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

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Background: Multiple treatments are available for chronic hepatitis C virus (HCV) infection.

Purpose: To compare benefits and harms of antiviral regimens for chronic HCV infection in treatment-naive adults.

Data Sources: English-language literature from MEDLINE (1947 to August 2012), the Cochrane Library Database, Embase, Scopus, PsychINFO, and clinical trial registries.

Study Selection: Randomized trials of antiviral treatments and cohort studies examining associations between sustained virologic response (SVR) after therapy and clinical outcomes.

Data Extraction: Several investigators abstracted study details and quality by using predefined criteria.

Data Synthesis: No trial evaluated effectiveness of treatment on long-term clinical outcomes. Dual therapy with pegylated interferon alfa-2b plus ribavirin was associated with a lower likelihood of SVR than was pegylated interferon alfa-2a plus ribavirin (absolute difference, 8 percentage points [95% CI, 3 to 14 percentage points]) on the basis of 7 poor- to fair-quality trials. For genotype 2 or 3 infection, dual therapy for 12 to 16 weeks was associated with a lower likelihood of SVR than was therapy for 24 weeks, and lower doses of pegylated interferon alfa-2b were less effective than standard doses (2 to 4 fair-quality trials). For genotype 1 infection, fair-quality trials found that triple therapy with pegylated interferon, ribavirin, and either boceprevir (2 trials) or telaprevir (4 trials) was associated with a higher likelihood of SVR than was dual therapy (absolute difference, 22 to 31 percentage points). Compared with dual therapy, boceprevir triple therapy increased risk for hematologic adverse events and telaprevir triple therapy increased risk for anemia and rash. A large well-designed cohort study and 18 smaller cohort studies found that an SVR after antiviral therapy was associated with lower risk for all-cause mortality than was no SVR.

Limitations: Trials involved highly selected populations. Observational studies did not always adequately control for confounders.

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

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Chronic hepatitis C virus (HCV) infection is a leading cause of complications from chronic liver disease, including cirrhosis, liver failure, hepatocellular carcinoma, and death (1, 2). The goal of antiviral treatment is to eradicate viremia and prevent long-term complications. Genotype 1 infection predominates in the United States (about 75% of cases) but is more difficult to treat than genotype 2 or 3 infection.

In the early 2000s, dual therapy with the combination of pegylated interferon plus ribavirin became the standard HCV treatment (3–6). Pegylation refers to the cross-linking of polyethylene glycol molecules to the interferon molecule, which delays renal clearance, permitting once-weekly dosing (7). Two pegylated interferons are available: alfa-2a and alfa-2b. Interferon-based treatment is associated with a high rate of adverse effects, including influenza-like symptoms, fatigue, and neuropsychiatric and hematologic effects (8). In 2011, the U.S. Food and Drug Administration approved the first direct-acting antiviral agents, boceprevir (9) and telaprevir (10), for chronic genotype 1 infection.

Understanding the effectiveness of antiviral regimens is critical for making informed treatment decisions for HCV infection. This review focuses on comparative effectiveness in antiviral-naive patients and examines how effectiveness varies depending on clinical and demographic characteristics.

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Methods

Scope

We developed a review protocol and analytic framework (**Appendix Figure 1,** available at www.annals.org) that included the following key questions:

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

2. What is the comparative effectiveness of antiviral treatments on the rate of sustained virologic response (SVR), and does it vary according to patient subgroup characteristics?

3. What are the comparative harms associated with antiviral treatments, and do they vary according to patient subgroup characteristics?

4. Have improvements in SVR been shown to reduce the risk for or rates of adverse health outcomes from HCV infection?

The protocol was developed by using a standardized process with input from experts and the public. Details, including full search strategies, inclusion criteria, and evidence tables and quality ratings, are provided in the full report, as are results of studies comparing induction versus fixed-dose regimens and study outcomes related to quality of life and histologic changes (11).

Data Sources and Searches

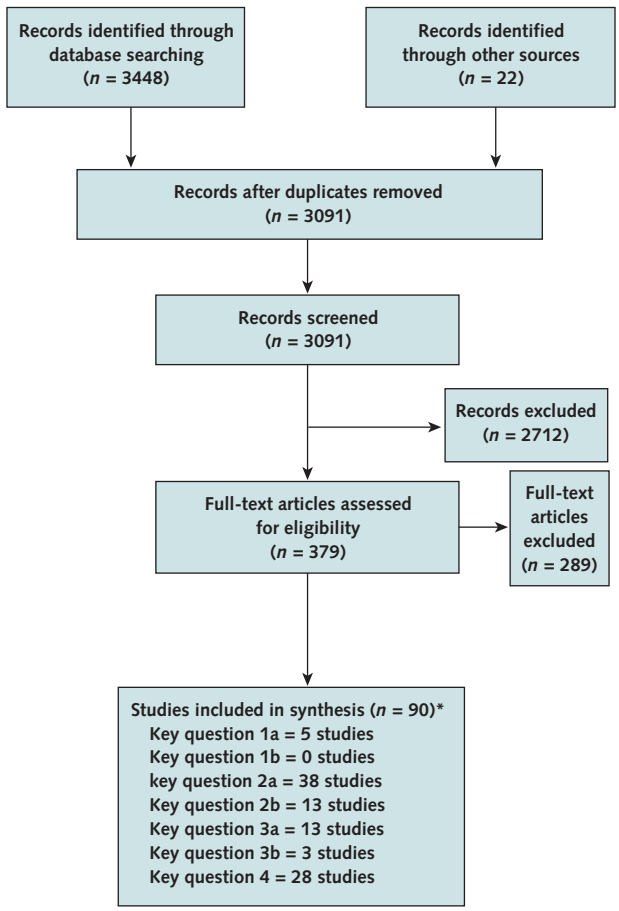
A research librarian searched Ovid MEDLINE from 1947 to August 2012, the Cochrane Library Database (through the first quarter of 2012), Embase (1976 to August 2012), Scopus (1960 to August 2012), PsychINFO (1806 to August 2012), clinical trials registries, and grants databases.

Study Selection

At least 2 reviewers independently evaluated studies for inclusion. For the first 3 questions, we included randomized trials of antiviral-naive patients that compared dual therapy with pegylated interferon alfa-2b plus ribavirin versus pegylated interferon alfa-2a plus ribavirin; triple therapy with pegylated interferon (alfa-2a or -2b), ribavirin, and either telaprevir or boceprevir versus dual therapy; or different doses or durations of dual or triple therapy. Dose and duration comparisons of dual therapy focused on genotype 2 or 3 infection. For the last question, we included cohort studies that reported adjusted risk estimates for the association between an SVR after antiviral treatment versus no SVR and clinical outcomes. Clinical outcomes were mortality, cirrhosis, hepatic decompensation, hepatocellular carcinoma, and need for transplantation. Sustained virologic response, the primary intermediate outcome, was defined as the absence of detectable HCV RNA in the serum 6 months after the end of a course of therapy (4). Harms included withdrawals due to adverse events, serious adverse events, neutropenia, anemia, psychological adverse events, influenza-like symptoms, and rash.

We restricted inclusion to English-language articles and included studies published as conference abstracts only in sensitivity analyses. We excluded studies of pregnant women (12), patients who received a transplant, HIV-infected patients, patients undergoing hemodialysis, and previously treated patients. We excluded regimens with antiviral drugs not approved in the United States for HCV infection.

Figure 1. **Summary of evidence search and selection.**



For key questions, see **Appendix Figure 1** (available at www.annals.org). Reproduced from reference 11.

* Some studies applied to more than 1 key question. Studies of induction versus fixed-dose regimens and outcomes related to quality of life and histologic changes are not reported here but can be found in the full report (11).

Data Extraction and Quality Assessment

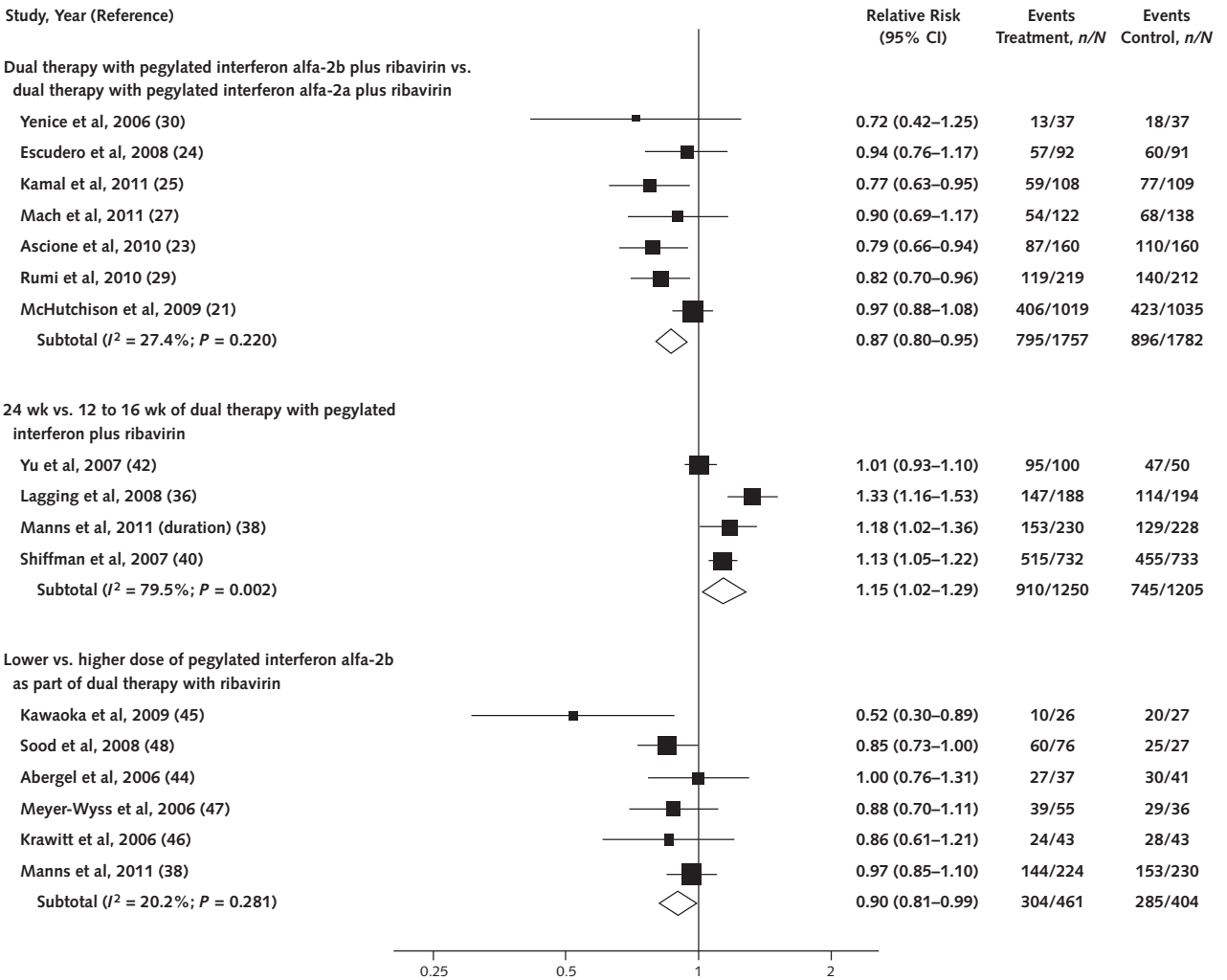
One investigator abstracted details about the study design, population, setting, interventions, analysis, follow-up, and results. A second investigator reviewed data for accuracy. Two investigators independently applied predefined criteria (13–15) to assess study quality as good, fair, or poor. Discrepancies were resolved through consensus.

Data Synthesis and Analysis

We assessed the overall strength of each body of evidence as "high," "moderate," "low," or "insufficient" in accordance with the AHRQ "Methods Guide for Effectiveness and Comparative Effectiveness Reviews" (16) on the basis of the quality of studies, consistency between studies, precision of estimates, and directness of evidence.

We performed meta-analyses of trials that evaluated similar populations, interventions, comparisons, and outcomes to estimate pooled relative risks (RRs) using the

Figure 2. **Sustained virologic response, comparisons of dual-therapy regimens.**



Relative risks >1 favor dual therapy with pegylated interferon alfa-2b over dual therapy with pegylated interferon alfa-2a, 24 wk over 12 to 16 wk, and lower-dose versus higher-dose pegylated interferon alfa-2b.

DerSimonian–Laird method in a random-effects model (17). Heterogeneity was assessed with the I^2 statistic (18). Statistical heterogeneity was explored through sensitivity and subgroup analyses based on study quality, differences in dosing or drugs, and outlier trials. We did not produce funnel plots because of small numbers (<10) of studies (19), but we performed sensitivity analyses that included studies published only as abstracts. Analyses were performed with Stata software, version 11.0 (StataCorp, College Station, Texas).

Role of the Funding Source

The AHRQ's Effective Health Care Program funded this work. Investigators worked with AHRQ staff to develop and refine the scope, analytic framework, and key questions. The AHRQ staff had no role in study selection, quality assessment, synthesis, or development of conclusions and provided project oversight and reviewed the draft report and manuscript. The investigators are solely responsible for the manuscript's content and the decision to submit it for publication.

RESULTS

Figure 1 shows the search and selection results and **Appendix Table 1** (available at www.annals.org) shows the strength of evidence ratings. No study evaluated the comparative effectiveness of current antiviral treatments on long-term clinical outcomes. Three trials found no differences between various dual- or triple-therapy regimens in short-term (6 months after regimen completion) mortality but reported few deaths (20 total) (20–22).

Virologic Outcomes

Ten trials (n = 66 to 3070) compared dual therapy with pegylated interferon alfa-2b plus ribavirin versus dual

therapy with pegylated interferon alfa-2a plus ribavirin (6, 21, 23–30) (**Appendix Table 2**, available at www.annals.org). Four trials were restricted to genotype 1 infection (21, 27, 28, 30). The prevalence of baseline cirrhosis ranged from less than 5% to 20% (23, 29, 31, 32), and the prevalence of elevated aminotransferase levels ranged from 60% to 100% (23–25, 29, 30, 32). Eleven trials (n = 117 to 1465) (33–43) compared different durations of dual therapy, 6 trials (n = 53 to 454) (38, 44–48) compared different doses of pegylated interferon as part of dual therapy, and 4 trials (n = 60 to 1831) (35, 49–51) compared different doses of ribavirin as part of dual therapy for genotype 2 or 3 infection (**Appendix Table 2**). One trial was rated as good quality (40), 4 trials as poor quality (24, 30, 38, 47), and the remainder as fair quality. Methodologic shortcomings included open-label design or inadequately described blinding (23–25, 27–29, 33–39, 42–52), high or unclear attrition (21, 23, 24, 29, 35, 38, 51), and unclear or inadequate randomization or methods for allocation concealment (24, 25, 27–30, 34, 36–39, 41–48).

Dual therapy with standard-dose (1.5 mcg/kg per week) pegylated interferon alfa-2b was associated with a slightly lower likelihood of SVR than was dual therapy with standard-dose (180 mcg per week) pegylated interferon alfa-2a (pooled relative risk [RR], 0.87 [95% CI, 0.80 to 0.95]; I^2 = 27%) (**Figure 2**), with a pooled absolute difference of 8 percentage points (CI, 3 to 14 percentage points), on the basis of 7 trials (5 fair-quality and 2 poor-quality) (21, 23–25, 27, 29, 30). Results were similar when the meta-analysis included a trial (31) that evaluated triple-therapy regimens, a trial (6) published only as an abstract, and 2 trials that evaluated nonstandard doses of pegylated interferon alfa-2b (26, 28) or when the analysis excluded poor-quality trials (24, 30).

The largest trial (n = 3070), the Individualized Dosing Efficacy vs. Flat Dosing to Assess Optimal Pegylated Interferon Therapy (IDEAL) study, found no difference in likelihood of SVR for genotype 1 infection between 2 doses of pegylated interferon alfa-2b (1.0 mcg/kg per week or 1.5 mcg/kg per week) plus ribavirin, 800 to 1400 mg/d, or pegylated interferon alfa-2a, 180 mcg per week, plus ribavirin, 1000 to 1200 mg/d (range, 38% to 41%) (21). Excluding IDEAL because of differential ribavirin dosing had little effect on the pooled estimate but eliminated statistical heterogeneity (6 trials; pooled RR, 0.83 [CI, 0.76 to 0.90]; I^2 = 0%) (23–25, 27, 29, 30).

Duration Effects

Two fair-quality trials found no difference between 48 and 24 weeks of dual therapy in the likelihood of SVR in genotype 2 or 3 infection (pooled RR, 0.97 [CI, 0.84 to 1.1]; I^2 = 43%) (35, 43). Four trials (1 good-quality and 3 fair-quality) found that 24 weeks of dual therapy was associated with a higher likelihood of SVR than was 12 to 16 weeks (pooled RR, 1.2 [CI, 1.0 to 1.3]), but the lower limit of the CI nearly crossed 1 and statistical heterogeneity was present (I^2 = 80%) (**Figure 2**) (36, 38, 40, 42). The 1 trial that found no difference (RR, 1.0 [CI, 0.93 to 1.1]) reported high overall SVR rates (94% to 95%), was restricted to genotype 2 infection, and used a somewhat different ribavirin dosing regimen (42). Excluding this trial reduced statistical heterogeneity, but the estimate was similar (3 trials; pooled RR, 1.2 [CI, 1.1 to 1.3]; I^2 = 47%) (36, 38, 40).

Three fair-quality trials of rapid virologic responders (undetectable HCV RNA by week 4) found no difference in the likelihood of SVR between 24 and 12 to 16 weeks of dual therapy (pooled RR, 0.99 [CI, 0.86 to 1.1]; I^2 = 66%) (34, 39, 41). Absolute differences ranged up to 10 percentage points in either direction.

Dose Effects

Lower-dose pegylated interferon alfa-2b as part of dual therapy was associated with a lower likelihood of SVR than was a higher dose (typically 1.5 mcg/kg per week) in genotype 2 or 3 infection, although the upper limit of the CI nearly crossed 1.0 (pooled RR, 0.90 [CI, 0.81 to 0.99]; I^2 = 20%), on the basis of 6 trials (4 fair-quality and 2 poor-quality) (**Figure 2**) (38, 44–48). Excluding the poor-quality trials (38, 47) or 1 trial that evaluated an atypical dosing regimen (46) had little effect on the pooled estimate.

Two fair-quality trials found no clear difference between induction regimens of pegylated interferon alfa-2b (higher initial doses followed by lower doses) plus ribavirin versus standard fixed-dose dual therapy (53, 54).

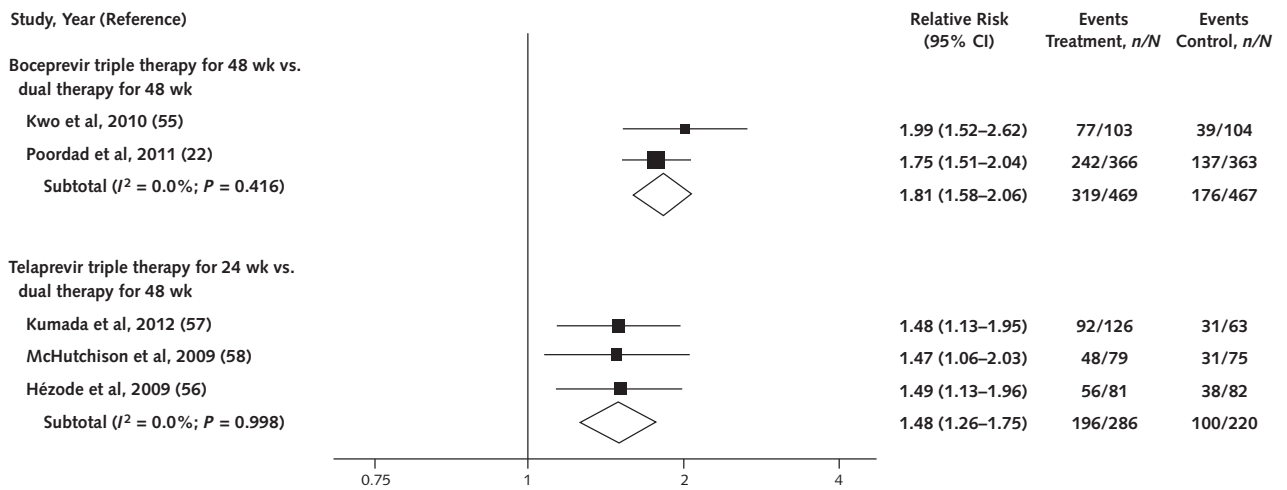
Two fair-quality trials of pegylated interferon alfa-2a found no difference between 1000 to 1200 mg and 800 mg of ribavirin daily (n = 492), or between 400 mg and 800 mg daily, in likelihood of SVR (n = 282) (35, 49). One fair-quality trial (n = 1831) of pegylated interferon alfa-2b found no difference between ribavirin, 800 mg/d (flat dose), and 800 to 1400 mg/d (weight-dosed) (51).

One fair-quality trial (n = 60) that primarily enrolled patients with advanced fibrosis or cirrhosis found pegylated interferon alfa-2a plus ribavirin, 600 to 800 mg/d, to be associated with a lower likelihood of SVR than was ribavirin, 1000 to 1200 mg/d (45% versus 72%; RR, 0.62 [CI, 0.40 to 0.98]) (50).

Triple Therapy

Two fair-quality trials (n = 1097 and 520) compared triple therapy with boceprevir, pegylated interferon alfa-2b, and ribavirin versus dual therapy for antiviral treatment–naive patients with genotype 1 infection (**Appendix Table 3**, available at www.annals.org) (22, 55). Seven percent to 10% of patients had cirrhosis or severe fibrosis at baseline. Methodological shortcomings included open-label design (55) or high attrition (22). A 48-week boceprevir regimen (4 weeks of dual-therapy lead-in followed by 44 weeks of triple therapy) was associated with a higher likelihood of SVR than was 48 weeks of dual therapy (pooled RR, 1.8 [CI, 1.6 to 2.1]; I^2 = 0%), with a pooled absolute increase

Figure 3. **Sustained virologic response, triple therapy with a protease inhibitor versus dual therapy.**



The boceprevir regimen consisted of 4 wk of dual-therapy lead-in with pegylated interferon alfa-2b plus ribavirin, followed by the addition of boceprevir for 44 more wk. The telaprevir regimen consisted of 12 wk of telaprevir, pegylated interferon alfa-2a or -2b, and ribavirin, followed by 12 wk of dual therapy (pegylated interferon plus ribavirin without telaprevir). Relative risks >1 favor triple therapy.

of 31 percentage points (CI, 23 to 39 percentage points) (22, 55) (**Figure 2**). Other triple-therapy regimens evaluated in the trials (28 weeks with or without dual-therapy lead-in, 48 weeks without dual-therapy lead-in, or response-guided triple therapy for 28 or 48 weeks) were associated with lower or similar SVR rates compared with the 48-week regimen with lead-in.

One trial ($n = 75$) found that triple therapy with weight-based ribavirin, 400 to 1000 mg/d, was associated with a trend toward lower likelihood of SVR compared with triple therapy with standard-dose (800 to 1400 mg/d) ribavirin (36% versus 50%; RR, 0.71 [CI, 0.39 to 1.3]) (55).

Six randomized trials compared triple therapy with telaprevir, pegylated interferon, and ribavirin versus dual therapy for genotype 1 infection (**Appendix Table 3**) (20, 31, 56–59). One trial used pegylated interferon alfa-2b (57), 1 evaluated regimens with pegylated interferon alfa-2a or alfa-2b (31), and the remainder used pegylated interferon alfa-2a. The prevalence of baseline cirrhosis ranged from 0% to 11%. One trial (58) was rated as good-quality and the remainder as fair-quality. Methodological shortcomings included open-label design or unclear blinding procedures (31, 56, 59), unclear randomization methods (56, 58), and unclear attrition (57, 58). In all triple-therapy regimens, telaprevir was administered with pegylated interferon plus ribavirin for the first 8 to 12 weeks. For regimens longer than 12 weeks, dual therapy was continued to the end of treatment.

Three trials ($n = 189$ to 323) found that a 24-week fixed-duration telaprevir regimen was associated with a higher likelihood of SVR than was 48 weeks of dual therapy (pooled RR, 1.5 [CI, 1.3 to 1.8]; $I^2 = 0\%$) (**Figure 3**), with an absolute increase of 22 percentage points (CI, 13 to 31 percentage points) (56–58). Excluding a trial that evaluated pegylated interferon alfa-2b instead of alfa-2a had no effect on the estimate (57). Two trials found no difference between 12 weeks of triple therapy and 48 weeks of dual therapy (56, 58), and 1 trial found no difference between 48 and 24 weeks of telaprevir triple therapy (58).

One trial ($n = 1088$) found response-guided triple therapy with telaprevir (triple therapy for 8 or 12 weeks followed by dual therapy for a total of 24 or 48 weeks, depending on extended rapid virologic response) to be associated with a higher likelihood of SVR than was dual therapy for 48 weeks (RR, 1.6 [CI, 1.4 to 1.9]), with an absolute increase of 25 to 31 percentage points (20).

One trial found similar SVR rates (81% to 85%) for response-guided triple-therapy regimens that varied on telaprevir dose (750 mg 3 times daily versus 1125 mg 2 times daily) and type of pegylated interferon (alfa-2a versus alfa-2b) (31). Another trial of extended rapid virologic responders to initial triple therapy with telaprevir reported similar, high SVR rates with 24- and 48-week regimens (92% and 88%, respectively) (59).

Effectiveness in Subgroups

In patients with genotype 1 infection, 1 trial of dual therapy with pegylated interferon alfa-2b versus alfa-2a (21), 2 trials of 48 weeks of triple therapy with boceprevir and dual-therapy lead-in versus 48 weeks of dual therapy (22, 55), and 2 trials of triple therapy with telaprevir (response-guided or fixed duration) versus 48 weeks of dual therapy (20, 57) found no clear differences in RR estimates based on race, sex, age, baseline fibrosis, and weight. For boceprevir, the RR estimate was higher with a baseline

HCV RNA viral load greater than 600 to 800,000 IU/mL (pooled RR, 2.0 [CI, 1.7 to 2.3]; $I^2 = 0\%$) than with a lower viral load (pooled RR, 1.3 [CI, 1.0 to 1.5]; $I^2 = 0\%$) (22, 55), but there was no clear difference in RR estimates for telaprevir triple therapy versus dual therapy according to baseline viral load in 2 trials (20, 57). Across regimens, absolute SVR rates were lower in older patients, black patients, patients with more advanced fibrosis, and patients with higher viral load. Four trials of dual therapy with pegylated interferon alfa-2b versus alfa-2a found no clear difference in RR estimates according to genotype, although absolute SVR rates were lower by 24% to 42% with genotype 1 (6, 23, 24, 29).

Harms of Antiviral Treatments

Six head-to-head trials of dual therapy with pegylated interferon alfa-2b versus alfa-2a found no difference in risk for withdrawal due to adverse events (6 trials; pooled RR, 1.1 [CI, 0.73 to 1.7]; $I^2 = 42\%$) (21, 23, 24, 28–30). Excluding 1 outlier trial (RR, 4.2 [CI, 1.5 to 12]) (23) eliminated statistical heterogeneity, but the pooled estimate was similar (5 trials; pooled RR, 0.88 [CI, 0.7 to 1.1]; $I^2 = 0\%$).

Two trials found dual therapy with pegylated interferon alfa-2b to be associated with lower risk for serious adverse events than was dual therapy with pegylated interferon alfa-2a (pooled RR, 0.76 [CI, 0.61 to 0.95]; $I^2 = 0\%$) (21, 29). There were no differences between dual-therapy regimens in risk for anemia, thrombocytopenia, depression, fatigue, myalgia, or influenza-like symptoms (**Appendix Table 4**, available at www.annals.org). Dual therapy with pegylated interferon alfa-2b was associated with higher risk for headache (3 trials; pooled RR, 1.1 [CI, 1.1 to 1.2]; $I^2 = 0\%$) (21, 23, 28) and lower risk for rash (2 trials; pooled RR, 0.79 [CI, 0.71 to 0.88]; $I^2 = 0\%$) (21, 28) and neutropenia (5 trials; pooled RR, 0.61 [CI, 0.46 to 0.83]; $I^2 = 38\%$). In the largest study (the IDEAL trial), dual therapy with either pegylated interferon was associated with serious adverse events in about 4% of patients, fatigue in 65%, headache in 45%, nausea in 40%, myalgia in 25%, neutrophil count less than 500 cells/mm^3 in 5%, and hemoglobin level less than 85 g/L in 3% (21).

Excluding the low-dose pegylated interferon alfa-2b group from the IDEAL trial had little effect on pooled estimates, except that pegylated interferon alfa-2b became associated with increased risk for depression (3 trials; pooled RR, 1.2 [CI, 1.0 to 1.4]; $I^2 = 0\%$) (21, 23, 28). Excluding 2 poor-quality trials had little effect on pooled estimates (24, 30).

Two trials found a 48-week boceprevir regimen with dual-therapy lead-in was associated with higher risk for neutropenia (pooled RR, 1.8 [CI, 1.5 to 2.3]; $I^2 = 0\%$), dysgeusia (pooled RR, 2.5 [CI, 2.0 to 3.2]; $I^2 = 0\%$), anemia (pooled RR, 2.0 [CI, 1.4 to 2.8]; $I^2 = 0\%$), and thrombocytopenia (pooled RR, 3.2 [CI, 1.2 to 8.2]; $I^2 = 0\%$) than dual therapy for 48 weeks (22, 55) (**Appendix Table 4**). About 25% of patients receiving triple therapy experienced anemia (4% to 5% severe, defined as hemoglobin level less than 80 or less than 85 g/L) and about 33% neutropenia (8% to 15% severe, defined as neutrophil count <500 cells/L). There were no differences in risk for withdrawal due to adverse events, serious adverse events, or other adverse events.

A 24-week regimen of triple therapy with telaprevir was associated with higher risk for anemia (3 trials; pooled RR, 1.3 [CI, 1.1 to 1.5]; $I^2 = 0\%$) and rash (3 trials; pooled RR, 1.4 [CI, 1.1 to 1.7]; $I^2 = 0\%$) than was dual therapy for 48 weeks, but there were no statistically significant differences in risk for serious adverse events, withdrawal due to adverse events, neutropenia, depression, fatigue, headache, chills/rigors, or influenza-like symptoms (56–58) (**Appendix Table 4**). Triple therapy was also associated with increased risk for thrombocytopenia in 1 trial (RR, 1.8 [CI, 1.2 to 2.5]) (57). About half of the patients randomly assigned to telaprevir experienced rash (severe rash in 7% to 10%) and about half had anemia (severe anemia in 4% to 11%) (56–58).

One trial found that response-guided therapy with telaprevir for 24 to 48 weeks was associated with higher risk for withdrawal due to adverse events (RR, 3.8 [CI, 2.6 to 5.7]), anemia (RR, 2.0 [CI, 1.6 to 2.5]), rash (RR, 1.5 [CI, 1.2 to 1.8]), and severe rash (5% versus 1%; RR, 4.6 [CI, 1.6 to 13]) than dual therapy for 48 weeks (20).

No trial reported harms in patient subgroups. Three trials of dual therapy with pegylated interferon alfa-2b versus alfa-2a for genotype 1 infection reported pooled estimates for harms similar to the estimates based on all trials (21, 30, 31).

Association Between SVR and Clinical Outcomes

Nineteen cohort studies ($n = 105$ to 16 864) evaluated the association between an SVR after antiviral therapy and mortality or complications of chronic HCV infection (**Appendix Table 5**, available at www.annals.org) (60–78). Duration of follow-up ranged from 3 to 9 years. Ten studies were conducted in Asia (60, 67–72, 75, 77, 78). Eight (64–66, 72, 75–78) were rated as poor-quality and the remainder as fair-quality. Although all studies reported adjusted risk estimates, only 8 (60, 61, 63, 67–70, 73) evaluated 5 key confounders (age, sex, genotype, viral load, and fibrosis stage). No study clearly described assessment of outcomes blinded to SVR status.

The largest study ($n = 16\,864$) had the fewest methodologic shortcomings (61). It adjusted for multiple potential confounders, including age, sex, viral load, presence of cirrhosis, multiple comorbid conditions, aminotransferase levels, and others. It also stratified results by genotype. In a predominantly male, Veterans Affairs population, SVR after antiviral therapy was associated with lower risk for all-cause mortality than was no SVR, after a median of 3.8 years (adjusted hazard ratio, 0.71 [CI, 0.60 to 0.86], 0.62

[CI, 0.44 to 0.87], and 0.51 [CI, 0.35 to 0.75] for genotypes 1, 2, and 3, respectively). Mortality curves began to separate as soon as 3 to 6 months after SVR assessment.

Eighteen other cohort studies also found SVR to be associated with decreased risk for all-cause mortality (adjusted hazard ratios, 0.07 to 0.39) (60, 69, 72, 73, 75–78), liver-related mortality (adjusted hazard ratios, 0.04 to 0.27) (60, 62, 63, 69, 70, 72, 74, 76, 77), hepatocellular carcinoma (adjusted hazard ratios, 0.12 to 0.46) (60, 62, 63, 67, 68, 71, 73–76, 78), and other complications of end-stage liver disease versus no SVR, with effects larger than in the Veterans Affairs study. The subgroup of studies that focused on patients with advanced fibrosis or cirrhosis at baseline (62, 63, 65–68, 74–76) or that were conducted in Asia (60, 67–72, 75, 77, 78) reported similar ranges of risk estimates.

Discussion

Antiviral therapy for chronic HCV infection continues to evolve. No study evaluated comparative effectiveness of current antiviral regimens on long-term clinical outcomes. Such trials are a challenge to carry out because of the long time course over which complications of HCV infection develop.

In lieu of direct evidence on long-term clinical outcomes, SVR rates are the primary outcome measure with which to evaluate comparative effectiveness. For treatment-naive patients, dual therapy with pegylated interferon alfa-2b is associated with a lower likelihood of SVR than is dual therapy with pegylated interferon alfa-2a (absolute difference, about 8 percentage points). Although there was no difference between dual-therapy regimens in risk for withdrawals due to adverse events, pegylated interferon alfa-2b was associated with a lower risk for serious adverse events, suggesting potential tradeoffs between benefits and harms. However, serious adverse events were reported in only 2 trials (21, 29), the absolute difference was only about 1%, and antiviral-related adverse events are generally self-limited.

For genotype 2 or 3 infection, standard doses and durations (24 weeks) of pegylated interferon as part of dual therapy are more effective than shorter regimens or lower doses, lending support to current dosing guidance (4, 79, 80). Evidence on differential effects of ribavirin dose is limited, although differences were small in most studies.

The relative ineffectiveness of dual therapy for genotype 1 infection has led to ongoing efforts to identify more effective treatments. Recent trials found triple therapy with boceprevir or telaprevir superior to dual therapy, with SVR approaching the 70% to 80% rates observed in trials of dual therapy for genotype 2 or 3 infection (20, 22, 31, 55–59). This has important implications for treatment, as well as for screening, because screening benefits depend in part on the effectiveness of available treatments (81).

Triple therapy for genotype 1 infection is also associated with shorter duration of treatment, an important consideration given the high frequency of adverse effects associated with interferon-based therapy. However, triple therapy is also associated with increased risk for hematologic adverse events with boceprevir (neutropenia, anemia, and thrombocytopenia) and anemia and rash with telaprevir (including severe rash in less than 10% of patients), although there was no clear increase in risk for serious adverse events overall. Across all antiviral regimens, absolute treatment response rates are lower in older patients; black patients; and patients with higher baseline viral load, genotype 1 infection, or more advanced fibrosis.

The strongest evidence on the association between virologic and clinical outcomes is a large Veterans Affairs cohort study that found SVR to be associated with a 30% to 50% reduction in mortality risk, after adjustment for many confounders (61). The rapid separation of mortality curves in this study suggests possible residual confounding, given the typically protracted course of HCV infection. Therefore, estimates of benefit may be exaggerated, although it is not possible to determine to what degree. Eighteen other cohort studies also found that SVR was associated with decreased risk for serious complications of chronic HCV infection, but these studies had more methodological shortcomings than did the Veterans Affairs study.

Our study has limitations. We excluded non–English-language articles. We did not perform formal analyses for publication bias because of the small numbers of trials, but analyses of abstracts and searches of clinical trials registries did not suggest publication bias. Meta-analyses were performed by using the DerSimonian–Laird random-effects model, which results in CIs that are slightly too narrow when heterogeneity is present, so that pooled estimates with 95% CIs close to 1.0 should be interpreted cautiously (82). Estimates and conclusions based on small numbers of trials should also be interpreted cautiously. For example, pooled estimates based on 2 trials can be unreliable, particularly when statistical heterogeneity is present. The trials generally met criteria for efficacy studies, which could limit their applicability because of exclusion of patients with comorbid conditions, and greater adherence than typically observed in clinical practice. Almost all of the randomized trials were funded by pharmaceutical companies (83, 84).

Additional research would help clarify the comparative effectiveness of antiviral treatments. Studies are needed to understand the long-term clinical outcomes associated with different antiviral treatments, the long-term harms of telaprevir and boceprevir, the comparative effectiveness of triple therapy with telaprevir versus boceprevir, and effective strategies to improve adherence (85). Other direct-acting antiviral agents, including second-generation protease inhibitors, polymerase inhibitors, NS5A inhibitors, and others, are in active development, with all-oral, interferon-sparing regimens expected within the next few years (86).

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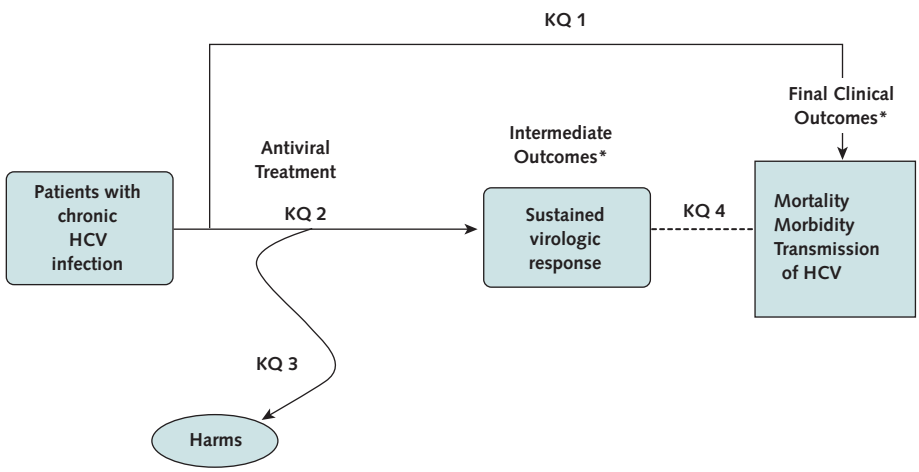
Appendix Figure 1. **Analytic framework for treatment of HCV in adults.**



Key Questions:
1a. What is the comparative effectiveness of antiviral treatment in improving health outcomes in patients with HCV infection?
1b. How does the comparative effectiveness of antiviral treatment for health outcomes vary according to patient subgroup characteristics?†
2a. What is the comparative effectiveness of antiviral treatments on intermediate outcomes on the rate of SVR?
2b. How does the comparative effectiveness of antiviral treatment for intermediate outcomes vary according to patient subgroup characteristics?†
3a. What are the comparative harms associated with antiviral treatments?
3b. Do these harms differ according to patient subgroup characteristics?†
4. Have improvements in SVR been shown to reduce the risk or rates of adverse health outcomes from HCV infection?

This analytic framework outlines the population, interventions, and outcomes considered in the review. It is a modified version of a larger framework depicting the effect of both screening for and treatment of hepatitis C in adults. This figure focuses on the treatment portion of the framework. The population includes adults with chronic HCV infection. The interventions include pegylated interferon alfa-2a with ribavirin or pegylated interferon alfa-2b with ribavirin, with or without the protease inhibitors telaprevir or boceprevir. Intermediate outcomes include liver function, sustained virologic remission, and histologic changes. Final outcomes include morbidity and mortality from HCV (including hepatic cirrhosis, hepatocellular carcinoma, liver transplantation rates, and quality of life) and harms of antiviral therapies (including influenza-like symptoms, hematologic effects, and psychiatric effects). HCV = hepatitis C virus; KQ = key question.
* Including but not limited to HCV genotype, age, race, sex, stage of disease, or genetic markers.

Appendix Table 1. **Summary of Evidence on Comparative Effectiveness of Treatment for Hepatitis C**

Therapy	Strength of Evidence of Findings*	Studies Identified, *n* Participants, *n*	Overall Quality	Consistency (High, Moderate, Low)	Directness (Direct or Indirect)	Precision (High, Moderate, Low)	Summary of Findings
Comparative effectiveness of antiviral treatments for SVR							
Dual therapy with pegylated interferon α-2a plus ribavirin vs. pegylated interferon α-2b plus ribavirin	Moderate	7 randomized trials 4660	Fair	High	Direct	High	Dual therapy with standard-dose pegylated interferon α-2b associated with lower likelihood of achieving SVR than standard-dose pegylated interferon α-2a (pooled RR, 0.87 [95% CI, 0.80–0.95]; I^2 = 27%), with an absolute difference of 8 percentage points (95% CI, 3–14 percentage points)
Duration effects, dual therapy with pegylated interferon plus ribavirin (genotype 2 or 3)							
SVR: 48 vs. 24 wk	Moderate	2 randomized trials 609	Fair	High	Direct	Moderate	No difference in likelihood of achieving SVR (pooled RR, 0.97 [95% CI, 0.84–1.1]; I^2 = 43%)
SVR: 24 vs. 12–16 wk	Moderate	4 randomized trials 2599	Fair	High	Direct	Moderate	24 wk of dual therapy more effective than 12–16 wk for achieving SVR (pooled RR, 1.2 [95% CI, 1.0–1.3; I^2 = 80%); RR estimates ranged from 1.0 to 1.3
SVR: 24 vs. 12–16 wk in patients with rapid virologic response	Moderate	3 randomized trials 583	Fair	High	Direct	Moderate	No difference between 24 vs. 12–16 wk of dual therapy (pooled RR, 0.99 [95% CI, 0.86–1.1]; I^2 = 66%); RR estimates ranged from 0.89 to 1.1
Dose effects, dual therapy with pegylated interferon plus ribavirin (genotype 2 or 3)							
SVR: Lower- vs. higher-dose pegylated interferon	Moderate	6 randomized trials 865	Fair	High	Direct	Moderate	Lower doses of pegylated interferon α-2b associated with lower likelihood of achieving SVR than higher doses (pooled RR, 0.90 [95% CI, 0.81–0.99]; I^2 = 20%)
SVR: Lower- vs. higher-dose ribavirin	Moderate	3 randomized trials 2605	Fair	Moderate	Direct	Moderate	No clear difference in likelihood of SVR between lower versus higher doses of ribavirin
SVR: Lower- vs. higher-dose ribavirin, patients with advanced fibrosis or cirrhosis	Low	1 randomized trial 60	Fair	Unknown (1 study)	Direct	Low	600–800 mg of ribavirin daily associated with lower likelihood of SVR than 1000–1200 mg daily (45% vs. 72%; RR, 0.62 [95% CI, 0.40–0.98])
Triple therapy with boceprevir for genotype 1 infection							
SVR: Triple therapy with boceprevir vs. dual therapy	Moderate	2 randomized trials 1608	Fair	High	Direct	Moderate	Triple therapy with boceprevir for 48 wk associated with higher likelihood of SVR than dual therapy for 48 wk (pooled RR, 1.8 [95% CI, 1.6–2.1]; I^2 = 0%), with an absolute increase in SVR rate of 31 percentage points (95% CI, 23–39 percentage points)
Triple therapy with telaprevir for genotype 1 infection							
SVR: 24 wk of fixed-duration triple therapy with telaprevir vs. 48 wk of dual therapy	Moderate	3 randomized trials 506	Fair	High	Direct	Moderate	Triple therapy with telaprevir for 24 wk associated with higher likelihood of SVR than dual therapy for 48 wk (pooled RR, 1.5 [95% CI, 1.3–1.8]; I^2 = 0%), with an absolute increase in SVR rate of 22 (95% CI, 13–31) percentage points
SVR: response-guided triple therapy with telaprevir vs. dual therapy	Low	1 randomized trial 1088	Fair	Unknown (1 study)	Direct	Low	Response-guided triple therapy with telaprevir associated with higher likelihood of SVR than dual therapy for 48 wk (RR, 1.6 [95% CI, 1.4–1.9]), with an absolute increase in SVR rate ranging from 25 to 31 percentage points

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Appendix Table 1—**Continued**

Therapy	Strength of Evidence of Findings*	Studies Identified, *n* Participants, *n*	Overall Quality	Consistency (High, Moderate, Low)	Directness (Direct or Indirect)	Precision (High, Moderate, Low)	Summary of Findings
Effectiveness in patient subgroups							
SVR: Effects of race, sex, age, baseline fibrosis stage, or baseline viral load	Low to moderate†	9 randomized trials 7116	Fair	High (low for viral load and telaprevir)	Direct	Moderate to high	Across regimens, absolute SVR rates were lower in older patients, black patients, patients with more advanced fibrosis, and patients with higher viral load
Harms of antiviral treatments							
Dual therapy with pegylated interferon α-2b plus ribavirin vs. pegylated interferon α-2a plus ribavirin	Moderate	5 randomized trials, depending on specific harm 4047	Fair	High	Direct	Moderate	Dual therapy with pegylated interferon α-2b was associated with slightly higher risk for headache (3 trials; pooled RR, 1.1 [95% CI, 1.1–1.2]; I^2 = 0%), and lower risk for serious adverse events (2 trials; pooled RR, 0.74 [95% CI, 0.57–0.95]; I^2 = 0%), neutropenia (5 trials; pooled RR, 0.61 [95% CI, 0.46–0.83]), rash (2 trials; pooled RR, 0.79 [95% CI, 0.71–0.88]; I^2 = 0%) than dual therapy with pegylated interferon α-2a
Triple therapy with boceprevir for 48 wk (4-wk lead-in plus 44 wk dual therapy) vs. dual therapy for 48 wk	Moderate	2 randomized trials 3501	Fair	High	Direct	Moderate	Triple therapy with boceprevir for 48 wk was associated with higher risk for neutropenia (2 trials; pooled RR, 1.8 [95% CI, 1.5– 2.3]; I^2 = 0%), dysgeusia (2 trials; pooled RR, 2.5 [95% CI, 2.0–3.2]; I^2 = 0%), anemia (2 trials; pooled RR, 2.0 [95% CI, 1.4–2.8]; I^2 = 0%), and thrombocytopenia (2 trials; pooled RR, 3.2 [95% CI, 1.2–8.2]) than dual therapy for 48 wk
24 wk of fixed duration triple therapy with telaprevir vs. 48 wk of dual therapy	Moderate	3 randomized trials 3591	Fair	High	Direct	Moderate	Triple therapy with telaprevir for 24 wk was associated with increased risk for anemia (3 trials; pooled RR, 1.3 [95 CI, 1.1–1.5]; I^2 = 0%) and rash (3 trials; pooled RR, 1.4 [95% CI, 1.1–1.7]) versus dual therapy for 48 wk
Response-guided triple therapy with telaprevir vs. dual therapy	Low	1 randomized trial 189	Fair	Unknown (1 study)	Direct	Low	Response-guided triple therapy with telaprevir was associated with increased risk for withdrawal due to adverse events (RR, 3.8 [95% CI, 2.6–5.7]), anemia (RR, 2.0 [95% CI, 1.6–2.5]), any rash (RR, 1.5 [95% CI, 1.2–1.8]), and severe rash (RR, 4.6 [95% CI, 1.6–13]) vs. dual therapy for 48 wk
Association between SVR and clinical outcomes							
Mortality and long-term hepatic complications	Moderate	19 cohort studies 27 992	Fair	High	Direct	High	One large study that controlled well for potential confounders found SVR after antiviral therapy associated with lower risk for all-cause mortality vs. no SVR (adjusted HR, 0.71 [95% CI, 0.60–0.86], 0.62 [95% CI, 0.44–0.87], and 0.51 [95% CI, 0.35–0.75] for genotypes 1, 2, and 3, respectively); 18 other cohort studies found SVR associated with decreased mortality and liver complications than no SVR but did not control as well for confounders

HR = hazard ratio; RR = relative risk; SVR = sustained virologic response.
* Outcomes related to quality of life and histologic changes are not reported in this publication but can be found in the full report (11).
† Details about strength of evidence for subgroup effects for specific drug comparisons are available in the full report (11).

Appendix Table 2. Trials Comparing Dual-Therapy Regimens

Study, Year; Country (Reference)	Quality	Sample Sizes, *n*	Cirrhosis at Baseline, %	Elevated Aminotransferase Levels at Baseline, %	Genotype Mix, %	Weekly Pegylated Interferon Dose	Daily Ribavirin Dose, *mg*	Duration, *wk*	Sustained Virologic Response Rate, %
Pegylated interferon α-2a plus ribavirin versus pegylated interferon α-2b plus ribavirin									
Ascione et al, 2010; Italy (23)	Fair	A: 160 B: 160	A: 21 B: 16	100	~60 genotype 1 or 4	A: α-2a, 180 mcg B: α-2b, 1.5 mcg/kg	1000–1200	24–48 by genotype*	A: 69 B: 54
Escudero et al, 2008; Spain (24)	Poor	A: 91 B: 92	Not reported	100	~75 genotype 1 or 4	A: α-2a, 180 mcg B: α-2b, 1.5 mcg/kg	800–1200	24–48 by genotype*	A: 66 B: 62
Kamal et al, 2011; Egypt (25)	Fair	A: 109 B: 108	Not reported	100	100 genotype 4	A: α-2a, 180 mcg B: α-2b, 1.5 mcg/kg	1000–1200	48	A: 71 B: 55
Khan et al, 2007; Pakistan (26)	Not assessed†	A: 33 B: 33	Not reported	Not reported	100 genotype 3	A: α-2a, 180 mcg B: α-2b, 1.0 mcg/kg	800	24	A: 79 B: 82
Mach et al, 2011; Poland (27)	Fair	A: 138 B: 122	Not reported	Not reported	100 genotype 1b	A: α-2a, 180 mcg B: α-2b, 1.5 mg/kg	1000–1200	48	A: 49 B: 44
Magni et al, 2009; Italy (6)	Not assessed†	A: 100 B: 118	Not reported	Not reported	~55 genotype 1 or 4	A: α-2a, 180 mcg B: α-2b, 1.5 mcg/kg	10.5/kg	24–48 by genotype*	A: 68 B: 67
McHutchison and Sulkowski, 2008 (IDEAL); United States (21, 32)	Fair	A: 1035 B: 1019 C: 1016	A: 10‡ B: 11‡ C: 11‡	A: 80 B: 81 C: 81	100 genotype 1	A: α-2a, 180 mcg B: α-2b, 1.5 mcg/kg C: α-2b, 1.0 mcg/kg	A: 1000–1200 B: 800–1400 C: 800–1400	48	A: 41 B: 40 C. 38
Miyase et al, 2012; Japan (28)	Fair	A: 101 B: 100	A. 20 B. 17	Not reported	100 genotype 1	A: α-2a, 180 mcg B: α-2b, 60-150 mcg/kg (weight-based)	600–1000	48	A: 65 B: 51
Rumi et al, 2010; Italy (29)	Fair	A: 212 B: 219	A: 20 B: 18	A: 59§ B: 59§	~50 genotype 1 or 4	A: α-2a, 180 mcg B: α-2b, 1.5 mcg/kg	A: 1000–1200 (genotypes 1 or 4) and 800 mg (genotypes 2 or 3) B: 800–1200	24–48 by genotype*	A: 66 B: 54
Yenice et al, 2006; Turkey (30)	Poor	A: 37 B: 37	Not reported (all had at least minimal fibrosis)	A: 70 B: 76	100 genotype 1	A: α-2a, 180 mcg B: α-2b, 1.5 mcg/kg	800–1200	48	A: 49 B: 35
Duration effects‖									
48 wk vs. 24 wk									
Hadziyannis et al, 2004 (PEGASYS); worldwide (35)	Fair	A: 99 B: 153 C: 96 D: 144	A: 7 B: 8 C: 5 D: 7	100	38 genotype 2 or 3	α-2a, 180 mcg	A: 800 B: 1200 C: 800 D: 1200	A/B: 48 C/D: 24	A/B: 75 C/D. 82
Zeuzem et al, 2004 (PEGASYS); Australia, Europe, New Zealand, North and South America (43)	Fair	A: 59 B: 58	A: 1 B: 0	0	28 genotype 2 or 3	α-2a, 180 mcg	800	A: 48 B: 24	A: 78 B: 72
24 wk vs. 12–16 wk									
Lagging et al, 2008; Denmark and Finland (36)	Fair	A: 188 B: 194	A: 13 B: 13	Not reported	100 genotype 2 or 3	α-2a, 180 mcg	800	A: 24 B: 12	A: 78 B: 59
Manns et al, 2011; international (38)	Poor	A: 230 B: 228	Not reported	100	100 genotype 2 or 3	α-2b, 1.5 mcg/kg	800–1400	A: 24 B: 16	A: 67 B: 57
Shiffman et al, 2007; 132 centers worldwide (40)	Good	A: 732 B: 733	A: 23‡ B: 25‡	100	100 genotype 2 or 3	α-2a, 180 mcg	800	A: 24 B: 16	A: 70 B: 62
Yu et al, 2007; Taiwan (42)	Fair	A: 100 B: 50	A: 20‡ B: 22‡	100	100 genotype 2 or 3	α-2a, 180 mcg	1000–1200	A: 24 B: 16	A: 95 B: 94
24 wk vs. 12–16 weeks among those with undetectable virus by wk 4									
Dalgard et al, 2008; Denmark, Sweden, Norway (34)	Fair	A: 150 B: 148	Not reported	100	100 genotype 2 or 3	α-2b, 1.5 mcg/kg	800–1400	A: 24 B: 14	A: 91 B: 81
Mecenate et al, 2010 (CLEO); Italy (39)	Fair	A: 71 B: 72	10 (overall)	100	100 genotype 2 or 3	α-2a, 180 mcg	800–1200	A: 24 B: 12	A: 75 B: 83
von Wagner et al, 2005; Germany (41)	Fair	A: 71 B: 71	Not reported	100	100 genotype 2 or 3	α-2a, 180 mcg	800–1200	A: 24 B: 16	A: 80 B: 82
Other duration comparisons									
Andriulli et al, 2009¶; Italy (33)	Fair	A: 61 B: 59	Not reported	100	100 genotype 2 or 3	α-2a, 180 mcg	A: 1000–1200 for 12 wk B: 1000–1200 for 6 wk	12	A: 82 B: 54

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Appendix Table 2—Continued

Study, Year; Country (Reference)	Quality	Sample Sizes, *n*	Cirrhosis at Baseline, %	Elevated Aminotransferase Levels at Baseline, %	Genotype Mix, %	Weekly Pegylated Interferon Dose	Daily Ribavirin Dose, *mg*	Duration, *wk*	Sustained Virologic Response Rate, %
Mangia et al, 2005; Italy (37)	Fair	A: 70 B: 213	A: 23‡ B: 16‡	100	100 genotype 2 or 3	α-2b, 1.0 mcg/kg	1000–1200	A. 24 B. 12–24**	A: 76 B: 77
Dose effects: pegylated interferon‖ Higher vs. lower doses of pegylated interferon α-2b									
Abergel et al, 2006; France (44)	Fair	A: 37 B: 41	A: 46 B: 57	100	38 genotype 2 or 3	A: α-2b, 0.75 mcg/kg B: α-2b, 1.5 mcg/kg	800	48	A: 73 B: 73
Kawaoka et al, 2009; Japan (45)	Fair	A: 26 B: 27	None	Not reported	100 genotype 2 or 3	A: α-2b, 1.0 mcg/kg B: α-2b, 1.5 mcg/kg	600–1000	24	A: 39 B: 74
Krawitt et al, 2006; United States (46)	Fair	A: 43 B: 43	A: 17 B: 10	A: 88†† B: 88††	29 genotype 2 or 3	A: α-2b, 50 mcg B: α-2b, 100-150 mcg	1000	48	A: 56 B: 65
Meyer-Wyss, 2006; Switzerland (47)	Poor	A: 55 B: 36	None	100	42 genotype 2 or 3	A: α-2b, 1.0 mcg/kg B: α-2b, 1.5 mcg/kg	800	24–48 by genotype*	A: 71 B: 81
Sood et al, 2008; India (48)	Fair	A: 76 B: 27	Not reported	100	100 genotype 2 or 3	A: α-2b, 1.0 mcg/kg B: α-2b, 1.5 mcg/kg	10–12/kg	24	A: 79 B: 93
Manns et al, 2011; international (38)	Poor	A: 224 B: 230	Not reported	100	100 genotype 2 or 3	A: α-2b, 1.0 mcg/kg B: α-2b, 1.5 mcg/kg	800–1400	24	A: 64 B: 67
Dose effects: ribavirin‖									
Ferenci et al, 2008; Austria (49)	Poor	A: 141 B: 141	Not reported	100	100 genotype 2 or 3	α-2a, 180 mcg	A: 400 B: 800	24	A: 64 B: 69
Hadziyannis et al, 2004 (PEGASYS); worldwide (35)	Fair	A: 96 B: 144 C: 99 D: 153	A: 5 B: 7 C: 7 D: 8	100	38 genotype 2 or 3	α-2a, 180 mcg	A/C. 800 B/D. 1000–1200	A: 24 B: 24 C: 48 D: 48	A/C: 80 B/D: 77
Helbling et al, 2006; Switzerland (50)	Fair	A: 31 B: 29	A: 57 B: 52	100	48 genotype 2 or 3	α-2a, 180 mcg	A: 600–800 B: 1000–1200	24–48 by genotype*	A: 45 B: 72
Jacobson et al, 2007 (WIN-R); United States (51)	Fair	A: 911 B: 920	A: 10 B: 10	100	37 genotype 2 or 3	α-2b, 1.5 mcg/kg	A: 800 B: 800–1400	24–48 by genotype*	A: 60 B: 62

Cirrhosis = METAVIR (Meta-analysis of Histologic Data in Viral Hepatitis) F4, Ishak 5–6, or equivalent; Minimal or no fibrosis = METAVIR F0–F1, Ishak 0–2, or equivalent; CLEO = Club Epatologi Ospedalieri; HCV = hepatitis C virus; IDEAL = Individualized Dosing Efficacy vs. Flat Dosing to Assess Optimal Pegylated Interferon Therapy; WIN-R = Weight-based dosing of pegINterferon α-2b and Ribavirin.

* Treatment duration varied according to genotype: typically 48 wk for genotype 1 or 4 and 24 wk for genotype 2 or 3.

† Published as abstract only; only included in sensitivity analysis.

‡ Severe fibrosis or cirrhosis.

§ More than 2 times the upper limit of normal.

‖ Sample sizes and results are restricted to patients with genotype 2 or 3 infection.

¶ Patients who had undetectable virus by wk 4 were randomly assigned to 12 or 6 wk of ribavirin.

** Treatment for 12 wk if HCV RNA undetectable at 4 wk and for 24 wk if detectable.

†† Alanine aminotransferase level >40 IU/L.

Appendix Table 3. **Trials of Triple Therapy With Boceprevir or Telaprevir, Pegylated Interferon, and Ribavirin**

Study, Year; Country (Reference)	Quality	Sample Sizes, *n*	Cirrhosis, %	Elevated Aminotransferase Levels, %	Boceprevir or Telaprevir Dose/Duration	Weekly Pegylated Interferon Dose	Daily Ribavirin Dose, *mg*	Duration, *wk*	Sustained Virologic Response Rate, %
Trials of triple therapy with pegylated interferon α-2b, ribavirin, and boceprevir versus dual therapy with pegylated interferon α-2b plus ribavirin									
Kwo et al, 2010, SPRINT-1; United States, Canada, Europe (55)	Fair	A: 103 B: 107 C: 103 D: 103 E: 104	7 overall	Not reported	A: 800 mg tid wk 1–48 B: 800 mg tid wk 1–28 C: 800 mg tid wk 5–48* D: 800 mg tid wk 5–28 E: placebo	α-2b, 1.5 mcg/kg	800–1400	A: 48 B: 28 C: 48 D: 28 E: 48	A: 67 B: 54 C: 75* D: 56 E: 38
Poordad et al, 2011, SPRINT-2; United States and Europe (22)	Fair	A: 366 B: 368 C: 363	A: 11† B: 9† C: 7†	A: 74 B: 80 C: 77	A: 800 mg tid wk 5–48 B: 800 mg tid wk 5–28 C: placebo	α-2b, 1.5 mcg/kg	A: 600–1400 wk 5–48 B: 600–1400 wk 5–28 C: 600–1400	A: 48 B: 28/48‡ C: 48	A: 66* B: 63 C: 38
Trials of triple therapy with pegylated interferon α-2b, ribavirin, and telaprevir									
Hézode et al, 2009; Europe (56)	Fair	A: 82 B: 81 C: 78 D: 82	A: 0 B: 0 C: 1 D: 0	Not reported	A: 750 mg tid wk 1–12 B: 750 mg tid wk 1–12 C: 750 mg tid wk 1–12 D: placebo	α-2a, 180 mcg	A: 1000–1200 B: 1000–1200 C: placebo D: 1000–1200	A: 12 B: 24 C: 12 D: 48	A: 60 B: 69 C: 36 D: 46
Jacobson et al, 2011; worldwide (20)	Good	A: 364 B: 363 C: 361	6 overall	Not reported	A: 750 mg tid wk 1–8 B: 750 mg tid wk 1–12 C: placebo	α-2a, 180 mcg	1000–1200	A: 24/48§ B: 24/48§ C: 48	A: 69 B: 75 C: 44‖
Kumada et al, 2012; Japan (57)	Fair	A: 126 B: 63	Not reported (decompensated cirrhosis excluded)	Not reported	A: 750 mg tid wk 1–12 B: placebo	α-2b, 1.5 mcg/kg	600–1000	A: 24 B: 48	A: 73 B: 49
Marcellin et al, 2011; Europe (31)	Fair	A: 40 B: 42 C: 40 D: 39	A: 2.5 B: 2.4 C: 0 D: 5.1	Not reported	A: 750 mg tid wk 1–12 B: 750 mg tid wk 1–12 C: 1125 mg bid wk 1–12 D: 1125 mg bid wk 1–12	A: α-2a, 180 mcg B: α-2b, 1.5 mcg/kg C: α-2a, 180 mcg D: α-2b, 1.5 mcg/kg	A: 1000–1200 B: 800–1200 C: 1000–1200 D: 800–1200	24/48¶	A: 85 B: 81 C: 83 D: 82
McHutchison et al, 2009, PROVE1; United States (58)	Fair	A: 17 B: 79 C: 79 D: 75	None	Not reported	A: 750 mg tid wk 1–12 B: 750 mg tid wk 1–12 C: 750 mg tid wk 1–12 D: placebo	α-2a, 180 mcg	1000–1200	A: 12 B: 24 C: 48 D: 48	A: 35 B: 61 C: 67 D: 41
Sherman et al, 2011, ILLUMINATE; United States (59)**	Fair	A: 162 B: 160	A: 11 B: 8	Not reported	A: 750 mg tid wk 1–12 B: 750 mg tid wk 1–12	α-2a, 180 mcg	1000–1200	A: 24 B: 48	A: 92 B: 88

bid = twice daily; HCV = hepatitis C virus; ILLUMINATE = Illustrating the Effects of Combination Therapy with Telaprevir; PROVE = Protease Inhibition for Viral Evaluation; SPRINT = Serine Protease Inhibitor Therapy; tid = thrice daily. Cirrhosis = METAVIR (Meta-analysis of Histologic Data in Viral Hepatitis) F4, Ishak 5–6, or equivalent. Minimal or no fibrosis = METAVIR F0–F1, Ishak 0–2, or equivalent.

* Dosing recommended by the U.S. Food and Drug Administration for boceprevir in antiviral-naive patients with cirrhosis at baseline.

† Severe fibrosis or cirrhosis.

‡ Response-guided duration: 28 wk of pegylated interferon/ribavirin if HCV RNA is negative from wk 8–24. Patients not meeting these criteria continued until wk 48.

§ Response-guided duration: 24 wk of pegylated interferon/ribavirin if HCV RNA negative from week 4 through week 12. Patients not meeting these criteria continued until week 48.

‖ Dosing regimen recommended by the U.S. Food and Drug Administration for telaprevir.

¶ Response-guided duration: 24 weeks of treatment with pegylated interferon/ribavirin if HCV RNA is negative from wk 4–20. Patients not meeting these criteria continued until wk 48.

** Patients with undetectable HCV RNA at wk 4 and wk 12 randomly assigned to 24 or 48 wk of dual therapy.

Appendix Table 4. **Harms of Triple Therapy With Boceprevir or Telaprevir With Pegylated Interferon, and Ribavirin Versus Dual Therapy With Pegylated Interferon α-2b Plus Ribavirin**

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

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

Appendix Table 5. Sustained Virologic Response and Clinical Outcomes Summary Results*

Study, Year; Country (Reference)	Quality	Study Type Patients Analyzed, *n* Duration of Follow-up Proportion With Cirrhosis: SVR vs. no SVR, %	Adjusted Hazard Ratio (95% CI)				Results Adjusted for at Least Age, Sex, Viral Load, Genotype, and Fibrosis Stage, or No Association Found in Univariate Analyses
			Hepatocellular Carcinoma	Liver-Related Mortality	All-Cause Mortality	Other Clinical Outcomes	
Studies of general populations of treated patients with HCV infection							
Arase et al, 2007; Japan (60)	Fair	Retrospective cohort 500 Mean, 7.4 y Cirrhosis: 9 vs. 16	SVR vs. no SVR: 0.19 (0.08–0.45)	SVR vs. no SVR: 0.13 (0.03−0.59)	SVR vs. no SVR: 0.39 (0.16−0.93)	NR	Yes
Backus et al, 2011; United States (61)†	Fair	Retrospective cohort 16 864 Median, 3.8 y Cirrhosis: 9−12 vs. 12−20	NR	NR	SVR vs. no SVR (genotypes 1, 2, and 3, respectively): 0.71 (0.60−0.86), 0.62 (0.44−0.87), and 0.51 (0.35−0.75)	NR	Yes
Coverdale et al, 2004; Australia (64)‡	Poor	Prospective cohort (some patients originally enrolled in randomized trials) 343 Median, 9 y Cirrhosis: Not reported, Median, fibrosis score F2 (Scheuer)	SVR vs. response—relapse vs. nonresponse Adjusted HR not reported ($P > 0.05$)	SVR vs. response–relapse vs. nonresponse Liver transplant or liver-related death: Adjusted HR not reported ($P = 0.20$)	NR	SVR vs. response relapse vs. nonresponse Liver-related complications§: Adjusted HR not reported ($P = 0.06$)	Unclear
Imazeki et al, 2003; Japan (69)	Fair	Retrospective cohort 459 Mean, 8.2 y Cirrhosis: 13 overall	NR	SVR vs. no SVR: 0.11 (0.01−0.96)‖	SVR vs. no SVR: 0.12 (0.01−1.3)‖	NR	Yes
Innes et al, 2011; United Kingdom (70)	Fair	Retrospective cohort 1215 Mean, 5.3 y Cirrhosis: 10 vs. 18	NR	SVR vs. no SVR: 0.22 (0.09−0.58)	NR	SVR vs. no SVR Liver-related hospital episode: 0.22 (0.15−0.34)	Yes
Izumi et al, 2005; Japan (71)	Fair	Cohort study, appears retrospective 495 Follow-up NR Cirrhosis: 5.1 overall	SVR vs. no SVR: 0.36 (0.04–0.83)	NR	NR	NR	Unclear
Kasahara et al, 2004; Japan (72)	Poor	Retrospective cohort 2698 Mean, 6 y Cirrhosis: 3.0 vs. 5.4	NR	SVR vs. no SVR: 0.04 (0.005−0.30)	SVR vs. no SVR: 0.14 (0.06−0.35)	NR	No
Maruoka et al, 2012; Japan (73)	Fair	Retrospective cohort 577 Mean, 9.9 y Cirrhosis: 10 overall	SVR vs. no SVR: 0.12 (0.04–0.40)‖	NR	SVR vs. no SVR: 0.20 (0.08−0.54)‖	NR	Yes
Yoshida et al, 2002; Japan (77)	Poor	Retrospective cohort 2889 Mean, 5.4 y Cirrhosis: 6.5 vs. 11	NR	SVR vs. no SVR: 0.13 (0.02−0.66)‖	SVR vs. no SVR: 0.32 (0.12−0.86)‖	NR	No
Yu et al, 2006; Taiwan (78)	Poor	Retrospective cohort 1057 Mean, 5.2 y Cirrhosis: 16 overall	SVR vs. no SVR: 0.25 (0.13–0.50)‖	NR	SVR vs. no SVR: 0.28 (0.08−1.0)‖	NR	No
Studies of populations with advanced fibrosis and cirrhosis							
Bruno et al, 2007; Italy (62)	Fair	Retrospective cohort study 883 Mean, 8 y Cirrhosis: All	SVR vs. no SVR: 0.39 (0.17–0.88)	SVR vs. no SVR: 0.14 (0.04−0.59)	NR	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)	No

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Appendix Table 5—**Continued**

Study, Year; Country (Reference)	Quality	Study Type Patients Analyzed, *n* Duration of Follow-up Proportion With Cirrhosis: SVR vs. no SVR, %	Adjusted Hazard Ratio (95% CI)				Results Adjusted for at Least Age, Sex, Viral Load, Genotype, and Fibrosis Stage, or No Association Found in Univariate Analyses
			Hepatocellular Carcinoma	Liver-Related Mortality	All-Cause Mortality	Other Clinical Outcomes	
Cardoso et al, 2010; France (63)	Fair	Retrospective cohort study (of patients originally enrolled in clinical trials) 307 Median, 3.5 y Cirrhosis: 53 vs. 61	SVR vs. no SVR: 0.33 (0.23–0.89)	SVR vs. no SVR: 0.27 (0.08–0.95)	NR	SVR vs. no SVR Ascites or variceal bleeding: 0.21 (0.05–0.92)	Yes
Braks et al, 2007; France (65)	Poor	Retrospective cohort study 113 Mean, 7.7 y Cirrhosis: All	NR	NR	NR	SVR vs. no SVR Clinical events (hepatocellular cancer, ascites, hepatic encephalopathy, or death): 0.14 (0.04–0.45)	No
Fernández–Rodríguez, 2010; Spain (66)†	Poor	Retrospective cohort study 509 Median, 35 mo Cirrhosis: All	NR	NR	NR	SVR vs. no SVR Combined clinical endpoint¶: 0.38 (0.18–0.76)	Unclear
Hasegawa et al, 2007; Japan (67)**	Fair	Retrospective cohort study 105 Median, 4.6 y Cirrhosis: All	SVR vs. no SVR: 0.18 (0.04–0.81)	NR	NR	NR	Yes
Hung et al, 2006; Taiwan (68)	Fair	Cohort study (unclear if retrospective or prospective) 132 Median, 37 mo Cirrhosis: All	SVR vs. no SVR: 0.28 (0.09–0.92)	NR	NR	NR	Yes
Morgan et al, 2010; United States (74)†	Fair	Prospective cohort study of patient enrolled in a randomized trial 526 Median, 79 to 86 mo Cirrhosis: 21 vs. 43	SVR vs. no SVR: 0.19 (0.04–0.80)	SVR vs. no SVR Liver-related mortality or liver transplantation: 0.12 (0.03–0.48)	SVR vs. no SVR All-cause mortality or liver transplantation: 0.17 (0.06–0.46)	SVR vs. no SVR Any liver-related outcome:†† 0.15 (0.06–0.38) Decompensated liver disease: 0.13 (0.03–0.53)	Unclear
Shiratori et al, 2005; Japan (75)	Poor	Prospective cohort study of patients enrolled in randomized trials 271 Median, 6.8 y Cirrhosis: All	SVR vs. no SVR: 0.40 (0.18–0.89)‖	NR	SVR vs. no SVR: 0.07 (0.01–0.56)‖	NR	No
Veldt et al, 2007; Europe and Canada (76)	Fair	Retrospective cohort 479 Median, 2.1 y Cirrhosis: 71 vs. 77	SVR vs. no SVR: 0.46 (0.12–1.7)	SVR vs. no SVR: 0.19 (0.02–1.4)	SVR vs. no SVR: 0.31 (0.07–1.4)	SVR vs. no SVR Any event (death, liver failure, and hepatocellular cancer): 0.20 (0.07–0.58)	No

HCV = hepatitis C virus; HR = hazard ratio; NR = not reported; SVR = sustained virologic response.

* SVR defined in all studies as undetectable HCV RNA in serum 6 mo after the end of antiviral therapy, except as noted.

† Study primarily evaluated patients who received pegylated interferon plus ribavirin.

‡ SVR defined as undetectable HCV RNA on at least 2 occasions at least 2 years after completion of therapy.

§ Hepatic decompensation, complications of portal hypertension, hepatocellular carcinoma, liver transplantation, and liver-related mortality.

‖ Calculated from estimates for SVR vs. untreated and no SVR vs. untreated.

¶ Hepatic decompensation, upper gastrointestinal bleeding secondary to rupture of esophageal or gastric varices, hepatocellular carcinoma, liver transplantation, and liver-related or liver-unrelated mortality.

** Duration of undetectability to meet criteria for SVR not reported.

†† Decompensated liver disease (ascites, variceal bleeding, hepatic encephalopathy, spontaneous bacterial peritonitis), hepatocellular carcinoma, liver transplantation, and liver-related mortality.