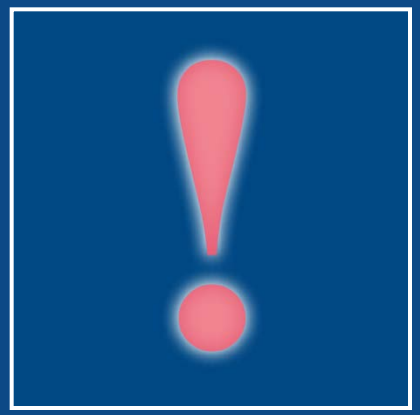
Nephro Update Europe 2018

5-6 October, Budapest

Hot Topic: Hepatitis C



Michel Jadoul, Belgium

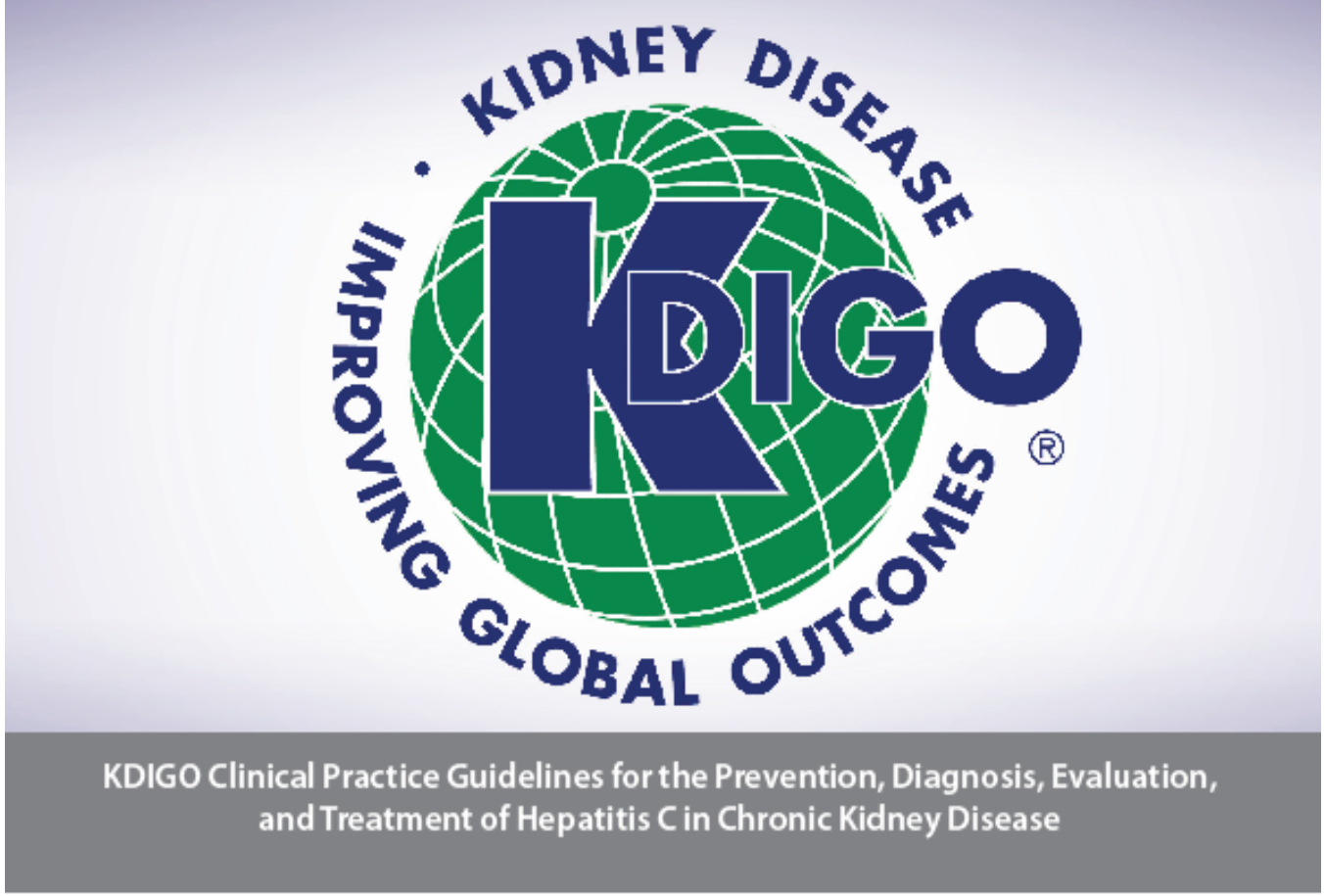
Conflicts of Interest

Research Support: Alexion, Amgen, Janssen-Cilag, MSD, Otsuka, Roche

Lecturing: Abbvie, Amgen, Menarini, MSD

Consulting activities: Astellas, Vifor-FMCRP, MSD

Other : I have cochaired the 2018 update of the HCV in CKD KDIGO Guideline and am KDIGO Co-chair elect



KDIGO clinical practice guidelines for the prevention, diagnosis, evaluation, and treatment of hepatitis C in chronic kidney disease. *Kidney Int Suppl* 2008: S1-99

Logo used with permission: D. Green

Hepatitis C

Daniel P Webster, Paul Klenerman, Geoffrey M Dusheiko

PI= protease inhibitors

Direct-Acting Antiviral Agents(DAAs)

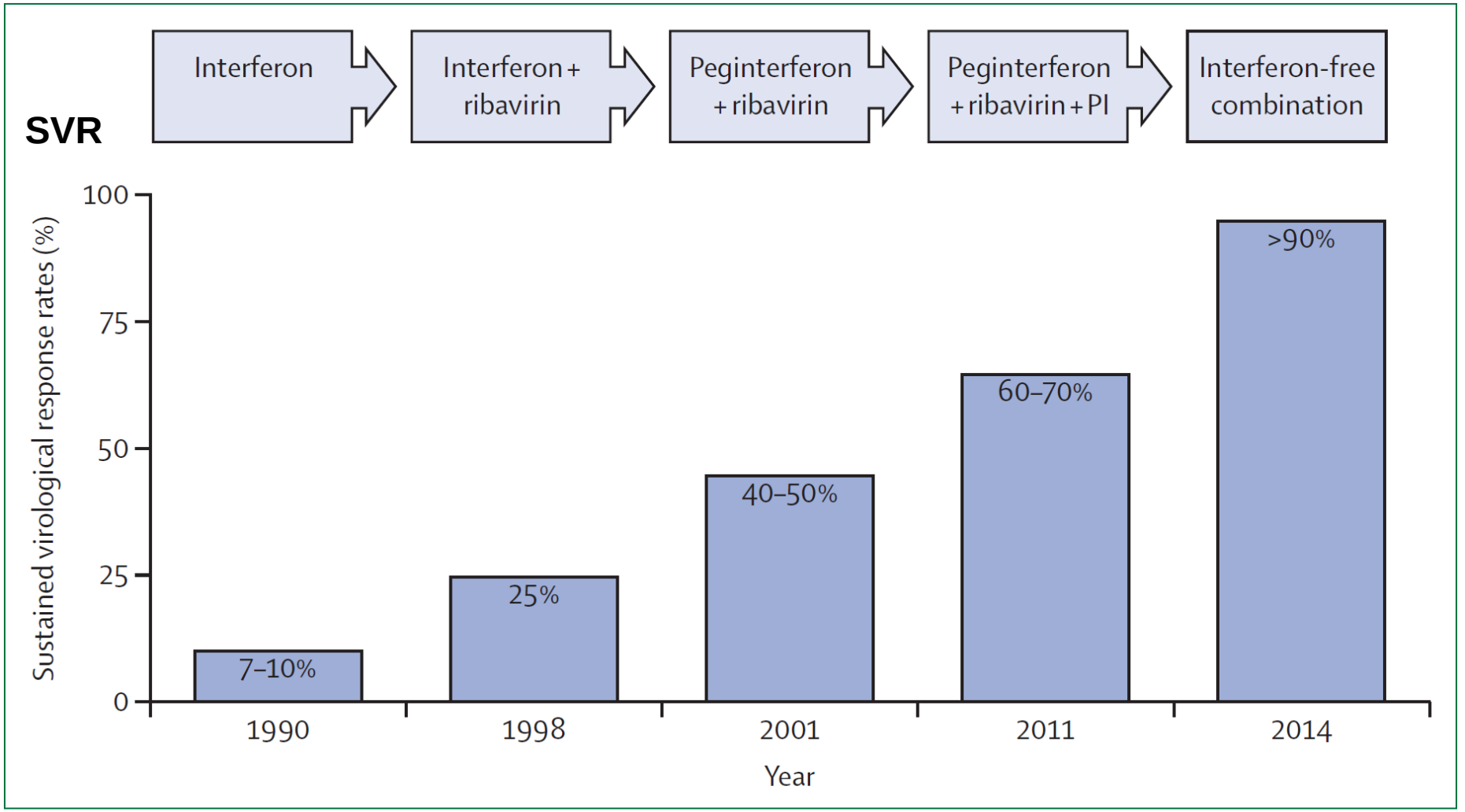


Figure 1: **Changes in standard of care for HCV, and improvements in numbers of sustained virological responses**
Data from references 9–12. PI=protease inhibitor.

Lancet 2015; 385: 1124–35

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Outline

- Screening for HCV in CKD
- Treating HCV in CKD
- Preventing HCV transmission in HD
- Managing HCV before and after kidney TP
- Treating HCV-associated GN

Screening for HCV in CKD

Detection and Evaluation of HCV in CKD

1.1 Screening patients with CKD for HCV infection

1.1.1: We recommend screening all patients for hepatitis C virus (HCV) infection at the time of initial evaluation of chronic kidney disease (CKD) (*1C*).

1.1.1.1:We recommend using an immunoassay followed by nucleic acid testing (NAT) if immunoassay is positive (*1A*).

1.1.2: We recommend screening all patients for HCV infection upon initiation of in-center hemodialysis or upon transfer from another dialysis facility or modality (*1A*).

1.1.2.1: We recommend using NAT alone or an immunoassay followed by NAT if immunoassay is positive (*1A*). Repeat /6months

Kidney Disease: Improving Global Outcomes (KDIGO) Hepatitis C Work Group. KDIGO 2018 Clinical Practice Guideline on the Prevention, Diagnosis, Evaluation, and Treatment of Hepatitis C in CKD. *Kidney Int Suppl.* 2018; in press

Rationale for screening CKD non D patients for HCV

- HCV may cause Membranoprolif. GN
- Greater prevalence of HCV in late CKD stages than in general population
- Consistent association of
  - HCV+ with worse liver, kidney and CV outcomes
  - anti-HCV treatment with better outcomes (liver, kidney, CV)
- Low cost of single EIA for HCV
- Thus testing once for this modifiable risk factor is recommended (1C)

HCV prevalence in prevalent vs. incident (<120 days) patients

DOPPS 1+ Countries: France, Germany, Italy, Japan, Spain, UK, US

	DOPPS Phase				
Region/Country	**1**	**2**	**3**	**4**	**5**
Prevalent patients	14.3 (7894)	12.1 (6682)	9.5 (6245)	9.4 (8617)	8.4 (10042)
Incident patients	5.2 (6186)	5.5 (3018)	5.2 (898)	4.8 (3102)	4.8 (4767)

DOPPS 1 (1996-2001); DOPPS 2 (2002-2004; DOPPS 3 (2005-2008); DOPPS 4 (2009-2012); DOPPS 5 (2012-20015)

M Jadoul et al. submitted

Chronic Hepatitis C Virus (HCV) Increases the Risk of Chronic Kidney Disease (CKD) While Effective HCV Treatment Decreases the Incidence of CKD

Haesuk Park,[1] Chao Chen,[1] Wei Wang,[1] Linda Henry,[1] Robert L. Cook,[2] and David R. Nelson[2]

US study : administrative claims database + Medicare database
Propensity matching, Cox model with time- varying covariates

TABLE 2. Incidence Rate and Hazard Ratio (HR) for CKD in the HCV and Non-HCV Cohorts

Study Population	HCV Status	No. of Patients	Person-Years	No. of CKD Events	Mean Time to CKD Event (Months)	Crude Incidence of CKD*	Adjusted HR of CKD (95% CI)	
							Baseline Covariates	Baseline and Time-Varying Covariates
All patients	HCV	56,448	140,468	1455	20.53	10.36	1.57 (1.47-1.68)	1.27 (1.18-1.37)
	Non-HCV	169,344	440,495	2518	22.37	5.72	Reference	Reference
Age, years								
18-49	HCV	15,869	37,643	139	19.53	3.69	1.87 (1.49-2.35)	1.47 (1.13-1.90)
	Non-HCV	48,044	122,666	216	22.78	1.76	Reference	Reference
50-59	HCV	27,344	72,630	685	21.95	9.43	1.75 (1.58-1.93)	1.32 (1.18-1.47)
	Non-HCV	82,304	227,193	1086	22.81	4.78	Reference	Reference
≥60	HCV	13,235	30,194	631	19.22	20.90	1.38 (1.25-1.53)	1.19 (1.06-1.33)
	Non-HCV	38,996	90,636	1216	21.91	13.42	Reference	Reference

Park H, et al. ***Hepatology*** 2018; 67(2): 492–504

TABLE 4. HCV Treatment Association with Incidence of CKD Using Time-Varying Cox-Proportional Hazards Model

Treatment Status*	Person-Years	No. of CKD Events	Crude Incidence of CKD†	Adjusted HR of CKD (95% CI)
All HCV patients (N = 55,818)				
Minimum Effective TX	11,737	79	6.73	0.70 (0.55-0.88)
Insufficient TX	6854	69	10.07	0.85 (0.66-1.09)
No TX	119,698	1291	10.79	Reference
Dual therapy (n = 3666)				
Minimum Effective TX	6115	34	5.56	0.60 (0.43-0.85)
Insufficient TX	3245	34	10.48	0.92 (0.65-1.31)
No TX	108,813	1190	11.10	Reference
Triple therapy (n = 3534)				
Minimum Effective TX	3469	19	5.48	0.59 (0.37-0.94)
Insufficient TX	3023	25	8.27	0.72 (0.48-1.07)
No TX	110,623	1197	10.82	Reference
All-oral therapy (n = 4628)				
Minimum Effective TX	2154	26	12.07	1.03 (0.68-1.55)
Insufficient TX	585	10	17.09	0.85 (0.39-1.82)
No TX	114,224	1254	10.98	Reference

Park H, et al. ***Hepatology*** 2018; 67(2): 492–504

TABLE 5. Incidence Rate and Hazard Ratio for MPGN and Cryoglobulinemia in the HCV and Non-HCV Cohorts, Adjusting for Baseline Characteristics

Secondary Outcomes	HCV Status	No. of Patients	Person-Years	No. of Events	Crude Incidence*	Mean Time to Event (Months)	Adjusted HR (95% CI)	
							Baseline Covariates	Baseline and Time-Varying Covariates
MPGN	HCV	55,618	140,408	120	0.833	17.39	3.74 (2.84-4.93)	2.23 (1.84-2.71)
	Non-HCV	166,854	438,153	97	0.221	19.03	Reference	Reference
Men	HCV	33,395	84,325	83	0.984	18.40	3.50 (2.54-4.84)	1.74 (1.37-2.19)
	Non-HCV	101,422	266,423	73	0.274	18.81	Reference	Reference
Women	HCV	22,223	56,082	37	0.660	15.11	4.40 (2.59-7.47)	3.78 (2.66-5.36)
	Non-HCV	65,432	171,730	24	0.140	19.72	Reference	Reference
Cryoglobulinemia	HCV	55,646	140,435	123	0.876	14.17	17.25 (10.91-27.26)	16.91 (12.00-23.81)
	Non-HCV	166,938	438,946	22	0.050	24.69	Reference	Reference
Men	HCV	33,423	84,363	75	0.889	14.96	21.00 (11.10-39.73)	20.03 (12.28-32.67)
	Non-HCV	100,824	265,142	11	0.041	27.25	Reference	Reference
Women	HCV	22,223	56,072	48	0.856	12.95	13.11 (6.76-25.40)	14.07 (8.68-22.81)
	Non-HCV	66,114	173,804	11	0.063	22.12	Reference	Reference

Park H, et al. ***Hepatology*** 2018; 67(2): 492–504

Outcomes for HCV+ versus HCV- patients

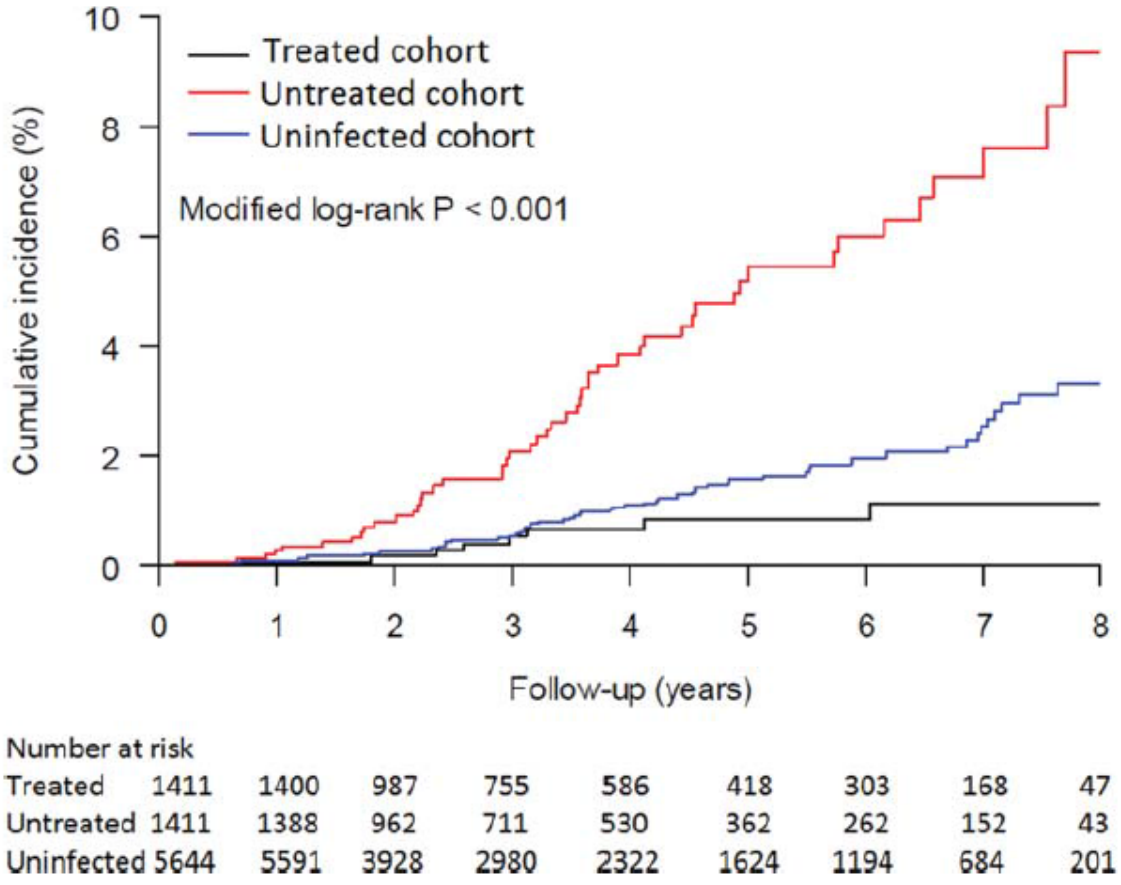
Hemodialysis DOPPS 1-5 (1996-2015)

Event	Unadjusted HR[a] (95% CI)	Adjusted HR[b] (95% CI)
All-cause mortality	1.02(0.95-1.09)	1.12(1.05-1.20)
Cardiovascular	0.97(0.87-1.07)	1.10(0.98-1.22)
Infection	1.05(0.88-1.27)	1.11(0.91-1.34)
Hepatic-related	5.88(3.84-8.99)	5.90(3.67-9.50)

Goodkin D, Bieber B, Jadoul M, *et al*. Mortality, hospitalization, and quality of life among patients with hepatitis c infection on hemodialysis. *Clin J Am Soc Nephrol* 2017; 12: 287-297.

Antiviral treatment for HCV infection is associated with improved outcomes in diabetics

ESRD



Hsu YC, *et al. Hepatology* 2014; 59: 1293-1302.

Treating HCV in CKD

protease inh. , NS5A inh. , polymerase inh.

- PREVIR , -ASVIR , -BUVIR

Characteristics: variable between molecules

- **antiviral activity on some vs all genotypes**
- **extent of elimination by the kidney**
- **potential to cause drug-drug interactions (liver)**
- **barriers to viral resistance (and thus need to add ribavirin)**
- **≥ 2 drugs in all regimens (to reduce risk of HCV resistance)**

- - Sofosbuvir (SOF) cleared by the kidney
  - - eGFR < 30 ml/'= off label use
  - - some reports (case series) that SOF -based regimens safe and effective in late CKD
  - - optimal dosage of SOF not fully clear
  - - worsening of CKD progression by SOF not completely excluded

Grazoprevir plus elbasvir in treatment-naive and treatment-experienced patients with hepatitis C virus genotype 1 infection and stage 4–5 chronic kidney disease (the C-SURFER study): a combination phase 3 study

David Roth, David R Nelson, Annette Bruchfeld, AnnMarie Liapakis, Marcelo Silva, Howard Monsour Jr, Paul Martin, Stanislas Pol, Maria-Carlota Londoño, Tarek Hassanein, Philippe J Zamor, Eli Zuckerman, Shuyan Wan, Beth Jackson, Bach-Yen Nguyen, Michael Robertson, Eliav Barr, Janice Wahl, Wayne Greaves

- **First RCT of an oral, interferon-free DAA regimen in CKD stage 4 /5 patients**
- **<1% of grazoprevir and elbasvir renally excreted: no dose adjustment in CKD**
- **Single pill: Grazo 100mg/Elbas 50 mg**
- **primary endpoint = sustained viral response 12 weeks after stopping DAAs (SVR12)**

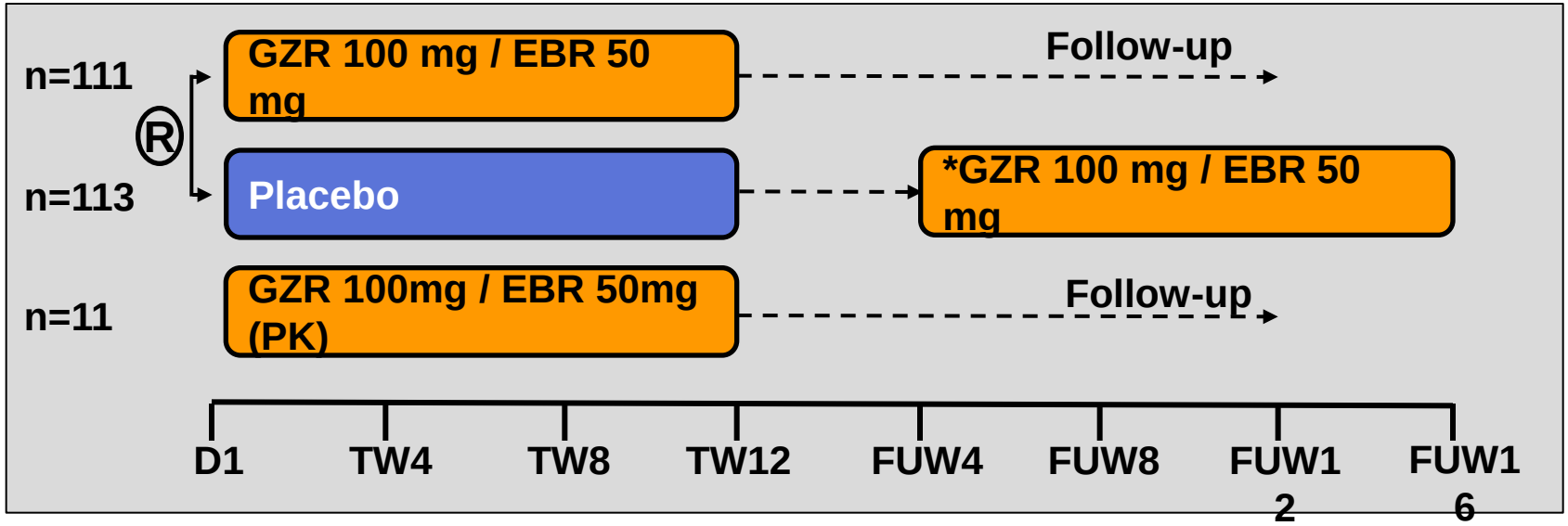
Roth D, et al. *Lancet* 2015; 386: 1537-1545.

PATIENTS CHARACTERISTICS

- HCV Genotype 1 infection (52% 1a, 48% 1b)
- treatment-naive and treatment-experienced patients
- CKD stage 4/5
  - CKD stage 4
  - CKD stage 5 non D, or on hemodialysis (76% of total n)
- Compensated cirrhosis allowed (6 %)
- All HBV and HIV negative

Roth D, et al. *Lancet* 2015; 386: 1537-1545.

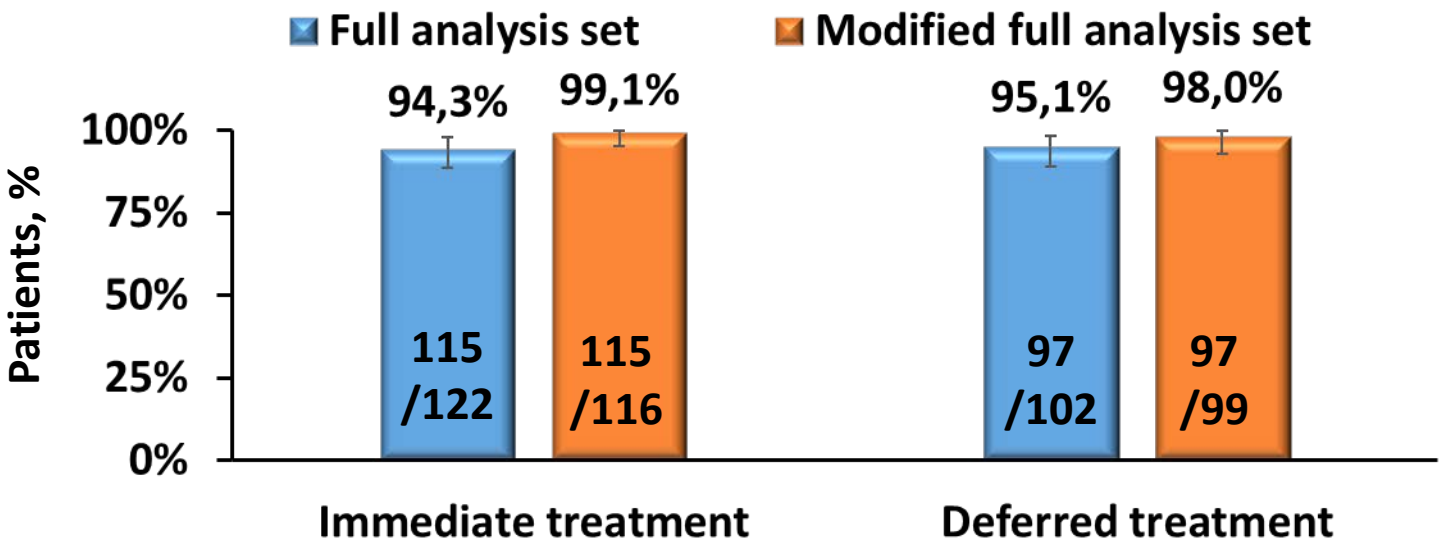
STUDY DESIGN



- Randomized, parallel-group, multi-site, placebo-controlled trial
- 12 weeks of study drug
- 11 patients in open-label GZR/EBR arm underwent intensive pharmacokinetic sampling

Roth D, et al. *Lancet* 2015; 386: 1537-1545.

C-SURFER SVR12 RESULTS IMMEDIATE AND DEFERRED TREATMENT ARMS



Relapse	1	1	2	2
D/c unrelated to treatment	6	0	3	0

Roth D, et al. *Lancet* 2015; 386: 1537-1545.

Bruchfeld A, et al; *Lancet Gastroenterol Hepatol* 2017; 2: 585-594.

SAFETY SUMMARY

- Tolerance better or similar to placebo
- A single SAE possibly ascribed to study drug, vs one due to placebo
- Clear improvement in ALT/AST with study drug vs placebo
- No difference in bilirubin, or anemia parameters

Roth D, et al. *Lancet* 2015; 386: 1537-1545.
Bruchfeld A, et al; *Lancet Gastroenterol Hepatol* 2017; 2: 585-594.

Glecaprevir and Pibrentasvir in Patients with HCV and Severe Renal Impairment

- **Open-label multicenter phase 3 study**
- **N = 104, 79% males, 25% Black**
- **HCV Genotype : 1 n= 54**
  2 n= 17
  3 n= 11
  4 n=20
  5 n= 1
  6 n= 1
- **88% on HD, 58% treatment naive**

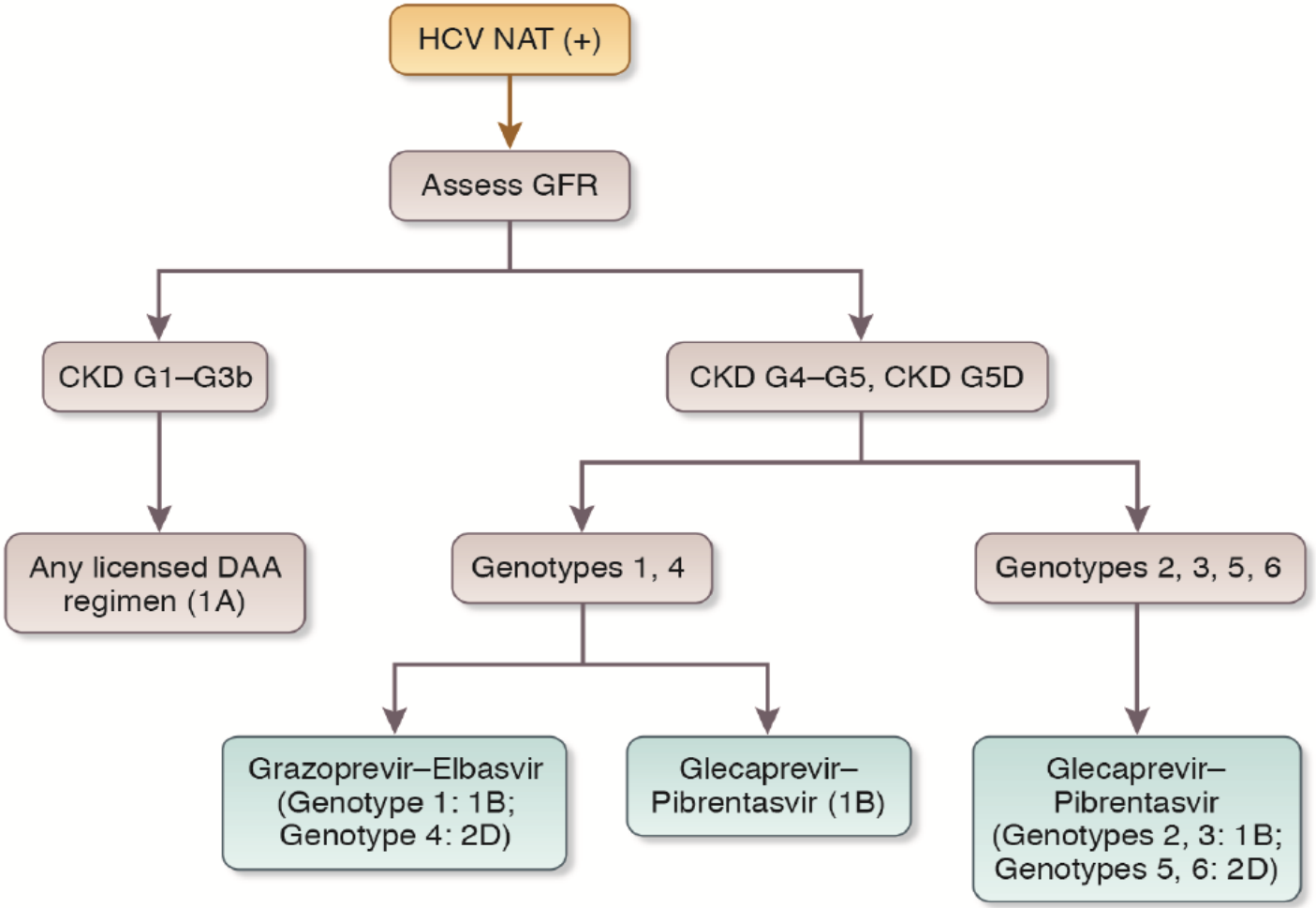
Gane E, *N Engl J Med* 2017; 377: 1448-1455

Table 2. Sustained Virologic Response Rate.

Time of measurement	Value
On-treatment response — no./total no. (%)*	
Week 1	37/101 (37)
Week 2	77/100 (77)
Week 4	98/103 (95)
Week 8	103/103 (100)
Final treatment	104/104 (100)
Posttreatment response — no./total no. (%)†	
Sustained virologic response at posttreatment week 4	103/104 (99)
Sustained virologic response at posttreatment week 12	102/104 (98)
Sustained virologic response at posttreatment week 24	100/104 (96)‡

Tolerance OK (pruritus 20%, fatigue 14%, nausea 12%)
No safety signal

Gane E et al. *N Engl J Med* 2017; 377: 1448-1455



Algorithm 1. Treatment scheme for CKD G1-G5D

Recommendation grading is provided for each specific treatment regimen and HCV genotype.
CKD G, chronic kidney disease, GFR category; DAA, direct-acting antiviral; GFR, glomerular filtration rate; GT, genotype; HCV, hepatitis C virus; NAT, nucleic acid testing.

KDIGO Working Group. Kidney Int Suppl. 2018; in press

Kidney function	HCV genotype	Recommended regimen(s)	Strength of evidence	Alternate regimen(s)	Strength of evidence
CKD G4–G5 (GFR < 30 ml/min/ 1.73 m²) including HD, KTR[b]	1a	Grazoprevir/elbasvir	1B	Ritonavir-boosted paritaprevir, ombitasvir, and dasabuvir (also known as PrOD or 3D regimen) with ribavirin	2D
		Glecaprevir/pibrentasvir	1B	Daclatasvir/asunaprevir	2C
	1b	Grazoprevir/elbasvir	1B	Ritonavir-boosted paritaprevir, ombitasvir, and dasabuvir (also known as ProD or 3D regimen)	2D
		Glecaprevir/pibrentasvir	1B	Daclatasvir/asunaprevir	2C
	2,3	Glecaprevir/pibrentasvir	1B		
	4	Grazoprevir/elbasvir	2D		
		Glecaprevir/pibrentasvir	1B		
	5,6	Glecaprevir/pibrentasvir	2D		
CKD G5 PD	n/a (reasonable to follow proposed regimens for HD)				
KTR (GFR ≥ 30 ml/min/ 1.73 m²)	1a	Sofosbuvir with ledipasvir, daclatasvir or simeprevir	1B	Sofosbuvir/ribavirin	2D
		Glecaprevir/pibrentasvir[c]	1C		
	1b	Sofosbuvir with ledipasvir, daclatasvir or simeprevir	1B		
		Glecaprevir/pibrentasvir[c]	1C		
	2, 3, 5, 6	Glecaprevir/pibrentasvir[c]	1D	Sofosbuvir/daclatasvir/ribavirin[d]	2D
	4	Sofosbuvir with ledipasvir, daclatasvir or simeprevir	1D		
		Glecaprevir/pibrentasvir[c]	1D		

KDIGO Working Group. Kidney Int Suppl. 2018; in press

Who should be treated ?

- In most CKD patients the potential benefits of treating HCV outweigh potential harm.
- Some patients, e.g., patients with metastatic cancer, may not live long enough to benefit from therapy.
- No minimum life expectancy would justify treatment: inaccuracy of predictions, need to individualize decision. However as in the AASLD/IDSA guidance, life expectancy of at least 12 months should be anticipated
- Indirect reduction of HCV transmission (but not primary aim of treatment)

Drug-drug interactions with DAAs

- 12 weeks treatment with DAAs
- Important to review the potential interactions, and available alternative drugs or need to adapt dosages of drugs coprescribed with DAAs

https://www.hep-druginteractions.org/checker##table-view-wrap

Accessed on May 22, 2018

	Elbasvir/Grazoprevir	Glecaprevir/Pibrentasvir	Ledipasvir/Sofosbuvir	OBV/PTV/r + DSV	Sofosbuvir/Velpatasvir	Sofosbuvir/Velpatasvir/ Voxilaprevir
Atorvastatin	■	●	■	●	■	●
Escitalopram	◆	◆	◆	◆	◆	◆
Levetiracetam	◆	◆	◆	◆	◆	◆
Moxonidine	◆	◆	◆	◆	◆	◆
Pantoprazole	◆	▲	■	▲	■	■

● Do Not Coadminister ■ Potential Interaction ▲ Potential Weak Interaction ◆ No Interaction Expected ◆ No Clear Data

○ Do Not Coadminister □ Potential Interaction △ Potential Weak Interaction ◇ No Interaction Expected ◇ No Clear Data

CHAPTER 2
TREATMENT OF HCV INFECTION IN PATIENTS WITH CKD

2.5: As hepatitis B reactivation has been described with DAA therapy, all treatment candidates should undergo testing for HBV infection prior to therapy. If hepatitis B surface antigen [HBsAg] is present, the patient should undergo assessment for HBV therapy. If HBsAg is absent but markers of prior HBV infection (HBcAb positive with or without HBsAb) are detected, monitor for HBV reactivation with serial HBV DNA and liver function tests during DAA therapy (*Not Graded*)

Bersoff-Matcha SJ, *et al.* HBV Reactivation Associated With Direct-Acting Antiviral Therapy for Chronic Hepatitis C Virus: A Review of Cases Reported to the U.S. Food and Drug Administration Adverse Event Reporting System. *Ann Intern Med* 2017; 166: 792-798.

Impact of HCV treatment on kidney TP timing

- Renewed interest for the use of HCV+ grafts , especially in the USA.
- Waiting time for deceased donor frequently > 5 years, whereas HCV+ graft may be available very rapidly (local epidemiology!)
- Good long-term results in Spain of HCV+ kidneys to HCV+ recipients (Morales JM, *et al.* Long-term experience with kidney transplantation from hepatitis C-positive donors into hepatitis C-positive recipients. *Am J Transplant* 2010; **10:** 2453-2462.)

- **2.1.3:Treat kidney transplant candidates in collaboration with the transplant center to optimize timing of therapy. (*Not Graded*)**

KDIGO Working Group. Kidney Int Suppl. **2018; in press**

Treatment With Ledipasvir–Sofosbuvir for 12 or 24 Weeks in Kidney Transplant Recipients With Chronic Hepatitis C Virus Genotype 1 or 4 Infection

A Randomized Trial

Massimo Colombo, MD; Alessio Aghemo, MD; Hong Liu, PhD; Jie Zhang, PhD; Hadas Dvory-Sobol, PhD; Robert Hyland, DPhil; Chohee Yun, MD; Benedetta Massetto, MD; Diana M. Brainard, MD; John G. McHutchison, MD; Marc Bourlière, MD; Markus Peck-Radosavljevic, MD; Michael Manns, MD; and Stanislas Pol, MD

Median of 10 years after kidney TP
Cockroft : median 56 ml/min
Tacrolimus 47%, Cyclosporin 39%, MMF 61%, Steroids 98%
Cirrhosis : 15%

Table 2. Response During and After Treatment

Variable	Ledipasvir-Sofosbuvir		Total (n = 114)
	12 wk (n = 57)	24 wk (n = 57)	
HCV RNA level less than the LLOQ during treatment, *n/N (%)*			
Baseline	0/57 (0)	0/57 (0)	0/114 (0)
Week 1	9/57 (16)	7/57 (12)	16/114 (14)
Week 2	31/57 (54)	33/57 (58)	64/114 (56)
Week 4	50/57 (88)	52/57 (91)	102/114 (89)
Week 8	56/56 (100)*	57/57 (100)	113/113 (100)
Week 12	56/56 (100)*	57/57 (100)	113/113 (100)
Week 16	NA	57/57 (100)	57/57 (100)
Week 20	NA	57/57 (100)	57/57 (100)
Week 24	NA	57/57 (100)	57/57 (100)
HCV RNA level less than the LLOQ after end of treatment, *n/N (% [95% CI])*			
SVR4	57/57 (100 [94–100])	57/57 (100 [94–100])	114/114 (100 [97–100])
SVR12	57/57 (100 [94–100])	57/57 (100 [94–100])	114/114 (100 [97–100])
Overall virologic failure (relapse), *n/N (%)*	0/0 (0)	0/0 (0)	0/0 (0)

Tolerance of DAA regimen OK

Colombo M, *et al*. *Ann Intern Med* 2017; 166: 109-117.

Preventing HCV transmission in HD

CHAPTER 3: PREVENTING HCV TRANSMISSION IN HEMODIALYSIS UNITS

3.1: We recommend that hemodialysis facilities adhere to standard infection control procedures including hygienic precautions that effectively prevent transfer of blood and blood-contaminated fluids between patients to prevent transmission of blood-borne pathogens (see Table 2) (*1A*).

3.1.1: We recommend regular observational audits of infection control procedures in hemodialysis units (*1C*).

3.1.2: We recommend *not* using dedicated dialysis machines for HCV-infected patients (*1D*).

3.1.3: We suggest *not* isolating HCV-infected hemodialysis patients (*2C*).

3.1.4: We suggest that the dialyzers of HCV-infected patients can be reused if there is adherence to standard infection control procedures (*2D*).

KDIGO Working Group. Kidney Int Suppl. 2018; in press

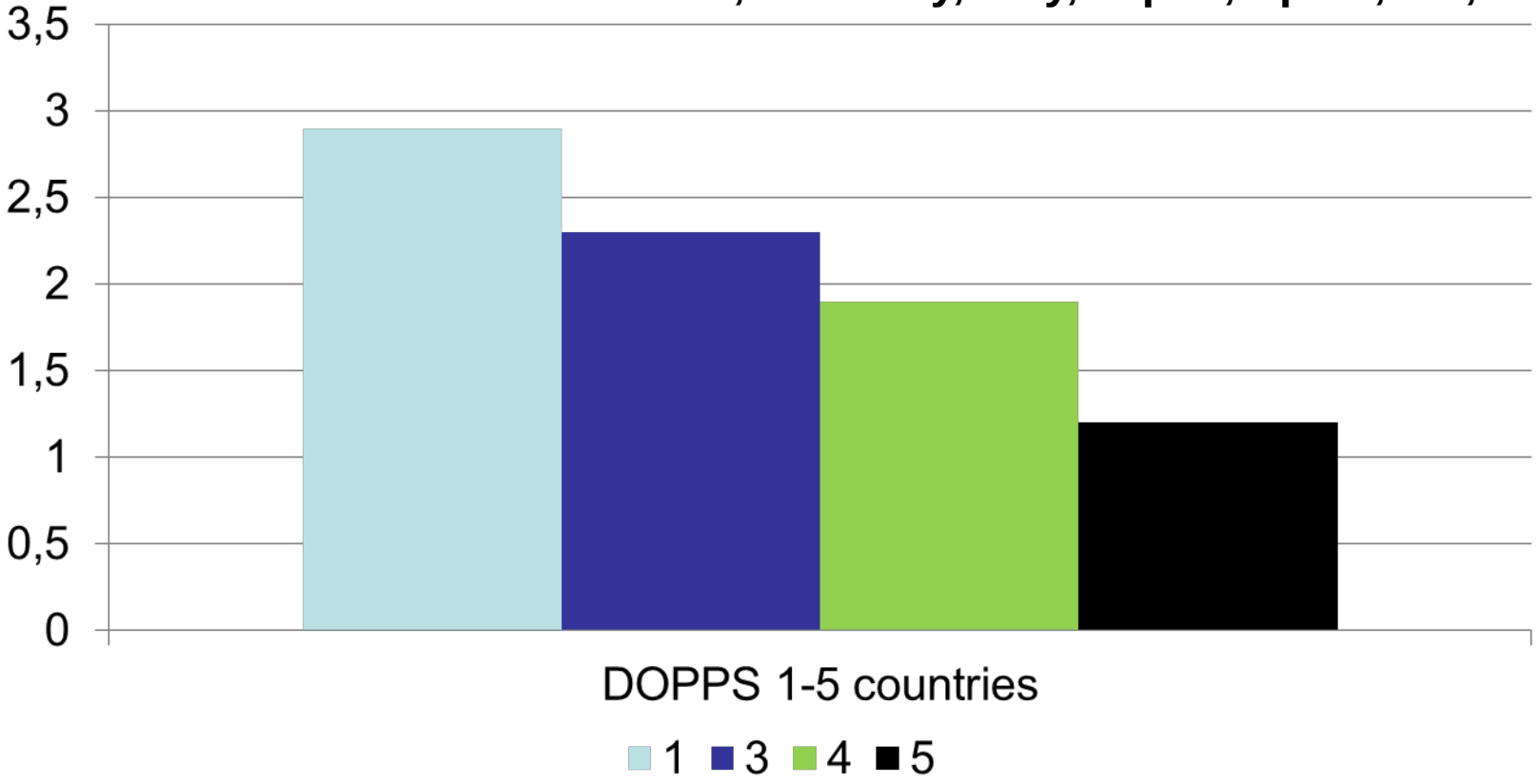
Table 1. Infection control practices (“hygienic precautions”) particularly relevant in preventing HCV transmission

- Proper hand hygiene and glove changes, especially between patient contacts, before invasive procedures, and after contact with blood and potentially blood-contaminated surfaces/supplies
- Proper injectable medication preparation practices following aseptic technique and in an appropriate clean area, and proper injectable medication administration practice
- Thorough cleaning and disinfection of surfaces at the dialysis station, especially high-touch surfaces
- Adequate separation of clean supplies from contaminated materials and equipment

KDIGO Working Group. Kidney Int Suppl. 2018; in press

HCV incidence per 100 patients years, by DOPPS region/country and phase

DOPPS 1-5 Countries : France, Germany, Italy, Japan, Spain, UK, US



DOPPS 1	DOPPS 3	DOPPS 4	DOPPS 5
1996-2001	2005-08	2009-11	2012-15

M Jadoul et al. submitted

Arguments for Nosocomial transmission

- DOPPS HCV incidence rates, by facility practice:
  - Do not accept HCV+ patients: 0.6 (0.3,1.3)
  - HCV+ pts treated at a general station: 2.3 (2.1,2.5)

- Clustering of HCV seroconversions in some facilities (mini-outbreaks)
  - 60% of facilities had 0 cases over ~3 years follow-up
  - 3% of facilities had 5+ cases

- Transfusional HCV transmission: currently < 1 case per per million transfusions in high income countries

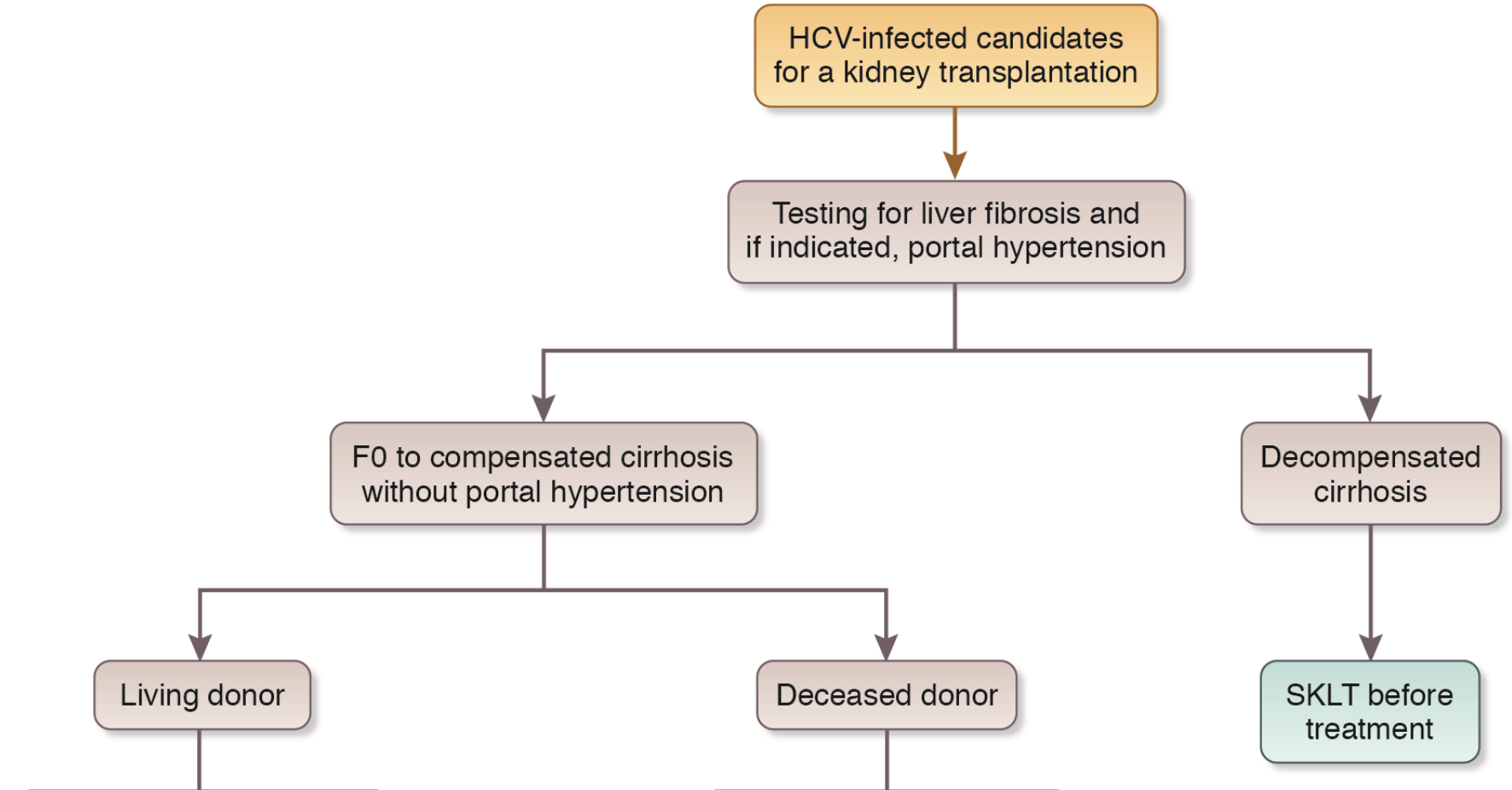
- IV drug users generally much younger than the HD DOPPS patients with HCV seroconversion

M Jadoul et al. submitted

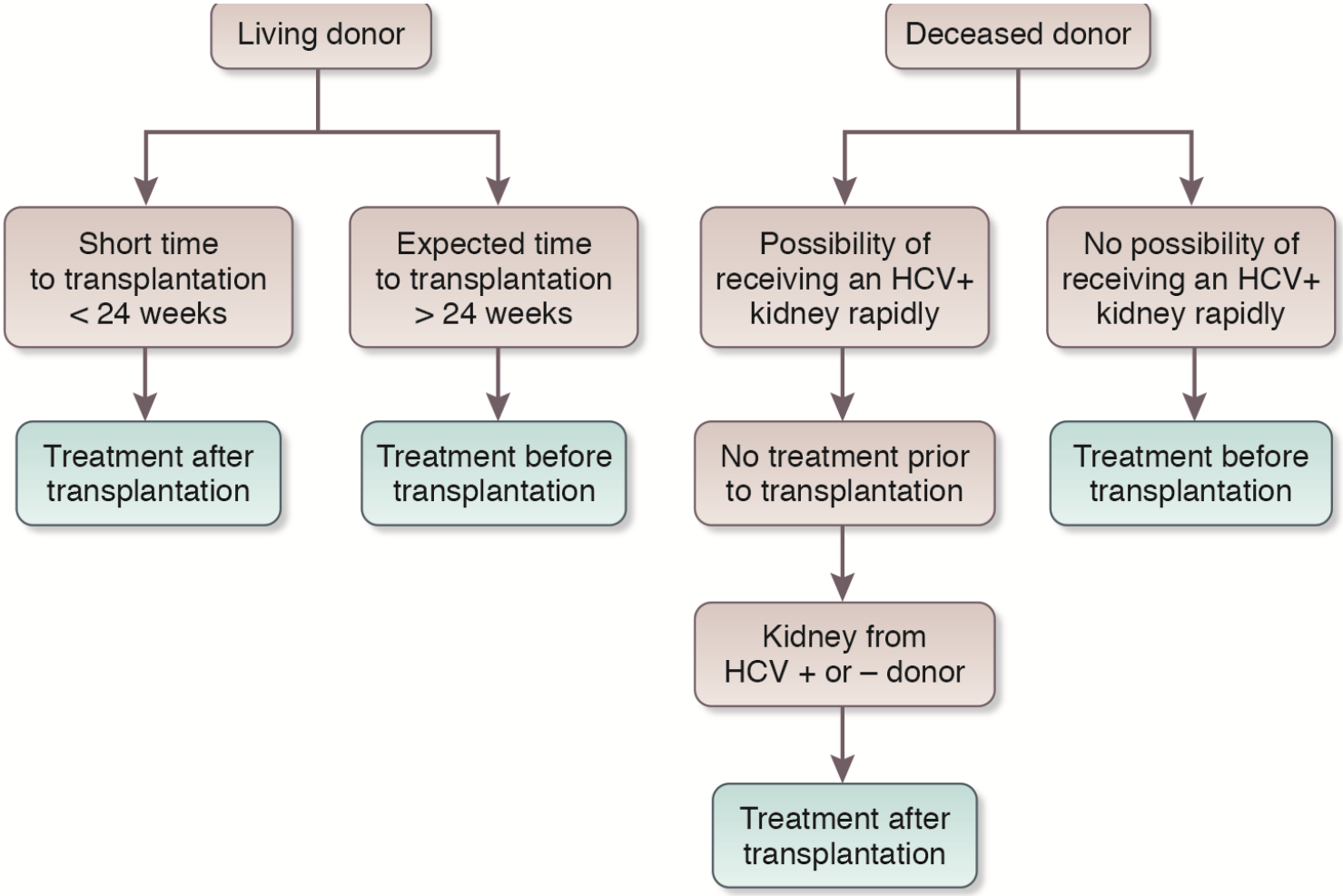
Managing HCV before and after kidney TP

KDIGO Working Group. Kidney Int Suppl. 2018; in press

CHAPTER 4: MANAGEMENT OF HCV-INFECTED PATIENTS BEFORE AND AFTER KIDNEY TRANSPLANTATION



CHAPTER 4: MANAGEMENT OF HCV-INFECTED PATIENTS BEFORE AND AFTER KIDNEY TRANSPLANTATION



KDIGO Working Group. Kidney Int Suppl. 2018; in press

Use of kidneys from HCV-infected donors

4.4.1: We recommend all kidney donors be screened for HCV infection with both immunoassay and NAT (if NAT is available). (1A)

4.4.2: We recommend that transplantation of kidneys from HCV RNA-positive donors be directed to recipients with positive NAT. (1A)

4.4.3: After the assessment of liver fibrosis, potential HCV-positive living kidney donors who do not have cirrhosis should undergo HCV treatment before donation; they can be accepted for donation if they achieve sustained virologic response (SVR) and remain otherwise eligible to be a donor. (Not Graded)

KDIGO Working Group. Kidney Int Suppl. 2018; in press

Transplanting HCV-RNA(+) kidneys into HCV(-) recipients ?

- Preliminary exciting results from 2 US TP Centers (Philadelphia and Hopkins)
- total : around 30 patients
- Very short waiting time for TP (weeks)
- DAAs immediately before or after TP, for 12 weeks, with SVR12 in all pts
- No safety signal
- Strategy as yet investigational according to KDIGO WG

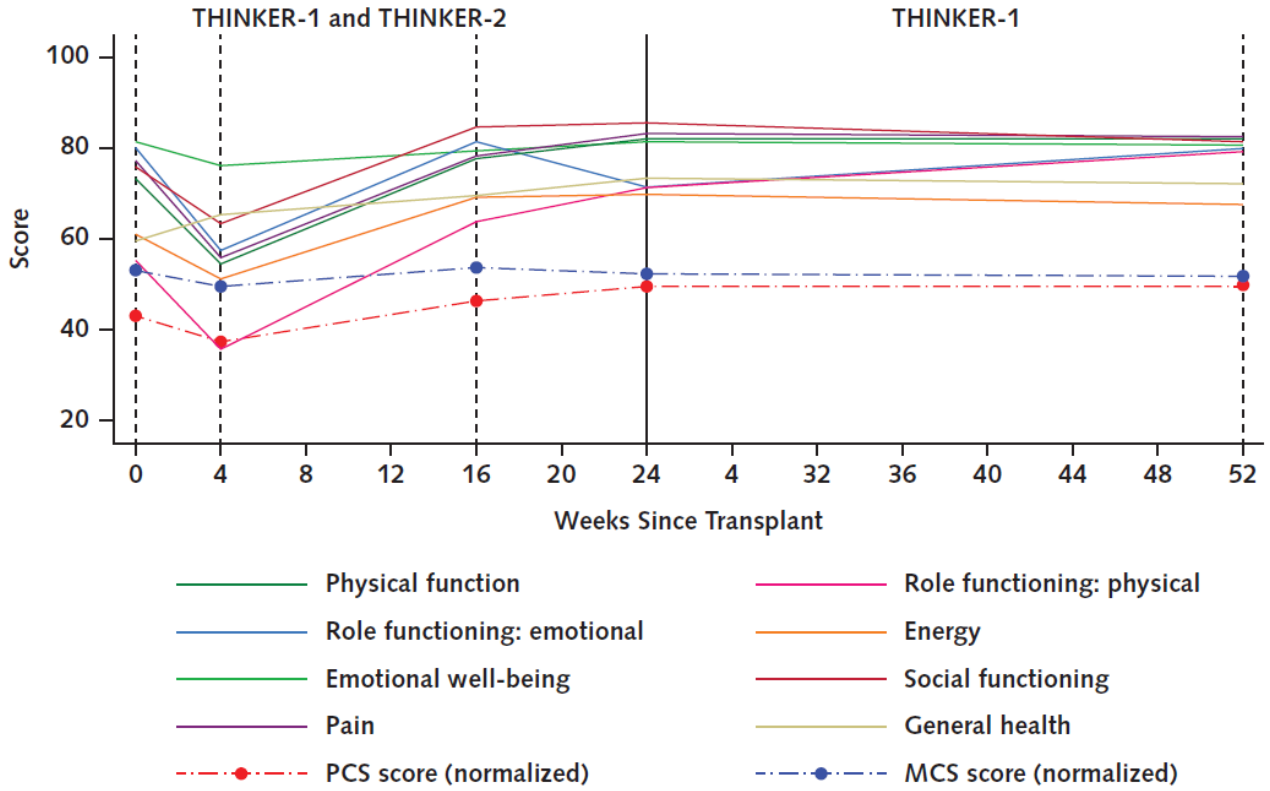
Durand C et al. *Ann Intern Med.* 2018; doi:10.7326/M17-2871
Reese P et al. *Ann Intern Med. 2018;* doi:10.7326/M18-0749

Table 2. Comparison of eGFRs and Creatinine Levels at 6 and 12 Months Between THINKER Participants and Matched Comparator Recipients of Kidneys From HCV-Negative Donors

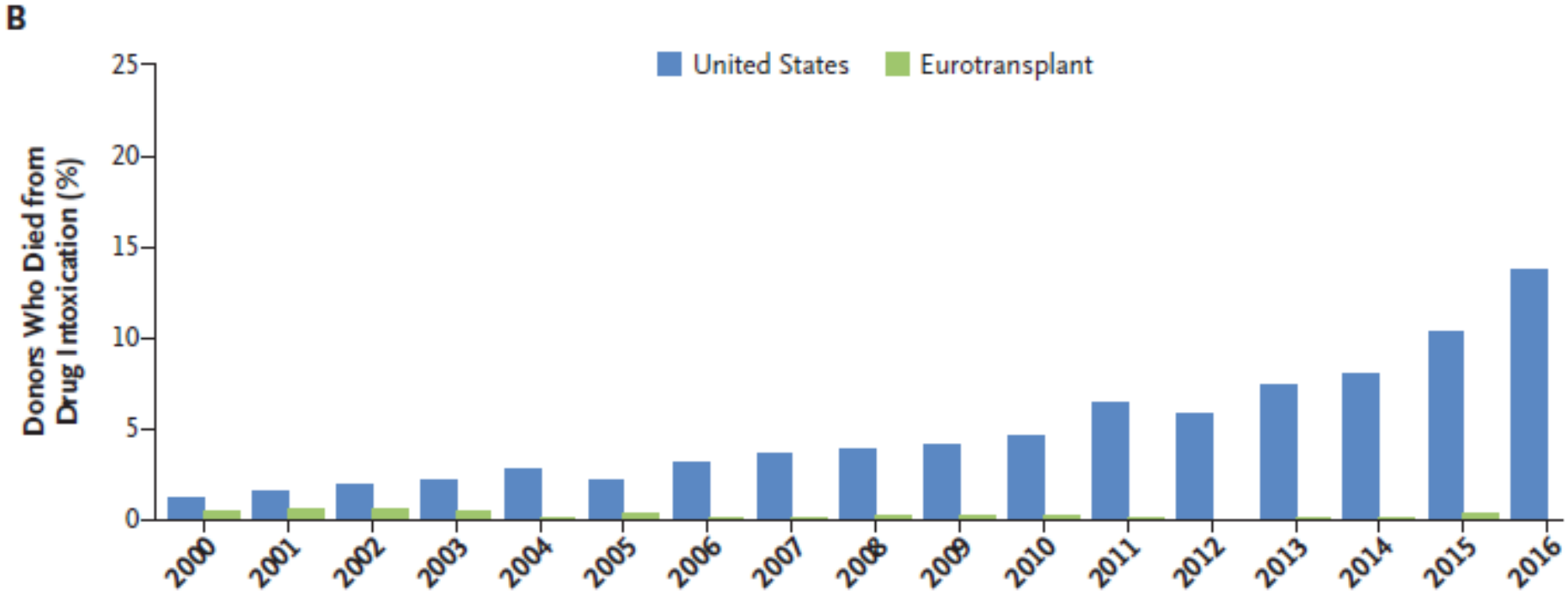
Variable	Median Value (IQR)			Difference Between Matched Sets of THINKER Recipients and Allocation Comparators (95% CI)‡	*P* Value for Comparison With Allocation Comparators‡	Difference Between Matched Sets of THINKER Recipients and Optimal Comparators (95% CI)‡	*P* Value for Comparison With Optimal Comparators‡
	THINKER Recipients (n = 10 or 20)*	Matched Allocation KDPI Comparators (n = 50 or 100)*	Matched Optimal KDPI Comparators (n = 50 or 100)*†				
6-mo outcomes							
Creatinine level					<0.001		0.37
µmol/L	103 (90 to 118)	117 (95 to 150)	106 (88 to 124)	−20 (−29 to −11)		−4 (−11 to 4)	
mg/dL	1.2 (1.0 to 1.3)	1.3 (1.1 to 1.7)	1.2 (1.0 to 1.4)	−0.2 (−0.3 to −0.1)		−0.04 (−0.1 to 0.1)	
eGFR, *mL/min/1.73 m²*	67.5 (57.8 to 85.7)	56.6 (48.3 to 74.6)	66.2 (55.3 to 81.9)	10.5 (4.8 to 16.2)	<0.001	1.6 (−4.2 to 7.5)	0.56
12-mo outcomes							
Creatinine level					<0.001		0.33
µmol/L	98 (84 to 111)	106 (95 to 141)	97 (80 to 115)	−21 (−31 to −12)		−4 (−12 to 4)	
mg/dL	1.1 (1.0 to 1.3)	1.2 (1.1 to 1.6)	1.1 (0.9 to 1.3)	−0.2 (−0.4 to −0.1)		−0.04 (−0.1 to 0.1)	
eGFR, *mL/min/1.73 m²*	72.8 (58.6 to 74.4)	57.7 (46.0 to 68.6)	67.2 (55.8 to 78.3)	13.6 (7.9 to 19.2)	<0.001	1.4 (−7.2 to 9.8)	0.76
Delayed graft function, *n* (%)	5 (25)	45 (45)	32 (32)	NA	0.076	NA	0.59

Reese P et al. *Ann Intern Med. 2018;* doi:10.7326/M18-0749

Figure 3. Trajectories of PCS, MCS, and domain scores over time among 20 HCV-negative recipients of HCV-infected kidneys.



Reese P et al. *Ann Intern Med. 2018;* doi:10.7326/M18-0749



Mehra M et al The drug intoxication epidemic and solid organ transplantation NEJM 2018; 378;1943-1945

Treating HCV-associated GN

CHAPTER 5: DIAGNOSIS AND MANAGEMENT OF KIDNEY DISEASES ASSOCIATED WITH HCV INFECTION

5.1: We recommend that a kidney biopsy be performed in HCV-infected patients with clinical evidence of glomerular disease (*Not Graded*).

5.2: We recommend that patients with HCV-associated glomerular disease be treated for HCV (*1A*).

Mild (kidney) disease : DAAs first (1C)
Severe (kidney) disease : DAAs and IS agents (+ plasma exchange?) (1C)
We recommend rituximab as the first-line immunosuppressive treatment (*1C*).

5.2.3: We recommend immunosuppressive therapy in patients with histologically active HCV-associated glomerular disease who do not respond to antiviral therapy, particularly those with cryoglobulinemic kidney disease (*1B*).

5.2.3.1: We recommend rituximab as the first-line immunosuppressive treatment (*1C*).

KDIGO Working Group. Kidney Int Suppl. 2018; in press

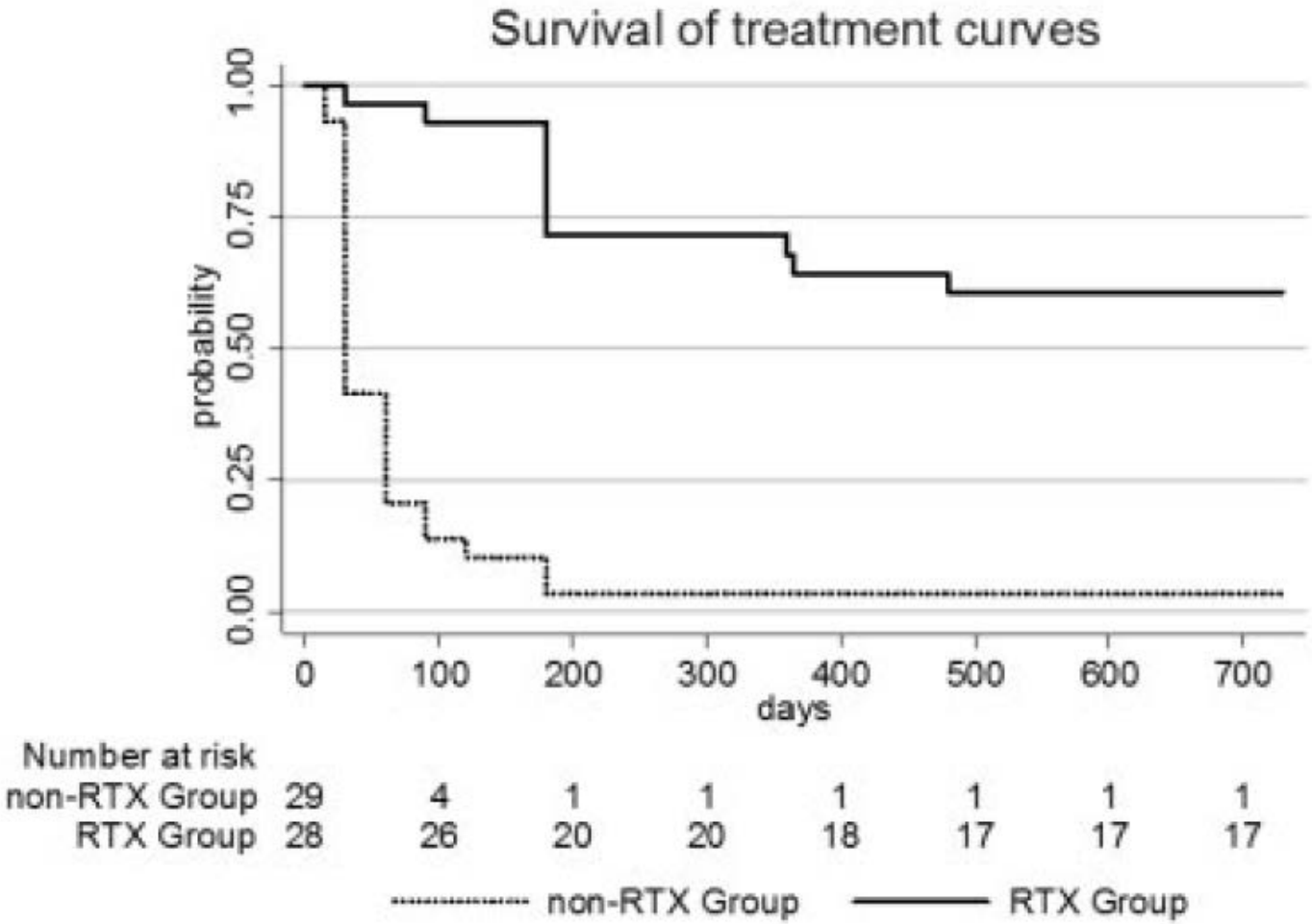
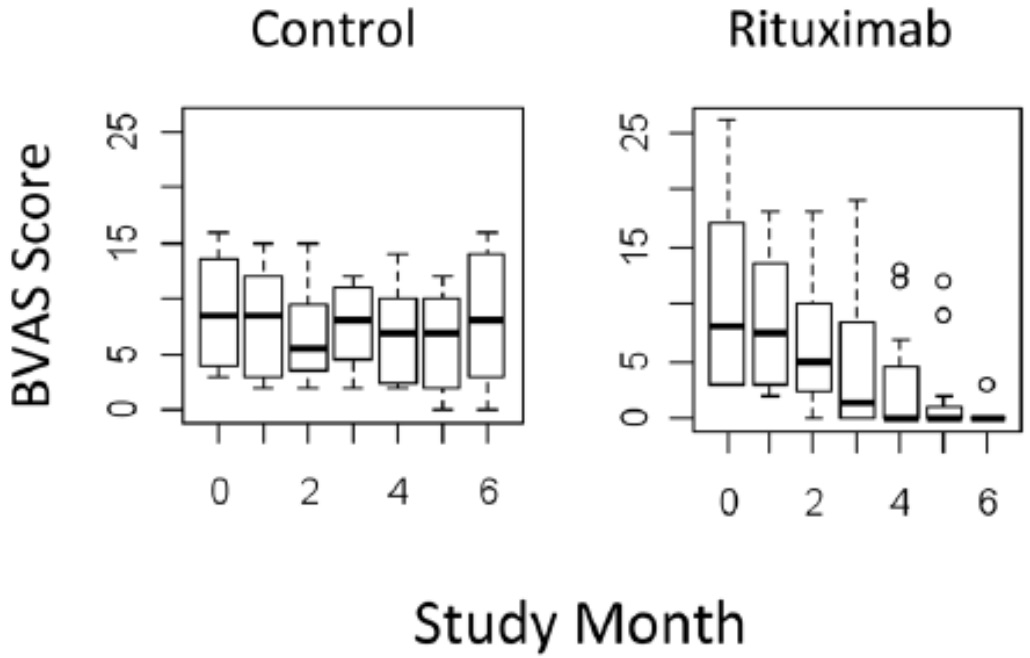


Figure 2. Survival curves in patients randomized to receive rituximab (RTX) therapy or conventional therapy (non-rituximab [non-RTX]), consisting of glucocorticoids, azathioprine, cyclophosphamide, or plasmapheresis.

De Vita S, *et al.* A randomized controlled trial of rituximab for the treatment of severe cryoglobulinemic vasculitis. *Arthritis Rheum* 2012; 64: 843-853.

A Randomized Controlled Trial of Rituximab Following Failure of Antiviral Therapy for Hepatitis C-Associated Cryoglobulinemic Vasculitis

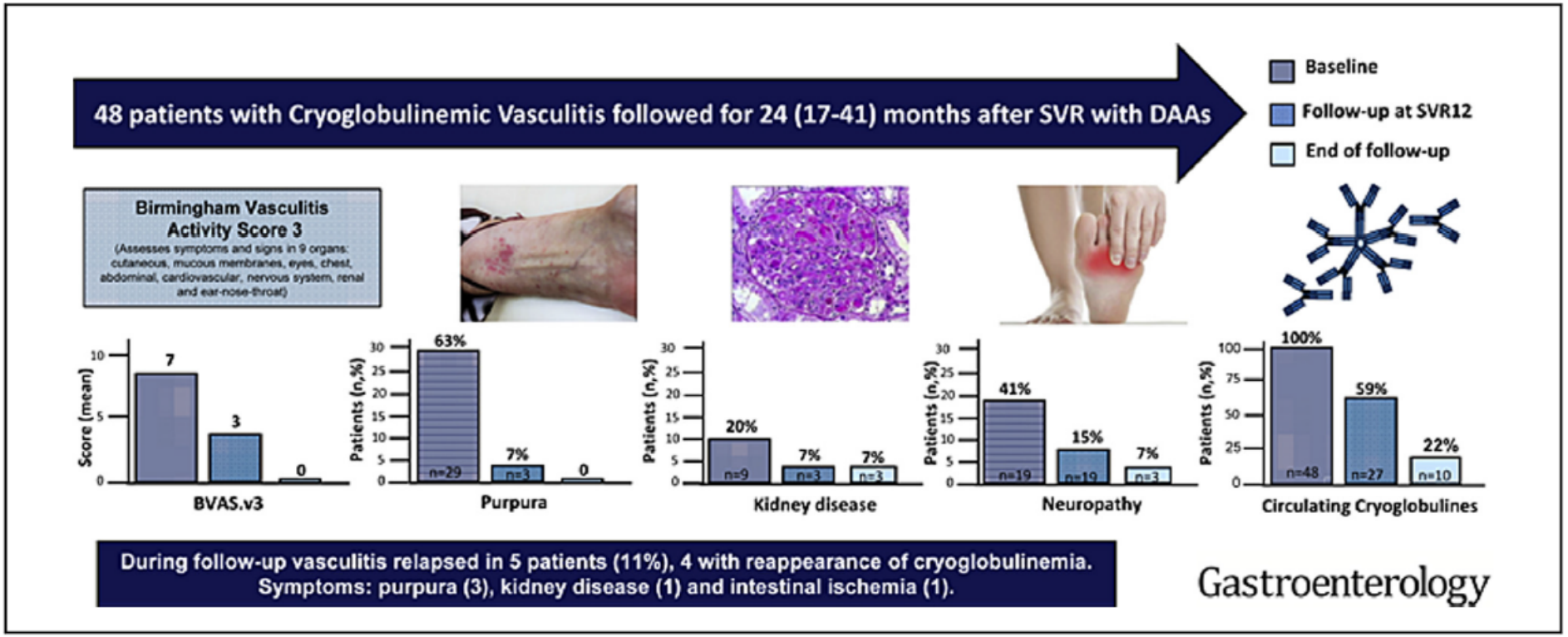
Michael C. Sneller, M.D., **Zonghui Hu, Ph.D.**, and **Carol A. Langford, M.D., M.H.S.**
Laboratory of Immunoregulation (M.C.S.) and Biostatistics Research Branch (Z.H), National Institute of Allergy and Infectious Diseases, Bethesda, MD, and Cleveland Clinic, Cleveland, OH (C.A.L.)



Sneller MC et al. *Arthritis Rheum* 2012; 64: 835-842.

Long-Term Outcomes of Patients With HCV-Associated Cryoglobulinemic Vasculitis After Virologic Cure

Martín Bonacci,[1] Sabela Lens,[1] Zoe Mariño,[1] María-Carlota Londoño,[1] Sergio Rodriguez-Tajes,[1] José M. Sánchez-Tapias,[1] Manel Ramos-Casals,[2] José Hernández-Rodríguez,[3] and Xavier Forns[1]



Gastroenterology 2018;155:311–315

Table 2. Features of Patients Who Experienced a Clinical Relapse After HCV Eradication

	At baseline							FU at PT12				Relapse				
Patient, Symptoms at Baseline	Sex	DAAs	TE (*kPa*)	Cryocrit (%)	IS	BVAS.v3	MELD/CP scores[a]	Cryocrit (%)	BVAS.v3	CR	IS	Months after DAAs	Cryocrit (%)	BVAS.v3	IS	Symptoms/signs
1, Purpura	F	SOF/RBV	12.7	1.2	No	3	8/A5	0	0	C	No	22	0.7	3	No	Repetitive purpura episodes
2, Purpura	F	SOF/SIM	17	7.7	No	3	14/A6	2.1	0	C	No	24	2.5	3	No	Repetitive purpura episodes
3, Purpura/neuropathy	F	SOF/VEL	4	3.5	Cort	9	—	0	3	C	No	6	0.7	6	No	Purpura
4, Nephropathy	F	SOF/DAC	43	1.7	Cort	12	8/A5	1.0	4	C	No	12	1.3	10	Cort	Nephrotic syndrome
5, Neuropathy	F	3D/RBV	29	0.6	No	9	6/A5	0	3	C	No	15	0	11	Cort	Acute mesenteric ischemia/purpura

3D, paritaprevir/ritonavir/ombitasvir/dasabusvir; C, complete; Cort, corticosteroids; CP, Child-Pugh score; CR, clinical response; DAC, daclatasvir; F, female; FU, follow-up; IS, immunosuppression; MELD, Model for End-Stage Liver Disease; PT12, 12 weeks after antiviral therapy; RBV, ribavirin; SIM, simeprevir; SOF, sofosbuvir; TE, transient elastography; VEL, velpatasvir.

[a]None of the patients with cirrhosis had a previous decompensation.

Bonacci M et al. *Gastroenterology* 2018; 155:311-315

Take-Home Messages

- Exciting time for those involved in the battle against HCV in CKD/dialysis/ kidney TP
- Major progress in the treatment of HCV in CKD patients: impressive new evidence
- No complacency anymore: right time to get rid of HCV from nephrology field , in line with WHO commitment to eliminate viral hepatitis as a public health problem by 2030
- Combining treatment and prevention (HD !)

KDIGO 2018 Clinical Practice Guideline for the Prevention, Diagnosis, Evaluation, and Treatment of Hepatitis C in Chronic Kidney Disease

VOLUME 8 | ISSUE 3 | OCTOBER 2018

www.kisupplements.org

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List of Abbreviations (1)

AASLD : American Association for the Study of Liver Disease
ALT : Alanine Aminotransferase
AST : Aspartate Transaminase
CI : Confidence Interval
CKD : Chronic Kidney Disease
CV : Cardiovascular
DAAs : Direct-Acting Antiviral Agents
DOPPS : Dialysis Outcomes and Practice Patterns Study
EBR : Elbasvir
EIA : Enzyme Immunoassay
ESRD : End-Stage Renal Disease
GFR : Glomerular Filtration Rate
GN : Glomerulonephritis
GT : Genotype
GZR : Grazoprevir
HBV : Hepatitis B Virus
HCV : Hepatitis C Virus
HD : Hemodialysis

List of Abbreviations (2)

HIV : Human Immunodeficiency Virus
HR : Hazard Ratio
IDSA : Infectious Disease Society of America
IS agents : Immunosuppressive agents
KDIGO : Kidney Disease Improving Global Outcomes
KDPI : Kidney Donor Profile Index
MMF : Mycophenolate Mofetil
MPGN : Membranoproliferative Glomerulonephritis
NAT : Nucleic Acid Testing
PI : Protease Inhibitors
RCT : Randomized Controlled Trial
RNA : Ribonucleic Acid
RTX : Rituximab
SAE : Serious Adverse Event
SOF : Sofosbuvir
SVR : Sustained Virologic Response
TP : Transplantation
WHO : World Health Organization