

Lower response to simeprevir and sofosbuvir in HCV genotype 1 in routine practice compared with clinical trials

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ABSTRACT

Background: High sustained virological response at 12 weeks after end of treatment (SVR12) with 12 weeks of simeprevir and sofosbuvir±ribavirin (SMV+SOF±RBV) has been demonstrated in hepatitis C virus genotype 1 (HCV-1) but is based on limited data. Therefore, we performed a meta-analysis of available data evaluating the effectiveness of SMV+SOF±RBV in HCV-1.

Methods: We performed a comprehensive literature search in June 2015 to identify randomised controlled trials (RCTs) and observational studies of HCV-1 patients treated with 12 weeks of SMV+SOF±RBV. Original studies with SVR12 data in ≥5 HCV-1 patients were included. We excluded studies on liver transplant recipients and/or patients co-infected with HIV or hepatitis B/D. We estimated pooled effect sizes using a random-effects model and evaluated heterogeneity with Cochrane Q-test, $p \leq 0.10$ and I^2 statistic $\geq 50\%$.

Results: Pooled SVR12 was 85.6% (CI 81.3% to 89.0%) in 1389 HCV-1 patients from 15 studies. On subgroup analysis, SVR12 was 83.9% (CI 79.4% to 87.5%) in observational studies, which was lower than 93.5% (CI 85.7% to 97.2%) in RCTs. A trend showed SVR12 was higher in mild fibrosis, 93.0% (CI 86.2% to 96.6%) compared with advanced fibrosis, 81.5% (CI 75.7% to 86.1%), OR 2.22 (CI 0.79 to 6.25, $p=0.131$). There was no significant difference in SVR12 rates between HCV-1a, 89.9% (CI 81.9% to 94.6%) and HCV-1b, 89.0% (CI 78.9% to 94.6%) with OR 1.35 (CI 0.75 to 2.42, $p=0.322$). The most common pooled side effects were: headache 15.2% ($n=55/361$), fatigue 12.1% ($n=78/646$), nausea 9.5% ($n=50/527$) and rash 9.3% ($n=68/728$).

Conclusions: SMV+SOF±RBV is an effective regimen in HCV-1 patients. The SVR12 rate in observational studies was lower than that in RCTs, which may reflect the more diverse patient population in real-world settings.

INTRODUCTION

Hepatitis C virus (HCV) is a major global public health issue that affects approximately

Summary box

What is already known about this topic?

- ▶ Newer direct-acting agents including simeprevir (SMV) and sofosbuvir (SOF) have demonstrated greater efficacy and better tolerability in patients with hepatitis C.
- ▶ In randomised controlled trials (RCTs) of hepatitis C virus genotype 1 (HCV-1) patients, sustained virological response at 12 weeks after end of treatment (SVR12) rates greater than 90% have been achieved with 12 weeks of SMV and SOF.
- ▶ However, less is known about the effectiveness of this regimen in a real-life setting.

What are the new findings?

- ▶ In the current meta-analysis based on a total of 15 studies with 1389 HCV-1 patients treated with 12 weeks of SMV+SOF±ribavirin, we demonstrate a pooled SVR12 rate of 86%.
- ▶ Observational studies had a lower SVR12 rate at 84% compared with RCTs at 94%.
- ▶ In subgroup analysis, we demonstrated a trend favouring SVR12 in patients with mild fibrosis.

185 million people worldwide.¹ Chronic infection can lead to significant morbidity (cirrhosis, end-stage liver disease and hepatocellular carcinoma) and mortality.² Historically, the HCV genotype 1 (HCV-1) has been one of the most difficult genotypes to treat, with sustained virological response (SVR) rates ranging from 24% to 45% on previous standard of care therapy with pegylated-interferon and ribavirin (PEG-IFN+RBV).^{3 4} The recent development of direct-acting agents (DAAs) has led to dramatically improved treatment outcomes and better tolerated options.²

Protease-inhibitor-based therapies were part of this new age of highly potent oral agents and carried much promise for

patients with HCV.⁵ While SVR12 rates of up to 80% brought a great deal of enthusiasm to the field,⁵ universal adoption of this treatment regimen was tempered by significant rates of treatment-limiting adverse events,^{6 7} and the expectation of newer and safer drugs being developed in the near future.⁸

In late 2013, the Food and Drug Administration (FDA) approved second generation DAAs—simeprevir (SMV) and sofosbuvir (SOF)—for use with PEG-IFN and/or RBV.⁹ Then, in the phase II Combination Of SiMeprevir and sOfosbuvir in HCV genotype 1 infected patientS (COSMOS) trial, the all-oral, IFN-free combination of SMV and SOF with or without RBV (SMV+SOF ±RBV) demonstrated SVR12 rates greater than 90% with few adverse events.¹⁰ These findings prompted major changes in clinical guidelines by the American Association for the Study of Liver Diseases (AASLD)/ Infectious Disease Society of America (IDSA) and European Association for the Study of the Liver (EASL), recommending the use of SMV+SOF±RBV in HCV-1 patients with IFN ineligibility/intolerance or prior treatment failure.^{11 12} Shortly after these recommendations were made, the FDA approved SMV+SOF±RBV for HCV-1 as a 12-week regimen in patients without cirrhosis and a 24-week regimen in patients with cirrhosis.⁹

Evidence supporting the recommendations made by professional societies and FDA approval were mostly based on limited data from randomised controlled trials (RCTs) with small sample sizes and heterogeneous study designs. Currently, less is known regarding treatment outcomes in real-world cohorts. Therefore, we sought to perform a meta-analysis of available data to evaluate the effectiveness of SMV+SOF±RBV for 12 weeks in HCV-1 patients from real-world settings compared with RCTs.

METHODS

Literature search

In June 2015, we performed a literature search to evaluate studies of SMV and SOF combination therapy. We identified articles through a search of MEDLINE and EMBASE databases using the term: 'simeprevir'. We used the same search term to manually identify relevant abstracts from major scientific conferences held in 2014 by the AASLD, Digestive Disease Week (DDW), Asian Pacific Association for the Study of the Liver (APASL), EASL and World Transplant Congress, and, in 2015, by EASL. No restrictions on language, date or geography were applied.

Study selection

After duplicate studies were removed, the remaining records were evaluated based on titles and abstracts. Criteria for inclusion were original studies with SVR12 data on ≥5 patients treated with 12 weeks of SMV+SOF ±RBV. Studies were excluded if patients were co-infected with HIV, hepatitis B and/or hepatitis D, or if they were liver transplant recipients. Two authors (BEY and NHN) independently screened articles for inclusion.

Discrepancies were evaluated by a third author (MHN) and resolved by consensus.

Data abstraction

A data abstraction form was designed for this study to collect the following data: study design, study type, practice setting, collaboration (single vs multicentre) and patient demographics including age, gender, ethnicity, viral load, degree of fibrosis/cirrhosis and (sub) genotype. We also obtained data on treatment outcomes including end of treatment response, SVR at 4 weeks after end of treatment and SVR12, as well as safety and tolerability data on side effects, dose reductions, interruptions and/or withdrawals from treatment.

Statistical analysis

The primary outcome of this study was the pooled rate of SVR12. Secondary outcomes included subgroup analysis of characteristics between studies (ie, study design and study type) and characteristics within studies (ie, severity of fibrosis and subgenotype). We calculated pooled event rates for each outcome, using a random-effects model with corresponding 95% CIs.¹³ We assessed for heterogeneity using the Cochrane Q-statistic with $p \leq 0.10$ and I^2 statistic $\geq 50\%$.¹³ We produced ORs with corresponding 95% CIs for subgroup analyses. Additionally, we utilised funnel plots of $\ln(\text{OR})$ against SE with Egger's test to assess for publication bias and one-study removed method to evaluate for the disproportionate influence of any included studies. All statistical analyses were conducted using Comprehensive Meta-analysis Software, V.2 (Biostat, Englewood, New Jersey, USA).

RESULTS

Results of literature search

From our literature search, we identified 1139 studies (1014 articles from MEDLINE/EMBASE and 125 abstracts from major liver meetings held in 2014 and 2015). After removing duplicates, 882 records were screened for eligibility. A total of 47 studies were assessed in their entirety. Of those, 32 were excluded for reasons described in figure 1. Ultimately, 15 studies (4 full-length articles and 11 abstracts) met all eligibility criteria.

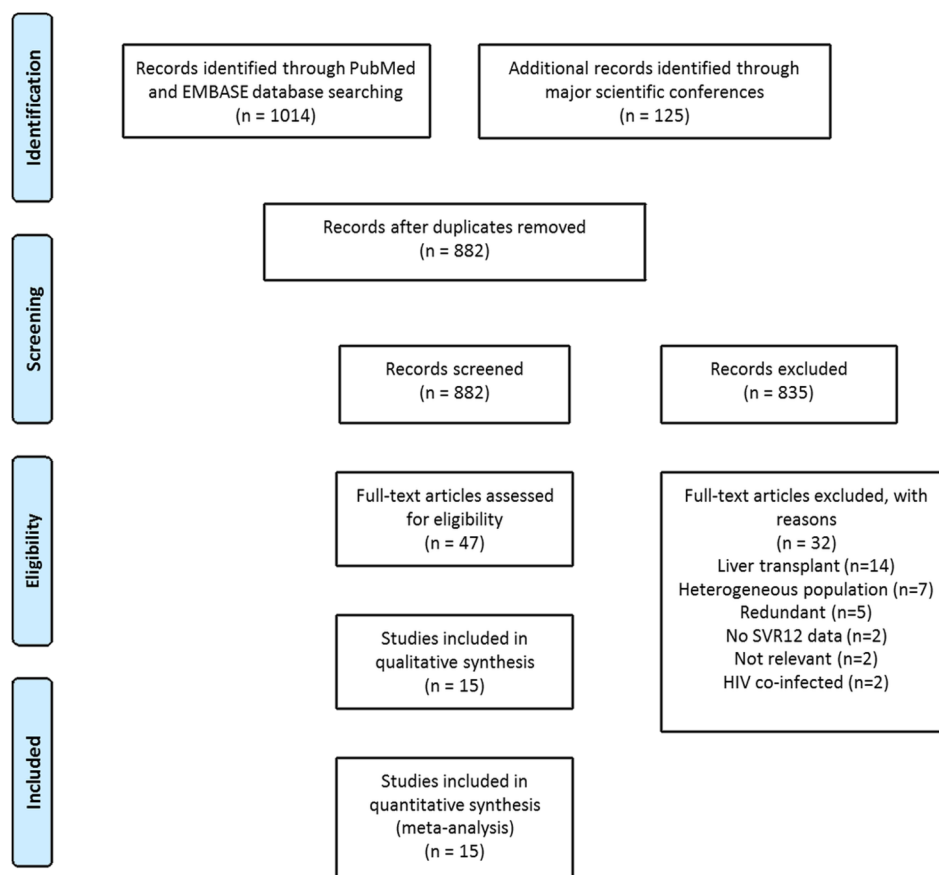
Characteristics of included studies

Fifteen studies with a total of 1389 HCV-1 patients treated with 12 weeks of SMV+SOF±RBV were included in this meta-analysis.^{10 14–27} Study characteristics are summarised in table 1. All were conducted in the USA. Two were RCTs.^{10 24} Thirteen were observational studies: seven were prospective^{16–20 22 23} and six were retrospective.^{14 15 21 25–27} Mean age ranged from 58 to 63 years. Most patients were male (53–81%).

SVR12

The overall rate of SVR12 was 85.6% (CI 81.3% to 89.0%) based on 1389 HCV-1 patients pooled from 15

Figure 1 PRISMA flow diagram of study selection. SVR12, sustained virological response at 12 weeks after end of treatment.



studies. Significant heterogeneity (Q -statistic=48.035, $p=0.000$, $I^2=70.85\%$; [figure 2](#)) and publication bias (Egger's two-tailed $p=0.033$) were observed among the eligible studies. On one-study removed influence analysis, the pooled rate of SVR12 varied by no more than approximately 2%. On subgroup analysis by study design, we found an SVR12 rate of 93.5% (CI 85.7% to 97.2%)

based on 2 RCTs, compared with 83.9% (CI 79.4% to 87.5%) based on 13 observational studies ([figure 3](#)).

Mild compared with advanced fibrosis

Five studies^{10 18 19 21 25} provided SVR12 data on a total of 343 patients with mild fibrosis. The pooled rate of SVR12 was 93.0% (CI 86.2% to 96.6%). Significant

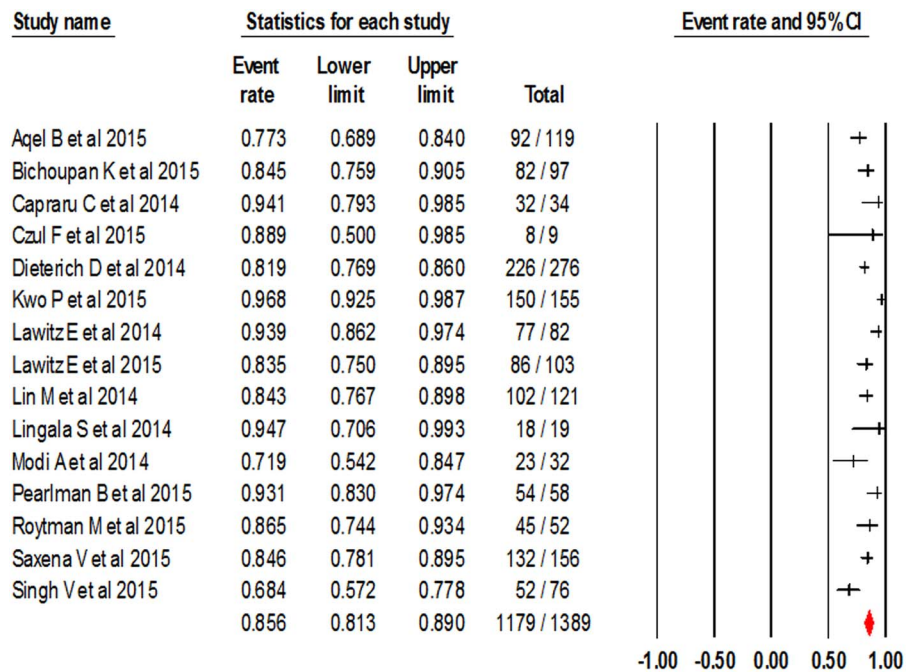
Table 1 Characteristics of included studies

First author, year published	Study design	Collaboration	Patients with SVR12 data	Mean age (years)	Male N (%)	Advanced fibrosis N (%)
Aqel, 2015 ¹⁴	Retrospective	Multicentre	119	60	73 (61)	119 (100)
Bichoupan, 2015 ¹⁵	Retrospective	Single centre	97	60*	Not reported	278 (54)
Capraru, 2014 ¹⁶	Prospective	Single centre	34	57.7	31 (66)	Not reported
Czul, 2015 ¹⁷	Prospective	Single centre	9	Not reported	Not reported	16 (89)
Dieterich, 2014 ¹⁸	Prospective	Multicentre	276	59	181 (57)	145 (45)
Kwo, 2015 ¹⁹	Prospective	Multicentre	155	56*	82 (53)	0 (0)
Lawitz, 2014 ¹⁰	RCT	Multicentre	82	Not reported	58 (81)	41 (50)
Lawitz, 2015 ²⁰	Prospective	Multicentre	103	58*	83 (81)	103 (100)
Lin, 2014 ²¹	Retrospective	Multicentre	121	57.7	103 (70)	84 (57)
Lingala S <i>et al</i> , 2014 ²²	Prospective	Single centre	19	59	16 (64)	Not reported
Modi, 2014 ²³	Prospective	Multicentre	32	59*	34 (76)	Not reported
Pearlman, 2015 ²⁴	RCT	Single centre	58	58	38 (66)	58 (100)
Roytman, 2015 ²⁵	Retrospective	Single centre	52	61.5	63 (64)	62 (63)
Saxena, 2015 ²⁶	Retrospective	Multicentre	156	62*	95 (61)	156 (100)
Singh, 2015 ²⁷	Retrospective	Single centre	76	62.8	Not reported	78 (100)

*Median age presented.

RCT, randomised controlled trial; SVR12, sustained virological response at 12 weeks after end of treatment.

Figure 2 Pooled rate of sustained virological response at 12 weeks after end of treatment in all hepatitis C virus genotype 1 patients treated with simeprevir and sofosbuvir±ribavirin.



heterogeneity was observed among these studies (Q-statistic=9.867, p=0.043, I²=59.46%).

Nine studies^{10 14 18 20 21 24–27} provided SVR12 data on a total of 711 patients with advanced fibrosis. These studies used different definitions to classify patients with advanced fibrosis; seven defined advanced fibrosis as presence of cirrhosis^{14 18 20 21 25–27} while two used the METAVIR scoring system.^{10 24} The pooled rate of SVR12 was 81.5% (CI 75.7% to 86.1%) for patients with advanced fibrosis. Significant heterogeneity was observed among these studies (Q-statistic=22.68, p=0.004, I²=64.72%).

In direct comparison of four studies with a total of 387 patients (188 with mild fibrosis; 199 with advanced

fibrosis), a trend favouring SVR12 in patients with mild fibrosis over advanced fibrosis was found, OR 2.22 (CI 0.78 to 6.25, p=0.131; figure 4). There was significant heterogeneity among these studies (Q-statistic=6.29, p=0.098, I²=52.31%).

Subtypes of hepatitis C genotype 1

On subgroup analysis of hepatitis C genotype 1a compared with genotype 1b, the pooled rates of SVR12 were 89.9% (CI 81.9% to 94.6%) in HCV-1a and 89.0% (CI 78.9% to 94.6%) in HCV-1b. No significant association between hepatitis C genotype 1 subtype and SVR12 was observed, OR 1.35 (CI 0.75 to 2.42, p=0.322; figure 5).

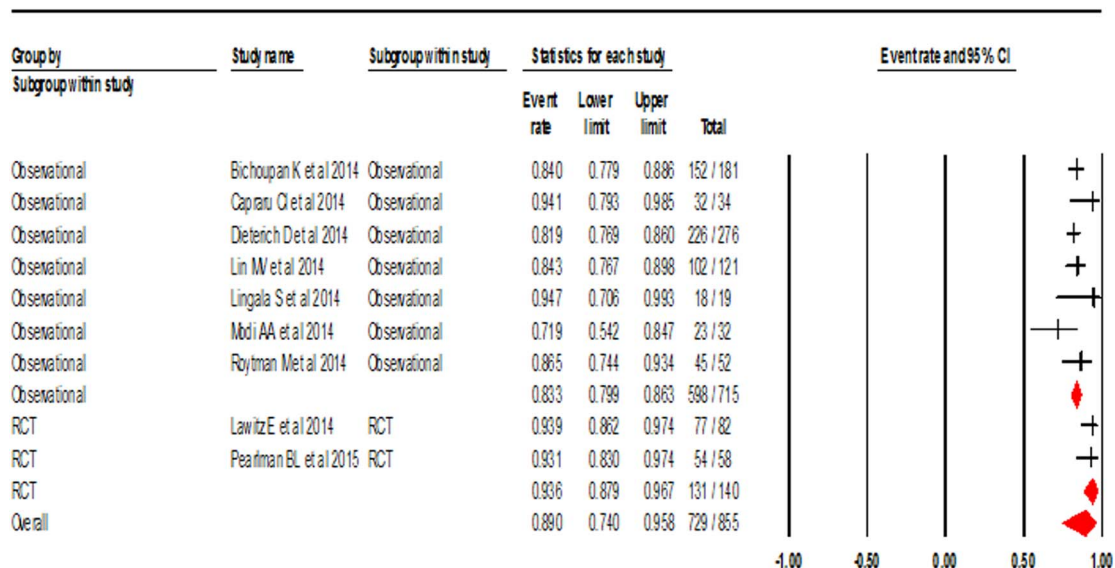


Figure 3 Sustained virological response at 12 weeks after end of treatment subgroup analysis by study design: observational versus randomised controlled trial (RCT).

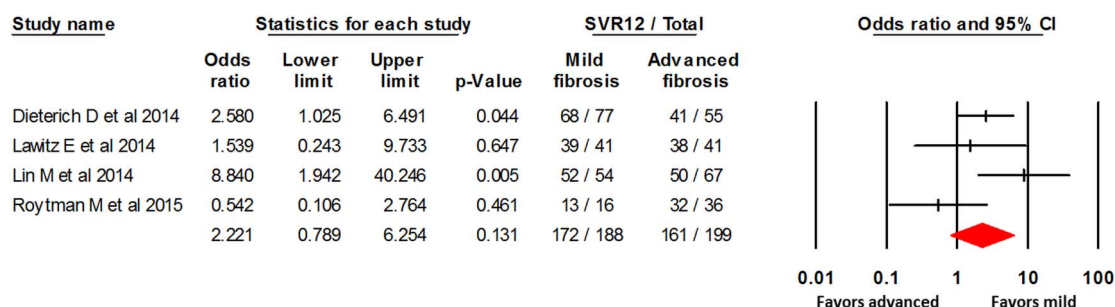


Figure 4 Odds of sustained virological response at 12 weeks after end of treatment (SVR12) by severity of fibrosis: mild versus advanced fibrosis.

Tolerability

Based on available tolerability data, the most common pooled side effects were: headache 15.2% (n=55/361), fatigue 12.1% (n=78/646), nausea 9.49% (n=50/527) and rash 9.3% (n=68/728). Insufficient data were available to evaluate for withdrawal from treatment and serious adverse events.

DISCUSSION

Currently, there are few published studies with treatment data on SMV+SOF±RBV.^{10 14 24 26} While findings from the COSMOS study were highly promising, study patients were recruited, and stratified into different treatment durations and severity of fibrosis, and only 82 patients received SMV+SOF±RBV for 12 weeks.¹⁰ In a separate RCT by Pearlman *et al*,²⁴ the authors recruited 58 patients to the treatment arm with 12 weeks of SMV+SOF±RBV and only included patients with chronic HCV genotype 1a infection and child's grade A cirrhosis. Two additional studies on patients with cirrhosis were recently published, but have been limited to retrospective cohorts.^{14 26} Therefore, given the small sample sizes and heterogeneous study designs of the aforementioned studies, we performed a meta-analysis of available data to provide a more robust estimate of SVR12 in a 12-week regimen of SMV+SOF±RBV.

In our analysis, the overall pooled SVR12 rate was 86%, which was lower than rates reported by the COSMOS trial¹⁰ and RCT by Pearlman *et al*.²⁴ This estimate was robust, varying by no more than 2.1% on

one-study removed influence analysis. In subgroup analysis comparing observational studies and RCTs, the pooled SVR12 rate was 89%, which reflects a difference in weights due to the dispersion of studies within each subgroup. When evaluating treatment outcomes based on study design, observational studies had a lower SVR12 rate at 84% compared with RCTs at 94%. While this finding is limited since this was not a head-to-head comparison, it may reflect the lower treatment rates of real-world settings.

Our meta-analysis was inclusive of patients with genotypes 1a and 1b as well as varying degrees of fibrosis. Given the more diverse nature of the study population and the uncontrolled environment in which all of the observational studies were conducted, it is not surprising to see that the pooled SVR12 rate is slightly lower than those from RCTs.^{10 24} However, our treatment rate is still better compared with historical cohorts treated with protease-inhibitor-based therapies,⁵ which suggests that SMV+SOF±RBV is a more effective treatment option.

In our subgroup analysis of patients with SVR12 and fibrosis data, we observed a higher SVR12 rate in patients with mild fibrosis (93%) compared with those with advanced fibrosis (82%), with a trend favouring SVR12 in patients with mild fibrosis, OR 2.22 (95% CI 0.79 to 6.25, p=0.131). Of the nine studies with SVR12 data on patients with advanced fibrosis, both RCTs^{10 24} had SVR12 rates greater than 90% while the seven observational studies^{14 18 20 21 25-27} had lower SVR12 rates ranging from 68.4% to 88.9%. This finding is likely due to the diversity of real-world patients with more

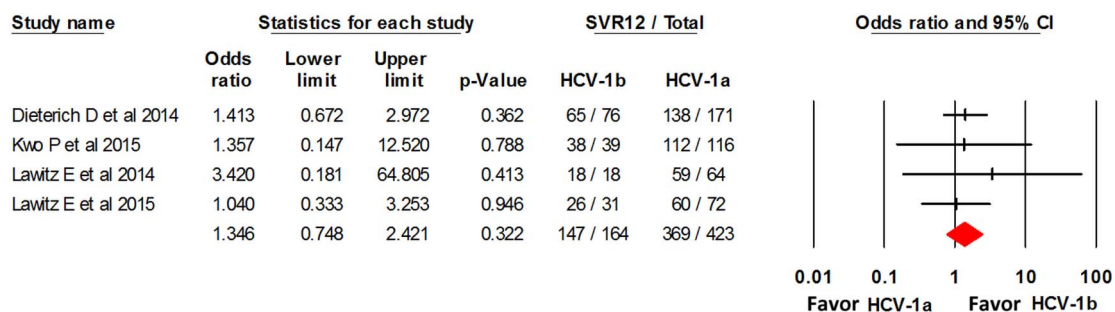


Figure 5 Odds of sustained virological response at 12 weeks after end of treatment (SVR12) by subtype: hepatitis C virus genotype 1a (HCV-1a) versus genotype 1b (HCV-1b).

variability in terms of medication adherence, follow-up and comorbidities, compared with the highly selective patients included in clinical trials.

This meta-analysis exclusively evaluated outcomes in HCV-1, the most prevalent genotype in the USA.²⁸ While HCV-1a has been considered the more difficult-to-treat subtype due to NS3 polymorphisms associated with decreased SMV activity¹ and a higher likelihood of developing resistance against protease inhibitors,^{24–29} clinical trials including COSMOS,¹⁰ ION-1³⁰ and ION-2³¹ have shown minimal differences in SVR rates between HCV-1a and HCV-1b. Similarly, our subgroup analysis showed no significant association between HCV-1 subtype and the likelihood of achieving SVR, OR 1.35 (95% CI 0.75 to 2.42, $p=0.322$), suggesting that a nucleotide polymerase inhibitor such as SOF may serve as an added barrier against the development of resistant variants,^{1–24} abrogating subclinical differences between subtypes.

Limitations to our study include insufficient data to evaluate serious adverse events, perform subgroup analysis of treatment with or without RBV, and compare outcomes in treatment naïve and experienced patients. An additional limitation was publication bias in our pooled estimate of SVR12, where smaller studies with larger than average effect sizes were more likely to be published, and this finding was statistically significant. In conducting our literature search, we attempted to be as comprehensive as possible, including preliminary data from abstracts presented at major scientific conferences in addition to four full-length articles. We also attempted to give a more conservative estimate of the pooled effect by using a random-effects model. More information on SMV+SOF±RBV will become available in the future, with clinical trials underway to address the efficacy and tolerability of SMV+SOF±RBV in special populations including those with cirrhosis,³² HIV co-infection,³³ liver transplantation³⁴ and HCV genotype 4.^{35–37} In the meantime, and despite the limitations described above, our study is currently the largest to evaluate the effectiveness of SMV+SOF±RBV for 12 weeks in HCV-1 patients in real-world settings, which included several university centres and the TRIO network data gathered from patients managed by practitioners from the community ($n=152$) as well as from academic centres ($n=82$).

In summary, our results support SMV+SOF±RBV as a treatment option for HCV-1 patients. While this rate is slightly lower than that seen in the COSMOS trial alone, our findings are likely more representative of the diverse patient population encountered in routine clinical settings. Given the rapid evolution in HCV therapy and need to optimise treatment, our meta-analysis provides a robust estimate of SVR12 in HCV-1 patients treated with SMV+SOF±RBV.

Contributors MHN is the guarantor of the article. BEY was involved in study design, data collection, data analysis and interpretation, and drafting of the manuscript. NHN was involved in data collection, data analysis and

interpretation, and participation in drafting of the manuscript. MJ was involved in data analysis and interpretation, and critical revision of the manuscript. GL was involved in data analysis and interpretation, and critical revision of the manuscript. JKL was involved in data analysis and interpretation, and critical revision of the manuscript. MHN was involved in concept development, study design, data collection, data analysis and interpretation, and critical revision of the manuscript. All the authors identified above have critically reviewed and approve the final version of this paper, including the authorship statement.

Competing interests Authors' declaration of personal interests: (1) GL has served as a consultant and as an advisory board member for Gilead Sciences, Janssen and Abbvie. (2) JKL has received research support from Abbott, Boehringer-Ingelheim, Bristol-Myers Squibb, Gilead, Glaxo-Smith Kline and Janssen, and has served as a consultant and/or advisory board member for Bristol-Myers Squibb, Gilead, Janssen and Merck. (3) MHN has received research support from and served as a consultant and/or an advisory board member for Gilead Sciences, Janssen Pharmaceuticals and Bristol-Myers Squibb.

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