Draft Comparative Effectiveness Review

Number XX

Treatment for Hepatitis C Virus Infection in Adults: A Comparative Effectiveness Review

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Contract No. xxx-xxxx-xxxxx

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AHRQ Publication No. XX-EHCXXx
<Month Year>

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Financial Disclosure Statement

None of the investigators has any affiliations or financial involvement that conflicts with the material presented in this report.

Standard Suggested Citation of Your Report

Suggested citation: <Authors>. <Topic>. Evidence Report/Technology Assessment. No. <#>. (Prepared by <EPC Name> under Contract No. <##>.) Rockville, MD: Agency for Healthcare Research and Quality. <Month, Year>. http://www.ahrq.gov/clinic/epcix.htm. Accessed: <Date>. <URL>.

Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the Children's Health Insurance Program (CHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting comparative effectiveness reviews (CERs) of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see http://www.effectivehealthcare.ahrq.gov/reference/purpose.cfm

AHRQ expects that CERs will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

Transparency and stakeholder input from are essential to the Effective Health Care Program. Please visit the Web site (http://www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly.

We welcome comments on this CER. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to epc@ahrq.hhs.gov.

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The authors gratefully acknowledge the following individuals for their contributions to this project: <Acknowledgments>.

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Treatment for Hepatitis C Virus Infection in Adults: A Comparative Effectiveness Review

Structured Abstract

Objectives: This report systematically reviews the comparative benefits and harms of current antiviral treatment regimens for chronic hepatitis C virus (HCV) infection in treatment-naïve adults.

Data Sources: MEDLINE®, the Cochrane Central Register of Controlled Trials, clinical trial registries, and reference lists.

Review Methods: We selected randomized trials of dual therapy with pegylated interferon (alfa-2a or -2b) plus ribavirin or triple therapy with pegylated interferon (alfa-2a or -2b), ribavirin and boceprevir or telaprevir which reported clinical outcomes, sustained virologic response (SVR), or harms. We also selected randomized trials or cohort studies that compared clinical outcomes in patients who received antiviral therapy and experienced an SVR compared with those who did not experience an SVR.

Results: We included 71 randomized trials and observational studies. No study evaluated comparative effectiveness of current antiviral regimens on long-term clinical outcomes. In trials of treatment-naïve patients, the likelihood of achieving an SVR was slightly lower for dual therapy with pegylated interferon alfa-2b plus ribavirin compared with dual therapy with pegylated interferon alfa-2a plus ribavirin, with a difference in absolute SVR rates of about 6 percentage points. There were no clear differences in estimates of relative effectiveness in patient subgroups defined by demographic or clinical characteristics, though absolute response rates were lower in older patients, black persons, patients with high viral load, patients with more advanced fibrosis or cirrhosis, and patients with genotype 1 infection. Differences in harms were relatively small, with no differences in serious adverse events or in withdrawals due to adverse events. In patients with genotype 2 or 3 infection, trials found no clear differences between dual therapy with pegylated interferon for 24 weeks and either longer (48 weeks) or shorter (12 to 16 weeks) regimens. Lower doses of pegylated interferon alfa-2b were less effective than standard doses, and limited evidence showed no clear differential effects of ribavirin dosing.

Five trials found triple therapy with pegylated interferon (alfa-2a or -2b), ribavirin, and boceprevir or telaprevir associated with higher likelihood of SVR (66% to 80%) compared with dual therapy with pegylated interferon plus ribavirin for genotype 1 infection, with an absolute increase in SVR rate of 21 to 31 percentage points. Triple therapy with boceprevir was associated with increased risk of hematological adverse events and triple therapy with telaprevir with increased risk of rash compared with dual therapy, including severe rash.

A large cohort study that controlled well for confounders found experiencing an SVR after antiviral therapy associated with lower risk of all-cause mortality compared with not experiencing an SVR, with adjusted hazard ratio estimates ranging from 0.51 to 0.71 depending on genotype. Other cohort studies also found SVR associated with reduced risk of all-cause

mortality and long-term complications of HCV infection, but had more methodological shortcomings.

Conclusions: Although there is no evidence on the comparative effects of current antiviral regimens on long-term clinical outcomes, SVR rates are substantially higher in patients with HCV genotype 1 infection who receive triple therapy with pegylated interferon (alfa-2a or -2b), ribavirin, and boceprevir or telaprevir compared to dual therapy with pegylated interferon plus ribavirin. Achieving an SVR following antiviral therapy appears to be associated with decreased risk of all-cause mortality, although more evidence is needed to reliably estimate effects on other important clinical outcomes.

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Treatment for Hepatitis C Virus Infection in Adults: A Comparative Effectiveness Review

Executive Summary

The Effective Health Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders including consumers.

The full report and this summary are available at www.effectivehealthcare.ahrq.gov. Ahrq.gov/reports/final.cfm

Background

Hepatitis C virus (HCV) is the most common chronic bloodborne pathogen in the United States. It is primarily acquired by large or repeated percutaneous exposures to blood, with injection drug use the strongest risk factor. Approximately 1.6% of U.S. adults over 20 years of age have antibodies to HCV, indicating prior acute HCV infection.[1] About 78% of patients with acute HCV infection develop chronic HCV infection, defined by the presence of persistent viremia.

Chronic HCV infection has a variable course, but is a leading cause of complications from chronic liver disease, including cirrhosis, liver failure, and hepatocellular cancer. Chronic HCV infection was associated with an estimated 15,000 deaths each year in the United States[2] and is the most common indication for liver transplantation among American adults, accounting for more than 30 percent of cases.[3] The prevalence of chronic HCV infection is thought to have peaked in 2001 at 3.6 million people and the yearly incidence has declined from more than 200,000 cases per year in the 1980s to around 16,000 cases in 2009.[4, 5] However, complications related to chronic HCV infection, which frequently occur only after decades of infection, are expected to rise for another 10 to 13 years.[4]

The goals of antiviral treatment for chronic HCV infection are to prevent the long-term health complications associated with HCV infection such as cirrhosis, hepatic decompensation, and liver cancer, but it is extremely difficult to design and carry out clinical trials long and large enough to provide direct evidence related to these outcomes. The sustained virologic response (SVR) rate, typically defined as a decline in HCV RNA to undetectable levels 24 weeks following completion of antiviral treatment, is the standard marker of successful treatment in clinical trials because it is strongly associated with long-term absence of viremia.[6, 7] Recent studies have evaluated the association between achieving an SVR and reduced mortality, liver failure, and cancer.[8, 9]

In the early 2000's, the combination of "pegylated" interferon plus ribavirin became the standard antiviral treatment for HCV infection.[10-12] Pegylation refers to the cross-linking of polyethylene glycol molecules to the interferon molecule, which delays renal clearance, thereby permitting less frequent dosing (once weekly vs. three times a week with standard interferon).[13] Dual therapy with pegylated interferon plus ribavirin is associated with higher SVR rates (about 55 to 60 percent overall) than either standard interferon plus ribavirin or pegylated interferon monotherapy. Currently, two pegylated interferons are available: pegylated interferon alfa-2a or pegylated interferon alfa-2b. Although previous reviews found insufficient evidence to determine whether combination therapy with pegylated interferon alfa-2a or pegylated interferon alfa-2b plus ribavirin is more effective,[14, 15] more head-to-head trials directly comparing these two regimens are now available.[16-19]

A number of factors affect response to antiviral treatment. The two major predictors of SVR are the viral genotype and the pretreatment viral load.[11] In the United States, genotype 1 infection is found in around three-quarters of HCV-infected patients.[20] HCV genotype 1 infection is associated with a substantially lower response to antiviral treatment than infection with genotypes 2 and 3, which are present in about 20% of HCV-infected patients. A pretreatment viral load of <600,000 IU/mL is associated with higher likelihood of achieving an SVR.[11] Other factors less consistently or less strongly associated with increased likelihood of SVR include female sex, age <40 years, non-African-American race, lower body weight (<=75 kg), absence of insulin resistance, elevated alanine aminotransferase (ALT) levels, and absence of bridging fibrosis or cirrhosis on liver biopsy.[11] Effects of race on the likelihood of SVR may be due in part to polymorphisms in the interleukin-28B (IL28B) gene.[21, 22]

An issue complicating antiviral treatment is the high rate of adverse effects observed with interferon-based therapy, including flu-like symptoms, fatigue, and neuropsychiatric and hematologic adverse effects.[23] Such adverse effects can be difficult to tolerate and can lead to premature discontinuation of therapy.

In 2011, the U.S. Food and Drug Administration approved the first direct acting antiviral agents, boceprevir (trade name Victrelis®) and telaprevir (trade name Incivek®), for treatment of chronic HCV genotype 1 infection.[24, 25] Both drugs are classified as nonstructural 3/4A protease inhibitors, with a potential advantage of shorter duration of therapy (24 weeks) compared with standard dual therapy with pegylated interferon (alfa-2a or 2b) plus ribavirin for genotype 1 infection (48 weeks).[26-28] Either drug is administered in combination with pegylated interferon (alfa-2a or 2b) plus ribavirin.

Understanding the comparative benefits and harms of the various antiviral regimens is critical for making informed treatment decisions in patients with chronic HCV infection, particularly given the availability of new treatment options. This review will assess the comparative effectiveness of antiviral treatments in adults with chronic HCV infection who have not received previous antiviral drug treatment. In addition to assessing the comparative effectiveness of different drug regimens, the review will evaluate effects of different medication doses, durations of therapy, and dosing strategies (such as weight-based or response-guided vs. fixed treatment). To help with individualized clinical decision-making regarding antiviral therapy for chronic HCV infection, it will also evaluate how comparative effectiveness varies depending on HCV genotype, viral load and other demographic and clinical characteristics. This review will be used together with a separate review on HCV screening [29] by the U.S. Preventive Services Task Force to update its HCV screening recommendations, given the need to

understand the effects of treatment in persons with HCV infection identified by screening in order to understand the potential benefits and harms of screening.

Objectives

The following key questions are the focus of our report:

Key Question 1

This key question has two parts:

a. What is the comparative effectiveness of antiviral treatment in improving health outcomes in patients with HCV infection?
b. How does the comparative effectiveness of antiviral treatment for health outcomes vary according to patient subgroup characteristics, including but not limited to HCV genotype, age, race, sex, stage of disease or genetic markers?

Key Question 2

This key question has two parts:

a. What is the comparative effectiveness of antiviral treatments on intermediate outcomes, such as the rate of SVR or histologic changes in the liver?
b. How does the comparative effectiveness of antiviral treatment for intermediate outcomes vary according to patient subgroup characteristics, including but not limited to HCV genotype, age, race, sex, stage of disease or genetic markers?

Key Question 3

This key question has two parts:

a. What are the comparative harms associated with antiviral treatments?
b. Do these harms differ according to patient subgroup characteristics, including HCV genotype, age, race, sex, stage of disease, or genetic markers?

Key Question 4

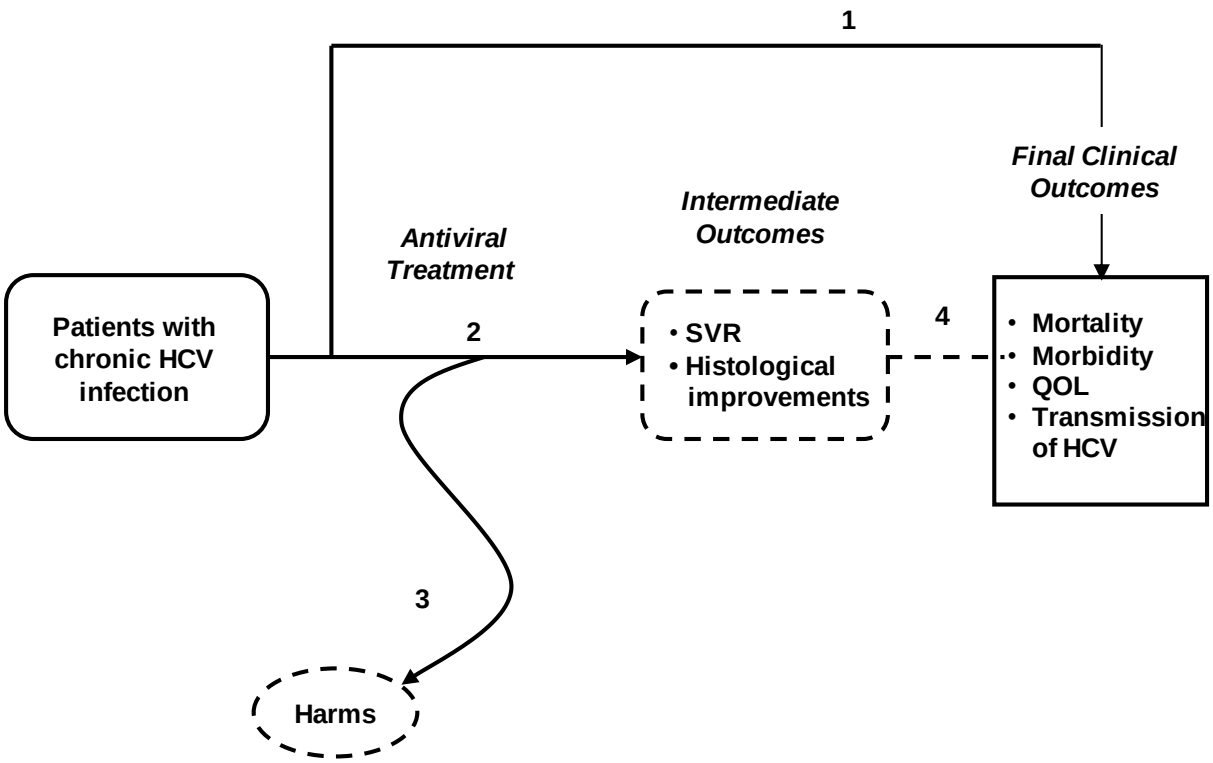
Have improvements in intermediate outcomes (SVR, histologic changes) been shown to reduce the risk or rates of adverse health outcomes from HCV infection?

Analytic Framework

The analytic framework used to guide this report is shown below in Figure A. The numbers in the analytic framework indicate the key questions listed above. The population was patients with chronic HCV infection receiving antiviral therapy. The interventions were dual therapy with pegylated interferon (alfa-2a or -2b) plus ribavirin or triple therapy with pegylated interferon (alfa-2a or alfa-2b), ribavirin plus a protease inhibitor approved by the U.S Food and Drug Administration (FDA) (boceprevir or telaprevir). Comparisons were between different regimens,

as well as between regimens including the same drugs administered at different doses or for different durations. Intermediate outcomes were sustained virologic response and hepatic histological improvement. Final outcomes were morbidity and mortality from HCV (including hepatic cirrhosis, hepatocellular carcinoma, liver transplantation rates, and quality of life) and harms of antiviral therapies including flu-like symptoms, hematologic effects, rash and psychiatric effects.

Figure A. Analytic framework for treatment of hepatitis C infection in adults



Abbreviations: HCV, hepatitis C virus; QOL, quality of life; SVR, sustained virologic response.

Methods

Input from stakeholders

The topic of hepatitis C virus (HCV) treatment was nominated for a comparative effectiveness review in a public process. The key questions were proposed in the public nomination process and developed by investigators from the Evidence-based Practice Center (EPC) with input from expert Key Informants (KI) who helped to refine key questions, identify important methodological and clinical issues, and define parameters for the review of evidence. The revised key questions were then posted to a public Web site for comment. The Agency for Healthcare Research and Quality (AHRQ) and the EPC agreed upon the final key questions after reviewing the public comments and receiving additional input from a Technical Expert Panel

(TEP) convened for this report. Prior to participation in this report, the TEP members disclosed all financial or other conflicts of interest. The AHRQ Task Order Officer and the authors reviewed all of these disclosures and determined the panel members had no significant conflicts of interest that precluded participation. KIs and TEP members had expertise in the areas of hepatology, epidemiology, screening, and primary care.

Search Strategy and Study Selection

To identify articles relevant to each Key Question, a research librarian searched the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, and Ovid MEDLINE® (see Appendix A for search strategy) from 1947 to present. The search strategies were peer reviewed by another information specialist and revised prior to finalization. Unpublished trials were sought by searching clinical trial registries (ClinicalTrials.gov, Current Controlled Trials, Clinical Trial Results, WHO Trial Registries) and grants databases (NIHRePORTER, HSRProj, and AHRQ GOLD). Scientific Information Packets on unpublished and published trials were solicited from manufacturers of included antiviral drugs through the Scientific Resource Center. We also hand-searched the reference lists of relevant studies.

Searches will be updated prior to finalization of the report to identify any relevant new publications.

Data Extraction and Quality Assessment

We assessed the quality of each study based on predefined criteria (Appendix E). We adapted criteria from methods proposed by Downs and Black (observational studies),[30] the USPSTF, [31] and the Quality Assessment of Diagnostic Accuracy Studes-2 Group.[32] The criteria used are consistent with the approach recommended by AHRQ in the Methods Guide for Comparative Effectiveness Reviews.[33] We used the term "quality" rather than the alternate term "risk of bias." Although both refer to internal validity, "quality" may be more familiar to most users and has potential advantages in terms of readability.

We rated the quality of each randomized trial based on the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to followup; the use of intent-to-treat analysis; and ascertainment of outcomes.[31]

We rated the quality of each cohort study based on whether it used nonbiased selection methods to create an inception cohort; whether it evaluated comparable groups; whether rates of loss to followup were reported and acceptable; whether it used accurate methods for ascertaining exposures, potential confounders, and outcomes; and whether it performed appropriate statistical analyses of potential confounders[31]

Following assessment of individual quality criteria, individual studies were rated "good," "fair," or "poor" quality, as defined below:[34]

Good-quality studies are considered likely to be valid. Good-quality studies clearly describe the population, setting, interventions, and comparison groups; use a valid method for allocation of patients to interventions; clearly report dropouts and have low dropout rates; use appropriate methods for preventing bias; and appropriately measure outcomes and fully report results.

Fair-quality studies have some methodological deficiencies, but no flaw or combination of flaws judged likely to cause major bias. The study may be missing information, making it difficult to assess its methods or assess limitations and potential problems. The fair-quality

category is broad, and 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 probably valid.

Poor-quality studies have significant flaws that may invalidate the results. They have a serious or "fatal" flaw in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting. The results of these studies are judged to be at least as likely to reflect flaws in the study design as true effects of the interventions under investigation. We did not exclude studies rated poor-quality *a priori*, but they were considered to be the least reliable studies when synthesizing the evidence, particularly when discrepancies between studies were present.

We recorded factors important for understanding the applicability of studies, such as whether the publication adequately described the study population, how similar patients were to populations likely to be targeted by screening, whether differences in outcomes were clinically (as well as statistically) significant, and whether the interventions and tests evaluated were reasonably representative of standard practice.[48] We also recorded the funding source and role of the sponsor. We did not assign a rating of applicability (such as "high" or "low") because applicability may differ based on the user of this report.

Data Synthesis and Rating the Strength of the Body of Evidence

We performed meta-analysis of trials that evaluated similar populations, interventions, comparisons, and outcomes to estimate pooled relative risks.[35] When present, statistical heterogeneity was explored through subgroup and sensitivity analyses, as well as qualitatively. Subgroup analyses were performed in groups stratified by HCV genotype as well as by race, age, body weight, viral load, stage/severity of disease, and IL-28b status when these data were available. We performed sensitivity analysis by excluding poor-quality studies and by excluding outlier trials, and by adding results from studies published only as abstracts to evaluate the stability of estimates and conclusions. We did not perform meta-analyses Key Question 4 because all studies were observational and had important methodologic shortcomings. These studies were synthesized qualitatively.

We rated the strength of evidence for each key question using the four categories recommended in the AHRQ Methods guide.[34] We synthesized the overall quality of each body of evidence, based on the type and quality of studies (graded good, fair, or poor); the precision of the estimate of effect, based on the number and size of studies and confidence intervals for the estimates (graded high, moderate, or low); the consistency of results between studies (graded high, moderate, or low); and the directness of the evidence linking the intervention and health outcomes (graded direct or indirect). We were not able to formally assess for publication bias due to small number of studies, methodological shortcomings, or differences across studies in designs, measured outcomes, and other factors. We rated the strength of evidence for each comparison and outcome using the four categories recommended in the AHRQ guide: [34] A "high" grade indicates high confidence that the evidence reflects the true effect and that further research is very unlikely to change our confidence in the estimate of effect. A "moderate" grade indicates moderate confidence that the evidence reflects the true effect and further research may change our confidence in the estimate of effect and may change the estimate. A "low" grade indicates low confidence that the evidence reflects the true effect and further research is likely to change the confidence in the estimate of effect and is likely to change the estimate. An "insufficient" grade indicates evidence either is unavailable or is too limited to permit any conclusion.

Results

The search and selection of articles are summarized in the study flow diagram (Figure B). Of the 1,177 citations identified at the title and abstract level, we screened and reviewed, 294 studies were selected for full-length articles. A total of 71 studies met inclusion criteria.

No study evaluated comparative effectiveness of current antiviral regimens on long-term clinical outcomes such as mortality, complications of chronic HCV infection, or quality of life.

In trials of treatment-naïve patients, dual therapy with pegylated interferon alfa-2b plus ribavirin was associated with a slightly lower likelihood of achieving an SVR compared with dual therapy with pegylated interferon alfa-2a plus ribavirin, with a difference in absolute SVR rates of about 8 percentage points. In patients with genotype 2 or 3 infection, trials found no clear differences between dual therapy with pegylated interferon alfa-2a or -2b for 24 weeks and either longer (48 weeks) or shorter (12 to 16 weeks) duration of therapy. In trials comparing different doses of dual therapy with pegylated interferon plus ribavirin, lower doses of pegylated interferon alfa-2b were less effective than standard doses, and limited evidence found no clear differential effects of ribavirin dosing.

There were no clear differences in estimates of relative effectiveness between dual therapy with pegylated interferon alfa-2a plus ribavirin compared with dual therapy with pegylated interferon alfa-2b plus ribavirin in patient subgroups defined by demographic or clinical characteristics, although absolute response rates were lower in older patients, black patients, patients with high viral load, patients with more advanced fibrosis or cirrhosis, and patients with genotype 1 infection.

Differences in harms between dual therapy with pegylated interferon alfa-2a plus ribavirin compared with pegylated interferon alfa-2b plus ribavirin were relatively small, with no differences in serious adverse events or in withdrawals due to adverse events.

Trials of antiviral regimens including boceprevir or telaprevir have only been conducted in patients with genotype 1 infection. Triple antiviral regimens (pegylated interferon alfa-2a or -2b, ribavirin, and boceprevir or telaprevir) were associated with substantially increased likelihood of achieving an SVR compared to dual therapy with pegylated interferon alfa-2a or -2b plus ribavirin.

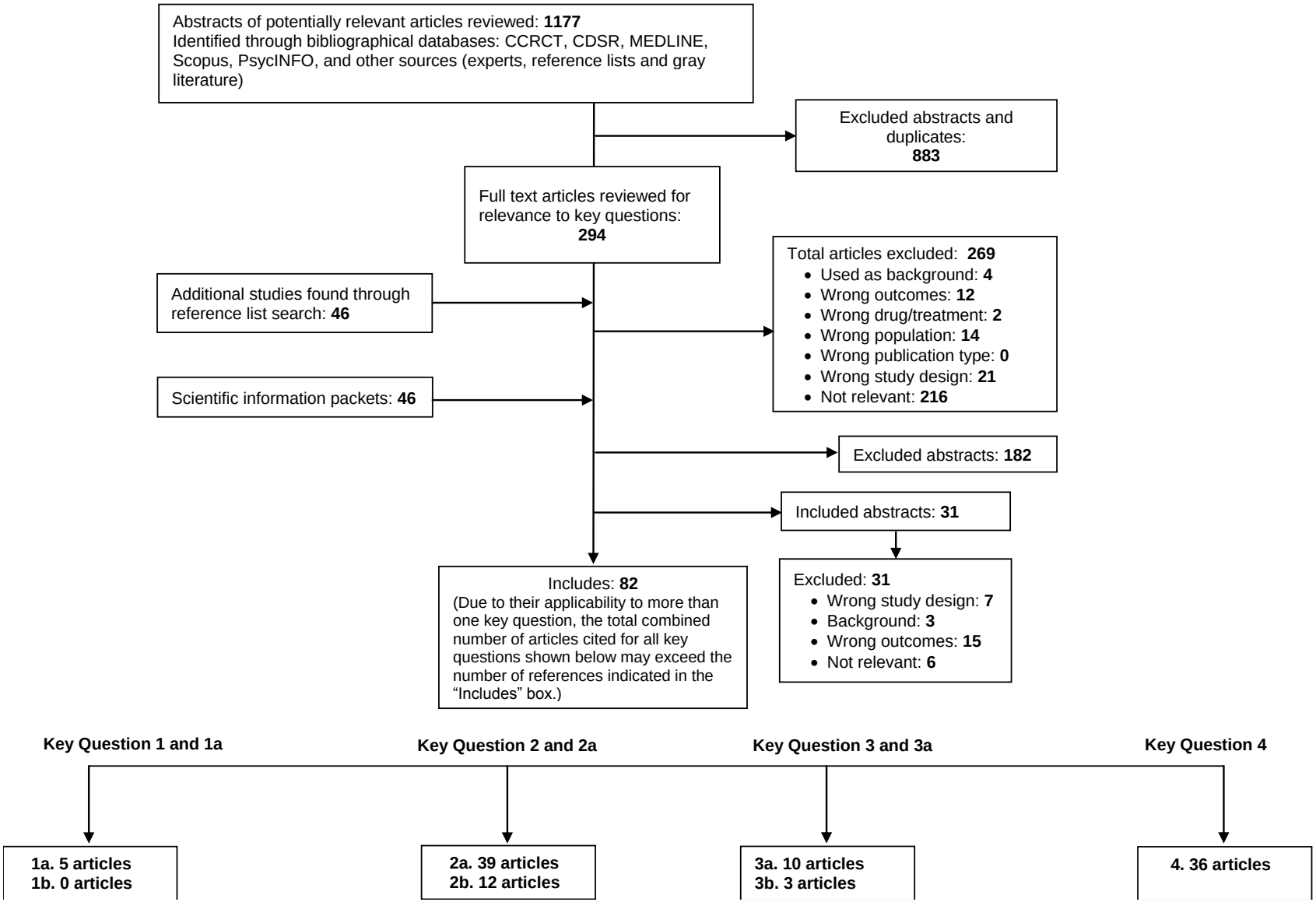
Two trials found triple therapy with boceprevir for 48 weeks (dual therapy with pegylated interferon alfa-2b plus ribavirin for 4 weeks followed by 44 weeks of triple therapy with the addition of boceprevir) associated with higher likelihood of SVR compared with dual therapy with pegylated interferon alfa-2b plus ribavirin for 48 weeks (pooled RR 1.8, 95% CI 1.6 to 2.1), with an absolute increase in SVR rate of 31 percentage points (95% CI 23 to 39 percentage points).

Two trials found triple therapy with telaprevir for 24 weeks (pegylated interferon alfa-2a, ribavirin, and telaprevir triple therapy for 12 weeks followed by 12 weeks of pegylated interferon alfa-2a plus ribavirin without telaprevir) associated with higher likelihood of SVR compared with dual therapy with pegylated interferon alfa-2a plus ribavirin for 48 weeks (pooled RR 1.5, 95% CI 1.2 to 1.8), with an absolute increase in SVR rate of 21 percentage points (95% CI 10 to 32 percentage points). One trial found response-guided telaprevir triple therapy (8 or 12 weeks of pegylated interferon alfa-2a, ribavirin, plus telaprevir followed by 12 or 36 weeks of response guided dual therapy with pegylated interferon alfa-2a plus ribavirin) associated with higher likelihood of SVR compared with dual therapy with pegylated interferon alfa-2a plus ribavirin for 48 weeks (RR 1.6, 95% CI 1.4 to 1.9), with an absolute increase in SVR rate of 25 to 31 percentage points.

Relative estimates of effects of triple therapy with either boceprevir or telaprevir compared with dual therapy were similar across subgroups except in patients with low viral load, in whom triple therapy was no more effective than dual therapy in achieving an SVR. Triple therapy with boceprevir was associated with increased risk of hematological adverse events and triple therapy with telaprevir with increased risk of rash (including severe rash) compared with dual therapy; adverse events were generally self-limited with discontinuation of therapy. All antiviral regimens were associated with a high incidence of flu-like symptoms, with small or no clear differences in risk.

A large cohort study that controlled well for confounders found an SVR after antiviral therapy associated with lower risk of all-cause mortality compared with no SVR (adjusted hazard ratio estimates 0.51 to 0.71). Sixteen other cohort studies also found SVR associated with reduced risk of all-cause mortality, liver-related mortality, and other hepatic complications compared with no SVR, but had more methodological shortcomings. Nine of the studies were conducted in Asian countries and might not be directly applicable to U.S. populations.

Figure B. Study flow diagram: Treatment for hepatitis C virus infection in adults



Discussion

Key Findings and Strength of Evidence

The evidence reviewed in this study is summarized in Table A. Details about the factors used to determine the overall strength of evidence for each key question are provided in Appendix E of the main report.[36] We identified no studies that evaluated comparative effectiveness of current antiviral regimens on long-term clinical outcomes such as mortality, complications of chronic HCV infection, or quality of life. Such trials would be difficult to design and carry out due to the long time required for complications of chronic HCV infection in most patients.

In lieu of direct evidence on long-term clinical outcomes, SVR rates are the primary outcome to assess comparative benefits of different antiviral regimens. In trials of treatment-naïve patients, the likelihood of achieving an SVR was slightly lower with dual therapy with pegylated interferon alfa-2b plus ribavirin compared with dual therapy with pegylated interferon alfa-2a plus ribavirin (pooled RR 0.90, 95% CI 0.84 to 0.96), with a difference in absolute SVR rates of about seven percentage points. Although the largest study, the IDEAL trial, found no difference in SVR rates between dual therapy with pegylated interferon alfa-2a plus ribavirin compared with dual therapy with pegylated interferon alfa-2b plus ribavirin, findings could have been confounded by differential ribavirin dosing.[18] Nonetheless, excluding the IDEAL trial from pooled analyses resulted in similar effect estimates.

Trials found no clear difference in estimates of relative effectiveness of dual therapy with pegylated interferon alfa-2a plus ribavirin compared with dual therapy with pegylated interferon alfa-2b plus ribavirin in patient subgroups stratified by age, sex, race, viral load, fibrosis stage, and genotype, although absolute response rates were lower in older patients, black patients, patients with high viral load, patients with more advanced fibrosis or cirrhosis, and patients with genotype 1 infection. SVR rates ranged from 24 to 42 percentage points lower in patients with genotype 1 infection compared with patients with genotype 2 or 3.[16, 17, 19, 37]

In patients with genotype 2 or 3 infection, there do not appear to be major differences in SVR rates between 24 weeks and either longer or shorter courses of dual therapy. Standard doses of pegylated interferon alfa-2b as part of dual therapy were more effective than lower doses (no trials compared different doses of pegylated interferon alfa-2a). Although trials comparing different ribavirin doses as part of dual therapy found no clear differences, they evaluated different dose comparisons, precluding firm conclusions. Differences in harms between dual therapy with pegylated interferon alfa-2a plus ribavirin compared with pegylated interferon alfa-2b plus ribavirin were relatively small, with no differences in serious adverse events or withdrawals due to adverse events.

Trials of triple therapy regimens with the protease inhibitors boceprevir or telaprevir (both approved by the FDA in 2011) in treatment-naïve patients with genotype 1 infection found each associated with substantially higher SVR rates than standard dual therapy without a protease inhibitor, with SVR rates with triple therapy approaching the 70 to 80% observed with dual therapy in patients with genotype 2 or 3 infection.[23, 26-28, 38-42] Trials evaluating the telaprevir regimen recommended by the FDA (12 weeks of triple therapy with telaprevir followed by response guided duration of 12 or 36 weeks of dual therapy) reported SVR rates of 75% to 80%.[39, 41] Trials evaluating the boceprevir regimen recommended by the FDA for antiretroviral-naïve patients with cirrhosis (4 weeks of dual therapy lead-in followed by 44 weeks of triple therapy with boceprevir) reported SVR rates of 66% to 75%.[26, 28] Trials that evaluated other

regimens in antiretroviral naïve patients, including fixed duration telaprevir regimens, shorter fixed duration triple therapy boceprevir therapy, and boceprevir without dual therapy lead-in, reported similar or lower SVR rates.

As in the head-to-head trials of dual therapy with pegylated interferon alfa-2a plus ribavirin compared with pegylated interferon alfa-2b plus ribavirin, relative risk estimates for triple compared with dual therapy were similar (or there were no clear differences) in patient subgroups based on age, sex, or race, although absolute SVR rates were lower in older patients and black patients. Triple therapy with either boceprevir or telaprevir was no more effective than dual therapy in the subgroup of patients with lower HCV RNA viral load (<600,000 or <800,000 IU/mL).[26, 28, 39] There was insufficient evidence to evaluate relative effectiveness of triple compared with dual therapy based on fibrosis stage.

In addition to a higher likelihood of SVR, another advantage of triple therapy regimens in patients with genotype 1 infection is the potential for shorter duration of treatment (24 or 28 weeks in patients with early virologic response, compared with the standard 48 weeks of dual therapy with pegylated interferon plus ribavirin). Shorter courses of treatment would likely be of high relevance to patients, given the frequency of bothersome flu-like symptoms associated with interferon-based therapy. On the other hand, triple therapy regimens were associated with increased risk of certain harms, in particular hematological adverse events (neutropenia, anemia, and thrombocytopenia) with boceprevir and rash (including severe rash in <10% of patients that could result in treatment discontinuation) with telaprevir. However, there was no clear increase in risk of serious adverse events with use of protease inhibitors, and the adverse events appear to be self-limited following drug discontinuation.

The strongest evidence on the association between achieving an SVR and improved clinical outcomes is a large U.S. Department of Veterans Affairs (VA) cohort study (n=16,864) that adjusted for many confounders and found decreased risk of all-cause mortality compared with no SVR across patient groups stratified by genotype (adjusted HR 0.71 [0.60-0.86], 0.62 [0.44-0.87] and 0.51 [0.35-0.75] for genotypes 1, 2, and 3, respectively).[8] Sixteen other cohort studies also found achievement of SVR associated with decreased risk of all-cause mortality and hepatic complications associated with chronic HCV infection, including studies of populations specifically of patients with baseline cirrhosis, but had more methodological shortcomings. In addition, nine of the sixteen studies were conducted in Asia, where the incidence of hepatocellular carcinoma in patients with chronic HCV infection is higher than in the United States,[43] potentially limiting their generalizability. Other studies found an SVR after antiviral therapy associated with better scores on measures of quality of life compared with no SVR, but focused on short-term outcomes, and typically did not adjust for confounders or blind patients to SVR status when assessing outcomes.

Table A. Summary of evidence on comparative effectiveness of treatment for hepatitis C

Key Question	Outcome	Summary of Evidence	Strength of Evidence
Key Question 1a What is the comparative effectiveness of antiviral treatment in	**Long-term clinical outcomes**	No evidence.	Insufficient
	Short-term mortality	Three trials that compared current antiviral regimens [a] found no differences in risk of short-term mortality, but reported very few (20 total) events.	Low

Key Question	Outcome	Summary of Evidence	Strength of Evidence
improving health outcomes in patients with HCV infection?	**Short-term quality of life**	One open-label randomized trial of patients with genotype 4 infection found dual therapy with pegylated interferon alfa-2a plus ribavirin associated with slightly better short-term scores on some quality of life assessments compared with dual therapy with pegylated interferon alfa-2b plus ribavirin.	Low
Key Question 1b How does the comparative effectiveness of antiviral treatment for health outcomes vary according to patient subgroup characteristics?	**Any clinical outcome**	No evidence.	Insufficient
Key Question 2a What is the comparative effectiveness of antiviral treatments on intermediate outcomes?		***Dual therapy with pegylated interferon alfa-2b plus ribavirin vs. dual therapy with pegylated interferon alfa-2a plus ribavirin***	
	Sustained virologic response	Seven trials of patients with genotype 2 or 3 infection found dual therapy with standard doses of pegylated interferon alfa-2b plus ribavirin associated with lower likelihood of achieving an SVR than pegylated interferon alfa-2a plus ribavirin (pooled RR 0.88, 95% CI 0.81 to 0.96; I^2=37%), with an absolute difference in SVR rates of 7.8 percentage points (95% CI 2.2 to 13.4 percentage points).	Moderate
		Dual therapy with pegylated interferon alfa-2a or -2b plus ribavirin: duration effects	
	Sustained virologic response	Two trials of patients with genotype 2 or 3 infection found no difference in likelihood of achieving an SVR between 48 versus 24 weeks of dual therapy with pegylated interferon alfa-2a plus ribavirin (pooled RR 0.97, 95% CI 0.84 to 1.1; I^2=43%)	Moderate
	Sustained virologic response	Three trials of patients with genotype 2 or 3 infection found no differences between 24 versus 12-16 weeks of dual therapy with pegylated interferon alfa-2a plus ribavirin (pooled RR=0.88, 95% CI 0.76 to 1.0; I^2=86%). Relative risk estimates ranged from 0.75 to 0.99 in the three trials and may have varied in part due to different methods of ribavirin dosing.	Moderate
	Sustained virologic response	Three trials of patients with genotype 2 or 3 infection with a rapid virologic response (undetectable HCV RNA by week 4) found no differences between 24 versus 12-16 weeks of dual therapy with pegylated interferon (alfa-2a or alfa-2b) plus ribavirin (pooled RR=0.99, 95% CI 0.86 to 1.1, I^2=66%). Relative risk estimates ranged from 0.89 to 1.1.	Moderate

Key Question	Outcome	Summary of Evidence	Strength of Evidence
		Dual therapy with pegylated interferon alfa-2a or -2b plus ribavirin: dose effects	
	Sustained virologic response	Five trials of patients with genotype 2 or 3 infection found lower doses of pegylated interferon alfa-2b (0.75-1.0 mcg/kg or 50 mcg) associated with lower likelihood of achieving an SVR than higher doses (1.5 mcg/kg or 100-150 mcg) (pooled RR 0.86; 95% CI 0.76 to 0.98; I^2=17%).	Moderate
	Sustained virologic response	Three trials of patients with genotype 2 or 3 infection who did not specifically have advanced fibrosis or cirrhosis found no clear difference in likelihood of SVR between lower doses of ribavirin (400 or 800 mg flat dose or 600 to 800 mg weight-based dose) compared with higher doses (800 or 1200 mg flat dose or 800 to 1400 mg weight-based dose).	Moderate
	Sustained virologic response	One small trial (n=124) of patients with genotype 2 or 3 infection and advanced fibrosis or cirrhosis (Ishak stage 4-6) found 1000 to 1200 mg daily of ribavirin associated with greater likelihood of SVR compared with 600 to 800 mg daily (72% vs. 45%; p=0.002).	Low
		Triple therapy with pegylated interferon alfa-2b, ribavirin, and boceprevir vs. dual therapy with pegylated interferon alfa-2b plus ribavirin	
	Sustained virologic response	Two trials of patients with genotype 1 infection found triple therapy with boceprevir (pegylated interferon alfa-2b plus ribavirin for 4 weeks, followed by the addition of boceprevir for 44 weeks) associated with higher likelihood of SVR compared with dual therapy with pegylated interferon alfa-2b plus ribavirin therapy for 48 weeks (pooled RR 1.8; 95% CI 1.6 to 2.1; I^2=0%), with an absolute increase in SVR rate of 31 percentage points (95% CI 23 to 39 percentage points).	Moderate
	Sustained virologic response	A single trial of patients with genotype 1 infection found that 48 weeks of triple therapy with boceprevir using low dose of ribavirin (400-1000 mg daily) associated with a non-statistical trend towards lower likelihood of SVR compared to 48 weeks of triple therapy with a standard ribavirin dose (800-1400 mg daily) (36% vs 50%, RR 0.71, 95% CI 0.39 to 1.3)	Low
		Triple therapy with pegylated interferon alfa-2b, ribavirin, and telaprevir vs. dual therapy with pegylated interferon alfa-2b plus ribavirin	

Key Question	Outcome	Summary of Evidence	Strength of Evidence
	Sustained virologic response	Two trials of patients with genotype 1 infection found triple therapy with telaprevir for 24 weeks (12 weeks of pegylated interferon alfa-2a, ribavirin, and telaprevir followed by 12 weeks of pegylated interferon alfa-2a plus ribavirin) associated with higher likelihood of SVR compared with dual therapy with pegylated interferon alfa-2a plus ribavirin for 48 weeks (pooled RR 1.5, 95% CI 1.2 to 1.8; I^2=0%), with an absolute increase in SVR rate of 21 percentage points (95% confidence interval 10 to 32 percentage points).	Moderate
	Sustained virologic response	One trial of patients with genotype 1 infection found no difference in likelihood of SVR between triple therapy with pegylated interferon, ribavirin, and telaprevir for 12 weeks versus dual therapy with pegylated interferon alfa-2a plus ribavirin for 48 weeks.	Moderate
	Sustained virologic response	One trial of patients with genotype 1 infection found triple therapy with telaprevir (pegylated interferon alfa-2a, ribavirin, and telaprevir for 8 or 12 weeks followed by response-guided dual therapy with pegylated interferon alfa-2a plus ribavirin for an additional 12 or 36 weeks) associated with higher likelihood of SVR compared with dual therapy with pegylated interferon alfa-2a plus ribavirin for 48 weeks (RR 1.6, 95% CI 1.4 to 1.9), with an absolute increase in SVR rate ranging from 25 to 31 percentage points. The regimen with 8 weeks of telaprevir was associated with a slightly lower SVR rate than the 12 week telaprevir regimen (69% vs. 75%).	Low
		Triple therapy with pegylated interferon alfa-2b, ribavirin, and telaprevir: duration effects	
	Sustained virologic response	One trial of patients with genotype 1 infection found no difference in likelihood of SVR between triple therapy with telaprevir for 48 weeks (12 weeks of triple therapy with pegylated interferon alfa-2a, ribavirin, and telaprevir followed by 36 weeks of dual therapy with pegylated interferon alfa-2a plus ribavirin) and triple therapy with telaprivir for 24 weeks (12 weeks of triple therapy followed by 12 weeks of dual therapy).	Low
	Sustained virologic response	One trial of patients with an extended rapid virologic response to initial triple therapy with telaprevir reported similar, high (92% and 88%) SVR rates in patients randomized to a total of 24 or 48 weeks of therapy.	Low

Key Question	Outcome	Summary of Evidence	Strength of Evidence
Key Question 2b How does the comparative effectiveness of antiviral treatment for intermediate outcomes vary according to patient subgroup characteristics?		***Dual therapy with pegylated interferon alfa-2b plus ribavirin vs. dual therapy with pegylated interferon alfa-2a plus ribavirin***	
	Sustained virologic response	The largest randomized trial (n=3070) of dual therapy with pegylated interferon alfa-2a plus ribavirin versus dual therapy with pegylated interferon alfa-2b plus ribavirin found no clear differences in relative risk estimates for SVR in genotype 1 patients stratified by race, sex, age, baseline fibrosis stage, or baseline viral load, although absolute SVR rates for either pegylated interferon were lower in older patients (38%), black patients (23% to 26%), persons with advanced fibrosis or cirrhosis (21% to 24%), and persons with high baseline viral load (35% to 36%).	Moderate
	Sustained virologic response	Four randomized trials of dual therapy with pegylated interferon alfa-2a plus ribavirin versus dual therapy with pegylated interferon alfa-2b plus ribavirin found no clear differences in relative risk estimates for SVR in patients stratified by genotype, although absolute rates of SVR were lower by 24 to 42 percentage points in genotype 1 infection compared with genotypes 2 and 3 infection.	Moderate
		Triple therapy with pegylated interferon alfa-2b, ribavirin, and boceprevir vs. dual therapy with pegylated interferon alfa-2b plus ribavirin	
	Sustained virologic response	Two trials of triple therapy with boceprevir for 48 weeks (four weeks of dual therapy lead-in with pegylated interferon plus ribavirin followed by 44 weeks of triple therapy with pegylated interferon, ribavirin, and boceprevir) found no difference in relative risk estimates for SVR in men compared with women, and no clear difference in relative risk estimates for black patients compared with non-black patients, although the absolute SVR rate was lower in black patients (53%) compared with non-black patients (63% to 78%).	Moderate
	Sustained virologic response	Two trials found triple therapy with pegylated interferon alfa-2b, ribavirin, and boceprevir asssociated with higher likelihood of achieving SVR than dual therapy with pegylated interferon alfa-2b plus ribavirin in patients with high baseline HCV RNA viral load (>600,000 or ≥800,000 IU/mL), but found no difference in likelihood of SVR in patients with lower viral load.	Moderate
		Triple therapy with pegylated interferon alfa-2b, ribavirin, and telaprevir vs. dual therapy with pegylated interferon alfa-2b plus ribavirin	

Key Question	Outcome	Summary of Evidence	Strength of Evidence
	Sustained virologic response	One trial of response-guided triple therapy with telaprevir (12 weeks of pegylated interferon alfa-2a, ribavirin, and telaprevir followed by response-guided dual therapy with pegylated interferon alfa-2a and ribavirin) vs. dual therapy with pegylated interferon plus ribavirin for 48 weeks found no clear differences in relative risk estimates in patients stratified by age, sex, race, baseline fibrosis status, or body mass index, although absolute SVR rates were higher in persons younger than 45 years compared with those older (83% vs. 70%), whites compared with black patients (75% vs. 62%), persons with no or minimal fibrosis compared with advanced fibrosis or cirrhotics (81% vs. 62%), and those with body mass index<25 compared with those with higher body mass index (83% vs. 69%).	Low
	Sustained virologic response	Two trials found triple therapy with pegylated interferon alfa-2a, ribavirin, and telaprevir associated with higher likelihood of achieving an SVR than dual therapy with pegylated interferon alfa-2a plus ribavirin in patients with high baseline HCV RNA viral load (≥800,000 IU/mL), but found no difference in patients with lower viral load.	Moderate
Key Question 3a What are the comparative harms associated with antiviral treatments?		***Dual therapy with pegylated interferon alfa-2b plus ribavirin vs. dual therapy with pegylated interferon alfa-2a plus ribavirin***	
	Harms	Dual therapy with pegylated interferon alfa-2b was associated with slightly greater risk of headache (3 trials, pooled RR 1.2, 95% CI 1.1 to 1.3, I^2=0%) and myalgia (2 trials, pooled RR 1.2, 95% CI 1.0 to 1.4, I^2=0%) and slightly lower risk of rash (2 trials, pooled RR 0.80, 95% CI 0.71 to 0.89; I^2=0%) compared with dual therapy with pegylated interferon alfa-2a plus ribavirin, with no differences in risk of serious adverse events or withdrawals due to adverse events.	Moderate
		Triple therapy with pegylated interferon alfa-2b, ribavirin, and boceprevir vs. dual therapy with pegylated interferon alfa-2b plus ribavirin	

Key Question	Outcome	Summary of Evidence	Strength of Evidence
	Harms	Triple therapy with boceprevir for 48 weeks (pegylated interferon alfa-2b plus ribavirin for 4 weeks followed by addition of boceprevir for 44 weeks) weeks was associated with increased risk of neutropenia (2 trials, pooled RR 1.8, 95% CI 1.5 to 2.3, I^2=0%), dysgeusia (2 trials, pooled RR 2.5, 95% CI 2.0 to 3.2, I^2=0%), anemia (2 trials, pooled RR 2.0, 95% CI 1.4 to 2.8, I^2=0%), and thrombocytopenia (2 trials, pooled RR 3.3, 95% CI 1.3 to 8.6) compared to dual therapy with pegylated interferon alfa-2b plus ribavirin. The incidence of anemia was about 50% with triple therapy and the incidence of neutropenia about 25%, with severe anemia in 4% to 5% and severe neutropenia in 8% to 15%.	Moderate
		Triple therapy with pegylated interferon alfa-2b, ribavirin, and telaprevir vs. dual therapy with pegylated interferon alfa-2b plus ribavirin	
	Harms	In two trials, there were no statistically significant differences between a twelve week regimen of triple therapy with pegylated interferon alfa-2a, ribavirin, and telaprevir compared with dual therapy with pegylated interferon alfa-2a plus ribavirin in risk of any assessed adverse event.	Moderate
		In two trials, there was a 24 week regimen of triple therapy with telaprevir (pegylated interferon alfa-2a, ribavirin, and telaprevir for 12 weeks followed by pegylated interferon alfa-2a plus ribavirin for 12 weeks) was associated with increased risk of anemia (2 trials, pooled RR 1.5, 95% CI 1.0 to 2.1, I^2=0%), decreased risk of myalgia (2 trials, pooled RR 0.56, 95% CI 0.34 to 0.93, I^2=0%), and increased risk of rash (2 trials, pooled RR 1.4, 95% CI 1.1 to 1.8) compared with dual therapy with pegylated interferon alfa-2a plus ribavirin for 48 weeks, and trends towards increased risk of withdrawal due to adverse events (RR estimate around 2), primarily due to rash. Among patients randomized to the 24 week telaprevir regimen, one-half to three-quarters of patients experienced a rash (7% to 11% experienced a severe rash) and 27% to 37% experienced anemia (4% experienced severe anemia).	Moderate

Key Question	Outcome	Summary of Evidence	Strength of Evidence
		In one trial, response-guided triple therapy with telaprevir (pegylated interferon alfa-2a, ribavirin, and telaprevir for 8 or 12 weeks followed by response-guided pegylated interferon alfa-2a and ribavirin) was associated with increased risk of withdrawal due to adverse events (27% vs. 7.2%, RR 3.8, 95% CI 2.6 to 5.7), anemia (38% vs. 19%, RR 2.0, 95% CI 1.6 to 2.5), any rash (36% vs. 24%, RR 1.5 , 95% CI 1.2 to 1.8), and severe rash (5% vs. 1%, RR 4.6, 95% CI 1.6 to 13) compared with dual therapy with pegylated interferon alfa-2a plus ribavirin for 48 weeks.	Low
Key Question 3b Do these harms differ according to patient subgroup characteristics?		***Dual therapy with pegylated interferon alfa-2b plus ribavirin vs. dual therapy with pegylated interferon alfa-2a plus ribavirin***	
	Harms	No trial of dual therapy with pegylated interferon alfa-2b plus ribavirin vs. dual therapy with pegylated interferon alfa-2a plus ribavirin reported harms in patients stratified by factors such as HCV genotype, age, race, sex, stage of disease, or genetic markers. Three trials that restricted enrollment to patients with genotype 1 infection reported risk estimates for risk of harms that were similar to the risk estimates based on all trials.	Insufficient
		Triple therapy with pegylated interferon alfa-2a or -2b, ribavirin, and telaprevir or boceprevir vs. dual therapy with pegylated interferon alfa-2a or -2b plus ribavirin	
	Harms	No trials evaluated harms associated with triple therapy with pegylated interferon, ribavirin, and boceprevir or telaprevir versus dual therapy with pegylated interferon plus ribavirin in patient subgroups. All trials evaluated patients with genotype 1 infection.	Insufficient

Key Question	Outcome	Summary of Evidence	Strength of Evidence
Key Question 4 Have improvements in intermediate outcomes been shown to reduce the risk or rates of adverse health outcomes from HCV infection?	**Mortality and long-term hepatic complications**	A large Veterans Affairs (VA) study that controlled well for potential confounders found achieving an SVR associated with lower risk of all-cause mortality compared with not achieving an SVR (adjusted HR 0.71 [0.60-0.86], 0.62 [0.44-0.87] and 0.51 [0.35-0.75] for genotypes 1, 2, and 3, respectively). Sixteen other cohort studies found achieving an SVR associated with decreased risk of all-cause mortality, liver-related mortality, hepatocellular carcinoma, and other complications of end-stage liver disease compared with not achieving an SVR, with stronger effect estimates than the VA study (adjusted HRs generally ranged from around 0.10 to 0.33). However, the studies had methodological shortcomings, including inadequate handling of confounders, and 9 were conducted in Asia.	Moderate
	Short-term quality of life	Nine studies found achieving an SVR associated with greater improvement in measures related to quality of life (generic or disease-specific) 24 weeks after the end of antiviral treatment, with differences averaging less than 5 to 10 point on various SF-36 domains. All studies were poor-quality and were characterized by failure to adjust for confounders, high loss to followup, and failure to blind patients to SVR status.	Low

Abbreviations: CI, confidence interval; HCV, hepatitis C virus; HCV-RNA, Hepatitis C virus ribonucleic acid test; HR, hazard ratio; RR, relative risk; SVR, sustained virologic response.
[a] "Current antiviral treatment regimen" refers to dual therapy with pegylated interferon (alfa-2a or -2b) plus ribavirin, or triple therapy with pegylated interferon (alfa-2a or -2b) plus ribavirin and boceprevir or telaprevir.

Findings in Relationship to What Is Already Known

Our findings regarding the comparative effectiveness of dual therapy with pegylated interferon alfa-2b plus ribavirin compared with dual therapy with pegylated interferon alfa-2a plus ribavirin are consistent with recent systematic reviews that also found the former associated with a lower likelihood of SVR.[14, 44] Our findings of no clear difference in comparative effectiveness between 12 to 16 weeks compared with 24 weeks of response-guided dual therapy with pegylated interferon plus ribavirin in hepatitis C genotype 2 or 3 infection with rapid virologic response are discordant with a recent systematic review, which found a shorter duration of treatment associated with a lower likelihood of achieving an SVR.[45] The discrepancy may be explained by the inclusion in the other systematic review of a study that we excluded because it evaluated a non-standard dose of pegylated interferon,[46] as well as its inclusion of subgroup analyses from trials of patients randomized to different fixed durations of therapy prior to assessment of rapid virologic response,[47-49] which we considered separately because they did not represent randomized comparisons of response-guided treatment.

Because telaprevir and boceprevir are so new, we are unaware of other published systematic reviews on the comparative benefits and harms of regimens including these drugs, compared to

standard dual therapy. Our findings on the association between achieving an SVR and reduced risk of mortality or complications associated with chronic HCV infection are consistent with a recent review that used some systematic methods.[50]

Applicability

The trials included in this review generally met criteria for efficacy studies, based on the exclusion of patients with common comorbidities (such as serious psychiatric conditions or recent or ongoing substance abuse). In addition, the trials may have overestimated efficacy compared to what would be seen in typical practice due to improved adherence as a result of closer followup, effects of trial participation, selection of patients, or other factors. A separate review funded by AHRQ will be focusing on issues related to adherence in the treatment of HCV infection.[51]

The severity of baseline liver disease in the patients enrolled in the trials suggests that they enrolled a broad range of patients. In trials of triple therapy with boceprevir or telaprevir, the proportion of patients with cirrhosis at enrollment ranged from <1% to 11%.[26-28, 38, 39, 41, 42] Trials that reported the proportion of patients with minimal or no fibrosis reported rates of 27 percent to 39 percent.[27, 38, 39, 41, 42]

Evidence to evaluate potential differences in comparative benefits or harms in patient subgroups based on age, sex, race, and other clinical factors was relatively limited, precluding strong conclusions in these specific subgroups. The strongest evidence on the association between achieving an SVR and reduced mortality comes from a study performed in a VA population, which might limit generalizability to other settings.[8] As described above, studies conducted in Asia on the association between an SVR after antiviral therapy compared with no SVR and risk of clinical outcomes may be of limited applicability to U.S. populations because some studies indicate a higher incidence of hepatocellular cancer in Asian patients with chronic HCV infection.[43]

The results of this CER are not applicable to populations excluded from the review, including patients previously treated with antiviral therapies and excluded populations such as patients with HIV coinfection, post-transplant patients, or hemodialysis patients.

Implications for Clinical and Policy Decisionmaking

Our review has potential implications for clinical and policy decisionmaking. For patients with genotype 1 infection, triple therapy regimens with pegylated interferon (alfa-2a or -2b), ribavirin, and telaprevir or boceprevir may be considered an alternative to dual therapy with pegylated interferon alfa-2a or -2b plus ribavirin as standard treatment due to substantially superior efficacy for achieving SVR compared to dual therapy with pegylated interferon alfa-2a or -2b, as well as a shorter duration of treatment. Factors that may affect decisions to utilize regimens with boceprevir or telaprevir include cost and specific harms associated with use of these drugs (such as hematologic adverse events with boceprevir and rash with telaprevir). For patients with genotype 2 or 3 infection, dual therapy with pegylated interferon alfa-2b plus ribavirin appears to be associated with higher likelihood of achieving SVR compared to dual therapy with pegylated interferon alfa-2a plus ribavirin, but absolute differences were relatively small. Therefore, decisions about which pegylated interferon to use may be relatively more affected by other considerations, such as cost, patient preferences, or other factors.

The findings that absolute SVR rates are lower in certain subgroups (such as older patients, black patients, patients with worse baseline fibrosis, and patients with high viral load) can be

used to inform individualized decisionmaking. Patients who are less likely to achieve a SVR may make different informed decisions about therapy compared to those more likely to achieve an SVR, given the adverse effects associated with treatment.

The findings of the review are also relevant to screening recommendations, which are based in part on the effectiveness of treatments in persons found to have HCV infection by screening. Important new evidence that may affect assessments regarding potential benefits of screening include stronger evidence on the link between achieving an SVR and improvement in clinical outcomes as well as evidence showing substantially higher SVR rates with newer triple therapy regimens with boceprevir or telaprevir in patients with genotype 1 infection, the predominant type of HCV infection in the United States.

Limitations of the Comparative Effectiveness Review Process

Our review had some potential limitations. We excluded non English language articles, which could result in language bias, although we identified no non English language studies that would have met inclusion criteria (Appendix B) and a recent systematic review found little empirical evidence that exclusion of non English language articles leads to biased estimates for non-complementary or alternative medicine interventions.[52]

We did not formally assess for publication bias with funnel plots due to small numbers (<10) of studies for all comparisons. Small numbers of studies can make interpretation of funnel plots unreliable, and experts suggest 10 studies as the minimum number of studies to perform funnel plots.[53] However, we included some studies which were published only as abstracts and found that their inclusion or exclusion from analyses did not change conclusions. In addition, we searched trial registries and solicited drug manufacturers for additional unpublished trials and identified none.

Another potential limitation is that we included cohort studies to evaluate the association between SVR and mortality or hepatic complications associated with chronic HCV infection. Such studies are susceptible to confounding if factors associated with SVR (such as age, race, viral load, or fibrosis stage) are also associated with these outcomes. Therefore, we only included studies that reported adjusted risk estimates, and evaluated how well studies addressed key potential confounders as part of our quality assessment. Nonetheless, residual confounding is a possibility even in cohort studies that adjust for potential confounding.

Limitations of the Evidence Base

We identified several important limitations of the evidence base. First, studies assessing important long-term clinical outcomes associated with current antiviral treatments for chronic HCV infection are not available. In the case of antiviral regimens involving newly approved antiviral drugs, such studies are not possible yet because of the extended followup required to adequately evaluate effects on clinical outcomes. Second, no trials directly compared regimens with boceprevir compared with regimens with telaprevir. Given the increased efficacy of these regimens in patients with genotype 1 infection, trials directly comparing their effects would be helpful for informing treatment choices between these drugs. In addition, few trials have evaluated the regimens approved specifically by the FDA for these drugs, limiting confidence in conclusions regarding estimates of benefits and harms for the regimens likely to be used in clinical practice. Finally, few methodologically rigorous studies conducted in settings applicable to U.S. populations evaluated the association between achieving an SVR and improvements in clinical outcomes. Such studies would be very helpful for confirming the results of the recent,

large, well-conducted VA cohort study showing an association between achieving an SVR and reduced mortality risk.[8]

Future Research

Evaluating the comparative effectiveness of current antiviral regimens on clinical outcomes in randomized trials or cohort studies is a challenge due to the long lead-time and large samples necessary to adequately assess these outcomes, but might be more feasible if the studies focus on populations at higher risk for complications from chronic HCV infection (e.g., patients with baseline cirrhosis, high viral load, or other risk factors for progression).

For all trials of antiviral treatments, studies that enroll broader populations with medical and psychological comorbidities, as frequently encountered in clinical practice, are needed to better understand comparative effectiveness, rather than just comparative efficacy. Studies designed using an effectiveness paradigm would also be helpful for understanding real-world effects of antiviral regimens, including effects related to the poorer adherence than expected from efficacy trials.

Trials directly comparing triple therapy with telaprevir compared with triple therapy with boceprevir would be very helpful for understanding comparative effectiveness of these two protease inhibitors. In addition, trials evaluating the boceprevir regimen recommended by the FDA in antiretroviral-naïve patients without baseline cirrhosis are needed to verify that results from studies of previously treated patients were appropriately generalized. Prolonged followup of patients exposed to telaprevir and boceprevir is needed to understand the long-term harms associated with these medications. A number of other protease inhibitors and other newer drugs for treatment of hepatitis C virus infection are currently in active development and further studies with new drugs and drug regimens are expected, including regimens without interferon.[54]

It is critical that future studies comparing clinical outcomes in patients who experience an SVR compared with those who do not experience an SVR adequately control for other factors that influence clinical outcomes in patients with chronic HCV infection. Studies on effects of achieving an SVR on long-term quality of life would be very helpful for understand other potential clinical benefits of antiviral therapy, but a significant challenge is whether it is possible to ethically blind patients to virologic status, which may have an important impact on assessments of quality of life.

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Internet Citation

[Provided by AHRQ] Authoring EPC, Title, Comparative Effectiveness Review: Number ##. AHRQ Publication Number No. 0#-###, Month 200#. Agency for Healthcare Research and Quality, Rockville, MD. http://www.effectivehealthcare.ahrq.gov/xxxxxxx

Introduction

Hepatitis C virus (HCV) is the most common chronic blood borne pathogen in the United States. It is primarily acquired by large or repeated percutaneous exposures to blood, with injection drug use the strongest risk factor. Approximately 1.6% of U.S. adults over 20 years of age have antibodies to HCV, indicating prior acute HCV infection.[1] About 78% of patients with acute HCV infection develop chronic HCV infection, defined by the presence of persistent viremia.

Chronic HCV infection has a variable course, but is a leading cause of complications from chronic liver disease, including cirrhosis, liver failure, and hepatocellular cancer. Chronic HCV infection was associated with an estimated 15,000 deaths in the United States in 2007[2] deaths each year in the United States,[3] and is the most common indication for liver transplantation among American adults, accounting for more than 30 percent of cases.[4] The prevalence of chronic HCV infection is thought to have peaked in 2001 at 3.6 million people and the yearly incidence has declined from more than 200,000 cases per year in the 1980s to around 16,000 cases in 2009.[3, 5] However, complications related to chronic HCV infection, which frequently occur only after decades of infection, are expected to rise for another 10 to 13 years.[5]

The goals of antiviral treatment for chronic HCV infection are to prevent the long-term health complications associated with HCV infection such as cirrhosis, hepatic decompensation, and liver cancer, but it is extremely difficult to design and carry out clinical trials long and large enough to provide direct evidence related to these outcomes. The sustained virologic response (SVR) rate, typically defined as a decline in HCV RNA to undetectable levels 24 weeks following completion of antiviral treatment, is the standard marker for successful treatment in clinical trials because it is strongly associated with long-term absence of viremia.[6, 7] Recent studies have evaluated the association between achieving an SVR and reduced mortality, liver failure, and cancer.[8, 9]

The treatment of HCV infection has evolved dramatically over the past several decades. Recombinant type I interferons were introduced as monotherapy in the mid-1980's, but were only modestly successful at achieving SVR (overall <20%).[10-13] Subsequent trials found dual therapy with interferon and the synthetic nucleoside analogue ribavirin more effective than monotherapy with interferon, although the sustained virologic response (SVR) rates remained under 50%.[10-13]

In the early 2000's, the combination of "pegylated" interferon plus ribavirin became the standard antiviral treatment for HCV infection.[14-16] The first pegylated interferon was approved by the FDA in 2001. Pegylation refers to the cross-linking of polyethylene glycol molecules to the interferon molecule, which delays renal clearance, thereby permitting less frequent dosing (once weekly vs. three times a week with nonpegylated interferon).[17] Currently, two pegylated interferons are available: pegylated interferon alfa-2a and pegylated interferon alfa-2b. Both are Type I alfa interferons, but differ in the size and structure of the interferon and polyethylene glycol molecules, as well as in their pharmacokinetic properties (Table 1).[17] One pegylated interferon consists of 31-kilodalton (kDa) interferon alfa-2b conjugated to 12-kilodalton (kDa) polyethylene glycol (trade name PEG-intron®). The other consists of recombinant 20-kDa interferon alfa-2a linked to 40-kDa polyethylene glycol (trade name Pegasys®). The dosing schedule is fixed for pegylated interferon alfa-2a and is based on weight for pegylated interferon alfa-2b. Each pegylated interferon is approved for dual therapy with ribavirin. Although each pegylated interferon is approved for combination therapy with a specific brand of ribavirin

manufactured by the respective manufacturer (Copegus® for pegylated interferon alfa-2a and Rebetol® for alfa-2b), the ribavirin is pharmacologically identical.

Dual therapy with pegylated interferon (alfa-2a or -2b) plus ribavirin is associated with higher SVR rates (about 55 to 60 percent overall) than either nonpegylated interferon plus ribavirin or pegylated interferon (alfa-2a or -2b) monotherapy. Although previous reviews found insufficient evidence to determine whether dual therapy with pegylated interferon alfa-2a or pegylated interferon alfa-2b is more effective,[18, 19] more head-to-head trials directly comparing these two regimens are now available.[20-23]

A number of factors affect response to antiviral treatment. The two major predictors of SVR are the viral genotype and the pretreatment viral load.[15] In the United States, genotype 1 infection is found in around three-quarters of HCV-infected patients.[24] HCV genotype 1 infection is associated with a substantially lower response to antiviral treatment than infection with genotypes 2 and 3, which are present in about 20% of HCV-infected patients. A pretreatment viral load of <600,000 IU/mL is associated with higher likelihood of achieving an SVR.[15] Other factors less consistently or strongly associated with increased likelihood of SVR include female sex, age <40 years, non-African-American race, lower body weight (<=75 kg), absence of insulin resistance, elevated ALT levels, and absence of bridging fibrosis or cirrhosis on liver biopsy.[15] Effects of race on the likelihood of SVR may be due in part to polymorphisms in the interleukin-28B (IL28B) gene.[25, 26]

An issue complicating antiviral treatment is the high rate of adverse effects observed with interferon-based therapy, including flu-like symptoms, fatigue, and neuropsychiatric and hematologic adverse effects.[27] Such adverse effects can be difficult to tolerate and can lead to premature discontinuation of therapy.

In 2011, the U.S. Food and Drug Administration approved the first direct acting antiviral agents, boceprevir (trade name Victrelis®) and telaprevir (trade name Incivek®), for treatment of chronic HCV genotype 1 infection (Table 1).[28, 29] Both drugs are classified as non-structural (NS) 3/4A protease inhibitors, with a potential advantage of shorter duration of therapy (24 weeks) when used in combination with pegylated interferon (alfa-2a or -2b) compared with standard dual therapy with pegylated interferon (alfa-2a plus -2b) plus ribavirin for genotype 1 infection (48 weeks) (Table 1).[30-32]

Table 1. Pharmacokinetics, indications, and dosing of included drugs[33, 34]

Drug Trade Name	Indications Labeled by the US Food and Drug Administration	Dosing recommended by the US Food and Drug Administration
Pegylated interferon alfa-2a Pegasys®	Patients 5 years of age and older with chronic HCV infection with compensated liver disease not previously treated with interferon alfa	180 mcg once weekly in combination with ribavirin for 24 weeks with ribavirin for genotypes 2 or 3, or 48 weeks for genotype 1or 4 infection
Pegylated interferon alfa-2b PEG-Intron®	Patients 5 years of age and older with chronic HCV infection with compensated liver disease	1.5 mcg/kg weekly in combination with ribavirin for 24 weeks with ribavirin for genotypes 2 or 3, or 48 weeks for genotype 1infection
Boceprevir Victrelis®	Adults with chronic HCV genotype 2 infection with compensated liver disease, including cirrhosis, who are previously untreated or who have been previously treated with interferon and ribavirin therapy	Four weeks of treatment with pegylated interferon (alfa-2a or 2b) plus ribavirin, then the addition of boceprevir as follows:[a] In treatment-naïve patients without cirrhosis: - If HCV-RNA undetectable from treatment week 8 through week 24 complete triple therapy at treatment week 28 - If HCV-RNA detectable at treatment week 8 and undetectable at treatment week 24, continue triple therapy through treatment week 36 and continue pegylated interferon (alfa-2a or 2b)with ribavirin through treatment week 48 In treatment-naïve patients with cirrhosis: - 44 weeks of triple therapy
Telaprevir Incivek®	Adults with chronic HCV genotype 1 infection with compensated liver disease, including cirrhosis, who are previously untreated or who have been previously treated with interferon and ribavirin therapy	750 mg 3 times a day with pegylated interferon (alfa-2a or 2b) and ribavirin for all patients for 12 weeks, followed by response-guided regimen of pegylated interferon and ribavirin[a] In treatment-naïve patients without cirrhosis: - If HCV-RNA is undetectable at weeks 4 and 12 then continue dual therapy for 12 more weeks (total treatment 24 weeks) - If HCV-RNA is detectable at week 4 and/or week 12 then continue dual therapy for 36 more weeks (total treatment 48 weeks) In treatment-naïve with cirrhosis: - Continue dual therapy for 36 more weeks (total treatment 48 weeks)

Abbreviations: HCV, hepatitis C virus; HCV-RNA, HCV ribonucleic acid.

[a] While boceprevir was tested exclusively with pegylated interferon alfa-2b and telaprevir primarily with pegylated interferon alfa-2a, the manufacturer packaging and dosage information does not specify a particular pegylated interferon (alfa 2a or 2b) for either drug.

Understanding the comparative benefits and harms of the various antiviral regimens is critical for making informed treatment decisions in patients with chronic HCV infection, particularly given the availability of new treatment options. This review will assess the comparative effectiveness of antiviral treatments in adults with chronic HCV infection who have not received previous antiviral drug treatment. In addition to assessing the comparative effectiveness of different drug regimens, the review will evaluate effects of different medication doses, durations of therapy, and dosing strategies (such as weight-based or response-guided vs. fixed treatment). To help with individualized clinical decision-making regarding antiviral therapy for chronic HCV infection, it will also evaluate how comparative effectiveness varies depending on HCV genotype, viral load and other demographic and clinical characteristics. This

review will be used together with a separate review on HCV screening[35] by the U.S. Preventive Services Task Force to update its HCV screening recommendations, given the need to understand the effects of treatment in persons with HCV infection identified by screening in order to understand the potential benefits and harms of screening.

Scope and Key Questions

The analytic framework and key questions used to guide this report are shown below (Figure 1). The analytic framework shows the target populations, interventions, and intermediate and health outcome measures we examined.

The following key questions are the focus of our report:

Key Question 1
This key question has two parts:
a. What is the comparative effectiveness of antiviral treatment in improving health outcomes in patients with HCV infection?
b. How does the comparative effectiveness of antiviral treatment for health outcomes vary according to patient subgroup characteristics, including but not limited to HCV genotype, age, race, sex, stage of disease or genetic markers?

Key Question 2
This key question has two parts:
a. What is the comparative effectiveness of antiviral treatments on intermediate outcomes, such as the rate of SVR or histologic changes in the liver?
b. How does the comparative effectiveness of antiviral treatment for intermediate outcomes vary according to patient subgroup characteristics, including but not limited to HCV genotype, age, race, sex, stage of disease or genetic markers?

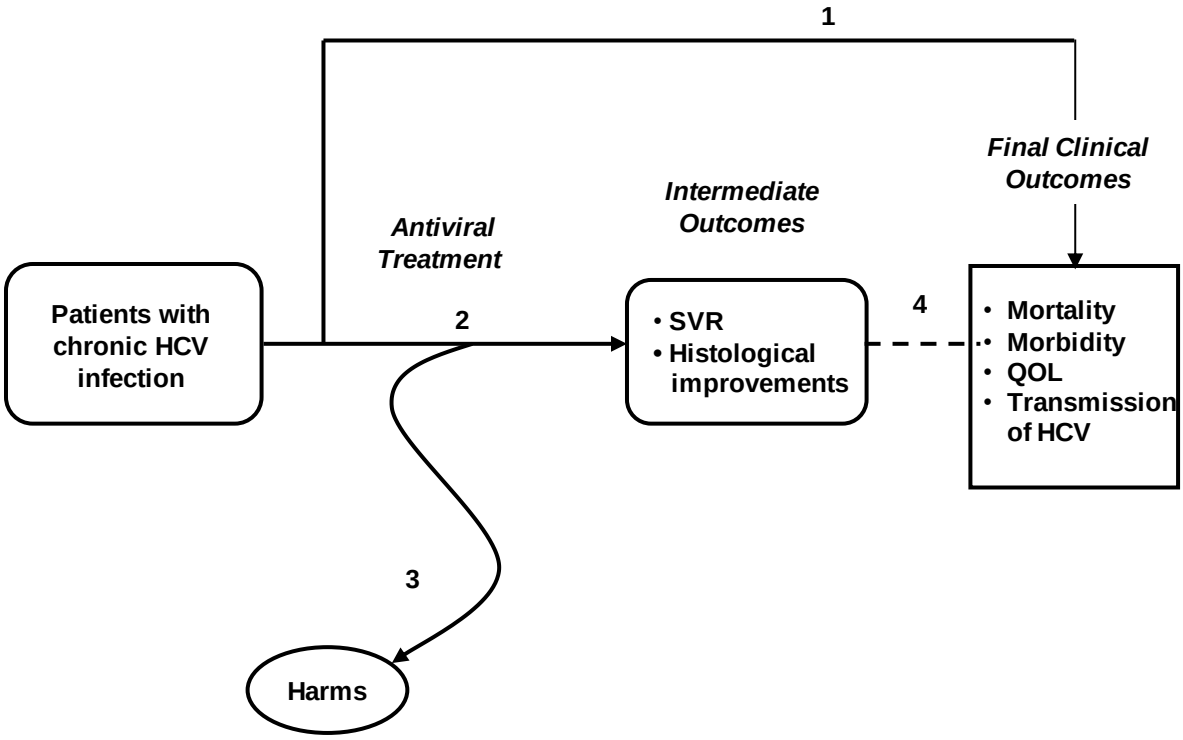
Key Question 3
This key question has two parts:
a. What are the comparative harms associated with antiviral treatments?
b. Do these harms differ according to patient subgroup characteristics, including HCV genotype, age, race, sex, stage of disease, or genetic markers?

Key Question 4
Have improvements in intermediate outcomes (SVR, histologic changes) been shown to reduce the risk or rates of adverse health outcomes from HCV infection?

Key Question 1 focuses on direct evidence on the comparative effectiveness of antiviral treatments for chronic HCV infection on health outcomes (such as death, cirrhosis, hepatic decompensation, hepatocellular cancer, need for transplantation, or quality of life). Because of the long duration (typically decades) necessary develop major hepatic complications related to chronic HCV infection, it is difficult to assess for such outcomes in clinical trials. In addition, dual therapy with pegylated interferon (alfa-2a or 2b) plus ribavirin has only been available since 2001, and protease inhibitors only became approved by the FDA in 2011, which might not be enough time to adequately evaluate some long-term clinical outcomes. Therefore, Key Question 2 focuses on evidence on the comparative effectiveness of antiviral treatments for chronic HCV

infection on intermediate outcomes (SVR and histological improvements). Key Question 4 assesses the link between intermediate and clinical outcomes, in order to facilitate interpretation of results obtained for Key Question 2. Key Question 3 focuses on the comparative harms of different antiviral treatments.

Figure 1. Analytic framework for treatment of hepatitis C infection in adults



Abbreviations: HCV, hepatitis C virus; QOL, quality of life; SVR, sustained virologic response.

Methods

Input from Stakeholders

The topic of hepatitis C virus (HCV) treatment was nominated for a comparative effectiveness review in a public process. The key questions were proposed in the public nomination process and developed by investigators from the Evidence-based Practice Center (EPC) with input from expert Key Informants, who helped to refine key questions, identify important methodological and clinical issues, and define parameters for the review of evidence. The revised key questions were then posted to a public Web site for comment. The Agency for Healthcare Research and Quality and the EPC agreed upon the final key questions after reviewing the public comments and receiving additional input from a Technical Expert Panel (TEP) convened for this report. Prior to participation in this report, the TEP members disclosed all financial or other conflicts of interest. The AHRQ Task Order Officer and the authors reviewed all of these disclosures and determined the panel members had no significant conflicts of interest that precluded participation.

Search Strategy

To identify articles relevant to each Key Question, a research librarian searched the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, and Ovid MEDLINE® (see Appendix A for search strategy) from 1947 to present. The search strategies were peer reviewed by another information specialist and revised prior to finalization. Unpublished trials were sought by searching clinical trial registries (ClinicalTrials.gov, Current Controlled Trials, Clinical Trial Results, WHO Trial Registries) and grants databases (NIHRePORTER, HSRProj, and AHRQ GOLD). Scientific Information Packets on unpublished and published trials were solicited from manufacturers of included antiviral drugs through the Scientific Resource Center. We also hand-searched the reference lists of relevant studies.

Searches will be updated prior to finalization of the report to identify any relevant new publications.

Study Selection

We developed criteria for inclusion and exclusion of studies based on the key questions and the populations, interventions, comparators, outcomes, timing, and setting (PICOTS) approach. Inclusion and exclusion criteria, summarized below, are described in more detail by key question in Appendix B. Papers were selected for full review if they were about chronic HCV infection, were relevant to key questions in the analytic framework, and met the pre-defined inclusion criteria. To evaluate potential effects of publication bias, we included trials published only as conference abstracts as sensitivity analyses. We restricted inclusion to English language articles. Studies of non-human subjects were also excluded, and studies had to include original data. Abstracts and full-text articles were reviewed in duplicate for inclusion and exclusion for each key question (Appendix B). Full-text articles were obtained for all studies that either investigator identified as potentially meeting inclusion criteria. Two investigators independently reviewed all full-text articles for final inclusion or exclusion (Appendix C). A list of excluded studies with primary reasons for exclusion can be found in Appendix D. Discrepancies were resolved through discussion and consensus, with a third investigator making the final decision if necessary.

Population and Conditions of Interest

The target population for key questions 1 through 3 was non-pregnant adults with chronic HCV infection who have not had previous antiviral drug treatment. Pregnant women were excluded as no antiviral treatment for HCV infection is currently recommended during pregnancy due to potential teratogenic effects.[36] We also evaluated comparative benefits and harms in patient subgroups defined by HCV genotype, race, sex, stage or severity of disease, viral load, weight, genetic markers (i.e., polymorphisms in the IL28b gene), and other factors (such as body weight). For key question 4, the target population was adults with chronic HCV infection who had received a course of interferon-based antiviral therapy. We excluded post-transplant patients, HIV patients, and hemodialysis patients, because treatment considerations and response to therapy may differ from what is observed in the general population of patients with chronic HCV infection without these conditions.

Interventions and Comparisons

We included antiviral regimens recommended in current guidelines for treatment of HCV infection, specifically dual therapy with pegylated interferon alfa-2a or alfa-2b plus ribavirin.[15] We also included triple therapy antiviral regimens with the recently approved protease inhibitors telaprevir and boceprevir, which are used in combination with pegylated interferon alfa-2a or -2b plus ribavirin. We included studies of interferon monotherapy and standard interferon plus ribavirin only for key question 4, which evaluated the association between intermediate and clinical outcomes. We excluded regimens that involved antiviral drugs that are not approved in the United States for treatment of chronic HCV infection.

For key questions 1 through 3, we included studies that compared dual therapy with pegylated interferon alfa-2a plus ribavirin versus dual therapy with pegylated interferon alfa-2b plus ribavirin, or that compared triple therapy with pegylated interferon (alfa-2a or 2b), ribavirin, and a protease inhibitor (telaprevir or boceprevir) versus dual therapy with pegylated interferon (alfa-2a or 2b) plus ribavirin. We also included studies that evaluated different doses or dosing protocols (i.e., weight-based vs. standardized) of the same antiviral drugs, or different durations of therapy or methods (e.g., response-guided therapy vs. fixed-duration therapy) for guiding duration of therapy. We focused on dose and duration comparisons of dual therapy with pegylated interferon (alfa-2a or 2b) plus ribavirin in patients with HCV genotypes 2 and 3. For key question 4, we included studies of patients with chronic HCV infection that received antiviral treatment that compared outcomes between those that achieved an SVR after antiviral therapy (or improved histological findings) compared with those who did not.

Outcomes

Clinical outcomes were mortality, cirrhosis, hepatic decompensation, hepatocellular cancer, need for transplantation, and quality of life. We classified clinical outcomes assessed 1 year or earlier after the end of antiviral treatment as "short-term" and those assessed after at least 1 year as "long-term." Intermediate outcomes were SVR rates and improvements in histological outcomes. We defined a sustained virologic response (SVR) as the absence of detectable HCV RNA in the serum six months after the end of a course of therapy.[15] We did not evaluate measures of earlier virologic response (such as undetectable HCV RNA before or through week 12 of therapy or at the end of therapy). Although such early virologic outcomes predict whether a patient will achieve an SVR and can be used to guide therapy decisions (e.g., whether to

continue therapy or duration of therapy), they are less accurate than the SVR for predicting long-term remission.[15] Histological response has been defined as a 2-point or greater decrease in the inflammatory score or fibrosis score, or a 1-point decrease in the fibrosis score, although relatively few trials evaluate histological response and definitions are less standardized compared with SVR.[15, 37] We did not evaluate improvement in liver function tests as an intermediate outcome (e.g., sustained biochemical response, or normalization of liver transaminases six months after the end of a course of therapy), due to its poor correlation with SVR. Harms of treatment included withdrawals due to adverse events, serious adverse events such as neutropenia, anemia, psychological adverse events, flu-like symptoms, and dermatologic adverse events.

Timing

We did not apply a minimum threshold for duration of studies. We defined long-term outcomes as those measured one year or more after the completion of antiviral therapy and short-term outcomes as those measured prior to one year after theh completion of antiviral therapy.

Setting

Studies conducted in primary care and specialty settings were included.

Types of Studies

We included randomized trials for all key questions. For Key Question 4, we included cohort studies that compared clinical outcomes between patients who achieved an SVR compared with those who did not achieve an SVR, or that compared clinical outcome between patients who achieved a histological response compared with those that did not. Because many factors (such as age, race, viral load, and fibrosis stage) may be associated with both the likelihood of achieving an SVR as well as the likelihood of hepatic complications, we excluded studies on the association between achieving an SVR and mortality or hepatic complications that only reported unadjusted risk estimates, given the strong potential for confounding. Because almost no studies on the association between SVR and quality of life reported adjusted risk estimates, we included studies that reported unadjusted risk estimates for this association.

Data Extraction

We extracted the following data from included studies into Excel spreadsheets: study design, setting, population characteristics, eligibility and exclusion criteria, the antiviral regimen (including duration and dose), and results for each outcome. Data abstraction for each study was completed by two investigators: the first abstracted the data, and the second reviewed the abstracted data for accuracy and completeness against the original articles.

For Key Question 4, some studies reported adjusted HRs for the association between achieving an SVR and clinical outcomes relative to untreated patients, and for no SVR and clinical outcomes relative to untreated patients, but did not report a risk estimate for SVR compared with no SVR. We calculated the HR for SVR compared with no SVR based on the two HRs and their reported confidence intervals, assuming zero correlation between the two reported HRs. Such HRs are usually positively correlated; an assumption of zero correlation results in the most conservative (widest) confidence interval for the HR for SVR vs. no SVR.

Assessing Quality

We assessed quality for each study based on the predefined criteria listed in Appendix E. We adapted criteria from methods proposed by Downs and Black[38] and the USPSTF.[39] The criteria used are consistent with the approach recommended in AHRQ's Methods Guide for Comparative Effectiveness Reviews.[40] We used the term "quality" rather than the alternate term "risk of bias." Although both refer to internal validity, "quality" may be more familiar to most users and has potential advantages in terms of readability.

We rated the quality of each randomized trial based on the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to followup; the use of intent-to-treat analysis; and ascertainment of outcomes.[39]

We rated the quality for each cohort study based on whether it used nonbiased selection methods to create an inception cohort; whether it evaluated comparable groups; whether rates of loss to followup were reported and acceptable; whether it used accurate methods for ascertaining exposures, potential confounders, and outcomes; and whether it performed appropriate statistical analyses of potential confounders.[39] For key question 4, we considered studies to have performed adequate statistical analyses of potential confounders if they adjusted at a minimum for age, sex, genotype, viral load, and hepatic fibrosis stage in a multivariate model including SVR or histological response, evaluated these factors and excluded them from the multivariate model because there was no association in either univariate or step-wise multivariate analyses, or accounted for these factors using other methods such as stratification or restriction.

Following assessment of individual quality criteria, individual studies were rated as "good," "fair," or "poor" quality, as defined below:[39, 40]

Good quality studies are considered likely to be valid. Good quality studies clearly describe the population, setting, interventions, and comparison groups; use a valid method for allocating patients to interventions; clearly report dropouts and have low dropout rates; use appropriate methods for preventing bias; and appropriately measure outcomes and fully report results.

Fair quality studies have some methodological deficiencies, but no flaw or combination of flaws judged likely to cause major bias. The study may be missing information, making it difficult to assess its methods or assess limitations and potential problems. The fair quality category is broad, and 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 probably valid.

Poor quality studies have significant flaws that may invalidate the results. They have a serious or "fatal" flaw in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting. The results of these studies are judged to be at least as likely to reflect flaws in the study design as true effects of the interventions under investigation. We did not exclude poor quality studies *a priori*, but they were considered the least reliable studies when synthesizing the evidence, particularly when discrepancies between studies were present.

Assessing Research Applicability

We recorded factors important for understanding the applicability of studies such as whether the publication adequately described the study population, the country in which the study was conducted (studies indicate that the rate of hepatocellular cancer in patients with chronic HCV infection is higher in Japan and other Asian countries compared with the United States),[41] how

similar patients were to typical populations of those with chronic HCV infection, whether differences in outcomes were clinically (as well as statistically) significant, and whether the antiviral regimens and other aspects of care evaluated were reasonably representative of standard practice.[42] We also recorded the funding source and role of the sponsor. We did not assign a rating of applicability (such as "high" or "low") because applicability may differ based on the user of this report.

Data Synthesis

For Key Questions 1 through 3, we performed meta-analysis of trials that evaluated similar populations, interventions, comparisons, and outcomes to estimate pooled relative risks using the DerSimonian-Laird method in a random effects model.[43] A random effects model results in estimates that are similar to a fixed effects model when there is little or no between-study statistical heterogeneity, but results in more conservative estimates (wider confidence intervals) when statistical heterogeneity is present. Heterogeneity was assessed by calculating the Q-statistic and the percent of the total variance due to between study variability (I^2 statistic).[44] When present, statistical heterogeneity was explored through subgroup and sensitivity analyses, as well as qualitatively. Subgroup analyses were performed in groups stratified by HCV genotype as well as by race, age, body weight, viral load, stage/severity of disease, and IL-28b status when these data were available. We performed sensitivity analysis by excluding poor quality studies, excluding outlier trials, and adding results from trials published only as abstracts to evaluate the stability of estimates and conclusions. Funnel plots were produced to assess the likelihood of publication bias if there were an adequate number of studies (at least ten) to plot.[45] All analyses were performed using Stata 11.0 (StataCorp, College Station, TX, 2009).

For Key Question 4, we did not perform meta-analysis, since all studies were cohort studies, and many had methodological shortcoming (including failure to adjust for important confounders) and varied in populations assessed, treatments received, and other factors. Rather, these studies were synthesized qualitatively.

Strength of the Body of Evidence

We assessed the overall strength of evidence for a body of literature about a particular key question in accordance with AHRQ Methods Guide for Comparative Effectiveness Reviews.[40] The strength of evidence was based on the overall quality of each body of evidence, based on the type and quality of studies (graded good, fair, or poor); the consistency of results within and between study designs (graded high, moderate, or low); the directness of the evidence linking the intervention and health outcomes (graded direct or indirect); and the precision of the estimate of effect, based on the number and size of studies and confidence intervals for the estimates (graded high, moderate, or low). We rated the strength of evidence for each key question using the four categories recommended in the AHRQ guide:[40] A "high" grade indicates high confidence that the evidence reflects the true effect and that further research is very unlikely to change our confidence in the estimate of effect. A "moderate" grade indicates moderate confidence that the evidence reflects the true effect and further research may change our confidence in the estimate of effect and may change the estimate. A "low" grade indicates low confidence that the evidence reflects the true effect and further research is likely to change the confidence in the estimate of effect and is likely to change the estimate. An "insufficient" grade indicates evidence either is unavailable or is too limited to permit any conclusion.

Peer Review and Public Commentary

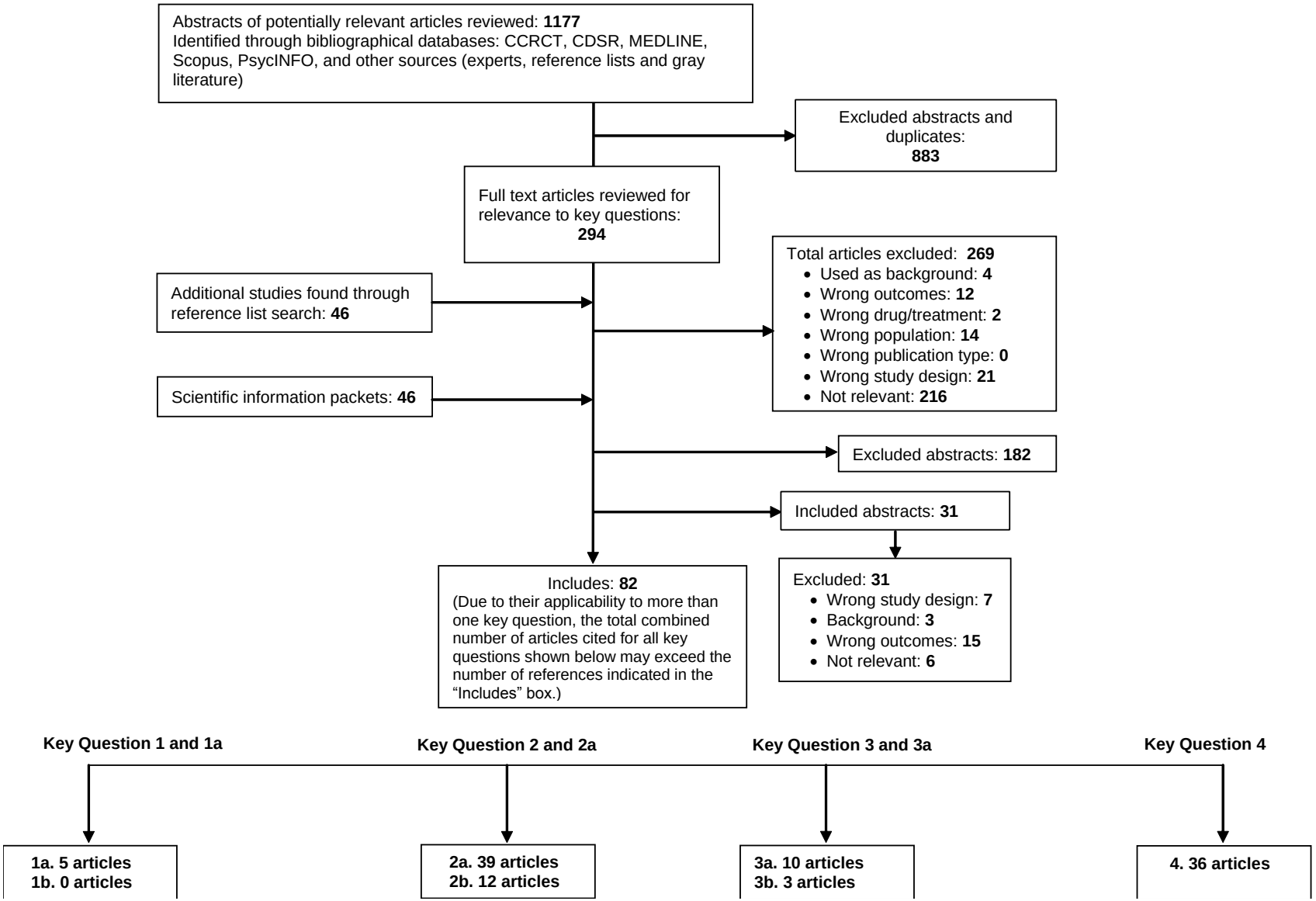
Experts in gastroenterology, hepatology, primary care, and prevention, and individuals representing stakeholder and user communities were invited to provide external peer review of this CER; AHRQ and an associate editoralso provided comments. The protocol was posted on the AHRQ Web site, and the draft report will be posted on the AHRQ Web site for 4 weeks to elicit public comment. All comments will be reviewed and addressed as documented in a disposition of comments report that will be made available 3 months after the Agency posts the final CER on the AHRQ website (http://effectivehealthcare.ahrq.gov/).

Results

Overview

The search and selection of articles are summarized in the study flow diagram (Figure 2). Database searches resulted in 1,177 potentially relevant articles. After dual review of abstracts and titles, 294 studies were selected for full text review, and 36 were determined by dual review at the full text level to meet inclusion criteria (Appendix B). In addition, 46 studies were found through reviewing reference lists of published studies. A total of 71 studies were included in this review.

Figure 2. Study flow diagram: Treatment for hepatitis C virus infection in adults



Key Question 1a. What is the comparative effectiveness of antiviral treatment in improving health outcomes in patients with HCV infection?

- No randomized trials or observational studies evaluated the comparative effectiveness of current antiviral treatment regimens for chronic HCV infection on improving long-term clinical outcomes. (strength of evidence: insufficient)
- Three trials that compared current antiviral regimens found no differences in risk of short-term mortality, but reported very few (20 total) events.(strength of evidence: low)
- One open-label randomized trial of patients with genotype 4 infection found dual therapy with pegylated interferon alfa-2a plus ribavirin associated with slightly better short-term scores on some generic and liver disease-specific quality of life assessments compared with dual therapy with pegylated interferon alfa-2b plus ribavirin. (strength of evidence: low).

No trial evaluated comparative effects of current antiviral treatment regimens for chronic HCV infection (dual therapy with pegylated interferon alfa-2a or 2b plus ribavirin or triple therapy with pegylated interferon alfa-2a or -2b, ribavirin, and a protease inhibitor) on risk of long-term clinical outcomes.

Three trials reported short-term mortality (through 6 months after the completion of antiviral therapy), but reported few deaths (20 total), resulting in very imprecise estimates (Appendix H: Evidence Table 1). One large trial found no difference between dual therapy with standard dose pegylated interferon alfa-2b (1.5 mcg/kg/week) plus ribavirin compared with pegylated interferon alfa-2a plus ribavirin in risk of short-term mortality (RR 0.85, 95% CI 0.26 to 2.8), based on 11 deaths in over 2000 subjects.[22] Another trial found no difference between triple therapy with boceprevir and dual therapy in risk of short-term all-cause mortality (RR 0.25, 95% CI 0.03 to 2.2), but only reported 5 deaths in over 700 patients.[32] One trial of response-guided triple therapy with telaprevir compared with dual therapy reported 4 deaths in over 1088 patients, resulting in a very imprecise estimate (RR 1.5, 95% CI 0.16 to 14).[46]

Two trials evaluated comparative effects of current antiviral regimens for chronic HCV infection on short-term quality of life (Appendix H: Evidence Table 11).[47, 48] One trial of patients with genotype 4 infection found dual therapy with pegylated interferon alfa-2a plus ribavirin associated with slightly higher (better) scores on some SF-36 subscales compared with dual therapy with pegylated interferon alfa-2b plus ribavirin 24 weeks after the end of treatment (differences of 3.2 to 5.7 points on the Bodily Pain, Vitality, Social Functioning, and Role Emotional subscales, each on a 0 to 100 scale).[48] Dual therapy with pegylated interferon alfa-2a was also associated with slightly higher scores on the Physical Component Summary score (3.2, points, $p<0.02$), but there was no difference on the Mental Component Summary score, or on 5 of 6 domains on the Chronic Liver Disease questionnaire, though dual therapy with pegylated interferon alfa-2a plus ribavirin was associated with a slightly higher overall score (difference 0.4 point on a 1 to 7 scale, $p=0.02$). The trial was open-label and patients do not appear to have been blinded to virologic response status, which could have affected quality of life assessments. A trial of patients with genotype 1 infection with undetectable HCV RNA after 24 weeks of pegylated interferon alfa-2a plus ribavirin found continuation of dual therapy for another 24

weeks associated with worse quality of life scores at the end of treatment compared with pegylated interferon alone for the last 24 weeks, but the clinical relevance of this finding is limited since the shorter regimen was associated with lower likelihood of achieving an SVR and is not considered the standard of care for genotype 1 infection.[47]

Key Question 1b. How does the comparative effectiveness of antiviral treatment for health outcomes vary according to patient subgroup characteristics, including but not limited to HCV genotype, age, race, sex, stage of disease or genetic markers?

- No randomized trials or observational studies evaluated comparative effects of current antiviral treatment regimens on any clinical outcomes in patients stratified by HCV genotype, age, race, sex, stage of disease, genetic markers, or other factors factors (strength of evidence: insufficient).

Key Question 2a. What is the comparative effectiveness of antiviral treatments on intermediate outcomes, such as the rate of SVR or histologic changes in the liver?

Dual Therapy with Pegylated Interferon (Alfa-2a or 2b) plus Ribavirin

- Seven trials of patients with genotype 2 or 3 infection found dual therapy with standard doses of pegylated interferon alfa-2b plus ribavirin associated with lower likelihood of achieving an SVR than pegylated interferon alfa-2a plus ribavirin (pooled RR 0.88, 95% CI 0.81 to 0.96; I^2=37%), with an absolute difference in SVR rates of 7.8 percentage points (95% CI 2.2 to 13.4 percentage points). (strength of evidence: moderate).

Dual Therapy with Pegylated Interferon Alfa-2a or -2b plus Ribavirin: Duration Effects

- Two trials of patients with genotype 2 or 3 infection found no difference in likelihood of achieving an SVR between 48 versus 24 weeks of dual therapy with pegylated interferon alfa-2a plus ribavirin (pooled RR 0.97, 95% CI 0.84 to 1.1; I^2=43%) (strength of evidence: moderate)Three trials of patients with genotype 2 or 3 infection found no differences between 24 versus 12-16 weeks of dual therapy with pegylated interferon alfa-2a plus ribavirin (pooled RR=0.88, 95% CI 0.76 to 1.0; I^2=86%). Relative risk estimates ranged from 0.75 to 0.99 in the three trials and may have varied in part due to different methods of ribavirin dosing. (strength of evidence: moderate)
- Three trials of patients with genotype 2 or 3 infection with a rapid virologic response (undetectable HCV RNA by week 4) found no differences between 24 versus 12-16 weeks of dual therapy with pegylated interferon (alfa-2a or alfa-2b) plus ribavirin (pooled

RR=0.99, 95% CI 0.86 to 1.1, I^2=66%). Relative risk estimates ranged from 0.89 to 1.1. (strength of evidence: moderate)

Dual Therapy with Pegylated Interferon Alfa-2a or -2b plus Ribavirin: Dose Effects

- Five trials of patients with genotype 2 or 3 infection found lower doses of pegylated interferon alfa-2b (0.75-1.0 mcg/kg or 50 mcg) associated with lower likelihood of achieving an SVR than higher doses (1.5 mcg/kg or 100-150 mcg) (pooled RR 0.86; 95% CI 0.76 to 0.98; I^2=17%). (strength of evidence: moderate)Three trials of patients with genotype 2 or 3 infection who did not specifically have advanced fibrosis or cirrhosis found no clear difference in likelihood of SVR between lower doses of ribavirin (400 or 800 mg flat dose or 600 to 800 mg weight-based dose) compared with higher doses (800 or 1200 mg flat dose or 800 to 1400 mg weight-based dose). (strength of evidence: moderate)One small trial (n=124) of patients with genotype 2 or 3 infection and advanced fibrosis or cirrhosis (Ishak stage 4-6) found 1000 to 1200 mg daily of ribavirin associated with greater likelihood of SVR compared with 600 to 800 mg daily (72% vs. 45%; p=0.002). (strength of evidence: low)

Trials of Triple Therapy with Pegylated Interferon (Alfa-2a or Alfa-2b), Ribavirin, and Boceprevir or Telaprevir

- Two trials of patients with genotype 1 infection found triple therapy with telaprevir for 24 weeks (12 weeks of pegylated interferon alfa-2a, ribavirin, and telaprevir followed by 12 weeks of pegylated interferon alfa-2a plus ribavirin) associated with higher likelihood of SVR compared with dual therapy with pegylated interferon alfa-2a plus ribavirin for 48 weeks (pooled RR 1.5, 95% CI 1.2 to 1.8; I^2=0%), with an absolute increase in SVR rate of 21 percentage points (95% confidence interval 10 to 32 percentage points). (strength of evidence: moderate)
- Two trials of patients with HCV genotype 1 infection found dual therapy lead-in with pegylated interferon (alfa-2a or 2b) plus ribavirin for 4 weeks followed by 44 weeks of triple therapy with boceprevir associated with higher likelihood of SVR compared with dual therapy for 48 weeks (pooled RR 1.8; 95% CI 1.6 to 2.1), with an absolute increase in SVR rate of 31 percentage points (95% CI 23 to 39 percentage points).(strength of evidence: moderate)
- A single trial of patients with genotype 1 infection found that 48 weeks of triple therapy with boceprevir using low dose of ribavirin (400-1000 mg daily) associated with a non-statistical trend towards lower likelihood of SVR compared to 48 weeks of triple therapy with a standard ribavirin dose (800-1400 mg daily) (36% vs 50%, RR 0.71, 95% CI 0.39 to 1.3) (strength of evidence: low)
- One trial of patients with genotype 1 infection found no difference in likelihood of SVR between triple therapy with pegylated interferon, ribavirin, and telaprevir for 12 weeks versus dual therapy with pegylated interferon alfa-2a plus ribavirin for 48 weeks. (strength of evidence: moderate)One trial of patients with genotype 1 infection found triple therapy with telaprevir (pegylated interferon alfa-2a, ribavirin, and telaprevir for 8 or 12 weeks followed by response-guided dual therapy with pegylated interferon alfa-2a plus ribavirin for an additional 12 or 36 weeks) associated with higher likelihood of SVR

compared with dual therapy with pegylated interferon alfa-2a plus ribavirin for 48 weeks (RR 1.6, 95% CI 1.4 to 1.9), with an absolute increase in SVR rate ranging from 25 to 31 percentage points. The regimen with 8 weeks of telaprevir was associated with a slightly lower SVR rate than the 12 week telaprevir regimen (69% vs. 75%). (strength of evidence: low)

- One trial of patients with genotype 1 infection found no difference in likelihood of SVR between triple therapy with telaprevir for 48 weeks (12 weeks of triple therapy with pegylated interferon alfa-2a, ribavirin, and telaprevir followed by 36 weeks of dual therapy with pegylated interferon alfa-2a plus ribavirin) and triple therapy with telaprivir for 24 weeks (12 weeks of triple therapy followed by 12 weeks of dual therapy). (strength of evidence: low)
- One trial of patients with an extended rapid virologic response to initial triple therapy with telaprevir reported similar, high (92% and 88%) SVR rates in patients randomized to a total of 24 or 48 weeks of therapy. (strength of evidence: low)

Dual Therapy with Pegylated Interferon Alfa-2a plus Ribavirin compared with Dual therapy with Pegylated Interferon Alfa-2b plus Ribavirin

Nine trials directly compared dual therapy with pegylated interferon alfa-2a plus ribavirin to dual therapy with pegylated interferon alfa-2b plus ribavirin and met inclusion criteria (Table 2, Appendix H: Evidence Table 1).[20-23, 48-52] Two trials were published only as abstracts and were only included in sensitivity analyses; we could not adequately assess their quality due to limited information ion the abstracts.[49, 50] Of the remaining seven trials, two[21, 52] were rated poor quality and the remainder fair quality (Appendix H: Evidence Table 1). Frequent methodologic shortcomings were open-label design,[20, 21, 23, 48] high or unclear loss to followup,[20-23] and unclear or inadequate methods of allocation concealment.[21, 23, 48, 52] Sample sizes ranged from 66 to 3070. Three trials included only patients with genotype 1 HCV infection;[22, 51, 52] the others enrolled either a mix of genotypes or a specific genotype other than genotype 1. The proportion of patients with cirrhosis at baseline ranged from <5% to 20%[20, 23, 51, 53] and the proportion of patients with elevated transminases ranged from 60% to 100%[20, 21, 23, 48, 52, 53] in trials that reported this information. All trials except for one[49] included at least one treatment arm that used a standard dose of pegylated interferon alfa-2a (180 mcg/week) or pegylated interferon alfa-2b (1.5 mcg/kg/week). One trial evaluated multiple pegylated interferon alfa-2b doses.[22] Ribavirin dosing varied across studies. All trials used weight-based dosing of ribavirin except for one, which used an 800 mg daily flat dose (it also enrolled only genotype 3 patients).[49] Two trials used different ribavirin doses with pegylated interferon alfa-2a and alfa-2b.[22, 51] Six trials evaluated fixed-duration regimens, with 48 weeks of treatment for genotypes 1 or 4 and 24 weeks for genotypes 2 or 3.[20, 21, 23, 48-50, 52] One trial of patients with genotype 1 infection compared pegylated interferon alfa-2a with pegylated alfa-2b as part of response-guided triple therapy with telaprevir.[51]

Table 2. Trials of dual therapy of pegylated interferon alfa-2a plus ribavirin vs. dual therapy of pegylated interferon alfa-2b plus ribavirin

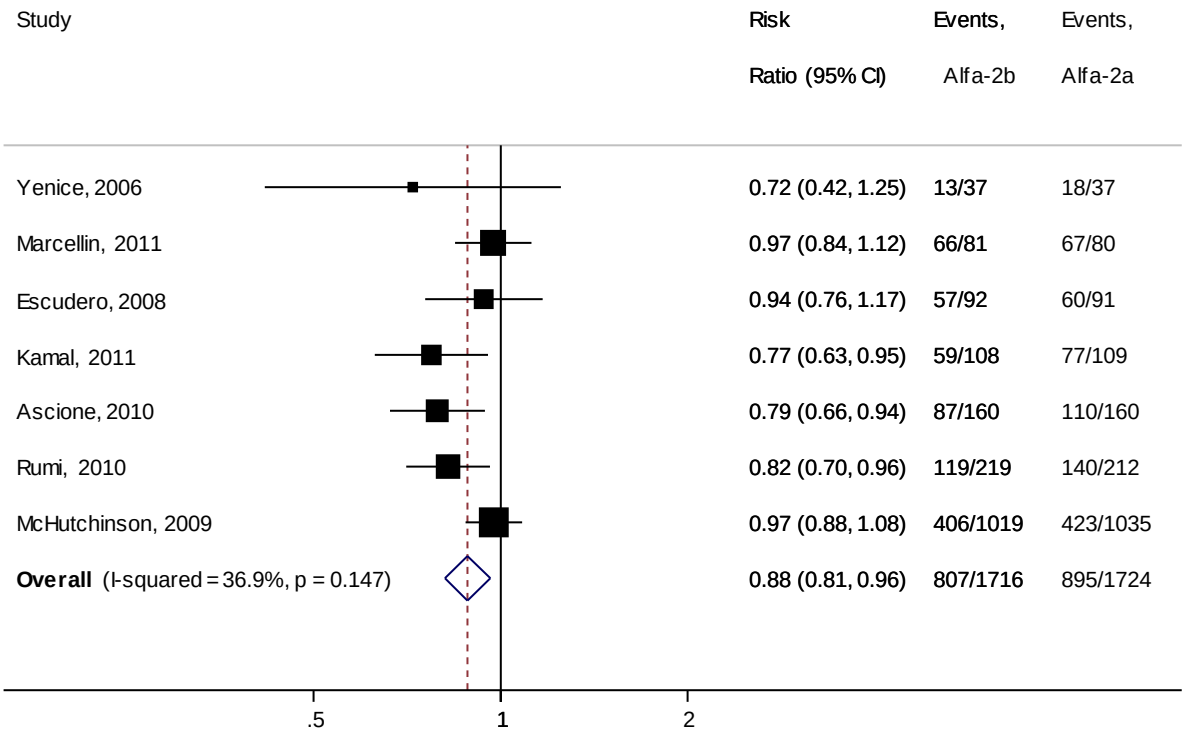
Trial Country N Quality	Population Characteristics	Genotype Mix	Weekly Pegylated Interferon Dose	Daily Ribavirin Dose	Duration (weeks)	Sustained Virologic Response Rate
Ascione, 2010[20] Italy N=320 Quality: Fair	A vs. B Age (mean): 51 vs. 49 years Female: 49% vs. 61% Race: Not reported Cirrhosis: 21% vs. 16% Minimal or no fibrosis: Not reported Elevated transaminases: 100%	~60% genotype 1 or 4	A. Alfa-2a 180 mcg B. Alfa-2b 1.5 mcg/kg	1000-1200 mg	24-48 by genotype	A. 69% B. 54%
Escudero, 2008[21] Spain N=183 Quality: Poor	A vs. B Age (mean): 44 vs. 44 years Female: 30% vs. 39% Race: Not reported Cirrhosis: Not reported Minimal or no fibrosis: Not reported (100% had at least periportal fibrosis) Elevated transaminases: 100%	~75% genotype 1 or 4	A. Alfa-2a 180 mcg B. Alfa-2b 1.5 mcg/kg	800-1200 mg	24-48 by genotype	A. 66% B. 62%
Kamal, 2011 Egypt [48] N=217 Quality: Fair	A vs. B Age (mean): 42 vs. 41 years Female: 46% vs. 56% Race: Not reported Cirrhosis: Not reported Minimal or no fibrosis: Not reported Elevated transaminases: 100%	100% genotype 4	A. Alfa-2a 180 mcg B. Alfa-2b 1.5 mcg/kg	1000-1200 mg	48 weeks	A. 71% B. 55%
Khan,2007[49] Pakistan N=66 Quality: Not assessed[b]	A vs. B Age: Not reported Female: Not reported Race: Not reported Cirrhosis: Not reported Minimal or no fibrosis: Not reported Elevated transaminases: Not reported	100% genotype 3	A. Alfa-2a 180 mcg B. Alfa-2b 1.0 mcg/kg	800 mg	24 weeks	A. 79% B. 82%
Magni, 2009 [50] Italy N=218 Quality: Not assessed[b]	A vs. B Age: Not reported Female: Not reported Race: Not reported Cirrhosis: Not reported Minimal or no fibrosis: Not reported Elevated transaminases: Not reported	~55% genotype 1 or 4	A. Alfa-2a 180 mcg B. Alfa-2b 1.5 mcg/kg	10.5 mg/kg	24-48 by genotype	A. 68% B. 67%

Trial Country N Quality	Population Characteristics	Genotype Mix	Weekly Pegylated Interferon Dose	Daily Ribavirin Dose	Duration (weeks)	Sustained Virologic Response Rate
Marcellin, 2011[51a] Europe N=161 Quality: Fair	A vs. B vs. C vs. D Age (median): 47 vs. 46 vs. 40 vs. 49 years Female: 50% vs. 52% vs. 48% vs. 51 Non-white race: 10% vs. 10% vs. 10% vs. 8% Cirrhosis: 2.5% vs. 2.4% vs. 0% vs. 5.1% Minimal or no fibrosis: 38% vs. 36% vs. 55% vs. 28% Elevated transaminases: Not reported	100% genotype 1	A. Alfa-2a 180 mcg B. Alfa-2b 1.5 mcg/kg C. Alfa-2a 180 mcg D. Alfa-2a 1.5 mcg/kg	A. 1000-1200 mg B. 800-1200 mg C. 1000-1200 mg D. 800-1200 mg	24/48[c]	A. 85% B. 81% C. 83% D. 82%
McHutchison, 2008 (IDEAL)[53] US N=3070 Quality: Fair	A vs. B vs. C Age (mean): 48 vs. 48 vs. 48 years Female: 40% vs. 40% vs. 41% Non-white race: 29% vs. 28% vs. 29% Cirrhosis: Not reported (10% vs. 11% vs. 11% severe fibrosis or cirrhosis) Minimal or no fibrosis: Not reported Elevated transaminases: 80% vs. 81% vs. 81%	100% genotype 1	A. Alfa-2a 180 mcg B. Alfa-2b 1.5 mcg/kg C. Alfa-2b 1.0 mcg/kg	A. 1000-1200 mg B. 800-1400 mg C. 800-1400 mg	Response guided[c]	A. 41% B. 40% C. 38%
Rumi,2010[23] Italy N=431 Quality: Fair	A vs. B Age (mean): 52 vs. 53 years Female: 40% vs. 45% Race: Not reported Cirrhosis: 20% vs. 18% Minimal or no fibrosis: Not reported Elevated transaminases (>2 times upper limit of normal): 59% vs. 59%	100% genotype 1	A. Alfa-2a 180 mcg B. Alfa-2b 1.0 mcg/kg C. Alfa-2b 1.5 mcg/kg	A. 1000-1200 mg B. 1000-1400 mg C. 1000-1400 mg	48 weeks	A. 41% B. 38% C. 40%
Yenice,2006[52] Turkey N=74 Quality: Poor	A vs. B Age (mean): 48 vs. 51 years Female: 35% vs. 27% Race: Not reported Cirrhosis: Not reported Minimal or no fibrosis: Not reported (all patients had at least minimal fibrosis) Elevated transaminases: 70% vs. 76%	~50% genotype 1 or 4	A. Alfa-2a 180 mcg B. Alfa-2b 1.5 mcg/kg	800-1200 mg	24-48 by genotype	A. 66% B. 54%

Abbreviations: HCV, hepatitis C virus; NA, not applicable; NR, not reported; SD, standard deviation.
Cirrhosis=METAVIR F4, Ishak 5-6, or equivalent. Minimal or no fibrosis=METAVIR F0-F1, Ishak 0-2, or equivalent
[a] All arms included 12 weeks of telaprevir.
[b] Published as abstract only.
[c] Response guided duration: 24 weeks of pegylated interferon/ribavirin if HCV RNA negative from week 4 through week 20. 48 weeks if positive at any point from week 4 through week 20.

Based on published trials that evaluated standard doses of pegylated interferon, dual therapy with pegylated interferon alfa-2b plus ribavirin was associated with slightly lower likelihood of achieving an SVR compared with pegylated interferon alfa-2a plus ribavirin (7 trials, pooled RR 0.88, 95% CI 0.81 to 0.96; I^2=67%) (Figure 3).[20-23, 48-52] The pooled absolute reduction in likelihood of SVR was 7.8 percentage points (95% CI 2.2 to 13 percentage points). Results were similar when the meta-analysis included a trial[50] only available as a conference abstract (8 trials, pooled RR=0.90, 95% CI 0.83 to0.97, I^2=32%) or excluded 2 poor-quality trials (6 trials, pooled RR=0.89, 95% CI 0.82 to 0.98, I^2=48%).[21, 52] One other trial only published as an abstract reported similar SVR rates for dual therapy with pegylated interferon alfa-2b compared with dual therapy with pegylated interferon alfa-2a, but was not included in sensitivity analyses because it only evaluated a lower dose of pegylated interferon alfa-2b (1.0 mcg/kg).[49]

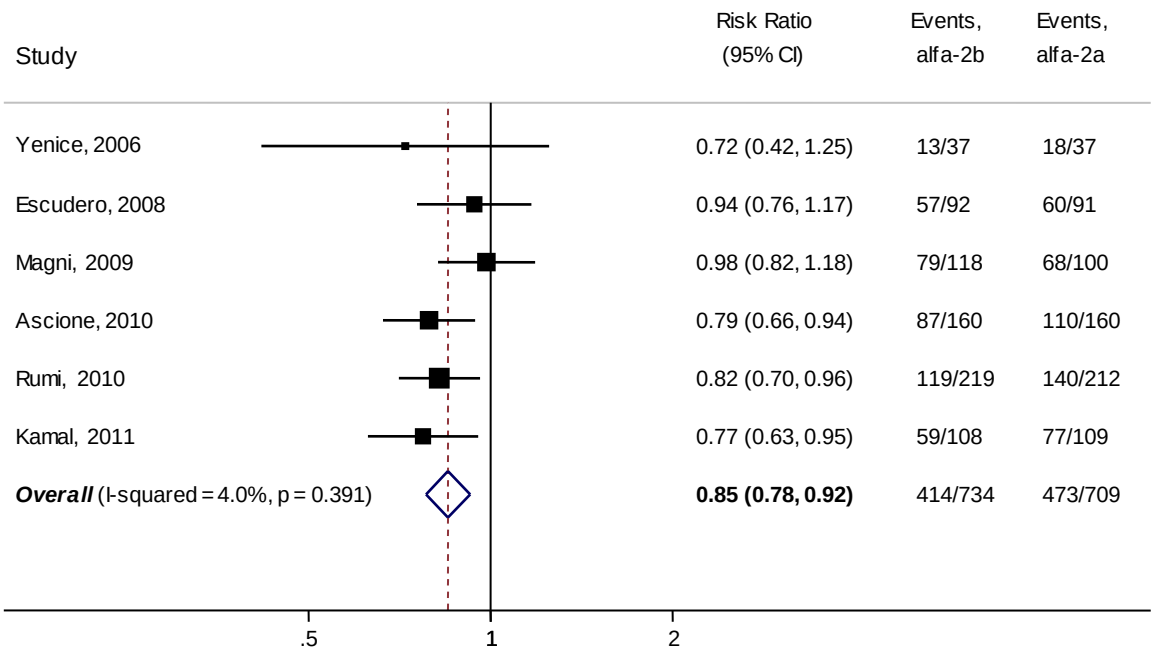
Figure 3. Sustained virologic response, dual therapy with pegylated interferon alfa-2b plus ribavirin compared with dual therapy with pegylated interferon alfa-2a plus ribavirin



The largest head-to-head trial was the Individualized Dosing Efficacy vs. Flat Dosing to Assess Optimal Pegylated Interferon Therapy (IDEAL) study (n=3070, compared with 66 to 477 in the other trials).[22] It was rated fair quality because loss to followup exceeded 20%. A three-armed trial, IDEAL randomized patients with HCV genotype 1 infection to one of two doses of pegylated interferon alfa-2b (1.0 mcg/kg/week or 1.5 mcg/kg/week) plus ribavirin 800 to1400 mg daily (800 mg 40 to 65 kg; 1000 mg >65 to 85 kg; 1200 mg >85 to 105 kg; 1400 >105 to 125 kg) or pegylated interferon alfa-2a 180 mcg/week plus ribavirin 1000 to 1200 mg/day (1000 mg <75 kg; 1200 mg ≥75 kg). Overall, SVR rates were similar at 38% to 41% in the three arms. However, differences in ribavirin dosing could have affected treatment comparability. Excluding IDEAL[22] and one other trial[51] that evaluated different ribavirin doses for pegylated interferon

alfa-2a and 2b had little effect on estimates, although statistical heterogeneity was slightly reduced (6 trials, pooled RR 0.85,95% CI 0.78 to 0.93; I^2= 4%) (Figure 4).[20, 21, 23, 48-50, 52] The latter trial also differed from the others because each treatment arm included twelve weeks of telaprevir.[51]

Figure 4. Sustained virologic response, dual therapy with pegylated interferon alfa-2b plus ribavirin compared with dual therapy with pegylated interferon alfa-2a plus ribavirin (excluding trials with differential ribavirin dosing or that evaluated triple therapy regimens)



Dual Therapy with Pegylated Interferon Alfa-2a or -2b plus Ribavirin: Duration Effects

Ten trials compared effects of different treatment durations of dual therapy with pegylated interferon (alfa-2a or 2b) plus ribavirin on SVR rates in patients with HCV genotype 2 or 3 infection (Table 3, Appendix H: Evidence Table 5). Eight trials[54-61] only enrolled patients with genotype 2 or 3 infection and the other two[62, 63] reported results in the subgroup of patients with genotype 2 or 3 infection. One other trial evaluated patients with HCV genotype 6 infection.[64] Sample sizes ranged from 60 to 1465 subjects. One trial[59] was rated good quality and the remainder fair quality (Appendix H: Evidence Table 5 and Evidence Table 6). Common methodological shortcomings included open-label design[54-58, 61, 63, 64] and inadequately described randomization or treatment allocation procedures.[55-58, 60, 61, 63] Most trials evaluated standard dosing of pegylated interferon alfa-2a (180 mcg/wk) and pegylated interferon alfa-2b (1.5 mcg/kg/week), although ribavirin dosing varied across the trials.

Table 3. Trials on effects of duration with dual therapy with pegylated interferon (alfa-2a or -2b) plus ribavirin

Trial Country N Quality	Population Characteristics	Percent Genotype 2 or 3	Weekly Pegylated Interferon Dose	Daily Ribavirin Dose	Duration	Sustained Virologic Response Among Patients with Genotype 2 or 3 Infection
48 weeks vs. 24 weeks						
Zeuzem, 2004 (PEGASYS) [63] Australia, Europe, New Zealand, North & South America N=117 with genotype 2 or 3 infection Quality: Fair	A vs. B Age (Mean): 44 vs. 44 Female: 58% vs. 61% Non-white race: 14% vs.14%Cirrhosis: 0% vs. 1% Minimal or no fibrosis: 66% vs. 69%	28%	Alfa-2a 180 mcg	800 mg	A. 24 weeks B. 48 weeks	A. 72% B. 78%
Hadziyannis, 2004[62] World-wide N=492 with genotype 2 or 3 infection Quality: Fair	A vs. B vs. C vs. D: Age (mean): 41 vs. 42 vs. 43 vs. 43 years Female: 32% vs. 34% vs. 27% vs. 34% Non-white race: 12% vs. 9% vs. 13% vs. 10% Cirrhosis: 5% vs. 7% vs. 8% Minimal or no fibrosis: Not reported	38%	Alfa-2a 180 mcg	A. 800 mg B. 1200 mg C. 800 mg D. 1200 mg	A/B. 24 weeks C/D. 48 weeks	A/B. 82% C/D. 75%
24 weeks vs. 12-16 weeks						
Shiffman, 2007[59] 132 Centers World-wide N=1465 Quality: Good	A vs. B: Age (mean): 46 vs. 45.6 years Female: 39% vs. 37% Non-white race: 13% vs. 13% Cirrhosis: Not reported (25% vs. 23% severe fibrosis or cirrhosis) Minimal or no fibrosis	100%	Alfa-2a 180 mcg	800 mg	A. 16 weeks B. 24 weeks	A. 62% B. 70%
Yu, 2007[61] Taiwan N=150 Quality: Fair	A vs. B: Age (mean): 49.4 vs. 50.2 years Female: 40% vs. 34% Non-white race: Not reported Cirrhosis: Not reported (severe fibrosis or cirrhosis 20% vs. 22%) Minimal or no fibrosis: Not reported (mild, minimal, or no fibrosis 80% vs. 78%)	100%	Alfa-2a 180 mcg	1000-1200 mg	A. 16 weeks B. 24 weeks	A. 94% B. 95%

Trial Country N Quality	Population Characteristics	Percent Genotype 2 or 3	Weekly Pegylated Interferon Dose	Daily Ribavirin Dose	Duration	Sustained Virologic Response Among Patients with Genotype 2 or 3 Infection
Lagging, 2008 [56] Denmark & Finland N=382 Quality: Fair	A vs. B: Age (mean): 42 vs. 42 years Female: 37% vs. 44%Non-white race: Not reported Cirrhosis: 13% vs. 13% Minimal or no fibrosis: Not reported	100%	Alfa-2a 180 mcg	800 mg	A. 12 weeks B. 24 weeks	A. 59% B. 78%
24 weeks vs. 12-14 weeks among those with undetectable virus by week 4						
Dalgard, 2008[55] Denmark, Sweden, Norway N=298 Quality: Fair	A vs. B:: Age (median): 38 vs. 38 years Female: 36% vs. 35% Non-white race: Not reported Cirrhosis: Not reported Minimal or no fibrosis: Not reported	100%	Alfa-2b 1.5 mcg/kg	800-1400 mg	A. 14 weeks B. 24 weeks	A. 81% B. 91%
von Wagner, 2005[60] Germany N=153 Quality: Fair	A vs. B: Age (mean): 38 vs. 39 Female: 26% vs. 42% Non-white race: Not reported Cirrhosis: Not reported Minimal or no fibrosis: Not reported	100%	Alfa-2a 180 mcg	800-1200 mg	A. 16 weeks B. 24 weeks	A. 82% B. 80%
Mecenate, 2010 (CLEO)[58] Italy N=210 Quality: Fair	Demographics reported overall only Age (mean): 43 years Female: 19%Non-white race: Not reported Cirrhosis: 10% (overall) Minimal or no fibrosis: Not reported	100%	Alfa-2a 180 mcg	800-1200 mg	A. 12 weeks B. 24 weeks	A. 83% B. 74%
Other duration comparisons						
Mangia, 2005 [57] Italy N=283 Quality: Fair	A vs. B: Age (mean): 49.7 vs. 46.6 years Female: 44% vs. 44% Race: Not reported Cirrhosis: Not reported (23% vs. 16% severe fibrosis or cirrhosis) Minimal or no fibrosis: Not reported	100%	Alfa-2b 1.0 mcg/kg	1000-1200 mg	A. response guided duration[a] B. 24 weeks	A. 76% B. 77%

Trial Country N Quality	Population Characteristics	Percent Genotype 2 or 3	Weekly Pegylated Interferon Dose	Daily Ribavirin Dose	Duration	Sustained Virologic Response Among Patients with Genotype 2 or 3 Infection
Andriulli, 2009 [54] Italy N=120 Quality: Fair	A vs. B: Age (mean): 53 vs. 53 years Female: 41% vs. 51% Race: Not reported Cirrhosis: Not reported Minimal or no fibrosis: Not reported	100%	Alfa-2a 180 mcg	A. 1000-1200 mg for 6 weeks B. 1000-1200 mg for 12 weeks	A. 6/12 weeks[b] B. 12 weeks	A. 54% B. 82%
Lam, 2010 [64] USA (limited to Southeast Asian populations) N=48 Quality: Fair	A vs. B: Age (mean): 50 vs. 53 years Female: 42% vs. 54% Southeast Asian race: 100% Cirrhosis: Not reported (26% vs. 27% severe fibrosis or cirrhosis) Minimal or no fibrosis: Not reported	0%(100% genotype 6)	Alfa-2a 180 mcg	800-1200 mg	A. 24 weeks B. 48 weeks	A. 70%[c] B. 79%

Abbreviations: ALT, HCV, hepatitis C virus; NA, not applicable; NR, not reported; SVR, sustained virologic response.
Cirrhosis=METAVIR F4, Ishak 5-6, or equivalent. Minimal or no fibrosis=METAVIR F0-F1, Ishak 0-2, or equivalent
[a] HCV RNA undetectable at 4 weeks received 12 weeks of dual therapy, otherwise 24 weeks if detectable.
[b] Those with undetectable HCV RNA at 4 weeks randomized to 6 or 12 weeks of ribavirin with 12 weeks of pegylated interferon.
[c] HCV genotype 6 SVR rates.

Five trials compared fixed-duration regimens of dual therapy with pegylated interferon alfa-2a plus ribavirin in patients with genotype 2 or 3 infection.[56, 59, 61-63] Two trials found no difference between 48 compared with 24 weeks of dual therapy in likelihood of achieving an SVR (pooled RR 0.97; 95% CI 0.84 to 1.1; I^2=43%) (Figure 5).[62, 63] Three other trials found no differences between 12 to16 compared with 24 weeks of dual therapy in likelihood of achieving an SVR (pooled RR 0.88; 95% CI 0.76 to 1.0),[56, 59, 61] but substantial statistical heterogeneity was present (I^2=86%) (Figure 6). Differences in ribavirin dosing may explain some of the heterogeneity. Specifically, two trials[56, 59] that used a flat ribavirin dose of 800 mg daily found 12 or 16 weeks of therapy associated with lower likelihood of achieving an SVR compared with 24 weeks of therapy, but also reported lower SVR rates (59% to 62% vs. 70% to 78%, respectively) compared to the third trial,[61] which used higher, weight-based doses of ribavirin (1000-1200 mg daily) and reported higher SVR rates that were similar with 16 compared with 24 weeks of treatment (94% vs. 95%). One of the trials[56] that found shorter duration of therapy less effective than 24 weeks also enrolled substantially more patients with bridging fibrosis or cirrhosis (~50%) compared with the other two trials (~20%).

Figure 5. Sustained virologic response, dual therapy with pegylated interferon (alfa-2a or -2b) plus ribavirin for 48 compared with 24 weeks in patients with genotype 2 or 3 infection

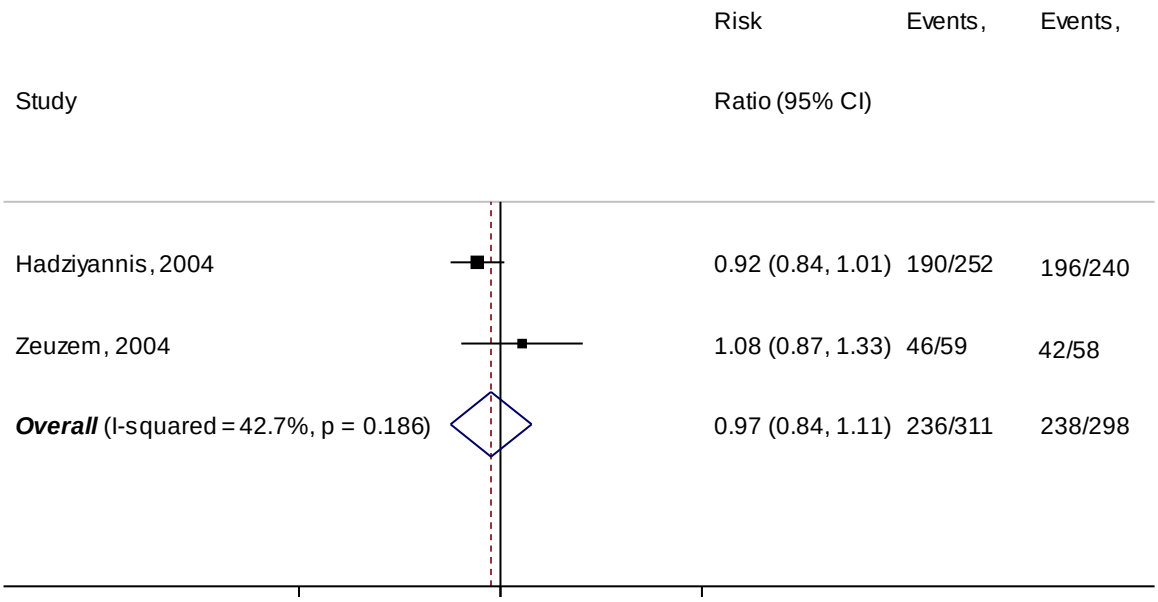
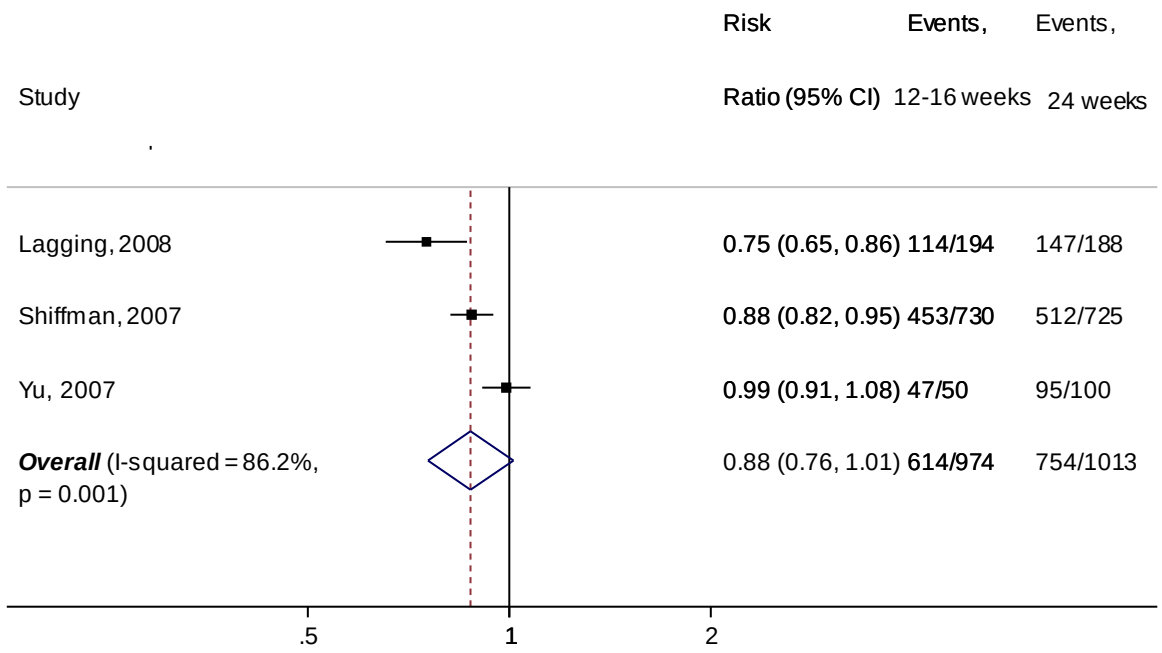
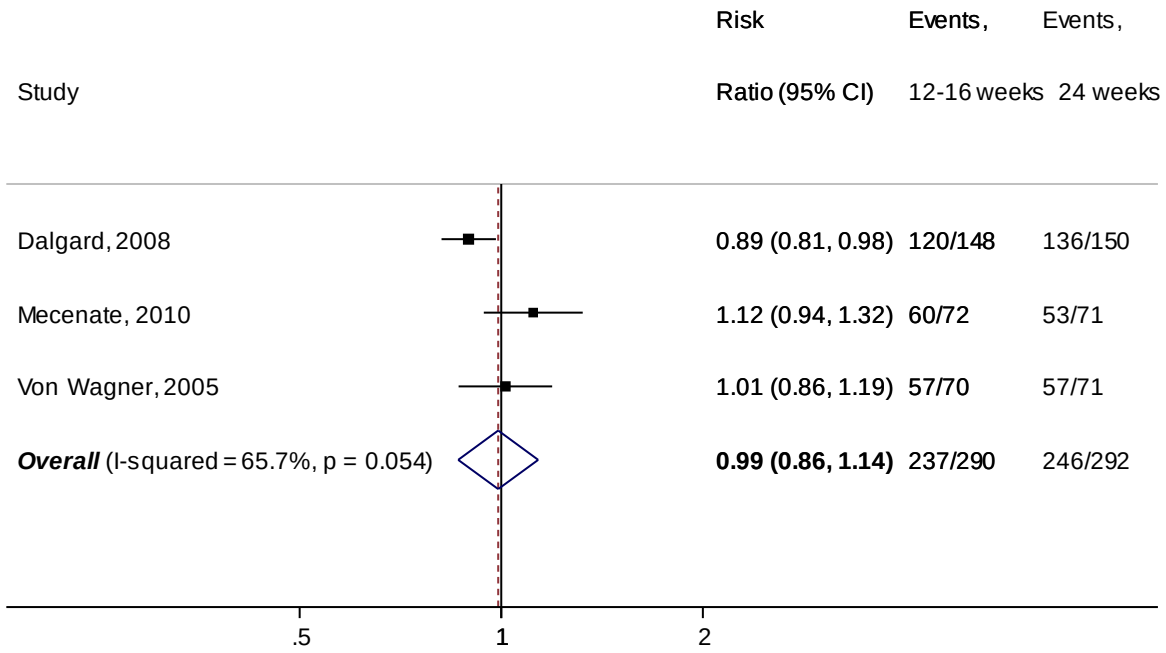


Figure 6. Sustained virologic response, dual therapy with pegylated interferon (alfa-2a or -2b) plus ribavirin for 12 to 16 compared with 24 weeks in patients with genotype 2 or 3 infection



Three trials of patients with genotype 2 or 3 infection who achieved a rapid virologic response (defined as undetectable HCV RNA by week 4) found no difference between patients randomized to a total of 24 compared with 12 to 16 weeks of dual therapy with pegylated interferon alfa-2a (two trials) or alfa-2b (one trial) plus ribavirin (pooled RR 0.99; 95% CI 0.86 to 1.14; I^2=66%) (Figure 7).[55, 58, 60] Although statistically heterogeneity was present, absolute differences were relatively small, ranging from 10% favoring 24 over 16 weeks of therapy[55] to 9% favoring 12 over 24 weeks of therapy.[58] One trial used the alfa-2b form of pegylated interferon and a somewhat different weight-based ribavirin dosing algorithm, which might account for some of the heterogeneity.[55]

Figure 7. Sustained virologic response, dual therapy with pegylated interferon (alfa-2a or -2b) plus ribavirin for a total of 24 compared with 12 to 16 weeks in patients with genotype 2 or 3 infection with a rapid virologic response



Two other trials evaluated other comparisons related to duration of dual therapy with pegylated interferon plus ribavirin in patients with HCV genotype 2 or 3 infection.[54, 57, 64] One trial found fixed duration therapy with low dose (1.0 mcg/kg/week) pegylated interferon alfa-2b plus ribavirin for 24 weeks associated with nearly identical likelihood of achieving an SVR compared with response-guided therapy for 12 or 24 weeks, based on absence or presence of a rapid virologic response (76% vs. 77%).[57] A trial of patients who experienced a rapid virologic response found 12 weeks of pegylated interferon alfa-2a with early discontinuation of ribavirin after 6 weeks associated with lower likelihood of SVR compared with dual therapy for 12 weeks (54% vs. 82%; RR 0.66; 95% CI 0.51 to 0.86).[54]

One trial of Asian Americans (ancestry southeast Asian) with HCV genotype 6 infection found no statistically significant difference in likelihood of achieving an SVR between 48 compared with 24 weeks of therapy with pegylated interferon alfa-2a plus ribavirin (79% vs. 70%; RR 1.1, 95% CI 0.83 to 1.5).[64]

Dual therapy with pegylated interferon alfa-2a or -2b plus ribavirin: dose effects pegylated interferon (alfa-2a or 2b)

Five trials of dual therapy with pegylated interferon plus ribavirin compared higher with lower doses of pegylated interferon alfa-2b in patients with genotype 2 or 3 infection (Table 4, Appendix H: Evidence Table 7).[65-69] Two trials[66, 69] restricted enrollment to patients with genotype 2 or 3 infection and three trials[65, 67, 68] enrolled other genotypes but reported results in the subgroup of patients with genotype 2 or 3 infection. Sample sizes ranged from 53 to 103 persons with genotype 2 or 3 infection. One trial[68] was rated poor quality and the remainder fair

quality (Appendix H: Evidence Table 7 and Evidence Table 8). Methodologic shortcomings included open-label or inadequately described blinding procedures[65-69] and unclear randomization methods.[65-69] Four trials compared standard dose pegylated interferon alfa-2b (1.5 mcg/kg/week) compared with lower doses (1.0 or 0.75 mcg/kg/week).[65, 66, 68, 69] The fifth trial evaluated an atypical pegylated interferon alfa-2b dosing regimen of 100-150 mcg weekly (100 mcg if <75 kg or 150 mcg if ≥75 kg) compared with 50 mcg weekly.[67]

Table 4. Dose effects of pegylated interferon, trials of with dual therapy with pegylated interferon (alfa-2a or -2b) plus ribavirin

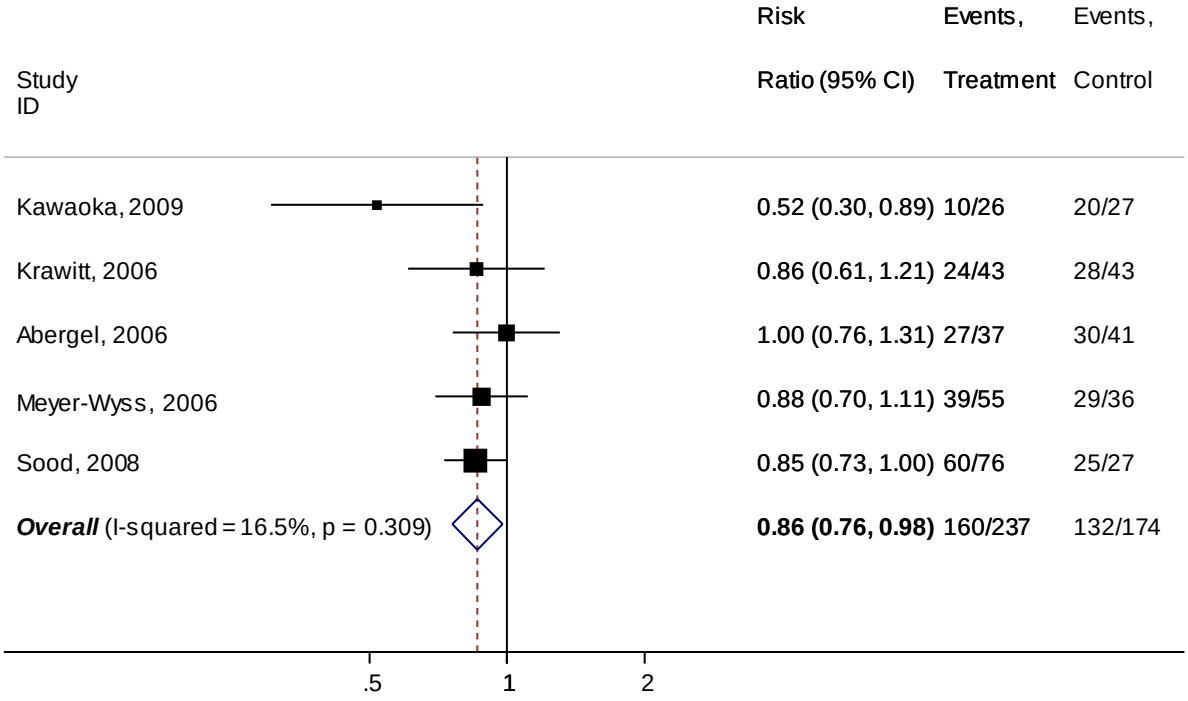
Author Country N Quality	Population Characteristics	Percent Genotype 2 or 3	Weekly Pegylated Interferon Dose	Daily Ribavirin Dose	Duration	Sustained Virologic Response Among Genotype 2 or 3
Trials of higher versus lower doses of pegylated interferon alfa-2b						
Abergel, 2006 [65] France N=78 with genotype 2 or 3 infection Quality: Fair	A vs. B Age (mean): 49.3 vs. 51.1 years Female: 36% vs. 32% Race: Not reported Cirrhosis: 46% vs. 57% Minimal or no fibrosis: Not reported	38%	A. Alfa-2b 0.75 mcg/kg B. Alfa-2b 1.5 mcg/kg	800 mg	48 weeks	A. 73% B. 73%
Krawitt, 2006 [67] US N=86 with genotype 2 or 3 infection Quality: Fair	A vs. B Age >50 years: 18% vs. 19% Female: 38% vs. 36% Non-white race: 4.6% vs. 3.1% Cirrhosis: 17% vs. 10% Minimal or no fibrosis: 30% vs. 33%	29%	A. Alfa-2b 50 mcg B. Alfa-2b 100-150 mcg	1000 mg	48 weeks	A. 56% B. 65%
Meyer-Wyss, 2006 [68] Switzerland N=91 with genotype 2 or 3 infection Quality: Poor	A vs. B Age (median): 39 vs. 42 years Female: 43% vs. 28% Race: Not reported Cirrhosis: None Minimal or no fibrosis: 58% vs. 49%	42%	A. Alfa-2b 1.0 mcg/kg B. Alfa-2b 1.5 mcg/kg	800 mg	24-48 weeks by genotype	A. 71% B. 81%
Sood, 2008 [69] India N=103 Quality: Fair	A vs. B Age (mean): 43 vs. 37 years Female: 12% vs. 22% Race: Not reported Cirrhosis: Not reported Minimal or no fibrosis: Not reported	100%	A. Alfa-2b 1.0 mcg/kg B. Alfa-2b 1.5 mcg/kg	10-12 mg/kg	24 weeks	A. 79% B. 93%

Author Country N Quality	Population Characteristics	Percent Genotype 2 or 3	Weekly Pegylated Interferon Dose	Daily Ribavirin Dose	Duration	Sustained Virologic Response Among Genotype 2 or 3
Kawaoka, 2009 [66] Japan N=53 Quality: Fair	A vs. B Age (median): 57 vs. 55 years Female: 65% vs. 44% Race: Not reported (study conducted in Japan) Cirrhosis: None Minimal or no fibrosis: 55% vs. 48%	100%	A. Alfa-2b 1.0 mcg/kg B. Alfa-2b 1.5 mcg/kg	600-1000 mg	24 weeks	A. 39% B. 74%
Trials of induction dosing regimens						
Mimidis (2006) [70] Greece N=120 Quality: Poor	A vs. B Age (mean): Not reported Female: : 49% vs 51% Race: Not reported Cirrhosis: Not reported Minimal or no fibrosis: Not reported	51%	A. Alfa-2b 3.0 mcg/kg x12 weeks, 1.5 mcg/kg x 36 weeks B. Alfa-2b 1.5 mcg/kg x48 weeks	800-1200 mg	48 weeks	A. 48% B. 59%
Manns, 2001 [71] US & UK N=1530 Quality: Fair	A vs. B Age (mean): Female: Non-white race: Cirrhosis: Not reported (29% vs. 30% severe fibrosis or cirrhosis) Minimal or no fibrosis: Not reported	29%	A. Alfa-2b 1.5 mcg/kg x4 weeks, then 0.5 mcg/kg x44 weeks B. Alfa-2b 1.5 mcg/kg x48 weeks	A. 1000-1200 mg B. 800 mg	48 weeks	A. 80% 88%

Abbreviations: HCV, hepatitis C virus; NA, not applicable; SD, standard deviation; U.K., United Kingdom; U.S., United States. Cirrhosis=METAVIR F4, Ishak 5-6, or equivalent. Minimal or no fibrosis=METAVIR F0-F1, Ishak 0-2, or equivalent

Lower dose pegylated interferon alfa-2b as part of dual therapy with ribavirin was associated with decreased likelihood of achieving an SVR compared with standard dose (five trials, pooled RR 0.86; 95% CI 0.76 to 0.98; I^2=17%) (Figure 8).[65-69] Excluding the poor quality trial[68] (4 trials, pooled RR 0.85; 95% CI 0.71 to 1.0; I^2=38%) or the trial[67] that evaluated an atypical dose (four trials, pooled RR 0.86; 95% CI 0.73 to 1.0; I^2=38%) had little effect on the point estimate.

Figure 8. Sustained virologic response, dual therapy with pegylated interferon (alfa-2a or 2b) plus ribavirin with lower dose pegylated interferon patients with genotype 2 or 3 infection with a rapid virologic response



Two other trials evaluated induction regimens of pegylated interferon alfa-2b (higher initial doses followed by lower doses until completion of therapy) plus ribavirin compared with standard fixed-dose regimens of pegylated interferon alfa-2b plus ribavirin.[70, 71] One good quality trial found dual therapy with pegylated interferon alfa-2b (3.0 mcg/kg/week) plus ribavirin for 12 weeks followed by 36 weeks of standard dose pegylated interferon alfa-2b plus ribavirin associated with a non-statistically significant trend towards decreased likelihood of SVR compared with standard fixed dose dual therapy for 48 weeks (48% vs. 59%, p>0.05).[70] Another trial found no clear difference in likelihood of achieving an SVR between dual therapy with standard dose pegylated interferon alfa-2b plus ribavirin for 4 weeks followed by 0.5 mcg/kg/week for 44 weeks compared with fixed dose dual therapy with standard doses of pegylated interferon alfa-2b for 48 weeks (82% vs. 80%), but results are difficult to interpret because ribavirin dosing was higher (1000 to 1200 mg daily) in the induction therapy arm compared with the standard therapy arm (800 mg daily).[71]

Ribavirin

Four trials compared effects of dual therapy with pegylated interferon plus ribavirin with different doses of ribavirin in patients with genotype 2 or 3 infection (Table 5, Appendix H: Evidence Table 5 and Evidence Table 6). One trial[72] restricted enrollment to patients with genotype 2 or 3 infection and three trials[62, 73, 74] enrolled other genotypes but reported results in the subgroup of patients with genotype 2 or 3 infection.Sample sizes ranged from 97 to 1831 with genotype 2 or 3 infection. All four trials were rated fair quality (Appendix H: Evidence

Table 5 and Evidence Table 6). Methodological shortcomings included open-label design or inadequately described blinding[62, 72-74] and high loss to followup.[62, 74] Three trials[62, 72, 73] evaluated ribavirin in combination with pegylated interferon alfa-2a and one trial in combination with pegylated interferon alfa-2b.[74]

Table 5. Dose effects of ribavirin, trials of with dual therapy with pegylated interferon (alfa-2a or -2b) plus ribavirin

Author Country Study Name N Quality	Population Characteristics	Percent Genotype 2 or 3	Pegylated Interferon Dose	Ribavirin Dose	Duration	Sustained Virologic Response Among Genotype 2 or 3
Hadziyannis, 2004 (PEGASYS) [62] Worldwide N=482 withgenotype 2 or 3 infection Quality: Fair	A vs. B vs. C vs. D: Age (mean): 41 vs. 42 vs. 43 vs. 43 years Female: 32% vs. 34% vs. 27% vs. 34% Non-white race: 12% vs. 9% vs. 13% vs. 10% Cirrhosis: 5% vs. 7% vs. 7% vs. 8% Minimal or no fibrosis: Not reported	38%	Alfa-2a 180 mcg	A/C. 800 mg B/D. 1200 mg	A. 24 weeks B. 24 weeks C. 48 weeks D. 48 weeks	A/C. 80% B/D. 77%
Helbling, 2006 [73] Switzerland N= 97 (genotype 2 or 3) Quality: Fair	A vs. B Age (median): 47 vs. 47 years Female: 30% vs. 40% Race: Not reported Cirrhosis: 57% vs. 52%Minimal or no fibrosis: 6% vs. 2%	48%	Alfa-2a 180 mcg	A. 600-800 mg B. 1000-1200 mg	24-48 weeks by genotype	A. 45% B. 72%
Jacobson, 2007a (WIN-R) [74] U.S. N=1831 with genotype 2 or 3 infection Quality: Fair	A vs. B Age (mean): 46 vs. 46 years Female - 37.7% vs. 36.2% Non-white race: 19% vs. 21% Cirrhosis: 10% vs. 10%Minimal or no fibrosis: Not reported (mild, minimal, or no fibrosis 70% vs. 70%)	37%	Alfa-2b 1.5 mcg	A. 800 mg B. 800-1400 mg	24-48 weeks by genotype	A. 62% B. 60%
Ferenci, 2008 [72] Austria N= 250 Quality: Poor	A vs. B Age (mean): 37 vs. 36 years Female: 40% vs. 38% Race: Not reported Cirrhosis: Not reported Minimal or no fibrosis: Not reported	100%	Alfa-2a 180 mcg	A. 400 mg B. 800 mg	24 weeks	A. 64% B. 69%

Abbreviations: HCV, hepatitis C virus; NA, not applicable; NR, not reported; U.S., United States.
Cirrhosis=METAVIR F4, Ishak 5-6, or equivalent. Minimal or no fibrosis=METAVIR F0-F1, Ishak 0-2, or equivalent.

The trials each evaluated a different ribavirin dose comparison, precluding pooled analyses. The two largest trials found no clear differences between lower flat doses of ribavirin compared

with higher or weight-based doses.[62, 74] One trial (n= 492 with genotype 2 or 3 infection) randomized patients to dual therapy with pegylated interferon alfa-2a 180 mcg/week plus flat-dose ribavirin, in one of four regimens: 24 weeks of with 800 mg of ribavirin, 24 weeks with 1200 mg of ribavirin, 48 weeks with 800 mg of ribavirin, and 48 weeks with 1200 mg of ribavirin.[62] Rates of SVR were very similar in the combined 1200 mg compared with the combined 800 mg arms (77% vs. 80%). Another trial (n=1831with genotype 2 or 3 infection) found no difference between dual therapy for 24 weeks with pegylated interferon alfa-2b 1.5 mcg/kg week and either flat-dose ribavirin 800 mg or weight-dosed ribavirin 800 to 1400 mg (60% vs. 62%).[74] One other smaller trial (n=250) found no difference between dual therapy with pegylated interferon alfa-2a with flat doses of ribavirin 400 mg compared with ribavirin 800 mg in likelihood of achieving an SVR (62% vs. 69%, p>0.05).[75]

One trial (n=97 with genotype 2 or 3 infection) found 1000-1200 mg daily of ribavirin associated with greater likelihood of SVR compared with 600-800 mg daily (72% vs. 45%; p=0.002),[73] but differed from the others in that it enrolled subjects primarily with advanced fibrosis or cirrhosis (Ishak stage F4-F6).[73]

Trials of triple therapy with pegylated interferon (alfa-2a or alfa-2b), ribavirin, and boceprevir or telaprevir

Two randomized trials compared triple therapy with boceprevir, pegylated interferon alfa-2b and weight-based ribavirin with dual therapy with pegylated interferon alfa-2b plus ribavirin in antiviral treatment-naïve patients with chronic HCV genotype 1 infection (Table 6, Appendix H: Evidence Table 3 and Evidence Table 4).[30, 32] The Serine Protease Inhibitor Therapy (SPRINT) 1[30] and SPRINT-2[32] trials (n=1097 and 520, respectively) were conducted in the US, Canada, and Europe. In SPRINT-1,[30] 7% of enrolled patients had cirrhosis at baseline and in SPRINT-2[32] about 10% had either severe fibrosis or cirrhosis. Both trials were rated fair quality (Appendix H: Evidence Table 3 and Evidence Table 4). SPRINT-1 was an open label trial and in SPRINT-2 24% of patients did not complete followup. Neither trial evaluated the FDA-recommended dosing regimen for boceprevir in antiviral-naïve patients without cirrhosis at baseline (four week dual therapy lead-in with pegylated interferon alfa-2a or 2b plus ribavirin, followed by triple therapy with the addition of boceprevir for either 24 or 32 weeks, based on virologic response at weeks 8 and 24),[76] although both trials evaluated the FDA-recommended dosing regimen for boceprevir in antiviral treatment-naïve patients with cirrhosis at baseline (4 week dual therapy lead-in, followed by triple therapy for the final 44 weeks).

Table 6. Trials of triple therapy with pegylated interferon alfa-2b, ribavirin, and boceprevir compared with dual therapy with pegylated interferon alfa-2b plus ribavirin

Trial Country Study Name N Quality	Population characteristics	Boceprevir Dose / Duration	Weekly Pegylated interferon dose	Daily Ribavirin Dose	Overall Duration of Therapy (weeks)	Sustained Virologic Response
Kwo, 2010 [30] US, Canada, Europe Serine Protease Inhibitor Therapy 1 (SPRINT-1) Trial N=520 Quality: Fair	A vs. B vs. C vs. D vs. E Age (mean): 47 vs. 46 vs. 48 vs. 48. vs. 48 years Female: 39% vs. 41% vs. 44% vs. 50% vs. 33% Non-White race: 16% vs. 20% vs. 17% vs. 17% vs. 20% Genotype 1: 100% Cirrhosis: 7% (overall) Minimal or no fibrosis: Not reported Elevated transaminases: Not reported	A. BCP 800 mg tid weeks 1-48 B. BCP 800 mg tid weeks 1-28 C. BCP 800 mg tid weeks 5-48[a] D.BCP 800 mg tid weeks 5-28 E. placebo	Alfa-2b 1.5 mcg/kg	800-1400 mg	A. 48 B. 28 C. 48 D. 28 E. 48	A. 67% B. 54% C. 75%[a] D. 56% E. 38%
Poordad, 2011[32] USA and Europe Serine Protease Inhibitor Therapy 2 (SPRINT-2) N=275 Quality: Fair	A vs. B vs. C Age (mean) 49 vs. 50 vs. 49 years Female: 40% vs. 38% vs. 43% Non-white race: 19% vs. 17% vs. 18% Genotype 1: 100% Cirrhosis: Not reported (Severe fibrosis or cirrhosis 11% vs. 9% vs. 7%) Minimal or no fibrosis: Elevated transaminases:	A. 800 mg tid weeks 5-48 B. 800 mg tid weeks 5-28 C. placebo	Alfa-2b 1.5 mcg/kg	A. 600-1400 mg weeks 5-48 B. 600-1400 mg weeks 5-28 C. 600-1400 mg	A.48 B.28/28[b] C.48	A. 66%[a] B. 63% C. 38%

Abbreviations: BCP, boceprevir; bid, twice daily; eRVR, extended rapid virologic response; TCP, telaprevir; tid, three times daily.

Cirrhosis=METAVIR F4, Ishak 5-6, or equivalent. Minimal or no fibrosis=METAVIR F0-F1, Ishak 0-2, or equivalent

[a] Dosing recommended by the US Food and Drug Administration for boceprevir in antiviral-naïve patients with cirrhosis at baseline.

[b] Response guided duration: 28 weeks of pegylated interferon/ribavirin if HCV RNA negative from week 8 through week 24. 48 weeks of pegylated interferon/ribavirin if HCV RNA positive at any point from week 8 up to, but not including, week 24.

SPRINT-1 randomized patients to five different antiviral regimens: 1) four week dual therapy lead in with pegylated interferon alfa-2b plus ribavirin followed by the addition of boceprevir for 24 weeks (total 28 weeks), 2) 28 weeks of triple therapy with pegylated interferon alfa-2b, ribavirin, and boceprevir with no lead-in, 3) four week dual therapy lead in followed by triple therapy for 44 weeks (total 48 weeks), 4) 48 weeks of triple therapy with no lead-in, or 5) dual therapy for 48 weeks.[30] SVR rates were 56% and 54% in the 28-week boceprevir treatment arms

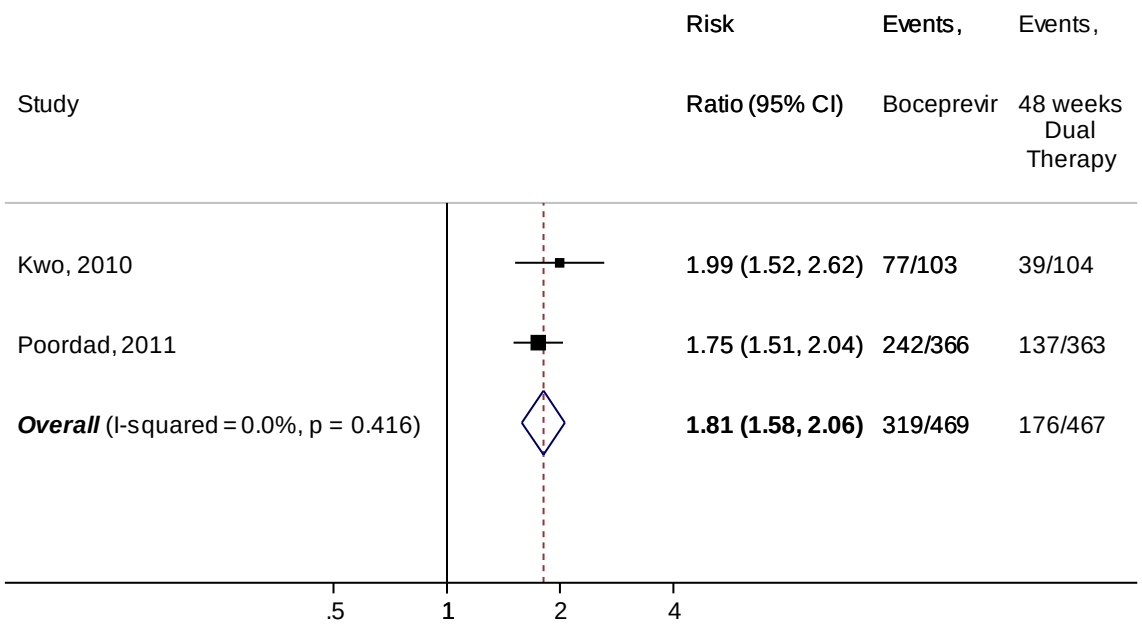
and 75% and 67% in the 48-week boceprevir treatment arms (with and without dual therapy lead in, respectively), compared with 38% with dual therapy ($p<0.01$ for each triple therapy arm vs. dual therapy), for an absolute risk difference for triple compared with dual therapy ranging from 19 to 37 percentage points. Compared with dual therapy, the relative risk for achieving an SVR for the two 48 week triple therapy arms combined was 1.9 (95% CI 1.5 to 2.5), and for the two 28 week triple therapy arms combined was 1.5 (95% CI 1.1 to 1.9). Four week dual therapy lead-in was associated with an increased absolute rate of achieving an SVR compared with no lead-in of 2 percentage points for the 28 week regimens and 8 percentage points for the 48 week regimens.

SPRINT-2 compared a fixed duration triple therapy regimen, a response-guided triple therapy regimen, and dual therapy.[32] The fixed duration regimen consisted of four weeks of dual therapy lead-in with pegylated interferon alfa-2b plus ribavirin followed by the addition of boceprevir for 44 weeks (48 weeks total). The response-guided approach consisted of four week dual therapy lead-in, followed by triple therapy for 24 weeks. Patients with undetectable serum HCV RNA from weeks 8 through 24 completed their antiviral treatment at week 28. Patients with detectable HCV RNA at any time between weeks 8 and 24 continued dual therapy for another 20 weeks (48 weeks total). The third (control) arm consisted of dual therapy for 48 weeks. SVR rates for the three regimens were 66%, 63%, and 38%, respectively, ($p<0.001$ for either boceprevir regimen vs. dual therapy), with an absolute risk difference of 25 to 28 percentage points for triple compared with dual therapy. Compared with dual therapy, the relative risk for achieving an SVR for the two regimens with boceprevir combined was 1.7 (95% CI 1.5 to 2.0).

The only treatment regimen evaluated in both SPRINT trials was the 48 week regimen with dual therapy lead-in for the first 4 weeks and boceprevir added for the final 44 weeks. Based on data from both trials, triple therapy was associated with an increased likelihood of SVR compared with dual therapy (pooled RR=1.8, 95% CI 1.6 to 2.1, $I^2=0\%$), with a pooled absolute increase in SVR of 31 percentage points (95% CI 23 to 39 percentage points) (Figure 9).[30, 32]

SPRINT-1 also included a separate trial of 75 patients randomized to weight-based low dose (400-1000 mg) or standard dose (800-1400 mg) ribavirin as part of 48 weeks of triple therapy with boceprevir without dual therapy lead in. [30] Low dose ribavirin was associated with a non-statistically significant trend towards lower likelihood of SVR (36% vs. 50%, RR 0.71, 95% CI 0.39 to 1.3).

Figure 9. Sustained virologic response, 48 weeks of triple therapy with boceprevir (4 weeks of dual therapy lead-in with pegylated interferon alfa-2b followed by the addition of 44 weeks boceprevir) compared with 48 weeks of dual therapy in patients with genotype 1 infection



Telaprevir

Five randomized trials compared triple therapy with telaprevir, pegylated interferon alfa-2a or -2b and weight-based ribavirin compared with dual therapy with pegylated interferon alfa-2a or -2b and ribavirin for antiviral treatment-naïve patients with chronic HCV genotype 1 infection (Table 7, Appendix H: Evidence Table 3 and Evidence Table 4).[31, 46, 51, 77, 78] One trial[31] was rated good quality and the remainder fair quality (Appendix H: Evidence Table 3 and Evidence Table 4). The proportion of patients with cirrhosis at baseline ranged from 0% to 10%. Methodological shortcoming included open-label design or unclear blinding procedures,[51, 77, 78] unclear randomization methods,[31, 77] and unclear reporting of attrition.[31] Two trials (n=250 to 323) evaluated fixed duration triple compared with dual therapy regimens (12 weeks, 24 weeks, 48 weeks).[31, 77] Two other trials[46, 51] (n=161 and 1088) evaluated response-guided duration triple therapy regimens, including one trial[46] that compared the FDA-recommended telaprevir dosing regimen (12 weeks of triple therapy followed by 12 or 36 weeks of dual therapy, depending on early virologic response) to dual therapy.[76] The fifth trial compared different durations of antiviral therapy in patients who experienced an extended rapid virologic response.[78] In all evaluated triple therapy regimens, telaprevir was administered with pegylated interferon (alfa-2a or -2b) plus ribavirin for the first eight to twelve weeks. For regimens longer than 12 weeks, dual therapy with pegylated interferon alfa-2a or -2b plus ribavirin without telaprevir was continued for the remainder of the regimen.

Table 7. Trials of triple therapy with pegylated interferon alfa-2b, ribavirin, and telaprevir

Trial Country Study Name N Quality	Population Characteristics	Telaprevir Dose / Duration	Weekly Pegylated interferon Dose	Daily Ribavirin Dose	Overall Duration of Therapy (weeks)	Sustained Virologic Response
Hezode, 2009 [77] Europe N=209 Quality: Fair	A vs. B vs. C vs. D Age (median): 46 vs. 44 vs. 45 vs. 45 years Female: 33% vs. 40% vs. 45% vs. 44% Non-White race: 7% vs. 7% vs. 1% vs. 7% Genotype 1: 100% Cirrhosis: 0% vs. 0% vs. 1% vs. 0% Minimal or no fibrosis: 43% vs. 37% vs. 40% vs. 34% Elevated transaminases: Not reported	A. 750 mg tid weeks 1-12 B. 750 mg tid weeks 1-12 C. 750 mg tid weeks 1-12 D. placebo	Alfa-2a 180 mcg	A. 1000-1200 mg B. 1000-1200 mg C. placebo D. 1000-1200 mg	A. 12 B. 24 C. 12 D. 48	A. 69% B. 60% C. 36% D. 46%
Jacobson, 2011 [46] Worldwide N=1088 Quality: Good	A vs. B vs. C Age (median): 49 vs. 49 vs. 49 years Female: 41% vs. 42% vs. 42% Non-White race: 10% vs. 13% vs. 12% Genotype 1: 100% Cirrhosis: 6% overall Minimal or no fibrosis: 28% overall Elevated transaminases: Not reported	A. 750 mg tid weeks 1-8 B. 750 mg tid weeks 1-12[b] C. placebo	Alfa-2a 180 mcg	1000-1200 mg	A. 24/48[a] B. 24/48[a] C. 48	A. 69% B. 75%[b] C. 44%
Marcellin, 2011 [51] Europe N=161 Quality: Fair	A vs. B vs. C vs. D Age (median): 47 vs. 46 vs. 40 vs. 49 years Female: 50% vs. 52% vs. 48% vs. 51% Non-White race: 10% vs. 10% vs. 10% vs. 8% Genotype 1: 100% Cirrhosis: 2.5% vs. 2.4% vs. 0 vs. 5.1% Minimal or no fibrosis: 39% overall Elevated transaminases: Not reported	A. 750 mg tid weeks 1-12 B. 750 mg tid weeks 1-12^ C. 1125 mg bid weeks 1-12 D. 1125 mg bid weeks 1-12	A. Alfa-2a 180 mcg B. Alfa-2b 1.5 mcg/kg C. Alfa-2a 180 mcg D. Alfa-2a 1.5 mcg/kg	A. 1000-1200 mg B. 800-1200 mg C. 1000-1200 mg D. 800-1200 mg	24/48[c]	A. 85% B. 81%^ C. 83% D. 82%

Trial Country Study Name N Quality	Population Characteristics	Telaprevir Dose / Duration	Weekly Pegylated interferon Dose	Daily Ribavirin Dose	Overall Duration of Therapy (weeks)	Sustained Virologic Response
McHutchison, 2009 [22] U.S. PROVE1 N=3070 Quality: Fair	A vs. B vs. C vs. D Age (median): 49 vs. 50 vs. 49 vs. 49 years Female: 32% vs. 39% vs. 29% vs. 43% Non-White race: 24% vs. 24% vs. 24% vs. 21% Cirrhosis: 0% Minimal or no fibrosis: 31% (overall) Elevated transaminases: Not reported	A. 750 mg tid weeks 1-12 B. 750 mg tid weeks 1-12 C. 750 mg tid weeks 1-12 D. placebo	Alfa-2a 180 mcg	1000-1200 mg	A. 12 B. 24 C. 48 D. 48	A. 35% B. 61% C. 67% D. 41%
Sherman, 2011 [78] U.S. Name: ILLUMINATE n=322 Quality: Fair	A vs. B Age (median): 51 vs. 50 years Female: 36% vs. 39% Non-White race: 17% vs. 18% Cirrhosis: 11% vs. 8% Minimal or no fibrosis: 27% (overall) Elevated transaminases: Not reported	A. 750 mg tid weeks 1-12 B. 750 mg tid weeks 1-12 Patients with eRVR, randomized at week 20	Alfa-2a 180 mcg	1000-1200 mg	A.24 B.48	A. 92% B. 88%

Abbreviations: bid, two times daily; eRVR=extended rapid virologic response; HCV, hepatitis C virus; NA, not applicable; TCP, telaprevir; tid, three times daily.
Cirrhosis=METAVIR F4, Ishak 5-6, or equivalent. Minimal or no fibrosis=METAVIR F0-F1, Ishak 0-2, or equivalent
[a] Response guided duration: 24 weeks of pegylated interferon/ribavirin if HCV RNA negative from week 4 through week 12. 48 weeks if positive at week 4 through 12
[b] Dosing regimen recommended by the U.S. Food and Drug Administration for telaprevir.
[c] Response guided duration: 24 weeks of pegylated interferon/ribavirin if HCV RNA negative from week 4 through week 20. 48 weeks if positive at any point from week 4 through week 20.

Two trials found the 24 week fixed duration triple therapy with pegylated interferon alfa-2a, ribavirin, and telaprevir associated with increased likelihood of achieving an SVR compared with 48 weeks of dual therapy (pooled RR 1.48, 95% CI 1.20 to 1.83; I^2=0%) (Figure 10), but no difference between the 12 week fixed duration triple therapy regimen compared with 48 weeks of dual therapy (pooled RR 1.19, 95% CI 0.86 to 1.64; I^2=14%) (Figure 11).[31, 77] The pooled absolute increase in SVR rates for the 24 week regimen compared with dual therapy for 48 weeks was 21 percentage points (95% CI 10 to 32 percentage points). One of the trials also found a 48 week triple therapy regimen with telaprevir associated with similar likelihood of SVR compared with a 24 week triple therapy regimen (RR 1.1, 95% CI 0.87 to 1.4).[31] The other trial also found a twelve week triple therapy regimen of telaprevir plus pegylated interferon without ribavirin associated with a non-statistically significant trend towards lower likelihood of

achieving an SVR compared with pegylated interferon alfa-2a plus ribavirin for 48 weeks (RR 0.77, 95% CI 0.53 to 1.1).[77]

Figure 10. Sustained virologic response, triple therapy with pegylated interferon alfa-2a, ribavirin, and telaprevir for 12 weeks followed by dual therapy for 12 weeks compared with dual therapy with pegylated interferon alfa-2a plus ribavirin for 48 weeks in patients with genotype 1 infection

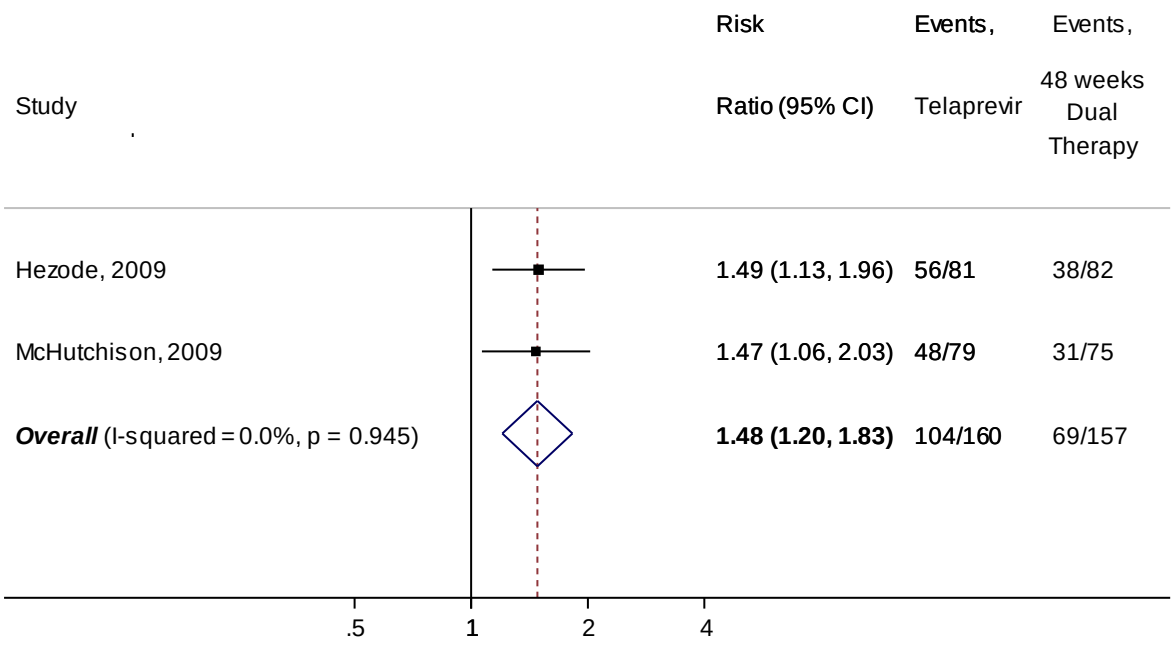
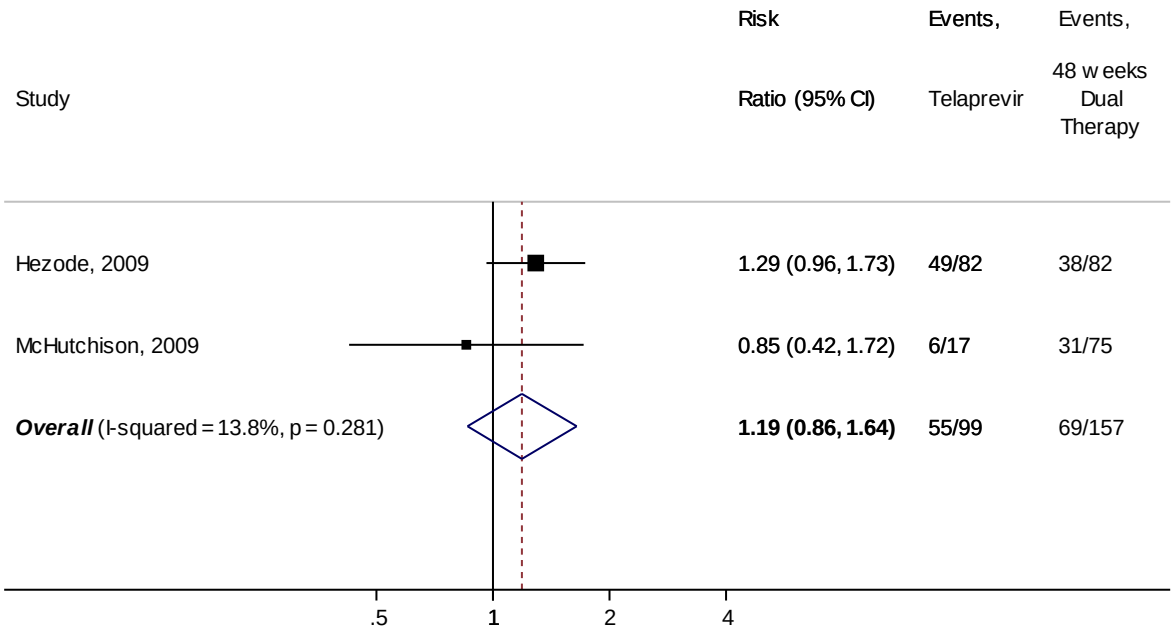


Figure 11. Sustained virologic response, triple therapy with pegylated interferon alfa-2a, ribavirin, and telaprevir for 12 weeks compared with dual therapy with pegylated interferon alfa-2a plus ribavirin for 48 weeks in patients with genotype 1 infection



One trial compared response-guided duration triple therapy with telaprevir compared with dual therapy.[46] Patients were randomized to 8 weeks of initial triple therapy with pegylated interferon alfa-2a, ribavirin, and telaprevir, 12 weeks of initial triple therapy, or dual therapy with pegylated interferon alfa-2a plus ribavirin. In the telaprevir arms, patients with an extended rapid viral response (HCV RNA undetectable between weeks 4 and 12) continued pegylated interferon plus ribavirin for a total of 24 weeks, while those without an extended rapid viral response continued dual therapy for a total of 48 weeks. Patients randomized to dual therapy received pegylated interferon alfa-2a plus ribavirin for a fixed duration of 48 weeks. Both telaprevir treatment-guided response regimens were associated with higher SVR rates compared with dual therapy (69%, 75%, and 44% for 8 weeks of telaprevir, 12 weeks of telaprevir, and dual therapy, respectively; $p<0.001$ for either telaprevir regimen vs. dual therapy), with an absolute increase in SVR rate ranging from 25 to 31 percentage points for triple therapy compared with dual therapy. Compared with dual therapy, the relative risk for achieving an SVR in the combined telaprevir arms was 1.6 (95% CI 1.4 to 1.9).

One trial of response-guided triple therapy with telaprevir (24 or 48 weeks, based on absence or presence of HCV RNA from weeks 4 through 20) found similar SVR rates (81% to 85%) for regimens that varied on telaprevir dose (750 mg tid vs. 1125 mg bid) and type of pegylated interferon (alfa-2a or alfa-2b).[51] Another trial of patients with an extended rapid virologic response to initial triple therapy with telaprevir reported similar, high (92% and 88%) SVR rates in patients randomized to a total of 24 or 48 weeks of therapy, meeting the study's pre-defined non-inferiority threshold.[78]

Key Question 2b. How does the comparative effectiveness of antiviral treatment for intermediate outcomes vary according to patient subgroup characteristics, including but not limited to HCV genotype, age, race, sex, stage of disease or genetic markers?

- The largest randomized trial (n=3070) of dual therapy with pegylated interferon alfa-2a plus ribavirin versus dual therapy with pegylated interferon alfa-2b plus ribavirin found no clear differences in relative risk estimates for SVR in genotype 1 patients stratified by race, sex, age, baseline fibrosis stage, or baseline viral load, although absolute SVR rates for either pegylated interferon were lower in older patients (38%), black patients (23% to 26%), persons with advanced fibrosis or cirrhosis (21% to 24%), and persons with high baseline viral load (35% to 36%).(strength of evidence:moderate)Four randomized trials of dual therapy with pegylated interferon alfa-2a plus ribavirin versus dual therapy with pegylated interferon alfa-2b plus ribavirin found no clear differences in relative risk estimates for SVR in patients stratified by genotype, although absolute rates of SVR were lower by 24 to 42 percentage points in genotype 1 infection compared with genotypes 2 and 3 infection. (strength of evidence:moderate)
- Two trials of triple therapy with boceprevir for 48 weeks (four weeks of dual therapy lead-in with pegylated interferon plus ribavirin followed by 44 weeks of triple therapy with pegylated interferon, ribavirin, and boceprevir) found no difference in relative risk estimates for SVR in men compared with women, and no clear difference in relative risk estimates for black patients compared with non-black patients, although the absolute SVR rate was lower in black patients (53%) compared with non-black patients (63% to 78%).(strength of evidence:moderate)
- Two trials found triple therapy with pegylated interferon alfa-2b, ribavirin, and boceprevir asssociated with higher likelihood of achieving SVR than dual therapy with pegylated interferon alfa-2b plus ribavirin in patients with high baseline HCV RNA viral load (>600,000 or ≥800,000 IU/mL), but found no difference in likelihood of SVR in patients with lower viral load. (strength of evidence:moderate)
- One trial of response-guided triple therapy with telaprevir (12 weeks of pegylated interferon alfa-2a, ribavirin, and telaprevir followed by response-guided dual therapy with pegylated interferon alfa-2a and ribavirin) vs. dual therapy with pegylated interferon plus ribavirin for 48 weeks found no clear differences in relative risk estimates in patients stratified by age, sex, race, baseline fibrosis status, or body mass index, although absolute SVR rates were higher in persons younger than 45 years compared with those older (83% vs. 70%), whites compared with black patients (75% vs. 62%), persons with no or minimal fibrosis compared with advanced fibrosis or cirrhotics (81% vs. 62%), and those with body mass index <25 compared with those with higher body mass index (83% vs. 69%).(strength of evidence:low)
- Two trials found triple therapy with pegylated interferon alfa-2a, ribavirin, and telaprevir associated with higher likelihood of achieving an SVR than dual therapy with pegylated interferon alfa-2a plus ribavirin in patients with high baseline HCV RNA viral load

(≥800,000 IU/mL), but found no difference in patients with lower viral load. (strength of evidence:moderate)

Dual Therapy with Pegylated Interferon Alfa-2a plus Ribavirin compared with Pegylated Interferon Alfa-2b plus Ribavirin

Five trials of dual therapy with pegylated interferon alfa-2a plus ribavirin compared with pegylated interferon alfa-2b evaluated SVR rates in patients subgroups defined by demographic and clinical characteristics (Appendix H: Evidence Table 1 and Evidence Table 2).[20-23, 50] The largest study (n=3070), the IDEAL trial, which only enrolled patients with genotype 1 infection, reported no clear differences in relative risk estimates for SVR dual therapy with pegylated interferon alfa-2b plus ribavirin vs. dual therapy with pegylated interferon alfa-2a plus ribavirin in patients stratified by race (RR 0.88 for black patients, 95% CI 0.59 to 1.3 and RR 0.98 for whites, 95% 0.84 to 1.2), sex (RR 0.92, 95% CI 0.77 to 1.1 for males and RR 1.1, 95% CI 0.86 to 1.3 for females), age (RR 0.95, 95% CI 0.77 to 1.2 for <40 years and RR 0.99, 95% CI 0.88 to 1.1 for age >40 years), baseline fibrosis (RR 0.88, 95% CI 0.53 to 1.4 for METAVIR F3 or F4 and RR 0.97, 95% CI 0.87 to 1.1 for METAVIR F0 to F2), and baseline viral load (RR 0.99, 95% CI 0.87 to 1.1 for HCV RNA >600,000 IU/mL and RR 0.93, 95% CI 0.79 to 1.1 for HCV RNA <=600,000 IU/mL).[22] However, absolute SVR rates across dual therapy regimens were lower in older (38%) compared with younger (53% to 56%) persons, black patients (23 to 26%) compared with white patients (53% to 55%), patients with F3 or F4 (21% to 24%) compared with F0 to F2 fibrosis (42 to 44%), and patients with high (35% to 36%) compared with low viral load (61% to 66%). The relative risk estimate was somewhat lower for patients 75 to 85 kg (RR 0.80, 95% CI 0.65 to 0.98) compared with other weight groups (RRs ranged from 0.89 to 1.1) but the confidence intervals for the estimates overlapped, and results were confounded by differential ribavirin dosing according to weight.

Four smaller (n=183 to 320) trials found no clear differences in relative risk estimates in patients stratified by genotype, although rates of SVR were lower by 24 to 42 percentage points with genotype 1 infection compared with genotypes 2 and 3 infection.[20, 21, 23, 50] One of these trials also found no clear differences in relative risk estimates in patient groups stratified by presence or absence of cirrhosis, or high or low viral load.[20]

Two trials that compared different durations of therapy in patients with genotype 2 or 3 infection reported risk estimates for SVR stratified by patient characteristics.[59, 61] They found no differences in relative risk estimates for 16 weeks of therapy versus 24 weeks of therapy when patients were stratified according to fibrosis stage, body mass index, sex, or age (all RR estimates close to 1). Although the pooled estimates suggested lower likelihood of SVR with 16 compared with 24 weeks of therapy in patients with HCV RNA >800,000 IU/mL (pooled RR 0.84, 95% CI 0.77 to 0.93; I^2=0%) but no difference in those with a viral load less than 800,000 IU/mL (pooled RR 0.99, 95% CI 0.93 to 1.06; I^2=0%) the estimates were imprecise and the confidence intervals overlapped.[59, 61]

Another large trial that compared 48 compared with 24 weeks of dual therapy with pegylated interferon alfa-2a plus ribavirin found similar rates of SVR in patients with genotype 2 or 3 infection regardless of baseline viral load.[62]

Triple Therapy with pegylated interferon (alfa-2a or -2b), ribavirin, and boceprevir or telaprevir

Boceprevir

Two trials (n=520 and 1097) of triple therapy with boceprevir for a total of 48 weeks (4 weeks dual therapy lead-in with pegylated interferon alfa-2b plus ribavirin followed by the addition of 44 weeks of boceprevir) compared with 48 weeks of dual therapy with pegylated interferon alfa-2b plus ribavirin found no difference in relative risk estimates for SVR in men (pooled RR 1.8, 95% CI 1.6 to 2.2; I^2=0%) compared with women (pooled RR 1.9, 95% CI 1.3 to 2.8; I^2=57%).[30, 32] There was also no clear difference in the relative risk estimates for black (pooled RR 2.5, 95% CI 1.5 to 4.2; I^2=0%) and non-black patients (pooled RR 1.7, 95% CI 1.5 to 2.0; I^2=0%), although the absolute SVR rate was lower in black (53%) compared with non black (63% to 78%) patients. The relative risk estimate was higher for patients with HCV RNA viral load >600-800,000 IU/mL at baseline (pooled RR 2.0; 95% CI 1.7 to 2.3; I^2=0%) compared with those with a lower viral load (pooled RR 1.3; 95% CI 1.0 to 1.5; I^2=0%), with an absolute SVR rate of 63% to 73% in persons with a high viral load and 85% to 91% in persons with a lower viral load. Although triple therapy with boceprevir was not associated with improved likelihood of SVR in the subgroup of patients with advanced fibrosis or cirrhosis, the number of patients randomized to triple therapy was small (n=30) and the estimate was imprecise (pooled RR=1.1; 95% CI 0.55 to 2.1; I^2=0%).

Telaprevir

One trial (n=1088) of response-guided duration triple therapy with telaprevir (12 weeks of pegylated interferon alfa-2a, ribavirin, and telaprevir followed by response-guided duration dual therapy) compared with 48 weeks of dual therapy with pegylated interferon alfa-2a plus ribavirin found no clear differences in relative risk estimates in patients stratified by age, sex, race, baseline fibrosis status, or body mass index.[46] Absolute SVR rates were higher in persons younger than 45 years compared with those older (83% vs. 70%), white patients compared with black patients (75% vs. 62%), persons with no or minimal fibrosis compared with those with advanced fibrosis or cirrhotics (81% vs. 62%), and those with body mass index <25 compared with those with higher body mass index (83% vs. 69%). Triple therapy was more effective than dual therapy in patients with a baseline HCV RNA viral load ≥800,000 IU/mL (RR=2.0, 95% CI 1.7 to 2.4), but there was no difference in likelihood of achieving an SVR in those with a baseline viral load <800,000 IU/mL (RR 1.1, 95% CI 0.93 to 1.3), with triple therapy associated with similar absolute SVR rates across viral load strata (78% and 74%).

Another trial of patients with an extended rapid virologic response on triple therapy with telaprevir reported similar, high (80% to 90%) SVR rates with either 12 compared with 36 additional weeks of dual therapy in patients stratified by race, body mass index, or fibrosis stage.[78]

Key Question 3a. What are the comparative harms associated with antiviral treatments?

- Dual therapy with pegylated interferon alfa-2b was associated with slightly greater risk of headache (3 trials, pooled RR 1.2, 95% CI 1.1 to 1.3, I^2=0%) and myalgia (2 trials,

pooled RR 1.2, 95% CI 1.0 to 1.4, I^2=0%) and slightly lower risk of rash (2 trials, pooled RR 0.80, 95% CI 0.71 to 0.89; I^2=0%) compared with dual therapy with pegylated interferon alfa-2a plus ribavirin, with no differences in risk of serious adverse events or withdrawals due to adverse events. (strength of evidence: moderate)

- Triple therapy with boceprevir for 48 weeks (pegylated interferon alfa-2b plus ribavirin for 4 weeks followed by addition of boceprevir for 44 weeks) weeks was associated with increased risk of neutropenia (2 trials, pooled RR 1.8, 95% CI 1.5 to 2.3, I^2=0%), dysgeusia (2 trials, pooled RR 2.5, 95% CI 2.0 to 3.2, I^2=0%), anemia (2 trials, pooled RR 2.0, 95% CI 1.4 to 2.8, I^2=0%), and thrombocytopenia (2 trials, pooled RR 3.3, 95% CI 1.3 to 8.6) compared to dual therapy with pegylated interferon alfa-2b plus ribavirin. The incidence of anemia was about 50% with triple therapy and the incidence of neutropenia about 25%, with severe anemia in 4% to 5% and severe neutropenia in 8% to 15%. (strength of evidence: moderate)
- In two trials, there were no statistically significant differences between a twelve week regimen of triple therapy with pegylated interferon alfa-2a, ribavirin, and telaprevir compared with dual therapy with pegylated interferon alfa-2a plus ribavirin in risk of any assessed adverse event. (strength of evidence: moderate)
- In two trials, there was a 24 week regimen of triple therapy with telaprevir (pegylated interferon alfa-2a, ribavirin, and telaprevir for 12 weeks followed by pegylated interferon alfa-2a plus ribavirin for 12 weeks) was associated with increased risk of anemia (2 trials, pooled RR 1.5, 95% CI 1.0 to 2.1, I^2=0%), decreased risk of myalgia (2 trials, pooled RR 0.56, 95% CI 0.34 to 0.93, I^2=0%), and increased risk of rash (2 trials, pooled RR 1.4, 95% CI 1.1 to 1.8) compared with dual therapy with pegylated interferon alfa-2a plus ribavirin for 48 weeks, and trends towards increased risk of withdrawal due to adverse events (RR estimate around 2), primarily due to rash. Among patients randomized to the 24 week telaprevir regimen, one-half to three-quarters of patients experienced a rash (7% to 11% experienced a severe rash) and 27% to 37% experienced anemia (4% experienced severe anemia).(strength of evidence: moderate)
- In one trial, response-guided triple therapy with telaprevir (pegylated interferon alfa-2a, ribavirin, and telaprevir for 8 or 12 weeks followed by response-guided pegylated interferon alfa-2a and ribavirin) was associated with increased risk of withdrawal due to adverse events (27% vs. 7.2%, RR 3.8, 95% CI 2.6 to 5.7), anemia (38% vs. 19%, RR 2.0, 95% CI 1.6 to 2.5), any rash (36% vs. 24%, RR 1.5 , 95% CI 1.2 to 1.8), and severe rash (5% vs. 1%, RR 4.6, 95% CI 1.6 to 13) compared with dual therapy with pegylated interferon alfa-2a plus ribavirin for 48 weeks.(strength of evidence: low)

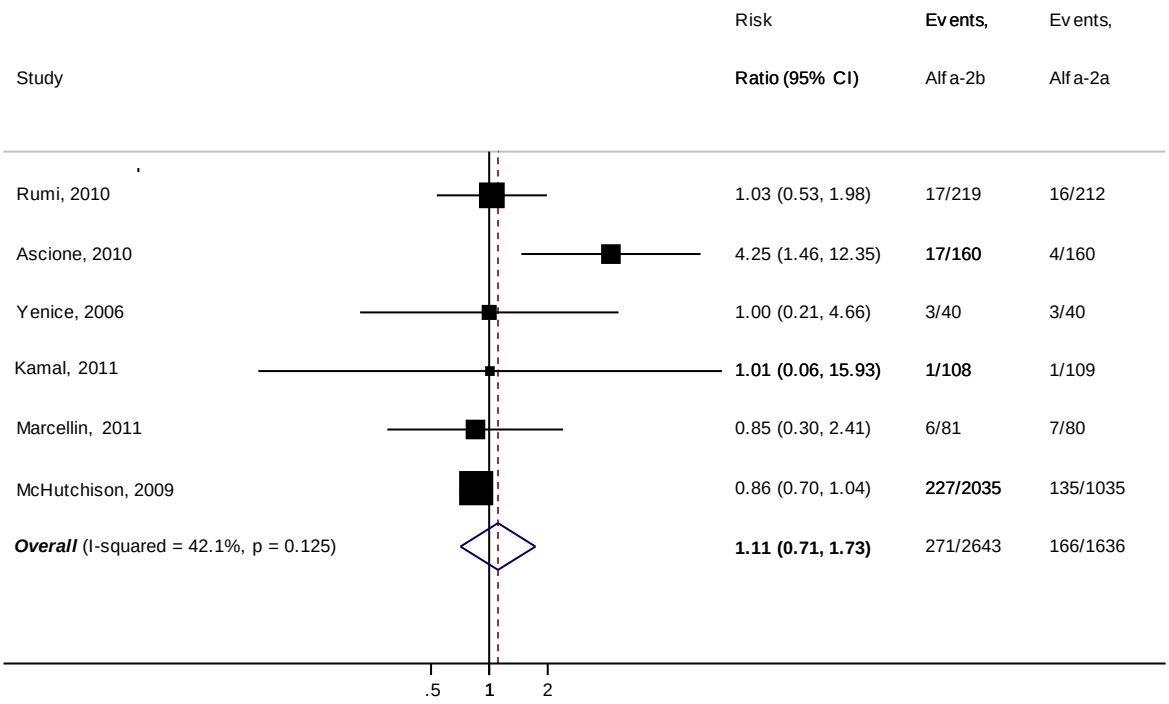
Dual Therapy with Pegylated Interferon Alfa-2b plus Ribavirin compared with Dual Therapy with Pegylated Interferon Alfa-2a plus Ribavirin

Six head-to-head randomized trials of dual therapy with pegylated interferon alfa-2b plus ribavirin compared with dual therapy with pegylated interferon alfa-2a plus ribavirin reported adverse events (Table 8, Appendix H: Evidence Table 1 and Evidence Table 2).[20-23, 51, 52] Characteristics of the trials were described earlier (see Key question 2a).

There was no difference between dual therapy with pegylated interferon alfa-2b compared with dual therapy with pegylated interferon alfa-2a in risk of withdrawal due to adverse events (6

trials, pooled RR 1.1, 95% CI 0.71 to 1.7; I^2=42%) (Figure 12).[20-23, 51, 52] In the largest study, the IDEAL trial, about 13% of patients randomized to dual therapy with standard doses pegylated interferon alfa-2b or pegylated interferon alfa-2a plus ribavirin withdrew due to adverse events, compared with about 10% in those randomized to low-dose pegylated interferon alfa-2b plus ribavirin.[22] Excluding the low-dose pegylated interferon alfa-2b arm of IDEAL from the pooled analysis resulted in a similar pooled estimate (6 trials, RR 1.1, 95% CI 0.77 to 1.7; I^2=31%).[20-23, 51, 52] One outlier trial found dual therapy with pegylated interferon alfa-2b associated with substantially higher risk of withdrawal due to adverse events compared with dual therapy with pegylated interferon alfa-2a (RR 4.2, 95% CI 1.5 to 12).[20] Excluding it also had little effect on the pooled estimate, although statistically heterogeneity was eliminated (5 trials, RR 0.97, 95% CI 0.79 to 1.2, I^2=0%).

Figure 12. Withdrawal due to adverse events, dual therapy with pegylated interferon alfa-2b plus ribavirin compared with dual therapy with pegylated interferon alfa-2a plus ribavirin



Serious adverse events were only reported in two trials.[22, 23] They found dual therapy with pegylated interferon alfa-2b plus ribavirin associated with decreased risk compared with dual therapy with pegylated interferon alfa-2a plus ribavirin (pooled RR 0.74, 95% CI 0.57 to 0.95, I^2=0%).[22, 23] In the IDEAL trial, serious treatment-related adverse events occurred in about 4% of patients.[22] There were no statistically significant differences between regimens in risk of neutropenia, thrombocytopenia, depression, fatigue, or flu-like symptoms (Table 8). Dual therapy with pegylated interferon alfa-2b plus ribavirin was associated with slightly greater risk of headache (three trials, pooled RR 1.2, 95% CI 1.1 to 1.3, I^2=0%)[20, 22, 51] and myalgia (two trials, pooled RR 1.2, 95% CI 1.0 to 1.4, I^2=0%),[20, 22] and slightly lower risk of rash (2 trials,

pooled RR 0.80, 95% CI 0.71 to 0.89, I^2=0%)[22, 51] compared with dual therapy with pegylated interferon alfa-2a plus ribavirin. In the IDEAL trial, dual therapy with either pegylated interferon (alfa-2a or 2b) was associated with fatigue in about 65% of patients, headache in about 45%, nausea in about 40%, and myalgia in about 25%, neutrophil count <500/mm^3 in about 5%, and hemoglobin <8.5 g/dL in about 3%.[22]

Table 8. Harms: Dual therapy with pegylated interferon alfa-2b plus ribavirin compared with dual therapy with pegylated interferon alfa-2a plus ribavirin

Outcome	RR (95% CI); I^2	Number of Trials
All-cause mortality	RR 0.85, 95% CI 0.26 to 2.8	1[22]
Serious adverse events	RR 0.74 (0.57 to 0.95); I^2=0%	2[22, 23]
Withdrawal due to adverse events	RR=1.1 (0.69 to 1.8); I^2=54%	5[20-23, 51, 52]
Neutropenia	RR 0.70 (0.48 to 1.0); I^2=45%	5[20-23, 51]
Anemia	RR 0.94 (0.68 to 1.3); I^2=64%	4[20, 22, 23, 51]
Thrombocytopenia	RR 0.74 (0.32 to 1.7); I^2=0%	2[20, 23]
Depression	RR 1.1 (0.94 to 1.2); I^2=0%	3[20, 22, 51]
Fatigue	RR 1.0 (0.98 to 1.1); I^2=0%	3[20, 22, 51]
Flu-like symptoms	RR 1.1 (0.79 to 1.6); I^2=70%	2[23, 51]
Headache	RR 1.2 (1.1 to 1.3); I^2=0%,	3[20, 22, 51]
Myalgia	RR 1.2 (1.0 to 1.4); I^2=0%	2[20, 22]
Rash	RR 0.80 (0.71 to 0.89); I^2=0%	2[22, 51]

Abbreviations: RR, relative risk.

Excluding data from patients who received pegylated interferon alfa-2b at a dose of 1.0 mcg/kg/week in the IDEAL trial[22] had little effect on pooled results, except the pooled estimate for depression became greater and statistically significant in favor of dual therapy with pegylated interferon alfa-2a (3 trials, RR 1.2, 95% CI 1.0 to 1.4; I^2=0%).[20, 22, 51] In addition, the decreased risk of neutropenia with dual therapy with pegylated interferon alfa-2b plus ribavirin became statistically significant, although the point estimate was unchanged (5 trials, pooled RR 0.71, 95% CI 0.51 to 0.98, I^2=30%).[20-23, 51] Excluding poor quality trials[21, 52] from the pooled analyses also had little effect on estimates. Excluding two trials[22, 51] with differential dosing of ribavirin for pegylated interferon alfa-2a and pegylated interferon alfa-2b eliminated statistical heterogeneity in the analysis of neutropenia, but the risk estimate was unchanged (3 trials, pooled RR 0.75, 95% CI 0.53 to 1.1; I^2=0%).[20, 21, 23]

Trials of triple therapy with pegylated interferon (alfa-2a or alfa-2b), ribavirin, and boceprevir or telaprevir

Four trials compared triple therapy with pegylated interferon (alfa-2a or -2b), ribavirin, and boceprevir or telaprevir compared with dual therapy with pegylated interferon (alfa-2a or -2b) plus ribavirin without a protease inhibitor in patients with genotype 1 infection and reported adverse events (Appendix H: Evidence Table 3 and Evidence Table 4).[30-32, 77] Characteristics of the trials were described earlier (see Key Question 2a).

Boceprevir

For boceprevir, two trials evaluated a 48-week fixed duration regimen consisting of dual therapy lead-in for 4 weeks with pegylated interferon alfa-2b plus ribavirin, with the addition of

from weeks 5 through 48.[30, 32] Triple therapy was associated with increased risk of neutropenia (2 trials, pooled RR 1.8, 95% CI 1.5 to 2.3, I^2=0%), dysgeusia (2 trials, pooled RR 2.5, 95% CI 2.0 to 3.2, I^2=0%), anemia (two trials, pooled RR 2.0, 95% CI 1.4 to 2.8, I^2=0%), and thrombocytopenia (2 trials, pooled RR 3.3, 95% CI 1.3 to 8.6, I^2=0%) compared with dual therapy with pegylated interferon alfa-2b plus ribavirin (Table 9). About 50% of patients on triple therapy experienced anemia and about 25% neutropenia, with an incidence of severe neutropenia (neutrophil count <500 cells per μL) that ranged from 8% to 15% and an incidence of severe anemia (hemoglobin <80 or <85 g/L) of 4% to 5%. In addition, more patients randomized to boceprevir triple therapy used erythropoietin (43% and 87%) compared with those randomized to dual therapy (24% and 33%), which could have attenuated the risk estimate for anemia. One of the trials reported similar use of granulocyte stimulating agents with boceprevir triple therapy and dual therapy (8% vs. 6%).[32] There was no statistically significant difference between triple therapy and dual therapy in risk of withdrawal due to adverse events, serious adverse events, depression, fatigue, headache, myalgia, chills/rigors, rash, or flu-like symptoms (Table 9).

Table 9. Harms: Triple therapy with boceprevir, pegylated interferon alfa-2b, and ribavirin compared with dual therapy with pegylated interferon alfa-2b plus ribavirin

Outcome	Triple therapy with pegylated interferon and ribavirin for 48 weeks with boceprevir from weeks 5 to 48 vs. dual therapy for 48 weeks: RR (95% CI); I^2	Number of Trials
Serious adverse events	RR 1.4 (0.93 to 2.2)	1[32]
Withdrawal due to adverse events	RR 1.1 (0.77 to 1.4); I^2=0%	2[30, 32]
Neutropenia	RR 1.8 (1.5 to 2.3); I^2=0%	2[30, 32]
Anemia	RR 2.0 (1.4 to 2.8); I^2=0%	2[30, 32]
Thrombocytopenia	RR 3.3 (1.3 to 8.6); I^2=0%),	2[30, 32]
Depression	RR 0.87 (0.65 to 1.2)	1[32]
Fatigue	RR 1.1 (0.82 to 1.5); I^2=82%	2[30, 32]
Flu-like symptoms	RR 0.80 (0.58 to 1.1); I^2=27%	2[30, 32]
Headache	RR 1.1 (0.96 to 1.3); I^2=0%	2[30, 32]
Myalgia	RR 0.97 (0.76 to 1.2)	1[32]
Rash	RR 1.1 (0.81 to 1.4)	1[32]
Dysgeusia	RR 2.5 (2.0 to 3.2); I^2=0%	2[30, 32]

Abbreviations: RR, relative risk.

Telaprevir

For fixed duration triple therapy with telaprevir (administered during the first 12 weeks in combination with pegylated interferon and ribavirin), we focused on 12 or 24 week regimens, as 48 week triple therapy regimens have not been shown to be more effective than 24 weeks.[31, 78] There were no differences between a twelve week regimen of triple therapy with telaprevir compared with dual therapy with pegylated interferon alfa-2a plus ribavirin for 48 weeks in risk of serious adverse events, neutropenia, anemia, depression, fatigue, headache, myalgia, chills/rigors, rash, or flu-like symptoms (Table 10). Rash was reported in 44% to 77% of patients randomized to 12 weeks of triple therapy with telaprevir, with 6% of patients reporting severe rash.[31, 77]

Table 10. Harms: Triple therapy with telaprevir, pegylated interferon (alfa-2a or alfa-2b), and ribavirin compared with dual therapy with pegylated interferon (alfa-2a or alfa-2b) plus ribavirin

Outcome	12-week regimen with telaprevir vs. dual therapy for 48 weeks: RR (95% CI); I^2	Number of trials	24-week regimen with telaprevir vs. dual therapy for 48 weeks: RR (95% CI); I^2	Number of Trials
All-cause mortality	No deaths reported	No deaths reported	No deaths reported	No deaths reported
Serious adverse events	RR 1.3 (0.68 to 2.5)	1[77]	RR 1.0, 95% CI 0.50 to 2.0)	**1**[77]
Withdrawal due to adverse events	RR 1.5 (0.56 to 4.0)	1[77]	RR 1.9 (0.72 to 4.8)	1[77]
Neutropenia	RR 0.11 (0.01 to 1.8)	1[31]	RR 0.58 (0.29 to 1.1)	1[31]
Anemia	RR 1.2 (0.72 to 1.9); I^2=0%	2[31, 77]	Pooled RR 1.5, 95% CI 1.0 to 2.1, I^2=0%)	2[31, 77]
Thrombocytopenia	Not reported	Not reported	Not reported	Not reported
Depression	RR 0.89 (0.53 to 1.5); I^2=0%	2[31, 77]	RR 1.0 (0.66 to 1.6); I^2=0%	2[31, 77]
Fatigue	RR 0.94 (0.63 to 1.4); I^2=61%	2[31, 77]	RR 0.94 (0.63 to 1.4); I^2=61%	2[31, 77]
Flu-like symptoms	RR 0.76 (0.56 to 1.0); I^2=0%	2[31, 77]	RR 0.93 (0.82 to 1.6); I^2=67%	2[31, 77]
Headache	RR 0.87 (0.65 to 1.2); I^2=0%	2[31, 77]	RR 0.87 (0.65 to 1.2); I^2=0%	2[31, 77]
Myalgia	RR 0.71 (0.40 to 1.3); I^2=0%	2[31, 77]	RR 0.56 (0.34 to 0.93); I^2=0%	2[31, 77]
Rash	RR 1.2 (0.92 to 1.7); I^2=0%	2[31, 77]	RR 1.4 (1.1 to 1.8); I^2=0%	2[31, 77]

Abbreviations: RR, relative risk.

A 24-week regimen of triple therapy with telaprevir was associated with increased risk of anemia (2 trials, pooled RR 1.5, 95% CI 1.0 to 2.1, I^2=0%),[31, 77] decreased risk of myalgia (2 trials, pooled RR 0.56, 95% CI 0.34 to 0.93, I^2=0%), and increased risk of rash (2 trials, pooled RR 1.4, 95% CI 1.1 to 1.8, I^2=0%) compared with dual therapy for 48 weeks, but there were no statistically significant differences in risk of serious adverse events, neutropenia, depression, fatigue, headache, chills/rigors, or flu-like symptoms (Table 10). One-half to three-quarters of patients randomized to the 24 week regimen with telaprevir experienced a rash, with the incidence of severe rash 7% to 11%.[31,77] The incidence of anemia with telaprevir was 27% to 37%,[31, 77] with one trial[77] reporting severe anemia in 4%. There was a trend towards increased risk of withdrawal due to adverse events in one trial (13% vs. 7%, RR 1.9, 95% CI 0.74 to 4.8), primarily due to rash.[77] The other trial did not report withdrawal due to adverse events separately for the 24 week telaprevir regimen, but reported a similar trend towards higher risk of withdrawal due to adverse events for all telaprevir regimens combined (12, 24, or 48 weeks) compared with dual therapy (21% vs. 11%, RR 2.0, 95% CI 0.97 to 4.1).[31]

One trial evaluated triple therapy with telaprevir for 8 or 12 weeks followed by response-guided dual therapy for 12 or 36 weeks compared with dual therapy.[46] Since the two telaprevir regimens were associated with similar rates of harms, results were combined.[46] The trial found response-guided therapy with telaprevir associated with increased risk of withdrawal due to adverse events (27% vs. 7.2%, RR 3.8, 95% CI 2.6 to 5.7), anemia (38% vs. 19%, RR 2.0, 95% CI 1.6 to 2.5), any rash (36% vs. 24%, RR 1.5 , 95% CI 1.2 to 1.8), and severe rash (5% vs. 1%, RR 4.6, 95% CI 1.6 to 13) compared with dual therapy for 48 weeks.

A trial of extended early virologic responders (undetectable HCV RNA levels at weeks 4 and 12) to telaprevir triple therapy reported very similar rates of adverse events in patients randomized to 4 compared with 28 more weeks of dual therapy.[78] The overall incidence of rash was 38% (severe rash 5%) and the incidence of anemia 42% (severe anemia 6%).

Key Question 3b. Do these harms differ according to patient subgroup characteristics, including HCV genotype, age, race, sex, stage of disease, or genetic markers?

- No trial of dual therapy with pegylated interferon alfa-2b plus ribavirin vs. dual therapy with pegylated interferon alfa-2a plus ribavirin reported harms in patients stratified by factors such as HCV genotype, age, race, sex, stage of disease, or genetic markers.
- Three trials that restricted enrollment to patients with genotype 1 infection reported risk estimates for risk of harms that were similar to the risk estimates based on all trials. (strength of evidence: insufficient)No trials evaluated harms associated with triple therapy with pegylated interferon, ribavirin, and boceprevir or telaprevir versus dual therapy with pegylated interferon plus ribavirin in patient subgroups. All trials evaluated patients with genotype 1 infection. (strength of evidence: insufficient)
- No trial reported harms in patients stratified by factors such as HCV genotype, age, race, sex, stage of disease, or genetic markers. A subgroup of three trials of dual therapy with pegylated interferon alfa-2a compared with pegylated interferon alfa-2b that restricted enrollment to patients with genotype 1 infection reported pooled estimates for risk of harms that were similar to the risk estimates based on all trials.[22, 51, 52] All trials of triple therapy including protease inhibitors restricted enrollment to patients with genotype 1 infection.

Key Question 4: Have improvements in intermediate outcomes (SVR, histologic changes) been shown to reduce the risk or rates of adverse health outcomes from HCV infection?

- A single trial of patients with genotype 1 infection found that 48 weeks of triple therapy with boceprevir using low dose of ribavirin (400-1000 mg daily) associated with a non-statistical trend towards lower likelihood of SVR compared to 48 weeks of triple therapy with a standard ribavirin dose (800-1400 mg daily) (36% vs 50%, RR 0.71, 95% CI 0.39 to 1.3) A large Veterans Affairs (VA) study that controlled well for potential confounders found achieving an SVR associated with lower risk of all-cause mortality compared with not achieving an SVR (adjusted HR 0.71 [0.60-0.86], 0.62 [0.44-0.87] and 0.51 [0.35-0.75] for genotypes 1, 2, and 3, respectively).
- Sixteen other cohort studies found achieving an SVR associated with decreased risk of all-cause mortality, liver-related mortality, hepatocellular carcinoma, and other complications of end-stage liver disease compared with not achieving an SVR, with stronger effect estimates than the VA study (adjusted HRs generally ranged from around 0.10 to 0.33). However, the studies had methodological shortcomings, including

inadequate handling of confounders, and 9 were conducted in Asia. (strength of evidence: moderate)

- Nine studies found achieving an SVR associated with greater improvement in measures related to quality of life (generic or disease-specific) 24 weeks after the end of antiviral treatment, with differences averaging less than 5 to 10 point on various SF-36 domains. All studies were poor-quality and were characterized by failure to adjust for confounders, high loss to followup, and failure to blind patients to SVR status.(strength of evidence: low).

All-Cause Mortality, Liver-Related Mortality, and Complications Related to Chronic Hepatitis C Virus Infection

Seventeen cohort studies evaluated the association between achieving an SVR following interferon-based antiviral therapy and mortality (all-cause or liver-related) or complications related to chronic HCV infection, such as hepatocellular carcinoma, ascites, hepatic encephalopathy, or gastrointestinal bleeding and reported risk estimates adjusted for potential confounders (Table 11, Appendix H: Evidence Table 9 and Evidence 12).[8, 9, 79-93] Sample sizes ranged from 105 to 16,864 subjects and duration of followup ranged from 3 to 9 years. Nine studies were conducted in Asia.[79, 85-90, 92, 93] Four studies focused on patients who received pegylated interferon (alfa-2a or 2b) plus ribavirin.[8, 9, 81, 84] The others evaluated patients who received non-pegylated interferon plus ribavirin, or either pegylated or non-pegylated interferon monotherapy. Eight studies[8, 79, 82, 87-89, 92, 93] evaluated general populations of HCV patients treated with antiviral therapy (baseline rate of cirrhosis ranged from 3% to 20%) and nine studies[9, 80, 81, 83-86, 90, 91] focused on patients with advanced fibrosis or cirrhosis at the time of antiviral treatment (six studies[80, 83-86, 90] only enrolled patients with cirrhosis and the baseline rate of cirrhosis ranged from 21% to 77% in three others[9, 81, 91]).

All studies had methodological shortcomings (Appendix H: Evidence Table 9, Evidence Table 10, Evidence Table 13, and Evidence Table 14). Eight studies were rated poor quality and the remainder fair quality.[82-84, 89-93] Although all of the studies reported adjusted risk estimates, only six[8, 79, 81, 85-87] of the seventeen studies evaluated five key potential confounders (at least age, sex, genotype, viral load, and fibrosis stage). No study clearly described assessment of outcomes blinded to SVR status, and only four studies[8, 84, 87, 90] reported the number of patients who met inclusion criteria but were excluded due to missing data or loss to followup.

For general populations of HCV patients treated with antiviral therapy, the largest study (n=16,864) had the fewest methodological shortcomings and was also conducted in the U.S. (Table 11).[8] It adjusted for multiple potential confounders, including age, sex, viral load, presence of cirrhosis, multiple comorbidities, AST and ALT levels, and others; and stratified results by genotype. In a predominantly male (>95%) population of veterans, it found SVR after antiviral therapy associated with decreased risk of all-cause mortality compared with no SVR, after a median followup of 3.8 years (adjusted HR 0.71 [0.60 to 0.86], 0.62 [0.44 to 0.87] and 0.51 [0.35 to 0.75] for genotypes 1, 2, and 3, respectively). Although point estimates showed somewhat smaller effects for genotype 1 compared with genotypes 2 or 3, the confidence intervals for the three genotypes overlapped. Clinical outcomes other than mortality were not assessed.

Seven other studies also evaluated the association between achieving an SVR and mortality or hepatic complications in general populations of HCV patients (Table 11).[79, 82, 87-89, 92, 93] One Australian study (poor quality) found no statistically significant association between virologic

response status (SVR, response-relapse, or non-response) and all-cause mortality, liver-related mortality, or hepatocellular carcinoma, although trends favored the SVR group.[82] The other six studies (three poor quality), all conducted in Asia, each found achieving an SVR associated with substantially lower risk of all-cause mortality, liver-related mortality, or hepatocellular carcinoma compared with no SVR.[79, 87-89, 92, 93] Five studies reported substantially lower risk for all-cause mortality than the U.S. study described above (adjusted HR range 0.12 to 0.39).[79, 87, 89, 92, 93] For liver-related mortality, four studies[79, 87, 89, 92] reported adjusted HRs that ranged from 0.04 to 0.17 and for hepatocellular carcinoma, three studies reported adjusted HRs that ranged from of 0.19 to 0.36.[79, 88, 93]

Six studies of European or North American populations (two poor quality) evaluated the association between achieving an SVR after antiviral therapy and clinical outcomes in patients with advanced fibrosis and cirrhosis prior to antiviral treatment (Table 11).[9, 80, 81, 83, 84, 91] One study (fair quality) found achieving an SVR associated with decreased risk of all-cause mortality or liver transplantation compared with no SVR (adjusted HR 0.17, 95% CI 0.06 to 0.46).[9] Another study (poor quality) found achieving an SVR associated with decreased risk of all-cause mortality (adjusted HR 0.31, 95% CI 0.07 to 1.4).[91] Four studies found achieving an SVR associated with decreased risk of liver-related mortality and hepatocellular carcinoma compared with not achieving an SVR (adjusted HRs ranged from 0.12 to 0.27 and from 0.19 to 0.46, respectively).[9, 80, 81, 91] For complications of chronic HCV infection (variably defined), six studies reported adjusted HRs that ranged from 0.13 to 0.38.[9, 80, 81, 83, 84, 91] Results from three Asian studies[85, 86, 90] (one poor quality) were consistent with the North American and European studies. One study[90] found achieving an SVR associated with lower risk of all-cause mortality compared with no SVR (adjusted HR 0.07, 95% CI 0.09 to 0.56) and three studies[85, 86, 90] found achieving an SVR associated with lower risk of hepatocellular carcinoma compared with no SVR (adjusted HR range 0.18 to 0.40).

One study stratified results according to presence or absence of cirrhosis of baseline. Although effects of achieving an SVR compared with not achieving an SVR on all-cause mortality appeared more favorable in patients with cirrhosis compared with those without cirrhosis, estimates were imprecise and confidence intervals overlapped substantially, precluding strong conclusions.[92]

The only study to evaluate the association between improvement in histological outcomes and clinical outcomes did not meet inclusion criteria because it did not report adjusted risk estimates.[94] In 96 patients with chronic HCV infection and cirrhosis, it found regression of cirrhosis (defined as a decrease in METAVIR fibrosis score from 4 to <=2) after interferon-based therapy associated with decreased risk of liver-related events (ascites, hepatic encephalopathy, variceal bleeding, spontaneous bacterial peritonitis, hepatocellular carcinoma, or liver transplantation) or death (0 vs. 4 events/100 patients-years, p=0.002) after a median followup of 10.5 years. Transplantation-free survival was 100% in patients with regression of cirrhosis compared with 74% in those without regression (p=0.02). In addition to failure to analyze potential confounders, the study only included patients who underwent a post-treatment biopsy, which could have resulted in selection bias, and cirrhosis regression only occurred in 13 patients, resulting in low precision.

Table 11. Sustained virologic response and clinical outcomes

Author Country N Quality	Comparison Definition of Sustained Virologic Response	Population Characteristics	Treatments	Results
Arase (2007)[79] Japan N=500 Quality: Fair	SVR vs. no SVR SVR=Undetectable HCV RNA 6 months after completion of long-term IFN therapy	SVR (n=140) vs. no SVR (n=360) Mean age (years): 63 vs. 64 (p=0.07) Female: 41% vs. 53% (p=0.01) Race: Not reported Genotype 1b: 34% vs. 71% (p<0.0001) Viral load (kIU/ml): 172 vs. 661 (p<0.0001) Cirrhosis (Knodell F4): 9% vs. 16% (p=0.009)	Interferon-2a or Interferon-2b monotherapy: 94% Interferon plus ribavirin combination therapy: 6%	SVR vs. no SVR Hepatocellular cancer: Adjusted HR 0.19 (0.08-0.45) All-cause mortality: Adjusted HR 0.39 (0.16-0.93) Liver-related mortality: Adjusted HR 0.13 (0.03-0.59)
Backus (2011)[8] U.S. N=16,864 Quality: Fair	SVR vs. no SVR SVR=Undetectable HCV RNA 6 months after completion of antiviral therapy	SVR vs. no SVR (genotypes 1 [n=12,166], 2 [n=2904], and 3 [n=1794], respectively) Mean age (years): 51 vs. 52, 53 vs. 53. and 51 vs. 51 Female: 5% vs. 4%, 4% vs. 3%, and 4% vs. 3% Non-white: 40% vs. 51%, 33% vs. 31%, and 30% vs. 29% Genotype: Results stratified by genotype Viral load >=500,000 IU/mL: 70% vs. 82%, 78% vs. 83%, and 64% vs. 68% Cirrhosis: 9% vs. 15%, 7% vs. 12%, and 12% vs. 20%	Pegylated interferon (alfa-2a or -2b) plus ribavirin	SVR vs. no SVR (genotypes 1, 2, and 3, respectively) All-cause mortality: Adjusted HR 0.71 (0.60-0.86), 0.62 (0.44-0.87), and 0.51 (0.35-0.75)
Bruno (2007)[80] Italy N=883 Quality: Fair	SVR vs. no SVR SVR=Undetectable HCV RNA 6 months after completion of antiviral therapy	SVR (n=124) vs. no SVR (n=759) Mean age (years): 53 vs. 44 (p=0.004) Female: 27% vs. 38% (p<0.001) Non-White: 0 (0%) vs. 0 (0%) Race: Not reported Genotypes 1 and 4: 37% vs. 63% (p<0.001) Viral load: Not reported Cirrhosis: All (inclusion criterion)	Interferon monotherapy	SVR vs. no SVR Ascites, encephalopathy, or gastrointestinal bleeding: Not calculated, 0 events/1061 person-years vs. 107 events/5703 person-years (1.88 events/100 person-years) Hepatocellular carcinoma: Adjusted HR 0.39 (0.17-0.88) Liver-related mortality: 0.14 (0.04-0.59)

Author Country N Quality	Comparison Definition of Sustained Virologic Response	Population Characteristics	Treatments	Results
Cardoso (2010)[81] France N=307 Quality: Fair	SVR vs. no SVR SVR=Undetectable HCV RNA 6 months after completion of antiviral therapy	SVR (n=103) vs. no-SVR (n=204) Mean age (years): 55 vs. 55 (p=0.93) Female: 30% vs. 34% (p=0.51) Race: Not reported Genotype 1: 36% vs. 72% (p<0.001) Viral load (log_{10} I/mI): 5.5 vs. 5.7 (p=0.08) Cirrhosis (METAVIR F4): 53% vs. 61% (p=0.19)	Pegylated interferon (alfa-2a or -2b) and ribavirin: 252 (82%) Pegylated interferon monotherapy: 22 (7%) Non-pegylated interferon with or without ribavirin: 33 (11%)	SVR vs. no SVR Hepatocellular carcinoma: Adjusted HR 0.33 (0.23-0.89) Ascites or variceal bleeding: Adjusted HR 0.21 (0.05-0.92) Liver-related mortality: Adjusted HR 0.27 (0.08-0.95)
Coverdale (2004)[82] Australia N=343 Quality: Poor	SVR vs. response relapse vs. nonresponse SVR=Undetectable HCV RNA on at least 2 occasions at least 2 years after completion of therapy	Demographics for all treated patients (not reported by SVR status) Median age (years): 37 Female: 33% Race: Not reported Genotype 1: 38% Viral load: Not reported Median fibrosis score (Scheuer): 2	Interferon-2a or Interferon-2b	SVR vs. response-relapse vs. nonresponse Liver-related complications (hepatic decompensation, complications of portal hypertension, hepatocellular carcinoma, liver transplantation, and liver-related mortality) at 10 years: Not statistically significant in multivariate analysis, adjusted HR not reported (p=0.06) Hepatocellular carcinoma at 10 years: Not statistically significant in multivariate analysis, adjusted HR and p value not reported Liver transplant or liver-related death at 10 years: Not statistically significant in multivariate analysis, adjusted HR not reported (p=0.20)

Author Country N Quality	Comparison Definition of Sustained Virologic Response	Population Characteristics	Treatments	Results
Di Marco (2007) [95] Italy N=102 Quality: Fair	SVR vs. no-SVR SVR=undetectable HCV-RNA 24 weeks after completion of antiviral therapy maintained throughout the remaining documented followup	Monotherapy (n=51) vs. Combination therapy (n=51) Mean age: 56±8.1 vs. 57±6.6 Female: 18 (35%) vs. 19 (37%)	Patients randomly assigned to receive pegylated interferon alfa-2b or pegylated interferon alfa-2b + ribavirin	Liver-related clinical events (increase of Child score =2 points, ascites, portosystemic encephalopathy, Hepatocellular carcinoma) SVR vs. no-SVR: 1/16 (6.2%) vs. 33/86 (38.3%), p=0.03
El Braks (2007) [83] France N=113 Quality:Poor	SVR vs. no SVR SVR=Undetectable HCV RNA 6 months after completion of antiviral therapy	SVR (n=37) vs. no SVR (n=76) Mean age (years): 51 vs. 56 (p=0.02) Female: 16% vs. 50% (p=0.0005) Race: Not reported HCV genotype 1: 36% vs. 73% (p=0.0001) Viral load: Not reported Cirrhosis: All (inclusion criterion)	Interferon monotherapy: 35/113 (31%) Interferon + ribavirin: 40/113 (35%) Pegylated interferon + ribavirin: 38/113 (34%)	SVR (n=37) vs. no SVR (n=76) Clinical events (hepatocellular cancer, ascites, hepatic encephalopathy, or death): Adjusted HR 0.14 (0.04-0.45)
Fernandez-Rodriguez (2010) [84] Spain N=509 Quality: Poor	SVR vs. no SVR SVR=Undetectable HCV RNA 6 months after completion of antiviral therapy	SVR (n=174) vs. no SVR (n=394) Mean age (years): 51 vs. 52 (p=0.31) Female: 69% vs. 73%, p=0.37 Genotype 1: 24% vs. 55% (p=0.001) Race: Not reported Viral load (10^6 IU/ml): 1.7 vs. 3.1 (p=0.001) Cirrhosis: All (inclusion criterion)	Pegylated interferon-2a or 2b	SVR vs. no SVR Combined clinical endpoint (hepatic decompensation, upper gastrointestinal bleeding secondary to rupture of esophageal or gastric varices, hepatocellular carcinoma, liver transplantation, and liver-related or liver-unrelated mortality): Adjusted HR 0.38 (0.18-0.76)
Hasegawa (2007) [85] Japan N=105 Quality: Fair	SVR vs. no SVR SVR=Sustained undetectable HCV RNA after completion of antiviral therapy (duration of undetectability not specified)	SVR (n=48) vs. no SVR (n=58) Age >56 years: 60% vs. 55% (p>0.05) Female: 35% vs. 34% (p>0.05) Race: Not reported Genotype 1b: 19% vs. 21% (p>0.05) Viral load >=100 KIU/ml or >=1 mg/mL: 25% vs. 62% (p<0.001) Cirrhosis: All (inclusion criterion)	Natural or recombinant interferon alfa: 67% Natural interferon-beta: 31% Both: 1.6%	SVR vs. no SVR Hepatocellular carcinoma: Adjusted HR 0.18 (0.04-0.81)

Author Country N Quality	Comparison Definition of Sustained Virologic Response	Population Characteristics	Treatments	Results
Hung (2006) [86] Taiwan N= 132 Quality: Fair	SVR vs. no SVR SVR=Undetectable HCV RNA 6 months after completion of antiviral therapy	SVR (n=73) vs. no SVR (n=59) Mean age (years): 55 vs. 58 (p=0.07) Female: 43% vs. 54% (p=0.12) Race: Not reported Genotype 1b: 27% vs. 78% (p<0.001) Viral load >=2 x 10^6 copies/ml: 21% vs. 51% (p<0.001) Cirrhosis: 100% (inclusion criterion)	Interferon-2b plus ribavirin	SVR vs. no SVR Hepatocellular carcinoma: Adjusted HR 0.28 (0.09-0.92)
Imazeki (2003) [87] Japan N=459 Quality: Fair	SVR vs. no SVR SVR=Undetectable HCV RNA 6 months after completion of antiviral therapy	Demographics for all treated patients (not reported by SVR status) Mean age (years): 49 Female: 36% Race: Not reported Genotype 1: 74% Viral load: Not reported Cirrhosis (Desmet F4): 13%	Interferon-2a: 84% Interferon-2b: 12% Both: 4%	SVR vs. untreated and no SVR vs. untreated Liver-related mortality: Adjusted HR 0.06 (0.007-0.43) and 0.55 (0.27-1.1) All-cause mortality: Adjusted HR 0.030 (0.003-0.27) and 0.26 (0.11-0.61)
Izumi (2005) [88] Japan N=495 Quality: Fair	SVR vs. no SVR SVR=Undetectable HCV RNA 6 months after completion of antiviral therapy	Demographics for patients treated with interferon monotherapy and interferon plus ribavirin combination therapy, respectively (not reported by SVR status) Mean age (years): 52 and 58 Female: 43% and 44% Race: Not reported Genotype 1b: 71% and 80% Median viral load (kIU/ml): 470 and 680 Cirrhosis: 35% and 2%	Interferon monotherapy:69% Interferon-2b plus ribavirin combination therapy: 34%	SVR vs. no SVR Hepatocellular carcinoma: Adjusted HR 0.36 (0.04-0.83)
Kasahara (2004) [89] Japan N=2698 Quality: Poor	SVR vs. no SVR SVR=Undetectable HCV RNA 6 months after completion of antiviral therapy	SVR (n=738) vs. no-SVR (n=1930) Median age (years): 51 vs. 54 (p=0.12) Female: 31% vs. 37% (p=0.32) Race: Not reported Genotype 1: Not reported Viral load: Not reported Cirrhosis (Desmet F4): 3.0% vs. 5.4% (p=0.34)	Interferon	SVR vs. no SVR Liver-related mortality: Adjusted HR 0.04 (0.005-0.30) All-cause mortality: Adjusted HR 0.14 (0.06-0.35)

Author Country N Quality	Comparison Definition of Sustained Virologic Response	Population Characteristics	Treatments	Results
Morgan (2010)[9] U.S. Name: HALT-C N=526 Quality: Fair	SVR vs. no SVR SVR=Undetectable HCV RNA 6 months after completion of antiviral therapy	SVR (n=140) vs. breakthrough/relapse (n=77) vs. no SVR (n=309) Mean age (years): 49 vs. 49 vs. 50 (p=0.23) Female: 24% vs. 26% vs. 30% (p=0.30) Non-white: 20% vs. 20% vs. 32% (p=0.001) Genotype 1: 72% vs. 86% vs. 94% (p<0.0001) Viral load: Not reported Cirrhosis (Ishak 5 or 6): 21% vs. 31% vs. 43% (p<0.0001)	Pegylated interferon-2a-180 µg/week + ribavirin 1000-12000 mg/day for 24weeks	SVR vs. no SVR All-cause mortality or liver transplantation: Adjusted HR 0.17 (0.06-0.46) Any liver-related outcome (decompensated liver disease [ascites, variceal bleeding, hepatic encephalopathy, spontaneous bacterial peritonitis], hepatocellular carcinoma, liver transplantation, liver-related mortality): Adjusted HR 0.15 (0.06-0.38) Decompensated liver disease: Adjusted HR 0.13 (0.03-0.53) Hepatocellular carcinoma: Adjusted HR 0.19 (0.04-0.80) Liver-related mortality or liver transplantation: Adjusted HR 0.12 (0.03-0.48)
Shiratori (2005)[90] Japan N=271 Quality: Poor	SVR vs. no SVR SVR=Undetectable HCV RNA 6 months after completion of antiviral therapy	For all treated patients (not reported by SVR status) Mean age (years): 57 Female: 62% Race: Not reported Genotype 1: 75% Viral load (log_{10} copies/ml): 5.8 Cirrhosis: 100% (inclusion criterion)	Interferon alfa-2a: 58% Natural interferon alfa: 42%	SVR vs. untreated patients and no SVR vs. untreated patients Hepatocellular carcinoma: Adjusted HR 0.31 (0.16-0.61) and 0.77 (0.51-1.2) All-cause mortality: Adjusted HR 0.05 (0.006-0.34) and 0.71 (0.43-1.2)

Author Country N Quality	Comparison Definition of Sustained Virologic Response	Population Characteristics	Treatments	Results
Veldt (2004)[96] Europe N=343 Quality: Fair	SVR vs. biochemical responders SVR=no detectable HCV-RNA at the end of treatment and after 6 months followup	SVR (n=286) vs. biochemical responders (n=50) Mean age: 41 (17-72) vs. 45 (23-72), p=0.04 Female: 41% vs. 48%, p=0.35	Interferon monotherapy	Standard morality ratios SVR vs. biochemical responders 1.4 (0.3-2.5) vs. 5.6 (0.0-12.6) *No statistically significant difference in mortality between sustained virologic responders and general population, matched for age and sex Change in fibrosis SVR vs. biochemical responders 2 points progression: 3% vs. 7% 1 point progression: 3% vs. 13% No change: 65% vs. 80% 1 point regression: 21% vs. 0% 2 points regression: 8% vs. 0% Multiple regression analysis of risk factors for fibrosis progression Biochemical response vs. SVR: HR 0.31 (0.3-1.49), p<0.01 (age, fibrosis stage pretreatment, activity score pretreatment also significant)

Author Country N Quality	Comparison Definition of Sustained Virologic Response	Population Characteristics	Treatments	Results
Veldt (2007)[91] Europe and Canada N=479 Quality: Poor	SVR vs. no SVR SVR=Undetectable HCV RNA 6 months after completion of antiviral therapy	SVR (n=142) vs. no-SVR (n=337) Mean age (years): 48 vs. 49 (p=0.45) Female: 27% vs. 32% (p=0.23) Race: Not reported Genotype 1: 39% vs. 67% (p<0.001) Viral load (x10^5 IU/mL): 8.5 vs. 8.0 (p=0.75) Cirrhosis (Ishak 5 or 6): 71% vs. 77% (p=0.45)	Interferon monotherapy: 27% Interferon and ribavirin: 27% Pegylated interferon monotherapy: 2.1% Pegylated interferon and ribavirin: 43%	SVR vs. no SVR Any event (death, liver failure, and hepatocellular cancer): Adjusted HR 0.20 (0.07-0.58) All-cause mortality: Adjusted HR 0.31 (0.07-1.4) Liver-related mortality: Adjusted HR 0.19 (0.02-1.4) Hepatocellular carcinoma: Adjusted HR 0.46 (0.12-1.70)
Yoshida (2002)[92] Japan Name: IHIT N=459 Quality: Poor	SVR vs. no SVR SVR=Undetectable HCV RNA 6 months after completion of antiviral therapy	SVR (817) vs. non-SVR (1613) Mean age (years): 48 vs. 51 Female: 30% vs. 40% Race: Not reported Genotype: Not reported Viral load: Not reported Cirrhosis (Desmet F4): 6.5% vs. 11%	Interferon-alfa: 84% Interferon-beta: 14% Both: 2%	SVR vs. untreated and no SVR vs. untreated Liver-related mortality: Adjusted HR 0.050 (0.01-0.22) and 0.39 (0.22-0.68) All-cause mortality: Adjusted HR 0.15 (0.06-0.34) and 0.47 (0.29-0.76)
Yu (2006)[93] Taiwan Name: NA N=1057 Quality: Poor	SVR vs. no SVR SVR=Undetectable HCV RNA 6 months after completion of antiviral therapy	For all treated patients (not reported by SVR status) Mean age (years): 47 Female: 40% Race: Not reported Genotype 1: 46% Viral load: Not reported Cirrhosis (criteria not reported): 16%	Interferon monotherapy: 28% Interferon plus ribavirin combination therapy: 72%	SVR vs. untreated and no SVR vs. untreated Hepatocellular carcinoma: Adjusted HR 0.25 (0.13-0.46) and 0.99 (0.64-1.5) All-cause mortality: Adjusted HR 0.37 (0.14-0.99) and 1.3 (0.56-3.1)

Abbreviations: HCV, hepatitis C virus; HR, hazard ratio; NA, not applicable; SVR, sustained virologic response.

Quality of Life

Nine cohort studies evaluated the association between achieving an SVR following interferon-based antiviral therapy and outcomes related to quality of life (Table 12, Appendix H: Evidence Table 11 and Evidence Table 12).[97-105] Only one study reported adjusted risk estimates, thus we included studies that reported unadjusted risk estimates. Eight studies[97, 98, 100-105] evaluated patients originally enrolled in randomized trials of antiviral treatments.[27, 106-110] Two studies evaluated the same cohort of patients[103, 105] and one study[104] evaluated a cohort of patients included in a study[98] that reported results for three pooled cohorts. One study included patients randomized to pegylated interferon (alfa-2a or -2b) plus ribavirin, although results were not stratified according to what type of antiviral therapy was received.[101] The remainder of the studies evaluated non-pegylated interferon plus ribavirin combination therapy, or non-pegylated or pegylated interferon monotherapy.

All studies were rated poor quality (Appendix H: Evidence Table 11, Evidence Table 12, Evidence Table 15, and Evidence Table 16). Only one study adjusted for potential confounders,[97] only one reported low loss to followup,[102] and only one study reported blinding of patients to virologic outcomes.[100] Followup was at 24 weeks after treatment (typically 72 weeks from start of treatment) in all studies. No study evaluated longer-term quality of life according to SVR status.

All of the studies found patients who achieved an SVR experienced better improvement from baseline on individual SF-36 domains as well as SF-36 physical and mental component summary scores compared with those who did not achieve an SVR (Table 12). In most studies, differences between patients who achieved an SVR and those who didn't on various SF-36 domains were less than 5 to 10 points. Patients who achieved an SVR also reported greater improvements from baseline on hepatitis C specific quality of life measures (health distress and limitations) and measures related to fatigue and sleep somnolence. However, results are subject to the methodological limitations of the studies.

One study also found achieving an overall response (defined as SVR plus 2-point improvement in the Histological Activity Index) associated with improved quality of life compared with those who did not achieve an overall response.[103]

Discussion

Table 13 summarizes the findings of this review. Details about the factors used to determine the overall strength of evidence for each key question are shown in Appendix E.

Antiviral therapy for chronic hepatitis C virus (HCV) infection continues to evolve. No study has evaluated comparative effectiveness of current antiviral regimens on long-term clinical outcomes such as mortality, complications of chronic HCV infection, or quality of life. Such trials would be difficult to design and carry out due to the long time required for complications of chronic HCV infection in most patients. In fact, the first pegylated interferon was only approved by the US Food and Drug Administration (FDA) in 2001, and the initial major trials of pegylated interferon plus ribavirin published in 2002. The protease inhibitors telaprevir and boceprevir were only approved in 2011. Although some trials reported short-term (prior to one-year after the end of antiviral therapy) mortality,[22, 32, 46] few events were reported, precluding reliable conclusions about comparative effectiveness.

In lieu of direct evidence on long-term clinical outcomes, sustained virologic response (SVR) rates are the primary outcome to assess comparative benefits of different antiviral regimens. In trials of treatment-naïve patients, the likelihood of achieving an SVR was slightly lower with dual therapy with pegylated interferon alfa-2b plus ribavirin compared with dual therapy with pegylated interferon alfa-2a plus ribavirin (pooled RR 0.90, 95% CI 0.84 to 0.96), with a difference in absolute SVR rates of about seven percentage points. Although the largest study, the IDEAL trial, found no difference in SVR rates between dual therapy with pegylated interferon alfa-2a compared with dual therapy with pegylated interferon alfa-2b, findings could have been confounded by differential ribavirin dosing.[22] Nonetheless, excluding the IDEAL trial from pooled analyses resulted in similar effect estimates.

Trials found no clear differences in estimates of relative effectiveness of dual therapy with pegylated interferon alfa-2a compared with dual therapy with pegylated interferon alfa-2b in patient subgroups stratified by age, sex, race, viral load, fibrosis stage, and genotype, although absolute response rates were lower in older patients, black patients, patients with high viral load, patients with more advanced fibrosis or cirrhosis, and genotype 1 infection. SVR rates ranged from 24 to 42 percentage points lower in patients with genotype 1 infection compared with patients with genotype 2 or 3.[20, 21, 23, 50]

In patients with genotype 2 or 3 infection, there do not appear to be major differences in SVR rates between 24 weeks and either longer or shorter courses of dual therapy. Standard doses of pegylated interferon alfa-2b were more effective than lower doses (no trials compared different doses of pegylated interferon alfa-2a). Although trials comparing different ribavirin doses found no clear differences, they evaluated different dose comparisons, precluding firm conclusions. Differences in harms between dual therapy with pegylated interferon alfa-2a compared with pegylated interferon alfa-2b were relatively small, with no differences in serious adverse events or withdrawals due to adverse events.

The relatively low SVR rates with pegylated interferon plus ribavirin dual therapy for genotype 1 infection (present in about three-quarters of U.S. patients with HCV infection) has led to ongoing efforts to identify more effective treatment alternatives. Recent trials found triple therapy regimens with boceprevir or telaprevir, pegylated interferon (alfa-2a or -2b), and ribavirin each associated with substantially higher SVR rates than standard dual therapy with pegylated interferon (alfa-2a or -2b) plus ribavirin in treatment-naïve patients with genotype 1 infection, with SVR rates with triple therapy approaching the 70 to 80 observed for dual therapy

in patients with genotype 2 or 3 infection.[30-32, 46, 51, 77, 78] Trials evaluating the FDA telaprevir regimen recommended by the FDA (12 weeks of triple therapy with telaprevir followed by response guided duration of 12 or 36 weeks of dual therapy) reported SVR rates of 75% to 80%.[46, 51] Trials evaluating the FDA-recommended boceprevir regimen for antiretroviral-naïve patients with cirrhosis (4 weeks of dual therapy lead-in followed by 44 weeks of triple therapy with boceprevir) reported SVR rates of 66% to 75%.[30, 32] Trials that evaluated other regimens in antiretroviral naïve patients, including fixed duration telaprevir regimens, shorter fixed duration triple therapy boceprevir therapy, and boceprevir without dual therapy lead-in, reported similar or lower SVR rates. The SVR rates with various antiviral regimens or placebo are summarized in Table 13.

Table 12. Sustained virologic response rates with different antiviral regimens for hepatitis C virus infection

Regimen	Sustained Virologic Response Rate 6 Months after Treatment (%)	Approximate Number Needed to Treat to Achieve One Sustained Virologic Response compared with Placebo	References
Placebo	<2	Not applicable	Poynard et al., 1996[12]
Interferon monotherapy	6-16	7-25	Chander, 2002[10] Kjaegard, 2000[11] Poynard et al., 1996[12] Shepherd et al., 2000[13]
Interferon plus ribavirin	33-41	2.6-3.2	Chander, 2002[10] Kjaergard et al., 2001[11] Shepherd et al., 2000[13]
Pegylated interferon plus ribavirin	54-61 overall, 42-52 in patients with genotype 1 infection	1.7-1.9 overall; 2.0-2.5 for genotype 1 infection	Shepherd et al., 2005[111] Siebert et al., 2005[112] Zaman et al., 2003[113]
Pegylated interferon plus ribavirin plus boceprevir or telaprevir[a]	66-80 (genotype 1 infection only)	1.3-1.6 (genotype 1 infection only)	Jacobson, 2011[46] Kwo et al, 2010[30] Marcellin, 2011[51] Poordad et al, 2011[32]

[a] Based on FDA-recommended regimens evaluated in trials of antiretroviral-naïve patients

The boceprevir regimen recommended by the FDA[76] for antiretroviral-naïve patients without baseline cirrhosis (4 weeks of dual therapy lead-in with pegylated interferon plus ribavirin followed by the addition of boceprevir for 24 weeks for virologic responders at weeks 8 to 24, or 4 weeks of dual therapy lead-in followed by the addition of boceprevir for 32 weeks and then 12 additional weeks of dual therapy for late virologic responders) has not been evaluated in a trial of antiretroviral-naïve patients. Rather, the FDA recommendation was based on a trial of previous partial responders to pegylated interferon plus ribavirin which found slightly higher SVR rates in late virologic responders who received 32 weeks of triple therapy followed by 12 weeks of dual therapy compared with those who received 44 weeks of triple therapy, each following 4 weeks of dual therapy lead-in (79% vs. 73%).[114]

As in the head-to-head trials of dual therapy with pegylated interferon alfa-2a plus ribavirin compared with pegylated interferon alfa-2b plus ribavirin, relative risk estimates were similar (or there was no clear difference) in patient subgroups based on age, sex, race, although absolute SVR rates were lower in older patients and black patients. Triple therapy with either boceprevir or telaprevir was no more effective than dual therapy in the subgroup of patients with lower HCV RNA viral load (<600,000 or <800,000 IU/mL).[30, 32, 46] There was insufficient evidence to evaluate relative effectiveness of triple compared with dual therapy based on fibrosis stage.

In addition to higher likelihood of SVR, another advantage of triple therapy regimens in patients with genotype 1 infection is the potential for shorter duration (24 or 28 weeks in patients with early virologic response compared with the standard 48 weeks of dual therapy with pegylated interferon plus ribavirin). Shorter courses of treatment would likely be of high relevance to patients, given the high frequency of bothersome flu-like symptoms associated with interferon-based therapy. On the other hand, triple therapy regimens were associated with increased risk of certain harms, in particular hematological adverse events (neutropenia, anemia, and thrombocytopenia) with boceprevir and rash (including severe rash in <10% of patients that could result in treatment discontinuation) with telaprevir. However, there was no clear increase in risk of serious adverse events with use of protease inhibitors, and the adverse events appear to be self-limited following drug discontinuation.

The strongest evidence on the association between achieving an SVR and improved clinical outcomes is a large U.S. Department of Veterans Affairs (VA) cohort study (n=16,864) that adjusted for many confounders and found decreased risk of all-cause mortality compared with no SVR across patient groups stratified by genotype (adjusted HR 0.71 [0.60-0.86], 0.62 [0.44-0.87] and 0.51 [0.35-0.75] for genotypes 1, 2, and 3, respectively).[8] Sixteen other cohort studies also found achieving an SVR associated with decreased risk of all-cause mortality and hepatic complications associated with chronic HCV infection, including studies of populations specifically of patients with baseline cirrhosis, but had more methodological shortcomings. In addition, nine of the sixteen studies were conducted in Asia, where the incidence of hepatocellular carcinoma in patients with chronic HCV infection is higher than in the United States,[41] potentially limiting their generalizability. Other studies found patients who achieved SVR had higher scores on various measures of quality of life compared with those with no SVR, but focused on short-term outcomes, and typically did not adjust for confounders or blind patients to SVR status when assessing outcomes.

Table 13. Summary of evidence on comparative effectiveness of treatment for hepatitis C

Key Question	Outcome	Summary of Evidence	Strength of Evidence
Key Question 1a What is the comparative effectiveness of antiviral treatment in improving health outcomes in patients with HCV infection?	**Long-term clinical outcomes**	No evidence.	Insufficient
	Short-term mortality	Three trials that compared current antiviral regimens [a] found no differences in risk of short-term mortality, but reported very few (20 total) events.	Low
	Short-term quality of life	One open-label randomized trial of patients with genotype 4 infection found dual therapy with pegylated interferon alfa-2a plus ribavirin associated with slightly better short-term scores on some quality of life assessments compared with dual therapy with pegylated interferon alfa-2b plus ribavirin.	Low
Key Question 1b How does the comparative effectiveness of antiviral treatment for health outcomes vary according to patient subgroup characteristics?	**Any clinical outcome**	No evidence.	Insufficient

Key Question	Outcome	Summary of Evidence	Strength of Evidence
Key Question 2a What is the comparative effectiveness of antiviral treatments on intermediate outcomes?		***Dual therapy with pegylated interferon alfa-2b plus ribavirin vs. dual therapy with pegylated interferon alfa-2a plus ribavirin***	
	Sustained virologic response	Seven trials of patients with genotype 2 or 3 infection found dual therapy with standard doses of pegylated interferon alfa-2b plus ribavirin associated with lower likelihood of achieving an SVR than pegylated interferon alfa-2a plus ribavirin (pooled RR 0.88, 95% CI 0.81 to 0.96; I^2=37%), with an absolute difference in SVR rates of 7.8 percentage points (95% CI 2.2 to 13.4 percentage points).	Moderate
		Dual therapy with pegylated interferon alfa-2a or -2b plus ribavirin: duration effects	
	Sustained virologic response	Two trials of patients with genotype 2 or 3 infection found no difference in likelihood of achieving an SVR between 48 versus 24 weeks of dual therapy with pegylated interferon alfa-2a plus ribavirin (pooled RR 0.97, 95% CI 0.84 to 1.1; I^2=43%)	Moderate
	Sustained virologic response	Three trials of patients with genotype 2 or 3 infection found no differences between 24 versus 12-16 weeks of dual therapy with pegylated interferon alfa-2a plus ribavirin (pooled RR=0.88, 95% CI 0.76 to 1.0; I^2=86%). Relative risk estimates ranged from 0.75 to 0.99 in the three trials and may have varied in part due to different methods of ribavirin dosing.	Moderate
	Sustained virologic response	Three trials of patients with genotype 2 or 3 infection with a rapid virologic response (undetectable HCV RNA by week 4) found no differences between 24 versus 12-16 weeks of dual therapy with pegylated interferon (alfa-2a or alfa-2b) plus ribavirin (pooled RR=0.99, 95% CI 0.86 to 1.1, I^2=66%). Relative risk estimates ranged from 0.89 to 1.1.	Moderate
		Dual therapy with pegylated interferon alfa-2a or -2b plus ribavirin: dose effects	
	Sustained virologic response	Five trials of patients with genotype 2 or 3 infection found lower doses of pegylated interferon alfa-2b (0.75-1.0 mcg/kg or 50 mcg) associated with lower likelihood of achieving an SVR than higher doses (1.5 mcg/kg or 100-150 mcg) (pooled RR 0.86; 95% CI 0.76 to 0.98; I^2=17%).	Moderate
	Sustained virologic response	Three trials of patients with genotype 2 or 3 infection who did not specifically have advanced fibrosis or cirrhosis found no clear difference in likelihood of SVR between lower doses of ribavirin (400 or 800 mg flat dose or 600 to 800 mg weight-based dose) compared with higher doses (800 or 1200 mg flat dose or 800 to 1400 mg weight-based dose).	Moderate

Key Question	Outcome	Summary of Evidence	Strength of Evidence
	Sustained virologic response	One small trial (n=124) of patients with genotype 2 or 3 infection and advanced fibrosis or cirrhosis (Ishak stage 4-6) found 1000 to 1200 mg daily of ribavirin associated with greater likelihood of SVR compared with 600 to 800 mg daily (72% vs. 45%; p=0.002).	Low
		Triple therapy with pegylated interferon alfa-2b, ribavirin, and boceprevir vs. dual therapy with pegylated interferon alfa-2b plus ribavirin	
	Sustained virologic response	Two trials of patients with genotype 1 infection found triple therapy with boceprevir (pegylated interferon alfa-2b plus ribavirin for 4 weeks, followed by the addition of boceprevir for 44 weeks) associated with higher likelihood of SVR compared with dual therapy with pegylated interferon alfa-2b plus ribavirin therapy for 48 weeks (pooled RR 1.8; 95% CI 1.6 to 2.1; I^2=0%), with an absolute increase in SVR rate of 31 percentage points (95% CI 23 to 39 percentage points).	Moderate
	Sustained virologic response	A single trial of patients with genotype 1 infection found that 48 weeks of triple therapy with boceprevir using low dose of ribavirin (400-1000 mg daily) associated with a non-statistical trend towards lower likelihood of SVR compared to 48 weeks of triple therapy with a standard ribavirin dose (800-1400 mg daily) (36% vs 50%, RR 0.71, 95% CI 0.39 to 1.3)	Low
		Triple therapy with pegylated interferon alfa-2b, ribavirin, and telaprevir vs. dual therapy with pegylated interferon alfa-2b plus ribavirin	
	Sustained virologic response	Two trials of patients with genotype 1 infection found triple therapy with telaprevir for 24 weeks (12 weeks of pegylated interferon alfa-2a, ribavirin, and telaprevir followed by 12 weeks of pegylated interferon alfa-2a plus ribavirin) associated with higher likelihood of SVR compared with dual therapy with pegylated interferon alfa-2a plus ribavirin for 48 weeks (pooled RR 1.5, 95% CI 1.2 to 1.8; I^2=0%), with an absolute increase in SVR rate of 21 percentage points (95% confidence interval 10 to 32 percentage points).	Moderate
	Sustained virologic response	One trial of patients with genotype 1 infection found no difference in likelihood of SVR between triple therapy with pegylated interferon, ribavirin, and telaprevir for 12 weeks versus dual therapy with pegylated interferon alfa-2a plus ribavirin for 48 weeks.	Moderate

Key Question	Outcome	Summary of Evidence	Strength of Evidence
	Sustained virologic response	One trial of patients with genotype 1 infection found triple therapy with telaprevir (pegylated interferon alfa-2a, ribavirin, and telaprevir for 8 or 12 weeks followed by response-guided dual therapy with pegylated interferon alfa-2a plus ribavirin for an additional 12 or 36 weeks) associated with higher likelihood of SVR compared with dual therapy with pegylated interferon alfa-2a plus ribavirin for 48 weeks (RR 1.6, 95% CI 1.4 to 1.9), with an absolute increase in SVR rate ranging from 25 to 31 percentage points. The regimen with 8 weeks of telaprevir was associated with a slightly lower SVR rate than the 12 week telaprevir regimen (69% vs. 75%).	Low
		Triple therapy with pegylated interferon alfa-2b, ribavirin, and telaprevir: duration effects	
	Sustained virologic response	One trial of patients with genotype 1 infection found no difference in likelihood of SVR between triple therapy with telaprevir for 48 weeks (12 weeks of triple therapy with pegylated interferon alfa-2a, ribavirin, and telaprevir followed by 36 weeks of dual therapy with pegylated interferon alfa-2a plus ribavirin) and triple therapy with telaprivir for 24 weeks (12 weeks of triple therapy followed by 12 weeks of dual therapy).	Low
	Sustained virologic response	One trial of patients with an extended rapid virologic response to initial triple therapy with telaprevir reported similar, high (92% and 88%) SVR rates in patients randomized to a total of 24 or 48 weeks of therapy.	Low
Key Question 2b How does the comparative effectiveness of antiviral treatment for intermediate outcomes vary according to patient subgroup characteristics?		***Dual therapy with pegylated interferon alfa-2b plus ribavirin vs. dual therapy with pegylated interferon alfa-2a plus ribavirin***	
	Sustained virologic response	The largest randomized trial (n=3070) of dual therapy with pegylated interferon alfa-2a plus ribavirin versus dual therapy with pegylated interferon alfa-2b plus ribavirin found no clear differences in relative risk estimates for SVR in genotype 1 patients stratified by race, sex, age, baseline fibrosis stage, or baseline viral load, although absolute SVR rates for either pegylated interferon were lower in older patients (38%), black patients (23% to 26%), persons with advanced fibrosis or cirrhosis (21% to 24%), and persons with high baseline viral load (35% to 36%).	Moderate

Key Question	Outcome	Summary of Evidence	Strength of Evidence
	Sustained virologic response	Four randomized trials of dual therapy with pegylated interferon alfa-2a plus ribavirin versus dual therapy with pegylated interferon alfa-2b plus ribavirin found no clear differences in relative risk estimates for SVR in patients stratified by genotype, although absolute rates of SVR were lower by 24 to 42 percentage points in genotype 1 infection compared with genotypes 2 and 3 infection.	Moderate
		Triple therapy with pegylated interferon alfa-2b, ribavirin, and boceprevir vs. dual therapy with pegylated interferon alfa-2b plus ribavirin	
	Sustained virologic response	Two trials of triple therapy with boceprevir for 48 weeks (four weeks of dual therapy lead-in with pegylated interferon plus ribavirin followed by 44 weeks of triple therapy with pegylated interferon, ribavirin, and boceprevir) found no difference in relative risk estimates for SVR in men compared with women, and no clear difference in relative risk estimates for black patients compared with non-black patients, although the absolute SVR rate was lower in black patients (53%) compared with non-black patients (63% to 78%).	Moderate
	Sustained virologic response	Two trials found triple therapy with pegylated interferon alfa-2b, ribavirin, and boceprevir asssociated with higher likelihood of achieving SVR than dual therapy with pegylated interferon alfa-2b plus ribavirin in patients with high baseline HCV RNA viral load (>600,000 or ≥800,000 IU/mL), but found no difference in likelihood of SVR in patients with lower viral load.	Moderate
		Triple therapy with pegylated interferon alfa-2b, ribavirin, and telaprevir vs. dual therapy with pegylated interferon alfa-2b plus ribavirin	
	Sustained virologic response	One trial of response-guided triple therapy with telaprevir (12 weeks of pegylated interferon alfa-2a, ribavirin, and telaprevir followed by response-guided dual therapy with pegylated interferon alfa-2a and ribavirin) vs. dual therapy with pegylated interferon plus ribavirin for 48 weeks found no clear differences in relative risk estimates in patients stratified by age, sex, race, baseline fibrosis status, or body mass index, although absolute SVR rates were higher in persons younger than 45 years compared with those older (83% vs. 70%), whites compared with black patients (75% vs. 62%), persons with no or minimal fibrosis compared with advanced fibrosis or cirrhotics (81% vs. 62%), and those with body mass index<25 compared with those with higher body mass index(83% vs. 69%).	Low

Key Question	Outcome	Summary of Evidence	Strength of Evidence
	Sustained virologic response	Two trials found triple therapy with pegylated interferon alfa-2a, ribavirin, and telaprevir associated with higher likelihood of achieving an SVR than dual therapy with pegylated interferon alfa-2a plus ribavirin in patients with high baseline HCV RNA viral load (≥800,000 IU/mL), but found no difference in patients with lower viral load.	Moderate
Key Question 3a What are the comparative harms associated with antiviral treatments?		***Dual therapy with pegylated interferon alfa-2b plus ribavirin vs. dual therapy with pegylated interferon alfa-2a plus ribavirin***	
	Harms	Dual therapy with pegylated interferon alfa-2b was associated with slightly greater risk of headache (3 trials, pooled RR 1.2, 95% CI 1.1 to 1.3, I^2=0%) and myalgia (2 trials, pooled RR 1.2, 95% CI 1.0 to 1.4, I^2=0%) and slightly lower risk of rash (2 trials, pooled RR 0.80, 95% CI 0.71 to 0.89; I^2=0%) compared with dual therapy with pegylated interferon alfa-2a plus ribavirin, with no differences in risk of serious adverse events or withdrawals due to adverse events.	Moderate
		Triple therapy with pegylated interferon alfa-2b, ribavirin, and boceprevir vs. dual therapy with pegylated interferon alfa-2b plus ribavirin	
	Harms	Triple therapy with boceprevir for 48 weeks (pegylated interferon alfa-2b plus ribavirin for 4 weeks followed by addition of boceprevir for 44 weeks) weeks was associated with increased risk of neutropenia (2 trials, pooled RR 1.8, 95% CI 1.5 to 2.3, I^2=0%), dysgeusia (2 trials, pooled RR 2.5, 95% CI 2.0 to 3.2, I^2=0%), anemia (2 trials, pooled RR 2.0, 95% CI 1.4 to 2.8, I^2=0%), and thrombocytopenia (2 trials, pooled RR 3.3, 95% CI 1.3 to 8.6) compared to dual therapy with pegylated interferon alfa-2b plus ribavirin. The incidence of anemia was about 50% with triple therapy and the incidence of neutropenia about 25%, with severe anemia in 4% to 5% and severe neutropenia in 8% to 15%.	Moderate
		Triple therapy with pegylated interferon alfa-2b, ribavirin, and telaprevir vs. dual therapy with pegylated interferon alfa-2b plus ribavirin	
	Harms	In two trials, there were no statistically significant differences between a twelve week regimen of triple therapy with pegylated interferon alfa-2a, ribavirin, and telaprevir compared with dual therapy with pegylated interferon alfa-2a plus ribavirin in risk of any assessed adverse event.	Moderate

Key Question	Outcome	Summary of Evidence	Strength of Evidence
		In two trials, there was a 24 week regimen of triple therapy with telaprevir (pegylated interferon alfa-2a, ribavirin, and telaprevir for 12 weeks followed by pegylated interferon alfa-2a plus ribavirin for 12 weeks) was associated with increased risk of anemia (2 trials, pooled RR 1.5, 95% CI 1.0 to 2.1, I^2=0%), decreased risk of myalgia (2 trials, pooled RR 0.56, 95% CI 0.34 to 0.93, I^2=0%), and increased risk of rash (2 trials, pooled RR 1.4, 95% CI 1.1 to 1.8) compared with dual therapy with pegylated interferon alfa-2a plus ribavirin for 48 weeks, and trends towards increased risk of withdrawal due to adverse events (RR estimate around 2), primarily due to rash. Among patients randomized to the 24 week telaprevir regimen, one-half to three-quarters of patients experienced a rash (7% to 11% experienced a severe rash) and 27% to 37% experienced anemia (4% experienced severe anemia).	Moderate
		In one trial, response-guided triple therapy with telaprevir (pegylated interferon alfa-2a, ribavirin, and telaprevir for 8 or 12 weeks followed by response-guided pegylated interferon alfa-2a and ribavirin) was associated with increased risk of withdrawal due to adverse events (27% vs. 7.2%, RR 3.8, 95% CI 2.6 to 5.7), anemia (38% vs. 19%, RR 2.0, 95% CI 1.6 to 2.5), any rash (36% vs. 24%, RR 1.5 , 95% CI 1.2 to 1.8), and severe rash (5% vs. 1%, RR 4.6, 95% CI 1.6 to 13) compared with dual therapy with pegylated interferon alfa-2a plus ribavirin for 48 weeks.	Low
Key Question 3b Do these harms differ according to patient subgroup characteristics?		***Dual therapy with pegylated interferon alfa-2b plus ribavirin vs. dual therapy with pegylated interferon alfa-2a plus ribavirin***	
	Harms	No trial of dual therapy with pegylated interferon alfa-2b plus ribavirin vs. dual therapy with pegylated interferon alfa-2a plus ribavirin reported harms in patients stratified by factors such as HCV genotype, age, race, sex, stage of disease, or genetic markers. Three trials that restricted enrollment to patients with genotype 1 infection reported risk estimates for risk of harms that were similar to the risk estimates based on all trials.	Insufficient
		Triple therapy with pegylated interferon alfa-2a or -2b, ribavirin, and telaprevir or boceprevir vs. dual therapy with pegylated interferon alfa-2a or -2b plus ribavirin	

Key Question	Outcome	Summary of Evidence	Strength of Evidence
	Harms	No trials evaluated harms associated with triple therapy with pegylated interferon, ribavirin, and boceprevir or telaprevir versus dual therapy with pegylated interferon plus ribavirin in patient subgroups. All trials evaluated patients with genotype 1 infection.	Insufficient
Key Question 4 Have improvements in intermediate outcomes been shown to reduce the risk or rates of adverse health outcomes from HCV infection?	**Mortality and long-term hepatic complications**	A large Veterans Affairs (VA) study that controlled well for potential confounders found achieving an SVR associated with lower risk of all-cause mortality compared with not achieving an SVR (adjusted HR 0.71 [0.60-0.86], 0.62 [0.44-0.87] and 0.51 [0.35-0.75] for genotypes 1, 2, and 3, respectively). Sixteen other cohort studies found achieving an SVR associated with decreased risk of all-cause mortality, liver-related mortality, hepatocellular carcinoma, and other complications of end-stage liver disease compared with not achieving an SVR, with stronger effect estimates than the VA study (adjusted HRs generally ranged from around 0.10 to 0.33). However, the studies had methodological shortcomings, including inadequate handling of confounders, and 9 were conducted in Asia.	Moderate
	Short-term quality of life	Nine studies found achieving an SVR associated with greater improvement in measures related to quality of life (generic or disease-specific) 24 weeks after the end of antiviral treatment, with differences averaging less than 5 to 10 point on various SF-36 domains. All studies were poor-quality and were characterized by failure to adjust for confounders, high loss to followup, and failure to blind patients to SVR status.	Low

Abbreviations: CI, confidence interval; HCV, hepatitis C virus; HCV-RNA, Hepatitis C virus ribonucleic acid test; HR, hazard ratio; RR, relative risk; SVR, sustained virologic response.
[a] "Current antiviral treatment regimen" refers to dual therapy with pegylated interferon (alfa-2a or -2b) plus ribavirin, or triple therapy with pegylated interferon (alfa-2a or -2b) plus ribavirin and boceprevir or telaprevir.

Findings in Relationship to What Is Already Known

Our findings regarding the comparative effectiveness of dual therapy with pegylated interferon alfa-2b plus ribavirin compared with dual therapy with pegylated interferon alfa-2a plus ribavirin are consistent with recent systematic reviews that also found the former associated with a lower likelihood of SVR.[18, 115] Our findings of no clear difference in comparative effectiveness between 12 to 16 weeks compared with 24 weeks of response-guided dual therapy with pegylated interferon plus ribavirin in hepatitis C genotype 2 or 3 infection with rapid virologic response are discordant with a recent systematic review, which found a shorter duration of treatment associated with a lower likelihood of achieving an SVR.[116] The discrepancy may be explained by the inclusion in the other systematic review of a study that we excluded because it

evaluated a non-standard dose of pegylated interferon,[57] as well as its inclusion of subgroup analyses from trials of patients randomized to different fixed durations of therapy prior to assessment of rapid virologic response,[56, 59, 61] which we considered separately because they did not represent randomized comparisons of response-guided treatment.

Because telaprevir and boceprevir are so new, we are unaware of other published systematic reviews on the comparative benefits and harms of regimens including these drugs, compared to standard dual therapy. Our findings on the association between achieving an SVR and reduced risk of mortality or complications associated with chronic HCV infection are consistent with a recent review that used some systematic methods.[117]

Applicability

The trials included in this review generally met criteria for efficacy studies, based on the exclusion of patients with common comorbidities (such as serious psychiatric conditions or recent or ongoing substance abuse). In addition, the trials may have overestimated efficacy compared to what would be seen in typical practice due to improved adherence as a result of closer followup, effects of trial participation, selection of patients, or other factors. A separate review funded by AHRQ will be focusing on issues related to adherence in the treatment of HCV infection.[118]

The severity of baseline liver disease in the patients enrolled in the trials suggests that they enrolled a broad range of patients. In trials of triple therapy with boceprevir or telaprevir, the proportion of patients with cirrhosis at enrollment ranged from <1% to 11%.[30-32, 46, 51, 77, 78] Trials that reported the proportion of patients with minimal or no fibrosis reported rates of 27% to 39%.[31, 46, 51, 78]

Evidence to evaluate potential differences in comparative benefits or harms in patient subgroups based on age, sex, race, and other clinical factors was relatively limited, precluding strong conclusions in these specific subgroups. The strongest evidence on the association between achieving an SVR and reduced mortality comes from a study performed in a VA population, which might limit generalizability to other settings.[9] As described above, studies conducted in Asia on the association between an SVR after antiviral therapy compared with no SVR and risk of clinical outcomes may be of limited applicability to U.S. populations because some studies indicate a higher incidence of hepatocellular cancer in Asian patients with chronic HCV infection.[42]

The results of this CER are not applicable to populations excluded from the review, including patients previously treated with antiviral therapies and excluded populations such as patients with HIV coinfection, post-transplant patients, or hemodialysis patients.

Implications for Clinical and Policy Decisionmaking

Our review has potential implications for clinical and policy decisionmaking. For patients with genotype 1 infection, triple therapy regimens with pegylated interferon (alfa-2a or -2b), ribavirin, and telaprevir or boceprevir may be considered an alternative to dual therapy with pegylated interferon alfa-2a or -2b plus ribavirin as standard treatment due to substantially superior efficacy for achieving SVR compared to dual therapy with pegylated interferon alfa-2a or -2b, as well as a shorter duration of treatment. Factors that may affect decisions to utilize regimens with boceprevir or telaprevir include cost and specific harms associated with use of these drugs (such as hematologic adverse events with boceprevir and rash with telaprevir). For patients with genotype 2 or 3 infection, dual therapy with pegylated interferon alfa-2b plus

ribavirin appears to be associated with higher likelihood of achieving SVR compared to dual therapy with pegylated interferon alfa-2a plus ribavirin, but absolute differences were relatively small. Therefore, decisions about which pegylated interferon to use may be relatively more affected by other considerations, such as cost, patient preferences, or other factors.

The findings that absolute SVR rates are lower in certain subgroups (such as older patients, black patients, patients with worse baseline fibrosis, and patients with high viral load) can be used to inform individualized decisionmaking. Patients who are less likely to achieve a PSVR may make different informed decisions about therapy compared to those more likely to achieve an SVR, given the adverse effects associated with treatment.

The findings of the review are also relevant to screening recommendations, which are based in part on the effectiveness of treatments in persons found to have HCV infection by screening. Important new evidence that may affect assessments regarding potential benefits of screening include stronger evidence on the link between achieving an SVR and improvement in clinical outcomes as well as evidence showing substantially higher SVR rates with newer triple therapy regimens with boceprevir or telaprevir in patients with genotype 1 infection, the predominant type of HCV infection in the United States.

Limitations of the Comparative Effectiveness Review Process

Our review had some potential limitations. We excluded non English language articles, which could result in language bias, although we identified no non English language studies that would have met inclusion criteria (Appendix B) and a recent systematic review found little empirical evidence that exclusion of non English language articles leads to biased estimates for noncomplementary or alternative medicine interventions.[120]

We did not formally assess for publication bias with funnel plots due to small numbers (<10) of studies for all comparisons. Small numbers of studies can make interpretation of funnel plots unreliable, and experts suggest 10 studies as the minimum number of studies to perform funnel plots.[46] However, we included some studies which were published only as abstracts and found that their inclusion or exclusion from analyses did not change conclusions. In addition, we searched trial registries and solicited drug manufacturers for additional unpublished trials and identified none.

Another potential limitation is that we included cohort studies to evaluate the association between SVR and mortality or hepatic complications associated with chronic HCV infection. Such studies are susceptible to confounding if factors associated with SVR (such as age, race, viral load, or fibrosis stage) are also associated with these outcomes. Therefore, we only included studies that reported adjusted risk estimates, and evaluated how well studies addressed key potential confounders as part of our quality assessment. Nonetheless, residual confounding is a possibility even in cohort studies that adjust for potential confounding.

Limitations of the Evidence Base

We identified several important limitations of the evidence base. First, studies assessing important long-term clinical outcomes associated with current antiviral treatments for chronic HCV infection are not available. In the case of antiviral regimens involving newly approved antiviral drugs, such studies are not possible yet because of the extended followup required to adequately evaluate effects on clinical outcomes. Second, no trials directly compared regimens with boceprevir compared with regimens with telaprevir. Given the increased efficacy of these regimens in patients with genotype 1 infection, trials directly comparing their effects would be

helpful for informing treatment choices between these drugs. In addition, few trials have evaluated the specifically FDA-approved regimens for these drugs, limiting confidence in conclusions regarding estimates of benefits and harms for the regimens likely to be used in clinical practice. Finally, few methodologically rigorous studies conducted in settings applicable to U.S. populations evaluated the association between achieving an SVR and improvements in clinical outcomes. Such studies would be very helpful for confirming the results of the recent, large, well-conducted VA cohort study showing an association between achieving an SVR and reduced mortality risk.[9]

Future Research

Evaluating the comparative effectiveness of current antiviral regimens on clinical outcomes in randomized trials or cohort studies is a challenge due to the long lead-time and large samples necessary to adequately assess these outcomes, but might be more feasible if the studies focus on populations at higher risk for complications from chronic HCV infection (e.g., patients with baseline cirrhosis, high viral load, or other risk factors for progression).

For all trials of antiviral treatments, studies that enroll broader populations with medical and psychological comorbidities, as frequently encountered in clinical practice, are needed to better understand comparative effectiveness, rather than just comparative efficacy. Studies designed using an effectiveness paradigm would also be helpful for understanding real-world effects of antiviral regimens, including effects related to the poorer adherence than expected from efficacy trials.

Trials directly comparing triple therapy with telaprevir compared with triple therapy with boceprevir would be very helpful for understanding comparative effectiveness of these two protease inhibitors. In addition, trials evaluating the boceprevir regimen by the FDA in antiretroviral-naïve patients without baseline cirrhosis are needed to verify that results from studies of previously treated patients were appropriately generalized. Prolonged followup of patients exposed to telaprevir and boceprevir is needed to understand the long-term harms associated with these medications. A number of other protease inhibitors and other newer drugs for treatment of hepatitis C virus infection are currently in active development and further studies with new drugs and drug regimens are expected, including regimens without interferon .[121]

It is critical that future studies comparing clinical outcomes in patients who experience an SVR compared with those who do not experience an SVR adequately control for other factors that influence clinical outcomes in patients with chronic HCV infection. Studies on effects of achieving an SVR on long-term quality of life would be very helpful for understand other potential clinical benefits of antiviral therapy, but a significant challenge is whether it is possible to ethically blind patients to virologic status, which may have an important impact on assessments of quality of life.

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Abbreviations and Acronyms

Abbreviation/Acronym	Definition
ACOG	American College of Obstetricians and Gynecologists
AHRQ	Agency for Healthcare Research and Quality
ALT	Alanine aminotransferase
APRI	Aspirate Aminotransferase-Platelet Ratio Index
ARV	Anti-retro viral drug therapy
AST	Aspirate Aminotransferase
AUROC	Area Under the Receiver Operator Characteristic
CBC	Complete blood count
CDC	Centers for Disease Control and Prevention
CDS	Cirrhosis Discriminant Score
CERs	Comparative Effectiveness Reviews
CHIP	Children's Health Insurance Program
CI	Confidence Interval
COPD	Chronic obstructive pulmonary disease
EIA	Enzyme immune assay
ELF	European Liver Fibrosis Index
ELISA	Enzyme-linked immunoassay
EPC	Evidence-based Practice Center
ESLD	End stage liver disease
ESRD	End-stage renal disease
GGT	Gamma-Glutamyl Transferase
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HCV-RNA	Hepatitis C virus ribonucleic acid test
HIV	Human immunodeficiency virus
INF	Interferon
IVD/IV users	Intra-venous drug users
Metavir/Ishak/Knodell/Scheur	Liver fibrosis and cirrhosis severity grading criterion
PCR	Polymerase Chain Reaction
PEG	Pegylated
PICOTS	Populations, Interventions, Comparators, Outcomes, Timing and Setting
RIBA	Recombinant Immunoblot Assay
Simplified ELF	Enhanced Liver Fibrosis Index
SVR	Sustained virologic response
TEP	Technical Expert Panel
TIMP	Tissue Inhibitor of Metalloproteinase
USPSTF	US Preventive Services Task Force