DAAs were uncommon, with high quality of evidence for SOF/VEL (0%); moderate quality of evidence for DCV/ASV (0.4%), GLE/PIB (0.5%), PrO±D (0.2%), and SOF/LDV (0%); low quality of evidence for GZR/EBR (0.6%); and very low quality of evidence for SOF, SOF/DCV, and SOF/SIM. Quality of evidence was downgraded primarily because of reporting bias and imprecision. Across 16 studies that evaluated SOF-based regimens and reported SAEs, none were reported in 803 hemodialysis patients (full-dose SOF in 628 patients). Rates of discontinuation because of adverse events were variable across studies and DAA regimens. We found high quality of evidence for DCV/ASV (3.8%) and SOF/DCV (0.4%); moderate quality of evidence for GLE/PIB (1.6%) and PrO±D (1.8%); low quality of evidence for GZR/EBR (2.5%), SOF/LDV (0%), and SOF/VEL (0%); and very low quality of evidence for SOF and SOF/SIM.

KTRs

We found 29 studies pertaining to KTRs.[29,30,99-125] The studies evaluated the following: GLE/PIB (1 study, $N = 20$), GZR/EBR (2 studies, $N = 21$), PrO ± D (2 studies, $N = 33$), SOF (6 studies, $N = 117$), SOF/DCV (7 studies, $N = 351$), SOF/LDV (9 studies, $N = 300$), and SOF/VEL (1 study, $N = 10$). Three retrospective, unadjusted studies also compared a variety of DAA regimens ($N = 86$), mostly SOF/LDV or SOF/DCV, to no DAA treatment ($N = 63$).[122-124] Conclusions about DAA treatment in KTRs are summarized in Table 3.

Based on the 3 studies comparing various DAA regimens to no treatment, there is low quality of evidence of a reduced risk of death across about 2 to 5 years of follow-up with DAA treatment (unadjusted OR, 0.16; 95% CI, 0.04–0.61). This may be an overestimate of the effect of DAA because patients who chose, or were chosen, to forgo DAA treatment may have been at higher underlying risk of death. There is low quality of evidence from 3 studies of low risk of allograft loss with SOF/LDV treatment (1.2%; 95% CI, 0.2–8.0), primarily evaluated at 12 weeks after end of therapy, but sparse evidence for other DAA regimens.

There is high quality of evidence that SOF/DCV and SOF/LDV achieve SVR12 of about 99.7% and 97.3%, respectively; and moderate quality of evidence that SOF achieves an SVR12 of about 95%. There is very low quality of evidence that GLE/PIB, GZR/EBR, PrO ± D, and SOF/VEL achieve SVR12 of about 100%.

SAEs ascribed to DAAs were uncommon but were incompletely reported across studies. Therefore, there is low quality of evidence regarding SOF/LDV (2.6%; 95% CI, 0.7–5.7), but very low quality of evidence for other DAA regimens. Across all SOF-based regimens, 5 of 437 (almost all on full-dose SOF) patients had SAEs (1.1%; 95% CI, 0.5–2.7). Similarly, treatment discontinuation because of adverse events were uncommon, but incompletely reported. There is moderate quality of evidence that approximately 1.7% (95% CI 0.4–3.7) of patients on SOF/LDV discontinued because of adverse events. There is very low quality of evidence for other DAA regimens and for other outcomes, primarily because of imprecision (Table 3).

DISCUSSION

DAA treatment has revolutionized the management of HCV in CKD populations.[126,127] Our systematic review found high SVR12 rates and low adverse event rates in patients with CKD G4–G5ND, patients undergoing dialysis, and KTRs for nearly all combinations of DAAs. Although, there were no direct comparisons of different DAA regimens within studies, SVR12 and adverse events were very similar across regimens; this includes pangenotypic regimens and regimens that undergo hepatic clearance and, with the addition of SOF-based regimens, renal clearance. Our review has enabled updated guidance from KDIGO regarding appropriate management of CKD patients with HCV infection.[2] Based on the strength of evidence for each DAA regimen, the 2022 KDIGO guidelines provide recommended treatments for each CKD stage.

Importantly, we found no evidence of higher rates of adverse events with SOF-based therapy despite theoretical concerns. This finding is of particular importance because for many lower and middle-income countries, SOF-based therapies are the only available DAA regimens. Additionally, the safety and efficacy of SOF in patients with CKD stages G4–G5ND and those on dialysis provides a treatment option for patients with cirrhosis.[20] Previously, patients with advanced CKD and cirrhosis had limited treatment options because of concerns about toxicity with GLE/PIB and GZR/EBR in patients with decompensated cirrhosis.

For KTRs with eGFR >30 ml/min per 1.73 m^2, efficacy and safety of evaluated DAA regimens remained high. Nevertheless, drug-drug interactions between DAA and immunosuppressive agents remain an important concern with both calcineurin inhibitors and mammalian target of rapamycin inhibitors. GZR/EBR generally should be avoided in combination with cyclosporine because of increased levels of both DAAs.[128] Close monitoring of tacrolimus levels with GZR/EBR is required because of a 40% increase in tacrolimus levels.[128] Useful resources that summarize potential drug-drug interactions can be found in the American Association for the Study of Liver Disease

Table 3. Evidence profile regarding DAA treatment in kidney transplant recipients

								Summary of findings		
Outcome	Regimen[a]	No. of studies[b]	Total N of patients on treatment	Methodological quality of studies	Consistency across studies	Directness of the evidence	Other considerations	Quality of evidence for outcome	Description of findings	Importance of outcome
Death, long-term	Any specific regimen	0							ND	Critical
	DAA vs. no DAA	3	86 vs. 63	Serious limitations[c]	Consistent	Direct	None	Low	Unadj OR 0.16 (0.04, 0.61)	Death rates may be much lower with DAA treatment than without.
Allograft loss	DCV/ASV	0							ND	Critical
	GLE/PIB	1	20	No limitations	N/A	Direct	Sparse	Very Low	0% (0, 30)	Allograft loss rates low (≤1%) but very sparse, imprecise estimates. Reporting bias may be inflating estimates, but follow-up duration mostly short (SVR12 or end of treatment). No evidence of differences among regimens. Allograft loss rate with DAA vs. no DAA unclear.
	GZR/EBR	1	11	No limitations	N/A	Direct	Sparse	Very Low	0.1% (1.3, 44)	
	PrO±D	0							ND	
	SOF	1	10	Serious limitations[d]	N/A	Direct	Sparse	Very Low	0% (0, 48)	
	SOF/DCV	2	141	Serious limitations[e]	Consistent	Direct	Imprecise	Very Low	0% (0, 5.4)	
	SOF/LDV	3	84	Serious limitations[d]	Consistent	Direct	None	Low	1.2% (0.2, 8.0)	
	SOF/SIM	0							ND	
	SOF/VEL	0							ND	
	DAA vs. no DAA	3	86 vs. 63	Serious limitations[c]	Consistent	Direct	Imprecise	Very Low	Unadj OR 0.50 (0.09, 2.73)	
SVR12	DCV/ASV	0							ND	High
	GLE/PIB	1	20	No limitations	N/A	Direct	Sparse	Very Low	100% (70, 100)	Very high SVR12 for evaluated treatments. Mostly 100%. No evidence of differences among regimens.
	GZR/EBR	2	21	No limitations	N/A	Direct	Imprecise	Very Low	100% (71, 100)	
	PrO±D	2	33	No limitations	Consistent	Direct	Imprecise	Very Low	100% (80, 100)	
	SOF	6	117	No limitations	Consistent	Direct	Imprecise	Moderate	94.8% (88.2, 98.8)	
	SOF/DCV	6	290	No limitations	Consistent	Direct	None	High	99.7% (97.6, 100)	
	SOF/LDV	10	300	No limitations	Consistent	Direct	None	High	97.3 (94.9, 99.0)	
	SOF/SIM	0							ND	
	SOF/VEL	1	10	No limitations	Consistent	Direct	Sparse	Very Low	100% (52, 100)	
Serious AE because of DAA	DCV/ASV	0							ND	High
	GLE/PIB	0							ND	Rare. No evidence of differences among regimens.
	GZR/EBR	2	21	No limitations	N/A	Direct	Sparse	Very Low	0% (0, 29)	
	PrO±D	2	33	No limitations	Consistent	Direct	Imprecise	Very Low	0% (0, 20)	
	SOF	4	91	Serious limitations[e]	Consistent	Direct	Imprecise	Very Low	2.9% (0.5, 7.2)	
	SOF/DCV	5	166	Some limitations[f]	Consistent	Direct	Imprecise	Very Low	0% (0, 4.6)	
	SOF/LDV	5	170	Serious limitations[d]	Consistent	Direct	None	Low	2.6% (0.7, 5.7)	
	SOF/SIM	0							ND	
	SOF/VEL	1	10	No limitations	N/A	Direct	Sparse	Very Low	0% (0, 48)	
Discontinued because of AE	DCV/ASV	0							ND	High
	GLE/PIB	0							ND	Rare. No evidence of differences among regimens.
	GZR/EBR	2	21	No limitations	N/A	Direct	Sparse	Very Low	4.8% (0.7, 27)	
	PrO±D	2	33	No limitations	Consistent	Direct	Imprecise	Very Low	0% (0, 20)	
	SOF	4	91	Serious limitations[e]	Consistent	Direct	Imprecise	Very Low	2.9% (0.5, 7.2)	
	SOF/DCV	5	186	Some limitations[f]	Consistent	Direct	Imprecise	Very Low	0% (0, 4.2)	
	SOF/LDV	7	224	Some limitations[f]	Consistent	Direct	None	Moderate	1.7% (0.4, 3.7)	
	SOF/SIM	0							ND	
	SOF/VEL	1	10	No limitations	N/A	Direct	Sparse	Very Low	0% (0, 48)	

ASV, asunaprevir; DAA, direct-acting antiviral; DCV, daclatasvir; EBR, elbasvir; GLE, glecaprevir; Gt, genotype; GZR, grazoprevir; LDV, ledipasvir; N/A, not applicable; ND, no data; PIB, pibrentasvir; PrO ± D, paritaprevir/ritonavir/ombitasvir±dasabuvir; SIM, simeprevir; SOF, sofosbuvir; SVR12, sustained virologic response at 12 weeks posttreatment; Unadj OR, unadjusted odds ratio; VEL, velpatasvir.

[a]Notation of inclusion of ribavirin omitted from this table. The outcome quality of life had sparse evidence from 2 studies providing very low quality of evidence for GLE/PIB and SOF/DCV; it is omitted from this table.

[b]Single groups, mostly retrospective.

[c]No adjustment for potential confounders.

[d]Reporting bias (many studies did not report outcome).

[e]Reporting bias (study with majority of patients did not report outcome).

[f]Reporting bias (larger study did not report outcome).

and Infectious Diseases Society of America joint guidelines (https://www.hcvguidelines.org) and at the University of Liverpool Hepatitis Drug Interactions website (http://www.hep-druginteractions.org).

Insufficient data exist on the role of DAA in KTRs with eGFR<30 ml/min per 1.73 m^2 because this population has not been extensively studied. However, data can be extrapolated from reports of donor-positive to recipient-negative (D+/R−) kidney transplantation with early DAA therapy. These patients initially have low eGFR and although they represent a very specialized population with short-lived HCV infection, viral, allograft as well as clinical and safety outcomes of DAA are excellent.[129]

The safety and efficacy of DAA across all CKD populations has transformed the field from selection of specific DAA regimen to optimal timing of therapy for the benefit of individual patients. Most patients with CKD will likely derive renal, hepatic, quality of life, and other clinical benefits from HCV treatment.[130,131] Patients with CKD G4–G5 likely benefit from a hepatic standpoint and may experience a small delay in time to progression to kidney failure, as has been observed in earlier stages of CKD[132]; although, there is scant evidence about the effect of DAA regimens on progression to kidney failure. For patients who are eligible for kidney transplantation, the timing of treatment should be individualized to provide the maximum benefit with the consideration of factors such as prevalence of HCV in deceased donor populations, national and transplant center policies about the use of HCV-infected donors, patient preferences, societal costs, and availability of DAA regimens. There is no downside to pretransplant treatment from the patient's perspective because they would still be eligible to receive a kidney from an HCV-positive donor. Although this scenario would incur a societal cost of requiring 2 treatment courses of DAA in the same individual (pretransplant treatment and then posttransplant treatment), this situation would be rare. Effective treatment of patients undergoing dialysis, regardless of their plans for transplantation, is available and has potential benefits ranging from eradication of HCV from the dialysis center[133,134] to potentially benefiting the patient because HCV treatment has been associated with lower risk of cardiovascular disease and with increased quality of life in the general population.[130,135] However, currently, there is scant evidence about the benefits of DAAs on long-term or patient-centered outcomes in the CKD population.

We have arrived at a new era of HCV management in CKD with highly effective and safe treatment for all CKD populations. Although questions of clinical benefit beyond viral eradication in patients with CKD remain unanswered, with declining costs of treatment and the known hepatic, renal, and other end-organ complications of ongoing viral replication, DAA treatment of patients with CKD appears to be a potentially important aspect of care of patients with CKD.

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AUTHOR CONTRIBUTIONS

Conception and design: CEG, EMB, MJ, PM; Data acquisition: CEG, EMB, GPA; Data analysis: EMB; Data interpretation: CEG, EMB, GPA, MJ, PM; EMB; Study supervision and mentorship: CEG, EMB, MJ, PM. Each author contributed important intellectual content during manuscript drafting or revision and gave final approval of the version to be submitted.

SUPPLEMENTARY MATERIAL

Supplementary File (Word)

Medline Literature Search (via PubMed)

Summary Table 1.1: DAAs in CKD G4-G5ND (non-dialysis) patients, part 1 (SVR12 and adverse events)

Summary Table 1.2: DAAs in CKD G4-G5 (non-dialysis) patients, part 2 (kidney outcomes)

Summary Table 2.1: DAAs in CKD G5D (dialysis) population, part 1 (SVR12 and adverse events)

Summary Table 2.2: DAAs in CKD G5D (dialysis) population, part 2 (Death)

Summary Table 2.3: DAAs in CKD G5D (dialysis) population, part 3 (Quality of Life)

Summary Table 3.1: DAAs in kidney transplant recipients, part 1 (SVR12 and adverse events)

Summary Table 3.2: DAAs in kidney transplant recipients, part 2 (allograft outcomes and death)
Summary Table 3.3: DAAs in kidney transplant recipients, part 3 (eGFR and proteinuria)
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