Terapia dell'epatite C nel nefropatico

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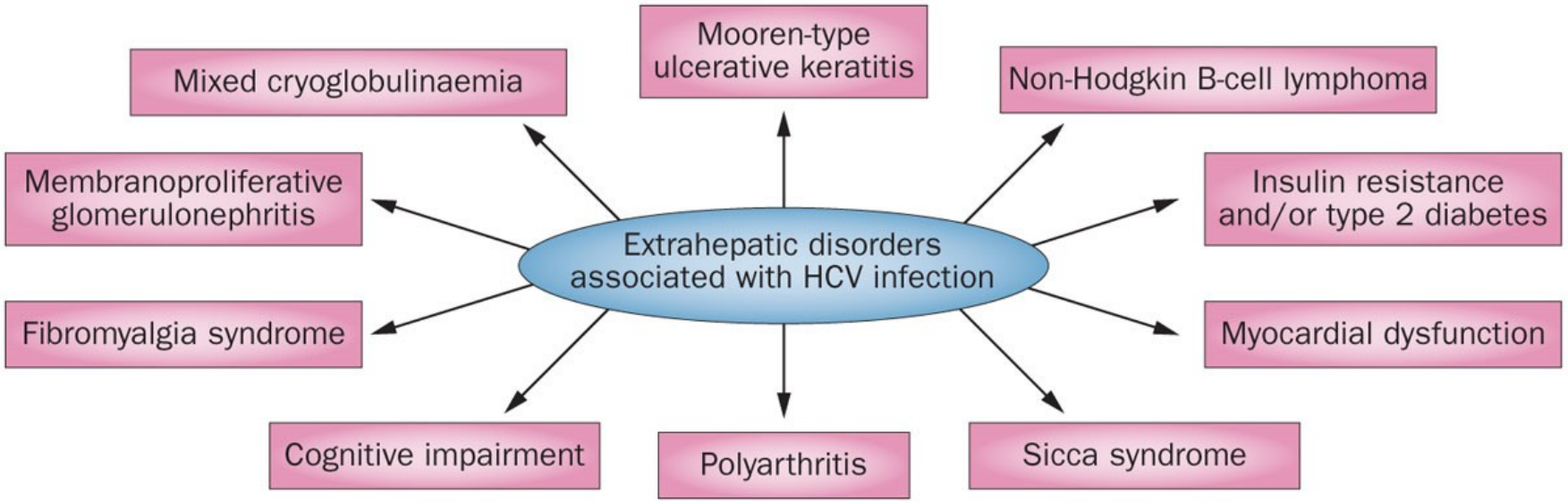
San Giovanni Rtondo

HCV, a hepatotropic virus

HCV, a multifaceted disease

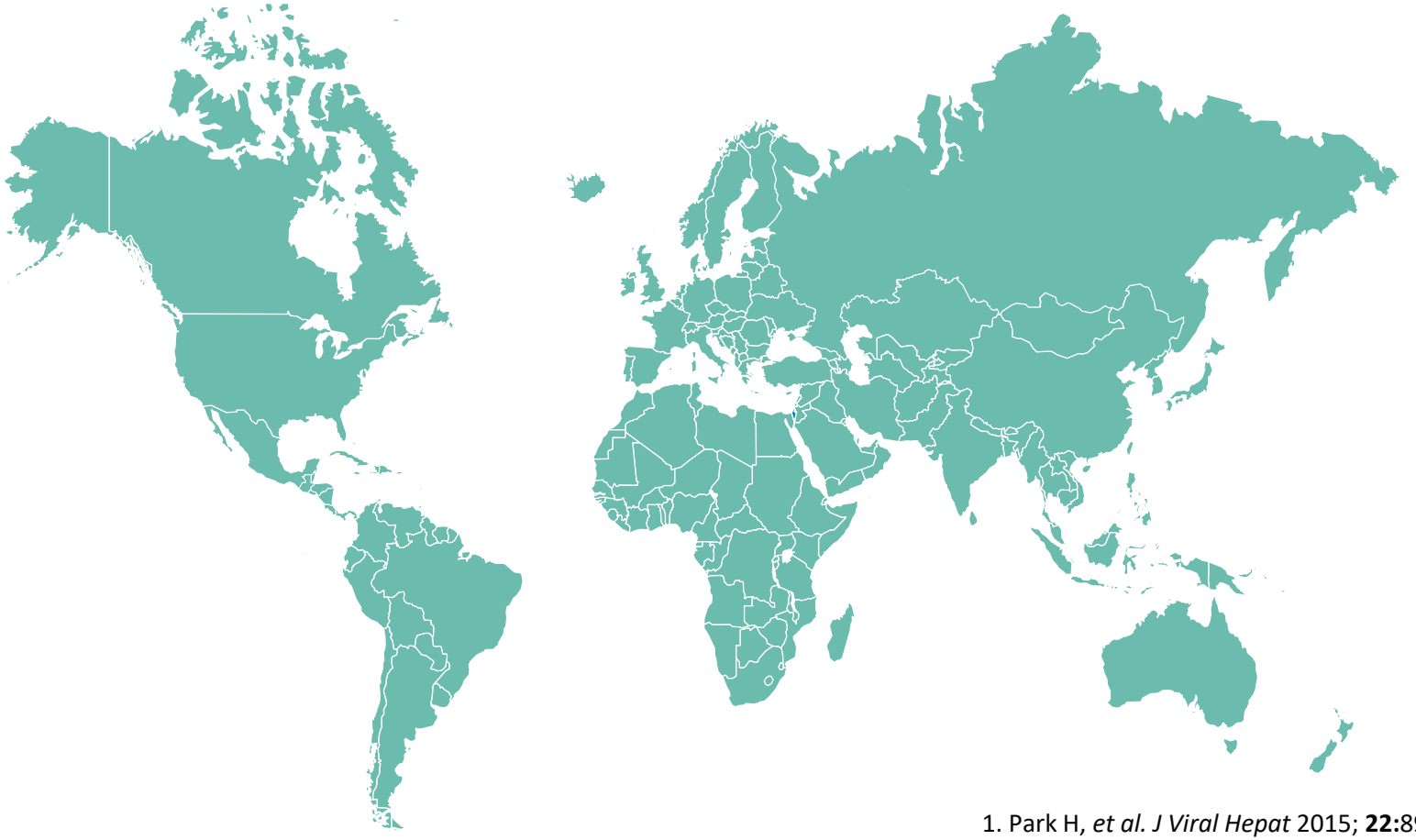
Non-exhaustive list of extrahepatic manifestations that have been associated with HCV infection



Negro, F. (2013) HCV causes systemic disorders that can be cured
Nat. Rev. Gastroenterol. Hepatol. doi:10.1038/nrgastro.2013.222

HCV Infection in Patients with CKD

HCV+ patients have a 23% higher risk of presenting with CKD vs. HCV– patients[1]



1. Park H, *et al. J Viral Hepat* 2015; **22:**897–905;
2. Molnar M, *et al. Hepatol* 2015; **61:**1495–502;
3. Kidney International 2008; **73:**Suppl 109 S1–99.

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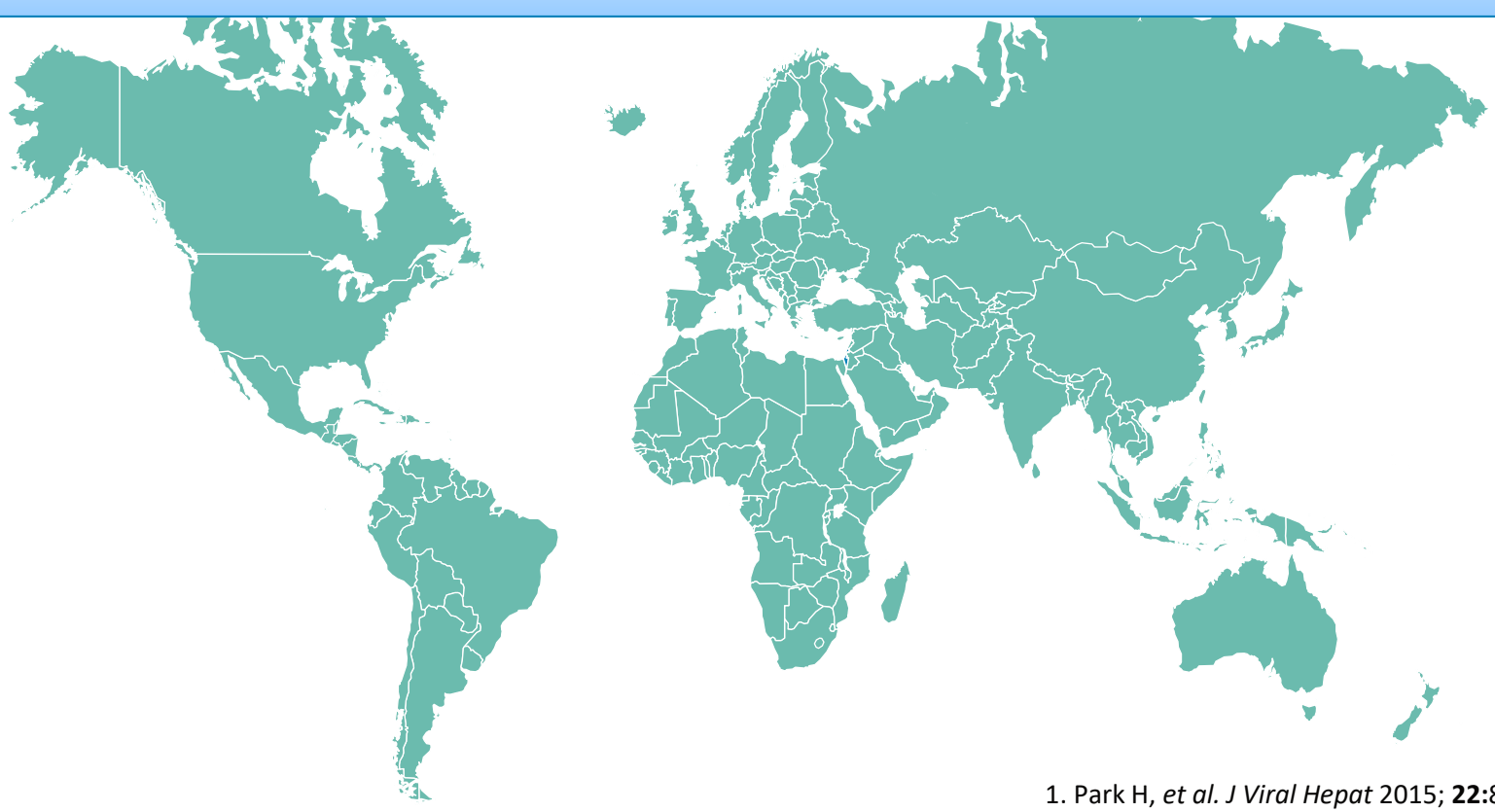
Among US veterans with HCV, 11.2% had renal impairment
(n=100,518; 2004–2006; incidence rate 16.7/1000 patient-years)[2]



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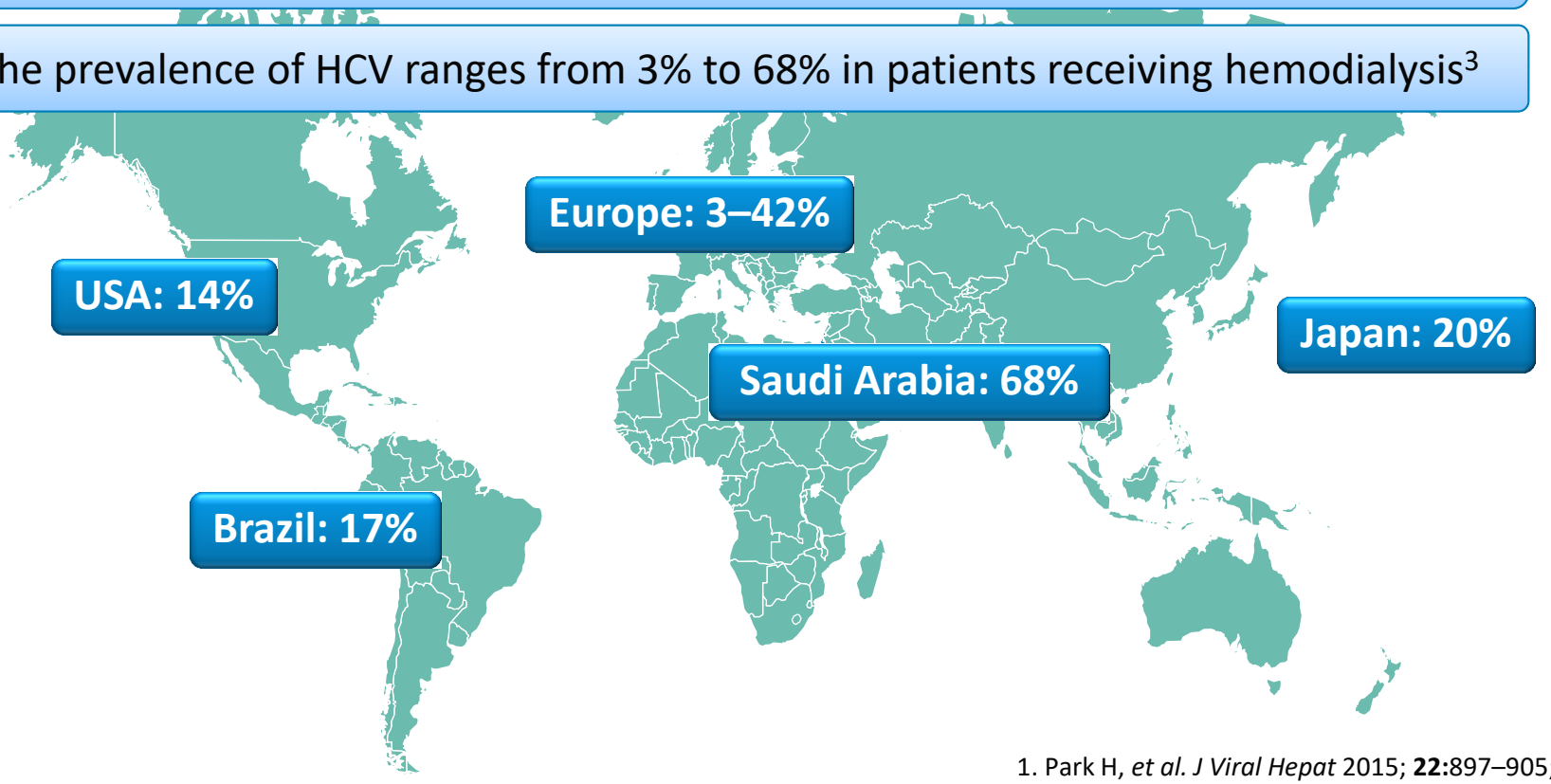
The prevalence of HCV ranges from 3% to 68% in patients receiving hemodialysis[3]



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ESITI DELLE TERAPIE ANTIVIRALI IN PAZIENTI CON INFEZIONE CRONICA DA HCV : uno studio collaborativo

Centro Coordinatore: San Giovanni Rotondo

No. 17 Centri Pugliesi

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- Bari (Milella/Angarano)
- Castellana Grotte (Cozzolongo)
- Bari (Di Leo/Barone)
- Foggia (Santantonio/Fasano)
- Galatina (Tundo)
- Ostuni (Gatti)
- Castellaneta (Termite)
- Bari (Sabba/Napoli)
- Bari (Lauletta)
- Andria (Francavilla)
- Barletta (Cuccorese)
- Casarano (Metrangolo/Bacca)
- Bisceglie (Francavilla)
- Martina Franca (Rizzo)
- Lecce (Romano/Carraturo/Maci)
- Scorrano (Paiano)

No. 7 Centri Nazionali

- Caserta (Messina)
- Bologna (Andreone)
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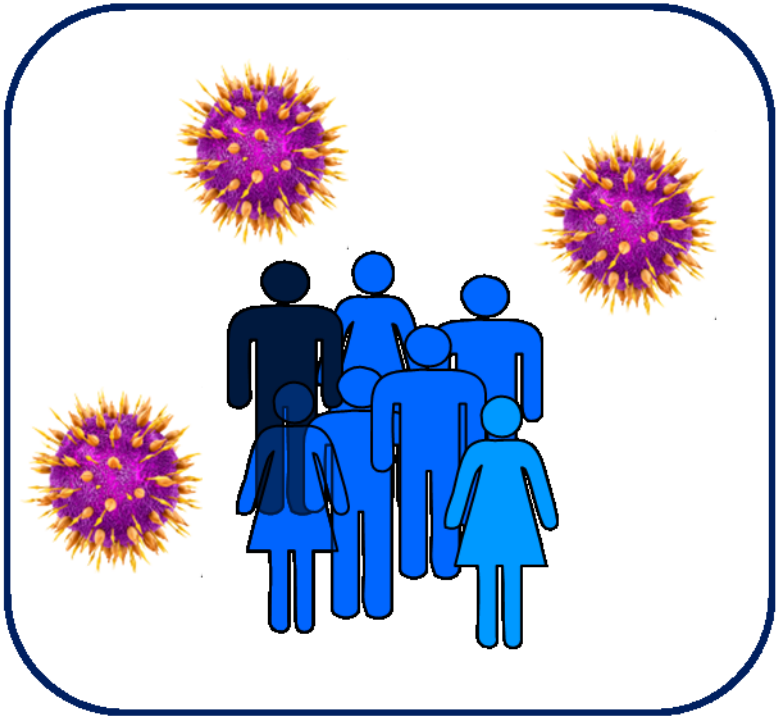
- Napoli (Gaeta/Brancaccio)
- Roma (Angelico/Masetti)
- Torino (Smedile)
- Venosa (Carretta)

ESITI DELLE TERAPIE ANTIVIRALI IN 2612 PAZIENTI CON INFEZIONE CRONICA DA HCV : uno studio collaborativo

Baseline Demographics

ALL (no.= 2612)	N (%)
Gender	
M	1498 (57.3)
F	1114 (42.6)
Age; ***(yrs) mean ± SD***	64,2 ± 11,5
>70 years	991 (37.9)
HCV genotype	
1a	224 (3.1)
1b	1590 (61.9)
2	494 (18.9)
3	157 (6.0)
4	135 (5.2)
GFR ***(C-G calculated)***	
(0-15)	-
(15,1-30)	8 (0.3)
(30,1-60)	**387 (14.8)**
(60,1-90)	981 (37.6)
(> 90)	1236 (47.3)

Key Considerations for HCV-Infected Patients with CKD



- ↓ eGFR rates
- ↑ Albuminuria
- ↑ CKD progression
- ↑ Mortality from renal diseases

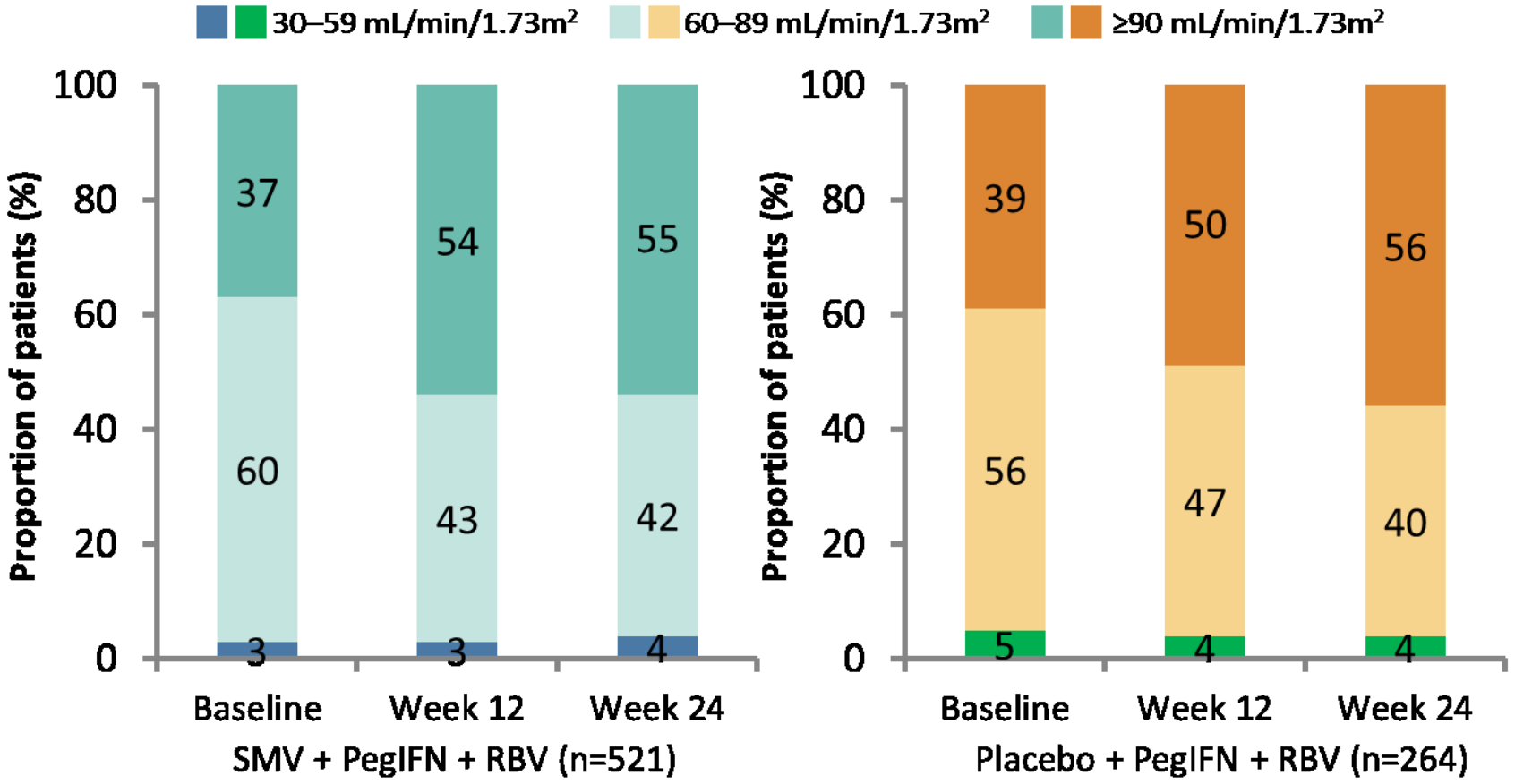
Prevalence:
In a recent analysis 8.5% of subjects aged 20–64 and 26.5% aged ≥65 years with HCV also had CKD[1]

HCV infection is associated with reduced renal function[2–5]

1. Senaka P, *et al. Hepatology* 2015; **62**(suppl):1120A;
2. Fabrizi F, *et al. New Journal of Science* 2014. doi:10.1155/2014/180203;
3. Tsui JI, *et al. J Am Soc Nephrol.* 2006; **17**:1168–1174;
4. Lucas GM, *et al. J Inf Dis* 2013; **208**:1240–1249; 5. Lee MH, *et al. J Inf Dis* 2012; **206**:469–477.

Antiviral Therapy Improves Renal Function*

Post-hoc analysis of Phase 3 studies* of SMV + PegIFN + RBV in treatment-naive patients with HCV GT1

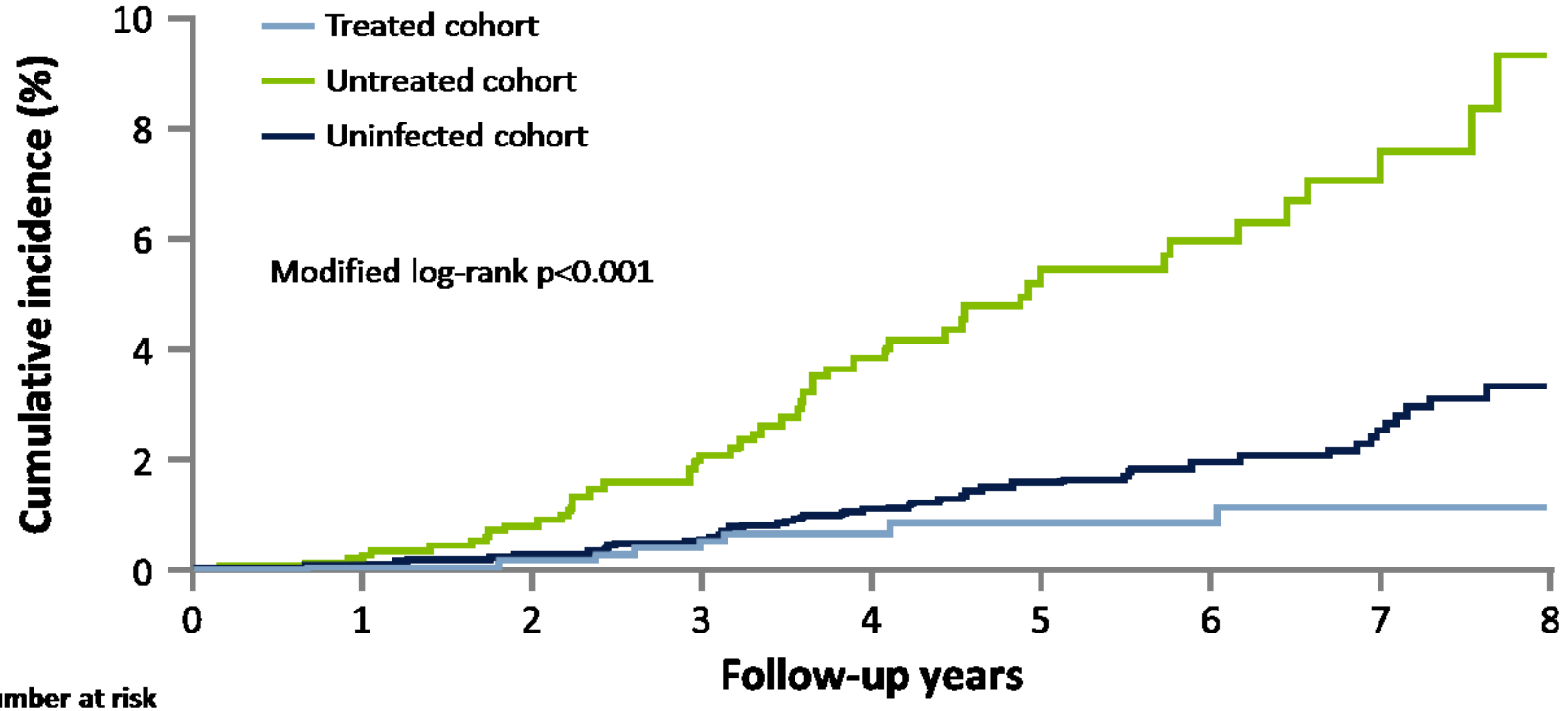


* Results from a historical studies (QUEST-I and QUEST-II), and have not yet been confirmed with the AbbVie regimen.

Mauss S, *et al.* VHC 2014; Poster presentation; P14.

Antiviral Therapy Improves End-Stage Renal Disease in Patients with Diabetes*

Cumulative incidence of ESRD in three study cohorts, analyzed by the modified log-rank test with death adjusted as a competing risk event



Number at risk									
Treated	1411	1400	987	755	586	418	303	168	47
Untreated	1411	1388	962	711	530	362	262	152	43
Uninfected	5644	5591	3928	2980	2322	1624	1194	684	201

* Results from a historical study, and have not yet been confirmed with the AbbVie regimen.

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

Is antiviral tx recommended for patients with ESRD ?

AASLD guidance → Antiviral treatment is imperative for those with cryoglobulinemia and symptoms or objective evidence of end-organ manifestations

EASL guidance → Treatment should be prioritized in patients with clinically significant extra-hepatic manifestations (e.g. HCV-related cryoglobulinemia)

Persons on long-term hemodialysis should also be prioritized/considered for HCV therapy due to an increased risk of nosocomial transmission

AASLD Recommendations for Testing, Managing, and Treating Hepatitis C; Available at http://www.hcvguidelines.org/fullreport (accessed March 2016);
EASL Recommendations on Treatment of Hepatitis C. *J Hepatol* 2015, Available at: http://www.easl.eu/research/our-contributions/clinical-practice-guidelines (accessed March 2016).

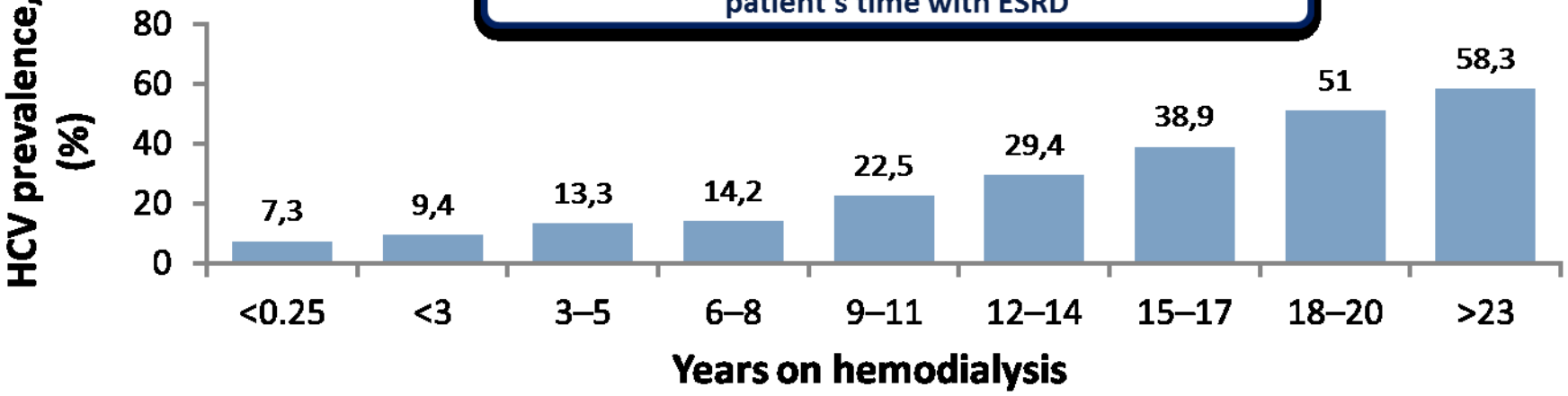
Patients with CKD on Hemodialysis are at Risk of Contracting HCV

Hemodialysis increases risk of HCV exposure and nosocomial transmission

Mean anti-HCV prevalence of **13.5%** in patients on hemodialysis in France, Germany, Italy, Japan, Spain, UK and US*

Risk factors: number of transfusions, duration of hemodialysis, type of hemodialysis, lack of compliance with universal precautions

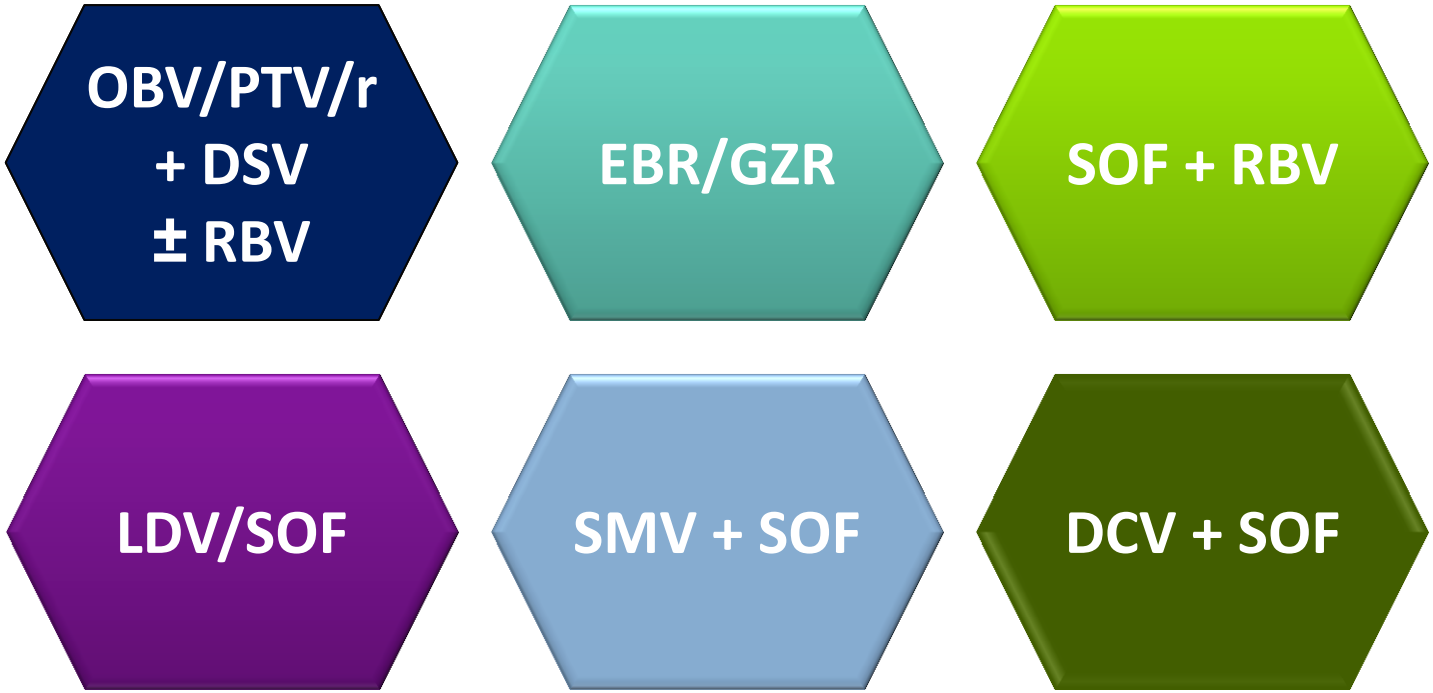
Variation in HCV prevalence by patient's time with ESRD



* Hemodialysis Outcomes and Practice Patterns Study 2004.
† The mean time on ESRD was 4.9 years, with a standard deviation of 5.4 years.

Fissell RB, *et al. Kidney International* 2004; **65**:2335–2342;
Aguirre Valadez J, *et al. Ther Clin Risk Manag* 2015; **11**:329–338.

A number of regimens are currently approved for use in patients with mild or moderate renal impairment



* eGFR ≥30 mL/min/1.73 m^2.
Zepatier is only approved in the US.

Viekirax, Exviera, Sovaldi , Harvoni, Olysio, and Daklinza SmPCs (all accessed March 2016);
Viekira Pak, Zepatier, Sovaldi , Harvoni, Olysio, and Daklinza US PIs (all accessed March 2016).

Dei nuovi antivirali, quali possono essere utilizzati nei pazienti con insufficienza renale cronica?

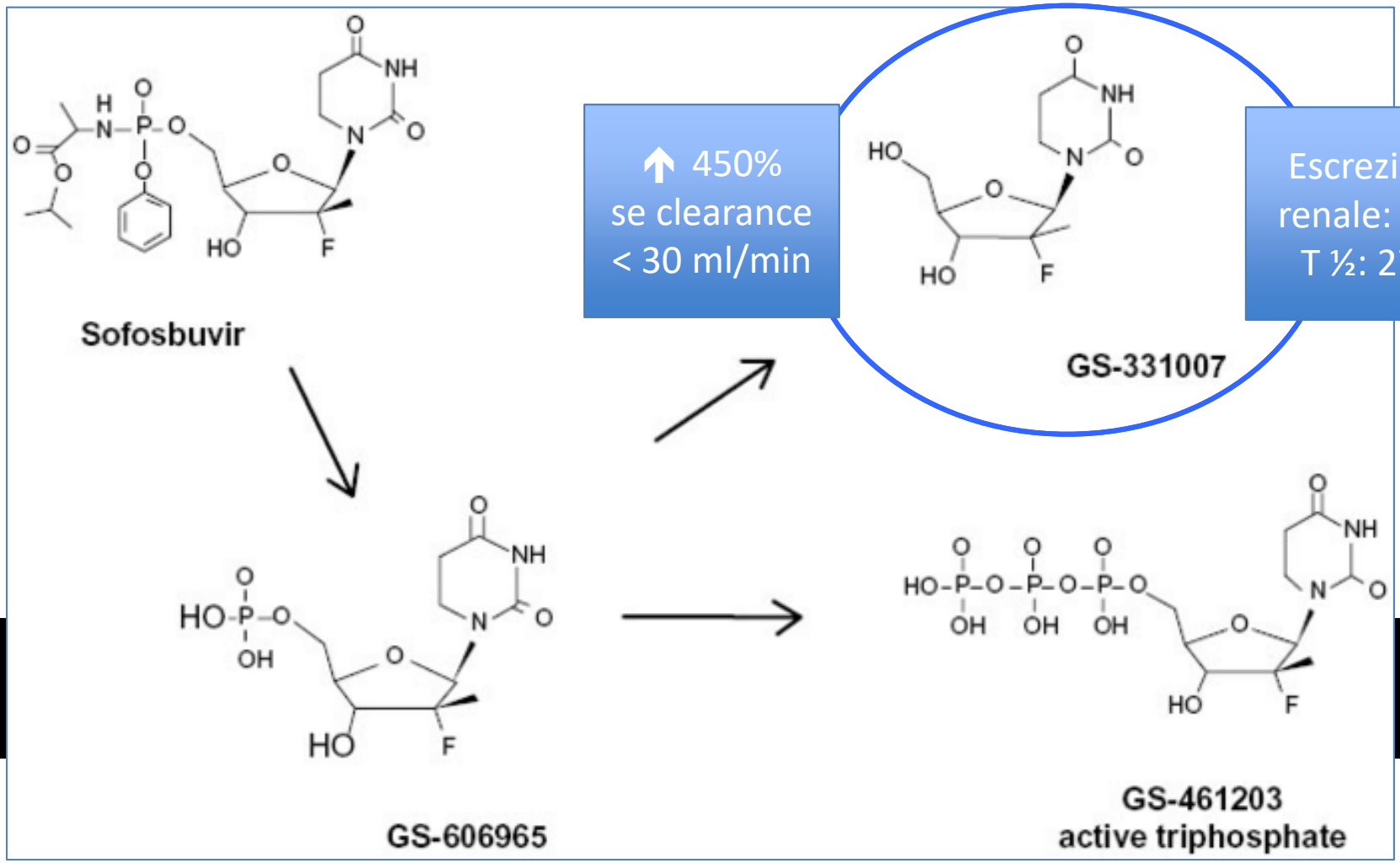
- **Sofosbuvir**
- **Simeprevir**
- **Daclatasvir**
- **Ombitasvir/paritaprevir/ritonavir**
- **Dasabuvir**
- **Ledipasvir**

Metabolismo

Emivita

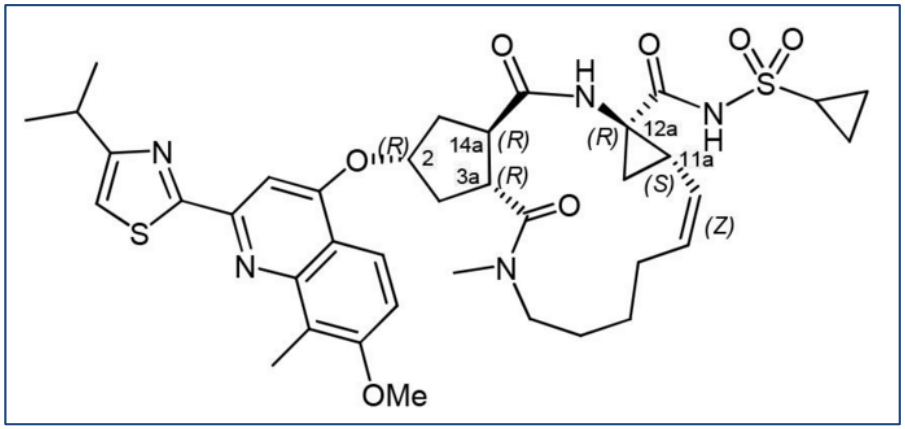
Escrezione

Sofosbuvir



Safety: Clearance renale > 30 ml/min

Simeprevir



Metabolismo epatico (CYP 3A4)

Escrezione biliare

91% nelle feci

< 1% nelle urine

Limite: associazione con Sofosbuvir

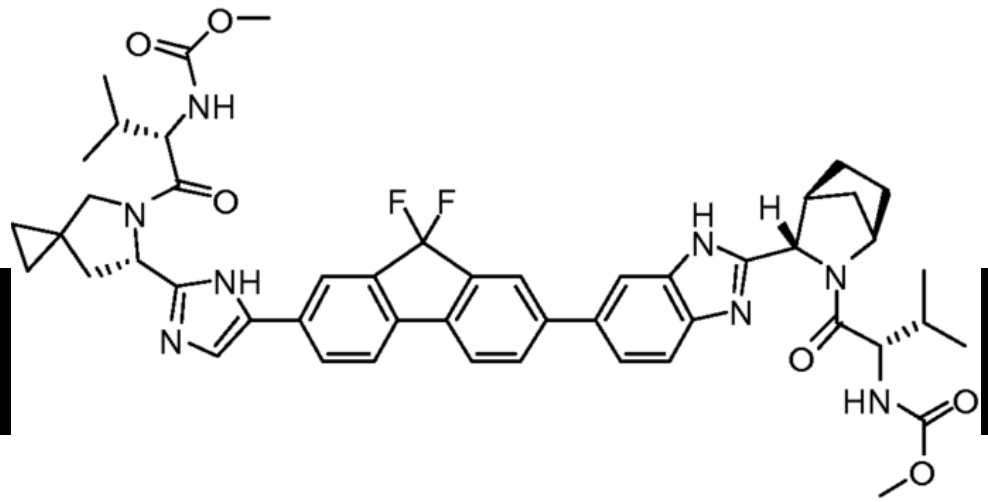
Daclatasvir

Pharmacokinetics	Summary
Once-daily dosing[1]	• Terminal half-life: ~12–15 h[1] • Single dose PD: beyond 24 h (potency)[2] • ≈ 99% protein-bound in HCV-infected subjects[1]
Metabolism* (Primarily mediated by CYP3A4)[3]	• Time-dependent inhibitor of CYP3A4[3]
	• Weak inducer of CYP3A4[3]
	• P-gp substrate[3] • Moderate inhibitor of P-gp and OATP1B1/B3[3] • Moderate to weak inhibitor of BCRP[3]
Elimination (hepatic metabolism and direct biliary excretion)[4]	• ≈ 88% of dose excreted in feces (as parent and metabolites)[5] • ≈ 5% in urine[6]

Limite: associazione con sofosbuvir

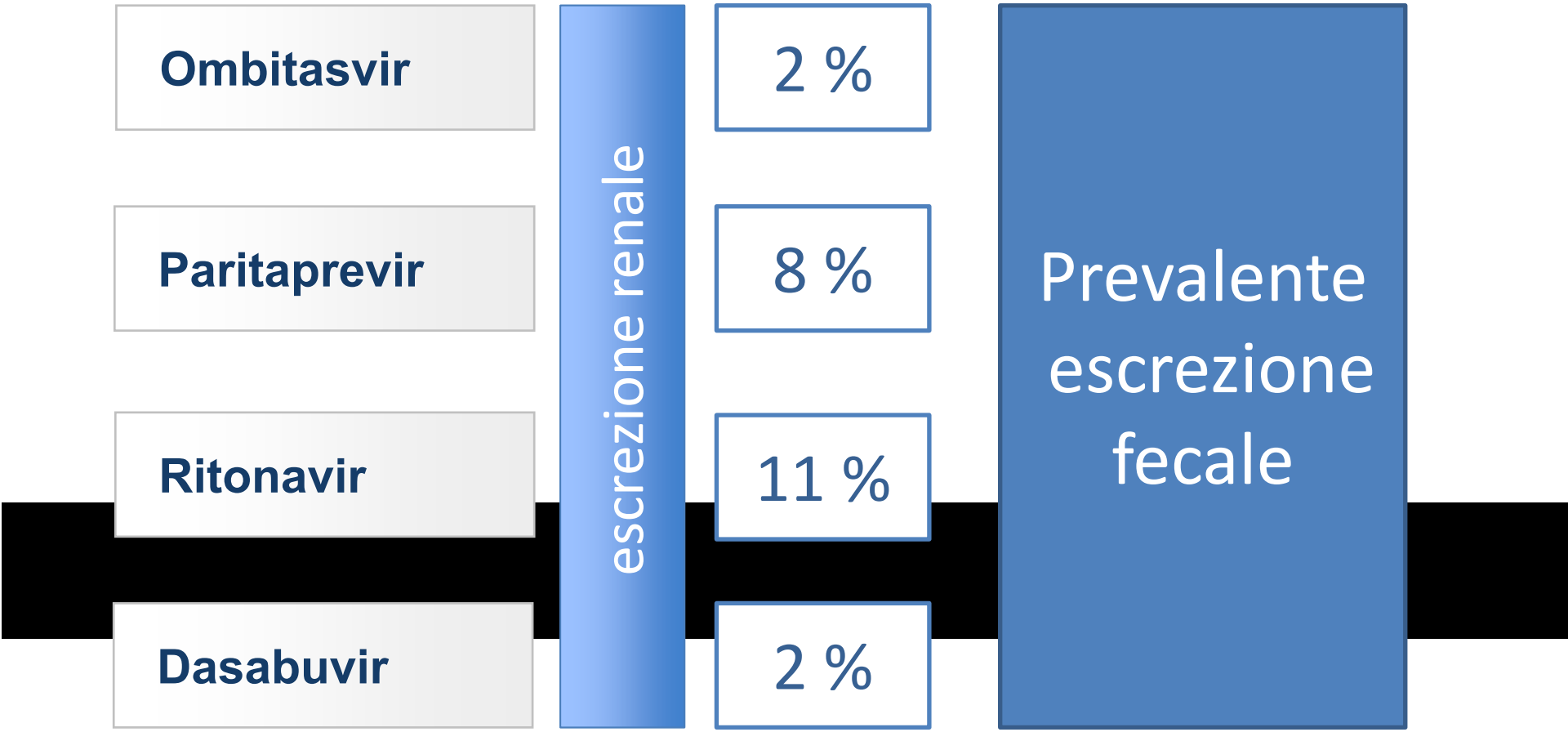
Ledipasvir

1. Escrezione renale < 1%
2. Associazione con sofosbuvir



Safety: Clearance renale < 30 ml/min non testata

Ombitasvir/paritaprevir/ritonavir e dasabuvir



Safety: Clearance renale < 30 ml/min

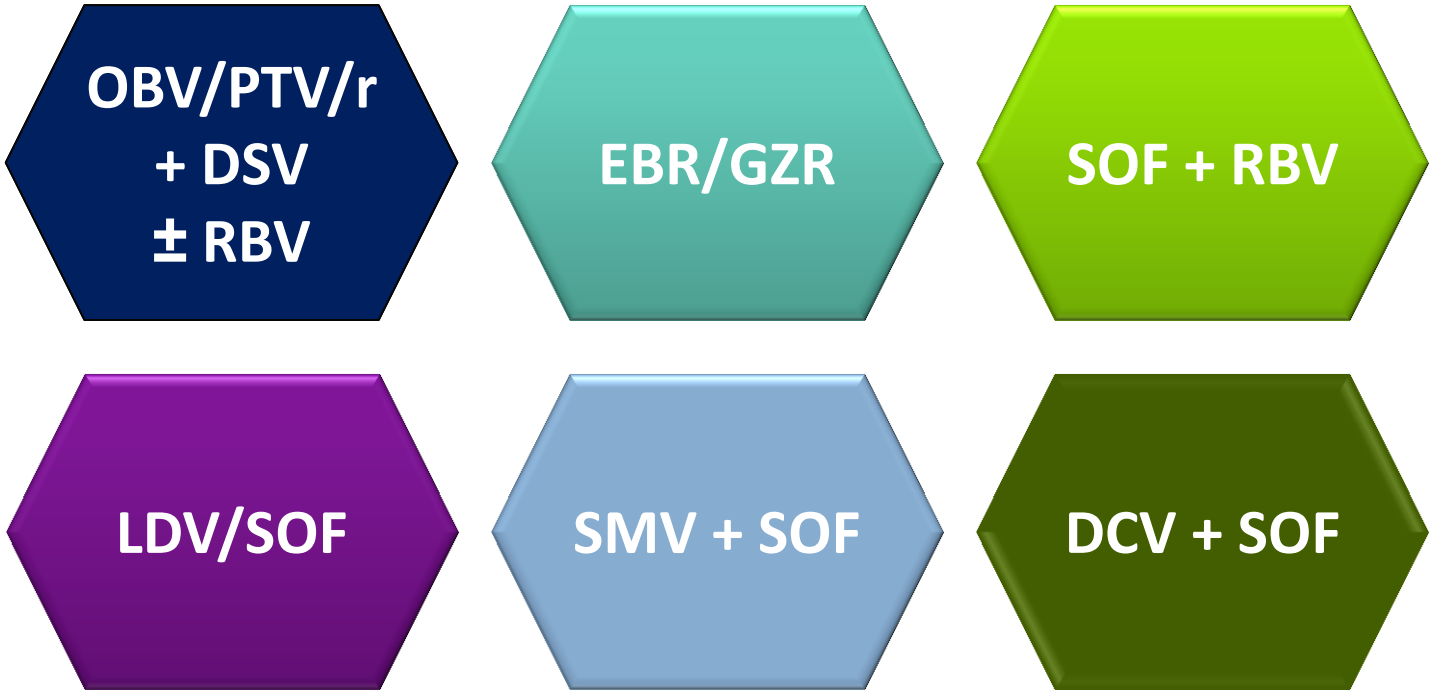
Pharmacokinetics of DAAs with Severe Renal Impairment

Change in AUC compared with healthy subjects, %	Severe renal impairment (eGFR <30 mL/min/1.73 m^2)
Ombitasvir	No change
Paritaprevir	↑ ≤50%
Ritonavir	↑114%
Dasabuvir	↑ ≤50%
Ledipasvir	Not relevant
Sofosbuvir GS-331007	↑171% ↑451%
Simeprevir	↑62%
Daclatasvir*	↑51%
Grazoprevir	↑65%
Elbasvir	↑86%

* Estimated for CrCl = 15 mL/min.

Khatri A, *et al. Hepatology* 2014; **60**(Suppl):320A;
Harvoni, Olysio, and Daklinza SMPC (accessed October 2015);
Yeh WW, *et al. Hepatology* 2014; **60**(Suppl 4):1940 (poster presentation).

A number of regimens are currently approved for use in patients with mild or moderate renal impairment



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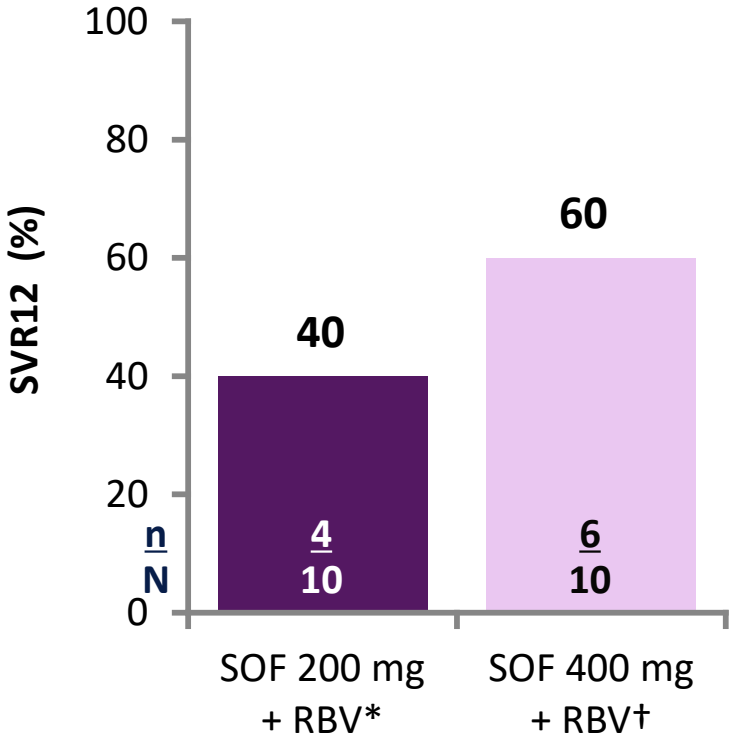
Phase 2b Study of **SOF + RBV** Patients with Severe Renal Impairment, Not on Dialysis

HCV GT1/3 treatment-naive/experienced patients
± cirrhosis treated for 24 weeks



No treatment-related SAEs occurred with either regimen

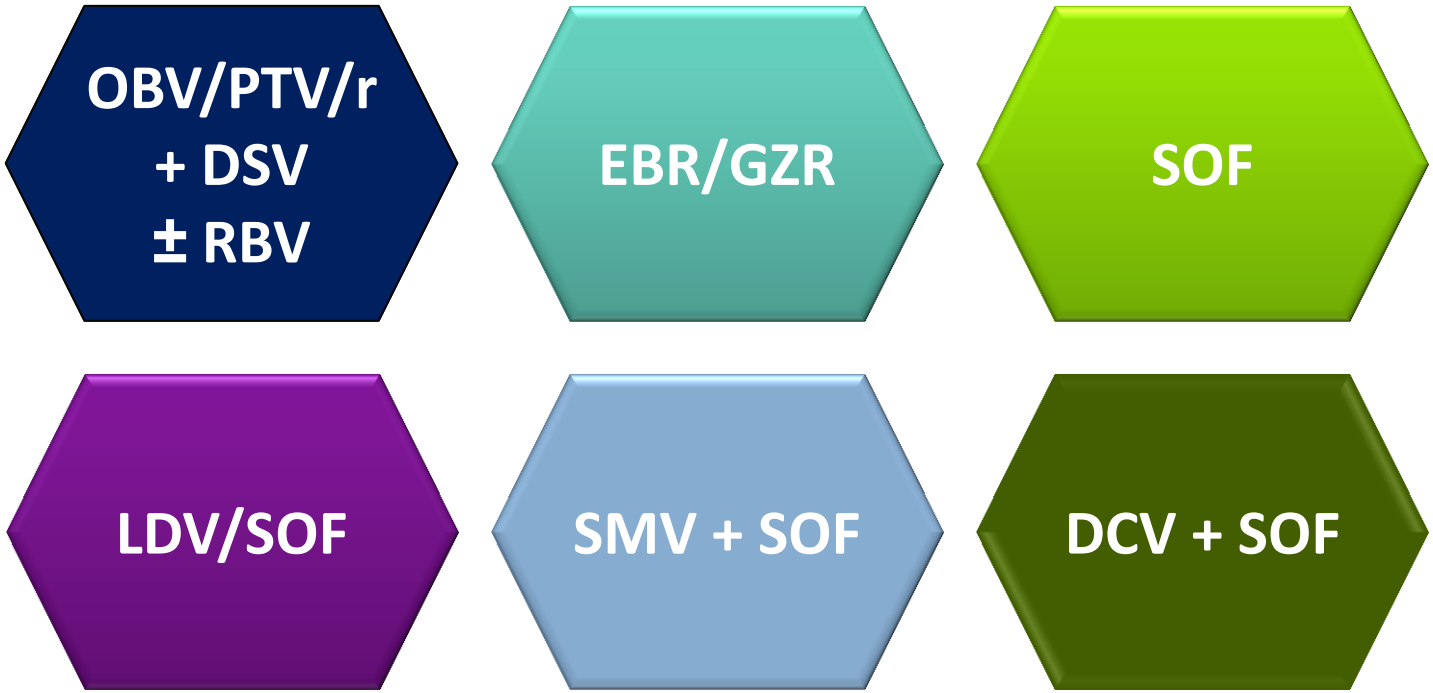
Discontinuations due to AEs:
0 for SOF 200 mg (1 discontinued RBV);
2 for SOF 400 mg‡

4 patients on SOF 200 mg + RBV and 3 patients on SOF 400 mg + RBV experienced a decline in hemoglobin <8.5 g/dL

* 5 patients relapsed with SOF 200 mg + RBV (one patient who withdrew was counted as failure);
† 2 patients relapsed with SOF 400 mg + RBV and 2 patients discontinued due to AEs;
‡ Grade 2 fatigue, Grade 3 renal failure and pneumonia.

Gane EJ, *et al. Hepatology* 2014; **60**(suppl):667A;
Martin P, *et al. Hepatology* 2015; **62**(suppl):765A.

OBV/PTV/r + DSV ± RBV and **EBR/GZR** are approved treatment options for patients with severe renal impairment*



*eGFR <30 mL/min/1.73 m^2; Zepatier is only approved in the US;
The safety and dose of SOF has not been established in patients with severe renal impairment or ESRD.

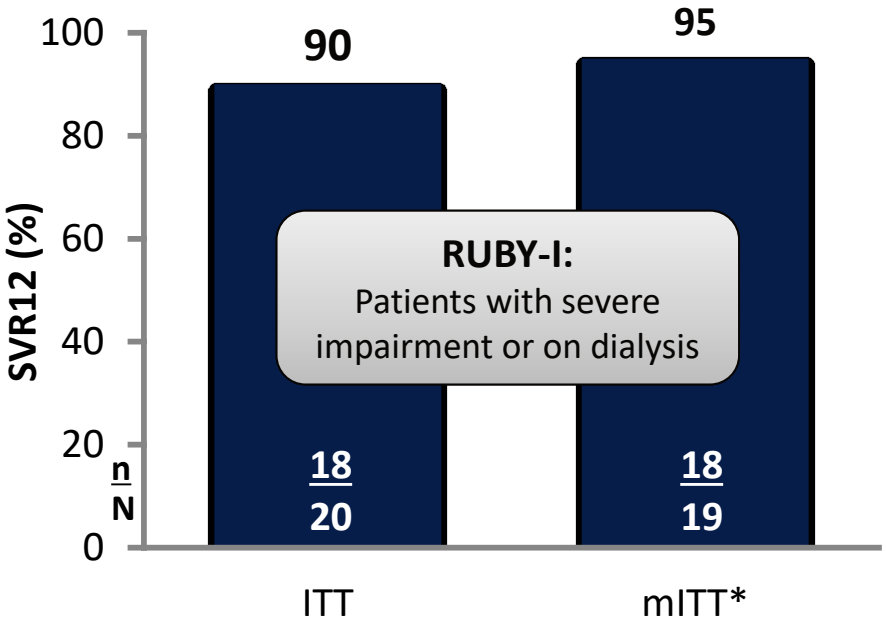
Viekirax, Exviera, Sovaldi , Harvoni, Olysio, and Daklinza SmPCs (all accessed March 2016); Viekira Pak, Zepatier, Sovaldi , Harvoni, Olysio, and Daklinza US PIs (all accessed March 2016).

Treatment Options For Patients with Severe Renal Impairment and ESRD

OBV/PTV/r + DSV EU SMPC

Renal impairment

No dose adjustment of Viekirax is required for patients with mild, moderate, or severe renal impairment (see section 5.2).



AEs were mild or moderate with no study drug discontinuations

One patient died 14 days post-treatment due to cardiac causes unrelated to the study drug†

No clinically significant changes in markers of liver or kidney function

* mITT = modified ITT (patients with post-treatment data availability).;
† Death due to left ventricular systolic dysfunction not attributed to DAAs or RBV.

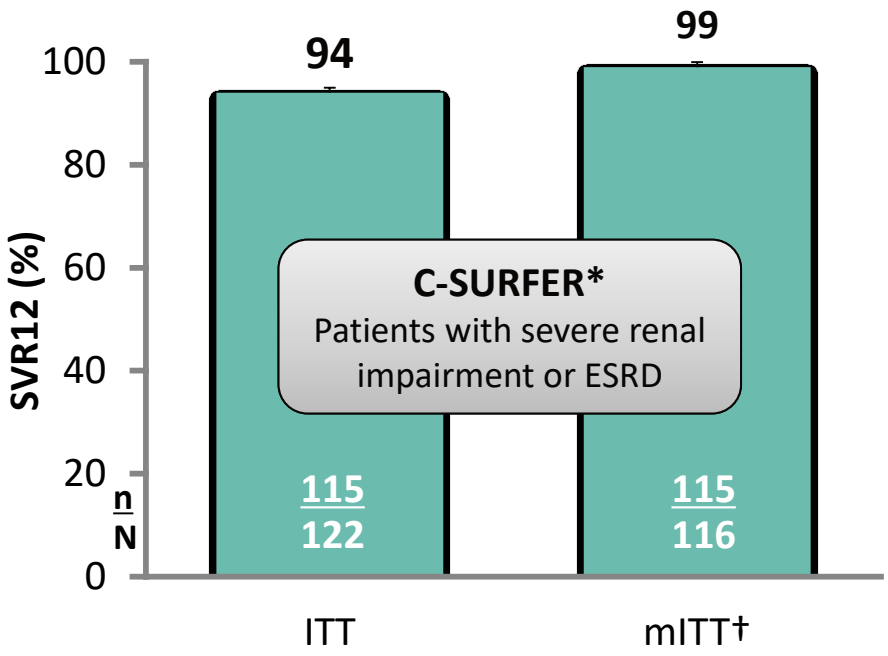
Viekirax and Eviera SmPC (accessed March 2016);
Pockros PJ, *et al. Gastroenterology* 2016; Epub ahead of print.

Treatment Options For Patients with Severe Renal Impairment and ESRD

EZR + GBR US Prescribing Information

Renal Impairment

No dosage adjustment of ZEPATIER is recommended in patients with any degree of renal impairment including patients on hemodialysis.



AEs were mild or moderate

No AEs leading to study drug discontinuations in the immediate treatment group (5 in the deferred treatment group)

SAEs occurred in 16 (14%) patients in the immediate treatment group; none were considered to be drug-related

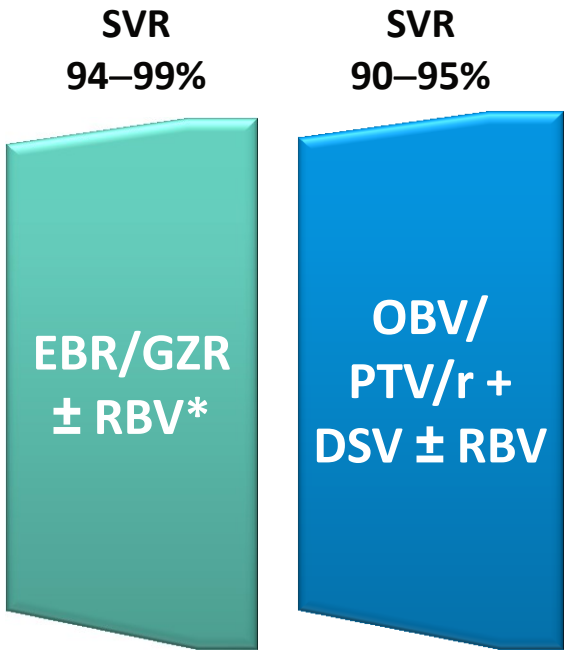
SAEs occurred in 19 (17%) patients in the deferred treatment group; 1 (increased lipase) was considered drug-related

* Zepatier is only approved in the US, excerpt from US PI.
† Modified full analysis set includes patients who received ≥1 dose of study drug, excluding those with missing data due to death or early discontinuation for reasons unrelated to the study drug.

Roth D, *et al. Lancet* 2015; **386:**1537–1545; Zepatier US PI (accessed March 2016).

What Have We Achieved in Clinical Trials?

Following successful clinical trials, HCV treatments are now available for patients with severe renal impairment



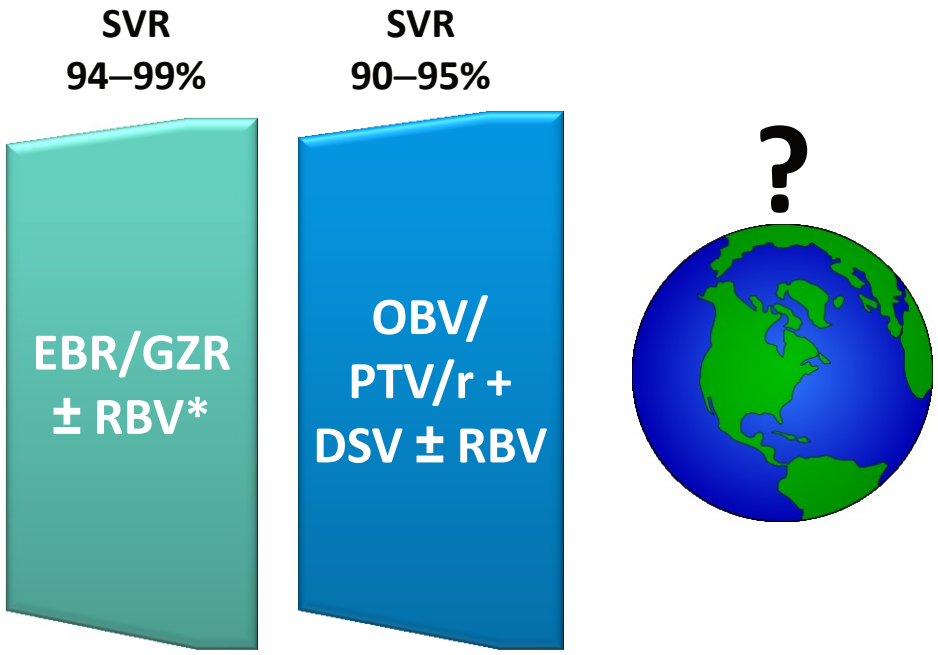
High SVR12 rates in patients with severe renal impairment in clinical trials

* Zepatier is only approved in the US.

Pockros PJ, *et al. Gastroenterology* 2016; Epub ahead of print.
Roth D, *et al. Lancet* 2015; **386:**1537–1545.

What Have We Achieved in Clinical Trials?

Can we replicate this in clinical practice?



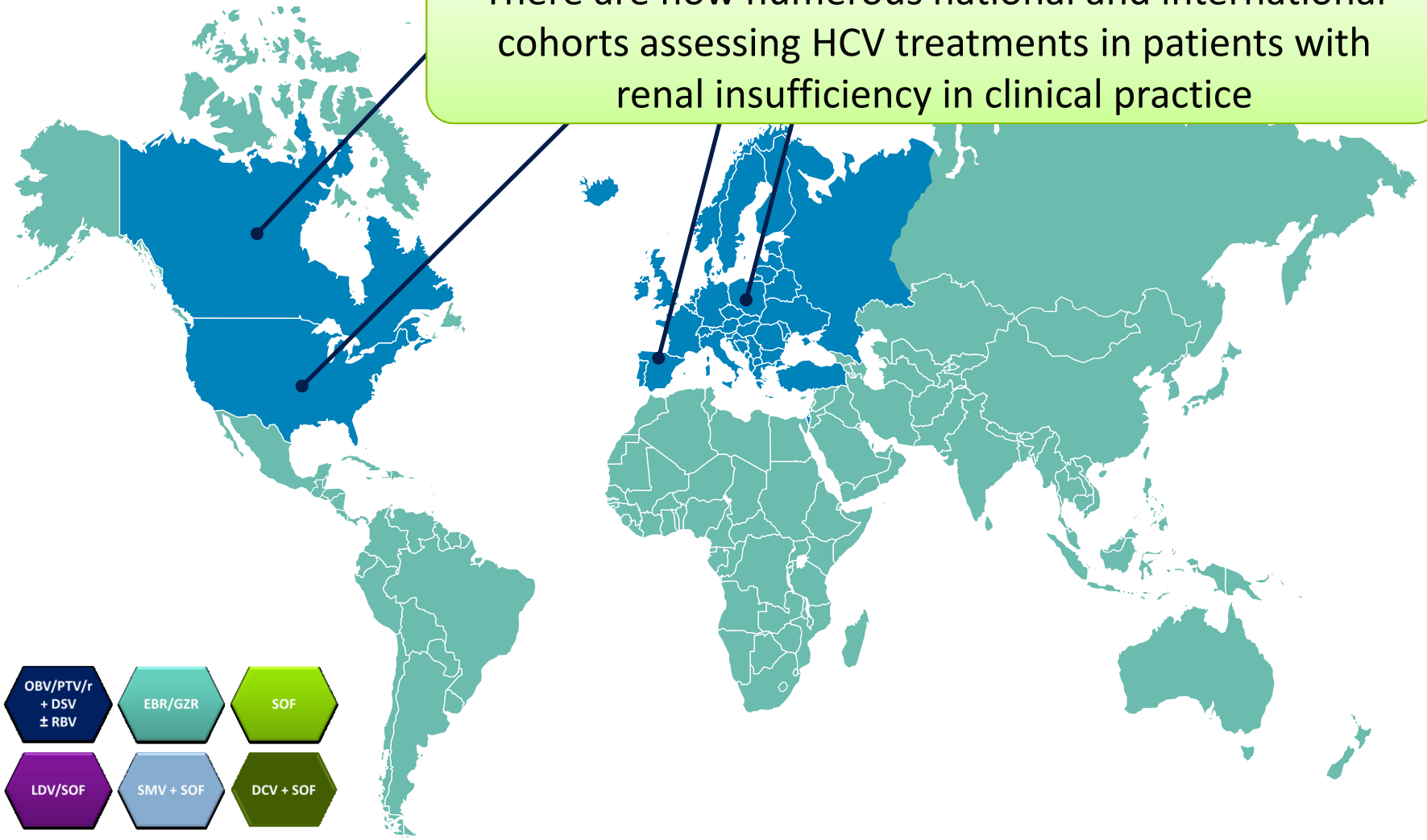
In patients with renal impairment evidence is now emerging from the real world…

* Zepatier is only approved in the US.

Pockros PJ, *et al. Gastroenterology* 2016; Epub ahead of print.
Roth D, *et al. Lancet* 2015; **386:**1537–1545.

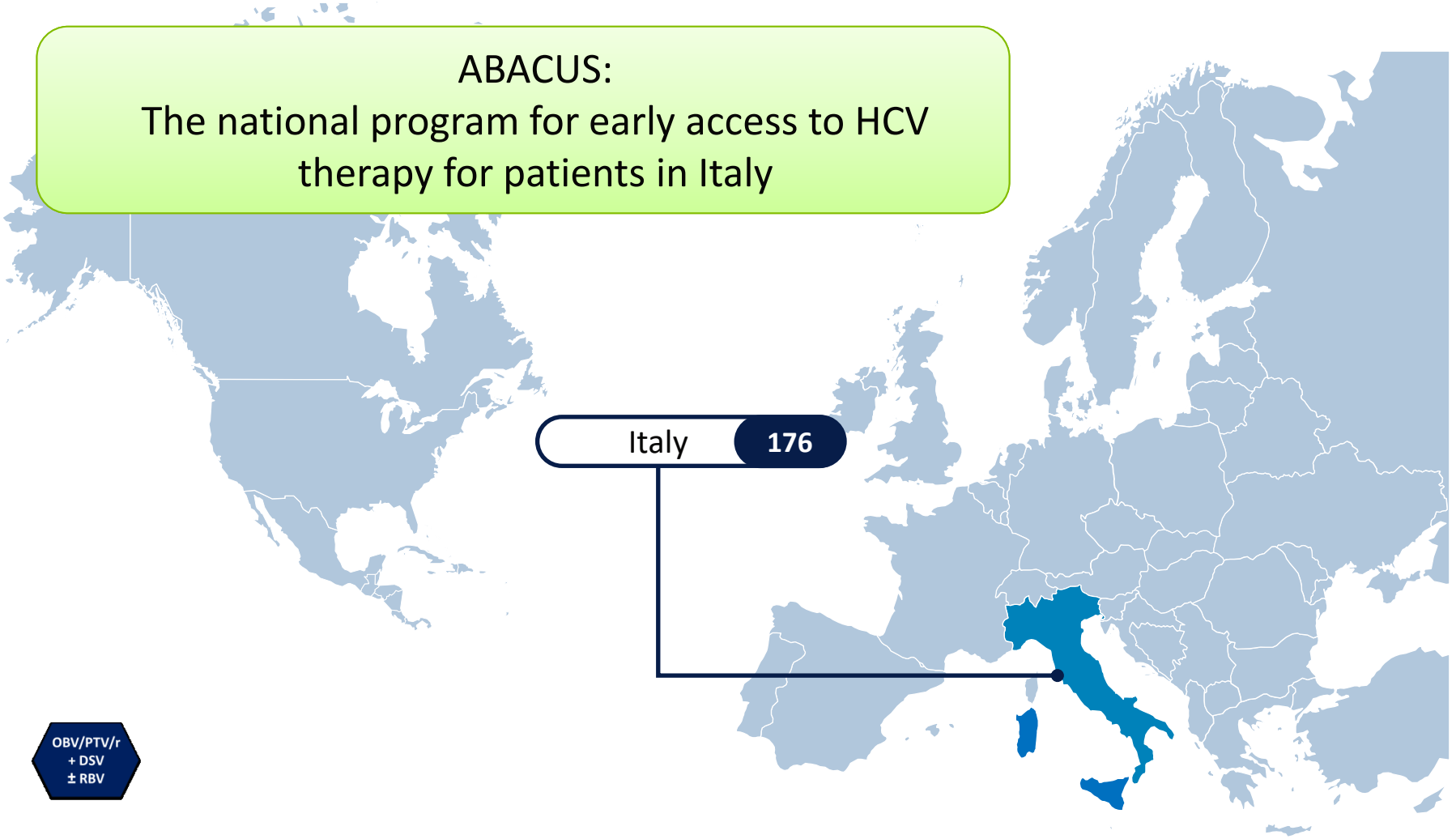
RWE Cohorts with Renally Impaired Patients

There are now numerous national and international cohorts assessing HCV treatments in patients with renal insufficiency in clinical practice



ABACUS – Italian Compassionate Use Study

ABACUS:
The national program for early access to HCV therapy for patients in Italy



Numbers indicate participating centers.

Petta S, AISF Annual Meeting , Rome 17–19 February 2016.

ABACUS – Italian Compassionate Use Study

>1000 patients enrolled in the compassionate use program

Primary efficacy analysis in **762** cirrhotic patients

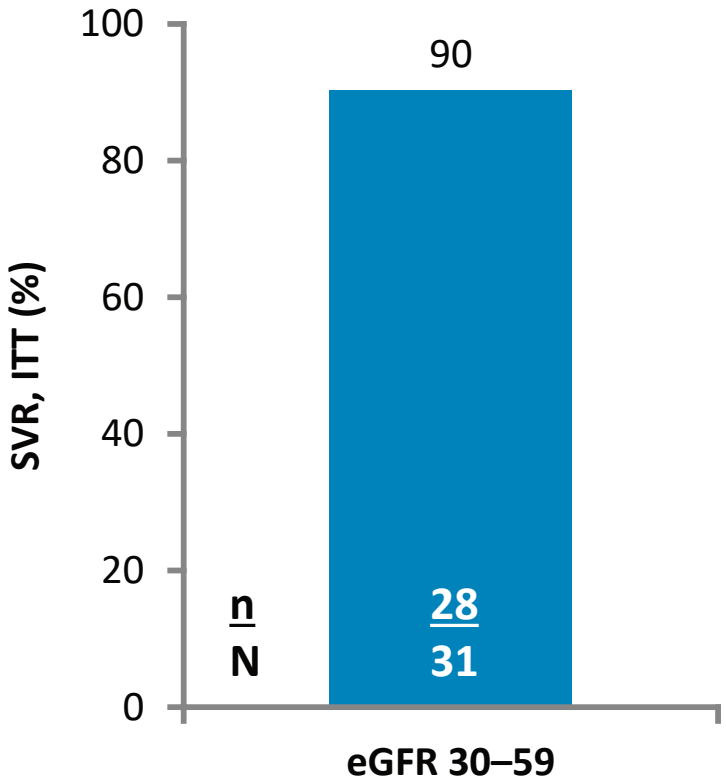
Patients received OBV/PTV/r + DSV + RBV for 12 (GT1b) or 24 (GT1a) weeks

Variable	Cirrhotic patients N=762
Creatinine, mg/dL	0.8 ± 0.5
Creatinine clearance (CrCl)*, mL/min	92.4 ± 16.9
CrCl*, n (%)	
≥90 mL/min	501 (65.7)
60–89 mL/min	226 (29.7)
30–59 mL/min	31 (4.1)
<30 mL/min	4 (0.5)

* eGFR by CKD-EPI.

Petta S, AISF Annual Meeting , Rome 17–19 February 2016.

ABACUS – Italian Compassionate Use Study



All 4 patients with
eGFR <30 achieved SVR

Petta S, AISF Annual Meeting , Rome 17–19 February 2016.

ESITI DELLE TERAPIE ANTIVIRALI IN 2612 PAZIENTI CON INFEZIONE CRONICA DA HCV : uno studio collaborativo

Sustained viral clearance by therapy

ALL (no.= 2612)	N (%)
Gender	
M	1498 (57.3)
F	1114 (42.6)
Age; *(yrs) mean ± SD*	64,2 ± 11,5
>70 years	991 (37.9)
HCV genotype	
1a	224 (3.1)
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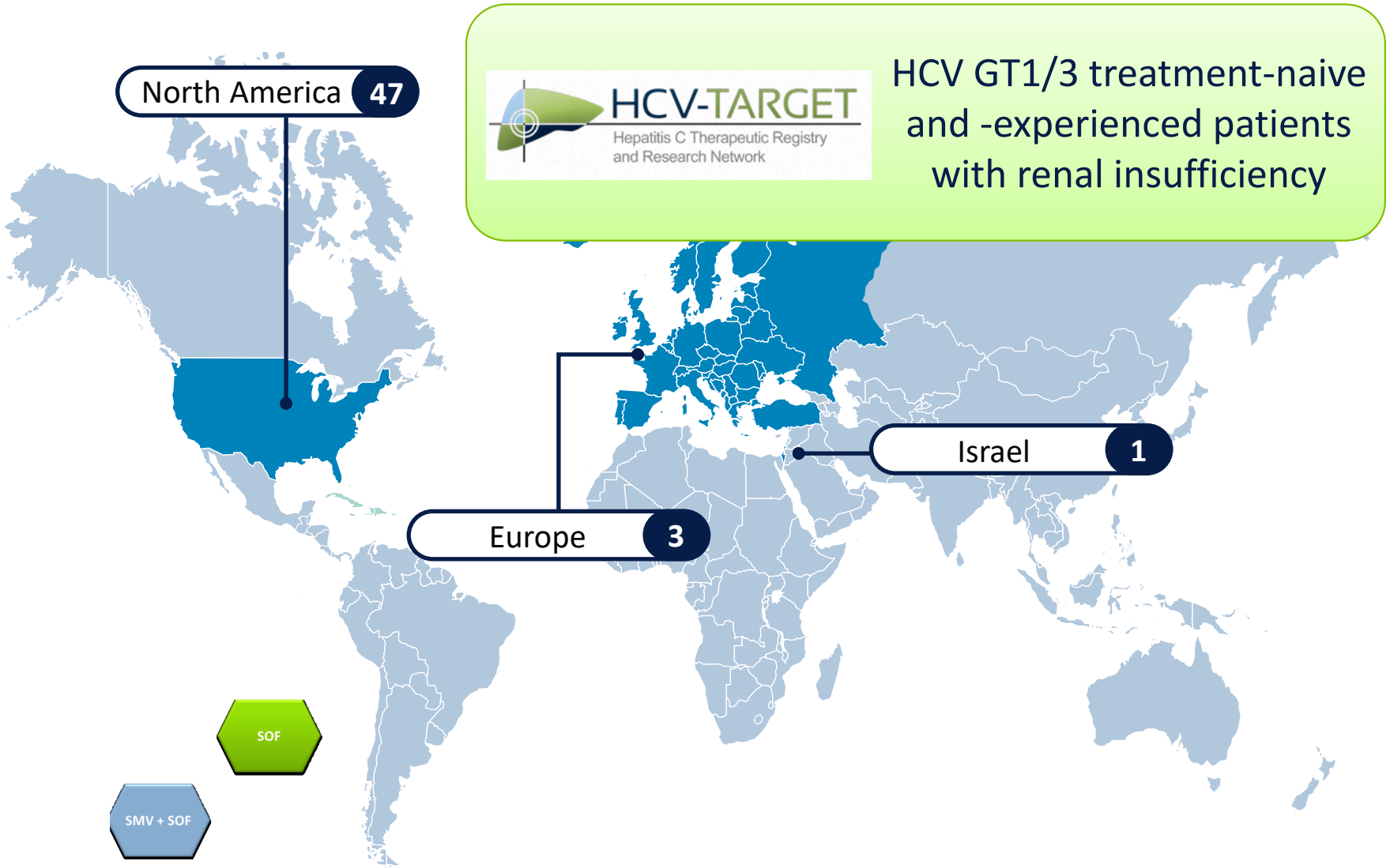
(15,1-30)	8 (0.3)
(30,1-60)	**387 (14.8)**
(60,1-90)	981 (37.6)
(> 90)	1236 (47.3)

SVR12

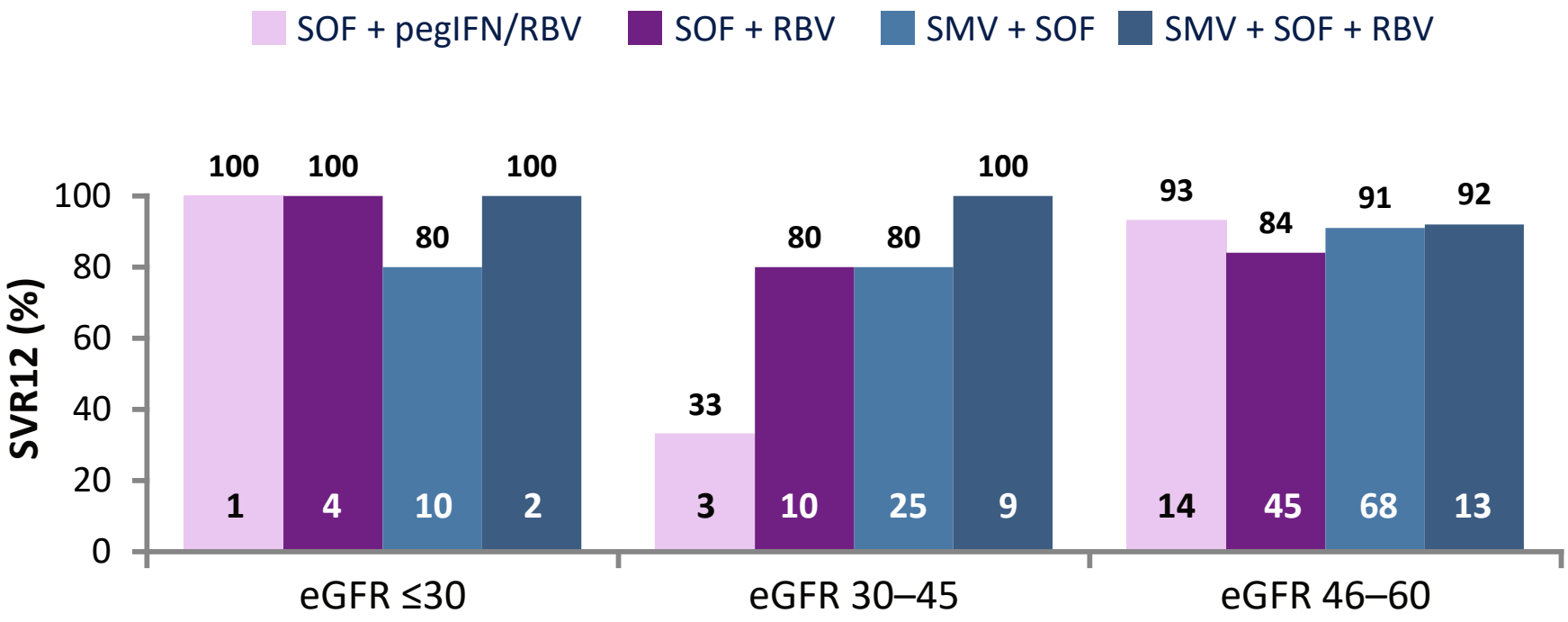
6/8 = 75%
368/387 = 95%
954/ 981 = 97%
1188/1236 = 96%

HCV TARGET: SOF-Based Regimens in Patients with Renal Insufficiency in the Real World



Numbers indicate participating centers.

HCV-TARGET: SVR12 Rates by Baseline eGFR and Treatment Regimen*

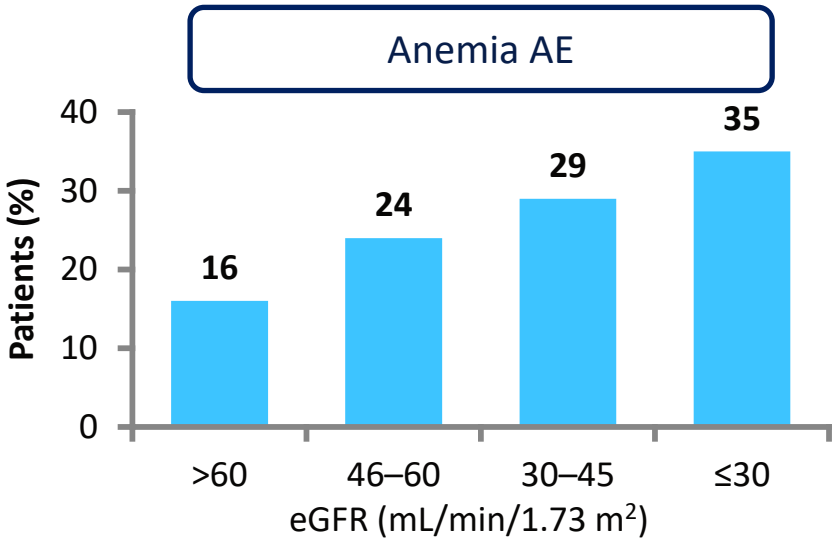


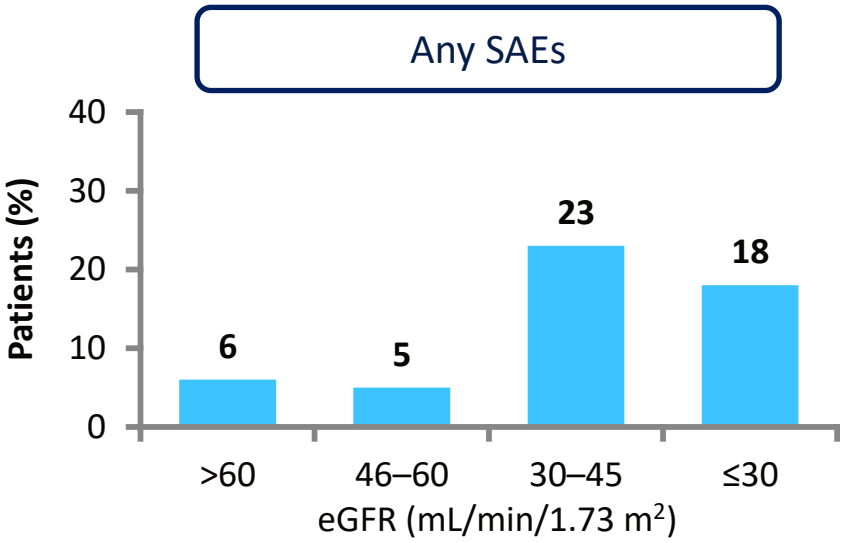
Real world SVR12 rates of 80–100% were achieved in patients treated with SMV + SOF ± RBV

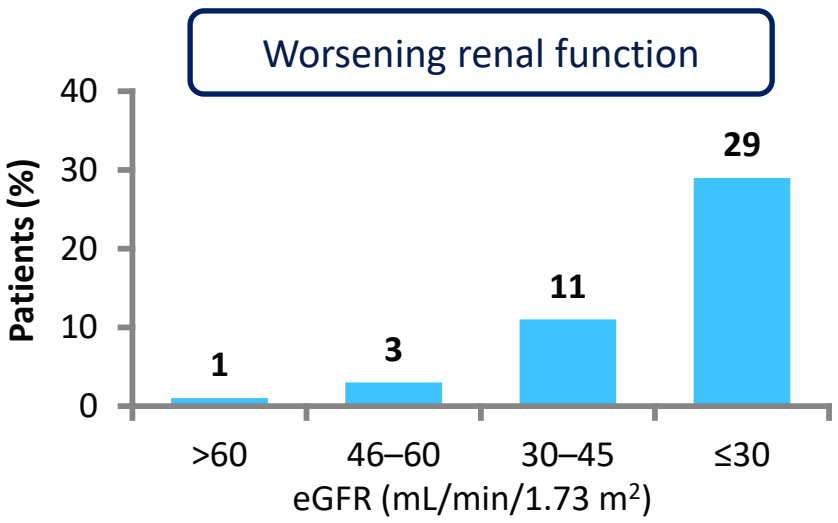
* Among patients with known outcome.

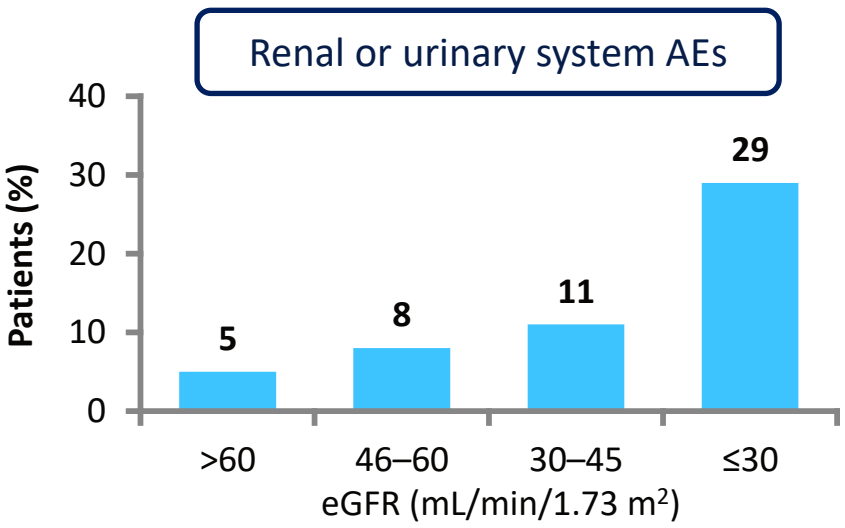
Saxena V, *et al. J Hepatol* 2015; **62**(Suppl):S267.

HCV-TARGET: Safety Overview by Baseline eGFR









Saxena V, *et al. J Hepatol* 2015; **62**(Suppl):S267.

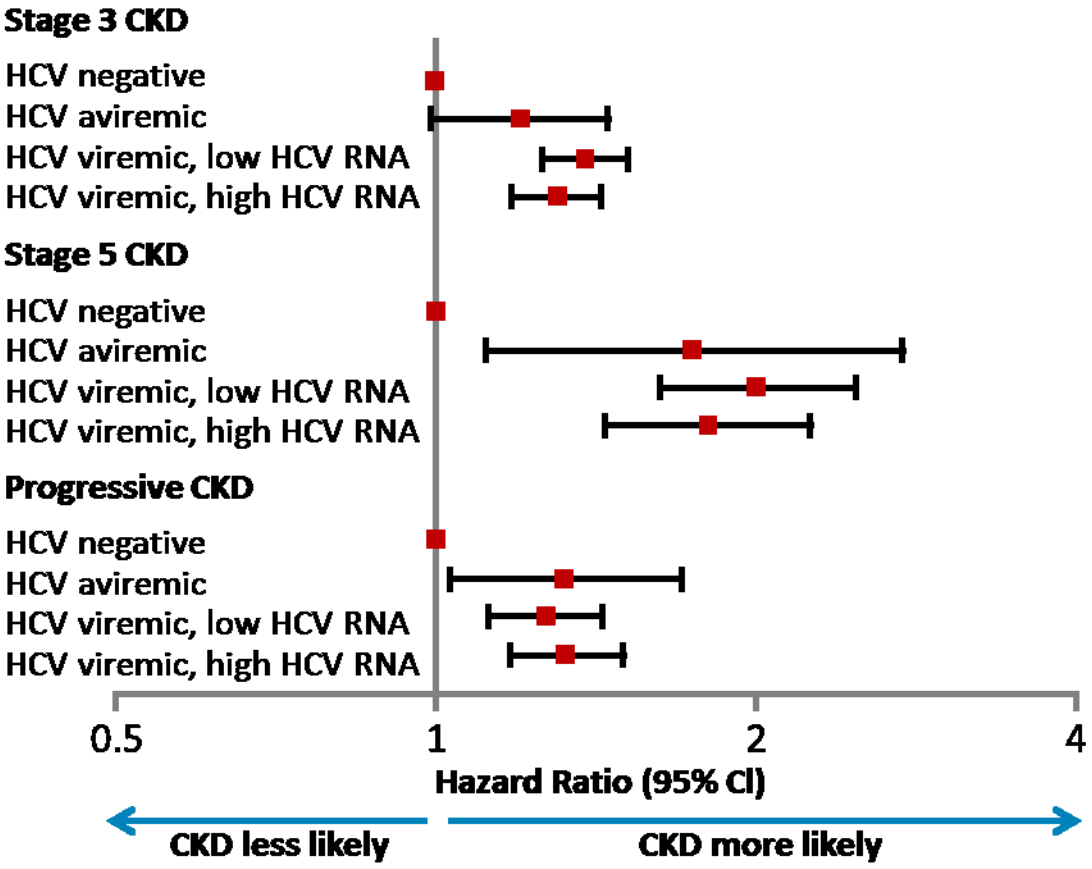
What Have We Learned About Treating HCV-Patients with CKD?

High SVR rates in HCV-infected patients with CKD

It is critical to consider the safety profile of DAA regimens to be used in patients with severe renal impairment

HCV Infection is Associated with an Increased Risk of CKD Progression

CKD outcomes from 52,602 HCV seronegative, 9,508 HCV viremic and 913 HCV aviremic HIV-infected subjects from NA-ACCORD



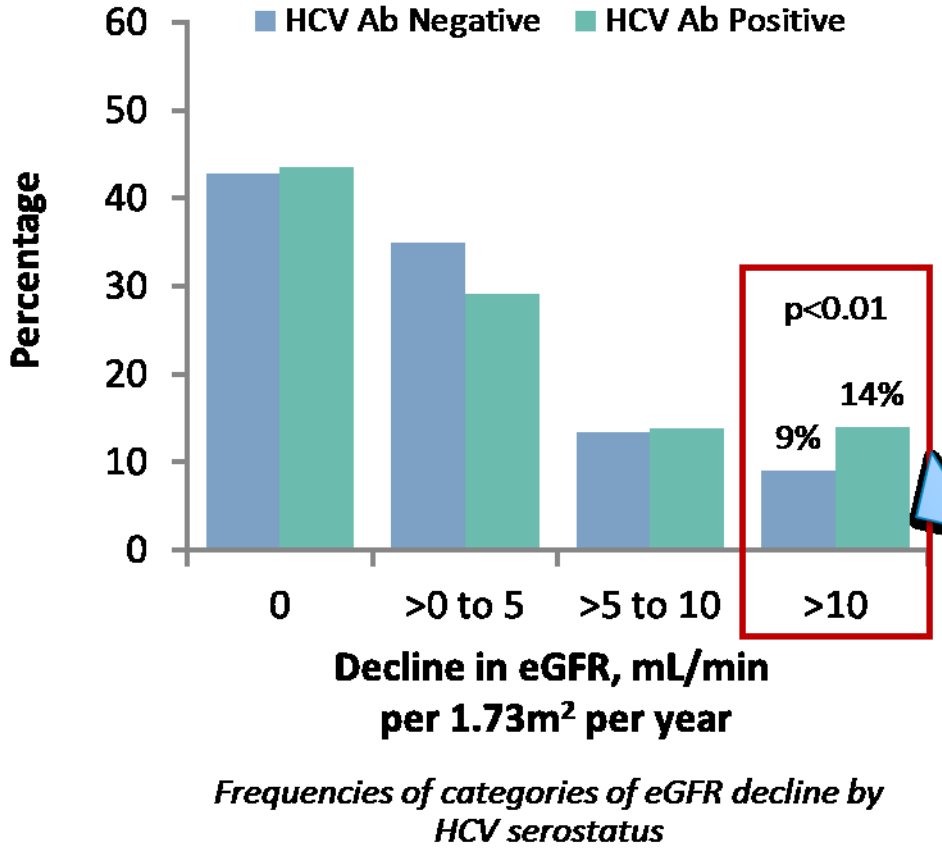
Compared with HIV-infected subjects who were HCV seronegative, both HCV viremic and HCV aviremic individuals were at increased risk for moderate, advanced and progressive CKD

HCV viremic = detectable HCV RNA; HCV aviremic = HCV seropositive, undetectable HCV RNA; NA-ACCORD = North American AIDS Cohort Collaboration on Research and Design.

Lucas GM, *et al. J Inf Dis* 2013; **208**:1240–1249.

HCV Infection is Associated with an Increased Risk of CKD Progression

Retrospective cohort of 474,369 US veterans: HCV seropositive = 11%



Frequencies of categories of eGFR decline by HCV serostatus

Prevalence:
9% of subjects with HCV also had CKD at baseline

Significantly more HCV-positive subjects had an annual decline of eGFR >10 mL/min/1.73m^2 compared with those who were HCV-negative

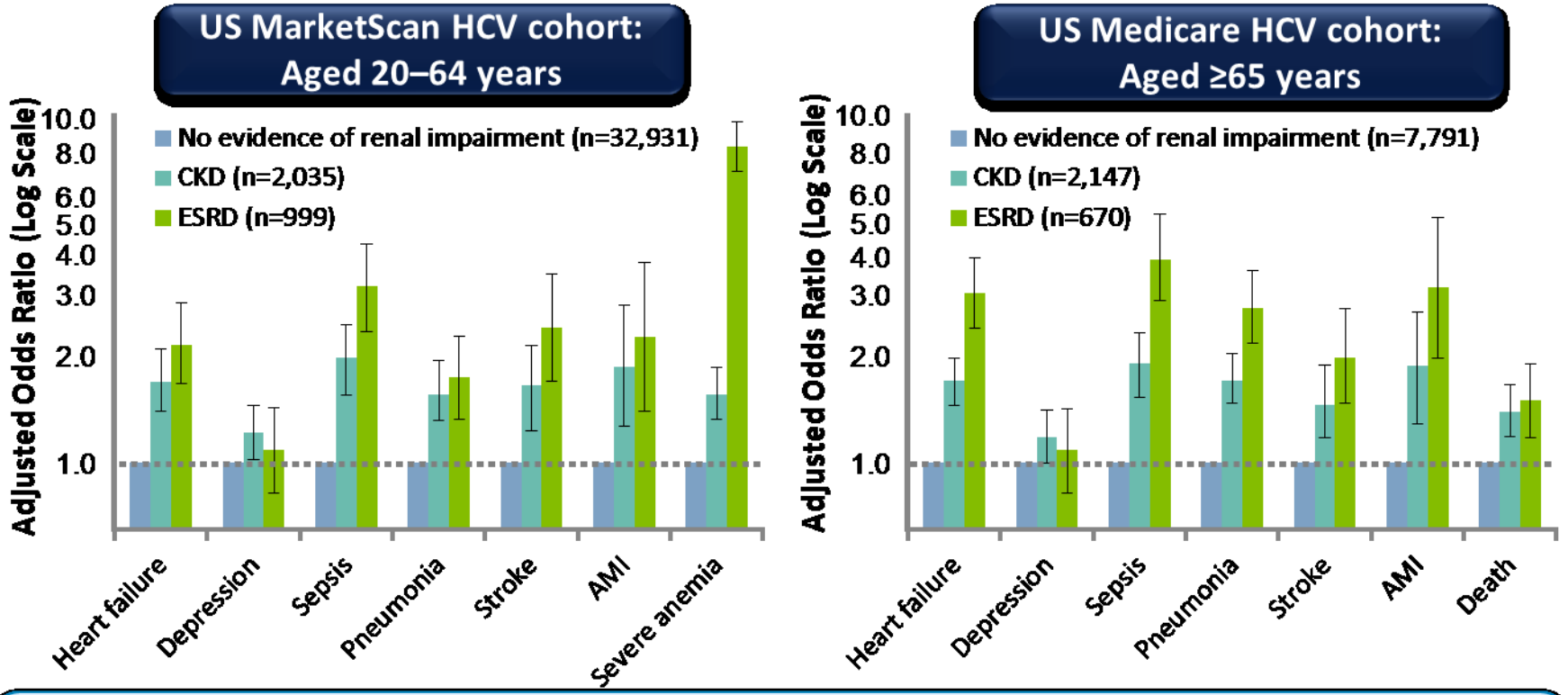
In subjects with baseline eGFR >30 mL/min/1.73m^2:
HCV seropositivity increased the risk of developing ESRD almost 3-fold (adjusted HR 2.8; 95% CI 2.43–3.23)

Ab = antibody; HR = hazard ratio.
ESRD defined as the onset of chronic hemodialysis or renal transplantation.

Tsui JI, *et al. Arch Intern Med* 2007; **167**:1271–1276.

Patients with HCV and CKD Have a Higher Comorbidity Burden and Worse Outcomes than Those without CKD

Risk of clinical events in US patients with HCV with and without renal impairment during 1 year of follow up in 2012 (adjusted odds ratio)*



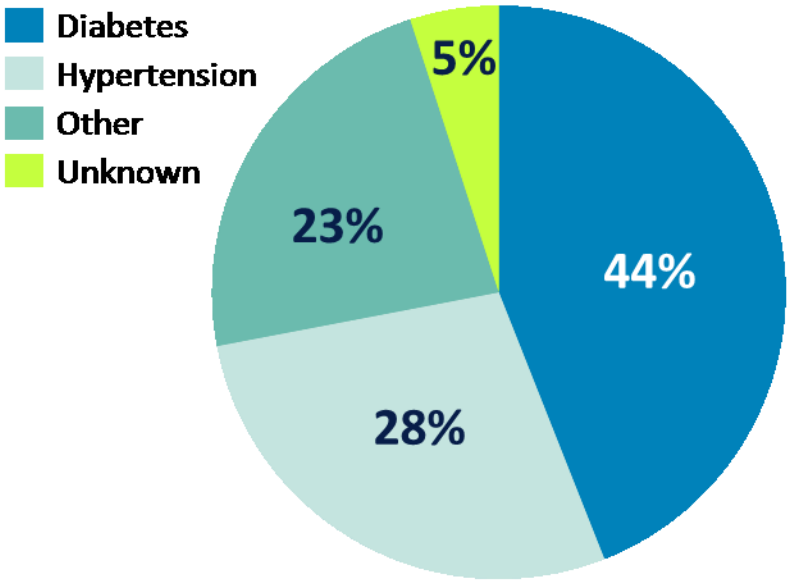
Patients with HCV and CKD or ESRD were more likely to have baseline co-infections, cardiovascular diseases, liver-related diseases (younger cohort), and COPD (older cohort) than those with HCV without renal impairment

AMI = acute myocardial infarction. * Diagnosis of HCV, CKD and ESRD identified via ICD-9 and CPT code.

Senaka P, *et al. Hepatology* 2015; **62**(Suppl):1120A.

Hypertension and Diabetes are Common Comorbidities of HCV and CKD

Approximately 33% of US adults with diabetes and 20% with hypertension have CKD[1]



New cases of kidney failure in the US in 2011 by primary diagnosis[1]

The risk of developing CKD is higher for HCV-infected individuals than for those without HCV infection[2]

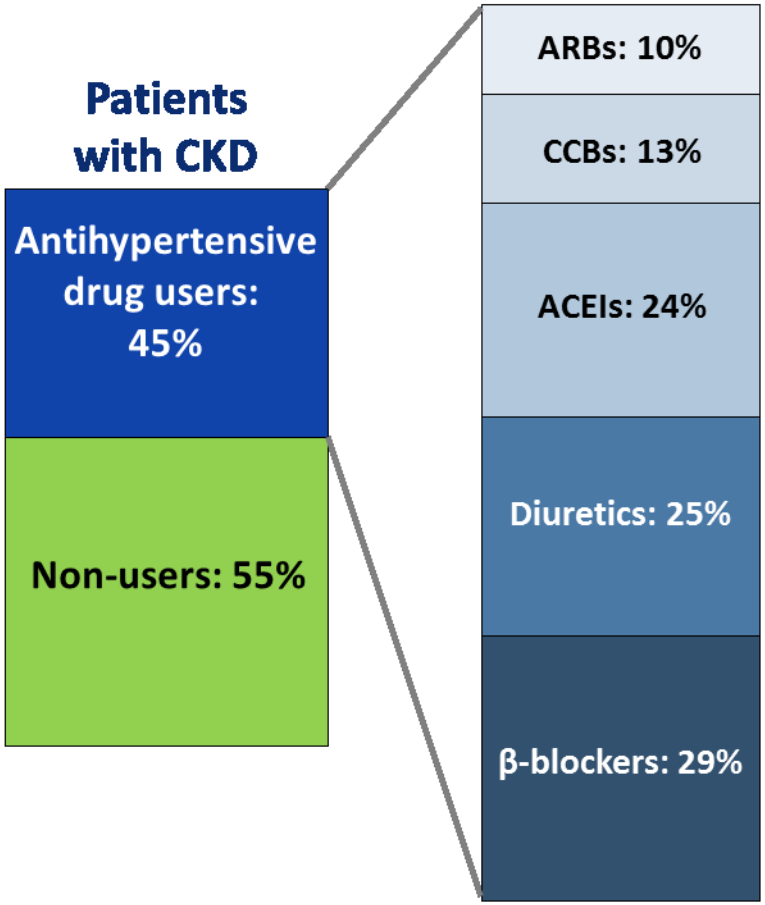
33% of HCV-infected individuals in the US have hypertension and 14% have diabetes[3]

The risk of CKD is further increased in HCV-infected individuals with diabetes[2]

1. Centers for Disease Control and Prevention (CDC). Factsheet 2014. Available at: http://www.cdc.gov/diabetes/pubs/pdf/kidney_factsheet.pdf (accessed January 2016);
2. Chen YC, *et al. Kidney Int* 2014; 85:1200–1207;
3. Louie KS, *et al. BMC Infect Dis* 2012; 12:86.

Patients with CKD Often Take Antihypertensive Medications Such as CCBs and ARBs: NHANES Data, 2005–2010

Retrospective cross-sectional study representing a weighted sample of >116 million US adults with CKD



Of patients with Stage 4 CKD (4.6%), 95% were users of antihypertensive medication

33% were taking ARBs or CCBs and 67% were taking β-blockers, diuretics, or ACEIs

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; CCB = calcium channel blocker; HTN = hypertension.

*Patients with CKD Stage V were excluded from analysis.

Sonawane KB, *et al. Clin Ther* 2015; 37:188–196.

Definition of CKD: Kidney Damage ± Impaired Kidney Function for ≥3 Months

Renal function is evaluated using the eGFR

	eGFR* (mL/min/1.73m^2)	CKD stage
Normal renal function	≥90	1
Mild renal impairment	60–89	2
Moderate renal impairment	30–59	3
Severe renal impairment	15–29	4
End stage renal disease (ESRD)	<15 or on dialysis	5