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Global Hepatitis Programme

Guideline development for Hepatitis C virus Screening, Care and Treatment in low- and middle-income countries

PICO 7: Treatment

Direct acting antiviral therapy versus pegylated interferon and ribavirin treatment for chronic hepatitis C infection: a meta-analytical systematic review

Conducted by the Burnet Institute, Melbourne and Health Protection Scotland, Glasgow
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Review Members

Dr Joseph Doyle	Burnet Institute, Melbourne
Dr Alexander Thompson	St Vincent's Hospital, University of Melbourne, and Victorian Infectious Diseases Reference Laboratory, Melbourne
Dr Esther Aspinall	Health Protection Scotland, Glasgow
Prof Sharon Hutchinson	Caledonian University, Glasgow
Prof Margaret Hellard	Burnet Institute, Melbourne

Review Advisory Group

Dr Mark Stoove	Burnet Institute, Melbourne
Prof David Goldberg	Health Protection Scotland
Prof Stanley Luchters	Burnet Institute, Melbourne
Dr Stefan Wiktor	WHO Global Hepatitis Program
Mr Tim Nguyen	WHO Global Hepatitis Program
Dr Bryce Smith	Centre for Disease Control and Prevention, Atlanta
Dr Yngve Falck-Ytter	Case Western Reserve University,
Ms Rebecca Morgan	Centre for Disease Control and Prevention, Atlanta

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BACKGROUND

The World Health Organization (WHO) estimates that between 130 and 150 million people are chronically infected with hepatitis C (HCV) virus worldwide (World Health Organization 2012). People with untreated HCV are at increased risk of liver cirrhosis, hepatocellular carcinoma, and liver-related mortality (Grebely and Dore 2011). The combination of pegylated interferon and ribavirin, where available, has been the standard of care for treating individuals with chronic HCV for many years (European Association for the Study of the Liver 2011). However newer direct acting antiviral agents in development and approved for therapeutic use promise to further improve virological response to treatment, but may add to treatment complexity, adverse effects, monitoring requirements and cost. This review will assess the available evidence in an effort to determine whether the addition of regimens containing direct acting antiviral agents are more effective at treating HCV compared to pegylated interferon/ribavirin therapy with respect to virological response, morbidity, mortality and adverse effects.

METHODS

Narrative review question

Among people with chronic HCV, is treatment containing direct acting antiviral agents (DAA) more effective than treatment with pegylated interferon and ribavirin (PR) alone?

PICO Question

Population: Adults and children with chronic HCV infection

Intervention*:* Direct-acting antiviral (DAA) therapy in addition to pegylated interferon (PEG) and ribavirin (RBV) therapy

Comparison*:* Pegylated interferon and ribavirin therapy alone

Outcomes: Number achieving sustained virological response; number of cases of decompensated liver disease/hepatocellular carcinoma/all-cause mortality; treatment-related serious adverse events leading to discontinuation of therapy; and quality of life. Cost outcomes will require economic modelling which will be conducted separately from this protocol.

Study type/limits*:* Experimental studies (human) published between 1994 and the present; limited to published phase 3 studies of licensed anti-HCV drugs

Search strategy

A systematic review was carried out using the following electronic databases and information sources:

- OVID MEDLINE, OVID EMBASE, and the Cochrane Library (CENTRAL and DARE) (without language restrictions);
- Reference lists of all relevant articles and reviews;
- Recommendations from Guideline Development Group (GDG) members and other experts in the field;
- Relevant articles identified during the conduct of the other systematic reviews.

Search terms included combinations of free text and medical subject heading terms (MeSH, Emtree), briefly summarized as: Hepatitis C AND Direct Acting Antiviral Agents.

Conduct of the review

The review process followed the Cochrane methodology for conducting a systematic review and the PRISMA guidelines on reporting. The review was prospectively registered with the systematic reviews registry PROPSPERO (CRD42013004725, University of York). All article assessment for eligibility, data extraction and quality appraisal was performed by two independent reviewers and disagreement resolved by consensus. Two reviewers assessed all search results and include those studies that meet population, intervention, and at least one outcome criteria. The bibliographic records and abstracts were used to filter studies that clearly did not meet the inclusion criteria. Full articles were obtained and assessed to confirm eligibility of potentially relevant studies.

Quality appraisal

All experimental studies were assessed using the Cochrane Risk of Bias assessment tool, which grades studies as having a low, high, or unclear level of bias.

Data extraction

Data was extracted from each study by the reviewers acting independently to a standardised spread sheet noting:

- Study characteristics (country, study design, study objectives, funding source);
- Study population (adults vs. children, people who inject drugs [PWID], genotype);
- Setting (community clinic, hospital clinic; harm reduction and community services, low- and middle-income country [LMIC] vs. high-income country [HIC] setting);

- Participant details (age, sex, ethnicity);
- Inclusion/exclusion criteria for study;
- Sample size;
- Intervention (type of HCV treatment);
- Control (selection and characteristics of control group);
- Analysis (number offered intervention, number accepted intervention, reason for refusal, time to follow-up, study data collection method, statistical analyses, primary and secondary outcomes of study);
- Outcomes (SVR, decompensated cirrhosis, hepatocellular carcinoma, all-cause mortality, treatment-related serious adverse events, quality of life);

GRADE process

The quality of the body of evidence as a whole was assessed using Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology. GRADE rates the quality of evidence for each outcome of interest (i.e., SVR, decompensated cirrhosis, hepatocellular carcinoma, liver-related mortality, all-cause mortality, serious adverse events, quality of life) as high, moderate, low or very low, depending on a number of criteria. These include study design, study quality, study consistency (the similarity of estimates of effect across studies) and study directness (the extent to which the evidence is relevant to the population, intervention, and outcome of interest).

Data synthesis

A random effects meta-analysis of individual study risk ratios was conducted to create pooled estimates of effect for each outcome. Stratification, proposed *a priori,* was carried out to assess the effects of cirrhosis and genotype on SVR, however an absence of data limited any further stratification by HIV status, injecting behaviour, country income level, or comparing adults with children. A sensitivity analysis was conducted to explore effects of methodological factors on outcome estimates.

RESULTS

The citation search identified a total of 420 citations (Figure 1). Initial review excluded 87 duplicated and 155 irrelevant citations. Subsequent screening by title and abstract excluded a further 169 citations which did not meet population, intervention, comparison, or at least one outcome criteria. Nine studies advanced to full text review, of which four full text articles directly met the PICO criteria. A further five full text articles were excluded from the review as two RCTs used sofosbuvir (an as yet unlicensed NS5B polymerase inhibitor) making different comparisons: Lawitz *et al* (2013) studied both sofosbuvir plus PR without a control arm, and compared sofosbuvir plus RBV alone to PR; Jacobson *et al.* (2013) compared sofosburvir plus RBV to placebo. Three other RCTs were excluded as since they only presented more detailed sub-analyses of already included RCTs (Sulkowski *et al.* 2013, Pol *et al.* 2013, Poordad *et al.* 2012).

The four included studies provide estimates of the effect of DAA on SVR; adverse events including severe anaemia, neutropenia, rash or treatment discontinuation; and mortality within 72 weeks of commencing treatment (Table 1). There were no data found comparing the effects of DAA therapy on long-term liver related morbidity, hepatocellular carcinoma incidence, long-term mortality or quality of life.

These papers comprise two studies of the first generation HCV protease inhibitors boceprevir (BOC) plus PR and two studies of telaprevir (TPV) plus PR, compared to PR alone. They contained data on 3305 individuals followed for a median of 72 weeks. Two articles reported comparisons among treatment naïve individuals, and two among treatment experienced individuals who had previously received 12 weeks of PR therapy but not achieved a SVR. All were conducted in high income settings in North America and Europe. Individuals with HIV co-infection, active PWID, and children were excluded from all studies, however subgroup data are available on degree of fibrosis (early F0-2 versus advanced F3-4). Since these DAA act primarily against HCV genotype-1 infection, there are no comparative data by HCV genotypes.

Sustained virological response

Overall, DAA+PR was associated with fewer treatment failures than PR alone (RR 0.51, 95%CI 0.47 to 0.55, $I^{2=}$20%). Both drugs were independently associated with improvements in SVR, in treatment naïve and treatment experienced individuals (Figures 2-4). Given an estimate of 643 virological failures per 1000 HCV genotype-1 infected patients treated with PR alone, 315 fewer (95%CI 289 to

341 fewer) virological failures could be anticipated using DAA+PR treatment. The improvement in virological response held for those with mild fibrosis (RR 0.49, 95%CI 0.45 to 0.53; I^2=0.3%) and advanced fibrosis (RR 0.56, 95%CI 0.52 to 0.66; I^2=68%).

Adverse events

Grade 3 or 4 anaemia (<85g/dl) occurred more frequently among DAA+PR therapy than PR alone therapy (RR 2.84, 95%CI 1.78 to 4.54; I^2=5.6%). Severe anaemia occurred in 22 per 1000 individuals treated with PR alone, and could be anticipated to increase by 41 more cases (95%CI 18 to 79 more) per 1000 using BOC or TPV plus PR (Figure 5).

Grade 3 or 4 neutropenia (<750 cells/mm^3) occurred more frequently in DAA+PR treatment than PR alone (RR 1.61, 95%CI 1.29 to 2.00, I^2=11%). Severe neutropenia on these laboratory parameters was not necessarily related to treatment failure or infection rates. It occurred in 174 individuals per 1000 treated with PR, and could be anticipated to increase by 106 (95%CI 50 to 174) per 1000 treated with BOC or TPV plus PR (Figure 6).

Treatment discontinuation due to any adverse events was measured in all four RCTs but was not clearly associated with the use of DAAs compared to PR alone (RR 1.18, 95%CI 0.93 to 1.49; I^2=57%). Given 95 treatment discontinuations due to adverse events with PR treatment, there may be 17 more (95%CI 7 fewer and 47 more) discontinuations when using DAA+PR (Figure 7).

Rash was defined and reported differently across studies precluding any statistical synthesis of the results. Comparing BOC+PR to PR, any rash was more common in the BOC+PR recipients (14-17%) than PR alone recipients (5%, p<0.05)(Bacon *et al.* 2011). In the TPV studies, severe rash (defined as toxic skin eruptions) occurred in two treatment experienced patients receiving TPV for 12 weeks but not among the PR arm (Zeuzem *et al.* 2011). Among treatment naïve patients, grade 3 rash occurred in 6% and 4% of individuals receiving TPV for 12 and 8 weeks respectively, and only 1% among the PR control group (Jacobson *et al.* 2011).

Mortality at 72 weeks

DAA therapy using BOC or TPV was not associated with changes in mortality during therapy or in 24 weeks post therapy (RR 0.51, 95%CI 0.15 to 1.76; I^2=0%, 3 RCTs). Overall, there were very few deaths observed in either treatment (6/1784 individuals) or control arms (5/804) (Figure 8). Four deaths (2 in DAA+PR, 2 in PR study arms) were attributed to suicide potentially related to interferon, one

death in the DAA+PR arm to liver disease and the remaining six deaths thought to be unrelated to therapy by the studies' investigators.

Study quality

All included studies were of high methodological quality with the primary aim of determining efficacy (defined by SVR) and safety of DAA+PR therapy. There was no evidence of publication bias for any outcome on inspection of funnel plot. Sensitivity analysis based on pre-specified study design characteristics did not change any results. The limited number of mortality events, and

CONCLUSIONS

DAA therapy using first generation protease inhibitors (BOC or TPV) is clearly associated with improved virological response measured by SVR among HCV genotype-1 infection, with or without advanced fibrosis and in both treatment naïve and experienced individuals. There are however increased serious adverse events including anaemia and neutropenia, but with no clear change in treatment discontinuation in the trial setting. There is no data on effectiveness and safety from low or middle income countries, which might limit the generalizability of these findings to those settings.

Implications for practice

Where resources permit, DAA+PR has become the standard of care treatment for HCV genotype-1. However, the side effect profile of current DAA+PR regiments requires experience clinical monitoring and management during therapy.

Implications for research

Improvements in virological response may lead to improvements in liver related morbidity and mortality however there are no direct data available from these studies to make definite conclusions about these longer term outcomes. The significance of severe neutropenia on HCV treatment remains unclear.

FIGURES

Figure 1: Flow chart describing selection of included studies

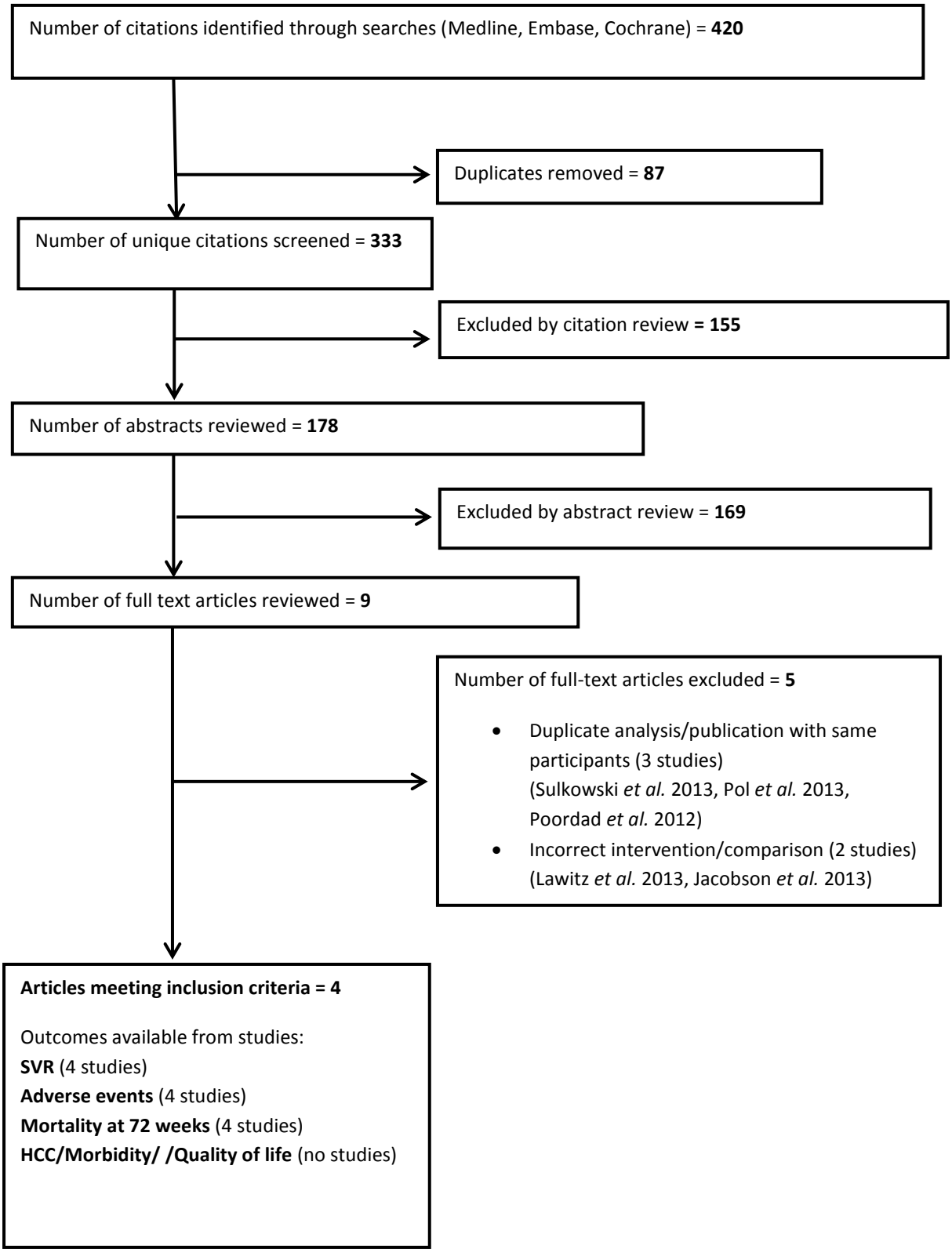


Figure 2: Failure to achieve SVR using DAA+PR versus PR treatment for chronic HCV

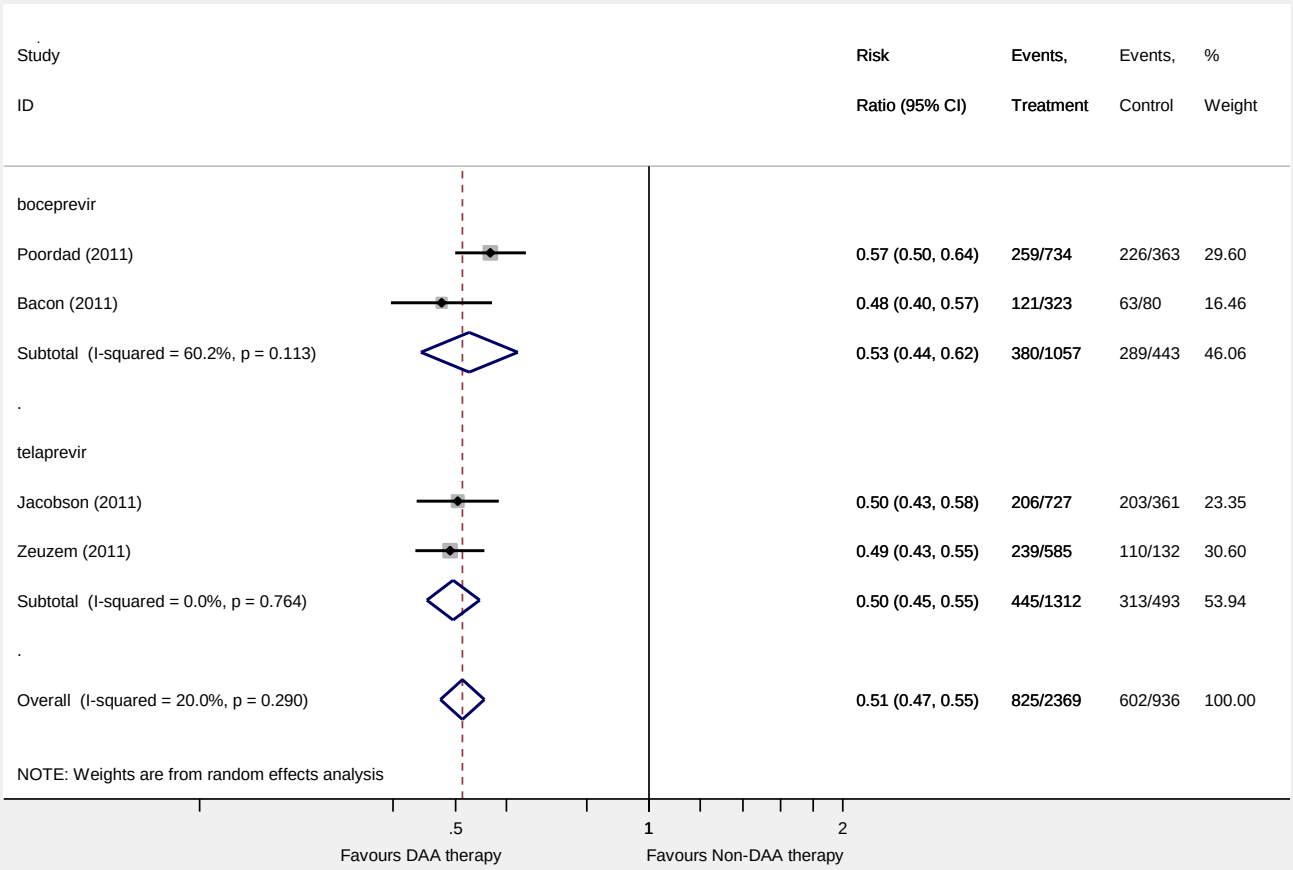


Figure 3a: Failure to achieve SVR using DAA+PR versus PR for chronic HCV, among treatment naïve individuals

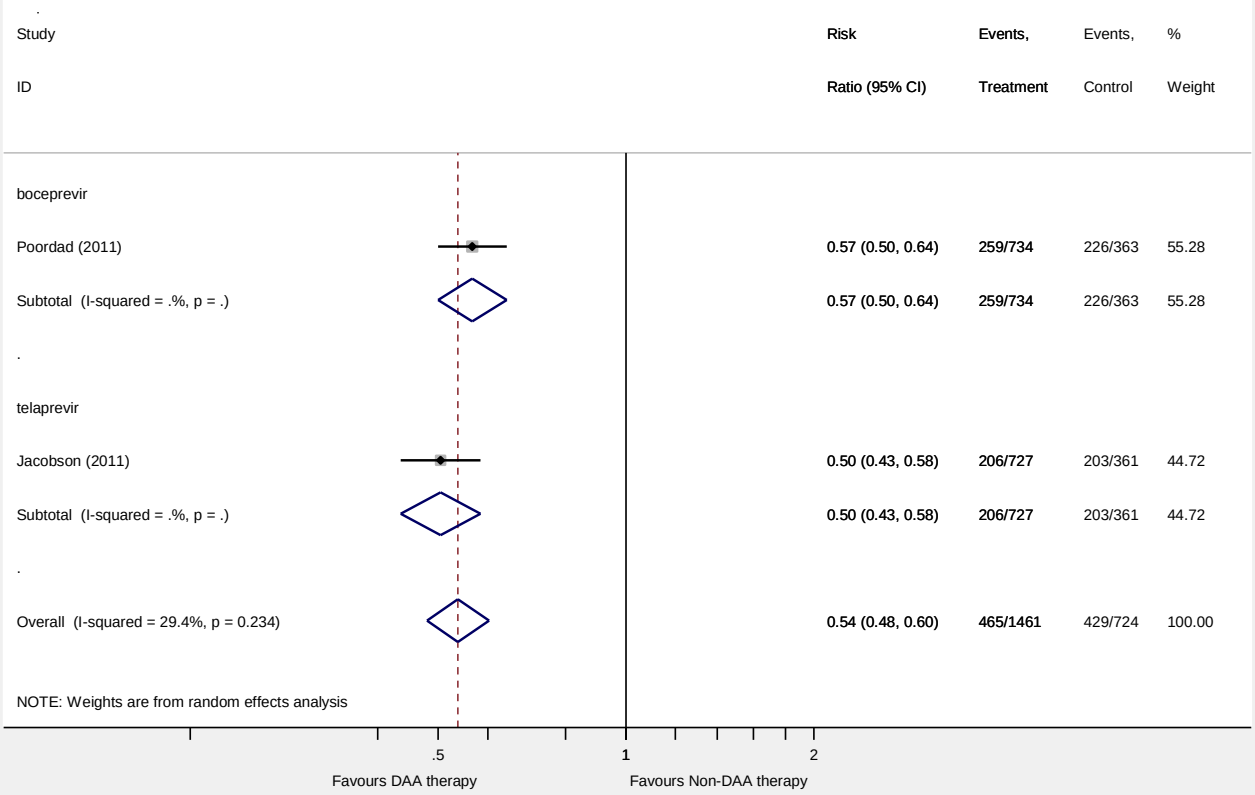


Figure 3b: Failure to achieve SVR using DAA+PR versus PR for chronic HCV, among treatment experience individuals

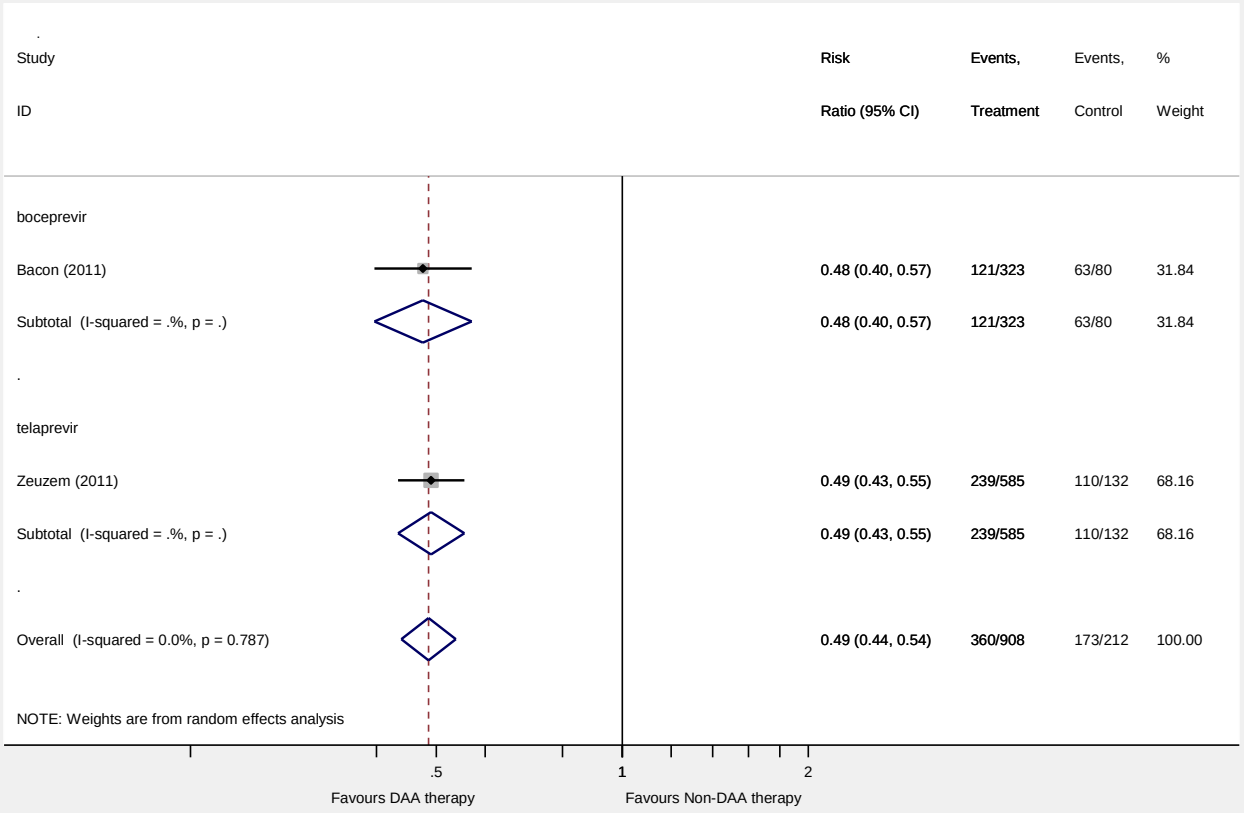


Figure 4a: Failure to achieve SVR using DAA+PR versus PR for chronic HCV, with mild fibrosis (F0-2)

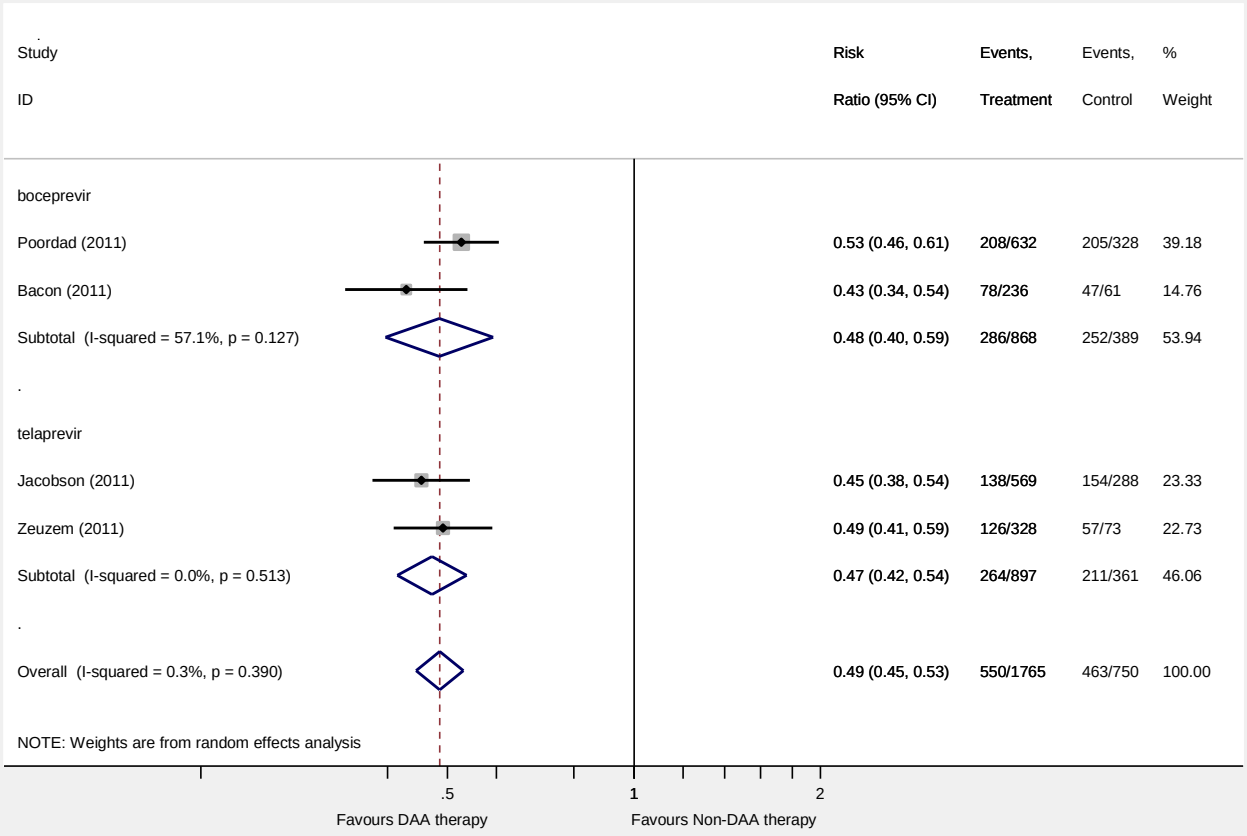
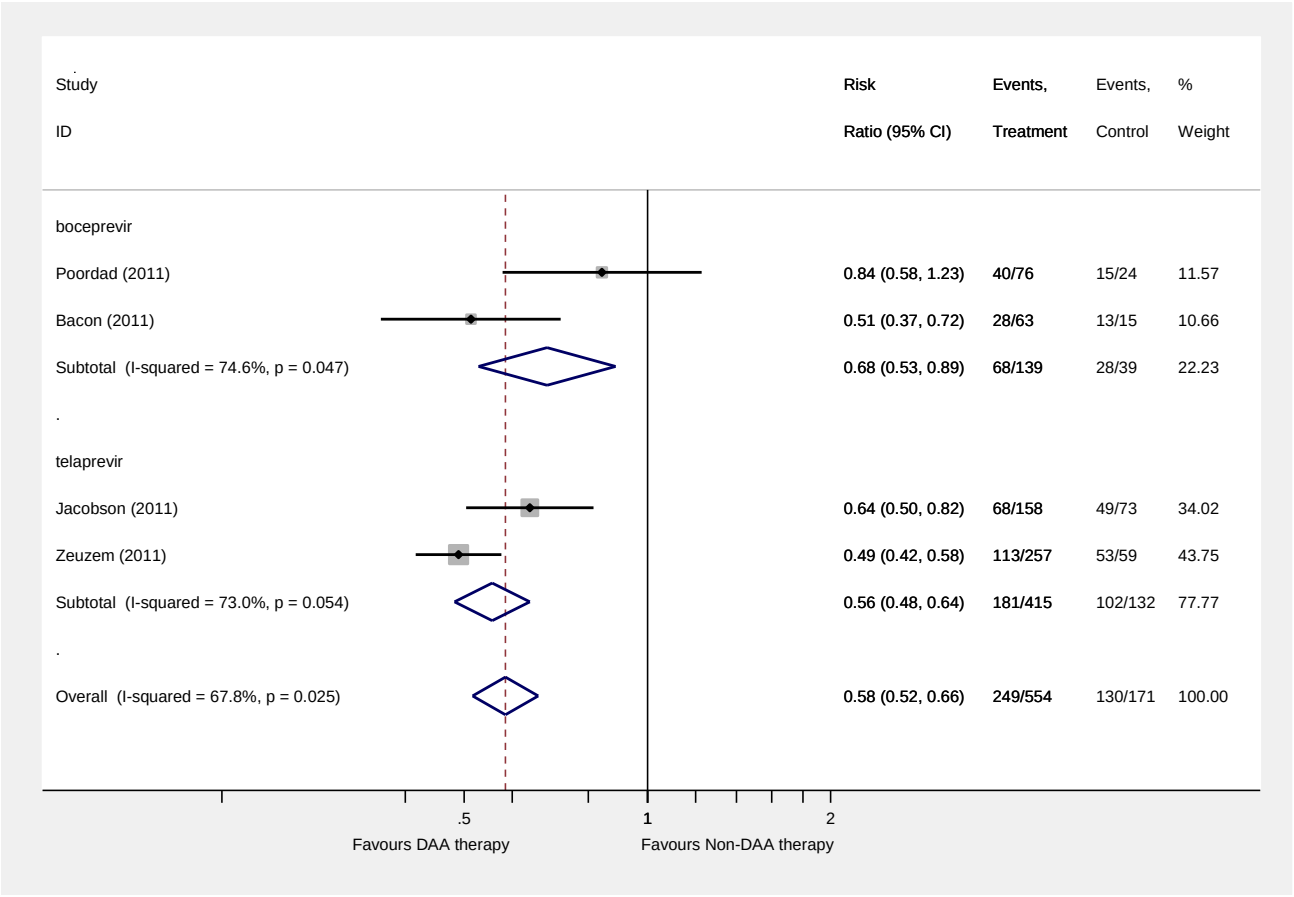


Figure 4b: Failure to achieve SVR using DAA+PR versus PR for chronic HCV, with advanced fibrosis (F3-4)



NB Fixed effects model used given n=2 with broad heterogeneity in this analysis

Figure 5: Adverse Events (Grade 3/4 anaemia) using DAA+PR versus PR for chronic HCV

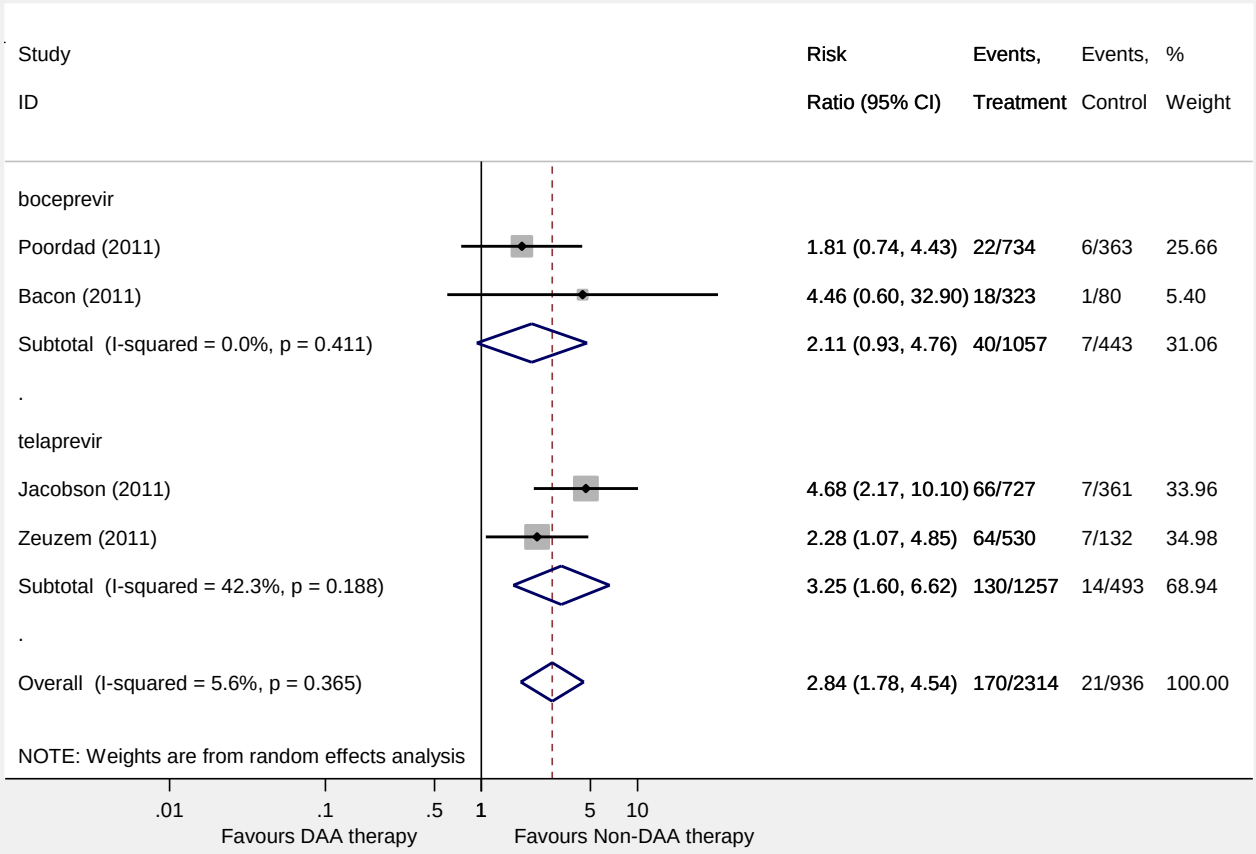


Figure 6: Adverse Events (Grade 3/4 neutropenia) using DAA+PR versus PR for chronic HCV

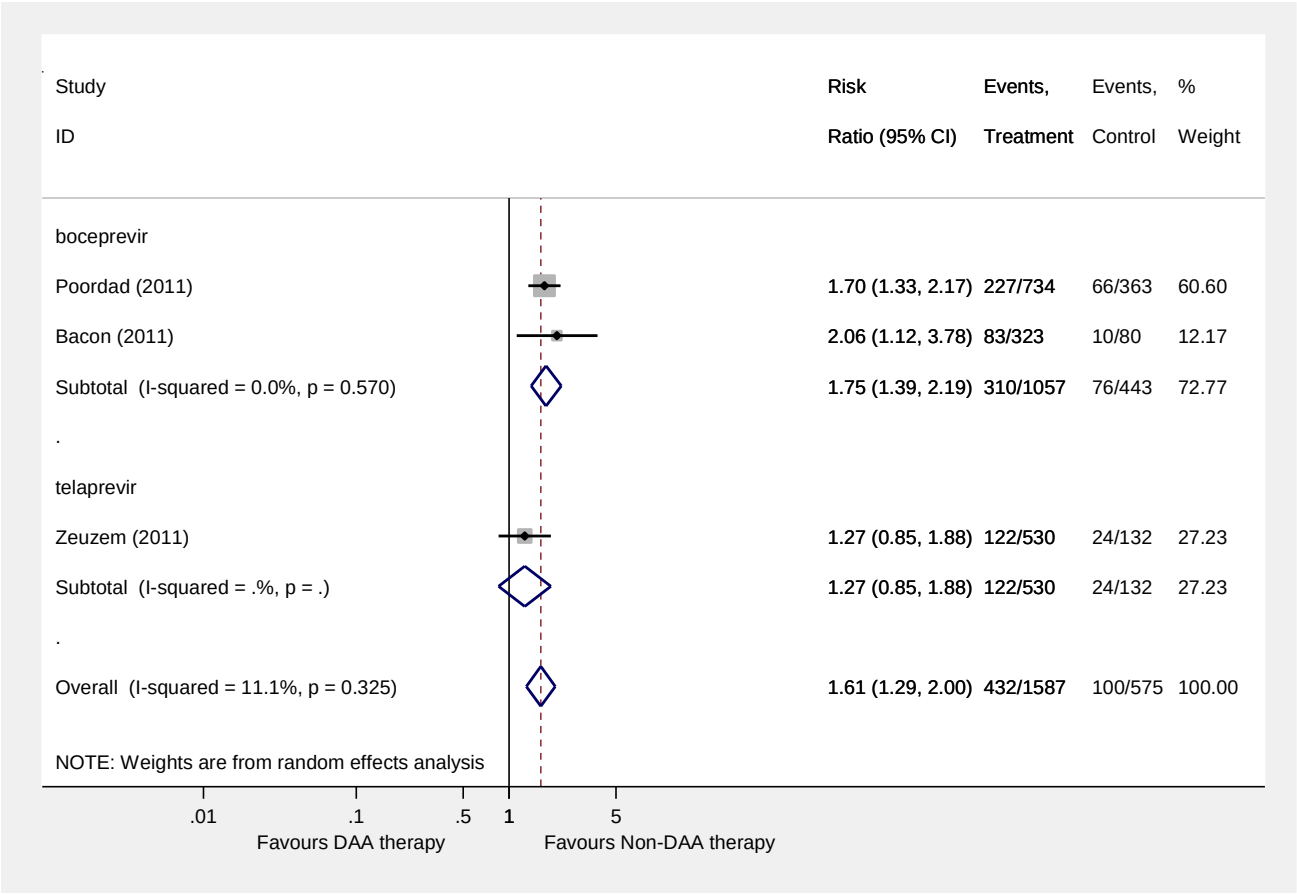
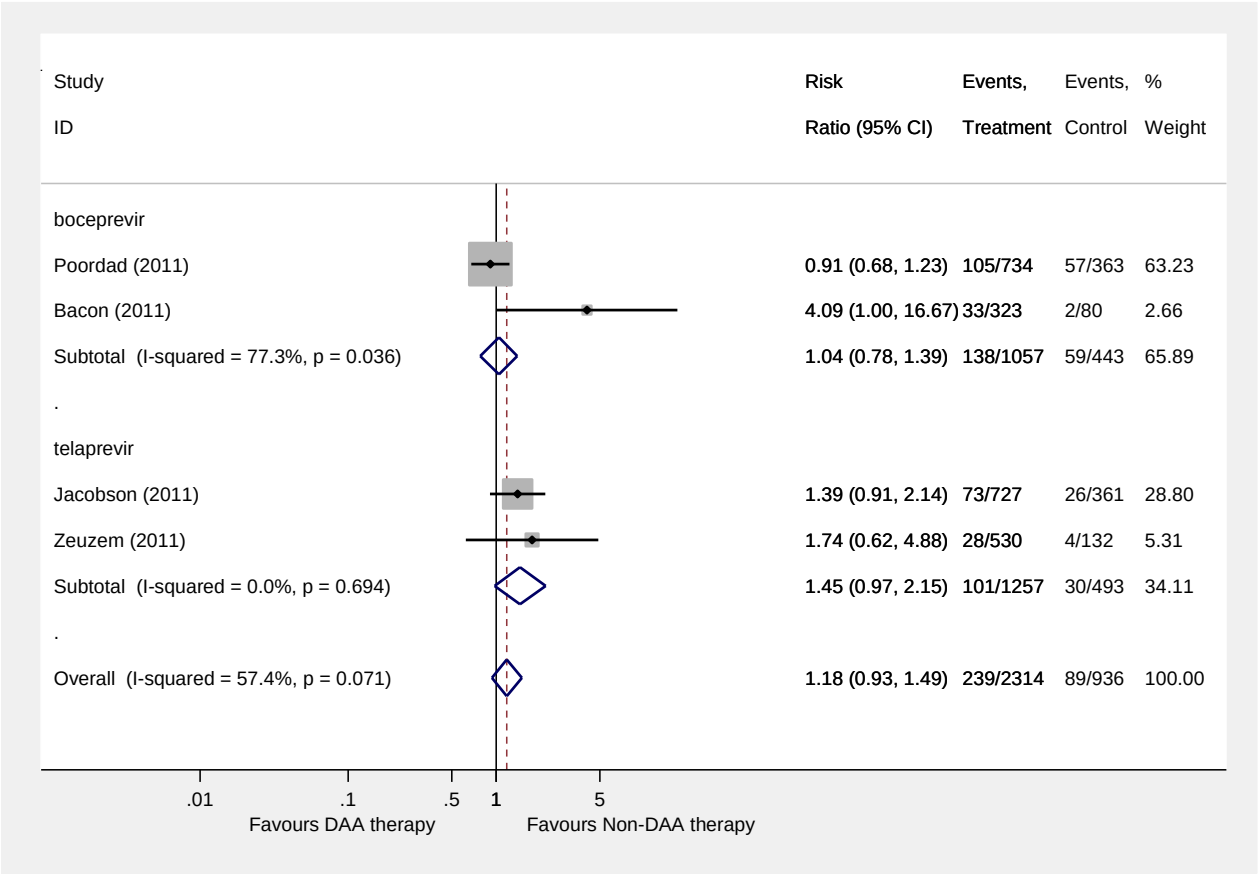


Figure 7a: Adverse Events (Treatment discontinuation) using DAA+PR versus PR for chronic HCV



NB Fixed effects model used given n=2 with broad heterogeneity in this analysis

Figure 7b: Adverse Events (Treatment discontinuation) using DAA+PR versus PR for chronic HCV, sensitivity analysis removing 1 outlier (Bacon *et al.* 2011)

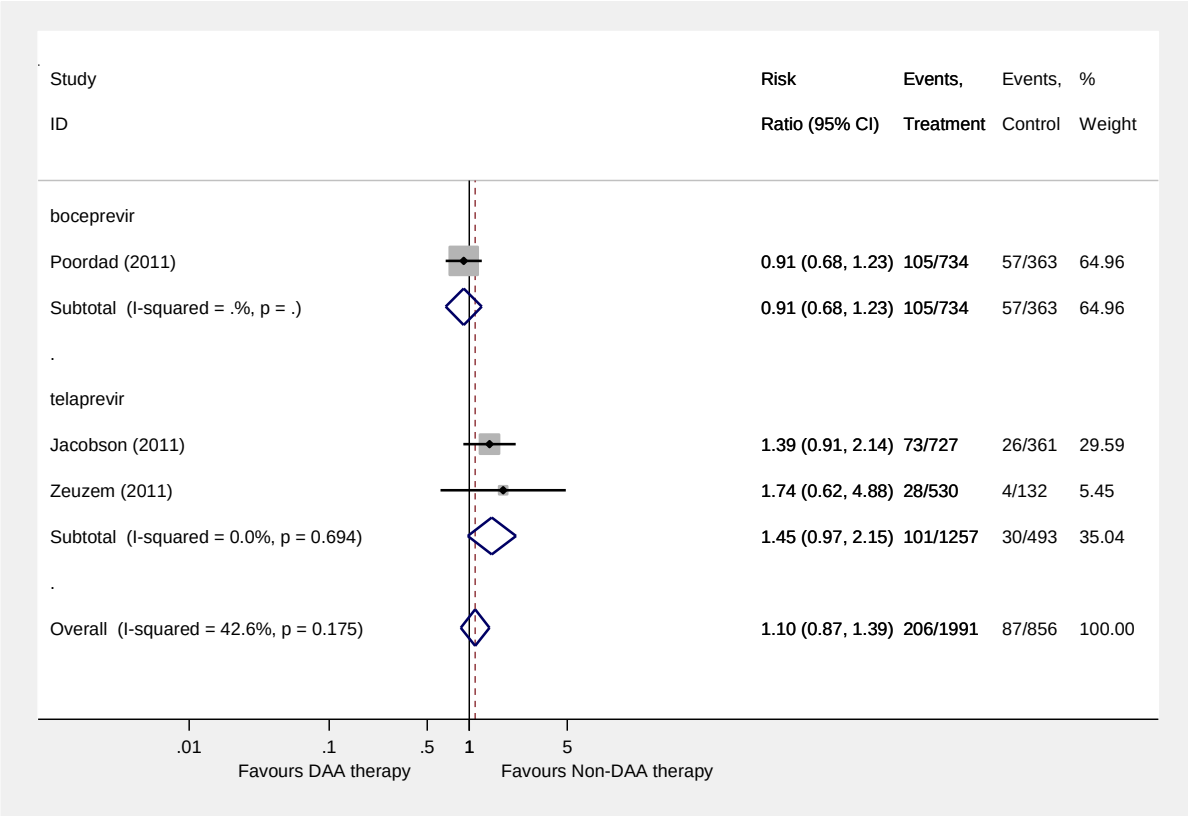
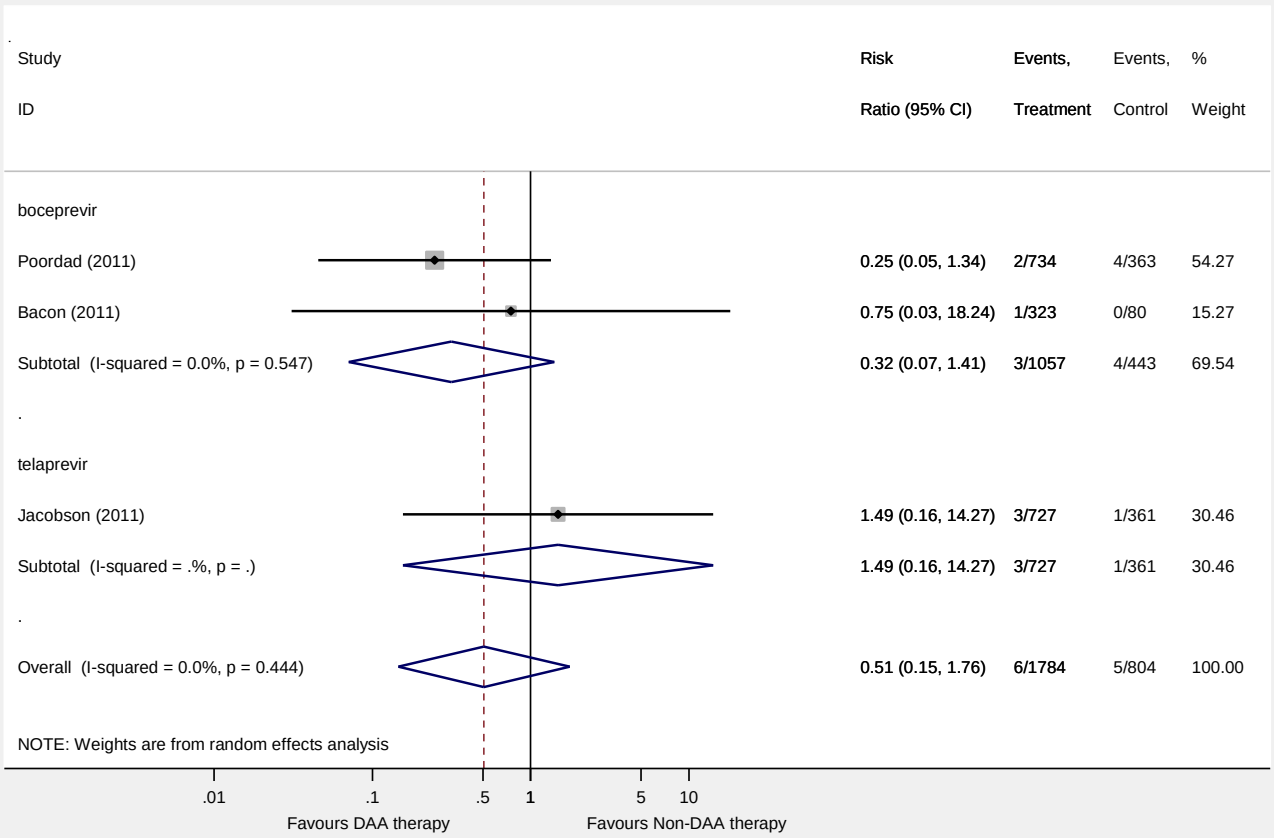


Figure 8: Mortality (to 72 weeks) using DAA+PR versus PR for chronic HCV



TABLES

Table 1: Characteristics of included studies

STUDY	**Poordad *et al.* 2011**	
PARTICIPANTS	Setting and location: USA, Europe Intervention period: 2008-2010 Population: Chronic HCV treatment naïve, HCV Gt-1, adults Study population characteristics: 60% male, 86% Caucasian, 9% advanced fibrosis Study size: 1097 participants, 1:1:1 (experimental 1: experimental 2: control)	
INTERVENTIONS	1. Response guided arm: Lead-in PR (4 weeks) + PR+BOC (800mg orally 8 hourly) for a further 24-44 weeks according to week 8 response (those with detectable HCV RNA at week 8 received a further 20 weeks of PR therapy) 2. Fixed dose arm: Lead-in PR (4 weeks)+ PR + BOC (800mg orally 8 hourly) for a further 44 weeks	
COMPARISON	Peginterferon (2b, 1.5ug/kg/wk) + RBV (600 - 1400mg) plus placebo for 48 weeks	
OUTCOMES	SVR, anaemia, neutropenia, treatment discontinuation, mortality	
COCHRANE RISK OF BIAS ASSESSMENT	Sequence generation?	Low
	Allocation concealment?	Low
	Blinding?	Low
	Incomplete outcome data addressed?	Low
	Free of selective reporting?	Low
	Free of other bias?	Low
QUALITY SUMMARY	Low risk of bias	

STUDY	**Bacon *et al.* 2011**	
PARTICIPANTS	Setting and location: USA, Europe Intervention period: 2008-2010 Population: Chronic HCV Gt-1, adults, treatment experienced with minimum 12 weeks PR with no SVR Study population characteristics: 67% male, 88% Caucasian, 10% advanced fibrosis Study size: 403 participants, 2:2:1 (experimental 1: experimental 2: control)	
INTERVENTIONS	1. Response guided arm: Lead-in PR (4 weeks) + PR+BOC (800mg orally 8 hourly) for 32 weeks, and patients with detectable HCV RNA at week 8 received placebo plus PR for additional 12 weeks 2. Fixed dose arm: Lead-in PR (4 weeks)+ PR + BOC (800mg orally 8 hourly) for a further 44 weeks	
COMPARISON	PEG alpha2b (1.5ug/kg/wk) + RBV (600-1400mg) plus placebo for 48 weeks	
OUTCOMES	SVR, anaemia, neutropenia, treatment discontinuation, mortality	
COCHRANE RISK OF BIAS ASSESSMENT	Sequence generation?	Low
	Allocation concealment?	Low
	Blinding?	Low
	Incomplete outcome data addressed?	Low
	Free of selective reporting?	Low
	Free of other bias?	Low
QUALITY SUMMARY	Low risk of bias	

STUDY	**Jacobson *et al.* 2011**	
PARTICIPANTS	Setting and location: USA, Europe Intervention period: 2008-2010 Population: Chronic HCV Treatment naïve, HCV Gt-1, adults Study population characteristics: 59% male, 88% Caucasian, 20% advanced fibrosis Study size: 1088 participants, 1:1:1 (experimental 1: experimental 2: control)	
INTERVENTIONS	1. Telaprevir 12 group: TPV + PR for 12 weeks, followed by PR alone for 12 weeks if HCV RNA was undetectable at weeks 4 and 12, or for 36 weeks if HCV RNA was detectable at either time point 2. Telaprevir 8 group: TPV + PR for 8 weeks and placebo with PR for 4 weeks, followed by 12 or 36 weeks PR on the basis of the same HCV RNA criteria	
COMPARISON	PEG alpha2a (180ug/wk) + RBV (1000-1200mg/day) plus placebo for 48 weeks	
OUTCOMES	SVR, anaemia, treatment discontinuation, mortality	
COCHRANE RISK OF BIAS ASSESSMENT	Sequence generation?	Low
	Allocation concealment?	Low
	Blinding?	Low
	Incomplete outcome data addressed?	Low
	Free of selective reporting?	Low
	Free of other bias?	Low
QUALITY SUMMARY	Low risk of bias	

STUDY	**Zeuzem *et al.* 2011**	
PARTICIPANTS	Setting and location: USA, Europe Intervention period: 2008-2010 Population: Chronic HCV Gt-1, adults; treatment experienced (minimum 12 weeks PR without achieving SVR) Study population characteristics: 70% male, 93% Caucasian, 48% advanced fibrosis Study size: 717 participants, 2:2:1 (experimental 1: experimental 2: control)	
INTERVENTIONS	1. Telaprevir 12 group: TPV+PR for 12 weeks, followed by PR alone for 36 2. Lead-in Telaprevir 12 group: 4 weeks PR, followed by TPV+PR for 12 weeks, followed by 32 weeks PR alone	
COMPARISON	PEG alpha2a (180ug/wk) + RBV (1000-1200mg/day) plus placebo for 48 weeks	
OUTCOMES	SVR, anaemia, neutropenia, treatment discontinuation, mortality	
COCHRANE RISK OF BIAS ASSESSMENT	Sequence generation?	Low
	Allocation concealment?	Low
	Blinding?	Low
	Incomplete outcome data addressed?	Low
	Free of selective reporting?	Low
	Free of other bias?	Low
QUALITY SUMMARY	Low risk of bias	

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Table 2: Evidence Profile – DAA+PR versus PR in chronic HCV infection

Question: Should direct acting antiviral therapy with PEG/RBV vs PEG/RBV be used for chronic HCV infection?

Quality assessment							Summary of Findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With PEG/RBV	With Direct acting antiviral therapy with PEG/RBV		Risk with PEG/RBV	Risk difference with Direct acting antiviral therapy with PEG/RBV (95% CI)
Failure to achieve SVR (CRITICAL OUTCOME; assessed with: HCV RNA test 6 months post treatment)											
3305 (4 studies) 72 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊕⊕⊕ **HIGH**	602/936 (64.3%)	825/2369 (34.8%)	**RR 0.51** (0.47 to 0.55)	**643 virological failures per 1000**	**315 fewer virological failures per 1000** (from 289 fewer to 341 fewer)
AE (Grade 3 or 4 anaemia) (IMPORTANT OUTCOME; assessed with: Hb <8.5g/dl during treatment)											
3250 (4 studies) 72 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊕⊕⊕ **HIGH**	21/936 (2.2%)	170/2314 (7.3%)	**RR 2.84** (1.78 to 4.54)	**22 anaemia per 1000**	**41 more anaemia per 1000** (from 18 more to 79 more)
AE (Grade 3 or 4 neutropenia) (IMPORTANT OUTCOME; assessed with: Neutrophil count <750/mm3 during therapy)											
2162 (3 studies) 72 weeks	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	undetected	⊕⊕⊕⊖ **MODERATE**[1] due to indirectness	100/575 (17.4%)	432/1587 (27.2%)	**RR 1.61** (1.29 to 2)	**174 neutropenia per 1000**	**106 more neutropenia per 1000** (from 50 more to 174 more)
Adverse event leading to treatment discontinuation (CRITICAL OUTCOME)											
3250 (4 studies) 72 weeks	no serious risk of bias	no serious inconsistency[2]	no serious indirectness	serious[3]	undetected	⊕⊕⊕⊖ **MODERATE**[2,3] due to imprecision	89/936 (9.5%)	239/2314 (10.3%)	**RR 1.18** (0.93 to 1.49)	**95 discontinuation per 1000**	**17 more discontinuation per 1000** (from 7 fewer to 47 more)
Mortality during study (CRITICAL OUTCOME)											
2588 (3 studies) 72 weeks	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision[4]	undetected	⊕⊕⊕⊕ **HIGH**[4]	5/804 (0.62%)	6/1784 (0.34%)	**RR 0.51** (0.15 to 1.76)	**6 deaths per 1000**	**3 fewer deaths per 1000** (from 5 fewer to 5 more)

[1] Neutropenia not clearly related to infections or changes in management
[2] Inconsistency in finding due to imprecision in effect, so this outcome was only rated down for imprecision
[3] Imprecision due to definitions of adverse events and relationship to outcome
[4] This outcome was not marked down for imprecision despite only a few events because of the large sample size

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APPENDICIES

Appendix 1: Search Syntax

OVID EMBASE

1996 to 16 May 2013

281 Records

1 exp hepatitis c/
2 hepatitis c.ti,ab.
3 hcv.ti,ab
4 1 or 2 or 3
5 direct acting antiviral or daa or direct acting.ti,ab.
6 protease inhibitor.ti,ab.
7 boceprevir or victrelis.ti,ab.
8 telaprevir or incivo.or incivek.ti,ab.
9 nucleo*ide analogue or nucleoside analogue or nucleotide analogue.ti,ab
10 ns5a inhibitor.ti,ab.
11 ns5b inhibitor.ti,ab
12 polymerase inhibitor.ti,ab.
13 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14 4 and 13
15 limit 14 to (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or controlled clinical trial or randomized controlled trial)

OVID MEDLINE

1946 to 16 May 2013

137 Records

1 exp hepatitis c/
2 hepatitis c.ti,ab.
3 hcv.ti,ab
4 1 or 2 or 3
5 direct acting antiviral or daa or direct acting.ti,ab.
6 protease inhibitor.ti,ab.
7 boceprevir or victrelis.ti,ab.
8 telaprevir or incivo.or incivek.ti,ab.
9 nucleo*ide analogue or nucleoside analogue or nucleotide analogue.ti,ab
10 ns5a inhibitor.ti,ab.
11 ns5b inhibitor.ti,ab
12 polymerase inhibitor.ti,ab.
13 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14 4 and 13

15 limit 14 to (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or controlled clinical trial or randomized controlled trial)

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1 MeSH descriptor: [Hepatitis C] explode all trees
2 hepacivirus:ti,ab,kw (Word variations have been searched)
3 HCV:ti,ab,kw (Word variations have been searched)
4 Hepatitis C:ti,ab,kw (Word variations have been searched)
5 HepC:ti,ab,kw (Word variations have been searched)
6 hep C:ti,ab,kw (Word variations have been searched)
7 #1 or #2 or #3 or #4 or #5 or #6
8 MeSH descriptor: [Antiviral Agents] explode all trees
9 antiviral agents:ti,ab,kw (Word variations have been searched)
10 MeSH descriptor: [Interferon-alpha] explode all trees
11 "pegylated interferon" or :interferon-alpha":ti,ab,kw
12 "direct-acting antiviral".ti.ab.kw
13 #8 or #9 or #10 or #11 or #12
14 #7 and #13

Appendix 2: Cochrane Collaboration's tool for assessing risk of bias

Domain	Description	Review authors' judgement
Sequence generation.	Describe the method used to generate the allocation sequence in sufficient detail to Allow an assessment of whether it should produce comparable groups.	Was the allocation sequence adequately generated?
Allocation concealment.	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.	Was allocation adequately concealed?
Blinding of participants, personnel and outcome assessors *Assessments should be made for each main outcome (or class of outcomes).*	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Was knowledge of the allocated intervention adequately prevented during the study?
Incomplete outcome data *Assessments should be made for each main outcome (or class of outcomes).*	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.	Were incomplete outcome data adequately addressed?
Selective outcome reporting.	State how the possibility of selective outcome reporting was examined by the review authors, and what was found.	Are reports of the study free of suggestion of selective outcome reporting?
Other sources of bias.	State any important concerns about bias not addressed in the other domains in the tool. If particular questions/entries were pre-specified in the review's protocol, responses should be provided for each question/entry.	Was the study apparently free of other problems that could put it at a high risk of bias?

Appendix 3: GRADE approach to assessing the quality of evidence across studies

<table>
<tr><th>Quality of Evidence (summary score)</th><th>Study Design</th><th>Downgrading Factors</th><th>Upgrading Factors</th></tr>
<tr><td>High (4) =Further research is very unlikely to change our confidence in the estimate of effect.</td><td>Randomized trials or valid accuracy studies for diagnostic tests begin with a score of High (4)</td><td rowspan="4">Study Limitations:
-1 Serious
-2 Very serious

Consistency:
-1 Serious
-2 Very serious

Directness:
-1 Serious
-2 Very serious

Precision:
-1 Serious
-2 Very serious

Publication Bias:
-1 Serious
-2 Very serious</td><td rowspan="4">Large effect
+1 Large
+2 Very large

Plausible confounding would change the effect
+1

Dose-response gradient
+1 if Present</td></tr>
<tr><td>Moderate (3) = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.</td><td></td></tr>
<tr><td>Low (2) = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.</td><td>Observational studies or indirect accuracy studies for diagnostic tests begin with a score of low (2).</td></tr>
<tr><td>Very low (1) = Any estimate of effect is very uncertain.</td><td></td></tr>
</table>