Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2016-07-15-D-247 Sofosbuvir/Velpatasvir

Stand: Januar 2016

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

Sofosbuvir/Velpatasvir
[chronische Hepatitis C bei Erwachsenen]

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)
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche*

II. 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>Sofosbuvir/
Velpatasvir</td><td>Geplantes Anwendungsgebiet laut Beratungsanforderung:
Behandlung der chronischen Hepatitis C (CHC) Infektion bei Erwachsenen (Genotyp 1 bis Genotyp 6)</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>

II. 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.

Ribavirin	Rebetol ist in Kombination mit anderen Arzneimitteln bestimmt zur Behandlung der chronischen Hepatitis C (CHC) bei Erwachsenen (siehe

II. Zugelassene Arzneimittel im Anwendungsgebiet	
J05AB04 Rebetol®	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.
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. ***Anzuwendende Dosierung*** Ribavirin-ratiopharm® muss entweder in Kombination mit Peginterferon alfa-2b (1,5 Mikrogramm/kg/Woche) oder Interferon alfa-2b (3 Millionen Internationale Einheiten (Mio I.E.) dreimal in der Woche) angewendet werden. Die Wahl der Kombinations- Dosierungsschemata hängt von der Charakteristik des Patienten ab. Die Fachinformation zu Peginterferon alfa-2b oder Interferon alfa-2b ist für Informationen zur Verschreibung des jeweiligen Produktes ebenfalls zu beachten.

II. 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-Filmtabletten
< 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-Filmtabletten
< 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. […]

Telaprevir J05AE11 Incivo®	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; - 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)
Boceprevir J05AE12 Incivo®	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.

II. Zugelassene Arzneimittel im Anwendungsgebiet

Simeprevir
J05AE14
Olysio®

OLYSIO ist bei erwachsenen Patienten in Kombination mit anderen Arzneimitteln zur Behandlung der chronischen Hepatitis C (CHC) indiziert

Tabelle 1: Empfohlene Arzneimittel und Therapiedauer im Rahmen der Kombinationstherapie mit OLYSIO

Patientengruppe	Behandlung	Dauer
Therapienaive Patienten, vorherige Relapser[1] und vorherige Non-Responder[2] (einschließlich partieller und Null-Responder) mit HCV-Genotyp 1 oder 4, mit oder ohne Zirrhose, mit oder ohne HIV-Koinfektion	OLYSIO + Sofosbuvir (+/– Ribavirin)[3]	12 Wochen[4] (siehe Abschnitte 4.4, 4.8 und 5.1)
Therapienaive Patienten und vorherige Relapser[1] mit HCV-Genotyp 1 oder 4		
mit oder ohne Zirrhose und ohne HIV-Koinfektion ohne Zirrhose aber mit HIV-Koinfektion	OLYSIO + Peginterferon alfa + Ribavirin[5]	24 Wochen[6] Die Behandlung mit OLYSIO muss in Kombination mit Peginterferon alfa und Ribavirin begonnen und über einen Zeitraum von 12 Wochen fortgeführt werden, gefolgt von einer weiteren 12-wöchigen Behandlung mit Peginterferon alfa und Ribavirin.
mit Zirrhose und mit HIV-Koinfektion	OLYSIO + Peginterferon alfa + Ribavirin[5]	48 Wochen[6] Die Behandlung mit OLYSIO muss in Kombination mit Peginterferon alfa und Ribavirin begonnen und über einen Zeitraum von 12 Wochen fortgeführt werden, gefolgt von einer weiteren 36-wöchigen Behandlung mit Peginterferon alfa und Ribavirin.
Vorherige Non-Responder[2] (einschließlich partieller und Null-Responder) mit HCV-Genotyp 1 oder 4, mit oder ohne Zirrhose, mit oder ohne HIV-Koinfektion	OLYSIO + Peginterferon alfa + Ribavirin[5]	48 Wochen[6] Die Behandlung mit OLYSIO muss in Kombination mit Peginterferon alfa und Ribavirin begonnen und über einen Zeitraum von 12 Wochen fortgeführt werden, gefolgt von einer weiteren 36-wöchigen Behandlung mit Peginterferon alfa und Ribavirin.

1 Relapse nach vorheriger Therapie mit Interferon (pegyliert oder nicht pegyliert), mit oder ohne Ribavirin (siehe Abschnitt 5.1).
2 Zu Non-Response nach vorheriger Behandlung mit Interferon (pegyliert oder nicht pegyliert), mit oder ohne Ribavirin, siehe Abschnitt 5.1.
3 Basierend auf einer klinischen Bewertung jedes einzelnen Patienten kann Ribavirin hinzugefügt werden (siehe Abschnitte 4.4, 4.8 und 5.1). Die empfohlene Behandlungsdauer beträgt 12 Wochen. Eine längere Behandlungsdauer mit OLYSIO zusammen mit Sofosbuvir (mit oder ohne Ribavirin) (bis zu 24 Wochen) kann im Einzelfall in Betracht gezogen werden (siehe Abschnitte 4.4, 4.8 und 5.1).
4 Für die Kombination von OLYSIO und Sofosbuvir sind keine Abbruchregeln etabliert.
5 Wird eine Kombinationstherapie mit 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).
6 Empfohlene Behandlungsdauer unter der Voraussetzung, dass der Patient keine der Abbruchregeln (siehe Tabelle 2 auf Seite 2) erfüllt.

II. 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 zu Behandlungsregimen und Behandlungsdauer für die Kombinationstherapie mit Daklinza

HCV-Genotyp und Patientenpopulation*	Behandlung	Behandlungsdauer
Genotyp 1 oder 4 ohne Zirrhose	Daklinza + Sofosbuvir	12 Wochen Bei vorbehandelten Patienten, deren Therapie auch einen NS3/4A-Proteaseinhibitor beinhaltete, ist zu erwägen, die Behandlung auf 24 Wochen zu verlängern (siehe Abschnitte 4.4 und 5.1).
Genotyp 1 oder 4 mit kompensierter Zirrhose	Daklinza + Sofosbuvir	24 Wochen Bei vorher unbehandelten Patienten mit Zirrhose und positiven Prognosefaktoren, wie IL28B-CC-Genotyp und/oder niedrige Ausgangsvirenlast, kann erwogen werden, die Behandlung auf 12 Wochen zu verkürzen. Bei Patienten mit weit fortgeschrittener Lebererkrankung oder anderen negativen Prognosefaktoren, wie Vorbehandlung, kann die zusätzliche Anwendung von Ribavirin erwogen werden.
Genotyp 3 ohne Zirrhose	Daklinza + Sofosbuvir	12 Wochen
Genotyp 3 mit Zirrhose	Daklinza + Sofosbuvir +/- Ribavirin	24 Wochen Ribavirin kann je nach klinischer Beurteilung des einzelnen Patienten zusätzlich gegeben werden.
Genotyp 4	Daklinza + Peginterferon alfa + Ribavirin	24 Wochen Daklinza in Kombination mit 24 – 48 Wochen Peginterferon alfa und Ribavirin 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.

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

Sofosbuvir
J05AX15
Sovaldi®

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).

Zur spezifischen Aktivität gegen die verschiedenen Genotypen des Hepatitis-C-Virus (HCV) siehe Abschnitte 4.4 und 5.1.
Abschnitt 4.2 der Fachinformation:

II. Zugelassene Arzneimittel im Anwendungsgebiet

Tabelle 1: Empfohlene(s) gleichzeitig angewendete(s) Arzneimittel und Behandlungsdauer für die Kombinationstherapie mit Sovaldi

Patientengruppe* Behandlung Dauer	**Behandlung**	**Dauer**
Patienten mit CHC vom Genotyp 1, 4, 5 oder 6	Sovaldi + Ribavirin + Peginterferon alfa	12 Wochen [a, b]
	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)	24 Wochen
Patienten mit CHC vom Genotyp 2	Sovaldi + Ribavirin	12 Wochen[b]
	Sovaldi + Ribavirin + Peginterferon alfa	12 Wochen[b]
Patienten mit CHC vom Genotyp 3	Sovaldi + Ribavirin	24 Wochen
Patienten mit CHC, die auf eine Lebertransplantation warten	Sovaldi + Ribavirin	Bis zur Lebertransplantation[c]

* 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 alfa und Ribavirin) assoziiert waren.
[c] Siehe unten: „Besondere Patientengruppen – Patienten, die auf eine Lebertransplantation warten“.

II. Zugelassene Arzneimittel im Anwendungsgebiet

Dasabuvir
J05AX16
Exviera®

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

Patientenpopulation	Therapie*	Dauer
Genotyp-1b-Patienten ohne Zirrhose	Exviera + Ombitasvir/Paritaprevir/Ritonavir	12 Wochen
Genotyp-1b-Patienten mit kompensierter Zirrhose	Exviera + Ombitasvir/Paritaprevir/Ritonavir + Ribavirin	12 Wochen
Genotyp-1a-Patienten ohne Zirrhose	Exviera + Ombitasvir/Paritaprevir/Ritonavir + Ribavirin*	12 Wochen
Genotyp-1a-Patienten mit kompensierter Zirrhose	Exviera + Ombitasvir/Paritaprevir/Ritonavir + Ribavirin*	24 Wochen (siehe Abschnitt 5.1)

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

<u>HIV-1-Koinfektion</u>
Es gelten die Dosierungsempfehlungen in Tabelle 1. Zu Dosierungsempfehlungen zusammen mit antiviralen Arzneimitteln gegen HIV

<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.

II. Zugelassene Arzneimittel im Anwendungsgebiet

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 oder Genotyp 4	
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 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).

II. Zugelassene Arzneimittel im Anwendungsgebiet

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	Viekirax + Dasabuvir	12 Wochen
Genotyp-1b-Patienten mit kompensierter Zirrhose	Viekirax + Dasabuvir + Ribavirin	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	Viekirax + Ribavirin	12 Wochen
Genotyp-4-Patienten mit kompensierter Zirrhose	Viekirax + Ribavirin	24 Wochen

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

<u>HIV-1-Koinfektion</u>
Es gelten die Dosierungsempfehlungen in Tabelle 1.

<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.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Interferon alfa-2a L03AB04 Roferon-A®	Histologisch nachgewiesene chronische Hepatitis C bei *erwachsenen Patienten*, bei denen HCV-Antikörper oder HCVRNA 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.
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**.**
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. *Erwachsene – Zu verabreichende Dosierung* PegIntron 1,5 Mikrogramm/kg/Woche in Kombination mit Ribavirin-Kapseln.

II. Zugelassene Arzneimittel im Anwendungsgebiet

Tabelle 1 Dosierungsschema für die Duale Therapie*

Körpergewicht (kg)	PegIntron		Ribavirin-Kapseln	
	PegIntron Stärke (µg/0,5 ml)	Wöchentlich zu verabreichende Dosis (ml)	Tägliche Ribavirin-Gesamtdosis (mg)	Anzahl der Kapseln (200 mg)
< 40	50	0,5	800	4[a]
40–50	80	0,4	800	4[a]
51–64	80	0,5	800	4[a]
65–75	100	0,5	1.000	5[b]
76–80	120	0,5	1.000	5[b]
81–85	120	0,5	1.200	6[c]
86–105	150	0,5	1.200	6[c]
> 105	150	0,5	1.400	7[d]

a: 2 morgens, 2 abends
b: 2 morgens, 3 abends
c: 3 morgens, 3 abends
d: 3 morgens, 4 abends
* Für detaillierte Angaben zur Dosierung von Boceprevir im Rahmen einer 3-fach-Kombinationstherapie beachten Sie bitte die Fachinformation zu Boceprevir.

Erwachsene – Dauer der Behandlung – Nicht-vorbehandelte Patienten
Duale Therapie:
Genotyp 2 oder 3: Es wird empfohlen, dass alle Patienten im Rahmen einer dualen Therapie für 24 Wochen behandelt werden, außer HCV/HIV-co-infizierte Patienten, die eine Behandlung über 48 Wochen erhalten sollten.

Erwachsene – Dauer der Behandlung –Re-Therapie
Duale Therapie:
Unabhängig vom Genotyp sollten alle Patienten, deren HCV-RNA-Serumspiegel in Woche 12 unter der Nachweisgrenze liegen, im Rahmen einer dualen Therapie 48 Wochen lang therapiert werden.

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

II. Zugelassene Arzneimittel im Anwendungsgebiet

Eine Monotherapie gegen Hepatitis C sollte nur in Fallen von Kontraindikationen gegen andere Arzneimittel in Betracht gezogen werden.

Chronische Hepatitis C – unvorbehandelte erwachsene Patienten

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

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,

II. Zugelassene Arzneimittel im Anwendungsgebiet	
	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.

Quellen: Fachinformationen

Gemeinsamer Bundesausschuss

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie (zVT):

Inhalt

Indikation für die Recherche bei Sofosbuvir/Velpatasvir:

Behandlung der chronischen Hepatitis C (CHC) Infektion bei Erwachsenen.

Berücksichtigte Wirkstoffe/Therapien:

siehe Unterlage zur Beratung in AG: Übersicht zVT, Tabellen „I. Zweckmäßige Vergleichstherapie“ und „II. Zugelassene Arzneimittel im Anwendungsgebiet.“

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 07.10.2015 abgeschlossen. Die Suche erfolgte in folgenden Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane

Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database), MEDLINE (PubMed), AWMF, Clinical Evidence, DAHTA, CADTH, G-BA, GIN, IQWiG, NGC, NICE, TRIP. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Bei der Recherche wurde keine Sprachrestriktion vorgenommen. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 839 Quellen, die anschließend nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Davon wurden 230 Quellen eingeschlossen. Insgesamt ergab dies 68 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Abkürzungen

AE	Adverse Events
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
ÄZQ	Ärztliches Zentrum für Qualität in der Medizin
BOC	Boceprevir
BSC	Best supportive care
cEVR	complete early virological response
CHC	Chronic Hepatitis C
CADTH	Canadian Agency for Drugs and Technologies in Health
DAHTA	Deutsche Agentur für Health Technology Assessment
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
HCV	Hepatitis C Virus
IFN	Interferon
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
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
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
SoC	Standard of care
SVR	Sustained virological response
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; 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, 2012 [20]. 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) Telaprevir Vom 29. März 2012 **Siehe auch:** **IQWiG, 2012 [35].** Telaprevir – Nutzenbewertung gemäß § 35a SGB V (Auftrag A11-25)	***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; – 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, 2013 [19]. 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	***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

(SGB V) Boceprevir Vom 1. März 2012 **Siehe auch:** **IQWiG, 2011 [34].** Boceprevir – Nutzenbewertung gemäß § 35a SGB V (Auftrag A11-17)	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 [21]. 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 [39].** Simeprevir – Nutzenbewertung gemäß § 35a SGB V (Auftrag A14-18) sowie **Addendum zum Auftrag A14-18 (Auftrag A14-39) [38].**	***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 [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 – Sofosbuvir **siehe auch:** **IQWiG, 2014 [41].** Sofosbuvir – Nutzenbewertung gemäß § 35a SGB V (Auftrag A14-05) sowie **Addendum zum Auftrag A14-05 (Auftrag A14-20) [40]**	***Sofosbuvir*** **Zugelassenes Anwendungsgebiet:** 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 [23]. 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 – Daclatasvir **siehe auch:** **IQWiG, 2014 [36].** Daclatasvir – Nutzenbewertung gemäß § 35a SGB V (Auftrag A14-31) sowie **Addendum zum Auftrag A14-31 (Auftrag A15-02) [42].**	***Daclatasvir*** **Zugelassenes Anwendungsgebiet:** 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 [24]. 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 [37].** Dasabuvir – Nutzenbewertung gemäß § 35a SGB V (Auftrag A15-03) sowie **Addendum zu den Aufträgen A15-03 und A15-04 (Auftrag A15-21) [43].**	***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 [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 – Ledipasvir/Sofosbuvir **siehe auch:** **IQWiG, 2015 [45].** Ledipasvir/Sofosbuvi	***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) **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

r – Nutzenbewertung gemäß § 35a SGB V (Auftrag A14-44). sowie **Addendum zum Auftrag A14-44 (Auftrag A15-14) [44].**	**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 [26]. Beschluss des Gemeinsamen	***Ombitasvir/Paritaprevir/Ritonavir*** **Zugelassenes Anwendungsgebiet:** Ombitasvir/Paritaprevir/Ritonavir (Viekirax®) wird in Kombination mit anderen Arzneimitteln zur Behandlung der chronischen Hepatitis C

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 [46].** Ombitasvir/ Paritaprevir/ Ritonavir – Nutzenbewertung gemäß § 35a SGB V (Auftrag A15-04) sowie **Addendum zu den Aufträgen A15-03 und A15-04 (Auftrag A15-21) [43].**	(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 [32]. Peginterferon plus ribavirin versus interferon plus ribavirin for chronic hepatitis C	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 *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 *Endpunkt* 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

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.

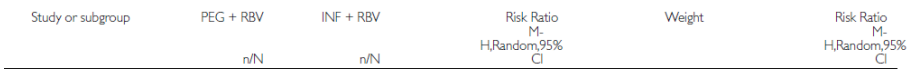
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Non-pegylated	Corresponding risk Peginterferon				
Liver-related morbidity plus all-cause mortality	Five per 1000	Six per 1000 (two to 17)	OR 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.

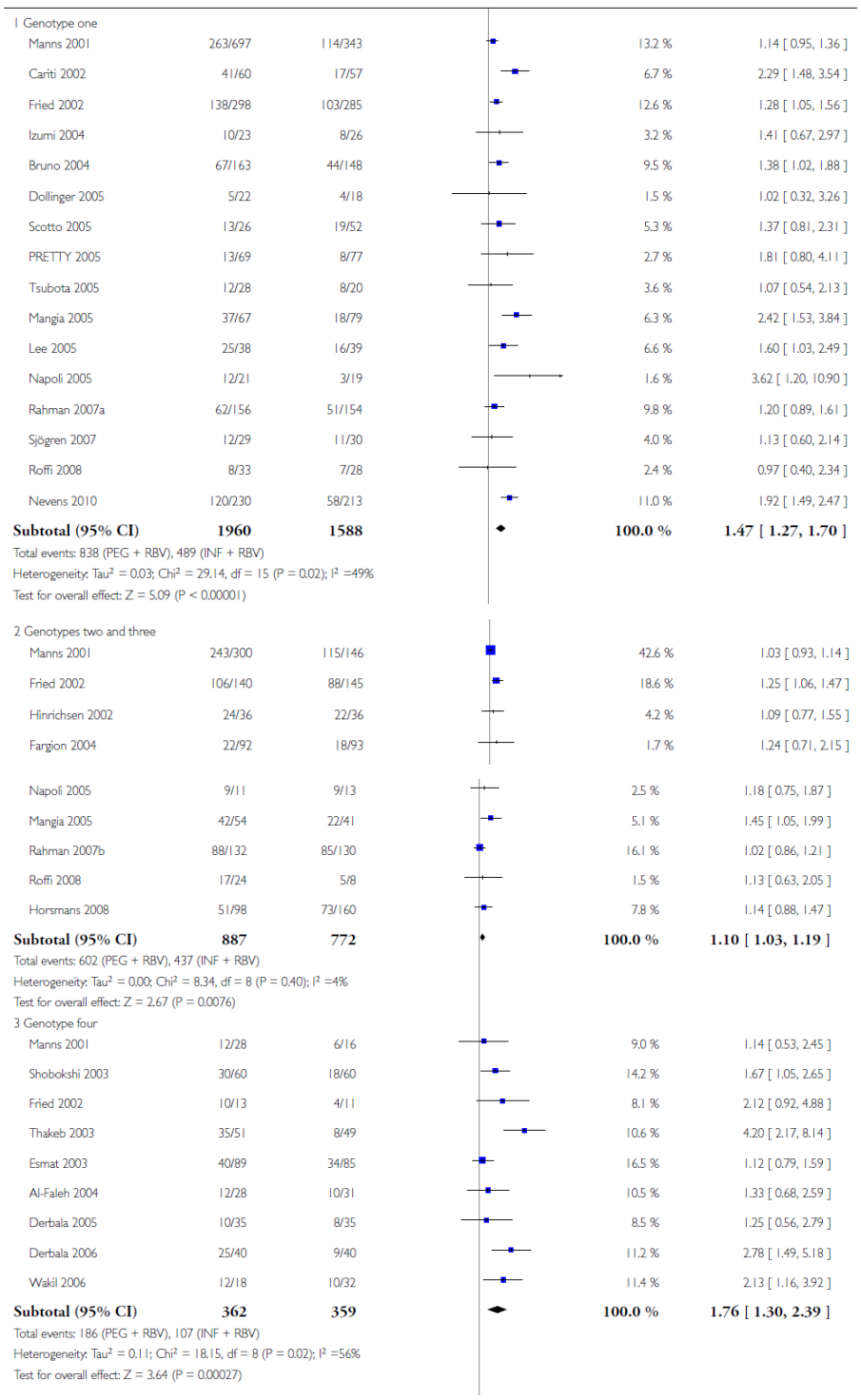
*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence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

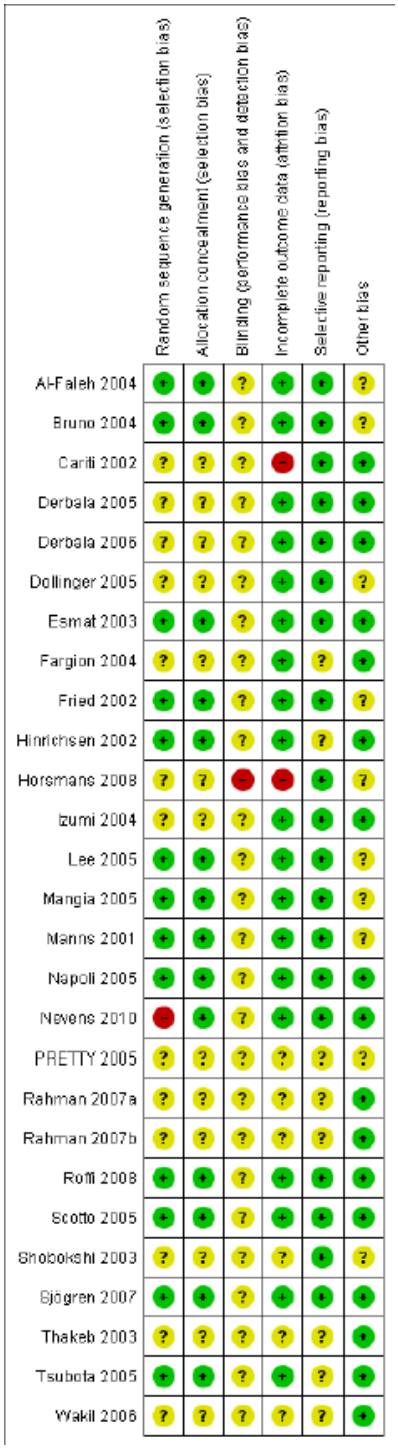
Sustained virological response according to genotype





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]
Napoli 2005	9/11	9/13		2.5 %	1.18 [0.75, 1.87]
Mangia 2005	42/54	22/41		5.1 %	1.45 [1.05, 1.99]
Rahman 2007b	88/132	85/130		16.1 %	1.02 [0.86, 1.21]
Roffi 2008	17/24	5/8		1.5 %	1.13 [0.63, 2.05]
Horsmans 2008	51/98	73/160		7.8 %	1.14 [0.88, 1.47]
Subtotal (95% CI)	**887**	**772**		**100.0 %**	**1.10 [1.03, 1.19]**
Total events: 602 (PEG + RBV), 437 (INF + RBV)					
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 8.34$, df = 8 (P = 0.40); $I^2 = 4\%$					
Test for overall effect: Z = 2.67 (P = 0.0076)					
3 Genotype four					
Manns 2001	12/28	6/16		9.0 %	1.14 [0.53, 2.45]
Shobokshi 2003	30/60	18/60		14.2 %	1.67 [1.05, 2.65]
Fried 2002	10/13	4/11		8.1 %	2.12 [0.92, 4.88]
Thakeb 2003	35/51	8/49		10.6 %	4.20 [2.17, 8.14]
Esmat 2003	40/89	34/85		16.5 %	1.12 [0.79, 1.59]
Al-Faleh 2004	12/28	10/31		10.5 %	1.33 [0.68, 2.59]
Derbala 2005	10/35	8/35		8.5 %	1.25 [0.56, 2.79]
Derbala 2006	25/40	9/40		11.2 %	2.78 [1.49, 5.18]
Wakil 2006	12/18	10/32		11.4 %	2.13 [1.16, 3.92]
Subtotal (95% CI)	**362**	**359**		**100.0 %**	**1.76 [1.30, 2.39]**
Total events: 186 (PEG + RBV), 107 (INF + RBV)					
Heterogeneity: $Tau^2 = 0.11$; $Chi^2 = 18.15$, df = 8 (P = 0.02); $I^2 = 56\%$					
Test for overall effect: Z = 3.64 (P = 0.00027)					

Critical appraisal



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 [33]. 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 could have 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. *Endpunkt* 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

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	

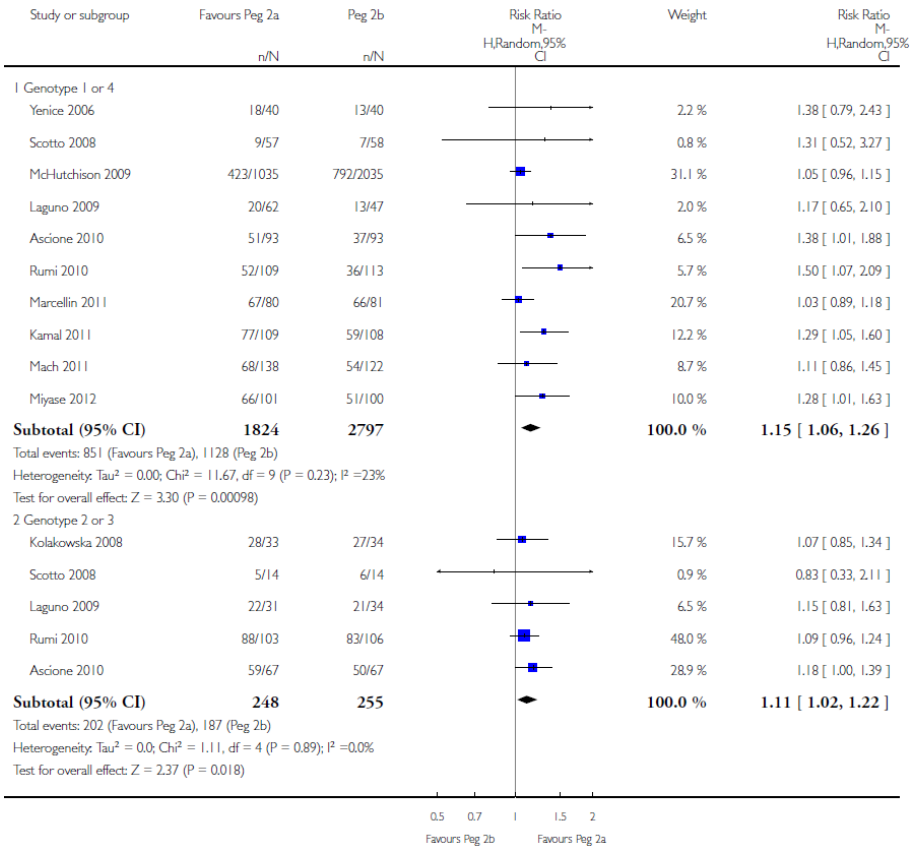
421 per 1000	480 per 1000 (451 to 510)
Moderate	
510 per 1000	581 per 1000 (546 to 617)

*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.

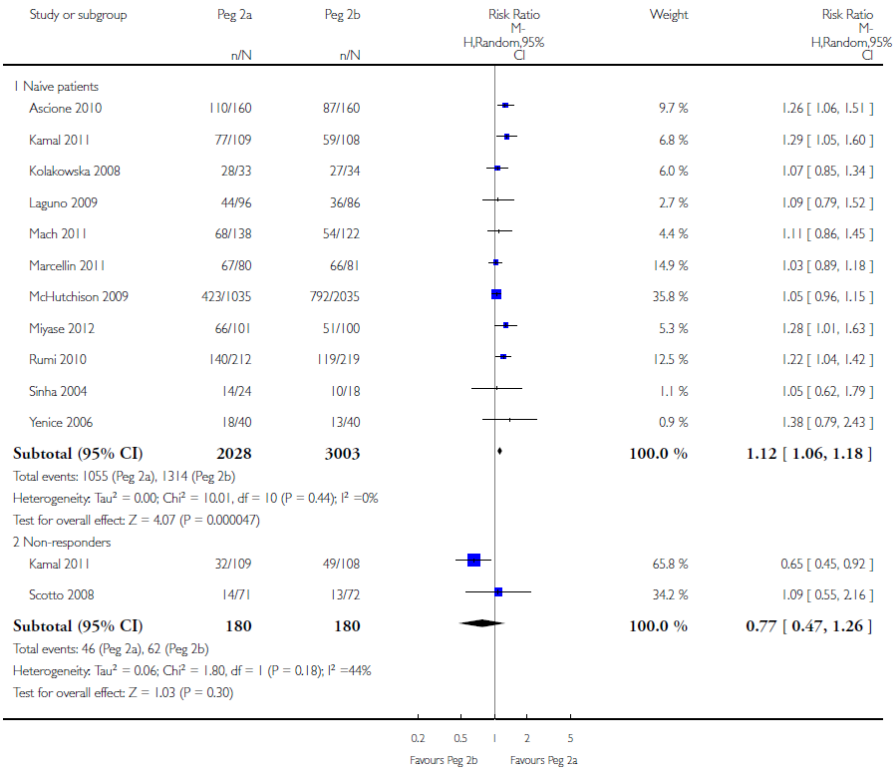
GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further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

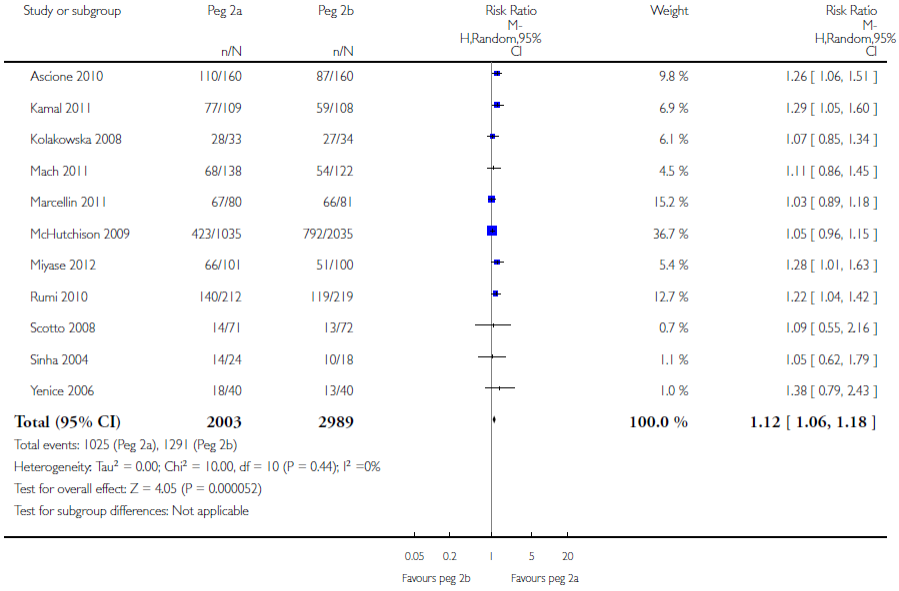
Sustained virological response according to genotype



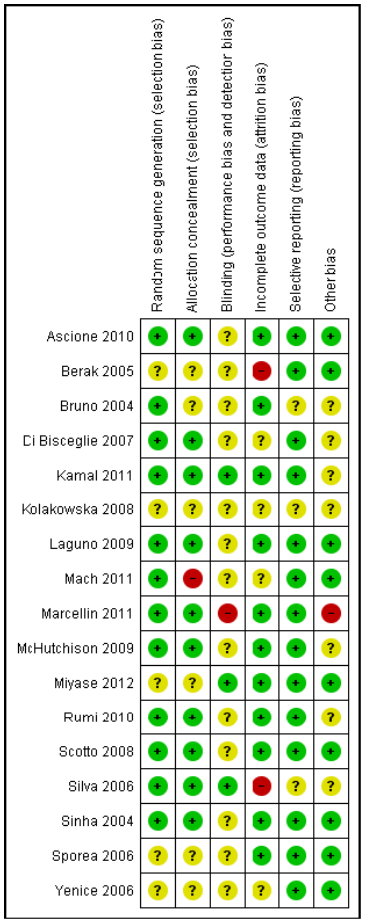
Sustanied virological response according to treatment history



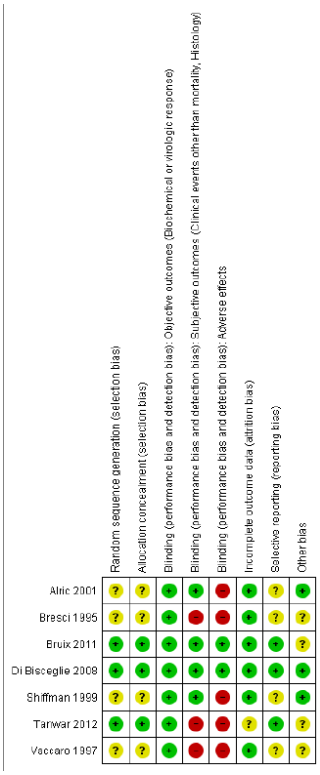
Sustained virological response in patients without HIV co-infection



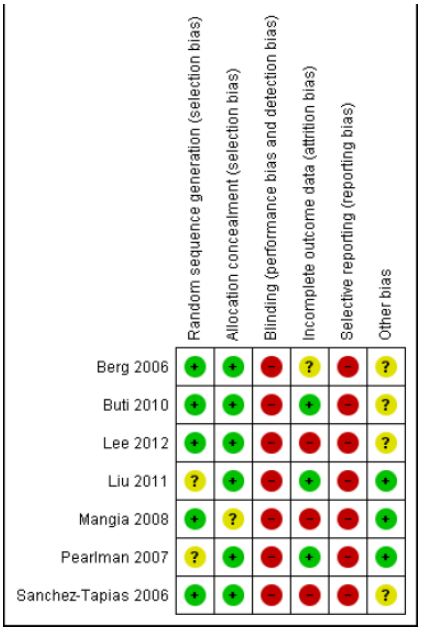
Critical appraisal

	
	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 [52] Interferon for interferon nonresponding and relapsing patients with chronic hepatitis	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*

C.	Patients with chronic Hep C, **non-responder and relapsing** *Intervention / Komparator* interferon monotherapy with no treatment *Endpunkt* 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 • 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 **Critical appraisal**

	
	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 [48]. Extended peginterferon plus ribavirin treatment for 72 weeks versus standard peginterferon plus ribavirin treatment for 48 weeks in	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*

chronic hepatitis C genotype 1 infected slowresponder adult patients.	Peginterferon (alfa-2a or alfa-2b) and ribavirin for 72 weeks v. peginterferon (alfa-2a or alfa-2b) and ribavirin for 48 weeks *Endpunkt* Primäre Endpunkte: 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 • 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. **Critical appraisal**

	
	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.
Brok et al., 2010 [6]. Ribavirin plus interferon versus interferon for chronic hepatitis C. **Siehe auch:** **Brok J et al. 2010 [5]** Meta-analysis: ribavirin plus interferon vs. interferon	1. Fragestellung To assess the beneficial and harmful effects of ribavirin and interferon combination therapy versus interferon monotherapy for chronic hepatitis C.
	2. Methodik *Population* Patients with chronic hepatitis C *Intervention / Komparator* Comparisons of any type, dose, or duration of ribavirin plus interferon alpha therapy versus interferon alpha monotherapy *Endpunkt* Primäre Endpunkte: failure of serum (or plasma) sustained virological response (SVR); liver-related morbidity plus all-cause mortality; all adverse events

monotherapy for chronic hepatitic C – an updated Cochrane review	Sekundäre Endpunkte: failure of end-of-treatment virological response; failure of histological response; quality of life. *Suchzeitraum (Aktualität der Recherche)* Systematische Literaturrecherche bis März 2009; The Cochrane Hepato-Biliary Group Controlled Trials Register (Gluud 2009), The Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library, MEDLINE, EMBASE, and Science Citation Index Expanded *Anzahl eingeschlossene Studien/Patienten (Gesamt):* 83 Studien (12.707 Patienten) *Qualitätsbewertung der Studien:* Allocation sequence generation, Allocation concealment, Blinding
	3. Ergebnisdarstellung **Failure of serum sustained virological response** • Combination therapy significantly reduced the number with failure of SVR when all patients were combined (RR 0.75, 95% CI 0.71 to 0.79; 67 trials) • Combination therapy had a significant effect on the response in subgroups of **naive** (RR 0.72, 95% CI 0.68 to 0.75; 25 trials, I^2 = 34%), **relapsers** (RR 0.62, 95% CI 0.54 to 0.70; 14 trials, I^2 = 57%), and **non-responders** (RR 0.89, 95% CI 0.84 to 0.93; 22 trials, I^2 = 63%) • Sensitivity analyses of trials with genotype 1 (RR 0.67, 95% CI 0.56 to 0.80, 7 trials) and trials with many cirrhotic patients (> 25%) (RR 0.80, 95% CI 0.72 to 0.90, 14 trials) gave the same overall results showing that adding ribavirin significantly reduced the number with failure of SVR. • Subgroup analyses with test of interaction found that adding ribavirin was significantly more beneficial in naive (P < 0.0001) and relapsers (P < 0.0001) compared to non-responders **Liver-related morbidity plus all-cause mortality** • Few patients developed cirrhosis, hepatocellular carcinoma, or died • On combination therapy the number of outcomes was 16 out of 7482 patients, and on monotherapy the number of outcomes was 29 out of 5225 patients. • Combination therapy significantly reduced morbidity plus mortality (Peto OR 0.43, 95% CI 0.23 to 0.79, I^2 = 0%). • Excluding patients with cirrhosis events provided similar result (Peto OR 0.39, 95%CI 0.17 to 0.92). • The results were not significant for **naive alone** (Peto OR 0.55, 95% CI 0.20 to 1.55), **relapsers alone** (Peto OR 0.13, 95% CI 0.00 to 6.78), or **non-responders alone** (Peto OR 0.56, 95% CI 0.17 to 1.19). **Adverse events and reactions** • The most frequent adverse reaction was anaemia, which occurred in 727 out of 4448 patients (16%) on combination therapy and 43 out of 2944 (1%) on monotherapy (RR 9.45, 95% CI 7.42 to 12.05; 35 trials). • Combination therapy significantly increased the risk of leukopenia (RR 3.42, 95% CI 1.38 to 8.49; 3 trials), but not neutropenia or thrombocytopenia.

	• Combination therapy increased the risk of several dermatological adverse reactions, eg,dermatitis (RR 1.67, 95% CI 1.21 to 2.30; 3 trials), pruritus (RR 1.62, 95% CI 1.29 to 2.02; 18 trials), and rash (RR 1.74, 95%CI 1.17 to 2.61; 12 trials). • Combination therapy also led to a significant increase in gastrointestinal adverse reactions (dyspepsia and anorexia or nausea), insomnia, and miscellaneous adverse events (cough, dyspnoea, and fatigue). **Failure of end-of-treatment virological response** • Combination therapy significantly reduced the number of patients with failure of virological response (RR 0.72, 95%CI 0.69 to 0.77; 78 trials). • Combination therapy also had a significant effect on virological response of **naive patients**, **relapsers**, and **non-responders** individually. **Failure of histological response** • All post-treatment biopsies were performed between 3 to 12 months after the end of treatment. Combination therapy significantly reduced the number of patients with failure on both inflammation score (grading) (RR 0.84, 95% CI 0.77 to 0.91; 11 trials) and fibrosis score (staging) (RR 0.95, 95% CI 0.92 to 0.97; 9 trials). • Combination therapy also had a significant effect on liver histology of **naive patients**, **relapsers**, and **non-responders** individually. **Quality of life** • Only one trial with 257 relapsers reported data on quality of life. • Combination therapy had a significant beneficial effect on some subscales. These included scales on general health (MD 7.00, 95% CI 0.67 to 13.33), social functioning (MD 6.00, 95% CI 1.22 to 10.78), and mental health (MD 5.00, 95% CI 1.53 to 8.47).
	4. Anmerkungen/Fazit der Autoren Compared with interferon alone, ribavirin plus interferon is more effective in clearing hepatitis C virus from the blood. Combination therapy may reduce liver-related morbidity and all-cause mortality, but we need more evidence. The number needed to treat to obtain a beneficial effect is considerable considering the increased risk of several severe adverse reactions and costs. 5. Hinweise durch FB Med Subgruppenanalysen für „Failure of serum sustained virological response“ für Patienten mit Genotyp 1 Patienten wurden durchgeführt. The proportion of patients with histological cirrhosis was reported in 59 trials (median 14%; range 0 to 74%). The proportion of patients with hepatitis C virus genotype 1 was reported in 72 trials (median 61%; range 0 to 100%).
Iorio A et al., 2010 [47]. Antiviral treatment for chronic hepatitis C in patients with human	1. Fragestellung To assess the benefits and harms of antiviral treatment for **chronic hepatitis C in patients with HIV.**
	2. Methodik

immunodeficiency virus.	*Population* Patients with chronic hepatitis C and **stable HIV co-infection**. *Intervention / Komparator* • Randomised comparisons of peginterferon (any type, ie, alpha 2a or 2b) plus ribavirin versus peginterferon or interferon (any type, ie, alpha 2a or 2b) plus ribavirin • randomised comparisons of peginterferon plus ribavirin given for different doses or treatment durations *Endpunkt* Primäre Endpunkte: Virologic response defined as loss of hepatitis C virus RNA: • at the end of treatment • at least six months after treatment (sustained virological response). Sekundäre Endpunkte: Mortality; Progression to acquired immunodeficiency syndrome (AIDS) related illness; Hospitalisation; Histological response; Biochemical response (normalisation of transaminases); Level of CD4-positive T-Lymphocytes; Level of HIV RNA; All adverse events; Withdrawals and dropouts *Suchzeitraum (Aktualität der Recherche)* Systematische Literaturrecherche bis Mai 2009; The Cochrane Hepato-Biliary Group Controlled Trials Register (Gluud 2009), the Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library, MEDLINE, EMBASE, and Science Citation Index Expanded *Anzahl eingeschlossene Studien/Patienten (Gesamt):* 14 Studien (2269 Patienten) *Qualitätsbewertung der Studien:* Cochrane risk of bias tool
	3. Ergebnisdarstellung Peginterferon plus ribavirin versus interferon plus ribavirin: **Virologic response defined as loss of hepatitis C virus RNA from the blood** • Peginterferon plus ribavirin was more effective in achieving end of treatment and sustained virological response compared with interferon plus ribavirin (5 trials, 1340 patients). • The benefit of peginterferon plus ribavirin was seen irrespective of HCV genotype although patients with **genotype 1 or 4** had lower response rates (26%) than patients with **genotype 2 or 3** (56%). ➔ Peginterferon plus interferon increased the risk of achieving a sustained virological response for both subgroups (**genotype 1 or 4** RR 3.36, 95% CI 2.33 to 4.86 and **genotype 2 or 3** RR 1.70, 95% CI 1.36 to 2.12). **Mortality** • No significant difference was found between patients randomized to peginterferon plus ribavirin versus interferon plus ribavirin (RR 1.27, 95% CI 0.49 to 3.30; Chi^2 statistic = 0.35). **Adverse events** • The most frequent adverse events were anaemia, flu-like

	symptoms, and depression • Fourteen per cent of patients randomised to peginterferon plus ribavirin developed anaemia and 64% flu-like symptoms. • Both anaemia and flu-like symptoms occurred significantly more frequently among patients randomized to peginterferon plus ribavirin (RR 1.57, 95% CI 1.16 to 2.14 and RR 1.16, 95% CI 1.07 to 1.26, respectively). • The risk of depression was not significantly different in the two treatment groups (RR 0.97, 95% 0.80 to 1.17). **Withdrawals and dropouts** • The proportion of patients who dropped out or were withdrawn for any reason was significantly lower among patients randomized to peginterferon plus ribavirin compared with interferon plus ribavirin (30% and 36%; RR 0.82, 95% CI 0.71 to 0.96). **Other secondary outcome measures** • No data were available allowing analysis of the outcomes progression to AIDS, hospitalisation, biochemical response, level of CD4-positive lymphocytes, or levels of HIV RNA. <u>Peginterferon plus ribavirin versus peginterferon alone:</u> **Virologic response defined as loss of hepatitis C virus RNA from the blood** • Peginterferon plus ribavirin was more effective in achieving end of treatment and sustained virological response compared with peginterferon (2 trials, 714 patients). • The proportion of patients with a sustained virological response was highest among patients randomised to peginterferon plus ribavirin (131 of 359), versus peginterferon alone (64 of 355, RR 2.03, 95% CI 1.57 to 2.63). • The difference was seen for patients with **genotype 1 or 4** (RR 1.71, 95% CI 1.24 to 2.38) as well as patients with **genotype 2 or 3** (RR 1.26, 95% CI 1.00 to 1.58) **Mortality** • Five deaths were reported in the two treatment groups (RR 1.00, 95% CI 0.29 to 3.41) **Histological response** • The number of patients with improved histology and paired liver biopsies was 77 of 135 (57%) in the peginterferon plus ribavirin group and 52 of 134 (39%) in the peginterferon group. **Adverse events, withdrawals, and dropouts** • In total, 113 patients randomised to peginterferon plus ribavirin and 129 patients randomised to peginterferon were lost to follow up (RR 0.86, 95% CI 0.71 to 1.05) • Six patients in both treatments groups became anaemic (RR 1.00,

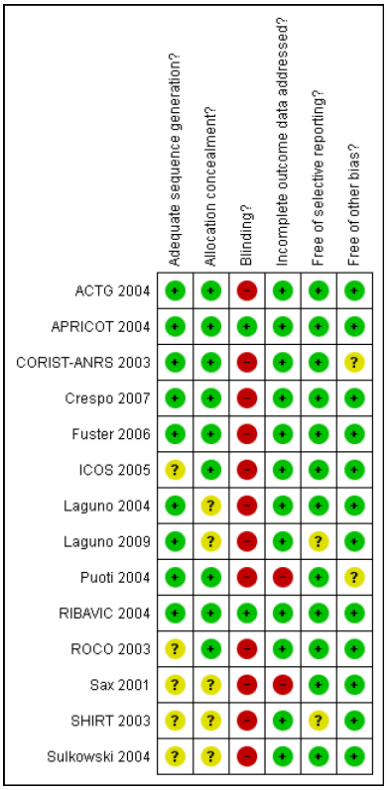
95% CI 0.33 to 3.05).

- No significant differences were seen in occurrence of flu-like symptoms (RR 2.40, 95% CI 0.35 to 16.58) or depression (RR 0.76, 95% CI 0.57 to 1.03).

Other secondary outcome measures

- No data were available for any of the remaining outcomes.

Critical appraisal



4. Anmerkungen/Fazit der Autoren

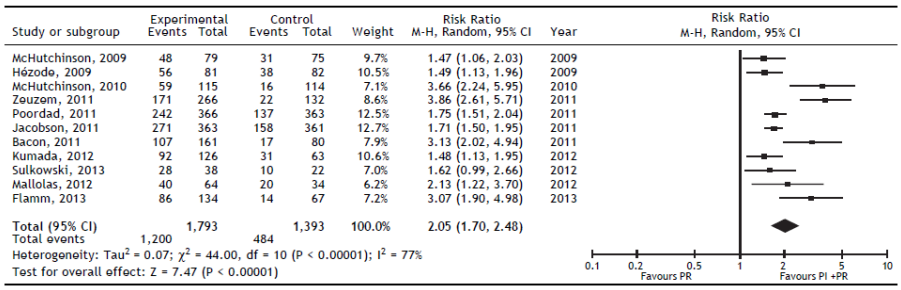
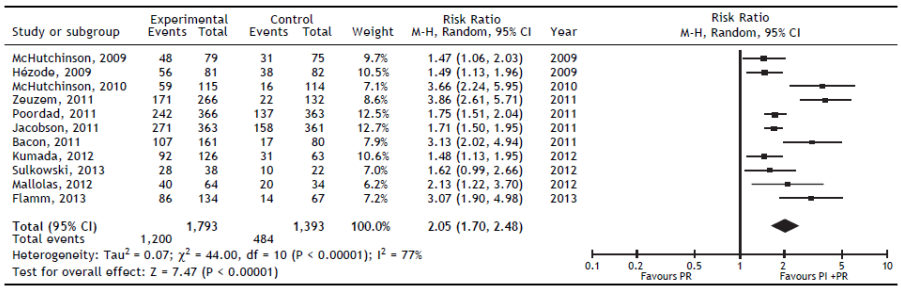
Peginterferon plus ribavirin may be considered a treatment for patients with chronic hepatitis C and stable HIV who have not received treatment for hepatitis C as the intervention may clear the blood of HCV RNA. Supporting evidence comes mainly from the analysis of this non-validated surrogate outcome assessed in comparisons against other antiviral treatments. There is no evidence on treatment of patients who have relapsed or did not respond to previous therapy. Careful monitoring of adverse events is warranted.

5. Hinweise durch FB Med

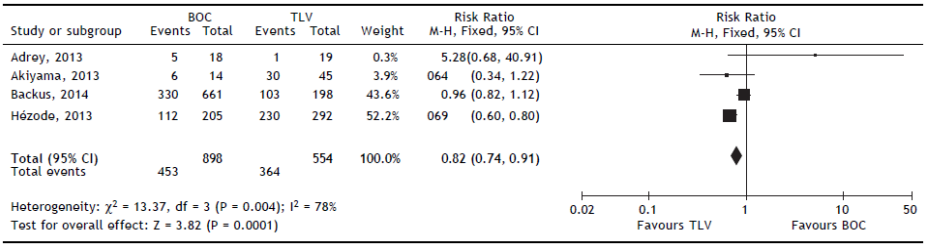
Subgruppenanalysen für die anhaltende virologische Ansprechrate der Patienten mit Genotyp 1 und 4 Patienten wurden durchgeführt.
The mean proportion of patients with hepatitis C genotype 1 ranged from 44% to 78%.
The proportion of patients with cirrhosis ranged from 7% to 45%.

Systematische Reviews

Genotyp 1

Manzano-Robleda MC et al., 2015 [54]. 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 *Endpunkt* 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 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

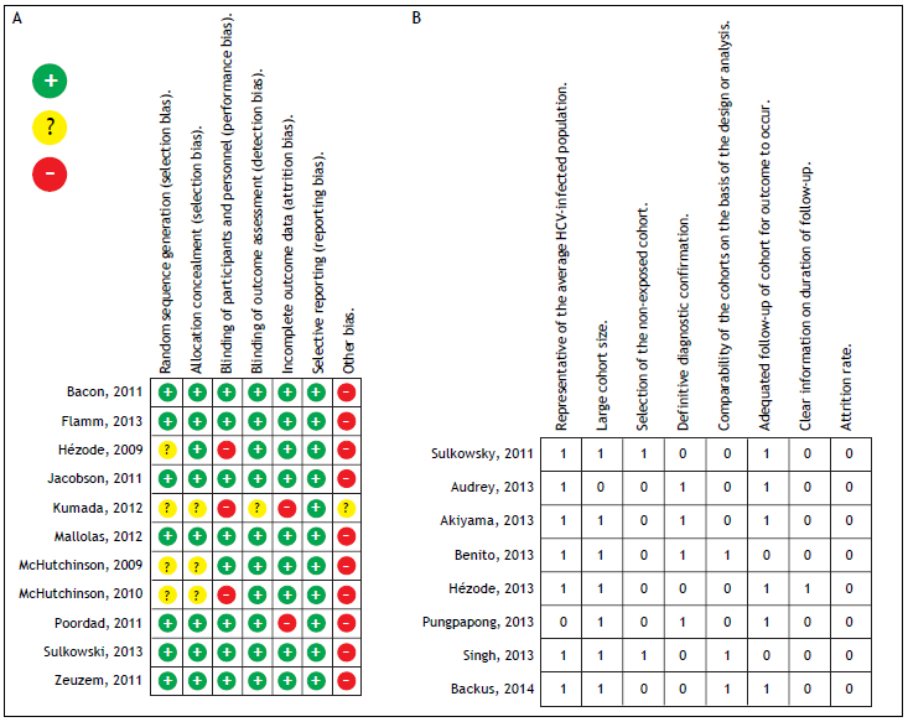


Safety analysis of protease inhibitor plus pegylated interferon plus ribavirin vs. pegylated interferon plus ribavirin in all patients, naie patients, and pre-treated patients

	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.

Critical appraisal

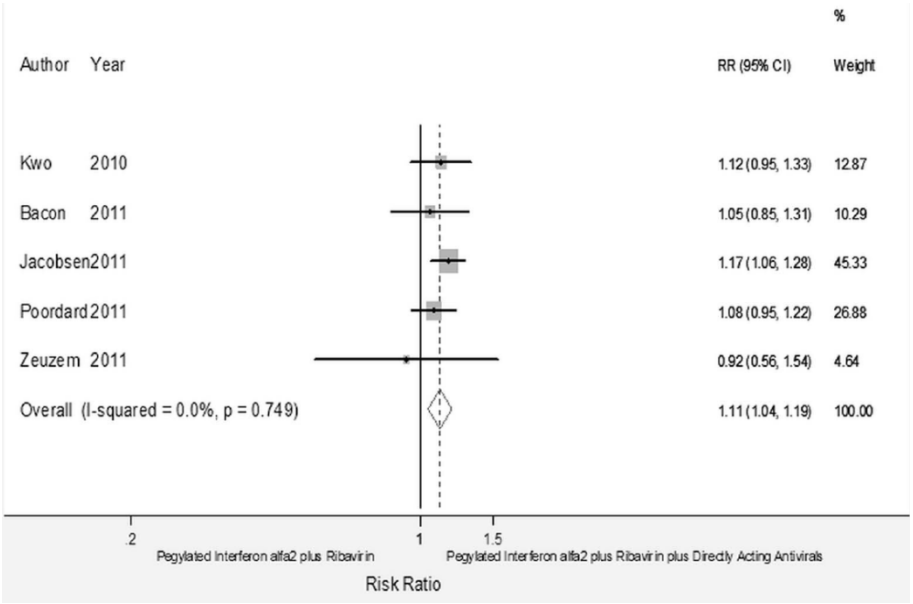


4. Anmerkungen/Fazit der Autoren

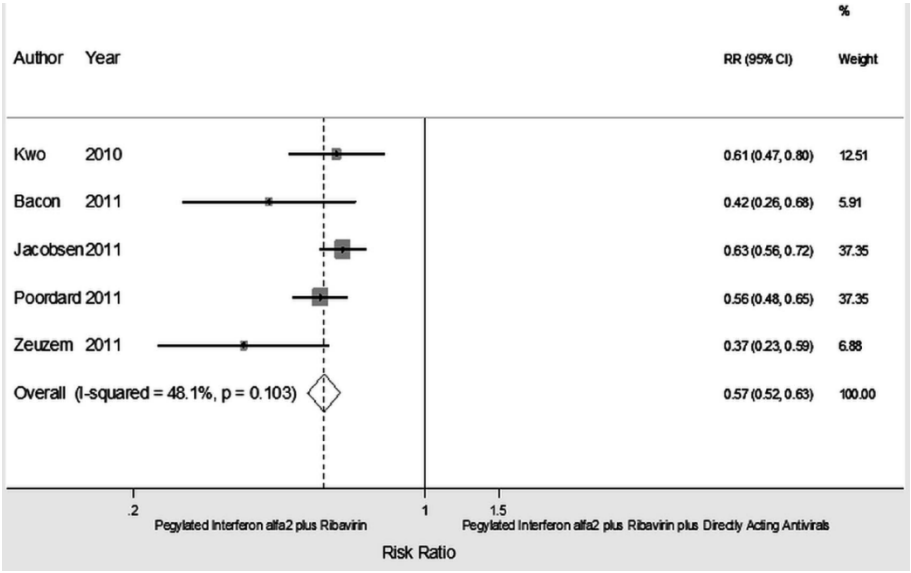
In conclusion SVR was higher in patients treated with PIs, patients previously exposed to PR showed superior response rates. Specific predictors will determine the best candidates for treatments that will offer real-life therapeutic alternatives.

Qu Y et al., 2015 [58]. Efficacy and safety of simeprevir for chronic hepatitis virus C genotype 1 infection: A meta-analysis	1. Fragestellung 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) *Endpunkt* 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.

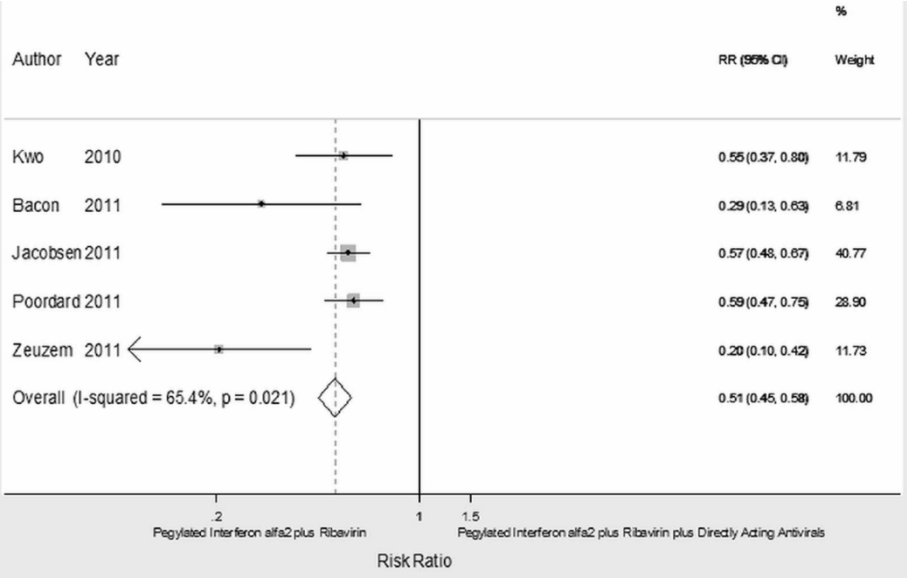
	Critical appraisal Studies | Method to generate the sequence of randomization | Randomization concealment | Blinding | Withdrawals and drop-outs Zeuzem, 2014 | Not clear | Not clear | Appropriate | Appropriate Manns, 2014 | Appropriate | Appropriate | Appropriate | Appropriate Jacobson, 2014 | Appropriate | 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 increase 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 [11]. 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) *Endpunkt* 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



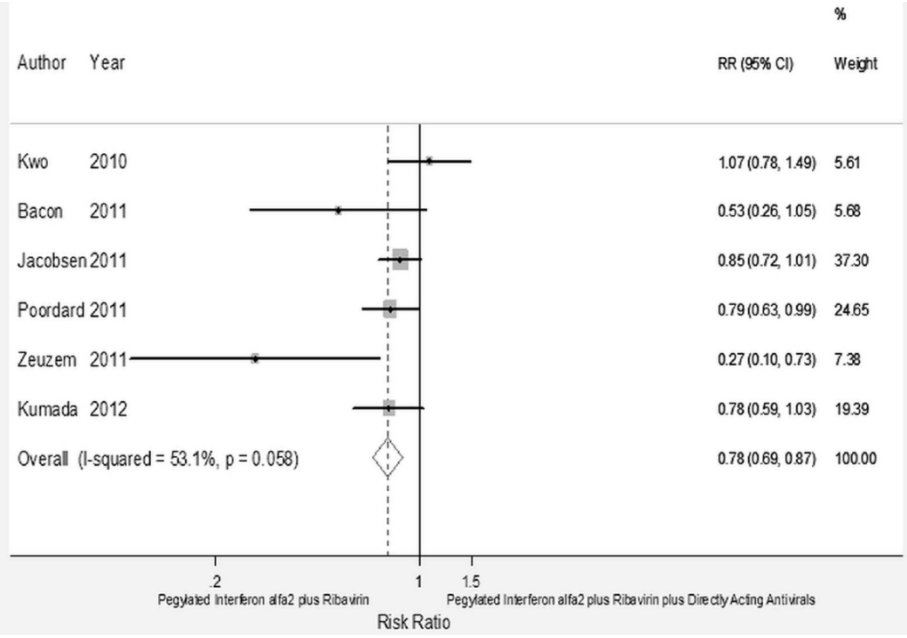
Achievement of SVR in CHC patients **without advanced liver fibrosis** treated with pegylated interferon a-2 plus ribavirin or pegylated interferon a-2 plus ribavirin plus a direct-acting antiviral



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



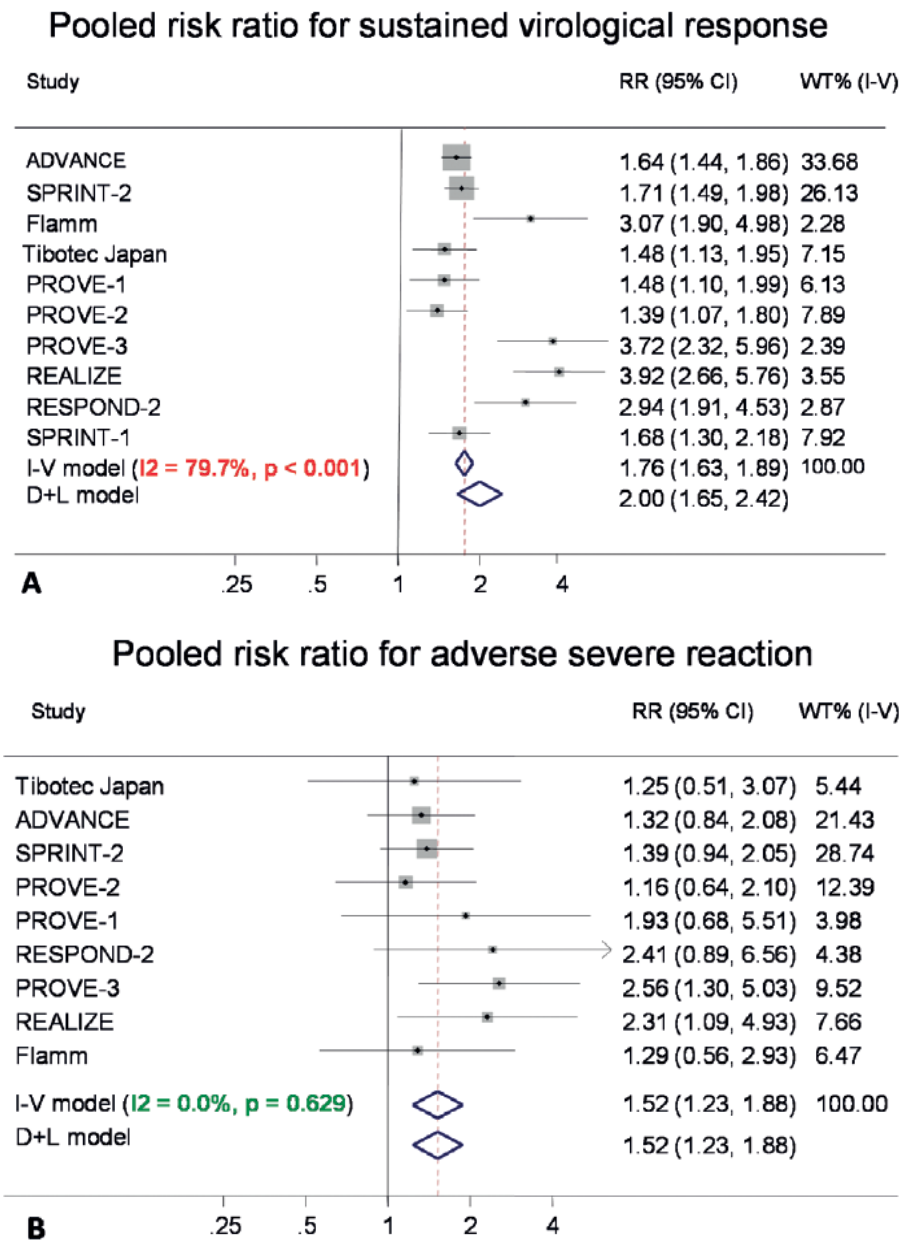
Critical appraisal

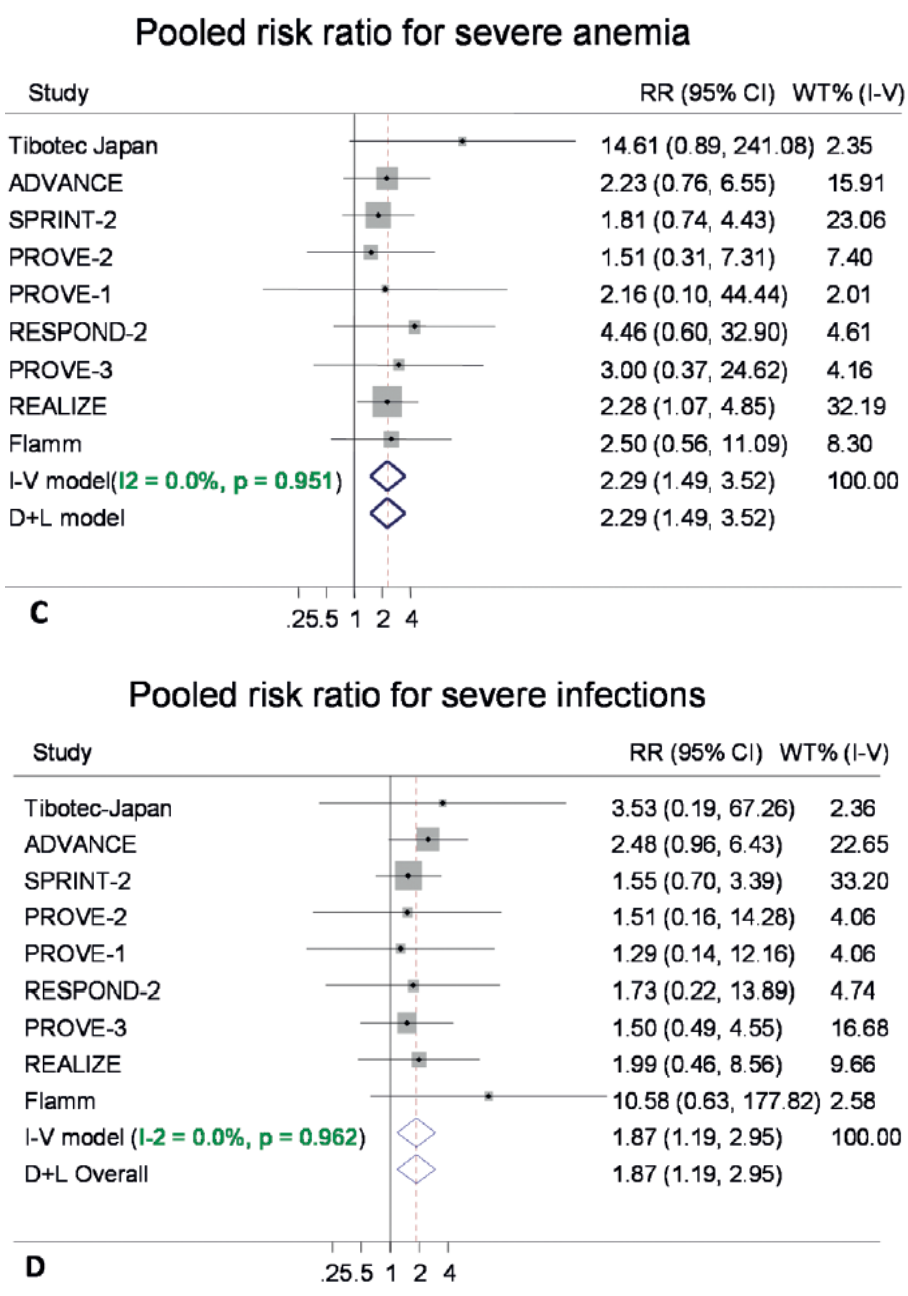
First Author [Reference No.]	Was the treatment randomly allocated?	Was the randomization procedure described and was it appropriate?	Was the trial described as double blind?	Was the method of blinding described and appropriate?	Was the number of withdrawals/ dropouts in each group mentioned?	Jadad Score, 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

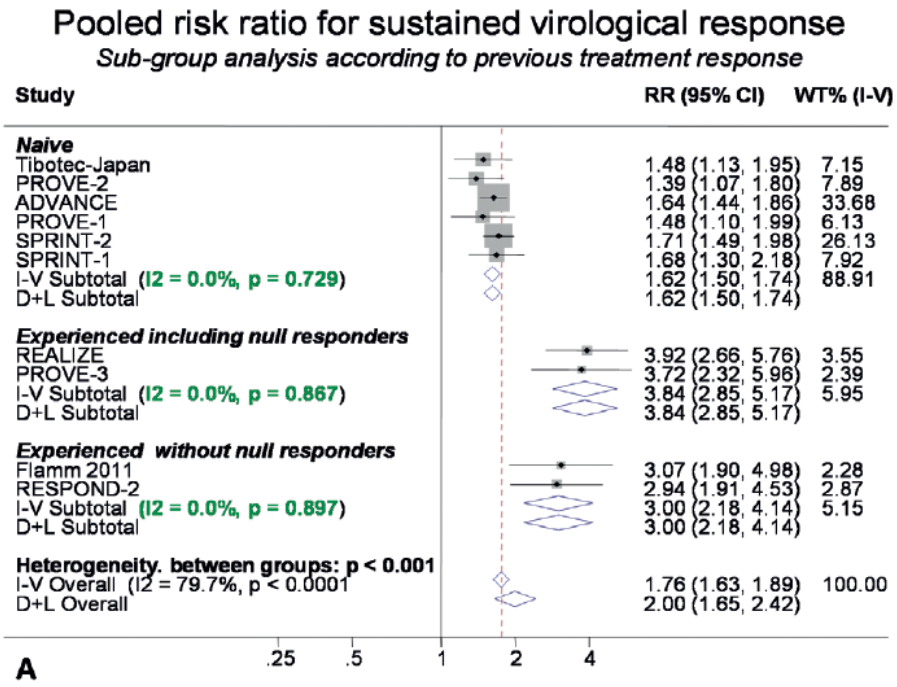
Triple therapy provides a significantly higher SVR rate than dual

	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 [53]. 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 *Endpunkt* 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 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.

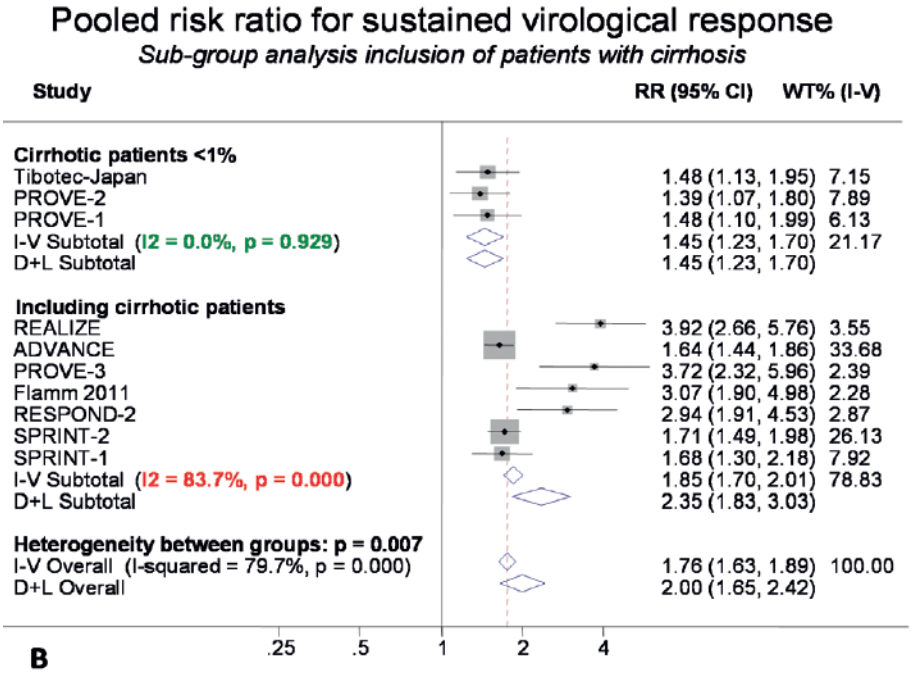

Pooled risk ratio for sustained virological response
Study
RR (95% CI)
WT% (I-V)
ADVANCE 1.64 (1.44, 1.86) 33.68
SPRINT-2 1.71 (1.49, 1.98) 26.13
Flamm 3.07 (1.90, 4.98) 2.28
Tibotec Japan 1.48 (1.13, 1.95) 7.15
PROVE-1 1.48 (1.10, 1.99) 6.13
PROVE-2 1.39 (1.07, 1.80) 7.89
PROVE-3 3.72 (2.32, 5.96) 2.39
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)
A
.25
.5
1
2
4
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)
B
.25
.5
1
2
4



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



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



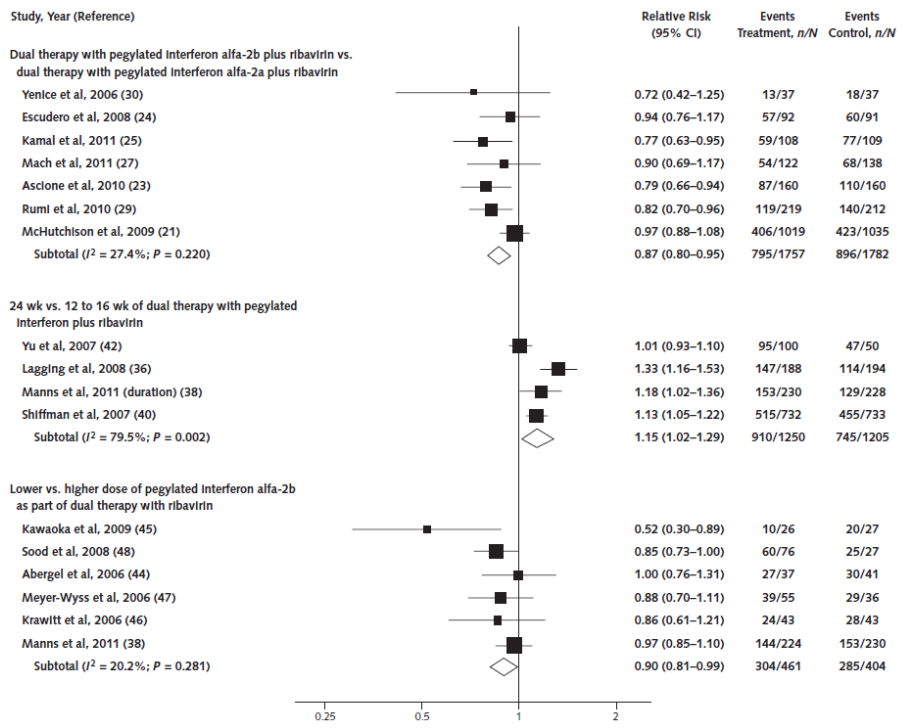
Critical appraisal

None of the studies are judged to be at low risk of bias.

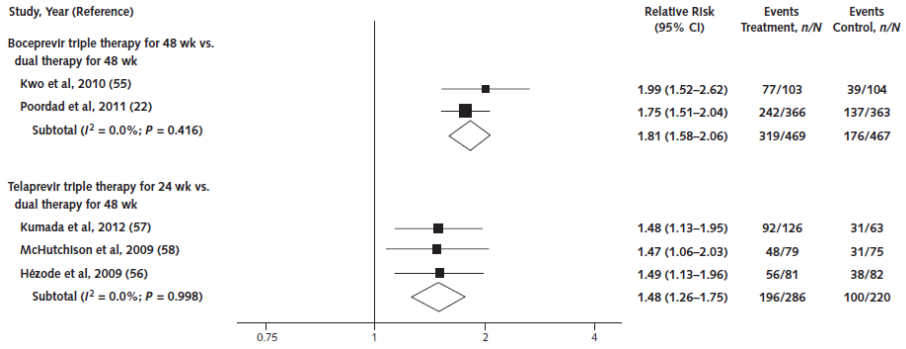
4. Anmerkungen/Fazit der Autoren

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 [10]. 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 *Endpunkt* 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

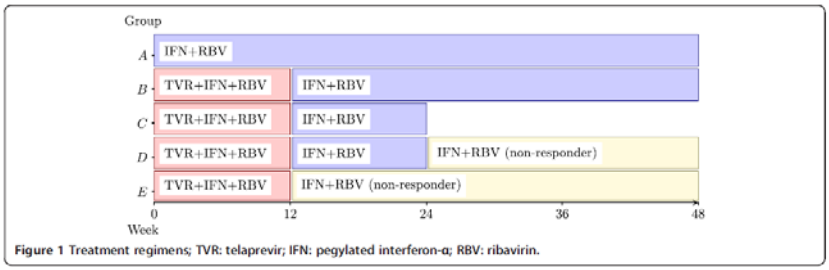


Sustained virologic response, triple therapy with a protease inhibitor versus dual therapy
Relative risks > 1 favor triple therapy

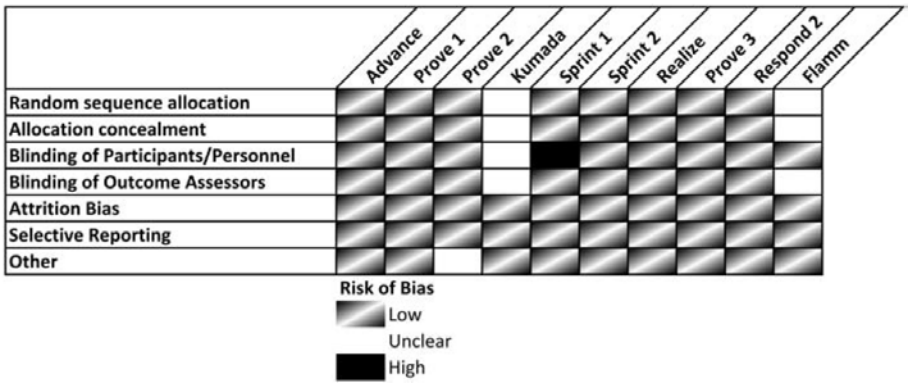


Harms of Triple Therapy With Boceprevir or Telaprevir With Pegylated Interferon, and Ribavirin Versus Dual Therapy With Pegylated Interferon α-2b Plus Ribavirin

	<table><tr><th>Therapy Harms</th><th>Relative Risk (95 CI); I², %</th><th colspan="2">Pooled Event Rates (95 CI), %</th><th>Risk Difference (95 CI), percentage points</th><th>Trials, n (References)</th></tr><tr><th></th><th></th><th>Intervention 1</th><th>Intervention 2</th><th></th><th></th></tr><tr><td>Dual therapy with pegylated interferon α-2b plus ribavirin versus dual therapy with pegylated interferon α-2a plus ribavirin*</td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Serious adverse events</td><td>0.76 (0.61 to 0.95); 0</td><td>4.7 (0 to 1.3)</td><td>6.3 (0 to 17)</td><td>−1.0 (−3.8 to 1.8)</td><td>2 (21, 29)</td></tr><tr><td>Withdrawal due to adverse events</td><td>1.1 (0.73 to 1.7); 42</td><td>7.7 (2.9 to 13)</td><td>6.6 (1.7 to 12)</td><td>0.8 (−2.0 to 3.6)</td><td>6 (21, 23, 25, 28–30)</td></tr><tr><td>Neutropenia</td><td>0.61 (0.46 to 0.83); 38</td><td>9.9 (4.5 to 15)</td><td>15 (7.4 to 22)</td><td>−3.0 (−6.1 to 0.0)</td><td>5 (21, 23, 24, 28, 29)</td></tr><tr><td>Anemia</td><td>0.97 (0.72 to 1.3); 64</td><td>26 (5.7 to 47)</td><td>24 (7.0 to 42)</td><td>0.9 (−3.9 to 5.7)</td><td>4 (21, 23, 28, 29)</td></tr><tr><td>Thrombocytopenia</td><td>0.87 (0.59 to 1.3); 0</td><td>8.8 (1.1 to 16)</td><td>10 (1.7 to 19)</td><td>−0.9 (−3.1 to 1.2)</td><td>3 (23, 28, 29)</td></tr><tr><td>Depression</td><td>1.1 (0.92 to 1.2); 0</td><td>12 (0 to 25)</td><td>12 (2.2 to 23)</td><td>0.6 (−1.9 to 3.1)</td><td>3 (21, 23, 28)</td></tr><tr><td>Fatigue</td><td>1.0 (0.96 to 1.1); 7</td><td>55 (40 to 69)</td><td>57 (48 to 66)</td><td>0.9 (−3.7 to 5.6)</td><td>3 (21, 23, 28)</td></tr><tr><td>Influenza-like symptoms</td><td>0.98 (0.85 to 1.1)</td><td>62 (56 to 68)</td><td>63 (57 to 70)</td><td>−1.1 (−10 to 8.0)</td><td>1 (29)</td></tr><tr><td>Headache</td><td>1.1 (1.1 to 1.2); 0</td><td>30 (7.2 to 53)</td><td>29 (10 to 47)</td><td>3.7 (−1.6 to 9.0)</td><td>3 (21, 23, 28)</td></tr><tr><td>Myalgia</td><td>1.1 (0.86 to 1.5); 33</td><td>18 (7.2 to 30)</td><td>18 (12 to 24)</td><td>1.9 (−3.8 to 7.5)</td><td>3 (21, 23, 28)</td></tr><tr><td>Rash</td><td>0.79 (0.71 to 0.88); 0</td><td>39 (5.4 to 72)</td><td>49 (7.5 to 90)</td><td>−7.6 (−14 to −1.2)</td><td>2 (21, 28)</td></tr><tr><td>Triple therapy with boceprevir versus dual therapy for 48 wk†</td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Serious adverse events</td><td>1.4 (0.93 to 2.2)</td><td>12 (8.9 to 16)</td><td>8.5 (5.7 to 11)</td><td>3.8 (−0.7 to 8.2)</td><td>1 (22)</td></tr><tr><td>Withdrawal due to adverse events</td><td>1.1 (0.77 to 1.4); 0</td><td>13 (5.3 to 20)</td><td>12 (4.1 to 20)</td><td>0.8 (−3.5 to 5.2)</td><td>2 (22, 55)</td></tr><tr><td>Neutropenia</td><td>1.8 (1.5 to 2.3); 0</td><td>33 (29 to 38)</td><td>18 (14 to 22)</td><td>15 (9.8 to 21)</td><td>2 (22, 55)</td></tr><tr><td>Anemia</td><td>2.0 (1.4 to 2.8); 0</td><td>25 (0 to 67)</td><td>12 (0 to 34)</td><td>12 (−18 to 41)</td><td>2 (22, 55)</td></tr><tr><td>Thrombocytopenia</td><td>3.2 (1.2 to 8.2); 0)</td><td>3.8 (2.1 to 5.6)</td><td>1.4 (0.2 to 2.6)</td><td>2.8 (0.8 to 4.8)</td><td>2 (22, 55)</td></tr><tr><td>Depression</td><td>0.87 (0.65 to 1.2)</td><td>19 (15 to 23)</td><td>22 (18 to 26)</td><td>−2.9 (−8.7 to 2.9)</td><td>1 (22)</td></tr><tr><td>Fatigue</td><td>1.1 (0.82 to 1.5); 83</td><td>64 (50 to 77)</td><td>59 (54 to 63)</td><td>5.9 (−12 to 2.4)</td><td>2 (22, 55)</td></tr><tr><td>Influenza-like symptoms</td><td>0.80 (0.58 to 1.1); 27</td><td>19 (11 to 27)</td><td>25 (21 to 29)</td><td>−4.7 (−10 to 1.0)</td><td>2 (22, 55)</td></tr><tr><td>Headache</td><td>1.1 (0.96 to 1.3); 0</td><td>48 (42 to 54)</td><td>42 (38 to 47)</td><td>4.7 (−1.6 to 11)</td><td>2 (22, 55)</td></tr><tr><td>Myalgia</td><td>0.97 (0.76 to 1.2)</td><td>25 (21 to 30)</td><td>26 (21 to 30)</td><td>−0.8 (−7.1 to 5.6)</td><td>1 (22)</td></tr><tr><td>Rash</td><td>1.1 (0.81 to 1.4)</td><td>24 (20 to 28)</td><td>23 (18 to 27)</td><td>1.2 (−5.0 to 7.3)</td><td>1 (22)</td></tr><tr><td>Dysgeusia</td><td>2.5 (2.0 to 3.2); 0</td><td>35 (20 to 50)</td><td>13 (4.6 to 22)</td><td>23 (17 to 29)</td><td>2 (22, 55)</td></tr><tr><td>Triple therapy with telaprevir for 24 weeks versus dual therapy for 48 wk†</td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Serious adverse events</td><td>1.0 (0.50 to 2.0)</td><td>16 (8.1 to 24)</td><td>16 (7.9 to 24)</td><td>0.2 (−11 to 11)</td><td>1 (56)</td></tr><tr><td>Withdrawal due to adverse events</td><td>1.1 (0.45 to 2.6); 60</td><td>15 (10 to 20)</td><td>14 (0 to 29)</td><td>1.0 (−11 to 13)</td><td>2 (56, 57)</td></tr><tr><td>Neutropenia</td><td>0.81 (0.51 to 1.3); 53</td><td>41 (0 to 94)</td><td>48 (0.4 to 96)</td><td>−7.7 (−17 to 1.5)</td><td>2 (57, 58)</td></tr><tr><td>Anemia</td><td>1.3 (1.1 to 1.5); 0</td><td>52 (6.4 to 97)</td><td>39 (6.5 to 71)</td><td>13 (5.8 to 21)</td><td>3 (56–58)</td></tr><tr><td>Thrombocytopenia</td><td>1.8 (1.2 to 2.5)</td><td>64 (56 to 73)</td><td>36 (25 to 48)</td><td>28 (13 to 42)</td><td>1 (57)</td></tr><tr><td>Depression</td><td>1.0 (0.66 to 1.6); 0</td><td>21 (14 to 27)</td><td>20 (14 to 26)</td><td>0.4 (−8.4 to 9.3)</td><td>2 (56, 58)</td></tr><tr><td>Fatigue</td><td>0.96 (0.74 to 1.2); 53</td><td>51 (26 to 76)</td><td>54 (29 to 78)</td><td>−2.5 (−15 to 9.8)</td><td>3 (56, 58)</td></tr><tr><td>Influenza-like symptoms</td><td>0.87(0.63 to 1.2); 50</td><td>35 (15 to 55)</td><td>40 (24 to 56)</td><td>−5.1 (−16 to 5.7)</td><td>3 (56–58)</td></tr><tr><td>Headache</td><td>0.83 (0.69 to 1.0); 0</td><td>42 (36 to 48)</td><td>52 (43 to 61)</td><td>−8.8 (−18 to −0.01)</td><td>3 (56–58)</td></tr><tr><td>Myalgia</td><td>0.76 (0.43 to 1.3); 57</td><td>18 (7.4 to 28)</td><td>23 (17 to 28)</td><td>−5.4 (−15 to 4.4)</td><td>3 (56, 58)</td></tr><tr><td>Rash</td><td>1.4 (1.1 to 1.7); 0</td><td>49 (36 to 61)</td><td>35 (28 to 42)</td><td>14 (5.0 to 22)</td><td>3 (56–58)</td></tr></table> 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 et al., 2013 [28]. 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

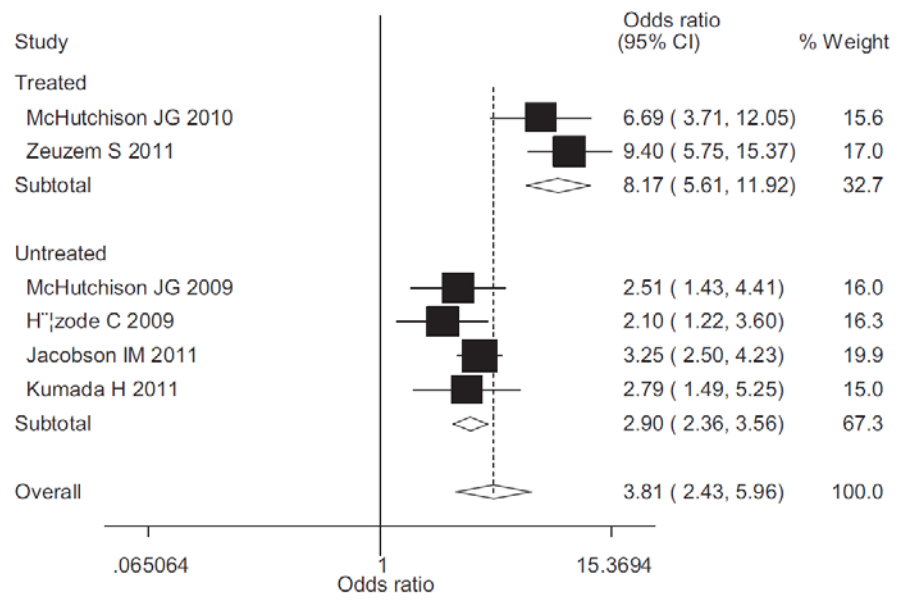
	restrictions from inception to 25 February 2013 in the following databases: Medline/PubMed and Web of Science. *Anzahl eingeschlossene Studien/Patienten (Gesamt):* 7 Studien (3505 Patienten) *Qualitätsbewertung der Studien:* Sequence generation, allocation concealment, blinding of participants and outcome, 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 [49]. The Relative Efficacy of Boceprevir and Telaprevir in the Treatment of Hepatitis C Virus Genotype 1	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** 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. *Endpunkt* 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 [63]. 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 [7].** Retreatment, Switching and Extended Therapy with Boceprevir and Telaprevir for Chronic Hepatitis C Infection: A Review of the Clinical	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 *Endpunkt* 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). *Suchzeitraum (Aktualität der Recherche)* MEDLINE, EMBASE, and Cochrane databases (January 1995 to October 2012) *Anzahl eingeschlossene Studien/Patienten (Gesamt):* 8 Studien (Patienten: k. A.)

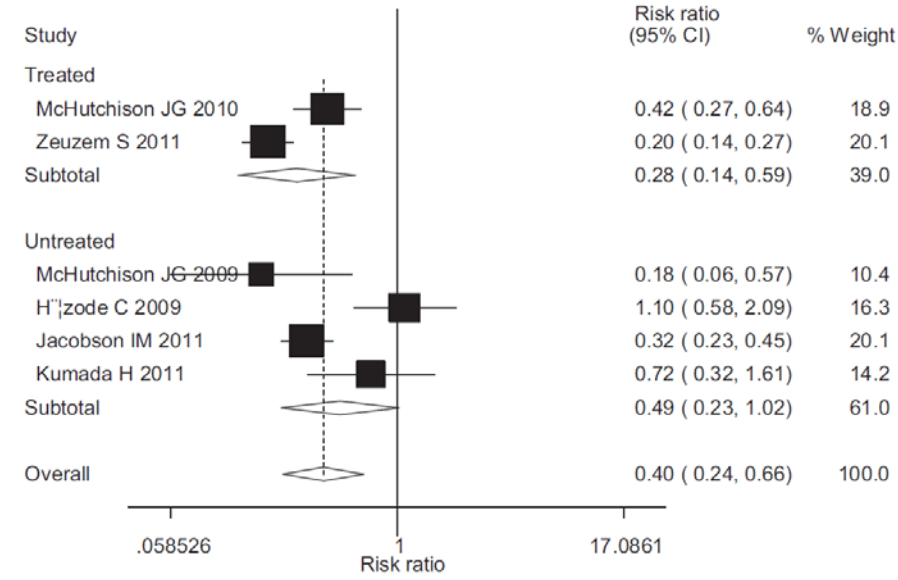
Effectiveness and Safety **Siehe auch:** **Park C et al., 2014 [56].** Efficacy and safety of telaprevir and boceprevir in patients with hepatitis C genotype 1: a meta-analysis	*Qualitätsbewertung der Studien:* Jadad scale
	3. Ergebnisdarstellung *Telaprevir* **Treatment-naïve** - SVR at 24 weeks was 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)

	Critical appraisal All of the included studies had a Jadad scale between 3 and 5.
	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 [65]. 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) *Endpunkt* 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 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)

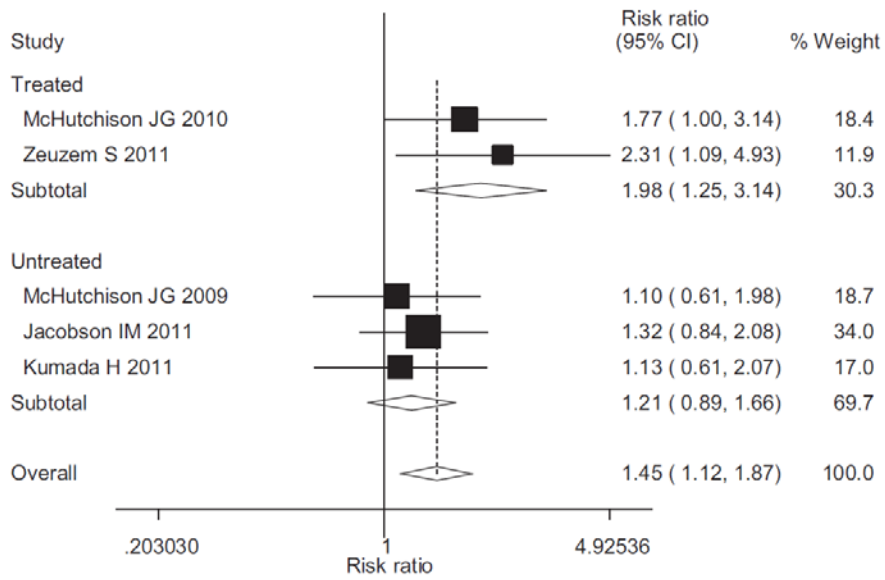


Meta-analysis of the relapse rate comparing the TPR group with the RP group

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

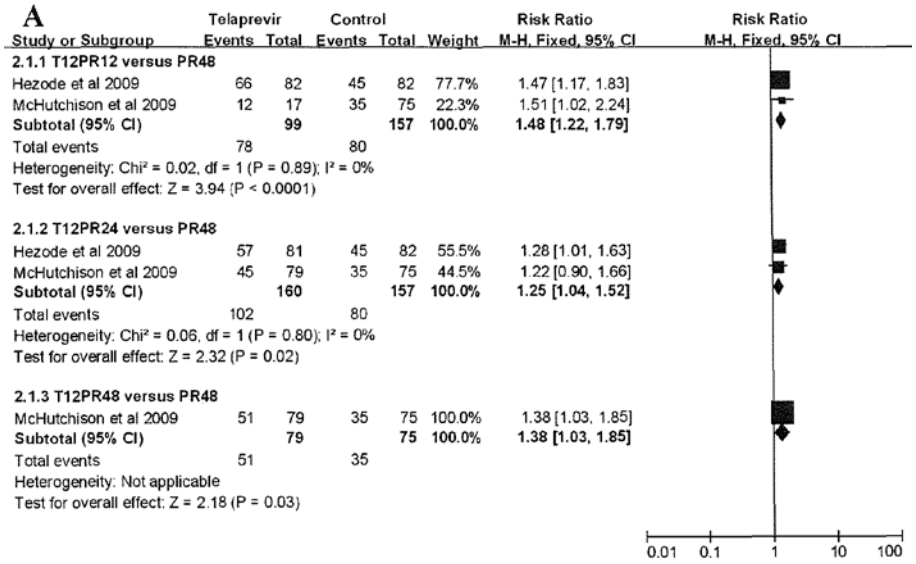
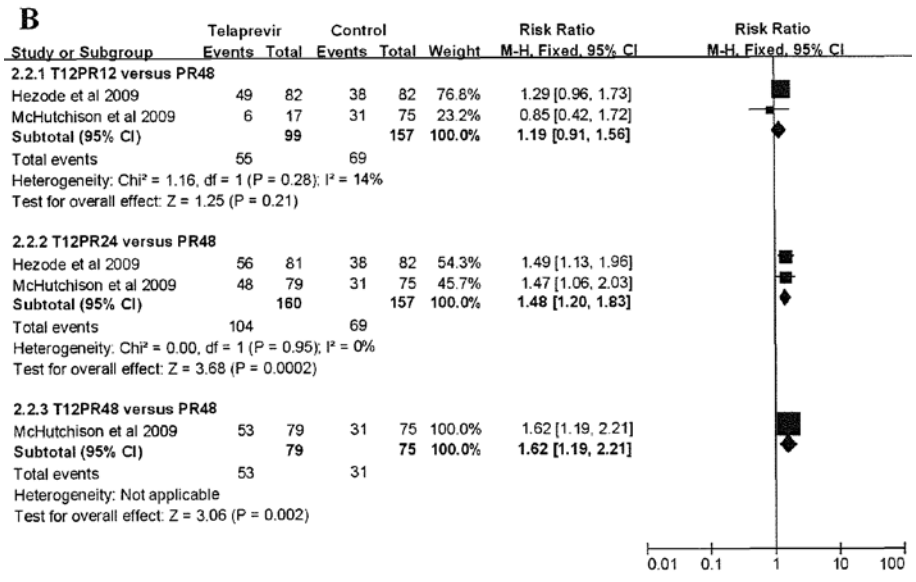


Meta-analysis of the rate of serious adverse events comparing the TPR group with the RP group (RRs are shown with 95% CIs, and an RR < 1 corresponds to an advantage towards the TPR group)

	 Critical appraisal All of the included studies had a Jadad scale of 5.
	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 [12]. 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 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. 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.
	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 [13]. 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 [14]. Telaprevir for Chronic Hepatitis C with Genotype 1: A Meta-Analysis **Siehe auch:** **Kong Y et al., 2012 [51].** 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** Telaprevir / Control / Risk Ratio / Risk Ratio Study or Subgroup — Events Total — Events Total Weight — M-H, Fixed, 95% CI — 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) 0.01 0.1 1 10 100 RCTs comparing the effect of regimens with telaprevir triple therapy on sustained response in **naïve patients** (B)  **B** Telaprevir / Control / Risk Ratio / Risk Ratio Study or Subgroup — Events Total — Events Total Weight — M-H, Fixed, 95% CI — M-H, Fixed, 95% CI **2.2.1 T12PR12 versus PR48** Hezode et al 2009 49 82 38 82 76.8% 1.29 [0.96, 1.73] McHutchison et al 2009 6 17 31 75 23.2% 0.85 [0.42, 1.72] **Subtotal (95% CI)** **99** **157** **100.0%** **1.19 [0.91, 1.56]** Total events 55 69 Heterogeneity: Chi² = 1.16, df = 1 (P = 0.28); I² = 14% Test for overall effect: Z = 1.25 (P = 0.21) **2.2.2 T12PR24 versus PR48** Hezode et al 2009 56 81 38 82 54.3% 1.49 [1.13, 1.96] McHutchison et al 2009 48 79 31 75 45.7% 1.47 [1.06, 2.03] **Subtotal (95% CI)** **160** **157** **100.0%** **1.48 [1.20, 1.83]** Total events 104 69 Heterogeneity: Chi² = 0.00, df = 1 (P = 0.95); I² = 0% Test for overall effect: Z = 3.68 (P = 0.0002) **2.2.3 T12PR48 versus PR48** McHutchison et al 2009 53 79 31 75 100.0% 1.62 [1.19, 2.21] **Subtotal (95% CI)** **79** **75** **100.0%** **1.62 [1.19, 2.21]** Total events 53 31 Heterogeneity: Not applicable Test for overall effect: Z = 3.06 (P = 0.002) 0.01 0.1 1 10 100

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 [29].

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

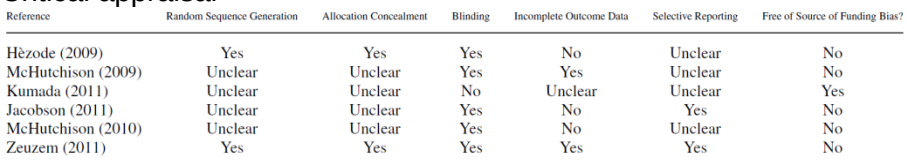
Anzahl eingeschlossene Studien/Patienten (Gesamt):

6 Studien (2775 Patienten)

Qualitätsbewertung der Studien:

Cochrane risk of bias tool

	3. Ergebnisdarstellung *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. Critical appraisal 

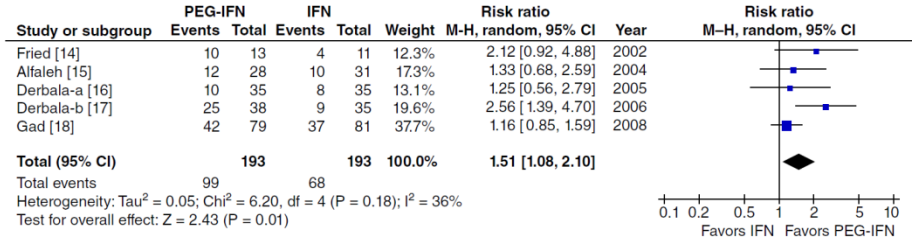
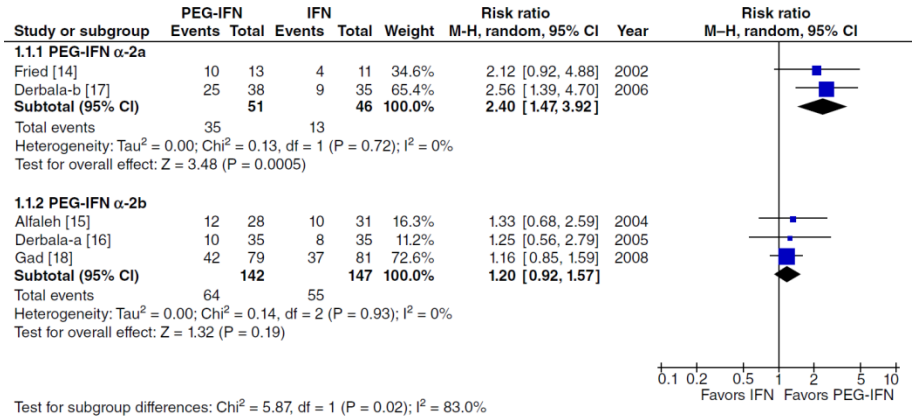
Reference	Random Sequence Generation	Allocation Concealment	Blinding	Incomplete Outcome Data	Selective Reporting	Free of Source of Funding Bias?
Hèzode (2009)	Yes	Yes	Yes	No	Unclear	No
McHutchison (2009)	Unclear	Unclear	Yes	Yes	Unclear	No
Kumada (2011)	Unclear	Unclear	No	Unclear	Unclear	Yes
Jacobson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

	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.
Singal AG et al., 2010 [62]. Meta-analysis: re-treatment of genotype I hepatitis C non-responders and relapsers after failing interferon and ribavirin combination therapy	1. Fragestellung To quantify sustained virological response (SVR) rates with different re-treatment regimens through meta-analysis of randomized controlled trials (RCTs).
	2. Methodik *Population* Study patients were **genotype I** HCV patients who **failed to achieve SVR with combination therapy** (note: studies were still included if a minority of study patients were nongenotype I) *Intervention / Komparator* Comparison of two-drug regimens using currently available

	treatments *Endpunkt* SVR rates *Suchzeitraum (Aktualität der Recherche)* OVID MEDLINE (from 1997 to September 2008), EMBASE (from 1997 to 2008) *Anzahl eingeschlossene Studien/Patienten (Gesamt):* 10 Volltexte und 8 Abstracts (Patienten: k. A.) *Qualitätsbewertung der Studien:* Jadad scale
	3. Ergebnisdarstellung Re-treatment of **nonresponders** to standard interferon and ribavirin therapy - Re-treatment with higher doses of PEG-IFN is more likely to produce SVR than combination therapy regimens with conventional doses of PEG-IFN: RR = 1.49; 95% CI: 1.09–2.04 (Q = 1.24, P = 0.98, I2 = 0.0%) Re-treatment of **relapsers** to combination therapy - In meta-analysis, SVR rates were increased with higher dose PEG-IFN combination therapy or prolonged (72 weeks) treatment with CIFN-based combination therapy: RR 1.57; 95% CI: 1.16–2.14 (Q = 1.19, P = 0.76, I^2 = 0.0%) Critical appraisal On quality assessment, the majority of the full manuscripts (7/11) were adequately randomized, but not double-blinded. The other four full manuscripts were randomized, but did not describe the method of randomization in detail and received Jadad scores of 2. The seven abstracts were possibly of similar quality, but only received Jadad scores of 1 given insufficient detail regarding randomization and withdrawals.
	4. Anmerkungen/Fazit der Autoren In genotype I HCV treatment failure patients who received combination therapy, re-treatment with high-dose PEG-IFN combination therapy is superior to re-treatment with standard combination therapy, although SVR rates are variable for nonresponders (£18%) and relapsers (43–69%). Re-treatment may be appropriate for select patients, especially relapsers and individuals with bridging fibrosis or compensated cirrhosis.

Genotyp 4

Aljumah AA et al., 2013 [2]. Pegylated versus standard interferon	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.

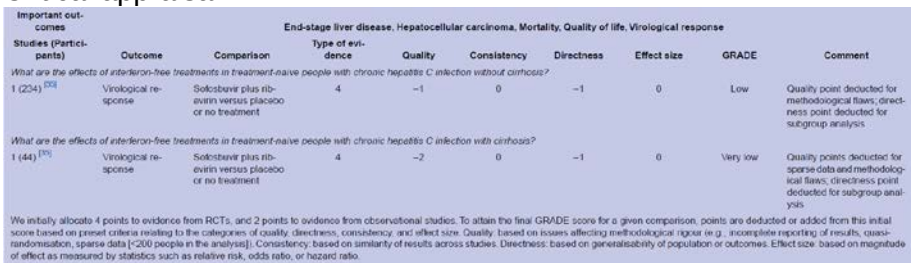
plus ribavirin in chronic hepatitis C genotype 4: A systematic review and meta-analysis	2. Methodik *Population* **Treatment-naïve HCV-G4** patients *Intervention / Komparator* PEG IFN plus RBV versus IFN plus RBV *Endpunkt* The outcome of interest is SVR *Suchzeitraum (Aktualität der Recherche)* The 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 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)  Critical appraisal

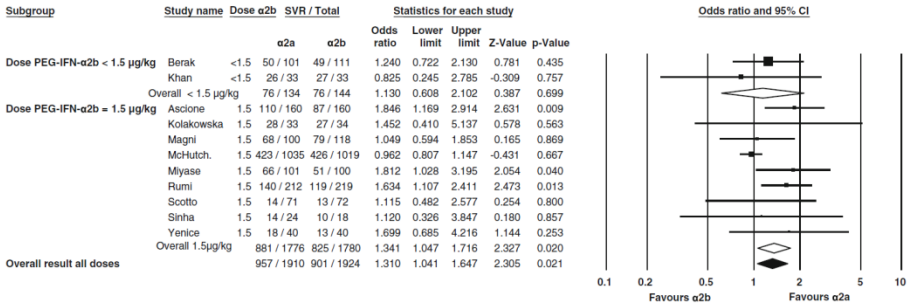
Study name	Sequence generation (randomization)	Allocation concealment	Blinding of participants, personnel and outcomes	Incomplete outcome data (attrition and exclusions)	Selective outcome reporting
Fried *et al.*[14]	Low risk	Low risk	Low risk	low risk	Low risk
Alfaleh *et al.*[15]	Low risk	Low risk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

	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. 5. Hinweise durch FB Med

Subgruppe Genotyp 1 oder 4 und/oder 2 oder 3

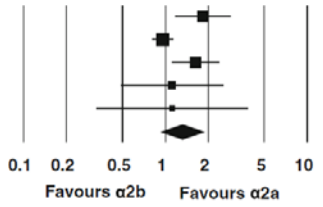
Yau AHL et al., 2015 [67]. Hepatitis C (chronic)	1. Fragestellung What are the effects of interferon-free treatments in treatment-naïve people with chronic hepatitis C infection without cirrhosis? What are the effects of interferon-free treatments in treatment-naïve people with chronic hepatitis C infection 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 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 o 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

	o Sofosbuvir plus ribavirin appears to be safe and well tolerated, with an adverse event profile consistent with ribavirin alone. o 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** o 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 o 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. o Sofosbuvir plus ribavirin appears to be safe and well tolerated, with an adverse event profile consistent with ribavirin alone. o 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) Critical appraisal 
	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].	1. Fragestellung Our objective was to determine which PEG-IFN (α2a or α2b), in

Pegylated Interferon-α2a and Ribavirin versus Pegylated Interferon-α2b and Ribavirin in Chronic Hepatitis C	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 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

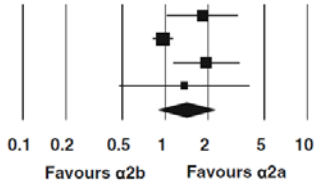
All genotypes

Study name	SVR / Total α2a	SVR / Total α2b	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Ascione	110 / 160	87 / 160	1.846	1.169	2.914	2.631	0.009
McHutch.	423 / 1035	426 / 1019	0.962	0.807	1.147	-0.431	0.667
Rumi	140 / 212	119 / 219	1.634	1.107	2.411	2.473	0.013
Scotto	14 / 71	13 / 72	1.115	0.482	2.577	0.254	0.800
Sinha	14 / 24	10 / 18	1.120	0.326	3.847	0.180	0.857
	701 / 1502	655 / 1488	1.310	0.924	1.857	1.517	0.129



Genotypes 1 and 4

Study name	SVR / Total α2a	SVR / Total α2b	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Ascione	51 / 93	37 / 93	1.838	1.027	3.290	2.048	0.041
McHutch.	423 / 1035	426 / 1019	0.962	0.807	1.147	-0.431	0.667
Rumi	52 / 109	36 / 113	1.951	1.131	3.368	2.401	0.016
Scotto	9 / 57	7 / 58	1.366	0.472	3.957	0.575	0.565
	535 / 1294	506 / 1283	1.408	0.892	2.224	1.468	0.142



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).

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

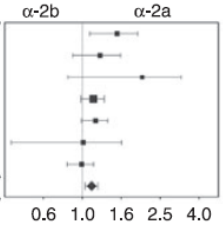
4. Anmerkungen/Fazit der Autoren

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

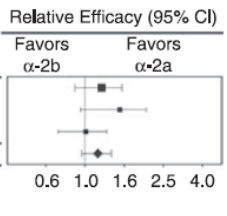
Forest Graph of cEVR results. All HCV genotypes

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				



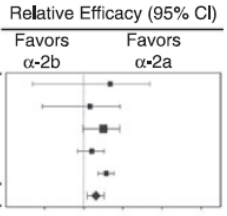
Forest Graph of cEVR results. HCV genotypes 1 and 4

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				



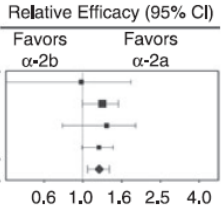
Forest Graph of RVR results. All HCV genotypes

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				



Critical appraisal

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

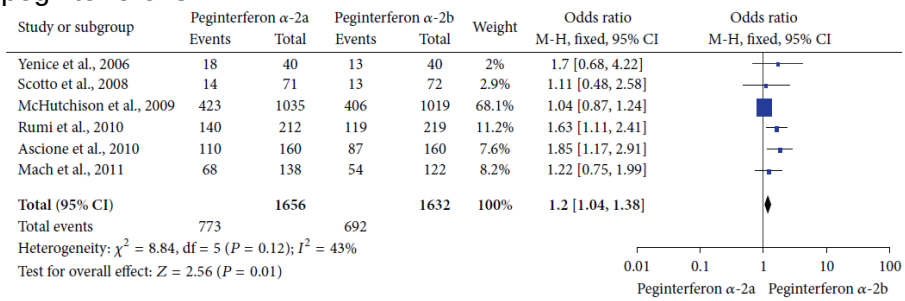
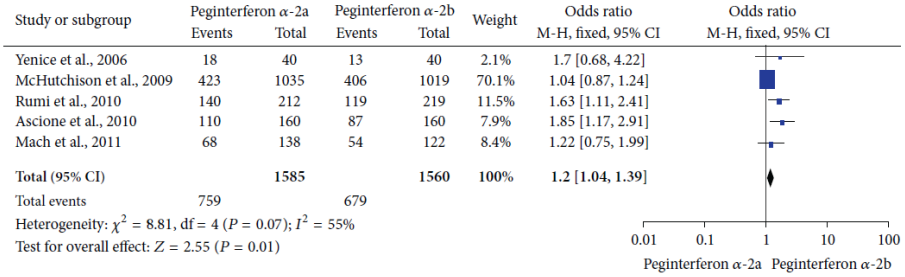
* Studies that report cEVR and EVR of all genotypes and also 1 and 4 independently.

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

Maximum value, 5 points, indicates highest quality.

4. Anmerkungen/Fazit der Autoren

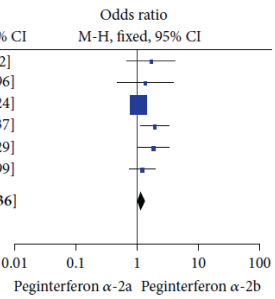
Peginterferon α-2a may be associated with a higher cEVR and RVR than peginterferon α-2b. These findings could help to achieve higher SVR rates and support clinical decision-making in the present scenario

	of triple combination therapy.
Yang Z et al., 2013 [66]. 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 The overall SVR rate of CHC patients treated with the two types of peginterferons  The SVR rate of **naïve** CHC patients  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: $Z = 2.12$ ($P = 0.03$)

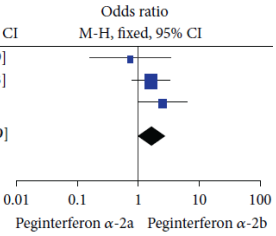


The SVR rate of CHC patients with HCV **genotype 2 or 3**

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: $Z = 2.01$ ($P = 0.04$)

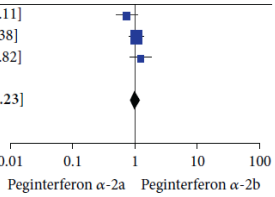


RVR rate comparison

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: $Z = 0.11$ ($P = 0.91$)

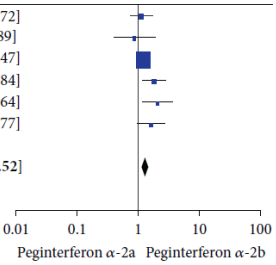


EVR rate comparison

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	125	189	121	191	11.7%	1.13 [0.74, 1.72]
Scotto et al., 2008	16	71	18	72	4%	0.87 [0.4, 1.89]
McHutchison et al., 2009	466	1035	407	1019	64.6%	1.23 [1.03, 1.47]
Rumi et al., 2010	170	212	151	219	8.4%	1.82 [1.17, 2.84]
Ascione et al., 2010	136	160	117	160	5%	2.08 [1.19, 3.64]
Mach et al., 2011	99	138	74	122	6.4%	1.65 [0.98, 2.77]
Total (95% CI)		**1805**		**1783**	**100%**	**1.32 [1.15, 1.52]**
Total events	1012		888			

Heterogeneity: $\chi^2 = 7.54$, df = 5 ($P = 0.18$); $I^2 = 34\%$

Test for overall effect: $Z = 3.98$ ($P < 0.0001$)

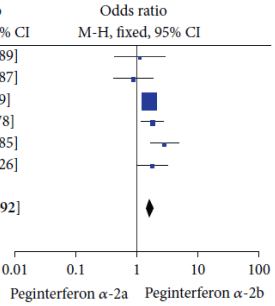


ETR rate comparison

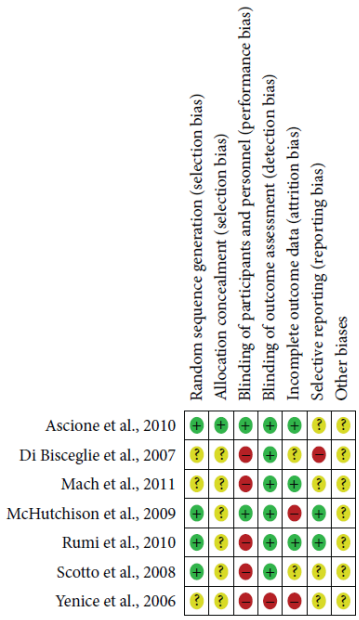
Study or subgroup	Peginterferon α-2a Events	Peginterferon α-2a Total	Peginterferon α-2b Events	Peginterferon α-2b Total	Weight	Odds ratio M-H, fixed, 95% CI
Yenice et al., 2006	28	40	27	40	2.9%	1.12 [0.44, 2.89]
Scotto et al., 2008	17	71	19	72	5.1%	0.88 [0.41, 1.87]
McHutchison et al., 2009	667	1035	542	1019	69%	1.6 [1.34, 1.9]
Rumi et al., 2010	166	212	146	219	11.1%	1.8 [1.17, 2.78]
Ascione et al., 2010	134	160	103	160	6%	2.85 [1.68, 4.85]
Mach et al., 2011	113	138	87	122	5.9%	1.82 [1.01, 3.26]
Total (95% CI)		**1656**		**1632**	**100%**	**1.66 [1.43, 1.92]**
Total events	1125		924			

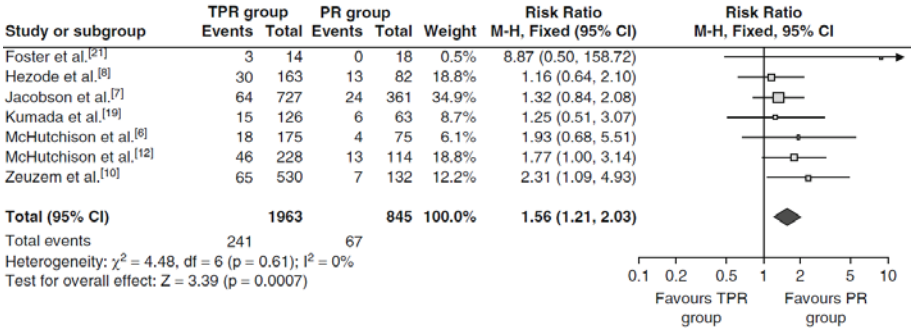
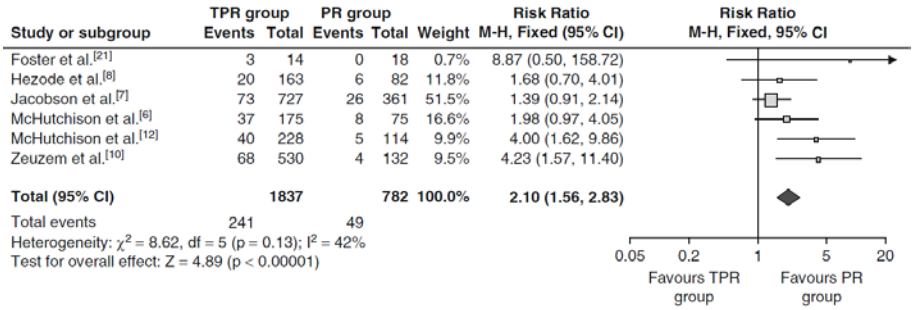
Heterogeneity: $\chi^2 = 7.81$, df = 5 ($P = 0.17$); $I^2 = 36\%$

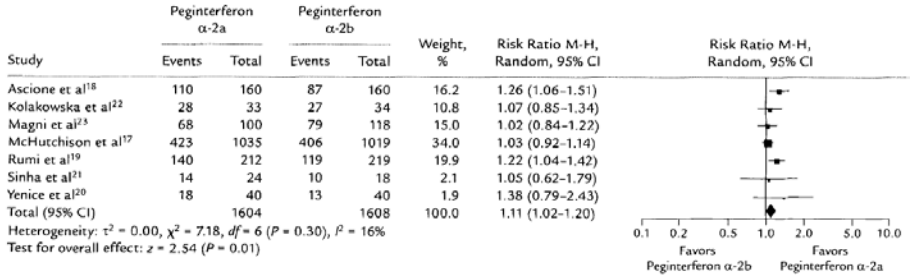
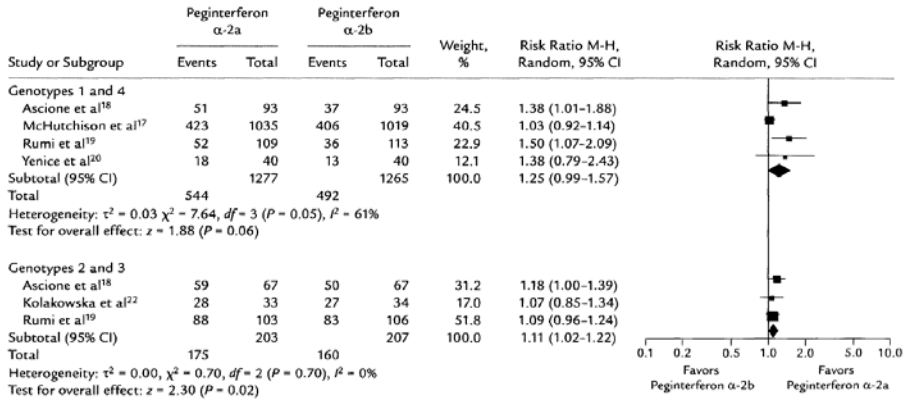
Test for overall effect: $Z = 6.78$ ($P < 0.00001$)



Critical appraisal

	
	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 [57]. 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)

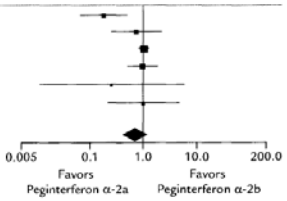
	Qualitätsbewertung der Studien: Jadad scale
	3. Ergebnisdarstellung Meta-analysis of serious adverse events in the TPR group compared with the PR group CI = confidence interval; df = degrees of freedom; I^2 = percentage of the total variation across studies due to heterogeneity; M-H = Mantel-Haenszel; peginterferon = pegylated interferon; PR= peginterferon plus ribavirin; TPR = combination telaprevir with peginterferon plus ribavirin; Z = test of overall treatment effect  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  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.
	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.
Zhao S et al., 2010 [68]. A Comparison of Peginterferon α-2a and α-2b for Treatment-Naïve Patients With Chronic Hepatitis C	1. Fragestellung The aim of this study was to perform a meta-analysis of randomized controlled trials (RCTs) comparing peginterferon α-2a and α-2b (in combination with ribavirin) treatments for chronic HCV.
	2. Methodik *Population*

Virus: A Meta-Analysis of Randomized Trials	**Treatment-naive** patients with chronic HCV *Intervention / Komparator* Peginterferon α-2a (180 µg/wk) and Peginterferon α-2b (1.5 µg/kg/wk) *Endpunkt* The primary outcome was the SVR, and the other measures included liver-related morbidity, all-cause mortality, and adverse events leading to treatment discontinuation. *Suchzeitraum (Aktualität der Recherche)* The Cochrane Central Registerof Controlled Trials, MEDLINE, Science Citation Index, and EMBASE were searched (1966 - April 2010) *Anzahl eingeschlossene Studien/Patienten (Gesamt):* 7 Studien (3212 Patienten) *Qualitätsbewertung der Studien:* adequate sequence generation, allocation concealment, blinding, incomplete outcome data addressed, and early stopping for benefit
	3. Ergebnisdarstellung Forest plot illustrating sustained virologic response in patients with chronic hepatitis C virus receiving peginterferon α-2a plus ribavirin or peginterferon α-2b plus ribavirin. M-H = Mantel-Haenszel Quality of the evidence (GRADE): high  Forest plot illustrating subgroup analysis of the hepatitis C virus (HCV) genotypes (**genotypes 1 and 4** or **2 and 3**) in patients with chronic HCV receiving peginterferon α-2a plus ribavirin or peginterferon α-2b plus ribavirin. M-H = Mantel-Haenszel  Forest plot illustrating discontinuation for adverse events in patients with chronic hepatitis C virus receiving peginterferon α-2a plus ribavirin or peginterferon α-2b plus ribavirin. M-H = Mantel-Haenszel

Quality of the evidence (GRADE): low

Study	Peginterferon α-2a Events	Peginterferon α-2a Total	Peginterferon α-2b Events	Peginterferon α-2b Total	Weight, %	Risk Ratio M-H, Random, 95% CI
Ascione et al[18]	4	160	22	160	15.3	0.18 (0.06–0.52)
Magni et al[23]	5	100	8	118	14.6	0.74 (0.25–2.18)
McHutchison et al[17]	135	1035	129	1019	34.6	1.03 (0.82–1.29)
Rumi et al[19]	16	212	17	219	23.7	0.97 (0.50–1.87)
Sinha et al[21]	0	24	1	18	2.7	0.25 (0.01–5.88)
Yenice et al[20]	3	40	3	40	9.1	1.00 (0.21–4.66)
Total (95% CI)		1571		1574	100.0	0.71 (0.42–1.22)
Total events	163		180			

Heterogeneity: $\tau^2 = 0.20$, $\chi^2 = 11.23$, $df = 5$ ($P = 0.050$), $I^2 = 55\%$
Test for overall effect: $z = 1.24$ ($P = 0.21$)



Critical appraisal

Parameter	Ascione et al[18]	Kolakowska et al[22]	Magni et al[23]	McHutchison et al[17]	Rumi et al[19]	Sinha et al[21]	Yenice et al[20]
Adequate sequence generation?	Adequate	Not reported	Not reported	Adequate	Adequate	Adequate	Not reported
Allocation concealment?	Adequate	Not reported	Not reported	Adequate	Adequate	Adequate	Not reported
Blinding?	Adequate	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Incomplete outcome data addressed?	Adequate	Not reported	Not reported	Adequate	Adequate	Adequate	Not reported
Stopping early to benefit results	Inadequate	Inadequate	Inadequate	Inadequate	Inadequate	Inadequate	Inadequate

4. Anmerkungen/Fazit der Autoren

The evidence reviewed in this meta-analysis suggests that peginterferon α-2a treatment was associated with a higher SVR rate than peginterferon α-2b treatment in patients with chronic HCV also treated with ribavirin. However, the available evidence on adverse events was insufficient to make recommendations.

HIV/HCV-Koinfektion

Hartwell D et al. 2011 [30]. Peginterferon alfa and ribavirin for chronic hepatitis C in patients eligible for shortened treatment, re-treatment or in HCV/HIV co-infection: a systematic review and economic evaluation.	1. Fragestellung To assess the clinical effectiveness and cost-effectiveness of peginterferon alfa and ribavirin for the treatment of chronic hepatitis C virus (HCV) in three specific patient subgroups affected by recent licence changes: those eligible for shortened treatment courses [i.e. those with low viral load (LVL) and who attained a rapid virological response (RVR) at 4 weeks of treatment], those eligible for re-treatment following previous nonresponse or relapse, and those co-infected with human immunodeficiency virus (HIV).
	2. Methodik *Population* Patienten vom **Genotyp 1, 2 und 3**. Patienten mit einer **HIV/HCV-Koinfektion**. *Intervention* - Combination therapy comprising ribavirin and either peginterferon alfa-2a or peginterferon alfa-2b. - Peginterferon alfa-2a or peginterferon alfa-2b monotherapy (for patients who are unable to tolerate or are contraindicated to ribavirin) Komparator

	- BSC (e.g. symptomatic treatment, monitoring, treatment without any form of interferon therapy) - standard-duration courses of peginterferon alfa and ribavirin combination therapy (up to 24 or 48 weeks, as appropriate) *Endpunkt* sustained virological response (SVR), relapse rate and adverse events *Suchzeitraum (Aktualität der Recherche)* Search up to October 2009; Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL), Centre for Reviews and Dissemination (CRD) (University of York) databases: Database of Abstracts of Reviews of Effects (DARE), NHS Economic Evaluation Database (NHS EED) and the HTA database. MEDLINE (Ovid), EMBASE (Ovid), PREMEDLINE In-Process & Other Non-Indexed Citations (Ovid), Web of Science with Conference Proceedings: Science Citation Index Expanded (SCIE) and Conference Proceedings Citation Index – Science (CPCI) (ISI Web of Knowledge). Biosis Previews (ISI Web of Knowledge), National Institute for Health Research (NIHR), Clinical Research Network Portfolio, ClinicalTrials.gov, Current Controlled Trials. *Anzahl eingeschlossene Studien/Patienten (Gesamt):* 4 Studien (Patienten: k. A.) *Qualitätsbewertung der Studien:* CRD criteria for assessment of risk of bias in RCTs
	3. Ergebnisdarstellung - All six included RCTs were in patients who were eligible for shortened treatment duration. - No RCTs comparing peginterferon alfa with or without ribavirin with BSC were identified for the HCV/HIV co-infection or re-treatment patient groups. - In the subgroup of patients who achieved an RVR and had LVL at baseline, SVR rates were comparable (i.e. no statistically significant differences) between groups who received the standard duration of treatment and those who received shortened courses, for both **genotype 1** and **genotypes 2 and 3**. This implies that this patient group can receive shortened courses of peginterferon combination therapy without compromising SVR rates. - For both **genotype 1** and **genotype 2 and 3** patients, there were no statistically significant differences in rates of RVR between treatment groups who received the standard duration of treatment and those who received shortened courses. Rates of RVR in **genotype 2/3** patients were observed to be generally higher than in **genotype 1** patients. - Relapse rates in the subgroup of patients with LVL and RVR (one trial) were low and not significantly different between those treated for 24 versus 48 weeks. - Treatment for 24 weeks resulted in a significantly lower biochemical response rate (reduction of ALT to normal levels) and histological response rate than 48 weeks of treatment in one trial of **genotype 1** patients. Shortening the treatment duration had no

	effect on biochemical response in one trial of **genotype 2/3** patients. Rates of biochemical and histological response should be treated with caution, as the results relate only to those patients with available data and rates were not reported in the subgroup of patients with LVL and RVR. - Adverse events were presented for treatment groups as a whole and the reporting of statistical tests varied. However, the most frequently occurring adverse events were similar across all the trials and included flu-like symptoms, insomnia, anorexia, dermatological symptoms and alopecia. - There was a trend for a lower incidence of adverse events in patients who were treated for a shorter duration (three trials), although statistically they were comparable between treatment arms. The incidence of dose discontinuations was significantly lower in those receiving a shortened treatment regimen in one trial.
	4. Anmerkungen/Fazit der Autoren The clinical trial evidence indicates that patients may be successfully treated with a shorter course of peginterferon combination therapy without compromising the likelihood of achieving an SVR.

Therapiedauer

Hartwell D et al., 2012 [31]. Shortened peginterferon and ribavirin treatment for chronic hepatitis c	1. Fragestellung We assessed the clinical and cost-effectiveness of peginterferon alfa and ribavirin for the treatment of chronic HCV in patients eligible for shortened treatment to help inform UK policy recommendations
	2. Methodik *Population* Adults with chronic HCV who were eligible for shortened treatment (i.e., with baseline low viral load (LVL) and an rapid virological load (RVR) at week 4 of treatment) *Intervention / Komparator* Studies had to evaluate standard peginterferon alfa and ribavirin combination therapy (or monotherapy for those unable to tolerate ribavirin) compared with shortened duration courses of combination therapy (24 weeks for genotype 1; 16 weeks for genotype 2/3, as per the licenses). *Endpunkt* Outcomes included measures of virological response (RVR and SVR), relapse rate, and adverse events. *Suchzeitraum (Aktualität der Recherche)* A sensitive literature search was applied to fourteen electronic bibliographic databases (including TheCochrane Library, Medline and Embase) from 2000 to October 2009 *Anzahl eingeschlossene Studien/Patienten (Gesamt):* 6 Studien (Patienten: k. A.)

	Qualitätsbewertung der Studien: Cochrane risk of bias tool
	3. Ergebnisdarstellung Sustained Virological Response - In the sub-group of patients with LVL who attained an RVR, SVR rates were comparable between groups who received the standard duration of treatment (range, 83 percent to 100 percent) and shortened courses (range 84 percent to 96 percent), with no statistically significant differences between treatment arms. - In addition, SVRs were broadly similar regardless of genotype with the exception of one trial of **genotype 1 patients** where SVRs were noticeably lower for standard compared with shortened treatment (42 percent versus 57 percent, respectively) Rapid virological response - For both **genotype 1** and **genotype 2/3** patients, rates of RVR were observed to be similar between groups who received standard treatment (range, 26 percent to 63 percent) versus those who received shortened courses (range, 27 percent to 68 percent) (not statistically significant in two trials; not statistically tested in four trials). - There was a large range in reported RVR rates between the studies, but the proportion of patients achieving an RVR was generally higher in those with **genotype 2/3** than in those with **genotype 1** Relapse rate - In the one trial reporting virological relapse rates in the LVL/RVR sub-group, rates were low and not statistically significantly different between those treated for 24 versus 48 weeks (3.6 percent versus 0, respectively, difference 3.6 percent (95 percent confidence interval, -7.2 percent to 6.6 percent), p = 1.000). Adverse Events - The most frequently occurring adverse eventswere similar across all the trials and included flu-like symptoms, insomnia, anorexia, dermatological symptoms, and alopecia. On the whole, the frequency of adverse eventswere not statistically different between treatment arms (where reported), although there was a trend for a lower incidence of adverse events and fewer dose discontinuations in patients receiving a shortened treatment regimen. *Critical appraisal* Methodological reporting and quality varied between the included studies, although quality was judged to be good overall.
	4. Anmerkungen/Fazit der Autoren For chronic HCV patients who have LVL and achieve an RVR, shortened peginterferon and ribavirin combination therapy could be considered as a viable treatment option

Parikh M et al. 2011 [55].

Extended treatment duration for treatment naive chronic hepatitis C genotype 1 late viral responders: a meta-analysis comparing 48 weeks vs 72 weeks of pegylated interferon and ribavirin

Siehe auch:

Alavian SM et al., 2011 [1].

Optimal Duration of Treatment for HCV Genotype 1 Infection in Slow Responders: A Meta-Analysis

Sowie

Gevers TJG et al., 2011 [27].

Treatment extension benefits HCV genotype 1 patients without rapid virological response: a systematic review

sowie

Farnik H et al., 2010 [17].

Meta-analysis Shows Extended Therapy Improves Response of

1. Fragestellung

We undertook a systematic review of the literature and performed a metaanalysis to compare 72 weeks of treatment to the standard duration of 48 weeks in HCV genotype I patients with late viral response (LVR)

2. Methodik

Population

Genotype 1 HCV treatment naive patients achieving LVR

Intervention / Komparator

Treatment duration – comparing standard 48 weeks treatment and extended duration 72 weeks treatment with pegylated interferon and ribavirin

Endpunkt

End of treatment response (ETR), sustained virological response and relapse rates (RR)

Suchzeitraum (Aktualität der Recherche)

Medline, Cochrane Reviews, and EMBASE, ISI Web of science from 2004 to 2010

Anzahl eingeschlossene Studien/Patienten (Gesamt):

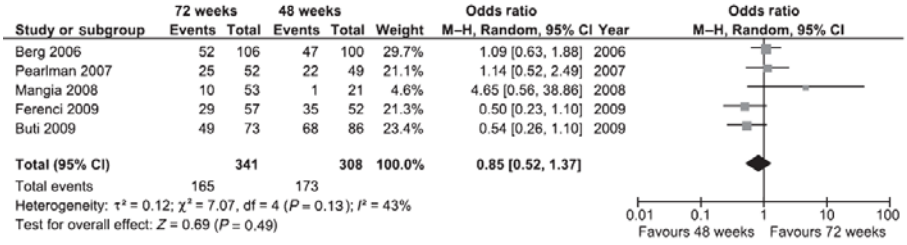
5 Studien (Patienten: k. A.)

Qualitätsbewertung der Studien:

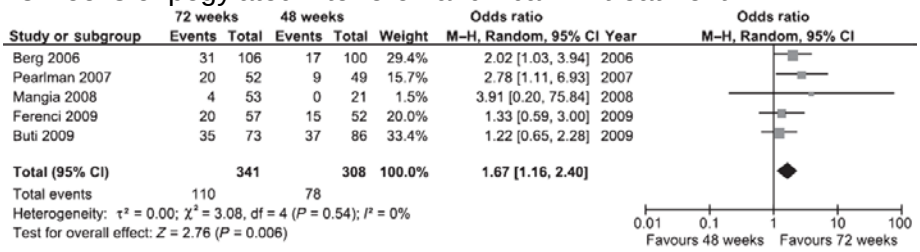
Jadad scale

3. Ergebnisdarstellung

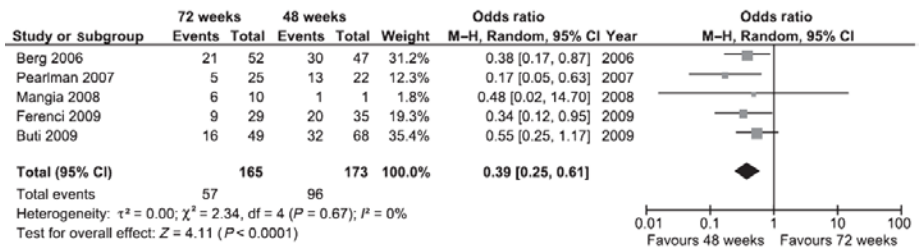
Forest plot for end of treatment response comparing 72 weeks vs 48 weeks of pegylated interferon and ribavirin treatment



Forest plot for sustained virological response comparing 72 weeks vs 48 weeks of pegylated interferon and ribavirin treatment



Forest plot for relapse rates comparing 72 weeks vs 48 weeks of pegylated interferon and ribavirin treatment

Patients With Chronic Hepatitis C Virus Genotype 1 Infection	 *Critical appraisal* Four studies scored 3 and one study scored 2 points on the Jadad scale
	4. Anmerkungen/Fazit der Autoren Therapy extension in genotype 1 late viral responders (LVR) may be a consideration to improve treatment response; however, the proportion of patients with LVR that might benefit from 72-week therapy appears to be small.

Leitlinien

Sarrazin C et al., 2015 [60]. **Deutsche Gesellschaft für Gastroenterologie:** Aktuelle 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	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

Diseases, 2014 [3].	data, information, and tools and treatments become available.
Recommendations for Testing, Managing, and Treating Hepatitis C **Siehe auch:** **Canadian Agency for Drugs and Technologies in Health, 2014 [9].** 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	Methodik Grundlage der Leitlinie – Panel members o 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 o 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
	Freitext/Empfehlungen/Hinweise ***Initial Treatment*** **Genotype 1a**

	Several options with similar efficacy in general are recommended for treatment-naïve patients with HCV genotype 1a infection: • Daily daclatasvir (60 mg*) and sofosbuvir (400 mg) for 12 weeks (no cirrhosis) or with or without weight-based RBV (1000 mg [<75 kg] to 1200 mg [>75 kg]) for 24 weeks (cirrhosis) is recommended for treatment-naive patients with HCV genotype 1a infection and without cirrhosis. Rating: Class I, Level B (no cirrhosis); Class IIa, Level B (cirrhosis) • Daily fixed-dose combination of ledipasvir (90 mg) /sofosbuvir (400 mg) for 12 weeks is recommended for treatment-naive patients with HCV genotype 1a infection. 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) and weight-based RBV for 12 weeks (no cirrhosis) or 24 weeks (cirrhosis) is recommended for treatment-naïve patients with HCV genotype 1a infection. Rating: Class I, Level A • Daily simeprevir (150 mg) and sofosbuvir (400 mg) for 12 weeks (no cirrhosis) or 24 weeks (cirrhosis without the Q80K polymorphism) with or without weight-based RBV is recommended for treatment-naive patients with HCV genotype 1a infection. 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 1b** Several options with similar efficacy in general are recommended for treatment-naïve patients with HCV genotype 1b infection: • Daily daclatasvir (60 mg*) and sofosbuvir (400 mg) for 12 weeks is recommended for treatment-naive patients with HCV genotype 1b infection who do not have cirrhosis. Rating: Class I, Level B • Daily daclatasvir (60 mg*) and sofosbuvir (400 mg) for 24 weeks with or without weight-based RBV is recommended for treatment-naive patients with HCV genotype 1b infection and cirrhosis. Rating: Class IIa, Level B • Daily fixed-dose combination of ledipasvir (90 mg) /sofosbuvir (400 mg) for 12 weeks is recommended for treatment-naive patients with HCV genotype 1b infection. 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 recommended for treatment-naive patients with HCV genotype 1b infection. Rating: Class I, Level A • Daily simeprevir (150 mg) plus sofosbuvir (400 mg) plus simeprevir (150 mg) for 12 weeks (no cirrhosis) or 24 weeks with or without weight-based RBV (cirrhosis) is recommended for treatment-naive patients with HCV genotype 1b infection.

Rating: Class I, Level A

*The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochromeP450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

The following regimens are NOT recommended for treatment-naive patients with HCV genotype 1:

- Daily sofosbuvir (400 mg) and weight-based RBV for 24 weeks.
  Rating: Class IIb, Level A
- PEG-IFN and RBV with or without sofosbuvir, simeprevir, telaprevir, or boceprevir for 12 weeks to 48 weeks.
  Rating: Class IIb, Level A
- Monotherapy with PEG-IFN, RBV, or a direct-acting antiviral.
  Rating: Class III, Level A

Genotype 2

Recommended regimen for treatment-naive patients with HCV genotype 2 infection:

- Daily daclatasvir (60 mg*) and sofosbuvir (400 mg) for 12 weeks is recommended for treatment-naive patients with HCV genotype 2 infection who cannot tolerate RBV.
  Rating: Class IIa, Level B
- Daily sofosbuvir (400 mg) and weight-based RBV for 12 weeks is recommended for treatment-naive patients with HCV genotype 2 infection.
  Rating: Class I, Level A
- Extending treatment to 16 weeks is recommended in patients with cirrhosis.
  Rating: Class IIb, Level C

The following regimens are NOT recommended for treatment-naive patients with HCV genotype 2:

- PEG-IFN and RBV for 24 weeks
  Rating: Class IIb, Level A
- Monotherapy with PEG-IFN, RBV, or a direct-acting antiviral
  Rating: Class III, Level A
- Telaprevir-, boceprevir-, or ledipasvir-containing regimens
  Rating: Class III, Level A

Genotype 3

Recommended regimens for treatment-naive patients with HCV genotype 3 infection:

- Daily daclatasvir (60 mg*) and sofosbuvir (400 mg) for 12 weeks is recommended for treatment-naive patients with HCV genotype 3 infection and without cirrhosis.
  Rating: Class I, Level A
- Daily daclatasvir (60 mg*) and sofosbuvir (400 mg) for 24 weeks with or without weight-based RBV is recommended for treatment-naive patients with HCV genotype 3 infection and cirrhosis.
  Rating: Class IIa, Level C
- Daily sofosbuvir (400 mg) and weight-based RBV plus weekly PEG-IFN for 12 weeks is recommended for IFN-eligible, treatment-naive patients with HCV genotype 3 infection.

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.

Alternative regimen for treatment-naive patients with HCV genotype 3 infection:

- Daily sofosbuvir (400 mg) and weight-based RBV for 24 weeks is an alternative regimen for treatment-naive patients with HCV genotype 3 infection who are IFN-ineligible.
  Rating: Class I, Level A

The following regimens are NOT recommended for treatment-naive patients with HCV genotype 3 infection:

- PEG-IFN and RBV for 24 weeks to 48 weeks
  Rating: Class IIb, Level A
- Monotherapy with PEG-IFN, RBV, or a direct-acting antiviral
  Rating: Class III, Level A
- Telaprevir-, boceprevir-, or simeprevir-based regimens should not be used for patients with genotype 3 HCV infection.
  Rating: Class III, Level A

Genotype 4

Three options with similar efficacy in general are recommended for treatment-naïve patients with HCV genotype 4 infection:

- Daily fixed-dose combination of ledipasvir (90 mg) /sofosbuvir (400 mg) for 12 weeks is recommended for treatment-naive patients with HCV genotype 4 infection.
  Rating: Class IIb, Level B
- Daily fixed-dose combination of paritaprevir (150 mg) /ritonavir (100 mg)/ombitasvir (25 mg) and weight-based RBV for 12 weeks is recommended for treatment-naïve patients with HCV genotype 4 infection.
  Rating: Class I, Level B
- Daily sofosbuvir (400 mg) and weight-based RBV for 24 weeks is recommended for treatment-naive patients with HCV genotype 4 infection.
  Rating: Class IIa, Level B

Alternative regimen for treatment-naive patients with HCV genotype 4 infection:

- Daily sofosbuvir (400 mg) and weight-based RBV plus weekly PEG-IFN for 12 weeks is an acceptable regimen for treatment-naive patients with HCV genotype 4 infection.
  Rating: Class II, Level B

The following regimens are NOT recommended for treatment-naive patients with HCV genotype 4 infection:

- PEG-IFN and RBV with or without simeprevir for 24 weeks to 48 weeks
  Rating: Class IIb, Level A
- Monotherapy with PEG-IFN, RBV, or a direct-acting antiviral
  Rating: Class III, Level A
- Telaprevir- or boceprevir-based regimens

	Rating: Class III, Level A **Genotype 5 or 6** Recommended regimen for treatment-naive patients with HCV genotype 5 or 6 infection: • Daily fixed-dose combination of ledipasvir (90 mg) /sofosbuvir (400 mg) for 12 weeks is recommended for treatment-naive patients with HCV genotype 5 or 6 infection. Rating: Class IIa, Level B Alternative regimen for treatment-naive patients with HCV genotype 5 or 6 infection: • Daily sofosbuvir (400 mg) and weight-based RBV plus weekly PEG-IFN for 12 weeks is an alternative regimen for treatment-naive patients with HCV genotype 5 or 6 infection. Rating: Class IIa, Level B The following regimens are NOT recommended for treatment-naive patients with HCV genotype 5 or 6 infection: • PEG-IFN and RBV with or without simeprevir for 24 weeks to 48 weeks Rating: Class IIb, Level A • Monotherapy with PEG-IFN, RBV, or a direct-acting antiviral Rating: Class III, Level A • Telaprevir- or boceprevir-based regimens Rating: Class III, Level A ***Retreatment*** **Genotype 1a** Several options with similar efficacy in general are recommended for patients with HCV genotype 1a infection who do not have cirrhosis, in whom prior PEG-IFN and RBV treatment has failed: • Daily daclatasvir (60 mg) plus sofosbuvir (400 mg) for 12 weeks is recommended for patients with HCV genotype 1a infection who do not have cirrhosis, in whom prior PEG-IFN and RBV treatment has failed. Rating: Class IIa, Level B • Daily fixed-dose combination of ledipasvir (90 mg) /sofosbuvir (400 mg) for 12 weeks is recommended for patients with HCV genotype 1a infection who do not have cirrhosis, in whom prior PEG-IFN and 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 (1000 mg [<75 kg] to 1200 mg [>75 kg]) for 12 weeks is recommended for patients with HCV genotype 1a infection who do not have cirrhosis, in whom prior PEG-IFN and RBV treatment has failed. Rating: Class I, Level A • Daily simeprevir (150 mg) plus sofosbuvir (400 mg) for 12 weeks is recommended for patients with HCV genotype 1a infection who do not have cirrhosis, in whom prior PEG-IFN and RBV treatment has failed.

	Rating: Class IIa, Level B **Genotype 1b** Several options with similar efficacy are recommended for patients with HCV genotype 1b infection who do not have cirrhosis, in whom prior PEG-IFN and RBV treatment has failed: • Daily daclatasvir (60 mg) plus sofosbuvir (400 mg) for 12 weeks is recommended for patients with HCV genotype 1b infection who do not have cirrhosis, in whom prior PEG-IFN and RBV treatment has failed. Rating: Class IIa, Level B • Daily fixed-dose combination of ledipasvir (90 mg) /sofosbuvir (400 mg) for 12 weeks is recommended for patients with HCV genotype 1b infection who do not have cirrhosis, in whom prior PEG-IFN and 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 recommended for patients with HCV genotype 1b infection who do not have cirrhosis, in whom prior PEG-IFN and RBV treatment has failed. Rating: Class I, Level A • Daily simeprevir (150 mg) plus sofosbuvir (400 mg) for 12 weeks is recommended for patients with HCV genotype 1b infection who do not have cirrhosis, in whom prior PEG-IFN and RBV treatment has failed. Rating: Class IIa, Level B **Genotype 1 (regardless of subtype)** Recommended regimens for patients with HCV genotype 1a or 1b infection who have compensated cirrhosis, in whom prior PEG-IFN and RBV treatment has failed: • Daily daclatasvir (60 mg) plus sofosbuvir (400 mg) for 24 weeks with or without weight-based RBV is recommended for patients with HCV genotype 1a or 1b infection who have compensated cirrhosis, in whom prior PEG-IFN and RBV treatment has failed. Rating: Class IIa, Level B • Daily fixed-dose combination of ledipasvir (90 mg) /sofosbuvir (400 mg) for 24 weeks is recommended for patients with HCV genotype 1a or 1b infection who have compensated cirrhosis, in whom prior PEG-IFN and 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 recommended for patients with HCV genotype 1a or 1b infection who have compensated cirrhosis, in whom prior PEG-IFN and RBV treatment has failed. Rating: Class I, Level B • 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 recommended for patients with HCV genotype 1a infection and for 12 weeks without RBV for patients with HCV genotype 1b infection who

	have compensated cirrhosis, in whom prior PEG-IFN and RBV treatment has failed. Rating: Class I, Level A • Daily simeprevir (150 mg) plus sofosbuvir (400 mg) with or without weight-based RBV for 24 weeks is recommended for patients with HCV genotype 1a infection who are negative for the Q80K variant by commercially available resistance assays and for patients with HCV genotype 1b infection, in whom prior PEG-IFN and RBV treatment has failed. 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 Recommended regimens for patients in whom a previous sofosbuvir plus RBV with or without PEG-IFN treatment has failed: No Cirrhosis: • Daily fixed-dose combination of ledipavir (90 mg)/sofosbuvir (400 mg) with weight-based RBV for 12 weeks is recommended for patients without cirrhosis, in whom a previous sofosbuvir plus RBV–containing regimen with or without PEG-IFN has failed. Rating: Class IIb, Level C Cirrhosis: • Daily fixed-dose combination of ledipasvir (90 mg) /sofosbuvir (400 mg) with weight-based RBV for 24 weeks is recommended for patients with cirrhosis, in whom a previous sofosbuvir-containing regimen has failed. Rating : Class IIa, Level C Recommended regimen for patients without cirrhosis who have HCV genotype 1 infection, regardless of subtype, in whom prior treatment with an HCV nonstructural protein 3 (NS3) protease inhibitor (telaprevir, boceprevir, or simeprevir) plus PEG-IFN and RBV or simeprevir plus sofosbuvir has failed (no prior NS5A treatment): • Daily daclatasvir (60 mg) plus sofosbuvir (400 mg) for 12 weeks is recommended 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 PEGIFN, and RBV has failed. Rating: Class I, Level A • Daily fixed-dose combination ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks is recommended for retreatment 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 and RBV has failed. Based on limited data, the addition of weight-based RBV to ledipasvir/sofosbuvir is recommended for patients without cirrhosis, in whom prior treatment with the HCV protease inhibitor simeprevir plus sofosbuvir has failed. Rating: Class I, Level A Three regimens with similar efficacy are recommended for patients with cirrhosis who have HCV genotype 1 infection, regardless of subtype, in whom prior treatment with an HCV nonstructural protein 3 (NS3) protease inhibitor (telaprevir, boceprevir, or simeprevir) plus PEG-IFN

	and RBV or simeprevir plus sofosbuvir has failed (no prior NS5A treatment): • Daily daclatasvir (60 mg) plus sofosbuvir (400 mg) for 24 weeks with or without weight-based RBV is recommended for patients with HCV genotype 1a or 1b infection with compensated cirrhosis, in whom prior treatment with an HCV protease inhibitor plus PEG-IFN and RBV has failed. Rating: Class IIa, Level B • Daily fixed-dose combination ledipasvir (90 mg)/sofosbuvir (400 mg) for 24 weeks is recommended for retreatment of patients with cirrhosis who have HCV genotype 1 infection, regardless of subtype, in whom a prior treatment with an HCV protease inhibitor plus PEG-IFN and RBV has failed. Based on limited data, the addition of weight-based RBV to ledipasvir/sofosbuvir is recommended for patients with cirrhosis, in whom prior treatment with the HCV protease inhibitor simeprevir plus sofosbuvir has failed. Rating: Class I, Level A • Daily fixed-dose combination ledipasvir (90 mg)/sofosbuvir (400 mg) plus weight-based RBV for 12 weeks is recommended for patients with cirrhosis who have HCV genotype 1 infection, regardless of subtype, in whom a prior treatment with an HCV protease inhibitor plus PEG-IFN and RBV has failed. Patients with cirrhosis who have HCV genotype 1 infection, in whom prior treatment with the HCV protease inhibitor simeprevir plus sofosbuvir has failed should not be treated with this 12-week regimen. Rating: Class IIa, Level B The following regimens are NOT recommended for patients with HCV genotype 1 infection in whom prior treatment that included an HCV protease inhibitor has failed: • Any regimen containing PEG-IFN, including o Simeprevir, PEG-IFN, and RBV o Sofosbuvir, PEG-IFN, and RBV o Telaprevir or boceprevir, PEG-IFN, and RBV o PEG-IFN and RBV alone Rating: Class IIb Level A • Monotherapy with PEG-IFN, RBV, or a direct-acting antiviral Rating: Class III, Level A • Any IFN-free regimen containing an HCV protease inhibitor o Simeprevir o Paritaprevir Rating: Class IIb, Level A Recommended regimen for patients in whom previous treatment with any HCV nonstructural protein 5A (NS5A) inhibitors has failed (including daclatasvir plus sofosbuvir, ledipasvir/sofosbuvir, or paritaprevir/ritonavir/ombitasvir plus dasabuvir): • For patients with minimal liver disease, deferral of treatment is recommended, pending availability of data. Rating: Class IIb, Level C • For patients with cirrhosis or other patients who require

	retreatment urgently, testing for resistance-associated variants that confer decreased susceptibility to NS3 protease inhibitors and to NS5A inhibitors is recommended. The specific drugs used in the retreatment regimen should be tailored to the results of this testing as described below. Treatment duration of 24 weeks is recommended and, unless contraindicated, weight-based RBV should be added. Rating: Class IIb, Level C **Genotype 2** Recommended regimen for patients with HCV genotype 2 infection in whom prior PEG-IFN and RBV treatment has failed: • Daily sofosbuvir (400 mg) and weight-based RBV for 16 weeks or 24 weeks is recommended for patients with HCV genotype 2 infection, in whom prior PEG-IFN and RBV treatment has failed. Rating: Class I, Level A Alternative regimen for patients with HCV genotype 2 infection who are eligible to receive IFN, and in whom prior PEG-IFN and RBV treatment has failed: • Retreatment with daily sofosbuvir (400 mg) and weight-based RBV plus weekly PEG-IFN for 12 weeks is an alternative for patients with HCV genotype 2 infection who are are eligible to receive PEG-IFN, in whom previous PEG-IFN and RBV treatment failed. Rating: Class IIa, Level B Recommended regimens for patients with HCV genotype 2 infection in whom prior sofosbuvir and RBV treatment has failed: • Daily daclatasvir (60 mg) plus sofosbuvir (400 mg) for 24 weeks with or without weight-based RBV is recommended for patients with HCV genotype 2 infection who are not eligible to receive IFN, in whom previous treatment with sofosbuvir and RBV has failed. Rating: Class IIa, Level C • Retreatment with daily sofosbuvir (400 mg) and weight-based RBV plus weekly PEG-IFN for 12 weeks is recommended for patients who have HCV genotype 2 infection, who are eligible to receive IFN, and in whom previous treatment with sofosbuvir and RBV has failed. Rating: Class IIa Level C The following regimens are NOT recommended for patients with HCV genotype 2 infection in whom prior HCV therapy with PEG-IFN and RBV has failed: • PEG-IFN and RBV with or without telaprevir or boceprevir Rating: Class IIb, Level A • Ledipasvir/sofosbuvir Rating: Class III, Level A • Monotherapy with PEG-IFN, RBV, or a direct-acting antiviral Rating: Class III, Level A **Genotype 3**

	Recommended regimens for patients with HCV genotype 3 infection without cirrhosis, in whom prior treatment with PEG-IFN and RBV has failed: • Daily daclatasvir (60 mg) and sofosbuvir (400 mg) for 12 weeks is recommended for patients with HCV genotype 3 infection without cirrhosis, in whom prior treatment with PEG-IFN and RBV has failed. Rating: Class I, Level A • Daily sofosbuvir (400 mg) and weight-based RBV plus weekly PEG-IFN for 12 weeks is recommended for IFN-eligible patients with HCV genotype 3 infection, in whom prior treatment with PEG-IFN and RBV has failed. Rating: Class I Level A Recommended regimens for patients with HCV genotype 3 infection with cirrhosis, in whom prior treatment with PEG-IFN and RBV has failed: • Daily daclatasvir (60 mg) and sofosbuvir (400 mg) for 24 weeks with weight based RBV is recommended for patients with cirrhosis and HCV genotype 3 infection, in whom prior treatment with PEG-IFN 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 recommended for patients with HCV genotype 3 infection, in whom prior treatment with PEG-IFN and RBV has failed and who are IFN eligible. Rating: Class I, Level A Recommended regimens for patients with HCV genotype 3 infection, in whom prior treatment with sofosbuvir and RBV has failed: • Daily daclatasvir (60 mg) and sofosbuvir (400 mg) for 24 weeks with weight-based RBV is recommended for IFN-ineligible patients with HCV genotype 3 infection, in whom prior treatment with sofosbuvir and RBV has failed. Rating: Class IIa Level C • Daily sofosbuvir (400 mg) and weight-based RBV plus weekly PEG-IFN for 12 weeks is recommended for IFN-eligible patients with HCV genotype 3 infection, in whom prior treatment with sofosbuvir and RBV has failed. Rating: Class IIa Level C The following regimens are NOT recommended for patients with HCV genotype 3 infection, in whom prior treatment with PEG-IFN and RBV has failed: • PEG-IFN and RBV for 24 weeks to 48 weeks Rating: Class IIb, Level A • Monotherapy with PEG-IFN, RBV, or a direct-acting antiviral Rating: Class III, Level A • Telaprevir-, boceprevir-, or simeprevir-based regimens. Rating: Class III, Level A **Genotype 4** Several options with similar efficacy in general are recommended for

	patients with HCV genotype 4 infection, in whom prior treatment with PEG-IFN and RBV has failed: • Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks is recommended for patients with HCV genotype 4 infection, in whom prior treatment with PEG-IFN and RBV treatment has failed. Rating: Class IIa, Level B • Daily fixed-dose combination of paritaprevir (150 mg) /ritonavir (100 mg)/ombitasvir (25 mg) (PrO) and weight-based RBV for 12 weeks is recommended for patients with HCV genotype 4 infection, in whom prior treatment with PEG-IFN and RBV has failed. Rating: Class IIa, Level B • Daily sofosbuvir (400 mg) for 12 weeks and daily weight-based RBV plus weekly PEG-IFN for 12 weeks is recommended for retreatment of IFN-eligible patients with HCV genotype 4 infection, in whom prior treatment with PEG-IFN and RBV has failed. Rating: Class IIa, Level B • Daily sofosbuvir (400 mg) and weight-based RBV for 24 weeks is recommended for retreatment of patients with HCV genotype 4 infection, in whom prior treatment with PEG-IFN and RBV has failed. Rating: Class IIa, Level B The following regimens are NOT recommended for patients with HCV genotype 4 infection, in whom prior treatment with PEG-IFN and RBV has failed: • PEG-IFN and RBV with or without telaprevir or boceprevir Rating: Class IIb, Level A • Monotherapy with PEG-IFN, RBV, or a direct-acting antiviral Rating: Class III, Level A **Genotype 5 and 6** Recommended regimen for patients with HCV genotype 5 or 6 infection, in whom prior treatment has failed: • Daily fixed-dose combination ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks is recommended for patients with HCV genotype 5 or 6 infection, in whom prior treatment with PEG-IFN and RBV has failed. Rating: Class IIa, Level C Alternative regimen for IFN-eligible patients with HCV genotype 5 or 6 infection, in whom prior treatment has failed: • Daily sofosbuvir (400 mg) and weight-based RBV plus weekly PEG-IFN for 12 weeks is an alternative regimen for IFN-eligible patients with HCV genotype 5 or 6 infection, in whom prior treatment has failed. Rating: Class IIa, Level C The following regimens are NOT recommended for patients with HCV genotype 5 or 6 infection in whom prior treatment has failed:

	• Monotherapy with PEG-IFN, RBV, or a direct-acting antiviral Rating: Class III, Level A • Telaprevir- or boceprevir-based regimens Rating: Class III, Level A ***Patients with HIC/HCV coinfection*** Recommendations related to HCV medication interactions with HIV antiretroviral medications: • Antiretroviral drug switches, when needed, should be done in collaboration with the HIV practitioner. For HIV antiretroviral and HCV direct-acting antiviral combinations not addressed below, expert consultation is recommended. Rating: Class I, Level A • Daclatasvir: o Daclatasvir requires dose adjustment with ritonavir-boosted atazanavir (adecrease to 30 mg daily) and efavirenz or etravirine (an increase to 90 mg daily). Rating: Class IIa, Level B • Fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg): o Because ledipasvir increases tenofovir levels, when given as tenofovir disoproxil fumarate, concomitant use mandates consideration of creatinine clearance (CrCl) rate and should be avoided in those with CrCl below 60 mL/min. Because potentiation of this effect occurs when tenofovir is used with ritonavir-boosted HIV protease inhibitors, ledipasvir should be avoided with this combination (pending further data) unless antiretroviral regimen cannot be changed and the urgency of treatment is high. Rating: Class IIa, Level C • For combinations expected to increase tenofovir levels, baseline and ongoing assessment for tenofovir nephrotoxicity is recommended. Rating: Class IIa, Level C • Daily fixed-dose combination of paritaprevir (150 mg) /ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) (paritaprevir/ritonavir/ombitasvir plus dasabuvir or PrOD): o Paritaprevir/ritonavir/ombitasvir plus dasabuvir should be used with antiretroviral drugs with which they do not have substantial interactions: atazanavir, dolutegravir, emtricitabine, enfuvirtide, lamivudine, raltegravir, and tenofovir. o The dose of ritonavir used for boosting of HIV protease inhibitors may need to be adjusted (or held) when administered with aritaprevir/ritonavir /ombitasvir plus dasabuvir and then restored when HCV treatment is completed. The HIV protease inhibitor should be administered at the same time as the fixed-dose HCV combination. Rating: Class IIa, Level C • Simeprevir:

	o Simeprevir should be used with antiretroviral drugs with which it does not have clinically significant interactions: abacavir, emtricitabine, enfuvirtide, lamivudine, maraviroc, raltegravir (and probably dolutegravir), rilpivirine, and tenofovir. Rating: Class IIa, Level B The following are NOT recommended or should not be used: • Antiretroviral treatment interruption to allow HCV therapy is NOT recommended. • Rating: Class III, Level A • Ledipasvir/sofosbuvir should NOT be used with cobicistat when given with tenofovir disoproxil fumarate. • Rating: Class III, Level C • Sofosbuvir or ledipasvir/sofosbuvir should NOT be used with tipranavir. • Rating: Class III, Level B • Paritaprevir/ritonavir/ombitasvir plus dasabuvir should NOT be used with darunavir, efavirenz, ritonavir-boosted lopinavir, or rilpivirine. • Rating: Class III, Level B • Paritaprevir/ritonavir/ombitasvir with or without dasabuvir should NOT be used in HIV/HCV-coinfected individuals who are not taking antiretroviral therapy. • Rating: Class III, Level B • RBV should NOT be used with didanosine, stavudine, or zidovudine. • Rating: Class III, Level B • Simeprevir should NOT be used with cobicistat, efavirenz, etravirine, nevirapine, or any HIV protease inhibitor. • Rating: Class III, Level B Recommended regimens for HIV/HCV-coinfected individuals: • HIV/HCV-coinfected persons should be treated and retreated the same as persons without HIV infection, after recognizing and managing interactions with antiretroviral medications (see Initial Treatment of HCV Infection and Retreatment of Persons in Whom Prior Therapy Has Failed sections). • Rating: Class I, Level B • Daily daclatasvir (refer above for dose) and sofosbuvir (400 mg), with or without RBV (refer to Initial Treatment of HCV Infection and Retreatment of Persons in Whom Prior Therapy Has Failed sections for duration) is recommended when antiretroviral regimen changes cannot be made to accommodate alternative HCV direct-acting antivirals. • Rating: Class I, Level B The following regimens are NOT recommended for treatment-naive or –experienced HIV/HCV-coinfected patients: • Treatment courses shorter than 12 weeks, such as the use of 8 weeks of ledipasvir/sofosbuvir Rating: Class IIb, Level C • Monotherapy with PEG-IFN, RBV, or a direct-acting antiviral

	Rating: Class III, Level A • PEG-IFN and RBV with or without simeprevir, telaprevir, or boceprevir for 24 weeks to 48 weeks Rating: Class IIb, Level A ***Patients with decompensated cirrhosis*** **Genotype 1 and 4** Recommended regimens for patients with genotype 1 or 4 HCV infection with decompensated cirrhosis (moderate or severe hepatic impairment; CTP class B or C) who may or may not be candidates for liver transplantation, including those with hepatocellular carcinoma: • Daily daclatasvir (60 mg), sofosbuvir (400 mg), and low initial dose of RBV (600 mg, increased as tolerated) for 12 weeks is recommended for patients with HCV genotype 1 or 4 with decompensated cirrhosis. Rating: Class II, Level A • Daily fixed-dose combination ledipasvir (90 mg)/sofosbuvir (400 mg) and low initial dose of RBV (600 mg, increased as tolerated) for 12 weeks is recommended for patients with HCV genotype 1 or 4 with decompensated cirrhosis. Rating: Class IIb, Level C Recommended regimen for patients with genotype 1 or 4 HCV infection with decompensated cirrhosis who are RBV intolerant or ineligible: • Daily daclatasvir (60 mg) and sofosbuvir (400 mg) for 24 weeks is recommended for patients with decompensated cirrhosis who are RBV intolerant or ineligible. Rating: Class IIb, Level C Recommended regimen patients with genotype 1 or 4 HCV infection with decompensated cirrhosis in whom prior sofosbuvir-based treatment has failed: • Daily fixed-dose combination ledipasvir (90 mg)/sofosbuvir (400 mg) and low initial dose of RBV (600 mg, increased as tolerated) for 24 weeks is recommended for patients with genotype 1 or 4 HCV infection with decompensated cirrhosis in whom prior sofosbuvir-based treatment has failed. Rating: Class IIb, Level C **Genotype 2 and 3:** Recommended regimens for patients with HCV genotype 2 or 3 infection who have decompensated cirrhosis (moderate or severe hepatic impairment; CTP class B or C) and who may or may not be candidates for liver transplantation, including those with hepatocellular carcinoma: • Daily daclatasvir (60 mg), sofosbuvir (400 mg), and low initial dose of RBV (600 mg, increased as tolerated) for 12 weeks is recommended for patients with HCV genotype 2 or 3 infection who have decompensated cirrhosis and who may or may not be candidates for liver transplantation, including those with hepatocellular carcinoma. Rating: Class II, Level A • Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75

	kg] to 1200 mg [>75 kg]) (with consideration of the patient's creatinine clearance rate and hemoglobin level) for up to 48 weeks is recommended for patients with HCV genotype 2 or 3 infection who have decompensated cirrhosis and who may or may not be candidates for liver transplantation, including those with hepatocellular carcinoma. Rating: Class IIb, Level B The following regimens are NOT recommended for patients with decompensated cirrhosis (moderate or severe hepatic impairment; Child Turcotte Pugh class B or C): • Any IFN-based therapy Rating: Class III, Level A • Monotherapy with PEG-IFN, RBV, or a direct-acting antiviral Rating: Class III, Level A • Telaprevir-, boceprevir-, or simeprevir-based regimens Pariteprevir-, ombitasvir-, or dasabuvir-based regimens Rating: Class III, Level A ***Patients with renal impairment*** Recommended dosage adjustments for patients with renal impairment, including severe renal impairment (creatinine clearance [CrCl] <30 mL/min) or end-stage renal disease (ESRD): • For patients with mild to moderate renal impairment (CrCl 30 mL/min-80 mL/min), no dosage adjustment is required when using daclatasvir, fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg), or fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) with (or without for HCV genotype 4 infection) twice-daily dosed dasabuvir (250 mg), simeprevir, or sofosbuvir to treat or retreat HCV infection in patients with appropriate genotypes. Rating: Class I, Level A Recommended regimen for patients with CrCl below 30 mL/min who do not have cirrhosis but for whom the urgency to treat (or retreat) is high and renal transplant is not an immediate option: • For patients with CrCl below 30 mL/min who do not have cirrhosis but for whom the urgency to treat (or retreat) is high and renal transplant is not an immediate option, daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg) /ombitasvir (25 mg) with twice-daily dosed dasabuvir (250 mg) (for HCV genotype 1b infection) or without dasabuvir (for HCV genotype 4 infection) is recommended. However, this recommendation is based on limited data on safety and efficacy. Rating: Class IIb, Level B • For HCV genotype 1a infection, daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) with RBV at reduced doses (200 mg thrice weekly to daily*) is recommended. However, caution is recommended in this group, owing to the potential for hemolysis in this population, and RBV should be restricted to those with a baseline hemoglobin concentration above 10 g/dL. Rating: Class IIb, Level B

<table>
<tr><td></td><td>
For patients with HCV genotype 2, 3, 5, or 6 infection and CrCl below 30 mL/min, PEG-IFN and dose-adjusted RBV is recommended if treatment is necessary and transplantation cannot be performed.
Rating: Class IIb, Level B
*RBV should be discontinued if hemoglobin level declines by more than 2 g/dL despite the use of erythropoietin.

Recommended regimen for patients with CrCl below 30 mL/min who do not have cirrhosis but for whom the urgency to treat (or retreat) is high and renal transplant is not an immediate option, who are RBV intolerant or ineligible:
For patients with CrCl below 30 mL/min who do not have cirrhosis but for whom the urgency to treat (or retreat) is high, consultation with an expert is recommended, to assess the appropriateness of a sofusbuvir-containing regimen, because safety and efficacy data are not available in this setting.
Rating: Class IIb, Level C
</td></tr>
<tr><td rowspan="2">EASL, 2014 [15].

EASL Clinical Practice Guidelines: management of hepatitis C virus infection

EASL, 2015 [16].

Recommendations on Treatment of Hepatitis C 2015</td><td>Leitlinie der European Association for the Study of the Liver (EASL)</td></tr>
<tr><td>
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):
<table>
<tr><th>Evidence quality</th><th>Notes</th><th>Grading</th></tr>
<tr><td>High</td><td>Further research is very unlikely to change our confidence in the estimate of effect</td><td>A</td></tr>
<tr><td>Moderate</td><td>Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate</td><td>B</td></tr>
<tr><td>Low</td><td>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</td><td>C</td></tr>
<tr><th>Recommendation</th><th>Notes</th><th>Grading</th></tr>
<tr><td>Strong</td><td>Factors influencing the strenght of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost</td><td>1</td></tr>
<tr><td>Weak</td><td>Variability in preferences and values, or more uncertainty. Recommendation is made with less certainty, higher cost or resource consumption</td><td>2</td></tr>
</table>

Keine genauen Angaben zur Literaturrecherche und zum Suchzeitraum!
</td></tr>
</table>

	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) **Haemodialysis patients** Haemodialysis patients, particularly those who are suitable candidates for renal transplantation, should be considered for antiviral therapy. (B1) Haemodialysis patients should receive an IFN-free, if possible ribavirin-free regimen, for 12 weeks in patients without cirrhosis, for 24 weeks in patients with cirrhosis. (B1) Simeprevir, daclatasvir, and the combination of ritonavir boosted paritaprevir, ombitasvir and dasabuvir are cleared by hepatic metabolism and can be used in patients with severe renal disease. (A1) Sofosbuvir should not be administered to patients with an eGFR <30

<table>
<tr><td></td><td>ml/min/1.73 m2 or with end-stage renal disease until more data is available. (B2)

The need for dose adjustments for the approved HCV DAAs in patients on dialysis is unknown. No safety dosing and efficacy data is available in this population. These drugs should thus be used with extreme caution in patients with severe renal disease, and only in extreme life-threatening situations for patients on dialysis. (B1)</td></tr>
<tr><td rowspan="2">Berden FAC et al., 2014 [4].

Dutch guidance for the treatment of chronic hepatitis C virus infection in a new therapeutic era</td><td>This paper may serve as a current guidance for the therapeutic management of chronic hepatitis C. This update of the earlier guidance 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>
</table>

	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) **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 [50]. 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
SIGN, 2013 [61]. Management of hepatitis C	The guideline provides evidence based recommendations covering all stages of the patient care pathway; screening, testing, diagnosis, referral, treatment, care and follow up of infants, children and adults with, or exposed to, HCV infection.
	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 LoE **1++** High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias **1+** well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias

1 -	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++	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
2+	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2 -	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, eg case reports, case series
4	Expert opinion

GoR

A	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
B	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+
C	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++
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+
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 [64]. 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

Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren wurden durch die Suche nicht identifiziert.

Primärstudien

Eine Suche nach Primärstudien wurde nicht in Auftrag gegeben.

Detaillierte Darstellung der Recherchestrategie:

Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database) **am 07.10.2015**

Suchschritt	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 and (c):ti,ab,kw
4	#1 or #2 or #3
5	#4 from 2010 to 2015

SR, HTAs in Medline (PubMed) am 07.10.2015

Suchschritt	Suchfrage
1	("Hepatitis C, Chronic/drug therapy"[Mesh])
2	((chronic[Title/Abstract]) AND hepatitis[Title/Abstract]) AND c[Title/Abstract]
3	„HCV“[Title/Abstract]
4	(#2) OR #3
5	(((((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	(#4) AND #5
7	(#1) OR #6
8	"Hepatitis C, Chronic"[Mesh]
9	"drug therapy"[MeSH Terms]
10	(#8) AND #9
11	(#7) OR #10
12	(#11) AND (Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp])
13	(#11) AND (((((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]))))
14	(#12) OR #13
15	(#14) AND ("2010/08/01"[PDAT] : "2015/10/07"[PDAT])

Leitlinien in Medline (PubMed) am 07.10.2015

Suchschritt	Suchfrage
1	"Hepatitis C, Chronic"[Mesh]
2	((chronic[Title/Abstract]) AND hepatitis[Title/Abstract]) AND c[Title/Abstract]
3	((#1) OR #2
4	(#3) 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])
5	(#4) AND ("2010/08/01"[PDAT] : "2015/10/07"[PDAT])

Literatur:

1. **Alavian SM, Tabatabaei SV, Behnava B, Mahboobi N**. Optimal duration of treatment for HCV genotype 1 infection in slow responders: a meta-analysis. Hepat Mon 2011; 11 (8): 612-9.

2. **Aljumah AA, Murad MH**. Pegylated versus standard interferon plus ribavirin in chronic hepatitis C genotype 4: A systematic review and meta-analysis. Hepatol Res 2013; 43 (12): 1255-63.

3. **American Association for the Study of Liver Diseases (AASLD), Infectious Diseases Society of America (IDSA)**. Recommendations for Testing, Managing, and Treating Hepatitis C (Stand: 09/2014). Alexandria (USA): AASLD, IDSA (hcvguidelines org) 2014; http://www.hcvguidelines.org/full-report-view, Zugriff am 10.10.2015.

4. **Berden FA, Kievit W, Baak LC, Bakker CM, Beuers U, Boucher CA, Brouwer JT, Burger DM, van Erpecum KJ, van Hoek B, Hoepelman AI, Honkoop P, Kerbert-Dreteler MJ, de Knegt RJ, Koek GH, van Nieuwkerk CM, van Soest H, Tan AC, Vrolijk JM, Drenth JP**. Dutch guidance for the treatment of chronic hepatitis C virus infection in a new therapeutic era. Neth J Med 2014; 72 (8): 388-400.

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