Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2017-08-01-D-301 Glecaprevir/Pibrentasvir

Stand: August 2017

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Glecaprevir/Pibrentasvir [chronische Hepatitis C]	
Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	*Siehe Tabelle II. Zugelassene Arzneimittel im Anwendungsgebiet*
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	nicht angezeigt
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Verfahren nach § 35a SGB V: - Boceprevir (Beschluss vom 01.03.2012) - Telaprevir (Beschluss vom 29.03.2012) - Sofosbuvir (Beschluss vom 17.07.2014) - Simeprevir (Beschluss vom 20.11.2014) - Daclatasvir (Beschluss vom 19.02.2015) - Ledipasvir/Sofosbuvir (Beschluss vom 21.05.2015) - Dasabuvir (Beschluss vom 16.07.2015) - Ombitasvir/Paritaprevir/Ritonavir (Beschluss vom 16.07.2015) - Sofosbuvir/Velpatasvir (Beschluss vom 05.01.2017) - Elbasvir/Grazoprevir (Beschluss vom 15.06.2017)
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche*

1. Zugelassene Arzneimittel im Anwendungsgebiet

<table>
<tr><th>Wirkstoff
ATC-Code
Handelsname</th><th>Anwendungsgebiet
(Text aus Fachinformation)</th></tr>
<tr><td colspan="2">Zu bewertendes Arzneimittel:</td></tr>
<tr><td>Glecaprevir/
Pibrentasvir
Maviret®</td><td>Maviret wird bei Erwachsenen zur Behandlung der chronischen Hepatitis-C-Virus (HCV)-Infektion angewendet (siehe Abschnitte 4.2, 4.4 und 5.1).</td></tr>
<tr><td>Ribavirin
J05AB04
Copegus®</td><td>Copegus wird in Kombination mit anderen Arzneimitteln zur Behandlung von chronischer Hepatitis C (CHC) angewendet.
Beachten Sie auch die Fachinformationen der Arzneimittel, die in Kombination mit Copegus zur Behandlung von Hepatitis C angewendet werden.

<table>
<tr><th colspan="3">Tabelle 1 Copegus Dosierungsempfehlung je nach dem in Kombination verwendeten Arzneimittel</th></tr>
<tr><th>Arzneimittel, das in Kombination verwendet wird</th><th>Tägliche Copegus Dosis</th><th>Anzahl an 200/400-mg-Tabletten</th></tr>
<tr><td>Direkt wirkende antivirale Arzneimittel (DAA)</td><td>< 75 kg = 1.000 mg

=> 75 kg = 1.200 mg</td><td>5 × 200 mg
(2 morgens, 3 abends)
6 × 200 mg
(3 morgens, 3 abends)</td></tr>
<tr><td></td><td></td><td></td></tr>
<tr><td>PegIFN alfa-2a mit DAA</td><td>< 75 kg = 1.000 mg

=> 75 kg = 1.200 mg</td><td>5 × 200 mg
(2 morgens, 3 abends)
6 × 200 mg
(3 morgens, 3 abends)</td></tr>
</table>
</td></tr>
</table>

1. Zugelassene Arzneimittel im Anwendungsgebiet

PegIFN alfa-2a ***ohne DAA***	**Genotyp 2/3 nicht vorbehandelt** **Genotyp 2/3/4 mit HIV-Koinfektion** 800 mg	4 × 200 mg (2 morgens, 2 abends) oder 2 × 400 mg (1 morgens, 1 abends)
	Genotyp 1/4 **Genotyp 2/3 vorbehandelt** **Genotyp 1 HIV-Koinfektion** < 75 kg = 1.000 mg => 75 kg = 1.200 mg	 5 × 200 mg (2 morgens, 3 abends) 6 × 200 mg (3 morgens, 3 abends)
IFN alfa-2a ***ohne DAA***	< 75 kg = 1.000 mg => 75 kg = 1.200 mg	5 × 200 mg (2 morgens, 3 abends) 6 × 200 mg (3 morgens, 3 abends)
PegIFN alfa-2b ***mit oder ohne DAA***	< 65 kg = 800 mg	4 × 200 mg (2 morgens, 2 abends) oder 2 × 400 mg (1 morgens, 1 abends)
	65 – 80 kg = 1.000 mg	5 (2 morgens, 3 abends)
	81 – 105 kg = 1.200 mg	6 (3 morgens, 3 abends)
	> 105 kg = 1.400 mg	7 (3 morgens, 4 abends)

Behandlungsdauer

Die Behandlungsdauer ist abhängig von den Arzneimitteln, die in Kombination mit Copegus angewendet werden und kann zudem von verschiedenen Eigenschaften der Patienten oder des Virus abhängen, einschließlich Genotyp, Koinfektionen, Vorgeschichte der Behandlung und Ansprechen auf die Behandlung. Beachten Sie auch die Fachinformation des Arzneimittels, das in Kombination mit Copegus angewendet wird.

1. **Zugelassene Arzneimittel im Anwendungsgebiet**	
	(Fachinformation, Stand 01/2015)
Ribavirin J05AB04 Rebetol®	Rebetol ist in Kombination mit anderen Arzneimitteln bestimmt zur Behandlung der chronischen Hepatitis C (CHC) bei Erwachsenen (siehe Abschnitte 4.2, 4.4 und 5.1). Rebetol ist in Kombination mit anderen Arzneimitteln bestimmt zur Behandlung der chronischen Hepatitis C (CHC) bei Kindern und Jugendlichen (Kinder ab dem Alter von 3 Jahren und Jugendliche), die nicht vorbehandelt sind und keine Leberdekompensation zeigen (siehe Abschnitte 4.2, 4.4 und 5.1). Rebetol muss in einer Kombinationstherapie angewendet werden, wie in Abschnitt 4.1beschrieben. Die entsprechenden Fachinformationen der Arzneimittel, die in Kombination mit Rebetol angewendet werden, sind für zusätzliche Informationen zur Verschreibung dieser Arzneimittel und für weitere Dosierungsempfehlungen bei gleichzeitiger Gabe mit Rebetol zu beachten. (Fachinformation, Stand 10/2015)
Ribavirin J05AB04 Ribavirin-ratiopharm®	Ribavirin-ratiopharm® ist indiziert zur Behandlung der chronischen Hepatitis-C-Virusinfektion (HCV-Infektion) bei Erwachsenen und darf nur als Teil eines Kombinations- Dosierungsschemas mit Peginterferon alfa-2b oder Interferon alfa-2b angewendet werden. Eine Ribavirin-ratiopharm®-Monotherapie darf nicht angewendet werden. […] Es liegen keine Informationen zur Unbedenklichkeit oder Wirksamkeit für die Anwendung von Ribavirin-ratiopharm® mit anderen Formen von Interferon (d.h. kein alfa-2b) vor. <u>Vorbehandelte Patienten</u> <u>Erwachsene Patienten</u> Ribavirin-ratiopharm® wird angewendet: • in Kombination mit Peginterferon alfa-2b zur Behandlung von Patienten mit chronischer Hepatitis C, die auf eine vorangegangene Therapie mit Interferon alfa (pegyliert oder nicht-pegyliert) allein oder in Kombination mit Ribavirin nicht angesprochen haben • in Kombination mit Interferon alfa-2b indiziert zur Behandlung von Patienten mit chronischer Hepatitis C, die zunächst auf eine Interferon-alfa-Monotherapie angesprochen haben (mit Normalisierung der ALT-Werte am Ende der Behandlung), jedoch später einen Rückfall erlitten haben. ***Dosierung und Art der Anwendung*** […] Ribavirin-ratiopharm® muss entweder in Kombination mit Peginterferon alfa-2b oder Interferon alfa-2b angewendet werden. Die Fachinformation zu Peginterferon alfa-2b oder Interferon alfa-2b ist für Informationen zur Verschreibung des jeweiligen Produktes ebenfalls zu beachten.

1. Zugelassene Arzneimittel im Anwendungsgebiet

200 mg

Tabelle 1

Ribavirin-Dosierung basierend auf dem Körpergewicht bei HCV mono-infizierten Patienten, unabhängig vom Genotyp

Gewicht des Patienten (kg)	Tägliche *Ribavirin-ratiopharm®*-Dosis	Anzahl der 200 mg-Film-tabletten
< 65	800 mg	4[a]
65 – 80	1.000 mg	5[b]
81 – 105	1.200 mg	6[c]
> 105	1.400 mg	7[d]

[a]: 2 morgens, 2 abends
[b]: 2 morgens, 3 abends
[c]: 3 morgens, 3 abends
[d]: 3 morgens, 4 abends

400 mg

Tabelle 2

Ribavirin-Dosierung basierend auf dem Körpergewicht bei HCV mono-infizierten Patienten, unabhängig vom Genotyp

Gewicht des Patienten (kg)	Tägliche *Ribavirin-ratiopharm®*-Dosis	Anzahl der 400 mg-Film-tabletten
< 65	800 mg	2[a]
65 – 80	1.000 mg	–*
81 – 105	1.200 mg	3[b]
> 105	1.400 mg	–*

[a]: 1 morgens, 1 abends
[b]: 1 morgens, 2 abends
* Die SmPC zu *Ribavirin-ratiopharm®* 200 mg Filmtabletten ist zu beachten

Ribavirin-ratiopharm® in Kombination mit Peginterferon alfa-2b: Dauer der Behandlung – Re-therapierte Patienten
Vorhersagbarkeit für ein anhaltendes virologisches Ansprechen: Unabhängig vom Genotyp sollten alle Patienten, deren HCVRNA- Serumspiegel in Woche 12 unter der Nachweisgrenze liegen, 48 Wochen lang therapiert werden. […]
(Fachinformation, Stand 11/2016)

Boceprevir J05AE12 Victrelis®	Victrelis ist indiziert zur Behandlung der chronischen Hepatitis C(CHC)-Infektion vom Genotyp 1 in Kombination mit Peginterferon alfa und Ribavirin bei erwachsenen Patienten mit kompensierter Lebererkrankung, die nicht vorbehandelt sind oder die nicht auf eine vorangegangene Therapie angesprochen bzw. einen Rückfall erlitten haben. (Fachinformation, Stand 02/2015)
Simeprevir J05AE14	OLYSIO ist bei erwachsenen Patienten in Kombination mit anderen Arzneimitteln zur Behandlung der chronischen Hepatitis C (CHC) indiziert

Olysio®

Tabelle 1: Empfohlene Behandlungsdauer bei einer Kombinationstherapie aus OLYSIO und Sofosbuvir bei HCV-Genotyp-1- oder -4-Patienten mit oder ohne Ribavirin

Patientengruppe	Behandlungsdauer
Patienten ohne Zirrhose	12 Wochen OLYSIO + Sofosbuvir
Patienten mit Zirrhose[1]	24 Wochen OLYSIO + Sofosbuvir oder 12 Wochen OLYSIO + Sofosbuvir + Ribavirin[2] 12 Wochen OLYSIO + Sofosbuvir (ohne Ribavirin) können bei Patienten mit nachfolgenden Wiederbehandlungsoptionen in Betracht gezogen werden, für die das Risiko einer klinischen Progression der Erkrankung als niedrig erachtet wird (siehe Abschnitte 4.4 und 5.1)

[1] Bei HCV-Genotyp-1a-infizierten Patienten mit Zirrhose, kann ein Nachweis auf das Vorhandensein des Q80K-Polymorphismus vor Beginn der Therapie mit OLYSIO in Kombination mit Sofosbuvir erwogen werden (siehe Abschnitt 4.4).

[2] Die tägliche Dosis an Ribavirin ist gewichtsabhängig (< 75 kg = 1.000 mg und ≥ 75 kg = 1.200 mg) und ist in 2 Dosen aufgeteilt und oral mit Nahrung einzunehmen; dazu sollte auch die Zusammenfassung der Merkmale (Fachinformation) von Ribavirin beachtet werden.

1. Zugelassene Arzneimittel im Anwendungsgebiet

Tabelle 2: Empfohlene Behandlungsdauer bei einer Kombinationstherapie aus OLYSIO, Peginterferon alfa und Ribavirin[1] bei HCV-Genotyp-1- oder -4

Patientengruppe	Behandlungsdauer
Therapienaive Patienten und vorherige Relapser[2]	
mit oder ohne Zirrhose und ohne HIV-Koinfektion	24 Wochen[3] Die Behandlung mit OLYSIO muss in Kombination mit Peginterferon alfa + Ribavirin begonnen und über einen Zeitraum von 12 Wochen fortgeführt werden, gefolgt von einer weiteren 12-wöchigen Behandlung mit Peginterferon alfa + Ribavirin.
ohne Zirrhose aber mit HIV-Koinfektion	
mit Zirrhose und mit HIV-Koinfektion	48 Wochen[3] Die Behandlung mit OLYSIO muss in Kombination mit Peginterferon alfa + Ribavirin begonnen und über einen Zeitraum von 12 Wochen fortgeführt werden, gefolgt von einer weiteren 36-wöchigen Behandlung mit Peginterferon alfa + Ribavirin.
Vorherige Non-Responder (einschließlich partieller und Null-Responder[2])	
mit oder ohne Zirrhose und mit oder ohne HIV-Koinfektion	48 Wochen[3] Die Behandlung mit OLYSIO muss in Kombination mit Peginterferon alfa + Ribavirin begonnen und über einen Zeitraum von 12 Wochen fortgeführt werden, gefolgt von einer weiteren 36-wöchigen Behandlung mit Peginterferon alfa + Ribavirin.

[1] Wird eine Kombinationstherapie aus OLYSIO, Peginterferon alfa und Ribavirin bei Patienten mit HCV-Genotyp 1a erwogen, soll vor Behandlungsbeginn eine Untersuchung auf einen NS3-Q80K-Polymorphismus durchgeführt werden (siehe Abschnitt 4.4).

[2] Nach vorheriger Behandlung mit Interferon (pegyliert oder nicht pegyliert), mit oder ohne Ribavirin (siehe Abschnitt 5.1).

[3] Empfohlene Behandlungsdauer unter der Voraussetzung, dass der Patient keine der Abbruchregeln (siehe Tabelle 3) erfüllt.

(Fachinformation, Stand 08/2016)

1. Zugelassene Arzneimittel im Anwendungsgebiet

Daclatasvir
J05AX14
Daklinza®

Daklinza wird in Kombination mit anderen Arzneimitteln zur Behandlung der chronischen Infektion mit dem Hepatitis-C-Virus (HCV) bei Erwachsenen angewendet

Tabelle 1: Empfehlungen zur Interferon-freien Kombinationstherapie mit Daklinza

Patientenpopulation*	**Regimen und Behandlungsdauer**
HCV GT 1 oder 4	
Patienten ohne Zirrhose	Daklinza + Sofosbuvir für 12 Wochen
Patienten mit Zirrhose *CP A oder B*	Daklinza + Sofosbuvir + Ribavirin für 12 Wochen oder Daklinza + Sofosbuvir (ohne Ribavirin) für 24 Wochen
CP C	Daklinza + Sofosbuvir ± Ribavirin für 24 Wochen (siehe Abschnitte 4.4 und 5.1)
HCV GT 3	
Patienten ohne Zirrhose	Daklinza + Sofosbuvir für 12 Wochen
Patienten mit Zirrhose	Daklinza + Sofosbuvir ± Ribavirin für 24 Wochen (siehe Abschnitt 5.1)
Rezidivierende HCV-Infektion nach einer Lebertransplantation (GT 1, 3 oder 4)	
Patienten ohne Zirrhose	Daklinza + Sofosbuvir + Ribavirin für 12 Wochen (siehe Abschnitt 5.1)
Patienten mit CP A oder B Zirrhose GT 1 oder 4 GT 3	 Daklinza + Sofosbuvir + Ribavirin für 12 Wochen Daklinza + Sofosbuvir ± Ribavirin für 24 Wochen
Patienten mit CP C Zirrhose	Daklinza + Sofosbuvir ± Ribavirin für 24 Wochen (siehe Abschnitte 4.4 und 5.1)

GT: Genotyp; CP: Child-Pugh

* Einschließlich Patienten mit Koinfektion mit dem humanen Immundefizienzvirus (HIV). Zu Dosierungsempfehlungen zusammen mit antiviralen Arzneimitteln gegen HIV siehe Abschnitt 4.5.

1. Zugelassene Arzneimittel im Anwendungsgebiet

<table>
<tr><td></td><td>Daklinza + Peginterferon alfa + Ribavirin: Dieses Regime ist eine alternativ empfohlenes Behandlungsregimen für mit Genotyp 4 infizierte Patienten ohne Zirrhose oder mit kompensierter Zirrhose. Daklinza wird 24 Wochen lang in Kombination mit 24 – 48 Wochen Peginterferon alfa und Ribavirin angewendet:
– wenn der Patient nicht-nachweisbare HCV-RNA-Titer sowohl in Woche 4 als auch in Woche 12 erreicht, sollten alle 3 Komponenten des Regimes insgesamt 24 Wochen angewendet werden.
– wenn der Patient nicht-nachweisbare HCV-RNA-Titer erreicht, jedoch nicht in Woche 4 sowie in Woche 12, sollte Daklinza nach 24 Wochen abgesetzt werden, aber die Behandlung mit Peginterferon alfa und Ribavirin für eine Gesamtdauer von 48 Wochen weitergeführt werden. (Fachinformation, Stand 09/2016)</td></tr>
<tr><td>Sofosbuvir
J05AX15
Sovaldi®</td><td>Sovaldi wird in Kombination mit anderen Arzneimitteln zur Behandlung der chronischen Hepatitis C (CHC) bei Erwachsenen angewendet (siehe Abschnitte 4.2, 4.4 und 5.1).

Abschnitt 4.2 der Fachinformation:
Tabelle 1: Empfohlene(s) gleichzeitig angewendete(s) Arzneimittel und Behandlungsdauer für die Kombinationstherapie mit Sovaldi
<table>
<tr><th>Patientengruppe* Behandlung Dauer</th><th>Behandlung</th><th>Dauer</th></tr>
<tr><td rowspan="2">Patienten mit CHC vom Genotyp 1, 4, 5 oder 6</td><td>Sovaldi + Ribavirin + Peginterferon alfa</td><td>12 Wochen [a, b]</td></tr>
<tr><td>Sovaldi + Ribavirin
Nur zur Anwendung bei Patienten, die für eine Therapie mit Peginterferon alfa ungeeignet sind oder eine Unverträglichkeit gegenüber Peginterferon alfa haben (siehe Abschnitt 4.4)</td><td>24 Wochen</td></tr>
<tr><td>Patienten mit CHC vom Genotyp 2</td><td>Sovaldi + Ribavirin</td><td>12 Wochen[b]</td></tr>
<tr><td rowspan="2">Patienten mit CHC vom Genotyp 3</td><td>Sovaldi + Ribavirin + Peginterferon alfa</td><td>12 Wochen[b]</td></tr>
<tr><td>Sovaldi + Ribavirin</td><td>24 Wochen</td></tr>
<tr><td>Patienten mit CHC, die auf eine Lebertransplantation warten</td><td>Sovaldi + Ribavirin</td><td>Bis zur Lebertransplantation[c]</td></tr>
</table>
* Einschließlich Patienten mit Koinfektion mit dem humanen Immundefizienzvirus (HIV).
[a] Für vorbehandelte Patienten mit einer HCV-Genotyp 1 Infektion liegen keine Daten zur Kombination von Sovaldi mit Ribavirin und Peginterferon alfa vor (siehe Abschnitt 4.4).
[b] Es ist zu erwägen, die Dauer der Therapie möglicherweise über 12 Wochen hinaus auf bis zu 24 Wochen verlängern; dies gilt insbesondere für Subgruppen mit einem oder mehreren der negativen prädiktiven Faktoren, die in der Vergangenheit mit niedrigeren Ansprechraten auf Interferon-haltige Therapien (z. B. fortgeschrittene Fibrose/Zirrhose, hohe Ausgangsviruslast, schwarze Hautfarbe, IL28B-Non-CC-Genotyp, früheres Nichtansprechen auf Peginterferon</td></tr>
</table>

<table>
<tr><th colspan="2">1. Zugelassene Arzneimittel im Anwendungsgebiet</th></tr>
<tr><td></td><td>alfa und Ribavirin) assoziiert waren.
[c] Siehe unten: „Besondere Patientengruppen – Patienten, die auf eine Lebertransplantation warten“.
(Fachinformation, Stand 09/2016)</td></tr>
<tr><td>Dasabuvir
J05AX16
Exviera®</td><td>Exviera wird in Kombination mit anderen Arzneimitteln zur Behandlung der chronischen Hepatitis C (CHC) bei Erwachsenen angewendet

Tabelle 1. Empfohlene(s) Kombinationsarzneimittel und Behandlungsdauer für Exviera nach Patientenpopulation
<table><tr><th>Patientenpopulation</th><th>Therapie*</th><th>Dauer</th></tr><tr><td>Genotyp-1b-Patienten ohne Zirrhose oder mit kompensierter Zirrhose</td><td>Exviera + Ombitasvir/Paritaprevir/Ritonavir</td><td>12 Wochen</td></tr><tr><td>Genotyp-1a-Patienten ohne Zirrhose</td><td>Exviera + Ombitasvir/Paritaprevir/Ritonavir + Ribavirin*</td><td>12 Wochen</td></tr><tr><td>Genotyp-1a-Patienten mit kompensierter Zirrhose</td><td>Exviera + Ombitasvir/Paritaprevir/Ritonavir + Ribavirin*</td><td>24 Wochen (siehe Abschnitt 5.1)</td></tr><tr><td colspan="3">* Hinweis: Bei Patienten mit unbekanntem Genotyp-1-Subtyp oder einer gemischten Genotyp-1-Infektion sind die Dosierungsempfehlungen für Genotyp 1a zu befolgen.</td></tr></table>
<u>Lebertransplantierte Patienten</u>
Für lebertransplantierte Patienten wird eine Behandlung mit Exviera und Ombitasvir/Paritaprevir/Ritonavir in Kombination mit Ribavirin über 24 Wochen hinweg empfohlen. Initial kann eine niedrigere Ribavirindosis angezeigt sein. In der Studie an Patienten nach einer Lebertransplantation wurde Ribavirin individuell dosiert; die meisten Studienteilnehmer erhielten 600 bis 800 mg pro Tag.
(Fachinformation, Stand 01/2017)</td></tr>
</table>

Ledipasvir/ Sofosbuvir
J05AX65
Harvoni®

Harvoni wird bei Erwachsenen zur Behandlung der chronischen Hepatitis C (CHC) angewendet.

Tabelle 1: Empfohlene Dauer der Behandlung mit Harvoni und empfohlene kombinierte Anwendung mit Ribavirin bei bestimmten Subgruppen

Patientengruppe*	Behandlung und Dauer
Patienten mit CHC vom Genotyp 1, 4, 5 oder 6	
Patienten ohne Zirrhose	Harvoni für 12 Wochen. – Harvoni kann für 8 Wochen bei therapienaiven Patienten mit einer Infektion vom Genotyp 1 in Betracht gezogen werden (siehe Abschnitt 5.1, ION-3-Studie). – Harvoni + Ribavirin für 12 Wochen oder Harvoni (ohne Ribavirin) für 24 Wochen sind bei vorbehandelten Patienten mit ungewissen nachfolgenden Optionen für eine Wiederbehandlung in Betracht zu ziehen (siehe Abschnitt 4.4).
Patienten mit kompensierter Zirrhose	Harvoni + Ribavirin für 12 Wochen oder Harvoni (ohne Ribavirin) für 24 Wochen. – Harvoni (ohne Ribavirin) kann für 12 Wochen bei Patienten mit einem geringen Risiko einer klinischen Krankheitsprogression, die nachfolgend Optionen für eine Wiederbehandlung haben, in Betracht gezogen werden (siehe Abschnitt 4.4).
Patienten nach Lebertransplantation ohne Zirrhose oder mit kompensierter Zirrhose	Harvoni + Ribavirin für 12 Wochen (siehe Abschnitt 5.1). – Harvoni (ohne Ribavirin) kann für 12 Wochen (bei Patienten ohne Zirrhose) oder 24 Wochen (bei Patienten mit Zirrhose) bei Patienten in Betracht gezogen werden, für die Ribavirin nicht in Frage kommt oder bei denen eine Ribavirin-Unverträglichkeit besteht.
Patienten mit dekompensierter Zirrhose, unabhängig vom Transplantationsstatus	Harvoni + Ribavirin für 12 Wochen (siehe Abschnitt 5.1). – Harvoni (ohne Ribavirin) kann für 24 Wochen bei Patienten in Betracht gezogen werden, für die Ribavirin nicht in Frage kommt oder bei denen eine Ribavirin-Unverträglichkeit besteht.
Patienten mit CHC vom Genotyp 3	
Patienten mit kompensierter Zirrhose und/oder Versagen einer vorherigen Behandlung	Harvoni + Ribavirin für 24 Wochen (siehe Abschnitte 4.4 und 5.1).

* Einschließlich Patienten mit Koinfektion mit dem humanen Immundefizienzvirus (HIV).

1. Zugelassene Arzneimittel im Anwendungsgebiet

(Fachinformation, Stand 07/2016)

Ombitasvir/ Paritaprevir/ Ritonavir
J05AX67
Viekirax®

Viekirax wird in Kombination mit anderen Arzneimitteln zur Behandlung der chronischen Hepatitis C (CHC) bei Erwachsenen angewendet

Tabelle 1. Empfohlene(s) Kombinationsarzneimittel und Behandlungsdauer für Viekirax nach Patientenpopulation

Patientenpopulation	Therapie*	Dauer
Genotyp-1b-Patienten ohne Zirrhose oder mit kompensierter Zirrhose	Viekirax + Dasabuvir	12 Wochen
Genotyp-1a-Patienten ohne Zirrhose	Viekirax + Dasabuvir + Ribavirin*	12 Wochen
Genotyp-1a-Patienten mit kompensierter Zirrhose	Viekirax + Dasabuvir + Ribavirin*	24 Wochen (siehe Abschnitt 5.1)
Genotyp-4-Patienten ohne Zirrhose oder mit kompensierter Zirrhose	Viekirax + Ribavirin	12 Wochen

* Hinweis: Bei Patienten mit unbekanntem Genotyp-1-Subtyp oder einer gemischten Genotyp-1-Infektion sind die Dosierungsempfehlungen für Genotyp 1a zu befolgen.

<u>Lebertransplantierte Patienten</u>
Für lebertransplantierte Patienten mit einer HCV-Infektion vom Genotyp 1 wird eine Behandlung mit Viekirax und Dasabuvir in Kombination mit Ribavirin über 24 Wochen hinweg empfohlen. Bei einer Infektion vom Genotyp 4 wird Viekirax in Kombination mit Ribavirin empfohlen. Initial kann eine niedrigere Ribavirindosis angezeigt sein. In der Studie an Patienten nach einer Lebertransplantation wurde Ribavirin individuell dosiert; die meisten Studienteilnehmer erhielten 600 bis 800 mg pro Tag.
(Fachinformation, Stand 11/2016)

1. Zugelassene Arzneimittel im Anwendungsgebiet

Sofosbuvir/ Velpatasvir Epclusa®

Epclusa wird bei Erwachsenen zur Behandlung der chronischen Hepatitis C Virusinfektion (HCV) angewendet.

Tabelle 1: Empfohlene Behandlung und Dauer für alle HCV-Genotypen

Patientengruppe[a]	Behandlung und Dauer
Patienten ohne Zirrhose und Patienten mit kompensierter Zirrhose	Epclusa für 12 Wochen Die Zugabe von Ribavirin kann bei Patienten mit einer Infektion vom Genotyp 3 und kompensierter Zirrhose erwogen werden (siehe Abschnitt 5.1.).
Patienten mit dekompensierter Zirrhose	Epclusa + Ribavirin für 12 Wochen

[a] Einschließlich Patienten mit Koinfektion mit dem humanen Immundefizienzvirus (HIV) und Patienten mit rezidivierender HCV-Infektion nach Lebertransplantation (siehe Abschnitt 4.4.).

(Fachinformation, Stand 07/2016)

Elbasvir/
Grazoprevir
J05AX68
Zepatier®

ZEPATIER wird zur Behandlung der chronischen Hepatitis C (CHC) bei Erwachsenen angewendet.

Tabelle 1: Empfohlene ZEPATIER Therapie für die Behandlung der chronischen Hepatitis-C-Infektion bei Patienten mit bzw. ohne kompensierte Zirrhose (nur Child-Pugh A)

HCV-Genotyp	Behandlung und Behandlungsdauer
1a	ZEPATIER über 12 Wochen Eine Behandlung mit ZEPATIER über 16 Wochen plus Ribavirin[A] zur Senkung des Risikos eines Therapieversagens sollte in Betracht gezogen werden bei Patienten mit einer Ausgangsviruslast > 800.000 IE/ml und/oder dem Vorliegen bestimmter NS5A-RAVs, die die Elbasvir-Aktivität um mindestens den Faktor 5 verringern (siehe Abschnitt 5.1).
1b	ZEPATIER über 12 Wochen
4	ZEPATIER über 12 Wochen Eine Behandlung mit ZEPATIER über 16 Wochen plus Ribavirin[A] zur Senkung des Risikos eines Therapieversagens sollte bei Patienten mit einer Ausgangsviruslast > 800.000 IE/ml in Betracht gezogen werden (siehe Abschnitt 5.1).

[A] In den klinischen Studien wurde Ribavirin gewichtsadaptiert dosiert (< 66 kg = 800 mg/Tag; 66 – 80 kg = 1.000 mg/Tag; 81 – 105 kg = 1.200 mg/Tag; > 105 kg = 1.400 mg/Tag) und die Tagesdosis auf zwei Dosen verteilt, die zusammen mit Nahrung eingenommen wurden.

(Fachinformation, Stand 12/2016)

1. Zugelassene Arzneimittel im Anwendungsgebiet

Interferon alfa-2a L03AB04 Roferon-A®	Histologisch nachgewiesene chronische Hepatitis C bei erwachsenen Patienten, bei denen HCV-Antikörper oder HCV-RNA und erhöhte Serumspiegel der Alaninaminotransferase (ALT) ohne Leberdekompensation vorliegen. Die Wirksamkeit von Interferon alfa-2a bei der Behandlung der Hepatitis C wird durch die Kombination mit Ribavirin erhöht. Roferon-A sollte als Monotherapie nur bei Intoleranz oder Kontraindikationen gegen Ribavirin angewendet werden. (Fachinformation, Stand 12/2016)
Interferon alfa-2b L03AB05 IntronA®	Vor Behandlungsbeginn mit IntronA sollten die Ergebnisse von klinischen Studien zum Vergleich von IntronA mit pegyliertem Interferon berücksichtigt werden. *Erwachsene* IntronA ist indiziert zur Behandlung von erwachsenen Patienten mit chronischer Hepatitis C, die erhöhte Transaminasenwerte ohne Leberdekompensation haben und die Hepatitis C-Virus-RNA (HCV-RNA)-positiv sind. Die beste Art, IntronA bei dieser Indikation anzuwenden, ist die Kombination mit Ribavirin**.** (Fachinformation, Stand 12/2015)
Peginterferon alfa-2b L03AB10 PegIntron®	*Erwachsene (3-fach-Kombinationstherapie):* PegIntron ist, in Kombination mit Ribavirin und Boceprevir (3-fach-Kombinationstherapie), indiziert zur Behandlung der chronischen Hepatitis-C(CHC)-Infektion vom Genotyp 1 bei erwachsenen Patienten (18 Jahre und älter) mit kompensierter Lebererkrankung, die nicht vorbehandelt sind oder die nicht auf eine vorangegangene Therapie angesprochen bzw. einen Rückfall erlitten haben. Bitte beachten Sie die Fachinformationen zu Ribavirin und Boceprevir, wenn Sie PegIntron in Kombination mit diesen Arzneimitteln anwenden. *Erwachsene (Duale Therapie und Monotherapie):* PegIntron ist indiziert zur Behandlung erwachsener Patienten (18 Jahre und älter) mit CHC, die Hepatitis-C-Virus-RNA(HCVRNA)- positiv sind, einschließlich Patienten mit kompensierter Zirrhose und/oder Patienten, die klinisch stabil mit HIV co-infiziert sind. PegIntron in Kombination mit Ribavirin (Duale Therapie) ist indiziert zur Behandlung der CHC-Infektion bei nicht vorbehandelten erwachsenen Patienten, einschließlich Patienten, die klinisch stabil mit HIV co-infiziert sind, und bei erwachsenen Patienten, die nicht auf eine vorangegangene Kombinationstherapie mit Interferon alfa (pegyliert oder nicht-pegyliert) und Ribavirin oder auf eine Interferon alfa-Monotherapie angesprochen bzw. einen Rückfall erlitten haben. Die Interferon-Monotherapie, einschließlich PegIntron, ist hauptsächlich indiziert im Fall einer Intoleranz oder einer Gegenanzeige gegenüber Ribavirin. Bitte beachten Sie die Fachinformation zu Ribavirin, wenn PegIntron in Kombination mit Ribavirin angewendet wird. (Fachinformation, Stand 07/2015)

1. **Zugelassene Arzneimittel im Anwendungsgebiet**	
Peginterferon alfa-2a L03AB11 Pegasys®	Pegasys ist in Kombination mit anderen Arzneimitteln für die Behandlung der chronischen Hepatitis C (CHC) bei Patienten mit kompensierter Lebererkrankung indiziert (siehe Abschnitte 4.2, 4.4 und 5.1). Zur spezifischen Aktivität gegen die verschiedenen Genotypen des Hepatitis C Virus (HCV), siehe Abschnitte 4.2 und 5.1. **4.2 Dosierung und Art der Anwendung** Eine Monotherapie gegen Hepatitis C sollte nur in Fallen von Kontraindikationen gegen andere Arzneimittel in Betracht gezogen werden.

1. Zugelassene Arzneimittel im Anwendungsgebiet

Tabelle 1: Dosierungsempfehlungen für die Kombinationstherapie bei HCV-Patienten

Genotyp	Pegasys Dosis	Ribavirin Dosis	Behandlungs-dauer
Genotyp 1 niedrige Viruslast mit raschem virologischem Ansprechen*	180 Mikrogramm	< 75 kg = 1.000 mg ≥ 75 kg = 1.200 mg	24 Wochen oder 48 Wochen
Genotyp 1 hohe Viruslast mit raschem virologischem Ansprechen*	180 Mikrogramm	< 75 kg = 1.000 mg ≥ 75 kg = 1.200 mg	48 Wochen
Genotyp 4 mit raschem virologischem Ansprechen*	180 Mikrogramm	< 75 kg = 1.000 mg ≥ 75 kg = 1.200 mg	24 Wochen oder 48 Wochen
Genotyp 1 oder 4 ohne rasches virologisches Ansprechen*	180 Mikrogramm	< 75 kg = 1.000 mg ≥ 75 kg = 1.200 mg	48 Wochen
Genotyp 2 oder 3 ohne rasches virologisches Ansprechen**	180 Mikrogramm	800 mg	24 Wochen
Genotyp 2 oder 3 niedrige Viruslast mit raschem virologischem Ansprechen**	180 Mikrogramm	800 mg[(a)]	16 Wochen[(a)] oder 24 Wochen
Genotyp 2 oder 3 hohe Viruslast mit raschem virologischem Ansprechen**	180 Mikrogramm	800 mg	24 Wochen

* Rasches virologisches Ansprechen (HCV-RNA nicht nachweisbar) nach 4 Wochen und HCV-RNA nicht nachweisbar nach 24 Wochen;

** Rasches virologisches Ansprechen (HCV-RNA negativ) in Woche 4

Niedrige Viruslast = ≤ 800.000 I.E./ml; hohe Viruslast = > 800.000 I.E./ml

[(a)] Derzeit ist noch unklar, ob bei einer Verkürzung der Behandlung auf 16 Wochen eine höhere Dosierung von Ribavirin (z. B. 1.000/1.200 mg/Tag je nach Körpergewicht) zu einer höheren Rate von anhaltendem virologischen Ansprechen führt als 800 mg/Tag.

Dauer der Behandlung – duale Therapie mit Pegasys und Copegus

1. **Zugelassene Arzneimittel im Anwendungsgebiet**	
	Patienten, die mit HC-Viren vom Genotyp 1 infiziert sind und bei denen in Woche 4 der Behandlung noch HCV-RNA nachweisbar ist, sollten ungeachtet der Ausgangsviruslast 48 Wochen therapiert werden. Eine Behandlung über 24 Wochen kann für Patienten in Betracht gezogen werden, die eine Infektion aufweisen mit Genotyp 1 mit niedriger Ausgangsviruslast (LVL) (≤ 800.000 I.E./ml) oder Genotyp 4 und die bis Woche 4 HCV-RNA-negativ werden und bis Woche 24 HCV-RNA-negativ bleiben. […] Patienten, die mit HC-Viren vom **Genotyp 2 oder 3** infiziert sind und bei denen in Woche 4 der Behandlung noch HCV-RNA nachweisbar ist, sollten ungeachtet der Ausgangsviruslast 24 Wochen therapiert werden. Eine Behandlungsdauer von nur 16 Wochen kann bei bestimmten Patienten in Betracht gezogen werden, die mit dem Genotyp 2 oder 3 infiziert sind, eine niedrige Ausgangsviruslast (≤ 800.000 I.E./ml) aufweisen, bis Woche 4 HCV-negativ geworden sind und bis Woche 16 HCV-negativ bleiben.[…] Es sind nur begrenzt Daten von Patienten mit einer Infektion vom **Genotyp 5 oder 6** verfügbar; deshalb wird eine Kombinationstherapie mit 1.000/1.200 mg Ribavirin über 48 Wochen empfohlen. ***Chronische Hepatitis C – vorbehandelte erwachsene Patienten*** Die empfohlene Dosis von Pegasys in Kombination mit Ribavirin beträgt 180 Mikrogramm einmal wöchentlich als subkutane Injektion. Patienten < 75 kg bzw. ≥ 75 kg sollten 1.000 mg/Tag bzw. 1.200 mg/Tag Ribavirin unabhängig vom Genotyp anwenden. […] Die empfohlene Gesamtdauer der Behandlung beträgt 48 Wochen. (Fachinformation, Stand 10/2016)

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V :

Auftrag von: Abt. AM

bearbeitet von: Abt. FB Med

Datum: 02.08.2017

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Anhang 179

Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und Evidenz-basierten systematischen Leitlinien zur Indikation *chronische Hepatitis C* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 29.11.2016 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database), MEDLINE (PubMed), AWMF, Clinical Evidence, DAHTA, G-BA, GIN, IQWiG, NGC, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 1169 Quellen, die anschließend in einem zweistufigen Screening Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies 73 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Indikation

zur Behandlung der chronischen Hepatitis C (CHC)

Abkürzungen

AE	Adverse Events
ABT12	ABT-530 for 12 wks
ASU12	asunaprevir 12 wks

ASU24	asunaprevir 24 wks
ASV	asunaprevir
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
ÄZQ	Ärztliches Zentrum für Qualität in der Medizin
B24 PR28	PR × 4 wks then boceprevir + PR × 24 wks
B24 PR28 RGT eRVR	PR × 4 wks then boceprevir + PR × 24 wks if eRVR achieved RGT
B24 PR28-48 RGT	PR × 4 wks then boceprevir + PR × 24 or 44 wks RGT
B24 PR48 RGT no eRVR	PR × 4 wks then boceprevir + PR × 24 wks, then PR × 20 wks if no eRVR achieved RGT
B32 PR36 RGT eRVR	PR × 4 wks then boceprevir + PR × 32 wks if eRVR achieved RGT
B32 PR36-48 RGT	PR × 4 wks then boceprevir × 32 wks with PR 32 to 44 wks RGT
B32 PR36-48 RGT no eRVR	PR × 4 wks then boceprevir + PR × 32 wks, then PR × 12 wks if no eRVR achieved RGT
B44 PR48	PR × 4 wks then boceprevir + PR × 44 wks
BCV	boceprevir
BEC	beclabuvir
BEC12	beclabuvir 12 wks
BEC12 (150 mg b.i.d.)	beclabuvir (150 mg b.i.d.) 12 wks
BEC12 (75 mg b.i.d.)	beclabuvir (75 mg b.i.d.) 12 wks
BOC	Boceprevir
BSC	Best supportive care
CADTH	**Canadian Agency for Drugs and Technologies in Health**
CDEC	**CADTH Canadian Drug Expert Committee**
cEVR	complete early virological response
CHC	Chronic Hepatitis C
DAHTA	Deutsche Agentur für Health Technology Assessment
DAS12	dasabuvir 12 wks
DCV	daclatasvir
DCV12	daclatasvir 12 wks
DCV24	daclatasvir 24 wks
ELB12	elbasvir 12 wks
ELB12 (20 mg)	elbasvir (20 mg q.d.) 12 wks
ELB12 (50 mg)	elbasvir (50 mg q.d.) 12 wks
ELB18	elbasvir 18 wks
ELB18 (20 mg)	elbasvir (20 mg q.d.) 18 wks
ELB18 (50 mg)	elbasvir (50 mg q.d.) 18 wks

ELB8	elbasvir 8 wks
ELB8 (20 mg)	elbasvir (20 mg q.d.) 8 wks
ELB8 (50 mg)	elbasvir (50 mg q.d.) 8 wks
FDV	faldaprevir
GALEXOS	simeprevir
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GRZ12	grazoprevir (100 mg q.d.) 12 wks
GRZ18	grazoprevir (100 mg q.d.) 18 wks
GRZ8	grazoprevir (100 mg q.d.) 8 wks
GS8	GS-5816 for 8 wks
GS-9451(6)	GS-9451 for 6 wks
GS-9669(6)	GS-9669 for 6 wks
Harvoni	ledipasvir/sofosbuvir
HCV	Hepatitis C Virus
HOLKIRA PAK	ombitasvir/paritaprevir/ritonavir (fixed-dose single tablet) and dasabuvir
IFN	Interferon
Incivek	telaprevir
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
k.A.	keine Angabe
LDV	ledipasvir
Lead-in T12PR48	Peginterferon/ribavirin for 4 weeks, followed by telaprevir for 12 wk and peg-interferon and ribavirin up to a total of 48 weeks.
LVL	Low viral load
LVR	Late viral response
NGC	National Guideline Clearinghouse
NHS CRD	National Health Services Center for Reviews and Dissemination
NICE	National Institute for Health and Care Excellence
Peg	Peginterferon
PR	Peginterferon + Ribavirin
PR	peginterferon-ribavirin
PR48	Placebo/Pegifn-2a/Ribavirin for 24 weeks, followed by Pegifn-2a/Ribavirin for 24 weeks
RBV	Ribavirin
RNA	Ribonucleic acid
RVR	Rapid virologic response
SAE	Serious adverse event
SMV	simeprevir
SoC	Standard of care

SOF	SOF
SVR	Sustained virological response
SVR	SVR
T12PR	Telaprevir/Pegifn-2a/Ribavirin for 12 weeks, followed by Pegifn-2a/Ribavirin for 12 weeks if HCV RNA was undetectable at weeks 4 and 12 or for 36 weeks if HCV RNA was detectable at either time point
T12PR12	Telaprevir / PeglFN-2a / Ribavirin for 12 weeks, followed by Placebo/Pegifn-2a/Ribavirin for 12 weeks
T12PR24	Telaprevir / PeglFN-2a / Ribavirin for 12 weeks, followed by Placebo / PegIFN-2a/Ribavirin for 24 weeks
T12PR48	Telaprevir / PeglFN-2a / Ribavirin for 12 weeks, followed by Placebo / PegIFN-2a/Ribavirin for 48 weeks
T24PR48,	Telaprevir/Pegifn-2a/Ribavirin for 24 weeks, followed by Pegifn-2a/Ribavirin for 48 weeks
T8PR	Telaprevir/Pegifn-2a/Ribavirin for 8 weeks and Placebo/Pegifn-2a/Ribavirin for 4 weeks, followed by 12 or 36 weeks of Pegifn-2a/Ribavirin on the basis of the same HCV RNA criteria
TLV	telaprevir
TLV; TVR	Telaprevir
TPR	Combination of telaprevir with peginterferon plus ribavirin
TRIP	Turn Research into Practice Database
WHO	World Health Organization

IQWiG Berichte/ G-BA Beschlüsse

G-BA, 2016 [25]. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Sofosbuvir/Velpatasvir vom 05.01.2017 **Siehe auch:** **IQWiG, 2016 [47].** Sofosbuvir/Velpatasvir (chronische Hepatitis C) – Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag: A16-48	**Zugelassenes Anwendungsgebiet (laut Zulassung vom 06. Juli 2016):** Epclusa wird bei Erwachsenen zur Behandlung der chronischen Hepatitis C Virusinfektion (HCV) angewendet (siehe Abschnitte 4.2, 4.4 und 5.1 der Fachinformation). Zusatznutzen des Arzneimittels im Verhältnis zur zweckmäßigen Vergleichstherapie **a) Patienten ohne Zirrhose, Genotyp 1:** Zweckmäßige Vergleichstherapie: Für therapienaive und therapieerfahrene Patienten die Kombination aus Ledipasvir/Sofosbuvir oder die Kombination aus Ombitasvir/Paritaprevir/Ritonavir plus Dasabuvir (ggf. plus Ribavirin). Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Sofosbuvir/Velpatasvir gegenüber Ledipasvir/Sofosbuvir: Ein Zusatznutzen ist nicht belegt. **b) Patienten mit kompensierter Zirrhose, Genotyp 1:** Zweckmäßige Vergleichstherapie: Für therapienaive und therapieerfahrene Patienten die Kombination aus Ledipasvir/Sofosbuvir. Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Sofosbuvir/Velpatasvir gegenüber Ledipasvir/Sofosbuvir: Ein Zusatznutzen ist nicht belegt. **c) Patienten ohne Zirrhose oder mit kompensierter Zirrhose, Genotyp 2:** Zweckmäßige Vergleichstherapie: Für therapienaive und therapieerfahrene Patienten die Kombination aus Sofosbuvir plus Ribavirin. Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Sofosbuvir/Velpatasvir gegenüber Sofosbuvir plus Ribavirin: Anhaltspunkt für einen geringen Zusatznutzen. **d) Patienten ohne Zirrhose oder mit kompensierter Zirrhose, Genotyp 3:** Zweckmäßige Vergleichstherapie: Für therapienaive und therapieerfahrene Patienten die Kombination aus Sofosbuvir plus Ribavirin. Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Sofosbuvir/Velpatasvir gegenüber Sofosbuvir plus Ribavirin: Anhaltspunkt für einen beträchtlichen Zusatznutzen. **e) Patienten ohne Zirrhose, Genotyp 4:** Zweckmäßige Vergleichstherapie: Für therapienaive und therapieerfahrene Patienten die Kombination aus Ledipasvir/Sofosbuvir oder die Kombination aus Ombitasvir/Paritaprevir/Ritonavir plus Ribavirin.

	Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Sofosbuvir/Velpatasvir gegenüber Ombitasvir/Paritaprevir/Ritonavir plus Ribavirin: Ein Zusatznutzen ist nicht belegt. **f) Patienten mit kompensierter Zirrhose, Genotyp 4:** Zweckmäßige Vergleichstherapie: Für therapienaive und therapieerfahrene Patienten die Kombination aus Ledipasvir/Sofosbuvir. Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Sofosbuvir/Velpatasvir gegenüber Ledipasvir/Sofosbuvir: Ein Zusatznutzen ist nicht belegt. **g) Patienten ohne Zirrhose oder mit kompensierter Zirrhose, Genotyp 5 oder Genotyp 6:** Zweckmäßige Vergleichstherapie: Für therapienaive und therapieerfahrene Patienten die Kombination aus Ledipasvir/Sofosbuvir. Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Sofosbuvir/Velpatasvir gegenüber Ledipasvir/Sofosbuvir: Ein Zusatznutzen ist nicht belegt. **h) Patienten mit dekompensierter Zirrhose, Genotyp 1:** Zweckmäßige Vergleichstherapie: Die Kombination aus Ledipasvir/Sofosbuvir plus Ribavirin. Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Sofosbuvir/Velpatasvir plus Ribavirin gegenüber Ledipasvir/Sofosbuvir plus Ribavirin: Ein Zusatznutzen ist nicht belegt. **i) Patienten mit dekompensierter Zirrhose, Genotyp 2, 3, 4, 5 oder 6:** Zweckmäßige Vergleichstherapie: Best Supportive Care. Als „Best Supportive Care“ (BSC) wird diejenige Therapie verstanden, die eine bestmögliche, patientenindividuell optimierte, unterstützende Behandlung zur Linderung von Symptomen und Verbesserung der Lebensqualität gewährleistet. Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Sofosbuvir/Velpatasvir plus Ribavirin gegenüber Best Supportive Care: Anhaltspunkt für einen nicht quantifizierbaren Zusatznutzen.
G-BA, 2012 [27]. Beschlusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII – Beschlüsse über die	***Telaprevir*** **Zugelassenes Anwendungsgebiet:** Incivo® ist in Kombination mit Peginterferon alfa und Ribavirin zur Behandlung der chronischen Hepatitis C vom Genotyp 1 bei erwachsenen Patienten mit kompensierter Lebererkrankung (einschließlich Zirrhose) indiziert: – die nicht vorbehandelt sind;

Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a des Fünften Buches Sozialgesetzbuch (SGB V) Telaprevir Vom 29. März 2012 **Siehe auch:** **IQWiG, 2012 [48].** Telaprevir – Nutzenbewertung gemäß § 35a SGB V (Auftrag A11-25)	– die entweder mit Interferon alfa (pegyliert oder nicht-pegyliert) allein oder in Kombination mit Ribavirin vorbehandelt wurden, einschließlich Patienten, die einen Rückfall (Relaps) erlitten haben, Patienten mit partiellem Ansprechen oder Patienten mit fehlendem Ansprechen (Null-Responder). **Zusatznutzen des Arzneimittels im Verhältnis zur zweckmäßigen Vergleichstherapie** a) In Kombination mit Peginterferon + Ribavirin gegenüber Peginterferon + Ribavirin bei *therapienaiven* Patienten mit chronischer Hepatitis-C-Virus (cHCV) Infektion (*Genotyp 1*) **Zweckmäßige Vergleichstherapie:** Peginterferon plus Ribavirin **Ausmaß und Wahrscheinlichkeit des Zusatznutzens** gegenüber Peginterferon plus Ribavirin: Hinweis auf einen Zusatznutzen von Telaprevir, Ausmaß nicht quantifizierbar. b) In Kombination mit Peginterferon + Ribavirin gegenüber Peginterferon + Ribavirin bei *therapieerfahrenen* Patienten mit chronischer HCV-Infektion (*Genotyp 1*) **Zweckmäßige Vergleichstherapie:** Peginterferon plus Ribavirin **Ausmaß und Wahrscheinlichkeit des Zusatznutzens** gegenüber Peginterferon plus Ribavirin: Hinweis auf einen Zusatznutzen von Telaprevir, Ausmaß nicht quantifizierbar.
G-BA, 2012 [26]. Beschlusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII – Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach §35a des Fünften Buches Sozialgesetzbuch (SGB V) Boceprevir Vom 1. März 2012 **Siehe auch:** **IQWiG, 2011 [37].** Boceprevir – Nutzenbewertung gemäß § 35a SGB V (Auftrag A11-17)	***Boceprevir*** **Zugelassenes Anwendungsgebiet:** Victrelis® ist indiziert zur Behandlung der chronischen Hepatitis C (CHC)-Infektion vom Genotyp 1 in Kombination mit Peginter feron alfa und Ribavirin bei erwachsenen Patienten mit kompensierter Lebererkrankung, die nicht vorbehandelt sind oder die nicht auf eine vorangegangene Therapie angesprochen bzw. einen Rückfall erlitten haben. **Zusatznutzen des Arzneimittels im Verhältnis zur zweckmäßigen Vergleichstherapie** a) In Kombination mit PegInterferon + Ribavirin gegenüber PegInterferon + Ribavirin bei *therapienaiven* Patienten mit chronischer Hepatitis-C-Virus (cHCV) Infektion (*Genotyp 1*) **Zweckmäßige Vergleichstherapie:** Peginterferon plus Ribavirin **Ausmaß und Wahrscheinlichkeit des Zusatznutzens** gegenüber Peginterferon plus Ribavirin: Hinweis auf einen Zusatznutzen von Boceprevir, Ausmaß nicht quantifizierbar.

	b) In Kombination mit PegInterferon + Ribavirin gegenüber PegInterferon + Ribavirin bei *therapieerfahrenen* Patienten mit cHCV-Infektion (*Genotyp 1*) **Zweckmäßige Vergleichstherapie:** Peginterferon plus Ribavirin **Ausmaß und Wahrscheinlichkeit des Zusatznutzens** gegenüber Peginterferon plus Ribavirin: Hinweis auf einen Zusatznutzen von Boceprevir, Ausmaß nicht quantifizierbar.
G-BA, 2014 [23]. Beschluss über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Simeprevir **siehe auch:** **IQWiG, 2014 [45].** Simeprevir – Nutzenbewertung gemäß § 35a SGB V (Auftrag A14-18) sowie **Addendum zum Auftrag A14-18 (Auftrag A14-39) [36].**	***Simeprevir*** **Zugelassenes Anwendungsgebiet:** Simeprevir (Olysio®) ist bei erwachsenen Patienten in Kombination mit anderen Arzneimitteln zur Behandlung der chronischen Hepatitis C (CHC) indiziert. **Zusatznutzen des Arzneimittels im Verhältnis zur zweckmäßigen Vergleichstherapie** a) *Therapienaive* Patienten (*mit und ohne Zirrhose*), *Genotyp 1*: Simeprevir in Kombination mit Peginterferon alfa + Ribavirin gegenüber Peginterferon alfa + Ribavirin **Zweckmäßige Vergleichstherapie:** ▪ Therapienaive Patienten ohne Zirrhose Duale Therapie (Kombination aus Peginterferon alfa und Ribavirin) **oder** Triple-Therapie (Kombination aus einem Proteaseinhibitor (Boceprevir oder Telaprevir), Peginterferon alfa und Ribavirin) ▪ Therapienaive Patienten mit Zirrhose Duale Therapie (Kombination aus Peginterferon alfa und Ribavirin) **Ausmaß und Wahrscheinlichkeit des Zusatznutzens** gegenüber Peginterferon alfa + Ribavirin: Hinweis für einen beträchtlichen Zusatznutzen. b) *Therapieerfahrene* Patienten (*Relapse*), *Genotyp 1*: Simeprevir in Kombination mit Peginterferon alfa + Ribavirin gegenüber Peginterferon alfa + Ribavirin **Zweckmäßige Vergleichstherapie:** Duale Therapie (Kombination aus Peginterferon alfa und Ribavirin) **oder** Triple-Therapie (Kombination aus einem Proteaseinhibitor (Boceprevir oder Telaprevir), Peginterferon alfa und Ribavirin) **Ausmaß und Wahrscheinlichkeit des Zusatznutzens** gegenüber Peginterferon alfa + Ribavirin: Hinweis für einen beträchtlichen Zusatznutzen. c) *Therapieerfahrene* Patienten (*vorherige Non-Responder*), *Genotyp 1*: Simeprevir in Kombination mit Peginterferon alfa + Ribavirin gegenüber Peginterferon alfa + Ribavirin + Proteaseinhibitor (Boceprevir oder Telaprevir) **Zweckmäßige Vergleichstherapie:**

	Duale Therapie (Kombination aus Peginterferon alfa und Ribavirin) **oder** Triple-Therapie (Kombination aus einem Proteaseinhibitor (Boceprevir oder Telaprevir), Peginterferon alfa und Ribavirin) **Ausmaß und Wahrscheinlichkeit des Zusatznutzens** gegenüber Peginterferon alfa + Ribavirin + Proteaseinhibitor (Boceprevir oder Telaprevir): Hinweis für einen beträchtlichen Zusatznutzen. d) *Therapienaive* Patienten und *therapieerfahrene* Patienten (*Relapse*), *Genotyp 4*: Simeprevir in Kombination mit Peginterferon alfa + Ribavirin gegenüber Peginterferon alfa + Ribavirin **Zweckmäßige Vergleichstherapie:** Duale Therapie (Kombination aus Peginterferon alfa und Ribavirin) **Ausmaß und Wahrscheinlichkeit des Zusatznutzens** gegenüber Peginterferon alfa + Ribavirin: Anhaltspunkt für einen geringen Zusatznutzen. e) *Therapieerfahrene* Patienten (*vorherige Non-Responder*), *Genotyp 4*: Simeprevir in Kombination mit Peginterferon alfa + Ribavirin gegenüber Peginterferon alfa + Ribavirin **Zweckmäßige Vergleichstherapie:** Duale Therapie (Kombination aus Peginterferon alfa und Ribavirin) **Ausmaß und Wahrscheinlichkeit des Zusatznutzens** gegenüber Peginterferon alfa + Ribavirin: Ein Zusatznutzen ist nicht belegt. f) *Therapienaive* Patienten (*ohne Zirrhose*) und *therapieerfahrene* Patienten (*Relapse ohne Zirrhose*) mit einer *HIV-Koinfektion*, *Genotyp 1, 4*: Simeprevir in Kombination mit Peginterferon alfa + Ribavirin gegenüber Peginterferon alfa + Ribavirin **Zweckmäßige Vergleichstherapie:** Duale Therapie (Kombination aus Peginterferon alfa und Ribavirin) **Ausmaß und Wahrscheinlichkeit des Zusatznutzens** gegenüber Peginterferon alfa + Ribavirin: Anhaltspunkt für einen geringen Zusatznutzen. g) *Therapienaive* Patienten (*mit Zirrhose*) und *therapieerfahrene* Patienten (*vorherige Non-Responder mit/ohne Zirrhose*; *Relapse mit Zirrhose*) mit einer *HIV-Koinfektion*, *Genotyp 1, 4*: Simeprevir in Kombination mit Peginterferon alfa + Ribavirin gegenüber Peginterferon alfa + Ribavirin **Zweckmäßige Vergleichstherapie:** Duale Therapie (Kombination aus Peginterferon alfa und Ribavirin) **Ausmaß und Wahrscheinlichkeit des Zusatznutzens** gegenüber Peginterferon alfa + Ribavirin: Ein Zusatznutzen ist nicht belegt.
G-BA, 2014 [24]. Beschluss	***Sofosbuvir*** **Zugelassenes Anwendungsgebiet:**

des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Sofosbuvir **siehe auch: IQWiG, 2014 [46].** Sofosbuvir – Nutzenbewertung gemäß § 35a SGB V (Auftrag A14-05) sowie **Addendum zum Auftrag A14-05 (Auftrag A14-20) [35].**	Sofosbuvir (Sovaldi®) wird in Kombination mit anderen Arzneimitteln zur Behandlung der chronischen Hepatitis C (CHC) bei Erwachsenen angewendet (siehe Abschnitte 4.2, 4.4 und 5.1 der Fachinformation von Sovaldi®). **Zusatznutzen des Arzneimittels im Verhältnis zur zweckmäßigen Vergleichstherapie** a) In Kombination mit Peginterferon alfa + Ribavirin gegenüber Peginterferon alfa + Ribavirin + Proteaseinhibitor (Boceprevir oder Telaprevir) bei *therapienaiven* Patienten *ohne Zirrhose* mit chronischer Hepatitis-C-Virus (cHCV) Infektion (*Genotyp 1*) **Zweckmäßige Vergleichstherapie:** Duale Therapie (Kombination aus Peginterferon alfa und Ribavirin) **oder** Triple-Therapie (Kombination aus einem Proteaseinhibitor (Boceprevir oder Telaprevir), Peginterferon alfa und Ribavirin) **Ausmaß und Wahrscheinlichkeit des Zusatznutzens** gegenüber Peginterferon alfa + Ribavirin + Proteaseinhibitor (Boceprevir oder Telaprevir): Anhaltspunkt für einen geringen Zusatznutzen. b) In Kombination mit Peginterferon alfa + Ribavirin gegenüber Peginterferon alfa + Ribavirin bei *therapienaiven* Patienten *mit Zirrhose* mit chronischer Hepatitis-C-Virus (cHCV) Infektion (*Genotyp 1*) **Zweckmäßige Vergleichstherapie:** Duale Therapie (Kombination aus Peginterferon alfa und Ribavirin) **Ausmaß und Wahrscheinlichkeit des Zusatznutzens** gegenüber Peginterferon alfa + Ribavirin: Anhaltspunkt für einen geringen Zusatznutzen. c) In Kombination mit Peginterferon alfa + Ribavirin gegenüber Peginterferon alfa + Ribavirin + Proteaseinhibitor (Boceprevir oder Telaprevir) bei *therapieerfahrenen* Patienten mit chronischer Hepatitis-C-Virus (cHCV) Infektion (*Genotyp 1*) **Zweckmäßige Vergleichstherapie:** Duale Therapie (Kombination aus Peginterferon alfa und Ribavirin) oder Triple-Therapie (Kombination aus einem Proteaseinhibitor (Boceprevir oder Telaprevir), Peginterferon alfa und Ribavirin) **Ausmaß und Wahrscheinlichkeit des Zusatznutzens** gegenüber Peginterferon alfa + Ribavirin + Proteaseinhibitor (Boceprevir oder Telaprevir): Ein Zusatznutzen ist nicht belegt. d) In Kombination mit Ribavirin gegenüber Peginterferon alfa + Ribavirin *bei therapienaiven* Patienten mit chronischer Hepatitis-C-Virus (cHCV) Infektion *(Genotyp 2)* **Zweckmäßige Vergleichstherapie:** Duale Therapie (Kombination aus Peginterferon alfa und Ribavirin) **Ausmaß und Wahrscheinlichkeit des Zusatznutzens** gegenüber Peginterferon alfa + Ribavirin: Hinweis für einen beträchtlichen Zusatznutzen.

	e) In Kombination mit Ribavirin gegenüber Peginterferon alfa + Ribavirin bei t*herapieerfahrenen* Patienten mit chronischer Hepatitis-C-Virus (cHCV) Infektion *(Genotyp 2)* **Zweckmäßige Vergleichstherapie:** Duale Therapie (Kombination aus Peginterferon alfa und Ribavirin) **Ausmaß und Wahrscheinlichkeit des Zusatznutzens** gegenüber Peginterferon alfa + Ribavirin: Anhaltspunkt für einen geringen Zusatznutzen. f) In Kombination mit Ribavirin gegenüber Peginterferon alfa + Ribavirin bei *therapienaiven* und *therapieerfahrenen* Patienten mit chronischer Hepatitis-C-Virus (cHCV) Infektion (*Genotyp 3*) **Zweckmäßige Vergleichstherapie:** Duale Therapie (Kombination aus Peginterferon alfa und Ribavirin) **Ausmaß und Wahrscheinlichkeit des Zusatznutzens** gegenüber Peginterferon alfa + Ribavirin: Anhaltspunkt für einen geringen Zusatznutzen. g) In Kombination mit Peginterferon alfa + Ribavirin gegenüber Peginterferon alfa + Ribavirin bei *therapienaiven* und *therapieerfahrenen* Patienten mit chronischer Hepatitis-C-Virus (cHCV) Infektion (*Genotyp 3*) **Zweckmäßige Vergleichstherapie:** Duale Therapie (Kombination aus Peginterferon alfa und Ribavirin) **Ausmaß und Wahrscheinlichkeit des Zusatznutzens** gegenüber Peginterferon alfa + Ribavirin: Ein Zusatznutzen ist nicht belegt. h) In Kombination mit Peginterferon alfa + Ribavirin gegenüber Peginterferon alfa + Ribavirin bei *therapienaiven* und *therapieerfahrenen* Patienten mit chronischer Hepatitis-C-Virus (cHCV) Infektion (*Genotyp 4, 5 und 6*) **Zweckmäßige Vergleichstherapie:** Duale Therapie (Kombination aus Peginterferon alfa und Ribavirin) **Ausmaß und Wahrscheinlichkeit des Zusatznutzens** gegenüber Peginterferon alfa + Ribavirin: Ein Zusatznutzen ist nicht belegt. i) In Kombination mit Peginterferon alfa + Ribavirin bzw. Kombination mit Ribavirin gegenüber Peginterferon alfa + Ribavirin bei Patienten mit einer *HIV-Koinfektion* (*therapienaiv, therapieerfahren*) mit chronischer Hepatitis-C-Virus (cHCV) Infektion (*Genotyp 1 bis 6*) **Zweckmäßige Vergleichstherapie:** Duale Therapie (Kombination aus Peginterferon alfa und Ribavirin) **Ausmaß und Wahrscheinlichkeit des Zusatznutzens** gegenüber Peginterferon alfa + Ribavirin: Anhaltspunkt für einen geringen Zusatznutzen.
G-BA, 2015 [19]. Beschluss	***Daclatasvir*** **Zugelassenes Anwendungsgebiet:**

des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Daclatasvir **siehe auch: IQWiG, 2014 [38].** Daclatasvir – Nutzenbewertung gemäß § 35a SGB V (Auftrag A14-31) sowie **Addendum zum Auftrag A14-31 (Auftrag A15-02) [39].**	Daclatasvir (Daklinza®) wird in Kombination mit anderen Arzneimitteln zur Behandlung der chronischen Infektion mit dem Hepatitis-C-Virus (HCV) bei Erwachsenen angewendet. **Zusatznutzen des Arzneimittels im Verhältnis zur zweckmäßigen Vergleichstherapie** a) *Therapienaive* Patienten (*ohne Zirrhose*), *Genotyp 1*: Daclatasvir in Kombination mit Sofosbuvir **Zweckmäßige Vergleichstherapie:** Duale Therapie (Kombination aus Peginterferon alfa und Ribavirin) **oder** Triple-Therapie (Kombination aus einem Proteaseinhibitor (Boceprevir oder Telaprevir), Peginterferon alfa und Ribavirin) **Ausmaß und Wahrscheinlichkeit des Zusatznutzens** gegenüber Peginterferon alfa + Ribavirin + Proteaseinhibitor (Boceprevir oder Telaprevir): Anhaltspunkt für einen geringen Zusatznutzen. b) *Therapienaive* Patienten (*mit kompensierter Zirrhose*), *Genotyp 1*: Daclatasvir in Kombination mit Sofosbuvir (gegebenenfalls + Ribavirin) **Zweckmäßige Vergleichstherapie:** Duale Therapie (Kombination aus Peginterferon alfa und Ribavirin) **Ausmaß und Wahrscheinlichkeit des Zusatznutzens** gegenüber Peginterferon alfa + Ribavirin: Ein Zusatznutzen ist nicht belegt. c) *Therapieerfahrene* Patienten, *Genotyp 1*: Daclatasvir in Kombination mit Sofosbuvir (gegebenenfalls + Ribavirin) **Zweckmäßige Vergleichstherapie:** Duale Therapie (Kombination aus Peginterferon alfa und Ribavirin) **oder** Triple-Therapie (Kombination aus einem Proteaseinhibitor (Boceprevir oder Telaprevir), Peginterferon alfa und Ribavirin) **Ausmaß und Wahrscheinlichkeit des Zusatznutzens** gegenüber Peginterferon alfa + Ribavirin sowie Peginterferon alfa + Ribavirin + Proteaseinhibitor (Boceprevir oder Telaprevir): Ein Zusatznutzen ist nicht belegt. d) *Therapienaive* Patienten (*mit kompensierter Zirrhose*) und *therapieerfahrene* Patienten, *Genotyp 3*: Daclatasvir in Kombination mit Sofosbuvir + Ribavirin **Zweckmäßige Vergleichstherapie:** Duale Therapie (Kombination aus Peginterferon alfa und Ribavirin) **Ausmaß und Wahrscheinlichkeit des Zusatznutzens** gegenüber Peginterferon alfa + Ribavirin: Ein Zusatznutzen ist nicht belegt. e) *Therapienaive* Patienten und *therapieerfahrene* Patienten, *Genotyp 4*: Daclatasvir in Kombination mit Sofosbuvir (gegebenenfalls + Ribavirin) **Zweckmäßige Vergleichstherapie:** Duale Therapie (Kombination aus Peginterferon alfa und Ribavirin)

	Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Peginterferon alfa + Ribavirin: Ein Zusatznutzen ist nicht belegt. f) *Therapienaive* Patienten, *Genotyp 4*: Daclatasvir in Kombination mit Peginterferon alfa + Ribavirin **Zweckmäßige Vergleichstherapie:** Duale Therapie (Kombination aus Peginterferon alfa und Ribavirin) **Ausmaß und Wahrscheinlichkeit des Zusatznutzens** gegenüber Peginterferon alfa + Ribavirin: Anhaltspunkt für einen beträchtlichen Zusatznutzen. g) *Therapieerfahrene* Patienten, *Genotyp 4*: Daclatasvir in Kombination mit Peginterferon alfa + Ribavirin **Zweckmäßige Vergleichstherapie:** Duale Therapie (Kombination aus Peginterferon alfa und Ribavirin) **Ausmaß und Wahrscheinlichkeit des Zusatznutzens** gegenüber Peginterferon alfa + Ribavirin: Ein Zusatznutzen ist nicht belegt.
G-BA, 2015 [20]. Beschluss über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Dasabuvir **siehe auch: IQWiG, 2015 [40].** Dasabuvir – Nutzenbewertung gemäß § 35a SGB V (Auftrag A15-03) sowie **Addendum zu den Aufträgen A15-03 und A15-04 (Auftrag A15-21) [41].**	***Dasabuvir*** **Zusatznutzen des Arzneimittels im Verhältnis zur zweckmäßigen Vergleichstherapie** a) *Therapienaive* Patienten (*ohne Zirrhose*), *Genotyp 1a/1b*: • Dasabuvir in Kombination mit Ombitasvir/Paritaprevir/Ritonavir plus Ribavirin (Genotyp 1a) • Dasabuvir in Kombination mit Ombitasvir/Paritaprevir/Ritonavir (Genotyp 1b) **Zweckmäßige Vergleichstherapie:** Duale Therapie (Kombination aus Peginterferon alfa und Ribavirin) **oder** Triple-Therapie (Kombination aus einem Proteaseinhibitor (Boceprevir oder Telaprevir), Peginterferon alfa und Ribavirin) **Ausmaß und Wahrscheinlichkeit des Zusatznutzens** gegenüber Peginterferon alfa + Ribavirin + Proteaseinhibitor (Boceprevir oder Telaprevir): Hinweis für einen beträchtlichen Zusatznutzen. b) *Therapienaive* Patienten (*mit kompensierter Zirrhose*), *Genotyp 1a/1b*: Dasabuvir in Kombination mit Ombitasvir/Paritaprevir/Ritonavir plus Ribavirin **Zweckmäßige Vergleichstherapie:** Duale Therapie (Kombination aus Peginterferon alfa und Ribavirin) **Ausmaß und Wahrscheinlichkeit des Zusatznutzens** gegenüber Peginterferon alfa + Ribavirin: Anhaltspunkt für einen geringen Zusatznutzen. c) *Therapieerfahrene* Patienten (*ohne Zirrhose*), *Genotyp 1a/1b*: • Dasabuvir in Kombination mit Ombitasvir/Paritaprevir/Ritonavir plus Ribavirin (Genotyp 1a)

	• Dasabuvir in Kombination mit Ombitasvir/Paritaprevir/Ritonavir (Genotyp 1b) **Zweckmäßige Vergleichstherapie:** Duale Therapie (Kombination aus Peginterferon alfa und Ribavirin) **oder** Triple-Therapie (Kombination aus einem Proteaseinhibitor (Boceprevir oder Telaprevir), Peginterferon alfa und Ribavirin) **Ausmaß und Wahrscheinlichkeit des Zusatznutzens** gegenüber Peginterferon alfa + Ribavirin + Proteaseinhibitor (Boceprevir oder Telaprevir): Anhaltspunkt für einen beträchtlichen Zusatznutzen. d) *Therapieerfahrene* Patienten (*mit kompensierter Zirrhose*), *Genotyp 1a/1b*: Dasabuvir in Kombination mit Ombitasvir/Paritaprevir/Ritonavir plus Ribavirin **Zweckmäßige Vergleichstherapie:** Duale Therapie (Kombination aus Peginterferon alfa und Ribavirin) **oder** Triple-Therapie (Kombination aus einem Proteaseinhibitor (Boceprevir oder Telaprevir), Peginterferon alfa und Ribavirin) **Ausmaß und Wahrscheinlichkeit des Zusatznutzens** gegenüber Peginterferon alfa + Ribavirin + Proteaseinhibitor (Boceprevir oder Telaprevir): Anhaltspunkt für einen geringen Zusatznutzen. e) *Therapienaive* Patienten und *therapieerfahrene* Patienten mit einer *HIV-Koinfektion*, *Genotyp 1a/1b*: • Dasabuvir in Kombination mit Ombitasvir/Paritaprevir/Ritonavir (Genotyp 1b ohne Zirrhose) • Dasabuvir in Kombination mit Ombitasvir/Paritaprevir/Ritonavir plus Ribavirin (Genotyp 1a, Genotyp 1b mit kompensierter Zirrhose) **Zweckmäßige Vergleichstherapie:** Duale Therapie (Kombination aus Peginterferon alfa und Ribavirin) **Ausmaß und Wahrscheinlichkeit des Zusatznutzens** gegenüber Peginterferon alfa + Ribavirin: Anhaltspunkt für einen geringen Zusatznutzen.
G-BA, 2015 [21]. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen	***Ledipasvir/Sofosbuvir*** **Zugelassenes Anwendungsgebiet:** Ledipasvir/Sofosbuvir (Harvoni®) wird bei Erwachsenen zur Behandlung der chronischen Hepatitis C (CHC) angewendet. **Zusatznutzen des Arzneimittels im Verhältnis zur zweckmäßigen Vergleichstherapie** a) *Therapienaive* Patienten (*ohne Zirrhose*), *Genotyp 1*: Ledipasvir/Sofosbuvir **Zweckmäßige Vergleichstherapie:** Duale Therapie (Kombination aus Peginterferon alfa und Ribavirin) **oder** Triple-Therapie (Kombination aus einem Proteaseinhibitor (Boceprevir oder Telaprevir), Peginterferon alfa und Ribavirin)

nach § 35a SGB V – Ledipasvir/Sofosbuvir **siehe auch: IQWiG, 2015 [42].** Ledipasvir/Sofosbuvir – Nutzenbewertung gemäß § 35a SGB V (Auftrag A14-44). sowie **Addendum zum Auftrag A14-44 (Auftrag A15-14) [43].**	**Ausmaß und Wahrscheinlichkeit des Zusatznutzens** gegenüber Peginterferon alfa + Ribavirin + Proteaseinhibitor (Boceprevir oder Telaprevir): Anhaltspunkt für einen beträchtlichen Zusatznutzen. b) *Therapienaive* Patienten (*mit kompensierter Zirrhose*), *Genotyp 1*: Ledipasvir/Sofosbuvir **Zweckmäßige Vergleichstherapie:** Duale Therapie (Kombination aus Peginterferon alfa und Ribavirin) **Ausmaß und Wahrscheinlichkeit des Zusatznutzens** gegenüber Peginterferon alfa + Ribavirin: Anhaltspunkt für einen beträchtlichen Zusatznutzen. c) *Therapieerfahrene* Patienten (*ohne Zirrhose, mit kompensierter Zirrhose*), *Genotyp 1*: Ledipasvir/Sofosbuvir **Zweckmäßige Vergleichstherapie:** Duale Therapie (Kombination aus Peginterferon alfa und Ribavirin) **oder** Triple-Therapie (Kombination aus einem Proteaseinhibitor (Boceprevir oder Telaprevir), Peginterferon alfa und Ribavirin) **Ausmaß und Wahrscheinlichkeit des Zusatznutzens** gegenüber Peginterferon alfa + Ribavirin + Proteaseinhibitor (Boceprevir oder Telaprevir): Anhaltspunkt für einen beträchtlichen Zusatznutzen. d) *Therapienaive* Patienten (*mit kompensierter Zirrhose*) und *therapieerfahrene* Patienten, *Genotyp 3*: Ledipasvir/Sofosbuvir in Kombination mit Ribavirin **Zweckmäßige Vergleichstherapie:** Duale Therapie (Kombination aus Peginterferon alfa und Ribavirin) **Ausmaß und Wahrscheinlichkeit des Zusatznutzens** gegenüber Peginterferon alfa + Ribavirin: Ein Zusatznutzen ist nicht belegt. e) *Therapienaive* Patienten und *therapieerfahrene* Patienten, *Genotyp 4*: Ledipasvir/Sofosbuvir **Zweckmäßige Vergleichstherapie:** Duale Therapie (Kombination aus Peginterferon alfa und Ribavirin) **Ausmaß und Wahrscheinlichkeit des Zusatznutzens** gegenüber Peginterferon alfa + Ribavirin: Anhaltspunkt für einen geringen Zusatznutzen. f) *Therapienaive* Patienten und *therapieerfahrene* Patienten mit einer *HIV-Koinfektion*, *Genotyp 1*: Ledipasvir/Sofosbuvir **Zweckmäßige Vergleichstherapie:** Duale Therapie (Kombination aus Peginterferon alfa und Ribavirin) **Ausmaß und Wahrscheinlichkeit des Zusatznutzens** gegenüber Peginterferon alfa + Ribavirin: Anhaltspunkt für einen nicht quantifizierbaren Zusatznutzen. g) Patienten mit *dekompensierter Zirrhose*, *Genotyp 1*: Ledipasvir/Sofosbuvir in Kombination mit Ribavirin **Zweckmäßige Vergleichstherapie:**

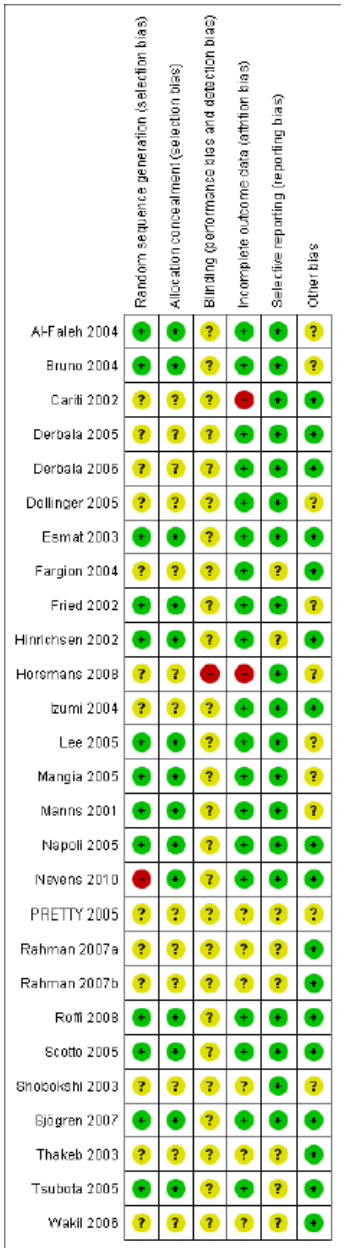
	Best-Supportive-Care **Ausmaß und Wahrscheinlichkeit des Zusatznutzens** gegenüber Best-Supportive-Care: Anhaltspunkt für einen nicht quantifizierbaren Zusatznutzen.
G-BA, 2015 [22]. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Ombitasvir/ Paritaprevir/ Ritonavir **siehe auch:** **IQWiG, 2015 [44].** Ombitasvir/ Paritaprevir/ Ritonavir – Nutzenbewertung gemäß § 35a SGB V (Auftrag A15-04) sowie **Addendum zu den Aufträgen A15-03 und A15-04 (Auftrag A15-21) [41].**	***Ombitasvir/Paritaprevir/Ritonavir*** **Zugelassenes Anwendungsgebiet:** Ombitasvir/Paritaprevir/Ritonavir (Viekirax®) wird in Kombination mit anderen Arzneimitteln zur Behandlung der chronischen Hepatitis C (CHC) bei Erwachsenen angewendet. **Zusatznutzen des Arzneimittels im Verhältnis zur zweckmäßigen Vergleichstherapie** a) *Therapienaive* Patienten (*ohne Zirrhose*), *Genotyp 1a/1b*: • Ombitasvir/Paritaprevir/Ritonavir in Kombination mit Dasabuvir plus Ribavirin (Genotyp 1a) • Ombitasvir/Paritaprevir/Ritonavir in Kombination mit Dasabuvir (Genotyp 1b) **Zweckmäßige Vergleichstherapie:** Duale Therapie (Kombination aus Peginterferon alfa und Ribavirin) **oder** Triple-Therapie (Kombination aus einem Proteaseinhibitor (Boceprevir oder Telaprevir), Peginterferon alfa und Ribavirin) **Ausmaß und Wahrscheinlichkeit des Zusatznutzens** gegenüber Peginterferon alfa + Ribavirin + Proteaseinhibitor (Boceprevir oder Telaprevir): Hinweis für einen beträchtlichen Zusatznutzen. b) *Therapienaive* Patienten (*mit kompensierter Zirrhose*), *Genotyp 1a/1b*: Ombitasvir/Paritaprevir/Ritonavir in Kombination mit Dasabuvir plus Ribavirin **Zweckmäßige Vergleichstherapie:** Duale Therapie (Kombination aus Peginterferon alfa und Ribavirin) **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Peginterferon alfa + Ribavirin:** Anhaltspunkt für einen geringen Zusatznutzen. c) *Therapieerfahrene* Patienten (*ohne Zirrhose*), *Genotyp 1a/1b*: • Ombitasvir/Paritaprevir/Ritonavir in Kombination mit Dasabuvir plus Ribavirin (Genotyp 1a) • Ombitasvir/Paritaprevir/Ritonavir in Kombination mit Dasabuvir (Genotyp 1b) **Zweckmäßige Vergleichstherapie:** Duale Therapie (Kombination aus Peginterferon alfa und Ribavirin) **oder** Triple-Therapie (Kombination aus einem Proteaseinhibitor (Boceprevir oder Telaprevir), Peginterferon alfa und Ribavirin) **Ausmaß und Wahrscheinlichkeit des Zusatznutzens** gegenüber Peginterferon alfa + Ribavirin + Proteaseinhibitor (Boceprevir oder Telaprevir): Anhaltspunkt für einen beträchtlichen Zusatznutzen.

	d) *Therapieerfahrene* Patienten (*mit kompensierter Zirrhose*), *Genotyp 1a/1b*: Ombitasvir/Paritaprevir/Ritonavir in Kombination mit Dasabuvir plus Ribavirin **Zweckmäßige Vergleichstherapie:** Duale Therapie (Kombination aus Peginterferon alfa und Ribavirin) **oder** Triple-Therapie (Kombination aus einem Proteaseinhibitor (Boceprevir oder Telaprevir), Peginterferon alfa und Ribavirin) **Ausmaß und Wahrscheinlichkeit des Zusatznutzens** gegenüber Peginterferon alfa + Ribavirin + Proteaseinhibitor (Boceprevir oder Telaprevir): Anhaltspunkt für einen geringen Zusatznutzen. e) *Therapienaive* Patienten und *therapieerfahrene* Patienten (*ohne Zirrhose*), *Genotyp 4*: Ombitasvir/Paritaprevir/Ritonavir in Kombination mit Ribavirin **Zweckmäßige Vergleichstherapie:** Duale Therapie (Kombination aus Peginterferon alfa und Ribavirin) **Ausmaß und Wahrscheinlichkeit des Zusatznutzens** gegenüber Peginterferon alfa + Ribavirin: Anhaltspunkt für einen geringen Zusatznutzen. f) *Therapienaive* Patienten und *therapieerfahrene* Patienten (*mit kompensierter Zirrhose*), *Genotyp 4*: Ombitasvir/Paritaprevir/Ritonavir in Kombination mit Ribavirin **Zweckmäßige Vergleichstherapie:** Duale Therapie (Kombination aus Peginterferon alfa und Ribavirin) **Ausmaß und Wahrscheinlichkeit des Zusatznutzens** gegenüber Peginterferon alfa + Ribavirin: Ein Zusatznutzen ist nicht belegt. g) *Therapienaive* Patienten und *therapieerfahrene* Patienten mit einer *HIV-Koinfektion*, *Genotyp 1a/1b*: • Ombitasvir/Paritaprevir/Ritonavir in Kombination mit Dasabuvir (Genotyp 1b ohne Zirrhose) • Ombitasvir/Paritaprevir/Ritonavir in Kombination mit Dasabuvir plus Ribavirin (Genotyp 1a, Genotyp 1b mit kompensierter Zirrhose) **Zweckmäßige Vergleichstherapie:** Duale Therapie (Kombination aus Peginterferon alfa und Ribavirin) **Ausmaß und Wahrscheinlichkeit des Zusatznutzens** gegenüber Peginterferon alfa + Ribavirin: Anhaltspunkt für einen geringen Zusatznutzen.

Cochrane Reviews

Hauser G et al., 2014 [31]. Peginterferon plus ribavirin versus interferon plus ribavirin for	1. Fragestellung To systematically evaluate the benefits and harms of peginterferon plus ribavirin versus interferon plus ribavirin for patients with chronic hepatitis C.
	2. Methodik

chronic hepatitis C	*Population:* Patients with chronic hepatitis C *Intervention / Komparator:* Peginterferon alpha-2a or peginterferon alpha-2b plus ribavirin versus interferon plus ribavirin for participants with chronic hepatitis C *Endpunkte* Primary outcomes • Liver-related morbidity plus all-cause mortality: number of participants who developed cirrhosis, ascites, variceal bleeding, hepatic encephalopathy, or hepatocellular carcinoma, or who died. • Adverse events leading to treatment discontinuation. ◦ Numbers and types of adverse events ◦ Other adverse events: haematological effects, fatigue, flu-like symptoms, psychiatric symptoms, dermatological symptoms, thyroid malfunction, gastrointestinal symptoms (other than liver related). • Quality of life. Secondary outcomes • Sustained virological response: number of participants with undetectable hepatitis C virus RNA in serum by sensitive tests six months after the end of treatment. *Suchzeitraum (Aktualität der Recherche):* We searched the Cochrane Hepato-Biliary Group Controlled Trials Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (from 1946), EMBASE (from 1974), Science Citation Index-Expanded (from 1900), and LILACS (from 1980). The searches were conducted until September 2013. *Anzahl eingeschlossene Studien/Patienten (Gesamt):* 27 Studien (5938 Patienten) *Qualitätsbewertung der Studien:* Cochrane risk of bias tool
	3. Ergebnisdarstellung <u>Qualität der Studien:</u>



Summary of findings for the main comparison

Peginterferon plus ribavirin versus non-pegylated interferon plus ribavirin for chronic hepatitis C

Patient or population: patients with chronic hepatitis C.
Settings: mainly outpatients.
Intervention: peginterferon.
Comparison: non-pegylated.

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Non-pegylated	Peginterferon				
Liver-related morbidity plus all-cause mortality	Five per 1000	Six per 1000 (two to 17)	OR 1.14 (0.38 to 3.42)	1789 (five studies)	⊕⊕◯◯ low[1]	
Adverse events leading to treatment discontinuation	207 per 1000	178 per 1000 (141 to 226)	RR 0.86 (0.68 to 1.09)	4571 (15 studies)	⊕⊕◯◯ low[2,3]	
Sustained virological response	386 per 1000	537 per 1000 (482 to 602)	RR 1.39 (1.25 to 1.56)	6104 (27 studies)	⊕◯◯◯[4,5] very low	All trials had high risks of bias. Only an unvalidated surrogate outcome.

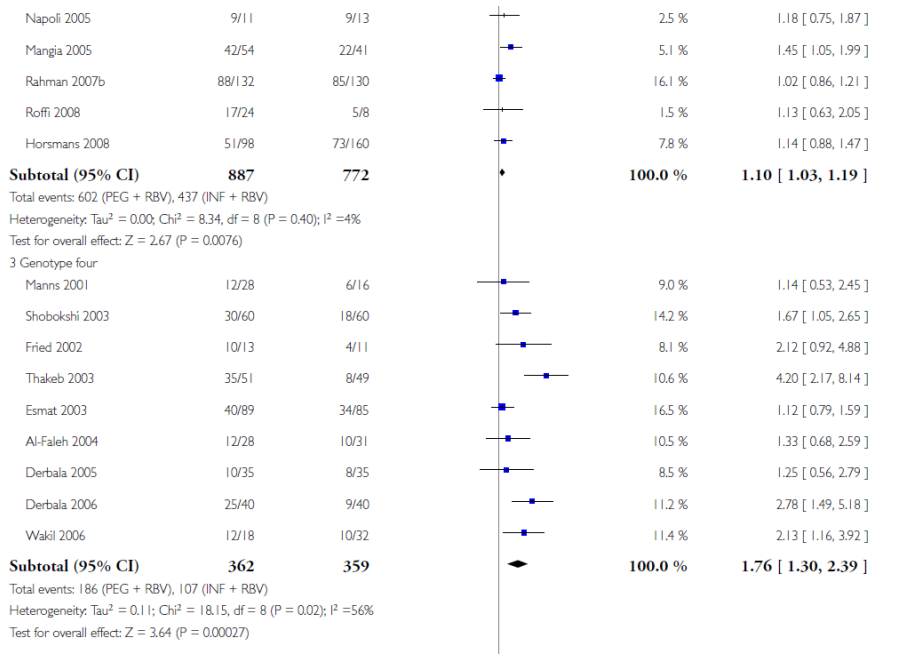
*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio.

GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Low due to imprecision and indirectness wide confidence interval. The meta-analysis included only nine events.
[2]Low due to imprecision and indirectness.The proportions of observed adverse events differ substantially across trials, and the direction of effect is heterogeneous. However, because the event rate is still relatively low across trials, all of the included trials may be subject to considerable random error, thus explaining the apparent heterogeneity in the direction of estimates.
[3]The observed treatment effects differ in both direction and magnitude, but most confidence intervals have considerable overlap. Low due to indirectness.
[4]Sustained virological response does not seem to be a valid surrogate marker for assessing hepatitis C virus treatment efficacy of interferon treatment. Very low due to high risk of bias in all trials and imprecision and indirectness due to surrogate
[5]Only randomised clinical trials were included.

Sustained virological response according to genotype

Study or subgroup	PEG + RBV n/N	INF + RBV n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Genotype one					
Manns 2001	263/697	114/343		13.2 %	1.14 [0.95, 1.36]
Cariti 2002	41/60	17/57		6.7 %	2.29 [1.48, 3.54]
Fried 2002	138/298	103/285		12.6 %	1.28 [1.05, 1.56]
Izumi 2004	10/23	8/26		3.2 %	1.41 [0.67, 2.97]
Bruno 2004	67/163	44/148		9.5 %	1.38 [1.02, 1.88]
Dollinger 2005	5/22	4/18		1.5 %	1.02 [0.32, 3.26]
Scotto 2005	13/26	19/52		5.3 %	1.37 [0.81, 2.31]
PRETTY 2005	13/69	8/77		2.7 %	1.81 [0.80, 4.11]
Tsubota 2005	12/28	8/20		3.6 %	1.07 [0.54, 2.13]
Mangia 2005	37/67	18/79		6.3 %	2.42 [1.53, 3.84]
Lee 2005	25/38	16/39		6.6 %	1.60 [1.03, 2.49]
Napoli 2005	12/21	3/19		1.6 %	3.62 [1.20, 10.90]
Rahman 2007a	62/156	51/154		9.8 %	1.20 [0.89, 1.61]
Sjögren 2007	12/29	11/30		4.0 %	1.13 [0.60, 2.14]
Roffi 2008	8/33	7/28		2.4 %	0.97 [0.40, 2.34]
Nevens 2010	120/230	58/213		11.0 %	1.92 [1.49, 2.47]
Subtotal (95% CI)	**1960**	**1588**		**100.0 %**	**1.47 [1.27, 1.70]**
Total events: 838 (PEG + RBV), 489 (INF + RBV)					
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 29.14$, df = 15 (P = 0.02); $I^2 = 49\%$					
Test for overall effect: Z = 5.09 (P < 0.00001)					
2 Genotypes two and three					
Manns 2001	243/300	115/146		42.6 %	1.03 [0.93, 1.14]
Fried 2002	106/140	88/145		18.6 %	1.25 [1.06, 1.47]
Hinrichsen 2002	24/36	22/36		4.2 %	1.09 [0.77, 1.55]
Fargion 2004	22/92	18/93		1.7 %	1.24 [0.71, 2.15]

	
	4. Anmerkungen/Fazit der Autoren: Peginterferon plus ribavirin versus interferon plus ribavirin seems to significantly increase the proportion of patients with sustained virological response, as well as the risk of certain adverse events. However, we have insufficient evidence to recommend or reject peginterferon plus ribavirin for liver-related morbidity plus all-cause mortality compared with interferon plus ribavirin. The clinical consequences of achieved sustained virological response are unknown, as sustained virological response is still an unvalidated surrogate outcome. We found no evidence of the potential benefits on quality of life in patients with achieved sustained virological response. Further high-quality research is likely to have an important impact on our confidence in the estimate of patient-relevant outcomes and is likely to change our estimates. There is very low quality evidence that peginterferon plus ribavirin increases the proportion of patients with sustained virological response in comparison with interferon plus ribavirin. There is evidence that it also increases the risk of certain adverse events.
Hauser G et al., 2014 [32]. Peginterferon alpha-2a versus peginterferon alpha-2b for chronic hepatitis C.	1. Fragestellung To systematically evaluate the benefits and harms of peginterferon alpha-2a versus peginterferon alpha-2b in head-to-head randomized clinical trials in patients with chronic hepatitis C.
	2. Methodik *Population:* Patients with chronic hepatitis C were included. Patients couldhave been treatment **naive** (not previously treated with antivirals), **relapsers** (patients with a transient response to previous antiviral treatment), or **non-responders** (patients without a response to previous antiviral treatment). We also included patients with comorbidities such as **liver cirrhosis** and **human immunodeficiency virus (HIV)** co-infection. Patients who had undergone liver

transplantation or were positive for chronic hepatitis B infection were excluded.

Intervention / Komparator: Peginterferon alpha-2a compared with peginterferon alpha-2b given with or without co-intervention(s) (for example, ribavirin, telaprevir) regardless of the dose or the duration of the interventions.

Endpunkte

Primary outcomes

- All-cause mortality.
- Liver-related morbidity: number of patients who developed ascites, variceal bleeding, progression of bilirubinaemia, hepatic encephalopathy, or hepatocellular carcinoma.
- Adverse events: serious adverse events, adverse events leading to treatment discontinuation, and all other (non-serious) adverse events.
- Quality of life as defined in the individual trials.

Secondary outcomes

- Sustained virological response: number of patients with undetectable hepatitis C virus RNA in their serum by a sensitive test six months after the end of treatment.

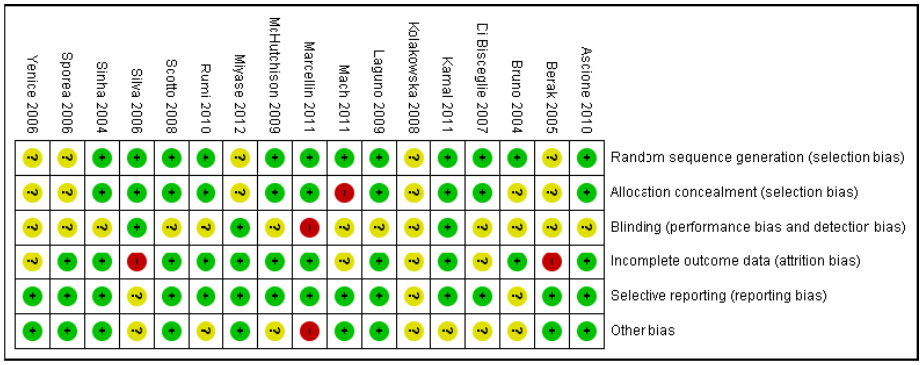
Suchzeitraum (Aktualität der Recherche): We searched the Cochrane Hepato-Biliary Group Controlled Trials Register, Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library, MEDLINE (from 1946), EMBASE (from 1974), Science Citation Index Expanded (from 1900), and LILACS. The last search was conducted in October 2013 (from 1982).

Anzahl eingeschlossene Studien/Patienten (Gesamt): 17 Studien (5847 Patienten)

Qualitätsbewertung der Studien: Cochrane risk of bias tool

3. Ergebnisdarstellung

<u>Qualität der Studien:</u>



Summary of findings for the main comparison

Peginterferon alpha-2a versus peginterferon alpha-2b for chronic hepatitis C

Patient or population: patients with chronic hepatitis C.
Settings: mainly out-patients in tertiary and teaching hospitals.
Intervention: peginterferon alpha-2a versus peginterferon alpha-2b.

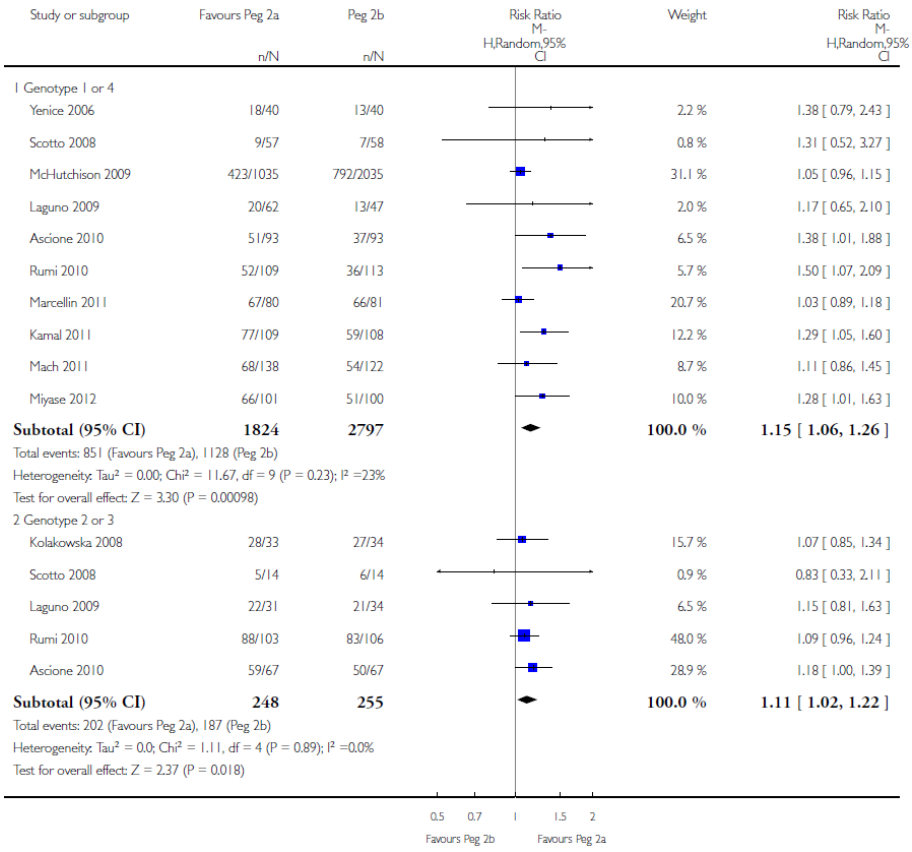
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (trials)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Peginterferon alpha-2b	Peginterferon alpha-2a				
All-cause mortality Deaths during and after the treatment Follow-up: 48 to 72 weeks	**Study population**		**RR 1.97** (0.64 to 6.08)	3070 (1 study)	⊕○○○ **very low**[1,2]	
	3 per 1000	**6 per 1000** (2 to 18)				
	Moderate					
	3 per 1000	**6 per 1000** (2 to 18)				
Liver-related morbidity Number of events Follow-up: 8 weeks	**Study population**		**RR 3** (0.7 to 12.93)	36 (1 study)	⊕○○○ **very low**[2]	
	111 per 1000	**333 per 1000** (78 to 1000)				
	Moderate					
	111 per 1000	**333 per 1000** (78 to 1000)				
Serious adverse events Number of events Follow-up: 48 to 72 weeks	**Study population**		**RR 1.12** (0.95 to 1.3)	3900 (4 studies)	⊕⊕○○ **low**[3,4]	
	114 per 1000	**127 per 1000** (108 to 148)				
	Moderate					
	70 per 1000	**78 per 1000** (66 to 91)				
Adverse events leading to treatment discontinuation Number of events Follow-up: 48-72 weeks	**Study population**		**RR 0.84** (0.57 to 1.22)	5340 (12 studies)	⊕⊕○○ **low**[1,4,5,6]	
	99 per 1000	**83 per 1000** (56 to 120)				
	Moderate					
	80 per 1000	**67 per 1000** (46 to 98)				
All other (non-serious) adverse events Follow-up: 48 to 72 weeks	See comment	See comment	Not estimable	4981 (9 studies)	⊕○○○ **very low**[4,5,6]	
Quality of life SF 36 and CLDQ Follow-up: 48 to 71 weeks	See comment	See comment		434 (1 study)	⊕○○○ **very low**[7,8]	
Sustained virological response Absence of viraemia 24 weeks after the treatment Follow-up: 48 to 72 weeks	**Study population**		**RR 1.12** (1.06 to 1.18)	5013 (12 studies)	⊕⊕⊕○[9,10] **moderate**	
	421 per 1000	**480 per 1000** (451 to 510)				
	Moderate					
	510 per 1000	**581 per 1000** (546 to 617)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio.

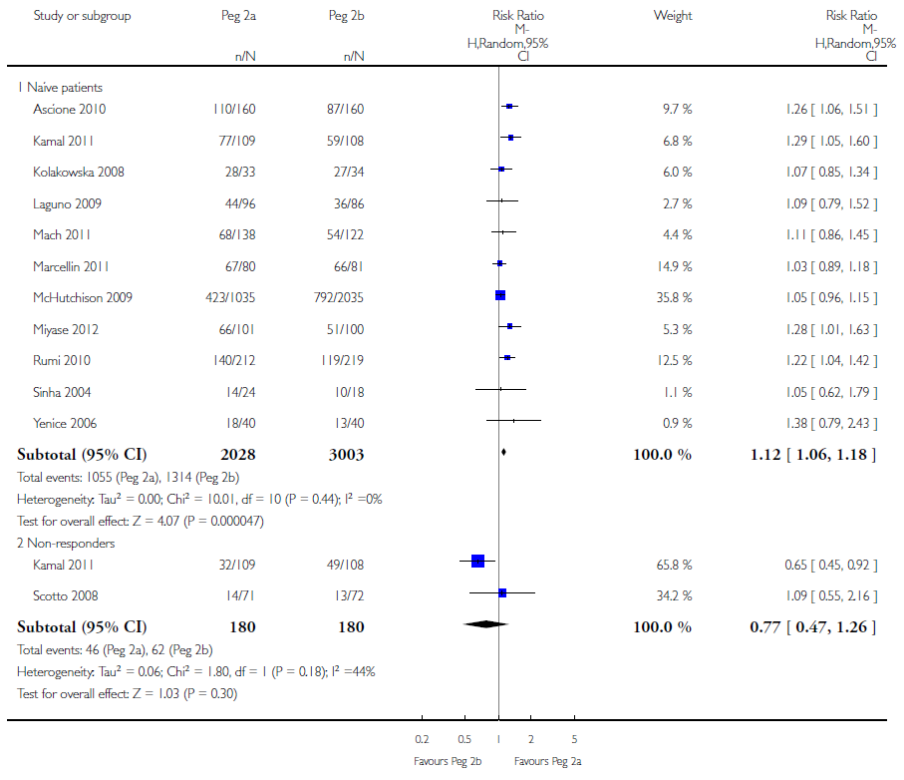
GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] The trial is at low risk of bias due to the allocation sequence generation and allocation concealment.
[2] Data from only one trial, wide confidence interval. Incomplete outcome data. Very low due to imprecision.
[3] Post hoc required information size calculation based on a 10% risk of adverse events in the peginterferon alpha-2b group, a minimally important difference of 10%, a 5% type I error, and a 80% power, suggests that a minimum of 27,000 patients need to be randomised for a conclusive meta-analysis on adverse events. The current number of patients is only approximately 5000.
[4] Wide confidence interval. Low due to imprecision.
[5] Trials yield widely differing estimates of effect. Low due to imprecision.
[6] Reporting of all other adverse events was poor and inconsistent across all included trials. The proportions of observed adverse events differ substantially across the trials, and the direction of effect is heterogeneous. Because the event proportion is relatively low across all trials, all of the included trials may be subject to considerable random errors, thus explaining the apparent heterogeneity in direction of estimates.
[7] Data from only one trial. Low due to imprecision
[8] Investigators fail to report the details necessary for calculating the effect estimate of the quality of life assessment. Very low due to imprecision.
[9] Sustained virological response does not seem to be a valid surrogate marker for assessing HCV treatment efficacy of interferon retreatment. Moderate quality of evidence due to indirectness due to surrogate and risk of bias.
[10] All trials are with high risk of bias. Sensitivity analyses did not show any important change in the intervention effects when we focused on trials with lower risk of bias.

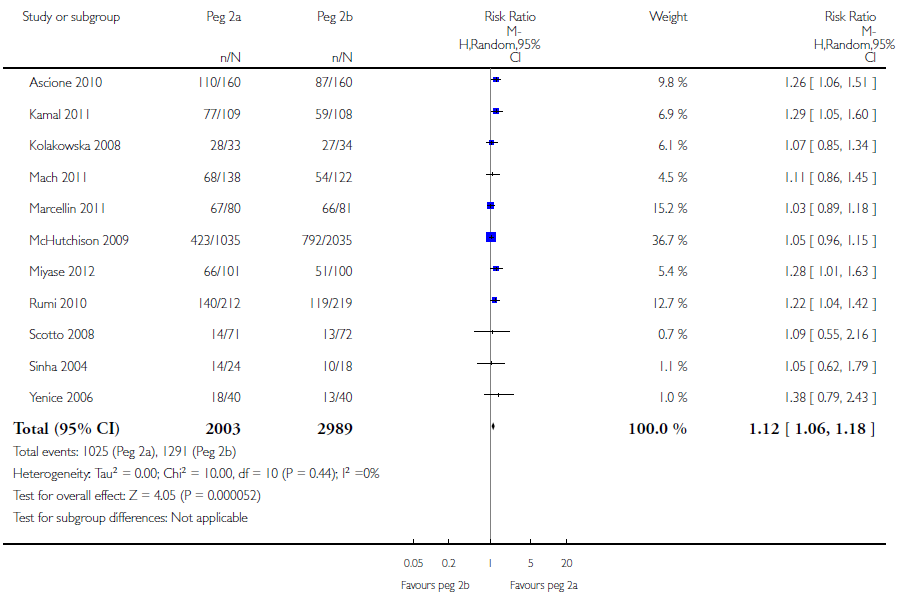
Sustained virological response according to genotype



Sustanied virological response according to treatment history



Sustained virological response in patients without HIV co-infection

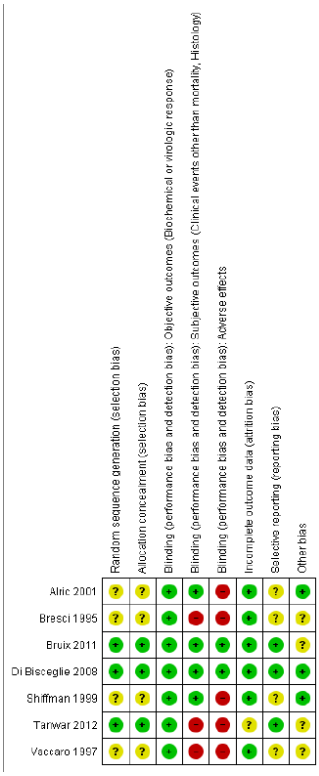
	
	4. Anmerkungen/Fazit der Autoren There is lack of evidence on patient-important outcomes and paucity of evidence on adverse events. Moderate quality evidence suggests that peginterferon alpha-2a is associated with a higher sustained virological response in serum than with peginterferon alpha-2b. This finding may be affected by the high risk of bias of the included studies. The clinical consequences of peginterferon alpha-2a versus peginterferon alpha-2b are unknown, and we cannot translate an effect on sustained virological response into comparable clinical effects because sustained virological response is still an unvalidated surrogate outcome for patient-important outcomes. The lack of evidence on patient-important outcomes and the paucity of evidence on adverse events means that we are unable to draw any conclusions about the effects of one peginterferon over the other.
Koretz RL et al., 2013 [53]. Interferon for interferon nonresponding and relapsing patients with chronic hepatitis C.	1. Fragestellung To assess the benefits and harms of interferon monotherapy retreatment in chronic hepatitis C patients who are nonresponders and relapsers to previous interferon therapy.
	2. Methodik *Population* Patients with chronic Hep C, **non-responder and relapsing** *Intervention / Komparator* interferon monotherapy with no treatment *Endpunkte* Mortality (all-cause and liver-related), Quality of life (however defined by authors), Adverse events *Suchzeitraum (Aktualität der Recherche)* Systematische Literaturrecherche im Suchzeitraum bis 2012

Anzahl eingeschlossene Studien/Patienten (Gesamt):
7 Studien (1976 Patienten)

Qualitätsbewertung der Studien:
Cochrane risk of bias tool

3. Ergebnisdarstellung

<u>Qualität der Studien:</u>



- Based on all trials reporting the outcomes, no significant difference was observed in either all-cause mortality (78/843 (9.3%) versus 62/867 (7.2%); risk ratio (RR) 1.30, 95% confidence interval (CI) 0.95 to 1.79; 3 trials) or hepatic mortality (41/532 (7.7%) versus 40/552 (7.2%); RR 1.07, 95% CI 0.70 to 1.63; 2 trials);
- When only the two trials at low risk of bias were combined, all-cause mortality was significantly higher in the recipients of the pegylated interferon (78/828 (9.4%) versus 57/848 (6.7%); RR 1.41, 95% CI 1.02 to 1.96) although trial sequential analysis could not exclude the possibility of random error.
- There was less variceal bleeding in the recipients of the interferon (4/843 (0.5%) versus 18/867 (2.1%); RR 0.24, 95% CI 0.09 to 0.67; 3 trials), although again trial sequential analysis could not exclude the presence of a type I error and the effect could not be confirmed in a random-effects model meta-analysis.
- No significant differences were seen with regard to the development of ascites, encephalopathy, hepatocellular carcinoma, or the need for liver transplantation.
- The recipients of interferon had significantly more sustained viral responses (20/557 (3.6%) versus 1/579 (0.2%); RR 15.38, 95% CI

	2.93 to 80.71; 4 trials) and a type I error was excluded by trial sequential analysis. • There was a trend for serious adverse events to occur more commonly in the pegylated interferon arm (RR 1.18, 95% CI 0.99 to 1.41, P = 0.07) • Neutropenia and thrombocytopenia more commonly occurred in the pegylated interferon recipients in one trial (RR 2.42, 95% CI 1.43 to 4.10 and RR 2.63, 95% CI 1.61 to 4.30) although there was no significant difference in "hematological adverse events" in the other large trial. • No significant differences were seen in psychiatric adverse events • Infections were more common in the recipients of pegylated interferon in both large trials (RR 1.51, 95% CI 1.05 to 2.16<<9
	4. Anmerkungen/Fazit der Autoren The clinical data were limited to patients with histologic evidence of **severe fibrosis** who were retreated with pegylated interferon. In this scenario, retreatment with interferon did not appear to provide significant clinical benefit and, when only the trials at low risk of bias were considered, retreatment for several years may even have increased all-cause mortality. Such treatment also produced adverse events. On the other hand, the treatment did result in improvement in some surrogate outcomes, namely sustained viral responses and histologic evidence of inflammation. Interferon monotherapy retreatment cannot be recommended for these patients. No clinical data are available for patients with less severe fibrosis. The sustained viral response cannot be used as a surrogate marker for hepatitis C treatment in this clinical setting with low sustained viral response rates and needs to be validated in others in which higher sustained viral response rates are reported.
Katz LH et al., 2012 [49]. Extended peginterferon plus ribavirin treatment for 72 weeks versus standard peginterferon plus ribavirin treatment for 48 weeks in chronic hepatitis C genotype 1 infected slowresponder adult patients.	1. Fragestellung To compare the therapeutic benefits and harms of different antiviral regimens in patients with hepatitis C re-infected grafts after liver transplantation.
	2. Methodik *Population* People of both sexes and all ethnic origins that are chronic **HCV genotype 1 infected naive patients and slow responders** *Intervention / Komparator* Peginterferon (alfa-2a or alfa-2b) and ribavirin for 72 weeks v. peginterferon (alfa-2a or alfa-2b) and ribavirin for 48 weeks *Endpunkte* <u>Primäre Endpunkte:</u> Overall mortality; HCV-related mortality; Liver-related morbidity

Sekundäre Endpunkte: Number of participants with sustained virological response (SVR); Number of participants with end of treatment response (EOR); Number of participants who relapsed; Adherance to treatment; Reduction of treatment dose; Occurrence of adverse events

Suchzeitraum (Aktualität der Recherche)

Systematische Literaturrecherche bis November 2011; Cochrane Hepato-Biliary Group Controlled Trials Register (Gluud 2012), Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library*, MEDLINE, EMBASE, Science Citation Index Expanded (SCI Expanded), and LILACS

Anzahl eingeschlossene Studien/Patienten (Gesamt):

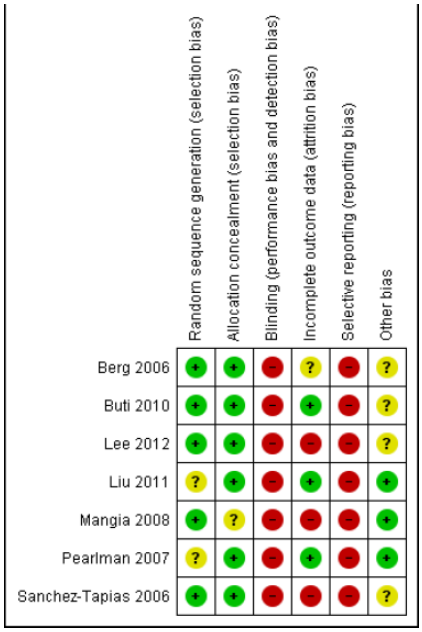
7 Studien (1369 Patienten)

Qualitätsbewertung der Studien:

Cochrane risk of bias tool

3. Ergebnisdarstellung

Qualität der Studien:



- None of the included trials mentioned primary outcomes.

Sustained virological response

- extension of the treatment period to 72 weeks increased the sustained virological response according to both definitions (71/217 (32.7%) versus 52/194 (26.8%); risk ratio (RR) 1.43, 95% CI 1.07 to 1.92, P = 0.02, I^2 = 8%; and 265/499 (53.1%) versus 207/496 (41.7%); RR 1.27, 95% CI 1.07 to 1.50, P = 0.006, I^2 = 38%), with a risk difference of 0.11 and calculated number needed to treat of nine.

End of treatment response and number of participants who experienced virological relapse after treatment

	• The end of treatment response was not significantly different between the two treatment groups. • The number of participants who relapsed virologically was found to be lower in the groups that had been treated for 72 weeks using both definitions (27/84 (32.1%) versus 46/91 (50.5%); RR 0.59, 95% CI 0.40 to 0.86, P = 0.007, I^2 = 18%, 3 trials; and 85/350 (24.3%) versus 146/353 (41.4%); RR 0.59, 95% CI 0.47, 0.73, P < 0.000001, I^2 = 0%, 3 trials). **Adherence to treatment, reduction of treatment dose, and adverse events** • The length of treatment did not significantly affect the adherence (247/279 (88.5%) versus 252/274 (92.0%); RR 0.95, 95% CI 0.84 to 1.07, P = 0.42, I2 = 69%, 3 trials). • In the single trial that reported adverse events, no significant difference was seen between the two treatment groups.
	4. Anmerkungen/Fazit der Autoren This review demonstrates higher a proportion of sustained virological response after extension of treatment from 48 weeks to 72 weeks in **HCV genotype 1** infected patients in whom HCV RNA was still detectable but decreased by ≥ 2 log after 12 weeks and became negative after 24 weeks of treatment, and in patients with detectable HCV RNA after four weeks of treatment with peginterferon plus ribavirin. The observed intervention effects can be caused by both systematic error (bias) and random errors (play of chance). There was no reporting on mortality and the reporting of clinical outcomes and adverse events was insufficient. More data are needed in order to recommend or reject the policy of extending the treatment period for slow responders. 5. Hinweise durch FB Med The mean proportion of **genotype 1 was 79.9%** in the nine trials that reported the genotype.

Systematische Reviews

Wells G et al., 2016 [68]. **(Canadian Agency for Drugs and Technologies in Health (CADTH))** Drugs for Chronic Hepatitis C Infection: Clinical Review	**1. Fragestellung** The objective of this systematic review was to assess the comparative efficacy and safety of currently available and emerging regimens for the treatment of CHC infection (genotypes 1 to 6). Five research questions were developed to address the aforementioned policy issues: 1. What is the comparative efficacy and safety of treatment regimens for patients with CHC infection (genotypes 1 to 6) who are treatment-naive? 2. What is the comparative cost-effectiveness of treatment regimens for patients with CHC infection (genotypes 1 to 4) who are treatment-naive? 3. What is the comparative efficacy and safety of treatment regimens for patients with CHC infection (genotypes 1 to 6) who have relapsed or had a partial or null response to prior PR or DAA + PR or DAA-only therapy? 4. What is the comparative cost-effectiveness of treatment regimens for patients with CHC infection (genotypes 1 to 4) who have relapsed or had a partial or null response to prior PR or DAA + PR or DAA-only therapy? 5. For questions 1 to 4, how do the comparative efficacy, safety, and cost-effectiveness of treatment regimens vary across population subgroups based on fibrosis level (METAVIR score ≤ F1, F2, F3, or F4), cirrhosis stage (e.g., compensated versus decompensated), genotype subtype, post-liver transplant, baseline viral load, HIV and CHC coinfection, hepatitis B (HBV) and CHC coinfection, and tuberculosis (TB) and CHC coinfection? This Clinical Review Report addresses the questions related to comparative efficacy and safety. Questions related to cost-effectiveness are addressed in the accompanying Cost-Effectiveness Analysis Report.
	2. Methodik This report updates CADTH's previous Therapeutic Review report on DAA agents for CHC genotype 1 infection, published in October 2014, and expands the scope to include hepatitis C virus (HCV) genotypes 2 to 6, as well as recently approved and emerging regimens. The systematic review followed a protocol written a priori and vetted by clinical experts and methodologists. The review was conducted in line with the *Cochrane Handbook for Systematic Reviews of Interventions*. Population: CHC Intervention*:* Nicht präspezifiziert Komparator: Nicht präspezifiziert Endpunkte: The main efficacy outcome of interest was SVR at 12 or 24 weeks. Key safety outcomes were rash, depression, and anemia. Suchzeitraum (Aktualität der Recherche): Bis 04/2015

	Anzahl eingeschlossene Studien/Patienten (Gesamt): 67 (n=k.A.). Included studies predominantly reported on patients with CHC genotype 1 infection, or a mix of patients with genotype 1 and other genotypes. Eleven studies reported on patients with CHC genotype 2 infection, 11 on genotype 3, eight on genotype 4, two on genotype 5, and three on genotype 6. Qualitätsbewertung der Studien: Cochrane Risk of Bias
	3. Ergebnisdarstellung Separate analyses were performed for each genotype for SVR, and within each genotype, analyses were separated by subpopulations based on prior treatment experience with PR (with or without DAA) or DAA alone, as follows: • Treatment-naive • Treatment-experienced • Treatment-experienced with prior relapse • Treatment-experienced with prior partial response • Treatment-experienced with prior null response. Within each of these five subpopulations, analyses were further separated by the presence or absence of cirrhosis. The analyses for genotype 1 were further separated by genotype subtype (1a and 1b). Analysis of safety events was performed separately in treatment-naive and treatment-experienced patients; however, data were pooled across genotypes. The lack of head-to-head trials in this therapeutic area, combined with the use of single-arm cohort studies, made it difficult to compare the relative efficacy of the different treatment regimens. We performed a Bayesian NMA to assess the various treatment options for CHC infection. This method allowed for comparisons between regimens based on direct and indirect evidence. We made adjustments to conventional NMA methodology in order to incorporate the single-arm evidence. The single-arm studies were included in the NMA by creating a “virtual” study in which a comparator arm matched for patient characteristics was selected for each single arm incorporated into the analysis. Where the available studies for a particular genotype could not be assembled into an NMA due to the lack of a common reference treatment, supplemental literature searches were conducted to identify evidence from meta-analyses or key primary studies (including observational studies, if needed) for a clinically appropriate reference treatment that would allow construction of a network.

Exhibit 1: Genotype 1 Patients: Summary of the Results for SVR With Reference to Harvoni, HOLKIRA PAK, and Daclatasvir

Patient Population	Harvoni (SOF12 + LDV12) Significantly Improved SVR Compared With	HOLKIRA PAK (PAR/RIT12 + OMB12 + DAS12) Significantly Improved SVR Compared With	Daclatasvir (DCV24 + ASU24) Significantly Improved SVR Compared With
Treatment-Naive Patients			
All	PR48 SOF24 + RBV24 SOF12 + PR12 SIM12 + PR24-48 RGT DCV24 + ASU24	PR48 SIM12 + PR24-48 RGT (with RBV12) PR48 SOF24 + RBV24 SOF12 + PR12 SIM12 + PR24-48 RGT DCV24 + ASU24	PR48 SIM12 + PR24-48 RGT (for DCV12 + SOF12) PR48
Genotype 1a	PR48 SOF12 + PR12 SIM12 + PR24-48 RGT	(with RBV12) PR48 SOF12 + PR12	
Genotype 1b	PR48 SOF12 + PR12 SIM12 + PR24-48 RGT DCV24 + ASU24	PR48	PR48 SIM12 + PR24-48 RGT
Cirrhotic	PR48 SOF24 + RBV24 SIM12 + PR24-48 RGT		PR48
Non-cirrhotic	PR48 SOF24 + RBV24 SOF12 + PR12 SIM12 + PR24-48 RGT DCV24 + ASU24	PR48 (with RBV12) PR48 SOF24 + RBV24 SIM12 + PR24-48 RGT	PR48 SIM12 + PR24-48 RGT (for DCV12 + SOF12) PR48
Treatment-Experienced Patients			
All	PR48 SOF12 + PR12 SIM12 + PR24-48 RGT SIM12 + PR48 DCV24 + ASU24 (24 weeks) PR48	PR48 (with RBV12) PR48 SOF12 + PR12 SIM12 + PR24-48 RGT SIM12 + PR48 DCV24 + ASU24	PR48 SIM12 + PR48 (with PR24) PR48 SIM12 + PR48 SIM12 + PR24-48 RGT
Genotype 1a	PR48 SIM12 + PR24-48 RGT SIM12 + PR48 (24 weeks) PR48	(with RBV12) PR48 SIM12 + PR24-48 RGT SIM12 + PR48 SOF12 + PR12	(with PR24) PR48
Genotype 1b	PR48 (24 weeks) PR48	PR48 SIM12 + PR24-48 RGT	PR48 (with PR24) PR48 SOF12 + LDV12

Exhibit 1: Genotype 1 Patients: Summary of the Results for SVR With Reference to Harvoni, HOLKIRA PAK, and Daclatasvir

Patient Population	Harvoni (SOF12 + LDV12) Significantly Improved SVR Compared With	HOLKIRA PAK (PAR/RIT12 + OMB12 + DAS12) Significantly Improved SVR Compared With	Daclatasvir (DCV24 + ASU24) Significantly Improved SVR Compared With
			SOF24 + LDV24 SIM12 + PR24-48 RGT SIM12 + PR48 SOF12 + PR12 DCV24 + ASU24
Cirrhotic	PR48 (24 weeks) PR48		PR48 (with PR24) PR48 SIM12 + PR48
Non-Cirrhotic	PR48 SIM12 + PR24-48 RGT	PR48 SIM12 + PR24-48 RGT SIM12 + PR48 SOF12 + PR12 DCV24 + ASU24 SIM12 + SOF12 (with RBV12) PR48 SOF12 + LDV12 SIM12 + PR24-48 RGT SIM12 + PR48 SOF12 + PR12 DCV24 + ASU24 DCV24 + ASU24 + PR24 SIM12 + SOF12	PR48 (with PR24) PR48 SIM12 + PR24-48 RGT
Treatment-Experienced Patients With Prior Relapse			
All	PR48	PR48 SIM12 + PR24-48 RGT (with RBV12) PR48 SIM12 + PR24-48 RGT	
Genotype 1a		(with RBV12) PR48	
Genotype 1b			
Cirrhotic			
Non-cirrhotic		PR48 SIM12 + PR24-48 RGT (with RBV12) PR48 SIM12 + PR24-48 RGT	
Treatment-Experienced Patients With Prior Partial Response			
All		PR48	PR48

Exhibit 1: Genotype 1 Patients: Summary of the Results for SVR With Reference to Harvoni, HOLKIRA PAK, and Daclatasvir

Patient Population	Harvoni (SOF12 + LDV12) Significantly Improved SVR Compared With	HOLKIRA PAK (PAR/RIT12 + OMB12 + DAS12) Significantly Improved SVR Compared With	Daclatasvir (DCV24 + ASU24) Significantly Improved SVR Compared With
		(with RBV12) PR48 SIM12 + PR48	(with PR24) PR48
Genotype 1a		(with RBV12) PR48 SIM12 + PR48	
Genotype 1b			
Cirrhotic			
Non-cirrhotic		PR48 (with RBV12) PR48	
Treatment-Experienced Patients With Prior Null Response			
All		PR48 (with RBV12) PR48 SOF12 + PR12 SIM12 + PR48	PR48 SOF12 + PR12 (with PR24) PR48 SOF12 + PR12
Genotype 1a		(with RBV12) PR48 SIM12 + PR48 (24 weeks with RBV24) PR48 SIM12 + PR48	
Genotype 1b			
Cirrhotic			
Non-cirrhotic		PR48 SIM12 + PR48 (with RBV12) PR48 SIM12 + PR48	(with PR24) SIM12 + PR48

ASU = asunaprevir; DAS = dasabuvir; DCV = daclatasvir; LDV = ledipasvir; OMB = ombitasvir; PAR = paritaprevir; PR = pegylated interferon plus ribavirin; RBV = ribavirin; RGT = response-guided therapy; RIT = ritonavir; SIM = simeprevir; SOF = sofosbuvir; SVR = sustained virologic response.
Note: Please refer to Treatment Regimen Nomenclature table for description of dosages.

Exhibit 3: All Patients — Summary of the Results for Rash, Anemia, and Depression With Reference to Harvoni, HOLKIRA PAK, and Daclatasvir

Safety Event	Harvoni (SOF12 + LDV12) Significantly Associated With Fewer Events Compared With	HOLKIRA PAK (PAR/RIT12 + OMB12 + DAS12) Significantly Associated With Fewer Events Compared With	Daclatasvir (DCV24 + ASU24) Significantly Associated With Fewer Events Compared With
Treatment-Naive Patients — All Genotypes			
Rash	PR48 SOF12 + PR12 SIM12 + PR24-48 RGT PAR/RIT12 + OMB12 + DAS12 + RBV12	PR48 SOF12 + PR12 SIM12 + PR24-48 RGT PAR/RIT12 + OMB12 + DAS12 + RBV12	PR48 SOF12 + PR12 SIM12 + PR24-48 RGT PAR/RIT12 + OMB12 + DAS12 + RBV12
Anemia	PR48 SOF12 + PR12	PR48 SOF12 + PR12	(with DCV12 + SOF12) PR48

Exhibit 3: All Patients — Summary of the Results for Rash, Anemia, and Depression With Reference to Harvoni, HOLKIRA PAK, and Daclatasvir

Safety Event	Harvoni (SOF12 + LDV12) Significantly Associated With Fewer Events Compared With	HOLKIRA PAK (PAR/RIT12 + OMB12 + DAS12) Significantly Associated With Fewer Events Compared With	Daclatasvir (DCV24 + ASU24) Significantly Associated With Fewer Events Compared With
	SOF24 + RBV24 SIM12 + PR24-48 RGT PAR/RIT12 + OMB12 + DAS12 ± RBV12	SOF24 + RBV24 SIM12 + PR24-48 RGT (with RBV12) PR48 SOF12 + PR12	SOF12 + PR12 SOF24 + RBV24 SIM12 + PR24-48 RGT
Depression	PR48 SOF12 + PR12 SIM12 + PR24-48 RGT SOF24 + RBV24 DCV24 + ASU24 DCV12 + SOF12 PAR/RIT12 + OMB12 + DAS12 + RBV12		PR48
Treatment-Experienced Patients — All Genotypes			
Rash	PR48 SOF12 + PR12 SIM12 + PR24-48 RGT SOF24 + RBV24 DCV24 + ASU24 + PR24	PR48 SOF12 + PR12 SIM12 + PR24-48 RGT DCV24 + ASU24 +PR24 PAR/RIT12 + OMB12 + DAS12 + RBV12 (with RBV12) PR48 DCV24 + ASU24 + PR24	PR48 DCV24 + ASU24 + PR24 SOF12 + PR12
Anemia	PR48 SOF12 + PR12 SIM12 + PR24-48 RGT SOF24 + RBV24 DCV24 + ASU24 +PR24 PAR/RIT12 + OMB12 + DAS12 + RBV12	PR48 SOF12 + PR12 SIM12 + PR24-48 RGT SOF24 + RBV24 DCV24 + ASU24 +PR24 PAR/RIT12 + OMB12 + DAS12 + RBV12 (with RBV12) PR48 SOF12 + PR12	(with PR24) PR48 SOF12 + PR12
Depression		(with RBV12) PR48	PR48

ASU = asunaprevir; DAS = dasabuvir; DCV = daclatasvir; OMB = ombitasvir; PAR = paritaprevir; PR = pegylated interferon plus ribavirin; RBV = ribavirin; RGT = response-guided therapy; RIT = ritonavir; SIM = simeprevir; SOF = sofosbuvir; SVR = sustained virologic response.
Note: Please refer to Treatment Regimen Nomenclature table for description of dosages.

4. Anmerkungen/Fazit der Autoren

In terms of efficacy (as measured by SVR):

• For treatment-naive and -experienced patients with **genotype 1** infection, SOF + LDV, PAR/RIT + OMB + DAS and DCV were superior to PR-based treatments. SOF + LDV and PAR/RIT + OMB + DAS were better than DCV-based regimens in some patient subgroups. There was limited evidence for patients with cirrhosis.

• The data available for **genotype 2 to 4** were limited. For patients with genotype 2 infection, SOF12 + RBV12 significantly improved SVR rates over PR24 in treatment-naive patients, but SOF12 + PR12 did not. In treatment-experienced patients, neither SOF16 + RBV16 nor SOF12 + PR12 were significantly different from SOF12+ RBV12.

	RBV24, DCV12 + SOF12, and SOF12 + PR12 significantly improved SVR compared with PR48, and there were no significant differences between these regimens. • For **genotype 4** patients, DCV24 + ASU24 + PR24 and SOF12 + PR12 were superior to SOF12 + RBV12 in treatment-experienced and -naive patients, respectively. • The data for **genotype 5 and 6** infection were insufficient for analysis. • Data were limited for the evaluation of **patients with HIV coinfection**; however, SOF + LDV, PAR/RIT + OMB + DAS + RBV, and SOF24 + RBV24 significantly improved SVR compared with PR48 in treatment-naive patients with genotype 1 infection, and there was some indication that PAR/RIT + OMB + DAS + RBV is efficacious for treatment-experienced patients with genotype 1 infection and HIV coinfection. NMA could not be performed for patients infected with other genotypes and coinfected with HIV, although the following regimens demonstrated high rates of SVR in treatment-naive patients in individual trials: SOF12 + RBV12 in genotype 2; SOF24 + RBV24 in genotype 3; SOF24 + RBV24 and SOF12 + PR12 in genotype 4. There were no data for treatment-experienced patients with non-genotype 1 infection and HIV coinfection. • There were limited data to inform optimal **re-treatment of patients after failure to achieve SVR** on a previous DAA-based regimen. SOF12 + PR12, SOF + LDV ± RBV for 12 or 24 weeks, and SOF24 + RBV24 demonstrated high SVR rates in studies of patients with genotype 1 infection who had failed prior DAA-PR therapy. Preliminary evidence suggests that SOF12 + LDV12 may be associated with high SVR rates in patients with CHC genotype 1 infection previously treated unsuccessfully with SOF + RBV. • **No evidence** was available to allow analysis of efficacy for the following regimens: DCV24 + SOF24 for genotype 1 infection; DCV + ASU + PR for treatment-naive patients with genotype 1 infection; DCV12 + SOF12 for treatment-experienced patients with genotype 1 infection; DCV + SOF for genotype 2 infection; SOF12 + LDV12 + RBV12 and DCV24 + SOF24 ± RBV24 for genotype 3 infection regardless of treatment experience; SOF12 + LDV12 and DCV12 + ASU12 + PR12 for patients with genotype 4 infection; and SOF12 + PR12 for treatment-experienced patients with genotype 4 infection. **In terms of safety:** • Adverse events, fatigue, and pruritus were frequently reported across all treatments. • Withdrawals due to adverse events, mortality, and liver-related complications of CHC infection (e.g., HCC) were infrequently reported across all treatments.

	• For treatment-naive and -experienced patients, SOF + LDV, PAR/RIT + OMB + DAS and DCV-based regimens were associated with lower risks for rash and anemia than PR-based treatments, but only SOF + LDV and DCV-based regimens were associated with less depression compared with PR-based treatments. In particular, PAR/RIT + OMB + DAS with RBV was less favourable than SOF + LDV. • For treatment-experienced patients, SOF + LDV, PAR/RIT + OMB + DAS and DCV-based regimens were associated with less rash and anemia than PR-based treatments, but evidence was sparse for depression. For rash, DCV with PR was less favourable than SOF + LDV, PAR/RIT + OMB + DAS and DCV without PR. For anemia, PAR/RIT + OMB + DAS with RBV was less favourable than SOF + LDV and PAR/RIT + OMB + DAS without RBV.
Peng Q et al., 2016 [58]. Daclatasvir combined with peginterferon-α and ribavirin for the treatment of chronic hepatitis C: a meta-analysis	**1. Fragestellung** to quantitatively assess the efficacy and safety of daclatasvir combined with pegIFN-α and ribavirin in the treatment of CHC.
	2. Methodik Population: patients aged 18–70 years who had chronic HCV infection over 6 months with positive anti-HCV. Additional inclusion criteria included HCV-RNA ≥ 105 IU/ml. Meanwhile, serum urea nitrogen, creatinine and prothrombin activity were at normal levels. Intervention: daclatasvir in combination with peg-IFN/RBV Komparator: placebo in combination with peg-IFN/RBV Endpunkt: Nicht präspezifiziert Suchzeitraum (Aktualität der Recherche): k.A. („no year restriction“) Anzahl eingeschlossene Studien/Patienten (Gesamt): 6 (n= 926) Qualitätsbewertung der Studien: Jadad Score; trials were excluded if: (a) the study belonged to nonrandomized controlled trial (NRCT) or the Jadad score of RCTs was less than three points. Statistical heterogeneity between studies was examined using the I^2 value. I^2 ranges of 25–<50, 50–<75 and ≥75 % were considered to represent low, moderate, and high heterogeneity, respectively. If heterogeneity is low, we choose fixed-effects model, and if heterogeneity is moderate or high, we choose random-effects model.
	3. Ergebnisdarstellung Übersicht der Einzelstudien- vgl. Anhang 3

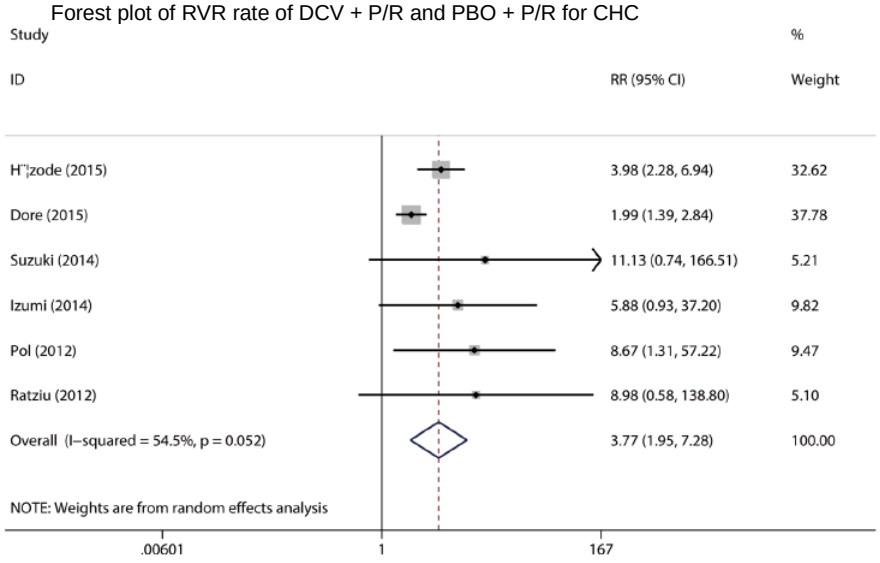
Table 2 Jadad score of clinical trials

Trial	Randomization	Double-blinding	Withdraw and drop out	Jadad score
Hézode et al. (2015)	Method of randomization was mentioned and it was appropriate (2)	Method of blinding was identical placebo (2)	There was a description of withdraws and drop outs (1)	5
Dore et al. (2015)	Method of randomization was mentioned and it was appropriate (2)	Method of blinding was identical placebo (2)	There was a description of withdraws and drop outs (1)	5
Suzuki et al. (2014)	Method of randomization was mentioned and it was appropriate (2)	Method of blinding was identical placebo (2)	There was a description of withdraws and drop outs (1)	5
Izumi et al. (2014)	Method of randomization was mentioned and it was appropriate (2)	Method of blinding was identical placebo (2)	There was a description of withdraws and drop outs (1)	5
Pol et al. (2012)	Method of randomization was mentioned but not described (1)	Method of blinding was identical placebo (2)	There was a description of withdraws and drop outs (1)	4
Ratziu et al. (2012)	Method of randomization was mentioned but not described (1)	Method of blinding was identical placebo (2)	There was a description of withdraws and drop outs (1)	4

Rapid virological response (RVR)

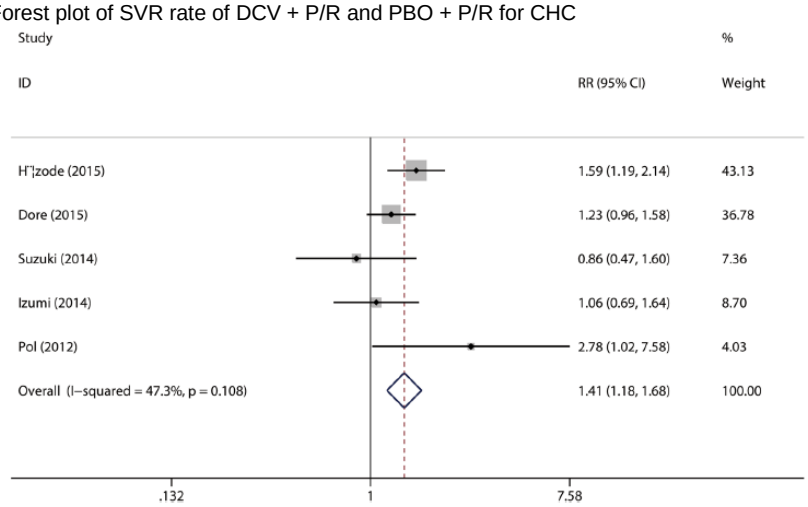
RVR was defined as an undetectable HCV-RNA level at 4 weeks after treatment initiation.

Forest plot of RVR rate of DCV + P/R and PBO + P/R for CHC



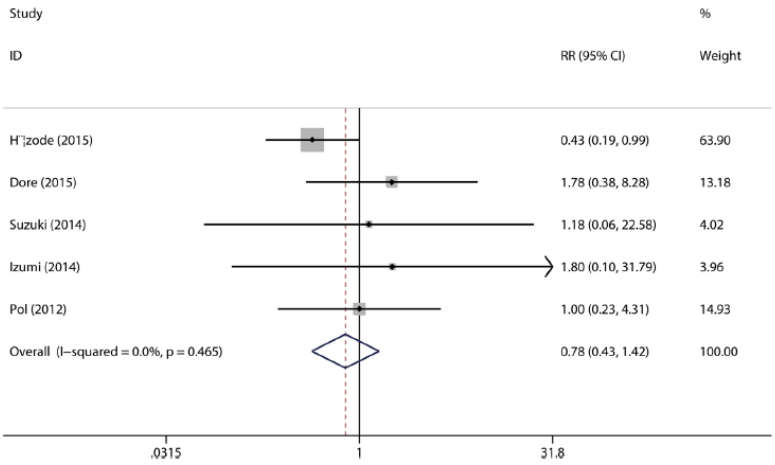
Sustained virological response at post-treatment week 24 (SVR_{24})

Forest plot of SVR rate of DCV + P/R and PBO + P/R for CHC

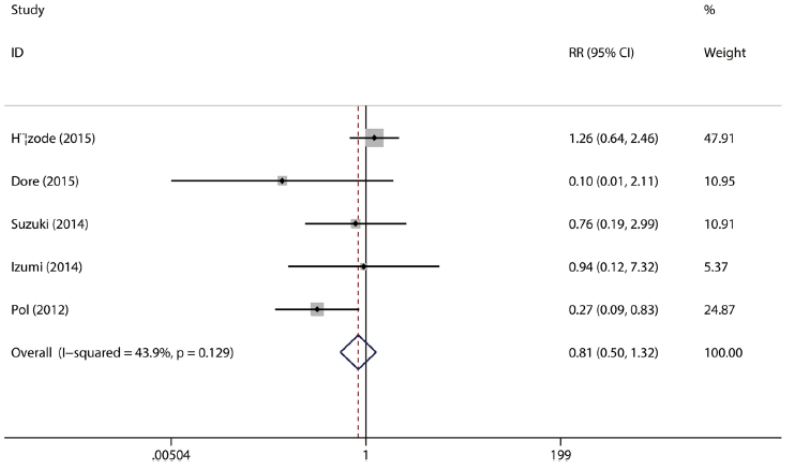


Treatment discontinuation due to an adverse event (TDAE)

Forest plot of TDAE rate of DCV + P/R and PBO + P/R for CHC



Forest plot of relapse rate of DCV + P/R and PBO + P/R for CHC



AEs

Table 3 Detailed adverse events of the included studies

Category	Concrete forms	Events/total (incidence rate, %)		RR (95 % CI)	*p* values
		DCV + P/R	PBO + P/R		
Nonspecific AEs	Fatigue	211 (49.76)	62 (58.49)	0.86 (0.72–1.03)	0.11
	Headache	184 (43.40)	48 (45.28)	0.96 (0.76–1.21)	0.73
	Insomnia	132 (31.13)	36 (33.96)	0.86 (0.64–1.14)	0.29
	Nausea	126 (32.31)	29 (29.59)	0.79 (0.37–1.68)	0.53
	Diarrhea	90 (23.20)	54 (57.45)	0.52 (0.20–1.36)	0.18
	Decreased appetite	104 (24.53)	26 (24.53)	0.99 (0.69–1.44)	0.98
	Cough	72 (18.60)	53 (54.08)	0.66 (0.18–2.37)	0.52
	Arthralgia	66 (17.01)	24 (25.53)	0.67 (0.44–1.01)	0.06
Liver dysfunction	Elevated ALT	9 (1.84)	1 (0.69)	1.51 (0.34–6.68)	0.59
	Elevated bilirubin	4 (0.82)	1 (0.69)	0.87 (0.19–4.07)	0.86
Hematologic abnormalities	Anemia	45 (8.59)	14 (8.92)	0.92 (0.53–1.59)	0.77
	Thrombocytopenia	12 (2.46)	6 (4.14)	0.63 (0.24–1.65)	0.34
	Neutropenia	139 (26.53)	46 (29.30)	0.89 (0.67–1.19)	0.44
Skin abnormalities	Rash	147 (28.05)	46 (29.30)	0.93 (0.71–1.23)	0.63
	Pruritus	179 (34.16)	49 (31.21)	1.06 (0.81–1.38)	0.67
	Alopecia	116 (27.36)	23 (21.70)	1.06 (0.50–2.24)	0.88

AE adverse event, *DCV* daclatasvir, *P* pegylated interferon-α, *R* ribavirin, *PBO* placebo

4. Anmerkungen/Fazit der Autoren

Daclatasvir combined with pegIFN-α/RBV is effective and safe in treating adult patients with CHC, especially HCV genotype 1 infection, and daclatasvir (60 mg/day) is a better choice as compared with daclatasvir (10 mg/day).

5. Hinweise durch FB Med

	• Keine Auswertung mit Genotypen • Keine Angaben zur Vorbehandlung

Genotyp 1

Borba HH et al., 2016 [5]. Network meta-analysis of first- and second-generation protease inhibitors for chronic hepatitis C genotype 1: efficacy based on RVR and SVR 24	**1. Fragestellung** This study aimed to compare the efficacy among direct-acting antiviral agents (first and second-generation direct-acting antiviral agents (DAAs)) with placebo and with standard dual therapy (pegylated interferon + ribavirin (Peg- IFN + RBV)) in terms of rapid virologic response (RVR) and sustained virologic response (SVR) in chronic hepatitis C genotype 1 treatment.
	2. Methodik Population: treatment-naive and treatment-experienced patients chronically infected with HCV genotype 1 Intervention / Komparator: nicht präspezifiziert Endpunkte: nicht präspezifiziert Suchzeitraum (Aktualität der Recherche): bis 04/2016 Anzahl eingeschlossene Studien/Patienten (Gesamt): x (n=dddd); RCTs Qualitätsbewertung der Studien The studies included in the meta-analysis had acceptable methodological quality (Jadad score ≥ 3), except for one study with score of 2. It was not clear whether the study was performe as a double-blind trial. Regarding the risk of bias, all included studies were considered as low risk, except for the itemb „Free of other bias," because almost all of them were supported by pharmaceutical companies.
	3. Ergebnisdarstellung Meta-analyses were conducted using ADDIS 1.16.5 software (Aggregate Data Drug Information System, http://drugis.org/addis) Übersicht über die Primärstudien – vgl. Anhang 6 **RVR (13 Studien)**

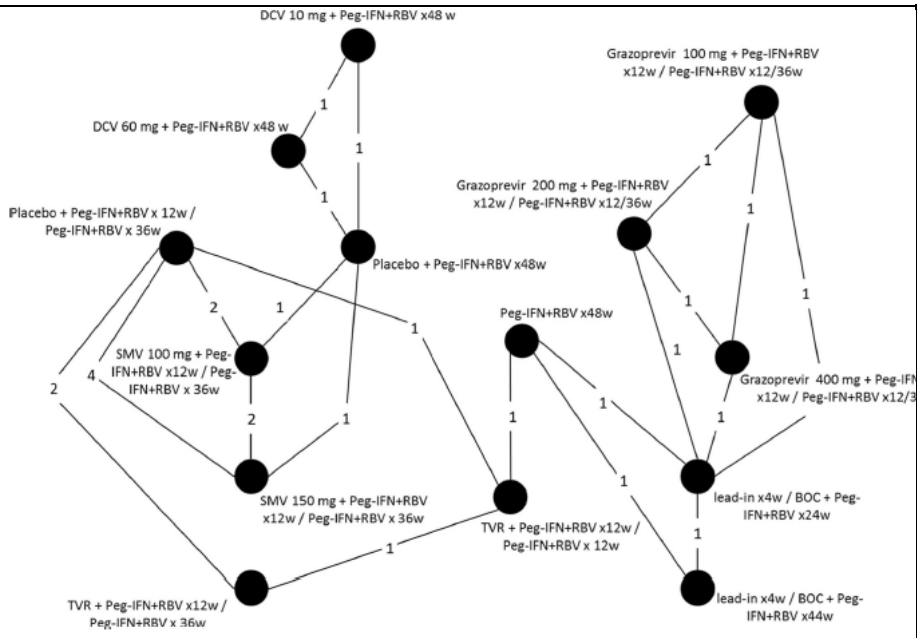


Fig. 1 RVR network. *BOC* boceprevir, *DCV* daclatasvir, *TVR* telaprevir, *SMV* simeprevir, *Peg-IFN* pegylated interferon, *RBV* ribavirin, *w* weeks. Each *node* corresponds to a treatment regimen. *Lines* indicate direct comparisons between nodes. The *numbers along the line* specif number of studies included in each direct comparison

Statistically significant favourable results were obtained for the regimens with DCV (10 mg), and for all the evaluated dosages of grazoprevir, SMV, TVR and BOC versus therapies with placebo or standard dual therapy (Peg-IFN + RBV ×48w; Placebo + Peg-IFN + RBV ×12w/Peg-IFN + RBV ×36w; Placebo + Peg-IFN + RBV ×48w). The ranking of the treatments regarding RVR is presented in Table 2. The most efficacious treatment in terms of RVR was DCV 10 mg + Peg-IFN + RBV ×48 w, whereas the least efficacious treatment was Placebo + Peg-IFN + RBV ×48w.

Table 2 Rank probability of the treatments for RVR. The best treatment is ranked first

Drug	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5	Rank 6	Rank 7	Rank 8	Rank 9	Rank 10	Rank 11	Rank 12	Rank 13	Rank 14
DCV 10 mg + Peg–IFN + RBV × 48 w	*0.37*	0.09	0.04	0.04	0.04	0.04	0.04	0.13	0.07	0.08	0.05	0.02	0.01	0
Grazoprevir 200 mg + Peg–IFN + RBV × 12 w/Peg–IFN + RBV × 12 w	0.18	*0.21*	0.13	0.08	0.07	0.08	0.12	0.09	0.03	0	0	0	0	0
SMV 100 mg + Peg–IFN + RBV × 12 w/Peg–IFN + RBV × 36 w	0.1	0.14	*0.19*	0.18	0.15	0.11	0.06	0.03	0.02	0	0	0	0	0
SMV 150 mg + Peg–IFN + RBV × 12 w/Peg–IFN + RBV × 36 w	0.03	0.1	0.16	*0.2*	0.18	0.16	0.1	0.05	0.01	0.01	0	0	0	0
TVR + Peg–IFN + RBV × 12 w/Peg–IFN + RBV × 12 w	0.03	0.05	0.12	0.15	*0.19*	0.19	0.13	0.09	0.06	0.01	0	0	0	0
TVR + Peg–IFN + RBV × 12 w/Peg–IFN + RBV × 36 w	0.01	0.01	0.05	0.1	0.16	*0.18*	0.22	0.15	0.09	0.02	0.01	0	0	0
Grazoprevir 400 mg + Peg–IFN + RBV × 12 w/Peg–IFN + RBV × 12 w	0.01	0.04	0.12	0.1	0.08	0.08	*0.15*	0.15	0.24	0.02	0.01	0	0	0
Grazoprevir 100 mg + Peg–IFN + RBV × 12 w/Peg–IFN + RBV × 12 w	0.19	0.17	0.15	0.09	0.08	0.08	0.1	*0.1*	0.03	0	0	0	0	0
lead–in 4w /BOC + Peg –IFN + RBV × 44 w	0	0	0	0.01	0.01	0.01	0.02	0.07	*0.15*	0.35	0.34	0.03	0.01	0
lead–in 4w/BOC + Peg–IFN + RBV × 24 w	0	0	0	0.01	0.01	0.01	0.01	0.07	0.15	*0.37*	0.31	0.04	0.01	0
DCV 60 mg + Peg–IFN + RBV × 48 w	0.09	0.18	0.04	0.05	0.04	0.06	0.05	0.07	0.12	0.07	*0.18*	0.03	0.02	0
Placebo + Peg–IFN + RBV × 12 w/Peg–IFN + RBV × 36 w	0	0	0	0	0	0	0	0	0.01	0.06	0.07	*0.75*	0.1	0
Peg–IFN + RBV × 48 w	0	0	0	0	0	0	0	0	0	0	0.01	0.06	*0.44*	0.49
Placebo + Peg–IFN + RBV × 48 w	0	0	0	0	0	0	0	0	0	0	0.01	0.06	0.41	*0.51*

Peg-IFN pegylated interferon, *RBV* ribavirin, *BOC* boceprevir, *DCV* daclatasvir, *TVR* telaprevir, *SMV* simeprevir, *w* weeks

SVR24

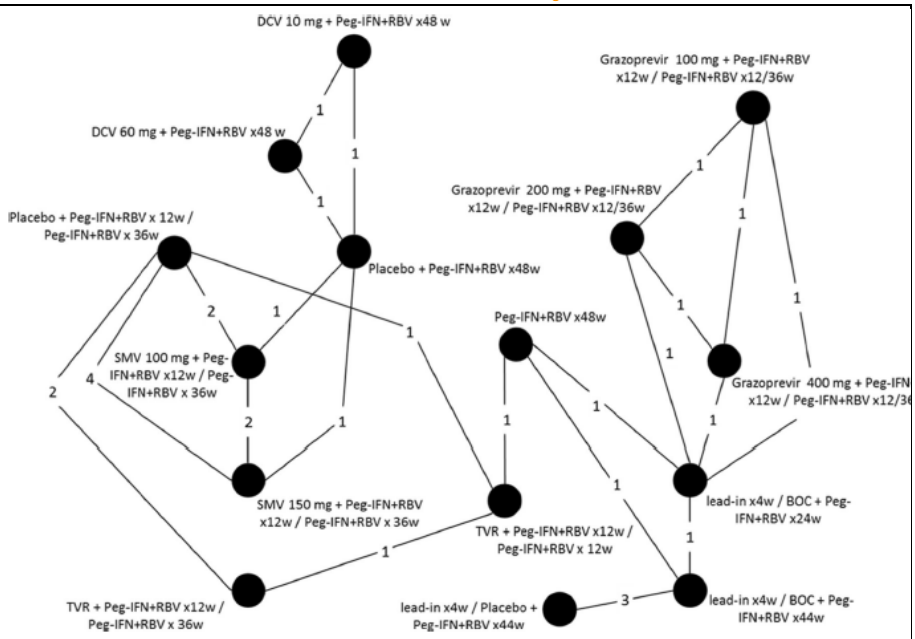


Fig. 2 SVR 24 network. *BOC* boceprevir, *DCV* daclatasvir, *TVR* telaprevir, *SMV* simeprevir, *Peg-IFN* pegylated interferon, *RBV* ribavirin, *w* weeks. Each *node* corresponds to a treatment regimen. *Lines* indicate direct comparisons between nodes. The *numbers* on the line specify the number of studies included in each direct compa

The network regarding SVR 24 as a treatment outcome is presented in Fig. 2. The analysis of this outcome involved 15 studies that reported data on SVR 24 rates [23, 25–33, 35–39]. The results of this meta-analysis are exhibited in Table 3. Statistically significant differences favouring the treatments with SMV (both evaluated regimens) and BOC (lead-in ×4w/BOC +Peg-IFN + RBV ×44w) versus placebo (Placebo + Peg-IFN +RBV x12w/Peg-IFN + RBV x36w; Placebo + Peg-IFN + RBV ×48 w and lead-in ×4w/Placebo + Peg-IFN + RBV ×44w) were observed. The ranking of the treatments regarding SVR 24 ispresented in Table 4. The most efficacious treatment regarding SVR 24 in the present meta-analysis was DCV 10 mg + Peg- IFN + RBV ×48 w, whereas the least efficacious was lead-in x4 w/Placebo + Peg-IFN + RBV x44 w.

The benefit-risk analysis included the most common safety outcomes reported by the clinical trials (anaemia, neutropenia, rash and pruritus). Daclatasvir stood out when compared tothe other appraised DAA regimens, with the best result in the rank acceptability. The regimen with telaprevir provided the worst result in terms of benefit-risk.

Table 4 Rank probability of the treatments for SVR 24. The best treatment is ranked first

Drug	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5	Rank 6	Rank 7	Rank 8	Rank 9	Rank 10	Rank 11	Rank 12	Rank 13	Rank 14	Rank 15
DCV 10 mg + Peg–IFN + RBV × 48 w	**0.25**	0.19	0.09	0.09	0.08	0.06	0.05	0.04	0.04	0.03	0.02	0.02	0.02	0.02	0.01
DCV 60 mg + Peg–IFN + RBV × 48 w	0.24	**0.19**	0.09	0.1	0.08	0.06	0.05	0.04	0.04	0.03	0.02	0.02	0.02	0.02	0.01
Grazoprevir 100 mg + Peg–IFN + RBV × 12 w/Peg–IFN + RBV × 12 w	0.09	0.13	**0.17**	0.12	0.11	0.08	0.07	0.06	0.05	0.04	0.03	0.02	0.01	0.01	0.01
Grazoprevir 200 mg + Peg–IFN + RBV × 12 w/Peg–IFN + RBV × 12 w	0.21	0.18	**0.17**	0.11	0.08	0.06	0.05	0.04	0.03	0.03	0.02	0.01	0.01	0	0
Grazoprevir 400 mg + Peg–IFN + RBV × 12 w/Peg–IFN + RBV × 12 w	0.14	0.17	**0.16**	0.12	0.09	0.07	0.07	0.05	0.04	0.03	0.02	0.02	0.01	0.01	0
SMV 150 mg + Peg–IFN + RBV × 12 w/Peg–IFN + RBV × 36 w	0.03	0.06	0.13	0.14	0.13	**0.15**	0.12	0.09	0.06	0.04	0.03	0.01	0.01	0	0
SMV 100 mg + Peg–IFN + RBV × 12 w/Peg–IFN + RBV × 36 w	0.02	0.04	0.09	0.12	0.12	0.12	**0.13**	0.11	0.09	0.07	0.05	0.04	0.02	0	0
TVR + Peg–IFN + RBV × 12 w/Peg–IFN + RBV × 36 w	0.01	0.01	0.03	0.05	0.09	0.1	0.11	**0.14**	0.14	0.12	0.09	0.06	0.05	0.02	0
TVR + Peg–IFN + RBV × 12 w/Peg–IFN + RBV × 12 w	0	0	0.01	0.02	0.04	0.06	0.09	0.12	**0.15**	0.17	0.15	0.1	0.06	0.03	0.01
lead–in 4 w/BOC + Peg–IFN + RBV × 44 w	0.02	0.03	0.05	0.1	0.1	0.11	0.1	0.1	0.11	**0.09**	0.06	0.06	0.03	0.01	0
lead–in 4 w/BOC + Peg–IFN + RBV × 24 w	0	0	0	0.03	0.05	0.06	0.06	0.08	0.09	**0.11**	0.13	0.12	0.14	0.09	0.04
Placebo + Peg–IFN + RBV × 12 w/Peg–IFN + RBV × 36 w	0	0	0	0	0	0.01	0.03	0.03	0.05	0.07	0.12	**0.15**	0.17	0.23	0.13
Peg –IFN + RBV × 48 w	0	0	0	0	0.01	0.01	0.02	0.03	0.04	0.05	0.09	**0.15**	0.2	0.24	0.17
Placebo + Peg–IFN + RBV × 48 w	0	0	0	0.01	0.01	0.02	0.03	0.04	0.05	0.06	0.08	0.1	0.12	**0.17**	0.31
lead–in × 4 w/Placebo + Peg–IFN + RBV × 44 w	0	0	0	0.01	0.01	0.03	0.03	0.04	0.04	0.06	0.08	0.11	0.13	0.16	**0.31**

Therapies with the highest probability for each rank order are highlighted in the table

Peg-IFN pegylated interferon, *RBV* ribavirin, *BOC* boceprevir, *DCV* daclatasvir, *TVR* telaprevir, *SMV* simeprevir, *w* weeks

4. Anmerkungen/Fazit der Autoren

The superiority of DAAs over placebo or standard dual therapy with Peg-IFN + RBV was confirmed, indicating the greater efficacy of DCV. This study is the first network meta-analysis that included RVR as an outcome in the evaluation of these agents via indirect comparison. Further investigation should be carried out addressing safety and tolerability outcomes.

Through a robust network meta-analysis, we confirmed thesuperiority of DAAs over placebo and standard dual therapy, as well as the greater efficacy and benefit-risk of daclatasvir in comparison with other DAAs and standard dual therapy with Peg-IFN + RBV. This study is the third network meta-analysis evaluating the efficacy of first- and second-generation DAAs in association with Peg-IFN + RBV but the first that included RVR as a treatment outcome in a comparison of these agents.

The results of the present network meta-analysis highlight the need for further investigation regarding these antiviral agents, including regimens with grazoprevir and boceprevir, which exhibited similar results regarding SVR 24. Considering the superiority of DAAs over placebo/standard therapy in terms of efficacy, future research should include evaluation of the safety and tolerability of these treatments through a metaanalysis approach, as well as observational studies to evaluate their effectiveness.

Ferreira VL et al., 2016 [17].

Ledipasvir/sofosbuvir with or without ribavirin for the treatment of chronic hepatitis C genotype 1: a pairwise meta-analysis

1. Fragestellung

Ledipasvir with sofosbuvir (LED/SOF) for the treatment of patients infected with genotype 1 hepatitis C virus (HCV) can be used with or without ribavirin (RBV). RBV is well known to promote significant adverse events (AE). The aim of this study was to compare the efficacy and safety of treatment with LED/SOF, with or without RBV, in patients infected with HCV genotype 1.

2. Methodik

Population: patients infected with HCV genotype 1, with or without cirrhosis but without comorbidities. Patients could have received previous treatment or be treatment-naïve.

Intervention/ Komparator: LED/SOF without or with ribavirin (LED/SOF versus LED/SOF + RBV)

Endpunkte:
Efficacy outcomes: SVR12 (primary outcome), SVR4, RVR and viral relapse;
Safety outcomes: any AE, serious AE, discontinuation due to AE and anemia, rash and other mentioned side effects.

Suchzeitraum (Aktualität der Recherche): k.A.

Anzahl eingeschlossene Studien/Patienten (Gesamt): x (n=dddd), nur RCT

Qualitätsbewertung der Studien: Jadad Score

3. Ergebnisdarstellung

Table 1. Characteristics of included studies

Author, year (reference number)	Therapy	Treatment duration (weeks)	Jadad score	Study Location	Population	Male	Mean age (years)	Cirrhotic (%)	TE (%)
Afdhal, 2014 [18]	LED/SOF	12 or 24	2	United States	218	68%	56	20%	100%
	LED/SOF + RBV				222	63%	56	20%	100%
Afdhal, 2014b [19]	LED/SOF	12 or 24	2	> 2 countries	431	62%	52.5	15%	0%
	LED/SOF + RBV				434	57%	52.5	16%	0%
Bourliere, 2015 [13]	LED/SOF	24	5	France	78	72%	56	100%	100%
	LED/SOF + RBV	12			77	75%	57	100%	100%
Gane, 2014 [20]	LED/SOF	12	3	New Zealand	10	100%	61	100%	100%
	LED/SOF + RBV	12			9	89%	57	100%	100%
Lawitz, 2014 [11]	LED/SOF	8 or 12	3	United States	58	69%	49.3	19%	32%
	LED/SOF + RBV				42	62%	51	26%	50%
Mizokami, 2015 [12]	LED/SOF	12	3	Japan	171	40%	60	24%	51%
	LED/SOF + RBV				170	43%	59	21%	51%
Kowdley, 2014 [21]	LED/SOF	8 or 12	2	United States	431	60%	53	0%	0%
	LED/SOF + RBV	8			216	54%	51	0%	0%

Abbreviations: LED, ledipasvir; SOF, sofosbuvir; RBV, ribavirin; TE, treatment experienced.

<u>Qualität der Primärstudien:</u>

Overall, the quality assessment showed a moderate quality resulting in a mean Jadad score of 2.85 (range from 2 to 5). All studies scored

at least for randomization and properly reported exclusions and dropouts, but almost all failed for double blind request.

As most of the RCTs were open label studies (6 of 7), there was a high risk of bias in assessing participants and in personnel and outcome blinding, according to the Cochrane Tool to evaluate bias risk (Supporting information 3).

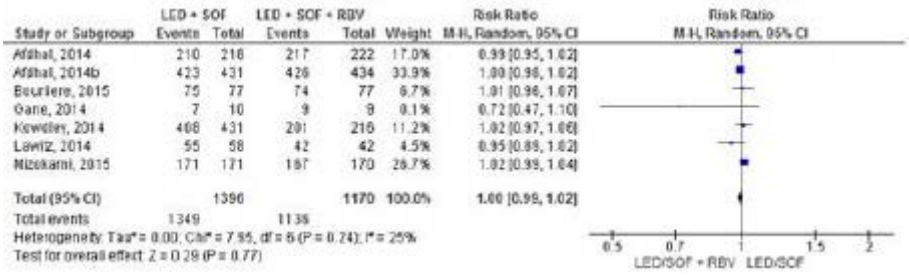
Additionally, all the included RCTs were sponsored by pharmaceutical companies, which contributed to another risk of bias. Due to the lack of information regarding allocation concealment, all studies were classified as “unclear risk” of bias for this topic. The following other items often presented low risk of bias: random sequence generation, incomplete outcome data and free of selective reporting.

Table 2. Meta-analyses of LED/SOF versus LED/SOF + RBV.

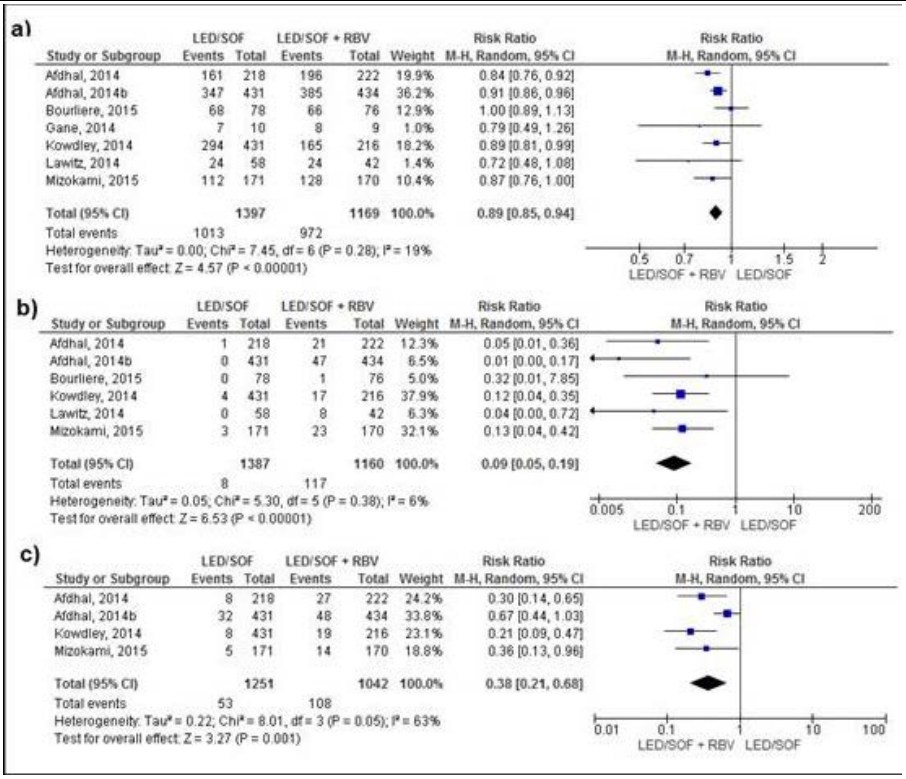
Outcome	Participants	Effect Estimate (LED/SOF vs. LED/SOF + RBV)	p-value	I^2
RVR	2,560	1.00 [95% CI 1.00-1.01]	0.89	0%
SVR4	2,566	1.00 [95% CI 0.99-1.02]	0.68	0%
Viral Relapse	2,566	1.12 [95% CI 0.62-2.01]	0.51	0%
Serious AE	2,566	1.57 [95% CI 0.96-2.54]	0.73	0%

Note: Seven studies were included for all outcome meta-analysis [11-13, 18-21].

Forest plot for the outcome of efficacy (SVR12) for LED/SOF versus LED/SOF + RBV treatment.



Safety of LED/SOF versus LED/SOF + RBV treatment, (a) any adverse event, (b) anemia and (c) rash

	
	4. Anmerkungen/Fazit der Autoren In conclusion, our meta-analysis showed no benefit, in terms of efficacy, of the addition of RBV to LED/SOF (12 weeks) treatment for HCV genotype 1 treatment-naïve patients, with or without cirrhosis, or treatment-experienced patients without cirrhosis. The results of subgroup analysis involving only cirrhotic patients (SVR12) showed similar efficacy profiles, indicating that the use of RBV does not enhance treatment efficacy in this group of patients. The results of SVR12 regarding treatment-experienced patients with compensated cirrhosis were inconclusive due to the small number of patients in this analysis. However, based on the discrepancies between the results of individual trials, this topic should be more thoroughly investigated in the future. In all analyses, the combination of LED/SOF with RBV presented a lower safety profile when compared to the same treatment without RBV. Risk-benefits and cost-analysis concerning the use of LED/SOF combined with RBV should be considered for patients infected with HCV genotype 1.
Gimeno-Ballester V et al., 2016 [28]. Sofosbuvir plus simeprevir for the treatment of	**1. Fragestellung** A systematic review of the literature was conducted to evaluate the available evidence about SOF/SIM combinations for both clinical trials and observational studies.
	2. Methodik

genotype 1 chronic hepatitis C: a review of evidence	Population: genotype 1 hepatitis C patients; all kinds of subpopulations were considered (naïve and pretreated, cirrhotic and non-cirrhotic, transplant, and coinfected). Intervention / Komparator: SOF/SIM ± RBV Endpunkt: only studies that reported effectiveness in terms of SVR12 were included Suchzeitraum (Aktualität der Recherche): 01/2011 – 04/2016 Anzahl eingeschlossene Studien/Patienten (Gesamt): 19 (n= 5766); 4 clinical trials, 6 observational studies Qualitätsbewertung der Studien: Consolidated Standards of Reporting Trials (CONSORT); Cochrane Collaboration tool
	3. Ergebnisdarstellung -Übersicht zu den Einzelstudien: vgl. Anhang 5 Clinical trials Four clinical trials were identified: one phase II clinical trial (COSMOS) [14], two phase III clinical trials (OPTIMIST 1 and 2) [31,33], and one clinical trial performed by independent researchers [32]. The COSMOS clinical trial analyzed the use of SOF/SIM ± RBV for both 12 and 24 weeks. The overall SVR was 92% overall, varying slightly by fibrosis stage (non-cirrhotic patients: 90%; cirrhotic patients: 94%) and by the presence of Q80K baseline polymorphism (positive: 88%; negative: 94%). Using RBV and prolonging the treatment to 24 weeks did not significantly increase the effectiveness of the treatment. During treatment, no patient experienced virologic failure, defined as either a confirmed and quantifiable HCV RNA increase after previously being below the lower limit of quantification or a confirmed increase in HCV RNA of greater than 1 log 10 from the lowest level on two consecutive occasions up to the end of the treatment. Five of the six relapsed patients had developed mutations associated with resistance to SIM. The OPTIMIST-1 clinical trial assessed the efficacy and safety of SOF/SIM in non-cirrhotic patients. A total of 310 patients were randomized to receive treatment for 8 or 12 weeks, and the results were compared with a historical cohort. SVR rates were 97% in patients treated for 12 weeks and 83% in patients treated for 8 weeks. A subgroup analysis showed that SVR in genotype 1a patients who had been treated for 8 weeks (79%) was significantly lower than the SVR for patients who had been treated for 12 weeks

	(97%), mainly due to the high rate of relapse (17% for the 8-week treatment compared to 3% for the 12-week treatment). Patients with Q80K polymorphism had lower SVR rates than those without it (73% vs. 92%) The OPTIMIST-2 clinical trial focused on a cirrhotic population of 103 patients, who were treated with SOF/SIM for 12 weeks. SVR was achieved in 83% of patients, and no difference was seen between patients with genotypes 1a and 1b (83% vs. 84%). The probability of achieving SVR decreased in genotype 1a patients who had the Q80K polymorphism at baseline (74%, compared to 92% for those without the polymorphism). One of the major predictors of response was the baseline serum albumin concentration, as patients with figures above 40 g/l showed higher SVR rates (94%) than did patients with levels below this limit (74%). Most relapses were related to SIM, and no mutations were associated with SOF. The Pearlman et al. clinical trial [32] compared the effectiveness of SOF/SIM to that of pIFN/RBV/SOF in Child–Pugh A cirrhotic patients over 12 weeks of treatment. The SVR obtained for SOF/SIM combination (93%) was higher than that achieved for pIFN/RBV/SOF (75%), and this was shown to be statistically significant. This clinical trial included 'healthrelated quality of life' measurements using the Chronic Liver Disease Questionnaire – HCV Version. Although quality of life decreased during the study for both groups, the disutility was higher for the pIFN/RBV/SOF group.
	4. Anmerkungen/Fazit der Autoren The SVR ranged from 67% to 100% depending on the patients' viral subtype and cirrhosis status. Adverse effects were common, but treatment discontinuation related to drug toxicity occurred in less than 5% of cases. Expert commentary: The SOF/SIM combination exhibits efficacy and tolerability profiles that are similar to those of the other available interferon-free combinations used for non-cirrhotic genotype 1b patients. Meanwhile, for patients with advanced cirrhosis or genotype 1a, this approach cannot be considered a routine treatment option due to the unsatisfactory results. **5. Hinweise durch FB Med** • Ergebnisse hier nur für klinische Studien extrahiert
He Q-F et al., 2016 [33]. Efficacy and Safety of Ribavirin with	**1. Fragestellung** Sofosbuvir and ledipasvir with or without ribavirin (RBV) regimens (SLR vs. SL) have exhibited promising results for the treatment of patients with hepatitis C virus (HCV) genotype 1 infection. Aim:To

Sofosbuvir Plus Ledipasvir in Patients with Genotype 1 Hepatitis C: A Meta-Analysis	comprehensively compare the efficacy and safety of the SL and SLR regimen for the treatment of chronic HCV genotype 1 infections.

2. Methodik

Population: patients with genotype 1 HCV infections

Intervention: triple therapy (SLR)

Komparator: dual therapy (SL)

Endpunkt: sustained virological response weeks 12 after the end of treatment (SVR12);AEs. The secondary outcomes were as follows: (1) virological relapse (post-treatment HCV RNA concentrations [25 IU/mL at any time during follow-up after a serum HCV RNA \25 IU/mL was recorded at the end of treatment); (2) treatment discontinuation due to the adverse events; and (3) five main AEs (nausea, headache, insomnia, fatigue, and anemia).

Suchzeitraum (Aktualität der Recherche): 01/2015 – 03/2016

Anzahl eingeschlossene Studien/Patienten (Gesamt): 7 (2601)

Qualitätsbewertung der Studien: Jadad score

3. Ergebnisdarstellung

Table 1 Main characteristics of the studies and patients enrolled in this meta-analysis

Author	Year	Country	Study design	No. of patients	Age (year)	Male (%)	White race (%)	BMI (kg/m^2)	HCV RNA (log10 IU/ml)
Eric et al. [24]	2014	America	RCT	42/58	51.0 ± 10.4/ 49.0 ± 10.3	56.5/ 70.0	95.2/87.9	30.7 ± 6.4/ 29.4 ± 6.0	6.1 ± 0.6/ 6.2 ± 0.7
Edward et al. [25]	2014	New Zealand	RCT	43/10	49.0 ± 10.6/ 61.0 ± 4.9	53.5/ 100.0	95.0/80.0	25.1 ± 4.1/ 31.0 ± 6.8	6.2 ± 0.9/ 6.5 ± 0.6
Kris et al. [26]	2014	America	RCT	216/431	51.0 ± 8.3/ 53.0 ± 8.6	54.2/ 62.5	81.5/62.9	28.0 ± 6.3/ 28.0 ± 4.2	6.4 ± 0.7/ 6.5 ± 0.8
Nezam et al. [27]	2014	France	RCT	434/431	53.0 ± 9.4/ 53.0 ± 9.6	56.9/ 61.7	85.5/84.5	27.0 ± 4.6/ 27.0 ± 4.5	6.4 ± 0.7/ 6.3 ± 0.7
Nezam et al. [28]	2014	America	RCT	222/218	54.0 ± 7.6/ 56.0 ± 7.2	62.6/ 67.9	82.4/80.3	28.0 ± 4.3/ 28.0 ± 4.2	6.5 ± 0.6/ 6.5 ± 0.5
Marc et al. [29]	2015	France	RCT	77/78	56.0 ± 7.4/ 57.0 ± 10.7	75.3/ 71.8	98.7/96.2	27.9 ± 5.5/ 26.3 ± 4.2	6.5 ± 0.5/ 6.5 ± 0.6
Masashi et al. [30]	2015	Japan	RCT	170/171	59.0 ± 9.5/ 60.0 ± 9.2	42.7/ 40.4	NA	23.3 ± 3.1/ 23.3 ± 3.6	6.6 ± 0.5/ 6.6 ± 0.5

Author	Year	Country	SLR drug dosage (mg/day)	Duration of treatment (weeks)
Eric et al. [24]	2014	America	SOF + LDV + RBV1000 (weight < 75 kg)/1200 mg (weight ≥ 75 kg)	8
Edward et al. [25]	2014	New Zealand	SOF + LDV + RBV1000 (weight < 75 kg)/1200 mg (weight ≥ 75 kg)	12
Kris et al. [26]	2014	America	SOF + LDV + RBV1000 (weight < 75 kg)/1200 mg (weight ≥ 75 kg)	8–12
Nezam et al. [27]	2014	France	SOF + LDV + RBV1000 (weight <75 kg)/1200 mg (weight ≥ 75 kg)	12–24
Nezam et al. [28]	2014	America	SOF + LDV + RBV1000 (weight < 75 kg)/1200 mg (weight ≥ 75 kg)	12–24
Marc et al. [29]	2015	France	SOF + LDV + RBV1000 (weight < 75 kg)/1200 mg (weight ≥ 75 kg)	12–24
Masashi et al. [30]	2015	Japan	SOF + LDV + RBV600 (weight ≤ 60 kg) SOF + LDV + RBV800 (60 kg < weight ≤ 80 kg) SOF + LDV + RBV1000 (weight > 80 kg)	12

SLR = SOF + LDV + RBV; SL = SOF + LDV. Values denote patients in the SLR group (before slash) and those in the SL group (after slash). Values of age, BMI, and HCV RNA presented as means. The drug dosage for SOF, 400 mg/day; and for LDV, 90 mg/day in SL and SLR regimen

NA not available, *BMI* body mass index

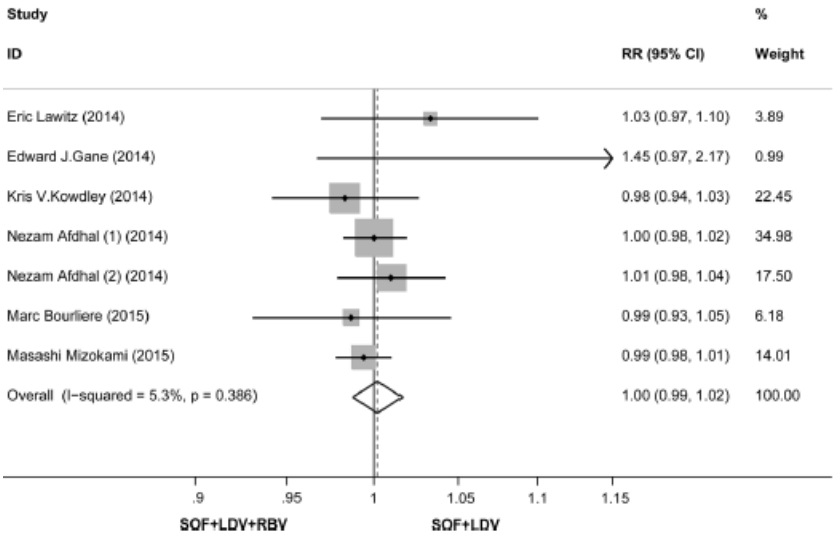
Table 2 Assessment of the quality of the studies included in the meta-analysis

Author	Year	Randomization			Allocation concealment			Blinding method			Withdrawals		Total score
		A	Un	In	A	Un	In	A	Un	In	Description	Undescribed	
Eric et al. [24]	2014	Yes			Yes			Yes			Yes		7
Edward et al. [25]	2014	Yes			Yes			Yes			Yes		7
Kris et al. [26]	2014		Yes		Yes			Yes				Yes	5
Nezam et al. [27]	2014		Yes		Yes			Yes				Yes	5
Nezam et al. [28]	2014		Yes		Yes			Yes			Yes		6
Marc et al. [29]	2015	Yes			Yes			Yes			Yes		7
Masashi et al. [30]	2015	Yes			Yes			Yes			Yes		7

In the randomization, allocation concealment and blinding method, if the method adequate = 2 scores, unclear = 1 score and inadequate = 0 score

A adequate, *Un* unclear, *In* inadequate

SVR12 in the SL and SLR Groups

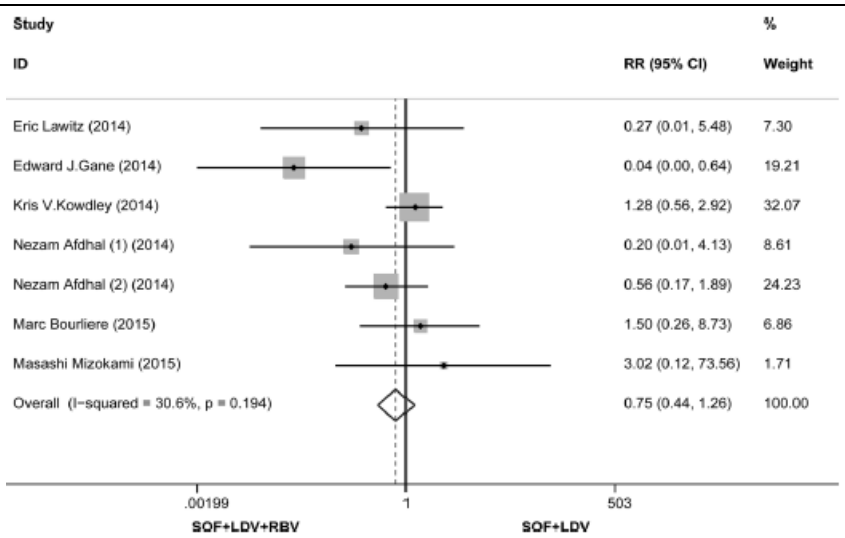


Subgroup analyses evaluating the difference in SVR12 based on treatment history, the presence or absence of cirrhosis, and duration of treatment in patients with HCV genotype 1 infection

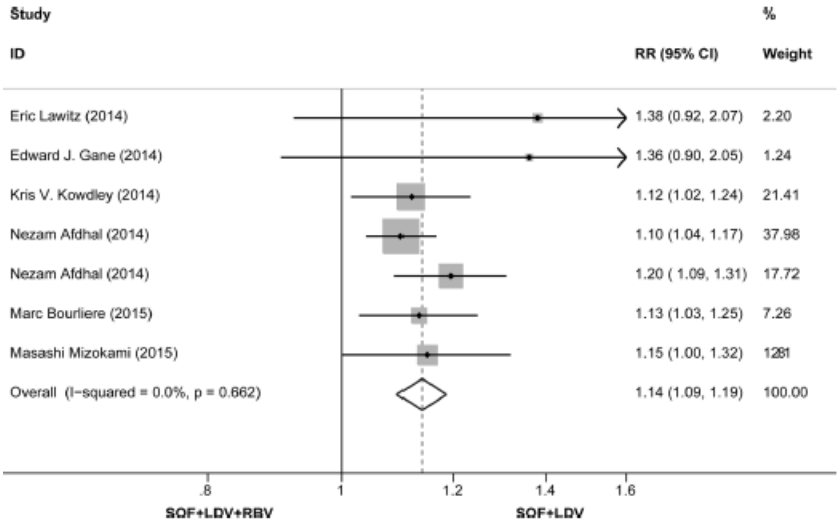
Subgroups	Number of study SLR/SL	RR	I^2 (%)	*P* value	95 % CI	
					Lower	Upper
Treatment history						
TN patients	671/901	0.994	0.00	0.567	0.975	1.014
PT patients	338/325	1.020	32.60	0.201	0.990	1.051
The presence or absence of cirrhosis						
With cirrhosis	868/868	1.003	0.00	0.629	0.990	1.016
Cirrhosis only	80/88	1.022	70.90	0.528	0.955	1.094
Duration of treatment						
8 weeks	237/451	1.040	0.00	0.047	1.001	1.081
12 weeks	540/542	1.010	59.00	0.374	0.989	1.031
24 weeks	328/326	1.010	44.60	0.496	0.988	1.025

Treatment Safety in the SL and SLR Groups

Relapse Rate



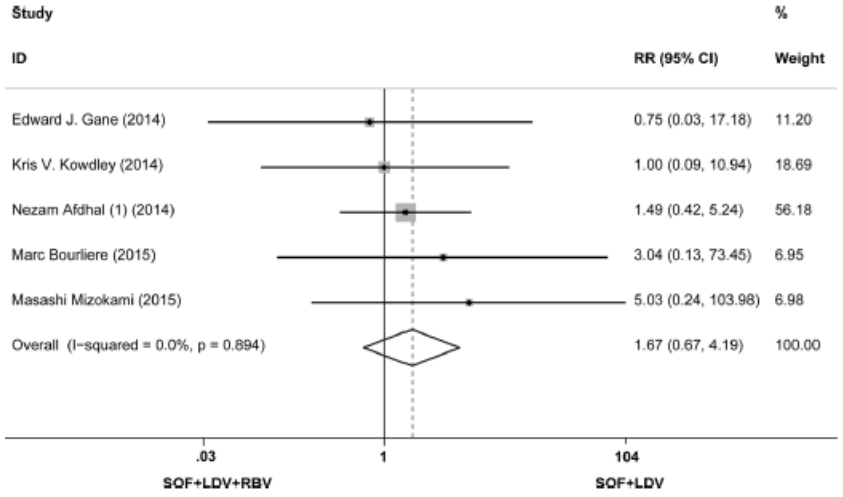
Drug safety



Subgroup analyses evaluating the rate of AEs in patients with HCV genotype 1 infection between SLR and SL groups

AEs	Number of study SLR/SL	RR	I^2 (%)	P value	95 % CI	
					Lower	Upper
Nausea	194/128	1.725	0.0	0.000	1.395	2.132
Insomnia	181/96	2.075	0.0	0.000	1.639	2.627
Anemia	108/8	15.244	4.2	0.000	7.530	30.859
Headache	288/272	1.162	49.6	0.043	1.005	1.343
Fatigue	352/256	1.623	60.0	0.000	1.411	1.866

discontinuation rate due to AEsin the SL and SLR groups

	 **4. Anmerkungen/Fazit der Autoren** The 12-week or 24-week SL regimen with a low incidence of AEs is as effective and well tolerated as the SLR regimen for the treatment of patients with chronic HCV genotype 1 infection. **5. Hinweise durch FB Med** • Es ist unklar, ob eine chronische Erkrankung (mindestens 6 Monate seit Erstnachweis von HCV) bestand.
Hsu CS, Kao JH et al., 2016 [34]. Management of hepatitis C patients with decompensated live disease	**1. Fragestellung** To this end, we conducted a narrative review regarding the treatment of hepatitis C patients with decompensated liver disease. Because the recurrence of HCV infection remains a major issue in patients with decompensated liver disease who successfully receive liver transplantation, we will also address the treatments of HCV infection in this special clinical setting.
	2. Methodik Population: hepatitis C patients with decompensated liver disease Intervention: Antiviral therapy included mono-therapy with IFN or Peg-IFN alfa; dual therapy with IFN plus RBV or Peg-IFN alfa plus RBV; triple therapy with Peg-IFN (alfa-2a or − 2b), RBV, and DAA; and regimens using DAA combination. Komparator: Nicht präspezifiziert Endpunkte: therapeutic efficacy, including SVR and AEs of antiviral therapy. SVR was defined as the absence of detectable serum HCV RNA12 weeks (SVR12) or 24 weeks (SVR24) after the end of a course of therapy. AEs included withdrawals due to AEs, serious AEs, hematological, psychological,

gastroenterological, or dermatological AEs, and influenza-like symptoms.

Suchzeitraum (Aktualität der Recherche): 1947 – 08/2015

Anzahl eingeschlossene Studien/Patienten (Gesamt): 14 (k.A.)
Including 10 on patients with genotype 1 and 4 HCV infection, and six on patients with genotype 2 and 3 HCV infection

Qualitätsbewertung der Studien: keine

3. Ergebnisdarstellung

Genotyp 1 oder 4

Table 1. Studies on the treatment of decompensated cirrhotic patients with genotype 1 or 4 HCV infection.

Study team name/ design/publication	Study population	Treatment	Therapeutic efficacy, n(%)	Adverse events	Ref No
SOLAR-1/RCT/Original	337 patients (99% with HCV GT-1 infection) including those with cirrhosis and moderate or severe hepatic impairment (non-transplant), or who had liver transplantation.	Assigned randomly (1:1) to receive 12 or 24 weeks of a daily LDV (90 mg), SOF (400 mg), and RBV	In non-transplant patients, SVR12 was 86–89%. In transplant recipients, SVR12 was 96–98% in patients without cirrhosis or with compensated cirrhosis, 85–88% in patients with moderate hepatic impairment, and 60–75% in patients with severe hepatic impairment. Response rates in the 12- and 24-week groups were similar.	Thirteen patients (4%) discontinued the LDV-SOF combination prematurely because of adverse events; 10 patients died, mainly from complications related to hepatic decompensation.	[16]
SOLAR-2/RCT/Abstract	108 patients with HCV GT-1 or GT-4 TN or -experienced, CTP class B cirrhosis (score 7–9) or CTP class C cirrhosis (score 10–12) decompensated cirrhosis	Daily LDV (90 mg), SOF (400 mg) and RBV (initial dose of 600 mg, increased as tolerated) for 12 weeks or 24 weeks.	In the 12-week treatment arm, SVR12 was 87%. In the 24-week treatment arm, SVR12 was 89%. Post-therapy virologic relapse occurred in 8% and 4% of the 12- and 24-week groups, respectively. Compared with baseline, total bilirubin and serum albumin levels improved at week 4 post-therapy in both treatment groups. Baseline CTP and MELD scores improved in more than 50% of the treated patients, but some patients did have worsening hepatic function.	Five (5%) patients died from various causes, but none of the deaths were attributed to antiviral therapy. Grade 3 or 4 adverse events were more common in the 24-week arm (34%) than in the 12-week arm (15%).	[17]
ALLY-1/RCT/Abstract	Adult HCV TN and TE patients predominantly had HCV GT-1 infection, in two specific populations: advanced cirrhosis (CTP class B and C; n = 60) and post-transplant with HCV recurrence (n = 53)	Daily Daclatasvir (60 mg) with SOF (400 mg) and low initial dose of RBV (600 mg) for 12 weeks	In advanced cirrhosis, SVR12 rate was 83% (76% in HCV GT-1a, 100% in HCV GT-1b, 94% in CTP class B cirrhosis, and 56% in CTP class C cirrhosis). In recurrent HCV infection post-transplant, SVR12 was 94%. In HCV GT- 3, SVR12 rates were 83% (advanced cirrhosis) and 91% (post-transplant with HCV recurrence).	No serious adverse events. The most common adverse events (≥10%) were headache (15%, 36%), fatigue (18%, 28%), anemia (20%, 19%), diarrhea (8%, 19%), nausea (17%, 6%), and arthralgia (2%, 13%) in the advanced cirrhotic and post-transplant cohorts, respectively.	[18]
UNITY-2/RCT/Original	Adult HCV GT-1-infected compensated cirrhotic patients with HCV TN (n = 112) or HCV TE (n = 90)	A 12-week treatment with daily daclatasvir (30 mg), asunaprevir (200 mg), and beclabuvir (75 mg), and randomly assigned (1:1) to receive double-blinded weight-based RBV (1000–1200 mg/d) or matching placebo.	When ribavirin was included in the regimen, in the TN group, the SVR12 rate was 98% (with RBV) and 93% (without RBV). In the TE group, SVR12 was 93% (with RBV) and 87% (without RBV).	There were 4 adverse event–related discontinuations, and 4 treatment-emergent grade 3 or 4 alanine aminotransferase elevations, including 1 had concomitant total bilirubin elevation.	[19]
Cohort/Original	14 patients with HCV GT-1 who relapsed after treatment with SOF-RBV for 24 weeks	Retreated with LDV-SOF for 12 weeks.	SVR12 was 100%.	Four grade 3 events (elevated serum creatinine in a patient with baseline renal insufficiency, hypercholesterolemia, and hypophosphatemia) occurred. No grade 4 events or treatment discontinuations.	[20]
Cohort/Original	51 patients with GT-1 HCV who did not achieve SVR after treatment in trials of SOF regimens. Fourteen (27%) had compensated cirrhosis at baseline.	LDV-SOF daily plus weight-based RBV (1,000 or 1,200 mg/day) for 12 weeks.	SVR12 was achieved by 50 of the 51 patients (98%) treated. Among the 45 patients who received SOF in earlier treatment, 44 (98%) achieved SVR12.	41/51 (80%) experienced at least one AE, but most events were mild to moderate in severity. The most common AEs were fatigue, headache, and diarrhea. One patient discontinued treatment because of an unrelated AE (bipolar disorder).	[21]

Study team name/ design/publication	Study population	Treatment	Therapeutic efficacy, n(%)	Adverse events	Ref No
Cohort/Abstract	64 liver transplant recipients with HCV GT-1 infection	Daclatasvir-containing regimens (60 mg/day) with either SOF or SMV for up to 24 weeks	SVR12 rate was 84% overall, 87% in the group that received daclatasvir and sofosbuvir, and 80% in the group that received daclatasvir and simeprevir.		[22]
Cohort/Original	Liver transplant recipients with recurrent hepatitis C. One with GT-1a and 5 with GT-1b	Daclatasvir, SMV, and RBV for 24 weeks	4 (67%) patients had SVR24	Adverse events were few and limited to moderate anemia caused by RBV	[23]
RCT/Abstract	154 HCV GT-1 patients with compensated cirrhosis for whom prior Peg-IFN and RBV treatment had failed	LDV-SOF for 24 weeks vs. LDV-SOF-RBV for 12 weeks plus a 12-week placebo phase.	The SVR12 rates were 96% with the 12-week regimen and 97% with the 24-week regimen.	The most common adverse events were asthenia, headache, and pruritus, but the frequency of severe adverse events and the need for early drug discontinuation were low in both treatment groups.	[24]
Sofosbuvir compassionate-use program /Cohort/ Abstract	78 patients with severe recurrent HCV infection following liver transplantation and were predicted to have a less than 6-month survival rate. The median MELD score was 16 (range, 6–43), and 20 with fibrosing cholestatic hepatitis.	44 patients were treated with SOF-RBV, and 32 patients also received PEG-IFN	After week 12 of treatment, 91% of patients treated with SOF-RBV and 75% of those treated with the addition of PEG-IFN achieved undetectable HCV RNA levels. 15/27 (56%) of patients achieved SVR12. 75% of patients had improved or stable clinical liver disease, including improved hyperbilirubinemia and coagulopathy and a decreased MELD score.	The most common adverse events in patients treated with SMV-Peg-IFN- RBV were fatigue, headache, and influenza-like illness. Eight patients died and most deaths were caused by liver disease progression.	[25]

Abbreviations: GT: genotype; CTP: Child Turcotte Pugh; SVR: sustained virologic response; SOF: sofosbuvir; SMV: simeprevir; RBV: ribavirin; Peg-IFN: pegylated interferon; LDV: ledipasvir; MELD: Model for End-Stage Liver Disease; AE: adverse event; TN: treatment-naïve; TE: treatment experienced

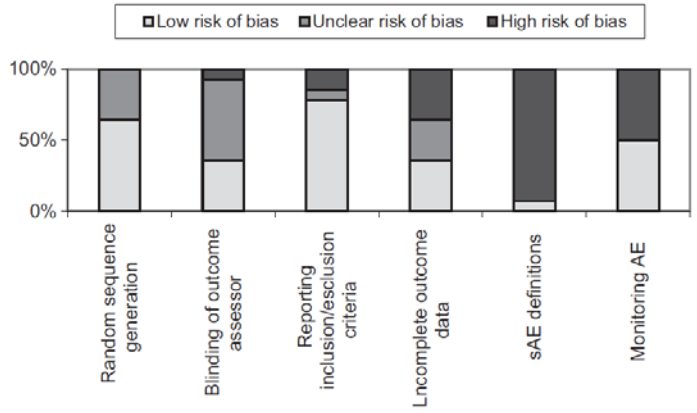
Genotyp 2 oder 3

Table 2. Studies on treatment of decompensated cirrhotic patients with genotype 2 or 3 HCV infection.

Study team name/ design/publication	Study population	Treatment	Therapeutic efficacy, n(%)	Adverse events	Ref No
ALLY-1/RCT/Abstract	Adult HCV TN and TE patients predominantly had HCV GT-1 infection, in two specific populations: advanced cirrhosis (CTP class B and C; n = 60) and post-transplant with HCV recurrence (n = 53)	Daily Daclatasvir (60 mg) with SOF (400 mg) and low initial dose of RBV (600 mg) for 12 weeks.	In advanced cirrhosis, SVR12 rate was 83% (76% in HCV GT-1a, 100% in HCV GT-1b, 94% in CTP class B cirrhosis, and 50% in CTP class C cirrhosis). In recurrent HCV infection post-transplant, SVR12 was 94%. In HCV GT- 3, SVR12 rates were 83% (advanced cirrhosis) and 91% (post-transplant with HCV recurrence).	No serious adverse events. The most common adverse events (≥ 10%) were headache (13%, 36%), fatigue (18%, 28%), anemia (20%, 19%), diarrhea (8%, 19%), nausea (17%, 6%), and arthralgia (2%, 13%) in the advanced cirrhotic and post-transplant cohorts, respectively.	[18]
PHOTON-1/Cohort/ Original	Adult TN (n = 182) and TE (n = 41) patients who had HCV-HIV coinfection. The number of patients with cirrhosis was five in GT-1, seven in naïve GT-2 or 3, and 10 in experienced GT-3.	SOF(400 mg) and weight-based RBV for 12 weeks in TN HCV GT-2 or GT-3 patients, and 24 weeks for TN GT-1 patients and TE GT-2 or GT-3 patients.	Among TN HCV patients, 87 /114 (76%) of GT-1, 23/26 (88%) of GT-2, and 28/42 (67%) of GT-3 achieved SVR12. Among TE HCV patients, 22/24 (92%) of GT-2 and 16/17 (94%) of GT-3 achieved SVR12.	The most common adverse events were fatigue, insomnia, headache, and nausea. Seven patients (3%) discontinued HCV treatment due to adverse events. No adverse effect on HIV disease or its treatment was observed.	[26]
ALLY-2/RCT/Original	Adult TN (n = 151) and TE (n = 52) patients who had HCV-HIV coinfection. Patients had HCV GT-1 through 4 (83% with GT-1), and 14% had compensated cirrhosis.	Daily daclatasvir (60 mg, adjustment for concomitant antiretroviral medication) plus SOF (400 mg) for 12 weeks or 8 weeks (randomly assigned in a 2:1 ratio) in TN patients, and 12 weeks for TE patients.	In TN patients with HCV GT-1 infection, the SVR12 rate was 96.4% (treated for 12 weeks) and 75.6% (treated for 8 weeks). In TE patients, SVR12 rate was 97.7% (treated for 12 weeks). SVR12 rates across all genotypes were 97.0%, 76.0%, and 98.1% (95% CI, 89.7–100), respectively.	The most common adverse events were fatigue, nausea, and headache. There were no study-drug discontinuations because of adverse events. HIV-1 suppression was not compromised.	[27]
ELECTRON-2/Cohort/ Abstract	50 TE GT-3 patients, and 25 GT-6 TN and TE patients.	GT-3 patients received LDV-SOF-RBV for 12 weeks. GT-6 patients received LDV-SOF for 12 weeks.	SVR12: 100% in the group that received LDV-SOF-RBV vs. 64% in the group that received LDV-SOF.	The adverse event profile was consistent with that seen in the Phase 3 program of fixed dose combination LDV-SOF ± RBV	[28]
Cohort/Original	61 patients with HCV and cirrhosis (CTP score ≤7) who were on waitlists for liver transplantation for hepatocellular carcinoma. The median MELD score was 8 (range, 6–14), 17 had CTP class B cirrhosis, 45 (73%) had HCV GT-1, eight (13%) had HCV GT-2, and seven (11%) had HCV GT-3.	Daily SOF (400 mg) and RBV before liver transplantation for 48 weeks.	46 received transplanted livers, and 43 patients had HCV-RNA level less than 25 IU/mL at the time of transplantation. 30/43 (70%) had a post-transplantation virologic response at 12 weeks, 10/11 (91%) subjects with HCV GT-2 or 3 achieved SVR12, and 19/29 (65%) patients with HCV GT- 1 achieved SVR12. 10 (23%) had recurrent infection. Of all 61 patients given SOF-RBV, 49% had a post-transplantation virologic response.	The most frequently reported adverse events were fatigue (in 38% of patients), headache (23%), and anemia (21%). Adverse effects led to treatment discontinuation for two patients (3%), and 12 patients (20%) required a dose reduction of RBV. Three (7%) died (two from nonfunction of the primary graft and one from complications of hepatic artery thrombosis).	[29]
Sofosbuvir compassionate-use program /Cohort/ Abstract	78 patients with severe recurrent HCV infection following liver transplantation and were predicted to have a less than 6-month survival rate. The median MELD score was 16 (range, 6–43), and 20 with fibrosing cholestatic hepatitis.	44 patients were treated with SOF-RBV, and 32 patients also received PEG-IFN.	After week 12 of treatment, 91% of patients treated with SOF-RBV and 75% of those treated with the addition of PEG-IFN achieved undetectable HCV RNA levels. 15/27 (56%) of patients achieved SVR12. 75% of patients had improved or stable clinical liver disease, including improved hyperbilirubinemia and coagulopathy and a decreased MELD score.	The most common adverse events in patients treated with SMV-Peg-IFN- RBV were fatigue, headache, and influenza-like illness. Eight patients died and most deaths were caused by liver disease progression.	[25]

Abbreviations: GT: genotype; CTP: Child Turcotte Pugh; SVR: sustained virologic response; SOF: sofosbuvir; SMV: simeprevir; RBV: ribavirin; Peg-IFN: pegylated interferon; LDV: ledipasvir; MELD: Model for End-Stage Liver Disease; AE: adverse event; TN: treatment-naïve; TE: treatment experienced

	4. Anmerkungen/Fazit der Autoren Although existing evidence supports the efficacy of oral DAA regimens in patients with decompensated cirrhosis, most of the evidence available today is retrieved from small studies and needs further validation. In addition, recent reports released by FDA have raised concerns about the safety of some DAA regimens in this special population. Moreover, the longterm effects of DAA regimens on disease progression, associated morbidity, and mortality remain largely unknown. Issues regarding multidrug-resistant HCV strains, mixed HCV genotype infection, drug–drug interactions, the optimal treatment regimens, and strategies for patients with severe comorbidities remain unsolved.
Pecoraro V et al., 2016 [57]. Optimisation of triple therapy for patients with chronic hepatitis C: a systematic review	**1. Fragestellung** The aim of this systematic review was to evaluate the evidence regarding the factors affecting response and rate of AEs associated with triple therapy.
	2. Methodik Population: patients with genotype 1 HCV infection Intervention: Triple therapy with Pegylated-Interferon a (PEG-IFNa)/Ribavirin (RBV) and Boceprevir (Boc) or Telaprevir (Tel) Komparator: PEG-IFNa/RBV alone (dual therapy) Endpunkte: improved sustained virological response (SVR) rates, AEs Suchzeitraum (Aktualität der Recherche): Bis 30.09.2014 Anzahl eingeschlossene Studien/Patienten (Gesamt): 14 (5419) Qualitätsbewertung der Studien: methods of the Cochrane Collaboration. The I^2 statistics indicates the percentage of the overall variability that is due to between-study (or interstudy) variability, as opposed to within-study (or intrastudy) variability. An I^2 value smaller than 50% reveals low heterogeneity, I^2 included between 50% and 75% moderate heterogeneity, and I^2 greater than 75% substantial heterogeneity. In the absence of heterogeneity between studies, we pooled data using Mantel–Haenszel methods for a fixed-effects model, otherwise we combined the studies using the random-effects model
	3. Ergebnisdarstellung Übersicht über die Einzelstudien – vgl. Anhang 4



Effektivität

Table 2 Rates of SVR to triple therapy compared to dual therapy

DAAs	*n* Studies	*n* Patients	OR*	95%CI	I^2 (%)	*P*
Tel	6	2885	3·16	1·84–5·42	87	< 0·00001
Boc	5	1117	3·89	2·31–6·55	63	< 0·00001
Tel + Boc	11	4002	3·42	2·36–4·97	80	< 0·00001

DAAs, direct acting antivirals; SVR, sustained virological response; Tel, Telaprevir; Boc, Boceprevir; *n*, number; OR, odds ratio; CI, confidence interval.
*Random effect model.

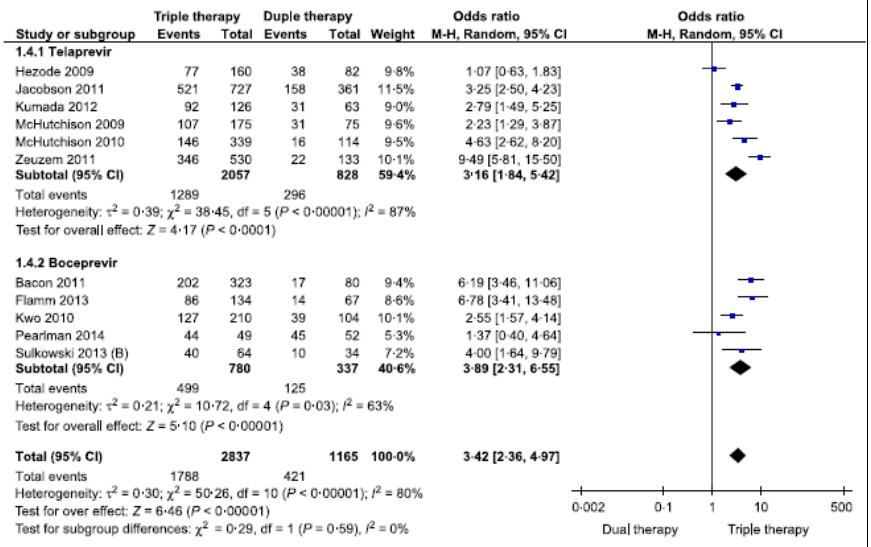


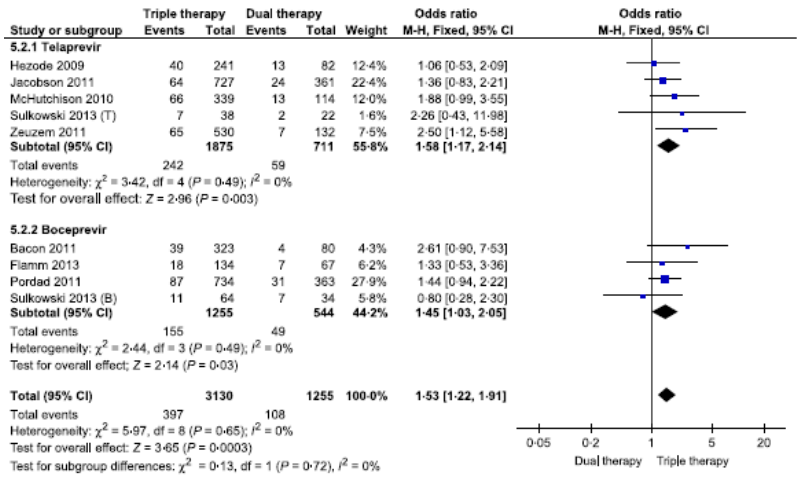
Figure 3 Meta-analysis of sustained virological response (SVR) rate in patients treated with triple therapy vs. dual therapy. B, Boceprevir.

Table 4 Meta-analysis of triple vs. dual therapy. Outcome: Efficacy of triple vs. dual therapy according to different patients' subgroups

	n Studies	*n* Patients	OR	95% CI	I^2 (%)	*P*	ROR	95%IC
Previous treatment								
Naïve	7	3232	2·70	2·32–5·15	63	< 0·00001	*	
Experienced	4	1720	6·73	5·06–8·95	17	< 0·00001	2·49	1·8–3·44
Gender								
Male	6	1923	3·29	2·69–4·03	18	< 0·00001	*	
Female	6	1266	3·18	2·48–4·09	0	< 0·00001	0·96	0·7–1·33
Ethnicity								
Nonblack	6	3002	3·58	2·80–4·59	41	< 0·00001	*	
Black	6	404	3·61	2·18–5·97	0	< 0·00001	0·97	0·54–1·7
IL28B genotype								
CC	3	117	2·07	0·67–6·41	0	0·21	*	
CT + TT	2	56	6·67	1·75–25·5	66	0·005	3·2	0·55–18·57
HCV genotype								
1a	5	1609	2·99	2·39–3·74	0	< 0·00001	*	
1b	5	1151	3·86	2·91–4·96	1	< 0·00001	1·27	0·89–1·8
Pretreatment viral load								
Low (≤ 800 000 IU/mL)	3	459	2·20	1·21–3·99	38	0·009	*	
High (> 800 000 IU/mL)	3	2127	4·13	2·94–5·81	58	< 0·0001	1·87	0·94–3·73
Cirrhosis								
No	5	1623	3·48	2·30–5·26	60	< 0·0000	*	
Yes	3	242	3·67	1·13–11·9	56	0·031	1·05	0·3–3·67
Fibrosis								
Early	2	1257	3·81	2·95–4·92	73	< 0·00001	*	
Advanced	2	807	2·23	1·37–3·63	68	0·001	0·58	0·33–1·01
Platelet count								
≤ 150 × 10^3/μL	3	164	3·03	1·41–6·51	0	0·005	*	
> 150 × 10^3/μL	3	1435	4·23	2·48–7·21	61	< 0·00001	1·39	0·54–3·54
ALT								
Normal	3	446	2·03	1·31–3·15	0	0·002	*	
Elevated	3	1200	4·56	2·66–7·81	51	< 0·00001	2·24	1·12–4·5

ALT, alanine amino-transferase; *n*, number; OR, odds ratio; CI, confidence interval; ROR, ratio of odds ratios.
*Reference category.

Unerwünschte Nebenwirkungen



Meta-analysis of serious adverse events in patients treated with Boceprevir or Telaprevir. B, Boceprevir; T, Telaprevir.

	Table 6 Meta-analysis of triple vs. dual therapy in naïve or previously treated patients. Outcome: Adverse events

	Naïve patients						Experienced patients					
	n Studies	*n* Patients	OR	95% CI	I^2 (%)	*P*	*n* Studies	*n* Patients	OR	95% CI	I^2 (%)	*P*
Any AEs	3	1984	2·76	1·14–6·7	0	0·02	5	1094	2·23	0·61–8·23	35	0·23
Any serious AE	3	2508	1·33	1–1·79	0	0·05	6	1877	1·85	1·28–2·65	0	0·0001
Treatment discontinuation due to AE	2	564	2·20	1·24–3·92	0	0·007	4	1719	4·28	2·45–7·50	0	< 0·00001
Anaemia	6	3261	2·13	1·64–2·76	48	< 0·00001	6	1877	2·48	1·80–3·44	0	< 0·00001
Fatigue	5	3061	0·91	0·78–1·06	0	0·22	4	1150	1·20	0·85–1·71	40	0·29
Headache	7	3269	1·01	0·88–1·18	35	0·84	4	1150	1·12	0·86–1·46	0	0·41
Rash	6	2955	1·38	1·12–1·71	21	0·003	5	1515	3·16	2·32–4·30	0	< 0·00001
Neutropenia	4	2385	1·07	0·65–1·76	77	0·79	3	697	1·83	1·16–2·90	0	0·010
Nausea	7	3269	1·45	1·11–1·89	53	0·006	4	1150	1·43	1·09–1·88	0	0·01
Insomnia	6	3257	0·96	0·81–1·15	15	0·69	2	654	1·05	0·43–2·57	77	0·92
Flu like symptoms	6	2897	0·86	0·73–1·03	0	0·10	4	1150	0·90	0·59–1·38	52	0·62
Dysgeusia	3	1600	3·04	2·33–3·97	0	< 0·00001	2	604	4·86	2·89–8·19	0	< 0·00001
Pruritus	5	2943	1·49	0·97–2·30	81	0·07	2	554	4·87	2·14–11·1	54	0·0002

AE, adverse event; *n*, number; OR; odds ratio; CI, confidence interval.

4. Anmerkungen/Fazit der Autoren

The present study shows how improved results of triple therapy are mainly observed in some patients' subsets and are accompanied by increased risk of AEs compared to dual therapy. These results might be useful for optimising treatment of chronic hepatitis C when IFN-free regimens are unavailable.

Characteristics of patients that might benefit from triple therapy:

1 Previous unsuccessful treatment with PEG-IFNa/RBV

2 IL28B genotype CT or TT

3 HCV genotype 1b

4 Early fibrosis

5 High pretreatment viral load

6 Platelet count > 150 000/lL

7 Elevated ALT levels

Suwanthawornkul T et al., 2015 [66].

Efficacy of Second Generation Direct-Acting Antiviral Agents for Treatment Naïve Hepatitis C Genotype 1: A Systematic Review and Network Meta-Analysis

1. Fragestellung

The treatment of hepatitis C (HCV) infections has significantly changed in the past few years due to the introduction of direct-acting antiviral agents (DAAs). DAAs could improve the sustained virological response compared to pegylated interferon with ribavirin (PR). However, there has been no evidence from randomized controlled trials (RCTs) that directly compare the efficacy among the different regimens of DAAs. Therefore, we performed a systematic review and network meta-analysis aiming to compare the treatment efficacy between different DAA regimens for treatment naïve HCV genotype 1.

2. Methodik

Population: treatment naïve HCV genotype 1

	Intervention*:* Treatment regimens of interest were divided into • DAA plus PR regimens (i.e. SMV plus PR, DCV plus PR, and SOF plus PR), • dual DAA combinations with and without ribavirin regimens (i.e. SOF plus LDV, SOF plus SMV, SOF plus DCV, SOF plus LDV and ribavirin, SOF plus SMV and ribavirin, and SOF plus DCV and ribavirin, PrOD and PrOD plusribavirin), • and PR alone. Komparator: k.A. Endpunkte: SVR12, SVR24 after the end of treatment and adverse drug events (i.e. serious adverse events, anemia, and fatigue). Suchzeitraum (Aktualität der Recherche) 25.05.2015 Anzahl eingeschlossene Studien/Patienten (Gesamt): 16 (n – k.A.) Qualitätsbewertung der Studien: Cochrane Collaboration's tool for assessing risk of bias in RCTs. Heterogeneity between studies was estimated using the Q test and I2 statistic and was considered present if the degree of heterogeneity (I2) was higher than 25%. Sources of heterogeneity were explored by fitting co-variables (i.e. mean age, BMI, baseline HCV RNA, and percent cirrhosis) one by one in a meta-regression.
	3. Ergebnisdarstellung Übersicht über die Einzelstudien: vgl. Anhang 2 <u>Qualität der Studien</u>: All studies reported low risk of bias in the domains of blinding participants and personnel, blinding of outcome assessment, selective outcome reporting, and other bias. For the domains of random sequence generation and allocation concealment, around 25% of the studies (4/16) had unclear risk of bias and the others had low risk of bias. Two out of the 16 studies (13%) had a high risk of bias in the domain of incomplete outcome data, while the others had low risk of bias. **DAA plus PR versus PR alone:** Compared with the PR regimen, SOF plus PR, SMV plus PR, and DVC plus PR regimens yielded significantly higher probability of having SVR24 with pooled risk ratios (RR) of 1.98 (95% CI 1.24, 3.14), 1.46 (95% CI: 1.22, 1.75), and 1.68 (95% CI: 1.14, 2.46), respectively.

Table 2. Pooled risk ratio of sustained virological response at weeks 12 and 24 after the end of treatment between simeprevir plus pegylated interferon-ribavirin and pegylated interferon-ribavirin.

Author	Year	SMV plus PR		PR		RR (95% CI)
		Response	Non-response	Response	Non-response	
Sustained virological response at 12 weeks						
Fried [11]	2013	252	57	51	26	1.23 (1.04, 1.46)
Hayashi [12]	2014	109	14	37	23	1.44 (1.17, 1.77)
Jacobson [13]	2014	210	54	65	65	1.59 (1.33, 1.91)
Manns [14]	2014	209	48	67	67	1.63 (1.36, 1.95)
Pooled RR						**1.46 (1.28, 1.67)**
Sustained virological response at 24 weeks						
Fried [11]	2013	250	59	50	27	1.24 (1.05, 1.48)
Hayashi [12]	2014	109	14	34	26	1.56 (1.24, 1.97)
Hayashi [10]	2013	63	16	6	7	1.73 (0.95, 3.14)
Jacobson [13]	2014	205	42	18	12	1.38 (1.03, 1.86)
Manns [14]	2014	206	47	28	33	1.77 (1.34, 2.34)
Pooled RR						**1.46 (1.26, 1.69)**

CI, confidence interval; PR, pegylated interferon-ribavirin; RR, risk ratio; SMV, simeprevir.

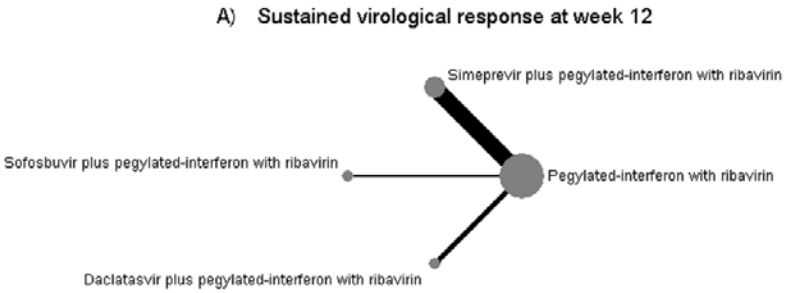
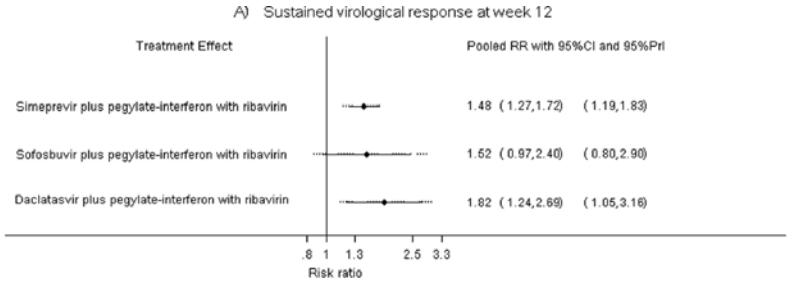


Table 3. Network meta-analysis of sustained virological response at week 12 after the end of treatment.

Treatment	No. of subjects	No. of SVR12	Pooled RR (95% CI)
DAA plus PR versus PR alone			
PR	525	271	1
SMV plus PR	953	780	1.48 (1.27, 1.71)
SOF plus PR	144	121	1.52 (0.97, 2.40)
DCV plus PR	329	209	1.82 (1.24, 2.70)
Among DAA plus PR regimens			
SOF plus PR vs SMV plus PR	-	-	1.03 (0.64, 1.66)
DCV plus PR vs SMV plus PR	-	-	1.23 (0.81, 1.87)
DCV plus PR vs SOF plus PR	-	-	1.20 (0.66, 2.18)

CI, confidence interval; DCV, daclatasvir; DAA, direct acting anti-viral agents; LDV, ledipasvir; PR, pegylated interferon-ribavirin; RR, risk ratio; SMV, simeprevir; SOF, sofosbuvir; SVR12, sustained virological response at week 12 after the end of treatment.



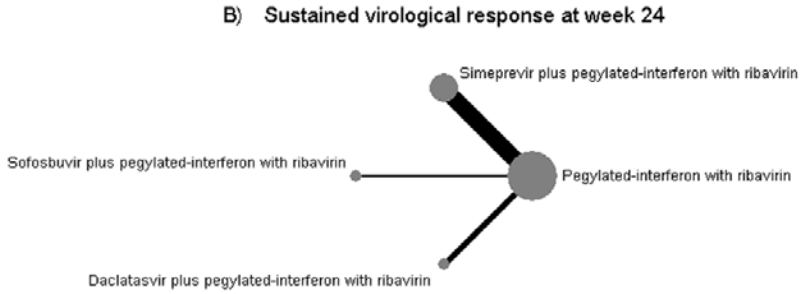
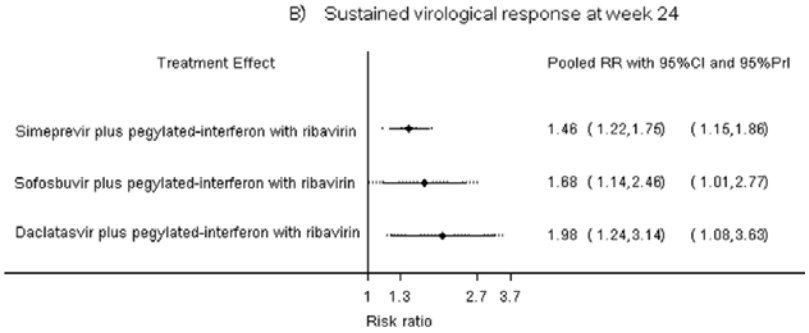


Fig 2. Network plots for sustained virological response at weeks 12 and 24 after the end of treatment.

Table 4. Network meta-analysis of sustained virological response at week 24 after the end of treatment.

Treatment	No. of subjects	No. of SVR12	Pooled RR (95% CI)
DAA plus PR versus PR alone			
PR	375	187	1
SMV plus PR	1011	833	1.46 (1.22, 1.75)
SOF plus PR	144	119	1.98 (1.24, 3.14)
DCV plus PR	329	199	1.68 (1.14, 2.46)
Among DAA plus PR regimens			
SOF plus PR vs SMV plus PR	-	-	1.35 (0.82, 2.23)
DCV plus PR vs SMV plus PR	-	-	1.15 (0.75, 1.76)
DCV plus PR vs SOF plus PR	-	-	0.85 (0.46, 1.55)

CI, confidence interval; DCV, daclatasvir; DAA, direct acting anti-viral agents; LDV, ledipasvir; PR, pegylated interferon-ribavirin; RR, risk ratio; SMV, simeprevir; SOF, sofosbuvir; SVR24, sustained virological response at week 24 after the end of treatment.



Dual DAA combinations with ribavirin versus dual DAA combinations without ribavirin: Pooled incidence rates of SVR12 and SVR24 in all treatment regimens without PR, i.e. SOF plus LDV with/without ribavirin, SOF plus SMV with/without ribavirin, SOF plus DCV with/without ribavirin, and PrOD with/without ribavirin, (pooled incidence of SVR12 ranging from 93% to 100%, and pooled incidence of SVR24 ranging from 89% to 96%) were much higher than the pooled incidence rates of SVR12 (51%) and SVR24 (48%) in PR alone. In comparing SOF plus LDV with ribavirin and SOF plus LDV without ribavirin, the chance of having SVR12 was not significantly different between these two regimens, with the pooled RR of 0.99 (95% CI: 0.97, 1.01).

Table 5. Pooled risk ratio of sustained virological response at week 12 after the end of treatment between sofosbuvir plus ledipasvir with ribavirin and sofosbuvir plus ledipasvir.

Author	Year	SOF plus LDV with RBV		SOF plus LDV		RR (95% CI)
		Response	Non-response	Response	Non-response	
Afdhal [18]	2014	426	8	423	8	1.00 (0.98, 1.02)
Kowdley [17]	2014	201	15	408	23	0.98 (0.94, 1.02)
Lawitz [19]	2014	21	0	37	2	1.04 (0.94, 1.15)
Mizokami [23]	2015	80	3	83	0	0.96 (0.92, 1.01)
Pooled RR						**0.99 (0.97, 1.01)**

CI, confidence interval; LDV, ledipasvir; RR, risk ratio; RBV, ribavirin; SOF, sofosbuvir; SVR24, sustained virological response at week 24 after the end of treatment.

S3 Table. Pooled incidence rate of sustained virological response at weeks 12 and 24 after the end of treatment

Treatment	Pooled SVR12 (95% CI)	Pooled SVR24 (95% CI)
PR	51% (43%, 59%)	48% (40%, 57%)
SMV plus PR	83% (79%, 86%)	83% (80%, 86%)
DCV plus PR	65% (57%, 73%)	62% (53%, 70%)
SOF plus PR	82% (63%, 100%)	81% (68%, 95%)
SOF plus LDV	98% (95%, 100%)	-
SOF plus SMV	97% (90%, 100%)	-
SOF plus DCV	100% (95%, 100%)	96% (88%, 99%)
PrOD	-	89% (79%, 95%)
SOF plus LDV with RBV	97% (95%, 100%)	-
SOF plus SMV with RBV	93% (86%, 100%)	-
SOF plus DCV with RBV	96% (92%, 100%)	95% (85%, 99%)
PrOD with RBV	-	95% (83%, 99%)

CI, confidence interval; DCV, daclatasvir; LDV, ledipasvir; PR, pegylated interferon-ribavirin; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR12, sustained virological response at week 12 after the end of treatment; SVR24, sustained virological response at week 24 after the end of treatment

Adverse drug events (14 Studien mit 3860 Patienten)
Regarding adverse drug events, risk of serious adverse drug events, anemia and fatigue were relatively higher in treatment regimens with PR than the treatment regimens without PR.

S6 Table. Pooled incidence rate of fatigue at entire of treatment

Treatment comparison	No. of studies	No. of subjects	No. of having events	Rate (%) of fatigue (95% CI)
PR	8	482	229	50.0 (42.9, 57.1)
SMV plus PR	4	892	383	44.8 (37.7, 51.9)
DCV plus PR	2	353	193	54.7 (49.5, 59.9)
SOF plus PR	2	144	86	56.7 (34.8, 78.7)
SOF plus LDV	2	862	191	22.2 (19.4, 24.9)
SOF plus DCV	1	100	39	39.0 (29.4, 48.6)
PrOD	1	79	16	20.3 (12.0, 30.8)
SOF plus LDV with RBV	2	650	236	36.3 (32.6, 40)
SOF plus DCV with RBV	1	70	24	34.3 (23.2, 45.4)
PrOD with RBV	1	40	10	25.0 (12.7, 41.2)

CI, confidence interval; DCV, daclatasvir; LDV, ledipasvir; PR, pegylated interferon-ribavirin; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir

S5 Table. Pooled incidence rate of anemia at entire of treatment

Treatment comparison	No. of studies	No. of subjects	No. of having events	Pooled incidence rate (%) (95% CI)
PR	9	544	107	25.4 (14.8, 36.0)
SMV plus PR	5	1,032	263	29.1 (18.6, 39.6)
DCV plus PR	2	353	33	21.5 (0.0, 53.6)
SOF plus PR	2	144	26	17.7 (11.5, 23.9)
SOF plus LDV	3	901	4	0.9 (0.0, 1.8)
PrOD	1	79	1	1.3 (0.0, 6.9)
SOF plus LDV with RBV	3	671	66	9.6 (7.4, 11.9)
PrOD with RBV	1	40	4	10.0 (2.8, 23.7)

CI, confidence interval; DCV, daclatasvir; LDV, ledipasvir; PR, pegylated interferon-ribavirin; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir

S4 Table. Pooled incidence rate of serious adverse event at entire of treatment

Treatment regimens	No. of studies	No. of subjects	No. of having events	Rate (%) of events (95% CI)
PR	9	544	42	7.5 (5.2, 9.7)
SMV plus PR	5	1,032	55	5.0 (3.6, 6.3)
DCV plus PR	2	353	28	7.9 (5.1, 10.7)
SOF plus PR	2	144	6	4.10 (0.0, 9.6)
SOF plus LDV	3	903	29	3.0 (1.3, 4.7)
SOF plus DCV	1	100	7	7.0 (2.0, 12.0)
PrOD	1	79	2	2.5 (0.3, 8.8)
SOF plus LDV with RBV	3	669	16	1.9 (0, 4.5)
SOF plus DCV with RBV	1	70	2	2.9 (1.0, 6.8)
PrOD with RBV	1	36	1	2.8 (0.1, 14.5)

CI, confidence interval; DCV, daclatasvir; LDV, ledipasvir; PR, pegylated interferon-ribavirin; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir

4. Anmerkungen/Fazit der Autoren

Both DAA plus PR and dual DAA regimens should be included in the first line drug for treatment naïve HCV genotype 1 because of the significant clinical benefits over PR alone.

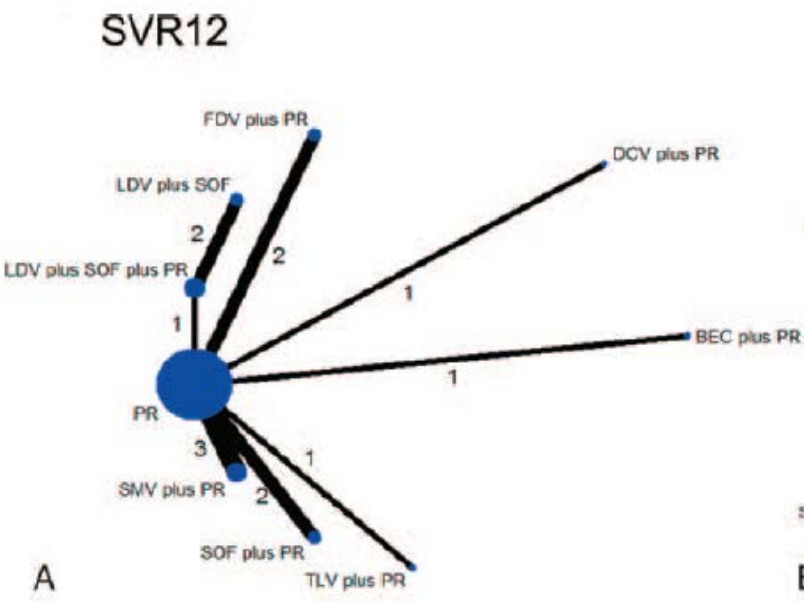
The main limitation of our study is that a subgroup analysis according to dosages and duration of treatment could not be performed. Therefore, the dose and duration of recommended treatment have been suggested in range and not in definite value.

Zhu G-Q et al., 2016 [73]. Systematic Review and Network Meta-Analysis of Randomized Controlled Trials. Comparative Effectiveness and

1. Fragestellung

All possible direct-acting antiviral agent (DAA) regimens for treatment-naive hepatitis C genotype 1 were evaluated by many randomized controlled trials (RCTs). However, the optimum regimen remains inconclusive. We aim to compare interventions in terms of sustained virological response at 12 (SVR12) and 24 (SVR24) weeks after the end of treatment and adverse effects (AEs) (fatigue, headache, nausea, insomnia).

2. Methodik

Safety of Direct-Acting Antiviral Agents for Treatment-Naive Hepatitis C Genotype 1	*Population:* CHC; treatment-naive HCV genotype 1 *Intervention / Komparator:* Combined direct-acting antiviral agent (DAA) with peginterferon-ribavirin (PR), combined dual DAAs with and without PR or PR alone DAAs: simeprevir (SMV), beclabuvir (BEC), faldaprevir (FDV), sofosbuvir (SOF), daclatasvir (DCV), asunaprevir (ASV), and ledipasvir (LDV) *Endpunkte:* SVR at week 12 (SVR12) or 24 (SVR24) after the end of treatment, AEs (fatigue, nausea, insomnia, or headache) *Suchzeitraum (Aktualität der Recherche):* Bis 07/2015 *Anzahl eingeschlossene Studien/Patienten (Gesamt):* 22 Studien in 7 Vergleichen (Anzahl der Patienten – siehe Anhang 1) *Qualitätsbewertung der Studien:* Cochrane Risk of Bias assessment tool. I^2 (presented as Q) were represented as markers of heterogeneity. I^2 values between 30% and 60% were defined as moderate heterogeneity, 60% to 75% as considerable heterogeneity, and values >75% assubstantial heterogeneity. Values <30% were considered unimportant
	3. Ergebnisse Einzelstudien: vgl. Anhang 1 

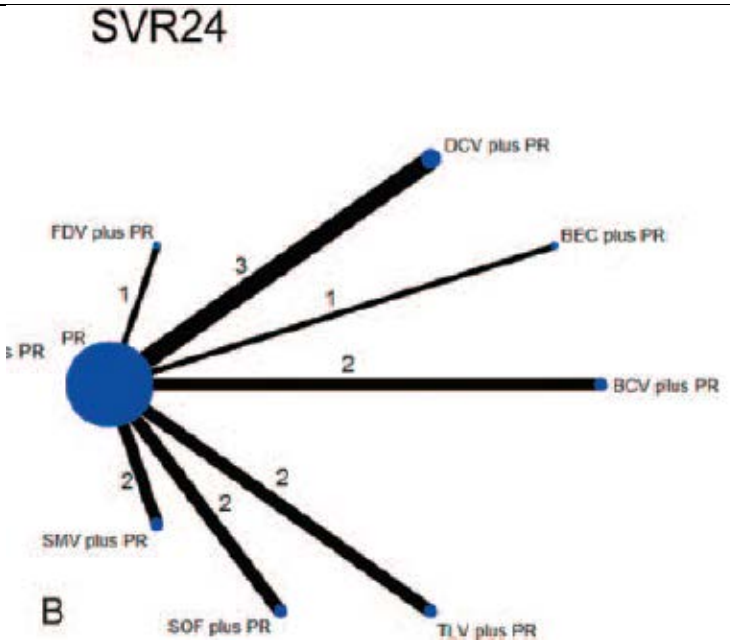


FIGURE 2. Evidence network of eligible comparisons for network meta-analysis. The numbers along the link lines indicate the number of trials or pairs of trial arms. Lines connect the interventions that have been studied in head-to-head (direct) comparisons in the eligible controlled trials. The width of the lines represents the cumulative number of trials for each comparison and the size of every node is proportional to the number of enrolled participants (sample size). Different nodes referred to different interventions accordingly. BCV=boceprevir, BEC=beclabuvir, DCV=daclatasvir, FDV=faldaprevir, LDV=ledipasvir, PR=peginterferon and ribavirin, SMV= simeprevir, SOF=sofosbuvir, SVR=sustained virological response, TLV=telaprevir.

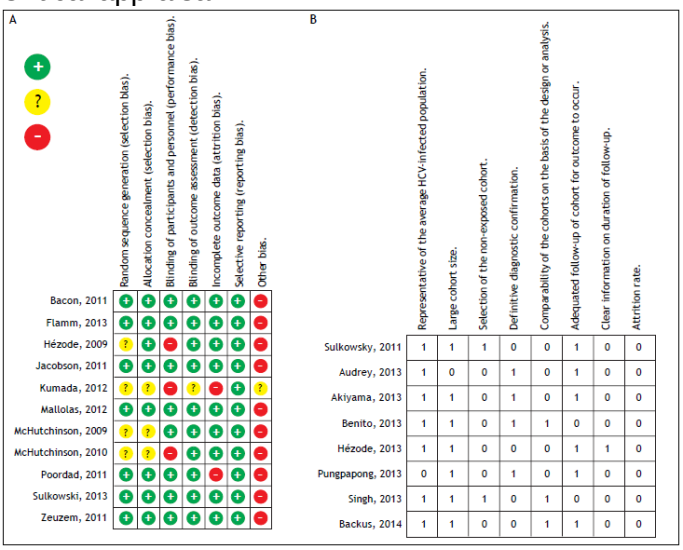
TABLE 3. Assessment of Heterogeneity and Publication Bias for Direct Comparisons and Comparison of Outcomes Between Pair-wise Meta-Analysis and Network Meta-Analysis

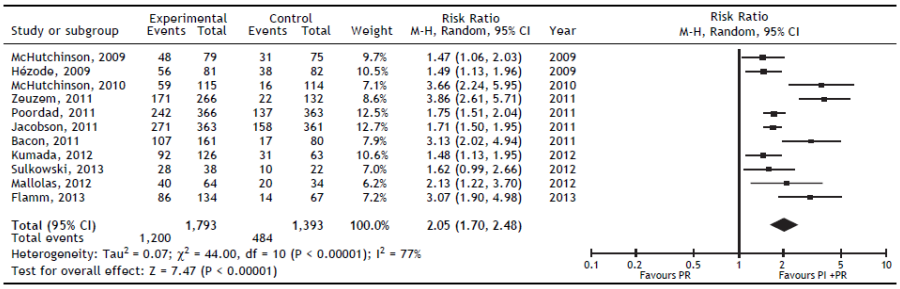
Treatment Comparisons	Results of Pair-Wise Meta-Analysis	Results of Network Meta-Analysis	I^2 (%)	Begg Test
SVR 12 weeks				
LDV plus SOF plus PR vs PR	0.76 (0.39, 1.48)	0.78 (0.15, 3.86)	NA	0.317
SMV plus PR vs PR	3.55 (2.22, 5.69)	3.59 (1.47, 8.99)	49.8	0.602
FDV plus PR vs PR	3.61 (1.74, 7.51)	3.72 (1.21, 10.63)	81.8	0.317
SOF plus PR vs PR	4.41 (1.61, 12.04)	4.69 (1.20, 17.05)	37.3	0.317
BEC plus PR vs PR	14.64 (10.58, 18.70)	13.92 (0.16, 26.15)	NA	NA
DCV plus PR vs PR	7.80 (1.75, 34.83)	8.90 (1.06, 84.37)	NA	NA
TLV plus PR vs PR	3.42 (2.03, 5.75)	3.49 (0.72, 18.16)	NA	NA
LDV plus SOF plus PR vs LDV plus SOF	0.99 (0.37, 2.67)	0.75 (0.12, 3.10)	NA	NA
SVR 24 weeks				
BCV plus PR vs PR	2.98 (2.38, 3.73)	2.93 (1.12, 7.36)	0.0	0.317
BEC plus PR vs PR	1.87 (0.48, 7.26)	1.95 (0.31, 12.60)	NA	NA
DCV plus PR vs PR	4.51 (1.58, 12.86)	4.77 (1.30, 17.96)	0.0	0.602
FDV plus PR vs PR	1.40 (0.14, 13.57)	1.43 (0.08, 22.74)	NA	NA
SMV plus PR vs PR	3.56 (1.40, 9.06)	3.49 (1.35, 9.97)	75.2	0.317
SOF plus PR vs PR	4.48 (2.07, 9.68)	4.51 (1.40, 14.76)	0.0	0.317
TLV plus PR vs PR	2.22 (0.99, 4.96)	2.33 (0.86, 5.65)	87.6	0.317

BCV = boceprevir, BEC = beclabuvir, DCV = daclatasvir, FDV = faldaprevir, LDV = ledipasvir, NA = not available, PR = peginterferon and ribavirin, SMV = simeprevir, SOF = sofosbuvir, SVR = sustained virological response, TLV = telaprevir.

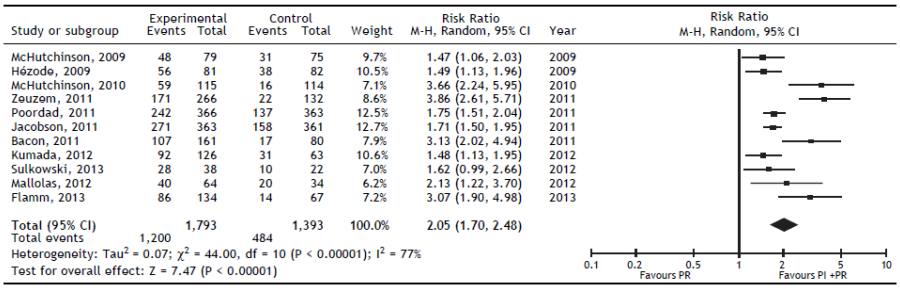
4. Fazit/ Schlussfolgerung der Autoren

Compared with peginterferon-ribavirin (PR), daclatasvir plus PR (OR 8.90, P<0.001), faldaprevir plus PR (OR 3.72, P<0.001), simeprevir plus PR (OR 3.59, P<0.001), sofosbuvir plus PR (OR 4.69, P<0.001) yield a significant effect in improving SVR12. Consistently, simeprevir plus PR (OR 3.49, P<0.001), sofosbuvir plus PR (OR 4.51, P<0.001), daclatasvir plus PR (OR 4.77, P<0.001) also improved the rates of SVR24 significantly compared with PR. With respect to AEs, compared with PR, ledipasvir plus sofosbuvir plus PR (OR 2.13, P<0.001) confer a significant AE in nausea, whereas daclatasvir plus PR (OR 0.20, P<0.001 and OR 0.18, P<0.001, respectively) lowered the incidence of fatigue and nausea significantly when compared with ledipasvir plus sofosbuvir plus PR.

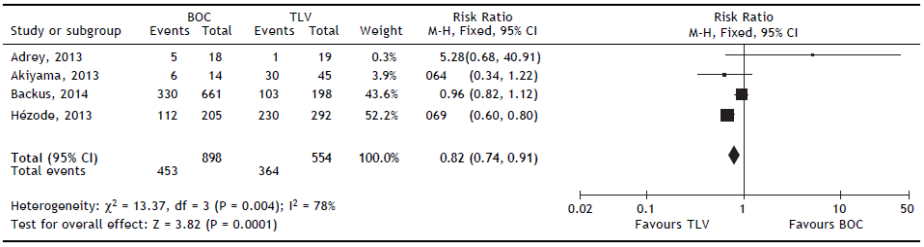
	Daclatasvir plus PR was the most effective in SVR12 and SVR24, but caused an increased AEs profile (headache and insomnia). Combined ledipasvir with sofosbuvir or combination of PR was associated with higher incidence of fatigue and nausea.
Manzano-Robleda MC et al., 2015 [55]. Boceprevir and telaprevir for chronic genotype 1 hepatitis C virus infection. A systematic review and meta-analysis	**1. Fragestellung** Assess benefits and harms of boceprevir (BOC) and telaprevir (TLV) in treatment of genotype 1 HCV infection, and identifying subgroups with mist benefit.
	2. Methodik *Population:* Patients with **genotype 1** HCV infection *Intervention / Komparator:* Comparison of BOC + PR versus TLV + PR *Endpunkte:* Primary outcome was SVR, secondary outcomes were the frequency and type of AEs, determination oft he predictors of SVR, and resistant variants to BOC or TLV *Suchzeitraum (Aktualität der Recherche):* PubMed and Embase (January 2009 to November 2013) *Anzahl eingeschlossene Studien/Patienten (Gesamt):* 822 Studien (Patienten: k. A.) *Qualitätsbewertung der Studien:* Cochrane risk of bias tool, modified Newcastle-Ottawa scale
	3. Ergebnisdarstellung Critical appraisal  SVR of protease inhibitor plus pegylated interferon plus ribavirin vs pegylated interferon plus ribavirin



Subgroup analysis of SVR with protease inhibitor plus pegylated interferon plus ribavirin vs. pegylated interferon plus ribavirin



Comparison of the SVR between boceprevir plus pegylated interferon plus ribavirin vs. telaprevir plus pegylated interferon plus ribavirin



Safety analysis of protease inhibitor plus pegylated interferon plus ribavirin vs. pegylated interferon plus ribavirin in all patients, naie patients, and pre-treated patients

	All patients			Naïve			Pre-treated		
	RR	95% CI	NNH	RR	95% CI	NNH	RR	95%CI	NNH
Any AE	1.01	1.00-1.03	77.594	1.01	1.00-1.02	92.40	1.02	1.00-1.05	NC
Anemia	1.67	1.53-1.83	5.286	1.52	1.36-1.70	5.74	2.17	1.70-2.76	4.77
Neutropenia	1.09	1.00-1.18	NC	1.04	0.95-1.12	NC	1.68	1.10-2.56	13.07
Thrombocytopenia	2.25	1.79-2.83	4.373	2.25	1.79-2.83	4.37	–	–	–
Rash	1.53	1.36-1.72	9.482	1.32	1.16-1.51	11.43	2.31	1.79-2.29	6.09
Pruritus	1.39	1.25-1.55	11.469	1.29	1.14-1.46	14.55	1.72	1.38-2.16	6.96
Death	0.82	0.24-2.84	NC	0.6	0.14-2.48	NC	2.52	0.12-51.73	NC
Fatigue	1.02	0.96-1.09	NC	0.96	0.89-1.04	NC	1.17	1.04-1.33	14.07
DC due to AE	1.69	1.36-2.10	18.036	1.34	1.06-1.70	27.56	3.84	2.19-6.75	9.80

AE: adverse event. DC: discontinuation. RR: risk ratio. CI: confidence interval. NNH: number needed to harm.

4. Anmerkungen/Fazit der Autoren

In conclusion SVR was higher in patients treated with PIs, patients previously exposed to PR showed superior response rates. Specific predictors will determine the best candidates for treatments that will offer real-life therapeutic alternatives.

1. Fragestellung

Qu Y et al., 2015 [60]. Efficacy and safety of simeprevir for chronic hepatitis virus C genotype 1 infection: A meta-analysis	We conducted a meta-analysis of the current published data in clinical trials to gain a profile of the efficacy and safety of simeprevir-based triple therapy in chronic HCV genotype 1 infected patients.
	2. Methodik *Population:* Chronic hepatitis virus C (HCV) **genotype 1** infected patients (aged ≥ 18 years) *Intervention / Komparator:* Simeprevir plus peginterferon and ribavirin combination therapy vs. the standard peginterferon and ribavirin therapy (the control group) *Endpunkte:* The numbers or rates of achieving SVR, rapidvirological response (RVR), incidence of discontinuationand severe adverse events (SAE) *Suchzeitraum (Aktualität der Recherche):* Medline, Embase, Cochranedatabase of systematic reviews, CINAHL, without year limitations (till 16 July 2014) *Anzahl eingeschlossene Studien/Patienten (Gesamt):* 6 Studien (2209 Patienten) *Qualitätsbewertung der Studien:* Jadad scale
	3. Ergebnisdarstellung SVR12 - Meta-analysis showed that the SVR rate at 12 weeks was significantly higher in the simeprevir group than in the control group (RR = 1.69, 95%CI: 1.37—2.08, P < 0.001), while the I^2 was 82.4% (P < 0.001), showing a significant heterogeneity. - In a subgroup analysis according to previous treatment status (**treatment-experienced** or **treatment-naïve**) the RR rates (simeprevir vs. control) were 2.45 (95% CI: 1.79—3.37, P < 0.001; I^2=42.8%) and 1.46 (95% CI: 1.28—1.67, P < 0.001; I^2=52.8%), respectively. RVR - Meta-analysis showed that the RVR rate was significantly higher in the simeprevir group than in the control group (RR = 9.57, 95% CI: 5.82—15.73, P < 0.001, I^2= 63.6%). - For the subgroup analysis according to treatment status, the RR rates (simeprevir vs. control) for **treatment-experienced** and **treatment-naïve** patients were 27.51 (95% CI: 11.57—65.40, P < 0.001) and 6.87 (95% CI: 5.19—9.08, P < 0.001), respectively, while the I^2 were both 0.0%. SAE - Meta-analysis showed that the incidence of SAE was a little lower in the simeprevir group than the control group (RR = 0.67, 95% CI: 0.47—0.94, P = 0.023, I^2= 0.0%), which indicated that there was no increased risk of serious adverse events for the addition of simeprevir.

Critical appraisal

Studies	Method to generate the sequence of randomization	Randomization concealment	Blinding	Withdrawals and drop-outs
Zeuzem, 2014	Not clear	Not clear	Appropriate	Appropriate
Manns, 2014	Appropriate	Appropriate	Appropriate	Appropriate
Jacobson, 2014	Appropriate	Appropriate	Appropriate	Appropriate
Fried, 2013	Appropriate	Not clear	Appropriate	Appropriate
Hayashi, 2014	Appropriate	Appropriate	Appropriate	Appropriate
Forns, 2014	Not clear	Appropriate	Appropriate	Appropriate

4. Anmerkungen/Fazit der Autoren

Simeprevir-based triple therapy significantly increases the SVR12 rate and RVR ratewithout increasing the incidences of SAE and treatment discontinuation due to adverse events. However, further inquiries on the long-term safety of simeprevir are required in future.

Coppola N et al., 2014 [12].

Peg-Interferon Plus Ribavirin with or without Boceprevir or Telaprevir for HCV Genotype 1: A Meta-Analysis on the Role of Response Predictors

1. Fragestellung

A meta-analysis of the currently available clinical trials was undertaken to compare the overall efficacy of triple and dual therapy in patients with CHC due to HCV-1 who were therapy-naive or relapsers to dual therapy in relation to the presence of constitutional, clinical and virological predictors of treatment response.

2. Methodik

Population: **HCV-1** chronic hepatitis patients who were **therapy-naive** or **relapsers** to previous Peg-IFN+ribavirin treatment

Intervention / Komparator: Conventional doses of Peg-IFN α-2a (180µg/week) or Peg-IFN α-2b (1.5µg/kg of body weight/week) plus ribavirin versus Peg-IFN α-2a or α-2b, ribavirin and conventional doses of telaprevir (750 mg three times a day) or boceprevir (800 mg three times a day)

Endpunkte: Sustained virological response

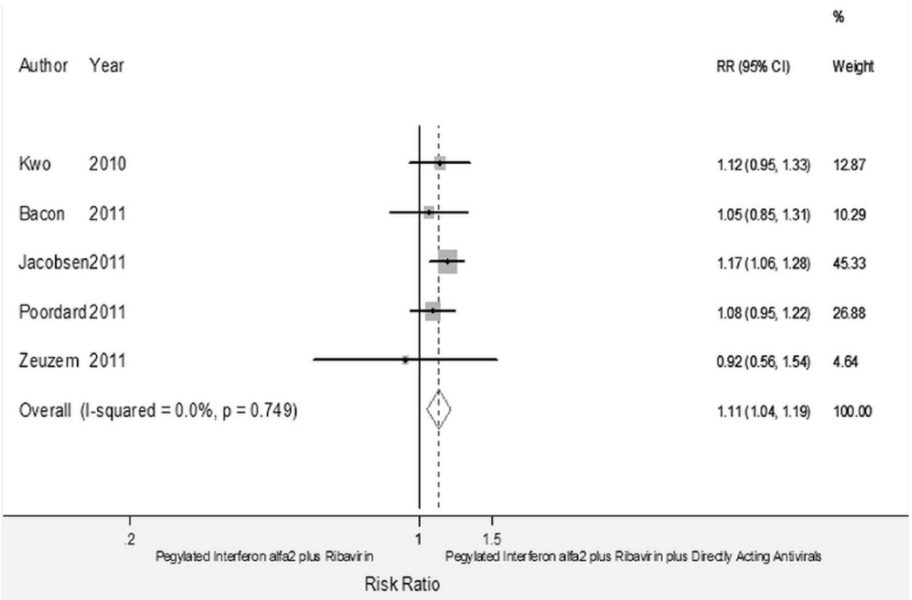
Suchzeitraum (Aktualität der Recherche): MEDLINE, EMBASE, LILACS, and the Cochrane Library (from January 2008 to June 2013)

Anzahl eingeschlossene Studien/Patienten (Gesamt): 7 Studien (Patienten: k. A.)

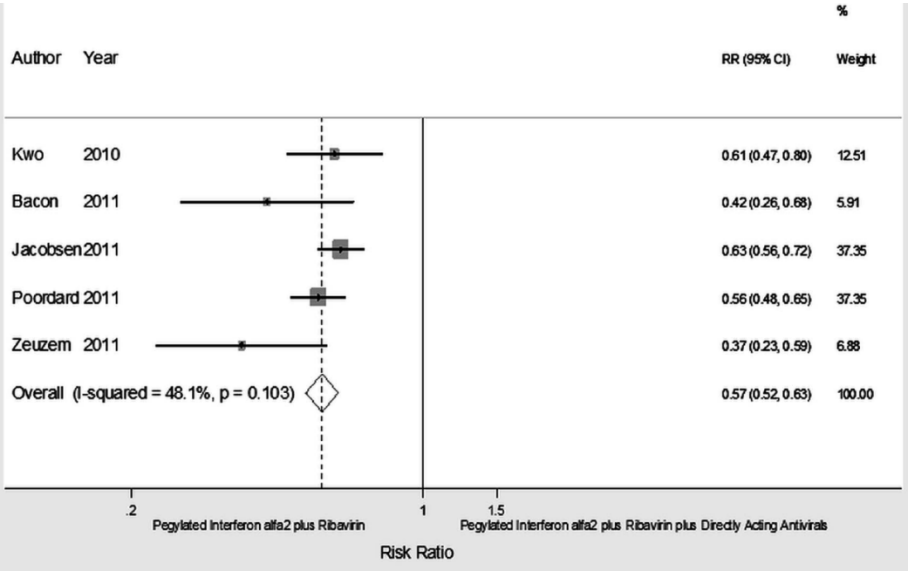
Qualitätsbewertung der Studien: Jadad scale

3. Ergebnisdarstellung

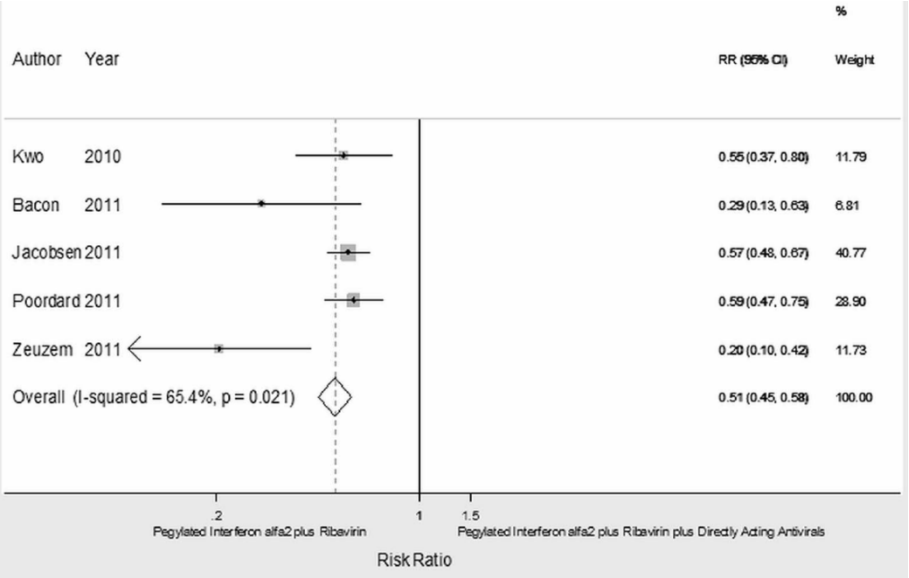
Achievement of SVR in CHC patients with a rapid virological response treated with pegylated interferon a-2 plus ribavirin or pegylated interferon a-2 plus ribavirin plus a direct-acting antiviral



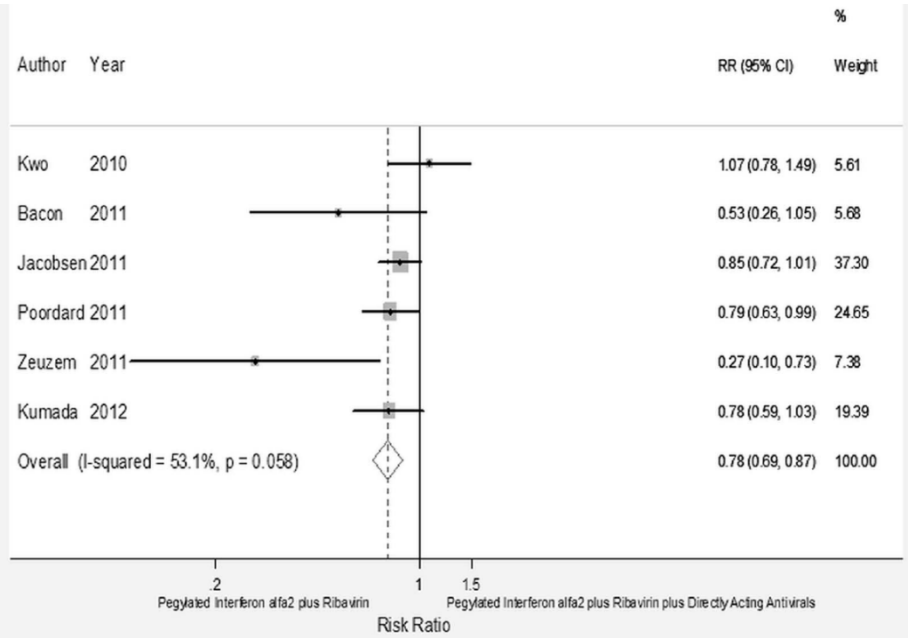
Achievement of SVR in CHC patients **without advanced liver fibrosis** treated with pegylated interferon a-2 plus ribavirin or pegylated interferon a-2 plus ribavirin plus a direct-acting antiviral



Achievement of SVR in CHC patients with **genotype 1b** treated with pegylated interferon a-2 plus ribavirin or pegylated interferon a-2 plus ribavirin plus a direct-acting antiviral



Achievement of SVR in CHC patients with low baseline HCV RNA treated with pegylated interferon a-2 plus ribavirin or pegylated interferon a-2 plus ribavirin plus a direct-acting antiviral



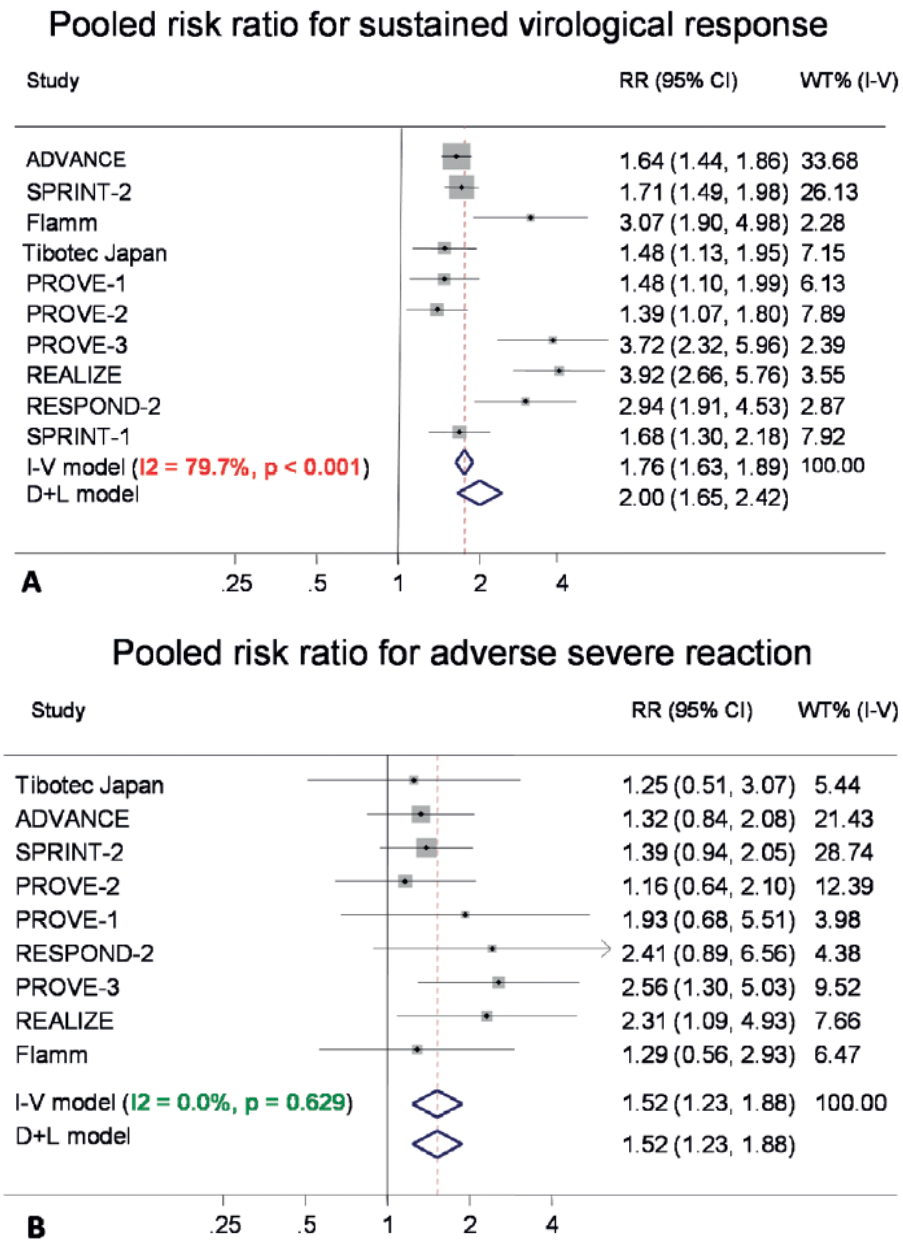
Critical appraisal

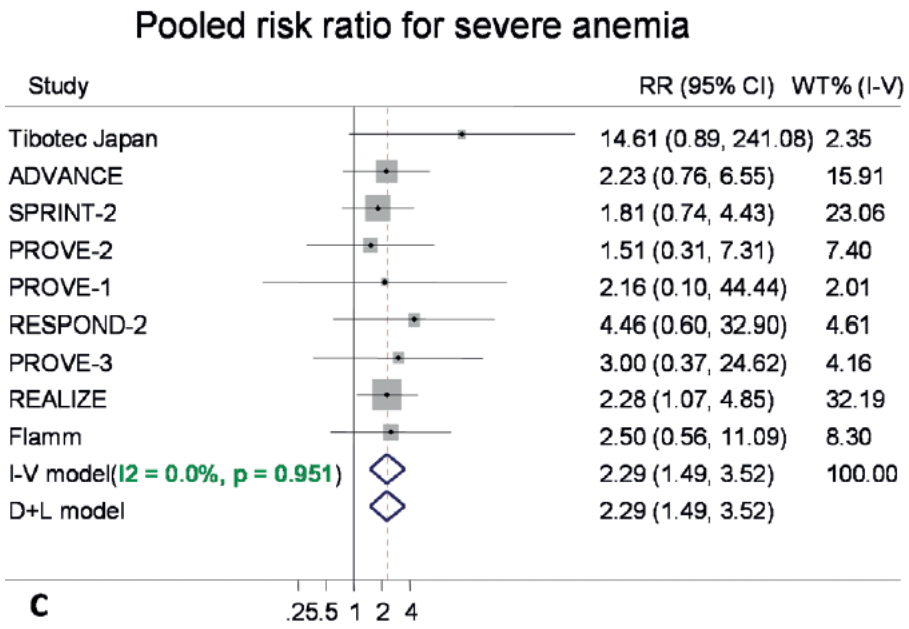
First Author [Reference No.]	Was the treatment randomly allocated?	Was the randomization procedure described and was it appropriate?	Was the trial described as double blind?	Was the method of blinding described and appropriate?	Was the number of withdrawals/ dropouts in each group mentioned?	Jadad Score, Maximum Score = 5
Kwo [28]	Yes	Yes	No	-	Yes	3
Poordad [29]	Yes	Yes	Yes	No	Yes	4
Bacon [30]	Yes	Yes	No	-	Yes	3
Jacobson [31]	Yes	Yes	Yes	No	Yes by group/No drop outs	4
Zeuzem [32]	Yes	Yes	Yes	No	Yes	4
Kumada [33]	Yes	No	No	-	Yes	2
Flamm [34]	Yes	Yes	Yes	No	Yes	4

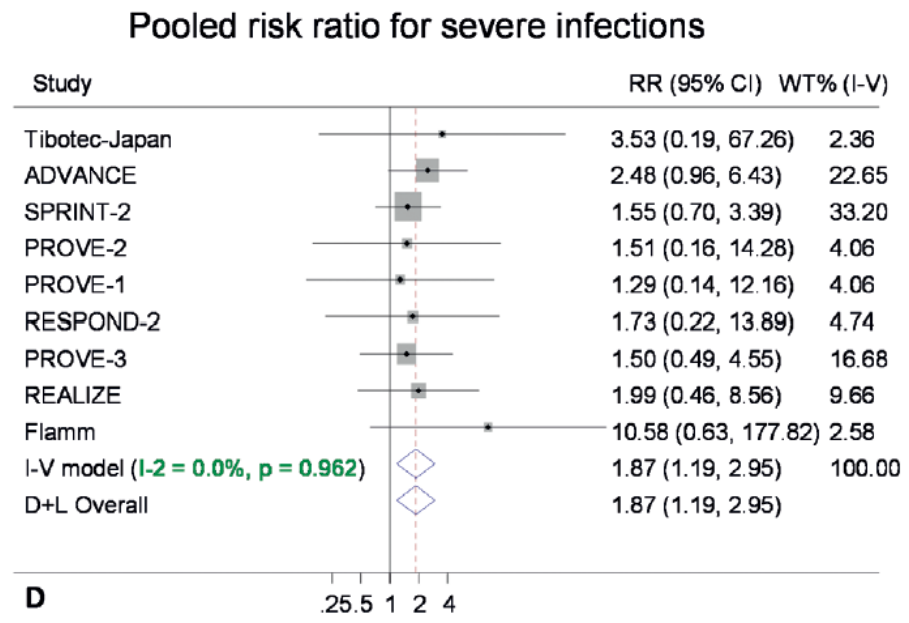
4. Anmerkungen/Fazit der Autoren

Triple therapy provides a significantly higher SVR rate than dual therapy, but dual therapy obtains a significantly higher SVR rate in

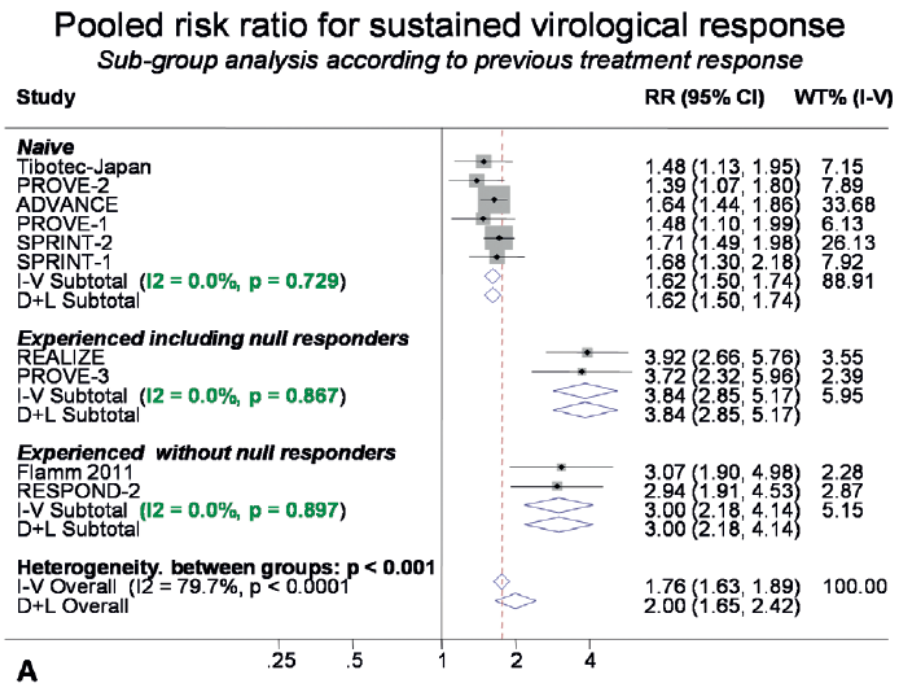
	patients with RVR. The data stress the clinical importance of a 4-week lead-in phase in direct-acting antiviral-based treatment.
Lanini S et al., 2014 [54]. Triple therapy for hepatitis C improves viral response but also increases the risk of severe infections and anaemia: a frequentist meta-analysis approach	**1. Fragestellung** This meta-analysis assesses the efficacy and safety of triple therapy with either boceprevir or telaprevir compared to the standard of care (SoC), pegylated interferon plus ribavirin, in patients chronically infected with genotype 1 hepatitis C virus (HCV).
	2. Methodik *Population:* Adult patients (aged 18 or more) who were infected with **genotype 1** HCV *Intervention / Komparator:* Comparison of Standard of care (SoC) with any combination of peg-IFN alpha and ribavirin plus either boceprevir or telaprevir *Endpunkte:* Sustained virological response, adverse events *Suchzeitraum (Aktualität der Recherche):* PubMed, the Cochrane Controlled Trials Register and the NIH National Clinical Trial Registry (NCT) until 15 April 2013 *Anzahl eingeschlossene Studien/Patienten (Gesamt):* 10 Studien (5312 Patienten) *Qualitätsbewertung der Studien:* sequence generation, allocation concealment, blinding, attrition and early termination
	3. Ergebnisdarstellung Critical appraisal: None of the studies are judged to be at low risk of bias. Meta-analyses for SVR (A), SAE (B), severe anaemia (C), and severe infections (D) The meta-analyses for SVR include 10 RCTs while other meta-analyses include 9 RCTs. SPRINT-1 is not included since all participants in the control arm with detectable HCV-RNA levels at week 24 were allowed to opt for boceprevir plus peg-IFN and ribavirin. RR: risk ratio; 95%CI: 95% confidence interval; I-V: inverse variance fixed effect model; D+L: derSimonian and Laird random effect model; WT%: proportion weight in the I-V model.


Pooled risk ratio for sustained virological response
Study
RR (95% CI)
WT% (I-V)
ADVANCE 1.64 (1.44, 1.86) 33.68
SPRINT-2 1.71 (1.49, 1.98) 26.13
Flamm 3.07 (1.90, 4.98) 2.28
Tibotec Japan 1.48 (1.13, 1.95) 7.15
PROVE-1 1.48 (1.10, 1.99) 6.13
PROVE-2 1.39 (1.07, 1.80) 7.89
PROVE-3 3.72 (2.32, 5.96) 2.39
REALIZE 3.92 (2.66, 5.76) 3.55
RESPOND-2 2.94 (1.91, 4.53) 2.87
SPRINT-1 1.68 (1.30, 2.18) 7.92
I-V model (I2 = 79.7%, p < 0.001) 1.76 (1.63, 1.89) 100.00
D+L model 2.00 (1.65, 2.42)
.25
.5
1
2
4
A
Pooled risk ratio for adverse severe reaction
Study
RR (95% CI)
WT% (I-V)
Tibotec Japan 1.25 (0.51, 3.07) 5.44
ADVANCE 1.32 (0.84, 2.08) 21.43
SPRINT-2 1.39 (0.94, 2.05) 28.74
PROVE-2 1.16 (0.64, 2.10) 12.39
PROVE-1 1.93 (0.68, 5.51) 3.98
RESPOND-2 2.41 (0.89, 6.56) 4.38
PROVE-3 2.56 (1.30, 5.03) 9.52
REALIZE 2.31 (1.09, 4.93) 7.66
Flamm 1.29 (0.56, 2.93) 6.47
I-V model (I2 = 0.0%, p = 0.629) 1.52 (1.23, 1.88) 100.00
D+L model 1.52 (1.23, 1.88)
.25
.5
1
2
4
B

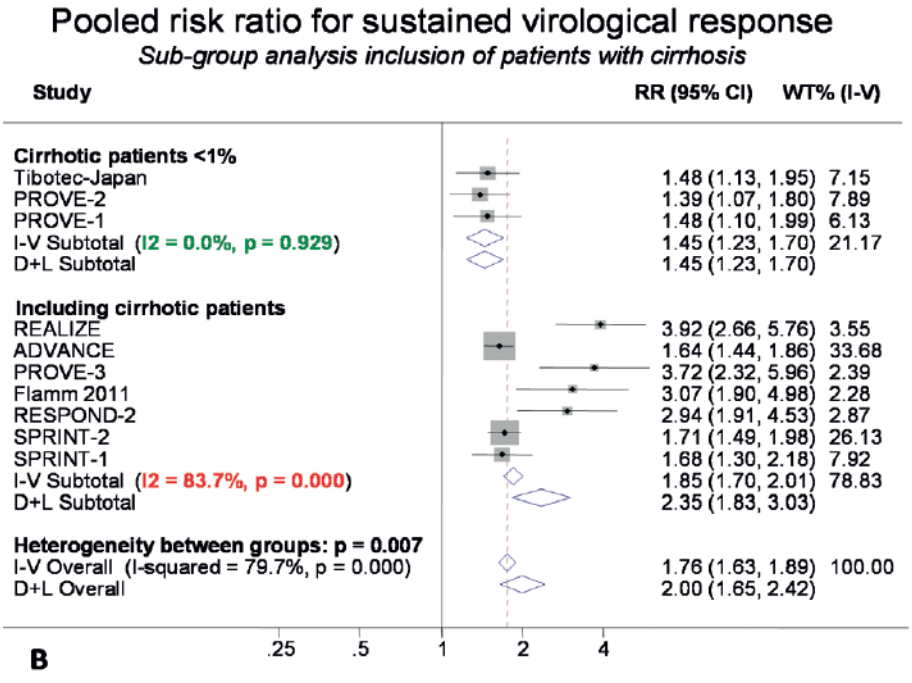




A: Subgroup analyses for **previous response** to interferon therapy



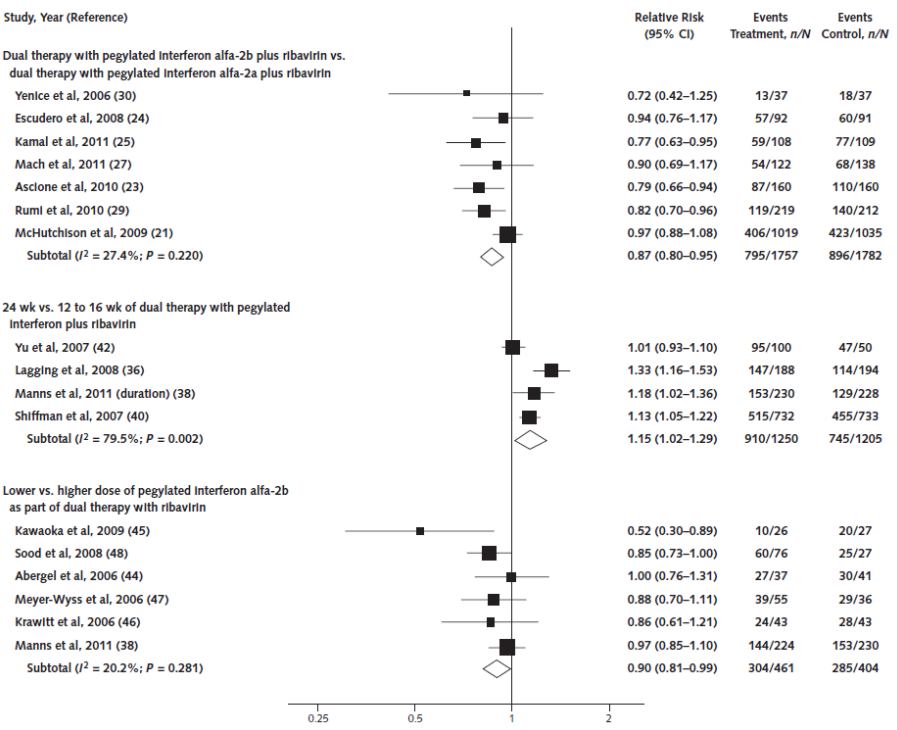
B: Subgroup analyses for having included **more than 1% of cirrhotic patients**



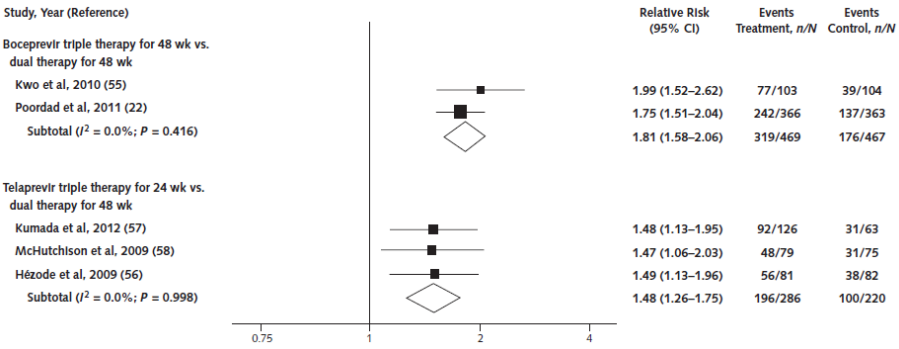
4. Anmerkungen/Fazit der Autoren

This study provides evidence that triple therapy with boceprevir and telaprevir can remarkably increase both the proportion of SVR and the occurrence of SAEs.

Chou R et al., 2013 [11]. Comparative Effectiveness of Antiviral Treatment for Hepatitis C Virus Infection in Adults: A Systematic Review	**1. Fragestellung** To compare benefits and harms of antiviral regimens for chronic HCV infection in treatment-naive adults. 1) What is the comparative effectiveness of antiviral treatment in improving health outcomes in patients with HCV infection, and does it vary according to patient subgroup characteristics (including, but not limited to, HCV genotype, age, race, sex, stage of disease, or genetic markers)? 2) What is the comparative effectiveness of antiviral treatments on the rate of sustained virologic response (SVR), and does it vary according to patient subgroup characteristics? 3) What are the comparative harms associated with antiviral treatments, and do they vary according to patient subgroup characteristics?
	2. Methodik *Population:* **Antiviral-naive** patients wih chronic HCV (nicht nur Genotyp 1 eingschlossen) *Intervention / Komparator:* Comparison of dual therapy with pegylated interferon alfa-2b plus ribavirin versus pegylated interferon alfa-2a plus ribavirin; triple therapy with pegylated interferon (alfa-2a or -2b), ribavirin, and either telaprevir or boceprevir versus dual therapy; or different doses or durations of dual or triple therapy *Endpunkte:* Sustained virologic response, adverse events *Suchzeitraum (Aktualität der Recherche):* Ovid MEDLINE from 1947 to August 2012, the Cochrane Library Database (through the first quarter of 2012), Embase (1976 to August 2012), Scopus (1960 to August 2012), PsychINFO (1806 to August 2012), clinical trials registries, and grants databases *Anzahl eingeschlossene Studien/Patienten (Gesamt):* 90 Studien (Patienten: k. A.) *Qualitätsbewertung der Studien:* Two investigators independently applied predefined criteria to assess study quality as good, fair, or poor. Discrepancies were resolved through consensus.
	3. Ergebnisdarstellung Sustained virologic response, comparisons of dual-therapy regimens Relative risks >1 favor dual therapy with pegylated interferon alfa-2b over dual therapy with pegylated interferon alfa-2a, 24 wk over 12 to 16 wk, and lower-dose versus higher-dose pegylated interferon alfa-2b



Sustained virologic response, triple therapy with a protease inhibitor versus dual therapy
Relative risks > 1 favor triple therapy



Harms of Triple Therapy with Boceprevir or Telaprevir With Pegylated Interferon, and Ribavirin Versus Dual Therapy With Pegylated Interferon α-2b Plus Ribavirin

Therapy Harms	Relative Risk (95 CI); I^2, %	Pooled Event Rates (95 CI), %		Risk Difference (95 CI), *percentage points*	Trials, *n* (References)
		Intervention 1	Intervention 2		
Dual therapy with pegylated interferon α-2b plus ribavirin versus dual therapy with pegylated interferon α-2a plus ribavirin*					
Serious adverse events	0.76 (0.61 to 0.95); 0	4.7 (0 to 1.3)	6.3 (0 to 17)	−1.0 (−3.8 to 1.8)	2 (21, 29)
Withdrawal due to adverse events	1.1 (0.73 to 1.7); 42	7.7 (2.9 to 13)	6.6 (1.7 to 12)	0.8 (−2.0 to 3.6)	6 (21, 23, 25, 28–30)
Neutropenia	0.61 (0.46 to 0.83); 38	9.9 (4.5 to 15)	15 (7.4 to 22)	−3.0 (−6.1 to 0.0)	5 (21, 23, 24, 28, 29)
Anemia	0.97 (0.72 to 1.3); 64	26 (5.7 to 47)	24 (7.0 to 42)	0.9 (−3.9 to 5.7)	4 (21, 23, 28, 29)
Thrombocytopenia	0.87 (0.59 to 1.3); 0	8.8 (1.1 to 16)	10 (1.7 to 19)	−0.9 (−3.1 to 1.2)	3 (23, 28, 29)
Depression	1.1 (0.92 to 1.2); 0	12 (0 to 25)	12 (2.2 to 23)	0.6 (−1.9 to 3.1)	3 (21, 23, 28)
Fatigue	1.0 (0.96 to 1.1); 7	55 (40 to 69)	57 (48 to 66)	0.9 (−3.7 to 5.6)	3 (21, 23, 28)
Influenza-like symptoms	0.98 (0.85 to 1.1)	62 (56 to 68)	63 (57 to 70)	−1.1 (−10 to 8.0)	1 (29)
Headache	1.1 (1.1 to 1.2); 0	30 (7.2 to 53)	29 (10 to 47)	3.7 (−1.6 to 9.0)	3 (21, 23, 28)
Myalgia	1.1 (0.86 to 1.5); 33	18 (7.2 to 30)	18 (12 to 24)	1.9 (−3.8 to 7.5)	3 (21, 23, 28)
Rash	0.79 (0.71 to 0.88); 0	39 (5.4 to 72)	49 (7.5 to 90)	−7.6 (−14 to −1.2)	2 (21, 28)
Triple therapy with boceprevir versus dual therapy for 48 wk†					
Serious adverse events	1.4 (0.93 to 2.2)	12 (8.9 to 16)	8.5 (5.7 to 11)	3.8 (−0.7 to 8.2)	1 (22)
Withdrawal due to adverse events	1.1 (0.77 to 1.4); 0	13 (5.3 to 20)	12 (4.1 to 20)	0.8 (−3.5 to 5.2)	2 (22, 55)
Neutropenia	1.8 (1.5 to 2.3); 0	33 (29 to 38)	18 (14 to 22)	15 (9.8 to 21)	2 (22, 55)
Anemia	2.0 (1.4 to 2.8); 0	25 (0 to 67)	12 (0 to 34)	12 (−18 to 41)	2 (22, 55)
Thrombocytopenia	3.2 (1.2 to 8.2); 0)	3.8 (2.1 to 5.6)	1.4 (0.2 to 2.6)	2.8 (0.8 to 4.8)	2 (22, 55)
Depression	0.87 (0.65 to 1.2)	19 (15 to 23)	22 (18 to 26)	−2.9 (−8.7 to 2.9)	1 (22)
Fatigue	1.1 (0.82 to 1.5); 83	64 (50 to 77)	59 (54 to 63)	5.9 (−12 to 2.4)	2 (22, 55)
Influenza-like symptoms	0.80 (0.58 to 1.1); 27	19 (11 to 27)	25 (21 to 29)	−4.7 (−10 to 1.0)	2 (22, 55)
Headache	1.1 (0.96 to 1.3); 0	48 (42 to 54)	42 (38 to 47)	4.7 (−1.6 to 11)	2 (22, 55)
Myalgia	0.97 (0.76 to 1.2)	25 (21 to 30)	26 (21 to 30)	−0.8 (−7.1 to 5.6)	1 (22)
Rash	1.1 (0.81 to 1.4)	24 (20 to 28)	23 (18 to 27)	1.2 (−5.0 to 7.3)	1 (22)
Dysgeusia	2.5 (2.0 to 3.2); 0	35 (20 to 50)	13 (4.6 to 22)	23 (17 to 29)	2 (22, 55)
Triple therapy with telaprevir for 24 weeks versus dual therapy for 48 wk‡					
Serious adverse events	1.0 (0.50 to 2.0)	16 (8.1 to 24)	16 (7.9 to 24)	0.2 (−11 to 11)	1 (56)
Withdrawal due to adverse events	1.1 (0.45 to 2.6); 60	15 (10 to 20)	14 (0 to 29)	1.0 (−11 to 13)	2 (56, 57)
Neutropenia	0.81 (0.51 to 1.3); 53	41 (0 to 94)	48 (0.4 to 96)	−7.7 (−17 to 1.5)	2 (57, 58)
Anemia	1.3 (1.1 to 1.5); 0	52 (6.4 to 97)	39 (6.5 to 71)	13 (5.8 to 21)	3 (56–58)
Thrombocytopenia	1.8 (1.2 to 2.5)	64 (56 to 73)	36 (25 to 48)	28 (13 to 42)	1 (57)
Depression	1.0 (0.66 to 1.6); 0	21 (14 to 27)	20 (14 to 26)	0.4 (−8.4 to 9.3)	2 (56, 58)
Fatigue	0.96 (0.74 to 1.2); 53	51 (26 to 76)	54 (29 to 78)	−2.5 (−15 to 9.8)	3 (56, 58)
Influenza-like symptoms	0.87(0.63 to 1.2); 50	35 (15 to 55)	40 (24 to 56)	−5.1 (−16 to 5.7)	3 (56–58)
Headache	0.83 (0.69 to 1.0); 0	42 (36 to 48)	52 (43 to 61)	−8.8 (−18 to −0.01)	3 (56–58)
Myalgia	0.76 (0.43 to 1.3); 57	18 (7.4 to 28)	23 (17 to 28)	−5.4 (−15 to 4.4)	3 (56, 58)
Rash	1.4 (1.1 to 1.7); 0	49 (36 to 61)	35 (28 to 42)	14 (5.0 to 22)	3 (56–58)

RR = relative risk.
* Intervention 1: interferon α-2b; intervention 2: interferon α-2a.
† Intervention 1: triple therapy with pegylated interferon and ribavirin for 48 wk with boceprevir from weeks 5 to 24; intervention 2: dual therapy for 48 wk.
‡ Intervention 1: triple therapy with telaprevir, pegylated interferon α-2, and ribavirin for 12 wk followed by dual therapy for 12 wk; intervention 2: dual therapy for 48 wk.

4. Anmerkungen/Fazit der Autoren

SVR rates for **genotype 1** infection are higher with triple therapy that includes a protease inhibitor than with standard dual therapy. An SVR after antiviral therapy appears associated with improved clinical outcomes.

Goralczyk AD et al., 2013 [29].

Treatment of chronic HCV genotype 1 infection with telaprevir: a Bayesian mixed treatment comparison of fixed-length and response-guided treatment regimens in treatment-naïve and –experienced patients.

1. Fragestellung

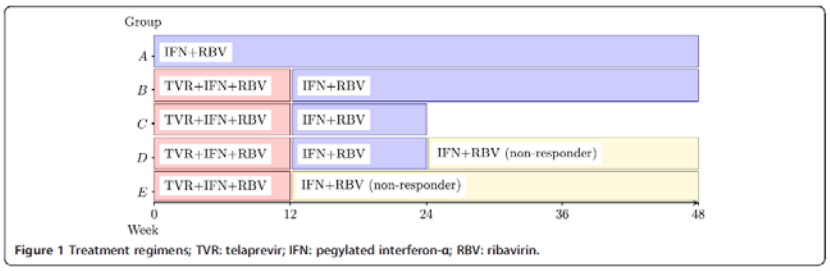
This systematic review and Bayesian mixed-treatment-comparison (MTC) aimed to compare the efficacy and safety of standard-therapy with pegylated-interferon-α/ribavirin (Peg-IFN-α/RBV (48 weeks), group A), FLT with TVR, Peg-IFN-α/RBV for 12 weeks with a long (+36 weeks, group B) or short (+12 weeks, group C) tail of Peg-IFN-α/RBV treatment, and RGT with 12 weeks of TVR, Peg-IFN-α/RBV followed by 12 weeks of Peg-IFN-α/RBV (group D) or no therapy (group E).

2. Methodik

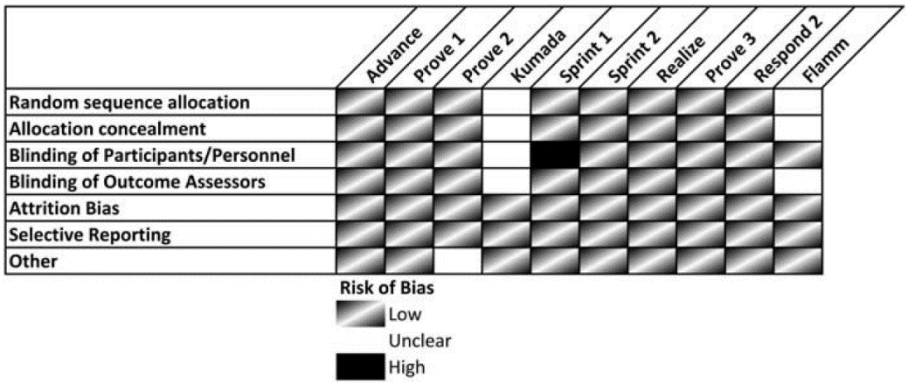
Population: Patients with a chronic HCV genotype 1 infection

Intervention / Komparator: Compare the efficacy of TVR with conventional doses of Peg-IFN-α-2a (180 µg/week) or Peg-IFN-α-2b (1.5 µg/kg of body weight/week), both in combination with RBV

Endpunkt: SVR

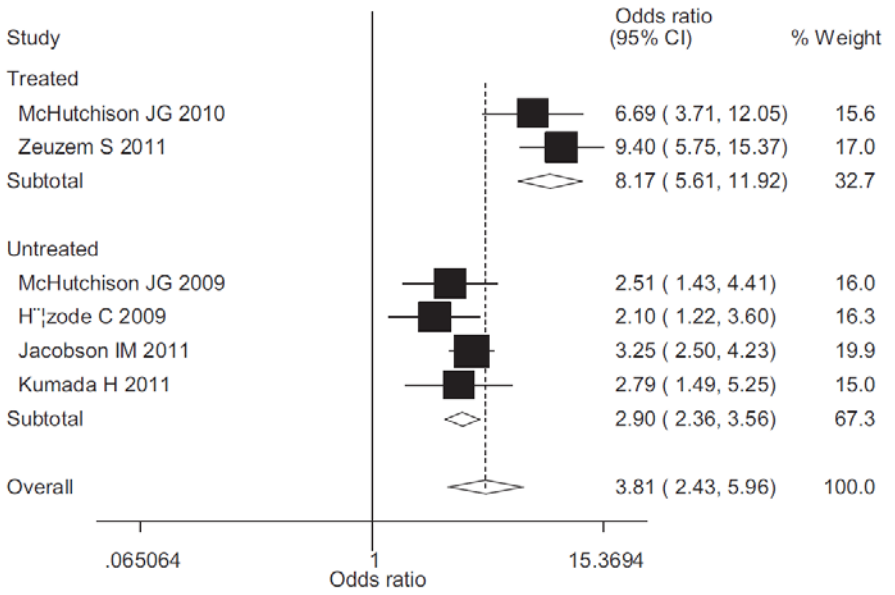
	Suchzeitraum (Aktualität der Recherche): A systematic literature search was performed without language restrictions from inception to 25 February 2013 in the following databases: Medline/PubMed and Web of Science. *Anzahl eingeschlossene Studien/Patienten (Gesamt):* 7 Studien (3505 Patienten) *Qualitätsbewertung der Studien:* Sequence generation, allocation concealment, blinding of participants and outcome, completeness of follow-up, incomplete outcome data
	3. Ergebnisdarstellung Behandlungsgruppen:  Figure 1 Treatment regimens; TVR: telaprevir; IFN: pegylated interferon-α; RBV: ribavirin. • Compared to standard-treatment (group A), treatment-naïve patients allocated to groups B, C, and D were significantly more likely to achieve sustained-virological-response (SVR, odds ratios (OR): B vs. A 3.5 (credibility interval [CrI] 2.2-5.4), C vs. A 3.0 (CrI 1.8-4.9), D vs. A 3.4 (CrI 2.5-4.6)) • Treatment-experienced patients achieved increased SVR rates when they were treated in group B (OR: 8.2 (CrI 5.0-13.5)), C (OR 7.0 (CrI 3.9-12.8)), or simulated group D (OR 8.2 (CrI 4.3-15.3)). • Patients treated with short RGT (simulated group E) did also have a significant improvement when they were treatment-experienced (simulated OR 3.6 (CrI 1.6-8.2)), whereas the effect was not significant in treatment-naïve patients (OR E vs. A 1.6 (CrI 0.9-2.7))
	4. Anmerkungen/Fazit der Autoren Long FLT and RGT regimens are useful treatment options for HCV-genotype-1 in both treatment-naïve and -experienced patients. A short 24-weeks FLT regimen does not seem to be inferior and should further be evaluated in clinical trials to reduce side effects and costs of treatment.
Kieran J et al., 2013 [50]. The Relative Efficacy of Boceprevir and Telaprevir in the Treatment of	**1. Fragestellung** We undertook a mixed treatment comparison to determine the relative differences in efficacy between boceprevir and telaprevir when used as a third agent in HCV genotype 1 treatment.
	2. Methodik *Population:* Studies of patients aged >18 y chronically infected with HCV **genotype 1**

Hepatitis C Virus Genotype 1	Subpopulations (1) patients with chronic HCV genotype 1 infection who were **treatment-naive** and **(2)** patients with chronic HCV genotype 1 infection who were **treatment-experienced** *Intervention / Komparator:* Studies where patients were treated with pegylated interferon and ribavirin in combination with either telaprevir or boceprevir. Study arms which evaluated telaprevir or boceprevir for unlicensed durations or without both pegylated interferon and ribavirin at standard doses were excluded. *Endpunkte:* Rates of sustained viral response in patients receiving pegylated interferon and ribavirin in combination with either telaprevir or boceprevir *Suchzeitraum (Aktualität der Recherche):* Medline/PubMed, Embase, The Cochrane Library, and Science Citation Index were searched on 1 November 2011 and the searches were re-run on 3 September 2012 *Anzahl eingeschlossene Studien/Patienten (Gesamt):* 10 Studien (Patienten: k. A.) *Qualitätsbewertung der Studien:* Cochrane risk of bias tool
	3. Ergebnisdarstellung **Treatment-Naive Patients** - In the total treatment-naive population (n = 2716), the addition of boceprevir to a backbone therapy of peg-IFN/RBV resulted in more efficacious treatment than peg-IFN/RBV alone (OR, 3.06 [95% CI, 2.43–3.87]). - Similarly, the addition of telaprevir to a backbone therapy of peg-IFN/RBV resulted in more efficacious treatment than peg-IFN/RBV alone (OR, 3.24 [95% CI, 2.56–4.10]). - There was insufficient evidence to detect a difference between telaprevir and boceprevir when added to standard of care (OR, 1.06 [95% CI, 0.75–1.47]). - The model did not detect a significant difference in efficacy between either triple therapy regimen in this subpopulation (telaprevir vs boceprevir: OR, 1.67 [95% CI, 0.48–6.05]) **Treatment-Experienced Patients** - In the overall treatment-experienced population (n = 1495), there was a significant improvement in SVR when the regimens including boceprevir were compared with standard of care (OR, 6.53 [95% CI, 4.20–10.32]) and when regimens containing telaprevir were compared with standard of care (OR, 8.32 [95% CI, 5.69–12.36]). - There was insufficient evidence to detect a difference in SVR between those regimens utilizing telaprevir as their third agent and those utilizing boceprevir as their third agent (OR, 1.27 [95% CI, 0.71–2.30]).

	- In the model considering those patients who had prior treatment relapse (n = 841), there was a significant difference in efficacy that favored telaprevir (telaprevir vs boceprevir: OR, 2.61 [95% CI, 1.24–5.52]). - Both agents were significantly better than standard of care (boceprevir vs standard of care: OR, 6.25 [95% CI, 3.79–10.53]; telaprevir vs standard of care: OR, 16.31 [95% CI, 9.52–28.51]). - In patients who did not have a prior treatment relapse (n = 654), there was no significant difference in efficacy detected between telaprevir and boceprevir (OR, 0.44 [95% CI, .09–1.72]). Critical appraisal 
	4. Anmerkungen/Fazit der Autoren Telaprevir had greater relative efficacy than boceprevir in patients who had previously relapsed. There was insufficient evidence to detect a difference in treatment outcomes between the 2 agents in the overall population. It was not possible to determine relative efficacy for subgroups such as patients with cirrhosis owing to small numbers.
Sitole M et al., 2013 [65]. Telaprevir Versus Boceprevir in Chronic Hepatitis C: A Meta-Analysis of Data from Phase II and III Trials **Siehe auch:** **Canadian Agency for Drugs and Technologies in Health, 2012 [9].** Retreatment, Switching and	**1. Fragestellung** This meta-analysis compared 24- and 48-week sustained viral responses (SVR) and drug-related adverse events (AEs) between telaprevir and boceprevir triple-therapy regimens in the treatment of chronic HCV infection.
	2. Methodik *Population:* **Treatment-naive** and **treatment-experienced** patients with chronic HCV **genotype 1** infection *Intervention / Komparator:* Telaprevir or boceprevir or placebo + Peg-IFN + RBV *Endpunkte:* SVR at 24 weeks was selected as an end point of interest, and SVR at 48 weeks, when available and reported, was also included. Other end points explored were AEs resulting in discontinuation of the study drug and AEs commonly reported with the use of either telaprevir (anemia, diarrhea, nausea, pruritis, and rash) or boceprevir (anemia, chills, diarrhea, and dysgeusia).

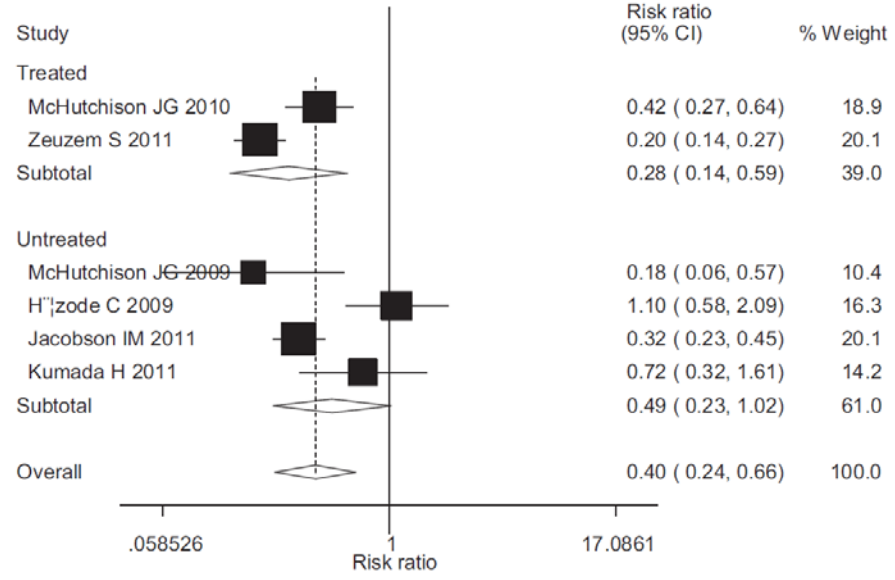
Extended Therapy with Boceprevir and Telaprevir for Chronic Hepatitis C Infection: A Review of the Clinical Effectiveness and Safety **Siehe auch:** **Park C et al., 2014 [56].** Efficacy and safety of telaprevir and boceprevir in patients with hepatitis C genotype 1: a meta-analysis	*Suchzeitraum (Aktualität der Recherche):* MEDLINE, EMBASE, and Cochrane databases (January 1995 to October 2012) *Anzahl eingeschlossene Studien/Patienten (Gesamt):* 8 Studien (Patienten: k. A.) *Qualitätsbewertung der Studien:* Jadad scale
	3. Ergebnisdarstellung Critical appraisal: All of the included studies had a Jadad scale between 3 and 5. *Telaprevir* **Treatment-naïve** - SVR at 24 weeks was greater in the telaprevir + Peg-IFN + RBV treated group compared with the control group (OR = 3.31; 95% CI, 2.27–4.82; P < 0.0001) - SVR at 48 weeks was greater in the telaprevir + Peg-IFN + RBV treated group c - ompared with the control group (OR = 1.98; 95% CI, 1.42–2.76; P < 0.0001) - There was less investigator-defined relapse among telaprevir-treated patients compared with the control group (OR = 0.24; 95% CI, 0.15–0.37; P < 0.0001) **Treatment-experienced** - SVR rates at 24 weeks were similar between the active and control groups (OR = 4.21; 95% CI, 1.83–9.72; P < 0.001) - 48-week SVR rates were similar between the triple-therapy and control groups (OR = 8.46; 95% CI, 5.72–12.50; P < 0.0001) - There was not less investigator-defined relapse among telaprevir-treated patients compared with the control group (OR = 0.61; 95% CI, 0.05–8.13; P < 0.71) *Boceprevir* **Treatment-naïve** - 24-week SVR was improved in the group that received boceprevir compared with controls (OR = 3.55; 95% CI, 2.66–4.56; P < 0.0001) - 48-week SVR was improved in the group that received boceprevir compared with the control group (OR = 1.98; 95% CI, 1.42–2.76) **Treatment-experienced** - 24-week SVR was improved in the group that received boceprevir compared with controls (OR = 7.34; 95% CI, 3.92–13.9; P < 0.0001) - 48-week SVR was improved in the group that received boceprevir compared with the control group (OR = 8.46; 95% CI, 5.72–12.5) *Telaprevir Versus Boceprevir* - An indirect treatment comparison between telaprevir and boceprevir favored telaprevir for inducing 24-week SVR in

	treatment-naive patients (OR = 1.78; 95% CI, 1.39–2.28; P < 0.0001) - however, the rates of 48-week SVR in treatment-naive patients were similar between telaprevir and boceprevir (OR = 0.82; 95% CI, 0.6–1.11; P = 0.2) - Telaprevir and boceprevir were also similar regarding discontinuation from ADRs (OR = 1.23; 95% CI, 0.95–1.6; P = 0.11)
	4. Anmerkungen/Fazit der Autoren Based on the findings from this meta-analysis, telaprevir or boceprevir combined with Peg-IFN + RBV had favorable short-term data on SVR while resulting in more drug-related AEs. Extended follow-up is required to determine whether these agents offer a reduction in the risk for chronic hepatitis C genotype 1–related mortality and/or hospitalization.
Yang D et al., 2013 [70]. The Efficacy and Safety of Telaprevir-based Regimens for Treating Chronic Hepatitis C Virus Genotype 1 Infection: A Meta-analysis of Randomized Trials	**1. Fragestellung** To assess the efficacy and safety of telaprevir in patients with chronic HCV genotype 1 infection.
	2. Methodik *Population:* Patients with chronic hepatitis C **genotype 1** according to established diagnostic criteria *Intervention / Komparator:* Comparing the standard PR regimen (24-48 weeks of peginterferon and ribavirin, PR group) with the addition of telaprevir (combination of telaprevir and the standard regimen of peginterferon and ribavirin, TPR group) *Endpunkte:* The primary outcomes included the rate of sustained virologic response (SVR) and viral relapse. The secondary outcomes included serious adverse events and the main types of adverse events. *Suchzeitraum (Aktualität der Recherche):* Pubmed (updated to August 2011), Embase (from 1980 to August 2011) and the Cochrane Central Register of Controlled Trials (Cochrane Library Issue 3, 2011) *Anzahl eingeschlossene Studien/Patienten (Gesamt):* 6 Studien (2758 Patienten) *Qualitätsbewertung der Studien:* Jadad scale
	3. Ergebnisdarstellung Critical appraisal: All of the included studies had a Jadad scale of 5. Meta-analysis of the sustained virologic response rate comparing the TPR group with the RP group (ORs are shown with 95% CIs, and an OR > 1 corresponds to an odds towards the TPR group)

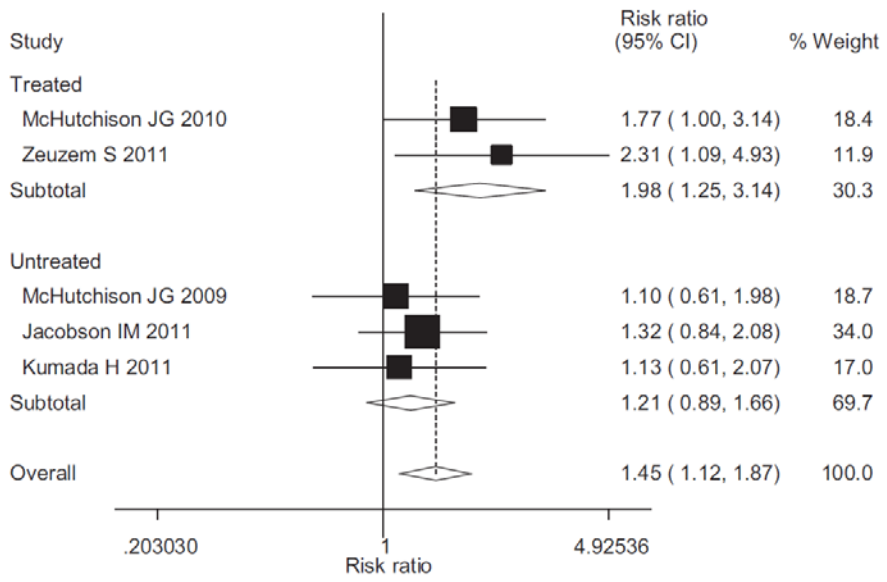


Meta-analysis of the relapse rate comparing the TPR group with the RP group

(RRs are shown with 95% CIs, and an RR < 1 corresponds to an advantage towards the TPR group)



Meta-analysis of the rate of serious adverse events comparing the TPR group with the RP group (RRs are shown with 95% CIs, and an RR < 1 corresponds to an advantage towards the TPR group)

	
	4. Anmerkungen/Fazit der Autoren Telaprevir-based regimens can significantly increase the SVR rate and reduce the relapse rate in patients with chronic HCV genotype 1 infection. However, the safety of telaprevir-based regimens still requires further study.
Coppola N et al., 2012 [13]. Efficacy of pegylated interferon α-2a and α-2b in patients with genotype 1 chronic hepatitis C: a meta-analysis	**1. Fragestellung** The purpose of this meta-analysis was to provide a systematic review of all randomized and non-randomized trials in which the efficacy of Peg-IFN α-2a had been compared with that of Peg-IFN α-2b, both in combination with ribavirin, in the treatment of patients with genotype 1 chronic HCV.
	2. Methodik *Population:* Antiviral **therapy-naïve HCV-genotype 1** patients *Intervention / Komparator:* Peg-IFN α-2a versus Peg-IFN α-2b in combination with ribavirin *Endpunkt:* Achievement of the virological outcomes *Suchzeitraum (Aktualität der Recherche):* MEDLINE, EMBASE, LILACS, and the Cochrane Library, from January 2000 to December 2011 *Anzahl eingeschlossene Studien/Patienten (Gesamt):* 7 Studien (Patienten: k. A.) *Qualitätsbewertung der Studien:* Jadad scale
	3. Ergebnisdarstellung Critical appraisal

First Author [Reference No.]	Chalmers 1	2	3	4	5	6	7	8	9	10	11	Protocol	12	13	14	15	16	17	18	19	20	21	22	Data analysis	Overall	Jadad score 1	2	3	Overall
Yenice [16]	1	0	1	0	0	0	0	0	0	1	0	0.17	0	1	0	0	0	0	0	1	0	0	0	0.23	0.2	1	0	0	1
Di Bisceglie [17]	1	0	1	0	0	0	0	1	1	1	n. a.	0.35	0	1	0	0	1	0	0	1	0	1	0	0.44	0.39	1	0	0	1
Escudero [18]	1	0	1	0	0	0	0	0	0	0	0	0.11	1	1	0	0	1	1	0	1	0	1	0	0.61	0.31	0	0	0	0
McHutchison [19]	1	1	1	1	0	0	0	1	1	1	0	0.58	1	1	0	0	1	1	0	1	0	1	0	0.61	0.6	2	0	1	3
Ascione [20]	1	1	1	1	0	0	0	1	1	1	0	0.54	1	1	0	n. a.	1	1	0	1	0	1	0	0.67	0.59	2	0	1	3
Lee [21]	1	0	1	0	0	0	1	0	0	1	0	0.15	1	1	0	0	0	1	0	1	0	1	0	0.54	0.37	0	0	0	0
Rumi [22]	1	1	1	1	0	0	0	1	1	1	0	0.54	1	1	0	n. a.	1	1	0	1	0	1	0	0.67	0.59	2	0	1	3

For the Chalmers et al. method: 0 is "Non adequate", 1 is "Adequate" for the following items: 1 Selection description; 2 Number and reasons for eligible patients not included in the study; 3 Regimen definition; 4 Blinding of Randomization; 5 Blinding of Patients to therapy; 6 Blinding of Physicians/observers to therapy; 7 Blinding of Physicians/observers to ongoing results; 8 Regimen definition; 9 Statistical estimate of sample size; 10 Testing randomization; 11 Testing compliance; 12 Dates of study; 13 Results of prerandomization; 14 Both test statistics and *P* value given; 15 Post beta estimate; 16 Confidence intervals given; 17 Regression/correlation; 18 Statistical analysis; 19 Number and reasons for patients withdrawn after randomization; 20 Withdrawals handled in several ways; 21 Side effects discussion; 22 Subgroups retrospective analysis. For the Jadad et al. the points are assigned for the following items: 1 Randomization; 2 Double-blinding; 3 Withdrawals and drop-out.
n.a. not applicable.

Summary of meta-analysis results in the achievement of the virological outcome by Pegylated interferon α-2a and α-2b plus ribavirin in patients with genotype 1 chronic hepatitis C

Outcomes	N° of studies	N° of patients α-2a/α-2b	N° and (%) of events α-2a/α-2b	RR (efficacy)	95% CI (efficacy)	*p*	Heterogeneity test (Q;*p*;I^2,%)
Rapid Virological Response	4 [17-19,22]	1,374/1,355	186(13.5)/174(12.8)	1.05	0.87–1.27	0.62	3.8;0.28;21.1
Early Virological Response	5[17-19,21,22]	1,395/1,371	649(46.5)/572(38.4)	1.12	1.03–1.22	0.011	7.58;0.14;42.8
End of Treatment Response	5[16,18,19,21,22]	1,243/1,217	782(62.9)/627(51.5)	1.22	1.14–1.31	<0.0001	7.6;0.11;47.3
	5*[16,18,19,21,22]	921/879	544(59)/403(45.8)	1.29	1.18–1.41	<0.0001	8.37;0.08;52.1
Sustained Virological Response	6[16,18-22]	1,336/1,310	574(43)/521(39.8)	1.08	0.99–1.18	0.098	9.97;0.08;49.8
	6**[16,18-22]	1,058/732	473(44.7)/306(41.8)	1.08	0.97–1.20	0.19	10.9;0.053;54.2
	6*[16,18-22]	1,014/972	406(40)/346(35.5)	1.13	1.01–1.26	0.04	8.59;0.13;41.8

* In McHutchison's study [19] only patients without ribavirin reduction were included.
** In McHutchison's study [19] only patients with adequate ribavirin dosage (≥13 mg/kg/die) were included.

4. Anmerkungen/Fazit der Autoren

The standard schedules of Peg-IFN α-2a and Peg-IFN α-2b, both in combination with ribavirin, can be used indifferently for patients with chronic HCV genotype 1 who are anti- to eliminate HIV-negative and antiviral treatment-naïve.

Cure S et al., 2012 [14].

Efficacy of telaprevir and boceprevir in treatment naïve and treatment-experienced genotype 1 chronic hepatitis C patients: an indirect comparison using Bayesian network meta-analysis

1. Fragestellung

The objective of this study was to indirectly compare the efficacy of telaprevir and boceprevir combined with PR in achieving SVR in both treatment-naive and experienced patients infected with G1 chronic HCV, using a Bayesian network meta-analysis framework.

2. Methodik

Population: Adult patients with HCV **G1** infection, naive to HCV treatment or having failed prior treatment with standard of care

Intervention / Komparator: Comparing PR (alfa-2a or 2b) to another PR or TVR- or BOC-based therapy

Endpunkt: SVR 24 weeks after the end of treatment

Suchzeitraum (Aktualität der Recherche): MEDLINE, EMBASE, the Cochrane library and the Centre for Review and Dissemination databases were searched from January 2000 to July 2011

	Anzahl eingeschlossene Studien/Patienten (Gesamt): 11 Studien (Patienten k. A.) *Qualitätsbewertung der Studien:* Cochrane risk of bias tool
	3. Ergebnisdarstellung Treatment-naive population - The OR (posterior median [95% CrI]) for TVR (12 weeks + RGT 24/48 weeks PR) and BOC (24 weeks + RGT 28/48 weeks PR) versus PR were respectively 3.80 (2.78–5.22) and 2.99 (2.23–4.01). The OR for the indirect comparison of TVR versus BOC was estimated at 1.42 (0.89–2.25), with a probability of TVR being superior (i.e., P[OR>1]) equal to 0.931. Treatment-experienced population - The median OR (95% CrI) of TVR (12 weeks + 48 weeks PR) and BOC (32 weeksþRGT 36/48 weeks PR) versus PR were respectively 13.11 (7.30–24.43) and 5.36 (2.90–10.30). The OR for the indirect comparison of TVR versus BOC was 2.45 (1.02–5.80), with a probability of TVR being superior of 0.978 in the pooled treatment-experienced patient population (partial responders + relapsers) - Separate analyses for prior relapsers and partial responders resulted in median OR of 3.16 (1.12–8.97) and 0.84 (0.08–6.05) for prior relapsers and partial responders, respectively.
	4. Anmerkungen/Fazit der Autoren In the absence of direct comparative head-to-head studies between telaprevir and boceprevir for the treatment of chronic HCV genotype 1 patients, an indirect comparison based on Bayesian network meta-analysis suggests better efficacy for telaprevir than boceprevir in both treatment-naive and treatmentexperienced patients.
Dang S et al., 2012 [15]. Telaprevir for Chronic Hepatitis C with Genotype 1: A Meta-Analysis **Siehe auch:** **Kong Y et al., 2012 [52].** Efficacy and Tolerability of Telaprevir for Chronic Hepatitis Virus C Genotype 1 Infection: A Meta-Analysis	**1. Fragestellung** In this systematic review, we sought to assess both the beneficial and harmful effect of telaprevir.
	2. Methodik *Population* Male or female patients, of any age or ethnic origin, who had chronic **genotype 1** HCV infection *Intervention / Komparator* Telaprevir administered at any dose, duration and route administration, given separately or in combination versus no intervention, placebo or other intervention *Endpunkt* Primary outcome assessed was viral response defined as loss of detectable HCV RNA, including SR and end of treatment response (ETR). Secondary outcome assessed was adverse events and discontinuation.

Suchzeitraum (Aktualität der Recherche)
MEDLINE, EMBASE, CENTRAL, the Web Science and the Chinese Biomedical Database to September 8 2010

Anzahl eingeschlossene Studien/Patienten (Gesamt):
5 Studien (1080 Patienten)

Qualitätsbewertung der Studien:
Cochrane risk of bias tool

3. Ergebnisdarstellung

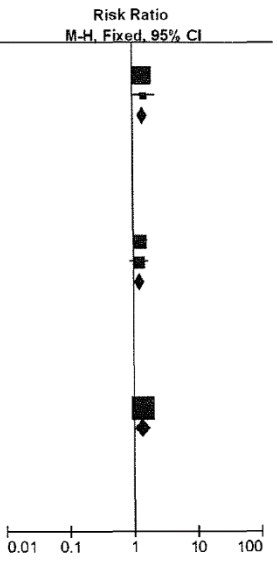
Abbreviations:

T12PR12, Telaprevir / PeglFN-2a / Ribavirin for 12 weeks, followed by Placebo / PegIFN-2a/Ribavirin for 12 weeks;
T12PR24, Telaprevir / PeglFN-2a / Ribavirin for 12 weeks, followed by Placebo / PegIFN-2a/Ribavirin for 24 weeks;
T12PR48, Telaprevir / PeglFN-2a / Ribavirin for 12 weeks, followed by Placebo / PegIFN-2a/Ribavirin for 48 weeks

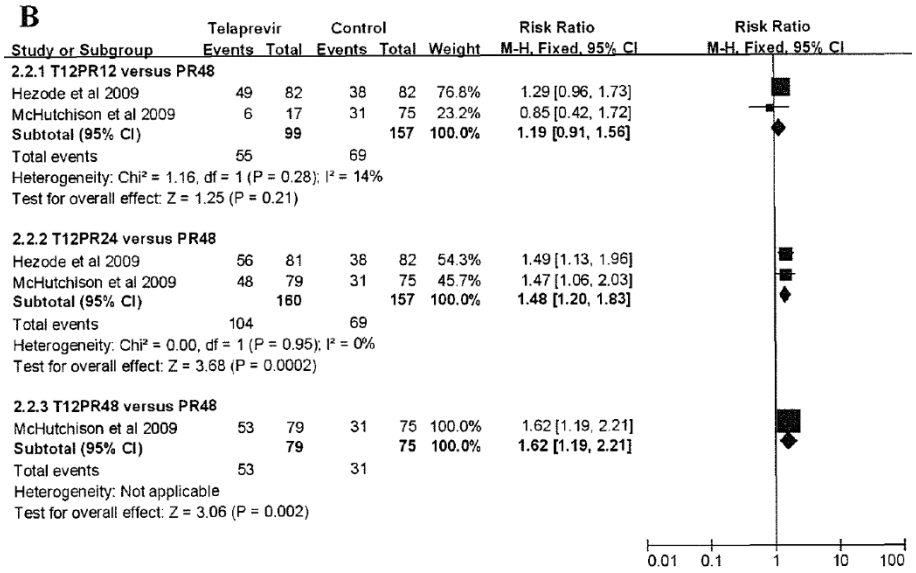
RCTs comparing the effect of regimens with telaprevir triple therapy on the end of treatment response (A)

A

Study or Subgroup	Telaprevir Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.1.1 T12PR12 versus PR48						
Hezode et al 2009	66	82	45	82	77.7%	1.47 [1.17, 1.83]
McHutchison et al 2009	12	17	35	75	22.3%	1.51 [1.02, 2.24]
Subtotal (95% CI)		**99**		**157**	**100.0%**	**1.48 [1.22, 1.79]**
Total events	78		80			
Heterogeneity: Chi² = 0.02, df = 1 (P = 0.89); I² = 0%						
Test for overall effect: Z = 3.94 (P < 0.0001)						
2.1.2 T12PR24 versus PR48						
Hezode et al 2009	57	81	45	82	55.5%	1.28 [1.01, 1.63]
McHutchison et al 2009	45	79	35	75	44.5%	1.22 [0.90, 1.66]
Subtotal (95% CI)		**160**		**157**	**100.0%**	**1.25 [1.04, 1.52]**
Total events	102		80			
Heterogeneity: Chi² = 0.06, df = 1 (P = 0.80); I² = 0%						
Test for overall effect: Z = 2.32 (P = 0.02)						
2.1.3 T12PR48 versus PR48						
McHutchison et al 2009	51	79	35	75	100.0%	1.38 [1.03, 1.85]
Subtotal (95% CI)		**79**		**75**	**100.0%**	**1.38 [1.03, 1.85]**
Total events	51		35			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.18 (P = 0.03)						



RCTs comparing the effect of regimens with telaprevir triple therapy on sustained response in **naïve patients** (B)



Meta-analysis of adverse events in the telaprevir group vs. the control group

Adverse Event	Studies	Patients	Statistical Method	Effect Estimate	*p*	Heterogeneity
Rash	4	1046	Risk Ratio (M-H, Random, 95% CI)	1.68 (1.19,2.37)	0.003	p=0.05, I^2=61%
Pruritus	3	1026	Risk Ratio (M-H, Fixed, 95% CI)	1.94 (1.55, 2.44)	<0.00001	p=0.27, I^2=23%
Hemorrhoids	2	703	Risk Ratio (M-H, Fixed, 95% CI)	6.95 (2.59, 18.64)	0.0001	p=0.49, I^2=0%
Nausea	4	1046	Risk Ratio (M-H, Fixed, 95% CI)	1.34 (1.12, 1.60)	0.001	p=0.15, I^2=43%
Diarrhea	3	755	Risk Ratio (M-H, Random, 95% CI)	1.14 (0.53, 2.47)	0.74	p<0.0001, I^2=90%
Pyrexia	3	755	Risk Ratio (M-H, Random, 95% CI)	0.88 (0.56, 1.38)	0.58	p=0.08, I^2=60%
Fatigue	2	555	Risk Ratio (M-H, Fixed, 95% CI)	0.90 (0.77, 1.05)	0.17	p=0.30, I^2=8%
Anemia	3	755	Risk Ratio (M-H, Random, 95% CI)	1.39 (0.85, 2.30)	0.19	p=0.07, I^2=62%

Critical appraisal

Source	Adequate Sequence Generation	Allocation Concealment	Blinding	Incomplete Outcome Data Addressed	Free of Selective Reporting	Free of Other Bias
McHutchison *et al.* 2010	Yes	Unclear	Yes	Yes	Yes	Yes
McHutchison *et al.* 2009	Yes	Unclear	Yes	Yes	Yes	Yes
Hezode *et al.* 2009	Yes	Unclear	Yes	Yes	Yes	Yes
Forestier *et al.* 2007	Yes	Yes	Yes	Yes	No	Yes
Reesink *et al.* 2006	Unclear	Unclear	Yes	Yes	No	Yes

4. Anmerkungen/Fazit der Autoren

Telaprevir combined with PegINF-2a plus ribavirin may improve sustained response in genotype 1 chronic hepatitis C. Regimen T12PR24 may be the best regimen in this respect. New randomized controlled trials are required to confirm this meta-analysis.

Gu L et al., 2012 [30].

Telaprevir for genotype 1 chronic hepatitis C: a systematic review and meta-analysis

1. Fragestellung

To assess the beneficial and harmful effects of telaprevir for patients with genotype 1 chronic hepatitis C.

2. Methodik

Population

Patients with **genotype 1** chronic hepatitis C

Intervention / Komparator

Telaprevir in combination with peginterferon alfa and ribavirin versus no intervention or placebo in combination with peginterferon alfa and ribavirin

Endpunkt

The primary outcome measures were viral response including sustained virologic response and virologic response at the end of treatment

Secondary outcome measures were: (i) relapse rate; (ii) severe adverse events; (iii) treatment discontinuations; (iiii) commonly reported adverse events, including anemia, neutropenia, rash and pruritus

Suchzeitraum (Aktualität der Recherche)

Cochrane Central Register of Controlled Trials (CENTRAL) on the Cochrane Library (Issue 4, 2012), MEDLINE, EMBASE, Chinese Biomedical Database (CBM), CNKI database and Chinese WanFang Database between 1980 and May 2012

Anzahl eingeschlossene Studien/Patienten (Gesamt):

6 Studien (2775 Patienten)

Qualitätsbewertung der Studien:

Cochrane risk of bias tool

3. Ergebnisdarstellung

Qualität der Studien:

Reference	Random Sequence Generation	Allocation Concealment	Blinding	Incomplete Outcome Data	Selective Reporting	Free of Source of Funding Bias?
Hèzode (2009)	Yes	Yes	Yes	No	Unclear	No
McHutchison (2009)	Unclear	Unclear	Yes	Yes	Unclear	No
Kumada (2011)	Unclear	Unclear	No	Unclear	Unclear	Yes
Jacobson (2011)	Unclear	Unclear	Yes	No	Yes	No
McHutchison (2010)	Unclear	Unclear	Yes	No	Unclear	No
Zeuzem (2011)	Yes	Yes	Yes	Yes	Yes	No

Abbreviations:

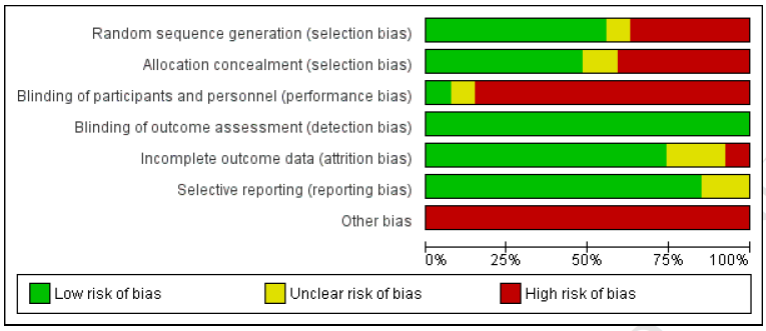
T12PR24, Telaprevir/Pegifn-2a/Ribavirin for 12 weeks, followed by Placebo/Pegifn-2a/Ribavirin for 12 weeks;
T24PR48, Telaprevir/Pegifn-2a/Ribavirin for 24 weeks, followed by Pegifn-2a/Ribavirin for 24 weeks;
PR48, Placebo/Pegifn-2a/Ribavirin for 24 weeks, followed by Pegifn-2a/Ribavirin for 24 weeks;
T12PR48, Telaprevir/Pegifn-2a/Ribavirin for 12 weeks, followed by Placebo/Pegifn-2a/Ribavirin for 36 weeks;
T12PR12, Telaprevir/Pegifn-2a/Ribavirin for 12 weeks;
T12PR, Telaprevir/Pegifn-2a/Ribavirin for 12 weeks, followed by Pegifn-2a/Ribavirin for 12 weeks if HCV RNA was undetectable at weeks 4 and 12 or for 36 weeks if HCV RNA was detectable at either time point;
T8PR, Telaprevir/Pegifn-2a/Ribavirin for 8 weeks and Placebo/Pegifn-2a/Ribavirin for 4 weeks, followed by 12 or 36 weeks of Pegifn-2a/Ribavirin on the basis of the same HCV RNA criteria;
Lead-in T12PR48, Peginterferon/ribavirin for 4 weeks, followed by telaprevir for 12 wk and peg-interferon and ribavirin up to a total of 48 weeks.

	Subgroup analysis of telaprevir effect in **naïve patients** - In naive patients, we found that telaprevir triple therapy presented a significantly higher rate of sustained virologic response than recommended PR48 regardless of T12PR24 (Odds Ratio (OR) 2.52; 95% CI 1.74 to 3.64), T12PR48 (OR 2.89; 95% CI 1.50 to 5.58), T12PR (OR 3.78; 95% CI 2.76 to 5.19) or T8PR (OR 2.82; 95% CI2.08 to 3.82), but not in T12PR12 (OR 1.41; 95% CI 0.83 to 2.40) - The rate of virologic response at the end of treatment was also significantly improved in T12PR12 (OR 3.20; 95% CI 1.76 to 5.80), T12PR24 (OR 1.88; 95% CI 1.24 to 2.87), T12PR48 (OR 2.08; 95% CI 1.09 to 3.97), T12PR (OR 3.69; 95% CI 2.55 to 5.34) and T8PR (OR 2.46; 95% CI 1.76 to 3.46) - In addition, telaprevir triple therapy also had a significant beneficial effect on the relapse rate in T12PR24 (OR 0.34; 95% CI 0.14 to 0.82), T12PR48 (OR 0.21; 95% CI 0.05 to 0.86), T12PR (OR 0.24; 95% CI 0.15 to 0.40), T8PR (OR 0.27; 95% CI 0.17 to 0.44), but not in T12PR12 (OR 1.55; 95% CI 0.71 to 3.36) - 127 of 1191 (11%) and 48 of 581 (8%) naive patients suffered from severe adverse events in telaprevir-based groups and control groups, respectively. There was no significant difference between them (OR 1.34, 95% CI 0.94 to 1.90). - 130 of 1028 (13%) naive patients in telaprevir-based groups discontinued the study treatment because of adverse events, as did 47 of 499 (9%) patients in the control group, there was no significant difference between them (OR 1.33, 95% CI0.74 to 2.38). - It also showed that telaprevir triple therapy significantly increased the risk of anemia, rash and pruritus both in naive patients, but it did not appear to increase the risk of neutropenia. Subgroup analysis of telaprevir effect in **patients previously treated unsuccessfully** - In previously treated patients, telaprevir triple therapy had a significant effect on the rate of sustained virologic response in subgroups of T12PR24 (OR 6.45; 95% CI 3.39 to 12.27), T24PR48 (OR 6.93; 95% CI 3.64 to13.21), T12PR48 (OR 9.00; 95% CI 5.34 to 15.17), and lead-in T12PR48 (OR 9.83; 95% CI 5.82 to 16.60) - The rate of virologic response at the end of treatment was also significantly improved in T12PR24 (OR 7.31; 95% CI 4.07 to 13.12), and T24PR48 (OR 4.83; 95% CI 2.76 to 8.47) - In addition, telaprevir triple therapy significantly reduced relapse rate in T12PR24 (OR 0.38; 95% CI 0.17 to 0.86), T24PR48 (OR 0.13; 95% CI 0.05 to 0.35), T12PR48 (OR 0.10; 95% CI 0.05 to 0.19), and lead-in T12PR48 (OR 0.10; 95% CI 0.05 to 0.19) - 109 of 758 (14%) and 20 of 246 (8%) previously treated patients experienced severe adverse events in telaprevir-based groups and control groups, respectively. There was a significant difference between them (OR 2.15, 95% CI1.29 to 3.58). - 69 of 530 (13%) patients previously treated unsuccessfully in telaprevir-based groups discontinued the study treatment because of adverse events, as did 4 of 132 (3%) patients in the control group, there was a significant difference between them (OR 4.79, 95% CI 1.72 to 13.37).

	- We also found that telaprevir triple therapy significantly increased the risk of anemia, rash and pruritus in previously treated patients, but the risk of neutropenia did not increase.
	4. Anmerkungen/Fazit der Autoren Telaprevir in combination with peginterferon alfa and ribavirin has been recommended as option for the treatment of genotype 1 chronic hepatitis C. It has been considered as effective to improve viral response and reduce relapse rate in patient who suffer genotype 1 chronic hepatitis C. However, the treatment should be monitored carefully as it may cause some severe adverse events. For further confirmation of its treatment effect and clarify its possible adverse events, more randomized clinical trials need to be carried out.

Genotyp 3

Berden FAC et al., 2016 [3]. Identification of the Best Direct-acting Antiviral Regimen for Patients With Hepatitis C Virus Genotype 3 Infection: a Systematic Review and Network Meta-analysis	**1. Fragestellung** Direct-acting antivirals (DAA) are effective in treatment of chronic hepatitis C virus (HCV) infection, although results for patients infected with genotype 3 are suboptimal. There are several regimens available but direct comparisons have not been made and are unlikely to occur. We aimed to identify the most effective DAA regimen for patients infected with HCV genotype 3 and to assess the role of ribavirin.
	2. Methodik Population: patients above 18 years with HCVgenotype 3 Intervention*:* at least one DAA Komparator: k.A. Endpunkt: The primary outcome was the mean estimated probability of SVR per studied regimen. SVR was defined as an undetectable HCV RNA 12 weeks after cessation of treatment. Suchzeitraum (Aktualität der Recherche): bis 03/2016 Anzahl eingeschlossene Studien/Patienten (Gesamt): 27 (n=3415), davon 16 RCT, 6 single-arm, 5 Observationsstudien Qualitätsbewertung der Studien Heterogeneity was assessed by the estimated between-study variation τ2 of the network meta-analysis and by I2 of the meta-analyses per regimen.
	3. Ergebnisdarstellung Übersicht über die Primärstudien – vgl. Anhang 7



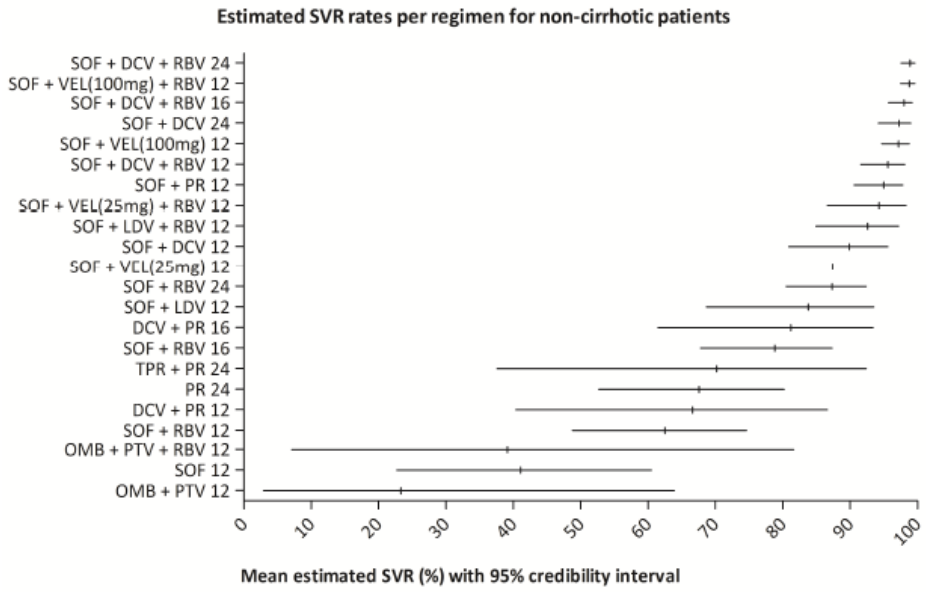
Sustained virological response in non-cirrhotic patients

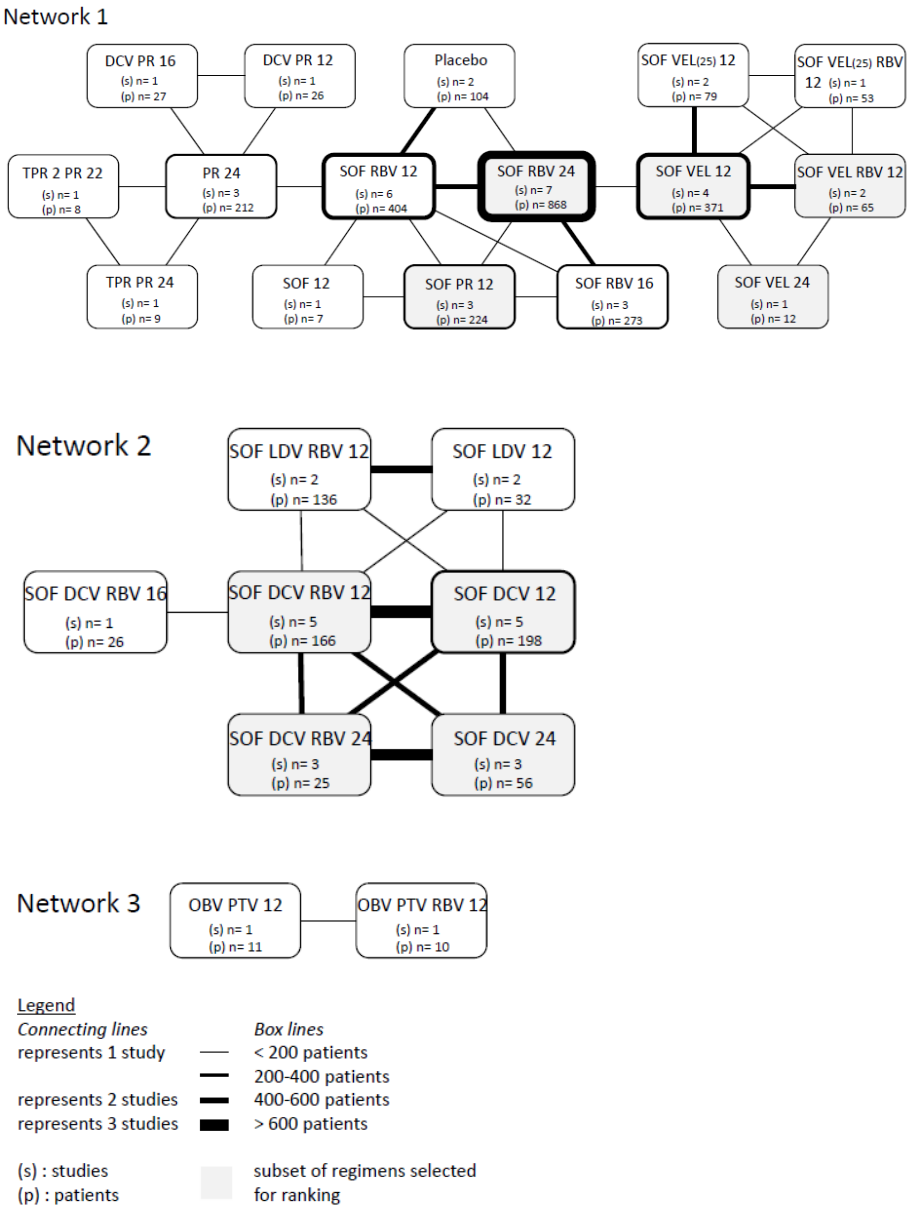
Twenty-two different regimens were studied in non-cirrhotic HCV genotype 3 patients. Highest SVR rates were estimated for sofosbuvir + daclatasvir + ribavirin for 24 weeks (98.9%, 95%CrI 97.6-99.6), sofosbuvir + velpatasvir + ribavirin for 12 weeks (98.8%, 95%CrI 97.5-99.6) and sofosbuvir + daclatasvir + ribavirin for 16 weeks (98.0%, 95%CrI 95.7-99.2)

Table 2. Mean difference in estimated SVR rate (%) between regimens in non-cirrhotic HCV genotype 3 patients (95%CrI)

Regimen SVR (95%CrI)	SOF+VEL+RBV 12 98.8 (97.5-99.6)	SOF+VEL 12 97.2 (94.7-98.8)	SOF+DCV+RBV 12 95.6 (91.6-98.1)	SOF+PR 12 95.0 (90.6-97.8)	SOF+DCV 12 89.9 (80.9-95.6)	SOF+RBV 24 87.3 (80.5-92.4)
1. **SOF+VEL+RBV 12** 98.8 (97.5-99.6)		**1.6 (0.4-3.5)***	**3.2 (0.7-7.1)***	**3.8 (1.1 – 8.1)***	**8.9 (3.0 – 18.2)***	**11.6 (6.8 – 18.0)***
2. **SOF+VEL 12** 97.2 (94.7-98.8)			1.5 (- 2.0 – 6.0)	2.2 (- 0.9 – 6.4)	**7.3 (1.5 – 16.3)***	**10.0 (5.5 – 16.0)***
3. **SOF+DCV+RBV 12** 95.6 (91.6-98.1)				0.6 (- 4.3 – 5.8)	**5.7 (1.3 – 12.7)***	**8.4 (2.0 – 15.7)***
4. **SOF+PR12** 95.0 (90.6-97.8)					5.1 (- 2.1 – 14.7)	**7.7 (3.3 – 13.2)***
5. **SOF+DCV 12** 89.9 (80.9-95.6)						2.7 (- 8.0 – 11.8)
6. **SOF+RBV 24** 87.3 (80.5-92.4)						

Subset of regimens are ordered based on ranking statistics (supplementary file 4). Mean differences between 2 regimens are presented (with 95%credibility interval). * and **bold** indicates a significantly higher estimated SVR rate. Abbreviations: SOF = sofosbuvir, VEL = velpatasvir 100 mg, RBV = ribavirin, PR = peginterferon and RBV, DCV = daclatasvir, 12 = 12 weeks, 24 = 24 weeks.

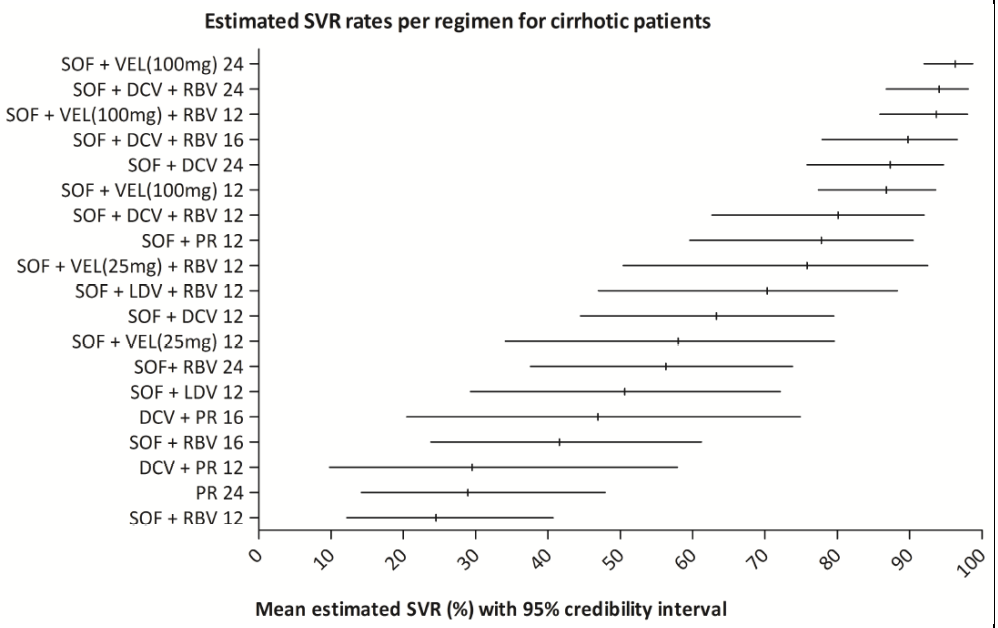




Sustained virological response in cirrhotic patients

In total, 19 different regimens were studied in cirrhotic HCV genotype 3 patients. Highest SVR rates were estimated for: sofosbuvir + velpatasvir for 24 weeks (96.3%, 95%CrI 92.0- 98.7), sofosbuvir + daclatasvir + ribavirin for 24 weeks (94.1%, 95%CrI 86.8-98.1) and sofosbuvir + velpatasvir + ribavirin for 12 weeks (93.7%, 95%CrI 85.9-98.0) (Figure 3b).

Ranking and comparison of the subset of clinically important regimens resulted in sofosbuvir + velpatasvir for 24 weeks to be ranked first, sofosbuvir + daclatasvir + ribavirin for 24 weeks to be ranked second and sofosbuvir + velpatasvir + ribavirin for 12 weeks to be ranked third, etcetera (supplementary file 4b). However, when we compared the regimens in the subset to each other, similar SVR rates were estimated for the first three ranked regimens (Table 3). sofosbuvir + velpatasvir for

	12 weeks resulted in 7% lower SVR, while sofosbuvir + peginterferon + ribavirin for 12 weeks resulted in 16% lower SVR than sofosbuvir +velpatasvir + ribavirin for 12 weeks. Sofosbuvir + ribavirin for 24 weeks was inferior to all other regimens, with 22-40% lower SVR estimates. 
	4. Anmerkungen/Fazit der Autoren An indirect comparison of DAA-based treatments, using Bayesian network metaanalysis, found regimens containing sofosbuvir and velpatasvir to be the best option for patients with HCV genotype 3 infection. Our analyses indicate that ribavirin significantly increases rates of SVR and should be considered if tolerated.

Genotyp 4

Van Sanden S. et al., 2016 [67]. Indirect comparison of the antiviral efficacy of peginterferon alpha 2a plus ribavirin used with or without simeprevir in genotype 4 hepatitis C virus infection, where	**1. Fragestellung** The need to assess relative efficacy in the absence of comparative clinical trials is a problem that is often encountered in economic modeling. The use of matching adjusted indirect comparison (MAIC) in this situation has been suggested. We present the results of a MAIC used to evaluate the incremental benefit offered by adding simeprevir (SMV) to standard therapy in the treatment of patients infected with genotype 4 hepatitis C virus (HCV).
	2. Methodik Population Patients with genotype 4 HCV monoinfection Intervention

common comparator study arms are lacking: a special application of the matching adjusted indirect comparison methodology	Dual therapy with pegylated interferon alpha 2a in combination with ribavirin. Planned treatment duration with PR of 48 weeks Komparator Nicht präspezifiziert Endpunkte SVR12 or SVR24 Suchzeitraum (Aktualität der Recherche) k.A. Anzahl eingeschlossene Studien/Patienten (Gesamt): 6 (zweichen 30 und 223) Qualitätsbewertung der Studien k.A. matching-adjusted indirect comparison (MAIC) matching criteria: Patient inclusion criteria similar to those used in RESTORE Data reported on baseline prevalence of patient and disease characteristics considered to be relevant to treatment response RESTORE-Studie: Moreno C, Hezode C, Marcellin P, et al. Efficacy and safety of simeprevir with PegIFN/ribavirin in naive or experienced patients infected with chronic HCV genotype 4. J Hepatol 2015;62:1047-55
	3. Ergebnisdarstellung Table 3. Studies reporting SVR results in HCV genotype 4 infected patients identified in the systematic literature review and meeting matching eligibility criteria. Study / Study objective / Patients randomized to PR (*N*) / PR-treated patients with HCV genotype 4 infection (*N*) / SVR24 for PR-treated patients: *N*, % Varghese *et al.*[14] — Single arm study of efficacy & safety of PR in genotype 4 HCV — 30 — 30 — 19 — 63.3 Rumi *et al.*[15] — Comparison of peginterferon alfa 2a vs 2b. All genotypes — 223 — 18 — 8 — 44.4 El Makhzangy *et al.*[16] — Single arm study of efficacy & safety of PR in genotype 4 HCV — 95 — 95 — 58 — 61.1 Rossignol *et al.*[17] — Comparison of efficacy of PR alone vs nitazoxanide + PR in genotype 4 HCV — 40 — 40 — 20 — 50 Kamal *et al.*[18] — Comparison of peginterferon alfa 2a vs 2b in genotype 4 HCV — 109 — 109 — 77 — 70.6 PR = peginterferon alfa 2a + ribavirin. 14. Varghese R, Al-Khaldi J, Asker H, et al. Treatment of chronic hepatitis C genotype 4 with peginterferon alpha-2a plus ribavirin. Hepatogastroenterology 2009;56:218-22 15. Rumi MG, Aghemo A, Prati GM, et al. Randomized study of peginterferonalpha2a plus ribavirin vs peginterferon-alpha2b plus ribavirin in chronic hepatitis C. Gastroenterol 2010;138:108-15 16. El Makhzangy H, Esmat G, Said M, et al. Response to pegylated interferon alfa-2a and ribavirin in chronic hepatitis C genotype 4. J Med Virol 2009;81:1576-83

17. Rossignol J, Elfert A, El-Gohary Y, Keeffe EB. Improved virologic response in chronic hepatitis C genotype 4 treated with nitazoxanide, peginterferon, and ribavirin. Gastroenterol 2009;136:856-62

18. Kamal SM, Ahmed A, Mahmoud S, et al. Enhanced efficacy of pegylated interferon alpha-2a over pegylated interferon and ribavirin in chronic hepatitis C genotype 4A randomized trial and quality of life analysis. Liver Int 2011;31:401-11

Table 4. Baseline patient characteristics for each pairing of RESTORE with the five comparator studies, after comparator inclusion/exclusion criteria have been applied to the IPD dataset.

Study	*N*	Mean age	% female	Mean BMI	Fibrosis assessment				Baseline viral load	G4 subtype				SVR24 *N* (%)
RESTORE + Varghese *et al.*[10,14]					F0–1	F2	F3	F4	Log_{10} viral load	n/a				
Varghese *et al.*	30	46.5	26.7	25.7	77%	17%	7%	0%	5.97					19 (63)
RESTORE	35	47.6	26.2	26.2	57%	17%	20%	6%	5.98					29 (83)
RESTORE + Rumi *et al.*[10,15]					S5–6/F3–4		S5–6/F4		% HCV RNA $<6 \times 10^5$ IU/ml					
Rumi *et al.*	18	43.0	16.7	26.4	28%		28%		72					8 (44)
RESTORE	35	47.6	25.7	26.2	26%		6%		43					29 (83)
RESTORE + El Makhzangy *et al.*[10,16]					F1	F2	F3	F4	Log_{10} viral load					
El Makhzangy *et al.*	77	17	7	0	38%	27%	20%	15%	5.40					58 (61)
RESTORE	57	17	20	6	55%	19%	19%	6%	5.99					27 (87)
RESTORE + Rossignol *et al.*[10,17]					S4–6/F3–4				Log_{10} viral load					
Rossignol *et al.*	40	40.0	10.0	28.0	3%				5.70					20 (50)
RESTORE	35	47.6	25.7	26.2	26%				6.19					29 (83)
RESTORE + Kamal *et al.*[10,18]					Median fibrosis score				Log_{10} viral load	4a	4d	4f	4o	
Kamal *et al.*	109	41.8	45.9	28.6	1				5.88	91%	6%	2%	2%	77 (71)
RESTORE	19	46.6	21.1	25.3	1				6.12	58%	32%	11%	0%	17 (89)

	Table 5. Results of the final matching model. Best fitting studies are listed first. **Matching parameters** / ***N*** / **Fibrosis** / **Baseline viral load** / **Mean BMI** / **Mean age** / **% female** / **SVR *N* (%)** **Best suited studies for matching – matched on fibrosis level, baseline viral load, BMI, age, sex** % F0–1; F2; F3; F4 / Log_{10} viral load Varghese *et al.*[14] / 30 / 77; 17; 7; 0 / 5.97 / 25.7 / 46.5 / 27 / 19 (63) RESTORE matched / 29* / 77; 16; 6; 0 / 5.97 / 25.64 / 46.24 / 27 / 85 % S5–6/F4 / % HCV RNA $<6 \times 10^5$ IU/ml Rumi *et al.*[15] / 18 / 28 / 72 / 26.4 / 43.00 / 17 / 8 (44) RESTORE matched / 15* / 28 / 72 / 26.4 / 43.01 / 17 / 77%** **Less suited studies matched on fibrosis level and baseline viral load only** % F0–1; F2; F3; F4 / Log_{10} viral load El Makhzangy *et al.*[16] / 95 / 38; 27; 20; 15 / 5.4 / 28.3 / 42 / 15 / 58 (61) RESTORE matched / 14* / 38; 27; 20; 15 / 5.4 / *27.00*** / *43.78*** / *0.26*** / 94% % S4–6/F3/F4 / Median viral load Rossignol *et al.*[17] / 40 / 3 / 501,187 / 28 / 40 / 10 / 20 (50) RESTORE matched / 26* / 3 / 394,000 (50% ≤501,187) / *25.93*** / *46.55*** / *29*** / 87% median S1/F1 / Median viral load Kamal *et al.*[18] / 109 / 1 / 765,610 / 28.62 / 41.83 / 46 / 77 (71) RESTORE matched / 17* / 1 (50% ≤1) / 503,000 (50% ≤765,610) / *25.24*** / *45.33*** / *24*** / 93% *For the RESTORE matched results, *N* represents the effective sample size of the pseudo-population after re-weighting. **In a sensitivity analysis, Ishak scores 5–6 were mapped to Metavir scores F3–4 rather than F4 alone, yielding an SVR of 87% for RESTORE. The more conservative estimate was used as the primary estimate. ***Not matched. **4. Anmerkungen/Fazit der Autoren** We have presented an alternative strategy, using a MAIC methodology, that allowed data from multiple clinical trials to be compared to individual patient data from a single-arm evaluation of simeprevir+PR in genotype 4 HCV infection. Using this approach, we have been able to generate robust estimates of incremental treatment benefit which, although falling short of the strength of direct comparative RCT evidence, represent a substantial improvement of previous approaches to this type of problem. Five potential comparator studies were identified. After applying the matching process, two emerged as offering the greatest equivalence with the generated RESTORE pseudosamples and were used to estimate SMVþPR efficacy, expressed as the percentage of patients achieving sustained viral response (SVR). In one comparison, SVR in the SMVþPR group was 85% versus 63% for PR alone. In the second comparison, the corresponding SVRs were 77% and 44% respectively. **5. Hinweise durch FB Med** Das primäre Ziel des Reviews war auf eine methodische Frage gerichtet. Die verwendete Methodik (MAIC) ist nicht etabliert; die Ergebnisse sollten lediglich i.S. eines qualitativen Reviews gewertet und mit Vorsicht interpretiert werden.
Aljumah AA et al., 2013 [1]. Pegylated versus standard interferon plus ribavirin in chronic hepatitis C genotype 4: A systematic	**1. Fragestellung** We conducted this systematic review and meta-analysis to compare the effect of a combination of Pegylated (PEG) Interferon (IFN) and Ribavirin (RBV) to that of IFN and RBV in patients with HCV-G4.
	2. Methodik *Population* **Treatment-naïve HCV-G4** patients *Intervention / Komparator*

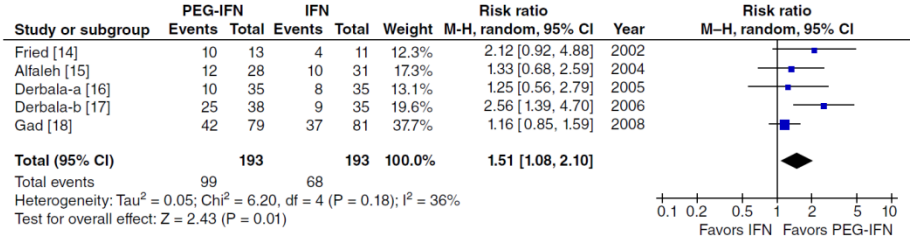
review and meta-analysis	PEG IFN plus RBV versus IFN plus RBV *Endpunkt* The outcome of interest is SVR *Suchzeitraum (Aktualität der Recherche)* The Cochrane Central Register of Controlled Trials in The Cochrane Library, PubMed, MEDLINE, EMBASE, SCIRUS, ProQuest, Google Scholar and reference lists of published trials; Our search included all published data from January 2000 through May 2012. *Anzahl eingeschlossene Studien/Patienten (Gesamt):* 5 Studien (386 Patienten) *Qualitätsbewertung der Studien:* Cochrane Risk of Bias tool

3. Ergebnisdarstellung

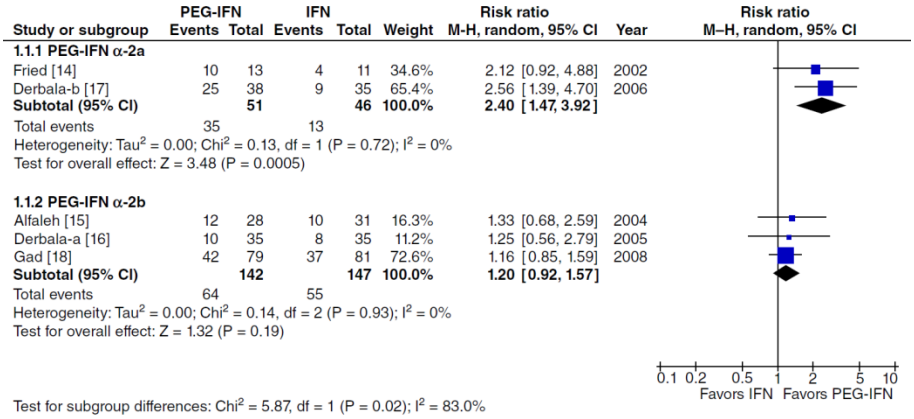
Qualität der Studien:

Study name	Sequence generation (randomization)	Allocation concealment	Blinding of participants, personnel and outcomes	Incomplete outcome data (attrition and exclusions)	Selective outcome reporting
Fried *et al.*[14]	Low risk	Low risk	Low risk	low risk	Low risk
Alfaleh *et al.*[15]	Low risk	Low risk	Low risk	Low risk	Low risk
Derbala *et al.*[16]	Low risk	Low risk	Low risk	Low risk	Low risk
Derbala *et al.*[17]	Low risk	Low risk	Low risk	Low risk	Low risk
Gad *et al.*[18]	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk

Comparison of pegylated interferon (PEG IFN) plus ribavirin with standard interferon (IFN) plus ribavirin in hepatitis C genotype 4 patients. (CI, confidence interval; M-H, Mantel–Haenszel)



Subgroup analysis of the summary effect of PEG IFN-α-2a versus PEG IFN-α-2b, random effect [M-H]. (CI, confidence interval; IFN, interferon; M-H, Mantel-Haenszel; PEG, pegylated; RR, risk ratio)



	4. Anmerkungen/Fazit der Autoren In treatment-naive patients with HCV-G4, treatment with PEG IFN plus RBV achieves higher SVR rate than treatment with IFN plus RBV.

Subgruppe Genotyp 1 oder 4 und/oder 2 oder 3

Yau AHL et al., 2015 [72]. Hepatitis C (chronic)	**1. Fragestellung** What are the effects of interferon-free treatments in treatment-naïve people with chronic hepatitis C infection without cirrhosis? What are the effects of interferon-free treatments in treatment-naïve people with chronic hepatitis C infection with cirrhosis?
	2. Methodik *Population* **Treatment-naïve** patients with hepatitis C infection **with or without cirrhosis** *Intervention / Komparator* Sofosbuvir plus ribavirin versus placebo/no treatment Sofosbuvir alone Sofosbuvir plus ribavirin versus peginterferon plus ribavirin Sofosbuvir plus ribavirin versus sofosbuvir plus peginterferon plus ribavirin Sofosbuvir plus simeprevir (with or without ribavirin) Sofosbuvir plus ledipasvir (with or without ribavirin) *Endpunkt* Virological response, defined as HCV RNA negativity and sustained virological response (SVR); hepatocellular carcinoma; end-stage liver disease; mortality; quality of life; adverse events *Suchzeitraum (Aktualität der Recherche)* Medline 1966 to August 2014, Embase 1980 to August 2014, The Cochrane Database of Systematic Reviews 2014, issue 8 (1966 to date of issue), the Database of Abstracts of Reviews of Effects (DARE), and Health Technology Assessment (HTA) database *Anzahl eingeschlossene Studien/Patienten (Gesamt):* k. A. *Qualitätsbewertung der Studien:* GRADE
	3. Ergebnisdarstellung <u>Qualität der Studien:</u>

Important outcomes	End-stage liver disease, Hepatocellular carcinoma, Mortality, Quality of life, Virological response								
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
What are the effects of interferon-free treatments in treatment-naive people with chronic hepatitis C infection without cirrhosis?									
1 (234) [33]	Virological response	Sofosbuvir plus ribavirin versus placebo or no treatment	4	−1	0	−1	0	Low	Quality point deducted for methodological flaws; directness point deducted for subgroup analysis
What are the effects of interferon-free treatments in treatment-naive people with chronic hepatitis C infection with cirrhosis?									
1 (44) [35]	Virological response	Sofosbuvir plus ribavirin versus placebo or no treatment	4	−2	0	−1	0	Very low	Quality points deducted for sparse data and methodological flaws; directness point deducted for subgroup analysis

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.

What are the effects of interferon-free treatments in **treatment-naïve** people with chronic hepatitis C infection **without cirrhosis**?

- Sofosbuvir plus ribavirin versus placebo or no treatment in treatment-naïve people with chronic HCV without cirrhosis
  - Sofosbuvir plus ribavirin may be more effective than placebo at reducing HCV RNA levels at the end of treatment, and increasing sustained virological response at up to 12 weeks (SVR12) after the end of treatment in treatmentnaïve people with HCV genotypes 2 or 3 without cirrhosis
  - Sofosbuvir plus ribavirin appears to be safe and well tolerated, with an adverse event profile consistent with ribavirin alone.
  - Sofosbuvir plus ribavirin may be more effective than placebo at reducing HCV RNA levels at the end of treatment, and at increasing sustained virological response at 12 weeks after the end of treatment in treatment-naïve people with HCV genotypes 2 and 3 without cirrhosis and who choose not to have interferon-based treatments, or for whom interferon-based treatments are not suitable (low quality evidence)
- Sofosbuvir plus ribavirin versus placebo or no treatment in **treatment-naïve** people with chronic HCV **without cirrhosis**
  - Sofosbuvir plus ribavirin may be more effective than placebo at reducing HCV RNA levels at the end of treatment in treatment-naïve people with HCV genotypes 2 or 3 with cirrhosis
  - Sofosbuvir plus ribavirin may be more effective than placebo at increasing sustained virological response at up to 12 weeks (SVR12) after the end of treatment in treatment-naïve people with HCV genotypes 2 and 3 with cirrhosis. However, this effect appears to be greater for HCV genotype 2 than for genotype 3.
  - Sofosbuvir plus ribavirin appears to be safe and well tolerated, with an adverse event profile consistent with ribavirin alone.
  - Sofosbuvir plus ribavirin may be more effective than placebo at reducing HCV RNA levels at the end of treatment, and at increasing sustained virological response at 12 weeks after the end of treatment, in treatment-naïve people with HCV genotypes 2 and 3 with cirrhosis and who choose not to have interferon-based treatments, or for whom interferon-based treatments are not suitable (very low quality evidence)

4. Anmerkungen/Fazit der Autoren

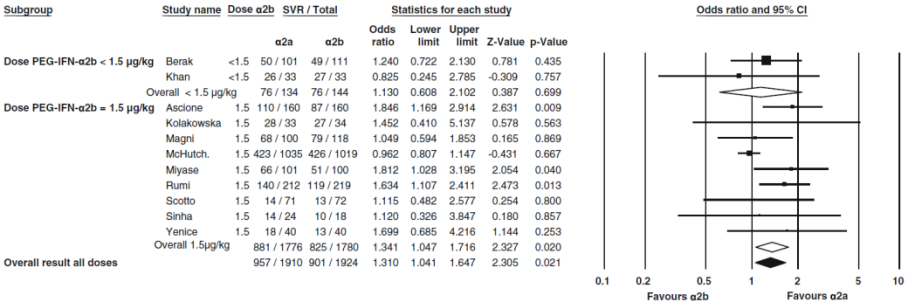
In this systematic overview, we categorised the efficacy for 12 different intervention/comparison combinations, based on information relating to the effectiveness and safety of sofosbuvir (with or without ribavirin), sofosbuvir (with or without ribavirin) plus ledipasvir, and sofosbuvir (with or without ribavirin) plus simeprevir, all in people with and without cirrhosis.

	5. Hinweise durch FB Med Die in den Ergbenissen nicht genannten Interventionen wurden wegen nicht vorhandener Evidenz mit „unknown effectiveness“ bewertet.
Flori N et al., 2013 [18]. Pegylated Interferon-α2a and Ribavirin versus Pegylated Interferon-α2b and Ribavirin in Chronic Hepatitis C	**1. Fragestellung** Our objective was to determine which PEG-IFN (α2a or α2b), in association with ribavirin, is the most effective for the treatment of chronic hepatitis C by performing an updated meta-analysis.
	2. Methodik *Population* Adult patients with HCV *Intervention / Komparator* Comparison of PEG-IFN-α2a with -α2b in association with ribavirin *Endpunkt* The primary outcome measure was the frequency of SVR. The secondary outcome measure was the frequency of adverse events leading to treatment discontinuation. *Suchzeitraum (Aktualität der Recherche)* MEDLINE (1950–2012) and EMBASE (1974–2012), as well the Cochrane Central Register of controlled trials and the Cochrane Database of Systematic Reviews; We performed the final search on 8 September 2012. *Anzahl eingeschlossene Studien/Patienten (Gesamt):* 26 Studien, davon 11 RCTs (18260 Patienten insgesamt) *Qualitätsbewertung der Studien:* The trial quality of RCTs was assessed by taking into account generation of allocation sequence, allocation concealment, efficacy of randomization, investigator blindness, description of withdrawals and dropouts and adherence to the intention-to-treat principle
	3. Ergebnisdarstellung Methodological quality of randomized controlled trials included NR not reported a Allocation was considered adequate when the sequence of random numbers was computer generated b The method used (central randomization, sealed envelopes) prevented the investigators from knowing which treatment would be allocated before the patient entered the study c Baseline characteristics of the two treatment groups were balanced d Investigator blinding was explicitly mentioned in the report e Numbers and reasons were reported

Study, year of publication	Generation of allocation sequence[a]	Allocation concealment[b]	Successful randomization[c]	Investigator blinding[d]	Withdrawals and dropouts[e]	Intention-to-treat analysis
Ascione et al. 2010 [3]	Yes	Yes	Yes	Unclear	Yes	Yes
Berak et al. 2007 [43]	Unclear	Unclear	No	Unclear	Yes	Yes
Khan et al. 2007 [50]	Unclear	Unclear	Yes	No	Yes	Unclear
Kolakowska et al. 2008 [46]	Unclear	Unclear	Yes	Unclear	NR	Unclear
Magni et al. 2009 [49]	Unclear	Unclear	Yes	NR	Yes	Yes
McHutchison et al. 2009 [4]	Yes	Yes	Yes	No	Yes	Yes
Miyase et al. 2012 [51]	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Rumi et al. 2010 [2]	Yes	Yes	Yes	Unclear	Yes	Yes
Scotto et al. 2008 [42]	Yes	Yes	Yes	No	Yes	Yes
Sinha et al. 2004 [47]	Unclear	Yes	Yes	Unclear	Yes	Yes
Yenice et al. 2006 [48]	Unclear	Unclear	Yes	Unclear	Yes	Unclear

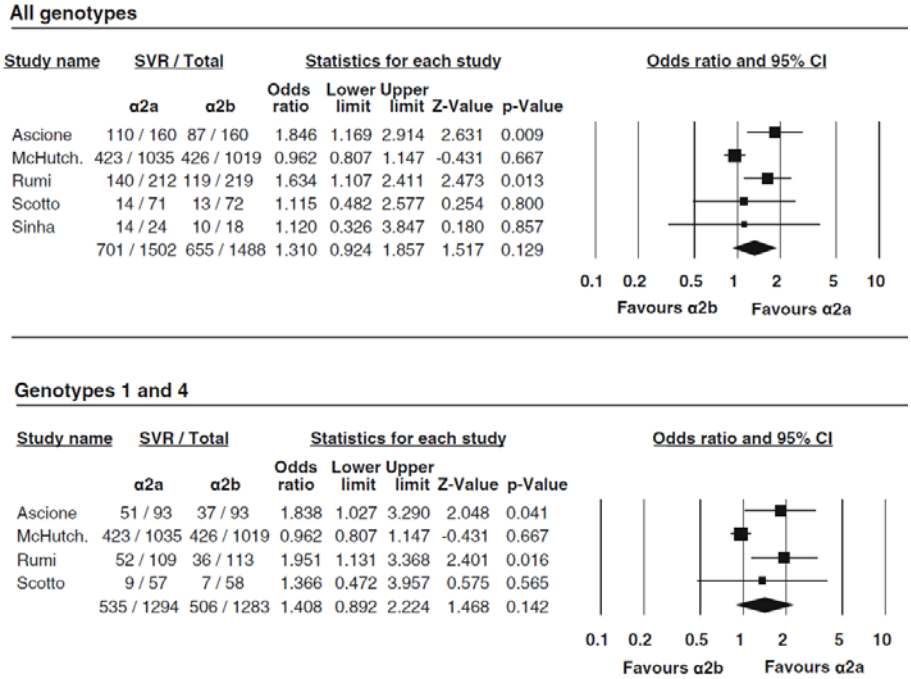
Meta-analysis of RCTs only for **all genotypes** comparing PEG-IFN-α2a and ribavirin with PEG-IFN-α2b and ribavirin, with subgroup analysis according to PEG-IFN-α2b dose (1.5 lg/kg/week or lower); outcome: sustained virological response.

PEG-IFN pegylated interferon, SVR sustained virological response



Meta-analysis including high-quality RCTs for **all genotypes**, and **genotypes 1 and 4**, comparing PEG-IFN-α2a and ribavirin with PEG-IFN-α2b and ribavirin; outcome: sustained virological response.

PEG-IFN pegylated interferon, SVR sustained virological response



Genotypes 2 and 3

The SVR was found to be higher for the PEG-IFN-a2a and ribavirin group, with the difference tending towards significance (OR 1.58; 95 % CI 0.98–2.53; p = 0.06, fixed-effects model). The subgroup analysis including three high-quality RCTs for which results for genotypes 2 and

	3 were available did not find any significant difference between the two groups (OR 1.60; 95 % CI 0.96–2.67; p = 0.07, fixed-effects model).
	4. Anmerkungen/Fazit der Autoren Current evidence suggests that PEG-IFN-α2a and ribavirin is associated with a higher SVR than PEG-IFN-α2b and ribavirin in patients mono-infected with hepatitis C, particularly for genotypes 1 and 4.
Romero-Gomez M et al., 2013 [61]. Meta-analysis: pegylated interferon α-2a achieves higher early virological responses than α-2b in chronic hepatitis C	**1. Fragestellung** We performed a meta-analysis of available randomized controlled trials comparing peginterferon α-2a and α-2b to explore the outcome in terms of RVR and cEVR.
	2. Methodik *Population* HCV-infected adults (>18 years) *(subgroup for genotype 1 or 4)* *Intervention / Komparator* The intervention arm was pegylated interferon α-2a and the comparison arm was pegylated interferon α-2b. *Endpunkt* The primary outcomes of interest were the Rapid virological response (RVR) rate (seronegativity of HCV RNA 4 weeks from initiation of treatment) and complete early virological response (cEVR) (undetectable HCV RNA within the initial 12 weeks of treatment) *Suchzeitraum (Aktualität der Recherche)* MEDLINE, EMBASE, LILACS and the Cochrane Central Register of Controlled Trials up to September 2011 *Anzahl eingeschlossene Studien/Patienten (Gesamt):* 8 Studien (4566 Patienten) *Qualitätsbewertung der Studien:* Jadad scale
	3. Ergebnisdarstellung <u>Studienqualität:</u>

Study	Year	Randomised (yes/no)	Appropriate Randomisation method	Double Blinded	Masked	Losses reported	Jadad scale
Ascione*	2010	1	1	0	0	1	3
Berak	2005	1	0	0	0	0	1
Bruno	2004	1	0	0	0	1	2
McHutchison*	2009	1	1	1	1	1	5
Rumi*	2010	1	1	0	0	1	3
Scotto	2008	1	1	0	0	1	3
Marcellin*,†	2011	1	1	0	0	1	3

* Studies that report cEVR and EVR of all genotypes and also 1 and 4 independently.

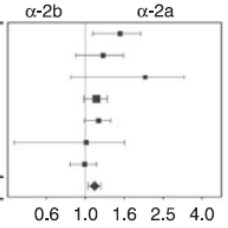
† Triple therapy study of peginterferon, RBV and Telaprevir 2.25 g/day.

Maximum value, 5 points, indicates highest quality.

Analysis of the relative efficacy of peginterferon α2a and α2b in terms of the different outcome measures and according to virus genotype

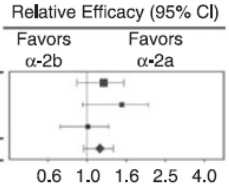
Forest Graph of cEVR results. All HCV genotypes

Study	Year	pegIFN-α2a Events	pegIFN-α2a Total	pegIFN-α2b Events	pegIFN-α2b Total	Total No. of Patients	Relative Efficacy	Confidence Interval 95%
Ascione	2010	121	160	104	160	320	1.164	(0.974; 1.391)
Berak	2005	58	101	53	111	212	1.203	(0.911; 1.588)
Bruno	2004	9	10	6	12	22	1.800	(0.977; 3.318)
McHutchison	2009	446	1035	773	2035	3070	1.134	(0.988; 1.303)
Rumi	2010	170	212	151	219	431	1.163	(0.998; 1.356)
Scoto	2008	16	70	18	72	143	0.901	(0.496; 1.639)
Marcellin	2012	70	80	72	81	161	0.984	(0.843; 1.149)
TOTAL		890	1669	1177	2690	4359	1.118	(0.039; 1.203)
Heterogeneity		Qh= 8.959		$P = 0.176$				
Association		QA= 8.909		$P = 0.003$				



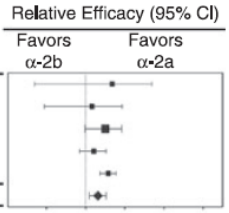
Forest Graph of cEVR results. HCV genotypes 1 and 4

Study	Year	pegIFN-α2a Events	pegIFN-α2a Total	pegIFN-α2b Events	pegIFN-α2b Total	Total No. of Patients	Relative Efficacy	Confidence Interval 95%
McHutchison	2009	466	1035	773	2035	3070	1.185	(0.903; 1.556)
Rumi	2010	60	91	40	87	178	1.434	(0.986; 2.085)
Marcellin	2012	70	80	72	81	161	0.984	(0.743; 1.304)
TOTAL		596	1206	885	2203	3409	1.151	(0.968; 1.369)
Heterogeneity		Qh= 9.802		$P = 0.007$				
Association		QA= 2.520		$P = 0.112$				



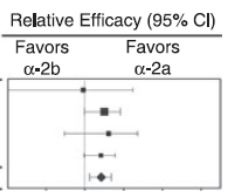
Forest Graph of RVR results. All HCV genotypes

Study	Year	pegIFN-α2a Events	pegIFN-α2a Total	pegIFN-α2b Events	pegIFN-α2b Total	Total No. of Patients	Relative Efficacy	Confidence Interval 95%
Bruno	2004	7	10	7	12	22	1.200	(0.641; 2.247)
Laguno	2009	27	77	25	72	149	1.010	(0.651; 1.566)
McHutchison	2009	123	1035	195	2035	3070	1.240	(1.002; 1.535)
Rumi	2010	132	212	125	219	431	1.091	(0.934; 1.274)
Marcellin	2012	65	80	55	81	161	1.197	(0.997; 1.437)
TOTAL		354	1414	407	2419	3833	1.151	(1.042; 1.272)
Heterogeneity		Qh= 1.461		$P = 0.834$				
Association		QA= 7.689		$P = 0.006$				



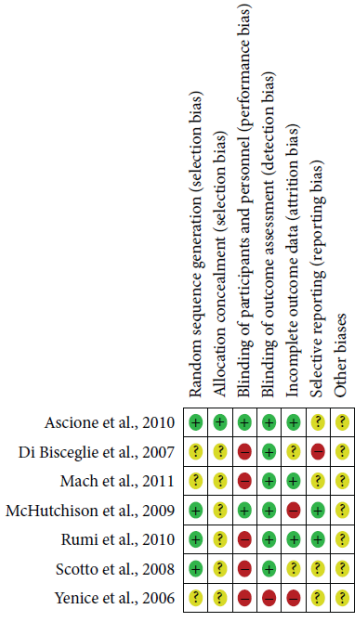
Forest Graph of RVR results. HCV genotypes 1 and 4

Study	Year	pegIFN-α2a Events	pegIFN-α2a Total	pegIFN-α2b Events	pegIFN-α2b Total	Total No. of Patients	Relative Efficacy	Confidence Interval 95%
Laguno	2009	8	51	8	39	90	0.315	(1.856; 0.765)
McHutchison	2009	123	1035	195	2035	3070	1.002	(1.345; 1.240)
Rumi	2010	34	91	26	87	178	0.823	(1.898; 1.250)
Marcellin	2012	65	80	55	81	161	0.997	(1.437; 1.197)
TOTAL		230	1257	284	2242	3499	1.206	(1.059; 1.374)
Heterogeneity		Qh= 1.115		$P = 0.773$				
Association		QA= 7.956		$P = 0.005$				



4. Anmerkungen/Fazit der Autoren

Peginterferon α-2a may be associated with a higher cEVR and RVR than peginterferon α-2b. These findings could help to achieve higher

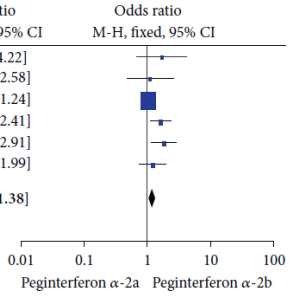
	SVR rates and support clinical decision-making in the present scenario of triple combination therapy.
Yang Z et al., 2013 [71]. Efficacy and Tolerability of Peginterferon α-2a and Peginterferon α-2b, Both plus Ribavirin, for Chronic Hepatitis C: A Meta-Analysis of Randomized Controlled Trials	**1. Fragestellung** We performed a meta-analysis of randomized controlled trials (RCTs) with critical inclusion and exclusion criteria to evaluate the efficacy and tolerability of peginterferon α-2a and peginterferon α-2b, both plus ribavirin.
	2. Methodik *Population* Chronic HCV virus monoinfection patients either **naive or retreatment** *Intervention / Komparator* Peginterferon α-2a and peginterferon α-2b, both plus ribavirin *Endpunkt* Rapid virologic response (RVR), early virologic response (EVR), end-of-treatment virologic response (ETR), SVR, relapse rate, and discontinuation rate *Suchzeitraum (Aktualität der Recherche)* PubMed, Ovid, and Cochrane libraries until August 30, 2012 *Anzahl eingeschlossene Studien/Patienten (Gesamt):* 7 Studien (3668 Patienten) *Qualitätsbewertung der Studien:* Cochrane risk of bias tool
	3. Ergebnisdarstellung Critical appraisal 

The overall SVR rate of CHC patients treated with the two types of peginterferons

Study or subgroup	Peginterferon α-2a Events	Peginterferon α-2a Total	Peginterferon α-2b Events	Peginterferon α-2b Total	Weight	Odds ratio M-H, fixed, 95% CI
Yenice et al., 2006	18	40	13	40	2%	1.7 [0.68, 4.22]
Scotto et al., 2008	14	71	13	72	2.9%	1.11 [0.48, 2.58]
McHutchison et al., 2009	423	1035	406	1019	68.1%	1.04 [0.87, 1.24]
Rumi et al., 2010	140	212	119	219	11.2%	1.63 [1.11, 2.41]
Ascione et al., 2010	110	160	87	160	7.6%	1.85 [1.17, 2.91]
Mach et al., 2011	68	138	54	122	8.2%	1.22 [0.75, 1.99]
Total (95% CI)		**1656**		**1632**	**100%**	**1.2 [1.04, 1.38]**
Total events	773		692			

Heterogeneity: $\chi^2 = 8.84$, df = 5 ($P = 0.12$); $I^2 = 43\%$

Test for overall effect: $Z = 2.56$ ($P = 0.01$)

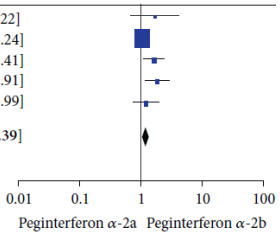


The SVR rate of **naïve** CHC patients

Study or subgroup	Peginterferon α-2a Events	Peginterferon α-2a Total	Peginterferon α-2b Events	Peginterferon α-2b Total	Weight	Odds ratio M-H, fixed, 95% CI
Yenice et al., 2006	18	40	13	40	2.1%	1.7 [0.68, 4.22]
McHutchison et al., 2009	423	1035	406	1019	70.1%	1.04 [0.87, 1.24]
Rumi et al., 2010	140	212	119	219	11.5%	1.63 [1.11, 2.41]
Ascione et al., 2010	110	160	87	160	7.9%	1.85 [1.17, 2.91]
Mach et al., 2011	68	138	54	122	8.4%	1.22 [0.75, 1.99]
Total (95% CI)		**1585**		**1560**	**100%**	**1.2 [1.04, 1.39]**
Total events	759		679			

Heterogeneity: $\chi^2 = 8.81$, df = 4 ($P = 0.07$); $I^2 = 55\%$

Test for overall effect: $Z = 2.55$ ($P = 0.01$)

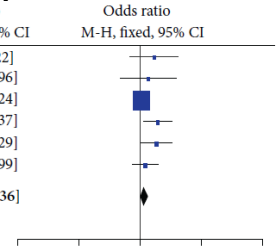


The SVR rate of CHC patients with HCV **genotype 1 or 4**

Study or subgroup	Peginterferon α-2a Events	Peginterferon α-2a Total	Peginterferon α-2b Events	Peginterferon α-2b Total	Weight	Odds ratio M-H, fixed, 95% CI
Yenice et al., 2006	18	40	13	40	2.2%	1.7 [0.68, 4.22]
Scotto et al., 2008	9	57	7	58	1.8%	1.37 [0.47, 3.96]
McHutchison et al., 2009	423	1035	406	1019	75.8%	1.04 [0.87, 1.24]
Rumi et al., 2010	52	109	36	113	5.8%	1.95 [1.13, 3.37]
Ascione et al., 2010	51	93	37	93	5.2%	1.84 [1.03, 3.29]
Mach et al., 2011	68	138	54	122	9.1%	1.22 [0.75, 1.99]
Total (95% CI)		**1472**		**1445**	**100%**	**1.17 [1.01, 1.36]**
Total events	621		553			

Heterogeneity: $\chi^2 = 8.06$, df = 5 ($P = 0.15$); $I^2 = 38\%$

Test for overall effect: $Z = 2.12$ ($P = 0.03$)

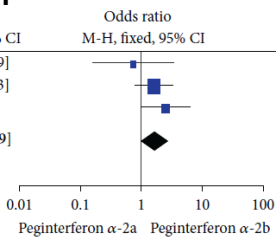


The SVR rate of CHC patients with HCV **genotype 2 or 3**

Study or subgroup	Peginterferon α-2a Events	Peginterferon α-2a Total	Peginterferon α-2b Events	Peginterferon α-2b Total	Weight	Odds ratio M-H, fixed, 95% CI
Scotto et al., 2008	5	14	6	14	17.7%	0.74 [0.16, 3.39]
Rumi et al., 2010	88	103	83	106	54.8%	1.63 [0.79, 3.33]
Ascione et al., 2010	59	67	50	67	27.5%	2.51 [1, 6.3]
Total (95% CI)		**184**		**187**	**100%**	**1.71 [1.01, 2.89]**
Total events	152		139			

Heterogeneity: $\chi^2 = 1.84$, df = 2 ($P = 0.4$); $I^2 = 0\%$

Test for overall effect: $Z = 2.01$ ($P = 0.04$)

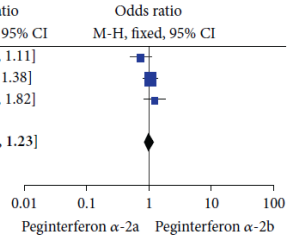


RVR rate comparison

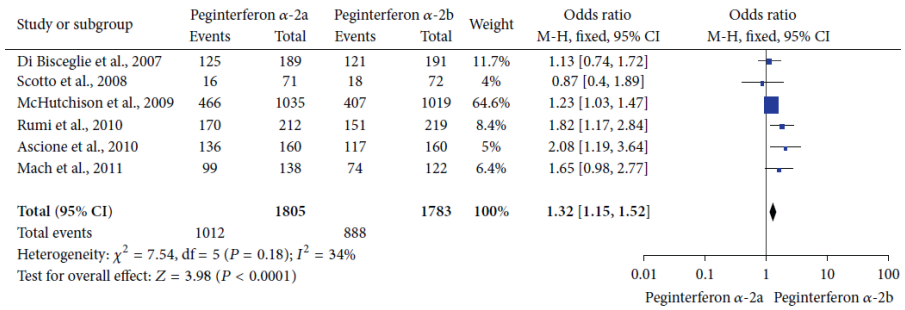
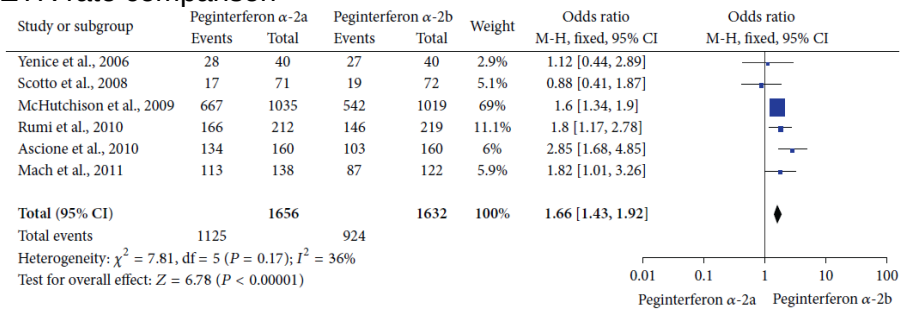
Study or subgroup	Peginterferon α-2a Events	Peginterferon α-2a Total	Peginterferon α-2b Events	Peginterferon α-2b Total	Weight	Odds ratio M-H, fixed, 95% CI
Di Bisceglie et al., 2007	79	189	94	191	26.7%	0.74 [0.49, 1.11]
McHutchison et al., 2009	123	1035	116	1019	50.5%	1.05 [0.8, 1.38]
Rumi et al., 2010	132	212	125	219	22.8%	1.24 [0.84, 1.82]
Total (95% CI)		**1436**		**1429**	**100%**	**1.01 [0.83, 1.23]**
Total events	334		335			

Heterogeneity: $\chi^2 = 3.42$, df = 2 ($P = 0.18$); $I^2 = 41\%$

Test for overall effect: $Z = 0.11$ ($P = 0.91$)



EVR rate comparison

	 ETR rate comparison 
	4. Anmerkungen/Fazit der Autoren Peginterferon α-2a has superior efficacy with higher EVR, ETR, and SVR than peginterferon α-2b for CHC patients, both plus ribavirin. Peginterferon α-2a might obtain a similar or even lower discontinuation rate than peginterferon α-2b. However, peginterferon α-2a had a higher relapse rate than peginterferon α-2b.
Qin H et al., 2012 [59]. Safety of Telaprevir for Chronic Hepatitis C Virus Infection	**1. Fragestellung** A meta-analysis was performed to assess the safety of the addition of telaprevir to a standard regimen of pegylated interferon (peginterferon) plus ribavirin (combination telaprevir with peginterferon plus ribavirin, the TPR group) compared with the standard regimen group (peginterferon plus ribavirin, the PR group).
	2. Methodik *Population* Patients with chronic HCV infection *(The HCV genotype in six RCTs was HCV genotype 1, and the other one was HCV genotype 2 and HCV genotype 3)* *Intervention / Komparator* Comparison of the standard PR regimen group (24- to 48-week course of peginterferon plus ribavirin, PR group) to the addition of telaprevir to the standard PR regimen group (combination of telaprevir with the standard regimen of peginterferon plus ribavirin, TPR group). *Endpunkt* Adverse events, serious adverse events

Suchzeitraum (Aktualität der Recherche)
PubMed (updated to September 2011), EMBASE (from 1980 to September 2011) and China Biology Medicine (CBM)

Anzahl eingeschlossene Studien/Patienten (Gesamt):
7 Studien (1963 Patienten)

Qualitätsbewertung der Studien:
Jadad scale

3. Ergebnisdarstellung

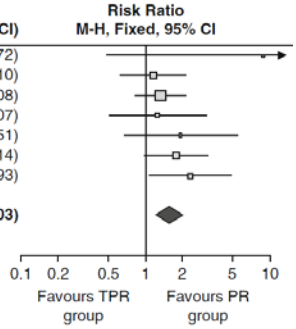
Critical appraisal
All RCTs were well designed and six RCTs scored 5 points on the Jadad scoring system, while the other one scored 3 points.

Meta-analysis of serious adverse events in the TPR group compared with the PR group

CI = confidence interval; df = degrees of freedom; I^2 = percentage of the total variation across studies due to heterogeneity; M-H = Mantel-Haenszel; peginterferon = pegylated interferon; PR= peginterferon plus ribavirin; TPR = combination telaprevir with peginterferon plus ribavirin; Z = test of overall treatment effect

Study or subgroup	TPR group Events	Total	PR group Events	Total	Weight	Risk Ratio M-H, Fixed (95% CI)
Foster et al.[21]	3	14	0	18	0.5%	8.87 (0.50, 158.72)
Hezode et al.[8]	30	163	13	82	18.8%	1.16 (0.64, 2.10)
Jacobson et al.[7]	64	727	24	361	34.9%	1.32 (0.84, 2.08)
Kumada et al.[19]	15	126	6	63	8.7%	1.25 (0.51, 3.07)
McHutchison et al.[6]	18	175	4	75	6.1%	1.93 (0.68, 5.51)
McHutchison et al.[12]	46	228	13	114	18.8%	1.77 (1.00, 3.14)
Zeuzem et al.[10]	65	530	7	132	12.2%	2.31 (1.09, 4.93)
Total (95% CI)		**1963**		**845**	**100.0%**	**1.56 (1.21, 2.03)**
Total events	241		67			

Heterogeneity: $\chi^2 = 4.48$, df = 6 (p = 0.61); $I^2 = 0\%$
Test for overall effect: Z = 3.39 (p = 0.0007)

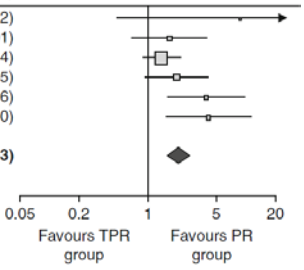


Meta-analysis of discontinued treatment because of an adverse event in the TPR group compared with the PR group

CI = confidence interval; df = degrees of freedom; I^2 = percentage of the total variation across studies due to heterogeneity; M-H = Mantel-Haenszel; peginterferon = pegylated interferon; PR= peginterferon plus ribavirin; TPR = combination telaprevir with peginterferon plus ribavirin; Z = test of overall treatment effect

Study or subgroup	TPR group Events	Total	PR group Events	Total	Weight	Risk Ratio M-H, Fixed (95% CI)
Foster et al.[21]	3	14	0	18	0.7%	8.87 (0.50, 158.72)
Hezode et al.[8]	20	163	6	82	11.8%	1.68 (0.70, 4.01)
Jacobson et al.[7]	73	727	26	361	51.5%	1.39 (0.91, 2.14)
McHutchison et al.[6]	37	175	8	75	16.6%	1.98 (0.97, 4.05)
McHutchison et al.[12]	40	228	5	114	9.9%	4.00 (1.62, 9.86)
Zeuzem et al.[10]	68	530	4	132	9.5%	4.23 (1.57, 11.40)
Total (95% CI)		**1837**		**782**	**100.0%**	**2.10 (1.56, 2.83)**
Total events	241		49			

Heterogeneity: $\chi^2 = 8.62$, df = 5 (p = 0.13); $I^2 = 42\%$
Test for overall effect: Z = 4.89 (p < 0.00001)



4. Anmerkungen/Fazit der Autoren

Our meta-analysis raises safety concerns about the potential for an increased risk of serious adverse events associated with the use of telaprevir among patients with chronic hepatitis C virus infection, and cautious use of telaprevir is warranted.

Leitlinien

Sarrazin C et al., 2014 [62]. **Deutsche Gesellschaft für Gastroenterologie:** Aktuelle Empfehlung zur Therapie der chronischen Hepatitis C *Siehe auch:* **Sarrazin C et al., 2015 [63].** Addendum zur aktuellen Empfehlung zur Therapie der chronischen Hepatitis C	Addendum zur Hepatitis-C-Leitlinie im Auftrag der folgenden Fachgesellschaften (2/15): Deutsche Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten (DGVS)/Berufsverband niedergelassener Gastroenterologen (bng), Kompetenznetz Hepatitis /Deutsche Leberstiftung, Deutsche Gesellschaft für Pathologie (DGP)/Berufsverband Deutscher Pathologen, Gesellschaft für Virologie (GfV), Gesellschaft für Pädiatrische Gastroenterologie und Ernährung (GPGE), Schweizerische Gesellschaft für Gastroenterologie (SGG), Österreichische Gesellschaft für Gastroenterologie und Hepatologie (ÖGGH), Deutsche Transplantationsgesellschaft (DTG), Deutsche Leberhilfe e.V. Durch die Zulassung der direkt antiviral wirksamen Medikamente gegen verschiedene Proteine des Hepatitis-C-Virus (HCV) wurde die Möglichkeit einer hocheffektiven, nebenwirkungsarmen interferonfreien Kombinationstherapie mit relativ kurzer Therapiedauer für praktisch alle Patienten mit einer chronischen Hepatitis-C-Virus-Infektion (HCV) eröffnet. Vor diesem Hintergrund kann eine interferonbasierte Therapie nicht mehr als Standardtherapie empfohlen werden. Die folgenden Empfehlungen gelten für erwachsene Patienten mit chronischer Hepatitis C.
	Methodik Grundlage der Leitlinie – Addendum zur abgelaufenen Leitlinie von 2010 – Vorgehen für die abgelaufene Leitlinie: kombinierter, formaler Prozess zur Konsensusfindung aus nominalem Gruppen- und Konsensusprozess, der multidisziplinär ausgerichtet war – Suchzeitraum: pubmed und web of science (2009 bis Januar 2015) – Weitere Kriterien für die Qualität einer LL: • Empfehlungen sind mit Literaturstellen verknüpft LoE / GoR

Empfehlungs-grad	Evidenz-grad	Beschreibung
A	Ia	„Evidenz“ durch systematisches Review randomisierter kontrollierter Studien (RCT)
	Ib	„Evidenz“ durch eine geeignet geplante RCT
	Ic	Alle-oder-Keiner-Prinzip
B	IIa	„Evidenz“ durch systematisches Review gut geplanter Kohortenstudien
	IIb	„Evidenz“ durch eine gut geplante Kohortenstudie/RCT mäßiger Qualität (z. B. < 80 % Follow-up)
	IIc	„Evidenz“ durch Outcome-Research-Studien
	IIIa	„Evidenz“ durch systematisches Review gut geplanter Fallkontrollstudien
	IIIb	„Evidenz“ durch eine Fallkontrollstudie
C	IV	„Evidenz“ durch Fallserien/Kohorten- und Fallkontrollstudien mäßiger Qualität
D	V	Expertenmeinung ohne explizite kritische Bewertung oder basierend auf physiologischen Modellen, Laborforschungsresultaten oder „first principles“

Freitext/Empfehlungen/Hinweise

Genotyp 1

Für Patienten mit einer HCV-Genotyp-1-Infektion werden unter Berücksichtigung des Zirrhosestatus, des Vortherapiestatus, des HCV Subtyps und viraler Resistenzen folgende Therapieoptionen empfohlen:

- Ledipasvir plus Sofosbuvir +/- Ribavirin für 8, 12 oder 24 Wochen (Evidenzgrad Ib)
- Paritaprevir/r plus Ombitasvir plus Dasabuvir +/- Ribavirin für 12 oder 24Wochen (Evidenzgrad Ib)
- Simeprevir plus Sofosbuvir +/- Ribavirin für 12 Wochen (Evidenzgrad IIb)
- Daclatasvir plus Sofosbuvir +/- Ribavirin für 12 bzw. 24 Wochen (Evidenzgrad IIb bzw. V)

Genotyp 2

Für Patienten mit einer HCV-Genotyp-2-Infektion wird in der Regel folgende Therapieoption empfohlen:

- Sofosbuvir und Ribavirin für 12 Wochen (Evidenzgrad Ib)

Genotyp 3

Für Patienten mit einer HCV-Genotyp-3-Infektion werden unter Berücksichtigung des Zirrhosestatus und des Vortherapiestatus folgende Therapieoptionen empfohlen:

- Sofosbuvir plus Ribavirin für 24 Wochen (Evidenzgrad Ib)
- Daclatasvir plus Sofosbuvir für 12 Wochen bei Patienten ohne Leberzirrhose (Evidenzgrad Ib)
- Daclatasvir plus Sofosbuvir plus Ribavirin für 24 Wochen bei Patienten mit Leberzirrhose (Evidenzgrad V)
- Ledipasvir plus Sofosbuvir plus Ribavirin für 24 Wochen bei Patienten mit Leberzirrhose (Evidenzgrad V)

	Genotyp 4 Für Patienten mit einer HCV-Genotyp-4-Infektion werden unter Berücksichtigung des Zirrhosestatus und des Vortherapiestatus folgende Therapieoptionen empfohlen: • Ledipasvir plus Sofosbuvir +/- Ribavirin für 12 Wochen (Evidenzgrad IIb) • Paritaprevir/r plus Ombitasvir und Ribavirin für 12 Wochen bei Patienten ohne Leberzirrhose (Evidenzgrad IIb) • Simeprevir plus Sofosbuvir +/- Ribavirin für 12 Wochen (Evidenzgrad V) • Daclatasvir plus Sofosbuvir +/- Ribavirin für 12 Wochen (Evidenzgrad V) **Genotyp 5 und 6** Für Patienten mit einer HCV-Genotyp-5- oder -6-Infektion werden unter Berücksichtigung der Interferonverträglichkeit folgende Therapieoptionen empfohlen: • Ledipasvir plus Sofosbuvir plus Ribavirin für 12 Wochen (IIb) **HIV/HCV-Koinfektion** HIV/HCV Koinfektion Genotyp 1 – 6: • Die antivirale Therapie sollte analog zu den Empfehlungen bei HCV monoinfizierten Patienten durchgeführt werden (Evidenzgrad IIb) **Therapie bei dekompensierter Leberzirrhose sowie vor und nach Lebertransplantation** Für Patienten mit dekompensierter Leberzirrhose sowie vor und nach Lebertransplantation werden unter Berücksichtigung der Interferonverträglichkeit folgende Therapieoptionen empfohlen: • Ledipasvir plus Sofosbuvir +/- Ribavirin über 12 – 24 Wochen (Evidenzgrad IIb) • Paritaprevir/r, Ombitasvir, Dasabuvir +/- Ribavirin nur bei maximal kompensierter Zirrhose für 12 – 24 Woche (Evidenzgrad IIb) • Sofosbuvir plus Ribavirin (Evidenzgrad IIb) • Simeprevir plus Sofosbuvir +/- Ribavirin für 12 – 24 Wochen (Evidenzgrad IIb bzw. V; s. u.) • Daclatasvir plus Sofosbuvir +/- Ribavirin für 12 – 24 Wochen (Evidenzgrad V)
American Association for the Study of Liver Diseases, 2016 [2]. Recommendations for Testing, Managing, and	The goal of the Guidance is to provide up-to-date recommendations to health care practitioners on the optimal screening, management, and treatment for adults with HCV infection in the United States, considering the best available evidence. The Guidance is updated regularly, as new data, information, and tools and treatments become available.
	Methodik Grundlage der Leitlinie – Panel members

Treating Hepatitis C

Siehe auch:

Canadian Agency for Drugs and Technologies in Health, 2014 [10].

Treatments for Patients with Genotype 1 Chronic Hepatitis C: A Review of Evidence-based Guidelines

sowie

Canadian Agency for Drugs and Technologies in Health, 2014 [8].

Interferon-free Regimens for Genotype 1 Chronic Hepatitis C: A Review of the Clinical Evidence and Cost-Effectiveness

- Panel members are chosen based on their expertise in the diagnosis, management, and treatment of HCV infection. Members from the fields of hepatology and infectious diseases are included, as well as HCV community representatives

– Data review and synthesis and preparation of recommendations and supporting information
  - Draft Recommendations are developed by subgroups of the full Panel with interest and expertise in particular sections of the Guidance. Following development of supporting text and references, the sections are reviewed by the full Panel and Chairs.
– CoI transparent
– Update
  Revised Date: December 19, 2014
– Suchzeitraum
  PubMed, Scopus, EMBASE, and Web of Science Databases; to be considered for inclusion, articles were required to have been published in English from 2010 to the present.
– Weitere Kriterien für die Qualität einer LL:
  - Empfehlungen sind mit Literaturstellen verknüpft

LoE / GoR

Recommendations are based on scientific evidence and expert opinion. Each recommended statement includes a Roman numeral (**I**, **II**, or **III**) that represents the level of the evidence that supports the recommendation, and a letter (**A**, **B**, or **C**) that represents the strength of the recommendation.

Classification	Description
Class I	Conditions for which there is evidence and/or general agreement that a given diagnostic evaluation, procedure, or treatment is beneficial, useful, and effective
Class II	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness and efficacy of a diagnostic evaluation, procedure, or treatment
Class IIa	Weight of evidence and/or opinion is in favor of usefulness and efficacy
Class IIb	Usefulness and efficacy are less well established by evidence and/or opinion
Class III	Conditions for which there is evidence and/or general agreement that a diagnostic evaluation, procedure, or treatment is not useful and effective or if it in some cases may be harmful
Level of Evidence	**Description**
Level A*	Data derived from multiple randomized clinical trials, meta-analyses, or equivalent
Level B*	Data derived from a single randomized trial, nonrandomized studies, or equivalent
Level C	Consensus opinion of experts, case studies, or standard of care

Initial Treatment

Genotype 1a

Genotype 1a Treatment-naïve Patients without Cirrhosis - Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- **Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 1a infection who do not have cirrhosis and in whom no baseline high fold-change NS5A RAVs[§] for elbasvir are detected.**
  Rating: Class I, Level A

- **Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 1a infection who do not have cirrhosis.**
  Rating: Class I, Level A

- **Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) with weight-based RBV for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 1a infection who do not have cirrhosis.**
  Rating: Class I, Level A

- **Daily simeprevir (150 mg) plus sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 1a infection who do not have cirrhosis.**
  Rating: Class I, Level A

- **Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 1a infection who do not have cirrhosis.**
  Rating: Class I, Level B

[§] Includes G1a polymorphisms at amino acid positions 28, 30, 31, or 93. Amino acid substitutions that confer resistance.
*The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

Genotype 1a Treatment-naïve Patients with Compensated Cirrhosis[ǂ] - Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- **Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 1a infection who have compensated cirrhosis and in whom no baseline high fold-change NS5A RAVs[§] for elbasvir are detected.**
  Rating: Class I, Level A

- **Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 1a infection who have compensated cirrhosis.**
  Rating: Class I, Level A

[ǂ] For decompensated cirrhosis, please refer to the appropriate section.
[§] Includes G1a polymorphisms at amino acid positions 28, 30, 31, or 93. Amino acid substitutions that confer resistance.

Genotype 1a Treatment-naïve Patients without Cirrhosis - Alternative

- **Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) with weight-based**

RBV for 16 weeks is an Alternative regimen for patients with HCV genotype 1a infection who do not have cirrhosis but have baseline high fold-change NS5A RAVs[§] for elbasvir.
Rating: Class IIa, Level B

[§] Includes G1a polymorphisms at amino acid positions 28, 30, 31, or 93. Amino acid substitutions that confer resistance.

Genotype 1a Treatment-naïve Patients with Compensated Cirrhosis[‡] - Alternative
Alternative regimens are listed in groups by level of evidence, then alphabetically.

- **Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) with weight-based RBV for 24 weeks is an Alternative regimen for treatment-naïve patients with HCV genotype 1a infection who have compensated cirrhosis.[†]**
  Rating: Class I, Level A

- **Daily simeprevir (150 mg) plus sofosbuvir (400 mg) with or without weight-based RBV for 24 weeks is an Alternative regimen for treatment-naïve patients with HCV genotype 1a infection who have compensated cirrhosis and in whom no Q80K polymorphism is detected.**
  Rating: Class I, Level A

- **Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) with or without weight-based RBV for 24 weeks is an Alternative regimen for treatment-naïve patients with HCV genotype 1a infection who have compensated cirrhosis.**
  Rating: Class IIa, Level B

- **Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) with weight-based RBV for 16 weeks is an Alternative regimen for treatment-naïve patients with HCV genotype 1a infection who have compensated cirrhosis and have baseline high fold-change NS5A RAVs[§] for elbasvir.**
  Rating: Class IIa, Level B

[‡] For decompensated cirrhosis, please refer to the appropriate section.
[†] Please see statement on FDA warning regarding the use of PrOD or PrO in patients with cirrhosis.
* The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.
[§] Includes G1a polymorphisms at amino acid positions 28, 30, 31, or 93. Amino acid substitutions that confer resistance.

Genotype 1b

Genotype 1b Treatment-naïve Patients without Cirrhosis - Recommended
Recommended regimens are listed in groups by level of evidence, then alphabetically.

- **Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 1b infection who do not have cirrhosis.**
  Rating: Class I, Level A

- **Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 1b infection who do not have cirrhosis.**
  Rating: Class I, Level A

- **Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 1b infection who do not have cirrhosis.**
  Rating: Class I, Level A

- **Daily simeprevir (150 mg) plus sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 1b infection who do not have cirrhosis.**
  Rating: Class I, Level A

- **Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 1b infection who do not have cirrhosis.**
  Rating: Class I, Level B

*The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

Genotype 1b Treatment-naïve Patients with Compensated Cirrhosis‡- Recommended
Recommended regimens are listed in groups by level of evidence, then alphabetically.

- **Daily fixed-dose combination of grazoprevir (100 mg)/elbasvir (50 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 1b infection who have compensated cirrhosis.**
  Rating: Class I, Level A

- **Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 1b infection who have compensated cirrhosis.**
  Rating: Class I, Level A

- **Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 1b infection who have compensated cirrhosis.†**
  Rating: Class I, Level A

‡ For decompensated cirrhosis, please refer to the appropriate section.
† Please see statement on FDA warning regarding the use of PrOD or PrO in patients with cirrhosis.

Genotype 1b Treatment-naïve Patients with Compensated Cirrhosis‡- Alternative
Alternative regimens are listed in groups by level of evidence, then alphabetically.

- **Daily simeprevir (150 mg) plus sofosbuvir (400 mg) with or without weight-based RBV for 24 weeks is an Alternative regimen for treatment-naïve patients with HCV genotype 1b infection who have compensated cirrhosis.**
  Rating: Class I, Level A

- **Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) with or without weight-based RBV for 24 weeks is an Alternative regimen for treatment-naïve patients with HCV genotype 1b infection who have compensated cirrhosis.**
  Rating: Class IIa, Level B

‡ For decompensated cirrhosis, please refer to the appropriate section.
* The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

Genotype 2

Genotype 2 Treatment-naïve Patients without Cirrhosis - Recommended
Recommended regimens are listed in groups by level of evidence, then alphabetically.

- **Daily sofosbuvir (400 mg) and weight-based RBV for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 2 infection who do not have cirrhosis.**
  Rating: Class I, Level A

- **Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 2 infection who do not have cirrhosis and who are not eligible to receive RBV.**
  Rating: Class IIa, Level B

* The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretoviral therapy.

Genotype 2 Treatment-naïve Patients with Compensated Cirrhosis‡ - Recommended
Recommended regimens are listed in groups by level of evidence, then alphabetically.

- **Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) for 16 weeks to 24 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 2 infection who have compensated cirrhosis and who are not eligible to receive RBV.**
  Rating: Class IIa, Level B

- **Daily sofosbuvir (400 mg) and weight-based RBV for 16 weeks to 24 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 2 infection who have compensated cirrhosis.**
  Rating: Class IIa, Level C

‡ For decompensated cirrhosis, please refer to the appropriate section.
* The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretoviral therapy.

Genotype 3

Genotype 3 Treatment-naïve Patients without Cirrhosis - Recommended
Recommended regimens are listed in groups by level of evidence, then alphabetically.

- **Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 3 infection who do not have cirrhosis.**
  Rating: Class I, Level A

- **Daily sofosbuvir (400 mg) and weight-based RBV plus weekly PEG-IFN for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 3 infection who do not have cirrhosis and who are eligible to receive PEG-IFN.**
  Rating: Class I, Level A

* The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretoviral therapy.

Genotype 3 Treatment-naïve Patients with Compensated Cirrhosis‡ - Recommended
Recommended regimens are listed in groups by level of evidence, then alphabetically.

- **Daily sofosbuvir (400 mg) and weight-based RBV plus weekly PEG-IFN for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 3 infection who have compensated cirrhosis and who are eligible to receive PEG-IFN.**
  Rating: Class I, Level A

- **Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) for 24 weeks with or without weight-based RBV is a Recommended regimen for treatment-naïve patients with HCV genotype 3 infection who have compensated cirrhosis.**
  Rating: Class IIa, Level B

‡ For decompensated cirrhosis, please refer to the appropriate section.
* The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretoviral therapy.

Genotype 3 Treatment-naïve Patients with or without Cirrhosis‡ - Alternative

- **Daily sofosbuvir (400 mg) and weight-based RBV for 24 weeks is an Alternative regimen for treatment-naïve patients with HCV genotype 3 infection, regardless of cirrhosis status, who are daclatasvir and IFN ineligible.**
  Rating: Class I, Level A

‡ For decompensated cirrhosis, please refer to the appropriate section.

Genotype 4

Genotype 4 Treatment-naïve Patients without Cirrhosis - Recommended
Recommended regimens are listed in groups by level of evidence, then alphabetically.

- **Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) and weight-based RBV for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 4 infection who do not have cirrhosis.**
  Rating: Class I, Level A
- **Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 4 infection who do not have cirrhosis.**
  Rating: Class IIa, Level B
- **Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 4 infection who do not have cirrhosis.**
  Rating: Class IIa, Level B

Genotype 4 Treatment-naïve Patients with Compensated Cirrhosis‡ - Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- **Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) and weight-based RBV for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 4 infection, with compensated cirrhosis.†**
  Rating: Class I, Level B
- **Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 4 infection with compensated cirrhosis.**
  Rating: Class IIa, Level B
- **Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 4 infection, with compensated cirrhosis.**
  Rating: Class IIa, Level B

‡ For decompensated cirrhosis, please refer to the appropriate section.
† Please see statement on FDA warning regarding the use of PrOD or PrO in patients with cirrhosis.

Genotype 4 Treatment-naïve Patients with or without Cirrhosis[‡] - Alternative

- **Daily sofosbuvir (400 mg) and weight-based RBV plus weekly PEG-IFN for 12 weeks is an Alternative regimen for treatment-naïve patients with HCV genotype 4 infection who are IFN eligible, regardless of cirrhosis status.**
  Rating: Class II, Level B

Genotype 5 or 6

Genotype 5/6 Treatment-naïve Patients with and without Cirrhosis - Recommended

- **Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 5 or 6 infection, regardless of cirrhosis status.**
  Rating: Class IIa, Level B

Genotype 5/6 Treatment-naïve Patients with and without Cirrhosis[‡] - Alternative

- **Daily sofosbuvir (400 mg) and weight-based RBV plus weekly PEG-IFN for 12 weeks is an Alternative regimen for treatment-naïve patients with HCV genotype 5 or 6 infection who are IFN eligible, regardless of cirrhosis status.**
  Rating: Class IIa, Level B

[‡] For decompensated cirrhosis, please refer to the appropriate section.

Retreatment

Genotype 1a PEG-IFN/RBV Treatment-experienced Patients without Cirrhosis - Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- **Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 1a infection who do not have cirrhosis, in whom prior PEG-IFN/RBV treatment has failed, and in whom no baseline high fold-change NS5A RAVs[§] for elbasvir are detected.**
  Rating: Class I, Level A

- **Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 1a infection who do not have cirrhosis, in whom prior PEG-IFN/RBV treatment has failed.**
  Rating: Class I, Level A

- **Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dasabuvir (250 mg) and weight-based RBV for 12 weeks is a Recommended regimen for patients with HCV genotype 1a infection who do not have cirrhosis, in whom prior PEG-IFN/RBV treatment has failed.**
  Rating: Class I, Level A

- **Daily simeprevir (150 mg) plus sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 1a infection who do not have cirrhosis, in whom prior PEG-IFN/RBV treatment has failed.**
  Rating: Class I, Level A

- **Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 1a infection who do not have cirrhosis, in whom prior PEG-IFN/RBV treatment has failed.**
  Rating: Class IIa, Level B

[5] Includes G1a polymorphisms at amino acid positions 28, 30, 31, or 93. Amino acid substitutions that confer resistance.
* The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

Genotype 1a PEG-IFN/RBV Treatment-experienced Patients with Compensated Cirrhosis[‡] - Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- **Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 1a infection who have compensated cirrhosis, in whom prior PEG-IFN/RBV treatment has failed, and in whom no baseline high fold-change NS5A RAVs[5] for elbasvir are detected.**
  Rating: Class I, Level A

- **Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 24 weeks is a Recommended regimen for patients with HCV genotype 1a infection who have compensated cirrhosis, in whom prior PEG-IFN/RBV treatment has failed.**
  Rating: Class I, Level A

- **Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) plus weight-based RBV for 12 weeks is a Recommended regimen for patients with HCV genotype 1a infection who have compensated cirrhosis, in whom prior PEG-IFN/RBV treatment has failed.**
  Rating: Class I, Level A

[‡] For decompensated cirrhosis, please refer to the appropriate section.
[5] Includes G1a polymorphisms at amino acid positions 28, 30, 31, or 93. Amino acid substitutions that confer resistance.

Genotype 1a PEG-IFN/RBV Treatment-experienced Patients without Cirrhosis - Alternative

- **Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) with weight-based RBV for 16 weeks is an Alternative regimen for patients with HCV genotype 1a infection who do not have cirrhosis, in whom prior PEG-IFN/RBV treatment has failed and who have baseline high fold-change NS5A RAVs[5] for elbasvir.**
  Rating: Class I, Level B

[5] Includes G1a polymorphisms at amino acid positions 28, 30, 31, or 93. Amino acid substitutions that confer resistance.

Genotype 1a PEG-IFN/RBV Treatment-experienced Patients with Compensated Cirrhosis‡ - Alternative

Alternative regimens are listed in groups by level of evidence, then alphabetically.

- **Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) and weight-based RBV for 24 weeks is an Alternative regimen for patients with HCV genotype 1a infection who have compensated cirrhosis, in whom prior PEG-IFN/RBV treatment has failed.†**
  Rating: Class I, Level A

- **Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) with weight-based RBV for 16 weeks is an Alternative regimen for patients with HCV genotype 1a infection who have compensated cirrhosis, in whom prior PEG-IFN/RBV treatment has failed and who have baseline high fold-change NS5A RAVs§ for elbasvir.**
  Rating: Class I, Level B

- **Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) with or without weight-based RBV for 24 weeks is an Alternative regimen for patients with HCV genotype 1a infection, who have compensated cirrhosis, in whom prior PEG-IFN/RBV treatment has failed.**
  Rating: Class IIa, Level B

- **Daily simeprevir (150 mg) plus sofosbuvir (400 mg) with or without weight-based RBV for 24 weeks is an Alternative regimen for patients with HCV genotype 1a infection with compensated cirrhosis who are negative for the Q80K variant by commercially available resistance assay, in whom prior PEG-IFN/RBV treatment has failed. Other Recommended or Alternative regimens should be used for patients with compensated cirrhosis and HCV genotype 1a infection in whom the Q80K variant is present.**
  Rating: Class IIa, Level B

†For decompensated cirrhosis, please refer to the appropriate section.

†Please see statement on FDA warning regarding the use of PrOD or PrO in patients with cirrhosis.
§ Includes G1a polymorphisms at amino acid positions 28, 30, 31, or 93. Amino acid substitutions that confer resistance.
* The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

Genotype 1b PEG-IFN/RBV Treatment-experienced Patients without Cirrhosis - Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- **Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 1b infection who do not have cirrhosis, in whom prior PEG-IFN/RBV treatment has failed.**
  Rating: Class I, Level A

- **Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 1b infection who do not have cirrhosis, in whom prior PEG-IFN/RBV treatment has failed.**
  Rating: Class I, Level A

- **Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 1b infection who do not have cirrhosis, in whom prior PEG-IFN/RBV treatment has failed.**
  Rating: Class I, Level A

- **Daily simeprevir (150 mg) plus sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 1b infection who do not have cirrhosis, in whom prior PEG-IFN/RBV treatment has failed.**
  Rating: Class I, Level A

- **Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 1b infection who do not have cirrhosis, in whom prior PEG-IFN/RBV treatment has failed.**
  Rating: Class IIa, Level B

* The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

Genotype 1b PEG-IFN/RBV Treatment-experienced with Compensated Cirrhosis‡ - Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- **Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 1b infection who have compensated cirrhosis, in whom prior PEG-IFN/RBV treatment has failed.**
  Rating: Class I, Level A

- **Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) plus weight-based RBV for 12 weeks is a Recommended regimen for patients with HCV genotype 1b infection who have compensated cirrhosis, in whom prior PEG-IFN/RBV treatment has failed.**
  Rating: Class I, Level A

- **Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 24 weeks is a Recommended regimen for patients with HCV genotype 1b infection who have compensated cirrhosis, in whom prior PEG-IFN/RBV treatment has failed.**
  Rating: Class I, Level A

- **Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 1b infection who have compensated cirrhosis, in whom prior PEG-IFN/RBV treatment has failed.**[†]
  Rating: Class I, Level A

[†]For decompensated cirrhosis, please refer to the appropriate section.

[†] Please see statement on FDA warning regarding the use of PrOD or PrO in patients with cirrhosis.

Genotype 1b PEG-IFN/RBV Treatment-experienced Patients with Compensated Cirrhosis[‡] - Alternative

Alternative regimens are listed in groups by level of evidence, then alphabetically.

- **Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) with or without weight-based RBV for 24 weeks is an Alternative regimen for patients with HCV genotype 1b infection, who have compensated cirrhosis, in whom prior PEG-IFN/RBV treatment has failed.**
  Rating: Class IIa, Level B

- **Daily simeprevir (150 mg) plus sofosbuvir (400 mg) with or without weight-based RBV for 24 weeks is an Alternative regimen for patients with HCV genotype 1b infection who have compensated cirrhosis, in whom prior PEG-IFN/RBV treatment has failed.**
  Rating: Class IIa, Level B

[†]For decompensated cirrhosis, please refer to the appropriate section.

* The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

Genotype 1 Sofosbuvir plus Ribavirin with or without PEG-IFN Treatment-experienced Patients - Recommended

- **No Cirrhosis:**
  Daily fixed-dose combination of ledipavir (90 mg)/sofosbuvir (400 mg) with weight-based RBV for 12 weeks is a Recommended regimen for patients with HCV genotype 1 infection, regardless of subtype, who do not have cirrhosis, in whom a previous sofosbuvir plus RBV-containing regimen with or without PEG-IFN has failed.
  Rating: Class IIa, Level B

- **Compensated Cirrhosis:**[‡]
  Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with weight-based RBV for 24 weeks is a Recommended regimen for patients with HCV genotype 1 infection, regardless of subtype, who have compensated cirrhosis, in whom a previous sofosbuvir

plus RBV-containing regimen has failed.
Rating: Class IIa, Level B

†For decompensated cirrhosis, please refer to the appropriate section.

Genotype 1 HCV nonstructural protein 3 (NS3) protease inhibitor (telaprevir, boceprevir, or simeprevir) plus PEG-IFN/RBV Treatment-experienced Patients without Cirrhosis - Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- **Daily fixed-dose combination ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for treatment of patients with HCV genotype 1 infection, regardless of subtype, who do not have cirrhosis, in whom prior treatment with an HCV protease inhibitor plus PEG-IFN/RBV has failed.**
  Rating: Class I, Level A

- **Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 1 infection, regardless of subtype, who do not have cirrhosis, in whom prior treatment with an HCV protease inhibitor plus PEG-IFN/RBV has failed.**
  Rating: Class IIa, Level B

- **Daily fixed-dose combination elbasvir (50 mg)/grazoprevir (100 mg) with weight-based ribavirin for 12 weeks is a Recommended regimen for patients with HCV genotype 1 infection, regardless of subtype, who do not have cirrhosis, in whom prior treatment with an HCV protease inhibitor plus PEG-IFN/RBV has failed. Genotype 1a patients who have baseline high fold-change NS5A RAVs[§] for elbasvir should have this treatment extended to 16 weeks.**
  Rating: Class IIa, Level B

* The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.
§ Includes G1a polymorphisms at amino acid positions 28, 30, 31, or 93. Amino acid substitutions that confer resistance.

Genotype 1 HCV nonstructural protein 3 (NS3) protease inhibitor (telaprevir, boceprevir, or simeprevir) plus PEG-IFN/RBV Treatment-experienced Patients with Compensated Cirrhosis‡ - Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- **Daily fixed-dose combination ledipasvir (90 mg)/sofosbuvir (400 mg) plus weight-based RBV for 12 weeks is a Recommended regimen for patients with HCV genotype 1 infection, regardless of subtype, who have compensated cirrhosis, in whom prior treatment with an HCV protease inhibitor plus PEG-IFN/RBV has failed.**
  Rating: Class I, Level A

- **Daily fixed-dose combination ledipasvir (90 mg)/sofosbuvir (400 mg) for 24 weeks is a Recommended regimen for retreatment of patients with HCV genotype 1 infection, regardless of subtype, who have compensated cirrhosis, in whom prior treatment with an HCV protease inhibitor plus PEG-IFN/RBV has failed.**
  Rating: Class I, Level A

- **Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) with or without weight-based RBV for 24 weeks is a Recommended regimen for patients with HCV genotype 1 infection, regardless of subtype, who have compensated cirrhosis, in whom prior treatment with an HCV protease inhibitor plus PEG-IFN/RBV has failed.**
  Rating: Class IIa, Level B

- **Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) plus weight-based RBV for 12 weeks is a Recommended regimen for patients with HCV genotype 1 infection, regardless of subtype, who have compensated cirrhosis, in whom a prior treatment with an HCV protease inhibitor plus PEG-IFN/RBV has failed. Genotype 1a patients who have baseline high fold-change NS5A RAVs[§] for elbasvir should have this treatment extended to 16 weeks.**
  Rating: Class IIa, Level B

[†]For decompensated cirrhosis, please refer to the appropriate section.

* The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.
[§] Includes G1a polymorphisms at amino acid positions 28, 30, 31, or 93. Amino acid substitutions that confer resistance.

Genotype 1 Simeprevir plus Sofosbuvir Treatment-experienced Patients - Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- **Deferral of treatment is recommended, pending availability of data, for patients with HCV genotype 1 infection, regardless of subtype, in whom prior treatment with the HCV protease inhibitor simeprevir plus sofosbuvir has failed (no prior NS5A treatment) who do not have cirrhosis,[‡] and do not have reasons for urgent retreatment.**
  Rating: Class IIb, Level C

- **Testing for resistance-associated variants that confer decreased susceptibility to NS3 protease inhibitors and to NS5A inhibitors is recommended for patients with HCV genotype 1 infection, regardless of subtype, in whom prior treatment with the HCV protease inhibitor simeprevir plus sofosbuvir has failed (no prior NS5A treatment), who have compensated cirrhosis,[‡] or have reasons for urgent retreatment. The specific drugs used in the retreatment regimen should be tailored to the results of this testing as described below.**

- **When using nucleotide-based (eg, sofosbuvir) dual DAA therapy a treatment duration of 24 weeks is recommended, and weight-based RBV, unless contraindicated, should be added.**

- **If available, nucleotide-based (eg, sofosbuvir) triple or quadruple DAA regimens may be considered. In these settings treatment duration ranges from 12 weeks to 24 weeks (see text), and weight-based ribavirin, unless contraindicated, are recommended.**

Rating: Class II, Level C

†For decompensated cirrhosis, please refer to the appropriate section.

Recommended for Genotype 1 HCV NS5A inhibitor Treatment-experienced Patients

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- **Deferral of treatment is recommended, pending availability of data for patients with HCV genotype 1, regardless of subtype, in whom previous treatment with any HCV nonstructural protein 5A (NS5A) inhibitors has failed, who do not have cirrhosis, and do not have reasons for urgent retreatment.**
  Rating: Class IIb, Level C

- **Testing for resistance-associated variants that confer decreased susceptibility to NS3 protease inhibitors and to NS5A inhibitors is recommended for patients with HCV genotype 1, regardless of subtype, in whom previous treatment with any HCV nonstructural protein 5A (NS5A) inhibitors has failed, and who have compensated cirrhosis,† or have reasons for urgent retreatment. The specific drugs used in the retreatment regimen should be tailored to the results of this testing as described below.**

- **When using nucleotide-based (eg, sofosbuvir) dual DAA therapy a treatment duration of 24 weeks is recommended, and weight-based RBV, unless contraindicated, should be added.**

- **If available, nucleotide-based (eg, sofosbuvir) triple or quadruple DAA regimens may be considered. In these settings treatment duration ranges from 12 weeks to 24 weeks (see text), and weight-based ribavirin, unless contraindicated, are recommended.**

Rating: Class IIb, Level C

†For decompensated cirrhosis, please refer to the appropriate section.

Genotype 2 PEG-IFN/RBV Treatment-experienced Patients without Cirrhosis - Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- **Daily sofosbuvir (400 mg) and weight-based RBV for 12 weeks is a Recommended regimen for patients with HCV genotype 2 infection, who do not have cirrhosis, in whom prior PEG-IFN/RBV treatment has failed.**
  Rating: Class I, Level A

- **Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 2 infection, who do not have cirrhosis, in whom prior PEG-IFN/RBV treatment has failed, and who are RBV ineligible.**
  Rating: Class IIa, Level B

* The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

Genotype 2 PEG-IFN/RBV Treatment-experienced Patients with Compensated Cirrhosis‡ - Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- **Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) for 16 weeks to 24 weeks is a Recommended regimen for patients with HCV genotype 2 infection, who have compensated cirrhosis, in whom prior PEG-IFN/RBV treatment has failed, and who are RBV ineligible.**
  Rating: Class IIa, Level B

- **Daily sofosbuvir (400 mg) and weight-based RBV for 16 weeks to 24 weeks is a Recommended regimen for patients with HCV genotype 2 infection, who have compensated cirrhosis, in whom prior PEG-IFN/RBV treatment has failed.**
  Rating: Class IIa, Level B

†For decompensated cirrhosis, please refer to the appropriate section.

* The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

Genotype 2 PEG-IFN/RBV Treatment-experienced Patients with Compensated Cirrhosis‡ - Alternative

- **Daily sofosbuvir (400 mg) and weight-based RBV plus weekly PEG-IFN for 12 weeks is an Alternative regimen for patients who have HCV genotype 2 infection, who have compensated cirrhosis, in whom previous treatment with PEG-IFN/RBV has failed, and who are IFN eligible.**
  Rating: Class IIa, Level B

†For decompensated cirrhosis, please refer to the appropriate section.

Genotype 2 Sofosbuvir plus Ribavirin Treatment-experienced Patients -

Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- **Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) with or without weight-based RBV for 24 weeks is a Recommended regimen for patients with HCV genotype 2 infection, regardless of cirrhosis status,† in whom previous treatment with sofosbuvir and RBV has failed, and who are ineligible to receive PEG-IFN and/or RBV.**
  Rating: Class IIa, Level C

- **Daily sofosbuvir (400 mg) and weight-based RBV plus weekly PEG-IFN for 12 weeks is a Recommended regimen for patients who have HCV genotype 2 infection, regardless of cirrhosis status,† in whom previous treatment with sofosbuvir and RBV has failed, and who are IFN eligible.**
  Rating: Class IIa, Level C

†For decompensated cirrhosis, please refer to the appropriate section.

* The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

Genotype 3 PEG-IFN/RBV Treatment-experienced Patients without Cirrhosis - Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- **Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 3 infection, who do not have cirrhosis, in whom prior treatment with PEG-IFN/RBV has failed.**
  Rating: Class I, Level A

- **Daily sofosbuvir (400 mg) and weight-based RBV plus weekly PEG-IFN for 12 weeks is a Recommended regimen for patients with HCV genotype 3 infection, who do not have cirrhosis, in whom prior treatment with PEG-IFN/RBV has failed, and who are IFN eligible.**
  Rating: Class I, Level A

* The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

Genotype 3 PEG-IFN/RBV Treatment-experienced Patients with Compensated Cirrhosis‡ - Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- **Daily sofosbuvir (400 mg) and weight-based RBV plus weekly PEG-IFN for 12 weeks is a**

Recommended regimen for patients with HCV genotype 3 infection, who have compensated cirrhosis, in whom prior treatment with PEG-IFN/RBV has failed, and who are eligible to receive PEG-IFN.
Rating: Class I, Level A

- **Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) with weight-based RBV for 24 weeks is a Recommended regimen for patients with HCV genotype 3 infection, who have compensated cirrhosis, in whom prior treatment with PEG-IFN/RBV has failed, and who are IFN ineligible.**
  Rating: Class IIa, Level B

†For decompensated cirrhosis, please refer to the appropriate section.

* The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

Genotype 3 Sofosbuvir and RBV Treatment-experienced Patients - Recommended
Recommended regimens are listed in groups by level of evidence, then alphabetically.

- **Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) with weight-based RBV for 24 weeks is a Recommended regimen for patients with HCV genotype 3 infection, regardless of cirrhosis status,† in whom prior treatment with sofosbuvir and RBV has failed, and who are IFN ineligible.**
  Rating: Class IIa, Level C

- **Daily sofosbuvir (400 mg) and weight-based RBV plus weekly PEG-IFN for 12 weeks is a Recommended regimen for patients with HCV genotype 3 infection, regardless of cirrhosis status,† in whom prior treatment with sofosbuvir and RBV has failed, and who are IFN eligible.**
  Rating: Class IIa, Level C

†For decompensated cirrhosis, please refer to the appropriate section.

* The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

Genotype 4 PEG-IFN/RBV Treatment-experienced Patients without Cirrhosis - Recommended
Recommended regimens are listed in groups by level of evidence, then alphabetically.

- **Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) (PrO) and weight-based RBV for 12 weeks is a Recommended regimen for patients with HCV genotype 4 infection, who do not have cirrhosis, in whom prior treatment with PEG-**

IFN/RBV has failed.
Rating: Class I, Level A

- Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for 12 weeks is a Recommended regimen for patients who have HCV genotype 4 infection, who do not have cirrhosis, who experienced virologic relapse after prior PEG-IFN/RBV therapy. Genotype 4 patients with prior on-treatment virologic failure (failure to suppress or breakthrough) while on PEG-IFN/RBV should be treated with 16 weeks and have weight-based RBV added to the treatment regimen.
  Rating: Class IIa, Level B

- Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 4 infection, who do not have cirrhosis, in whom prior treatment with PEG-IFN/RBV treatment has failed.
  Rating: Class IIa, Level B

Genotype 4 PEG-IFN/RBV Treatment-experienced Patients with Compensated cirrhosis‡ - Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) (PrO) and weight-based RBV for 12 weeks is a Recommended regimen for patients with HCV genotype 4 infection who have compensated cirrhosis, in whom prior treatment with PEG-IFN/RBV has failed.†
  Rating: Class I, Level A

- Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for 12 weeks is a Recommended regimen for patients who have HCV genotype 4 infection, who have compensated cirrhosis, and who experienced virologic relapse after prior PEG-IFN/RBV therapy. Genotype 4 patients with prior on-treatment virologic failure (failure to suppress or breakthrough) while on PEG-IFN/RBV should be treated with 16 weeks and have weight-based RBV added to the treatment regimen.
  Rating: Class IIa, Level B

- Daily ledipasvir (90 mg)/sofosbuvir (400 mg) and weight-based RBV for 12 weeks is a Recommended regimen for patients with HCV genotype 4 infection, in whom prior treatment with PEG-IFN/RBV has failed, and who are eligible for RBV.
  Rating: Class IIa, Level B

- Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 24 weeks is a Recommended regimen for patients with HCV genotype 4 infection, in whom prior treatment with PEG-IFN/RBV treatment has failed.
  Rating: Class IIa, Level B

†For decompensated cirrhosis, please refer to the appropriate section.

	†Please see statement on FDA warning regarding the use of PrOD or PrO in patients with cirrhosis. ***Genotype 4 Treatment-experienced Patients with or without cirrhosis‡ - Alternative*** *Alternative regimens are listed in groups by level of evidence, then alphabetically.* ▪ **Daily sofosbuvir (400 mg) and weight-based RBV plus weekly PEG-IFN for 12 weeks is an Alternative regimen for patients with HCV genotype 4 infection, who do not have cirrhosis, in whom prior treatment has failed, and who are eligible for PEG-IFN.** Rating: Class IIa, Level B ▪ **Daily sofosbuvir (400 mg) and weight-based RBV for 24 weeks is an Alternative regimen for patients with HCV genotype 4 infection, in whom prior treatment has failed, and who are IFN ineligible.** Rating: Class IIa, Level B †For decompensated cirrhosis, please refer to the appropriate section. ***Genotype 5 or 6 PEG-IFN/RBV Treatment-experienced Patients with or without Cirrhosis‡ - Recommended*** ▪ **Daily fixed-dose combination ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 5 or 6 infection regardless of cirrhosis status, in whom prior treatment with PEG-IFN/RBV has failed.** Rating: Class IIa, Level C †For decompensated cirrhosis, please refer to the appropriate section. ***Genotype 5 or 6 PEG-IFN/RBV Treatment-experienced Patients with or without Cirrhosis‡ - Alternative*** ▪ **Daily sofosbuvir (400 mg) and weight-based RBV plus weekly PEG-IFN for 12 weeks is an Alternative regimen for patients with HCV genotype 5 or 6 infection regardless of cirrhosis status, in whom prior treatment with PEG-IFN/RBV has failed, and are IFN eligible.** Rating: Class IIa, Level C †For decompensated cirrhosis, please refer to the appropriate section.
EASL, 2015 [16]. Recommendations on Treatment of Hepatitis C 2015	**1. Fragestellung:** Leitlinie der European Association for the Study of the Liver (EASL)
	2. Methodik Grundlage der Leitlinie: The evidence and recommendations in these guidelines have been graded according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. The strength of recommendations thus reflects the quality of underlying evidence. The principles of the GRADE system have been enunciated. The quality of the evidence in the CPG has been classified into one of three levels: high (A), moderate (B) or low (C). The GRADE system offers two grades of recommendation: strong (1) or weak (2). Evidence grading used in the EASL HCV Clinical Practice Guidelines (adapted from the GRADE system):

Evidence quality	Notes	Grading
High	Further research is very unlikely to change our confidence in the estimate of effect	A
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate	B
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Any change of estimate is uncertain	C
Recommendation	**Notes**	**Grading**
Strong	Factors influencing the strenght of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost	1
Weak	Variability in preferences and values, or more uncertainty. Recommendation is made with less certainty, higher cost or resource consumption	2

Keine genauen Angaben zur Literaturrecherche und zum Suchzeitraum!

3. Empfehlungen

Patients with **decompensated cirrhosis** (Child-Pugh B and C) should be urgently treated with an IFN-free regimen. (A1)

Indications for HCV treatment in **HCV/HIV coinfected** persons are identical to those in patients with HCV monoinfection. (A1)

Notwithstanding the respective costs of these options, IFN-free regimens are the best options when available in HCV-monoinfected and in **HIV-coinfected** patients **without cirrhosis** or **with compensated** (Child-Pugh A) or **decompensated** (Child-Pugh B or C) cirrhosis, because of their virological efficacy, ease of use and tolerability. (A1)

The same IFN-free treatment regimens can be used in **HIV-coinfected** patients as in patients without HIV infection, as the virological results of therapy are identical. (A1)

Genotype 1
Patients infected with HCV genotype 1 can be treated with a combination of weekly PegIFN-α, daily weightbased ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), and daily sofosbuvir (400 mg) 12 weeks. (A1)

Patients infected with HCV genotype 1 can be treated with a combination of weekly PegIFN-α, daily weightbased ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), and daily simeprevir (150 mg). (A1)
This combination is not recommended in patients infected with subtype 1a who have a detectable Q80K substitution in the NS3 protease sequence at baseline, as assessed by population sequencing (direct sequence analysis). (A1)

Simeprevir should be administered for 12 weeks in combination with PegIFN-α and ribavirin. PegIFN-α and ribavirin should then be administered alone for an additional 12 weeks (total treatment duration 24 weeks) in treatment-naïve and prior relapser patients, including cirrhotic patients, and for an additional 36 weeks (total treatment duration 48 weeks) in prior partial and null responders, including cirrhotic patients. (B1)

	HCV RNA levels should be monitored on treatment. Treatment should be stopped if HCV RNA level is ≥25 IU/ml at treatment week 4, week 12 or week 24. (A2) Patients infected with HCV genotype 1 can be treated with the IFN-free fixed-dose combination of sofosbuvir (400 mg) and ledipasvir (90 mg) in a single tablet administered once daily. (A1) Patients without cirrhosis, including treatment-naïve and treatment-experienced patients, should be treated with this fixed-dose combination for 12 weeks without ribavirin. (A1) Treatment may be shortened to 8 weeks in treatment-naïve patients without cirrhosis if their baseline HCV RNA level is below 6 million (6.8 Log) IU/ml. This should be done with caution, especially in patients with F3 fibrosis, pending demonstration of the accuracy of HCV RNA level determination within this range of values and real-life confirmation that 8 weeks of treatment are sufficient to achieve high SVR rates. (B1) Patients with compensated cirrhosis, including treatment-naïve and treatment-experienced patients, should be treated with this fixed-dose combination for 12 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively). (A1) Patients with compensated cirrhosis with contraindications to the use of ribavirin or with poor tolerance to ribavirin on treatment should receive the fixed-dose combination of sofosbuvir and ledipasvir for 24 weeks without ribavirin. (B1) Treatment with the fixed-dose combination of sofosbuvir and ledipasvir with ribavirin can be prolonged to 24 weeks in treatment-experienced patients with compensated cirrhosis and negative predictors of response, such as a platelet count <75 x 103/µl. (B2) Patients infected with HCV genotype 1 can be treated with an IFN-free regimen comprising the fixed-dose combination of ombitasvir (12.5 mg), paritaprevir (75 mg) and ritonavir (50 mg) in one single tablet (two tablets once daily with food), and dasabuvir (250 mg) (one tablet twice daily). (A1) Patients infected with subtype 1b without cirrhosis should receive this combination for 12 weeks without ribavirin. (A1) Patients infected with subtype 1b with cirrhosis should receive this combination for 12 weeks with daily weightbased ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively). (A1) Patients infected with subtype 1a without cirrhosis should receive this combination for 12 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively). (A1) Patients infected with subtype 1a with cirrhosis should receive this combination for 24 weeks with daily weightbased ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively). (A1)

	Patients infected with HCV genotype 1 can be treated with an IFN-free combination of daily sofosbuvir (400 mg) and daily simeprevir (150 mg) for 12 weeks. (A1) Based on data with other IFN-free combinations, adding daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) is recommended in patients with cirrhosis. (B1) In patients with cirrhosis with contra-indications to the use of ribavirin, extending duration of treatment to 24 weeks must be considered. (B1) Patients infected with HCV genotype 1 can be treated with an IFN-free combination of daily sofosbuvir (400 mg) and daily daclatasvir (60 mg) for 12 weeks. (A1) Based on data with other IFN-free combinations, adding daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) is recommended in patients with cirrhosis. (B1) In patients with cirrhosis with contra-indications to the use of ribavirin, extending duration of treatment to 24 weeks must be considered. (B1) **Genotype 2** Patients infected with HCV genotype 2 must be treated with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), and daily sofosbuvir (400 mg) for 12 weeks. (A1) Therapy should be prolonged to 16 or 20 weeks in patients with cirrhosis, especially if they are treatmentexperienced. (B1) Cirrhotic and/or treatment-experienced patients can be treated with weekly PegIFN-α, daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), and daily sofosbuvir (400 mg) 12 weeks. (B1) Cirrhotic and/or treatment-experienced patients can be treated with an IFN-free combination of daily sofosbuvir (400 mg) and daily daclatasvir (60 mg) for 12 weeks. (B1) **Genotype 3** Patients infected with HCV genotype 3 can be treated with a combination of weekly PegIFN-α, daily weightbased ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), and daily sofosbuvir (400 mg) 12 weeks. (B1) This combination is a valuable option in patients who failed to achieve an SVR after sofosbuvir plus ribavirin treatment. (B1) Patients infected with HCV genotype 3 can be treated with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), and daily sofosbuvir (400 mg) for 24 weeks. (A1) This therapy is suboptimal in treatment-experienced cirrhotic patients and in patients who failed to achieve an SVR after sofosbuvir plus

	ribavirin treatment, who should be offered an alternative treatment option. (B1) Patients infected with HCV genotype 3 without cirrhosis can be treated with an IFN-free combination of daily sofosbuvir (400 mg) and daily daclatasvir (60 mg) for 12 weeks. (A1) Treatment-naïve and treatment-experienced patients infected with HCV genotype 3 with cirrhosis should receive this combination with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) for 24 weeks, pending further data comparing 12 weeks with ribavirin and 24 weeks with and without ribavirin in this population. (B1) **Genotype 4** Patients infected with HCV genotype 4 can be treated with a combination of weekly PegIFN-α, daily weightbased ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), and daily sofosbuvir (400 mg) 12 weeks. (B1) Patients infected with HCV genotype 4 can be treated with a combination of weekly PegIFN-α, daily weightbased ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), and daily simeprevir (150 mg). (B1) Simeprevir should be administered 12 weeks in combination with PegIFN-α and ribavirin. PegIFN-α and ribavirin should then be administered alone for an additional 12 weeks (total treatment duration 24 weeks) in treatment-naïve and prior relapser patients, including cirrhotic patients, an additional 36 weeks (total treatment duration 48 weeks) in prior partial and null responders, including cirrhotic patients. (B1) HCV RNA levels should be monitored on treatment. Treatment should be stopped if HCV RNA level is ≥25 IU/ml at treatment week 4, week 12 or week 24. (A2) Patients infected with HCV genotype 4 can be treated with the IFN-free fixed-dose combination of sofosbuvir (400 mg) and ledipasvir (90 mg) in a single tablet administered once daily. (A1) Patients without cirrhosis, including treatment-naïve and treatment-experienced patients, should be treated with this fixed-dose combination for 12 weeks without ribavirin. (A1) Based on data in patients infected with HCV genotype 1, patients with compensated cirrhosis, including treatment-naïve and treatment-experienced patients, should be treated with this fixed-dose combination for 12 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively). (B1) Patients with compensated cirrhosis with contraindications to the use of ribavirin or with poor tolerance to ribavirin on treatment should receive the fixed-dose combination of sofosbuvir and ledipasvir for 24 weeks without ribavirin. (B1)

	Based on data in patients infected with HCV genotype 1, treatment with the fixed-dose combination of sofosbuvir and ledipasvir with ribavirin can be prolonged to 24 weeks in treatment-experienced patients with compensated cirrhosis and negative predictors of response, such as a platelet count <75 x 103/µl. (B1) Patients infected with HCV genotype 4 without cirrhosis can be treated with an IFN-free regimen comprising the fixed-dose combination of ombitasvir (12.5 mg), paritaprevir (75 mg) and ritonavir (50 mg) in one single tablet (two tablets once daily with food), for 12 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), without dasabuvir. (A1) Patients infected with HCV genotype 4 with cirrhosis should be treated with the fixed-dose combination of ombitasvir (12.5 mg), paritaprevir (75 mg) and ritonavir (50 mg) in one single tablet (two tablets once daily with food), for 24 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), without dasabuvir, pending further data. (B1) Patients infected with HCV genotype 4 can be treated with an IFN-free combination of daily sofosbuvir (400 mg) and daily simeprevir (150 mg) 12 weeks. (B2) Based on data with other combinations, adding daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) is recommended in patients with cirrhosis. (B2) In patients with cirrhosis with contra-indications to the use of ribavirin, extending duration of treatment to 24 weeks must be considered. (B2) Patients infected with HCV genotype 4 can be treated with an IFN-free combination of daily sofosbuvir (400 mg) and daily daclatasvir (60 mg) for 12 weeks. (B2) Based on data with other combinations, adding daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) is recommended in patients with cirrhosis. (B2) In patients with cirrhosis with contra-indications to the use of ribavirin, extending duration of treatment to 24 weeks must be considered. (B2) **Genotype 5 or 6** Patients infected with HCV genotype 5 or 6 can be treated with a combination of weekly PegIFN-α, daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), and daily sofosbuvir (400 mg) 12 weeks. (B1) Patients infected with HCV genotype 5 or 6 can be treated with the IFN-free fixed-dose combination of sofosbuvir (400 mg) and ledipasvir (90 mg) in a single tablet administered once daily. (A1)

	Patients without cirrhosis, including treatment-naïve and treatment-experienced patients, should be treated with this fixed-dose combination for 12 weeks without ribavirin. (B1) Based on data in patients infected with HCV genotype 1, patients with compensated cirrhosis, including treatment-naïve and treatment-experienced patients, should be treated with this fixed-dose combination for 12 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively). (B1) Patients with compensated cirrhosis with contraindications to the use of ribavirin or with poor tolerance to ribavirin on treatment should receive the fixed-dose combination of sofosbuvir and ledipasvir for 24 weeks without ribavirin. (B1) Based on data in patients infected with HCV genotype 1, treatment with the fixed-dose combination of sofosbuvir and ledipasvir with ribavirin can be prolonged to 24 weeks in treatment-experienced patients with compensated cirrhosis and negative predictors of response, such as a platelet count <75 x 103/µl. (B1) Patients infected with HCV genotype 5 or 6 can be treated with an IFN-free combination of daily sofosbuvir (400 mg) and daily daclatasvir (60 mg) for 12 weeks. (B1) Based on data with other combinations, adding daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) is recommended in patients with cirrhosis. (B1) In patients with cirrhosis with contra-indications to the use of ribavirin, extending duration of treatment to 24 weeks must be considered. (B1) **Retreatment of non-sustained virological responders** Patients who failed after PegIFN-α and ribavirin combination treatment must be retreated like treatment-naïve patients, according to the above recommendations by HCV genotype. (A1) Patients infected with HCV genotype 1 who failed after a triple combination regimen of PegIFN-α, ribavirin and either telaprevir or boceprevir should be retreated with the IFN-free combination of sofosbuvir and ledipasvir, or sofosbuvir and daclatasvir, with ribavirin for 12 weeks. (A1) Recommendations for retreatment after failure of second-wave DAA-based anti-HCV regimens are based on indirect evidence and subject to change when more data become available. (A1) Patients who failed on a second-wave DAA-containing regimen, with or without PegIFN-α, with or without ribavirin, should be retreated with an IFN-free regimen for 12 weeks with weight-based ribavirin. Extending therapy to 24 weeks with ribavirin may be considered, especially in patients with advanced liver disease, including extensive fibrosis (F3) and cirrhosis (F4). (B2)

	Patients who failed on sofosbuvir alone or sofosbuvir plus ribavirin or sofosbuvir plus PegIFN-α and ribavirin can be retreated with a combination of sofosbuvir plus simeprevir (genotype 1 or 4), sofosbuvir plus daclatasvir (all genotypes) or sofosbuvir plus ledipasvir (genotypes 1, 4, 5 or 6), or with ritonavir-boosted paritaprevir, ombitasvir and dasabuvir (genotype 1), or with ritonavirboosted paritaprevir and ombitasvir (genotype 4). (B2) Patients infected with HCV genotype 1 or 4 who failed on a regimen combining PegIFN-α, ribavirin and simeprevir should be retreated with a combination of sofosbuvir with daclatasvir or ledipasvir. (B2) Patients who failed on a regimen combining PegIFN-α, ribavirin and daclatasvir should be retreated with a combination of sofosbuvir and simeprevir (if they are infected with genotype 1 or 4). Patients infected with other genotypes should be retreated with the combination of sofosbuvir and daclatasvir (genotypes 2, 3, 5 and 6) or with the combination of sofosbuvir and ledipasvir (genotypes 5 and 6). (B2) Patients infected with genotype 1 or 4 who failed on a regimen containing sofosbuvir and simeprevir should be retreated with a combination of sofosbuvir with daclatasvir or ledipasvir. (B2) Patients who failed on a regimen containing sofosbuvir and daclatasvir or sofosbuvir and ledipasvir should be retreated with a combination of sofosbuvir and simeprevir (genotype 1 and 4). Patients infected with other genotypes should be retreated with the combination of sofosbuvir and daclatasvir (genotypes 2, 3, 5 and 6) or with the combination of sofosbuvir and ledipasvir (genotypes 5 and 6) for 24 weeks. (B2) Patients infected with genotype 1 who failed on the triple combination of ritonavir-boosted paritaprevir, ombitasvir and dasabuvir should be retreated with a sofosbuvir-based regimen, e.g. sofosbuvir and simeprevir, sofosbuvir and daclatasvir or sofosbuvir and ledipasvir. (B2) Patients infected with genotype 4 who failed on the double combination of ritonavir-boosted paritaprevir and ombitasvir should be retreated with a sofosbuvir-based regimen, e.g. sofosbuvir and simeprevir, sofosbuvir and daclatasvir or sofosbuvir and ledipasvir. (B2) Alternatively, patients without an urgent need for treatment can wait until more data and/or alternative therapeutic options become available. (A1) The efficacy and safety of a triple combination regimen including sofosbuvir, an NS3 protease inhibitor and an NS5A protease inhibitor in patients who failed on a DAA-containing regimen is unknown. (B2) The utility of HCV resistance testing (i.e. the determination of the sequence of the DAA target region) prior to retreatment in patients who failed on any of the DAA-containing treatment regimens is unknown. (B2)
	This paper may serve as a current guidance for the therapeutic management of chronic hepatitis C. This update of the earlier guidance

<table>
<tr><td rowspan="3">Berden FAC et al., 2014 [4].

Dutch guidance for the treatment of chronic hepatitis C virus infection in a new therapeutic era</td><td>is necessary given the wealth of new information that has become available since.</td></tr>
<tr><td>Methodik

Grundlage der Leitlinie

– The recommendations in this paper went through a formal approval process and were vetted by individual experts and all members of the NVMDL and representatives of the NIV
– Update der Leitlinie von 2013
– Suchzeitraum:
formal search through the databases PubMed, Web of Science and ClinicalTrials.gov (April 2014)
– Weitere Kriterien für die Qualität einer LL:
• Empfehlungen sind mit Literaturstellen verknüpft

LoE / GoR

<table>
<tr><th>Level</th><th>Evidence quality</th><th>Strength of recommendation</th></tr>
<tr><td>A1</td><td>High</td><td>Strong</td></tr>
<tr><td>B1</td><td>Moderate</td><td>Strong</td></tr>
<tr><td>C1</td><td>Low</td><td>Strong</td></tr>
<tr><td>A2</td><td>High</td><td>Weak</td></tr>
<tr><td>B2</td><td>Moderate</td><td>Weak</td></tr>
<tr><td>C2</td><td>Low</td><td>Weak</td></tr>
</table>
</td></tr>
<tr><td>Freitext/Empfehlungen/Hinweise

Genotype 1 treatment-naive patients
Recommendation: Sofosbuvir, peginterferon and weight-based ribavirin for 12 weeks (Level: B1)

Genotype 1 treatment-experienced patients
Recommendation: No recommendation based on data

Genotype 1 cirrhotic patients
Recommendation: Watchful waiting (Level: C1)

Genotype 2 treatment-naive patients
Recommendation: Sofosbuvir and weight-based ribavirin for 12 weeks (Level: A1)

Genotype 2 treatment-experienced patients
Recommendation: Sofosbuvir and weight-based ribavirin for 12 weeks (Level: B1)

Genotype 2 cirrhotic patients
Recommendation: Sofosbuvir and weight-based ribavirin for 12 weeks (Level: B1)</td></tr>
</table>

	Genotype 3 treatment-naive patients Recommendation: o Watchful waiting o Peginterferon and ribavirin (800 mg) for 24 weeks o Sofosbuvir and weight-based ribavirin for 24 weeks o Sofosbuvir, peginterferon and weight-based ribavirin for 12 weeks (Level A2) **Genotype 3 cirrhotic patients** Recommendation: Watchful waiting Alternative strategy: Sofosbuvir and weight-based ribavirin for 16 weeks OR sofosbuvir and weight-based ribavirin for 24 weeks (Level: B2) **Genotype 4 treatment-naive patients** Recommendation: Sofosbuvir, peginterferon and weight-based ribavirin for 12 weeks. (Level: C1) **Genotype 4 treatment-experienced patients** Recommendation: No recommendation based on data **Genotype 4 cirrhotic patients** Recommendation: No recommendation based on data **Genotype 5, 6 treatment-naive patients** Recommendation: o Genotype 5: No recommendation based on data, consider genotype 1 treatment regimen as template (Level: C2) o Genotype 6: sofosbuvir, peginterferon and weight-based ribavirin for 12 weeks (Level: C2) **Genotype 5,6 treatment-experienced patients** Recommendation: No recommendation based on data, consider genotype 1 treatment regimen as template (Level: C2) **Genotype 5, 6 cirrhotic patients** Recommendation: No recommendation based on data, consider genotype 1 treatment regimen as template (Level: C2)
Kohli A et al., 2014 [51]. Treatment of Hepatitis C	This review summarizes published data on interferon-based and oral interferon-free treatment regimens for patients infected with HCV genotypes 1, 2, or 3 from published phase 2, 3, and 4 randomized clinical trials (RCTs) and cohort studies of US Food and Drug Administration (FDA)–approved medications. We provide treatment recommendations for management of patients infected with HCV genotypes 1, 2, or 3.
	Methodik Grundlage der Leitlinie – Keine Angabe zum Konsensusprozess

	– Suchzeitraum: PubMed, Web of Science, Scopus, Embase, Agricola, Cochrane Library, Cinahl Plus, ClinicalTrials.gov, Conference Papers Index, Gideon, PsycINFO, Google Scholar, and Oaister (between January 1, 2009 and May 30, 2014) – Weitere Kriterien für die Qualität einer LL: • Empfehlungen sind mit Literaturstellen verknüpft LoE Level 1A, systematic reviews (with homogeneity of randomized clinical trials); level 1B, individual randomized clinical trials (with narrow confidence intervals); level 2A, systematic reviews (with homogeneity of cohort studies); level 2B, individual cohort studies (including low-quality randomized clinical trials) GoR A, consistent level 1 studies; B, consistent level 2 or 3 studies or extrapolations from level 1 studies; C, level 4 studies or extrapolations from level 2 or 3 studies; D, level 5 evidence or troublingly inconsistent or inconclusive studies of any level
	Freitext/Empfehlungen/Hinweise

Recommendation Based on This Review	Grade of This Review's Recommendation[a]
Genotype 1	
Therapy for treatment-naive patients with HCV genotype 1 should include sofosbuvir (400 mg/d) in combination with pegylated interferon + weight-based ribavirin	A
An alternative for treatment-naive patients with HCV genotype 1b or 1a without a baseline Q80K mutation is simeprevir (150 mg/d) for 12 weeks in combination with pegylated interferon + weight-based ribavirin for 24 weeks	A
All therapy for patients who receive simeprevir-containing regimens should be stopped for patients with an inadequate on-treatment virologic response (ie, quantifiable HCV viral load at week 4, 12, and/or 24)	B
For interferon-intolerant or -ineligible patients, therapy with sofosbuvir + ribavirin for 24 weeks can be considered	B
This combination may not be as effective in patients with advanced liver disease (metavir fibrosis stage 3-4)	C
Therapy for treatment-experienced patients with HCV genotype 1 should include sofosbuvir (400 mg/d) in combination with pegylated interferon + weight-based ribavirin	B
An alternative for treatment-experienced patients with HCV genotype 1b or 1a without a baseline Q80K mutation is simeprevir (150 mg/d) in combination with pegylated interferon + weight-based ribavirin for 48 weeks	A
Previous relapsers with HCV genotype 1b or 1a without a baseline Q80K mutation should be treated with a shorter duration of simeprevir (150 mg/d) for 12 weeks in combination with pegylated interferon + weight-based ribavirin for 24 weeks	A
All therapy should be stopped for patients with an inadequate on-treatment virologic response (ie, quantifiable HCV viral load at week 4, 12, and/or 24)	B
For interferon-intolerant or -ineligible patients, therapy with sofosbuvir + ribavirin for 24 weeks can be considered	B
This combination may not be as effective in patients with advanced liver disease (metavir fibrosis stage 3-4)	C
Therapy for treatment-experienced patients with HCV genotype 1 should include sofosbuvir (400 mg/d) in combination with pegylated interferon + weight-based ribavirin	B
An alternative for treatment-experienced patients with HCV genotype 1b or 1a without a baseline Q80K mutation is simeprevir (150 mg/d) in combination with pegylated interferon + weight-based ribavirin for 48 weeks	A
Previous relapsers with HCV genotype 1b or 1a without a baseline Q80K mutation should be treated with a shorter duration of simeprevir (150 mg/d) for 12 weeks in combination with pegylated interferon + weight-based ribavirin for 24 weeks	A
All therapy should be stopped for patients with an inadequate on-treatment virologic response (ie, quantifiable HCV viral load at week 4, 12, and/or 24)	B
In treatment-experienced patients, therapy with sofosbuvir + ribavirin alone should not be used	B
Genotypes 2 and 3	
Therapy for treatment-naive or treatment-experienced patients with HCV genotype 2 should consist of sofosbuvir + weight-based ribavirin for 12 weeks	A
Therapy for treatment-naive or treatment experienced patients with HCV genotype 3 should consist of sofosbuvir + weight-based ribavirin for 24 weeks	B
HIV-HCV Coinfection	
Therapy for HCV in patients coinfected with HIV and HCV genotypes 1, 2, or 3 should be with the same regimens recommended for patients without HIV after careful evaluation of drug-drug interactions by a specialist in this field	B
Cirrhosis[b]	
Patients with cirrhosis should be treated with the same regimen and duration as patients without cirrhosis	B

The guideline provides evidence based recommendations covering all stages of the patient care pathway; screening, testing, diagnosis,

<table>
<tr><td>SIGN, 2013 [64].
Management of hepatitis C</td><td>referral, treatment, care and follow up of infants, children and adults with, or exposed to, HCV infection.</td></tr>
<tr><td></td><td>Methodik
Grundlage der Leitlinie
– repräsentative Gremien - CoI-Erklärungen auf Anfrage einsehbar - öffentliche Konsultation und Expertenreview
– Update:
This guideline was issued in 2013 and will be considered for review in three years.
– Suchzeitraum:
Databases searched include Medline, Embase, Cinahl, PsycINFO and the Cochrane Library. The year range covered was 2006-2012.
– Weitere Kriterien für die Qualität einer LL:
• Empfehlungen sind mit Literaturstellen verknüpft
LoE
<table><tr><td colspan="2">LoE</td></tr><tr><td>1++</td><td>High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias</td></tr><tr><td>1+</td><td>well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias</td></tr><tr><td>1 -</td><td>Meta-analyses, systematic reviews, or RCTs with a high risk of bias</td></tr><tr><td>2++</td><td>High quality systematic reviews of case control or cohort studies, high quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal</td></tr><tr><td>2+</td><td>Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal</td></tr><tr><td>2 -</td><td>Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal</td></tr><tr><td>3</td><td>Non-analytic studies, eg case reports, case series</td></tr><tr><td>4</td><td>Expert opinion</td></tr></table>GoR
<table><tr><td>A</td><td>At least one meta-analysis, systematic review, or RCT rated as 1++,and directly applicable to the target population; or
A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results</td></tr><tr><td>B</td><td>A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or
Extrapolated evidence from studies rated as 1++ or 1+</td></tr><tr><td>C</td><td>A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or
Extrapolated evidence from studies rated as 2++</td></tr><tr><td>D</td><td>Evidence level 3 or 4; or
Extrapolated evidence from studies rated as 2+</td></tr></table></td></tr>
</table>

	GOOD PRACTICE POINTS — Recommended best practice based on the clinical experience of the guideline development group
	Freitext/Empfehlungen/Hinweise

Genotype 1

All treatment-naive patients infected with HCV genotype 1 should be considered for treatment with pegylated IFN and weight-based ribavirin with the addition of a protease inhibitor as triple therapy. (GoR: A)

All treatment-experienced patients infected with HCV genotype 1 should be considered for treatment with pegylated IFN and weight-based ribavirin with the addition of a protease inhibitor as triple therapy. (GoR: A)

Response-guided therapy can only be used in treatment-naive patients and previous treatment relapsers who are not cirrhotic. (GoR: A)

Genotype 2 and 3

For patients with HCV genotype 2 or 3 standard treatment should be pegylated IFN and weightbased ribavirin for 24 weeks. (GoR: A)

Non-cirrhotic patients, with genotype 2 or 3, who achieve an RVR at week 4 of therapy, could be considered for shortened duration of therapy of 12 to 16 weeks. (GoR: B)

Genotype 4, 5 and 6

For patients with HCV genotype 4, 5 or 6 infection, standard treatment should be 48 weeks of pegylated IFN and weight-based ribavirin. (GoR: A)

Patients with HIV co-infection

All patients co-infected with HCV and HIV should be considered for HCV treatment. (GoR: A)

For patients with HCV genotype 1 infection and HIV, who do not achieve an EVR, treatment should be stopped. (GoR: A)

Co-infected non-genotype 1 patients who are considered suitable for treatment should be offered treatment with pegylated IFN and weight-based ribavirin for 48 weeks. (GoR: A)

Co-infected genotype 2 or 3 patients who achieve an RVR may be considered for 24 weeks of treatment. (GoR: A)

All patients co-infected with HIV and HCV genotype 1 should be considered for treatment with a regimen which includes an HCV protease inhibitor. (GoR: C)

Treatment-naive patients co-infected with HIV and HCV genotype 1 who are unsuitable for treatment with a regimen which includes HCV protease inhibitors should be considered for treatment with pegylated IFN and weight-based ribavirin for 48-72 weeks depending on viral response. (GoR: B)

	Patients with cirrhosis Low-dose pegylated IFN maintenance monotherapy should not be used in patients with compensated cirrhosis. (GoR: A)
Wilkins E et al., 2013 [69]. British HIV Association guidelines for the management of hepatitis viruses in adults infected with HIV 2013	Leitlinie der British HIV Association (BHIVA)
	Methodik Grundlage der Leitlinie: BHIVA revised and updated the Association's guideline development manual in 2011. BHIVA has adopted the modified Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for the assessment, evaluation and grading of evidence and the development of recommendations. The scope, purpose and guideline topics were agreed by the Committee and key questions concerning each guideline topic were drafted and a systematic literature review undertaken by an information scientist. *Two-level grading system of recommendations:* **A Grade 1** recommendation is a strong recommendation to do (or not do) something, where benefits clearly outweigh risks (or vice versa) for most, if not all, patients. Most clinicians and patients would want to follow a strong recommendation unless there is a clear rationale for an alternative approach. A strong recommendation usually starts with the standard wording 'We recommend'. **A Grade 2** recommendation is a weaker or conditional recommendation, where the risks and benefits are more closely balanced or are more uncertain. Alternative approaches or strategies may be reasonable depending on the individual patient's circumstances, preferences and values. A weak or conditional recommendation usually starts with the standard wording 'We suggest'. *The quality of evidence is graded from A to D and for the purpose of these guidelines is defined as follows:* **Grade A** evidence means high-quality evidence that comes from consistent results from well- performed randomized controlled trials (RCTs), or overwhelming evidence from another source (such as well-executed observational studies with consistent strong effects and exclusion of all potential sources of bias). Grade A implies confidence that the true effect lies close to the estimate of the effect. **Grade B** evidence means moderate-quality evidence from randomised trials that suffers from serious flaws in conduct, inconsistency, indirectness, imprecise estimates, reporting bias, or some combination of these limitations, or from other study designs with specific strengths such as observational studies with consistent effects and exclusion of the majority of the potential sources of bias. **Grade C** evidence is low-quality evidence from controlled trials with several serious limitations, or observational studies with limited evidence on effects and exclusion ofmost potential sources of bias. **Grade D** evidence is based only on case studies, expert judgement or observational studies with inconsistent effects and a potential for substantial bias, such that there can be little confidence in the effect estimate

	Empfehlungen **Genotype 1** Recommendations • We recommend where there is a current clinical need for treatment (i.e., Metavir F4/cirrhosis), or if the patient wishes to be treated, the standard of care should be with triple therapy consisting of pegylated interferon, ribavirin, and either telaprevir or boceprevir (1C). • We recommend 48 weeks of total treatment with a telaprevir- or boceprevir-based regimen for patients who do not have cirrhosis (1C). Good practice points: • We recommend all patients should have the option of treatment, and have the pros and cons of opting for initiation of treatment and of deferring treatment discussed with them. • We recommend a total of 48 weeks of treatment in patients with cirrhosis and for those who do not achieve an RVR. • We suggest non-cirrhotic patients who were previously null responders, partial responders or who experienced breakthrough should, wherever possible, wait for the availability of interferon-sparing regimens or interferon-based regimens including at least two new agents. • We recommend that all patients with advanced or decompensated cirrhosis being treated with triple therapy are managed in a tertiary centre. • We suggest for patients with genotype 1 infection and non-cirrhotic disease, there is the option to defer treatment until newer funded therapies or a suitable clinical trial become available. Where deferred, close monitoring should take place with hepatic elastography or alternative non-invasive testing at least annually. Where there is confirmed progression of fibrosis, treatment initiation should be reconsidered **Genotype 2 and 3** Recommendations • We recommend where there is a current clinical need for treatment (i.e., Metavir F4/cirrhosis), or if the patient wishes to be treated, the standard of care should be with pegylated interferon and ribavirin (1C). • We recommend where patients receive pegylated interferon and ribavirin, the duration of treatment should be 48 weeks unless RVR is achieved, when treatment should be shortened to 24 weeks if the individual is non-cirrhotic (1C). Good practice points • We recommend all patients should have the option of treatment, and have the pros and cons of opting for initiation of treatment and of deferring treatment discussed with them. • We suggest for patients with non-cirrhotic disease there is the option to defer treatment until newer therapies or a suitable trial become available.

	• We recommend those deferring treatment are monitored by non-invasive tests at least annually and if they have confirmed progression of fibrosis are reconsidered for initiation of therapy. **Other genotypes** Good practice points • We suggest for patients with genotype 4 infection without cirrhosis, there is the option to defer treatment until newer therapies or a suitable clinical trial become available. • We recommend if treatment is given now, this should be with pegylated interferon and ribavirin. The duration of therapy should be 48 weeks if RVR is achieved. If the RNA is still detectable at 12 weeks, consideration should be given to discontinuing treatment. • For those with previous treatment failure, we recommend waiting for the availability of interferon-sparing regimens with active DAAs. • We recommend individuals coinfected with nongenotype 1–4 should be seen at a tertiary referral centre to determine treatment suitability, nature and duration and a treatment plan made in consultation with the referring hospital.

Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren

Canadian Agency for Drugs and Technologies in Health (CADTH), 2015 [6]. Drugs for ChronicHepatitis C Infection: Recommendations Report. Therapeutic Review Recommendations	The Therapeutic Review Recommendations or Advice are formulated following a comprehensive evidence-based review of the medication's efficacy or effectiveness and safety and an assessment of its cost-effectiveness. Therapeutic Review clinical and economic reports are based on published information available up to the time that CDEC made its recommendation. Input from stakeholders, such as drug manufacturers, patient groups, and health-related professional associations or organizations, is considered in the preparation of this recommendation document. CDEC is a committee of the Canadian Agency for Drugs and Technologies in Health (CADTH). It makes recommendations and provides advice to Canadian jurisdictions to use in making informed decisions. It is made up of experts in drug evaluation and drug therapy, and public members. **Summary of Recommendations** *Recommendation 1:* CDEC recommends that all patients with CHC infection should be considered for treatment, regardless of fibrosis score. Given the potential impact on health system sustainability of treating all patients with CHC infection on a first-come basis, priority for treatment should be given to patients with more severe disease. *Recommendation 2:* CDEC recommends ledipasvir/sofosbuvir and paritaprevir/ritonavir/ombitasvir + dasabuvir ± ribavirin as preferred regimens for treatment-naive and peginterferon plus ribavirin (PR)-experienced patients with CHC genotype 1 infection, regardless of cirrhosis status. The recommended duration of therapy is as per the Health Canada–approved monograph for each regimen. Conditions:

	Treatment should be initiated by physicians with experience in the management of patients with CHC infection. *Recommendation 3:* CDEC recommends the following as preferred regimens for patients with CHC infection genotypes 2 through 4: □ Genotype 2: sofosbuvir/ribavirin for 12 weeks □ Genotype 3, without cirrhosis: daclatasvir/sofosbuvir for 12 weeks □ Genotype 3, with cirrhosis: sofosbuvir/ribavirin for 24 weeks □ Genotype 4, treatment-naive without cirrhosis: sofosbuvir/pegylated interferon/ribavirin for 12 weeks □ Genotype 4, treatment-experienced or with cirrhosis regardless of treatment experience: insufficient evidence to make a recommendation. *Recommendation 4:* CDEC considered there to be insufficient evidence to make a recommendation for patients with CHC genotype 5 or 6 infection. *Recommendation 5:* CDEC recommends ledipasvir/sofosbuvir as the preferred regimen for patients with genotype 1 infection previously treated with a protease inhibitor-peginterferon/ribavirin regimen, regardless of cirrhosis status. CDEC considered there to be insufficient evidence to make a recommendation for patients previously treated with an all-oral DAA regimen. CDEC considered there to be insufficient evidence to make a recommendation for patients with non-genotype 1 CHC infection previously treated with a DAA-based regimen. Conditions: Treatment should be initiated by physicians with experience in the management of patients with CHC infection.
Canadian Agency for Drugs and Technologies in Health (CADTH), 2015 [7]. Ledipasvir/ Sofosbuvir (Harvoni). For the treatment of chronic infection with genotype 1 hepatitis C virus in adults	The report contains an evidence-based clinical and/or pharmacoeconomic drug review, based on published and unpublished material, including manufacturer submissions; studies identified through independent, systematic literature searches; and patient-group submissions. In accordance with *CDR Update — Issue 87*, manufacturers may request that confidential information be redacted from the CDR Clinical and Pharmacoeconomic Review Reports. The information in this report is intended to help Canadian health care decision-makers, health care professionals, health systems leaders, and policy-makers make well-informed decisions and thereby improve the quality of health care services. The information in this report should not be used as a substitute for the application of clinical judgment with respect to the care of a particular patient or other professional judgment in any decision-making process, nor is it intended to replace professional medical advice. Basierend auf einer systematischen Literaturrecherche bis 10/2014 mit regulären Alarmierungen bis 04/2015 Conclusions LDV/SOF administered for the Health Canada–approved durations was associated with high rates of SVR12 in patients with G1 CHC infection, in both treatment-naive and treatment-experienced patients. These rates were statistically significantly higher than historical

	control rates for DAA-containing regimens. The addition of RBV to LDV/SOF did not appear to improve SVR12 rates. LDV/SOF appeared to be better tolerated in a number of respects compared with RBV-containing regimens in the three pivotal trials. There were no direct comparative trials of LDV/SOF against existing DAA-containing regimens. The manufacturer-submitted NMA showed higher SVR rates with LDV/SOF than with PR-based DAA regimens; however, significant methodological limitations were noted that reduce confidence in the reported effect estimates. This renders it difficult to estimate the incremental benefit on SVR of LDV/SOF compared with other regimens. HRQoL scales demonstrated mixed and marginal changes from baseline to end of therapy. Relapse rates were low throughout all the trials, although the trials have limited long-term follow-up. Although some of the characteristic AEs associated with PR appeared to occur less frequently among patients treated with LDV/SOF, the lack of comparative data against existing regimens for CHC infection makes it difficult to judge the relative safety profile of LDV/SOF. **Standards of Therapy** The treatment paradigm for CHC infection continues to evolve rapidly. Prior to 2011, pegylated interferon plus ribavirin (PR) was the gold standard therapy for patients with CHC infection. Approximately half of patients infected with G1 HCV, the most prevalent type of CHC infection in Canada, could expect to achieve sustained virologic response (SVR) with a 48-week course PR therapy. However, a major limitation of existing treatment regimens has been the tolerability of those that include PR. In recent years, greater understanding of the hepatitis C viral replication cycle has resulted in the development of direct-acting antiviral (DAA) drugs that target several types of non-structural proteins used to support viral replication. These regimens resulted in a further advance in SVR rates as compared with PR regimens that did not include a DAA.9 Currently, there are four DAAs available in Canada for use in conjunction with PR for the treatment of G1 CHC infection. These include the protease inhibitors (PIs) telaprevir (TEL), boceprevir (BOC), and simeprevir (SIM), as well as sofosbuvir (SOF), which targets HCV polymerase.

Gemeinsamer Bundesausschuss

Detaillierte Darstellung der Recherchestrategie:

Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database) am 28.11.2016

#	Suchfrage
1	MeSH descriptor: [Hepatitis C, Chronic] explode all trees
2	(HCV):ti,ab,kw
3	chronic:ti,ab,kw and (hepatitis:ti,ab,kw next c:ti,ab,kw)
4	#1 or #2 or #3
5	#4 from 2011 to 2016

SR, HTAs in Medline (PubMed) am 29.11.2016

#	Suchfrage
1	hepatitis C, chronic/drug therapy[Mesh] OR hepatitis C, chronic/therapy[Mesh]
2	((chronic[Title/Abstract]) AND hepatitis[Title/Abstract]) AND c[Title/Abstract]
3	„HCV“[Title/Abstract]
4	(#2) OR #3
5	(#4) AND ((((((drug[Title/Abstract]) OR (drug therap*)[Title/Abstract]) OR therapy[Title/Abstract]) OR therapies[Title/Abstract]) OR treat[Title/Abstract]) OR treatment*[Title/Abstract])
6	(#1) OR #5
7	"hepatitis C, chronic"[Mesh] AND "drug therapy"[MeSH]
8	(#6) OR #7
9	(#8) AND ((Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp]) OR (((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR ((((((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR (systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-analy*[Title/Abstract]) OR (meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))) OR (((review*[Title/Abstract]) OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract]) AND based[Title/Abstract]))))))
10	(((#9) AND ("2011/11/01"[PDAT] : "2016/11/29"[PDAT])) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp]))

Leitlinien in Medline (PubMed) am 29.11.2016

#	Suchfrage
1	"hepatitis C, chronic"[Mesh] OR (((chronic[Title/Abstract]) AND hepatitis[Title/Abstract]) AND c[Title/Abstract])
2	(#1) AND (Guideline[ptyp] OR Practice Guideline[ptyp] or guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[Title/Abstract])
3	(((#2) AND ("2011/11/01"[PDAT] : "2016/11/29"[PDAT])) NOT ((comment[Publication Type]) OR letter[Publication Type])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp]))

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TABLE 1. Characteristics of Included Studies

Author (Year)	Region	Mean Age (Range)	Body Mass Index (Range)	Treatments	Treatment Duration		Study Size	SVR12	SVR24	Adverse Events			
					Treatment	Control		Treatment/ Control	Treatment/ Control	Insomnia Treatment/ Control	Headache Treatment/ Control	Nausea Treatment/ Control	Fatigue Treatment/ Control
Afdhal et al[11] (2014)	United States and Europe	52.5 (18–80)	26.75 (18–48)	LDV plus SOF plus PR vs LDV plus SOF	12–24 wk	12–24 wk	865	98/98	NR/NR	NR/NR	NR/NR	16/12	37/23
Fried et al[13] (2013)	North America, Europe, and Asia-Pacific regions	46.4 (18–69)	25.06 (16.8–42.2)	SMV plus PR vs PR	12–24 wk/24–48 wk	48 wk	386	82/66	81/65	NR/NR	46/52	28/27	42/48
Hayashi et al[14] (2014)	Japan	55.5 (23–69)	22.16 (16.9–33.2)	SMV plus PR vs PR	12/24–48 wk	48 wk	183	89/62	89/57	NR/NR	NR/NR	NR/NR	NR/NR
Hezode et al[15] (2009)	France, Germany, the United Kingdom, and Austria	45 (18–65)	23.75 (17–41)	TLV plus PR02 vs PR	12 wk/12–24 wk	48 wk	323	72/43	55/46	NR/NR	NR/NR	42/40	29/37
Jacobson et al[17] (2011)	international sites	49 (19–69)	26.1 (17–48)	TLV plus PR vs PR	8–12 wk/24–48 wk	48 wk	1088	NR/NR	72/44	NR/NR	NR/NR	28/31	57/57
Kowdley et al[18] (2014)	United States	52.3 (20–75)	28 (18–56)	LDV plus SOF plus PR vs PR	8 wk	8–12 wk	647	93/95	NR/NR	NR/NR	25/15	18/9	35/22
Kwo et al[47] (2010)	USA, Canada, and Europe	47.3 (18–60)	NR	BCV plus PR vs PR	24–48 wk/28–48 wk	48 wk	520	NR/NR	63/38	NR/NR	46/43	45/43	62/55
Lawitz et al[39] (2013)	USA	49.6 (18–70)	27.1 (NR)	SOF plus PR vs PR	12 wk/24–48 wk	24–48 wk	121	91/58	87/58	35/38	37/58	38/35	67/54
Manns et al[40] (2014)	Europe, North America, and South America	46.3 (18–73)	26 (18.1–53.5)	SMV plus PR vs PR	12 wk/24–48 wk	24–48 wk	391	81/50	NR/NR	24/31	39/37	NR/NR	37/42
Pol et al[41] (2012)	USA and France	51 (28–68)	NR	DCV plus PR vs PR	48 wk	48 wk	48	72/25	69/25	NR/NR	53/25	36/50	53/75
Poordad et al[10] (2011)	N	49.3 (NR)	NR	BCV plus PR vs PR	24–44 wk	48 wk	1097	NR/NR	65/38	36/50	46/42	46/42	55/60
Rodriguez-Torres et al[22] (2013)	United States (and Puerto Rico)	45 (18–65)	28.2 (19.3–35.6)	SOF plus PR vs PR	28 days/48 wk	48 wk	63	71/50	73/43	33/33	31/14	35/36	45/43
Sulkowski et al[43] (2014)	United States	54.9 (18–70)	NR	DCV plus SOF plus PR vs DCV plus SOF	12–24 wk	12–24 wk	126	96/100	95/96	14/14	NR/NR	NR/NR	NR/NR
Tatum et al[44] (2015)	N	48 (22–63)	28 (21–35)	BEC plus PR vs PR	48 wk	48 wk	39	58/38	54/NR	NR/NR	46/23	35/15	46/38
Zeuzem et al[45] (2013)	Europe, Australia, and New Zealand.	47.8 (18–75)	25.2 (20–30)	FDV plus DLV plus PR vs DCV plus DLV	16–40 wk	28 wk	362	60/39	NR/NR	35/23	NR/NR	NR/NR	23/26
Sulkowski et al[42] (2013)	Argentina, Australia, Austria, Canada, Czech Republic, and United States	46 (18–65)	26 (22–32)	FDV plus PR vs PR	24 wk/48 wk	48 wk	429	76/56	NR/NR	NR/NR	35/38	42/20	25/34
Ferenci et al[12] (2015)	European countries and Japan	47.8 (18–70)	25 (NR)	FDV plus PR vs PR	12–24 wk	24 wk	781	60/23	NR/NR	18/24	NR/NR	NR/NR	NR/NR
Nishiguchi et al[21] (2014)	N	52.3 (NR)	23 (NR)	FDV plus PR vs PR	4 wk/48 wk	48 wk	16	NR/NR	58/50	NR/NR	25/25	25/25	NR/NR
Izumi et al[16] (2014)	Antivir Ther	55.7 (28–67)	NR	DCV plus PR vs PR	24–48 wk	48 wk	25	NR/NR	94/75	17/25	18/50	NR/NR	35/50
Lawitz et al[19] (2014)	USA	48.1 (NR)	28.9 (NR)	LDV plus SOF plus PR vs LDV plus SOF	8 wk	8–12 wk	60	100/95	NR/NR	41/25	14/5	10/8	NR/NR
Muir et al[20] (2015)	United States, Canada, France, and Australia.	58.5 (19–76)	NR	DCV plus ASV plus BEC plus PR vs DCV plus ASV plus BEC	12 wk	12 wk	112	98/93	NR/NR	NR/NR	NR/NR	NR/NR	NR/NR
Suzuki et al[46] (2014)	Japan	52.2 (21–66)	NR	DCV plus PR vs PR	24–48 wk	48 wk	27	NR/NR	79/63	26/13	53/63	11/38	16/38

BCV = boceprevir, BEC = beclabuvir, DCV = daclatasvir, FDV = faldaprevir, LDV = ledipasvir, NR = not reported, PR = peginterferon and ribavirin, SMV = simeprevir, SOF = sofosbuvir, SVR = sustained virological response, TLV = telaprevir.

TABLE 2. Quality Assessment of Included Studies

	Random Sequence Generation (Selection Bias)	Allocation Concealment (Selection Bias)	Blinding of Participants and Personnel (Performance bias)	Blinding of Outcome Assessment (Detection Bias)	Incomplete Outcome data (Attrition Bias)	Selective Reporting (Reporting Bias)	Other Bias
Afdhal et al[11] 2014	0	0	2	2	0	0	0
Fried et al[13] (2013)	0	1	0	0	1	0	1
Hayashi et al[14] (2014)	0	1	0	0	0	0	0
Hézode et al[15] (2009)	0	1	2	2	0	0	0
Jacobson et al[17] (2011)	0	1	0	0	0	0	1
Kowdley et al[18] (2014)	0	0	2	2	0	0	1
Kwo et al[47] (2010)	0	0	2	2	0	0	0
Lawitz et al[39] (2013)	0	0	2	2	0	0	0
Manns et al[40] (2014)	0	0	0	0	0	0	0
Pol (2012)	0	0	0	0	0	0	0
Poordad et al[10] (2011)	0	0	2	0	0	0	0
Rodriguez-Torres (2013)	0	1	0	0	0	2	1
Sulkowski et al[43] (2014)	0	1	2	2	0	0	1
Tatum et al[44] (2015)	0	1	0	2	0	0	1
Zeuzem et al[45] (2013)	0	1	2	2	0	0	0
Sulkowski et al[42] (2013)	0	1	0	0	0	0	1
Ferenci et al[12] (2015)	0	0	0	2	0	0	1
Nishiguchi et al[21] (2014)	0	1	0	1	0	0	1
Izumi et al[16] (2014)	0	0	0	0	0	0	1
Lawitz et al[19] (2014)	0	0	2	2	0	0	0
Muir et al[20] (2015)	0	0	2	2	0	0	1
Suzuki et al[46] (2014)	0	1	0	1	0	0	1

0 = low risk of selection bias, 1 = moderate risk of selection bias, 2 = high risk of selection bias.

Table 1. Characteristics of included studies.

Author	Year	Setting	Intervention	Dose (mg/day)	Duration (week)	Comparator	Dose (mg/day)	Duration (week)	Mean Age (year)	Mean BMI, (kg/m^2)	Mean HCV RNA (log_{10} IU/mL)	Male (%)	HCV1 (%)	Cirrhosis (%)	CC/CT/TT (%)
Hayashi [10]	2013	Japan	SMV+PR[b]	50–100	12-24/24–48	PR[b]	-	48	50.33	-	6.17	46.8	0	0	
Fried [11]	2013	North America, Europe, Asia-Pacific	SMV+PR[b]	75–150	12-24/48	PR[b]	-	48	44.86	26.62	6.50	55.2	45.2	0	30/58/12
Hayashi [12]	2014	Japan	SMV+PR[b]	100	12/24-48	PR[b]	-	48	51.33	23.59	6.01	34.3	1.6	0	66/34[c]
Jacobso [13]	2014	Australia, North America Europe, Mexico, New Zealand	SMV+PR[b]	150	12/24-48	PR[b]	-	48	47	29.47		56.3	56.3	0	29/57/14
Manns [14]	2014	North & South America, Europe	SMV+PR[b]	150	12/24-48	PR[b]	-	48	47.35	30.59		55	41	8.4	30/54/16
Pol [15]	2012	U.S., France	DCV+PR[b]	30–60	48/48	PR[b]	-	48	51.25	-	6.50	66.8	66.8	0	35/51/14
Hézode [16]	2014	U.S., Australia, North America, Europe	DCV+PR[b]	20–60	12-24/24–48	PR[b]	-	48	47.55	-	6.48	67.1	75.5	7.4	30/52/12
Rodriguez-Torres [22]	2013	U.S., Puerto Rico	SOF+PR[b]	100–400	4/48	PR[b]	-	48	45	28.17	6.47	68.5	80.9	0	27/63[c]
Lawitz [4]	2013	U.S.	SOF+PR[b]	200–400	12-24/24–48	PR[b]	-	48	49.61	27.11	6.46	60.5	75.8	0	41/45/14
Kowdley [17]	2014	U.S.	SOF+LDV + RBV[a]	400/90	8	SOF+LDV	400/90	8–12	52.33	28	6.43	57.7	80	0	27/57/16
Afdhal [18]	2014	U.S., Europe	SOF+LDV + RBV[a]	400/90	12–24	SOF+LDV	400/90	12–24	50.76	29.07	6.35	59.3	67	15.7	30/52/18
Lawitz [19]	2014	U.S.	SOF+LDV + RBV[a]	400/90	8	SOF+LDV	400/90	8–12	48.07	28.9	6.07	61.7	88	0	20/62/18
Mizokami [23]	2015	Japan	SOF+LDV + RBV[a]	400/90	12	SOF+LDV	400/90	12	-	-	-	40.5	-	15	-
Lawitz [20]	2014	U.S.	SOF+SMV + RBV[a]	400/150	12–24	SOF+SMV	400/150	12–24	51.6	28.32	6.46	66.6	78.5	0	79/21[c]
Sulkowski [21]	2014	U.S.	SOF+DCV +RBV[a]	400/60	12–24	SOF+DCV	400/60	12–24	54.56	-	6.40	50.8	78.3	0	32/68[c]
Kowdley [24]	2014	U.S.	PrOD+RBV[a]	150/100/25/400	12	PrOD	150/100/25/500	12	49.21	-	6.45	58	67.3	-	-

DCV, daclatasvir; LDV, ledipasvir; PR, pegylated interferon-ribavirin; SMV, simeprevir; SOF, sofosbuvir; PrOD, paritaprevir/ritonavir/ombitasvir plus dasabuvir

[a]the dose of ribavirin was weight-base (1,000 mg/day in patients with body weight <75 kg and 1,200 mg/day in patients with a body weight ≥75 kg)

[b]the dose of pegylated interferon was 180 g/week and body weight adjusted dose for ribavirin

[c]CC/CT+TT

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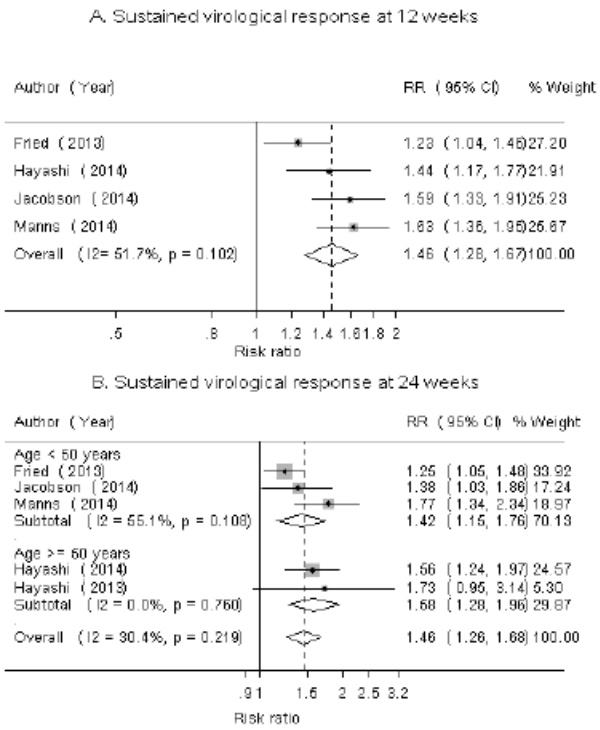
S1 Figure. Forest plot of pooled risk ratio for comparison between simeprevir plus pegylated-interferon with ribavirin and pegylated-interferon with ribavirin alone



S2 Table. Frequencies of patients who have sustained virological response at weeks 12 and 24 after the end of treatment for treatment regimens included in network meta-analysis

Author	Year	Treatment	No. of having SVR12	No. of not having SVR12	No. of having SVR24	No. of not having SVR24
Pol[7]	2012	DCV plus PR	26	10	25	11
		PR	3	9	3	9
Rodriguez-Torres[22]	2013	SOF plus PR	35	14	36	13
		PR	7	7	6	8
Lawitz[4]	2013	SOF plus PR	86	9	83	12
		PR	15	11	15	21
Hayashi[10]	2013	SMV plus PR	-	-	63	16
		PR	-	-	6	7
Fried[11]	2013	SMV plus PR	252	57	250	59
		PR	51	26	50	27
Hayashi[12]	2014	SMV plus PR	109	14	109	14
		PR	37	23	34	26
Jacobson[13]	2014	SMV plus PR	210	54	205	42
		PR	65	65	18	12
Manns[14]	2014	SMV plus PR	209	48	206	47
		PR	67	67	28	33
Hezode[16]	2014	DCV plus PR	183	110	174	119
		PR	26	46	27	45

DCV, daclatasvir; LDV, ledipasvir; PR, pegylated interferon-ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR24, sustained virological response at 24 weeks after the end of treatment

Table 1 Characteristics of the included studies

Study	Median age (range)	Gender (male, %)	HCV-RNA (median $\log_{10}$)	Genotype	Type of treatment and dose	Treatment duration (week)	RVR	SVR_{24}	Relapse	VB	TDAE	SAE
Hézode et al. (2015) (n = 395)	51 (22–70)	67.3	6.5	G1a, 275/395	D (20 mg/day) + P (180 μg/week) + R (1.0–1.2 g/day)	24	91 (57)	95 (60)	24 (15)	14 (9)	7 (4)	12 (8)
	50 (18–67)	65.2	6.5	G1b, 88/395	D (60 mg/day) + P (180 μg/week) + R (1.0–1.2 g/day)	24	87 (55)	99 (63)	22 (14)	15 (9)	7 (4)	13 (8)
	51 (25–66)	70.5	6.4	G4, 32/395	PBO + P (180 μg/week) + R (1.0–1.2 g/day)	24	11 (14)	30 (38)	9 (12)	2 (3)	8 (10)	6 (8)
Dore et al. (2015) (n = 151)	52 (28–64)	54.2	6.4	G2, 71/151	D (60 mg/day) + P (180 μg/week) + R (0.8 g/day)	12	43 (86)	38 (76)	0 (0)	8 (16)	4 (8)	4 (8)
	52 (25–67)	65.2	6.6	G3, 80/151	D (60 mg/day) + P (180 μg/week) + R (0.8 g/day)	16	35 (70)	37 (74)	0 (0)	7 (14)	3 (6)	0 (0)
	55 (20–63)	45.8	6.6		PBO + P (180 μg/week) + R (0.8 g/day)	24	20 (39)	31 (61)	2 (4)	5 (10)	2 (4)	3 (6)
Suzuki et al. (2014) (n = 45)	51 (21–68)	22.0	6.7	G1, 45/45	D (10 mg/day) + P (60–150 μg/week) + R (0.6–1 g/day)	24/48	12 (67)	8 (44)	4 (22)	5 (28)	1 (6)	1 (6)
	55 (36–70)	60.0	6.7		D (60 mg/day) + P (60–150 μg/week) + R (0.6–1 g/day)	24/48	11 (58)	12 (63)	3 (16)	4 (21)	1 (5)	0 (0)
	50 (42–66)	50.0	6.9		PBO + P (60–150 μg/week) + R (0.6–1 g/day)	48	0 (0)	5 (63)	2 (25)	1 (13)	0 (0)	0 (0)
Izumi et al. (2014) (n = 42)	56 (26–68)	44.0	6.8	G1, 42/42	D (10 mg/day) + P (180 μg/week) + R (0.6–1 g/day)	24	12 (71)	12 (71)	3 (18)	2 (12)	1 (6)	2 (12)
	57 (31–67)	25.0	6.6		D (60 mg/day) + P (180 μg/week) + R (0.6–1 g/day)	24	13 (76)	15 (88)	1 (6)	1 (6)	2 (12)	0 (0)
	54 (41–63)	38.0	6.5		PBO + P (180 μg/week) + R (0.6–1 g/day)	24	1 (13)	6 (75)	1 (13)	0 (0)	0 (0)	0 (0)

Table 1 continued

Study	Median age (range)	Gender (male, %)	HCV-RNA (median $\log_{10}$)	Genotype	Type of treatment and dose	Treatment duration (week)	RVR	SVR_{24}	Relapse	VB	TDAE	SAE
Pol et al. (2012) (n = 48)	52 (38–68)	75.0	6.3	G1a, 32/48	D (3 mg/day) + P (180 μg/week) + R (1.0–1.2 g/day)	12	5 (42)	5 (42)	2 (17)	2 (17)	1 (8)	1 (8)
	51 (37–68)	67.0	6.4		D (10 mg/day) + P (180 μg/week) + R (1.0–1.2 g/day)	12	11 (92)	10 (83)	1 (8)	0 (0)	1 (8)	1 (8)
	51 (43–67)	58.0	6.5	G1b, 16/48	D (60 mg/day) + P (180 μg/week) + R (1.0–1.2 g/day)	12	10 (86)	10 (83)	1 (8)	1 (8)	4 (33)	1 (8)
	50 (28–67)	67.0	6.7		PBO + P (180 μg/week) + R (1.0–1.2 g/day)	12	1 (8)	3 (25)	5 (42)	0 (0)	2 (17)	0 (0)
Ratziu et al. (2012) (n = 419)	NR	NR	NR	NR	D (20 mg/day) + P/R	12	47 (23)	NR	NR	NR	NR	12 (6)
					D (60 mg/day) + P/R	12	53 (27)					10 (5)
					PBO + P/R	12	0 (0)					3 (1.6)

The data of RVR, SVR24, relapse, VB, TDAE and SAE are presented as n (%)

Median age, gender, HCV-RNA, treatment duration, RVR, cEVR and SVR24 is respectively divided into different groups according to the type of treatment and dose; Genotype is divided into different groups according to G1a, G1b, G2, G3 and G4

D daclatasvir, *P* pegylated interferon-α, *R* ribavirin, *PBO* placebo, *RVR* rapid virological response, SVR_{24} sustained virological response at post-treatment week 24, *VB* virological breakthrough, *TDAE* treatment discontinuation due to an adverse event, *SAE* serious adverse event, *NR* not reported

Table 1 Characteristics of the studies included in the meta-analysis

DAAs	Author	Year	Study name	IFN	Previous treatments	Study phase	*n* pts TT	*n* pts DT	Mean FU (wks)	HCV subtype *n* 1a TT	1a DT	1b TT	1b DT	Fibrosis *n* None or minimal	Portal	Bridging	Cirrhosis *n* TT	Cirrhosis *n* DT	Viral load *n* TT	Viral load *n* DT
Tel	Forastier	2007		α 2a.	Naive	1	16	4	12	5	1	11	3	NR	NR	NR	NR	NR	NR	NR
Tel	McHutchinson	2009	PROVE1	α 2a	Naive	2	175	75	48	110	50	27	20	81	118	51	NR	NR	149	69
Tel	Hézode	2009	PROVE2	α 2a	Naive	2	241	82	36	108	35	133	45	123	172	26	1	0	203	68
Tel	McHutchinson	2010	PROVE3	α 2a	Experienced	2	339	114	48	194	71	11	34	96	161	1221	61	13	314	104
Tel	Jacobson	2011	ADVANCE	α 2a	Naive	3	727	361	36	423	208	300	151	409	448	163	47	21	560	279
Tel	Kumada	2012		α 2b	Naive	NR	126	63	48	2	124	0	63	NR	NR	NR	NR	NR	NR	NR
Tel	Zeuzem	2011	REALISE	α 2a	Experienced	3	530	133	48	239	59	236	59	154	192	147	139	30	472	114
Tel	Sulkowski*	2013		α 2a	NR	2	7	6	48	3	3	4	2	4	8	1	0	0	7	5
Boc	Bacon	2011	RESPOND 2	α 2b	Experienced	3	323	80	44	190	46	127	34	253	78	NR	39	10	288	65
Boc	Kwo	2010	SPRINT 1	α 2b	Naïve	2	416	104	48	235	53	134	42	NR	NR	NR	29	8	NR	NR
Boc	Poordad	2011	SPRINT 2	α 2b	Naïve	3	734	363	48	471	227	241	121	960	100	NR	40	13	627	308
Boc	Pearlman	2014		α 2b	Naïve	NR	49	52	24	19	20	30	32	NR	NR	NR	NR	NR	NR	NR
Boc	Flamm	2013		α 2a	Experienced	NR	134	67	44	75	38	55	27	NR	NR	NR	NR	NR	101	54
Boc	Sulkowski*	2013		α 2b	NR	2	64	34	44	51	25	12	9	NR	NR	NR	1	2	NR	NR

DAAs, direct acting antivirals; Boc, Boceprevir; Tel, Telaprevir; *n*, number; pts, patients; IFN, interferon; TT, triple therapy; DT, dual therapy; FU, follow-up; wks, weeks; NR, not reported.
*Patients coinfected with HIV.

Table 2. Characteristics and results of included studies.

	Basal characteristics		Treatment combination	Group of patients	SVR	Safety outcomes	
Lawitz el. Al (COSMOS) [14]	Male sex	107/167 (64%)	SOF/SIM ± RBV × 12 weeks	Overall	51/54 (64%)	Any AE leading to discontinuation	0/54 (0%)
	White origin	136/167 (81%)		Genotype 1a	40/43 (93%)	Total patients with any AE	46/54 (85%)
	Black and African American origin	31/167 (19%)		GT1a with baseline Q80K	15/17 (88%)	Total patients with any SAE,	0/54 (0%)
	Genotype 1a	130/167 (78%)		Genotype 1b	11/11 (100%)		
	GT1a with baseline Q80K	58/167 (45%)		Cirrhotic	25/27 (93%)		
	Genotype 1b	37/167 (22%)	SOF/SIM × 12 weeks	Overall	26/28 (93%)	Any AE leading to discontinuation	0/28 (0%)
	Treatment-experienced	127/167 (76%)		Genotype 1a	19/21 (91%)	Total patients with any AE	20/28 (71%)
	Cirrhotic	41/167 (25%)		GT1a with baseline Q80K	8/9 (89%)	Total patients with any SAE,	0/28 (0%)
				Genotype 1b	7/7 (100%)		
				Cirrhotic	13/14 (93%)		
			SOF/SIM ± RBV × 24 weeks	Overall	47/54 (87%)	Any AE leading to discontinuation	2/54 (4%)
				Genotype 1a	37/43 (86%)	Total patients with any AE	51/54 (94%)
				GT1a with baseline Q80K	19/23 (83%)	Total patients with any SAE,	3/54 (6%)
				Genotype 1b	10/11 (91%)		
				Cirrhotic	28/30 (93%)		
			SOF/SIM x 24 weeks	Overall	30/31 (97%)	Any AE leading to discontinuation	2/31 (7%)
				Genotype 1a	23/23 (100%)	Total patients with any AE	29/31 (94%)
				GT1a with baseline Q80K	9/9 (100%)	Total patients with any SAE,	1/31 (3%)
				Genotype 1b	7/8 (88%)		
				Cirrhotic	16/16 (100%)		
Kwo et al. (OPTIMIST-I) [33]	Male sex	169/310 (55%)	SOF/SIM x 8 weeks	Overall	128/155(83%)	Any AE leading to discontinuation	0/155 (0%)
	White origin	245/310 (79%)		Genotype 1a	92/116 (79%)	Total patients with any AE	97/155 (63%)
	Black and African American origin	55/310 (18%)		GT1a with baseline Q80K	36/49 (73%)	Total patients with any SAE,	3/155 (2%)
	Genotype 1a	232/310 (75%)		Genotype 1b	36/39 (92%)		
	GT1a with baseline Q80K	95/232 (41%)	SOF/SIM x 12 weeks	Overall	150/155(97%)	Any AE leading to discontinuation	0/155 (0%)
	Genotype 1b	78/310 (25%)		Genotype 1a	112/116 (97%)	Total patients with any AE	103/155 (66%)
	Treatment-experienced	92/310 (30%)		GT1a with baseline Q80K	44/46 (96%)	Total patients with any SAE,	1/155 (1%)
	Cirrhotic	27/310 (9%)		Genotype 1b	38/39 (97%)		
Lawitz et al. (OPTIMIST-II) [31]	Male sex	83/103 (81%)	SOF/SIM x 12 weeks	Overall	86/103 (83%)	Any AE leading to discontinuation	3/103 (3%)
	White origin	82/101 (81%)					
	Black and African American origin	19/101 (19%)					
	GT1a with baseline Q80K	34/72(47%)		Genotype 1a	60/72 (83%)	Total patients with any AE	72/103 (70%)
	Genotype 1b	31/103(30%)		GT1a with baseline Q80K	25/34(74%)		
	Treatment-experienced	53/103(51%)		Genotype 1b	26/31(84%)	Total patients with any SAE	5/103 (5%)
	Cirrhotic	103/103 (100%)					

(*Continued*)

Table 2. (Continued).

	Basal characteristics		Treatment combination	Group of patients	SVR	Safety outcomes	
Peafman et al. [32]	Male sex	53/82 (65%)	SOF/SIM × 12 weeks	Overall	54/58 (93%)	Any AE leading to discontinuation	0/58 (0%)
	White origin	Not reported				Total patients with any AE	46/58 (79%)
	Black and African American origin	39/82 (48%)		Treatment-experienced	33/36 (92%)	Total patients with any SAE	0/58 (0%)
	Genotype 1a	82/82 (100%)		Treatment-naive	21/22 (95%)		
	GT1a with baseline Q80K	23/58 (40%)	pIFN/RBV/SOF	Overall	18/24 (75%)	Any AE leading to discontinuation	3/24 (13%)
	Genotype 1b	0/82 (0%)				Total patients with any AE	22/24 (92%)
	Treatment-experienced	50/82 (61%)		Treatment-experienced	10/14 (64%)	Total patients with any SAE	1/24 (4%)
	Cirrhotic	82/82 (100%)		Treatment-naive	8/10(80%)		
Backus et al. [34]	Male sex	3068/3203 (96%)	SOF/SIM × 12 weeks	Overall	851/1130 (75%)	Any AE leading to discontinuation	Not reported
	White origin	1775/3203 (55%)		Genotype 1a	463/632 (73%)	Total patients with any AE	Not reported
	Black and African American origin	994/3203 (31%)		Genotype 1b	293/366 (80%)	Total patients with any SAE	Not reported
	Genotype 1a	1936/3203 (60%)		Cirrhotic	521/744 (70%)		
	GT1a with baseline Q80K	Not reported	SOF/SIM/RBV × 12 weeks	Overall	192/259 (74%)	Any AE leading to discontinuation	Not reported
	Genotype 1b	907/3203 (28%)		Genotype 1a	143/193 (74%)	Total patients with any AE	Not reported
	Treatment-experienced	1184/3203 (37%)		Genotype 1b	34/45 (76%)	Total patients with any SAE	Not reported
	Cirrhotic	1709/3203 (54%)		Cirrhotic	125/177 (71%)		
			pIFN/RBV/SOF	Overall	687/1028 (67%)	Any AE leading to discontinuation	Not reported
				Genotype 1a	435/623 (70%)	Total patients with any AE	Not reported
				Genotype 1b	159/273 (58%)	Total patients with any SAE	Not reported
				Cirrhotic	220/416 (53%)		
Sulkowski et al. [35]	Male sex	509/836 (61%)	SOF/SIM × 12 weeks	Overall	543/639 (85%)	Any AE leading to discontinuation	13/667 (2%)
	White origin	638/836 (76%)		Genotype 1a	308/371 (83%)	Total patients with any AE	499/667 (75%)
	Black and African American origin	112/836 (13%)		Genotype 1b	185/206 (90%)	Total patients with any SAE,	32/667 (5%)
	Genotype 1a	509/836 (61%)		Cirrhotic	296/367 (81%)		
	GT1a with baseline Q80K	42/90 (47%)	SOF/SIM/RBV × 12 weeks	Overall	132/163 (81%)	Any AE leading to discontinuation	4/169 (2%)
	Genotype 1b	242/836 (29%)		Genotype 1a	102/125 (82%)	Total patients with any AE	150/169 (89%)
	Treatment-experienced	487/836 (61%)		Genotype 1b	16/19 (84%)	Total patients with any SAE,	12/169 (7%)
	Cirrhotic	491/836 (59%)		Cirrhotic	88/110 (80%)		

(*Continued*)

Table 2. (Continued).

	Basal characteristics		Treatment combination	Group of patients	SVR	Safety outcomes	
Saxena et al. [36]	Male sex	95/156 (61%)	SOF/SIM ± RBV × 12 weeks	Overall	132/156 (85%)	Any AE leading to discontinuation	6/156 (4%)
	White origin	99/156 (63%)					
	Black and African American origin	26/156 (17%)					
	Genotype 1a	98/156 (63%)					
	GT1a with baseline Q80K	11/24 (46%)					
	Genotype 1b	58/156 (37%)		Child- Pugh A	92/101 (91%)	Total patients with any AE	Not reported
	Treatment-experienced	86/156 (55%)				Total patients with any SAE,	Not reported
	Cirrhotic	156/156 (100%)		Child- Pugh B-C	40/55 (73%)		
Shiffman et al. [37]	Male sex	76/120 (63%)	SOF/SIM±RBV × 12 weeks	Overall	97/120 (81%)	Any AE leading to discontinuation	4 /120 (3%)
	White origin	58/120 (48%)					
	Black and African American origin	53/120 (44%)					
	Genotype 1a	83/120 (69%)		Genotype 1a	66/82 (81%)	Total patients with any AE	Not reported
	GT1a with baseline Q80K	Not reported		Genotype 1b	28/34 (83%)		
	Genotype 1b	34/120 (28%)					
	Treatment-experienced	61/120 (51%)		Child Class A	70/81 (86%)	Total patients with any SAE	14/120 (12%)
	Cirrhotic	120/120 (100%)		Child Class B-C	28/39 (72%)		
Aqel et al. [38]	Male sex	73/119 (61%)	SOF/SIM ± RBV × 12 weeks	Overall	92/118 (78%)	Any AE leading to discontinuation	3/119 (3%)
	White origin	103/119 (87%)					
	Black and African American origin	Not reported					
	Genotype 1a	82/119 (69%)					
	GT1a with baseline Q80K	Not reported		Genotype 1a	65/82 (79%)		
				Genotype 1b	20/24 (83%)	Total patients with any AE	37/119 (31%)
	Treatment-experienced	80/119 (67%)					
	Cirrhotic	119/119 (71%)		Child- Pugh A	69/84 (82%)	Total patients with any SAE,	1/119 (1%)
				Child- Pugh B	23/34 (68%)		
Deterding et al. [39]	Male sex	47/80 (59%)	SOF/SIM ± RBV × 12 weeks	Overall	14/15 (93%)	Any AE leading to discontinuation	Not reported
	White origin	Not reported					
	Black and African American origin	Not reported				Total patients with any AE	Not reported
	Genotype 1	50/80 (63%)					
	Genotype 1a	Not reported				Total patients with any SAE	Not reported
	GT1a with baseline Q80K	Not reported	SOF/RBV × 12 weeks	Overall	13/28 (46%)	Any AE leading to discontinuation	Not reported
	Genotype 1b	Not reported					
	Treatment-experienced	54/80 (68%)				Total patients with any AE	Not reported
	Cirrhotic	80/80 (100%)				Total patients with any SAE	Not reported
Pungpapong et al. [40]	Male sex	93/123 (76%)	SOF/SIM ± RBV × 12 weeks	Overall	94/105 (90%)	Any AE leading to discontinuation	3/123 (2%)
	White origin	91/123 (74%)					
	Black and African American origin	12/123 (10%)					
	Genotype 1a	74/123 (60%)		Genotype 1a	ND (86%)		
	GT1a with baseline Q80K	ND		Genotype 1b	ND (95%)	Total patients with any AE	59/123 (48%)
	Genotype 1b	43/123 (35%)					
	Treatment-experienced	101/123 (82%)		Non-cirrhotic	ND (93%)	Total patients with any SAE	3/123 (2%)
	Cirrhotic	37/123 (30%)		Cirrhotic	ND (81%)		

(*Continued*)

Table 2. (Continued).

	Basal characteristics		Treatment combination	Group of patients	SVR	Safety outcomes	
Brown et al. [41]	Male sex	112/151 (74%)	SOF/SIM/RBV × 12 weeks	Overall	28/32 (88%)	Any AE leading to discontinuation	1/32 (3%)
	White origin	114/151 (75%)		Genotype 1a	17/20 (85%)	Total patients with any AE	28/32 (88%)
	Black and African American origin	14/151 (9%)		Genotype 1b	9/10 (90%)	Total patients with any SAE	6/32 (19%)
	Genotype 1a	87/151 (58%)		Cirrhotic	20/23 (87%)		
	GT1a with baseline Q80K	Not reported	SOF/SIM × 12 weeks	Overall	105/119 (88%)	Any AE leading to discontinuation	3/119 (3%)
	Genotype 1b	42/151 (28%)		Genotype 1a	57/67 (85%)	Total patients with any AE	86/119 (72%)
	Treatment-experienced	85/151 (56%)		Genotype 1b	30/32 (94%)	Total patients with any SAE	12/119 (10%)
	Cirrhotic	97/151 (64%)		Cirrhotic	63/74 (85%)		
Pillai et al. [42]	Male sex	114/170 (67%)	SOF/SIM ± RBV × 12 weeks (Post-transplant)	Overall	51/57 (89%)	Any AE leading to discontinuation	3/57 (5%)
	White origin	101/170 (59%)		Genotype 1a	36/41 (88%)	Total patients with any AE	86/119 (72%)
	Black and African American origin	60/170 (35%)		Genotype 1b	11/12 (92%)	Total patients with any SAE	12/119 (10%)
	Genotype 1a	105/170 (62%)		Cirrhotic	9/9 (100%)		
	GT1a with baseline Q80K	Not reported	SOF/SIM ± RBV × 12 weeks (Non-transplant)	Overall	95/113 (84%)	Any AE leading to discontinuation	2/113 (2%)
	Genotype 1b	45/170 (26%)		Genotype 1a	53/64 (83%)	Total patients with any AE	Not reported
	Treatment-experienced	80/170 (47%)		Genotype 1b	29/33 (88%)	Total patients with any SAE	Not reported
	Cirrhotic	99/170 (58%)		Cirrhotic	74/90 (82%)		
Gutierrez et al. [43]	Male sex	32/61 (52%)	SOF/SIM ± RBV × 12 weeks	Overall	57/61 (93%)	Any AE leading to discontinuation	0/61 (0%)
	White origin	31/61 (51%)					
	Black and African American origin	7/61 (11%)					
	Genotype 1a	35/61 (57%)		Genotype 1a	31/35 (89%)	Total patients with any AE	34/61 (56%)
	GT1a with baseline Q80K	Not reported		Genotype 1b	26/26 (100%)		
	Genotype 1b	26/61 (43%)					
	Treatment-experienced	42/61 (69%)		Cirrhotic	19/23 (83%)	Total patients with any SAE	6/61 (10%)
	Cirrhotic	23/61 (38%)					
Saab et al. [44]	Male sex	23/30 (77%)	SOF/SIM × 12 weeks	Overall	28/30 (93%)	Any AE leading to discontinuation	0/30 (0%)
	White origin	Not reported					
	Black and African American origin	Not reported					
	Genotype 1	30/30 (100%)					
	Genotype 1a	Not reported				Total patients with any AE	Not reported
	Genotype 1b	Not reported					
	Treatment-experienced	20/30 (67%)				Total patients with any SAE	Not reported
	Cirrhotic	5/30 (17%)					
Punzalan et al. [45]	Male sex	28/42 (67%)	SOF/SIM × 12 weeks	Overall	40/42 (95%)	Any AE leading to discontinuation	0/42 (0%)
	White origin	34/42 (81%)					
	Black and African American origin	1/42 (2%)					
	Genotype 1a	33/42 (79%)					
	GT1a with baseline Q80K	Not reported		Non-cirrhotic	33/34 (97%)	Total patients with any AE	14/42 (33%)
	Genotype 1b	8/42 (19%)					
	Treatment-experienced	20/42 (48%)		Cirrhotic	7/8 (88%)	Total patients with any SAE	Not reported
	Cirrhotic	8/42 (19%)					

(*Continued*)

Table 2. (Continued).

	Basal characteristics		Treatment combination	Group of patients	SVR	Safety outcomes	
Hundemer et al. [46]	Male sex	5/6 (83 %)	SOF/SIM × 12 weeks	Overall	2/3 (67%)	Any AE leading to discontinuation	0/3 (0%)
	White origin	5/6 (83%)					
	Black and African American origin	1/6 (17%)					
	Genotype 1a	3/6 (50%)				Total patients with any AE	Not reported
	GT1a with baseline Q80K	Not reported		Non-cirrhotic	1/1 (100%)		
	Genotype 1b	1/6 (17%)					
	Treatment-experienced	1/3 (33%)		Cirrhotic	1/2 (50%)	Total patients with any SAE	Not reported
	Cirrhotic	2/3 (67%)					
Gilmore et al. [47]	Male sex	Not reported	SOF/SIM ± RBV × 12 weeks Coinfectected patients	Overall	28/37 (76%)	Any AE leading to discontinuation	3/37 (8%)
	White origin	32/81 (40%)					
(HIV-coinfected patients)	Black and African American origin	48/81 (59%)				Total patients with any AE	Not reported
	Genotype 1a	52/81 (64%)				Total patients with any SAE	Not reported
	GT1a with baseline Q80K	Not reported	SOF/SIM±RBV × 12 weeks Monoinfected patients	Overall	34/44 (77%)	Any AE leading to discontinuation	1/44 (2%)
	Genotype 1b	29/81 (36%)				Total patients with any AE	Not reported
	Treatment-experienced	32/81 (40%)				Total patients with any SAE	Not reported
	Cirrhotic	56/81 (69%)					
Hezode et al. [48]	Male sex	13/16 (81%)	SOF/SIM × 12 weeks	Overall	12/14 (86%)	Any AE leading to discontinuation	Not reported
	White origin	Not reported					
	Black and African American origin	Not reported					
	Genotype 1a	11/16 (69%)				Total patients with any AE	Not reported
	Genotype 1b	3/16 (19%)					
	Treatment-experienced	16/16 (100%)				Total patients with any SAE	Not reported
	Cirrhotic	16/16 (100%)					

AE: adverse effect; CPT: Child–Pugh–Turcotte score; DAA: direct acting antivirals; GT1a: genotype 1a; HCV: hepatitis C virus; MELD: model for end-stage liver disease; NR: not reported; pIFN: peginterferon; RBV: ribavirin; SAE: serious adverse effect; SIM: simeprevir; SOF: sofosbuvir.

Table 3. Methodological quality of studies.

Clinical trials: the Cochrane collaboration's tool for assessing risk of bias							
	Random sequence generation	Allocation concealment	Blinding of participants and personnel.	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Lawitz et al. [14]	Low	Low	High	High	Low	Unclear	Unclear
Pearlman et al.[32]	Unclear	High	High	High	Low	Unclear	Unclear
Lawitz et al. [31]	High	High	High	High	Low	Unclear	Unclear
Kwo et al. [33]	High	High	High	High	Low	Unclear	Unclear

Observational studies: chambers tool								
	Were selection/ eligibility criteria adequately reported?	Was the selected population representative of that seen in normal practice?	Was an appropriate measure of variability reported?	Was loss to follow-up reported or explained?	Were at least 90% of those included at baseline followed up?	Were patients recruited prospectively?	Were patients recruited consecutively?	Did the study report relevant prognostic factors?
Backus et al. [34]	Yes	Yes	Yes	Yes	Yes	Yes	ND	Yes
Sulkowski et al. [35]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Saxena et al. [36]	Yes	Yes	Yes	No	NS	No	ND	Yes
Shiffman et al. [37]	Yes	Yes	Yes	No	NS	No	Yes	Yes
Aqel et al. [38]	No	Yes	Yes	Yes	Yes	No	ND	Yes
Deterding et al. [39]	No	Yes	Yes	No	NS	Yes	Yes	Yes
Pungpapong, et al. [40]	No	Yes	Yes	Yes	Yes	No	ND	Yes
Brown et al. [41]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Pillai et al. [42]	No	Yes	Yes	Yes	No	No	ND	Yes
Gutierrez et al. [43]	Yes	Yes	Yes	No	NS	No	ND	Yes
Saab et al. [44]	Yes	Yes	Yes	No	NS	No	Yes	Yes
Punzalan et al. [45]	Yes	Yes	Yes	Yes	Yes	No	Yes	No
Hundemer et al. [46]	No	Yes	No	No	NS	No	ND	No
Gilmore et al. [47]	Yes	Yes	Yes	No	NS	ND	ND	Yes
Hezode et al. [48]	No	Yes	Yes	Yes	Yes	ND	ND	Yes

ND: cannot determine; NS: no statement.

Study/Treatment	Study Design	Srudy Sites	Financial Support	Conflict of Interest	Jadad	HCV genotype (%)			Age (years)	Cirrhosis (%)	IL28B genotype (%)			Race (%)				Baseline viral load (log_{10} IU/mL)
						1a	1b	1			CC	CT	TT	Caucasian	Black	Asian	Other	
Bacon, 2011 (RESPOND-2)																		
• lead-in x4w / BOC + Peg-IFN+RBV x 32w / Peg-IFN+RBV x12w	RCT, multicentre, double-blind, placebo-controlled, phase III	80 sites in North America and Europe	Yes	Yes	4	58	41	0	52.9	10				88	11	0	1	
• lead-in x4w / BOC + Peg-IFN+RBV x44w						60	38	1	52.3	14		NR		84	12	0	4	NR
• lead-in x4w / Placebo + Peg-IFN+RBV x44w						58	42	2	52.9	12				84	15	0	1	
Flamm, 2013																		
• lead-in x4w / BOC + Peg-IFN+RBV x44w	RCT, multicentre, double-blind, placebo-controlled, phase III	53 sites in North America and Europe	Yes	Yes	4	56	41	3	52.0	NR	20	62	18	89	9	0	2	NR
• lead-in x4w / Placebo + Peg-IFN+RBV x44w						57	40	2	53.5	NR	20	67	14	87	12	0	1	
Forns, 2014 (PROMISE)																		
• SMV 150 mg + Peg-IFN+RBV x12w / Peg-IFN+RBV x36w	RCT, multicentre, double-blind, parallel group, placebo-controlled, phase III	14 countries in North America, Europe, and the Asia–Pacific regions	Yes	Yes	3	42.3	57.3	0.4	52.0	15.6	23.8	64.2	11.9	93.5	2.7	3.1	0.7	6.42
• Placebo + Peg-IFN+RBV x12w / Peg-IFN+RBV x36w						40.6	59.4	0	52.0	14.4	25.6	62.4	12.0	96.2	3.0	0.8	0	6.54
Hayashi, 2014b (CONCERTO-1)																		
• SMV 100 mg + Peg-IFN+RBV x12w / Peg-IFN+RBV x36w	RCT, multicentre, double-blind, placebo-controlled, phase III	37 sites in Japan	Yes	Yes	4	1.6	98.4	0	56.0	0	64.2	35.8		0	0	100	0	6.3
• Placebo + Peg-IFN+RBV x12 w / Peg-IFN+RBV x36 w						1.7	98.3	0	54.5	0	70.0	30.0		0	0	100	0	6.4
Jacobson, 2011 (ADVANCE)																		
• TVR + Peg-IFN+RBV x12w / Peg-IFN+RBV x36w	RCT, multicentre, double-blind, placebo-controlled, phase III	123 international sites	Yes	Yes	5	59	41	<1	49	6				90	7	1	2	6.3
• TVR + Peg-IFN+RBV x8w / Placebo + Peg-IFN+RBV x4w / Peg-IFN+RBV x36w						58	41	1	49	7		NR		87	11	1	1	6.3
• Placebo + Peg-IFN+RBV x12w / Peg-IFN+RBV x36w						58	42	1	49	6				88	8	3	1	6.3
Jacobson, 2014 (QUEST-1)																		
• SMV 150 mg + Peg-IFN+RBV x12w / Peg-IFN+RBV x12/36w	RCT, multicentre, double-blind, parallel group, placebo-controlled, phase III	71 sites in 13 countries (Australia, Canada, Germany, Italy, Mexico, New Zealand, Puerto Rico, Romania, Russia, Spain, Ukraine, the UK, and the USA)	Yes	Yes	4	56	44	0	48	12	29	57	14	86	10	2	2	NR
• Placebo + Peg-IFN+RBV x12 w / Peg-IFN+RBV x36w						57	43	0	48	13	28	58	13	94	3	2	1	
Kumada, 2012																		
• TVR + Peg-IFN+RBV x12w / Peg-IFN+RBV x12w	RCT, multicentre	41 institutions in Japan	No	No	2	1.6	98.4	0	53.0	NR		NR		0	0	100	0	6.7
• Peg-IFN+RBV x48 w						0	100	0	55.0	NR				0	0	100	0	6.9
Kwo, 2010 (SPRINT-1)																		
• lead-in x4w / BOC + Peg-IFN+RBV x24w	RCT, multicentre, open label, phase II	67 sites in the United States, Canada, and Europe	Yes	Yes	3	51	36	13	47.7	7				83	15	0	2	6.53
• lead-in x4w / BOC + Peg-IFN+RBV x44w						58	34	8	47.6	6				83	15	0	2	6.53
• BOC + Peg-IFN+RBV x28 w						63	28	9	46.4	7		NR		80	17	0	3	6.64
• BOC + Peg-IFN+RBV x48 w						53	35	12	46.7	9				84	14	0	2	6.54
• Peg-IFN+RBV x48 w						51	40	9	48.3	8				80	15	0	5	6.53
Manns, 2014 (QUEST-2)																		
• SMV 150 mg + Peg-IFN+RBV x12w / Peg-IFN+RBV x36w	RCT, multicentre, double-blind, parallel group, placebo-controlled, phase III	76 sites in 14 countries in Europe, North America, and South America	Yes	Yes	4	41	58	1	46	7	29	55	16	92	6	1	1	NR
• Placebo + Peg-IFN+RBV x12 w / Peg-IFN+RBV x36w						41	58	1	47	11	31	53	16	92	7	1	0	

Peg-IFN, pegylated interferon; RBV, ribavirin; RCT, randomized clinical trial; w, weeks; BOC, boceprevir; DCV, daclatasvir; SMV, simeprevir; TVR, telaprevir; NR, not reported.

Manns, 2014b																				
• Grazoprevir 100 mg + Peg-IFN+RBV x12w / Peg-IFN+RBV x12/36w	RCT, multicentre, double-blind, active-controlled, dose-ranging, phase II	United States, Canada, France, Germany, Italy, Israel, Argentina and Puerto Rico	Yes	Yes	4	65.2	NR	NR	49	0	25.8	74.2	87.9	9.1	NR	3	6.4
• Grazoprevir 200 mg + Peg-IFN+RBV x12w / Peg-IFN+RBV x12/36w						60.3	NR	NR	50	0	27.9	72.1	79.4	13.2	NR	7.4	6.4
• Grazoprevir 400 mg + Peg-IFN+RBV x12w / Peg-IFN+RBV x12/36w						55.2	NR	NR	49	0	25.4	74.6	86.6	11.9	NR	1.5	6.5
• Grazoprevir 800 mg + Peg-IFN+RBV x12w / Peg-IFN+RBV x12/36w						56.9	NR	NR	54	0	27.7	72.3	76.9	13.8	NR	9.3	6.3
• lead-in x4 w + BOC + Peg-IFN+RBV x24 w or 32 w / Peg-IFN+RBV x12 w						65.2	NR	NR	52	0	28.8	71.2	78.8	18.2	NR	3	6.4
McHutchison, 2009 (PROVE-1)																	
• TVR + Peg-IFN+RBV x12w / Peg-IFN+RBV x12w	RCT, multicentre, double-blind, placebo-controlled, phase IIb	37 centers in the United States	Yes	Yes	3	67	22	11	49	0			76	9	1	14	6.54
• TVR + Peg-IFN+RBV x12w / Peg-IFN+RBV x36w						61	34	5	50	0		NR	76	10	4	10	6.47
• TVR + Peg-IFN+RBV x12w						53	35	12	49	0			76	18	0	6	6.57
• Placebo + Peg-IFN+RBV x12 w / Peg-IFN+RBV x36w						67	27	7	49	0			79	12	0	9	6.68
Poi, 2012																	
• DCV 3 mg + Peg-IFN+RBV x48w	RCT, multicentre, parallel-group, double-blind, placebo-controlled, dose-finding, phase IIa	14 tertiary care centres in the USA and France	Yes	Yes	5	67	33	0	52.0	0	37.5	50.0 12.5	58	25	0	17	6.3
• DCV 10 mg + Peg-IFN+RBV x48w						67	33	0	50.5	0	45.4	36.4 18.2	75	17	8	0	6.4
• DCV 60 mg + Peg-IFN+RBV x48w						75	25	0	51.0	0	12.5	75.0 12.5	75	17	0	8	6.5
• Placebo + Peg-IFN+RBV x48w						58	42	0	49.5	0	44.4	44.4 11.1	83	17	0	0	6.7
Poordad, 2011 (SPRINT-2)																	
• lead-in x4w / BOC + Peg-IFN+RBV x24w / Placebo + Peg-IFN+RBV x20w	RCT, multicentre, double-blind, placebo-controlled, phase III	200 sites worldwide	Yes	Yes	4	64	34	3	50	0			83	14	1	2	6.5
• lead-in x4w / BOC + Peg-IFN+RBV x44w						65	32	3	49	0		NR	81	15	2	2	6.5
• lead-in x4w / Placebo + Peg-IFN+RBV x44w						63	33	4	49	0			82	14	2	2	6.5
Reddy, 2015 (ATTAIN)																	
• SMV 150 mg + Placebo + Peg-IFN+RBV x12w / Peg-IFN+RBV x36w	RCT, multicentre, double-blind, double-dummy, active-controlled, phase III	169 investigational sites in 24 countries	Yes	Yes	4	43	57	0	50	23	4	67 29	94	6	NR	0	6.56
• TVR + Placebo + Peg-IFN+RBV x12w / Peg-IFN+RBV x36w						42	57	1	52	20	5	63 32	95	4	NR	1	6.57
Wei, 2016 (TIGER)																	
• SMV 100 mg + Peg-IFN+RBV x12w / Peg-IFN+RBV x36w	RCT, multicentre, double-blind, double-dummy, placebo-controlled, phase III	27 sites in China and 13 sites in South Korea	Yes	Yes	4	1	99	0	45	6	80	19 1	0	0	100	0	6.0
• SMV 150 mg + Peg-IFN+RBV x12w / Peg-IFN+RBV x36w						1	99	0	44	3	78	21 1	0	0	100	0	6.0
• Placebo + Peg-IFN+RBV x12w / Peg-IFN+RBV x36w						1	99	0	45	8	80	19 1	0	0	100	0	6.7
Zeuzem, 2014 (ASPIRE)																	
• SMV 100 mg + Peg-IFN+RBV x12w / Peg-IFN+RBV x36w	RCT, multicentre, double-blind, placebo-controlled, phase IIb	14 countries in Europe, North America, Australia, and New Zealand	Yes	Yes	5	39.4	59.1	1.5	51.5	10.8	16.3	74.4 9.3	89.4	NR	NR	10.6	6.5
• SMV 100 mg + Peg-IFN+RBV x24w / Peg-IFN+RBV x24w						44.4	54.0	1.6	50.0	20.6	17.4	65.2 17.4	92.3	NR	NR	7.7	6.7
• SMV 100 mg + Peg-IFN+RBV x48w						38.5	60.0	1.5	50.0	21.2	17.0	59.6 23.4	93.9	NR	NR	6.1	6.6
• SMV 150 mg + Peg-IFN+RBV x12w / Peg-IFN+RBV x36w						45.5	54.5	0	48.0	19.7	11.6	69.8 18.6	92.4	NR	NR	7.6	6.6
• SMV 150 mg + Peg-IFN+RBV x24w / Peg-IFN+RBV x24w						44.6	52.3	3.0	51.5	19.4	18.0	64.0 18.0	89.7	NR	NR	10.3	6.6
• SMV 150 mg + Peg-IFN+RBV x48w						35.9	64.1	0	50.0	20.3	20.4	57.1 22.4	96.9	NR	NR	3.1	6.6
• Placebo + Peg-IFN+RBV x48w						40.9	59.1	0	50.5	15.6	22.0	64.0 14.0	93.9	NR	NR	6.1	6.6

Peg-IFN, pegylated interferon; RBV, ribavirin; RCT, randomized clinical trial; w, weeks; BOC, boceprevir; DCV, daclatasvir; SMV, simeprevir; TVR, telaprevir; NR, not reported

Anlage 7 – Übersicht über die Primärstudien in Berden et al. (2016)

Table 1. Baseline characteristics of included studies

Author	Acronym / NCT number	Year	Location	Population and design	Intervention	Duration in weeks	N	Cirrhosis - n (%)	SVR - n (%)*
Foster [22]	NCT00561015	2011	EU	Phase IIa RCT, TN G2-3 pts	TPR + PR vs. PR	24	26	1 (4)	14(54)
Lawitz [29]	FISSION	2013	NA, EU, ANZ	Phase III RCT, TN G2-3 pts	SOF + RBV vs. PR	12-24	359	NR	212 (59)
Jacobson [28]	POSITRON	2013	NA, ANZ	Phase III RCT, TN G2-3 pts in which interferon was not an option	SOF + RBV vs. Placebo	12	135	14 (10)	60 (61)
Jacobson [28]	FUSION	2013	NA, ANZ	Phase III RCT, TE G2-3 pts	SOF + RBV	12-16	127	49 (39)	58 (46)
Gane [26]	ELECTRON	2013	ANZ	Phase IIa RCT, TN G2-3 pts	SOF ± RBV / PR	12∫	42	0	40 (95)
Zeuzem [43]	VALENCE	2014	EU	Phase III RCT, later unblinded during study, TN and TE G2-3 pts	SOF + RBV vs. Placebo	12-24	328	62 (19)	216 (83)
Sulkowski [40]	PHOTON-1	2014	NA	Phase III single arm study with TN and TE HCV/HIV coinfected G1-3 pts	SOF + RBV	12-24	59	12 (20)	44 (75)
Sulkowski [39]	AI444040	2014	NA	RCT, TN G1-3 pts	SOF + DCV ± RBV	24	18	0	16 (89)
Foster [21]	ASTRAL-3	2015	NA, EU, ANZ	Phase III RCT, TN and TE G3 pts	SOF + VEL vs. SOF + RBV	12	552	163 (30)	485 (88)
Foster [24]	BOSON	2015	NA, EU, ANZ	Phase III RCT, TN and TE G3 pts	SOF + RBV / PR	12-24	544	171 (31)	449 (83)
Pianko [36]	NCT01909804	2015	NA, ANZ	Phase II RCT, TE G1 and 3 pts	SOF + VEL(25mg and 100 mg) ± RBV	12	210	103 (49)	186 (89)
Nelson [35]	ALLY-3	2015	NA	Phase III single arm study, TN and TE G3 pts	SOF + DCV	12	152	32 (21)	135 (89)
Molina [34]	PHOTON-2	2015	EU, ANZ	Phase III single arm study, TN and TE HCV/HIV co-infected G1-4 pts	SOF + RBV	24	106	26 (25)	94 (89)
Gane [25]	NCT01826981	2015	ANZ	Phase II RCT (TN) and single arm (TE) study in pts with G3 or G6	SOF + LDV ± RBV	12	101	32 (32)	83 (82)
Dore [19]	AI444031	2015	NA, EU, ANZ	Phase IIb RCT, TN G2-3 pts	DCV + PR vs. PR	12-24	80	18 (23)	53 (66)
Everson [20]	NCT01858766	2015	NA	Phase II RCT, TN G1-6 pts	SOF + VEL (25mg and 100mg)	12	54	0	50 (93)
Curry [18]	ASTRAL-4	2015	NA	Phase III RCT, TN and TE G1-6 pts with decompensated cirrhosis	SOF + VEL ± RBV	12-24	39	39 (100)	24 (62)
Lawitz [30]	NR	2015	NA	Phase II single arm study, TE G2-3 pts	SOF + PR	12	24	12 (50)	20 (83)
Lawitz [31]	NCT01458535	2015	NA	Phase II trial with sequential enrollment, TN G1-3 pts	OMB + ABT-450/r ± RBV	12	21	0	6 (29)
Lin [33]	NR	2015	NR	Single arm study, G2-3 pts, decompensated cirrhosis was included	SOF + RBV	24	8	NR	6 (75)
Welzel [41]	CUP	2015	EU	Observational cohort (compassionate use program), G3 pts both HCV and HCV/HIV coinfected, decompensated cirrhosis was included	SOF + DCV ± RBV	12-24	24	22 (92)	22 (92)
Hezode [27]	ATU	2015	EU (France)	Observational cohort (compassionate use program), TN and TE G3 pts both HCV and HCV/HIV coinfected, decompensated cirrhosis was included	SOF + DCV ± RBV	12-24	78	NR†	70 (90)
Poordad [37]	ALLY-1	2015	NA	Single arm study, TN and TE G1-6 pts with advanced fibrosis or post-liver transplant HCV recurrence	SOF + DCV + RBV	12	17	17 (100)	15 (88)
Wyles [42]	ALLY-2	2015	NA	Phase II RCT (TN) and single arm (TE), G1-4 HCV/HIV coinfected pts	SOF + DCV	12 ∫	13	2 (15)	12 (92)
Foster [23]	EAP	2016	EU	Observational cohort (expanded access programme), G1-6 TN and TE, both HCV and HCV/HIV coinfected pts, decompensated cirrhosis was included	SOF + LDV ± RBV vs. SOF + DCV ± RBV	12	192	172 (90)	132 (69)
Shah [38]	NR	2016	Asia (India)	RCT, TN G1 and G3 pts	SOF + RBV	16-24	59	14 (24)	57 (97)
Leroy [32]	ALLY-3+	2016	EU, ANZ	Phase IIIb RCT, TN and TE G3 pts	SOF + DCV + RBV	12-16	50	36 (72)	45 (90)

NR = Not Reported, EU = Europe, NA= North America, ANZ = Australia and New-Zealand, TN = treatment naive, TE = treatment experienced, HCV= hepatitis C virus, HIV = human immunodeficiency virus, RCT = randomized clinical trial, pts = patients, G = genotype.

Interventions: TPR = telaprevir, RBV = ribavirin, PR = peginterferon and RBV, SOF = sofosbuvir, DCV = daclatasvir, VEL = velpatasvir (100 mg unless otherwise indicated), LDV = ledipasvir, OMB = ombitasvir, ABT-450/r = paritaprevir/ritonavir.

* in case of placebo, these patients are excluded from SVR calculations

∫ The treatment arms with 8 weeks duration are excluded from the analysis