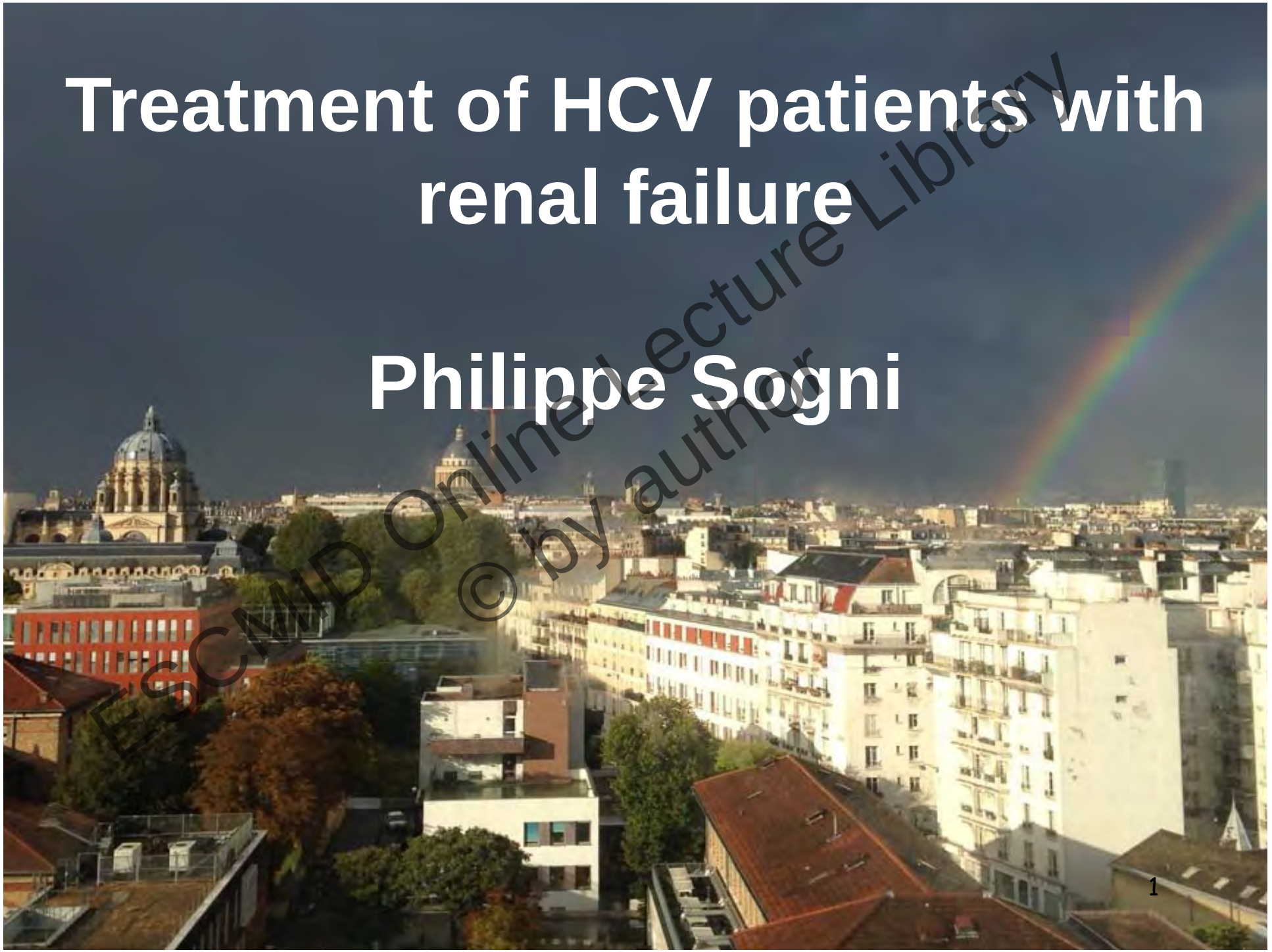
Treatment of HCV patients with renal failure

Philippe Sogni



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Disclosures

- Workshop or meeting invitation: Gilead, Bristol-Myers Squibb, Schering-Plough / MSD, Roche, Janssen, Mayoly-Spindler
- Board: Gilead, Bristol-Myers Squibb

Introduction

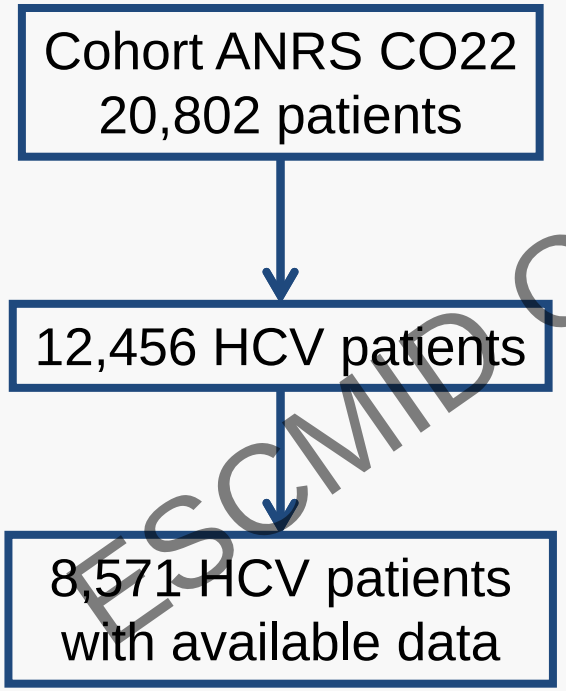
- The prevalence of HCV infection is more frequent but is decreasing overtime in patients with CKD

- HCV infection is associated with an increased risk of renal disease, ESRD and renal-related mortality[1]
- HCV increases mortality in hemodialysis patients[2]
- HCV increases mortality of kidney recipients and allografts[3,4,5]

[1] Lai TS et al. AASLD 2014 abstr. 172
[2] Nakayama E, et al. J Am Soc Nephrol 2000
[3] Pol S et al. Lancet 1991
[4] Legendre C et al. Transplantation 1997
[5] Mathurin P et al. Hepatology 1999

Prevalence of renal disease in HCV patients

ANRS CO22 HEPATHER cohort



Prevalence of GFR ≤ 60 mL/min = 6.3%
(95% CI: 5.8% - 6.9%)

Renal disease stage (GFR)	N
3A (45-59 mL/min)	305
3B (30-44 mL/min)	104
4 (15-29 mL/min)	48
5 (< 15 mL/min)	86

Fontaine H et al. AFEF 2016 / AASLD 2016

Factors associated with renal insufficiency stage ≥ 3 in HCV patients

ANRS CO22 HEPATHER cohort

Multivariate analysis	OR (CI 95 %)	p
Child score (B/C versus A)	1.2 (0.7-2.0)	0.41
Sex (homme vs femme)	1.1 (0.9-1.4)	0.36
Age (increase 10 years)	1.7 (1.6-1.9)	< 0.01
Arterial hypertension	4.4 (3.4-5.6)	< 0.01
Diabetes	1.8 (1.0-2.4)	< 0.01
Cardiopathy	1.6 (1.0-2.4)	< 0.03
Hypercholesterolemia	1.4 (1.0-1.9)	< 0.04

Fontaine H et al. AFEF 2016 / AASLD 2016

Questions

- How to treat HCV in patients with renal failure?
- When to treat HCV in patients with renal failure (i.e. before or after renal transplantation…)?
- ~~Benefit of virologic cure on kidney function?~~

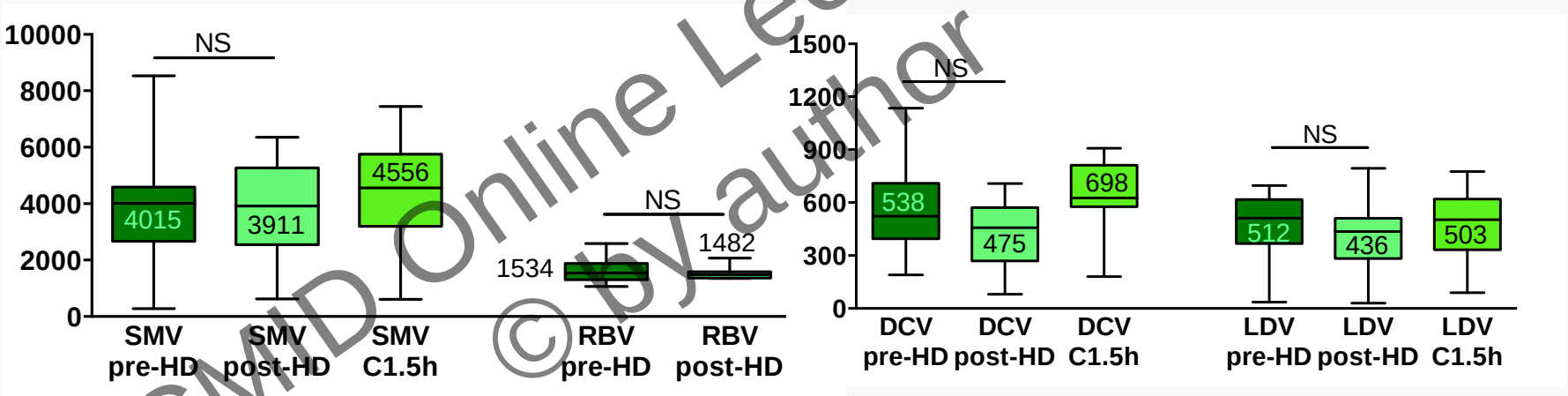
Focus on DAAs

How to use HCV DAAs when kidney function is impaired?

Molecule	NS5A inhibitor	Protease inhibitor
Renal insufficiency	No dose adjustment	No dose adjustment
Anticalcineurin drug	No dose adjustment	Dose adjustment

Pharmacokinetics of DAAs in dialysis

DAAs plasma concentrations (median, IQR; ng/ml)



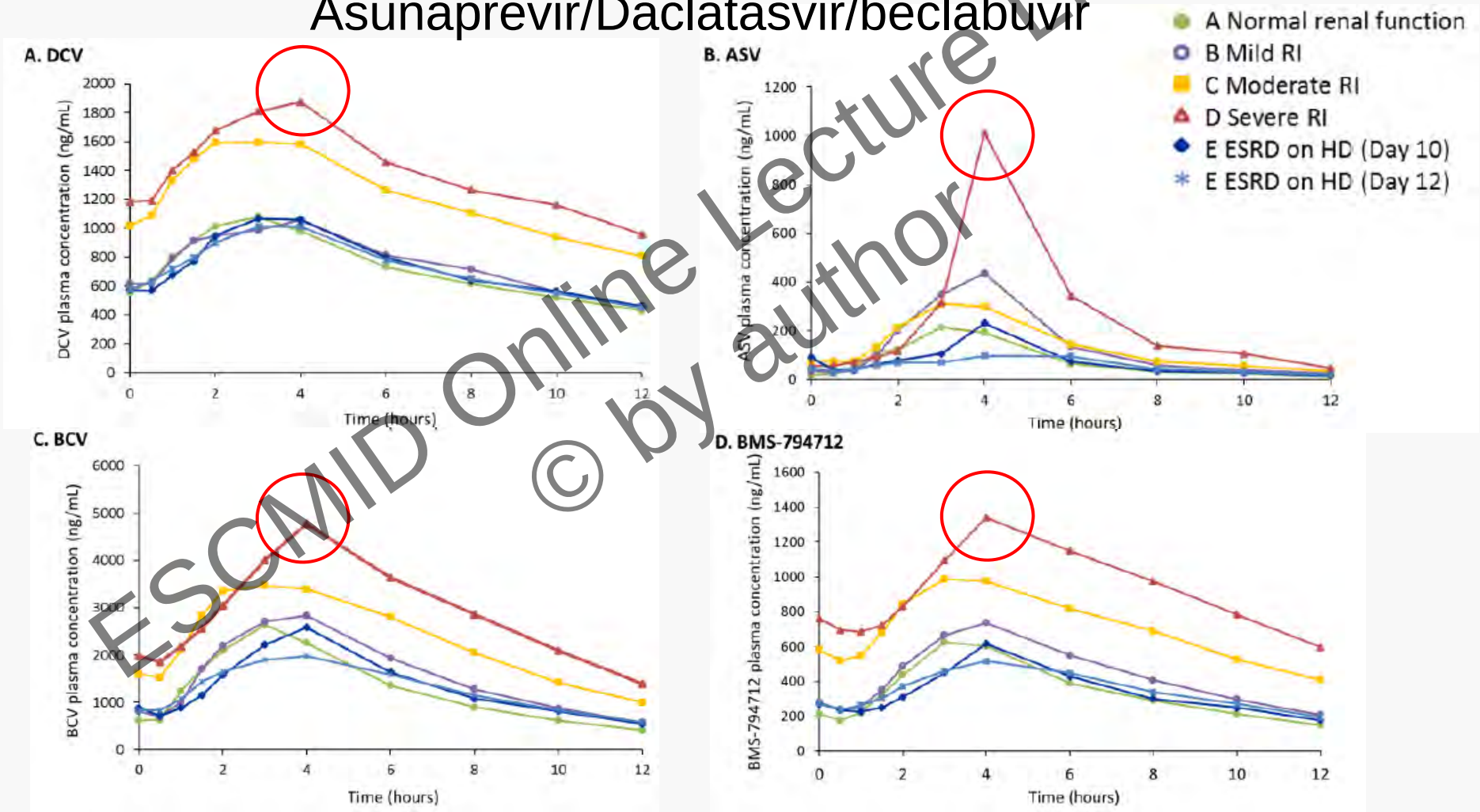
Patients (n)	2	2	2		1	1	8	8	4		1	1	1
Samples (n)	51	36	34		7	7	12	11	8		16	22	21

No difference between Pre-Hemodialysis and Post-Hemodialysis concentrations for SMV (Protease Inhibitor), and DCV or LDV (NS5A inhibitors)

Desnoyer A et al. J Hepatol 2016

How to use HCV DAAs when kidney function is impaired?

Asunaprevir/Daclatasvir/beclabuvir



Adamczyk R et al. ILC 2015; #PO790

How to use HCV DAAs when kidney function is impaired?

Molecule	NS5A inhibitor	Protease inhibitor	Polymerase inhibitor
Renal insufficiency	No dose adjustment	No dose adjustment	?
Anticalcineurin drug	No dose adjustment	Dose adjustment	No dose adjustment

Polymerase Inhibitor (non-nucleotide): Dasabuvir

- No dose adjustment to renal function

Polymerase Inhibitor (nucleotide): Sofosbuvir

- No dose adjustment for GFR > 30 mL/min
- For GFR < 30 mL/min: not recommended in the label [10]

Pharmacokinetics of SOF in HCV-negative patients with renal impairement

Patient Renal Impairment	Sofosbuvir AUC*	GS-331007 AUC*
Following Single 400 mg dose of sofosbuvir		
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 Dose 1 hour before hemodialysis Dose 1 hour after hemodialysis	 ⇧28% ⇧60%	 ⇧1280% ⇧2070%

* AUC given relative to subjects with normal renal function

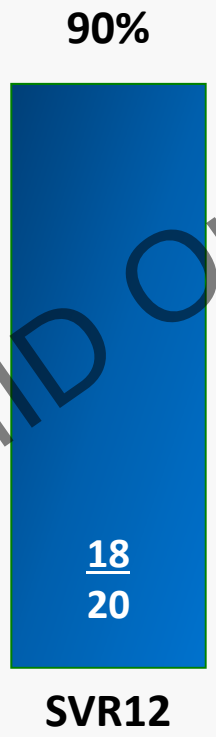
Sovaldi. 2015. Sofosbuvir. Summary of Product Characteristics, Gilead Sciences, Hayes, UK. Food & Drug Administration. Available at (last access September 2016): http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/204671s004lbl.pdf

How to use HCV DAAs when kidney function is impaired? In practice

- GFR > 30 mL/min: all the therapeutic options according to CPGs
- GFR < 30 mL/min:
  - Genotype 1a, 1b or 4 ➔ GZR/EBR or 2D/3D 12 weeks

3D when renal function is impaired: RUBY study

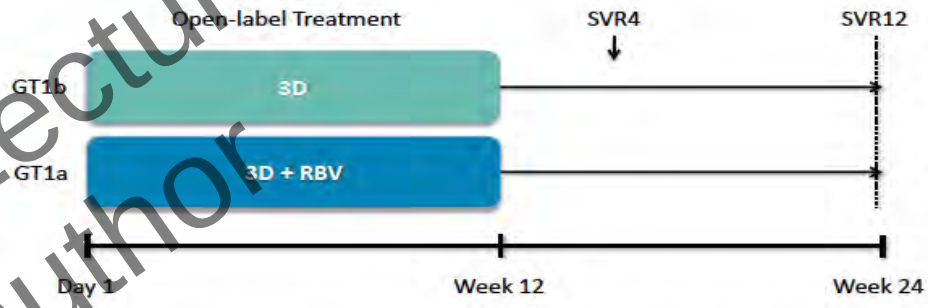
Ombitasvir/Paritaprevir/ritonavir (25/150/100 mg/j) + Dasabuvir (250 mg x 2/j) ± RBV



Pockros P et al. Gastroenterology 2016

Multicenter, Open-label, Phase 3b Study

- 9 sites, all in the United States

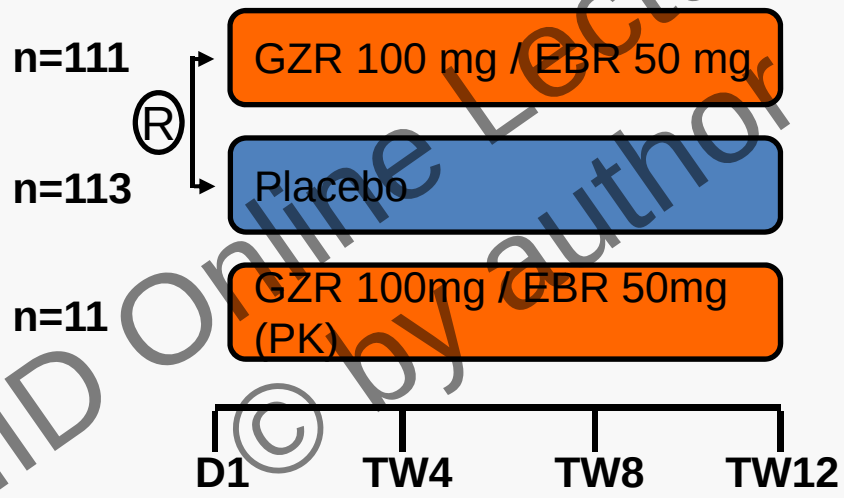


	3D±RBV N=20
Male; n (%)	17 (85)
Black; n (%)	14 (70)
Age, years; median (range)	60 (49-69)
Hispanic or Latino ethnicity; n(%)	3 (15)
Degree of fibrosis*; n(%)	
F0-F1	10 (50)
F2	6 (30)
F3	4 (20)
HCV viral load, log_{10} (IU/mL); median (range)	6.6 (5.5-7.6)
GT1a; n (%)	13 (65)
Hemoglobin, g/dL; mean (SD)	12.6 (1.8)
CKD stage; n (%)	
4 (eGFR 15-30 mL/min/1.73m²)	7 (35)
5 (eGFR <15 mL/min/1.73m² or requiring dialysis)	13 (65)
On dialysis; n (%)	13 (65)
eGFR, mL/min/1.73m²; median (range)	10.9 (5.4-29.9)
Creatinine, mg/dL; median (range)	6.2 (2.2-10.8)

*Biopsy: 5 patients; Fibroscan: 10 patients; Fibrotest: 5 patients.

GZR/EBR when renal function is impaired: C-SURFER study (1)

Grazoprevir/Elbasvir in patients with GFR < 30 mL/min



GT1/naïve/experienced

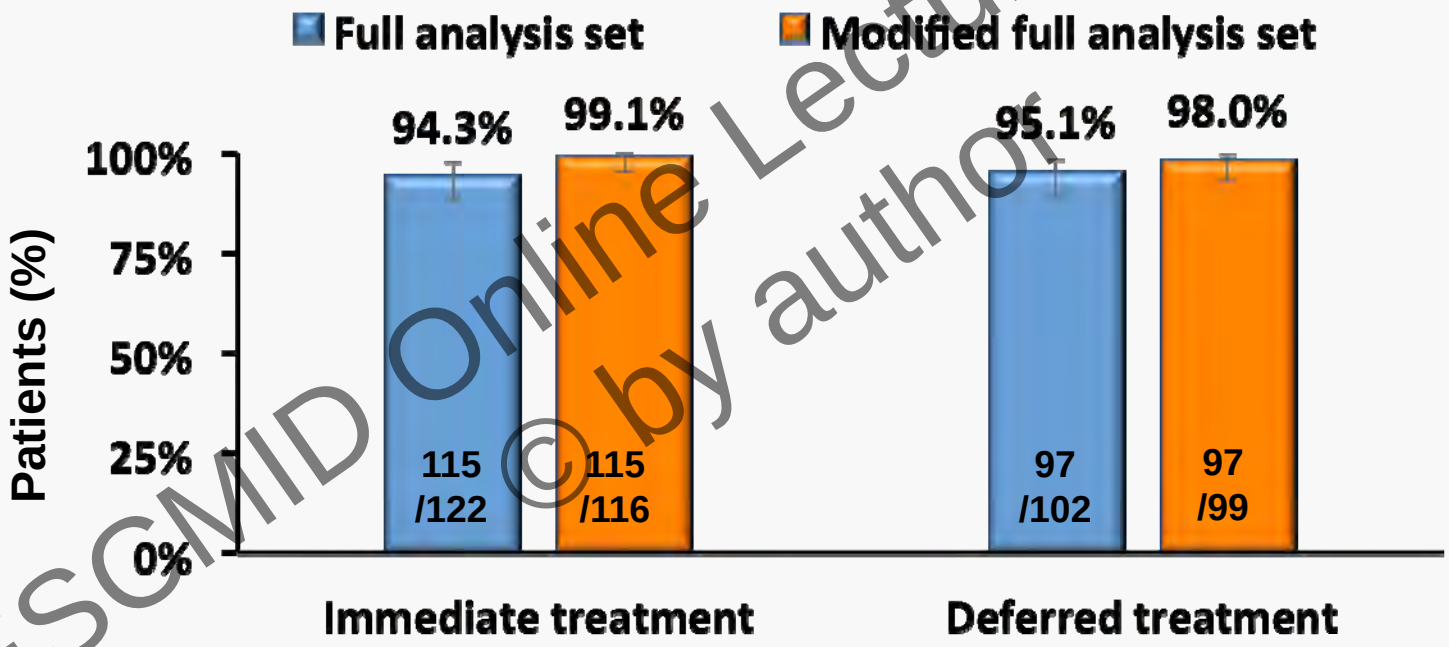
-CKD stage 4/5 (eGFR 15-29 mL/min/1.73m^2

-CKD stade 5: eGFR <15 mL/min/1.73m^2 or dialysis)

Roth D et al. Lancet 2015

GZR/EBR when renal function is impaired: C-SURFER study (2)

SVR12 in C-SURFER: EBR/GZR



Relapse	1[a]			2[c]	
D/c unrelated to treatment	6[b]			3[d]	

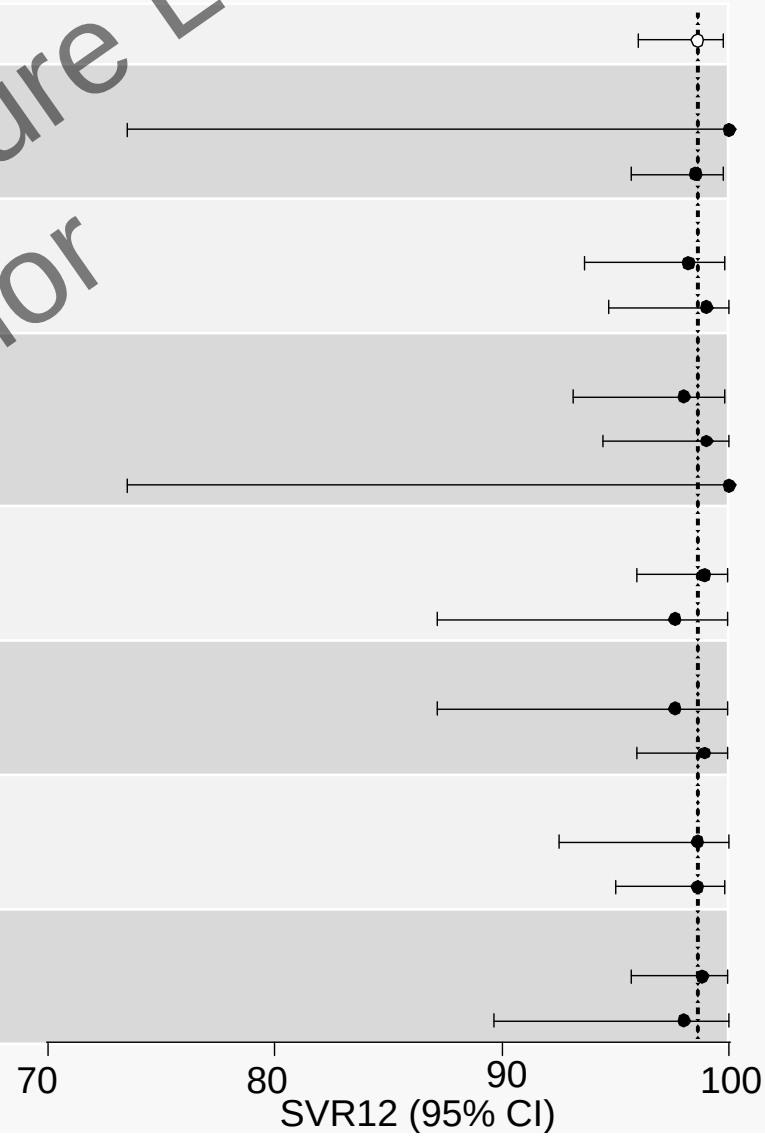
Roth D et al. Lancet 2015
Bruchfeld A et al. ESN 2016

[a]Noncirrhotic, interferon-intolerant patient with HCV GT1b infection relapsed at FUW12; [b]Lost to follow-up (n = 2), n = 1 each for death, noncompliance, withdrawal by subject, and withdrawal by physician (owing to violent behavior)
[c]Two patients in the DTG relapsed, both with G1a infection, relapsed at FUW4 and FUW12
[d]Withdrawal by subject, n = 1; AE (vomiting), n = 1; death, n = 1.

GZR/EBR when renal function is impaired: C-SURFER study (3)

SVR12 Key subgroup analyses

All Patients	**215/222**	**98.6% (96.0, 99.7)**
Cirrhosis		
Yes	**12/12**	**100% (73.5, 100)**
No	**200/203**	**98.5% (95.7. 99.7)**
HCV genotype		
G1a	**109/111**	**98.2% (93.6, 99.8)**
G1b	**102/103**	**99.0% (94.7, 100)**
Race		
White	**100/102**	**98.0% (93.1, 99.8)**
African American	**97/98**	**99.0% (94.4, 100)**
Asian	**12/12**	**100% (73.5, 100)**
Previous treatment		
Naïve	**172/174**	**98.9% (95.9, 99.9)**
Experienced	**40/41**	**97.6% (87.1, 99.9)**
CKD stage		
4	**40/41**	**97.6% (87.1, 99.9)**
5	**172/174**	**98.9% (95.9, 99.9)**
Diabetes		
Yes	**71/72**	**98.6% (92.5, 100)**
No	**141/143**	**98.6% (95.0, 99.8)**
Hemodialysis		
Yes	**162/164**	**98.8% (95.7, 99.9)**
No	**50/51**	**98.0% (89.6, 100)**



[a]Modified full analysis set population (mFAS)

How to use HCV DAAs when kidney function is impaired? In practice

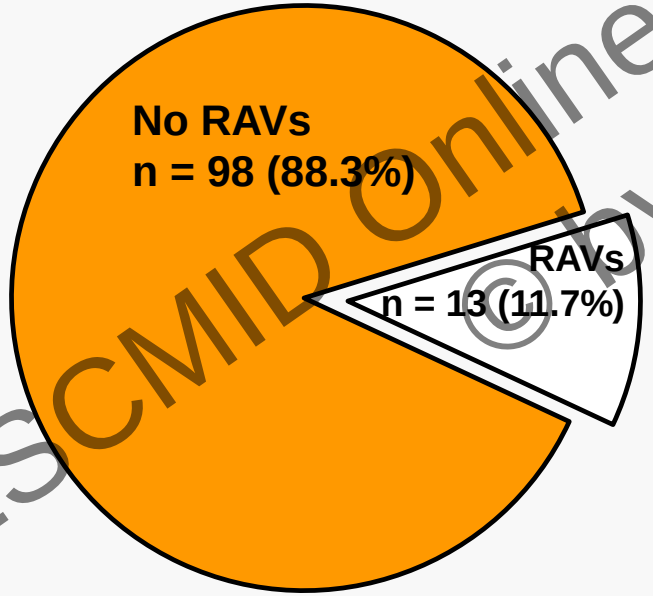
- GFR > 30 mL/min: all the therapeutic options according to CPGs

- GFR < 30 mL/min:
  - Genotype 1b or 4 ➔ GZR/EBR or 3D 12 weeks
  - Genotype 1a ➔ GZR/EBR 16 weeks or 3D 12 weeks + RBV?

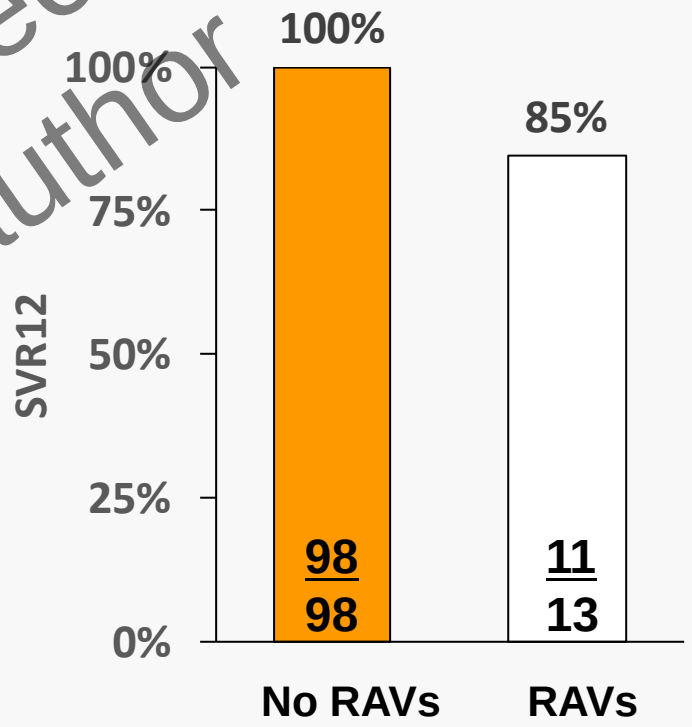
- RBV is difficult to manage
- NS5A RAVs which are mainly associated with relapse, should be tested in GT1a patients?

Impact of baseline NS5A RAVs* In patients with G1a infection

Prevalence of NS5A RAVs at baseline



Impact of baseline NS5A RAVs on SVR12



*Any variants at amino acids 28, 30, 31, or 93 by population sequencing (sensitivity threshold ~25%)

How to use HCV DAAs when kidney function is impaired? In practice

- GFR > 30 mL/min: all the therapeutic options according to CPGs
- GFR < 30 mL/min:
  - Genotype 1a, 1b or 4 ➔ GZR/EBR or 3D
  - Genotype 2, 3, 5 or 6 ➔ off-label Sofosbuvir included regimen?

Sofosbuvir: Safety? Dose adjustment to GFR?

How to use Sofosbuvir when kidney function is impaired?

Retrospective study: 90 pts treated with SOF/LDV for 8 (n = 15), 12 (n = 67) or 24 (n = 8) weeks: 17 pts with GFR < 60 mL/min

➔ 42% worsening of GFR

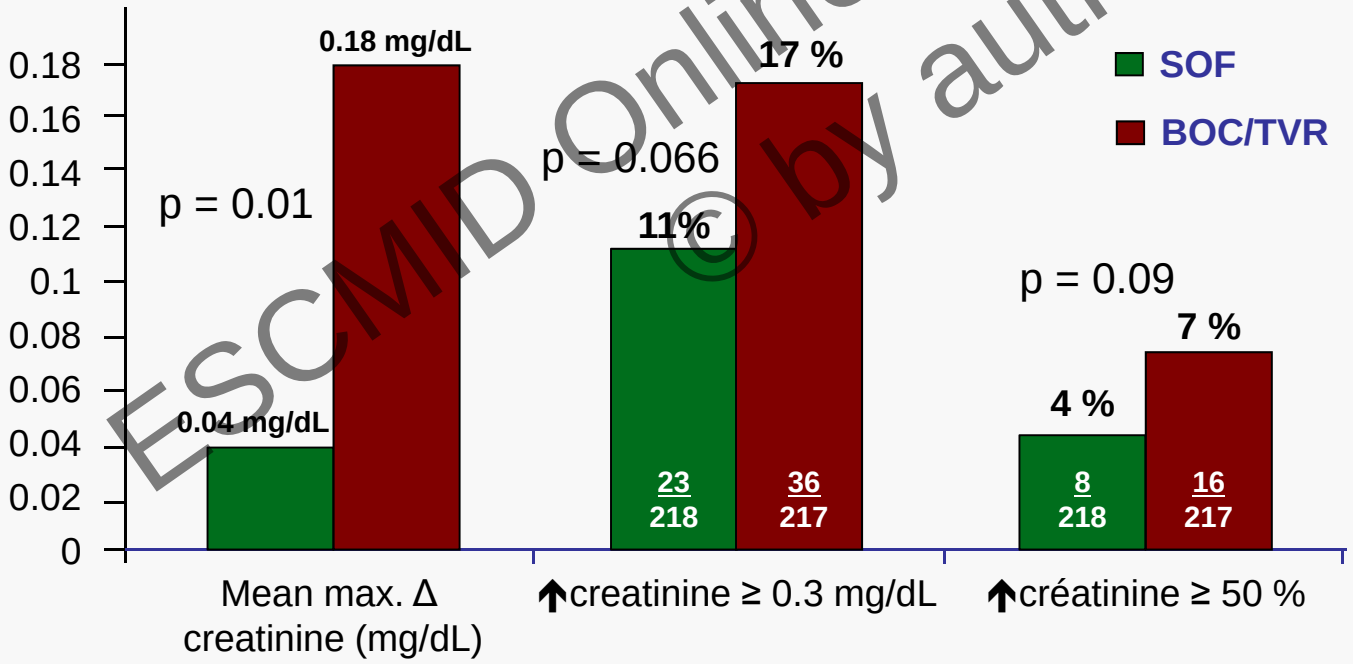
- GFR < 60 mL/min was associated with worsening renal function in uni- (p=0.016) and multivariate analysis (p=0.016)
- Baseline GFR predicts worsening renal function under SOF/LDV

Rosenblatt R et al. ILC/EASL 2016, Abs PS-262

How to use Sofosbuvir when kidney function is impaired?

- 219 patients with sofosbuvir-including regimen and 217 patients treated with boceprevir or telaprevir associated with PEG-IFN/RBV
- Renal impairement defined as an increase of creatinine ≥ 0.3 mg/dL or ≥ 50% vs. baseline

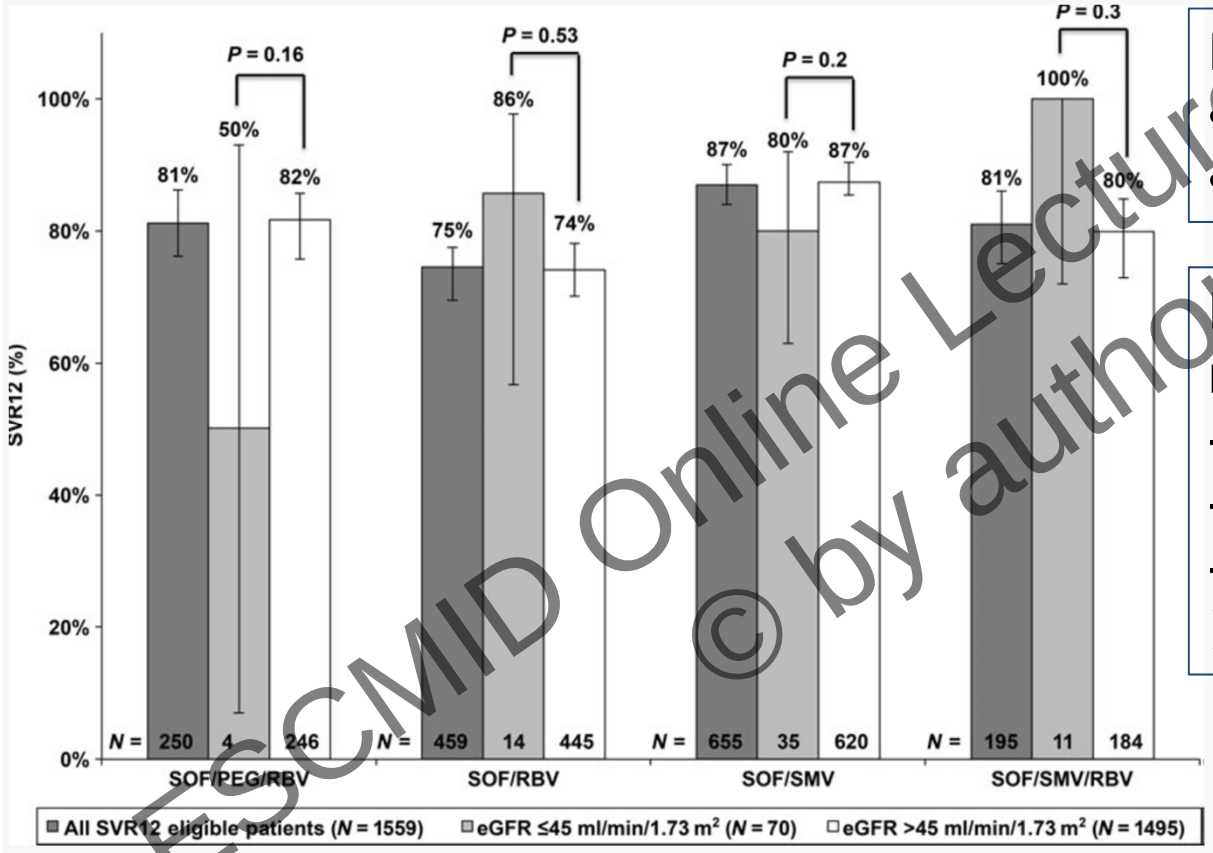
Evolution of GFR under therapy (GFR > 60 mL/min at baseline)



Renal dysfuntion or competition on reabsorption of creatinine?

Almarzooqi S et al. AASLD 2015, Abstract 1099

How to use Sofosbuvir when kidney function is impaired?



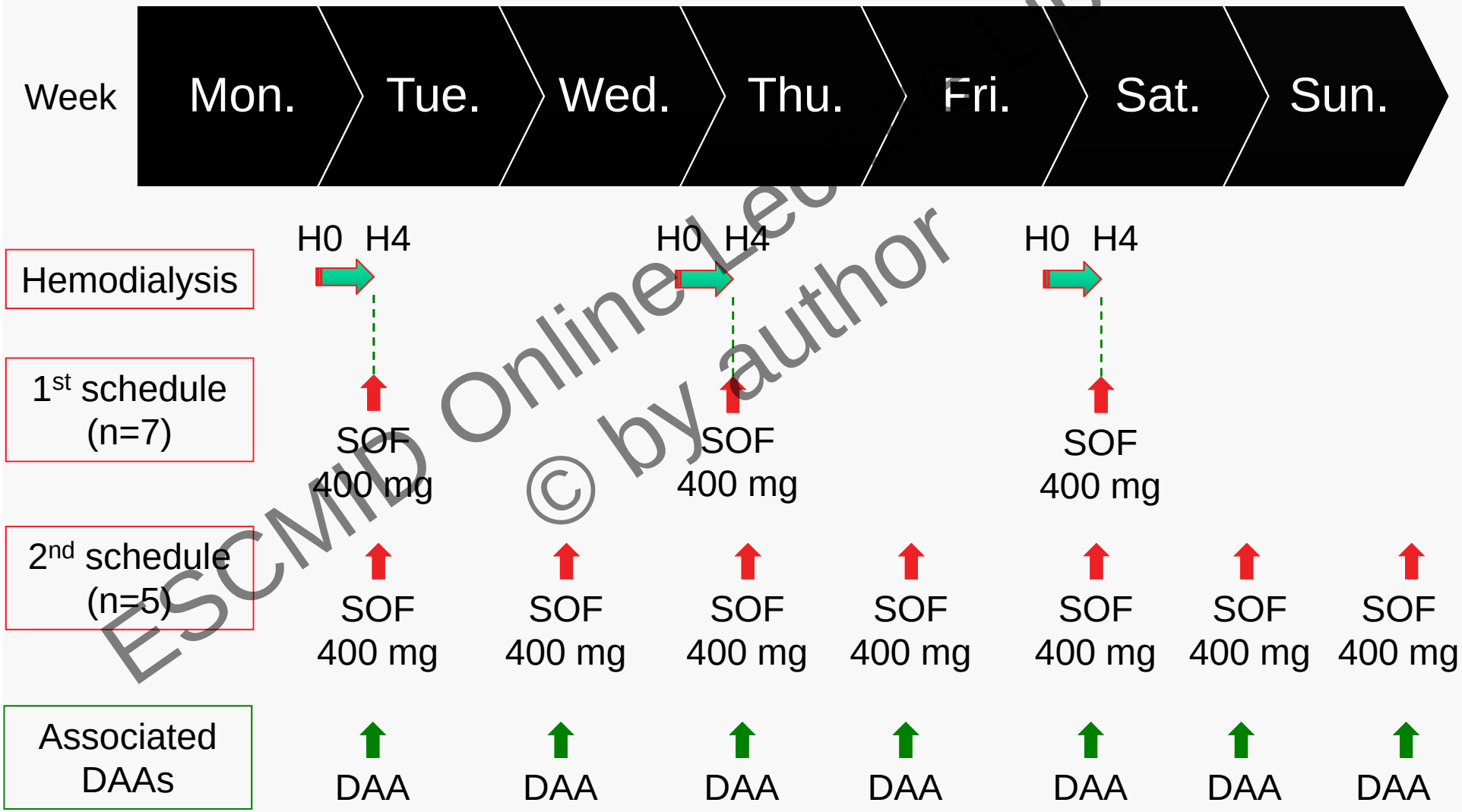
Real Life TARGET cohort
- SOF 400 mg/d
- RBV 800 (IQR 400-1200)

Patients with eGFR ≤ 45 mL/min (n=73)
-50 with eGFR 31-45
-18 with eGFR ≤ 30
-5 on dialysis
➢SVR = 83% (82-83%)

- Patients with eGFR ≤ 45 mL/min experienced more anaemia, worsening renal function and serious AEs
- Patients with baseline eGFR ≤ 30 and eGFR 31-45 had similar frequencies of efficacy and safety

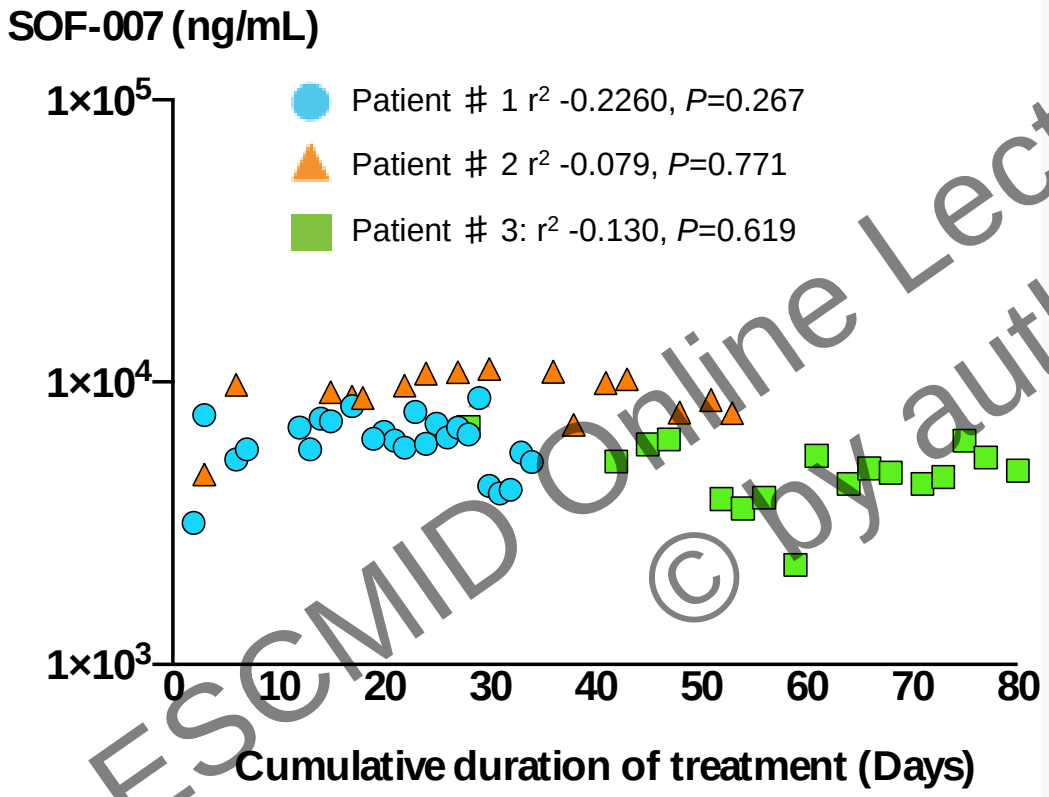
Saxena V et al. Liver Int 2016

Pharmacokinetics of SOF /GS-331007 during hemodialysis



Desnoyer A et al. J Hepatol 2016

Pharmacokinetics of SOF / GS-331007 during hemodialysis

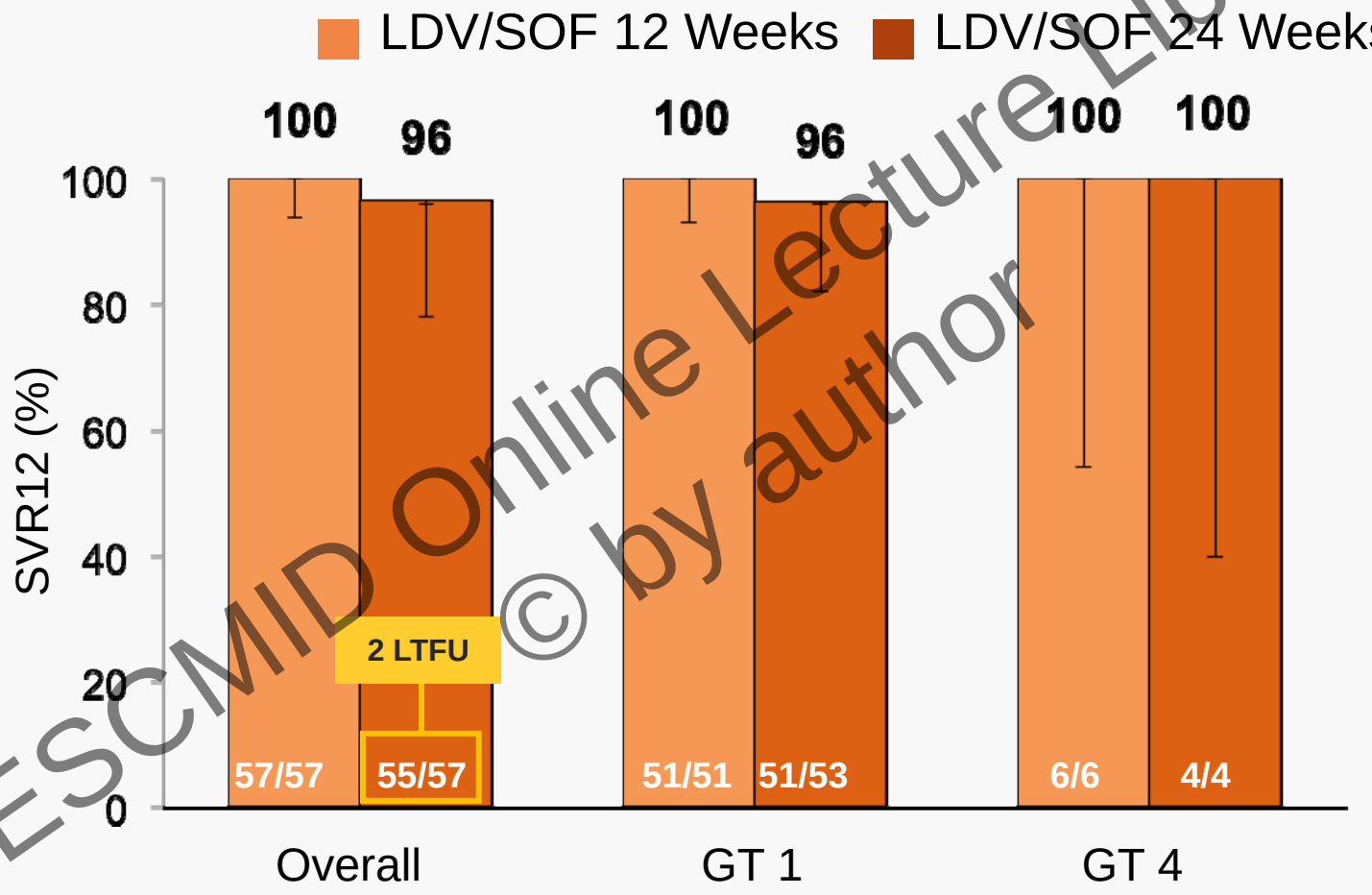


- No GS-331007 accumulation before hemodialysis in patients receiving SOF full dose every day
- No safety issue
- Efficacy issue:
  - SOF QD: SVR12 in 7/7
  - SOF TIW: SVR12 in 3/5

A regimen including sofosbuvir, 400 mg once daily, could be proposed for HCV-infected patients requiring hemodialysis and should be associated with close clinical, biological, cardiovascular, and therapeutic drug monitoring

Desnoyer A et al. J Hepatol 2016

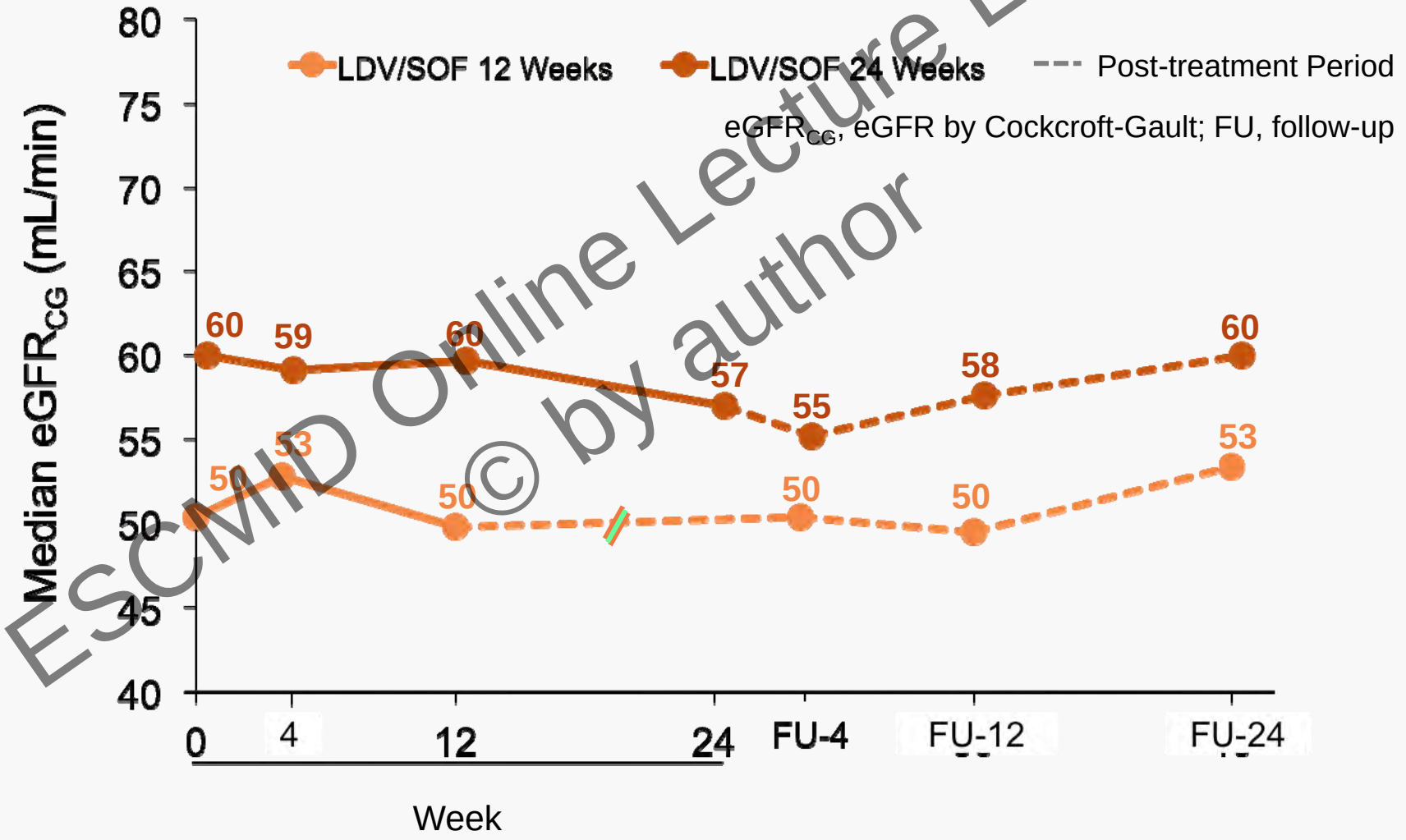
SOF/LDV & kidney recipients (1)



High efficacy and no impact on GFR in kidney recipients with GFR > 40 mL/min

Colombo M. et al. Ann Intern Med (in press)

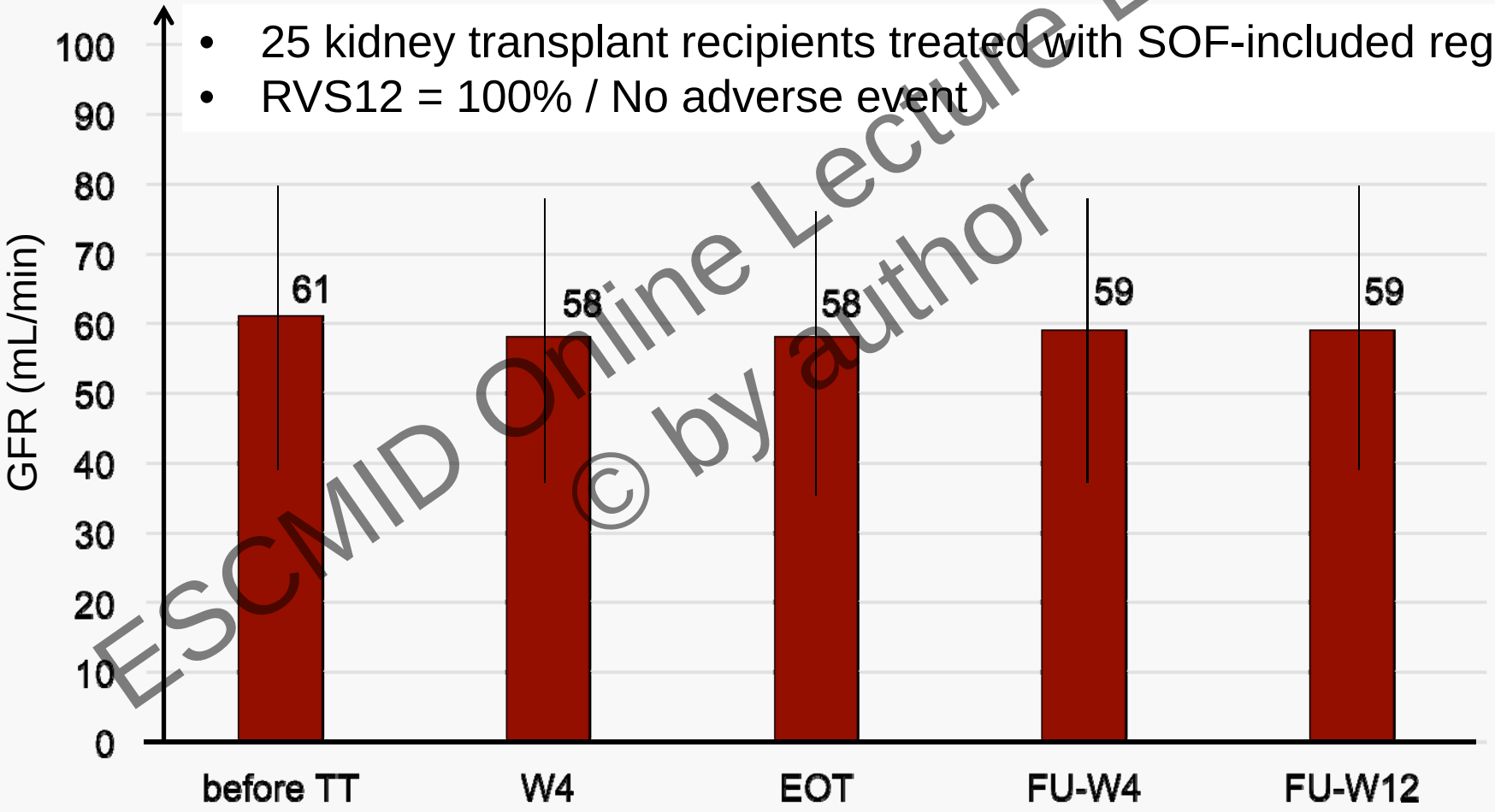
SOF/LDV & kidney recipients (2)



Colombo M. et al. Ann Intern Med (in press)

Sofosbuvir including regimen in kidney recipients

- 25 kidney transplant recipients treated with SOF-included regimen
- RVS12 = 100% / No adverse event



Kamar N et al. Am J Transplant 2016

Conclusion (1)

In HCV patients with impaired renal function

Patients with GFR > 30 mL/min (with or without renal transplantation)
- All the therapeutic options according to CPGs
- Renal Tx: Monitor HCV Protease Inhibitor / AntiCalcineurin

Patients with GFR < 30 mL/min or in hemodialysis
- Depends on genotype
- Depends on the severity of liver disease
- Depends on the indication of Renal Tx

Conclusion (2)

In HCV patients with impaired renal function

Patients with GFR < 30 mL/min or in hemodialysis
- With HCV genotype 1a, 1b or 4: GZR/EBR or 2/3D during 12 weeks*
- With HCV genotype 2, 3, 5 or 6: off-label

Patients with GFR < 30 mL/min or in hemodialysis, genotype 2, 3, 5 or 6
- Patients F3-F4: SOF-included regimen with drug monitoring
- Patients F0-F2 on Renal Tx waiting list: treat after renal Tx
- Patients F0-F2 without indication for Renal Tx: wait new data

Multidisciplinary discussion

Hepatology/Infectiology, Nephrology, Pharmacology, nurse for TPE**…

* For genotype 1a, discuss GZR/EBR during 16 weeks (without RBV) or RAVs
* For genotype 1a, discuss 3D during 12 weeks with or without RBV
* For genotype 4: 2D + RBV

** TPE: Therapeutic Patient Education