Pan-genotypic direct-acting antivirals for patients with hepatitis C virus infection and chronic kidney disease stage 4 or 5

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Abstract
Hepatitis C virus (HCV) infection is a major health problem with significant clinical and economic burdens in patients with chronic kidney disease (CKD) stage 4 or 5. Current guidelines recommend pan-genotypic direct-acting antivirals (DAAs) to be the first-line treatment of choice for HCV. This review summarizes the updated knowledge regarding the epidemiology, natural history, public health perspectives of HCV in patients with CKD stage 4 or 5, including those on maintenance dialysis, and the performance of pan-genotypic DAAs in these patients. The prevalence and incidence of HCV are much higher in patients with CKD stage 4 or 5 than in the general population. The prognosis is compromised if HCV patients are left untreated regardless of kidney transplantation (KT). Following treatment-induced HCV eradication, patient can improve the health-related outcomes by maintaining a long-term aviremic state. The sustained virologic response (SVR12) rates and safety profiles of pan-genotypic DAAs against HCV are excellent irrespective of KT. No dose adjustment of pan-genotypic DAAs is required across CKD stages. Assessing drug–drug interactions (DDIs) before HCV treatment is vital to secure on-treatment safety. The use of prophylactic or preemptive pan-genotypic DAAs in HCV-negative recipients who receive HCV-positive kidneys has shown promise in shortening KT waiting time, achieving excellent on-treatment efficacy and safety, and maintaining post-KT patient and graft survival. HCV elimination is highly feasible through multifaceted interventions, including mass screening, treatment scale-up, universal precautions, and post-SVR12 reinfection surveillance.

Keywords Hepatitis C virus · Chronic kidney disease · End-stage kidney disease · Dialysis · Direct-acting antiviral · Pan-genotypic · Glecaprevir · Pibrentasvir · Sofosbuvir · Velpatasvir · Voxilaprevir

Abbreviations
HCV Hepatitis C virus
CKD Chronic kidney disease
DAA Direct-acting antiviral
KT Kidney transplantation
SVR Sustained virologic response
HCC Hepatocellular carcinoma
IFN Interferon
RBV Ribavirin
GLE Glecaprevir
PIB Pibrentasvir
SOF Sofosbuvir
VEL Velpatasvir
VOX Voxilaprevir
RNA Ribonucleic acid
MPGH Membranoproliferative glomerulonephritis
MGN Membranous glomerulonephritis
IR Insulin resistance
DM Diabetes mellitus
ALT Alanine transaminase
ESKD End-stage kidney disease
GT Genotype
DDI Drug–drug interaction

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Introduction

Hepatitis C virus (HCV) infection is a global health problem that leads to cirrhosis, hepatic decompensation, and hepatocellular carcinoma (HCC) [1]. In addition to causing liver events, HCV can manifest with renal glomerulopathies and tubulointerstitial damages that contribute to a high prevalence of chronic kidney disease (CKD) [2]. Nonetheless, the risk of HCV infection tends to increase in patients with kidney failure who are on kidney replacement therapy because this blood-borne virus can be transmitted through parenteral routes. Due to poor tolerance and low antiviral responses, treatment uptake for HCV in patients with CKD stage 4 or 5 is limited in the interferon (IFN) era. Although genotype-specific direct-acting antivirals (DAAs) significantly improve HCV care, the limited antiviral spectrum, modest tolerance, and the need for ribavirin (RBV) in specific populations preclude the widespread use of these agents. Three pan-genotypic DAA regimens, including glecaprevir/pibrentasvir (GLE/PIB), sofosbuvir/velpatasvir (SOF/VEL), and sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX), have led to a paradigm shift of HCV care for the excellent efficacy and safety, broad antiviral spectrum, ease of use, and the approval to retreat patients with DAA failures.

Based on the rapidly growing knowledge of DAA treatment, this review will summarize the epidemiology and natural history, updated reports in clinical trials and real-world studies of pan-genotypic DAAs, and the path moving toward HCV elimination in patients with CKD stage 4 or 5.

Epidemiology

Since the identification of HCV in 1989, the serum anti-HCV and HCV ribonucleic acid (RNA) have been detected in a significant proportion of patients with kidney failure. While the global prevalence of HCV infection of 1.0% in the general population from the POLARIS survey in 2015, the prevalence of HCV infection in patients on hemodialysis was 9.9% between 2012 and 2015 in the Dialysis Outcome and Practice Pattern Study (DOPPS) [3, 4]. Among patients on hemodialysis, the prevalence ranges from 4% in Belgium to as high as 20% in the Middle East, with intermediate prevalence in China, Japan, Italy, Spain, and Russia. Although the annual incidence of HCV infection in patients on hemodialysis has decreased from 2.9% to 1.2% from 1996 to 2015, it remains much higher than the global incidence of 23.7 per 100,000 in the general population, which continues to be a significant public health threat in this special clinical setting [4–6].

Compared to the general population, the higher incidence and prevalence rates of HCV infection in patients with CKD stage 4 or 5 can be attributed to several factors. First, HCV is associated with various immune-mediated glomerular and tubulointerstitial damages, such as cryoglobulinemic nephropathy, membranoproliferative glomerulonephritis (MPGN), or membranous glomerulonephritis (MGN) [7–9]. In addition, HCV is associated with insulin resistance (IR), diabetes mellitus (DM), and cardiomyopathies that indirectly compromise kidney reserves [10]. Second, the risk of HCV transmission increases in patients with kidney failure receiving kidney replacement therapy. This is particularly relevant to patients on maintenance hemodialysis because inadequate hand washing or changing gloves before and after patient care by staff and the use of shared injection medications (heparin) in hemodialysis units increase the risk of nosocomial HCV transmission. Several global surveys have shown a higher prevalence rate of HCV infection among patients on hemodialysis than among patients on peritoneal dialysis [11–14]. Apart from the mechanistic relationship, many epidemiologic studies have confirmed a strong link between HCV and CKD [15–20].

Natural history

The natural history of HCV infection in patients with CKD stage 4 or 5 remains elusive because the course of HCV infection is usually indolent over decades. Following acute HCV infection, 65.4–92.0% of patients on maintenance dialysis develop chronic infection if left untreated [21–23]. Most infected patients are asymptomatic, and have serum alanine transaminase (ALT) levels below the reference limit for subjects without advanced kidney diseases, making the early diagnosis and the precise duration of HCV infection difficult to be identified [24–26]. Furthermore, it is also challenging to assess the long-term consequences of HCV infection because most patients with CKD stage 4 or 5 have complex comorbidities. Based on liver histologic analyses, current evidence indicates that the course of HCV infection is less aggressive in patients on hemodialysis than in non-uremic patients [27, 28]. While HCV viremia is unequivocally associated with progressive kidney damage, studies on the effects of HCV genotypes on the development of CKD or end-stage kidney disease (ESKD) remain controversial [29–31]. The REVEAL-HCV studies indicated that patients with HCV genotype (GT) 1 infection tended to develop ESKD. In
contrast, patients with HCV GT2 infection were associated with a higher risk of CKD stage 2 or more.

Mortality is a firm outcome of the natural history of HCV infection. Two meta-analyses conducted in 2007 and 2012 showed that the adjusted risk ratios of mortality were 1.37 and 1.35 in dialysis patients with HCV infection than those without HCV infection [32, 33]. Liver-related, infection-related and cardiovascular diseases mainly contributed to the higher mortality risk in dialysis patients with HCV infection. The DOPPS cohort study, which included 76,698 hemodialysis patients from 1996 to 2015, further corroborated the findings of meta-analysis studies showing a higher cumulative risk of death (adjusted hazard ratio: 1.12) due to more frequent in-hospital hepatic, infectious, and cardiovascular events in patients with HCV infection [34]. Moreover, the physical and mental health, and the kidney disease-related quality of life significantly compromised in hemodialysis patients with HCV infection [34]. With regard to HCC, two studies revealed that the incidence and prevalence of HCC were 0.2% and 2.0% in dialysis patients with HCV infection, respectively [35, 36].

While dialysis patients with active HCV infection who undergo kidney transplantation (KT) have survival advantages over those who are on maintenance dialysis, current evidence reveals that the patient and graft survival in KT recipients with active HCV infection are worse than that in KT recipients without HCV infection [37–39].

Based on the anticipated adverse clinical outcomes if HCV is left untreated in patients with CKD stage 4 or 5 regardless of KT, the prognosis following successful viral eradication in this vulnerable population is intriguing to healthcare providers. To date, several small-scaled studies have shown a survival benefit in patients with ESKD who received IFN-based treatment for HCV, compared to those who did not receive treatment [40–42]. However, none provided information about the effects of treatment-induced sustained virologic response (SVR) on patient survival, which is particularly important in the era of direct-acting antivirals (DAAs). Apart from survival, studies have shown that treatment-induced SVR can improve quality of life and hepatic inflammation/fibrosis in patients on hemodialysis [43, 44]. Concerning KT, current evidence also supports patient and graft survival benefits once HCV is cleared by antiviral agents [45].

Treatment overview

Prior to the advent of DAA, interferon (IFN)-based treatment was the standard of care for HCV in patients with CKD stage 4 or 5. Because the SVR rate and on-treatment tolerance were suboptimal, only 1.5% of patients with CKD stage 4 or 5 received IFN alfa-2a or alfa-2b treatment for HCV between 1996 and 2015 [40, 46–48]. Although IFN-free DAAs have revolutionized the HCV management by substantially improving the SVR rate and tolerance, current guidelines recommend pan-genotypic DAAs to be the prioritized treatment of choice based on their broad antiviral spectrum [49–52]. However, the healthcare providers should have knowledge of pan-genotypic DAA metabolism and drug–drug interactions (DDIs) with co-medication in patients with CKD stage 4 or 5.

Metabolism of pan-genotypic DAAs in patients with CKD stage 4 or 5

The pan-genotypic NS3/4A protease inhibitors (GLE and VOX), and NS5A inhibitors (PIB and VEL) undergo hepatic metabolism and are eliminated mainly through biliary excretion. Only a minority of these drugs (usually accounting for approximately 1.0%) are excreted through the kidneys [53]. Pharmacokinetic studies reveal that the maximal drug concentrations (Cmax) and the areas under the curve (AUCs) of GLE/PIB, VEL, and VOX in patients with CKD stage 4 or 5 regardless of maintenance dialysis are similar to patients with CKD stages 1–3 [54–56]. Therefore, there is no need to adjust the DAA dose in patients with CKD stage 4 or 5.

SOF is a nucleoside NS5B RNA-dependent RNA polymerase inhibitor for HCV. After intrahepatic phosphorylation of the monophosphate prodrug to the active triphosphate form (GS–461203), SOF acts as RNA chain terminator by inhibiting NS5B RNA-dependent RNA polymerase. Dephosphorylation of GS–461203 results in forming an inactive metabolite (GS–331007) that undergoes extensive renal excretion [57]. While administrating a single full-dose of SOF revealed slightly higher plasma SOF AUCs in patients with CKD stage 4 (2.73-fold) and CKD stage 5 (1.33-fold) than those in patients with an estimated glomerular filtration rate (eGFR) > 80 mL/min/1.73m², the plasma AUCs of GS–331007 were 5.56-fold and 6.83-fold higher in patients with CKD stages 4 and 5 than those with normal kidney reserve [56]. Based on the potential safety concerns, a dose recommendation of SOF cannot be made for patients with CKD stage 4 or 5. However, a multi-dose pharmacokinetic study with SOF at a dose of 400 mg per day or 400 mg trice weekly for 12–24 weeks in patients on hemodialysis revealed that the plasma GS–330017 concentration by a cumulative duration of treatment was similar to a single-dose treatment. Following the last dose of SOF, the plasma GS–331007 terminal half-life (T1/2) was about 38 h, which meant that patients on hemodialysis had only a 7-day delay of GS–331007 clearance compared to patients with normal kidney function [58, 59]. Furthermore, the clinical and biological tolerance was good for all patients. These encouraging results support the feasibility of multiple full-dose SOF administration in HCV patients with CKD stage 4 or 5.
Drug–drug interactions (DDIs)

Because the proportion of comorbidities in HCV patients with CKD stage 4 or 5 is high irrespective of KT, they are expected to have complex co-medication profiles. It is of particular importance before DAA treatment because the potential DDIs between DAAs and concomitant medications may significantly affect plasma drug levels by induction or inhibition of metabolic enzymes, or substrate competition, resulting in insufficient therapeutic effects or increased drug-related adverse events (AEs). Studies have indicated that the number of co-medication among dialysis patients with HCV was much higher than the general HCV individuals (6.0 versus 3.2) [60, 61]. The proportions of patients with red category (do not co-administered) and orange category (potential interaction) who received the same DAA regimen tended to be higher in patients on hemodialysis than in the general population, emphasizing the need of precarious DDI checks in patients with CKD stage 4 or 5. Table 1 shows the DDI categories between pan-genotypic DAAs and common co-medication in patients with CKD stage 4 or 5 according to the HEP Drug Interactions as proposed by the University of Liverpool [62].

Regarding antiviral agents against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), remdesivir and nirmatrelvir/ritonavir are not recommended for patients with CKD stage 4 or 5. If physicians judge to treat SARS-CoV-2 infection with nirmatrelvir/ritonavir in patients with CKD stage 4 or 5, GLE/PIB should not be co-administered because ritonavir, an organic anion transport protein 1B (OATP1B) inhibitor, may substantially increase the GLE concentration and lead to alanine transaminase (ALT) elevation. Molnupiravir can be used to treat SARS-CoV-2 infection in patients with CKD stage 4 or 5 without expected DDIs with pan-genotypic DAAs (Table 1) [63].

Pan-genotypic DAAs for HCV in patients with CKD stage 4 or 5

Glecaprevir/pibrentasvir (GLE/PIB)

The EXPEDITION-4 study was a phase III, open-label trial to assess the clinical performance of GLE/PIB for 12 weeks in 104 HCV patients with CKD stage 4 or 5. The SVR12 rates were 98% and 100% by intention-to-treat (ITT) modified ITT (mITT) analyses. Two participants failed to achieve SVR12 because of early discontinuation and loss of follow-up. The antiviral responses were not affected by CKD stage, pretreatment NS3 or NS5A resistant-associated substitutions (RASs), or type of kidney replacement therapy. Most patients tolerated GLE/PIB well, but 20% complained pruritus [64]. The EXPEDITION-5 study further explored the performance of GLE/PIB for 8 to 16 weeks according to the current label recommendations in 101 patients with CKD stages 3b-5 [65]. The SVR12 rates by ITT and mITT analyses were 97% and 100%, respectively (Table 2).

The SVR12 rates of GLE/PIB for HCV in real-world patients with CKD stage 4 or 5 ranged from 93 to 100%, comparable to the SVR12 rates in EXPEDITION-4 and EXPEDITION-5 trials (Table 2) [66–71]. The safety profiles were excellent, with low rates of treatment discontinuation and total bilirubin/ALT elevations. Approximately 3.0% to 62.8% of patients reported on-treatment pruritus, although the severity was mild in most patients with treatment discontinuation rate of 0% to 3.7%. The use of GLE/PIB did not adversely affect eGFR in patients with CKD stage 4 or 5 who were not on kidney replacement therapy [65, 67, 70].

Sofosbuvir/velpatasvir (SOF/VEL)

Borgia et al. conducted a phase II trial to treat 59 HCV patients on hemodialysis or peritoneal dialysis with full-dose SOF/VEL for 12 weeks [72]. The SVR12 rates by ITT and mITT analyses were 95% and 97%, respectively (Table 3). Two patients relapsed after treatment, including one HCV GT3 cirrhotic patient and the other HCV GT1b non-cirrhotic patient who had poor drug adherence. One patient committed suicide at off-treatment week 4 when the serum HCV RNA level remained undetectable. The tolerance was excellent, and no treatment discontinued due to AEs.

In real-world studies, the SVR12 rates of full-dose SOF/VEL in patients with CKD stage 4 or 5 and compensated liver diseases ranged from 90 to 97% and were comparable to the report in phase II trial (Table 3) [73–76]. Among patients with decompensated cirrhosis, the SVR12 rate by full-dose SOF/VEL combined with low-dose RBV for 12 weeks was 90%, implying that the antiviral responses remained excellent despite the presence of concomitant kidney and liver failures [73]. The overall tolerance was excellent, and the risks of total bilirubin/ALT elevations were low. Furthermore, the eGFR remained stable during full-dose SOF in CKD stage 4 or 5 patients not on maintenance dialysis, indicating that the renal safety of full-dose SOF/VEL remained excellent under poor kidney reserve [73, 77]. Recently, a meta-analysis reported an overall SVR12 rate of 98% in patients with CKD stage 5 on kidney replacement therapy receiving SOF/VEL for 12 weeks (Table 3) [78].

Full-dose SOF/VEL has been approved in Canada, Australia, South Korea, and Taiwan to treat HCV in patients with CKD stage 4 or 5 based on the updated evidence from clinical trials and real-world studies. Although SOF/VEL is not contraindicated for patients with CKD stage 4 or 5, no dose recommendation for SOF/VEL can be made by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for these patients. Furthermore, the EMA states that SOF/VEL can be used with no
Table 1  Drug–drug interactions (DDIs) between pan-genotypic DAAs and common co-medication in HCV patients with CKD stage 4 or 5

| Classification       | GLE/PIB | SOF/VEL | SOF/VEL/VOX |
|----------------------|---------|---------|-------------|
| **Anti-arrhythmics** |         |         |             |
| Amiodarone           |         |         |             |
| Dronedarone          |         |         |             |
| Digoxin              |         |         |             |
| Flecaïnide           |         |         |             |
| Propafenone          |         |         |             |
| Quinidine            |         |         |             |
| **Anti-platelets**   |         |         |             |
| Clopidogrel          |         |         |             |
| Prasugrel            |         |         |             |
| Ticagrelor           |         |         |             |
| **Anticoagulants**   |         |         |             |
| Dabigatran           |         |         |             |
| Edoxaban             |         |         |             |
| Rivaroxaban          |         |         |             |
| Warfarin             |         |         |             |
| Heparin              |         |         |             |
| **Lipid lowering agents** |         |         |             |
| Atorvastatin         |         |         |             |
| Fluvastatin          |         |         |             |
| Lovastatin           |         |         |             |
| Pitavastatin         |         |         |             |
| Pravastatin          |         |         |             |
| Rosuvastatin         |         |         |             |
| Simvastatin          |         |         |             |
| Ezetimibe            |         |         |             |
| Bezenafibrate        |         |         |             |
| Fenofibrate          |         |         |             |
| **Anti-hypertensives** |       |         |             |
| Doxazocin            |         |         |             |
| Bumetanide           |         |         |             |
| Furosemide           |         |         |             |
| Spironolactone       |         |         |             |
| Bisoprolol           |         |         |             |
| Carvedilol           |         |         |             |
| Metoprolol           |         |         |             |
| Nebivolol            |         |         |             |
|                      | Amlodipine | Felodipine | Nifedipine | Lercanidipine | Diatiazem | Verapamil | Candesartan | Irbesartan | Losartan | Olmesartan | Valsartan | Captopril | Enalapril |
|----------------------|------------|------------|------------|---------------|-----------|-----------|-------------|------------|-----------|------------|-----------|-----------|-----------|
| **Anti-diabetics**   |            |            |            |               |           |           |             |            |           |            |           |           |           |
| Glimepiride          |            |            |            |               |           |           |             |            |           |            |           |           |           |
| Rapaglinide          |            |            |            |               |           |           |             |            |           |            |           |           |           |
| Metformin            |            |            |            |               |           |           |             |            |           |            |           |           |           |
| Acarbose             |            |            |            |               |           |           |             |            |           |            |           |           |           |
| Pioglitazone         |            |            |            |               |           |           |             |            |           |            |           |           |           |
| Linagliptin          |            |            |            |               |           |           |             |            |           |            |           |           |           |
| Saxagliptin          |            |            |            |               |           |           |             |            |           |            |           |           |           |
| Sitagliptin          |            |            |            |               |           |           |             |            |           |            |           |           |           |
| Vildagliptin         |            |            |            |               |           |           |             |            |           |            |           |           |           |
| Canaglifozin         |            |            |            |               |           |           |             |            |           |            |           |           |           |
| Dapaglifozin         |            |            |            |               |           |           |             |            |           |            |           |           |           |
| Empaglifozin         |            |            |            |               |           |           |             |            |           |            |           |           |           |
| Liraglutide          |            |            |            |               |           |           |             |            |           |            |           |           |           |
| Dulaglutide          |            |            |            |               |           |           |             |            |           |            |           |           |           |
| Lixisenatide         |            |            |            |               |           |           |             |            |           |            |           |           |           |
| Exenatide            |            |            |            |               |           |           |             |            |           |            |           |           |           |
| Insulin              |            |            |            |               |           |           |             |            |           |            |           |           |           |
| **Anticonvulsants**  |            |            |            |               |           |           |             |            |           |            |           |           |           |
| Carbamazepine        |            |            |            |               |           |           |             |            |           |            |           |           |           |
| Eslicarbazepine      |            |            |            |               |           |           |             |            |           |            |           |           |           |
| Oxcarbazepine        |            |            |            |               |           |           |             |            |           |            |           |           |           |
| Phenobarbital        |            |            |            |               |           |           |             |            |           |            |           |           |           |
| Phenytoin            |            |            |            |               |           |           |             |            |           |            |           |           |           |
| Primidone            |            |            |            |               |           |           |             |            |           |            |           |           |           |
| **Anxiolytics**      |            |            |            |               |           |           |             |            |           |            |           |           |           |
| Alprazolam           |            |            |            |               |           |           |             |            |           |            |           |           |           |
| Drug Name      | 1 | 2 | 3 | 4 | 5 |
|---------------|---|---|---|---|---|
| Diazepam      |   |   |   |   |   |
| Estazolam     |   |   |   |   |   |
| Lorazepam     |   |   |   |   |   |
| Midazolam     |   |   |   |   |   |
| Oxazepam      |   |   |   |   |   |
| Zolpidem      |   |   |   |   |   |
| Zopiclone     |   |   |   |   |   |
| **Gastrointestinal agents** | | | | | |
| Esomeprazole  |   |   |   |   |   |
| Lansoprazole  |   |   |   |   |   |
| Omeprazole    |   |   |   |   |   |
| Pantoprazole  |   |   |   |   |   |
| Rabeprazole   |   |   |   |   |   |
| Famotidine    |   |   |   |   |   |
| Ranitidine    |   |   |   |   |   |
| Bisacodyl     |   |   |   |   |   |
| Domperidone   |   |   |   |   |   |
| Metoclopramide|   |   |   |   |   |
| Loperamide    |   |   |   |   |   |
| Simethicone   |   |   |   |   |   |
| **Herbal medicine** | | | | | |
| St John’s wort|   |   |   |   |   |
| Silymarin     |   |   |   |   |   |
| Ginkgo biloba |   |   |   |   |   |
| **Immunosuppressants** | | | | | |
| Azathioprine  |   |   |   |   |   |
| Cyclosporine  |   |   |   |   |   |
| Etanercept    |   |   |   |   |   |
| Mycophenolate |   |   |   |   |   |
| Sirolimus     |   |   |   |   |   |
| Tacrolimus    |   |   |   |   |   |
| Everolimus    |   |   |   |   |   |
| Rituximab     |   |   |   |   |   |
| Prednisone    |   |   |   |   |   |
| Methylprednisolone |   |   |   |   |   |
| Dexamethasone |   |   |   |   |   |
| Budesonide    |   |   |   |   |   |
| **Cancer therapy** | | | | | |
| Cisplatin     |   |   |   |   |   |
| Doxorubicin   |   |   |   |   |   |
dose adjustment when no other relevant treatment options are available for patients with CKD stage 4 or 5.

**Sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX)**

There are no clinical trials or real-world studies reporting the clinical performance of SOF/VEL/VOX in HCV patients with CKD stage 4 or 5.

**Risk of mortality with pan-genotypic DAA treatment**

Although the overall safety profiles of GLE/PIB and SOF/VEL for HCV are excellent in patients with CKD stage 4 or 5, several studies reported that the risk of mortality was 3.3% to 6.7% in patients with compensated liver disease and 10.0% in patients with decompensated liver disease during an about 6-month study interval (Tables 2 and 3) [70, 72–74]. While the higher mortality rate in patients with CKD stage 4 or 5 receiving GLE/PIB or SOF/VEL may raise concerns about the causal relationship between DAAs and deaths, the annual mortality rate in DOPPS is 13.95% in hemodialysis patients with or without HCV, which suggests that treatment with GLE/PIB or SOF/VEL is not associated with increased patient mortality [34].

**Pan-genotypic DAAs for HCV in patients with CKD stage 4 or 5 following KT**

The MAGELLAN-2 study was a phase III, open-label study to assess the efficacy and safety of GLE/PIB for 12 weeks in 20 kidney transplant recipients with chronic HCV infection. All participants completed the assigned treatment and achieved SVR12 [79]. No clinical trials to assess the efficacy and safety of SOF/VEL or SOF/VEL/VOX have been published till now in HCV patients following KT.

Data regarding the pan-genotypic DAAs in real-world studies are scarce. Greco et al. reported the outcomes of 10 patients with HCV after KT who received SOF/VEL for 12 weeks. All completed 12 weeks of treatment and achieved SVR12. There was no significant renal toxicity during treatment [80].

**HCV-negative recipients from HCV-positive kidney donors**

Kidneys from HCV-infected donors are exclusively transplanted into HCV-infected recipients in the era of IFN because most recipients poorly tolerate to IFN and the SVR12 rates are low. In addition, persistent post-KT HCV viremia accelerates the liver and kidney disease, and shortens the
## Table 2  Summary of efficacy/effectiveness and tolerance of glecaprevir/pibrentasvir in HCV patients with CKD stage 4 or 5

| Study/author | CKD stage | Regimen | Duration (week) | Genotype | Hepatic fibrosis | Patient No | SVR12 (ITT) (%)a | SVR12 (mITT) (%)b | Tolerance |
|--------------|-----------|---------|----------------|----------|------------------|------------|-----------------|------------------|-----------|
| **Clinical trial** | | | | | | | | | |
| Expedition-4 [64] | 4, 5 | GLE/PIB | 12 | 1–6 | F0-F4 | 104 | 98 | 100 | Death: 1% AE leading to drug discontinuation: 4% (pruritus: 1%) Serious AE: 24% Pruritus: 20% AST or ALT > 3 times ULN: 0% Total bilirubin > 3 times ULN: 1% |
| Expedition-5 [65] | 3b, 4, 5 | GLE/PIB | 8–16 | 1–4 | F0-F4 | 101 | 98 | 100 | Death: 0% AE leading to drug discontinuation: 2% (pruritus: 1%) Serious AE: 12% Pruritus: 16% AST or ALT > 5 times ULN: 0% Total bilirubin > 3 times ULN: 0% |
| **Real-world study** | | | | | | | | | |
| Liu et al. [66] | 4 | GLE/PIB | 8–12 | 1,2,3,6 | F0-F4 | 32 | 100 | 100 | Death: 0% AE leading to drug discontinuation: 0% Serious AE: 12.5% Pruritus: 18.8% ALT ≥ 3 times ULN: 0% Total bilirubin ≥ 3 times ULN: 0% |
| | 5 | GLE/PIB | 8–12 | 1,2,6 | F0-F4 | 76 | 99 | 100 | Death: 0% AE leading to drug discontinuation: 3% (skin eruption/pruritus: 1%) Serious AE: 15.8% Pruritus: 19.7% ALT ≥ 3 times ULN: 0% Total bilirubin ≥ 3 times ULN: 0% |
| Atsukawa, et al. [67] | 4 | GLE/PIB | 8–12 | 1–3 | F0-F4 | 32 | 100 | 100 | Death: 0% AE leading to drug discontinuation: 6.3% (pruritus: 0%) Serious AE: 0% Pruritus: 21.9% AST or ALT > 1–3 times ULN: 3.1% Total bilirubin > ULN: 0% |
patient and graft survival. However, the rapid increase of deceased donors due to the opioid epidemic and the availability of potent and safe DAAs after 2014 have challenged the conventional rules of organ allocation. Transplanting HCV-infected kidneys into uninfected recipients, followed by DAA treatment, is conceptually feasible and may enhance the organ procurement in patients with kidney failures by shorting the waiting time for KT [81].

**Table 2** (continued)

| Study/author | CKD stage | Regimen | Duration (week) | Genotype | Hepatic fibrosis | Patient No | SVR12 (ITT) (%)a | SVR12 (mITT) (%)b | Tolerance |
|--------------|-----------|---------|-----------------|----------|------------------|------------|-------------------|-------------------|-----------|
| Yen et al. [68] 5 GLE/PIB 8–12 1–3 F0-F4 109 99 100 Death: 0% AE leading to drug discontinuation: 0.9% (pruritus: 0.9%) Serious AE: 0% Pruritus: 33.0% AST or ALT > 1–3 times ULN: 0% Total bilirubin > ULN: 0% |
| Suda et al. [69] 5 GLE/PIB 8 2 F0-F3 13 100 100 Death: 0% AE leading to drug discontinuation: 7.4% (pruritus: 3.7%) Serious AE: 3.7% ALT > ULN: 0% Total bilirubin > 3 times ULN: 2.3% |
| Yap et al. [70] 4, 5 GLE/PIB 12 2, 3, 6 F4 20 90 100 Death: 5% AE leading to drug discontinuation: 4% (pruritus: 0%) Serious AE: 20% |
| Stein et al. [71] 4, 5 GLE/PIB 8–16 1–4 F0-F4 33 94 100 AE leading to drug discontinuation: 0% Pruritus: 3.0% AST or ALT > 3 times ULN: 0% Total bilirubin > 1.5 times ULN: 3.2% |

*CKD* chronic kidney disease, *SVR* sustained virologic response, *ITT* intention-to-treat, *mITT* modified intention-to-treat, *GLE/PIB* glecaprevir/pibrentasvir, *AE* adverse event, *AST* aspartate transaminase, *ALT* alanine transaminase, *ULN* upper limit of normal

*a Patients who received at least one dose of treatment were included in the analysis

*b Patients with non-virologic failures were excluded from the analysis
Because HCV viremia occurs in almost all recipients who receive kidneys from viremic donors, DAA can be initiated before KT (prophylactic therapy) or days to weeks after confirmation of viremia following KT (preemptive therapy). A total of 40 HCV-negative KT recipients in three proof-of-concept trials who received prophylactic or preemptive

**Table 3** Summary of efficacy/effectiveness and tolerance of sofosbuvir/velpatasvir in HCV patients with CKD stage 4 or 5

| Study/author       | CKD stage | Regimen       | Duration (week) | Genotype | Hepatic fibrosis | Patient No | SVR12 (ITT) (%)\(^a\) | SVR12 (mITT) (%)\(^b\) | Tolerance                                      |
|--------------------|-----------|---------------|-----------------|----------|------------------|------------|------------------------|------------------------|------------------------------------------------|
| Clinical trial     |           |               |                 |          |                  |            |                        |                        |                                                |
| Borgia et al. [72] | 5         | SOF/VEL       | 12              | 1,2,3,4,6 | F0-F4            | 59         | 95                     | 97                     | Death: 3% AE leading to drug discontinuation: 0% Serious AE: 19% |
| Liu et al. [73]    | 4, 5      | SOF/VEL       | 12              | 1,2,3,6  | F0-F4            | 181        | 95                     | 100                    | Death: 3.3% AE leading to drug discontinuation: 0.6% Serious AE: 9.9% ALT > 3 times ULN: 0.6% Total bilirubin > 1.5 times ULN: 2.2% |
|                    | 4, 5      | SOF/VEL + RBV | 12              | 1,2,6    | F4 (Child B or C) | 10         | 90                     | 100                    | Death: 6.7% AE leading to drug discontinuation: 9.5% Serious AE: 42.9% |
| Yu et al. [74]     | 5         | SOF/VEL       | 12              | 1,2,6    | F0-4             | 105        | 90                     | 96                     | Death: 0% AE leading to drug discontinuation: 0% |
| Gaur et al. [75]   | 5         | SOF/VEL       | 12              | 1,3      | F0-4             | 31         | 97                     | 97                     | Death: 0% AE leading to drug discontinuation: 0% |
| Taneja et al. [76] | 5         | SOF/VEL       | 12              | 1,3,4    | F0-4             | 51         | 96                     | 96                     | Death: 0% AE leading to drug discontinuation: 0% Serious AE: 0% |
| Real-world study   |           |               |                 |          |                  |            |                        |                        |                                                |
| Liu et al. [73]    | 4, 5      | SOF/VEL       | 12              | 1,2,3,6  | F0-F4            | 181        | 95                     | 100                    | Death: 3.3% AE leading to drug discontinuation: 0.6% Serious AE: 9.9% ALT > 3 times ULN: 0.6% Total bilirubin > 1.5 times ULN: 2.2% |
| Yu et al. [74]     | 5         | SOF/VEL       | 12              | 1,2,6    | F0-4             | 105        | 90                     | 96                     | Death: 6.7% AE leading to drug discontinuation: 9.5% Serious AE: 42.9% |
| Gaur et al. [75]   | 5         | SOF/VEL       | 12              | 1,3      | F0-4             | 31         | 97                     | 97                     | Death: 0% AE leading to drug discontinuation: 0% |
| Taneja et al. [76] | 5         | SOF/VEL       | 12              | 1,3,4    | F0-4             | 51         | 96                     | 96                     | Death: 0% AE leading to drug discontinuation: 0% Serious AE: 0% |
| Meta-analysis      |           |               |                 |          |                  |            |                        |                        |                                                |
| De et al. [78]     | 5         | SOF/VEL ± RBV | 12              | 1–6      | 7                | 410        | 98                     |                        | Publication year: 2019–2021 Additional findings: NA |

**CKD** chronic kidney disease. **SVR** sustained virologic response, **ITT** intention-to-treat, **mITT** modified intention-to-treat, **SOF/VEL** sofosbuvir/velpatasvir, **RBV** ribavirin, **AE** adverse event, **ALT** alanine transaminase, **ULN** upper limit of normal, **NA** not assessed

\(^a\)Patients who received at least one dose of treatment were included in the analysis

\(^b\)Patients with non-virologic failures were excluded from the analysis
### Table 4: Summary of efficacy/effectiveness and tolerance of pan-genotypic DAAs in HCV-negative recipient from HCV-positive kidney donors

| Study/author | Regimen | Duration (week) | Genotype | DAA Strategy | Donor type | Patient No | SVR12 (ITT) (%)<sup>a</sup> | SVR12 (mITT) (%)<sup>b</sup> | Tolerance |
|--------------|---------|-----------------|----------|--------------|------------|-------------|----------------------------|----------------------------|-----------|
| **Clinical trial** | | | | | | | | | |
| Mythic [85] | GLE/PIB | 8 | 1,2,4 | Preemptive | Deceased | 30 | 100 | 100 | Serious AE: 21 events <br> DAA-related serious AE: 0% <br> Acute cellular rejection: 10% |
| Rehanna [86] | GLE/PIB | 4 | 1,3 | Prophylactic | Deceased | 10 | 100 | 100 | AE leading to drug discontinuation: 0% <br> ≥ grade 3 treatment-related AE: 0% <br> Total bilirubin or AST/ALT ≥ 2.5 times ULN: 0% <br> Graft survival: 90% <br> Acute cellular rejection: 0% |
| Feld et al. [87] | GLE/PIB + ezetimibe | 1 | 1–3 | Prophylactic | NA | 10 | 100 | 100 | AE leading to drug discontinuation: 0% <br> Serious AE: 10% <br> Graft survival: 100% <br> Acute cellular rejection: 0% |
| Terrault. et al. [93] | SOF/VEL | 12 | NA | Preemptive | Deceased | 11 | 100 | 100 | Serious AE: 45% <br> DAA-related serious AE: 0% <br> Graft survival: 100% |
| Dapper [94] | SOF/VEL | 2–4 days | 1–3 | Prophylactic | Deceased | 50 | 88 | 88 | Patient survival: 98% <br> Graft survival: 98% <br> Acute cellular rejection: 4% <br> Transient ALT elevation: 4% |
| Reform HEPC [95] | SOF/VEL | 8 days | NA | Prophylactic | Deceased | 32 | 97 | 97 | Patient survival: 100% <br> Graft survival: 98% |
| | SOF/VEL + ezetimibe | | | | | 18 | 94 | 94 | |
| **Real-world study** | | | | | | | | | |
| Molnar et al. [88] | GLE/PIB | 12 | 1–3 | Median 76 days after KT | NA | 59 | 100 | 100 | Graft survival: 100% |
| Kapila, et al. [89] | GLE/PIB | 12–16 | 1–4 | NA | NA | 33 | 97 | 97 | Graft survival: 100% |
| Graham et al. [90] | GLE/PIB | 12 | 1–4 | Preemptive | Deceased | 29 | 100 | 100 | Patient survival: 100% <br> Graft survival: 100% <br> Acute cellular rejection: 7% |
Glecaprevir/pibrentasvir (GLE/PIB)

The MYTHIC trial recruited 30 HCV-negative recipients who received HCV-positive kidneys, followed by preemptive GLE/PIB for 8 weeks [85]. All recipients achieved SVR12, and no DAA-related serious AEs were reported. The REHANNA trial explored the feasibility of prophylactic GLE/PIB for 4 weeks in 10 kidney recipients. The SVR12 was 100%, and none discontinued GLE/PIB due to treatment-emergent AEs [86]. Feld et al. further shortened the treatment duration of prophylactic GLE/PIB to one week in combination with ezetimibe, a cholesterol absorption inhibitor that is active against HCV viral entry, in 10 participants. All achieved SVR12, and the tolerance was excellent (Table 4) [87].

Five real-world studies have reported the effectiveness and safety of preemptive GLE/PIB for 12 weeks in 172 HCV-negative recipients who received HCV-positive kidneys. In line with the reports in clinical trials, the SVR12 rates ranged from 97 to 100%, and the graft survival was excellent after GLE/PIB treatment (Table 4) [88–92].

Sofosbuvir/velpatasvir (SOF/VEL)

Terrault et al. conducted a multicenter study in the U.S. to treat 11 HCV-negative recipients from HCV-positive kidneys with preemptive SOF/VEL for 12 weeks. All recipients achieved SVR12, and none had DAA-related serious AEs [93]. The DAPPeR trial treated 50 participants with an ultra-short duration of prophylactic SOF/VEL for 2–4 days [94]. Three (12%) failed to clear HCV following KT. Because the SVR12 rate in the DAPPeR trial was suboptimal, the investigators conducted the REFORM HEPC trial by extending the prophylactic SOF/VEL to 8 days with or without ezetimibe combination in 50 participants. The SVR12 rates increased to 94% and 97% in participants receiving SOF/VEL with and without ezetimibe combination [95]. Patient tolerance was excellent in both trials (Table 4).

Six real-world studies to date have been reported in 44 patients receiving preemptive SOF/VEL for 12 weeks. All patients achieved SVR12, and the tolerance was also excellent (Table 4) [88–92, 96].

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**Table 4** (continued)

| Study/author | Regimen | Duration (week) | Genotype | DAA Strategy | Donor type | Patient No | SVR12 (ITT) (%) | SVR12 (mITT) (%) | Tolerance |
|--------------|---------|-----------------|----------|--------------|------------|------------|-----------------|-----------------|-----------|
| Jandovitz et al. [91] | GLE/PIB | 12 | 1,3 | Preemptive | Deceased | 3 | 100 | 100 | NA |
| | SOF/VEL | 12 | 1,3 | Preemptive | | 8 | 100 | 100 | |
| | SOF/VEL/VOX | 12 | 1a | - | | 1 | 100 | 100 | |
| Torabi et al. [92] | GLE/PIB | 12 | 1–4 | Preemptive | NA | 48d | 100 | 100 | Total bilirubin > 3 times ULN: 2% ALT > 3 times ULN: 17% Graft survival: 96% Acute cellular rejection: 6% |
| | SOF/VEL | 12 | 1–4 | Preemptive | | 100 | 100 | |
| | SOF/VEL/VOX | | | | | 100 | 100 | |
| Chen et al. [96] | SOF/VEL | 12 | 1–3 | Prophylactic | NA | 26 | 100 | 100 | AE leading to drug discontinuation: 0% Acute cellular rejection: 8% |
| Reform HEPC [95] | SOF/VEL/VOX | 12 | 1a,3 | - | Deceased | 3 | 100 | 100 | NA |

**SVR** sustained virologic response; **ITT** intention-to-treat; **mITT** modified intention-to-treat; **GLE/PIB** glecaprevir/pibrentasvir; **SOF/VEL** sofosbuvir/velpatasvir; **SOF/VEL/VOX** sofosbuvir/velpatasvir/voxilaprevir; **AE** adverse event; **DAA** direct-acting antiviral; **ALT** aspartate transaminase; **AST** alanine transaminase; **ULN** upper limit of normal; **NA** not assessed

*a* Patients who received at least one dose of treatment were included in the analysis

*b* Patients with non-virologic failures were excluded from the analysis

*c* The first dose of GLE/PIB plus ezetimibe was given before transplantation. GLE/PIB plus ezetimibe was continued for one week after transplantation

*d* Thirty-nine of fifty-two patients met criteria for SVR12, and all had achieved SVR12. All the remaining thirteen patients had undetectable HCV RNA at the last follow-up
Table 5  Summary of guideline recommendations for managing HCV in patients with CKD stage 4 or 5

| European Association for the Study of the Liver (EASL) | American Association for the Study of Liver Diseases (AASLD) | Asian Pacific Association for the Study of the Liver (APASL) |
|--------------------------------------------------------|-----------------------------------------------------------|----------------------------------------------------------|
| **Patients with HCV and an eGFR < 30 ml/min/1.73 m², including those on dialysis** | Patients should be treated in expert centers, with close monitoring by a multidisciplinary team  
Patients should be treated for HCV according to the general recommendations, with no need for DAA dose adjustments  
GLE/PIB or EBR/GZR are the preferred choices for HCV  
Patients with Child–Pugh B or C cirrhosis should be treated with SOF/VEL, without RBV for 24 weeks  
The risks and benefits of treating patients with ESKD and an indication for KT before or after KT require individual assessment | Patients can be treated with GLE/PIB, EBR/GZR and SOF-based DAAAs according to the general recommendations  
No dose adjustment in DAAs is required when using the recommended regimens  
The dose of RBV should be reduced according to the label recommendations | Maintenance hemodialysis confers a significant risk of nosocomial infection. Standard precautions must be rigorously observed  
Patients on hemodialysis should be screened with serological tests and RT-PCR at first hemodialysis or when transferring from another hemodialysis unit  
Maintenance hemodialysis patients and KT candidates should be tested for anti-HCV antibodies every 6–12 months, and RT-PCR should be performed for patients with unexplained elevated transaminase(s)  
| **HCV-positive kidney transplant recipients** | Patients should be treated for HCV before or after transplantation  
Before KT, patients on the waiting list can be treated for HCV according to the general recommendations  
After KT, recipients should be treated with the SOF/VEL for 12 weeks without immunosuppressant drug dose adjustments  
After KT, recipients can be treated with GLE/PIB for 12 weeks, but immunosuppressant drug levels need to be monitored and adjusted as needed during and after treatment | Non-DAA experienced GLE/PIB for genotypes 1–6 in compensated liver disease  
SOF/VEL for genotypes 1–6  
SOF/LDV for HCV genotypes 1, 4, 5, and 6 only  
EBR/GZR for HCV genotypes 1 and 4 only, and without baseline EBR RASs (alternative)  
DAA experienced SOF/VEL/VOX± RBV for genotypes 1–6 in compensated liver disease | No specific recommendations were provided  
| **HCV-negative kidney transplant recipients from HCV-positive donors** | No specific recommendations were provided | Informed consent should include:  
Risk of transmission from an HCV-viremic donor  
Risk of liver disease if HCV treatment is not available or treatment is unsuccessful  
Risk of graft failure  
Risk of extrahepatic complications, such as HCV-associated renal disease  
Risk of HCV transmission to partner  
Benefits, specifically reduced waiting time and possibly lower waiting list mortality  
Other unknown long-term consequences (hepatic and extrahepatic) of HCV exposure (even if cure is attained)  
Prophylactic or preemptive treatment with a pan-genotypic DAA regimen GLE/PIB for 8 weeks  
SOF/VEL for 12 weeks | No specific recommendations were provided  

HCV, hepatitis C virus; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; DAA, direct-acting antiviral; GLE/PIB, glecaprevir/pibrentasvir; SOF/VEL, sofosbuvir/velpatasvir; EBR/GZR, elbasvir/grazoprevir; SOF/LDV, sofosbuvir/ledipasvir; SOF/VEL/VOX, sofosbuvir/velpatasvir/voxilaprevir; DCV plus ASV, daclatasvir plus asunaprevir; RBV, ribavirin; KT, kidney transplantation; RAS, resistant-associated substitution; RT-PCR, reverse-transcriptase polymerase chain reaction
Sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX)

Because the antiviral responses with prophylactic or preemptive DAAs are nearly 100%, there have been no clinical trials to evaluate the efficacy and tolerance of SOF/VEL/VOX for HCV-negative recipients who received HCV-positive kidneys. Only five patients who received SOF/VEL/VOX for 12 weeks, of whom three relapsed in DAPPeR and REFORM HEPC trials, were reported in real-world studies, which showed an overall SVR12 rate of 100% (Table 4) [91, 92, 95].

Post-transplantation outcomes

The MYTHIC trial reported the 1-year post-KT outcome of 30 recipients who achieved SVR12 with GLE/PIB. No patients developed HCV-related kidney injury after viral eradication. The patient survival was 93%, and the graft function was excellent following KT [97]. Molnar et al. assessed the 1-year graft outcome in 65 HCV-negative recipients who achieved SVR12 with GLE/PIB, SOF/VEL, or SOF/ledipasvir (SOF/LDV) following KT from HCV-positive kidneys and 59 recipients underwent KT with HCV-negative kidneys [88]. The risks of patient deaths, delayed graft function, and the eGFR evolution were similar between groups. Interestingly, the proportion of graft loss in the HCV-positive kidney donor group was marginally lower than that in the HCV-negative kidney donor group (2% vs. 10%). Furthermore, a simulation model has proved that transplanting HCV-positive kidneys into HCV-negative recipients, followed by pan-genotypic DAAs, is cost-saving and can increase the quality-adjusted life expectancy [98].

HCV elimination in patients with CKD stage 4 or 5

Based on the significant impact on health-related outcomes in HCV-viremic patients, and the availability of potent and safe DAAs against HCV, the World Health Organization (WHO) has set a target of global HCV elimination by 2030. Current guidelines recommend DAA treatment for HCV without delay in patients with CKD stage 4 or 5 regardless of KT, although the statements about the choices of DAAs differ among professional societies (Table 5) [49–52]. Studies on HCV micro-elimination in the hemodialysis population showed promise through outreach services, mass screening, efficient link to care, and treatment scale-up [74, 99]. A long-term survey indicated that HCV reinfection in hemodialysis patients after treatment-induced SVR12 was comparably low to the general population through unrestricted DAAs and universal precautions in hemodialysis units [100]. Another study also indicated that the HCV RNA level remained undetectable in HCV-infected recipients once they achieved SVR12 with DAAs before or after KT [101].

Conclusion

HCV infection is prevalent and continues to be a significant threat for patients with CKD stage 4 or 5. Current evidence indicates that patients with CKD stage 4 or 5 have similar response rates and safety profiles to the general population with pan-genotypic DAAs before or after KT. There is no need for dose adjustment of pan-genotypic DAAs in patients with CKD stage 4 or 5, including those on maintenance dialysis. Regarding HCV-negative patients with CKD stage 4 or 5 who undergo KT with HCV-positive kidneys, the use of prophylactic or preemptive pan-genotypic DAAs can efficiently eradicate HCV after KT. While the performance of GLE/PIB has been well demonstrated by phase III trials and real-world studies in patients with CKD stage 4 or 5 before or after KT, data that assess the efficacy and safety of SOF/VEL and SOF/VEL/VOX from phase III trials or real-world studies are lacking or limited. Regarding the choice of GLE/PIB or SOF/VEL for HCV, the European Association for the Study of the Liver (EASL) prefers GLE/PIB for patients with CKD stage 4 or 5 before KT because evidence supporting the full-dose SOF/VEL in these patients is only modest. Moreover, the EASL highlights the need to monitor blood concentrations of immunosuppressive agents in KT recipients who are treated with GLE/PIB. Because patients with CKD stage 4 or 5 may take a higher number of concomitant medications, careful DDI checks between DAAs and co-medication are important to ensure on-treatment safety. Once SVR12 is achieved with antiviral therapies, most patients have durable long-term virologic remission and improved health-related outcomes. Despite the excellent performance of pan-genotypic DAAs for HCV in patients with CKS stage 4 or 5, continuous efforts on screening, treatment uptake, post-treatment surveillance, and hygiene precautions are needed to accelerate HCV elimination in this special clinical setting.

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