Drug Class Review

Comparative Effectiveness of Direct-Acting Antiviral Agents for Hepatitis C Infection

Final Original Report

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STRUCTURED ABSTRACT

Purpose

To compare the benefits and harms of direct-acting antiviral agents (DAAs) for hepatitis C virus (HCV) infection, including those currently available in the U.S. and those that have been submitted for US Food and Drug Administration approval.

Data Sources

To identify published studies, we searched MEDLINE® and the Cochrane Central Register of Controlled Trials (both through July 8, 2014), and reference lists of included studies. We searched ClinicalTrials.gov for additional unpublished data, and requested dossiers of information from pharmaceutical manufacturers.

Review Methods

Study selection, data abstraction, validity assessment, grading the strength of the evidence, and data synthesis were all carried out according to standard Drug Effectiveness Review Project methods.

Results

DAA compared with DAA

We found no difference in the rates of sustained virologic response (SVR) or relapse between the older DAA regimens (sofosbuvir, simeprevir, and boceprevir) in patients with HCV infection, regardless of prior treatment history. Some boceprevir regimens were associated with higher rates of anemia or rash than simeprevir regimens. In patients given all-oral DAA-containing regimens (simeprevir with sofosbuvir, ledipasvir/sofosbuvir, 3D regimen, or daclatasvir with another DAA), inclusion of ribavirin did not affect SVR and harms were reduced without it.

Treatment Duration

In treatment-naïve patients with HCV genotype 1, 8 weeks of treatment with ledipasvir/sofosbuvir was associated with increased risk of relapse, though treatment duration did not affect SVR or harms. Twelve weeks of treatment with simeprevir with pegylated interferon and ribavirin (PR) was equivalent to 24 weeks in effects on SVR and relapse, but associated with less neutropenia. However, patients treated with boceprevir with PR required 48 weeks of treatment; 28 weeks of treatment was associated with lower SVR.

In treatment-experienced patients with HCV genotype 1 and no cirrhosis given the 3D regimen, treatment duration did not affect SVR or relapse (1 trial, N=88). Data from another trial (N=380) including only patients with cirrhosis and mixed treatment history (both naïve and experienced) showed that relapse was more likely with 12 weeks of the 3D regimen compared with 24 weeks. A large trial (N=440) of treatment-experienced patients given ledipasvir/sofosbuvir fixed-dose combination also showed differences by stage of disease. Patients with cirrhosis treated for 12 weeks were less likely to achieve SVR and more likely to relapse than those treated for 24 weeks. However, in patients without cirrhosis duration did not affect SVR. (Data for relapse were sparse in patients without cirrhosis.) Thus, there are data to

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suggest that for both the 3D regimen and ledipasvir/sofosbuvir, treatment-experienced patients with cirrhosis require longer treatment duration. For simeprevir given with sofosbuvir, data from one trial (N=127) suggested that 12 weeks of treatment was as effective as 24 weeks of treatment in achieving SVR in treatment-experienced patients with any disease stage, though data for relapse were sparse.

Applicability

The trials included mostly white patients (85%) who were HIV negative and without other liver disease and provided no information on patients' history of substance abuse. Some trials also included only patients without cirrhosis (78% across trials without cirrhosis). Therefore, applicability to populations which may be less likely to respond to treatment may be limited.

SVR12, SVR24, and Long-Term Outcomes

In trials reporting both SVR12 and SVR24, we found good correlation between SVR12 and SVR24 in patients with genotype 1 treated with daclatasvir plus sofosbuvir, daclatasvir without other DAAs, the 3D regimen with ribavirin, or simeprevir without other DAAs. Additionally, we found moderate strength of evidence based on interferon given with or without ribavirin that SVR was associated with reduced all-cause mortality and reduced risk of hepatocellular carcinoma. There was no evidence on the relationship between SVR and cirrhosis or transplant in patients given interferon therapies, and no evidence on the relationship between SVR and any long-term outcome in patients given DAAs.

Conclusions

Direct, head-to-head evidence comparing one included DAA with another included DAA was lacking. Indirect evidence was limited to trials of sofosbuvir (1 trial), simeprevir (5 trials), and boceprevir (3 trials) with PR as a common comparator in treatment-naïve patients, and showed no difference in benefits between DAAs, though harms were increased with some boceprevir regimens.

In all-oral regimens, excluding ribavirin did not affect SVR but reduced harms. In treatment-naïve patients, 8 weeks of treatment with ledipasvir/sofosbuvir was associated with increased relapse rates compared with 12 weeks. In treatment-experienced patients with cirrhosis or patients with a mixed treatment history with cirrhosis, those treated for 12 weeks with ledipasvir/sofosbuvir or the 3D regimen, respectively were less likely to achieve SVR and/or more likely to relapse than those treated for 24 weeks. Treatment with sofosbuvir and ribavirin for 12 weeks was associated with lower rates of SVR compared to treatment for 16 weeks in patients with genotypes 3 who had not responded to previous interferon therapy.

We found evidence of good correlation between SVR12 and SVR24 in patients treated with DAAs, and evidence that SVR predicted some long-term outcomes in patients given interferon therapies, but no evidence on the relationship between SVR and long-term outcome in patients given DAAs.

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EVIDENCE TABLES

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INTRODUCTION

Chronic infection with the hepatitis C virus (HCV) is common, with potentially severe clinical consequences. New treatments have emerged over the last several years, with 5 regimens including direct-acting antiviral agents (DAAs) approved since 2011, two of which were approved since October 2014. The DAAs are more effective than previous treatments, but also more costly.

Virology

HCV is an enveloped, positive-stranded RNA virus first isolated in 1989. The viral genome encodes a polyprotein cleaved into structural and nonstructural (NS) viral proteins including NS3, 4A, 4B, 5A, and 5B, all of which are targets of DAAs discussed below. Viral polymerase lacks proofreading ability, leading to rapid mutation and genetic diversity. There are 6 or more HCV genotypes, and numerous subtypes including 1a and 1b. Genotype 1 is most prevalent in the United States, genotypes 2 and 3 less common, and genotypes 4, 5, and 6 uncommon. Treatment regimens and response vary across genotypes.[1-3]

Infection

Most patients infected with HCV (50% to 85%) fail to clear the acute infection and develop chronic HCV with persistent viremia.[3,4] Over time persistent infection leads to hepatic fibrosis and, in some patients, cirrhosis. The Metavir fibrosis scoring system requires liver biopsy and identifies histologic stages F0 (no fibrosis) through F4 (cirrhosis), with stage F3 showing bridging fibrosis and stage F4 showing both bridging fibrosis and regenerative nodules.[1] Non-invasive alternatives to biopsy using imaging or laboratory analysis are also available.[5]

Chronic HCV progresses slowly and variably, with an estimated 15% to 30% of patients developing cirrhosis over 20 to 30 years.[1,3] Complications of HCV infection occur primarily in patients with cirrhosis, and include hepatic decompensation (e.g., ascites, variceal bleeding, encephalopathy, and jaundice) or liver failure, as well as hepatocellular carcinoma.[1,3,4] Chronic HCV infection is the most common condition leading to liver transplantation among U.S. adults.[4,6] Mortality is increased, with nearly 18,000 HCV-associated deaths in the year 2011 alone.[3,7,8]

Epidemiology

HCV infection is the most common chronic blood-borne infection in the United States. The National Health and Nutrition Examination Survey (NHANES) is a large national survey conducted by the Centers for Disease Control collecting information on about 5,000 people annually, including blood samples. Samples testing positive or indeterminate for HCV antibodies, indicating current or past infection, are further tested for HCV RNA, which is positive with current infection. NHANES results from 2003 to 2010 produced an estimated prevalence of chronic HCV infection of 1.0% of the U.S. population, or 2.7 million people.[8] Because NHANES excludes some populations (e.g., those incarcerated or homeless), other estimates put the prevalence higher (5.2 to 7.1 million cases).[9]

Intravenous drug abuse is the major risk factor for HCV infection,[1,10] with IV drug users having 50 times the risk of non-users, and more than 60% of new infections occurring in recent

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IV drug users.[11] Alcohol abuse and blood transfusions received before 1992 are also risk factors.[10,11] Rates of sexual transmission are relatively low.[10,11]

Treatment

The goal of chronic HCV treatment is to prevent long-term health complications associated with infection. A more immediate measure of treatment success is viral eradication or sustained virologic response (SVR). SVR is defined as undetectable serum HCV RNA 12 or 24 weeks after the end of treatment, as measured by a sensitive polymerase chain reaction assay.[1,12]

Therapies to treat HCV infection have advanced substantially over the last several decades. In the mid-1980s, recombinant type I interferons were introduced as monotherapies to treat HCV infection, but had only modest success in achieving SVR.[13] Pegylation of alpha interferons, in which polyethylene glycol molecules are cross-linked to the interferon molecule, were developed to provide long-acting treatment.[13,14] In the 2000s, dual therapy with pegylated interferon and ribavirin (PR) became the standard of care for chronic HCV infection.[1,4,6] Pegylated interferon and ribavirin do not target a specific HCV gene or protein and are, therefore, not considered DAAs.[15] These dual therapies led to increases in SVR from <5% to approximately 50% in treatment-naïve patients with genotype 1.[1,13] Response rates were higher in genotypes 2 and 3 (70 to 80%)[16] However, adverse events are common and include fatigue, flu-like symptoms, mild anxiety, skin rash, and gastrointestinal symptoms such as nausea and diarrhea.[13] Hemolytic anemia is almost universal in patients treated with PR.[17] Neuropsychiatric effects including severe depression and suicidality have been reported with interferon, though may also be associated with underlying disease and/or elevated in patients at risk for HCV infection.[17,18] These adverse effects and the need to inject interferon reduce treatment adherence, especially in the context of treatment durations of up to 48 weeks.[1]

Treatment of chronic HCV infection advanced with the development and approval of oral DAAs (Table 1). Triple therapy treatments with PR and a DAA quickly became the standard of care, providing much higher SVR rates than the previous dual therapy with PR.[19] Boceprevir (Victrelis®) and telaprevir (Incivek®) were the first DAAs approved, both in May 2011. Boceprevir and telaprevir are both NS3/4A protease inhibitors and impede viral replication.[15] However, Vertex Pharmaceuticals discontinued sales of telaprevir in the United States on October 16, 2014, although it is still currently made available to patients who need to complete treatment. [20] Healthcare providers are advised not to start any new patients on Telaprevir. In 2013, simeprevir (Olysio®) and sofosbuvir (Sovaldi®) were approved by the US Food and Drug Administration (FDA). Simeprevir is also a NS3/4A protease inhibitor, while sofosbuvir is a nucleotide analog NS5B polymerase inhibitor. Currently, the three NS3/4A protease inhibitors are approved only for treating patients with genotype 1, while sofosbuvir has broader approval (Table 1). Some trials have shown higher response rates for sofosbuvir regimens among patients infected with genotype 2 than among those with genotype 3.[16]

Genetic variation in both virus and host can affect treatment response. Simeprevir efficacy in combination with peginterferon alfa and ribavirin is substantially reduced in patients infected with HCV genotype 1a with an NS3 Q80K polymorphism at baseline compared to patients infected with HCV genotype 1a without the Q80K polymorphism. The Q80K polymorphism of HCV is highly prevalent in North American populations, and it is not yet clear if this mutation also affects response to other NS3/4A protease inhibitors.[21,22] A polymorphism near the human interleukin-28B gene (*IL28B*, encoding an endogenous interferon) affects both spontaneous clearance and response to treatment, with both improved in patients with the CC

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compared with CT or TT genotype. The C allele is less common in black patients, and may contribute to lower response rates to interferon in this population.[1,3,23]

Alcohol abuse, liver transplant, and higher baseline viral load also predict lower response rates to interferon regimens.[1,11,16,24] HIV coinfection is associated with lower response rates to interferon and ribavirin,[16,23,24] though response to DAA regimens may be more comparable between HIV positive and negative patients.[23,24] Patients with cirrhosis and HCV genotype 1 have lower response rates for some DAA regimens.[16,23]

In 2014, new drug applications (NDAs) were submitted for 5 new DAAs, though 2 NDAs (for asunaprevir and faldaprevir) have since been withdrawn. Two of the remaining regimens are all-oral, given without pegylated interferon: a fixed-dose combination of ledipasvir and sofosbuvir (Harvoni®), and AbbVie's 3D regimen including 3 new DAAs and the HIV protease inhibitor ritonavir (all 4 packaged together as Viekira Pak™), with or without ribavirin (Table 1). The FDA approved ledipasvir/sofosbuvir on October 10, 2014 and the 3D regimen on December 19, 2014.

Table 1. Included drugs[a]

Drug(s)	Trade name	FDA NDA and/or approval status	Labeled indications	Mechanism of action
Boceprevir	Victrelis®	Approved 5/13/2011	CHC genotype 1 infection, in combination with peginterferon alfa and ribavirin, in adult patients with compensated liver disease, including cirrhosis, who are previously untreated or who have failed previous interferon and ribavirin therapy, including null responders, partial responders, and relapsers.[25]	NS3/4A protease inhibitor
Simeprevir	Olysio®	Approved 11/22/2013	CHC genotype 1 infection, in combination with peginterferon alfa and ribavirin for 12 weeks, followed by 12 or 36 additional weeks depending on prior response status. Also indicated in combination with sofosbuvir in treatment-naïve or treatment-experienced patients (12 without cirrhosis; 24 weeks with cirrhosis).[26]	NS3/4A protease inhibitor
Sofosbuvir	Sovaldi®	Approved 12/6/2013	Chronic HCV genotypes 1, 2, 3, or 4 infection, including those with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation) and those with HCV/HIV-1 co-infection.[27]	Nucleotide analog NS5B polymerase inhibitor
Ledipasvir/ Sofosbuvir (FDCP)	Harvoni®	Approved 10/10/2014	CHC genotype 1 infection in adults.[28]	NS5A inhibitor/nucleotide analog NS5B polymerase inhibitor

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Drug(s)	Trade name	FDA NDA and/or approval status	Labeled indications	Mechanism of action
Simeprevir with Sofosbuvir	Olysio® with Sovaldi®	Approved 11/5/2014	CHC genotype 1 infection in adults[26]	NS3/4A inhibitor with NS5B inhibitor
3D regimen: Paritaprevir/ Ritonavir/ Ombitasvir (FDCP) + Dasabuvir ± Ribavirin	Viekira Pak™	Approved 12/19/2014	Patients with chronic HCV genotype 1 infection, including those with compensated cirrhosis.[29]	NS3/4A protease inhibitor/NS5A inhibitor + non-nucleoside NS5B polymerase inhibitor
Daclatasvir	NA	NDA submitted 4/7/2014	NA	NS5A inhibitor

[a]Drugs excluded since DERP's hepatitis C review process began: asunaprevir: NDA withdrawn October 2014; faldaprevir: NDA withdrawn June 2014; telaprevir: manufacturer announced it would withdraw from U.S. market in October 2014
Abbreviations: CHC, chronic hepatitis C; FDA, U.S. Food and Drug Administration; FDCP, fixed-dose combination product; HCV, hepatitis C virus; NA = not applicable; NDA, new drug application; NS, non-structural (HCV viral proteins).

Drug Effective Review Project Reports

In mid-2014, Drug Effectiveness Review Project participating organizations, noting the rapid pace of new HCV drug development, new guidelines for treatment,[30] and the high cost of new drugs, asked the Pacific Northwest Evidence-based Practice Center (EPC) to compare the effectiveness and harms of DAA regimens, using an approach that could quickly incorporate new evidence as it emerged. The EPC began with a Summary Review completed in December 2014 using existing systematic reviews to establish an evidence baseline. The Drug Effectiveness Review Project Summary Review on the comparative effectiveness of drugs to treat Hepatitis C focused on a large, recently released (December 2014), good quality systematic review published by the Canadian Agency for Drugs and Technologies in Health (CADTH). The CADTH review includes only trials in patients with HCV genotype 1 infection, which is the majority population comprising the evidence base for hepatitis C.

After publication of the summary review, the EPC then began work on this original systematic review, which includes evidence from the Summary Review and adds recent primary evidence. This report is unique in that it is the first Drug Effectiveness Review Project review to include trials of drugs that have not yet been FDA approved. As mentioned previously, two drug regimens have been approved since this review began, making this review exceptionally timely. Drug treatments for hepatitis C is a also a unique topic for Drug Effectiveness Review Project as upon completion of this review, work will begin on an update report with the intention to create a living document that is updated as soon as sufficient new evidence is available. In this way participants will have the most current information at their fingertips.

Key Questions

In consultation with Drug Effectiveness Review Project participating organizations, the EPC drafted key questions and inclusion criteria reflecting populations, drugs, and outcome measures of interest to clinicians and patients. The following key questions were approved to guide this review:

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1. In patients with HCV genotype 1, what are the comparative benefits and harms of DAA-containing vs DAA-containing regimens?

2. In patients with HCV genotypes other than 1, what are the comparative benefits and harms of DAA-containing vs. DAA-containing regimens?

3. In patients with HCV genotypes other than 1, what are the comparative benefits and harms of DAA-containing vs. non-DAA containing regimens?

4. What are the comparative benefits and harms of varying doses and durations of DAA treatment within regimens in patients with hepatitis C virus?

5. What are the comparative benefits and harms of various DAA regimen changes based on virologic response at any time during antiviral therapy (i.e., response-guided therapy based on viral load)?
    a. Shortening DAA treatment
    b. Switching from one DAA to another

6. What are the comparative benefits and harms of DAAs for specific subpopulations of patients with hepatitis C virus (e.g., concomitant HIV or HBV infections or other comorbidities (e.g., chronic illnesses, inherited blood disorders, cancer), initial viral load, post-transplant, substance abuse, genetic polymorphisms (e.g., IL28B variants, Q80K mutation), or demographic characteristics such as age, gender, race or ethnicity)?

7. What are the comparative benefits and harms of DAAs in patients with early- vs. late-stage hepatitis C virus based on fibrosis scales (e.g., Metavir fibrosis score from liver biopsy) or presence of cirrhosis?

8. What evidence supports a correlation between 12- or 24-week post-treatment sustained virologic response (SVR) and long-term outcomes of mortality, cirrhosis, transplant, and hepatocellular carcinoma? Does SVR12 predict SVR24?

METHODS

Literature Search

We searched Ovid MEDLINE® (1946 through June 10, 2014 and July 8, 2014) and the Cochrane Central Register of Controlled Trials® (through June 10, 2014 and July 8, 2014) using names of included drugs as search terms. We also conducted a separate search of Ovid MEDLINE® (1946 through October 27, 2014) to identify additional studies relevant to Key Question 8 (SVR12 and 24). Please see Appendix C for complete search strategies. Because this is a streamlined review and because the first update will begin immediately after this original review is completed, we did not conduct bridge searches. We searched ClinicalTrials.gov to further identify trials of included drugs. We attempted to identify additional studies through hand searches of reference lists of included studies and reviews. Finally, we requested dossiers of published and unpublished information from the relevant pharmaceutical companies for this review. All

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received dossiers were screened for studies or data not found through other searches. All citations were imported into an electronic database (Endnote® X7, Thomson Reuters).

Study Selection

Selection of included studies was based on the inclusion criteria created in consultation with the Drug Effectiveness Review Project participants. Two reviewers independently assessed titles and abstracts of citations identified through literature searches for inclusion using the criteria below. Full-text articles of potentially relevant citations were retrieved and again were assessed for inclusion by both reviewers. Disagreements were resolved by consensus. Results published *only* in abstract form were not included because inadequate details were available for quality assessment; however, we did consider for inclusion abstracts that provided supplemental data from published trials.

Inclusion Criteria

Populations

- Adults with chronic infection with any genotype of hepatitis C virus (HCV)
- Either treatment-naïve or with any prior treatment for HCV

Interventions

- See Table 1. Included drugs

Comparators

Using a Best Evidence approach (see Study Designs), we prioritized head-to-head evidence. Where evidence for genotypes other than 1 or evidence comparing newer direct-acting anti-viral agents (DAAs) was sparse, we included trials with PR or placebo as a comparator. We also included these trials in indirect analysis when possible.

Benefits Outcomes

- Clinical outcomes: mortality, cirrhosis, liver transplantation, hepatocellular carcinoma
- SVR24: sustained virologic response at 24 weeks of follow-up (i.e. serum HCV RNA undetectable 24 weeks after therapy is completed); in the absence of data for SVR24 we included SVR12 data; we also included SVR12 data when both SVR12 and SVR24 evidence were reported to determine their magnitude of correlation
- Viral relapse or reinfection with HCV
- Serious extrahepatic manifestations (e.g., diabetes, renal disease, thyroid disease, lymphoma)

Harms Outcomes

- Withdrawals due to adverse events
- Specific adverse events (e.g. hematologic, dermatologic, drug interactions)

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Study Designs

- Using a Best Evidence approach,[31] we prioritized evidence from head-to-head randomized controlled trials (RCTs). Evidence from RCTs comparing a DAA to pegylated interferon and ribavirin (PR), observational studies, or other designs (e.g. pooled analyses) were only included when strength of evidence from head-to-head trials was deemed insufficient to assess benefits or harms.
- Good quality systematic reviews that included relevant studies according to this Best Evidence model were included wherever possible if search dates ended after the 2014 Canadian Agency for Drugs and Technologies in Health (CADTH) review's searches (January 2014). If the review included all relevant studies we cited those results. If additional trials were available we updated any existing analysis.
- Observational studies for harms and for clinical outcomes and for viral relapse or reinfection

We excluded trials with a single treatment arm for effectiveness or harms outcomes, as they do not provide comparative evidence. The Drug Effectiveness Review Project's methods have always focused on evidence that informs the comparison of one drug to an alternative drug.[32] For similar reasons, we also excluded trials that did have more than one arm, but where treatment was assigned based on patient characteristics like genotype, treatment history, or presence of cirrhosis. These trials do not allow comparison of one drug regimen to another within a given population. Table D2 (Appendix D) shows the six trials excluded because they were non-comparative.

Data Abstraction

We abstracted information on population characteristics, interventions, subject enrollment and discontinuation and results for efficacy, effectiveness, and harms outcomes for trials, observational studies, and systematic reviews. We recorded intent-to-treat results when reported. If true intent-to-treat results were not reported, but loss to follow-up was very small (<5%), we considered these results to be intent-to-treat. In cases where only per protocol results were reported, we calculated intent-to-treat results if the data for these calculations were available. Data abstraction was performed by one reviewer and independently checked by a second reviewer. Differences were resolved by consensus.

Validity Assessment (Quality Assessment)

We assessed the internal validity (quality) of trials based on predefined criteria (see www.ohsu.edu/drugeffectiveness). These criteria are based on the US Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination (United Kingdom) criteria.[33,34] We rated the internal validity of each trial based on the methods used for randomization, allocation concealment, and blinding, the similarity of compared groups at baseline, loss to follow-up, and the use of intent-to-treat analysis. Trials that had a fatal flaw were rated poor quality, trials that met all criteria were rated good quality, and the remainder were rated fair quality. As the fair-quality category is broad, studies with this rating vary in their strengths and weaknesses. The results of some fair-quality studies are *likely* to be valid, while others are only *possibly* valid. A poor-quality trial is not valid, as the results are at least as likely

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to reflect flaws in the study design as a true difference between the compared drugs. A fatal flaw is reflected by failure to meet combinations of items of the quality assessment checklist.

Two reviewers independently assessed the quality of each study and differences were resolved by consensus.

Grading the Strength of Evidence

We graded strength of evidence based on the guidance established for the Evidence-based Practice Center Program of the Agency for Healthcare Research and Quality.[35] Developed to grade the overall strength of a body of evidence, this approach incorporates 4 key domains: risk of bias (includes study design and aggregate quality), consistency, directness, and precision of the evidence. It also considers other optional domains that may be relevant for some scenarios, such as a dose-response association, plausible confounding that would decrease the observed effect, strength of association (magnitude of effect), and publication bias.

Table 2 describes the grades of evidence that can be assigned. Grades reflect the strength of the body of evidence to answer key questions on the comparative effectiveness, efficacy and harms of direct-acting antiviral agents for HCV infection. Grades do not refer to the general efficacy or effectiveness of pharmaceuticals. Two reviewers independently assessed each domain for each outcome and differences were resolved by consensus.

Strength of evidence was evaluated for the following key outcomes measure: SVR24 (SVR12 used if SVR24 not reported) in patients with HCV genotype 1 infection. Additional strength-of-evidence ratings will be included in future updates of this report.

Table 2. Definitions of the grades of overall strength of evidence[35]

Grade	Definition
High	High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate.
Low	Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate.
Insufficient	Evidence either is unavailable or does not permit estimation of an effect.

Data Synthesis

We constructed evidence tables showing the study characteristics, quality ratings, and results for all included studies. We reviewed studies using a hierarchy of evidence approach, where the best evidence is the focus of our synthesis for each question, population, intervention, and outcome addressed. Studies that evaluated 1 direct-acting antiviral agent or regimen for HCV infection against another, providing direct evidence of comparative effectiveness and adverse event rates, were preferred over indirect comparisons.

In theory, trials that compare direct-acting antiviral agents for HCV infection with other drug classes or with placebos can also provide evidence about comparative effectiveness of DAAs. This is known as an indirect comparison, and can be difficult to interpret for a number of reasons, primarily heterogeneity of trial populations, interventions, and outcomes assessment. Data from indirect comparisons are used to support direct comparisons, where they exist, and

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may be used as the primary comparison where no direct comparisons exist. Indirect comparisons should be interpreted with caution.

In addition to discussing the findings of individual studies, quantitative syntheses were conducted using Stata 10.0[36] or StatsDirect[37] when evidence was sufficient. In order to determine whether meta-analysis could be meaningfully performed, we considered the quality of the studies and the heterogeneity among studies in design, patient population, interventions, and outcomes. When meta-analysis could not be performed, the data were summarized qualitatively. Most of the available trial data was reported as counts (n/N). We converted this data to relative risks and reported them as individual or pooled relative risks. For sustained virologic response we used data for SVR24. If data for SVR24 were not available, we included SVR at 12 weeks post treatment. Random-effects models were used to estimate pooled effects.[38] When necessary, indirect meta-analyses were done to compare interventions for which there were no head-to-head comparisons and where there was a common comparator intervention across studies.[39] The Q statistic and the I^2 statistic (the proportion of variation in study estimates due to heterogeneity) were calculated to assess heterogeneity in effects between studies.[40,41] Potential sources of heterogeneity were examined with sensitivity analyses based on patient population and variation in interventions.

RESULTS

We identified 888 citations from database searches and 122 citations from other sources including ClinicalTrials.gov, dossiers from pharmaceutical companies, reference lists and hand searches. Ultimately, our literature searches yielded 1,010 citations. Of these publications, we included 26 randomized controlled trials (in 29 publications),[42-70] 7 observational studies,[71-77] and 1 systematic review.[78] In our search of ClinicalTrials.gov, we identified 3 unpublished trials.[52,53,61] We also received dossiers from AbbVie, Gilead Sciences, Inc., Janssen Pharmaceutical, and Merck & Co., Inc which provided information for 3 published studies[50,58,59] and 4 unpublished studies.[44,56,65,67] Figure 1 illustrates the flow of studies through the selection process. A list of studies excluded after full-text review, and reasons for exclusion, is provided in Appendix D.

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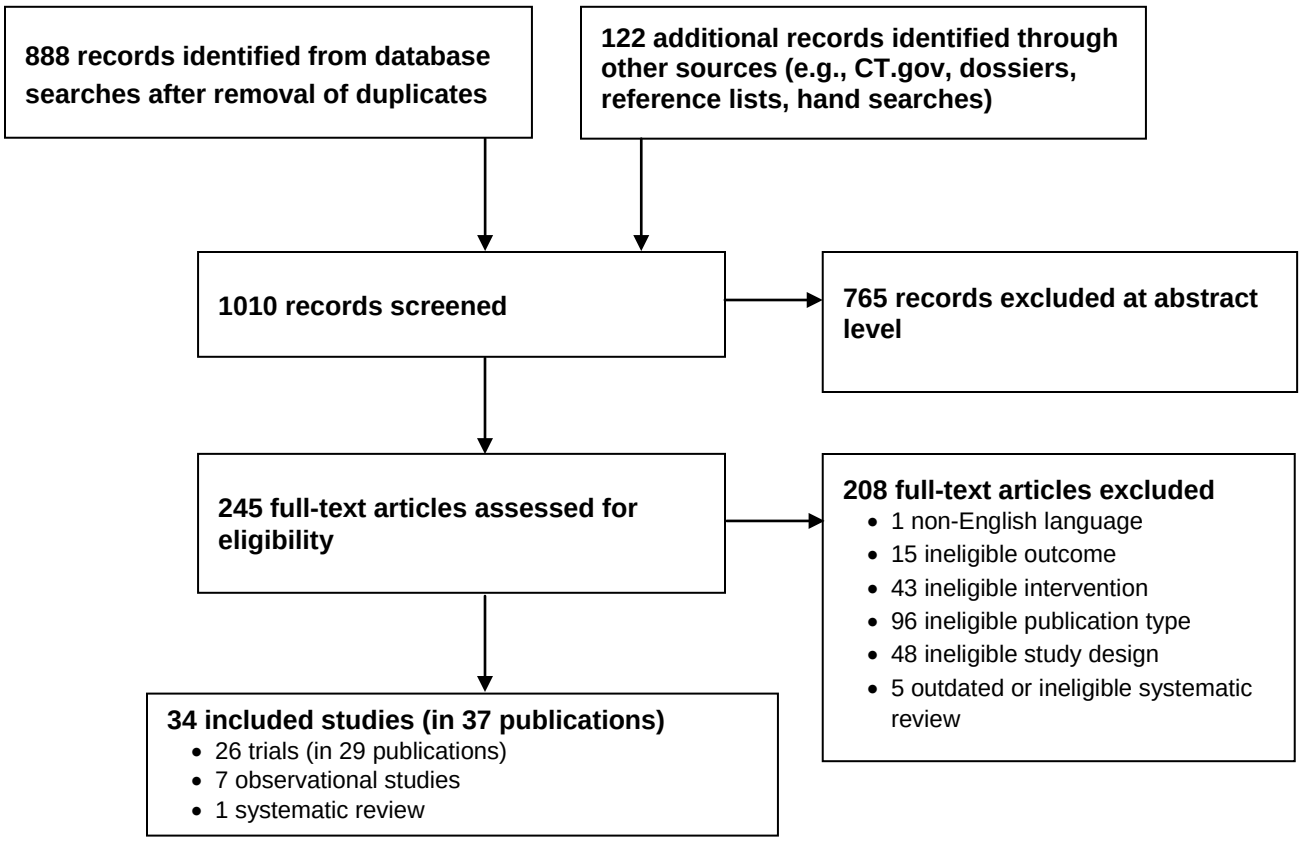
Figure 1. Results of literature search[a]



[a] The Drug Effectiveness Review Project uses a modified PRISMA flow diagram.[79]

None of the included trials compared one direct-acting antiviral agent (DAA) with a different DAA; instead they compared the same DAA with or without ribavirin, different doses of the same DAA, or different treatment durations of the same DAA with some treatment arms utilizing response-guided therapy (RGT). Indirect analysis was conducted in the absence of head-to-head evidence to compare one DAA with another in treatment-naive patients using trials that contained a PR-only arm as the common comparator. There was no common comparator to use in studies involving treatment-experienced patients with few trials employing a true control group

Most trials were rated fair quality and were primarily downgraded due to baseline differences between treatment groups, high and/or differential attrition, lack of clear randomization or allocation concealment methods, and lack of blinding. One trial was rated poor quality due to very high rates of attrition.[61]

Although we would have preferred evidence on clinical outcomes such as mortality, need for transplant, hepatocellular carcinoma, etc, there were very few, if any, such events reported as most trials followed patients through 72 weeks or less and may have concluded before clinical outcomes occurred. (Observational studies provided evidence for an association between treatment with pegylated interferon and ribavirin (PR) and mortality and hepatocellular carcinoma only.) The bulk of the evidence concerns sustained virologic response 24 weeks after the end of treatment, although studies of newer DAAs often reported only SVR12 data.

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Thirty-one trials enrolled only patients with HCV genotype 1; one trial enrolled patients with genotypes 1, 4 and 6; one trial enrolled patients with genotypes 1, 2, and 3; and one trial enrolled patients with genotypes 2 and 3. Ten trials included only treatment-naïve patients, 5 trials enrolled only treatment-experienced patients and 11 trials enrolled patients who were either treatment-naïve or experienced. Ten trials of both treatment naive and/or treatment-experienced patients stratified sustained virologic response (SVR) results by various subgroups. We reported comparisons between different DAA doses, different treatment durations and different treatment regimens (i.e., with and without ribavirin) and their effect on SVR by subgroup when data were available.

Strength of evidence for SVR was considered low (unless otherwise stated), generally due to the lack of head-to-head evidence, requiring indirect analyses for DAA comparisons and limited evidence for some DAAs with few trials or trials with small samples sizes per treatment arm. (Low strength of evidence implies that additional trial evidence may change the magnitude and/or direction of the estimate.) We did assess strength of the evidence for SVR in subgroups, including subgroups based on Metavir stage.

Below are the results by Key Question.

Key Question 1. In patients with HCV genotype 1, what are the comparative benefits and harms of DAA-containing versus DAA-containing regimens?

Summary of Evidence

Treatment Naïve

- No indirect comparisons were made with daclatasvir as evidence consisted of only 1 small trial (N=48) that had a substantially lower SVR rate in the PR arm compared with the PR arms of other trials precluding fair comparison (SOE: insufficient).
- Based on results from indirect meta-analyses:
    - Treatment with sofosbuvir plus PR was similar to treatment with simeprevir plus PR and treatment with boceprevir plus PR in all measured benefit and harm outcomes.
    - Boceprevir was superior to simeprevir in achieving SVR but there were no differences between the two DAAs in viral relapse or withdrawal due to adverse events. Treatment with boceprevir resulted in increased risk of anemia versus treatment with simeprevir.
- There was no difference between ledipasvir plus sofosbuvir with versus without ribavirin in SVR (SOE: Moderate) or in viral relapse. The risk of anemia was increased with the addition of ribavirin. Rash was also increased with the use of ribavirin with 8 weeks of treatment but not with 12 or 24 weeks. Treatment with 12 or 24 weeks of simeprevir plus sofosbuvir with versus without ribavirin in patients with Metavir scores F3-F4 resulted in similar rates of SVR and rash.
- The addition of ribavirin compared with not adding ribavirin to the 3D regimen increased SVR by 4%. However, there was a 12-fold increase in the risk of anemia.

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Treatment Experienced

- Based on a network meta-analysis in the CADTH report, indirect evidence on the comparative effectiveness of simeprevir and boceprevir (4 trials, N=1,129) showed no statistically significant difference between the 2 DAAs for SVR. However, some boceprevir regimens had higher risk of rash and anemia than simeprevir.
- Based on five trials, the addition of ribavirin to the following regimens did not appreciably change the effect of the following 4 DAA regiments on: the 3D regimen (1 trial), daclatasvir with sofosbuvir (1 trial), the fixed-dose combination of ledipasvir and sofosbuvir (2 trials), and simeprevir with sofosbuvir (1 trial). SVR24 was not reported.
- The addition of ribavirin to 4 DAA regimens increased adverse events, with effects on rash and anemia statistically significant for the 3D regimen (RR for rash 0.12, 95% CI 0.020 to 0.71, and for anemia 0.048, 95% CI 0.0048 to 0.46) and ledipasvir/sofosbuvir (RR 0.20, 95% CI 0.053 to 0.75 and RR 0.070, 95% CI 0.0096 to 0.52).

Detailed Assessment

Treatment Naïve

Daclatasvir compared with other DAAs

There were no head-to-head trials comparing daclatasvir with any other DAA. One small trial (N=48) of daclatasvir was available for comparisons.[64] The SVR rate for the PR group (the common comparison group) in the daclatasvir trial was 3/12 (25%). The SVR rates for the PR group in trials of other DAAs were 56% (range 46% to 65%) for simeprevir, 58% for sofosbuvir and 55% (range 38% to 88%) for boceprevir suggesting that indirect comparisons of daclatasvir to these other DAAs would not be valid. (SOE: insufficient for all comparisons with daclatasvir).

Sofosbuvir compared with simeprevir

Only 1 trial of sofosbuvir (N=121)[80] in treatment-naive patients was available for indirect comparison with simeprevir. We conducted indirect analyses and found no differences between sofosbuvir and simeprevir in SVR (6 trials, N=1304; RR 1.06, 95% CI 0.74 to 1.52)[49,50,52,59,80,81] or viral relapse (5 trials, N=1044; RR 2.58, 95% CI 0.12 to 57)[49,50,52,80,81] although the results for viral relapse were imprecise. See Table 3 for study characteristics. The SVR results are consistent with a recently published network meta-analysis (of fewer trials) by CADTH.[82]

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Table 3. DAA studies used in indirect analysis and their characteristics

Author, Year Study Name SVR used for comparison	N	Population (Treatment naïve)	DAA	Comparator
Lawitz, 2013[80] PROTON SVR24	121	Noncirrhotic Mean age 50 Male 60% HCV 1a 76% HCV 1b 24% SVR in PR group: 58%	Sofosbuvir 200 mg + Peg2aR x 12 weeks Sofosbuvir 400 mg + Peg2aR x 12 weeks Then Peg2aR x 12-36 weeks RGT	Peg2aR x 12 weeks Then Peg2aR x 36 weeks RGT
Fried, 2013[81] PILLAR SVR24	386	Noncirrhotic Mean age 47 Male 55% HCV1a 45% SVR in PR group: 65%	Simeprevir 150 mg + Peg2aR x 12 weeks, then Peg2a x 12 weeks Simeprevir 75 mg + Peg2aR x 12 weeks, then Peg2a x 12 weeks Simeprevir 150 mg + Peg2aR x 24 weeks Simeprevir 75 mg + Peg2aR 24-48 weeks	Peg2aR x 48 weeks
Hayashi, 2014[49] DRAGON SVR24	92	Noncirrhotic Mean age 54 Male 47% HCV1b 100% SVR in PR group: 46%	Simeprevir 50 mg x 12 weeks + Peg2aR x 24-48 weeks (RGT) Simeprevir 50 mg x 24 weeks + Peg2aR x 24-48 weeks (RGT) Simeprevir 100 mg x 12 weeks + Peg2aR x 24-48 weeks (RGT) Simeprevir 100 mg x 24 weeks + Peg2aR x 24-48 weeks (RGT)	Peg2aR x 48 weeks
Jacobson, 2014[50] QUEST-1 SVR12	394	Mean age 48 Male 56% HCV1a 56% HCV1b 44% SVR in PR group: 60%	Simeprevir 150 mg + Peg2aR x 12 weeks Then Peg2aR x 12-36 weeks (RGT)	Peg2aR x 48 weeks

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Author, Year Study Name SVR used for comparison	N	Population (Treatment naïve)	DAA	Comparator
Manns, 2011[60] OPERA-1 Did not report SVR	74	Median age 47 Male 66% HCV1a 41% HCV1b 55% HCV1e 1%	Simeprevir 25 mg x 1 week, then simeprevir 25 mg + Peg2aR x 3 weeks Simeprevir 25 mg + Peg2aR x 4 weeks Simeprevir 75 mg x 1 week, then simeprevir 75 mg + Peg2aR x 3 weeks Simeprevir 75 mg + Peg2aR x 4 weeks Simeprevir 200 mg x 1 week, then simeprevir 75 mg + Peg2aR x 3 weeks Simeprevir 200 mg + Peg2aR x 4 weeks Then could receive Peg2aR up to an additional 48 weeks	Peg2aR x 3 weeks Peg2aR x 4 weeks Then could receive Peg2aR up to 48 additional weeks
Manns, 2014[59] QUEST-2 SVR12	391	Median age 45 Male 56% HCV1a 32% HCV1b 66% HCV other 2% SVR in PR group: 52%	Simeprevir 150 mg + Peg2aR x 12 weeks, then Peg2aR x 12 or 36 weeks (RGT) Simeprevir 150 mg + Peg2bR x 12 weeks, then Peg2aR x 12 or 36 weeks (RGT)	Peg2bR x 12 weeks, then Peg2aR x 12 or 36 weeks (RGT)
NCT01292239[52] SVR24	183	Median age 55 Male 34% SVR in PR group: 57%	Simeprevir 100 mg + Peg2aR x 12 weeks, then Peg2aR x 12 weeks or 36 weeks (RGT)	Peg2aR x 48 weeks
Pol, 2012[64] SVR24	48	Noncirrhotic Median age 51 Male 67% HCV1a 67% HCV1b 33% SVR in PR group: 25%	Daclatasvir 3 mg + Peg2aR x 48 weeks Daclatasvir 10 mg + Peg2aR x 48 weeks Daclatasvir 60 mg + Peg2aR x 48 weeks	Peg2aR x 48 weeks
Kwo, 2010[14] SPRINT-1 SVR24	520	Mean age 47 Male 59% HCV1a 55% HCV1b 35% HCV1 no subtype 10% SVR in PR group: 38%	Peg2bR x 4 weeks, then Boceprevir 2400 mg + Peg2bR x 24 weeks Peg2bR x 4 weeks, then Boceprevir 2400 mg + Peg2bR x 44 weeks Boceprevir 2400 mg + Peg2bR x 28 weeks Boceprevir 2400 mg + Peg2bR x 48 weeks	Peg2bR x 48 weeks

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Author, Year Study Name SVR used for comparison	N	Population (Treatment naïve)	DAA	Comparator
Pearlman, 2014[63] SVR24	101	Noncirrhotic Mean age 53 Male 62% HCV1a 38% HCV1b 62% Low viral load (<600,000 IU/mL) with rapid virologic response to 4 weeks of Peg2bR before randomization SVR in PR group: 88%	Boceprevir 2400 mg + Peg2bR x 24 weeks (If previous 4 weeks RVR to Peg2bR)	Peg2bR x 24 weeks (If previous 4 weeks RVR to Peg2bR)
Poordad, 2011[83] SPRINT-2 SVR24	1097	No decompensated cirrhosis Mean age 49 Male 60% HCV1a 64% HCV1b 33% Missing data 3% SVR in PR group: 38%	Peg2bR x 4 weeks, then Boceprevir 2400 mg + Peg2bR for 24-44 weeks (RGT) Peg2bR x 4 weeks, then Boceprevir 2400 mg + Peg2bR for 44 weeks	Peg2bR x 48 weeks

Abbreviations: DAA , direct-acting antiviral agent; HCV, hepatitis C virus; RGT, response-guided therapy; SVR, sustained virologic response.

Indirect analyses showed no statistically significant differences between sofosbuvir and simeprevir in withdrawal from the study due to adverse events (5 trials, N=1,238; RR 0.58, 95% CI 0.13 to 2.51),[49,50,59,80,81] risk of anemia (5 trials, N=1,176; RR 0.91, 95% CI 0.39 to 2.40),[49,50,52,80,81] neutropenia (6 trials, N=1,250; RR 1.05, 95% CI 0.43 to 2.61),[49,50,52,60,80,81] or rash (6 trials, N=1,250; RR 1.91, 95% CI 0.70 to 5.17).[49,50,52,60,80,81] Statistical heterogeneity for the simeprevir studies was minimal except for rash (I^2=43%). Eliminating the smallest study (N=74)[60] that included the smallest and largest simeprevir doses of 25 mg and 200 mg and the shortest treatment with a DAA (4 weeks) reduced the heterogeneity (I^2=26%) without appreciably changing the estimate (5 trials, N=1,176; RR 1.86, 95% CI 0.69 to 4.98).

Sofosbuvir compared with boceprevir

One trial of sofosbuvir (N=121)[80] and 3 trials of boceprevir (N=1,790)[14,63,83] contributed data to indirect analyses. See Table 4 for study characteristics. Treatment with sofosbuvir was similar to treatment with boceprevir on numbers achieving SVR (3 trials, N=1,738, RR 0.89, 95% CI 0.62 to 1.27),[14,63,80,83]and viral relapse (3 trials, N=1,339, RR 1.73, 95% CI 0.07 to 42).[14,63,80,83] SVR results were also similar to those reported in an NMA by CADTH of fewer trials.[82]

Sensitivity analysis including the boceprevir trial conducted in patients with low viral load at baseline (<600,000 IU/mL)[63] changed the direction of the estimate for SVR (4 trials, N=1,839, RR 1.07, 95% CI 0.64 to 1.78)[14,63,80,83,14,80,83]but not for viral relapse (4 trials, N=1,440, RR 1.25, 95% CI 0.22 to 7.20).[63,80,83,14,80,83] These differences may be due to the greater treatment response in patients with initially low levels of HCV in the Pearlman trial[63] or because all enrolled patients had already demonstrated prior rapid viral response to PR prior to randomization.

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There were no differences between sofosbuvir and boceprevir in study withdrawal due to adverse events (2 trials, N=641, RR 0.26, 95% CI 0.06 to 1.21),[14,80] risk of anemia (3 trials, N=1,738, RR 0.63, 95% CI 0.26 to 1.54), or neutropenia (2 trials, N=641, RR0.58, 95% CI 0.21 to 1.64).[14,80]

Boceprevir compared with simeprevir

Three trials of boceprevir (N=1,790)[14,63,83] and 6 trials of simeprevir (N=1,495)[49,50,52,59,60,81] contributed to indirect comparisons. See Table 4 for study characteristics. Indirect analyses found no difference between boceprevir and simeprevir in SVR (8 trials, N=2,325, RR 1.00, 95% CI 0.67 to 1.48)[14,49,50,52,59,63,81,83] or viral relapse (7 trials, N=2,242, RR 1.50, 95% CI 0.66 to 3.43) with SVR results similar to those reported by NMA of fewer trials by CADTH.[82]

Sensitivity analyses excluding the trial conducted in patients with low initial viral load (<600,000 IU/mL) who had already demonstrated rapid viral response to PR[63] from our indirect analyses resulted in borderline increased SVR with boceprevir (7 trials, N=2,800; RR 1.20, 95% CI 1.01 to 1.45)[14,49,50,52,59,81,83] but little change in risk for viral relapse (6 trials, N=2,141, RR 1.49, 95% CI 0.57 to 3.92).[14,49,50,52,81,83]

Indirect analyses found an increased risk of anemia (6 trials, N=2,672, RR 1.55, 95% CI 1.21 to 1.98)[14,49,50,52,81,83] with boceprevir versus simeprevir but no difference between the 2 DAAs in study withdrawals due to adverse events (5 trials, N=1,637, RR 2.22, 95% CI 0.91 to 5.41) or neutropenia (6 trials, N=1,649, RR 1.80, 95% CI 0.97 to 3.34).[14,49,50,52,60,81] An additional boceprevir trial (N=1,097) found boceprevir associated with increased risk of neutropenia (RR 1.11; 95% CI 1.04 to 1.18) versus simeprevir but only grades 3 and 4 neutropenia were reported.[83]

DAA with or without ribavirin

Ledipasvir/sofosbuvir

One trial (N=865) compared treatment with 12 and 24 weeks of ledipasvir plus sofosbuvir without ribavirin compared with 12 and 24 weeks treatment with ledipasvir plus sofosbuvir with ribavirin.[43] The inclusion of ribavirin in the treatment regimen did not affect SVR for either 12 or 24 weeks treatment (RR 1.01, 95% CI 0.99 to 1.04; RR 0.99, 95% CI 0.96 to 1.01, respectively), viral relapse (RR 3.04, 95% CI 0.13 to 74; RR 3.00, 95% CI 0.12 to 73) or risk of rash (RR 0.77, 95% CI 0.42 to 1.44; RR 0.59, 95% CI 0.33 to 1.07). However, the risk of anemia was reduced when ribavirin was not included in the 12 week or 24 week treatment regimen (RR 0.02, 95% CI 0.001 to 0.33; RR 0.02, 95% CI 0.001 to 0.36).

Two trials compared 8 weeks treatment with ledipasvir plus sofosbuvir without versus with ribavirin and found no difference in SVR (N=472, RR 1.00, 95% CI 0.96 to 1.05, I^2=0) or viral relapse (RR 1.31, 95% CI 0.57 to 3.01, I^2=0).[54,57] Risk of anemia and rash were decreased without ribavirin (RR 0.13, 95% CI 0.04 to 0.49, I^2=0;[54,57] 1 trial, N=431, RR 0.16, 95% CI 0.05 to 0.53).[54]

Daclatasvir with sofosbuvir

One trial compared 24 weeks of treatment with daclatasvir plus sofosbuvir without ribavirin versus with ribavirin.[68] All patients achieved SVR (14/14 vs 15/15). There was also no difference in SVR among patients treated for 12 weeks without versus with ribavirin (1 trial, N=82, RR 1.03, 95% CI 0.92 to 1.15). (SOE: insufficient).

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Simeprevir with sofosbuvir
The COSMOS trial included a comparison of treatment with simeprevir plus sofosbuvir without ribavirin compared with simeprevir plus sofosbuvir with the addition of ribavirin for 12 and 24 weeks in treatment-naive patients with Metavir scores F3-F4 (N= 41, N=43, respectively).[58] Sustained virologic response rates were similar at both treatment lengths (12 weeks: RR 1.00, 95% CI 0.84 to 1.20; 24 weeks: 15/15 vs 28/28 achieved SVR). The risk of experiencing a rash was also similar without versus with ribavirin added to simeprevir plus sofosbuvir (12 weeks: RR 1.29, 95% CI 0.24 to 6.82; 24 weeks: RR 0.38, 95% CI 0.05 to 2.94).

3D regimen
Achievement of SVR was increased with the addition of ribavirin to 12 weeks treatment with the 3D regimen compared with the same treatment without ribavirin (3 trials, N=843, RR 1.04, 95% CI 1.02 to 1.07, I^2=87%) although the increase may not be clinically important.[47,55] Sensitivity analysis removing the trial in patients with genotype 1b eliminated the heterogeneity but did not appreciably change the estimate (2 trials, N=424, RR 1.07, 95% CI 1.02 to 1.13, I^2=0) including 1 trial in patients with genotype 1a and 1 trial of patients with mixed genotypes (66% had genotype 1a).

However, the risk of anemia was also significantly increased with the addition of ribavirin (3 trials, N=843, RR 12, 95% CI 7.43 to 20, I^2=0)[47,55], though there was no difference in risk of rash (3 trials, N=843, RR 1.44, 95% CI 0.82 to 2.53, I^2=0).[47,55]

DAA with regular compared with low-dose ribavirin

Boceprevir
One trial (N=75) randomized patients to boceprevir plus PR with regular dose ribavirin (800-1400 mg per day) or with low-dose ribavirin (400-1000 mg per day) for 48 weeks and found no difference in SVR rates (RR 1.41, 95% CI 0.77 to 2.56).[14]

Treatment Experienced

3D regimen

The SAPPHIRE-II trial of the 3D regimen with ribavirin met criteria for inclusion in this review, but could not be included in our primary analyses.[70] Though it was designed as a placebo-controlled trial, SVR and relapse were reported only for the active treatment arm, with comparison to historical controls. For efficacy it was thus excluded as a single-arm study, though we reported SVR and relapse rates in Table F1 (Appendix F). Harms could not be compared to other DAA regimens because no other trials in treatment-experienced genotype 1 patients included a placebo arm as a common comparator for indirect analysis.

Boceprevir compared with simeprevir

Sustained virologic response
Table 4 shows the effect on SVR of 4 regimens that included simeprevir or boceprevir for HCV genotype 1, based on network meta-analysis results from the 2014 CADTH review.[82] The review found no trials of sofosbuvir in treatment-experienced patients that met its inclusion criteria. For each of the 2 DAAs, 1 regimen used 48 weeks fixed duration of PR therapy, and 1 used response-guided therapy for PR. Results are presented for all treatment-experienced patients and,

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when possible, also stratified by prior treatment response. For any combination of simeprevir and boceprevir regimens, there was no difference between the 2 DAAs in their effect on SVR in treatment-experienced patients with HCV genotype 1. CADTH's NMAs did not include relapse, long-term clinical outcomes, or extrahepatic manifestations of hepatitis.

We did identify 1 study not included in CADTH's NMA that compared a DAA to PR.[61] However, we rated this study poor quality for its high study withdrawal rate (73%) and differences between treatment groups in baseline characteristics and do not consider it further in this report.

Table 4. The comparative effect of DAAs on SVR in treatment-experienced patients with HCV genotype 1: Results from network meta-analyses[82]

SVR[a]	Relative Risk (95% CrI)
All treatment-experienced patients (4 RCTs/N=1129)	
Boceprevir for 44 weeks + PR for 48 weeks vs. Simeprevir for 12 weeks + PR for 48 weeks	1.0 (0.71, 1.6)
Boceprevir for 44 weeks + PR for 48 weeks vs. Simeprevir for 12 weeks + PR as RGT for 24 or 48 weeks	1.0 (0.74, 1.5)
Boceprevir for 32 weeks + PR as RGT for 36 or 48 weeks vs. Simeprevir for 12 weeks + PR for 48 weeks	0.89 (0.56, 1.5)
Boceprevir for 32 weeks + PR as RGT for 36 or 48 weeks vs. Simeprevir for 12 weeks + PR as RGT for 24 or 48 weeks	0.91 (0.59, 1.4)
Patients with prior relapse (4 RCTs/N=850)	
Simeprevir for 12 weeks + PR for 48 week vs. Boceprevir for 32 weeks + PR as RGT for 36 or 48 weeks	1.1 (0.57, 1.7)
Boceprevir for 44 weeks + PR for 48 weeks vs. Simeprevir for 12 weeks + PR for 48 weeks	1.0 (0.72, 1.9)
Boceprevir for 44 weeks + PR for 48 weeks vs. Simeprevir for 12 weeks + PR as RGT for 24 or 48 weeks	1.0 (0.76, 1.4)
Boceprevir for 32 weeks + PR as RGT for 36 or 48 weeks vs. Simeprevir for 12 weeks + PR as RGT for 24 or 48 weeks	0.93 (0.62, 1.3)
Patients with prior partial response (3 RCTs/N=246)	
Boceprevir for 44 weeks + PR for 48 weeks vs. Simeprevir for 12 weeks + PR for 48 weeks	0.90 (0.40, 2.8)
Boceprevir for 32 weeks + PR as RGT for 36 or 48 weeks vs. Simeprevir for 12 weeks + PR for 48 weeks	0.73 (0.25, 2.4)
Patients with prior null response	NR

[a]CADTH 2014 "considered SVR12…an acceptable surrogate for SVR24…If both SVR12 and SVR24 were reported, SVR24 was used in the analyses."
Abbreviations: CADTH, Canadian Agency for Drugs and Technology in Health; CrI, credible interval; DAA, direct-acting antiviral agent; HCV, hepatitis C virus; PR, pegylated interferon and ribavirin; RCT, randomized controlled trial; RGT, response-guided therapy; SVR, sustained virologic response.

Adverse events

As reported by CADTH[82] boceprevir regimens were associated with increased rash (RRs 1.8 to 2.9) and anemia (RRs 2.4 to 2.7) compared with simeprevir regimens, though most comparisons were not statistically significant.

DAA with or without ribavirin

3D regimen

We found 1 study of the 3D regimen with or without ribavirin in treatment-experienced patients.[45] The trial randomized 187 patients with HCV genotype 1b and found no difference in SVR12 between patients who did not receive ribavirin and those who did (RR 1.0, 95% CI 0.98 to 1.1; SVR24 not reported). This finding did not depend on treatment history, with relative risks

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near 1.0 for those with no or partial response to prior treatment and those who had relapsed. SVR12 was achieved by 91 out of 91 patients not given ribavirin and 85 out of 88 of those given ribavirin. No patient relapsed. Patients not given ribavirin had fewer adverse effects, with differences statistically significant for anemia (RR 0.048, 95% CI 0.0048 to 0.46) and rash (RR 0.12, 95% CI 0.020 to 0.71). Few patients withdrew due to adverse events (2 total, both in the ribavirin arm).

Daclatasvir with sofosbuvir
In a single *trial*[68] of daclatasvir plus sofosbuvir with or without ribavirin (N=41) all patients achieved SVR12. No treatment-experienced patient relapsed. Three out of 20 patients given ribavirin had anemia versus 0/21 not given ribavirin, with similar results for rash (2/20 vs 0/21). No patient withdrew from the study.

Ledipasvir/sofosbuvir
One trial of fixed-dose ledipasvir/sofosbuvir included 2 randomized arms in 19 patients with cirrhosis and is discussed in Key Question 7.[48] A meta-analysis of 2 other trials[42,57] found no difference in SVR12 or relapse between patients given 12 weeks of ledipasvir/sofosbuvir without ribavirin compared with those given the combination with ribavirin (N=260; RR 0.97, 95% CI 0.91 to 1.0, I^2=0% for SVR; RR 1.8, 95% CI 0.59 to 5.7, I^2=0% for relapse). There were no withdrawals due to adverse events in either study. However, anemia was less common without ribavirin (RR 0.070, 95% CI 0.0096 to 0.52), as was rash (0.20, 95% CI 0.053 to 0.75). Please refer to Table 5 below for study characteristics.

Table 5. Trials of fixed-dose ledipasvir and sofosbuvir with and without ribavirin in treatment-experienced patients

Author, date Trial name	N Duration of treatment	Daily dose (mg): ledipasvir, sofosbuvir, ribavirin	Stage of disease	Quality rating
Afdhal, 2014[42] ION-2	441 12 vs. 24 weeks	Ledipasvir: 90; Sofosbuvir: 400; Ribavirin: weight-based (1000 or 1200)	Any (F0-F4)	Good
Gane, 2014[48] ELECTRON	19 12 weeks	Ledipasvir: 90; Sofosbuvir: 400; Ribavirin: weight-based (1000 or 1200)	All with cirrhosis (F4)	Fair
Lawitz, 2014[57] LONESTAR	40 12 weeks	Ledipasvir: 90; Sofosbuvir: 400; Ribavirin: weight-based (1000 or 1200)	Any (F0-F4)	Fair

Abbreviations: F0-F4, Metavir fibrosis score.

Simeprevir with sofosbuvir
We found 1trial (COSMOS) of the combination of simeprevir and sofosbuvir.[58] Cohort 1 of COSMOS randomized 81 treatment-experienced patients with early-stage disease (Metavir score F0-F2); Cohort 2 included both treatment-naïve (N=40) and treatment-experienced patients (N=47) with late-stage disease (F3-F4). Inclusion of ribavirin did not affect SVR12 for treatment-experienced patients with any disease stage given simeprevir and sofosbuvir without versus with ribavirin (N=127, RR 1.1, 95% CI 0.94 to 1.2). Relapse occurred in 4 patients, 3 of whom received ribavirin.

We analyzed harms data pooled across Cohorts 1 and 2 (N=167, 76% treatment-experienced, all stages of disease included). Study withdrawals due to adverse events were infrequent (N=4). Anemia was less likely without ribavirin, with the difference statistically

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significant for patients treated for 24 weeks (RR 0.11, 95% CI 0.019 to 0.58). There was no difference in risk of rash (RR 0.70, 95% CI 0.33 to 1.4, duration arms pooled).

Key Question 2. In patients with HCV genotypes other than 1, what are the comparative benefits and harms of DAA-containing versus DAA-containing regimens?

Summary of Evidence

- There was no difference in rates of SVR between daclatasvir plus sofosbuvir whether or not ribavirin was added to the treatment regimen in treatment-naïve patients with HCV genotype 2 or 3 infection.
- There was no evidence in treatment-experienced patients.

Detailed Assessment

Treatment Naïve

Daclatasvir with sofosbuvir ± ribavirin

One trial (N=28) compared treatment for 24 weeks with daclatasvir plus sofosbuvir without ribavirin to treatment with daclatasvir plus sofosbuvir with ribavirin in patients with HCV genotype 2 (61%) and genotype 3 (39%) and found no difference in SVR (14/14 vs 13/14, RR 1.07, 95% CI 0.89 to 1.30).[68] (SOE: insufficient)

Treatment Experienced

We found no evidence comparing DAA regimens in treatment-experienced patients with HCV genotypes other than 1.

Key Question 3. In patients with HCV genotypes other than 1, what are the comparative benefits and harms of DAA-containing versus non-DAA containing regimens?

Summary of Evidence

- Treatment with sofosbuvir plus ribavirin for 12 weeks versus treatment with PR for 24 weeks in treatment-naïve patients with HCV genotypes 2 and 3 was associated with similar rates of SVR and anemia but reduced risk of rash and neutropenia.
- Treatment with sofosbuvir plus ribavirin for 12 weeks in a mixed population was associated with increased rates of SVR12 and anemia compared with placebo. (SOE: moderate for SVR)

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Detailed Assessment

Treatment Naïve

Sofosbuvir

We identified 1 trial (N=499) of sofosbuvir plus ribavirin for 12 weeks versus PR for 24 weeks (FISSION) in patients with genotype 2 (27%) and genotype 3 (72%).[84] There was no difference in SVR between groups (RR 1.01. 95% CI 0.89 to 1.14). However, more patients with genotype 2 achieved SVR (97%) than did patients with genotype 3 (56%) in the groups receiving sofosbuvir plus ribavirin, although this difference was not statistically significant. In patients with HCV RNA <25 IU/ml at end of treatment, there was a borderline increase in viral relapse in patients treated with sofosbuvir and ribavirin for 12 weeks versus PR for 24 weeks (N=466, RR 1.40, 1.02 to 1.93). The trial authors conducted a sensitivity analysis of only those patients with viral load <25 IU/mL who completed treatment (N=430) and found similar results (RR 1.49, 95% CI 1.05 to 2.11). Sofosbuvir plus ribavirin for 12 weeks versus PR for 24 weeks was associated with a reduced risk of rash (RR 0.51, 95% CI 0.32 to 0.82) and neutropenia (RR 0.03, 95% CI 0.004 to 0.23) but not anemia (RR 0.68, 95% CI 0.39 to 1.17).

Treatment Experienced

We found no evidence in treatment-experienced patients with HCV genotypes other than 1 comparing DAA-containing versus non-DAA containing regimens.

Mixed Treatment History

Sofosbuvir

One trial (N=278) randomized patients with HCV genotypes 2 and 3 to 12 weeks of sofosbuvir and ribavirin or placebo.[51] Treatment with sofosbuvir and ribavirin was associated with increased SVR rates (RR 107, 95% CI 7 to 1700) and anemia (RR 19, 95% CI 1 to 300) compared with placebo, but there was no difference between groups in risk of rash (RR 1.03, 95% CI 0.43 to 2.49). (SOE: moderate for SVR).

The VALENCE trial[69] was designed as a placebo-controlled trial of 12 weeks of treatment with sofosbuvir and ribavirin in treatment-naïve or -experienced patients with HCV genotype 2 or 3. After the study began treatment duration was extended to 24 weeks for genotype 3 patients (except for 11 patients who had already completed 12 weeks of treatment). The study was unblinded and the placebo arm discontinued, leaving no randomized arms; for this reason we excluded the trial from this review. For comparison with other sofosbuvir trials, we included SVR and relapse rates in Table F1 (Appendix F). SVR rates appeared lower, and relapse rates higher, in patients with genotype 3, especially the few of these patients treated for 12 instead of 24 weeks. Treatment-experienced patients appeared less likely to achieve SVR than those who were treatment naive (relapse was not reported stratified by treatment history).

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Key Question 4. What are the comparative benefits and harms of varying doses and durations of DAA treatment within regimens in patients with hepatitis C virus?

Summary of Evidence

Genotype 1

Treatment naïve

Dose

- There was no statistically significant differences between the following DAA regimens:
  - Daclatasvir 3 mg, 10 mg and 60 mg in SVR (SOE: insufficient)
  - Sofosbuvir 200 mg and 400 mg in SVR and adverse events.
  - Simeprevir varying doses (3 trials ranging from 25 mg to 150 mg) in SVR, viral relapse, or adverse events.
  - Paritaprevir 100 mg and 150 mg as part of the 3D in SVR, anemia, or rash.

Duration

- Treatment for 12 weeks with either simeprevir 50 mg or 100 mg resulted in a lower risk of neutropenia than treatment with the same dose for 24 weeks.
- Treatment with ledipasvir plus sofosbuvir for 8 weeks was associated with increased risk of viral relapse compared with treatment for 12 weeks Treatment with 4 weeks of boceprevir followed by boceprevir plus PR for 24 versus 44 week resulted in reduced rates of SVR and neutropenia with shorter treatment duration.
- There were no statistically significant differences between the following DAA regimens:
  - Treatment with the 3D regimen plus ribavirin for 8 compared with 12 weeks in SVR, anemia and rash; 12 versus 24 weeks in SVR, anemia, and rash (SOE: Moderate for SVR); or 8 compared with 24 weeks in SVR
  - Treatment with simeprevir plus sofosbuvir with or without ribavirin in patients with Metavir F3 or F4 for 12 weeks compared with 24 weeks in SVR.
  - Treatment with simeprevir 50 mg, 75 mg, 100 mg, and 150 mg for 12 weeks compared with treatment for 24 weeks in SVR, viral relapse, anemia, and rash.
  - Treatment with sofosbuvir for 24 weeks plus 23 weeks treatment with daclatasvir compared with 24 weeks treatment of sofosbuvir plus daclatasvir in patients with genotype 1 and in those with genotypes 2 and 3 analyzed together (SOE: insufficient).

Treatment experienced

Dose

- The AVIATOR study found no difference in SVR24, anemia or rash between 100 mg versus 150 mg of paritaprevir as part of the 3D regimen plus ribavirin.

Duration

- All included studies comparing treatment duration in treatment-experienced patients compared 12 and 24 weeks of treatment. Effects of this duration comparison in specific drug regimens were as follows:

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  - 3D regimen: treatment duration did not affect SVR, anemia, or rash.
  - Ledipasvir/sofosbuvir: treatment duration did not affect SVR (SOE: Moderate), but relapse was more likely with 12 weeks of treatment.
  - Simeprevir with sofosbuvir: treatment duration did not affect SVR or rash, but anemia was less likely with 12 compared with 24 weeks of treatment among patients also treated with ribavirin.
  - Simeprevir: An unpublished study reported no effect of treatment duration on benefits or harms.
- Boceprevir: The 2014 CADTH review NMA found no statistically significant difference in SVR, anemia, or rash between 44 weeks of boceprevir and PR compared with 32 weeks of boceprevir with response-guided PR.

Genotypes Other Than 1

Treatment naïve

- In one small trial (N=30) in patients with genotypes 2 and 3, there was no difference in SVR with 7 days of sofosbuvir followed by 23 weeks of sofosbuvir plus daclatasvir compared with 24 weeks of sofosbuvir plus daclatasvir (SOE: insufficient).

Treatment experienced

- In patients with HCV genotypes 2 and 3, treatment with sofosbuvir and ribavirin for 12 weeks resulted in lower rates of SVR than treatment for 16 weeks.

Detailed Assessment

Genotype 1

Treatment naïve

Daclatasvir
We identified 2 small trials of daclatasvir in HCV genotype 1 patients that varied doses of the DAA.[62,64] One trial (N=48) randomized patients to daclatasvir 3, 10, or 60 mg in addition to PR[64] for 48 weeks while the other (N=30) treated with 1, 10, 30, 60, or 100 mg of daclatasvir for 14 days.[62] Data from the 2 trials were not eligible for pooling due to differences in the control groups (placebo plus PR vs. placebo).

Treatment with daclatasvir 3 mg was borderline non-significantly associated with reduced SVR compared with daclatasvir 10 mg and 60 mg (RR 0.50, 95% CI 0.24 to 1.02), which were not different from each other.[64] One patient out of 12 experienced viral relapse in each of the 10 mg and 60 mg arms compared with 2/12 patients in the 3 mg arm. There was no apparent dose-response regarding anemia, neutropenia and rash. (SOE: insufficient for SVR).

In the second trial[62], mean maximum decrease from baseline in HCV RNA seemed to increase with dose. When given daily, the maximum decrease was seen with 100 mg (-3.62 log IU/mL, N=4) compared with placebo (-1.32, N=6). However, treatment with twice daily daclatasvir 30 mg was associated with the greatest maximum decrease (-4.10, N=4). Frequency of adverse events was not apparently dose-related.

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Sofosbuvir
One trial of 12 weeks of sofosbuvir (N=121) plus PR in genotype 1 patients compared sofosbuvir 200 mg plus PR versus 400 mg plus PR (followed by 12-36 additional weeks of PR response-guided therapy [RGT]) and found no difference between the 2 doses in SVR (85% vs 89%, RR 0.96, 95% CI 0.82 to 1.11) or viral relapse (2% both groups).[80] There was also no difference between treatment with sofosbuvir 200 mg and 400 mg in anemia (23% vs 17%, RR 1.35, 95% CI 0.60 to 3.05), neutropenia (17% vs 30%, RR 0.56, 95% CI 0.26 to 1.21) or rash (27% for 200 mg and 26% for 400 mg).

Simeprevir
One trial (N=386) compared simeprevir 75 mg compared with 150 mg for 12 weeks and 24 weeks.[81] All 4 groups also received PR for 48 weeks. There were no statistically significant differences between 75 mg and 150 mg in SVR, viral relapse, anemia, neutropenia or rash (Table 6). A second trial (N=92) compared simeprevir 50 mg versus 100 mg for 12 and 24 weeks (groups received PR 24 or 48 weeks RGT) and also found no difference between doses in the same outcomes[49] while a third trial (N=37) found no difference between simeprevir 25 mg and 75 mg for 3 or 4 weeks (with up to 48 weeks PR) in risk of neutropenia or rash.[60]

Table 6. Dose compared with dose comparisons in HCV genotype-1 simeprevir trials in treatment-naive patients

Drug Study (N)	Outcome	Dose comparison			
		75 vs 150 mg % at 12 weeks	**75 vs 150 mg % at 24 weeks**	**75 vs 150 mg RR (CI) 12 weeks**	**75 vs 150 mg RR (CI) 24 weeks**
Simeprevir PILLAR[81] (386)	SVR	82 vs 81	75 vs 86	1.02 (0.88, 1.19)	0.87 (0.74, 1.02)
	Viral relapse	11vs 9	19 vs 8	1.28 (0.47, 3.49)	2.43 (0.99, 5.98)
	Anemia	19 vs 22	19 vs 24	0.87 (0.50, 1.62)	1.12 (0.60, 2.11)
	Neutropenia	19 vs 25	31 vs 23	0.78 (0.43, 1.42)	1.35 (0.79, 2.29)
	Rash	27 vs 21	13 vs 23	1.30 (0.73, 2.29)	0.59 (0.29, 1.19)
		50 vs 100 mg % at 12 weeks	**50 vs 100 mg % at 24 weeks**	**50 vs 100 mg RR (CI) 12 weeks**	**50 vs 100 mg RR (CI) 24 weeks**
Simeprevir DRAGON[49]	SVR	78 vs 77	77 vs 92	1.01 (0.76, 1.35)	0.83 (0.60, 1.17)
	Viral relapse	15 vs 15	17 vs 8	1.00 (0.28, 3.58)	2.17 (0.22, 21)
	Anemia	30 vs 23	39 vs 39	1.28 (0.52, 3.19)	1.00 (0.38, 2.64)
	Neutropenia	44 vs 54	77 vs 92	0.83 (0.48, 1.43)	0.83 (0.60, 1.17)
	Rash	63 vs 58	62 vs 62	1.09 (0.70, 1.69)	1.00 (0.55, 1.84)
		25 vs 75 mg % for 3 or 4 weeks		**25 vs 75 mg RR (CI) for 3 or 4 weeks**	
Simeprevir OPERA-1[60]	Neutropenia	6 vs 16		0.35 (0.04, 3.08)	
	Rash	0 vs 5		1.06 (0.07, 16)	

3D regimen
One trial (N=160) compared treatment with different doses (100 mg vs 150 mg) of paritaprevir as part of the 3D regimen with ribavirin for 12 and 24 weeks.[55] There was no difference between doses in SVR, anemia or rash at 12 weeks (RR 1.03, 95% CI 0.94 to 1.12; RR 0.77, 95% CI 0.18 to 3.22; RR 0.86, 95% CI 0.28 to 2.57, respectively) or 24 weeks (RR 1.03, 95% CI 0.90 to 1.18; RR 2.00, 95% CI 0.39 to 10; RR 1.33, 95% CI 0.51 to 3.50).

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Treatment duration

Simeprevir
One trial (N=386) that compared doses of simeprevir found little difference between treatment with either 75 mg or 150 mg for 12 weeks versus treatment for 24 weeks in SVR, viral relapse, anemia, neutropenia or rash.[81] Please refer to Table 7. A second trial (N=92) found similar results with either simeprevir 50 mg or 100 mg for 12 versus 24 weeks, with the exception that treatment with either dose of simeprevir for 12 weeks was associated with decreased risk of neutropenia than was treatment for 24 weeks.[49]

Table 7. Duration compared with duration comparisons in HCV genotype-1 trials in treatment-naive patients

Drug Study (N)	**Outcome**	**Duration comparison**			
Simeprevir PILLAR[81] (386)		**75 mg % 12 vs 24 weeks**	**150 mg % 12 vs 24 weeks**	**75 mg 12 vs 24 weeks RR (CI)**	**150 mg 12 vs 24 weeks RR (CI)**
	SVR	82 vs 75	81 vs 86	1.08 (0.92, 1.28)	0.91 (0.80, 1.05)
	Viral relapse	11 vs 19	9 vs 8	0.57 (0.26, 1.28)	1.09 (0.37, 3.21)
	Anemia	19 vs 21	22 vs 19	0.90 (0.48, 1.69)	1.16 (0.63, 2.16)
	Neutropenia	19 vs 31	25 vs 23	0.63 (0.36, 1.11)	1.08 (0.62, 1.90)
	Rash	27 vs 13	21 vs 23	**2.02 (1.02, 4.00)**	0.91 (0.50, 1.66)
Simeprevir DRAGON[49] (92)		**50 mg % 12 vs 24 weeks**	**100 mg % 12 vs 24 weeks**	**50 mg 12 vs 24 weeks RR (CI)**	**100 mg 12 vs 24 weeks RR (CI)**
	SVR	78 vs 77	77 vs 92	0.94 (0.65, 1.37)	0.83 (0.64, 1.08)
	Viral relapse	15 vs 17	15 vs 8	0.92 (0.20, 4.36)	2.00 (0.25, 16)
	Anemia	30 vs 39	23 vs 39	0.77 (0.31, 1.90)	0.60 (0.23, 1.60)
	Neutropenia	44 vs 77	54 vs 92	**0.58 (0.35, 0.97)**	**0.58 (0.40, 0.86)**
	Rash	63 vs 62	58 vs 62	1.02 (0.61, 1.72)	0.94 (0.55, 1.61)
Sofosbuvir Kowdley,2013[85] ATOMIC (177)		**400 mg % 12 vs 24 weeks**		**400 mg 12 vs 24 weeks RR (CI)**	
	SVR	89 vs 89		0.99 (0.88, 1.12)	
	Viral relapse	4 vs 1		4.19 (0.39, 45)	
	Anemia	14 vs 25		0.54 (0.26, 1.15)	
	Neutropenia	23 vs 20		1.15 (0.63, 2.12)	
	Rash	14 vs 21		0.65 (0.30,1.40)	
		60/400 mg 23 weeks+400 mg 1 week[b] vs 60/400 24 weeks %		**60/400 mg 23 weeks+400 mg 1 week[b] vs 60/400 24 weeks RR (CI)**	
Daclatasvir/ Sofosbuvir Sulkowski, 2014[68] (44)	SVR	93 vs 100		0.94 (0.78, 1.13)	

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Drug Study (N)	Outcome	Duration comparison			
3D regimen with ribavirin Kowdley, 2014[55] (318) Poordad, 2014[66] (160)		**Paritaprevir 100 mg 8 vs 12 weeks %**	**Paritaprevir 150 mg 12 vs 24 weeks %**	**Paritaprevir 100 mg 8 vs 12 weeks RR (CI)**	**Paritaprevir 150 mg 12 vs 24 weeks RR (CI)**
	SVR	88 vs 95	94 vs 93[c]	0.92 (0.83, 1.03)	1.01 (0.95, 1.08)[c]
	Anemia[d]	6 vs 10	10 vs 5	0.63 (0.18, 2.20)	2.00 (0.39, 10)
	Rash[d]	13 vs 15	15 vs 15	0.83 (0.33, 2.13)	1.00 (0.35, 2.84)
Simeprevir/ Sofosbuvir COSMOS[58] (24)		**150/400 mg 12 vs 24 weeks %**		**150/400 mg 12 vs 24 weeks RR (CI)**	
	SVR (F3-F4)	80 vs 100		0.80 (0.57, 1.12)	
	Rash (F3-F4)	14 vs 13		1.14 (0.18, 7.08)	
Simeprevir/ Sofosbuvir/ ribavirin COSMOS[58] (34)		**150/400 mg + ribavirin 12 vs 24 weeks %**		**150/400 mg + ribavirin 12 vs 24 weeks RR (CI)**	
	SVR (F3-F4)	94 vs 100		0.95 (0.81, 1.11)	
	Rash (F3-F4)	19 vs 23		0.79 (0.29, 2.21)	
Ledipasvir/ Sofosbuvir LONESTAR[57] Kowdley, 2014[54] (747)		**90/400 mg % 8 vs 12 weeks**		**90/400 mg 8 vs 12 weeks RR (CI)**	
	SVR	95 vs 95		0.99 (0.95, 1.03)	
	Viral relapse	5 vs 1		**3.53 (1.10, 11)**	
	Anemia[a]	0 vs 0			
	Rash[a]	1 vs 2		0.60 (0.15, 2.49)	
Ledipasvir/ Sofosbuvir Afdahl, 2014[43] ION-1		**90/400 mg % 12 vs 24 weeks**		**90/400 mg 12 vs 24 weeks RR (CI)**	
	SVR	99 vs 98		1.01 (0.98, 1.04)	
	Viral relapse	<1 vs <1		1.01 (0.06, 16)	
	Anemia	0 vs 0			
	Rash	7 vs 7		1.01 (0.52, 1.98)	
Ledipasvir/ Sofosbuvir/ Ribavirin Afdahl, 2014[43] ION-1		**90/400 mg % 12 vs 24 weeks**		**90/400 mg 12 vs 24 weeks RR (CI)**	
	SVR	97 vs 99		0.98 (0.96, 1.01)	
	Viral relapse	0 vs 0			
	Anemia	12 vs 10		1.14 (0.66, 1.95)	
	Rash	10 vs 12		0.78 (0.45, 1.33)	
Boceprevir plus PR Kwo, 2010[14] SPRINT-1(210)		**2400 mg + PR % 28 vs 48 weeks**		**2400 mg + PR 28 vs 48 weeks**	
	SVR	54 vs 67		0.81 (0.65, 1.01)	
	Anemia	56 vs 52		1.07 (0.83, 1.37)	
	Neutropenia	23 vs 25		0.93 (0.57, 1.49)	
Boceprevir plus PR Kwo, 2010[14] SPRINT-1(206)		**PR 4 weeks then 2400 mg + PR % 24 vs 44 weeks**		**PR 4 weeks then 2400 mg + PR 24 vs 44 weeks**	
	SVR	56 vs 75		**0.75 (0.61, 0.92)**	
	Anemia	53 vs 56		0.95 (0.74, 1.22)	
	Neutropenia	17 vs 30		**0.55 (0.33, 0.93)**	

[a] Kowdley, 2014 only (N=647)
[b] Leading week of Sofosbuvir 400 mg only
[c] Pooled analysis Kowdley and Poordad
[d] Kowdley only

Ledipasvir/sofosbuvir

Treatment with ledipasvir and sofosbuvir for 8 weeks was associated with increased risk of viral relapse when compared with treatment for 12 weeks (2 trials, N=747, RR 3.53, 95% CI 1.10 to

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11).[54,57] Please refer to Table 7. There was no difference between treatment for 8 versus 12 weeks in effects on SVR[54,57], anemia[54], or rash.[57]

There was also no difference between treatment with ledipasvir and sofosbuvir for 12 weeks versus 24 weeks in effects on SVR, viral relapse, risk of anemia or rash based on results from 1 trial (N=431).[42]

Ledipasvir/sofosbuvir + ribavirin

Results from 1 trial (N=434) indicate that treatment with ledipasvir and sofosbuvir plus ribavirin for 12 weeks was not different from treatment for 24 weeks in effects on SVR, viral relapse, anemia, or rash (Table 6).[42]

Daclatasvir with sofosbuvir

One trial randomized HCV genotype 1 treatment-naive patients to 7 days of sofosbuvir followed by 23 weeks of sofosbuvir plus daclatasvir (N=15) or to 24 weeks of sofosbuvir plus daclatasvir (N=14) and found no difference in SVR (RR 0.94, 95% CI 0.78 to 1.13; see Table 7).[68] (SOE: insufficient).

3D regimen

Pooled analysis of 2 trials (N=478) compared the 3D regimen plus ribavirin with paritaprevir (ABT-450r) 150/100 mg and found no difference between treatment with 12 weeks versus 24 weeks in effect on SVR, anemia, or rash (RR 1.02, 95% CI 0.97 to 1.08, I^2=3%, pooled paritaprevir 100 and 150 mg).[55,66] Please refer to Table 7 for relative risks by paritaprevir dose. One trial also found no difference between 8 and 12 weeks of treatment with the 3D regimen in effects on SVR, anemia, or rash (N=160).[66] Additionally, SVR was also similar when the treatment durations compared were 8 versus 24 weeks (RR 0.97, 95% CI 0.85 to 1.11) based on evidence from 1 trial (N=120).[55]

Simeprevir with sofosbuvir

Treatment-naive patients (Metavir F3-F4) who were treated with simeprevir plus sofosbuvir had similar rates of SVR when treated for 12 weeks (8/10) or 24 weeks (14/14) in the COSMOS trial (RR 0.80, 95% CI 0.57 to 1.12) (Table 7).[58] When ribavirin was added to simeprevir plus sofosbuvir in treatment-naive, Metavir F3-F4 patients, treatment with 12 versus 24 weeks also yielded similar effects on SVR (17/18 vs. 16/16, RR 0.95, 95% CI 0.81 to 1.11).[58] There was little difference in risk of rash whether treatment included or did not include ribavirin for 12 versus 24 weeks.

Boceprevir

Genotype 1, treatment-naive patients who were treated with PR for a 4-week lead-in period followed by either 24 or 44 weeks of boceprevir plus PR found that the shorter treatment regimen was associated with reduced risk of neutropenia (1 trial, N=206, RR 0.55, 95% CI 0.33 to 0.93**)** but also reduced rates of SVR (RR 0.75, 95% CI 0.61 to 0.92; see Table 7).[14] However, treatment with boceprevir plus PR for 24 or 48 weeks (without a PR lead-in period) did not show the same association in 2 different arms of the same trial. There was no difference in the risk of anemia with either comparison.

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Treatment experienced

Treatment dose

3D regimen
The AVIATOR study[55] (N=88; Table 8) compared 100 mg and 150 mg doses of paritaprevir in the 3D regimen, and showed that dose did not affect SVR24 in treatment-experienced patients (RR 0.94, 95% CI 0.81 to 1.1, pooled across durations). There were no relapses and 1 withdrawal due to adverse events in patients given the full 3D regimen, not reported by dose. Anemia occurred in 5.7% of patients and rash in 11%, with no statistically significant differences between dose arms.

Treatment duration

3D regimen
Three trials of the 3D regimen compared treatment durations, but because populations differed we did not combine them (Table 8). The AVIATOR study[55] excluded patients with cirrhosis and showed no difference in SVR24 between 12 and 24 weeks of treatment (RR 0.98, 95% CI 0.86 to 1.1, pooled across doses). There were no relapses, 2 serious adverse events, and 1 withdrawal due to adverse events in patients given the full 3D regimen, all in 24-week arms. Treatment duration did not affect rates of anemia or rash.

Table 8. Trials of the 3D regimen with and without ribavirin in treatment-experienced patients[a]

Author, date Trial name	N Duration of treatment	Daily dose (mg): paritaprevir/ ritonavir/ ombitasvir (FDCP), dasabuvir, ribavirin	Population	Quality rating
Kowdley, 2014[55] AVIATOR	88 12 vs. 24 weeks	Paritaprevir: **100 vs. 150**; Ritonavir: 100; Ombitasvir: 25; Dasabuvir: **800**; Ribavirin: 1000 or 1200 (weight-based)	Cirrhosis excluded (F0-F3)	Fair
Poordad, 2014[66] TURQUOISE-II	220 12 vs. 24 weeks	Paritaprevir: **150**; Ritonavir: 100; Ombitasvir: 25; Dasabuvir: **500**; Ribavirin: 1000 or 1200 (weight-based)	All with cirrhosis (F4)	Fair
Sulkowski, 2014[67] TURQUOISE-I	21 12 vs. 24 weeks	Paritaprevir: **150**; Ritonavir: 100; Ombitasvir: 25; Dasabuvir: **500**; Ribavirin: 1000 or 1200 (weight-based)	Any stage (F0-F4), and all with HIV-1	Fair

[a]Includes data only for treatment-experienced patients given full 3D regimen (both trials also include treatment-naïve patients).
Abbreviations: F0-F4, Metavir fibrosis score.

TURQUOISE-II[66] enrolled only patients with compensated cirrhosis and we report results with Key Question 7. Comparative SVR data are not yet available for TURQUOISE-I.[67] Relapse and harms data were reported pooled across treatment-naïve and -experienced populations for TURQUOISE-I, and are discussed below.

Ledipasvir/sofosbuvir
The ION-2 trial[42] (N=440) showed no difference in SVR12 between 12 and 24 weeks of treatment with fixed-dose ledipasvir/sofosbuvir (RR 0.96, 95% CI 0.92 to 1.0, pooled across

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arms with and without ribavirin). However, relapse was more likely in patients treated for 12 weeks, occurring in 11 patients treated for 12 weeks and no patient treated for 24-weeks. There were no withdrawals due to adverse events in the trial, but while no patient treated for 12 weeks had serious adverse events, 9 out of 220 patients treated for 24 weeks did. Anemia and rash also appeared less common with 12 weeks of treatment (RR 0.75 or less depending on inclusion of ribavirin), but confidence intervals included 1.0.

Simeprevir with sofosbuvir
The COSMOS trial[58] (N=127) described in Key Question 1 found that treatment duration did not affect SVR12 (RR 1.1, 95% CI 0.97 to 1.2 for 12 vs. 24 weeks of treatment, ribavirin arms pooled). Viral relapse occurred in 3 patients treated for 12 weeks and in 1 patient treated for 24 weeks. There were few withdrawals from the study due to adverse events (0 in patients treated for 12 weeks, 4 in patients treated for 24 weeks). One patient treated without ribavirin became anemic, but among patients treated with ribavirin 23 became anemic and the risk was higher with longer treatment (RR 0.44, 95% CI 0.20 to 0.94, 12 vs. 24 weeks). There were no statistically significant differences in rash between duration arms.

Simeprevir
An unpublished study (N=106)[53] conducted at 23 centers in Japan by Janssen Pharmaceuticals compared 12 with 24 weeks of treatment with 100 mg daily of simeprevir, each with response-guided PR. The design was similar to the PROMISE study included in CADTH,[82] but the simeprevir dose in PROMISE was higher (150 mg daily for 12 weeks) and populations more diverse, with 71 study locations worldwide. The Janssen study showed no difference in SVR24 between treatment durations, and no statistically significant differences in viral relapse or harms. SVR24 was lower than in PROMISE (occurring in 43% of all patients given simeprevir vs. 79% achieving SVR12 in PROMISE), and relapse rates higher (45% vs. 18%), perhaps because of the 100 daily dose; the current labeled dose is 150 mg, and simeprevir is only available as a 150 mg capsule. Neutropenia was uncommon in the Janssen study (4.7%), but anemia and rash were frequent (55% and 41%, respectively).

Boceprevir
CADTH's NMA compared durations of boceprevir treatment using data from 2 trials, Study P05685[86] and RESPOND2.[87] In the intervention arm of Study P05685, patients received boceprevir with PR for 44 weeks. The RESPOND2 trial had 2 active arms, 1 with the same intervention as P05685 (with peginterferon alfa2b instead of 2a) and the other arm with boceprevir with PR for 32 weeks, then response-guided PR. The NMA compared the 44-week arms from the 2 trials with the 32-week arm from RESPOND2, and found no statistically significant differences in SVR regardless of prior treatment history (RR 1.1, 95% CrI 0.87 to 1.6 for all treatment-experienced patients). Separate analyses showed no significant differences in rates of anemia or rash.

Mixed treatment history
Among the 63 HIV-positive, treatment-naïve or -experienced patients in TURQUOISE-I,[67] 1 patient experienced viral relapse and none withdrew due to adverse events.

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Genotypes Other Than 1

Treatment duration

Treatment naïve

Daclatasvir with sofosbuvir
One trial randomized HCV genotype 2 (17/30, 57%) and genotype 3 (13/30, 43%) patients who were treatment-naive to 7 days of sofosbuvir followed by 23 weeks of sofosbuvir plus daclatasvir (N=16) or to 24 weeks of sofosbuvir plus daclatasvir (N=14) and found no difference in SVR (RR 0.88, 95% CI 0.71 to 1.10).[68] (SOE: insufficient)

Treatment experienced

Sofosbuvir
One trial (FUSION) randomized patients with HCV genotypes 2 and 3 who had not responded to previous interferon therapy to 12 or 16 weeks of treatment with sofosbuvir and ribavirin (N=201).[51] Treatment for 12 weeks was associated with lower rates of SVR than treatment for 16 weeks (RR 0.70, 95% CI 0.55 to 0.88).

Key Question 5. What are the comparative benefits and harms of various DAA regimen changes based on virologic response at any time during antiviral therapy (i.e., response-guided therapy based on viral load)?

a. Shortening treatment

b. Switching from one DAA to another

Summary of Evidence

- We found no evidence for:
  - Switching from one DAA to another for either treatment-naïve or treatment-experienced patients
  - Shortening treatment in patients with HCV genotypes other than 1.

Treatment Naïve

- Based on a network meta-analysis by CADTH, there was no difference in SVR between boceprevir for 24 weeks plus PR for 28 weeks compared with boceprevir for 24 weeks plus response-guided PR for 24 or 48 weeks.

Treatment Experienced

- Based on network meta-analyses by CADTH, there were no differences in SVR between:
  - 12 weeks of simeprevir plus PR whether PR was given for 48 weeks fixed-duration or for 24 or 48 weeks RGT
  - Boceprevir given for 44 weeks with 48 weeks of fixed-duration PR compared with 32 weeks of boceprevir and response-guided PR.

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Detailed Assessment

Genotype 1

Treatment naïve

Shortening treatment with DAA regimens

Simeprevir
When response guided therapy was employed in simeprevir trials, it was applied to all simeprevir arms offering no comparison with longer simeprevir treatment.[50,59,81] Sustained virologic response in all who qualified for RGT ranged from 91%[59] to 93%.[81]

Boceprevir
Network meta-analysis performed by CADTH[82] found no difference in SVR between treatment with boceprevir for 24 weeks plus PR for 28 weeks versus treatment with boceprevir for 24 weeks plus PR for 24-48 weeks RGT (2 trials, N=1617, RR 0.92, 95% CI 0.69 to 1.16).

Treatment experienced

Shortening treatment with DAA regimens

Simeprevir
The CADTH review[82] network meta-analysis compared a simeprevir regimen with fixed-duration PR (48 weeks) to one with response-guided PR given for 24 or 48 weeks; simeprevir duration did not vary with response (12 weeks in each regimen). The NMA showed that SVR did not differ between fixed-dose and response-guided regimens for all treatment-experienced patients (RR 1.0, 95% CI 0.62 to 1.6). Results were similar for the subset with prior relapse (RR 0.98, 95% CI 0.54 to 1.5). There were no statistically significant differences in rates of anemia or rash between regimens.

Boceprevir
CADTH's[82] NMA also compared a regimen with boceprevir given for 44 weeks with 48 weeks of fixed-duration PR to one with 32 weeks of boceprevir and response-guided PR (36 or 48 weeks). The NMA showed that SVR did not differ between regimens (RR 1.1, 95% CI 0.87 to 1.6, fixed-duration vs. response-guided PR). Results were similar for subsets with prior viral relapse (RR 1.1, 95% CI 0.86 to 1.5) and prior partial response (RR 1.2, 95% CI 0.79 to 2.4). There were no statistically significant differences in rates of anemia or rash between regimens.

Switching from one DAA to another

We found no evidence for response-guided changes from one DAA to another in either treatment-naive or treatment-experienced patients.

Genotypes Other Than 1

We found no evidence in treatment-naive or treatment-experienced patients with HCV genotypes other than 1 for response-guided changes in DAA regimens.

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Key Question 6. What are the comparative benefits and harms of DAAs for specific subpopulations of patients with hepatitis C virus (e.g., concomitant HIV or HBV infections or other comorbidities (e.g., chronic illnesses, inherited blood disorders, cancer), initial viral load, post-transplant, substance abuse, genetic polymorphisms (e.g., IL28B variants, Q80K mutation), or demographic characteristics such as age, gender, race or ethnicity)?

Summary of Evidence

- In all trials reviewed (Table F1), substance use was either an exclusion criterion or not reported. Race was reported in most trials, and ranged from 1% to 37% non-white (mean 15%). About half of the trials included patients with cirrhosis, with a mean prevalence of 22%. HIV co-infected patients were excluded from almost all trials (N=27), though for one trial it was an inclusion criterion.[67]
- Confidence intervals overlapped (no significant difference) when comparing effects of different regimens changes within different subgroup strata (e.g., effects of 12 versus 24 weeks treatment duration in patients with higher viral loads compared to effects in patients with lower viral loads, or effects of inclusion of ribavirin in males compared with effects in females), for all subgroups stratified by viral load, IL28 genotype, age, gender, and race in treatment-naïve and treatment-experienced patients and in patients with a mixed treatment history. There were also no significant differences based on stratification by history of diabetes or presence of Q80K mutation in patients with a mixed treatment history.
- Only statistically significant comparisons are reported below (i.e., treatment duration may influence SVR in women but not in men, so only the effect in women is reported).

Genotype 1

Treatment naïve

- Viral load (low versus high): shorter treatment with boceprevir plus PR (24-48 weeks) and the 3D regimen plus ribavirin (8 weeks) was associated with lower rates of SVR in patients with higher baseline viral loads compared with longer treatments. Most patients had higher viral loads (n=509 vs. 65).
- Race (black/non-black): non-blacks experienced lower rates of SVR with boceprevir plus PR for 28 compared with 48 weeks treatment and with treatment with PR for 4 weeks followed by boceprevir for 24 weeks compared with 44 weeks treatment. Most patients were not black (n=354 vs. 62).
- IL28 genotype (CC, CT, TT): In patients with the CC genotype given the 3D regimen plus ribavirin, SVR was slightly higher with 12 weeks compared with 24 weeks treatment. Most patients had CT genotype (n=80), CC (n=44), TT (n=30).
- HCV genotypes (2 and 3): Patients with genotype 2 experienced increased SVR when treated with sofosbuvir and ribavirin for 12 weeks compared with PR therapy for 24 weeks.

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Treatment experienced

- Viral load (low vs. high): patients with higher baseline viral loads given ledipasvir and sofosbuvir plus ribavirin had lower SVR when treated for 12 weeks compared with 24 weeks treatment. Most patients had higher viral loads (n=390 vs. 50).
- Race (black/nonblack or Hispanic/non-Hispanic): non-black and non-Hispanics experienced reduced SVR when treated with ledipasvir and sofosbuvir with or without ribavirin for 12 weeks compared with 24 weeks treatment. Most patients were non-black (n=363 vs. 77) and non-Hispanic (n=396 vs. 41).
- IL28 genotype (CC/non-CC): patients with non-CC genotypes lower rates of SVR with 12 weeks of ledipasvir and sofosbuvir plus ribavirin compared with 24 weeks treatment. Most patients had HCV non-CC genotype (n=385 vs. 55).
- Age (<65/≥65): Younger patients treated with ledipasvir and sofosbuvir with or without ribavirin for 12 weeks had lower SVR rates than those treated for 24 weeks. Most patients were < 65 years of age (409 vs. 31).

Detailed Assessment

Treatment naïve

At higher initial HCV viral loads (>600,000 IU/mL or >800,000 IU/mL) patients were less likely to achieve SVR when treated with the 3D regimen plus ribavirin for 8 versus 12 weeks (RR 0.89, 95% CI 0.80 to 0.98),[55] boceprevir plus PR for 28 versus 48 weeks (RR 0.78, 95% CI 0.62 to 0.99),[14] or when treated with PR for 4 weeks the boceprevir plus PR for 24 vs 44 weeks (RR 0.74, 95% CI 0.60 to 0.93) (Table 9).[14] There was no reported effect of treatment duration on SVR in treatment-naive patients with lower initial viral loads. Achieved SVR rates were also similar across IL28 genotypes with different doses of simeprevir, with different durations of the 3D regimen, and with or without ribavirin included in the 3D regimen,[55,81] and treatment with ledipasvir and sofosbuvir with or without ribavirin.[43] Results were also similar in studies that stratified SVR results by HCV 1 genotype regardless of treatment duration.[14,43,54,55,66]

Table 9. SVR in specific subgroups in treatment-naive patients

Author, Year Trial Name	Drug Regimen	Comparison	Subgroup (N)	Relative Risk (95% CI)
Initial Viral Load				
Kwo, 2010[14] SPRINT-1	Boceprevir + PR	BPR for 28 vs 48 weeks	>600,000 (193) ≤600,000 (17)	**0.78 (0.62, 0.99)** 1.13 (0.61, 2.07)
Kwo, 2010[14] SPRINT-1	PR 4 weeks then Boceprevir + PR	PR 4 weeks then BPR for 24 vs 44 weeks	>600,000 (181) ≤600,000 (25)	**0.74 (0.60, 0.93)** 0.79 (0.54, 1.15)
Kowdley, 2014[55] AVIATOR	3D + Ribavirin	8 vs 12 weeks	≥800,000 (136) <800,000 (23)	**0.89 (0.80, 0.98)** 1.06 (0.85, 1.32)
Kowdley, 2014[55] AVIATOR	3D + Ribavirin	12 vs 24 weeks	≥800,000 (135) <800,000 (24)	1.06 (0.98, 1.15) 1.03 (0.80, 1.33)
Kowdley, 2014[55] AVIATOR	3D for 12 weeks	With or without ribavirin	≥800,000 (135) <800,000 (23)	0.91 (0.83, 1.01) 0.96 (0.73, 1.26)
Kowdley, 2014[54] ION-3	Ledipasvir + Sofosbuvir	8 vs 12 weeks	≥800,000 (353) <800,000 (78)	0.98 (0.93, 1.03) 1.02 (0.93, 1.11)
Kowdley, 2014[54] ION-3	Ledipasvir + Sofosbuvir 8 weeks	With or without ribavirin	≥800,000 (352) <800,000 (79)	1.01 (0.95, 1.07) 1.02 (0.93, 1.11)

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Author, Year Trial Name	Drug Regimen	Comparison	Subgroup (N)	Relative Risk (95% CI)
Afdhal, 2014 ION-1[43]	Ledipasvir + Sofosbuvir for 12 weeks	With or without ribavirin	≥800,000 (675) <800,000 (177)	1.01 (1.00, 1.02) 84/84 vs 93/93
Afdhal, 2014 ION-1[43]	Ledipasvir and Sofosbuvir	12 vs 24 weeks	≥800,000 (675) <800,000 (177)	1.00 (0.99, 1.01) 86/86 vs 91/91
IL28 Genotype				
Fried, 2013[81] PILLAR	Simeprevir	Simeprevir 75 mg vs 150 mg	CC genotype (66) CT genotype (124) TT genotype (26)	0.86 (0.73, 1.02) 0.98 (0.82, 1.17) 0.75 (0.39, 1.45)
Kowdley, 2014[55] AVIATOR	3D + Ribavirin	8 vs 12 weeks	CC genotype (44) CT genotype (80) TT genotype (35)	0.91 90.78, 1.06) 0.95 (0.84, 1.08) 0.81 (0.61, 1.08)
Kowdley, 2014[55] AVIATOR	3D + Ribavirin	12 vs 24 weeks	CC genotype (44) CT genotype (85) TT genotype (30)	**1.29 (1.01, 1.63)** 0.99 (0.90, 1.09) 0.96 (0.81, 1.14)
Kowdley, 2014[55] AVIATOR	3D for 12 weeks	With or without ribavirin	CC genotype (45) CT genotype (78) TT genotype (35)	0.92 (0.79, 1.06) 0.97 (0.87, 1.09) 0.81 (0.61, 1.08)
Kowdley, 2014[54] ION-3	Ledipasvir + Sofosbuvir	8 vs 12 weeks	CC genotype (112) CT genotype (244) TT genotype (75)	54/56 vs 54/56 0.98 (0.92, 1.04) 0.98 (0.87, 1.10)
Kowdley, 2014[54] ION-3	Ledipasvir + Sofosbuvir 8 weeks	With or without ribavirin	CC genotype (116) CT genotype (248) TT genotype (67)	1.02 (0.94, 1.10) 1.00 (0.93, 1.06) 1.08 (0.90, 1.29)
Afdhal, 2014[43] ION-1[a]	Ledipasvir and Sofosbuvir for 12 weeks	With or without ribavirin	CC genotype (251) CT genotype (445) TT genotype (156)	145/145 vs 106/106 1.00 (0.99, 1.02) 1.02 (0.98, 1.06)
Afdhal, 2014[43] ION-1[a]	Ledipasvir and Sofosbuvir	12 vs 24 weeks	CC genotype (251) CT genotype (445) TT genotype (156)	129/129 vs 122/122 1.00 (0.99, 1.02) 1.00 (0.97, 1.04)
Demographic Characteristics				
Kwo, 2010[14] SPRINT-1	Boceprevir + PR	BPR for 28 vs 48 weeks	Men (126) Women (84) Non-black (178) Black (32)	0.83 (0.61, 1.12) **1.41 (1.05, 1.89)** **0.79 (0.63, 0.98)** 1.36 (0.50, 3.74)
Kwo, 2010[14] SPRINT-1	PR 4 weeks then Boceprevir + PR	PR 4 weeks then BPR for 24 vs 44 weeks	Men (109) Women (97) Non-black (176) Black (30)	0.92 (0.71, 1.19) **0.60 (0.44, 0.83)** **0.75 (0.61, 0.93)** 0.75 (0.34, 1.64)
Poordad, 2011[83] SPRINT-2	PR 4 weeks then Boceprevir + PR	PR 4 weeks then BPR for 24 weeks (RGT for another 20 weeks) vs 44 weeks	Non-black (627) Black (107)	0.98 (0.88, 1.09) 0.80 (0.54, 1.20)
Kowdley, 2014[55] AVIATOR	3D + Ribavirin	8 vs 12 weeks	Non-black (137) Black (22)	0.93 (0.84, 1.03) 0.78 (0.54, 1.13)
Kowdley, 2014[55] AVIATOR	3D + Ribavirin	12 vs 24 weeks	Non-black (142) Black (17)	1.04 (0.95, 1.13) 1.38 (0.77, 2.47)
Kowdley, 2014[55] AVIATOR	3D for 12 weeks	With or without ribavirin	Non-black (132) Black (26)	0.91 (0.81, 1.01) 13/13 vs 13/13
Kowdley, 2014[54] ION-3	Ledipasvir + Sofosbuvir	8 vs 12 weeks	1a (343) 1b (87)	0.98 (0.93, 1.04) 1.00 (0.94, 1.07)
Kowdley, 2014[54] ION-3	Ledipasvir + Sofosbuvir 8 weeks	With or without ribavirin	1a (343) 1b (87)	159/172 vs 159/172 1.02 (0.95, 1.11)

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Author, Year Trial Name	Drug Regimen	Comparison	Subgroup (N)	Relative Risk (95% CI)
Afdhal, 2014[43] ION-1[a]	Ledipasvir and Sofosbuvir for 12 weeks	With or without ribavirin	Age < 65 (780)	1.01 (1.00, 1.02)
			Age ≥ 65 (72)	1.03 (0.95, 1.11)
			Men (506)	1.01 (1.00, 1.03)
			Women (346)	184/184 vs 162/162
			Non-black (742)	1.00 (1.00, 1.01)
			Black (107)	1.04 (0.97, 1.10)
			Not Hispanic/ Latino (774)	1.01 (1.00, 1.02)
			Hispanic/Latino (100)	45/45 vs 55/55
Afdhal, 2014[43] ION-1[a]	Ledipasvir and Sofosbuvir	12 vs 24 weeks	Age < 65 (780)	1.00 (0.99, 1.01)
			Age ≥ 65 (72)	1.03 (0.95, 1.11)
			Men (506)	1.00 (0.99, 1.02)
			Women (346)	173/173 vs 173/173
			Non-black (742)	1.00 (0.99, 1.01)
			Black (107)	1.04 (0.97, 1.10)
			Not Hispanic/ Latino (774)	1.00 (0.99, 1.01)
			Hispanic/Latino (100)	45/45 vs 55/55

Abbreviations: PR, pegylated interferon + ribavirin, RGT, response-guided therapy.
[a]Subgroups do not include those who withdrew consent or were lost to follow-up.

Women and non-black patients were less likely to achieve SVR when a 4 week lead-in treatment with PR was followed by boceprevir plus PR for 24 versus 44 weeks (RR 0.60, 95% CI 0.44 to 0.83; RR 0.75, 95% CI 0.61 to 0.93, respectively).[14] However, treatment with boceprevir plus PR for 28 versus 48 weeks was associated with increased SVR in women (RR 1.41, 95% CI 1.05 to 1.89). Treatment duration had a similar effect on non-black patients treated with boceprevir plus PR for 28 versus 48 weeks (RR 0.79, 95% CI 0.63 to 0.98).[14] However, there was no effect in a similar boceprevir regimen when the 28-week treatment arm allowed RGT for an additional 20 weeks versus total treatment for 44 weeks.[83] There was also little effect of treatment duration in either non-black or black patients treated with the 3D regimen with or without ribavirin[55] or with ledipasvir and sofosbuvir.[43]

In a trial enrolling only patients with lower baseline HCV viral loads (<600,000 IU/mL) who were treated with 4 weeks of PR and had a rapid virologic response and then randomized to 20 weeks of PR compared with an additional 24 weeks of boceprevir plus PR (N=101), there was no difference in SVR rates between 20 weeks of PR versus 24 weeks of boceprevir plus PR when stratified by IL28 (CC/Non-CC), genotype 1 subtype (1a/1b), or in African Americans.[63]

Treatment experienced

We found evidence in treatment-experienced patients for subgroups defined by history of diabetes, initial viral load, IL28 genotype, Q80K mutation, and demographic characteristics, but not by HIV or hepatitis B virus (HBV) coinfection, history of transplant, or substance abuse. All comparisons were from trials of a single DAA regimen with or without ribavirin, and/or with 12 vs. 24 weeks of treatment duration. Trials of the 3D regimen, ledipasvir/sofosbuvir, and simeprevir with sofosbuvir reported data by subgroup, though 2 trials[58,66] pooled results across treatment-naïve and-experienced patients (reported below). SVR was the only outcome assessed by subgroup.

Table 10 shows results for included comparisons by subgroup. Many groups were too small to give meaningful risk estimates; for example, in the AVIATOR study[55], 3 patients had the IL28 CC genotype, and all 3 achieved SVR24. For every comparison, relative risks were near 1.0, showing little or no effect of the regimen change on SVR, and confidence intervals for

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subgroups overlapped, meaning the effect of the regimen change on SVR did not differ across subgroups.

Table 10. Effects within subgroups of DAA regimen changes on SVR[a] in treatment-experienced patients

Author, Year Trial Name	Drug Regimen	Comparison	Subgroup (N)	Relative Risk (95% CI)
Initial Viral Load				
Kowdley, 2014[55] AVIATOR	3D with ribavirin	12 vs. 24 weeks[b]	≥ 800,000 IU/mL (85) < 800,000 IU/mL (3)	0.93 (0.75, 1.1) 1.0 (0, ∞)
Afdhal, 2014[42] ION-2	Ledipasvir/ sofosbuvir ± ribavirin	No ribavirin vs. ribavirin	≥ 800,000 IU/mL (390) < 800,000 IU/mL (50)	0.99 (0.95, 1.0) 0.95 (0.79, 1.1)
		12 vs. 24 weeks	≥ 800,000 IU/mL (390) < 800,000 IU/mL (50)	**0.96 (0.92, 0.99)** 0.94 (0.76, 1.1)
IL28 Genotype				
Andreone, 2014[45] PEARL-II	3D ± ribavirin	No ribavirin vs. ribavirin	CC genotype (17) CT genotype (120) TT genotype (42)	1.0 (0, ∞) 1.0 (0.96, 1.1) 1.0 (0.84, 1.3)
Kowdley, 2014[55] AVIATOR	3D with ribavirin	12 vs. 24 weeks	CC genotype (3) CT genotype (53) TT genotype (32)	1.0 (0, ∞) 0.93 (0.75, 1.1) 1.1 (0.79 to 1.3)
Afdhal, 2014[42] ION-2	Ledipasvir/ sofosbuvir ± ribavirin	No ribavirin vs. ribavirin	CC genotype (55) Non-CC genotype (385)	1.0 (0.87, 1.2) 0.98 (0.94, 1.0)
		12 vs. 24 weeks	CC genotype (55) Non-CC genotype (385)	1.0 (0.83, 1.2) **0.95 (0.91, 0.98)**
Demographic Subgroups				
Andreone, 2014[45] PEARL-II	3D ± ribavirin	No ribavirin vs. ribavirin	Male (97) Female (82) Black (8) Non-black (171)	1.1 (0.96, 1.2) 1.0 (0.90, 1.1) 1.0 (0, ∞) 1.0 (0.98, 1.1)
Kowdley, 2014[55] AVIATOR	3D with ribavirin	12 vs. 24 weeks	Black (9) Non-black (79)	1.0 (0, ∞) 0.97 (0.83, 1.1)
Afdhal, 2014[42] ION-2	Ledipasvir/ sofosbuvir ± ribavirin	No ribavirin vs. ribavirin	< 65 years (409) ≥ 65 years (31)	0.98 (0.94, 1.0) 1.1 (0.83, 1.4)
			Male (287) Female (153)	1.0 (0.94, 1.0) 0.97 (0.91, 1.0)
			Black (77) Non-black (363)	1.0 (0.90, 1.1) 0.98 (0.94, 1.0)
			Hispanic or Latino (41) Not Hispanic or Latino (396)	1.0 (0, ∞) 0.98 (0.94, 1.0)
		12 vs. 24 weeks	< 65 years (409) ≥ 65 years (31)	**0.96 (0.92, 0.99)** 0.93 (0.72, 1.2)
			Male (287) Female (153)	0.95 (0.90, 1.0) 0.97 (0.91, 1.0)
			Black (77) Non-black (363)	1.0 (0.89, 1.1) **0.95 (0.91, 0.98)**
			Hispanic or Latino (41) Not Hispanic or Latino (396)	1.0 (0, ∞) **0.95 (0.91, 0.99)**

[a]SVR24: Kowdley 2014; SVR12: Afdhal 2014, Andreone 2014
[b]Dose comparison not reported by subgroup.
Abbreviations: DAA, direct-acting antiviral agent; SVR, sustained virologic response; 3D, AbbVie regimen including 3 new DAAs

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Mixed treatment history

In a trial of the 3D regimen for 12 vs. 24 weeks in patients with cirrhosis[66] and 1 of simeprevir with sofosbuvir with vs. without ribavirin and for 12 vs. 24 weeks[58], subgroup data were pooled across treatment-naïve and -experienced patient populations. The effects of these regimen changes on SVR did not differ across subgroups defined by history of diabetes, baseline viral load, IL28 genotype, Q80K mutation, or demographic variables (Table 11).

Table 11. Effects within subgroups of DAA regimen changes on SVR12 in pooled treatment-naïve and treatment-experienced populations

Author, Year Trial Name	Drug Regimen	Comparison	Subgroup (N)	Relative Risk (95% CI)
Comorbidities				
Poordad, 2014[66] TURQUOISE-II ***All patients with cirrhosis***	3D with ribavirin	12 vs. 24 weeks	History of diabetes (60)	0.89 (0.71, 1.1)
			No history of diabetes (320)	0.97 (0.91, 1.0)
Initial Viral Load				
Poordad, 2014[66] TURQUOISE-II	3D with ribavirin	12 vs. 24 weeks	≥ 800,000 IU/mL (327)	0.95 (0.90, 1.0)
			< 800,000 IU/mL (53)	1.0 (0.84, 1.3)
IL28 Genotype				
Poordad, 2014[66] TURQUOISE-II	3D with ribavirin	12 vs. 24 weeks	CC genotype (69)	0.97 (0.84, 1.1)
			Non-CC genotype (311)	0.95 (0.90, 1.0)
Q80K Mutation				
Lawitz, 2014[58] COSMOS	Simeprevir + sofosbuvir ± ribavirin	No ribavirin vs. ribavirin	Mutation present (58)	1.1 (0.86, 1.3)
			Mutation absent (72)	1.0 (0.86, 1.2)
		12 vs. 24 weeks	Mutation present (58)	1.0 (0.80, 1.3)
			Mutation absent (72)	1.0 (0.87, 1.2)
Demographic Subgroups				
Poordad, 2014[66] TURQUOISE-II	3D with ribavirin	12 vs. 24 weeks	Male (267)	0.95 (0.89, 1.0)
			Female (113)	0.97 (0.87, 1.1)
			< 55 years (118)	0.98 (0.86, 1.1)
			≥ 55 years (262)	0.95 (0.89, 1.0)
			Black (12)	1.2 (0.62, 2.2)
			Non-black (368)	0.95 (0.90, 1.0)
			Hispanic or Latino (45)	0.88 (0.68, 1.1)
			Not Hispanic or Latino (335)	0.97 (0.91, 1.0)

Abbreviations: DAA, direct-acting antiviral agent; SVR, sustained virologic response; 3D, AbbVie regimen including 3 new DAAs

Genotypes Other Than 1

Treatment naïve

Treatment with sofosbuvir plus ribavirin for 12 weeks versus treatment with PR for 24 weeks resulted in no differences in SVR when patients were stratified by initial viral load, IL28 genotype, HCV genotype, age, gender, or race (Table 12)

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Table 12. Trials reporting SVR in treatment-naive patients with HCV genotypes other than 1

Author, Year Trial Name	Drug Regimen	Comparison	Subgroup (N)	Relative Risk (95% CI)
Initial Viral Load				
Lawitz, 2013[84] FISSION Genotypes 2, 3	Sofosbuvir + ribavirin	Sofosbuvir + ribavirin for 12 weeks vs PR for 24 weeks	≥600,000 (283) <600,000 (213)	0.93 (0.78, 1.11) 1.12 (0.94, 1.33)
IL28 Genotype				
Lawitz, 2013[84] FISSION Genotypes 2, 3	Sofosbuvir + ribavirin	Sofosbuvir + ribavirin for 12 weeks vs PR for 24 weeks	CC genotype (212) Non-CC genotype (281)	0.90 (0.77, 1.06) 1.14 (0.95, 1.37)
HCV Genotype				
Lawitz, 2013[84] FISSION Genotypes 2, 3	Sofosbuvir + ribavirin	Sofosbuvir + ribavirin for 12 weeks vs PR for 24 weeks	Genotype 2 (137) Genotype 3 (359)	**1.25 (1.09, 1.43)** 0.89 (0.75, 1.06)
Demographic Characteristics				
Lawitz, 2013[84] FISSION Genotypes 2, 3	Sofosbuvir + ribavirin	Sofosbuvir + ribavirin for 12 weeks vs PR for 24 weeks	Age<50 (244) Age≥50 (252) Men (324) Women (172) Non-black (479) Black (17) Not Hispanic/ Latino (425) Hispanic/Latino (71)	0.87 (0.73, 1.04) 1.17 (0.97, 1.40) 1.00 (0.84, 1.18) 1.04 (0.88, 1.22) 0.99 (0.88, 1.13) 1.88 (0.61, 5.76) 0.91 (0.79, 1.05) 1.12 (0.81, 1.55)

Abbreviations: HCV = hepatitis C virus.

Treatment with sofosbuvir plus ribavirin for 12 weeks versus treatment with PR for 24 weeks resulted in no differences in SVR when patients were stratified by initial viral load, IL28 genotype, HCV genotype, age, gender, race, or the presence or absence of cirrhosis.

Treatment experienced

We identified one trial[51] in patients with genotypes 2 and 3. The FUSION trial randomized patients who had not responded to prior interferon therapy to sofosbuvir plus ribavirin for either 12 or 16 weeks. See Table 13 for results by subgroup. Sustained virologic response rates were reduced in patients with higher viral loads, with non-CC genotypes, with genotype 3, in men, non-Blacks and non-Hispanics treated with 12 weeks of sofosbuvir and ribavirin compared with 16 weeks.

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Table 13. Trials reporting SVR in treatment-experienced patients with HCV genotypes other than 1

Author, Year Trial Name	Drug Regimen	Comparison	Subgroup (N)	Relative Risk (95% CI)
Initial Viral Load				
Jacobson, 2013 FUSION Genotypes 2, 3	Sofosbuvir + ribavirin	Sofosbuvir + ribavirin 12 vs 16 weeks	≥600,000 (140) <600,000 (55)	**0.65 (0.50, 0.84)** 0.81 (0.50, 1.30)
IL28 Genotype				
Jacobson, 2013 FUSION Genotypes 2, 3	Sofosbuvir + ribavirin	Sofosbuvir + ribavirin 12 vs 16 weeks	CC genotype (57) Non-CC genotype (138)	0.71 (0.46, 1.10) **0.68 (0.52, 0.90)**
HCV Genotype				
Jacobson, 2013 FUSION Genotypes 2, 3	Sofosbuvir + ribavirin	Sofosbuvir + ribavirin 12 vs 16 weeks	Genotype 2 (68) Genotype 3 (127)	0.92 (0.78, 1.08) **0.48 (0.31, 0.73)**
Demographic Characteristics				
Jacobson, 2013 FUSION Genotypes 2, 3	Sofosbuvir + ribavirin	Sofosbuvir + ribavirin 12 vs 16 weeks	Age<50 (44) Age≥50 (151) Men (135) Women (60) Non-black (189) Black (6) Not Hispanic/ Latino (176) Hispanic/Latino (18)	0.62 (0.35, 1.08) 0.88 (0.70, 1.11) **0.64 (0.47, 0.89)** 0.79 (0.60, 1.05) **0.65 (0.51, 0.84)** 5/5 vs 1/1 **0.70 (0.55, 0.89)** 0.64 (0.25, 1.62)

Key Question 7. What are the comparative benefits and harms of DAAs in patients with early-versus late-stage hepatitis C virus based on fibrosis scales (e.g., Metavir score from liver biopsy) or presence of cirrhosis?

Summary of Evidence

- Most included studies used biopsy-based Metavir scores to assess fibrosis, but occasionally non-invasive alternatives were used.

Genotype 1

Treatment naïve

- Network meta-analyses by CADTH in patients with Metavir scores F0-F2 found no differences between sofosbuvir, simeprevir, and boceprevir in SVR (the PROTON study was included in this analysis) while SVR rates were nonsignificantly reduced with boceprevir plus PR when compared with simeprevir in patients with Metavir scores F3-F4.
- Patients without cirrhosis given PR for 4 weeks followed by treatment with boceprevir plus PR for 24 weeks experienced reduced SVR compared with patients treated with PR for 4 weeks followed by boceprevir plus PR for 44 weeks. Most patients did not have

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cirrhosis (n=193 vs 13).Stage of disease had little effect on SVR when patients were treated with ledipasvir plus sofosbuvir.
- A trial in patients with genotypes 2 and 3 that compared sofosbuvir plus ribavirin for 12 weeks with PR for 24 weeks showed no difference in SVR between treatment arms, either for patients with cirrhosis or those without.

Treatment-experienced and mixed treatment history

- Patients with cirrhosis given the 3D regimen for 12 weeks were more likely to relapse than those treated for 24 weeks (RR 9.9, 95% CI 1.7 to 59), but duration did not affect SVR or harms.
- Patients with cirrhosis given ledipasvir/sofosbuvir for 12 weeks were less likely to achieve SVR12 than those treated for 24 weeks (RR 0.84, 95% CI 0.71 to 0.95), and were more likely to relapse. For patients without cirrhosis, duration did not affect SVR (RR 0.99, 95% CI 0.95 to 1.0). Inclusion of ribavirin had no statistically significant effect on SVR or relapse for any disease stage.
- Stage of disease had little effect on benefits and harms when patients were treated with simeprevir plus sofosbuvir, boceprevir, or when boceprevir plus PR was compared with simeprevir.

Genotypes Other Than 1

- In patients with genotype 3 who had not responded to prior interferon therapy, treatment with 12 weeks of sofosbuvir and ribavirin resulted in lower SVR rates compared with 16 weeks treatment regardless of the presence of cirrhosis; there were no statistically significant differences between 12 and 16 weeks treatment based on cirrhosis status in patients with genotype 2.

Detailed Assessment

Treatment naïve

We found evidence stratified by stage of disease in treatment-naïve patients given fixed-dose ledipasvir/sofosbuvir and older DAAs with PR (sofosbuvir, simeprevir, and boceprevir), but no evidence by disease stage for other all-oral DAA regimens. Comparisons for ledipasvir/ sofosbuvir were of treatment duration or inclusion of ribavirin. For older DAAs, indirect analysis allowed head to head comparisons.

Table 14 shows results for included comparisons by stage of disease. Some studies stratified by presence or absence of cirrhosis, and others by early-stage compared with late-stage disease; one study[54] presented results for each Metavir fibrosis category. For every comparison but one, confidence intervals included 1.0, showing no effect of the regimen change on SVR. For studies reporting more than one disease stage, all confidence intervals overlapped, meaning the effect of the regimen change on SVR did not differ by stage of disease.

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Table 14. SVR by stage of disease in treatment-naive patients with HCV genotype 1

Author, Year Trial Name	Comparison	Disease stage (N)	Relative Risk (95% CI)
Ledipasvir/Sofosbuvir			
Afdhal, 2014[43] ION-1[a]	12 weeks, with vs. without ribavirin	Cirrhosis (134) No cirrhosis (717)	1.03 (0.98, 1.09) 1.00 (1.00, 1.01)
	12 vs 24 weeks	Cirrhosis (134) No cirrhosis (717)	1.00 (0.96, 1.04) 1.00 (1.00, 1.01)
Kowdley, 2014[54] ION-3	8 weeks, with vs. without ribavirin	F0 (35) F1 (108) F2 (92) F3 (57)	1.02 (0.83, 1.25) 0.97 (0.88, 1.06) 1.03 (0.93, 1.14) 0.89 (0.75, 1.05)
	8 vs 12 weeks, without ribavirin	F0 (38) F1 (121) F2 (95) F3 (58)	0.92 (0.78, 1.08) 1.04 (0.96, 1.13) 0.95 (0.87, 1.04) 1.0 (0.85, 1.17)
Sofosbuvir compared with Simeprevir			
CADTH, 2014[82] Includes PROTON	Sofosbuvir for 12 weeks plus PR for 24-48 weeks RGT vs. simeprevir for 12 weeks plus PR for 24-48 weeks RGT	Early: F0-F2 (NR)	1.07 (0.78, 1.30)
Sofosbuvir compared with Boceprevir			
CADTH, 2014[82] Includes PROTON	Sofosbuvir for 12 weeks plus PR for 24-48 weeks RGT vs. boceprevir for 24 weeks plus PR for 28-48 weeks RGT	Early: F0-F2 (NR)	1.12 (0.81, 1.47)
Boceprevir compared with Simeprevir			
CADTH, 2014[82] Includes PROTON for F0-F2	Boceprevir for 24 weeks plus PR for 28-48 weeks RGT vs. simeprevir for 12 weeks plus 24-48 weeks RGT	Early: F0-F2 (NR) Late: F3-F4 (NR)	0.96 (0.74, 1.16) 0.58 (0.20, 1.19)
	Boceprevir for 44 weeks plus PR for 48 weeks vs. simeprevir for 12 weeks plus 24-48 weeks RGT	Late: F3-F4 (NR)	0.75 (0.31, 1.36)
Boceprevir + PR			
Kwo, 2010[14] SPRINT-1	28 vs 48 weeks	Cirrhosis (16) No cirrhosis (194)	0.74 (0.35, 1.53) 0.82 (0.65, 1.03)
	PR 4 weeks then boceprevir plus PR 24 vs 44 weeks	Cirrhosis (13) No cirrhosis (193)	1.14 (0.41, 3.19) **0.74 (0.60, 0.91)**
Poordad, 2011[83]	Boceprevir 24 weeks plus PR for 28-48 weeks RGT vs. boceprevir for 44 weeks plus PR for 48 weeks	F0-F2 (632) F3-F4 (76)	0.99 (0.89, 1.1) 0.79 (0.47, 1.3)
CADTH, 2014[82]	Boceprevir for 44 weeks plus PR for 48 weeks vs. boceprevir for 24 weeks plus PR for 28 to 48 weeks	F3-F4 (NR)	1.27 (0.64,2.85)

Abbreviations: F0-F4, Metavir fibrosis scores; HCV, hepatitis C virus; PR, pegylated interferon with ribavirin; RGT, response-guided therapy; SVR, sustained virologic response.

Treatment-experienced and mixed treatment history

3D regimen

TURQUOISE-II[66] (Tables 8 and 13) enrolled patients with compensated cirrhosis (Child-Pugh class A), and found that rates of SVR12 with 12 weeks of treatment are close to those with 24 weeks of treatment in treatment-experienced patients (RR 0.93, 95% CI 0.86 to 1.0). The trial reported relapse and harms data pooled across treatment-naïve (N=160) and -experienced (N=220) populations. Relapse was more likely in patients treated for 12 weeks, occurring in 12 patients compared with 1 in the 24-week arm (RR 9.9, 95% CI 1.7 to 59). There were no statistically significant differences in harms between patients treated for 12 and 24 weeks.

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Ledipasvir/sofosbuvir

The ION-2 trial of fixed-dose ledipasvir and sofosbuvir assessed both inclusion of ribavirin and treatment duration. There was no difference in the effect of ribavirin on SVR12 between patients with and without cirrhosis (Table 15). Four of 176 patients without cirrhosis treated for 12 weeks relapsed, all in the group not given ribavirin. We also pooled data from ION-2 patients with cirrhosis and 19 patients with cirrhosis in another trial[48] and found that inclusion of ribavirin did not affect SVR12 (RR 0.93, 95% CI 0.73 to 1.2). Relapse occurred in 10 of 63 patients with cirrhosis treated for 12 weeks across the 2 trials, 6 in patients not treated with ribavirin.

Effects of treatment duration in ION-2 did differ according to disease stage. For patients with cirrhosis, those treated for 12 weeks were less likely to achieve SVR12 than those treated for 24 weeks (RR 0.84, 95% CI 0.71 to 0.95). For patients without cirrhosis, there was no difference in SVR12 between 12 and 24 weeks of treatment (RR 0.99, 95% CI 0.95 to 1.0). Relapse appeared more likely with 12 weeks of treatment, particularly for patients with cirrhosis. All 11 patients who relapsed were treated for 12 weeks, 7 of 44 (16%) among those with cirrhosis and 4 of 176 (2.2%) in those without cirrhosis.

Table 15. Comparative effectiveness of DAA regimens by stage of disease in treatment-experienced patients and pooled treatment-naïve and -experienced populations

Author, Year Trial Name	Comparison	Population	Outcome	Disease stage (N)	Relative Risk (95% CI)
3D Regimen					
Poordad, 2014[66] TURQUOISE-II	12 vs. 24 weeks of treatment	TE	SVR12	Cirrhosis: F4 (220)	0.93 (0.86, 1.0)
		TN + TE	Relapse SAE WAE Rash Anemia	Cirrhosis: F4 (380)	**9.9 (1.7, 59)** 1.3 (0.59, 3.1) 0.83 (0.23, 3.0) 0.76 (0.45, 1.3) 0.74 (0.39, 1.4)
Ledipasvir/Sofosbuvir					
Afdhal, 2014[42] ION-2 Gane, 2014[48] ELECTRON	No ribavirin vs. ribavirin, 12 weeks of treatment	TE	SVR12	Cirrhosis: F4 (107)	0.93 (0.73, 1.2)
Afdhal, 2014[42] ION-2	No ribavirin vs. ribavirin[b]	TE	SVR12	No cirrhosis: F0-F3 (352) Cirrhosis: F4 (88)	0.98 (0.94, 1.0) 1.0 (0.89, 1.2)
	12 vs. 24 weeks of treatment[a]	TE	SVR12	No cirrhosis: F0-F3 (352) Cirrhosis: F4 (88)	0.99 (0.95, 1.0) **0.84 (0.71, 0.95)**
Simeprevir with Sofosbuvir					
Lawitz, 2014[58] COSMOS	No ribavirin vs. ribavirin[b]	TE	SVR12	Early: F0-F2 (80) Late: F3-F4 (47)	1.1 (0.87, 1.2) 1.1 (0.82, 1.3)
				No cirrhosis: F0-F3 (104) Cirrhosis: F4 (23)	1.1 (0.90, 1.2) 1.1 (0.69, 1.5)
		TE TN + TE	Rash	Early: F0-F2 (80) Late: F3-F4 (87)	0.78 (0.27, 2.1) 0.63 (0.23, 1.7)
	No ribavirin vs. ribavirin, 24 weeks of treatment	TE TN + TE	Anemia	Early: F0-F2 (39) Late: F3-F4 (46)	0.20 (0.019, 1.9) 0.38 (0.060, 2.1)
	12 vs. 24 weeks of treatment[a]	TE	SVR12	Early: F0-F2 (80) Late: F3-F4 (47)	1.1 (0.97, 1.4) 1.0 (0.84, 1.3)
				No cirrhosis: F0-F3 (104) Cirrhosis: F4 (23)	1.1 (0.99, 1.3) 0.96 (0.60, 1.3)
		TE TN + TE	Rash	Early: F0-F2 (80) Late: F3-F4 (87)	1.1 (0.42, 2.9) 0.87 (0.36, 2.1)
	12 vs. 24 weeks of treatment, with ribavirin	TE TN + TE	Anemia	Early: F0-F2 (51) Late: F3-F4 (57)	0.22 (0.035, 1.4) 0.44 (0.10, 1.8)

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Author, Year Trial Name	Comparison	Population	Outcome	Disease stage (N)	Relative Risk (95% CI)
Simeprevir vs. Boceprevir					
CADTH, 2014[82]	Boceprevir for 44 weeks plus PR for 48 weeks vs. Simeprevir for 12 weeks plus PR for 24-48 weeks RGT	TE	SVR24	Early: F0-F2 (585)	1.1 (0.77, 1.6)
				Late: F3-F4 (210)	1.1 (0.53, 2.6)
	Boceprevir for 32 weeks plus 36-48 weeks RGT vs. Simeprevir for 12 weeks plus PR for 24-48 weeks RGT	TE	SVR24	Early: F0-F2 (443)	1.0 (0.68, 1.6)
				Late: F3-F4 (164)	0.68 (0.23, 2.0)
Boceprevir					
CADTH, 2014[82]	Boceprevir for 44 weeks plus PR for 48 weeks vs. Boceprevir for 32 weeks plus 36-48 weeks RGT	TE	SVR24	Early: F0-F2 (437)	1.04 (0.84, 1.40)
				Late: F3-F4 (125)	1.56 (0.88, 3.63)

Abbreviations: DAA, direct-acting antiviral agent; PR, pegylated interferon + ribavirin; RGT, response-guided therapy; SVR, sustained virologic response; TE, treatment experienced; TN, treatment naïve.

Simeprevir with sofosbuvir

Using data from the COSMOS trial,[58] we compared patients with early-stage disease (F0-F2, Cohort 1 of COSMOS) to those with late-stage disease (F3-F4, Cohort 2), and also those with cirrhosis (F4) to those without (F0-F3). For treatment-experienced patients, there were no differences between these groups in effects of ribavirin or treatment duration on SVR12 (Table 15). Harms data were not reported by treatment history for late-stage patients, so we report pooled results for treatment-naïve and -experienced patients from Cohort 2 compared with the early-stage Cohort 1 patients, who were all treatment experienced. There were no differences between patients with early- and late-stage disease in the effects of ribavirin or duration on harms. Relapse occurred in just 4 treatment-experienced patients, 3 of them treated for 12 weeks. The six total patients relapsing in the trial had a range of disease stages: one had Metavir score F0-1, two F2, one F1, and two F4.

Simeprevir compared with boceprevir

The CADTH review's[82] NMA compared simeprevir and boceprevir regimens by stage of disease. There were no statistically significant differences in the effects of the 2 regimens on SVR, for patients with either early- or late-stage disease.

Boceprevir

CADTH[82] compared 2 boceprevir regimens and found no statistically significant difference in the effects of the 2 regimens on SVR, for patients with either early- or late-stage disease.

Genotypes Other Than 1

Sofosbuvir

One trial (FUSION) randomized patients with HCV genotypes 2 or 3 who had not responded to interferon therapy to treatment with sofosbuvir and ribavirin for 12 or 16 weeks (N=201).[51] For the 68 patients with genotype 2, achievement of SVR12 for patients without cirrhosis (N=49) was similar with 12 weeks of treatment compared with 16 weeks (RR 0.96, 95% CI 0.83 to 1.2). For genotype 2 patients with cirrhosis (N=19), achieving SVR appeared somewhat less

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likely with 12 weeks of treatment, but the difference was not statistically significant (RR 0.77, 95% CI 0.38 to 1.5). For patients with genotype 3, treatment with sofosbuvir and ribavirin for 12 weeks resulted in lower SVR compared with treatment for 16 weeks in patients with (N=49, RR 0.59, 95% CI 0.37 to 0.95) and without cirrhosis (N=78, RR 0.32, 95% CI 0.14 to 0.74).

Key Question 8. What evidence supports a correlation between 12- or 24-week post-treatment sustained virologic response (SVR) and long-term outcomes of mortality, cirrhosis, transplant, and hepatocellular carcinoma? Does SVR12 predict SVR24?

Summary of Evidence

- No evidence on the relationship between SVR and long-term outcomes with DAAs was found.
- Evidence based on interferon monotherapy or PR indicated
  - Moderate-strength evidence that SVR is associated with lower risk of all-cause mortality in genotypes 1 (adjusted HR 0.71, 95% CI, 0.60 to 0.86), 2 (adjusted HR 0.62; 95% CI, 0.44 to 0.87) and 3 (adjusted HR 0.51; 95% CI, 0.35 to 0.75)
  - Moderate-strength evidence that SVR was associated with lower risk of hepatocellular carcinoma; range of adjusted hazard ratios ranged from 0.12 (95% CI, 0.04 to 0.40) to 0.36 (95% CI, 0.04 to 0.83)
  - Low-strength evidence that in patients with advanced hepatic fibrosis or cirrhosis, SVR is associated with lower risk of all-cause mortality (adjusted HR 0.26; 95% CI, 0.14 to 0.49), liver-related mortality or transplant (adjusted HR, 0.06; 95% CI, 0.02 to 0.19) and hepatocellular carcinoma adjusted HR 0.16 (95% CI, 0.07 to 0.37).
- Evidence on the correlation of SVR12 and SVR24 with DAAs suggested a high level of correlation, with rates of positive predictive values from 98% to 100% and negative predictive values of 100% in patients with genotype 1. SVR rates were 0% to 3% lower at 24 weeks post-treatment compared with 12 weeks.
- Evidence from interferon-based regimens was similar, except that in an analysis including various forms of interferon, boceprevir, and telaprevir, negative predictive values were somewhat lower in patients with genotype 2 or 3 (95.4%). Across all evidence the range of PPVs was 97.5% to 100%, and for NPV was 95.4% to 100%.

Detailed Assessment

To date, no studies were identified that reported on long-term outcomes following treatment with DAAs, and the applicability of the identified evidence based on studies of interferon monotherapy and interferon plus ribavirin combination therapy to DAA treatment regimens is unclear. Based on studies of interferon monotherapy and interferon plus ribavirin combination therapy, the AHRQ review found that in treatment-naïve patients who are not co-infected with HIV, have not had a transplant, and who are not on dialysis, compared with no SVR, there is moderate strength evidence that SVR is associated with lower risk of all-cause mortality in genotypes 1 (adjusted HR 0.71, 95% CI, 0.60 to 0.86), 2 (adjusted HR 0.62; 95% CI, 0.44 to 0.87) and 3 (adjusted HR 0.51; 95% CI, 0.35 to 0.75).[4] The reported hazard ratios came from a

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large fair-quality US Veterans Affairs (VA) hospital cohort study of 16,864 patients that controlled well for potential confounders.[88] Findings from eighteen additional cohort studies that were smaller, lower quality and mostly conducted outside of the US were consistent with the VA study, with stronger adjusted hazard ratios (range, 0.10 to 0.33).[89-106] Similarly, a meta-analysis of only observational studies reported relative risk of liver-related mortality to be 0.23 (95% CI 0.10 to 0.52) in patients with SVR compared with those who had treatment failure (no SVR) at 6-months post-treatment with interferon +/- ribavirin.[107] Limiting to patients with 'advanced fibrosis or cirrhosis' the risk was further reduced (RR 0.19, 95% CI 0.10 to 0.37). This study does not meet Drug Effectiveness Review Project standards for a systematic review because the authors did not conduct quality assessments of included studies.

Similarly, an observational study of patients diagnosed with advanced hepatic fibrosis or cirrhosis who were treated with interferon +/- ribavirin provides low-strength evidence that SVR is associated with lower risk of all-cause mortality for those who achieved SVR compared with those who did not (adjusted HR 0.26; 95% CI, 0.14 to 0.49) and reduced risk of liver-related mortality or transplantation (HR, 0.06; 95% CI, 0.02 to 0.19).[108] The AHRQ report also rated the strength of the evidence as moderate for the association between SVR and lower risk of hepatocellular carcinoma. Adjusted hazard ratios for hepatocellular carcinoma were reported in 5 fair-quality cohort studies of 1516 total patients that were conducted primarily in Asian countries and ranged from 0.12 (95% CI, 0.04 to 0.40) to 0.36 (95% CI, 0.04 to 0.83). The meta-analysis that reported on liver-related mortality also reported on the risk of hepatocellular carcinoma in patients with SVR compared with those who had treatment failure (no SVR) at 6-months after the end of treatment with interferon +/- ribavirin and found a pooled relative risk of 0.21 (95% CI 0.16 to 0.27; I^2=0%, 19 studies) for all patients and 0.27 (95% CI 0.19 to 0.39, I^2=0%, 7 studies) for those with advanced fibrosis or cirrhosis. We also identified a single older observational study (N=2,400 treated patients) that was not included in either the AHRQ review or the meta-analysis, which found a relative risk of 0.52 (95% CI 0.36 to 0.74) in those with SVR compared with those without SVR at 6-months post-treatment with interferon.[77] The newer evidence does not change our assessment of the strength of the evidence, or the range of reduction expected, but this evidence is still based on interferon treatment and does not reflect current regimens. In patients with advanced hepatic fibrosis or cirrhosis, a single observational study provides low-strength evidence of a reduced risk of hepatocellular carcinoma in those with SVR after interferon +/- ribavirin treatment compared with those who did not (adjusted HR 0.16 [95% CI, 0.07-0.37]).[108,109]

Does SVR12 Predict SVR24?

There has been controversy over whether SVR at 12-weeks post-treatment is an accurate gauge of what the SVR would be at 24-weeks post-treatment, the historical standard for determining successful eradication of virus in hepatitis C.[71] Using SVR12 as the standard would allow shorter follow-up durations in studies that use this as the primary outcome and do not go on to measure clinical outcomes. There is some support for the use of shorter timeframes based on the concept that relapse (recurrence of detectable virus) actually occurs in the early weeks after treatment ends, e.g. by week 4, such that SVR at week 12 or 24 should be equivalent, barring re-infection. The discussion of this issue is complicated by the treatments themselves and the ability of the tests to detect virus. Much of the data on the correlation between SVR12 and SVR24 comes from use of interferons (various formulations and types) with or without ribavirin, with very little on DAAs with or without PR. Older studies used tests that were less sensitive to viral load – the

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level at which virus was undetectable with older tests was higher, while the current tests have the ability to detect virus at lower concentrations.

We found 6 studies that reported both SVR12 and SVR24 for at least 1 arm of the study (Table 16).[46,53,56,64,65,68] These are a mix of RCTs and observational studies, but the data from trials are mainly from a single arm. For DAA regimens in patients with genotype 1 virus, the difference between SVR12 and SVR24 was 0 to 3%, with the difference often related to loss to follow-up (counted as no longer SVR if failed to return for 24 week visit). Two of these studies[56,65] reported the positive predictive value (PPV), with a range of 97.5% to 100% and negative predictive values (NPV) of 100% (Table 17). An analysis undertaken by researchers at the US Food and Drug Administration (FDA) using individual patient-level data from studies submitted between 2002 and 2011 included 9 studies of either telaprevir or boceprevir and found PPVs of 98% to 100% for this subset of studies.[71]

The remainder of the evidence[71-76] included only data on interferons with or without ribavirin. Three observational studies found very little difference in SVR rates at 12 or 24 weeks post-treatment. While a meta-analysis found 5% to 6% difference, the analysis is based on qualitative indirect comparisons of pooled data from different studies; the SVR12s were measured in different patients than the SVR24s. The analysis conducted by researchers at the FDA included 3 studies of pegylated interferon, and the PPV's for these ranged from 96% to 98%.[71] The overall analysis, including data from these 3 studies, 3 studies of other forms of interferon, and telaprevir or boceprevir found a PPV of 98.3% for genotype 1 and 98.6% for genotypes 2 and 3, but somewhat lower NPVs in genotype 2 and 3 (95.4%) versus genotype 1 (98.8%). Separately, 3 observational studies of PR reported PPVs of 98% to 100%, and 1 reported an NPV of 100%. Across all evidence the range of PPVs was 97.5% to 100%, and for NPV was 95.4% to 100%.

Table 16. SVR12 and SVR24 rates in treatment studies for hepatitis C virus

Author, Year Study Design	DAA	Genotype	SVR12	SVR24	Difference (%)
DAAs					
Sulkowski, 2014[68] RCT	Daclatasvir + sofosbuvir +/- ribavirin for 12 or 24 weeks	Genotype 1 Treatment naïve	98%	95%	-3
Pol, 2012[64] RCT	Daclatasvir 60mg+PR for 48 weeks	Genotype 1 Treatment naïve	83%	83%	0
Dieterich, 2014[46] RCT	Faldaprevir + PR for 12 or 24 weeks, with extended PR depending on response	Genotype 1 Treatment naïve	12 weeks: 69% 24 weeks: 76%	12 weeks: 67% 24 weeks: 74%	-2 -2
Poordad, 2013[65] AVIATOR	3DAA+ribavirin for 12 or 24 weeks	Genotype 1 Combined treatment naïve and experienced	96%	94%	-2
Lawitz, 2014[56] PEARL-I	Paritaprevir+ritonavir+ombitasvir for 12 weeks	Genotype 1b	Treatment Naïve: 95.2% Treatment Experienced: 90%	Treatment Naïve: 92.9% Treatment Experienced: 90%	-2.3 -0
NCT01288209[53]	Simeprevir for 12 or 24 weeks + PR	Genotype 1 Treatment experienced	12 weeks treatment: 52% 24 weeks treatment: 36%	12 weeks treatment: 51% 24 weeks treatment: 36%	-1 0

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Author, Year Study Design	DAA	Genotype	SVR12	SVR24	Difference (%)
Interferons (+ribavirin)					
Giordanino, 2014[74] Observational	PR for 24-72 weeks	All genotypes	89%	88%	-1
Namikawa, 2012[76] Observational	PR for 24-72 weeks		74%	74%	-0
Campos-Varela, 2012[73] Observational	PR for 24-72 weeks		74%	74%	-0
Thorlund, 2014[72] Meta-analysis	PR (Peg-alpha2a and Peg alpha 2b separately)		Peg-alpha 2a: 53% Peg-alpha 2b: 45%	Peg-alpha 2a: 47% Peg-alpha 2b: 40%	-6% -5%

DAA, direct-acting antiviral agent; PR, pegylated interferon + ribavirin; SVR, sustained virologic response.

Table 17. SVR12 positive and negative predictive values for SVR24

Author, Year Study Name Study Design	Intervention details	Patient characteristics	Results
Chen, 2013[71] FDA IPD Meta-analysis	Data from Phase II and III studies submitted to FDA from 2002—2011 (N=15) of PR regimens, other interferons, boceprevir and telaprevir	All genotypes Combined treatment naïve and experienced	Genotype 1 PPV: 98.3% NPV: 98.8% Genotype2-3 PPV: 98.6% NPV: 95.4%
Poordad, 2013[65] 2 arms from AVIATOR study	3DAA+ribavirin for 12 or 24 weeks	Genotype 1 Combined treatment naïve and experienced	PPV: 98.3% NPV: 100% Sensitivity: 100% Specificity: 73.3%
Lawitz, 2014[56] 1 arm from PEARL-I study	Paritaprevir+ribavirin+ ombitasvir for 12 weeks	Genotype 1 Treatment naïve and experienced	PPV Treatment Naïve: 97.5% Treatment Experienced: 100% NPV: 100% for both
Namikawa, 2012[76] Observational	PR	All genotypes	PPV: 98% 1a and 1b: 100%
Martinot-Peignoux, 2010[75] Observational	PR	All genotypes	PPV: 99.7%
Campos-Varela, 2012[73] Observational	PR	All genotypes	PPV 100%

Abbreviations: DAA, direct-acting antiviral agent; FDA, US Food and Drug Administration; PR, pegylated interferon + ribavirin.

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LIMITATIONS OF THIS REVIEW

The conclusions we were able to draw in this review were limited by the evidence available. The major evidence gaps we identified included the following:

- We found no head-to-head trials of any included direct-acting antiviral agent (DAA) compared with another included DAA. Indirect analyses were required to compare older DAAs (boceprevir, simeprevir, sofosbuvir) using treatment with pegylated interferon with ribavirin (PR) as the common comparator arm.
- It was not possible to conduct indirect analysis with any all-oral DAA regimen (e.g., simeprevir with sofosbuvir, ledipasvir/sofosbuvir, 3D regimen) due to lack of a common comparator.
- For treatment-experienced patients, there were no included trials of sofosbuvir in a regimen without other DAAs, and no included trials in genotypes other than 1.
- Trials provided no information on treatment in hepatitis C virus (HCV) patients who abuse alcohol or drugs, and little information for patients co-infected with HIV.
- We found no evidence on associations between SVR and any long-term outcome in patients treated with DAAs.

Methodologic limitations of this review include exclusion of studies published in languages other than English.

STRENGTHS OF THIS REVIEW

This report is the first Drug Effectiveness Review Project review to include evidence on the comparative effectiveness and harms of drugs prior to US Food and Drug Administration (FDA) approval and included all direct-acting antiviral agents (DAAs) with New Drug Applications (NDA) submitted to the FDA. Two DAA drug regimens (ledipasvir/sofosbuvir and the 3D regimen) were approved during the conduct of the review and are included. This facilitates timely decision-making once these drugs become available to patients. We also included data from unpublished studies from ClinicalTrials.gov searches and manufacturers' dossiers.

Another strength of this review concerns the quality of the available evidence. Most trials were well-conducted. Additionally, many recent trials posted protocols and supplemental data online. Protocols frequently provided needed details on randomization and allocation concealment, and supplemental appendices often provided extensive subgroup information.

OVERALL SUMMARY

Direct, head-to-head evidence comparing one included direct-acting antiviral agent (DAA) with another included DAA was lacking. Indirect evidence was limited to trials of sofosbuvir (1 trial), simeprevir (5 trials), and boceprevir (3 trials) with pegylated interferon with ribavirin (PR) as a common comparator in treatment-naïve patients. There were no other common treatment arms in treatment-naïve or treatment-experienced patients that could be used to compare other DAA (e.g., 3D regimen, ledipasvir/sofosbuvir, simeprevir/sofosbuvir, daclatasvir/sofosbuvir). Indirect

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comparisons with daclatasvir were not conducted due to limited evidence from one very small trial with an unusually low sustained virologic response (SVR) rate in the control group. The strength of the evidence for all indirect comparisons was rated low.

We found moderate strength evidence in treatment-naïve patients that treatment with ledipasvir plus sofosbuvir with ribavirin versus without ribavirin did not affect rates of SVR. In both treatment-naïve and -experienced patients, moderate strength evidence showed that treatment with ledipasvir plus sofosbuvir for 12 weeks compared with 24 weeks also had minimal effect on SVR rates. There was moderate strength evidence in patients with a mixed treatment history that treatment with sofosbuvir plus ribavirin for 12 weeks resulted in increased SVR and anemia compared with placebo. Additionally, we found moderate strength evidence that achieving a sustained viral response was associated with lower risks of mortality and of hepatocellular carcinoma when treatment was interferon monotherapy or PR. There was no evidence reporting the association between any DAA and long-term clinical outcomes.

We found low strength of evidence in treatment-naïve patients that 8 weeks of treatment with ledipasvir/sofosbuvir was associated with increased relapse rates compared with 12 weeks, and that stage of disease did not affect outcomes. In both treatment-naïve and -experienced patients, we found that excluding ribavirin from all-oral DAA regimens did not affect SVR (low strength of evidence) and reduced harms.

We also found low strength of evidence in treatment-experienced patients that in patients with cirrhosis those treated for 12 weeks with ledipasvir/sofosbuvir were less likely to achieve SVR and more likely to relapse than those treated for 24 weeks. Similarly, in patients with cirrhosis and a mixed treatment history given the 3D regimen relapse was more likely with 12 weeks of treatment than with 24 weeks. Additionally, in patients with genotype 3 who had not responded to interferon therapy, treatment with sofosbuvir and ribavirin for 12 weeks resulted in lower rates of SVR than treatment for 16 weeks.

Although not formally assigned a strength-of-evidence rating, we did find evidence of good correlation between SVR12 and SVR24 in patients treated with DAAs. Summary of evidence by key question for treatment-naïve patients, treatment-experienced patients and those with mixed treatment history, and for the correlation between SVR12 and SVR24 and long-term outcomes are included below in Tables 18, 19, and 20, respectively.

Table 18. Summary of the evidence by key question for direct-acting antiviral agents for hepatitis C virus in treatment-naïve patients

Comparison	Strength of evidence	Conclusions
Key Question 1: Comparative effectiveness of DAAs in genotype 1		
Daclatasvir vs. other DAAs	Insufficient	One small trial (N=48) of daclatasvir versus PR was included; SVR in the PR of this trial was much lower (25%) than the PR arm of other DAA trials and therefore, indirect comparisons were not conducted
Sofosbuvir vs. Simeprevir	Low NA NA	**SVR:** There was no difference between sofosbuvir and simeprevir regimens in effects on SVR. **Relapse:** There was no difference in viral relapse. **Harms:** There were no differences between sofosbuvir and simeprevir on withdrawal due to adverse events, anemia, neutropenia, or rash.
Sofosbuvir vs. Boceprevir	Low NA NA	**SVR:** There was no difference between sofosbuvir and boceprevir in SVR. **Relapse:** There was no difference between sofosbuvir and boceprevir in viral relapse. **Harms:** There were no differences between sofosbuvir and boceprevir in withdrawal due to adverse events, anemia or neutropenia.

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Table 18. Summary of the evidence by key question for direct-acting antiviral agents for hepatitis C virus in treatment-naïve patients

Comparison	Strength of evidence	Conclusions
Boceprevir vs. Simeprevir	Low	**SVR:** There was no difference between boceprevir and simeprevir in SVR. Excluding the boceprevir trial in patients with lower viral load at baseline (<600,000 IU/mL) who demonstrated rapid virologic response to PR prior to randomization resulted in a ***borderline increase in SVR*** with boceprevir.
	NA	**Relapse:** Risk of viral relapse was similar between boceprevir and simeprevir.
	NA	**Harms:** Indirect analysis found an ***increased risk of anemia*** (RR 1.55, 1.21 to 1.98) with boceprevir versus simeprevir, but no difference in withdrawals due to adverse events or neutropenia.
Ledipasvir + Sofosbuvir ± Ribavirin	Moderate	**SVR:** There was no difference between ledipasvir plus sofosbuvir with ribavirin versus without ribavirin in SVR when treatment was between 8 and 24 weeks.
	NA	**Relapse:** There was no difference between ledipasvir plus sofosbuvir with or without ribavirin on viral relapse.
	NA	**Harms:** ***Anemia was reduced*** when ribavirin was not part of the treatment regimen compared to treatment with ledipasvir plus sofosbuvir with ribavirin when treatment was between 8 and 24 weeks. The ***risk of rash was also less*** without ribavirin with 8 weeks of treatment.
Simeprevir + Sofosbuvir ± Ribavirin	Low	**SVR:** In patients with Metavir Scores F3-F4, SVR rates were similar with versus without ribavirin with both 12 and 24 weeks of treatment.
	NA	**Harms:** The risk of rash was similar whether or not ribavirin was added to treatment with simeprevir plus sofosbuvir.
3D Regimen ± Ribavirin	Low	**SVR:** The addition of ribavirin to the 3D regimen increased SVR by 4% and although statistically significant (***RR 1.04, 95% CI 1.02 to 1.07***) this difference may not be clinically significant.
	NA	**Harms:** The ***risk of anemia was increased*** with the addition of ribavirin (RR 12, 95% CI 7.43 to 20) but there was no effect on risk of rash.
Boceprevir with regular or low dose ribavirin	Low	**SVR:** There was no difference between regular versus low dose ribavirin when added to boceprevir treatment for 48 weeks.
Key Question 2: Comparative effectiveness of DAAs in genotypes other than 1		
Daclatasvir + Sofosbuvir ± Ribavirin	Insufficient	**SVR:** There was no difference in SVR between daclatasvir plus sofosbuvir with versus without ribavirin in patients with genotypes 2 and 3.
Key Question 3: Comparative effectiveness of DAAs and non-DAAs in genotypes other than 1		
Sofosbuvir	Low	**SVR:** There was no difference between 12 weeks of treatment with sofosbuvir plus ribavirin versus 24 weeks treatment with PR in patients with genotypes 2 and 3 in effects on SVR.
	NA	**Relapse:** Treatment with sofosbuvir plus ribavirin for 12 weeks was associated with ***borderline increased viral relapse*** (RR 1.40, 95% CI 1.03 to 1.93).
	NA	**Harms:** There was ***reduced risk of rash*** (RR 0.51, 95% CI 0.32 to 0.82) ***and neutropenia*** (RR 0.03, 95% CI 0.004 to 0.23) but not anemia with 12 weeks of sofosbuvir plus ribavirin versus 24 weeks treatment with PR.
Key Question 4: Dose and duration genotype 1		
Daclatasvir 3 mg vs 10 mg vs 60 mg	Insufficient	**SVR:** 48 weeks of treatment with daclatasvir 10 mg resulted in the same number of patients achieving SVR as daclatasvir 60 mg (10/12 each) which was non-significantly increased over treatment with daclatasvir 3 mg (RR 0.50, 95% CI 0.24 to 1.02).
Daclatasvir 1 mg vs 10 mg vs 30 mg vs 60 mg vs 100 mg vs 30 mg twice/day	NA	**Relapse:** One patient out of 12 experienced viral relapse in each of the 10 mg and 60 mg arms and 2/12 in the 3 mg arm.
	NA	**HCV RNA:** In a small trial (N=30), the mean maximum decrease in HCV RNA appeared dose-related with treatment with daclatasvir 1 mg (-2.81) to daclatasvir 100 mg (-3.23). However, maximum decrease was seen with daclatasvir 30 mg given twice daily.

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Table 18. Summary of the evidence by key question for direct-acting antiviral agents for hepatitis C virus in treatment-naïve patients

Comparison	Strength of evidence	Conclusions
Sofosbuvir 200 mg vs 400 mg	Low NA	**SVR:** There was no difference in SVR between 12 weeks treatment with sofosbuvir 200 mg plus PR versus 400 mg plus PR (followed by additional 12-36 weeks treatment with PR). **Relapse:** There was also no difference between sofosbuvir doses in viral relapse (2% both groups).
	NA	**Harms:** Rates of anemia, neutropenia and rash were similar between sofosbuvir 200 and 400 mg.
Simeprevir 75 mg vs 150 mg **Simeprevir 50mg vs 100 mg** **Simeprevir 25 mg vs 75 mg**	Low NA NA	**SVR:** There was no difference between simeprevir 75 mg versus 150 mg with 12 or 24 weeks treatment along with PR for 48 weeks. SVR rates were also similar when 50 mg was compared with 100 mg along with PR for 24 or 48 weeks RGT. **Relapse:** There was no difference between simeprevir 75 mg versus 150 mg with 12 or 24 weeks treatment along with PR for 48 weeks. Relapse rates were also similar when 50 mg was compared with 100 mg along with PR for 24 or 48 weeks RGT. **Harms:** There was no difference between simeprevir 75 mg versus 150 mg with 12 or 24 weeks treatment along with PR for 48 weeks in risk of anemia, neutropenia or rash. Risk of anemia, neutropenia and rash was also similar when 50 mg was compared with 100 mg along with PR for 24 or 48 weeks RGT. Additionally there was no difference with 3 or 4 weeks treatment between simeprevir 25 mg versus 75 mg (plus PR for up to 48 weeks).
3D Regimen 100 mg vs. 150 mg Paritaprevir + Ribavirin	Low NA	**SVR:** There was no difference between 100 mg versus 150 mg of paritaprevir as part of the 3D regimen along with ribavirin when given for either 12 weeks or 24 weeks in SVR rates. **Harms:** There was no difference between doses of paritaprevir on risk of anemia or rash.
Simeprevir 12 vs 24 weeks	Low NA NA	**SVR:** There was no difference in rates of SVR between 12 weeks and 24 weeks treatment with simeprevir 75 mg or 150 mg (with PR for 48 weeks). There was no difference in SVR between 12 and 24 weeks of simeprevir 50 mg or 100 mg (with PR for 24/48 weeks RGT). **Relapse:** Viral relapse rates were similar between treatment durations with the same dosing regimens. **Harms:** Treatment with simeprevir 50 or 100 mg for 12 weeks was associated with ***reduced neutropenia*** compared with treatment for 24 weeks (RR 0.58, 0.35 to 0.97; RR 0.58, 0.40 to 0.86). There were no differences between treatment durations on anemia or rash.
Ledipasvir + Sofosbuvir 8 vs. 12 weeks **Ledipasvir + Sofosbuvir 12 vs. 24 weeks**	Moderate NA NA	**SVR:** There was no difference in SVR between treatment with ledipasvir plus sofosbuvir for 8 versus 12 weeks or for 12 versus 24 weeks **Relapse:** Treatment for 8 weeks was associated with ***increased risk of viral relapse*** versus treatment for 12 weeks (RR 3.53, 1.10 to 11) while there was no difference between 12 versus 24 weeks treatment. **Harms:** Risks of anemia and rash were similar between 8 versus 12 weeks treatment and between 12 versus 24 weeks treatment
Ledipasvir + Sofosbuvir + Ribavirin 12 vs 24 weeks	Low NA NA	**SVR:** There was no difference between 12 and 24 weeks treatment with ledipasvir and sofosbuvir plus ribavirin in effects on SVR. **Relapse:** 12 versus 24 weeks treatment had similar effects on risk of viral relapse. **Harms:** The 2 treatment durations had similar effects on risks of anemia and rash.
7 days of Sofosbuvir + 23 weeks Daclatasvir/ Sofosbuvir vs 24 weeks Daclatasvir/ Sofosbuvir	Low	**SVR:** There was no difference in SVR between a leading week of sofosbuvir followed by 23 weeks of daclatasvir/sofosbuvir versus 24 weeks of daclatasvir/sofosbuvir based on data from 1 small trial (N=29).

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Table 18. Summary of the evidence by key question for direct-acting antiviral agents for hepatitis C virus in treatment-naïve patients

Comparison	Strength of evidence	Conclusions
3D Regimen + Ribavirin 12 vs. 24 weeks	Moderate	**SVR:** There was no difference in SVR between treatment for 12 versus 24 weeks with the 3D regimen plus ribavirin regardless whether paritaprevir dose was 100 or 150 mg in a pooled analysis of 2 trials (N=478).
3D Regimen + Ribavirin 8 vs. 12 weeks; 8 vs. 24 weeks	Low NA	**SVR:** Treatment with the 3D Regimen resulted in similar rates of SVR when patients were treated for 8 versus 12 weeks (N=160) and when treatment was for 8 versus 24 weeks (N=120). **Harms:** Treatment with 8 versus 12 weeks of the 3D Regimen plus ribavirin resulted in similar rates of anemia and rash.
Simeprevir + Sofosbuvir ± Ribavirin 12 vs. 24 weeks	Low	**SVR:** In patients with Metavir F3-F4, SVR rates were similar whether treated with simeprevir plus sofosbuvir for 12 weeks or 24 weeks but sample sizes were very small (N=24). The addition of ribavirin to 12 weeks versus 24 weeks of treatment with simeprevir plus sofosbuvir also yielded similar results (N=34).
4 weeks Boceprevir then Boceprevir plus PR for 24 vs 44 weeks	Low NA	**SVR:** Treatment with boceprevir for 4 weeks lead-in period followed by 24 versus 44 weeks treatment with boceprevir plus PR resulted in ***reduced rates of SVR*** with the shorter treatment period (1 trial, N=206, RR 0.75, 95% CI 0.61 to 0.92). However, the same treatment regimen without the lead-in period resulted in decrease in SVR which did not reach statistical significance (RR 0.81, 95% CI 0.65 to 1.01). **Harms:** ***Neutropenia was decreased*** with shorter treatment duration along with the 4 week lead-in treatment with boceprevir (1 trial, N=206, RR 0.55, 95% CI 0.61 to 0.92).
Key Question 4: Dose and duration genotype other than 1		
7 days of Sofosbuvir + 23 weeks Daclatasvir/ Sofosbuvir vs 24 weeks Daclatasvir/ Sofosbuvir	Insufficient	**SVR:** There was no difference in SVR rates in patients with genotypes 2 and 3 who were randomized to a lead-in dose of sofosbuvir followed by 23 weeks of daclatasvir plus sofosbuvir versus 24 weeks of the 2 DAAs but the sample size was small (N=30).
Key Question 5: Response-guided therapy		
Simeprevir	Low	**SVR:** SVR in all who qualified for RGT ranged from 91% to 93% based on data from 3 trials
Boceprevir	Low	**SVR:** Network meta-analysis by CADTH found no difference in SVR between treatment with boceprevir for 24 weeks plus PR for 28 weeks versus boceprevir treatment for 24 weeks plus PR for 24-48 weeks RGT.
Key Question 6: Subgroups - genotype 1		
Initial viral load	NA	**3D with Ribavirin:** Treatment with 8 weeks versus 12 weeks resulted in ***reduced SVR*** in patients with higher initial viral load at baseline (≥800,000 IU/mL; RR 0.89, 95% CI 0.80 to 0.98). There were no differences between 12 versus 24 weeks at higher or lower baseline viral load **3D Regimen:** There were no differences based on initial viral load between 8 week treatment with versus without ribavirin **Ledipasvir/Sofosbuvir:** There were no differences based on baseline viral load in 12 versus 24 weeks or when treatment was with or without ribavirin for 8 or 12 weeks. **Boceprevir:** Treatment with boceprevir plus PR for 28 versus 48 weeks was associated with ***reduced SVR*** at higher initial viral loads (>600,000 IU/mL; RR 0.78, 95% CI 0.62 to 0.99). Results were similar when patients were initially treated with PR for 4 weeks followed by boceprevir plus PR for 24 versus 44 weeks with ***reduced SVR*** when baseline viral loads were higher (RR 0.74, 95% CI 0.60 to 0.93)

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Table 18. Summary of the evidence by key question for direct-acting antiviral agents for hepatitis C virus in treatment-naïve patients

Comparison	Strength of evidence	Conclusions
IL28 genotype	NA	**3D with Ribavirin:** Patients with CC genotype experienced ***increased SVR*** with 12 weeks treatment versus 24 weeks (RR 1.29, 95% CI 1.01 to 1.63) although unsure of the significance of this finding. There were no other differences between 12 versus 24 weeks or 8 versus 12 weeks when stratified by IL28 genotype. **3D Regimen:** When treatment duration was 12 weeks, there were no differences in SVR with ribavirin versus without ribavirin by IL28 genotype.
		Ledipasvir/Sofosbuvir: There were no differences in SVR when treatment duration was 12 versus 24 weeks or 8 versus 12 weeks by IL28 genotype. There were also no differences by genotype when treatment was for 8 weeks or 12 weeks of ledipasvir/sofosbuvir with ribavirin versus without ribavirin. **Simeprevir:** There were no differences in SVR between simeprevir 75 mg versus 150 mg when stratified by IL28 genotype.
Demographic subgroups	NA	**3D with Ribavirin:** There were no differences in SVR between 8 versus 12 weeks treatment or between 12 versus 24 weeks treatment when patients were stratified into non-black and black. **3D Regimen:** In patients treated for 12 weeks with or without the addition of ribavirin to the 3D regimen, there were no differences in SVR when patients were stratified into non-black and black. **Ledipasvir/Sofosbuvir:** There were no differences in SVR between treatment for 8 weeks versus 12 weeks or between treatment for 12 weeks versus 24 weeks when patients were stratified based on age, gender, or race. When treated for 8 weeks or 12 weeks with ledipasvir/sofosbuvir with versus without ribavirin, there were no differences in SVR when stratified by age, gender, or race. **Boceprevir:** Treatment with boceprevir plus PR for shorter durations (24 and 28 weeks) versus 44 or 48 weeks was associated with ***decreased SVR*** in non- black patients (RR 0.75, 95% CI 0.61 to 0.93; RR 0.79, 95% CI 0.63 to 0.98, respectively). Results were mixed for women with treatment with boceprevir plus PR for 28 associated with ***increased SVR*** versus 48 weeks (RR 1.41, 95% CI 1.05 to 1.89) whereas treatment with a leading 4 weeks of PR followed by 24 versus 44 weeks of boceprevir plus PR was associated with ***decreased SVR*** in women (RR 0.60, 95% CI 0.44 to 0.83).
Key Question 6: Subgroups - genotypes other than 1		
Initial viral load	NA	**Sofosbuvir plus Ribavirin:** There was no difference between treatment with sofosbuvir plus ribavirin for 12 weeks versus treatment with PR for 24 weeks in effects on SVR based on initial viral load.
IL28 genotype	NA	**Sofosbuvir plus Ribavirin:** There was no difference between treatment with sofosbuvir plus ribavirin for 12 weeks versus treatment with PR for 24 weeks in effects on SVR in patients with the CC or Non-CC genotype.
HCV genotype	NA	**Sofosbuvir plus Ribavirin:** There was no difference between treatment with sofosbuvir plus ribavirin for 12 weeks versus treatment with PR for 24 weeks in effects on SVR in patients with genotype 2 or genotype 3.
Demographic subgroups	NA	**Sofosbuvir plus Ribavirin:** There was no difference between treatment with sofosbuvir plus ribavirin for 12 weeks versus treatment with PR for 24 weeks in effects on SVR after stratifying patients by age, gender, or race.
Key Question 7: Stage of disease		
Ledipasvir + Sofosbuvir ± Ribavirin	NA	**SVR:** There was no difference in SVR in an 8-week trial of ledipasvir and sofosbuvir with versus without ribavirin when results were stratified by Metavir fibrosis score (F0-F3; no patients had cirrhosis). There was also no difference between 8 weeks of treatment versus 12 weeks of ledipasvir and sofosbuvir with ribavirin in effects on SVR by Metavir score. A trial of 12 versus 24 weeks of treatment ± ribavirin showed no effect of these regimen changes on SVR, either for patients with or without cirrhosis.

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Table 18. Summary of the evidence by key question for direct-acting antiviral agents for hepatitis C virus in treatment-naïve patients

Comparison	Strength of evidence	Conclusions
Sofosbuvir vs. Simeprevir	NA	**SVR:** A network meta-analysis by CADTH found no difference in SVR between sofosbuvir for 12 weeks plus PR for 24-48 weeks RGT and simeprevir for 12 weeks and the same PR regimen in patients with Metavir scores F0-F2.
Sofosbuvir vs. Boceprevir	NA	**SVR:** There was also no difference in SVR in patients with Metavir scores F0-F2 when treated with sofosbuvir for 12 weeks plus PR for 24-48 weeks RGT versus treatment with boceprevir for 24 weeks and PR for 28-48 weeks RGT.
Boceprevir vs. Simeprevir	NA	**SVR:** A NMA by CADTH found no difference in SVR in patients with Metavir scores F0-F2 between treatment with boceprevir for 24 weeks plus PR for 28-48 weeks RGT versus treatment with simeprevir for 12 weeks plus PR for 24-48 weeks RGT. There was also no differences between treatment with boceprevir for 44 weeks plus PR for 48 weeks or boceprevir for 24 weeks plus PR for 28-48 weeks RGT versus simeprevir for 12 weeks plus PR for 24-48 weeks RGT in patients with Metavir scores F3-F4.
Boceprevir with PR	NA	**SVR:** Effects of changes in duration or response-guided versus fixed-duration treatment did not differ by stage of disease or presence of cirrhosis.

Abbreviations: CI, confidence interval; DAA, direct-acting antiviral agent; NA, not applicable; PR, pegylated interferon with ribavirin; RGT, response-guided therapy; RR, relative risk; SVR, sustained virologic response.

Table 19. Summary of the evidence by key question for direct-acting antiviral agents for hepatitis C virus in treatment-experienced patients and those with mixed treatment history[a]

Comparison	Strength of evidence	Conclusions
Key Question 1: Comparative effectiveness of DAAs in genotype 1		
Boceprevir vs. Simeprevir	Low NA	**SVR:** There was no difference between boceprevir and simeprevir regimens in effects on SVR. **Harms:** Boceprevir regimens were associated ***with increased rash and anemia*** compared with simeprevir regimens, but most differences were not statistically significant.
3D Regimen ± Ribavirin	Low NA NA	**SVR:** In patients with genotype 1b, inclusion of ribavirin did not affect SVR. **Relapse:** In the 1 included trial, none of the 187 patients relapsed. **Harms:** Patients not given ribavirin had ***less anemia*** (RR 0.048, 95% CI 0.0048 to 0.46) and rash (RR 0.12, 95% CI 0.020 to 0.71)
Daclatasvir + Sofosbuvir ± Ribavirin	Low NA NA	**SVR:** In the 1 included trial, all of the 41 treatment-experienced patients achieved SVR. **Relapse:** None of the 41 patients relapsed. **Harms:** Three of 20 patients given ribavirin became anemic, and 2 of 20 developed rash; none of the 21 patients not given ribavirin had anemia or rash.
Ledipasvir/ Sofosbuvir ± Ribavirin	Low NA NA	**SVR:** Inclusion of ribavirin did not affect SVR. **Relapse:** Inclusion of ribavirin did not affect relapse rates. **Harms:** Patients not given ribavirin had ***less anemia*** (RR 0.070, 95% CI 0.0096 to 0.52) ***and rash*** (RR 0.20, 95% CI 0.053 to 0.75)
Simeprevir + Sofosbuvir ± Ribavirin	Low NA NA	**SVR:** Inclusion of ribavirin did not affect SVR. **Relapse:** In the 1 included trial, 4 of the 81 patients relapsed, 3 of whom received ribavirin. **Harms:** For patients with mixed treatment history (76% treatment experienced), inclusion of ribavirin did not affect rash. ***Anemia was less likely*** without ribavirin, with the difference statistically significant for 24 weeks of treatment duration (RR 0.11, 95% CI 0.019 to 0.58).

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Table 19. Summary of the evidence by key question for direct-acting antiviral agents for hepatitis C virus in treatment-experienced patients and those with mixed treatment history[a]

Comparison	Strength of evidence	Conclusions
Key Question 3: Comparative effectiveness of DAAs and non-DAAs in genotypes 2 and 3		
Sofosbuvir + Ribavirin	Moderate	**SVR:** In patients with genotypes 2 and 3, ***SVR was increased*** with sofosbuvir and ribavirin versus placebo (RR 107, 95% CI 7 to 1700).
	NA	**Harms:** The ***risk of anemia was greater*** with active treatment versus placebo (RR 19, 95% CI 1 to 300) but there was no difference in rash.
Key Question 4: Dose and duration genotype 1		
3D Regimen, Paritaprevir 100 vs 150 mg	NA	**SVR:** Paritaprevir dose did not affect SVR. **Relapse:** In the 1 included trial, none of the 88 patients relapsed. **Harms:** Paritaprevir dose did not affect rates of anemia or rash.
3D Regimen, 12 vs. 24 weeks of treatment	Low NA NA	**SVR:** Treatment duration did not affect SVR. **Relapse:** In the 1 included trial, none of the 88 patients relapsed. **Harms:** Treatment duration did not affect rates of anemia or rash.
Ledipasvir/ Sofosbuvir, 12 vs. 24 weeks of treatment	Moderate NA NA	**SVR:** Treatment duration did not affect SVR. ***Relapse was more likely*** with shorter treatment duration: 11/220 patients treated for 12 weeks and no patient treated for 24 weeks relapsed. ***Harms were more likely*** with 24 weeks of treatment, with serious adverse events occurring in no patients treated for 12 weeks and 9/220 treated for 24 weeks. There were no statistically significant differences in anemia or rash.
Simeprevir + Sofosbuvir, 12 vs. 24 weeks of treatment	Low NA NA	**SVR:** Treatment duration did not affect SVR in the 1 included trial (N=127) **Relapse** occurred in 3 patients treated for 12 weeks and 1 treated for 24 weeks. **Harms:** One patient treated without ribavirin became anemic, but ***among patients treated with ribavirin 23 became anemic, and the risk was higher with longer treatment*** (RR 0.44, 95% CI 0.20 to 0.94, 12 vs. 24 weeks). Duration did not affect rates of rash.
Simeprevir, 12 vs. 24 weeks of treatment + PR	Low NA NA	**SVR:** In patients given 100 mg/day simeprevir (vs. current labeled dose of 150 mg), treatment duration did not affect SVR. **Relapse:** Treatment duration did not affect relapse rates. **Harms:** Treatment duration did not affect harms.
Boceprevir, 32 vs. 44 weeks of treatment + PR	Low NA	**SVR:** Treatment duration did not affect SVR. **Harms:** Treatment duration did not affect rates of anemia or rash.
Key Question 4: Dose and duration genotypes 2 and 3		
Sofosbuvir + Ribavirin 12 vs. 16 weeks	Low	**SVR:** Treatment for 12 weeks resulted in ***lower SVR*** than treatment for 16 weeks in patients with genotypes 2 and 3 (RR 0.70, 95% CI 0.55 to 0.88)
Key Question 5: Response-guided therapy		
Simeprevir + 48 weeks PR vs. Simeprevir + response-guided PR	Low NA	**SVR:** Use of RGT did not affect SVR. **Harms:** Use of RGT did not affect rates of anemia or rash.
Boceprevir + 48 weeks PR vs. Boceprevir + response-guided PR	Low NA	**SVR:** Use of RGT did not affect SVR. **Harms:** Use of RGT did not affect rates of anemia or rash.

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Table 19. Summary of the evidence by key question for direct-acting antiviral agents for hepatitis C virus in treatment-experienced patients and those with mixed treatment history[a]

Comparison	Strength of evidence	Conclusions
Key Question 6: Subgroups genotype 1		
Comorbidities	NA	**3D with Ribavirin:** treatment duration did not affect SVR in patients with mixed treatment history, whether or not they had a history of diabetes.
Initial viral load	NA	**Ledipasvir/Sofosbuvir:** Patients with initial viral load ≥ 800,000 IU/mL were ***less likely to achieve SVR*** with 12 than 24 weeks of treatment (RR 0.96, 95% CI 0.92 to 0.99), but the effect of treatment duration did not differ significantly from that in patients with lower initial viral load. Inclusion of ribavirin did not affect SVR for either subgroup. **3D Regimen:** 12 vs. 24 weeks of treatment did not affect SVR for either subgroup.
IL28 genotype	NA	**3D Regimen:** neither inclusion of ribavirin nor treatment duration affected SVR for any IL28 genotype. **Ledipasvir/Sofosbuvir:** Patients with non-CC genotypes were ***less likely to achieve SVR*** with 12 than 24 weeks of treatment (RR 0.95, 95% CI 0.91 to 0.98), but the effect of treatment duration did not differ significantly from that in patients with the CC genotype. Inclusion of ribavirin did not affect SVR for either subgroup.
Q80K mutation	NA	**3D with Ribavirin:** neither inclusion of ribavirin nor treatment duration affected SVR in patients with mixed treatment history, whether or not the HCV Q80K mutation was present.
Demographic subgroups	NA	**3D Regimen:** Inclusion of ribavirin did not affect SVR for men, women, blacks, or non-blacks. **3D with Ribavirin:** Treatment duration did not affect SVR for blacks or non-blacks in treatment-experienced populations. In patients with mixed treatment history, duration did not affect SVR regardless of age, gender, race or ethnicity. **Ledipasvir/Sofosbuvir:** Inclusion of ribavirin did not affect SVR regardless of age, gender, race, or ethnicity. ***Some subgroups were less likely to achieve SVR*** with 12 vs. 24 weeks of treatment: those who were younger than 65 years (RR 0.96, 95% CI 0.92 to 0.99), non-black (RR 0.95, 95% CI 0.91 to 0.98), or non-Hispanic/Latino (0.95, 95% CI 0.91 to 0.99). However, few patients were ≥ 65 years, black, or Hispanic/Latino, and the effect of treatment duration in these groups was not significantly different from that in the majority groups. Treatment duration did not affect SVR for men or women.
Key Question 6: Subgroups genotypes 2 and 3		
Initial viral load	NA	**Sofosbuvir/Ribavirin:** Treatment with 12 weeks resulted in ***lower SVR*** than treatment for 16 weeks in patients with higher baseline viral load (RR 0.65, 95% CI 0.50 to 0.84).
IL28 genotype	NA	**Sofosbuvir/Ribavirin:** Treatment with 12 weeks resulted in ***lower SVR*** than treatment for 16 weeks in patients with non-CC genotype (RR 0.68, 95% CI 0.52 to 0.90).
HCV genotype	NA	**Sofosbuvir/Ribavirin:** Treatment with 12 weeks resulted in ***lower SVR*** than treatment for 16 weeks in patients with genotype 3 (RR 0.48, 95% CI 0.31 to 0.73).
Demographic subgroups	NA	**Sofosbuvir/Ribavirin:** Treatment with 12 weeks resulted in ***lower SVR*** than treatment for 16 weeks in men (RR 0.64, 95% CI 0.47 to 0.89), non-Blacks (RR 0.65, 95% CI 0.51 to 0.84), and non-Hispanics (RR 0.70, 95% CI 0.55 to 0.89).

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Table 19. Summary of the evidence by key question for direct-acting antiviral agents for hepatitis C virus in treatment-experienced patients and those with mixed treatment history[a]

Comparison	Strength of evidence	Conclusions
Key Question 7: Stage of disease genotype 1		
3D Regimen, 12 vs. 24 weeks of treatment	NA	**SVR:** For treatment-experienced patients with cirrhosis, treatment duration did not affect SVR. **Relapse:** For patients with mixed treatment history and cirrhosis, ***relapse was more likely*** with 12 weeks of treatment (RR 9.9, 95% CI 1.7 to 59). **Harms:** For patients with mixed treatment history and cirrhosis, treatment duration did not affect serious adverse events, withdrawals due to adverse events, anemia, or rash.
Ledipasvir/ Sofosbuvir ± Ribavirin	NA	**SVR:** Inclusion of ribavirin did not affect SVR for those with or without cirrhosis. **Relapse:** Ten of 63 patients with cirrhosis treated for 12 weeks relapsed; 6 of these did not receive ribavirin. Four of 176 patients without cirrhosis treated for 12 weeks relapsed, all in the group not given ribavirin.
Ledipasvir/ Sofosbuvir, 12 vs. 24 weeks of treatment	NA	**SVR:** Patients with cirrhosis treated for 12 weeks were ***less likely to achieve SVR*** than those treated for 24 weeks (RR 0.84, 95% CI 0.71 to 0.95). For patients without cirrhosis, duration did not affect SVR. **Relapse:** ***All 11 patients who relapsed were treated for 12 weeks, 7 of 44 (16%) in those with cirrhosis*** and 4 of 176 (2.2%) in those without cirrhosis
Simeprevir + Sofosbuvir ± Ribavirin	NA	**SVR:** For treatment-experienced patients, inclusion of ribavirin did not affect SVR for any disease stage. **Relapse** occurred in 4 of 127 treatment-experienced patients, 3 of whom received ribavirin. One of these patients had cirrhosis (treated with ribavirin for 12 weeks). **Harms:** For treatment-experienced patients with early-stage disease and patients with mixed treatment history and late-stage disease, inclusion of ribavirin did not affect incidence of rash. Anemia appeared less likely without ribavirin (RRs 0.20 and 0.38), but differences were not statistically significant.
Simeprevir + Sofosbuvir, 12 vs. 24 weeks of treatment	NA	**SVR:** For treatment-experienced patients, treatment duration did not affect SVR for any disease stage. **Relapse** occurred in 4 of 127 treatment-experienced patients, 3 of whom were treated for 12 weeks. One of these patients had cirrhosis (treated with ribavirin for 12 weeks). **Harms:** For treatment-experienced patients with early-stage disease and patients with mixed treatment history and late-stage disease, treatment duration did not affect incidence of rash. Anemia appeared less likely with 12 weeks of treatment (RRs 0.22 and 0.44), but differences were not statistically significant.
Boceprevir vs. Simeprevir	NA	**SVR:** There was no difference between boceprevir and simeprevir regimens in effects on SVR for early or late stage disease.
Boceprevir + fixed-duration PR vs. Boceprevir + response-guided PR	NA	**SVR:** Boceprevir regimen did not affect SVR for early or late-stage disease.
Key Question 7: Stage of disease for genotypes 2 and 3		
Sofosbuvir + Ribavirin 12 vs. 16 weeks	NA	**SVR:** Regardless of the presence or absence of cirrhosis, in patients with genotype 2 there were no differences in rates of SVR based on treatment duration. In patients with genotype 3, ***SVR was lower*** with 12 weeks of treatment in those with and without cirrhosis (RR 0.59, 95% CI 0.37 to 0.95; RR 0.32, 95% CI 0.14 to 0.74, respectively).

[a]Populations are treatment experienced unless otherwise indicated.
Abbreviations: CI, confidence interval; DAA, direct-acting antiviral agent; NA, not applicable; PR, pegylated interferon with ribavirin; RGT, response-guided therapy; RR, relative risk; SVR, sustained virologic response.

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Table 20. Summary of the evidence for Key Question 8 (correlation between SVR12 and SVR24 and long-term outcomes)

Outcome	Strength of evidence	Conclusions
All-cause mortality	Moderate	**Interferon monotherapy or PR:** SVR is associated with ***lower risk of all-cause mortality*** in genotypes 1 (adjusted HR 0.71, 95% CI, 0.60 to 0.86), 2 (adjusted HR 0.62; 95% CI, 0.44 to 0.87) and 3 (adjusted HR 0.51; 95% CI, 0.35 to 0.75)
Hepatocellular carcinoma	Moderate	**Interferon monotherapy or PR:** SVR was associated with ***lower risk of hepatocellular carcinoma***; range of adjusted hazard ratios ranged from 0.12 (95% CI, 0.04 to 0.40) to 0.36 (95% CI, 0.04 to 0.83)
Cirrhosis	Insufficient	No evidence was found on an association between SVR and cirrhosis.
Transplant	Insufficient	No evidence was found on an association between SVR and transplant.
Correlation between SVR12 and SVR24	NA	**DAAs:** evidence suggests a ***high level of correlation***, with rates of positive predictive values from 98% to 100% and negative predictive values of 100% in patients with genotype 1. SVR rates were 0% to 3% lower at 24 weeks post-treatment compared with 12 weeks **Interferon-based regimens:** in an analysis including various forms of interferon, boceprevir, and telaprevir, negative predictive values were somewhat lower in patients with genotype 2 or 3 (95.4%). Across all evidence the range of PPVs was 97.5% to 100%, and for NPV was 95.4% to 100%

Abbreviations: CI, confidence interval; DAA, direct-acting antiviral agent; NA, not applicable; PR, pegylated interferon + ribavirin; RR, relative risk; SVR, sustained virologic response.

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