بسم الله الرحمن الرحيم

# Direct-Acting Antiviral Agents for Treatment of Hepatitis C Virus Infection

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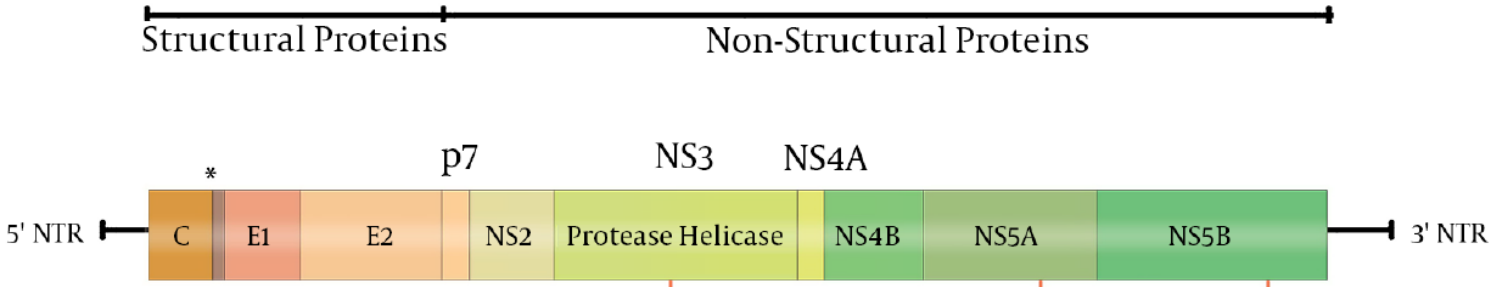
# Direct-Acting Antiviral Agents for Treatment of Hepatitis C Virus Infection




HCV Polyprotein Cleavage

Formation of Membranous Web, Replication, Virus Assembly

RNA Dependent RNA Polymerase

| NS3/4A Protease Inhibitors (-Previr) | | NS5A Inhibitors (-Asvir) | | NS5B Polymerase Inhibitors (-Buvir) | |
|---|---|---|---|---|---|
| Telaprevir | Vaniprevir | Daclatasvir | PPI-668 | **NIs** | **NNIs** |
| Boceprevir | Sovaprevir | Ledipasvir | PPI-461 | Sofosbuvir | Dasabuvir |
| Simeprevir | Grazoprevir | Ombitasvir | GSK2336805 | Mericitabine | BMS-791325 |
| Asunaprevir | ACH-2684 | Velpatasvir | Samatasvir | VX-135 | GS -9669 |
| Danoprevir | Narlaprevir | ACH-2928 | Elbasvir | Valopicitabin | VX-222 |
| Paritaprevir | Vedroprevir | ACH-3 102 | BMS-824393 | | Fillbuvir |
| | | | | | Setrobuvir |
| | | | | | Nesbuvir |
| | | | | | Tegobuvir |

- Goals of therapy
  - Sustained Virologic Response (SVR)
    - undetectable RNA level 12 weeks following the completion of therapy.

# Indications

- All patients with virologic evidence of chronic HCV infection (ie, detectable HCV viral level over a six-month period) should be considered for treatment

# EVALUATION TO GUIDE MANAGEMENT DECISIONS

- HCV genotype
- History of prior treatment
- Assessment of fibrosis stage

# SPECIAL SITUATIONS

- Treatment-experienced
  - can be retreated successfully.
- Mild liver disease
  - should be considered candidates for therapy.
- Bridging fibrosis and compensated cirrhosis
  - benefit the most
- Decompensated cirrhosis
  - Hepatologists can consider antiviral therapy.

# SPECIAL SITUATIONS

- Recurrence after liver transplantation
  - All patients should be considered for treatment
- Extrahepatic manifestations of HCV infection
  - Successful eradication of the virus results in improvement in extrahepatic manifestations in most patients

# SPECIAL SITUATIONS

- HIV coinfection
  - should be prioritized for treatment.
  - The potential for drug interactions
- HBV coinfection
  - Reactivation of HBV infection has been reported in patients receiving DAA therapy.
  - Prior to DAA regimen initiation, all patients should be tested for HBV coinfection.

# SPECIAL SITUATIONS

- Older adults
  - We follow the same general principles in deciding which older patients with HCV to treat and when as we do for the general population.

# Simeprevir

- NS3 protease inhibitor
- The most common side effects
  - Fatigue, headache, pruritus, influenza-like illness, nausea, myalgia, and dyspnea
  - Photosensitivity
  - Hyperbilirubinemia
  - Not recommended in patients with moderate or severe liver impairment (ChildPugh class B and C)

European Review for Medical and Pharmacological Sciences 2017; 21 (1 Suppl): 102-111

# Sofosbuvir

- NS5B polymerase inhibitor
- Few adverse effects
  - fatigue, nausea, insomnia, headache, anemia, pruritus and dizziness
    - more frequently when it is used in association with ribavirin
- Not recommended in patients with GFR< 30 ml/min and patients on hemodialysis
- The main interactions : Amiodarone

European Review for Medical and Pharmacological Sciences 2017; 21 (1 Suppl): 102-111

# Daclatasvir

- NS5A inhibitor
- Very few side effects,
  - headache, fatigue, and nausea
- No dose adjustment is required for renal neither hepatic impairment

European Review for Medical and Pharmacological Sciences 2017; 21 (1 Suppl): 102-111

# Daclatasvir

- A dose reduction to 30 mg once daily,
  - with strong CYP3A inhibitors like ritonavir-boosted atazanavir, clarithromycin, ketoconazole, rifabutin, calcium channel blockers
- A dose increase to 90 mg once daily
  - with moderate CYP3A inducers such as dexamethasone, carbamazepine, phenobarbital, phenytoin

European Review for Medical and Pharmacological Sciences 2017; 21 (1 Suppl): 102-111

# Ledipasvir

- NS5A polymerase inhibitor
- very few side effects
  - fatigue, headache, nausea, insomnia, and diarrhea
  - increased incidence of hyperbilirubinemia was reported in patients receiving LDV/SOF with RBV
- No dose adjustment is required for renal impairment

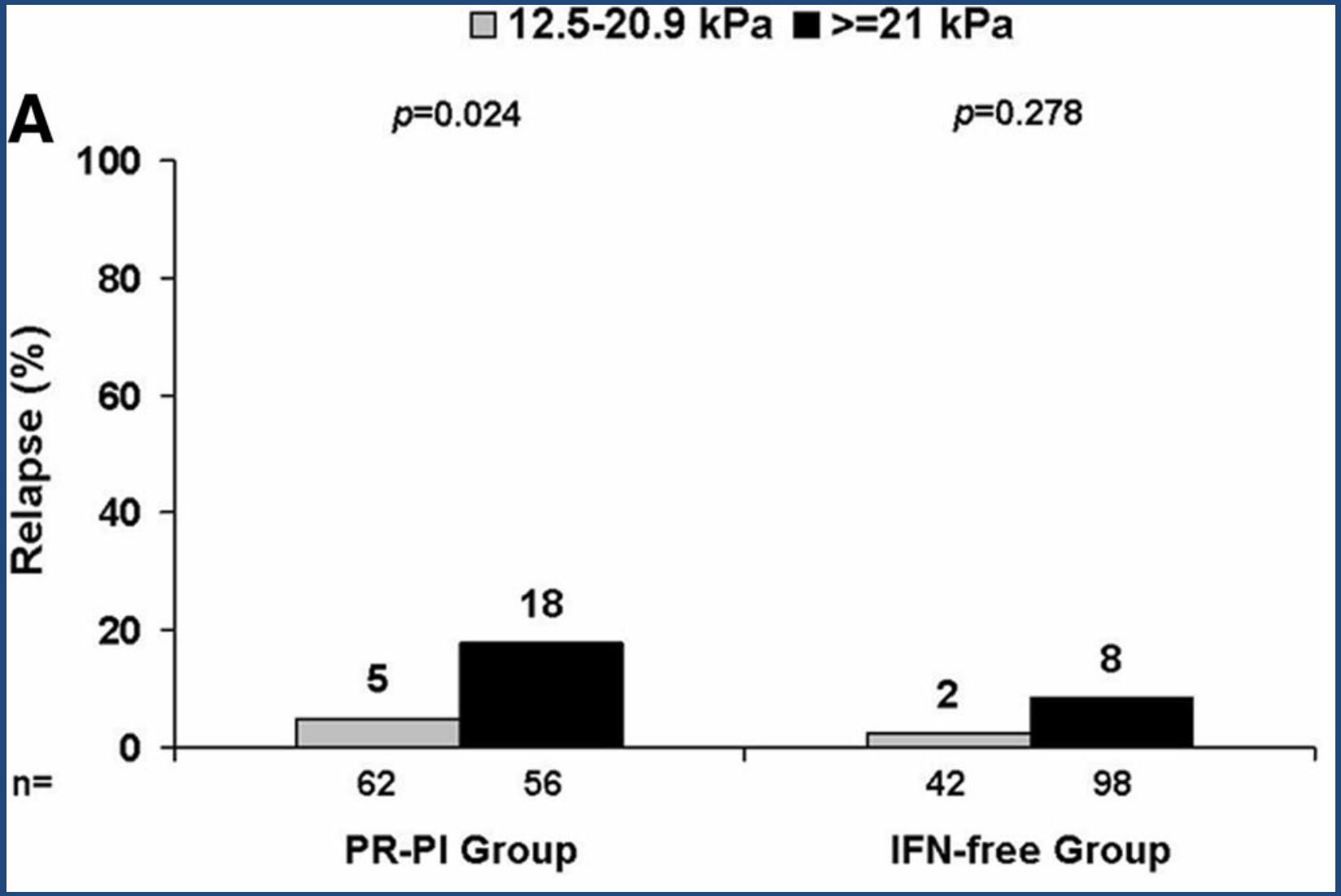
European Review for Medical and Pharmacological Sciences 2017; 21 (1 Suppl): 102-111

# Velpatasvir

- NS5A inhibitor,
- low rates of side effects
  - headache, fatigue, nausea, nasopharyngitis and insomnia
- contraindicated with rifampin, phenytoin, phenobarbital, carbamazepine

European Review for Medical and Pharmacological Sciences 2017; 21 (1 Suppl): 102-111

# Liver stiffness predicts the response to direct-acting antiviral-based therapy against chronic hepatitis C in cirrhotic patients




Eur J Clin Microbiol Infect Dis (2017) 36:853–861

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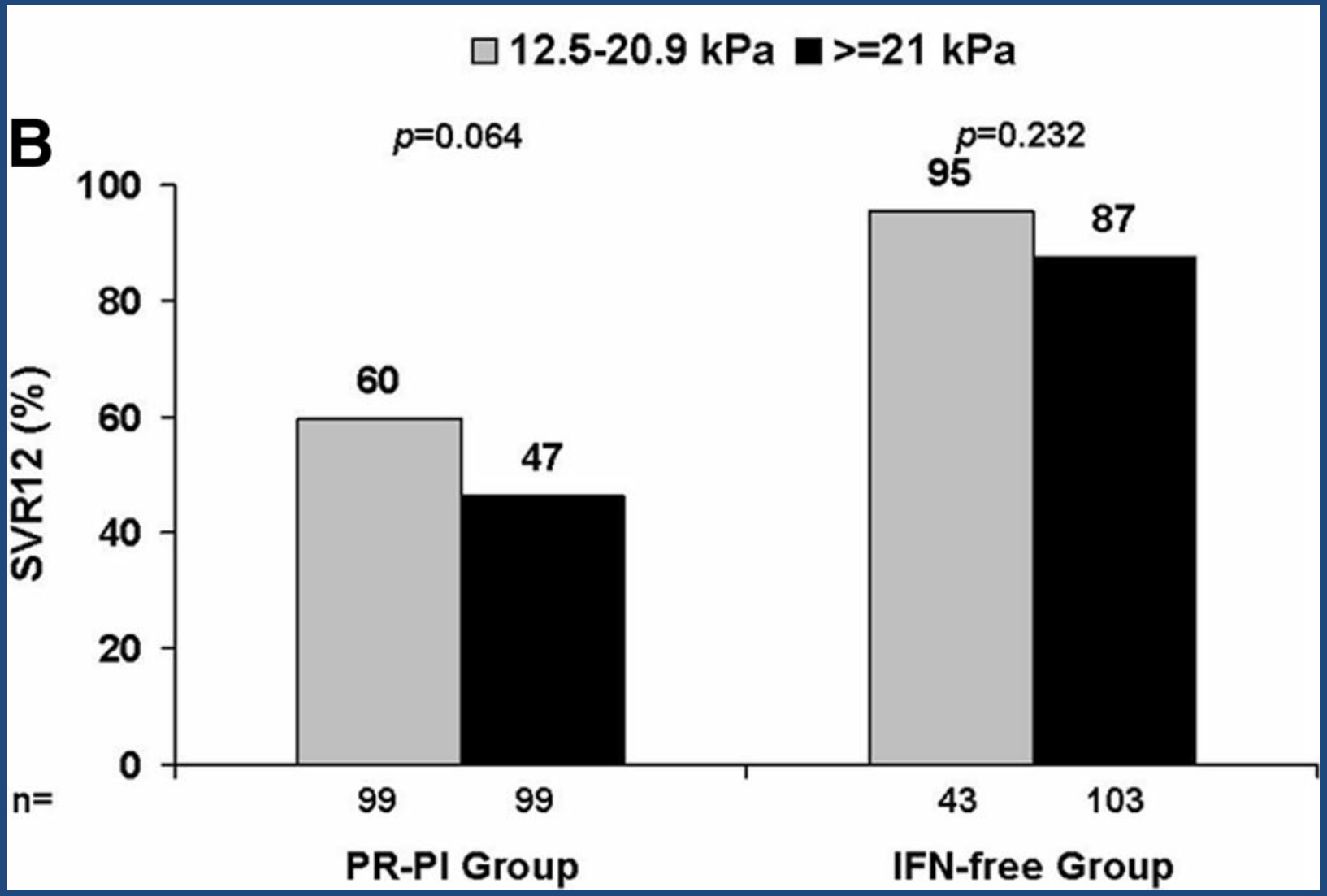


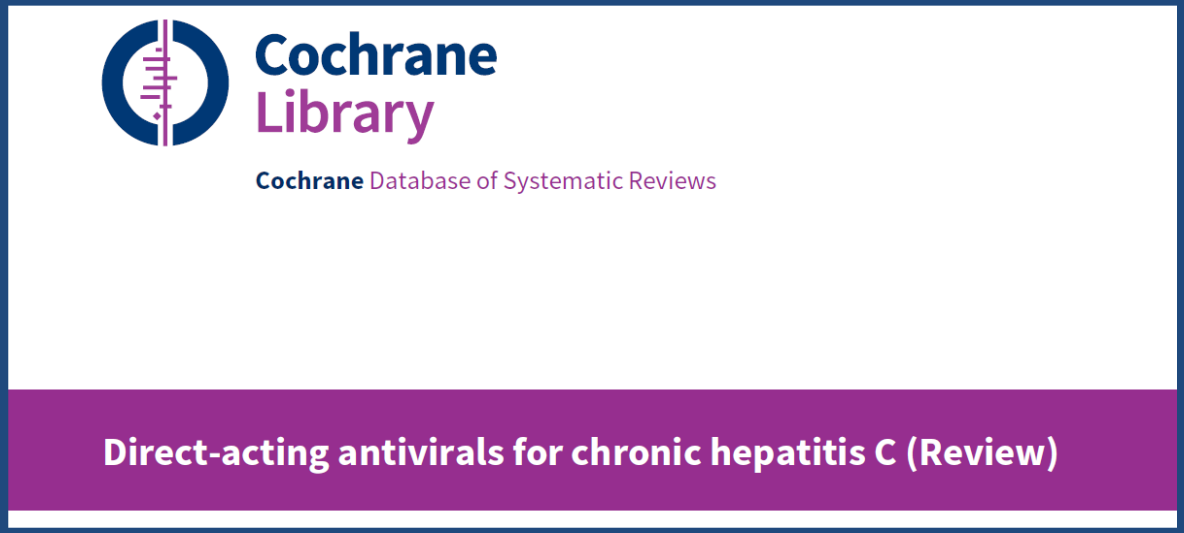

Eur J Clin Microbiol Infect Dis (2017) 36:853–861

# Superiority of Interferon-Free Regimens for Chronic Hepatitis C

## The Effect on Health-Related Quality of Life and Work Productivity

### Treatment-related adverse events.

| | IFN + SOF + RBV for 12 wk | IFN-free SOF + RBV for 12 or 24 wk | *P* |
|---|---|---|---|
| Blood or lymphatic system disorders | 26 (11.9%) | 24 (7.6%) | 0.10 |
| Fatigue or asthenia | 114 (52.0%) | 95 (30.2%) | <0.0001 |
| Flu-like symptoms | 80 (36.5%) | 10 (3.2%) | <0.0001 |
| Gastrointestinal system disorders | 83 (37.9%) | 75 (23.9%) | 0.0005 |
| Musculo-skeletal system disorders | 86 (39.3%) | 41 (13.1%) | <0.0001 |
| Nervous system disorders | 99 (45.2%) | 69 (22.0%) | <0.0001 |
| Psychiatric disorders | 99 (45.2%) | 96 (30.6%) | 0.0006 |
| Skin and subcutaneous tissue disorders | 79 (36.1%) | 75 (23.9%) | 0.0023 |
| Other disorders | 131 (59.8%) | 87 (27.7%) | <0.0001 |
| No treatment-related adverse events | 24 (11.0%) | 95 (30.2%) | <0.0001 |




- 138 trials randomising / 25,232 participants
- 51 different DAAs

Direct-acting antivirals for chronic hepatitis C (Review)

- Meta-analysis of the effects of all DAAs showed
  - no evidence of a difference when assessing hepatitis C-related morbidity or all-cause mortality (OR 3.72, 95% CI 0.53 to 26.18, P = 0.19
  - no evidence of a difference when assessing serious adverse events (OR 0.93, 95% CI 0.75 to 1.15, P = 0.52,
  - reduce the risk of no SVR (RR 0.44, 95% CI 0.37 to 0.52, P < 0.00001,
  - withdrawn DAAs seemed to increase the risk of serious adverse events (OR 1.45, 95% CI 1.22 to 1.73, P = 0.001,

Annals of Internal Medicine

REVIEW

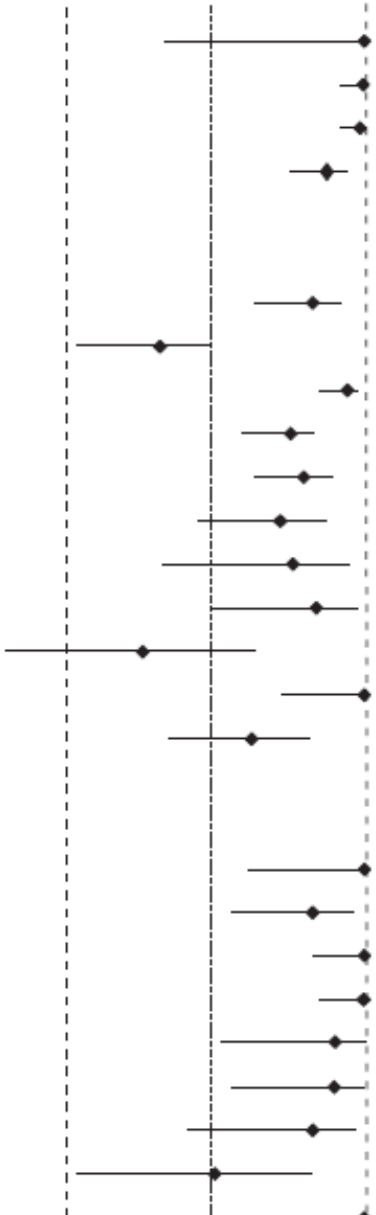
# Oral Direct-Acting Agent Therapy for Hepatitis C Virus Infection

## A Systematic Review

- 42 English-language studies
- At least 8 weeks of an FDA approved interferon-free HCV regimen that included at least 2 DAA
- Six DAA regimens showed
  - SVR rates >95% in HCV genotype 1 infection without cirrhosis
  - SVR rates (78% to 87%) in hepatic decompensation

*Figure 3.* HCV genotype 2 to 6 SVR12 rates and 95% CIs, by oral DAA regimen and clinical trial.

| Study, Year (Reference) | Regimen | Patients, *n* | Treatment Duration, *wk* | Cirrhosis Status | Treatment History | SVR12 Rate (95% CI), % |
|---|---|---|---|---|---|---|
| HCV-2 | | | | | | |
| ASTRAL-1, 2015 (24) | VEL–SOF | 10 | 12 | With | Both | 100.0 (69.0–100.0) |
| | VEL–SOF | 93 | 12 | Without | Both | 100.0 (96.0–100.0) |
| ASTRAL-2, 2015 (49) | VEL–SOF | 134 | 1 | With/without | Both | 99.0 (96.0–100.0) |
| | SOF + RBV | 132 | 12 | With/without | Both | 94.0 (88.0–97.0) |
| HCV-3 | | | | | | |
| ASTRAL-3, 2015 (49) | SOF–VEL | 80 | 12 | With | Both | 91.0 (83.0–96.0) |
| | SOF + RBV | 83 | 24 | With | Both | 66.0 (55.0–76.0) |
| | SOF–VEL | 197 | 12 | Without | Both | 97.0 (93.0–99.0) |
| | SOF + RBV | 187 | 24 | Without | Both | 87.0 (81.0–92.0) |
| ALLY-3, 2015 (16) | DCV + SOF | 101 | 12 | With | Naive | 90.0 (83.0–95.0) |
| | DCV + SOF | 51 | 12 | With | Experienced | 86.0 (74.0–94.0) |
| ALLY-3+, 2016 (42) | DCV + SOF + RBV | 24 | 12 | With | Both | 88.0 (68.0–97.0) |
| | DCV + SOF + RBV | 26 | 16 | With | Both | 92.0 (75.0–99.0) |
| Gane et al, 2015 (39) | LDV–SOF | 25 | 12 | With/without | Naive | 64.0 (43.0–82.0) |
| | LDV–SOF + RBV | 26 | 12 | With/without | Naive | 100.0 (87.0–100.0) |
| | LDV–SOF | 50 | 12 | With/without | Experienced | 82.0 (69.0–91.0) |
| HCV-4 | | | | | | |
| C-EDGE, 2015 (20) | GZP–EBV | 48 | 12 | With/without | Naive | 100.0 (82.0–100.0) |
| PEARL-I, 2015 (36) | PTV–r + OBV | 44 | 12 | Without | Naive | 91.0 (78.0–97.0) |
| | PTV–r + OBV + RBV | 42 | 12 | Without | Naive | 100.0 (92.0–100.0) |
| | PTV–r + OBV + RBV | 49 | 12 | Without | Experienced | 100.0 (93.0–100.0) |
| Kohli et al, 2015 (10) | LDV–SOF | 21 | 12 | With/without | Both | 95.0 (76.0–100.0) |
| Abergel et al, 2016 (19) | LDV–SOF | 22 | 12 | With/without | Naive | 95.0 (77.0–100.0) |
| | LDV–SOF | 22 | 12 | With/without | Experienced | 91.0 (71.0–99.0) |
| OSIRIS, 2017 (47) | SIM–SOF | 20 | 8 | Without | Both | 75.0 (51.0–91.0) |



Annals of Internal Medicine REVIEW

# Oral Direct-Acting Agent Therapy for Hepatitis C Virus Infection

## A Systematic Review

- The most effective DAA regimens for patients who have genotype 3 infection
  - without cirrhosis
    - sofosbuvir + velpatasvir or daclatasvir for 12 weeks
  - with cirrhosis
    - Velpatasvir + sofosbuvir

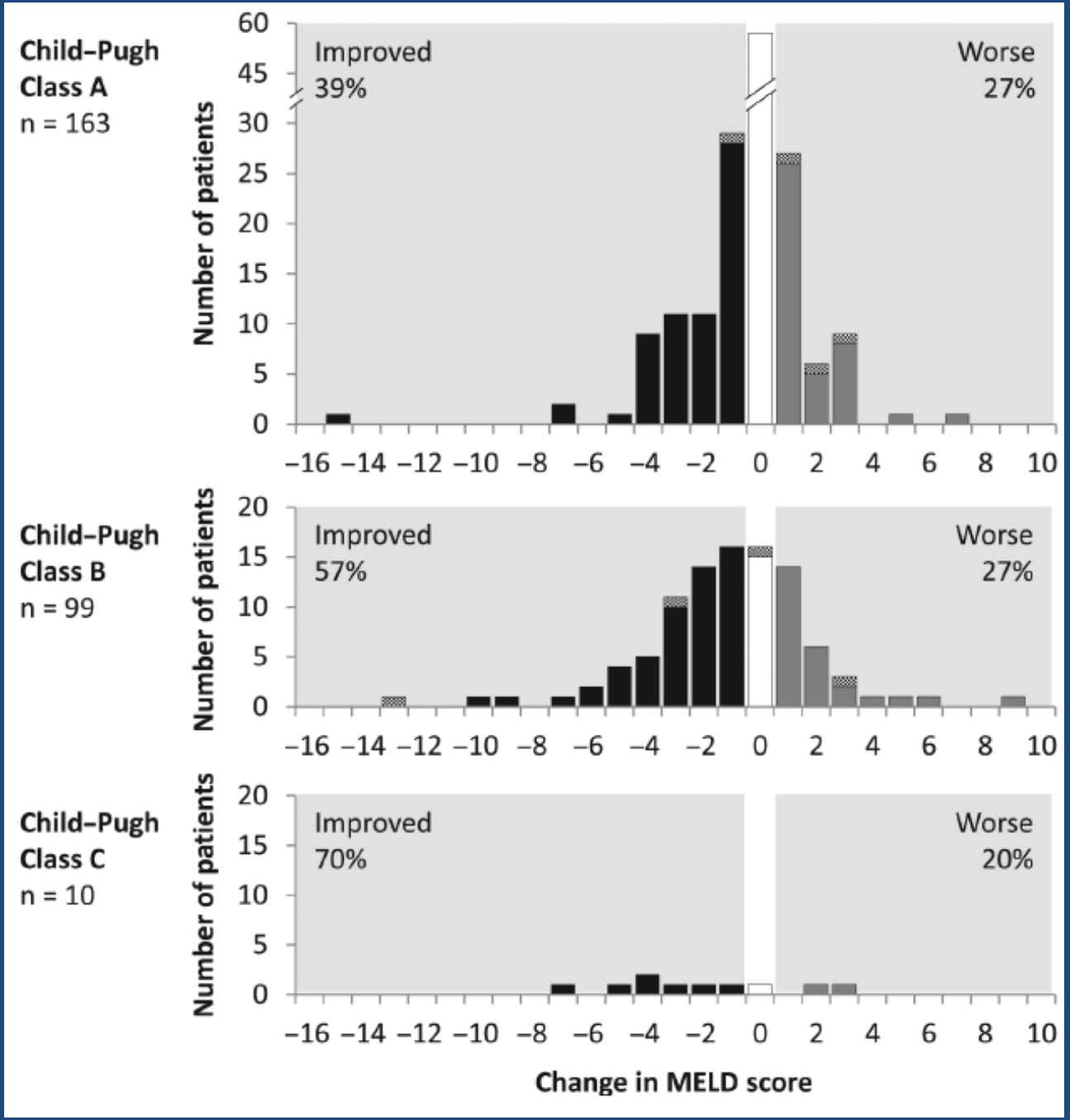
# Daclatasvir plus sofosbuvir, with or without ribavirin, achieved high sustained virological response rates in patients with HCV infection and advanced liver disease in a real-world cohort

| Parameter | n/N | % with SVR12 (95% CI) |
|---|---|---|
| Treatment group | | |
| DCV+SOF | 313/323 | 97 (94.4–98.5) |
| DCV+SOF+RBV | 106/110 | 96 (91.0–99.0) |
| HCV genotype | | |
| 1 | 312/319 | 98 (95.5–99.1) |
| 1a | 149/151 | 99 (95.3–99.8) |
| 1b | 150/155 | 97 (92.6–98.9) |
| 1 other/unknown subtype | 13/13 | 100 (75.3–100) |
| 3 | 82/89 | 92 (84.5–96.8) |
| 4 | 19/19 | 100 (82.4–100)) |
| Baseline HCV RNA, IU/mL | | |
| ≥2,000,000 | 113/116 | 97 (92.6–99.5) |
| <2,000,000 | 297/307 | 97 (94.1–98.4) |
| Cirrhosis status | | |
| Absent | 56/57 | 98 (90.6–100) |
| Present | 331/343 | 97 (94.0–98.2) |
| Indeterminate | 20/20 | 100 (83.2–100) |

Welzel TM, *et al*. *Gut* 2016;**65**:1861–1870. doi:10.1136/gutjnl-2016-312444

| | | |
|---|---|---|
| Child–Pugh class | | |
| A | 200/206 | 97 (93.8–98.9) |
| B | 115/121 | 95 (89.5–98.2) |
| C | 16/16 | 100 (79.4–100) |
| MELD score category | | |
| <10 | 147/152 | 97 (92.5–98.9) |
| 10–15 | 167/172 | 97 (93.3–99.0) |
| 16–20 | 14/16 | 88 (61.7–98.4) |
| Platelets $\times 10^9$/L | | |
| <50 | 56/60 | 93 (83.8–98.2) |
| <100 | 225/233 | 97 (93.3–98.5) |
| ≥100 | 182/187 | 97 (93.9–99.1) |
| Albumin, g/L | | |
| <35 | 129/136 | 95 (89.7–97.0) |
| ≥35 | 231/237 | 97 (94.6–99.1) |
| Prior HCV therapy | | |
| No | 125/127 | 98 (94.4–99.8) |
| Yes | 294/306 | 96 (93.3–98.0) |
| Protease inhibitor | 53/54 | 98 (90.1–100) |
| Liver transplant recipient | | |
| No | 339/353 | 96 (93.4–97.8) |
| Yes | 80/80 | 100 (95.5–100) |
| HIV/HCV coinfection | | |
| No | 346/359 | 96 (93.9–98.1) |
| Yes | 48/49 | 98 (89.1–99.9) |
| Renal insufficiency (CrCl, mL/min/1.73 $m^2$) | | |
| Severe (<30) | 5/5 | 100 (47.8–100) |
| Moderate (30–59) | 51/52 | 98 (89.7–100) |
| Mild (60–89) | 103/105 | 98 (93.3–99.8) |

Welzel TM, *et al*. *Gut* 2016;**65**:1861–1870. doi:10.1136/gutjnl-2016-312444




Welzel TM, *et al*. *Gut* 2016;**65**:1861–1870. doi:10.1136/gutjnl-2016-312444

# The effectiveness of daclatasvir based therapy in European patients with chronic hepatitis C and advanced liver disease

- The 249 patients
  - treatment experienced (65%)
  - decompensated cirrhosis (59%)
  - liver transplant before receiving daclatasvir (40%)

Young et al. BMC Infectious Diseases (2017) 17:45

**Table 2** Observed sustained virological response rates at 4 weeks (SVR4) and at 12 weeks (SVR12) after completing therapy with daclatasvir and sofosbuvir, with or without ribavirin

| Observed | SVR12 | | | |
|---|---|---|---|---|
| | As-treated | | Intent-to-treat | |
| Country | % | Fraction | % | Fraction |
| Austria | 100 | 13/13 | 93 | 13/14 |
| Denmark | 100 | 17/17 | 89 | 17/19 |
| Spain | 99 | 138/140 | 92 | 138/150 |
| Sweden | 100 | 15/15 | 94 | 15/16 |
| Switzerland | 85 | 22/26 | 85 | 22/26 |
| UK | 100 | 14/14 | 82 | 14/17 |
| Overall | 97 | 219/225 | 90 | 219/242 |

**Table 3** Observed sustained virological response rates in subgroups at 12 weeks (SVR12) after completing therapy with daclatasvir and sofosbuvir, with or without ribavirin

| Subgroups | | SVR12 | | | |
|---|---|---|---|---|---|
| | | As-treated | | Intent-to-treat | |
| | | % | Fraction | % | Fraction |
| Genotype[a] | 1 | 98 | 171/174 | 92 | 171/186 |
| | 3 | 94 | 33/35 | 85 | 33/39 |
| | Other | 94 | 15/16 | 88 | 15/17 |
| Cirrhosis | None or compensated | 100 | 93/93 | 99 | 93/94 |
| | Decompensated | 95 | 126/132 | 85 | 126/148 |
| Prior treatment | Naive | 99 | 75/76 | 88 | 75/85 |
| | Experienced | 99 | 144/149 | 92 | 144/157 |
| Ribavirin | Without | 96 | 157/163 | 88 | 157/178 |
| | With | 100 | 62/62 | 97 | 62/64 |
| Overall | | 97 | 219/225 | 90 | 219/242 |

# The Efficacy of 12 Weeks of Sofosbuvir, Daclatasvir, and Ribavirin in Treating Hepatitis C Patients with Cirrhosis, Genotypes 1 and 3

Shahin Merat,[1] Amir Houshang Sharifi,[1] Arghavan Haj-Sheykholeslami,[1] Hossein Poustchi,[1] Babak Fattahi,[1] Alireza Nateghi-Baygi,[1] Seyed Moayed Alavian,[2] and Reza Malekzadeh[1,*]

**Table 2.** Treatment Outcome in 100 Patients with HCV and Cirrhosis[a]

| Variable | Value |
|---|---|
| **Total number of patients** | 100 |
| **Treatment discontinued** | 1 |
| **Passed** | 1 |
| **Lost to follow-up** | 4 |
| **Completed study** | 94 |
| **SVR12** | 92 |
| Genotype 1 | 52/53 |
| Genotype 3 | 40/41 |
| **Per-protocol SVR** | 97.9% |
| **Intention-to-treat SVR** | 92.0% |

Hepatitis Mon. 2017; 17(1):e44564.

# Efficacy and Safety of Generic Sofosbuvir/Ledipasvir Fixed-Dose Combination in Iranian Patients with Chronic Hepatitis C Virus Infection

Heidar Sharafi,[1,2,3] Mehri Nikbin,[2,3] Seyed Hoda Alavian,[2,3] Bita Behnava,[2,3] and Seyed Moayed Alavian[1,2,3,*]

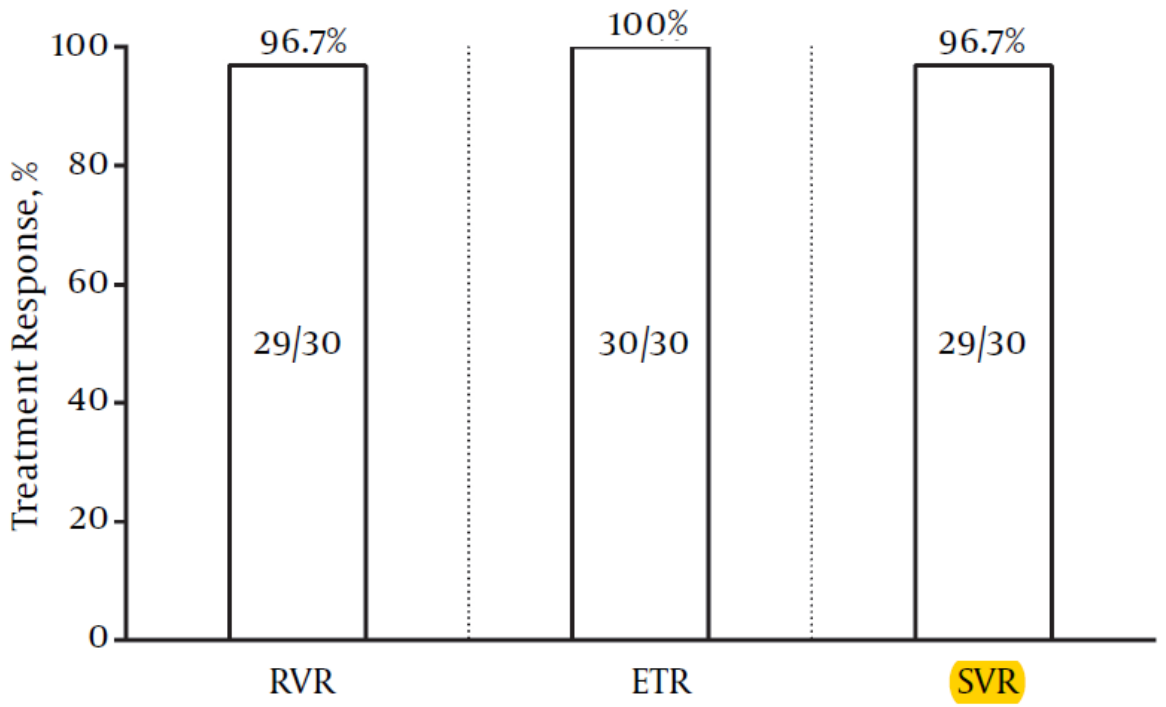
**Table 1.** Baseline Characteristics of the Study Population

| | | All Patients (N = 30) |
|---|---|---|
| **Gender** | Male | 22 (73.3%) |
| | Female | 8 (26.7%) |
| **Age[a], y** | Mean ± SD | 52.9 ± 15.6 |
| | Range (min - max) | 25 - 76 |
| **BMI[a], Kg/m$^2$** | Mean ± SD | 26.8 ± 4.8 |
| | Range (min - max) | 20.3 - 39.2 |
| **Serum ALT[a], IU/L** | Median (IQR) | 52.0 (40.5) |
| | Range (min-max) | 17 - 252 |
| **Serum AST[a], IU/L** | Median (IQR) | 43.0 (29.5) |
| | Range (min - max) | 13 - 214 |
| **Cirrhosis condition** | Non-cirrhotic | 14 (46.7%) |
| | Cirrhotic | 16 (53.3%) |
| **HCV RNA[a], Log IU/mL** | Median (IQR) | 6.5 (7.1) |
| | Range (min - max) | 3.7 - 7.7 |
| **HCV genotype** | HCV-1a | 14 (46.7%) |
| | HCV-1b | 8 (26.7%) |
| | Unsubtyped HCV-1 | 7 (23.3%) |
| | HCV-4 | 1 (3.3%) |
| **Previous history of treatment[a]** | Treatment-naive | 11 (37.9%) |
| | Relapse | 12 (41.4%) |
| | Non-responder | 6 (20.7%) |

# Efficacy and Safety of Generic Sofosbuvir/Ledipasvir Fixed-Dose Combination in Iranian Patients with Chronic Hepatitis C Virus Infection

Heidar Sharafi,[1,2,3] Mehri Nikbin,[2,3] Seyed Hoda Alavian,[2,3] Bita Behnava,[2,3] and Seyed Moayed Alavian[1,2,3,*]

**Figure 1.** Responses to Treatment with Sofosbuvir/Ledipasvir Fixed-dose Combination




Hepat Mon. 2017 June; 17(6):

# Efficacy of Ledipasvir Plus Sofosbuvir for 8 or 12 Weeks in Patients With Hepatitis C Virus Genotype 2 Infection

**Table 2.** Treatment Response

| | LDV–SOF 8 Weeks (n = 27) | LDV–SOF 12 Weeks (n = 26) |
|---|---|---|
| HCV RNA <15 IU/mL, n/n (%) | | |
| On treatment | | |
| Week 4 | 25/27 (93) | 23/25 (92)[a] |
| Week 8 | 26/27 (96) | 25/25 (100) |
| Week 12 | - | 25/25 (100) |
| After treatment | | |
| Week 2 | 26/27 (96) | 25/26 (96) |
| Week 4 | 22/27 (82) | 25/26 (96) |
| Week 8 | 20/27 (74) | 25/26 (96) |
| Week 12 (SVR) | 20/27 (74)[b] | 25/26 (96) |
| 95% CI | 54%–89% | 80%–100% |
| Virologic failure, n | | |
| On treatment | 0 | 0 |
| Relapse | 6 | 0 |

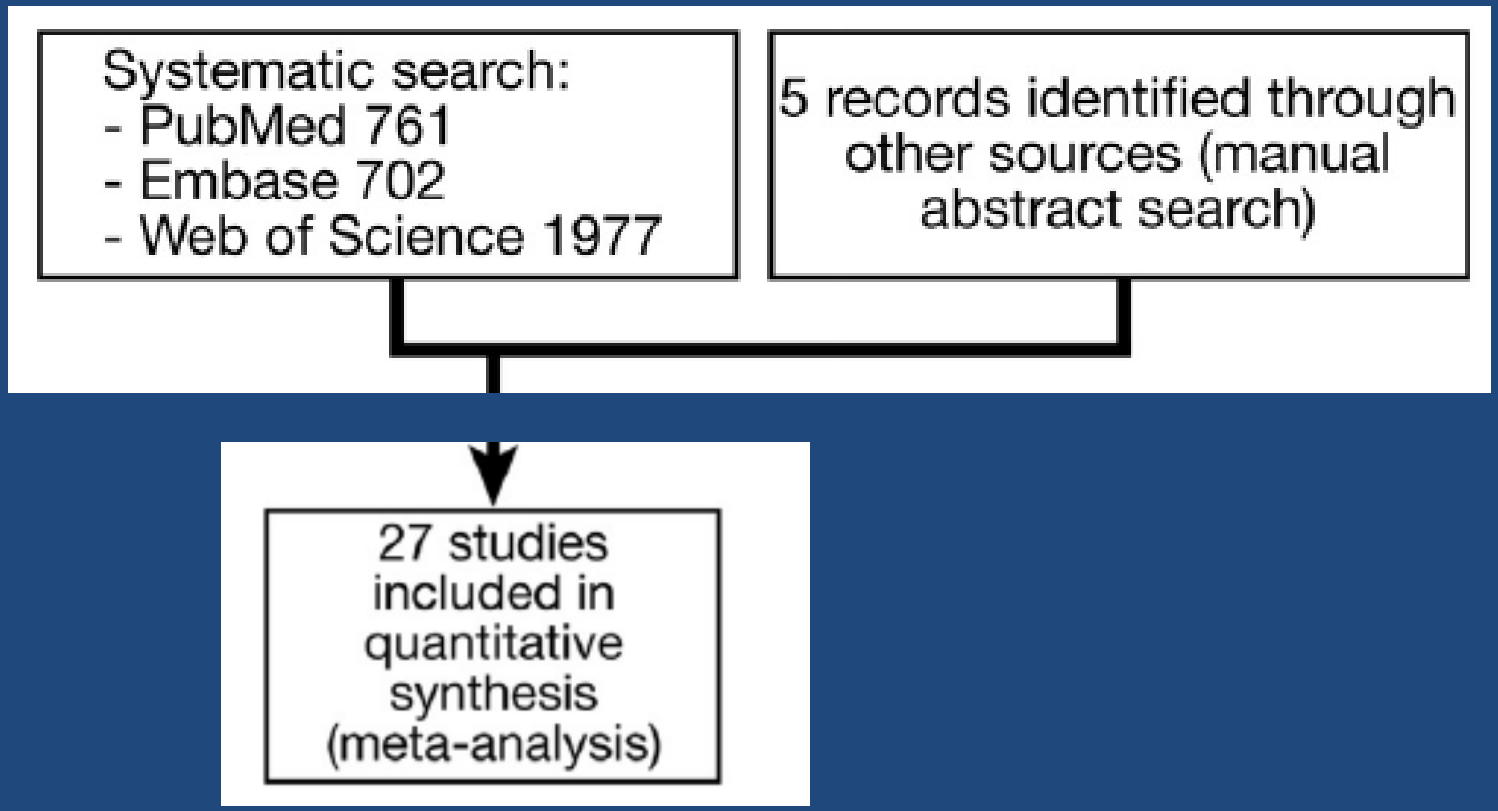
For treatment-naïve and -experienced patients, ledipasvir–sofosbuvir for 12 weeks is highly effective for the treatment of HCV genotype 2

Gastroenterology 2017;152:1366–1371

# SYSTEMATIC REVIEWS AND META-ANALYSES

*Fasiha Kanwal, Section Editor*

## Identification of the Best Direct-Acting Antiviral Regimen for Patients With Hepatitis C Virus Genotype 3 Infection: A Systematic Review and Network Meta-analysis



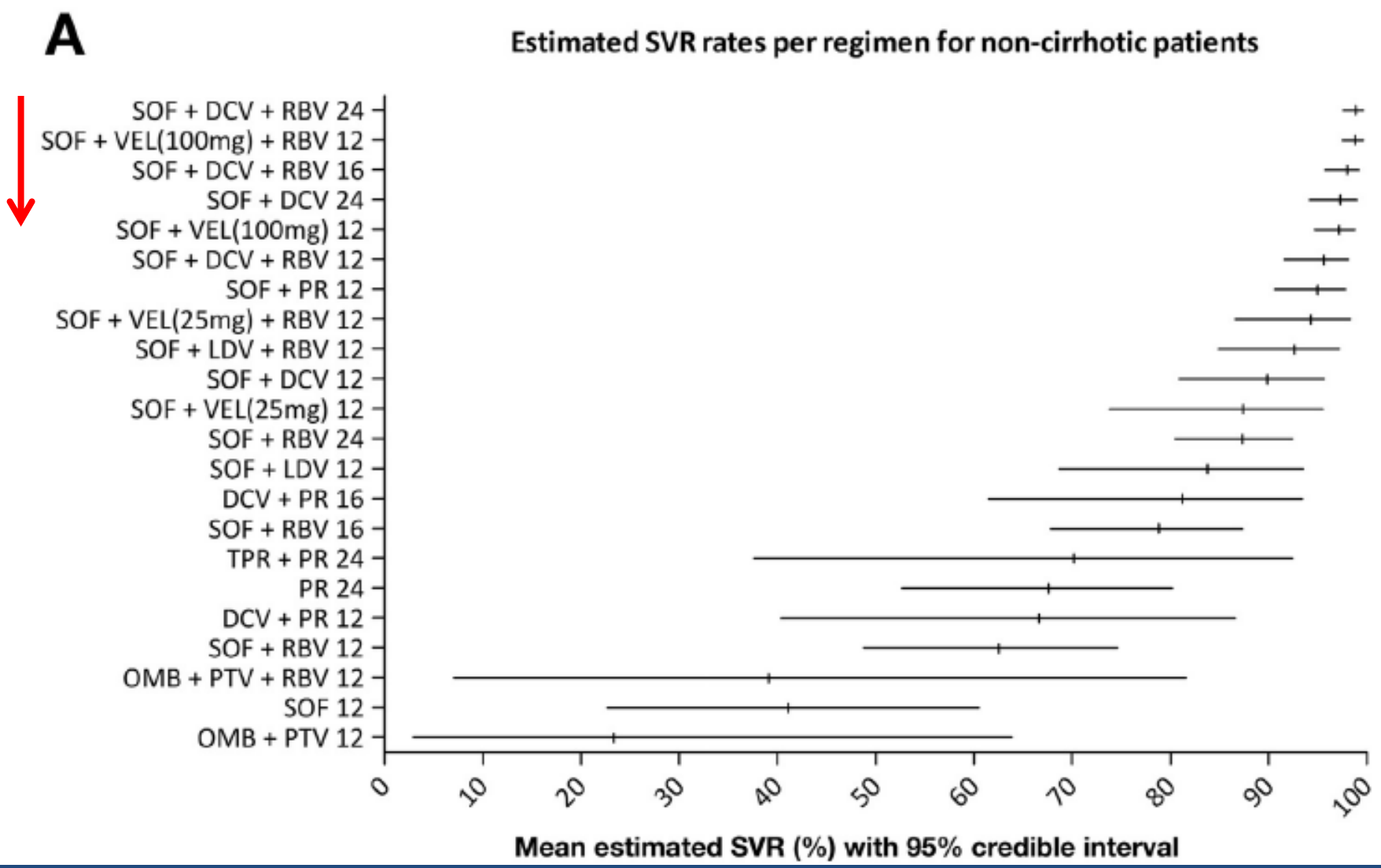

Clinical Gastroenterology and Hepatology 2017;15:349–3595

- Patients without cirrhosis, the greatest SVR
  - sofosbuvir + velpatasvir + ribavirin (99%; 95% CrI, 98%–100%)
  - sofosbuvir + velpatasvir without ribavirin (97%; 95% CrI, 95%–99%),
  - sofosbuvir + daclatasvir + ribavirin (96%; 95% CrI, 92%–98%),
  - sofosbuvir + peginterferon + ribavirin (95%; 95% CrI, 91%–98%),
  - all for 12 weeks.

Clinical Gastroenterology and Hepatology 2017;15:349–3595

- Patients with cirrhosis, the highest SVR
  - Sofosbuvir + velpatasvir for 24 weeks (96%; 95% CrI, 92%–99%),
  - sofosbuvir + daclatasvir + ribavirin for 24 weeks (94%; 95% CrI, 87%–98%),
  - Sofosbuvir + velpatasvir + ribavirin for 12 weeks (94%; 95% CrI, 86%–98%).
  - Ribavirin increases efficacy in patients with and without cirrhosis (odds ratio, 2.6–4.5).

Clinical Gastroenterology and Hepatology 2017;15:349–3595

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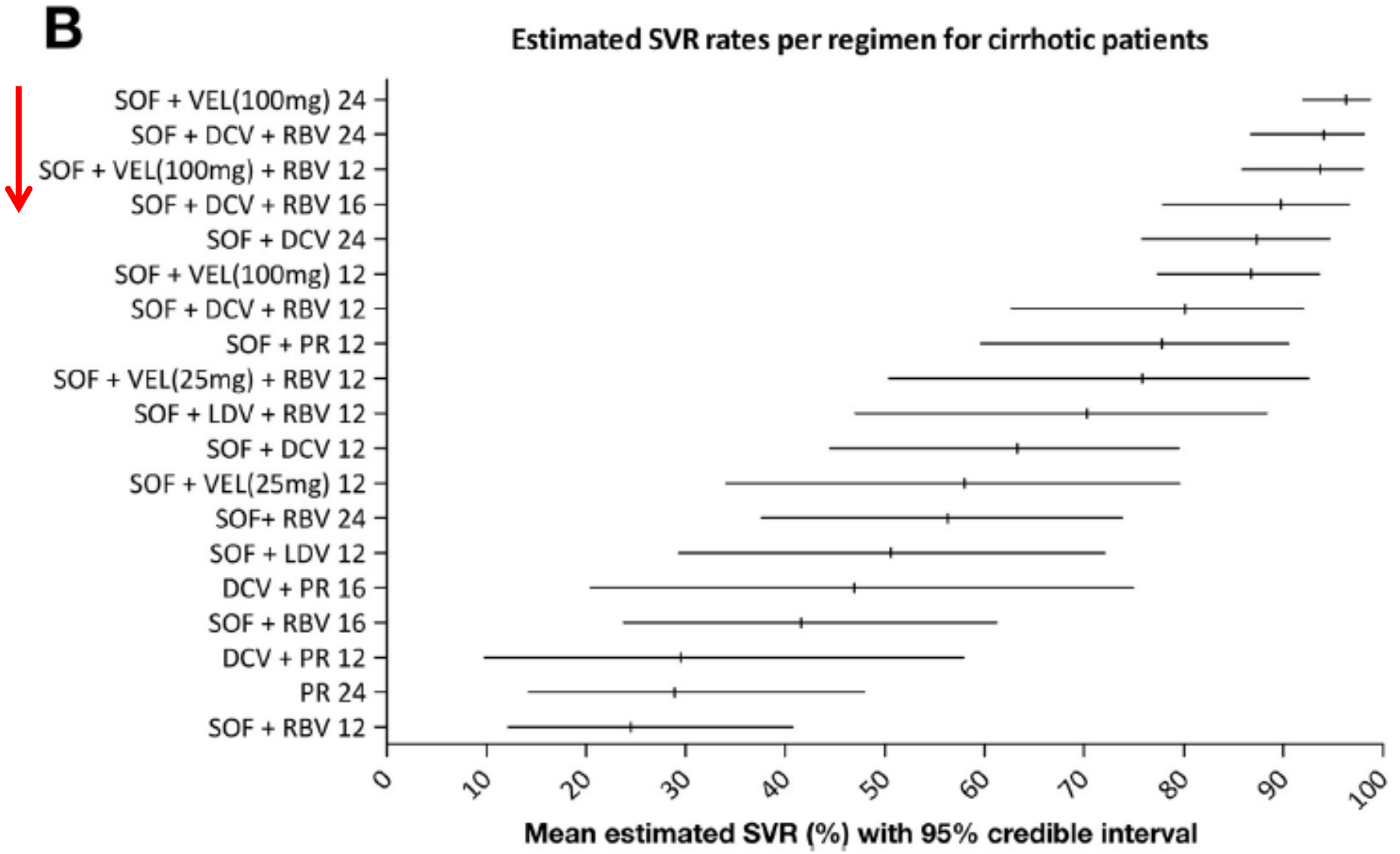
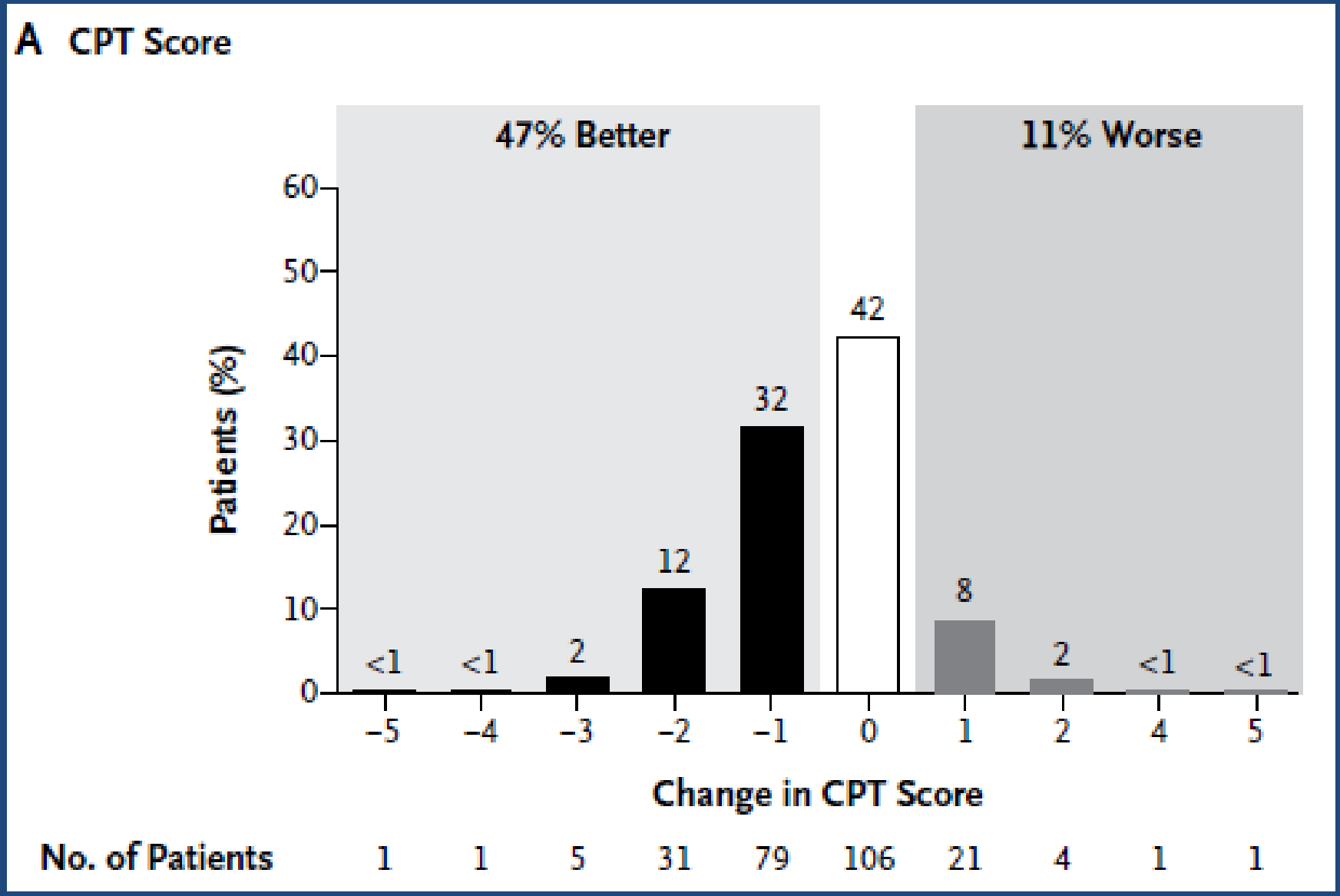


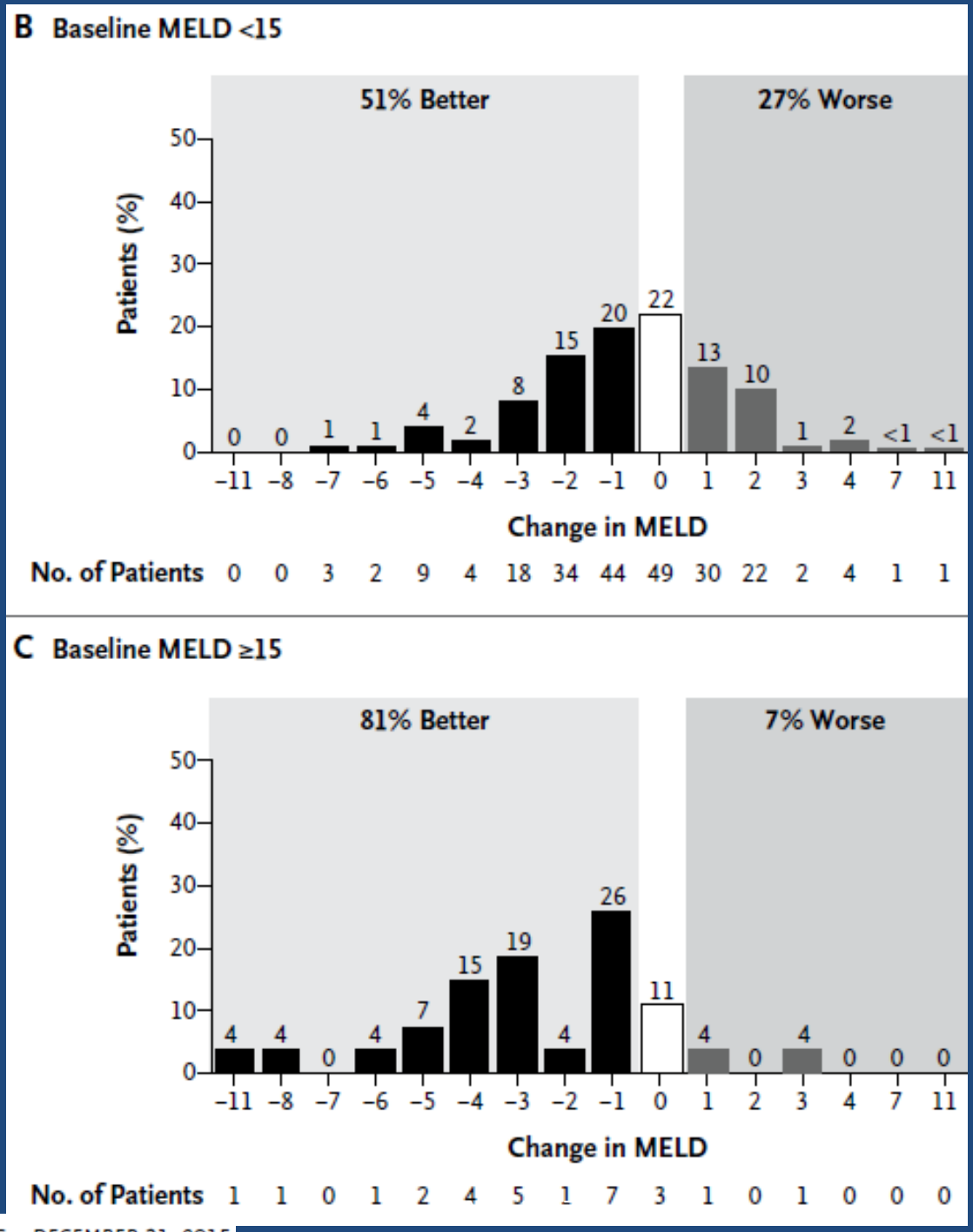

Clinical Gastroenterology and Hepatology 2017;15:349–3595

# Antiviral selection for HCV decompensated cirrhosis

# Sofosbuvir and Velpatasvir for HCV in Patients with Decompensated Cirrhosis

| Outcome | Sofosbuvir–Velpatasvir for 12 Wk (N=90) | | Sofosbuvir–Velpatasvir plus Ribavirin for 12 Wk (N=87) | | Sofosbuvir–Velpatasvir for 24 Wk (N=90) | |
|---|---|---|---|---|---|---|
| | *no./total no. (%)* | *95% CI* | *no./total no. (%)* | *95% CI* | *no./total no. (%)* | *95% CI* |
| **Sustained virologic response** | | | | | | |
| All genotypes | 75/90 (83) | 74–90 | 82/87 (94) | 87–98 | 77/90 (86) | 77–92 |
| Genotype 1a | 44/50 (88) | 76–96 | 51/54 (94) | 85–99 | 51/55 (93) | 82–98 |
| Genotype 1b | 16/18 (89) | 65–99 | 14/14 (100) | 77–100 | 14/16 (88) | 62–98 |
| Genotype 2 | 4/4 (100) | 40–100 | 4/4 (100) | 40–100 | 3/4 (75) | 19–99 |
| Genotype 3 | 7/14 (50) | 23–77 | 11/13 (85) | 55–98 | 6/12 (50) | 21–79 |
| Genotype 4 | 4/4 (100) | 40–100 | 2/2 (100) | 16–100 | 2/2 (100) | 16–100 |
| Genotype 6 | 0 | NA | 0 | NA | 1/1 (100) | 3–100 |
| **Virologic failure** | | | | | | |
| All genotypes | 11/90 (12) | | 3/87 (3) | | 8/90 (9) | |
| Genotype 1a | 3/50 (6) | | 1/54 (2) | | 2/55 (4) | |
| Genotype 1b | 2/18 (11) | | 0 | | 1/16 (6) | |
| Genotype 3 | 6/14 (43) | | 2/13 (15) | | 5/12 (42) | |
| **Other outcome** | | | | | | |
| Death | 3/90 (3) | | 2/87 (2) | | 2/90 (2) | |
| Loss to follow-up | 1/90 (1) | | 0 | | 3/90 (3) | |


A CPT Score
47% Better
11% Worse
Patients (%)
60
50
40
30
20
10
0
<1
<1
2
12
32
42
8
2
<1
<1
−5
−4
−3
−2
−1
0
1
2
4
5
Change in CPT Score
No. of Patients
1
1
5
31
79
106
21
4
1
1


B Baseline MELD <15
51% Better
27% Worse
Patients (%)
50
40
30
20
10
0
0 0 1 1 4 2 8 15 20 22 13 10 1 2 <1 <1
−11 −8 −7 −6 −5 −4 −3 −2 −1 0 1 2 3 4 7 11
Change in MELD
No. of Patients 0 0 3 2 9 4 18 34 44 49 30 22 2 4 1 1
C Baseline MELD ≥15
81% Better
7% Worse
Patients (%)
50
40
30
20
10
0
4 4 0 4 7 15 19 4 26 11 4 0 4 0 0 0
−11 −8 −7 −6 −5 −4 −3 −2 −1 0 1 2 3 4 7 11
Change in MELD
No. of Patients 1 1 0 1 2 4 5 1 7 3 1 0 1 0 0 0

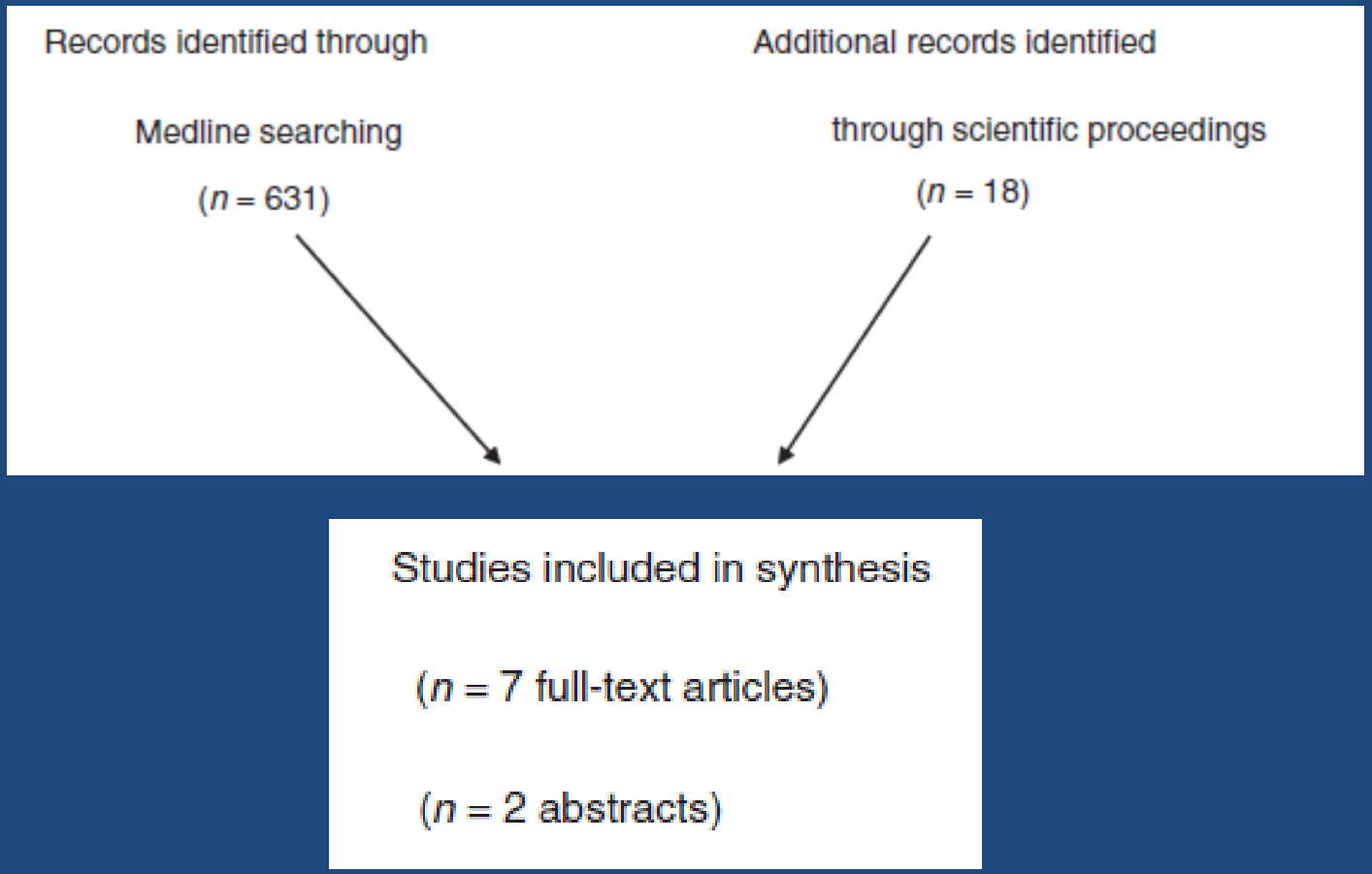
Clinical Gastroenterology and Hepatology 2017;15:421–430

# PANCREAS, BILIARY TRACT, AND LIVER

## Sofosbuvir and Velpatasvir Combination Improves Patient-reported Outcomes for Patients With HCV Infection, Without or With Compensated or Decompensated Cirrhosis

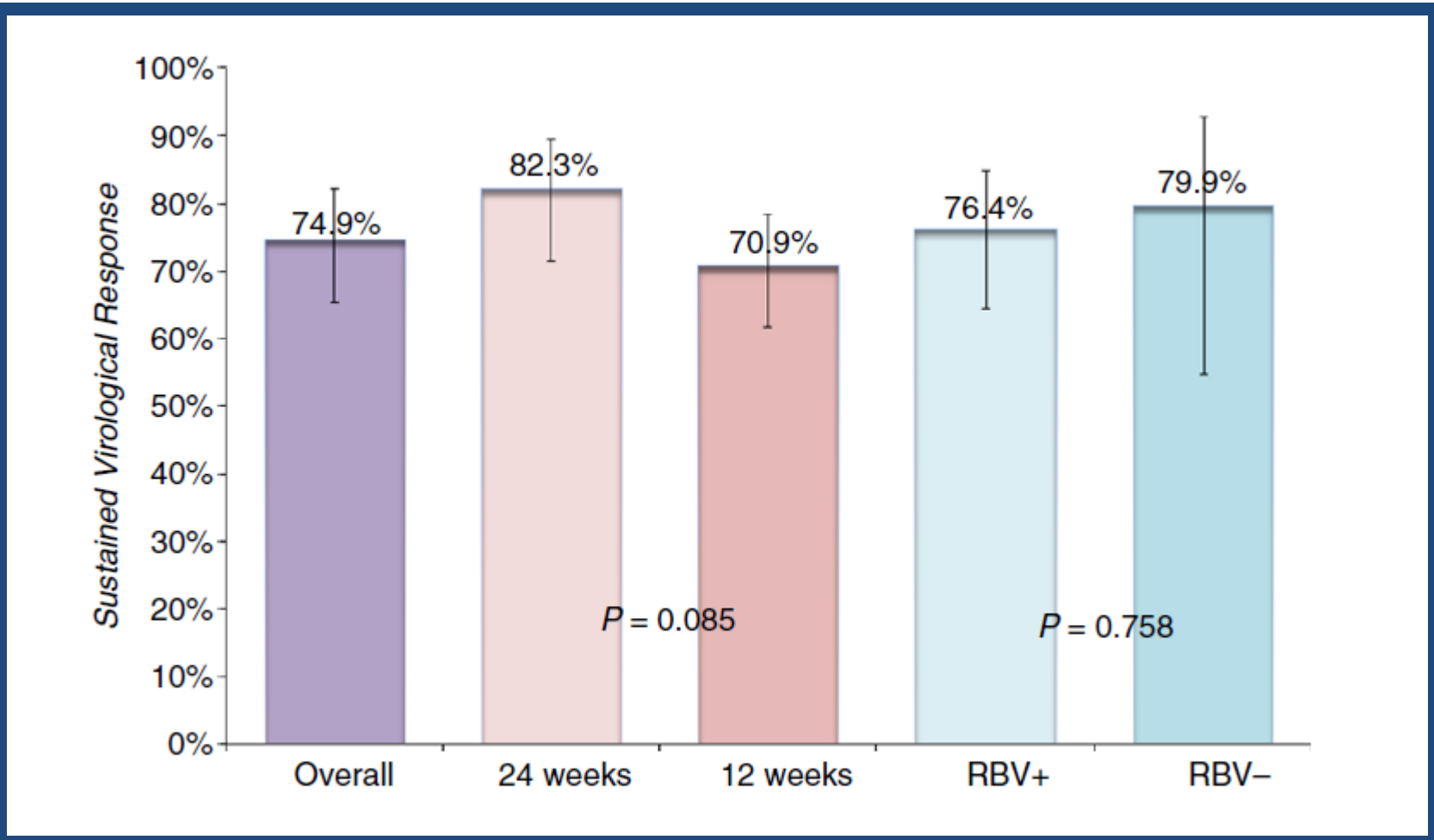
any time point (all 1-sided *P* values > .05). In multivariate analysis, compensated cirrhosis was associated with a 2.3% to 5.0% greater increase in PRO scores following treatment with sofosbuvir and velpatasvir ($P < .05$); decompensated cirrhosis was associated with a 5.5%–9.1% greater increase ($P < .002$). Clinicaltrials.gov number, NCT02201940, NCT02220998, NCT02201953, NCT02201901.

# Systematic review: interferon-free regimens for patients with HCV-related Child C cirrhosis




Aliment Pharmacol Ther 2017; 45: 1193–1200

# Systematic review: interferon-free regimens for patients with HCV-related Child C cirrhosis




SVR rates according to the different therapeutic regimens with new direct acting antivirals by treatment duration (24 vs. 12 weeks) or the inclusion or not of ribavirin in the regimens.

Aliment Pharmacol Ther 2017; 45: 1193–1200

# Systematic review: interferon-free regimens for patients with HCV-related Child C cirrhosis

Table 2 | Characteristics of Child C cirrhotic patients, enrolled in the studies selected for the meta-analysis

| | Regimen | Ribavirin | Duration of therapy (weeks) | Total no. of patients | No. of patients with SVR12 | No. of [illegible] | [illegible] |
|---|---|---|---|---|---|---|---|
| Charlton, 2015 | SOF/LDV | Yes | 12 | 22 | | | |
| | | Yes | 24 | | | | |
| Manns, 2016 | SOF/LDV | Yes | | | | | |
| | | [illegible] | | | | | |
| Shiffmann, 2015 | SOF/SMV | | | | | | |
| Foster, 2016 | | | | | | | |
| Mo[illegible] | | | | | | | – |
| Po[illegible] | | | | | | – | 7/13 |
| Sa[illegible] | | | | | | – | – |
| Ler[illegible] | | | | | 8 | – | 3/4 |
| Pete | | | | 20 | 15 | – | – |
| Ippol | | | 24 | 6 | 5 | 1 | 3/6 |
| | | | 24 | 5 | 5 | – | 4/5 |
| | | Yes | 24 | 3 | 3 | – | 3/3 |
| | | No | 24 | 7 | 7 | – | 3/7 |
| | SOF/SMV | Yes | 12 | 2 | 2 | – | 1/2 |
| | | No | 12 | 2 | 2 | – | – |

WILEY AP&T Alimentary Pharmacology & Therapeutics

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LETTERS TO THE EDITORS

## Letter: the efficacy of interferon-free regimens in HCV-related Child C cirrhosis needs careful interpretation

Aliment Pharmacol Ther 2017; 45: 1193–1200

# Treatment regimens for chronic hepatitis C virus genotype 1 infection in naïve adults

# Assess Liver fibrosis / Virus subtype

## Decompensated Cirrhosis

NO

### Subtype 1a

| No Cirrhosis (F 0-3) | Cirrhosis (F4) |
|---|---|
| *Sofosbuvir + Ledipasvir 12 w* | *Sofosbuvir + Ledipasvir 12 w* |
| *Sofosbuvir + Velpatasvir 12 wk* | *Sofosbuvir + Velpatasvir 12 wk* |
| *Sofosbuvir + Daclatasvir 12 wk* | *Sofosbuvir + Daclatasvir +/− Ribavirin 24 wk* |

### Subtype 1b

| No Cirrhosis (F 0-3) | Cirrhosis (F4) |
|---|---|
| *Sofosbuvir + Ledipasvir 12 w* | *Sofosbuvir + Ledipasvir 12 w* |
| *Sofosbuvir + Velpatasvir 12 wk* | *Sofosbuvir + Velpatasvir 12 wk* |
| *Sofosbuvir + Daclatasvir 12 wk* | *Sofosbuvir + Daclatasvir +/− Ribavirin 24 wk* |

# Antiviral selection for HCV genotype 2 infection in adults

# Assess Liver fibrosis

## Decompensated Cirrhosis

NO

| No Cirrhosis (F 0-3) | Cirrhosis(F4) |
| --- | --- |
| *Sofosbuvir +Velpatasvir* *12 wk* | *Sofosbuvir +Velpatasvir* *12 wk* |
| *Sofosbuvir +Daclatasvir* *12 wk* | *Sofosbuvir +Daclatasvir* *16-24 wk* |

# Antiviral selection for HCV genotype 3 infection in adults

# Assess Liver fibrosis

## Decompensated Cirrhosis

NO

No Cirrhosis (F 0-3)

Cirrhosis (F4)

Test for NS5A for RAS

*Sofosbuvir + Velpatasvir 12 wk*

*Sofosbuvir + Daclatasvir 12 wk*

Y93H absent

*Sofosbuvir + Velpatasvir 12 wk*

*Sofosbuvir + Daclatasvir + Ribavirin 24 wk*

Y93H present

*Sofosbuvir + Velpatasvir+ Ribavirin 12 wk*

*Sofosbuvir + Daclatasvir + Ribavirin 24 wk*