

HEPATITIS WEB STUDY  HEPATITIS C ONLINE

Treatment of Hepatitis C in Patients with Renal Insufficiency

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Robert Gish, MD: Relevant Disclosures To HCV

- **Consulting Board:** Bristol-Myers Squibb, Gilead, Merck & Co., Janssen, Abbvie
- **Honoraria for Promotional Talks:** Bristol-Myers Squibb, Gilead Sciences, Merck & Co., AbbVie, Janssen

Treatment of Hepatitis C in Patients with Renal Insufficiency

- Background and Staging of Renal Disease
- Treatment with Interferon-Based Regimens
- Treatment with Direct-Acting Antiviral Agents
- Hepatitis C and Renal Transplantation
- Summary

TREATMENT OF HCV IN PATIENTS WITH RENAL INSUFFICIENCY

Background and Staging Renal Disease

Hepatitis C Treatment Issues Related to Renal Disease

- **Hepatitis C may be associated with or cause renal disease**
- **Treatment of hepatitis C and renal disease**
 - (1) Treatment in patients with chronic renal insufficiency
 - (2) Treatment to prevent HCV causing renal disease
 - (3) Treatment post renal transplant for renal function and graft survival

Epidemiology of HCV in Patients on Hemodialysis (HD)

- In US, estimated HCV prevalence of 8%
 - (approximately 400,000 persons on HD)
- HCV prevalence 5X greater in HD patients than in general US population
- Risk factors for HCV infection among hemodialysis patients:
 - Number of years on dialysis
 - Number of blood product transfusions
 - Injection drug use
 - History of organ transplantation

Natural History of HCV Infection in Hemodialysis Patients

Impact of Hepatitis C Infection on Hemodialysis Patients:

- Increased overall risk of mortality
- Increased risk of cirrhosis
- Increased incidence of hepatocellular cancer

Hepatitis C and Renal Disease

Hepatitis C as a Cause of Renal Disease

- HCV infection in patients with advanced liver failure increases risk for renal disease
- Chronic HCV infection associated with increased risk for renal cell carcinoma
- Chronic HCV infection accelerated renal disease in HIV-infected patients

Source: (1) Ozkok A, et al. *Gastroenterol.* 2014;20:7544-54.
(2) Gordon SC, et al. *Cancer Epidemiol Biomarkers Prev.* 2010;19:1066-73.
(3) Peters L, et al. *AIDS.* 2012;26:1917-26.

Hepatitis C and Renal Disease

HCV as a Cause of Renal Disease: Immune Complex Disorders

- HCV-associated immune complex disorders that cause renal disease
 - Mixed Cryoglobulinemia: +RF as a screening test; reflex to qualitative or quantitative cryoglobulin (type II cryoglobulins)
 - Glomerulonephritis (Membranoproliferative [MPGN] is the most common)
 - Polyarteritis nodosa
- Uncommon HCV-associated immune complex disorders that cause renal disease
 - Focal segmental glomerular sclerosis
 - Proliferative glomerulonephritis
 - Membranous glomerulonephritis
 - Fibrillary and immunotactoid glomerulopathies

Source: (1) Ozkok A, et al. *Gastroenterol.* 2014;20:7544-54.

(2) Gordon SC, et al. *Cancer Epidemiol Biomarkers Prev.* 2010;19:1066-73.

(3) Peters L, et al. *AIDS.* 2012;26:1917-26.

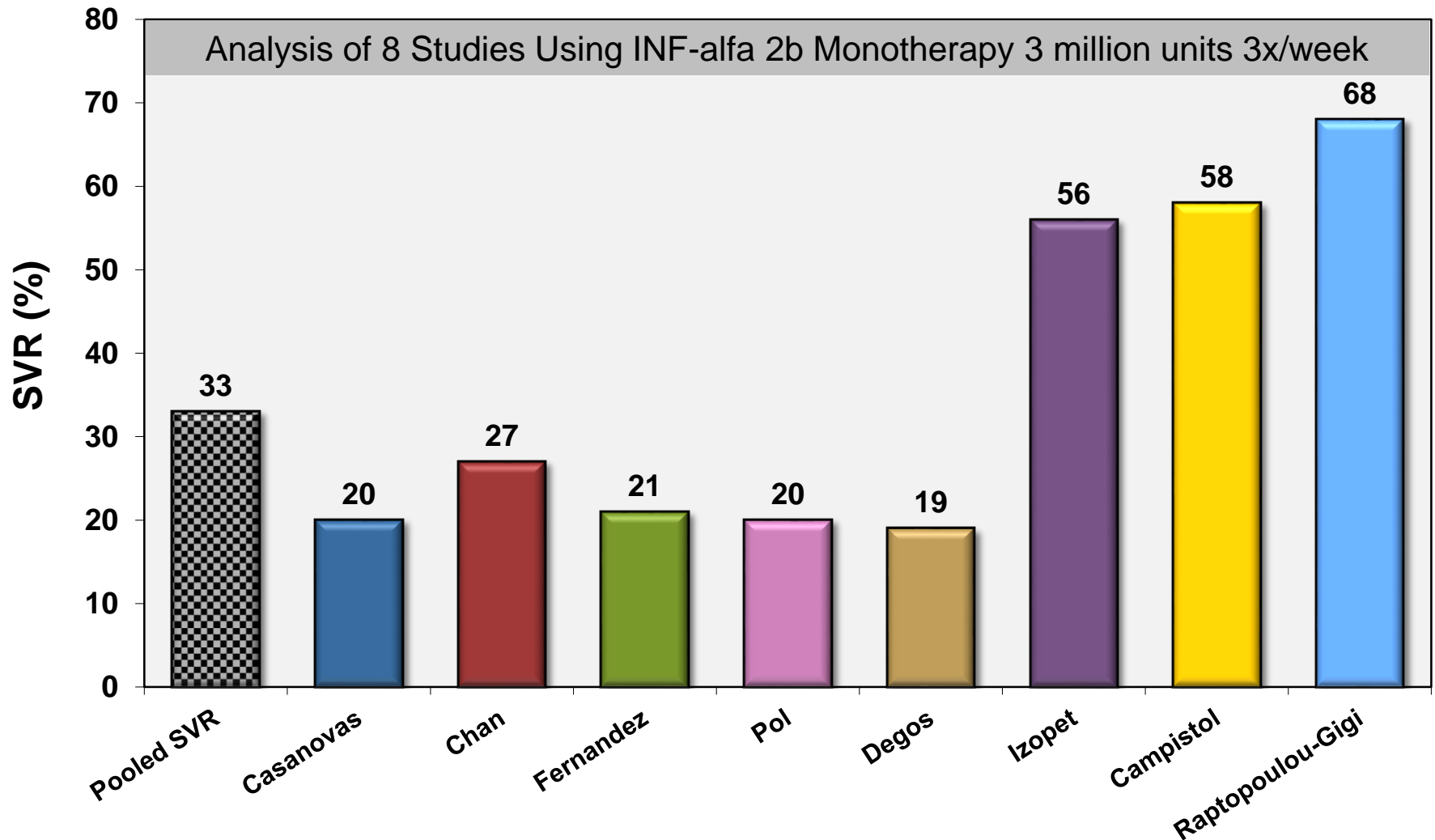
Stages of Chronic Kidney Disease

CKD Stage	Description	GFR (mL/min/1.73 m ²)
1	Kidney Damage with Normal or ↑ GFR	≥90
2	Kidney Damage with Mild ↓ GFR	60-89
3	Moderate ↓ GFR	30-59
4	Severe ↓ GFR	15-29
5	Kidney Failure	<15 (or dialysis)

TREATMENT OF HCV IN PATIENTS WITH RENAL INSUFFICIENCY
Experience with Interferon-Based Therapies

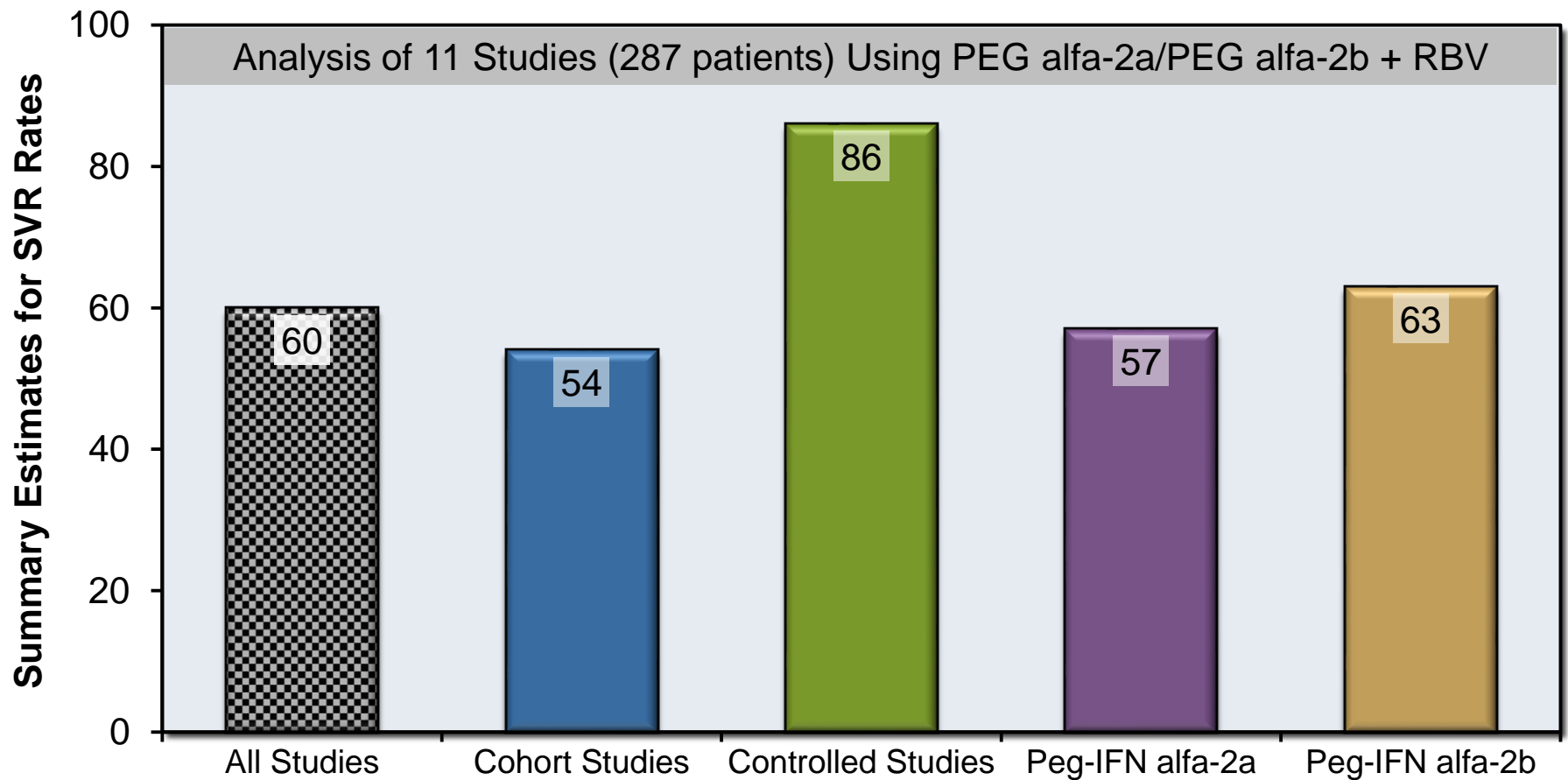
Interferon Monotherapy for HD Patients with Chronic HCV

Analysis of the Literature on Efficacy (SVR)

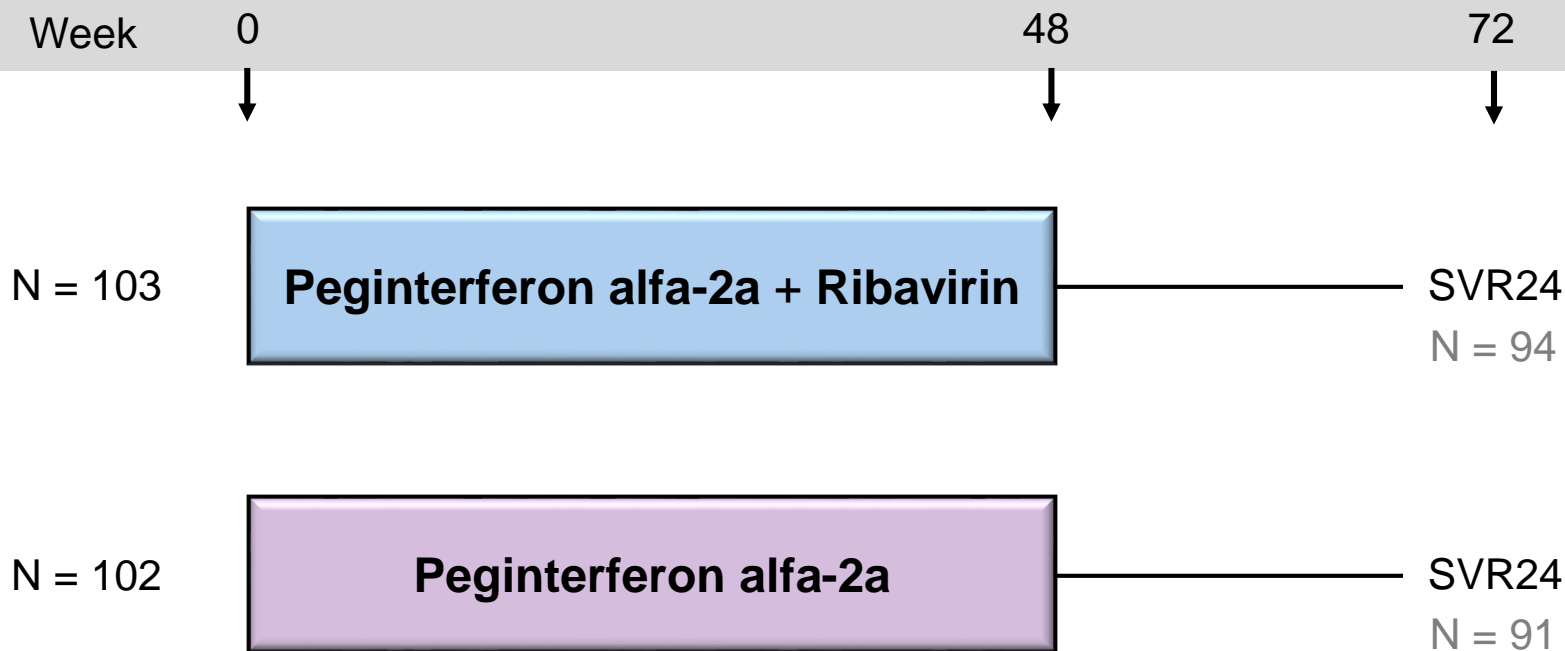


Source: Russo MW, et al. Am J Gastroenterol. 2003;98:1610-5.

Peginterferon + Ribavirin for HCV in Hemodialysis Patients Meta-Analysis of the Literature on Efficacy



PEG-IFN +/- Low-dose RBV (200 mg/day) in HCV GT1 on Hemodialysis HELPER-1 Trial: Study Regimens

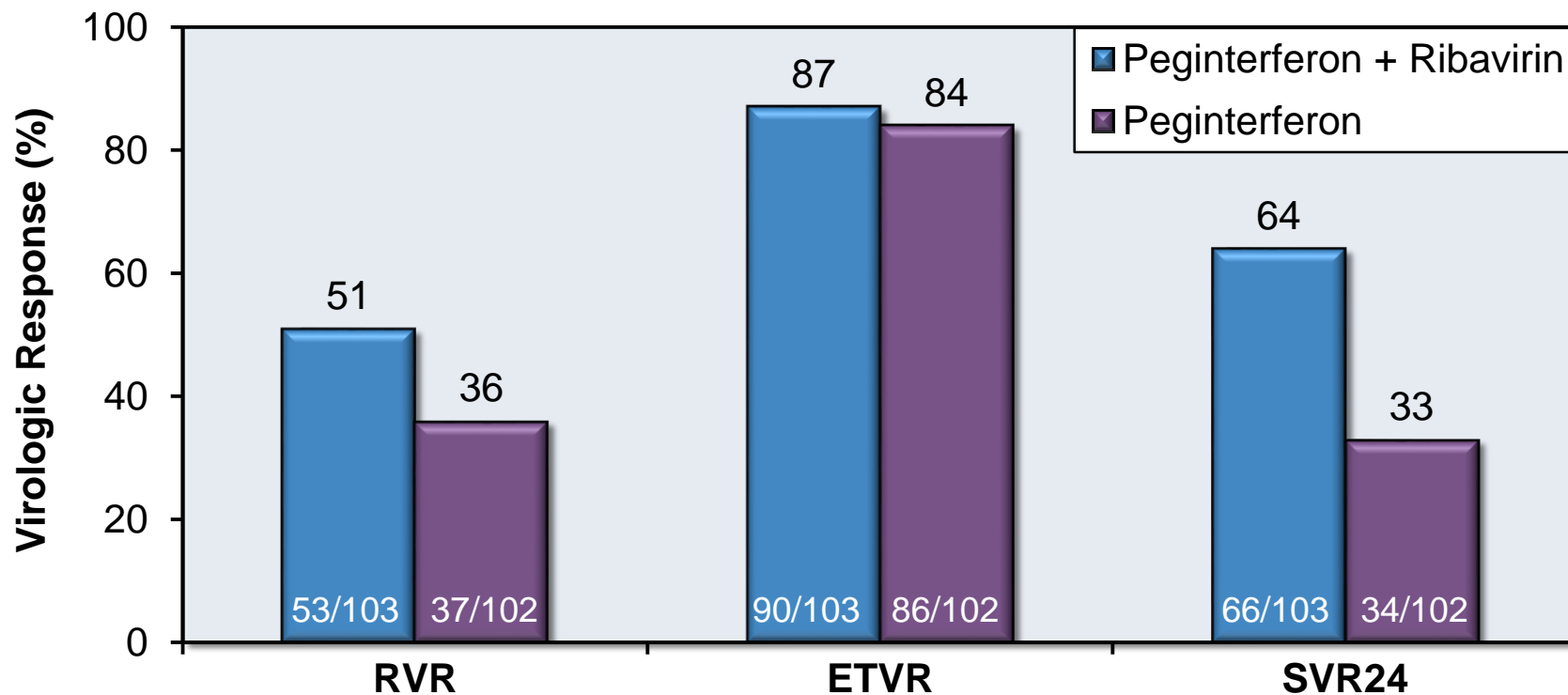


Drug Dosing

Peginterferon alfa-2a 135 µg 1x/week
Low-dose Ribavirin: 200 mg once daily

PEG-IFN +/- Low-dose RBV (200 mg/day) in HCV GT1 on Hemodialysis HELPER-1 Trial: Results

Virologic Responses



Drug Dosing

Peginterferon alfa-2a: 135 µg once weekly

Ribavirin: 200 mg daily

Controversies with Ribavirin Use in Advanced Renal Disease

- **Not recommended with eGFR < 50 ml/min/1.73 m² in:**
 - Package inserts for *Rebetol*, *Ribasphere*
 - KDIGO 2008 guidelines
 - 2009 AASLD guidelines
- **Permitted with eGFR < 50 ml/min/1.73 m² (with dose reduction) in:**
 - Package insert for *CoPegus*
 - 2014 AASLD/IDSA/IAS-USA guidelines

TREATMENT OF HCV IN PATIENTS WITH RENAL INSUFFICIENCY
Experience with Direct-Acting Antiviral Agents

Treatment of Hepatitis C in Patients with Renal Disease

Possible Options using Direct Acting Antiviral Agents

- Sofosbuvir plus Ribavirin
- Simeprevir plus Sofosbuvir
- Ombitasvir-Paritaprevir-Ritonavir plus Dasabuvir (genotype 1)
- Ledipasvir-Sofosbuvir (pangenotypic)
- Sofosbuvir plus Daclatasvir*

*Daclatasvir was not FDA approved in United States as of July 1, 2015

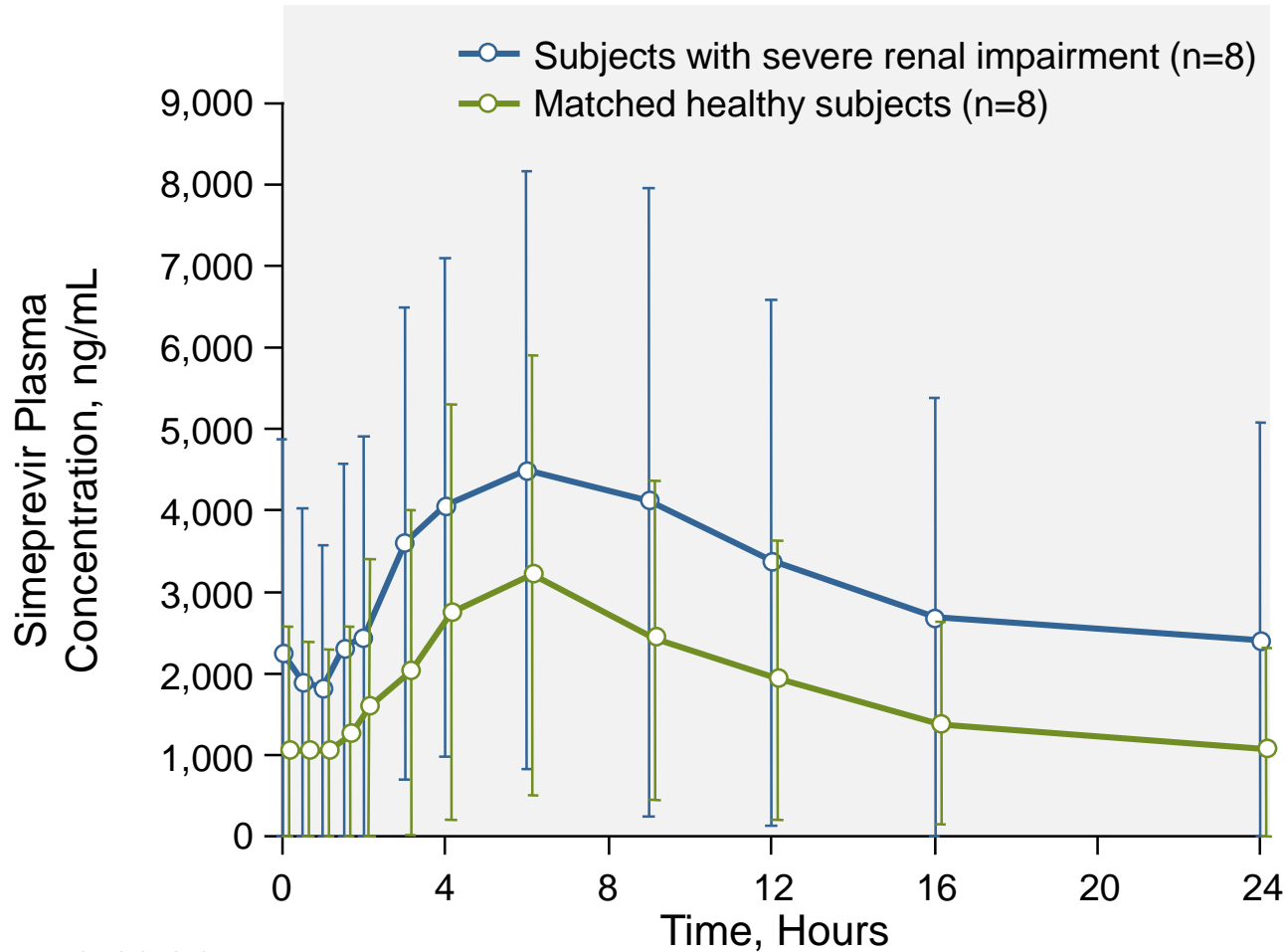
Sofosbuvir Pharmacokinetics HCV-Negative Patients with Renal Impairment

Sofosbuvir Pharmacokinetics in HCV-Negative Patients with Renal Impairment		
Patient Renal Impairment	Sofosbuvir AUC*	GS-3310007 AUC*
<i>Following Single 400 mg dose of sofosbuvir</i>		
eGFR ≥ 50 and < 80 mL/min/1.73 m ²	↑61%	↑55%
eGFR ≥ 30 and < 50 mL/min/1.73 m ²	↑107%	↑88%
eGFR < 30 mL/min/1.73 m ²	↑171%	↑451%
ESRD requiring hemodialysis		
Dosed 1 hour before hemodialysis	↑28%	↑1280%
Dosed 1 hour after hemodialysis	↑60%	↑2070%
*AUC given relative to subjects with normal renal function		

Simeprevir Pharmacokinetics

Severe Renal Impairment versus Healthy Subjects

Linear Mean Plasma Concentration-Time Profiles



Bars represent standard deviation

Source: Janssen Products

Sofosbuvir-Containing Regimens including Patients with Renal Disease

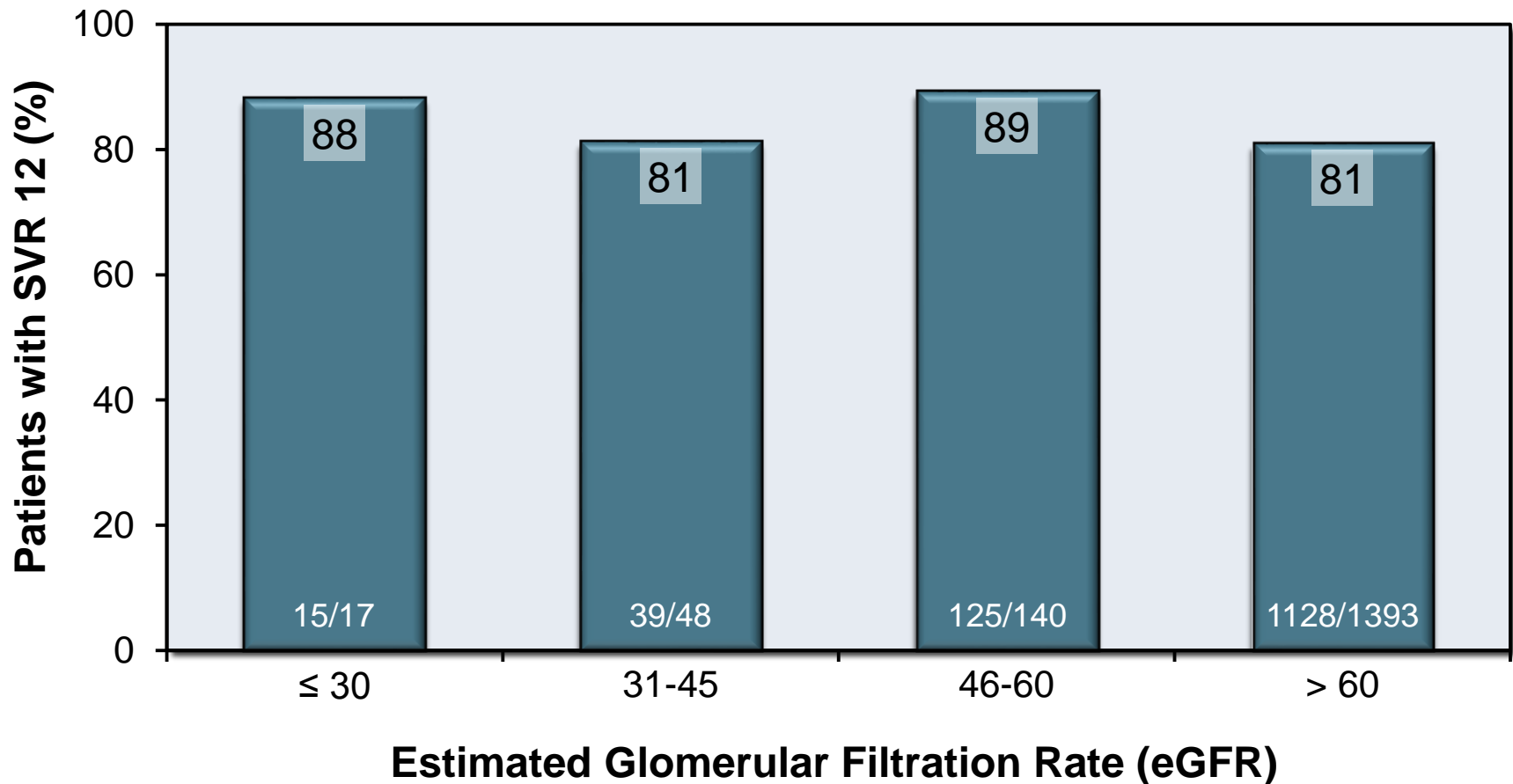
HCV-TARGET Trial: Study Features

HCV-Target and Patients with Renal Disease: Features

- **Design:** Longitudinal, cohort study with sofosbuvir-containing regimens, including patients with renal disease
- **Setting:** 56 centers in US, Germany, and Canada
- **Entry Criteria**
 - Chronic HCV treated with sofosbuvir-containing regimen
 - HCV genotype 1-6
 - Age 18 or older
 - Treatment naïve and treatment experienced
 - Includes patients with baseline renal insufficiency
 - Includes patients with cirrhosis
- **Primary End-Points**
 - Efficacy (SVR12), safety

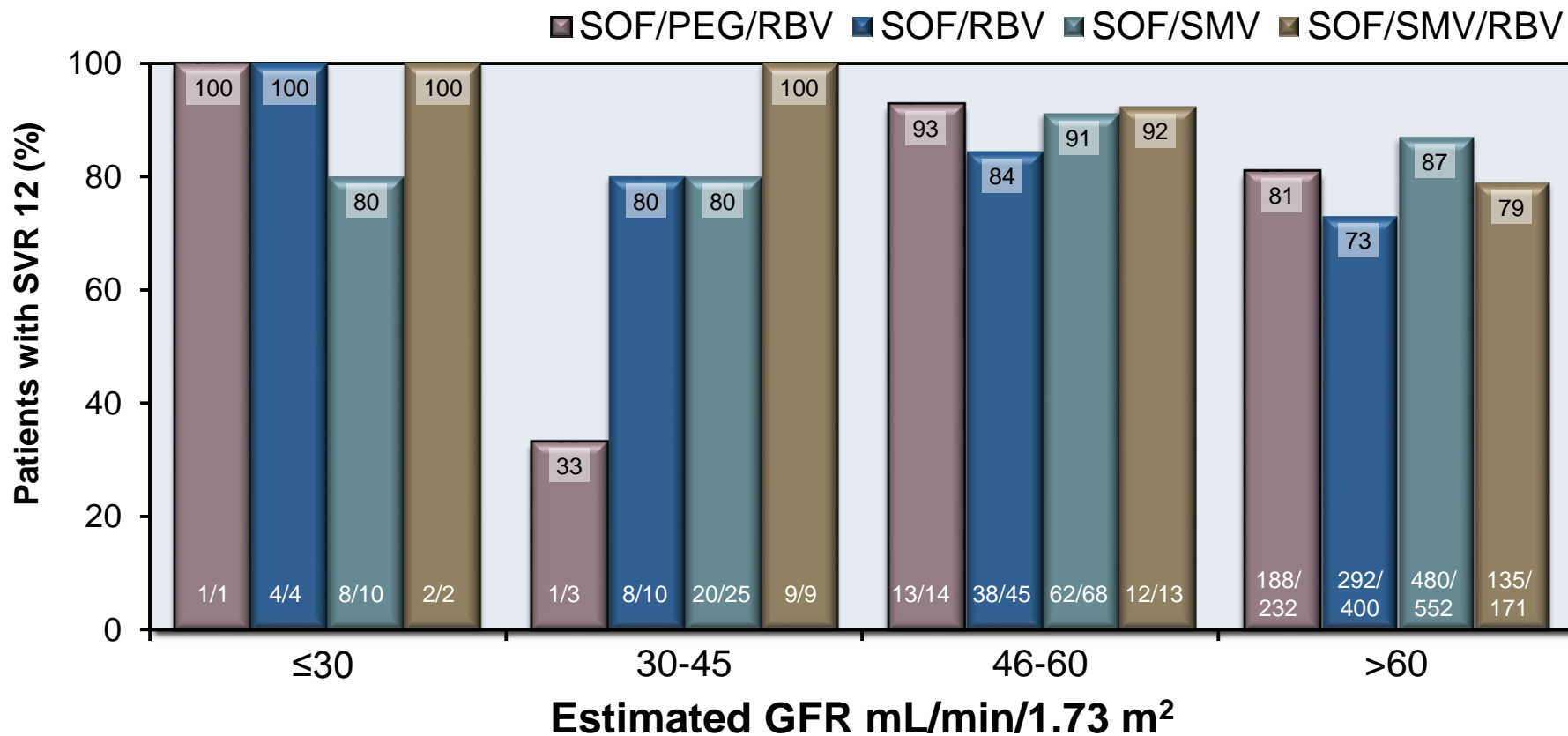
Sofosbuvir-Containing Regimens in Patients with Renal Disease HCV -TARGET

HCV TARGET: SVR12, by Baseline eGFR



Sofosbuvir-Containing Regimens including Patients with Renal Disease HCV-TARGET Trial: Result

HCV-TARGET Trial: SVR12 Results by Baseline eGFR and Regimen



Abbreviations: SOF = sofosbuvir; PEG = peginterferon; RBV = ribavirin; SMV = simeprevir

Source: Saxena V, et al. 50th EASL. 2015; Abstract LP08.

Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir in GT1 & Renal Disease

RUBY-I: Study Design

RUBY-I: Features

- **Design:** Phase 3b, randomized, open-label trial evaluating safety and efficacy of 3D (ombitasvir-paritaprevir-ritonavir and dasabuvir) with or without ribavirin for 12 weeks in treatment-naïve patients with chronic HCV GT1 and advanced kidney disease
- **Setting:** 9 sites in United States
- **Entry Criteria**
 - Adults with chronic HCV genotype 1 infection
 - Chronic kidney disease stage 4 or 5 (eGFR <30 mL/min/1.73 m²) +/- HD
 - Plasma HCV RNA greater than 1,000 IU/mL
 - Absence of cirrhosis
 - Absence of coinfection with HBV or HIV
 - Baseline Hb ≥10 g/dL
- **Primary End-Point:** SVR12

Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir in GT1 & Renal Disease RUBY-I: Regimens

Week 0

12

24

GT 1a
n = 13

Ombitasvir-Paritaprevir-Ritonavir
and Dasabuvir + Ribavirin

SVR12

GT 1b
n = 7

Ombitasvir-Paritaprevir-Ritonavir
and Dasabuvir

SVR12

Drug Dosing

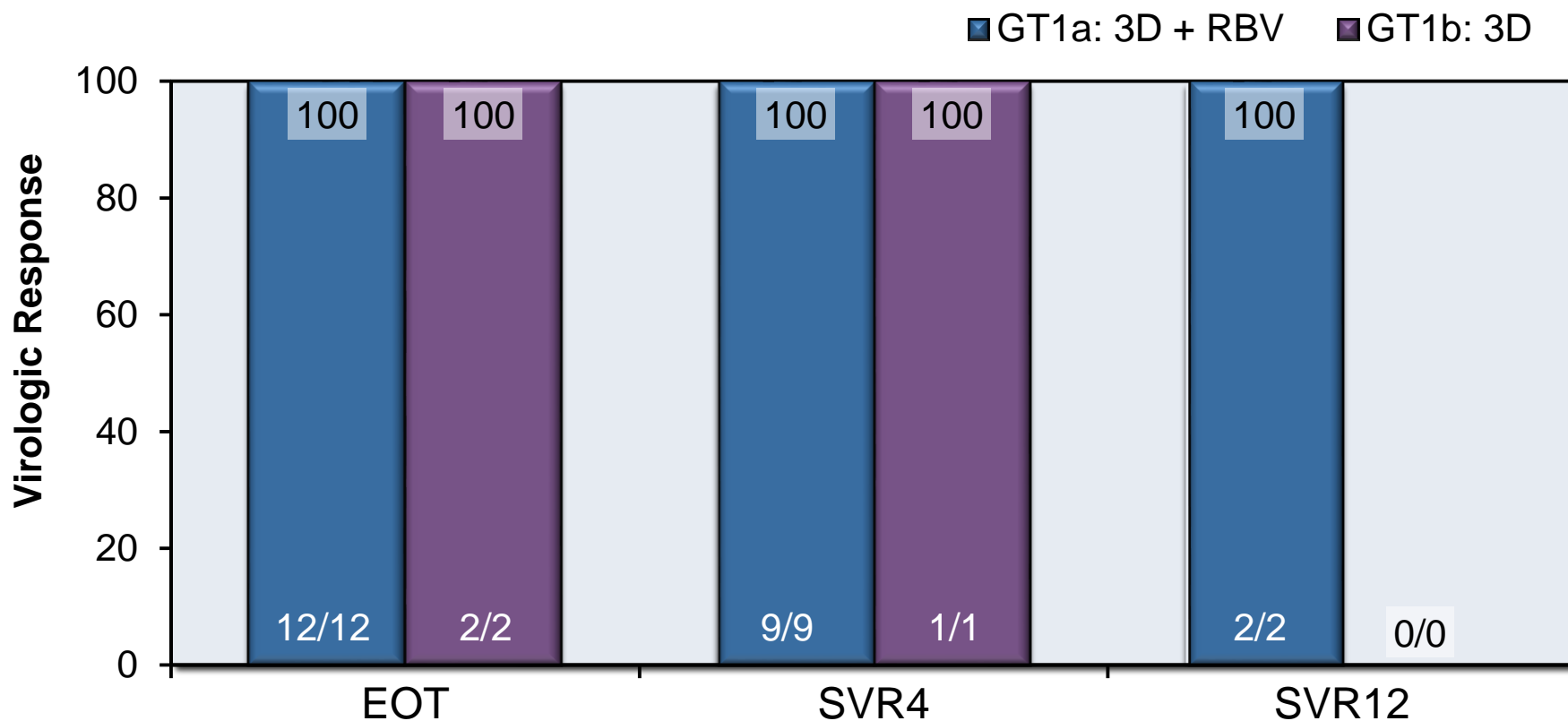
Ombitasvir-Paritaprevir-Ritonavir (25/150/100 mg once daily) + Dasabuvir: 250 mg twice daily

Ribavirin for patients not on hemodialysis: 200 mg once daily

Ribavirin for patients on hemodialysis: 200 mg given 4 hours before each hemodialysis session

Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir in GT1 & Renal Disease RUBY-I: Baseline Results

RUBY-I: SVR 12 Rates*



3D = Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir; RBV = ribavirin; EOT = end of treatment

Source: Pockros PJ, et al. 50th EASL. 2015; Abstract L01.

AASLD/IDSA/IAS-USA 2015 HCV Treatment Recommendations

Recommendations for Patients with Renal Impairment

AASLD/IDSA Recommendations for Patients with Renal Impairment*

Dosage adjustments for patients with mild to moderate renal impairment (CrCl 30 mL/min-80 mL/min)

Sofosbuvir: no dosage adjustment required

Simeprevir: no dosage adjustment required

Ledipasvir-sofosbuvir: no dosage adjustment required

Ombitasvir-paritaprevir-ritonavir + dasabuvir: no dosage adjustment required

Dosage adjustments for patients with severe renal impairment (CrCl <30 mL/min or ESRD)

Treatment can be contemplated after consultation with an expert, because safety and efficacy data are not available for these patients.

*Recommendations for patients with renal impairment, including severe renal impairment (creatinine clearance <30 mL/min) or end-stage renal disease requiring hemodialysis or peritoneal dialysis

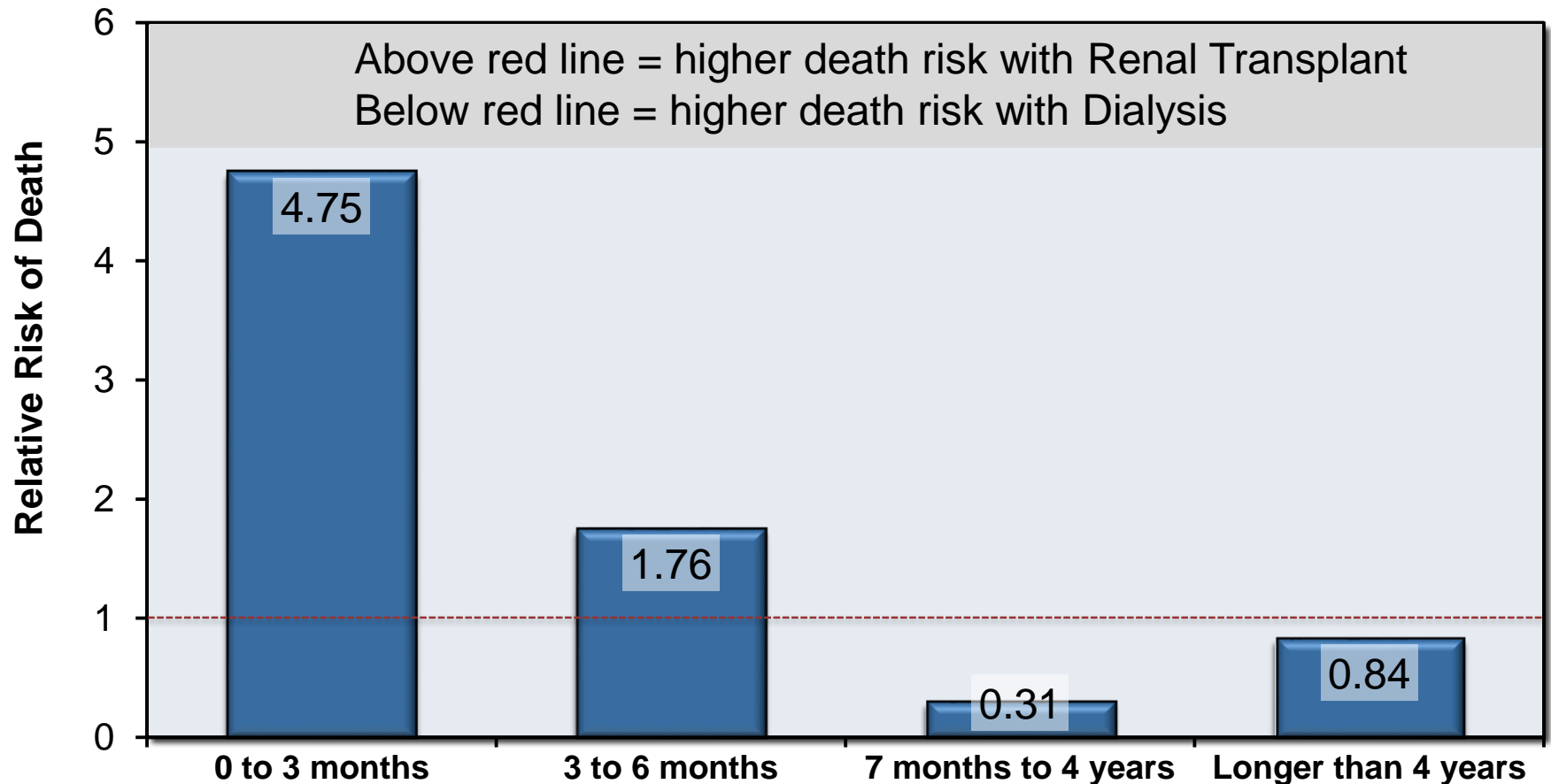
TREATMENT OF HCV IN PATIENTS WITH RENAL INSUFFICIENCY
HCV and Renal Transplantation

Impact of HCV on Outcome of Renal Transplantation

- HCV increases glomerulonephritis in transplanted kidney
 - HCV reduces renal allograft survival
 - HCV decreases long-term patient survival
- ❖ HCV infection is not a contraindication to renal transplantation unless portal hypertension is present or there is decompensated liver disease since patient survival with RT is better than with dialysis

Relative Risk of Death among Patients Undergoing Renal Transplantation versus those who Remained on Dialysis

Relative Risk of Death (all causes): Transplanted versus Dialysis



Hepatitis C and Renal Disease

Rationale for HCV Treatment in Renal Transplant Candidate

- Eradicate HCV as immunologic stimulus to B-cells to decrease immune complex formation and impact vasculitis or glomerulonephritis
- Decrease extrahepatic HCV-related complications
- Prevent HCV-related post-transplant complications
 - Interaction with HCV immune complexes and calcineurin inhibitor related renal toxicity
- HCV-related liver disease may accelerate with post-transplant immunosuppression
- Post-transplant treatment extremely difficult due to risk of graft rejection from interferon (historical)

Treatment of HCV after Renal Transplantation

- Interferon-based therapy relatively contraindicated because of risk of allograft rejection and loss
- Post-transplant interferon/ribavirin recommended only for
 - Fibrosing cholestatic hepatitis
 - ◆ IF daclatasvir compassionate use not available
 - Life-threatening vasculitis
- Interferon-free regimens will provide new options

Treatment of HCV Post-Renal Transplant

- Renal function less problematic depending on:
 - Use, dose, & blood levels of calcineurin inhibitor (cyclosporine, tacrolimus)
 - Improvement in GFR with graft recovery
 - History of rejection and residual renal damage
- Address drug-drug interactions per medication & drug class
- Higher HCV RNA levels due to immunosuppression may impact SVR rates
- No effective therapy yet published in controlled trials

TREATMENT OF HCV IN PATIENTS WITH RENAL INSUFFICIENCY
Summary and Recommendations

Treatment of Hepatitis C in Patients with Renal Insufficiency

Summary Points

- Renal disease severity should guide treatment decisions
- Interferon- and Peginterferon-based Rx of historical importance only
- Maximize EPO use when using ribavirin in this patient population
- First-generation HCV protease inhibitors not recommended
- No dose adjustments with DAAs if GFR \geq 30 mL/min
- Limited data with DAAs in patients with GFR <30 mL/min
- Obtain expert consultation if GFR <30 mL/min, especially HD patients
- Renal transplant candidates should receive HCV treatment with DAAs
 - Either before or after transplantation, depending on clinical scenario