Cochrane Library

Cochrane Database of Systematic Reviews

Pharmacological interventions for primary biliary cholangitis (Review)

Saffioti F, Gurusamy KS, Eusebi LH, Tsochatzis E, Davidson BR, Thorburn D

Saffioti F, Gurusamy KS, Eusebi LH, Tsochatzis E, Davidson BR, Thorburn D.
Pharmacological interventions for primary biliary cholangitis.
Cochrane Database of Systematic Reviews 2017, Issue 3. Art. No.: CD011648.
DOI: 10.1002/14651858.CD011648.pub2.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Pharmacological interventions for primary biliary cholangitis

Francesca Saffioti[1,2], Kurinchi Selvan Gurusamy[3], Leonardo Henry Eusebi[4,5], Emmanuel Tsochatzis[1], Brian R Davidson[3], Douglas Thorburn[1]

[1]Sheila Sherlock Liver Centre, Royal Free Hospital and the UCL Institute of Liver and Digestive Health, London, UK. [2]Department of Clinical and Experimental Medicine, Division of Clinical and Molecular Hepatology, University of Messina, Messina, Italy. [3]Department of Surgery, Royal Free Campus, UCL Medical School, London, UK. [4]The Royal Free Sheila Sherlock Liver Centre, Royal Free Hampstead NHS Foundation Trust and UCL Institute of Liver and Digestive Health, London, UK. [5]Department of Medical and Surgical Sciences (DIMEC), University of Bologna, Bologna, Italy

Contact: Kurinchi Selvan Gurusamy, Department of Surgery, Royal Free Campus, UCL Medical School, Royal Free Hospital, Rowland Hill Street, London, NW3 2PF, UK. k.gurusamy@ucl.ac.uk.

Editorial group: Cochrane Hepato-Biliary Group.
Publication status and date: Edited (no change to conclusions), published in Issue 4, 2017.

Citation: Saffioti F, Gurusamy KS, Eusebi LH, Tsochatzis E, Davidson BR, Thorburn D. Pharmacological interventions for primary biliary cholangitis. *Cochrane Database of Systematic Reviews* 2017, Issue 3. Art. No.: CD011648. DOI: 10.1002/14651858.CD011648.pub2.

ABSTRACT

Background

Primary biliary cholangitis (previously primary biliary cirrhosis) is a chronic liver disease caused by the destruction of small intra-hepatic bile ducts resulting in stasis of bile (cholestasis), liver fibrosis, and liver cirrhosis. The optimal pharmacological treatment of primary biliary cholangitis remains uncertain.

Objectives

To assess the comparative benefits and harms of different pharmacological interventions in the treatment of primary biliary cholangitis through a network meta-analysis and to generate rankings of the available pharmacological interventions according to their safety and efficacy. However, it was not possible to assess whether the potential effect modifiers were similar across different comparisons. Therefore, we did not perform the network meta-analysis and instead assessed the comparative benefits and harms of different interventions using standard Cochrane methodology.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 2), MEDLINE, Embase, Science Citation Index Expanded, World Health Organization International Clinical Trials Registry Platform, and randomised controlled trials registers to February 2017 to identify randomised clinical trials on pharmacological interventions for primary biliary cholangitis.

Selection criteria

We included only randomised clinical trials (irrespective of language, blinding, or publication status) in participants with primary biliary cholangitis. We excluded trials which included participants who had previously undergone liver transplantation. We considered any of the various pharmacological interventions compared with each other or with placebo or no intervention.

Data collection and analysis

We used standard methodological procedures expected by Cochrane. We calculated the odds ratio (OR) and rate ratio with 95% confidence intervals (CI) using both fixed-effect and random-effects models based on available-participant analysis with Review Manager 5. We assessed risk of bias according to Cochrane, controlled risk of random errors with Trial Sequential Analysis, and assessed the quality of the evidence using GRADE.

Main results

We identified 74 trials including 5902 participants that met the inclusion criteria of this review. A total of 46 trials (4274 participants) provided information for one or more outcomes. All the trials were at high risk of bias in one or more domains. Overall, all the evidence was low or very low quality. The proportion of participants with symptoms varied from 19.9% to 100% in the trials that reported this information. The proportion of participants who were antimitochondrial antibody (AMA) positive ranged from 80.8% to 100% in the trials that reported this information. It appeared that most trials included participants who had not received previous treatments or included participants regardless of the previous treatments received. The follow-up in the trials ranged from 1 to 96 months.

The proportion of people with mortality (maximal follow-up) was higher in the methotrexate group versus the no intervention group (OR 8.83, 95% CI 1.01 to 76.96; 60 participants; 1 trial; low quality evidence). The proportion of people with mortality (maximal follow-up) was lower in the azathioprine group versus the no intervention group (OR 0.56, 95% CI 0.32 to 0.98; 224 participants; 2 trials; $I^2 = 0\%$; low quality evidence). However, it has to be noted that a large proportion of participants (25%) was excluded from the trial that contributed most participants to this analysis and the results were not reliable. There was no evidence of a difference in any of the remaining comparisons. The proportion of people with serious adverse events was higher in the D-penicillamine versus no intervention group (OR 28.77, 95% CI 1.57 to 526.67; 52 participants; 1 trial; low quality evidence). The proportion of people with serious adverse events was higher in the obeticholic acid plus ursodeoxycholic acid (UDCA) group versus the UDCA group (OR 3.58, 95% CI 1.02 to 12.51; 216 participants; 1 trial; low quality evidence). There was no evidence of a difference in any of the remaining comparisons for serious adverse events (proportion) or serious adverse events (number of events). None of the trials reported health-related quality of life at any time point.

Funding: nine trials had no special funding or were funded by hospital or charities; 31 trials were funded by pharmaceutical companies; and 34 trials provided no information on source of funding.

Authors' conclusions

Based on very low quality evidence, there is currently no evidence that any intervention is beneficial for primary biliary cholangitis. However, the follow-up periods in the trials were short and there is significant uncertainty in this issue. Further well-designed randomised clinical trials are necessary. Future randomised clinical trials ought to be adequately powered; performed in people who are generally seen in the clinic rather than in highly selected participants; employ blinding; avoid post-randomisation dropouts or planned cross-overs; should have sufficient follow-up period (e.g. five or 10 years or more); and use clinically important outcomes such as mortality, health-related quality of life, cirrhosis, decompensated cirrhosis, and liver transplantation. Alternatively, very large groups of participants should be randomised to facilitate shorter trial duration.

PLAIN LANGUAGE SUMMARY

Medical treatment of primary biliary cholangitis

Background

Primary biliary cholangitis (previously called primary biliary cirrhosis) is a chronic liver disease caused by the destruction of small bile ducts within the liver (tubes that carry the bile produced by the liver) resulting in stagnation of bile (cholestasis) and liver damage and replacement of liver cells with scar tissue (liver cirrhosis). The best way to treat people with primary biliary cholangitis is unclear. We sought to resolve this issue by searching for existing trials on the topic. We included all randomised clinical trials (clinical studies where people are randomly put into one of two or more intervention groups) reported to February 2017. We included only trials in which participants with primary biliary cholangitis had not undergone liver transplantation previously. Apart from using standard Cochrane methods which allow comparison of only two treatments at a time (direct comparison), we planned to use an advanced method which allows comparison of the many different treatments that are individually compared in the trials (network meta-analysis). However, because of the nature of the information available, we could not determine whether the network meta-analysis results were reliable. Therefore, we used standard Cochrane methodology.

Study characteristics

We identified 74 randomised clinical trials (5902 participants). Of these, 46 randomised clinical trials (4274 participants) provided information for one or more measures (outcomes). The trials included people with primary biliary cholangitis with and without symptoms; with and without antimitochondrial antibody (AMA) (an indicator of primary biliary cholangitis) regardless of whether they received previous treatments. The average follow-up period in the trials ranged from one month to eight years in the trials that reported this information.

Funding: nine trials receive no additional funding or were funded by parties with no vested interest in the results. Thirty-one trials were partially or fully funded by the pharmaceutical companies that would benefit based on the results of the trial. The source of funding was not available from the remaining trials.

Quality of evidence

The overall quality of evidence was very low and all the trials were at high risk of bias, which means that there is possibility of making wrong conclusions overestimating benefits or underestimating harms of one treatment or the other because of the way that the trials were conducted.

Key results

There was no reliable evidence of decrease in the deaths between any of the interventions versus no intervention. There was no evidence of decrease in serious complications or complications of any severity between any of the treatments and no treatment. None of the trials reported health-related quality of life (a measure of a person's satisfaction with their life and health) at any time point.

Overall, there is currently no evidence of benefit of any intervention in primary biliary cholangitis. There is significant uncertainty in this issue and further high-quality randomised clinical trials are required.

Summary of findings for the main comparison. Ursodeoxycholic acid (UDCA) versus no intervention for primary biliary cholangitis

UDCA versus no intervention for primary biliary cholangitis

Patient or population: people with primary biliary cholangitis

Settings: secondary or tertiary care

Intervention: UDCA

Comparison: no intervention

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (trials)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	No intervention	UDCA			
Mortality at maximal follow-up Follow-up: 12 to 89 months	**208 per 1000**	**206 per 1000** (136 to 301)	**OR 0.99** (0.60 to 1.64)	**734** (6 trials)	⊕⊖⊖⊖ **Very low** [1,2]
Serious adverse events (proportion) Follow-up: 12 to 41 months	There were no events in either group			**380** (3 trials)	⊕⊖⊖⊖ **Very low** [1,2,3]
Serious adverse events (number of events)	None of the trials reported this outcome.				
Health-related quality of life	None of the trials reported this outcome.				

*The basis for the **assumed risk** is the mean control group proportion across all the trials. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **OR:** odds ratio; **UDCA:** ursodeoxycholic acid.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: 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.
Very low quality: We are very uncertain about the estimate.

[1] Risk of bias in the trial(s) was high (downgraded by two levels).
[2] Sample sizes were small and 95% confidence intervals overlapped clinically significant and clinically insignificant or no effect (downgraded by two levels).

[3] There was moderate heterogeneity (downgraded by one level).

Summary of findings 2. Azathioprine versus no intervention for primary biliary cholangitis

Azathioprine versus no intervention for primary biliary cholangitis

Patient or population: people with primary biliary cholangitis

Settings: secondary or tertiary care

Intervention: azathioprine

Comparison: no intervention

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (trials)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	No intervention	Azathioprine			
Mortality at maximal follow-up Follow-up: 63 months in 1 trial and not stated in 1 trial	**208 per 1000**	**128 per 1000** (78 to 205)	**OR 0.56** (0.32 to 0.98)	**224** (2 trials)	⊕⊖⊖⊖ **Very low** [1,2]
Serious adverse events (proportion)	None of the trials reported this outcome.				
Serious adverse events (number of events)	None of the trials reported this outcome.				
Health-related quality of life	None of the trials reported this outcome.				

*The basis for the **assumed risk** is the mean control group proportion across all the trials. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **OR:** odds ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: 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.
Very low quality: We are very uncertain about the estimate.

[1] Risk of bias in the trial(s) was high (downgraded by two levels).
[2] Sample sizes were small and 95% confidence intervals overlapped clinically significant and clinically insignificant or no effect (downgraded by two levels).

Summary of findings 3. Colchicine versus no intervention for primary biliary cholangitis

Colchicine versus no intervention for primary biliary cholangitis

Patient or population: people with primary biliary cholangitis

Settings: secondary or tertiary care

Intervention: colchicine

Comparison: no intervention

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (trials)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	No intervention	Colchicine			
Mortality at maximal follow-up Follow-up: 12 to 24 months	**208 per 1000**	**168 per 1000** (78 to 327)	**OR 0.77** (0.32 to 1.85)	**122** (2 trials)	⊕⊖⊖⊖ **Very low** [1,2]
Serious adverse events (proportion) Follow-up: 12 months	There were no events in either group			**64** (1 trial)	⊕⊖⊖⊖ **Very low** [1,2,3]
Serious adverse events (number of events)	None of the trials reported this outcome.				
Health-related quality of life	None of the trials reported this outcome.				

*The basis for the **assumed risk** is the mean control group proportion across all the trials. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **OR:** odds ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: 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.
Very low quality: We are very uncertain about the estimate.

[1] Risk of bias in the trial(s) was high (downgraded by two levels).
[2] Sample sizes were small and 95% confidence intervals overlapped clinically significant and clinically insignificant or no effect (downgraded by two levels).
[3] There was moderate heterogeneity (downgraded by one level).

Summary of findings 4. Ciclosporin versus no intervention for primary biliary cholangitis

Ciclosporin versus no intervention for primary biliary cholangitis

Patient or population: people with primary biliary cholangitis

Settings: secondary or tertiary care

Intervention: ciclosporin

Comparison: no intervention

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (trials)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	No intervention	Ciclosporin			
Mortality at maximal follow-up Follow-up: 31 to 35 months	**208 per 1000**	**188 per 1000** (118 to 283)	**OR 0.88** (0.51 to 1.50)	**390** (3 trials)	⊕⊖⊖⊖ **Very low** [1,2]
Serious adverse events (proportion)	None of the trials reported this outcome.				
Serious adverse events (number of events)	None of the trials reported this outcome.				
Health-related quality of life	None of the trials reported this outcome.				

*The basis for the **assumed risk** is the mean control group proportion across all the trials. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **OR:** odds ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: 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.
Very low quality: We are very uncertain about the estimate.

[1] Risk of bias in the trial(s) was high (downgraded by two levels).
[2] Sample sizes were small and 95% confidence intervals overlapped clinically significant and clinically insignificant or no effect (downgraded by two levels).

Summary of findings 5. D-Penicillamine versus no intervention for primary biliary cholangitis

D-Penicillamine versus no intervention for primary biliary cholangitis

Patient or population: people with primary biliary cholangitis

Settings: secondary or tertiary care

Intervention: D-penicillamine

Comparison: no intervention

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (trials)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	No intervention	D-Penicillamine			
Mortality at maximal follow-up (Follow-up 24 to 66 months)	**208 per 1000**	**191 per 1000** (130 to 274)	**OR 0.90** (0.57 to 1.44)	**423** (5 trials)	⊕⊖⊖⊖ **Very low** [1,2,3]
Serious adverse events (proportion) (Follow-up 24 months)	**4 per 1000**	**104 per 1000** (6 to 679)	**OR 28.77** (1.57 to 526.67)	**52** (1 trial)	⊕⊖⊖⊖ **Very low** [1,2,3]
Serious adverse events (number of events)	None of the trials reported this outcome.				
Health-related quality of life	None of the trials reported this outcome.				

*The basis for the **assumed risk** is the mean control group proportion across all the trials. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **OR:** odds ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: 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.
Very low quality: We are very uncertain about the estimate.

[1] Risk of bias in the trial(s) was high (downgraded by two levels).
[2] Sample sizes were small and 95% confidence intervals overlapped clinically significant and clinically insignificant or no effect (downgraded by two levels).
[3] There was moderate heterogeneity (downgraded by one level).

Summary of findings 6. Colchicine plus ursodeoxycholic acid (UDCA) versus UDCA for primary biliary cholangitis

Colchicine plus UDCA versus UDCA for primary biliary cholangitis

Patient or population: people with primary biliary cholangitis

Settings: secondary or tertiary care

Intervention: colchicine + UDCA

Comparison: UDCA

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (trials)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	UDCA	Colchicine + UDCA			
Mortality at maximal follow-up Follow-up: 24 months in 1 trial; not reported in 1 trial	**110 per 1000**	**185 per 1000** (45 to 524)	**OR 1.84** (0.38 to 8.91)	**158** (2 trials)	⊕⊖⊖⊖ **Very low** [1,2]
Serious adverse events (proportion) Follow-up: not stated	**14 per 1000**	**42 per 1000** (2 to 526)	**OR 3.08** (0.12 to 78.14)	**74** (1 trial)	⊕⊖⊖⊖ **Very low** [1,2,3]
Serious adverse events (number of events)	None of the trials reported this outcome.				
Health-related quality of life	None of the trials reported this outcome.				

*The basis for the **assumed risk** is the mean control group proportion across all the trials. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **OR:** odds ratio; **UDCA:** ursodeoxycholic acid.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: 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.
Very low quality: We are very uncertain about the estimate.

[1] Risk of bias in the trial(s) was high (downgraded by two levels).
[2] Sample sizes were small and 95% confidence intervals overlapped clinically significant and clinically insignificant or no effect (downgraded by two levels).
[3] There was moderate heterogeneity (downgraded by one level).

Summary of findings 7. Methotrexate plus ursodeoxycholic acid (UDCA) versus UDCA for primary biliary cholangitis

Methotrexate plus UDCA versus UDCA for primary biliary cholangitis

Patient or population: people with primary biliary cholangitis

Settings: secondary or tertiary care

Intervention: methotrexate + UDCA

Comparison: UDCA

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (trials)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	UDCA	Methotrexate + UDCA			
Mortality at maximal follow-up Follow-up: 11 to 91 months	**110 per 1000**	**126 per 1000** (64 to 237)	**OR 1.17** (0.55 to 2.51)	**290** (2 trials)	⊕⊖⊖⊖ **Very low** [1,2]
Serious adverse events (proportion)	None of the trials reported this outcome.				
Serious adverse events (number of events)	None of the trials reported this outcome.				
Health-related quality of life	None of the trials reported this outcome.				

*The basis for the **assumed risk** is the mean control group proportion across all the trials. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **OR:** odds ratio; **UDCA:** ursodeoxycholic acid.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: 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.
Very low quality: We are very uncertain about the estimate.

[1] Risk of bias in the trial(s) was high (downgraded by two levels).
[2] Sample sizes were small and 95% confidence intervals overlapped clinically significant and clinically insignificant or no effect (downgraded by two levels).
[3] There was moderate heterogeneity (downgraded by one level).

BACKGROUND

Description of the condition

Primary biliary cholangitis (previously named primary biliary cirrhosis) is a chronic liver disease caused by the destruction of small intrahepatic bile ducts resulting in stasis of bile (cholestasis), liver fibrosis, and liver cirrhosis (NCBI 2014). There is global variation in the incidence and prevalence of primary biliary cholangitis with annual incidence varying from 1.6 to 3.2 per 100,000 people and prevalence varying from 5 to 38 per 100,000 people, with a trend of increasing incidence and prevalence in many countries (Metcalf 1997; Boberg 1998; Kim 2000; Sood 2004; Lazaridis 2007; Pla 2007; Rautiainen 2007; Myers 2009; Baldursdottir 2012; Boonstra 2014). It is more common in women, particularly aged 25 to 40 years (Metcalf 1997; Kim 2000; Gershwin 2005; Pla 2007; Myers 2009; Baldursdottir 2012). The mean age at diagnosis is 40 to 60 years (Kim 2000; Parikh-Patel 2001; Gershwin 2005; Myers 2009; Baldursdottir 2012).

The aetiology of primary biliary cholangitis is unclear. The associations with primary biliary cholangitis include family history of primary biliary cholangitis, Sjögren's syndrome (autoimmune disease characterised by dry mouth and dry eyes), systemic lupus erythematosus (autoimmune connective tissue disorder), autoimmune thyroid disease, multiple sclerosis (autoimmune disorder of the central nervous system), scleroderma (autoimmune disease affecting the skin and internal organs), polymyositis (chronic inflammation of the muscles, possibly an autoimmune disease), history of cigarette smoking, history of hair dye use, and urinary tract infections (Parikh-Patel 2001; Gershwin 2005; Lazaridis 2007; Prince 2010; Lammert 2013). People with primary biliary cholangitis have other coexisting autoimmune disorders such as rheumatoid arthritis, systemic lupus erythematosus, autoimmune thyroid disease, multiple sclerosis, scleroderma, and polymyositis (Parikh-Patel 2001; Gershwin 2005; Prince 2010; Lammert 2013). Although the strong association between personal and family history of autoimmune diseases suggests that primary biliary cholangitis may have an autoimmune aetiology, the clustering of primary biliary cholangitis in certain areas and associations between primary biliary cholangitis and hair dye use, past smoking, and history of urinary tract infections have prompted people to consider environmental factors such as toxins and infections as possible aetiologies or triggering factors for primary biliary cholangitis (Leung 2005; Dronamraju 2010; Prince 2010; Selmi 2010).

A significant proportion of people with primary biliary cholangitis are asymptomatic at the time of diagnosis (up to about 60% in some studies (Pla 2007)). Itching and fatigue are the most common symptoms (Pla 2007; Myers 2009). Other ways of clinical presentation include Raynaud's syndrome (bluish discolouration of the fingers and toes due to vasospasm in response to cold or emotional stress); features of portal hypertension; osteoporosis; high cholesterol (particularly high ratio of high-density lipoprotein cholesterol (which is considered protective for the heart) to low-density lipoprotein cholesterol); and rarely deficiencies of vitamin A, vitamin D, vitamin E, and vitamin K (Kim 2000; Gershwin 2005; Pla 2007; Myers 2009; Baldursdottir 2012). Approximately 3% to 8% of people require liver transplantation in about five to six years from diagnosis (Kim 2000; Lindor 2009; Myers 2009; Baldursdottir 2012). Approximately 3% to 4% of people with primary biliary cholangitis die every year, usually because of liver-related causes such as decompensated liver disease or hepatocellular carcinoma (Rautiainen 2007; Myers 2009). Overall, approximately 21% to 50% of people are dead in about 10 to 11 years from diagnosis (Kim 2000; Rautiainen 2007; Myers 2009; Floreani 2011; Baldursdottir 2012).

The diagnosis of primary biliary cholangitis is made in the presence of any two of the following three criteria (Lindor 2009).

- Elevation of alkaline phosphatases.
- Presence of antimitochondrial antibody (AMA).
- Liver biopsy demonstrating non-suppurative destructive cholangitis and destruction of interlobular bile ducts.

Some variations of primary biliary cholangitis are AMA-negative primary biliary cholangitis that requires liver biopsy for establishing the diagnosis and the primary biliary cholangitis - autoimmune hepatitis overlap syndrome (Lindor 2009). However, there is currently no strong evidence that the course of the disease is different between the classic primary biliary cholangitis and these variants (Lindor 2009).

Description of the intervention

Various pharmacological interventions have been tried to treat people with primary biliary cholangitis. These include bile acids such as ursodeoxycholic acid (UDCA) (Kaplan 2004; Combes 2005; Rautiainen 2005; Rudic 2012a); fibrates such as bezafibrate (Kurihara 2000; Rudic 2012b); immunosuppressants or immunomodulators such as glucocorticosteroids (Prince 2005; Rautiainen 2005), colchicine (Almasio 2000; Gong 2004a; Kaplan 2004), methotrexate (Kaplan 2004; Combes 2005; Giljaca 2010), azathioprine (Gong 2007a), ciclosporin (Gong 2007b), chlorambucil (Li Wei 2012), mycophenolate mofetil (Jones 1999; Talwalkar 2005), and thalidomide (McCormick 1994); and copper-chelating agents such as D-penicillamine (Gong 2004b) and tetrathiomolybdate (Askari 2010). Several other interventions such as bisphosphonates and hormonal replacement to prevent or treat osteoporosis (Ormarsdottir 2004; Rudic 2011a; Rudic 2011b; Guanabens 2013); antidepressants such as fluoxetine and fluvoxamine to overcome fatigue (Ter Borg 2004; Talwalkar 2006); cholesterol-lowering agents such as simvastatin to decrease the high cholesterol (Cash 2013); and cholestyramine, rifampicin, and S-adenosyl methionine for pruritus (Bergasa 2000) have been evaluated for control of various symptoms. Liver transplantation is performed in some people with decompensated liver disease due to primary biliary cholangitis (Kim 2000; Lindor 2009; Myers 2009; Baldursdottir 2012).

How the intervention might work

Certain bile acids are protective while other bile acids are harmful to hepatocytes (liver cells), cholangiocytes (cells that line the bile duct), and gastrointestinal cells lining the oesophagus and stomach (Perez 2009). Bile acids such as UDCA may protect the cholangiocytes from the damage caused by hydrophobic bile acids by decreasing the oxidative stress (by direct antioxidant effect or an increase in antioxidant defences) (Paumgartner 2002; Perez 2009). Bile acids also stimulate the secretion of bile acids from hepatocytes, thereby decreasing their stasis and the resulting damage to the cells and inhibit apoptosis (programmed cell death) (Paumgartner 2002; Perez 2009). Fibrates inactivate hydrophobic bile acids and, therefore, decrease the damage to the cells (Kurihara 2000). Since primary biliary cholangitis

is considered an autoimmune disorder, altering the immunity and inflammatory response using glucocorticoids and other immunosuppressants may decrease the damage resulting from the inflammatory response. D-Penicillamine and tetrathiomolybdate might remove the excess copper, thereby protecting the cells from the damage caused by copper accumulation. They also have antifibrotic properties (Song 2008). In this Cochrane Review, we included only pharmacological interventions aimed at controlling the liver disease (i.e. we excluded symptomatic treatments, lifestyle modifications, and liver transplantation).

Why it is important to do this review

The optimal pharmacological treatment of primary biliary cholangitis is unknown. Currently, both the European Association for the Study of the Liver (EASL) and American Association for the Study of Liver Diseases (AASLD) recommend UDCA for the management of primary biliary cholangitis (EASL 2009; Lindor 2009). However, one Cochrane Review that compared UDCA versus placebo or no intervention reported that there was no survival or symptomatic benefit for UDCA (Rudic 2012a). Therefore, there is clearly a discordance between the evidence and guideline recommendation. Network meta-analysis allows combination of the direct evidence and indirect evidence, and allows ranking of different interventions in terms of the different outcomes (Salanti 2011; Salanti 2012). There has been no Cochrane Review on the different pharmacological interventions for primary biliary cholangitis. This systematic review and attempted network meta-analysis provides the best level of evidence for the role of different interventions used in the treatment of people with primary biliary cholangitis.

OBJECTIVES

To assess the comparative benefits and harms of different pharmacological interventions in the treatment of primary biliary cholangitis through a network meta-analysis and to generate rankings of the available pharmacological interventions according to their safety and efficacy. However, it was not possible to assess whether the potential effect modifiers were similar across different comparisons. Therefore, we did not perform the network meta-analysis, and, instead, assessed the comparative benefits and harms of different interventions using standard Cochrane methodology.

When more trials become available with adequate description of potential effect modifiers, we will attempt to conduct network meta-analysis to generate rankings of the available interventions according to their safety and efficacy. This is why we retained the planned methodology for network meta-analysis in our Appendix 1. Once data appear allowing for the conduct of network meta-analysis, this Appendix 1 will be moved back into the Methods section.

METHODS

Criteria for considering studies for this review

Types of studies

We considered randomised clinical trials only for this network meta-analysis, irrespective of the language, publication status, or date of publication. We excluded studies of other design because of the risk of bias in such studies. We are all aware that such exclusions make us focus much more on potential benefits and not fully assess the risks of serious adverse events as well as risks of adverse events.

Types of participants

We included randomised clinical trials with participants with primary biliary cholangitis irrespective of the method of diagnosis of the disease or the presence of symptoms. We excluded randomised clinical trials in which participants had undergone liver transplantation previously.

Types of interventions

Any of the following pharmacological interventions that are possible treatments used either alone or in combination for primary biliary cholangitis and can be compared with each other or with placebo or no intervention.

The interventions that we considered were:

- UDCA;
- obeticholic acid;
- bezafibrate;
- glucocorticosteroids;
- colchicine;
- methotrexate;
- azathioprine;
- ciclosporin;
- chlorambucil;
- mycophenolate mofetil;
- thalidomide;
- D-penicillamine;
- tetrathiomolybdate.

The above list was not exhaustive. If we identified pharmacological interventions that we were not aware of, we considered them as eligible and included them in the review if they were used primarily for the treatment of primary biliary cholangitis.

Types of outcome measures

We assessed the comparative benefits and harms of available pharmacological interventions aimed at treating people with primary biliary cholangitis for the following outcomes.

Primary outcomes

- Mortality at maximal follow-up.
- Mortality:
  - short-term mortality (up to one year);
  - medium-term mortality (one to five years).
- Adverse events (within three months after cessation of treatment). Depending on the availability of data, we attempted to classify adverse events as serious or non-serious. We defined a non-serious adverse event as any untoward medical occurrence not necessarily having a causal relationship with the treatment but resulting in a dose reduction or discontinuation of treatment (any time after commencement of treatment) (ICH-GCP 1997). We defined a serious adverse event as any event that would increase mortality; was life threatening; required hospitalisation; resulted in persistent or significant disability; was a congenital anomaly/birth defect; or any important

medical event that might jeopardise the person or require intervention to prevent it. We used the definition used by study authors for non-serious and serious adverse events:
  - proportion of participants with serious adverse events;
  - number of serious adverse events;
  - proportion of participants with any type of adverse event;
  - number of any type of adverse event.
- Health-related quality of life as defined in the included trials using a validated scale such as EQ-5D or 36-item Short Form (SF-36) (EuroQol 2014; Ware 2014):
  - short-term (up to one year);
  - medium-term (one to five years);
  - long-term (beyond five years).

We considered long-term quality of life more important than short-term or medium-term quality of life, although short-term and medium-term quality of life are also important primary outcomes.

Secondary outcomes

- Liver transplantation (maximal follow-up):
  - proportion of participants with liver transplantation;
  - time to liver transplantation.
- Decompensated liver disease (maximal follow-up):
  - proportion of participants with decompensated liver disease;
  - time to liver decompensation.
- Cirrhosis (maximal follow-up):
  - proportion of participants with cirrhosis;
  - time to cirrhosis.
- Hepatocellular carcinoma (maximal follow-up).

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, and Science Citation Index Expanded (Royle 2003) from inception to 27 February 2017 for randomised clinical trials comparing two or more of the above interventions without applying any language restrictions. We searched for all possible comparisons formed by the interventions of interest. To identify further ongoing or completed trials, we also searched the World Health Organization International Clinical Trials Registry Platform Search Portal (apps.who.int/trialsearch/), which searches various trial registers, including ISRCTN and ClinicalTrials.gov. Appendix 2 shows the search strategies we used.

Searching other resources

We searched the references of the identified trials and existing Cochrane Reviews on primary biliary cholangitis to identify additional trials for inclusion.

Data collection and analysis

Selection of studies

Two review authors (KG and FS) independently identified the trials for inclusion by screening the titles and abstracts. We sought full-text articles for any references that at least one of the review authors identified for potential inclusion. We selected trials for inclusion based on the full-text articles. We listed the excluded full-text references with reasons for their exclusion in the Characteristics of excluded studies table. We have also listed any ongoing trials identified primarily through the search of the clinical trial registers for further follow-up. We resolved discrepancies through discussion.

Data extraction and management

Two review authors (KG and FS or LHE) independently extracted the following data.

- Outcome data (for each outcome and for each treatment arm whenever applicable):
  - number of participants randomised;
  - number of participants included for the analysis;
  - number of participants with events for binary outcomes, mean and standard deviation for continuous outcomes, number of events for count outcomes, and the number of participants with events and the mean follow-up period for time-to-event outcomes;
  - definition of outcomes or scale used if appropriate.
- Data on potential effect modifiers:
  - participant characteristics such as age, sex, comorbidities, proportion of symptomatic participants, proportion with AMA-positive status, proportion of participants with overlap syndrome, and responders;
  - details of the intervention and control (including dose, frequency, and duration);
  - risk of bias (assessment of risk of bias in included studies).
- Other data:
  - year and language of publication;
  - country in which the participants were recruited;
  - year(s) in which the trial was conducted;
  - inclusion and exclusion criteria;
  - follow-up time points of the outcome.

If available, we planned to obtain the data separately for symptomatic participants and asymptomatic participants from the report. If available, we also planned to obtain the data separately for people with AMA-positive status and people with AMA-negative status and for responders and non-responders separately. We sought unclear or missing information by contacting the trial authors. If there was any doubt whether trials shared the same participants, completely or partially (by identifying common authors and centres), we attempted to contact the trial authors to clarify whether the trial report was duplicated. We resolved any differences in opinion through discussion.

Assessment of risk of bias in included studies

We followed the guidance given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and described in the Cochrane Hepato-Biliary Module (Gluud 2017) to assess the risk of bias in included trials. Specifically, we assessed the risk of bias in included trials for the following domains using the methods below (Schulz 1995; Moher 1998; Kjaergard 2001; Wood 2008; Savović 2012a; Savović 2012b; Lundh 2017).

Allocation sequence generation

- Low risk of bias: sequence generation was achieved using computer random number generation or a random number table. Drawing lots, tossing a coin, shuffling cards, and throwing

dice were adequate if performed by an independent person not otherwise involved in the trial.
- Unclear risk of bias: the method of sequence generation was not specified.
- High risk of bias: the sequence generation method was not random.

Allocation concealment

- Low risk of bias: the participant allocations could not have been foreseen in advance of, or during, enrolment. Allocation was controlled by a central and independent randomisation unit. The allocation sequence was unknown to the investigators (e.g. if the allocation sequence was hidden in sequentially numbered, opaque, and sealed envelopes).
- Unclear risk of bias: the method used to conceal the allocation was not described so that intervention allocations may have been foreseen in advance of, or during, enrolment.
- High risk of bias: the allocation sequence was likely to be known to the investigators who assigned the participants.

Blinding of participants and personnel

- Low risk of bias: any of the following: no blinding or incomplete blinding, but the review authors judged that the outcome was not likely to be influenced by lack of blinding; or blinding of participants and key study personnel ensured, and it was unlikely that the blinding could have been broken.
- Unclear risk of bias: any of the following: insufficient information to permit judgement of 'low risk' or 'high risk'; or the trial did not address this outcome.
- High risk of bias: any of the following: no blinding or incomplete blinding, and the outcome was likely to be influenced by lack of blinding; or blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome was likely to be influenced by lack of blinding.

Blinding of outcome assessors

- Low risk of bias: any of the following: no blinding of outcome assessment, but the review authors judged that the outcome measurement was not likely to be influenced by lack of blinding; or blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
- Unclear risk of bias: any of the following: insufficient information to permit judgement of 'low risk' or 'high risk'; or the trial did not address this outcome.
- High risk of bias: any of the following: no blinding of outcome assessment, and the outcome measurement was likely to be influenced by lack of blinding; or blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement was likely to be influenced by lack of blinding.

Incomplete outcome data

- Low risk of bias: missing data were unlikely to make treatment effects depart from plausible values. Sufficient methods, such as multiple imputation, were employed to handle missing data.
- Unclear risk of bias: there was insufficient information to assess whether missing data in combination with the method used to handle missing data were likely to induce bias on the results.
- High risk of bias: the results were likely to be biased due to missing data.

Selective outcome reporting

- Low risk of bias: the trial reported at least the following predefined outcomes: mortality, decompensated liver disease, requirement for transplantation, or treatment-related adverse events. If the original trial protocol was available, the outcomes should have been those called for in that protocol. If the trial protocol was obtained from a trial registry (e.g. www.clinicaltrials.gov), the outcomes sought should have been those enumerated in the original protocol if the trial protocol was registered before or at the time that the trial was begun. If the trial protocol was registered after the trial was begun, those outcomes were not considered to be reliable.
- Unclear risk: not all predefined, or clinically relevant and reasonably expected, outcomes were reported fully, or it was unclear whether data on these outcomes were recorded or not.
- High risk: one or more predefined or clinically relevant and reasonably expected outcomes were not reported, even though data on these outcomes were likely to have been available and even recorded.

For-profit bias

- Low risk of bias: the trial appeared to be free of industry sponsorship or other type of for-profit support that may manipulate the trial design, conductance, or results of the trial.
- Unclear risk of bias: the trial may or may not have been free of for-profit bias as no information on clinical trial support or sponsorship was provided.
- High risk of bias: the trial was sponsored by industry or received other type of for-profit support.

Other bias

- Low risk of bias: the trial appeared to be free of other components (e.g. inappropriate control or dose or administration of control) that could put it at risk of bias.
- Unclear risk of bias: the trial may or may not have been free of other components that could put it at risk of bias.
- High risk of bias: there are other factors in the trial that could put it at risk of bias (e.g. inappropriate control or dose or administration of control).

We considered a trial at low risk of bias if we assessed the trial to be at low risk of bias across all domains. Otherwise, we considered trials to be at unclear risk of bias or at high risk of bias regarding one or more domains as at high risk of bias.

Measures of treatment effect

For dichotomous variables (e.g. short-term and medium-term mortality, liver transplantation, proportion of participants with adverse events, decompensated liver disease, cirrhosis, or hepatocellular carcinoma), we calculated the odds ratio (OR) with 95% confidence intervals (CI). For continuous variables (e.g. quality of life reported on the same scale), we planned to calculate the mean difference with 95% CI. We planned to use standardised mean difference values with 95% CI for quality of life if included trials used different scales. For count outcomes (e.g. number of adverse events), we calculated the rate ratio with 95% CI. For time-to-event data (e.g. mortality at maximal follow-up or requirement

for liver transplantation, time to liver decompensation, and time to cirrhosis), we planned to use the hazard ratio (HR) with 95% CIs. We also calculated Trial Sequential Analysis-adjusted CI to control random errors (Thorlund 2011).

Unit of analysis issues

The unit of analysis was people with primary biliary cholangitis according to the intervention group to which they were randomly assigned.

Cluster randomised clinical trials

We found no cluster randomised clinical trials. However, if we had found them, we would have included them provided that the effect estimate adjusted for cluster correlation was available.

Cross-over randomised clinical trials

If we found cross-over randomised clinical trials, we included the outcomes after the period of first intervention only since primary biliary cholangitis is a chronic disease and the interventions could potentially have a residual effect.

Trials with multiple treatment groups

We collected data for all trial intervention groups that met our inclusion criteria.

Dealing with missing data

We performed an intention-to-treat analysis whenever possible (Newell 1992). Otherwise, we used the data that were available to us (e.g. a trial may have reported only per-protocol analysis results). As such per-protocol analyses may be biased, we planned to conduct best-worst case scenario analysis (good outcome in intervention group and bad outcome in control group) and worst-best case scenario analysis (bad outcome in intervention group and good outcome in control group) as sensitivity analyses whenever possible.

For continuous outcomes, we planned to impute the standard deviation from P values according to guidance given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). If the data were likely to be normally distributed, we planned to use the median for meta-analysis when the mean was not available. If it was not possible to calculate the standard deviation from the P value or the CIs, we planned to impute the standard deviation using the largest standard deviation in other trials for that outcome. This form of imputation may decrease the weight of the study for calculation of mean differences and may bias the effect estimate to no effect for calculation of standardised mean differences (Higgins 2011).

Assessment of heterogeneity

We assessed clinical and methodological heterogeneity by carefully examining the characteristics and design of included trials. We assessed the presence of clinical heterogeneity by comparing effect estimates in the presence or absence of symptoms, the presence or absence of AMA, responders versus non-responders, and the doses of the pharmacological interventions. Different study designs and risk of bias may contribute to methodological heterogeneity. We used the I^2 test and Chi^2 test for heterogeneity, and overlapping of CIs to assess heterogeneity.

Assessment of reporting biases

We planned to use visual asymmetry on a funnel plot to explore reporting bias in the presence of at least 10 trials that could be included for a direct comparison (Egger 1997; Macaskill 2001). In the presence of heterogeneity that could be explained by subgroup analysis, we planned to produce a funnel plot for each subgroup in the presence of an adequate number of trials (at least 10 trials). We planned to use the linear regression approach described by Egger 1997 to determine funnel plot asymmetry.

We also considered selective reporting as evidence of reporting bias.

Data synthesis

We performed the meta-analyses according to the recommendations of Cochrane (Higgins 2011), using the software package Review Manager 5 (RevMan 2014). We used a random-effects model (DerSimonian 1986) and a fixed-effect model (DeMets 1987). In the case of a discrepancy between the two models, we reported both results; otherwise, we reported only the results from the fixed-effect model.

Calculation of required information size and Trial Sequential Analysis

For calculation of the required information size, see Appendix 3. We performed Trial Sequential Analysis to control the risk of random errors when there were at least two trials included for mortality at maximal follow-up, serious adverse events (proportion) and health-related quality of life, the three outcomes that determine whether an intervention should be used (Wetterslev 2008; Thorlund 2011; TSA 2011; Wetterslev 2017). We used an alpha error as per guidance of Jakobsen 2014, power of 90% (beta error of 10%), a relative risk reduction of 20%, a control group proportion observed in the trials, and the diversity observed in the meta-analysis.

Subgroup analysis and investigation of heterogeneity

We planned to assess the differences in the effect estimates between the following subgroups.

- Trials at low risk of bias compared to trials at high risk of bias.
- Participants with symptomatic compared to participants with asymptomatic primary biliary cholangitis.
- AMA-positive participants compared to AMA-negative participants.
- Responders compared to non-responders to bile acids.
- Different doses of pharmacological interventions. For example, various doses of UDCA used in randomised clinical trials include 5 mg/kg to 7 mg/kg, 13 mg/kg to 15 mg/kg (moderate dose), and 23 mg/kg to 25 mg/kg (high dose) (Angulo 1999a; Lindor 1997).

We planned to use the Chi^2 test for subgroup differences to identify subgroup differences.

Sensitivity analysis

If a trial reported only per-protocol analysis results, we planned to re-analyse the results using the best-worst case scenario and worst-best case scenario analyses as sensitivity analyses whenever possible.

Presentation of results and GRADE assessments

We reported mortality, serious adverse events, and health-related quality of life, the three most important outcomes that determine the use of an intervention in a 'Summary of findings' table format, downgrading the quality of evidence for risk of bias, inconsistency, indirectness, imprecision, and publication bias using GRADE (Guyatt 2011). We have presented the 'Summary of findings' tables for all comparisons in which two trials were included for one of mortality at maximal follow-up, serious adverse events, or health-related quality of life.

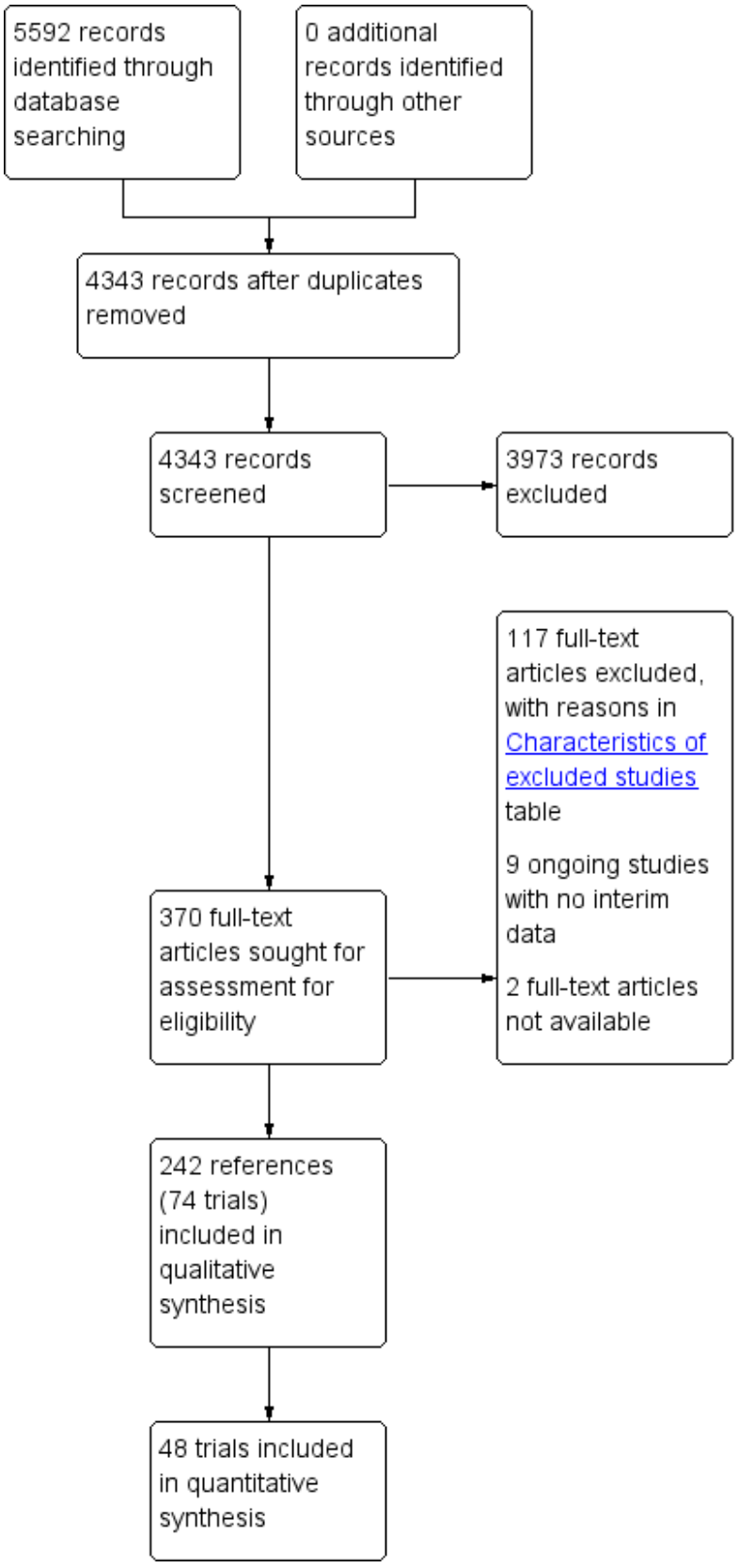
RESULTS

Description of studies

Results of the search

We identified 5592 references through electronic searches of CENTRAL (n = 1104), MEDLINE (n = 2383), Embase (n = 604), Science Citation Index Expanded (n = 1362), World Health Organization International Clinical Trials Registry Platform (n = 88), and ClinicalTrials.gov (n = 51). After the removal of 1249 duplicates we obtained 4343 references. We then excluded 3973 clearly irrelevant references through screening titles and reading abstracts. We retrieved 370 references for further assessment. No references were identified through scanning reference lists of the identified randomised trials. We excluded 117 references for the reasons stated in the Characteristics of excluded studies table. Nine references are an ongoing trial without any interim data (ChiCTR-IPR-16008935; EUCTR2015-002698-39-GB; NCT02308111; NCT02701166; NCT02823353; NCT02823366; NCT02937012; NCT02943447; NCT02965911). We were unable to obtain the full texts for two references (O'Brian 1990; Zaman 2006). In total, 242 references (74 trials) met the inclusion criteria. The reference flow is summarised in the study flow diagram (Figure 1).

Figure 1. Study flow diagram.



Included studies

The 74 trials that met the inclusion criteria for this review included 5902 participants. Some 28 trials did not contribute any information for this review leaving 4274 participants included in one or more outcomes in the review (Bodenheimer 1988; Arora 1990; Oka 1990; Smart 1990; Poupon 1991a; Senior 1991; Battezzati 1993; Manzillo 1993a; Manzillo 1993b; Bobadilla 1994; Goddard 1994; Lim 1994; McCormick 1994; Steenbergen 1994; Lindor 1997; Kaplan 1999; Leuschner 1999; Nakai 2000; Mazzarella 2002; Ueno 2005; Iwasaki 2008a; Iwasaki 2008b; Askari 2010; Liberopoulos 2010; Cash 2013; Bowlus 2014; Kowdley 2014a; Mayo 2015). In the main review unstratified by the dose of UDCA or obeticholic acid, 4060 participants were included in one or more outcomes in the review. The mean or median age of the participants ranged from 46 to 64 years in the trials that reported this information. The proportion of females ranged from 77.8% to 100% in the trials that reported this information. The proportion of participants with symptoms varied from 19.9% to 100% in the trials that reported this information. The proportion of participants who were AMA positive ranged from 80.8% to 100% in the trials that reported this information. Ten trials included non-responders to bile acids only (Van Hoogstraten 1998; Wolfhagen 1998; Kanda 2003; Ueno 2005; Iwasaki 2008b; Mason 2008; Liberopoulos 2010; Hirschfield 2015; Hosonuma 2015; Nevens 2016). The remaining trials did not state whether they included responders or non-responders, or both. However, it appeared that most trials included participants who had not received previous treatments or regardless of the previous treatments received. The interventions, controls, number of participants included in each trial, and the follow-up period reported in the different trials are listed in Table 1.

Source of funding: nine trials receive no additional funding or were funded by parties with no vested interest in the results (Heathcote 1976; Hoofnagle 1986; Almasio 2000; Nakai 2000; Iwasaki 2008a; Iwasaki 2008b; Askari 2010; Cash 2013; Hosonuma 2015). Thirty-one trials were partially or fully funded by the pharmaceutical companies that would benefit based on the results of the trial (Triger 1980; Matloff 1982; Christensen 1985; Dickson 1985; Bodenheimer 1988; Minuk 1988; Oka 1990; Wiesner 1990; Poupon 1991a; Senior 1991; Lombard 1993; Mitchison 1993; Heathcote 1994; Lindor 1994; McCormick 1994; Combes 1995a; Poupon 1996; Eriksson 1997; Van Hoogstraten 1998; Wolfhagen 1998; Leuschner 1999; Pares 2000; Papatheodoridis 2002; Combes 2005; Rautiainen 2005; Mason 2008; Bowlus 2014; Kowdley 2014a; Mayo 2015; Ma 2016; Nevens 2016). The source of funding was not available from the 34 remaining trials.

Excluded studies

The reasons for exclusion are summarised in the Characteristics of excluded studies table. While the reasons for exclusion for most references were self-explanatory, the reasons for exclusion of 15 references required some explanation (Poupon 1994; Lindor 1995a; Emond 1996; Lindor 1996; Angulo 1999b; Angulo 1999c; Degott 1999; Corpechot 2000; Jorgensen 2002; Kaplan 2004; Combes 2005b; Leung 2010; Leung 2011; Kowdley 2015; Carbone 2016). These 15 references were long-term follow-up reports of included trials, but the randomisation was not maintained and the 'no intervention' group received the intervention. While this is acceptable if some participants crossed over for specific reasons in an intention-to-treat analysis, it is not acceptable if the cross-over from one group to another was done in a systematic manner. Therefore, we excluded these references.

Risk of bias in included studies

The risk of bias is summarised in Figure 2, Figure 3, and Table 2.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

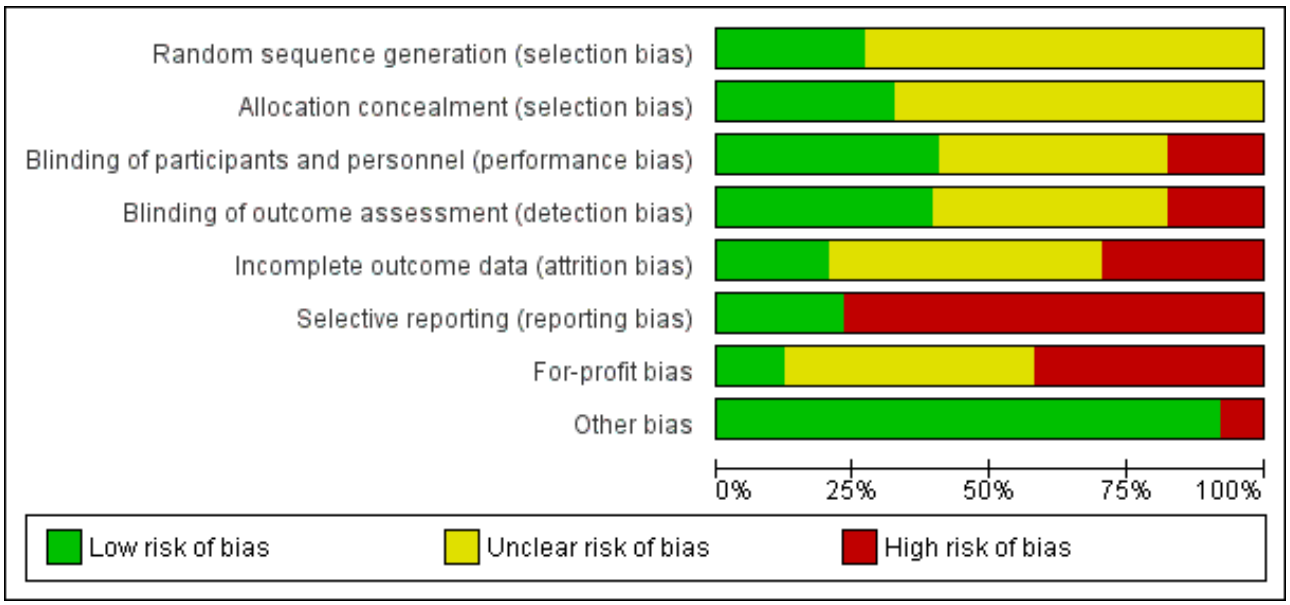


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

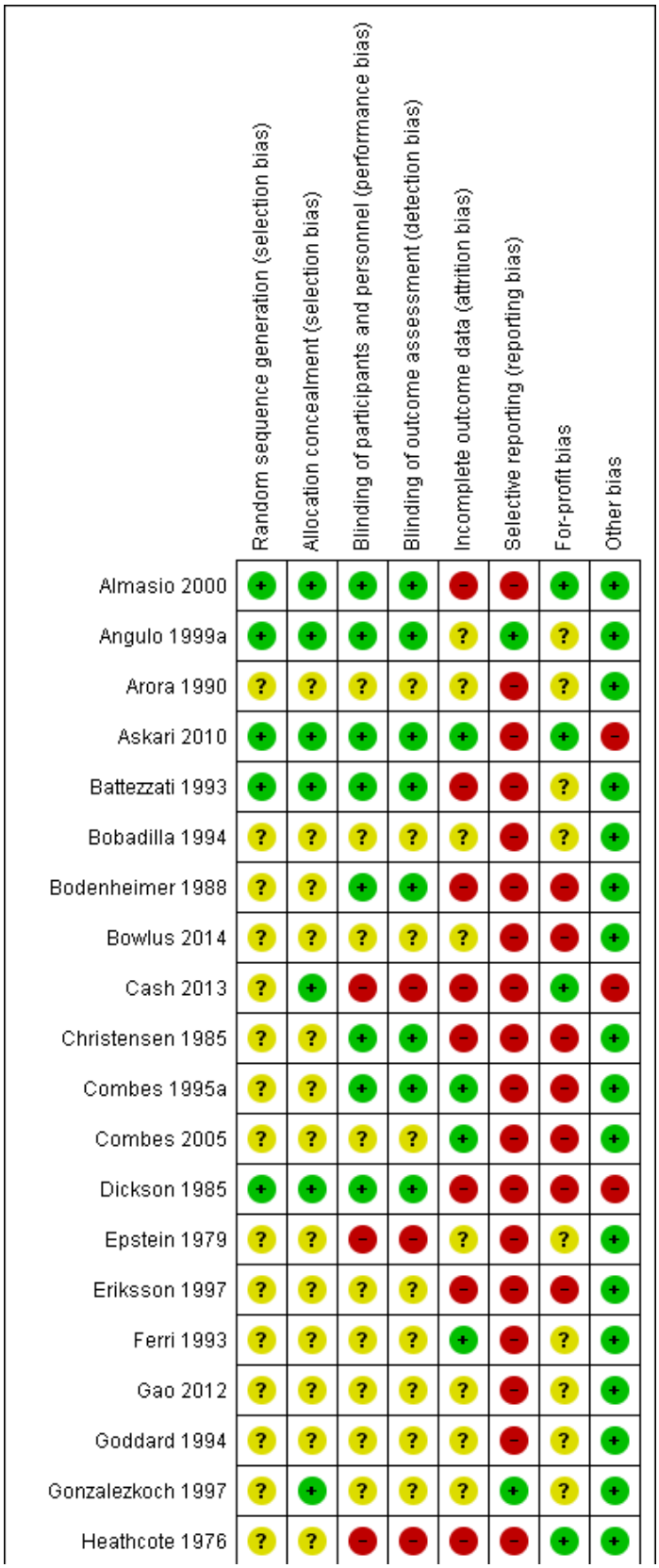


Figure 3. (Continued)

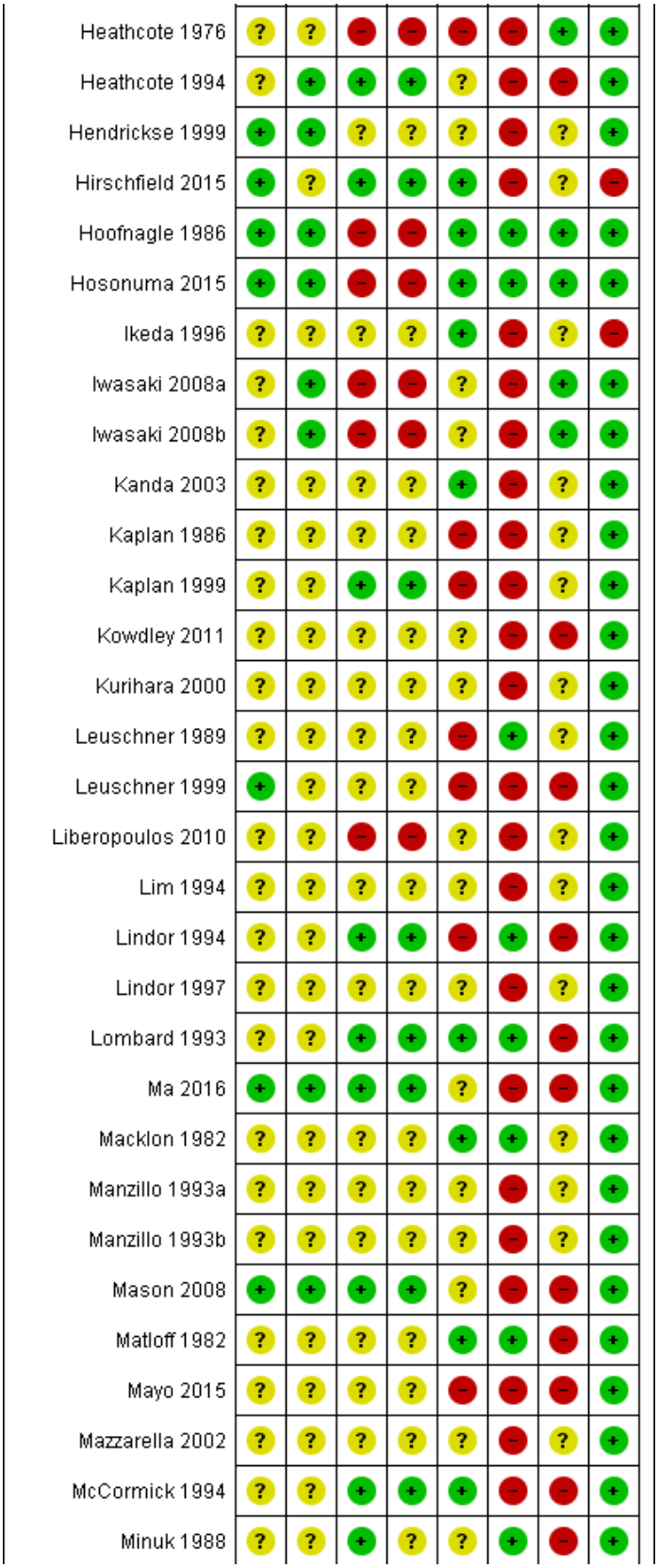
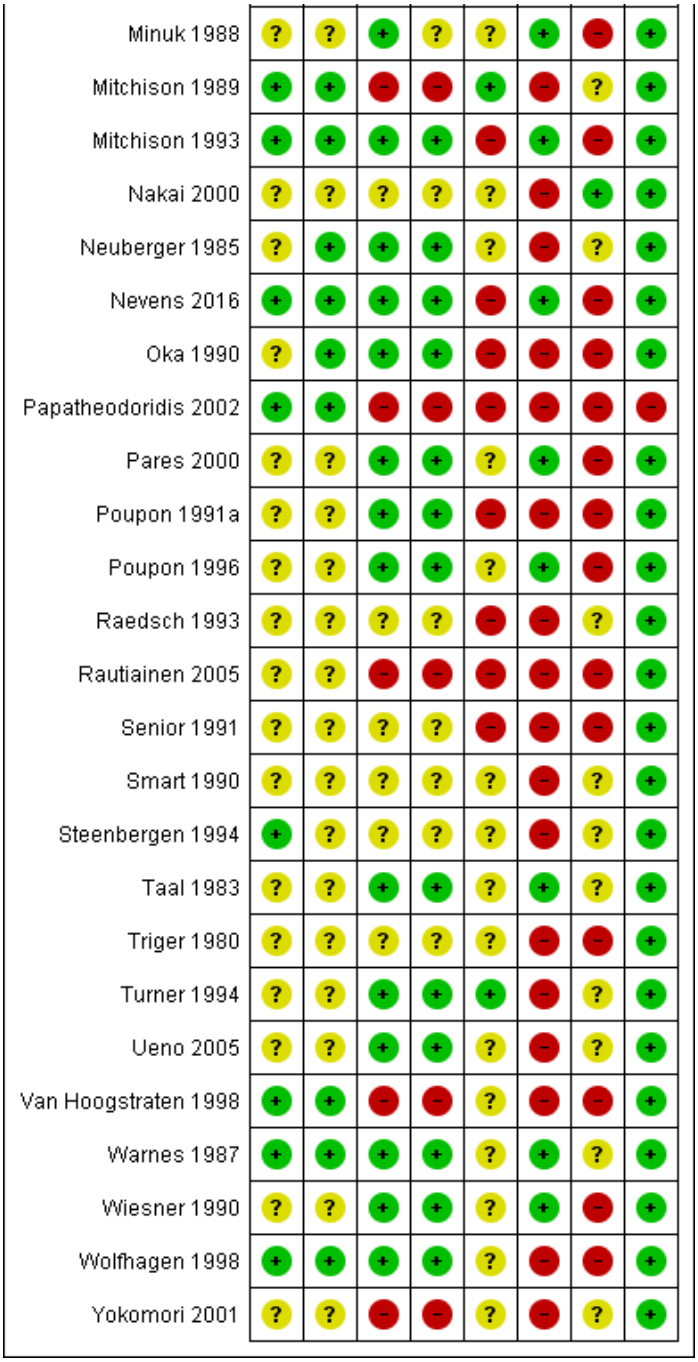


Figure 3. (Continued)



Allocation

Twenty trials were at low risk of bias due to random sequence generation (Dickson 1985; Hoofnagle 1986; Warnes 1987; Mitchison 1989; Battezzati 1993; Mitchison 1993; Steenbergen 1994; Van Hoogstraten 1998; Wolfhagen 1998; Angulo 1999a; Hendrickse 1999; Leuschner 1999; Almasio 2000; Papatheodoridis 2002; Mason 2008; Askari 2010; Hirschfield 2015; Hosonuma 2015; Ma 2016; Nevens 2016). The remaining trials were at unclear risk of bias.

Twenty-four trials were at low risk of bias due allocation concealment (Dickson 1985; Neuberger 1985; Hoofnagle 1986; Warnes 1987; Mitchison 1989; Oka 1990; Battezzati 1993; Mitchison 1993; Heathcote 1994; Gonzalezkoch 1997; Van Hoogstraten 1998; Wolfhagen 1998; Angulo 1999a; Hendrickse 1999; Almasio 2000; Papatheodoridis 2002; Iwasaki 2008a; Iwasaki 2008b; Mason 2008; Askari 2010; Cash 2013; Hosonuma 2015; Ma 2016; Nevens 2016). The remaining trials were at unclear risk of bias.

Sixteen trials were at low risk of both random sequence generation bias and allocation concealment bias (Dickson 1985; Warnes 1987; Mitchison 1989; Battezzati 1993; Mitchison 1993; Van Hoogstraten 1998; Wolfhagen 1998; Angulo 1999a; Hendrickse 1999; Almasio 2000; Papatheodoridis 2002; Mason 2008; Askari 2010; Hosonuma

2015; Ma 2016; Nevens 2016); these trials were considered to be at low risk of selection bias. The remaining trials were at unclear risk of selection bias.

Blinding

Thirty trials were at low risk of performance bias (Taal 1983; Christensen 1985; Dickson 1985; Neuberger 1985; Warnes 1987; Bodenheimer 1988; Minuk 1988; Oka 1990; Wiesner 1990; Poupon 1991a; Battezzati 1993; Lombard 1993; Mitchison 1993; Heathcote 1994; Lindor 1994; McCormick 1994; Turner 1994; Combes 1995a; Poupon 1996; Wolfhagen 1998; Angulo 1999a; Kaplan 1999; Almasio 2000; Pares 2000; Ueno 2005; Mason 2008; Askari 2010; Hirschfield 2015; Ma 2016; Nevens 2016). Thirteen trials were at high risk of performance bias (Heathcote 1976; Epstein 1979; Hoofnagle 1986; Mitchison 1989; Van Hoogstraten 1998; Yokomori 2001; Papatheodoridis 2002; Rautiainen 2005; Iwasaki 2008a; Iwasaki 2008b; Liberopoulos 2010; Cash 2013; Hosonuma 2015). The remaining trials were at unclear risk of performance bias.

Twenty-nine trials were at low risk of detection bias (Taal 1983; Christensen 1985; Dickson 1985; Neuberger 1985; Warnes 1987; Bodenheimer 1988; Oka 1990; Wiesner 1990; Poupon 1991a; Battezzati 1993; Lombard 1993; Mitchison 1993; Heathcote 1994; Lindor 1994; McCormick 1994; Turner 1994; Combes 1995a; Poupon 1996; Wolfhagen 1998; Angulo 1999a; Kaplan 1999; Almasio 2000; Pares 2000; Ueno 2005; Mason 2008; Askari 2010; Hirschfield 2015; Ma 2016; Nevens 2016). Thirteen trials were at high risk of detection bias (Heathcote 1976; Epstein 1979; Hoofnagle 1986; Mitchison 1989; Van Hoogstraten 1998; Yokomori 2001; Papatheodoridis 2002; Rautiainen 2005; Iwasaki 2008a; Iwasaki 2008b; Liberopoulos 2010; Cash 2013; Hosonuma 2015). The remaining trials were at unclear risk of detection bias.

Twenty-nine trials were at low risk of performance bias and detection bias (Taal 1983; Christensen 1985; Dickson 1985; Neuberger 1985; Warnes 1987; Bodenheimer 1988; Oka 1990; Wiesner 1990; Poupon 1991a; Battezzati 1993; Lombard 1993; Mitchison 1993; Heathcote 1994; Lindor 1994; McCormick 1994; Turner 1994; Combes 1995a; Poupon 1996; Wolfhagen 1998; Angulo 1999a; Kaplan 1999; Almasio 2000; Pares 2000; Ueno 2005; Mason 2008; Askari 2010; Hirschfield 2015; Ma 2016; Nevens 2016). Thirteen trials were at high risk of performance bias and detection bias (Heathcote 1976; Epstein 1979; Hoofnagle 1986; Mitchison 1989; Van Hoogstraten 1998; Yokomori 2001; Papatheodoridis 2002; Rautiainen 2005; Iwasaki 2008a; Iwasaki 2008b; Liberopoulos 2010; Cash 2013; Hosonuma 2015). The remaining trials were at unclear risk of performance and detection bias.

Incomplete outcome data

Fifteen trials were at low risk of attrition bias (Macklon 1982; Matloff 1982; Hoofnagle 1986; Mitchison 1989; Ferri 1993; Lombard 1993; McCormick 1994; Turner 1994; Combes 1995a; Ikeda 1996; Kanda 2003; Combes 2005; Askari 2010; Hirschfield 2015; Hosonuma 2015). Twenty-two trials were at high risk of attrition bias due to dropouts which may have been related to the intervention that the participant received (Heathcote 1976; Christensen 1985; Dickson 1985; Kaplan 1986; Bodenheimer 1988; Leuschner 1989; Oka 1990; Poupon 1991a; Senior 1991; Battezzati 1993; Mitchison 1993; Raedsch 1993; Lindor 1994; Eriksson 1997; Kaplan 1999; Leuschner 1999; Almasio 2000; Papatheodoridis 2002; Rautiainen 2005; Cash 2013; Mayo 2015; Nevens 2016). The remaining trials were at unclear risk of attrition bias.

Selective reporting

We were unable to find any protocols published prior to the full study reports. Seventeen trials were at low risk of due to selecting outcome reporting (Macklon 1982; Matloff 1982; Taal 1983; Hoofnagle 1986; Warnes 1987; Minuk 1988; Leuschner 1989; Wiesner 1990; Lombard 1993; Mitchison 1993; Lindor 1994; Poupon 1996; Gonzalezkoch 1997; Angulo 1999a; Pares 2000; Hosonuma 2015; Nevens 2016). The remaining trials were at high risk of bias due to selective reporting (reporting bias).

Other potential sources of bias

For profit bias: nine trials receive no additional funding or were funded by parties with no vested interest in the results and were at low risk of for-profit bias (Heathcote 1976; Hoofnagle 1986; Almasio 2000; Nakai 2000; Iwasaki 2008a; Iwasaki 2008b; Askari 2010; Cash 2013; Hosonuma 2015). Thirty-one trials partially or fully funded by the pharmaceutical companies that would benefit based on the results of the trial were at high risk of for-profit bias (Triger 1980; Matloff 1982; Christensen 1985; Dickson 1985; Bodenheimer 1988; Minuk 1988; Oka 1990; Wiesner 1990; Poupon 1991a; Senior 1991; Lombard 1993; Mitchison 1993; Heathcote 1994; Lindor 1994; McCormick 1994; Combes 1995a; Poupon 1996; Eriksson 1997; Van Hoogstraten 1998; Wolfhagen 1998; Leuschner 1999; Pares 2000; Papatheodoridis 2002; Combes 2005; Rautiainen 2005; Mason 2008; Bowlus 2014; Kowdley 2014a; Mayo 2015; Ma 2016; Nevens 2016). The remaining trials were at unclear risk of for-profit bias.

Six trials were at high risk of other bias: authors presented the results of only a subgroup of participants without explaining the reason for this approach (Dickson 1985; Ikeda 1996); a significant proportion of participants crossed over from placebo to UDCA (Papatheodoridis 2002); it was unclear whether the participants continued to take UDCA in both groups (Askari 2010); participants continued to take varying doses of UDCA (Hirschfield 2015); and participants were allowed to continue previous prescriptions for primary biliary cholangitis (it was unclear whether this was balanced across groups) (Cash 2013). The remaining trials were at low risk of other bias.

Overall risk of bias

All trials were at high risk of bias in one or more domains.

Effects of interventions

See: **Summary of findings for the main comparison** Ursodeoxycholic acid (UDCA) versus no intervention for primary biliary cholangitis; **Summary of findings 2** Azathioprine versus no intervention for primary biliary cholangitis; **Summary of findings 3** Colchicine versus no intervention for primary biliary cholangitis; **Summary of findings 4** Ciclosporin versus no intervention for primary biliary cholangitis; **Summary of findings 5** D-Penicillamine versus no intervention for primary biliary cholangitis; **Summary of findings 6** Colchicine plus ursodeoxycholic acid (UDCA) versus UDCA for primary biliary cholangitis; **Summary of findings 7** Methotrexate plus ursodeoxycholic acid (UDCA) versus UDCA for primary biliary cholangitis

Mortality at maximal follow-up

Twenty-eight trials including 2823 participants reported mortality at maximal follow-up (Heathcote 1976; Epstein 1979; Macklon 1982; Matloff 1982; Taal 1983; Christensen 1985; Neuberger 1985;

Hoofnagle 1986; Kaplan 1986; Warnes 1987; Minuk 1988; Leuschner 1989; Mitchison 1989; Wiesner 1990; Lombard 1993; Mitchison 1993; Heathcote 1994; Lindor 1994; Turner 1994; Poupon 1996; Gonzalezkoch 1997; Hendrickse 1999; Almasio 2000; Pares 2000; Papatheodoridis 2002; Combes 2005; Hosonuma 2015; Nevens 2016). The period of follow-up in these trials varied between 11 and 96 months. The proportion of people with mortality (maximal follow-up) was higher in the methotrexate group (adjusted proportion: 23.3%) than in the no intervention group (1/30 (3.3%)) (OR 8.83, 95% CI 1.01 to 76.96; 60 participants; 1 trial). The proportion of people with mortality (maximal follow-up) was lower in the azathioprine group (adjusted proportion: 53.5%) than in the no intervention group (72/107 (67.3%)) (OR 0.56, 95% CI 0.32 to 0.98; 224 participants; 2 trials; I^2 = 0%). There was no evidence of a difference in any of the remaining comparisons (Analysis 1.1).

Mortality (up to one year)

Eight trials including 655 participants reported mortality (up to year) (Heathcote 1976; Neuberger 1985; Warnes 1987; Minuk 1988; Leuschner 1989; Gonzalezkoch 1997; Almasio 2000; Nevens 2016). There was no evidence of a difference in any of the comparisons (Analysis 1.2).

Mortality (one to five years)

Twenty trials including 2168 participants reported mortality (one to five years) (Epstein 1979; Macklon 1982; Matloff 1982; Taal 1983; Christensen 1985; Hoofnagle 1986; Kaplan 1986; Mitchison 1989; Wiesner 1990; Lombard 1993; Mitchison 1993; Heathcote 1994; Lindor 1994; Turner 1994; Poupon 1996; Hendrickse 1999; Pares 2000; Papatheodoridis 2002; Combes 2005; Hosonuma 2015). The proportion of people with mortality (one to five years) was higher in the methotrexate group (adjusted proportion: 23.3%) than in the no intervention group (1/30 (3.3%)) (OR 8.83, 95% CI 1.01 to 76.96; 60 participants; 1 trial). There was no evidence of a difference in any of the remaining comparisons (Analysis 1.3).

Serious adverse events (proportion)

Eleven trials including 1076 participants reported serious adverse events (proportion) (Matloff 1982; Warnes 1987; Leuschner 1989; Lindor 1994; Poupon 1996; Kurihara 2000; Pares 2000; Kanda 2003; Mason 2008; Hirschfield 2015; Nevens 2016). The period of follow-up varied from three to 41 months. The proportion of people with serious adverse events (proportion) was higher in the D-penicillamine group (adjusted proportion: 28.8%; based on a control group proportion of 1%) versus the no intervention group (0/26 (0.0%)) (OR 28.77, 95% CI 1.57 to 526.67; 52 participants; 1 trial). The proportion of people with serious adverse events (proportion) was higher in the obeticholic acid plus UDCA group (adjusted proportion: 4.1%) versus the UDCA group (19/143 (13.3%)) (OR 3.58, 95% CI 1.02 to 12.51; 216 participants; 1 trial). There was no evidence of a difference in any of the remaining comparisons (Analysis 1.4).

Serious adverse events (number of events)

One trial including 216 participants reported serious adverse events (number of events) (Nevens 2016). The period of follow-up was 12 months. There was no evidence of a difference between the UDCA plus obeticholic acid versus the UDCA groups (Analysis 1.5).

Adverse events (proportion)

Nineteen trials including 1652 participants reported adverse events (proportion) (Macklon 1982; Dickson 1985; Minuk 1988; Leuschner 1989; Wiesner 1990; Ferri 1993; Lombard 1993; Mitchison 1993; Raedsch 1993; Lindor 1994; Ikeda 1996; Gonzalezkoch 1997; Kurihara 2000; Pares 2000; Yokomori 2001; Kanda 2003; Rautiainen 2005; Gao 2012; Hirschfield 2015). The proportion of people with adverse events (proportion) was higher in the ciclosporin group (adjusted proportion: 76.2%) versus the no intervention group (97/189 (51.3%) (OR 3.04, 95% CI 1.98 to 4.68; 390; 3 trials; I^2 = 27%), D-penicillamine group (adjusted proportion: 50.6%) versus the no intervention group (25/135 (18.5%)) (OR 4.51, 95% CI 2.56 to 7.93; 287 participants; 2 trials; I^2 = 0%); malotilate group (adjusted proportion: 19.2%) versus the no intervention group (1/49 (2.0%)) (OR 11.43, 95% CI 1.40 to 93.04; 101 participants; 1 trial); and obeticholic acid group (adjusted proportion: 96.1%) versus the no intervention group (32/38 (84.2%)) (OR 4.58, 95% CI 1.31 to 15.95; 165 participants; 1 trial). The proportion of people with adverse events (proportion) was higher in the glucocorticosteroids plus UDCA (adjusted proportion: 15.8%) versus the UDCA group (2/61 (3.3%) (OR 5.54, 95% CI 1.35 to 22.84; 135 participants; 2 trials; I^2 = 0%) and methotrexate plus UDCA (adjusted proportion: 100.0%) versus the UDCA group (0/12 (0.0%)) (OR 115.00, 95% CI 4.98 to 2657.48; 25 participants; 1 trial). The proportion of people with adverse events (proportion) was higher in the taurodeoxycholic acid (TUDCA) group (adjusted proportion: 60.0%) versus the UDCA group (1/15 (6.7%)) (OR 21.00, 95% CI 2.16 to 204.61; 30 participants; 1 trial). There was no evidence of a difference in any of the remaining comparisons (Analysis 1.6).

Adverse events (number)

Fourteen trials including 1304 participants reported adverse events (number) (Matloff 1982; Taal 1983; Dickson 1985; Hoofnagle 1986; Minuk 1988; Wiesner 1990; Lombard 1993; Mitchison 1993; Ikeda 1996; Gonzalezkoch 1997; Wolfhagen 1998; Hirschfield 2015; Hosonuma 2015; Ma 2016). The number of adverse events was higher in the chlorambucil group (adjusted rate: 57.9 events per 100 participants) versus the no intervention group (3/11 (27.3 events per 100 participants)) (rate ratio 3.67, 95% CI 1.04 to 12.87; 24 participants; 1 trial); ciclosporin group (adjusted rate: 84.4 events per 100 participants) versus the no intervention group (128/189 (67.7 events per 100 participants)) (rate ratio 2.58, 95% CI 1.26 to 5.31; 390 participants; 3 trials; I^2= 69%); D-penicillamine group (adjusted rate: 48.4 events per 100 participants) versus the no intervention group (37/155 (23.9 events per 100 participants)) (rate ratio 2.99, 95% CI 1.04 to 8.63; 303 participants; 3 trials; I^2 = 75%), malotilate group (adjusted rate: 20.7 events per 100 participants) versus the no intervention group (2/49 (4.1 events per 100 participants)) (rate ratio 6.13, 95% CI 1.38 to 27.14; 101 participants; 1 trial); and obeticholic acid group (adjusted rate: 175.0 events per 100 participants) versus the no intervention group (96/38 (252.6 events per 100 participants)) (rate ratio 1.41, 95% CI 1.13 to 1.75; 76 participants; 1 trial); ; ; ; . The number of adverse events was higher in the methotrexate plus UDCA group (adjusted rate: 30.6 events per 100 participants) versus the UDCA group (0/12 (0.0 events per 100 participants)) (rate ratio 30.64, 95% CI 1.84 to 510.76; 27 participants; 1 trial). There was no evidence of a difference in any of the remaining comparisons (Analysis 1.7).

Health-related quality of life

None of the trials reported health-related quality of life at any time point.

Liver transplantation

Eleven trials including 1561 participants reported liver transplantation (Neuberger 1985; Wiesner 1990; Lombard 1993; Heathcote 1994; Lindor 1994; Turner 1994; Eriksson 1997; Hendrickse 1999; Papatheodoridis 2002; Combes 2005; Hosonuma 2015). There was no evidence of a difference in any of the comparisons (Analysis 1.8).

Decompensated liver disease

Seven trials including 909 participants reported decompensated liver disease (Taal 1983; Combes 1995a; Almasio 2000; Papatheodoridis 2002; Combes 2005; Gao 2012; Nevens 2016). There was no evidence of a difference in any of the comparisons (Analysis 1.9).

Cirrhosis

Three trials including 103 participants reported cirrhosis (Heathcote 1976; Turner 1994; Wolfhagen 1998). There was no evidence of a difference in any of the comparisons (Analysis 1.10).

Hepatocellular carcinoma

None of the trials reported hepatocellular carcinoma.

Subgroup analysis

All the trials were at high risk of bias for one or more domains. None of the trials reported separate data for symptomatic and asymptomatic participants, AMA-positive and AMA-negative participants, or for responders and non-responders to bile acids. A secondary analysis performed by stratifying for the doses of UDCA and obeticholic acid revealed no differences between the main analysis except for the following.

There was no evidence of differences in the proportion of people with adverse events when stratified by the dose of obeticholic acid (obeticholic acid (high) versus no intervention: OR 16.60, 95% CI 0.90 to 305.59; 79 participants; 1 trial; obeticholic acid (moderate) versus no intervention: OR 8.81, 95% CI 1.01 to 76.73; 86 participants; 1 trial; and obeticholic acid (low) versus no intervention: OR 1.59, 95% CI 0.41 to 6.17; 76 participants; 1 trial). In addition, when stratified by dose, only obeticholic acid (high) had higher number of adverse events than no intervention (rate ratio 1.91, 95% CI 1.50 to 2.44; 79 participants; 1 trial). It also had higher number of adverse events than obeticholic acid (moderate) and obeticholic acid (low) (obeticholic acid (moderate) versus obeticholic acid (high): rate ratio 0.66, 95% CI 0.53 to 0.81; 89 participants; 1 trial; obeticholic acid (low) versus obeticholic acid (high): rate ratio 0.55, 95% CI 0.43 to 0.70; 79 participants; 1 trial).

Sensitivity analysis

We did not perform a sensitivity analysis of imputing information based on different scenarios because of paucity of data to carry out these analyses. We did not impute standard deviation; therefore, we did not perform a sensitivity analysis to assess the impact of imputing the standard deviation.

Reporting bias

We did not assess reporting bias by creating a funnel plot because of the few trials included under each comparison.

Using fixed-effect model versus random-effects model

The interpretation of results was not altered based on the model used for analysis.

Quality of evidence

The overall quality of evidence was very low for all the outcomes (Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3; Summary of findings 4; Summary of findings 5; Summary of findings 6; Summary of findings 7). This was because of the high risk of bias in all the trials (downgraded by two levels); small sample sizes for all outcomes and wide CIs (downgraded by two levels for imprecision) and heterogeneity (downgraded by two levels) for some of the outcomes.

Sample size calculations and Trial Sequential Analysis

The required sample size for identifying a 20% relative risk reduction in the different outcomes based on an alpha error of 5%, a beta error of 20%, and the control group proportion observed across trials were as follows.

- Mortality (up to one year) (control group proportion: 25.2%): 2166 participants.
- Mortality (one to five years) (control group proportion: 20.0%): 2894 participants.
- Mortality at maximal follow-up (control group proportion: 20.8%): 2758 participants.
- Serious adverse events (proportion) (control group proportion: 0.4%): 175,996 participants.
- Adverse events (proportion) (control group proportion: 27%): 1978 participants.
- Liver transplantation (control group proportion: 7.4%): 8910 participants.
- Decompensated liver disease (control group proportion: 20.8%): 2758 participants.
- Cirrhosis (control group proportion: 55.6%): 632 participants.

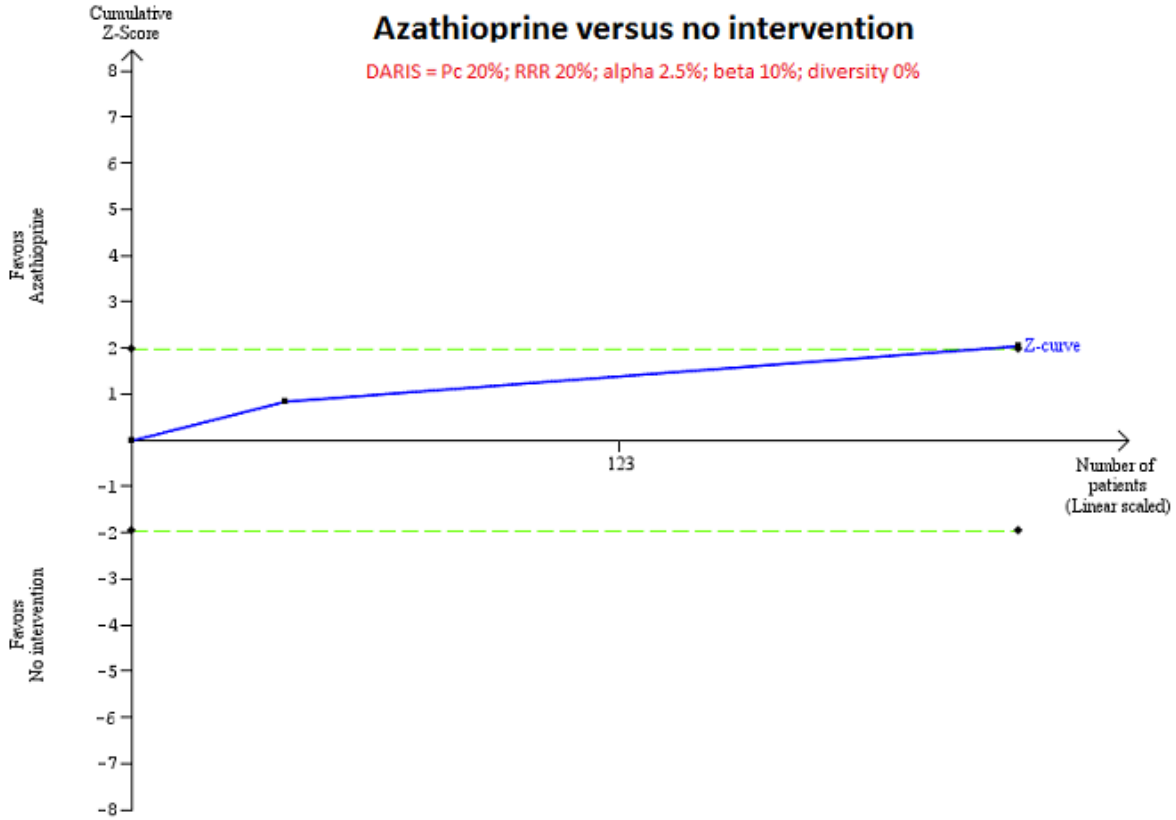
The above mentioned are sample sizes uncorrected for heterogeneity. In the presence of heterogeneity, for example, in the presence of a heterogeneity of 27%, the required information size for adverse events (proportion) is 1978/(1 - 0.27) = 2710 participants.

As shown in Figure 4, Figure 5, and Figure 6, the accrued sample sizes were only small fractions of the diversity-adjusted required information size (DARIS) and therefore, the boundaries could not be drawn. There was a high risk of random errors. The TSA-adjusted CI could not be calculated as there was too little information for the calculation (i.e. the CIs were wide).

Figure 4. Trial Sequential Analysis of mortality at maximal follow-up: azathioprine versus no intervention and colchicine versus no intervention. Based on an alpha error of 2.5%, power of 90% (beta error of 10%), a relative risk

reduction (RRR) of 20%, a control group proportion observed in the trials (Pc = 20%), and diversity observed in the analyses (0%), the accrued sample size (224 for azathioprine versus intervention and 122 for colchicine versus no intervention) was only a small fraction of the diversity adjusted required information size (DARIS) (4580 for both comparisons); therefore, the trial sequential monitoring boundaries were not drawn. The Z-curve (blue line) crossed the conventional boundaries (dotted green line) favouring azathioprine for azathioprine versus no intervention, but

did not cross the conventional boundaries for colchicine versus no intervention. This indicates that there is a high risk of random errors in both these comparisons.



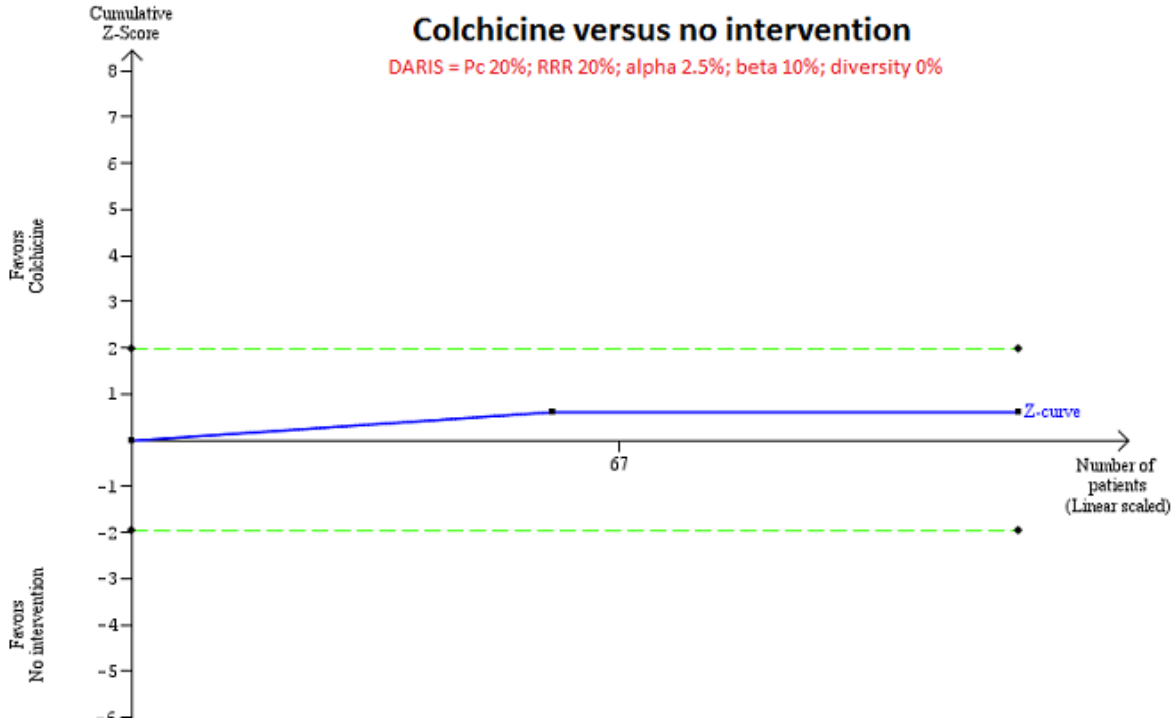


Figure 4. (Continued)

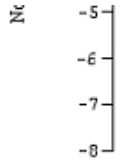
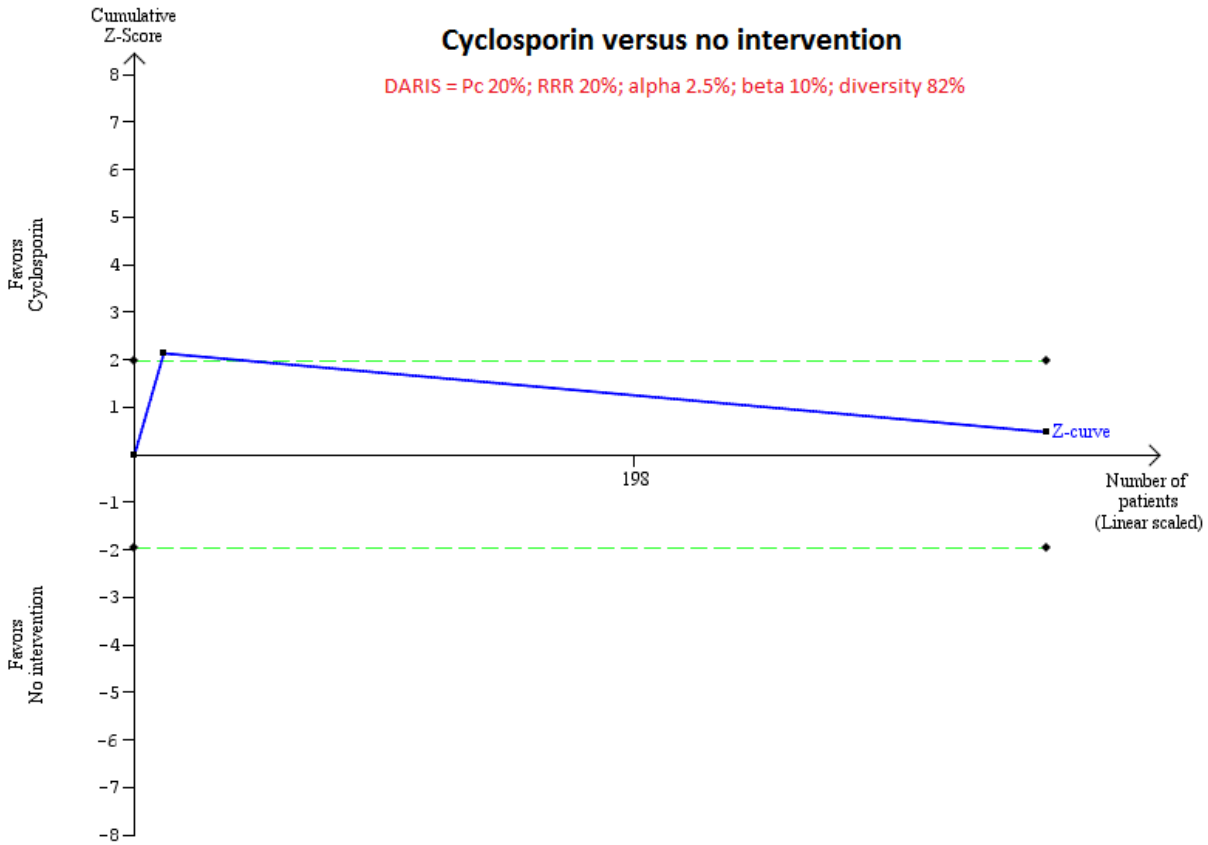


Figure 5. Trial Sequential Analysis of mortality at maximal follow-up: ciclosporin versus no intervention and D-penicillamine versus no intervention. Based on an alpha error of 2.5%, power of 90% (beta error of 10%), a relative risk reduction (RRR) of 20%, a control group proportion observed in the trials (Pc = 20%), and diversity observed in the analyses (82% for ciclosporin versus no intervention and 61% for D-penicillamine versus no intervention), the accrued sample size (394 for ciclosporin versus no intervention and 423 for D-penicillamine versus no intervention) was only a small fraction of the diversity adjusted required information size (DARIS) (25,098 for ciclosporin versus no intervention and 11,623 for D-penicillamine versus no intervention); therefore, the trial sequential monitoring boundaries were not drawn. The Z-curve (blue line) crossed the conventional boundaries (dotted green line) favouring ciclosporin for ciclosporin versus no intervention, but did not cross the conventional boundaries for

D-penicillamine versus no intervention. This indicates that there is a high risk of random errors in both these comparisons.



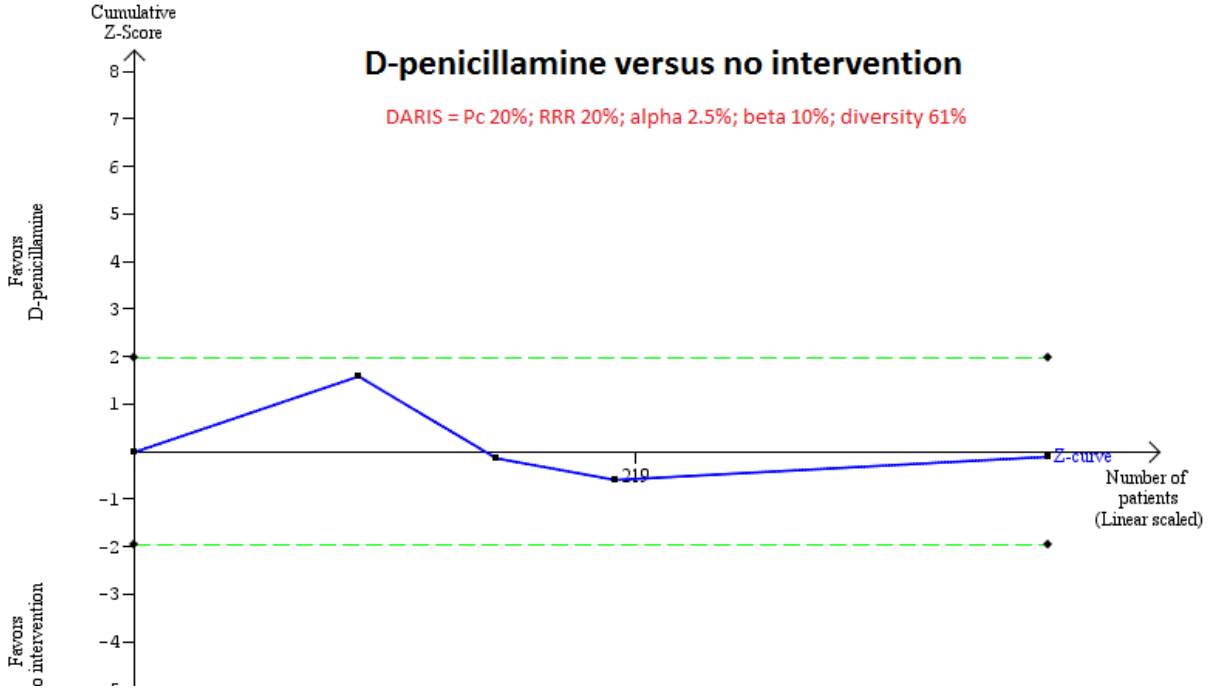


Figure 5. (Continued)

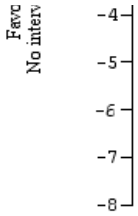
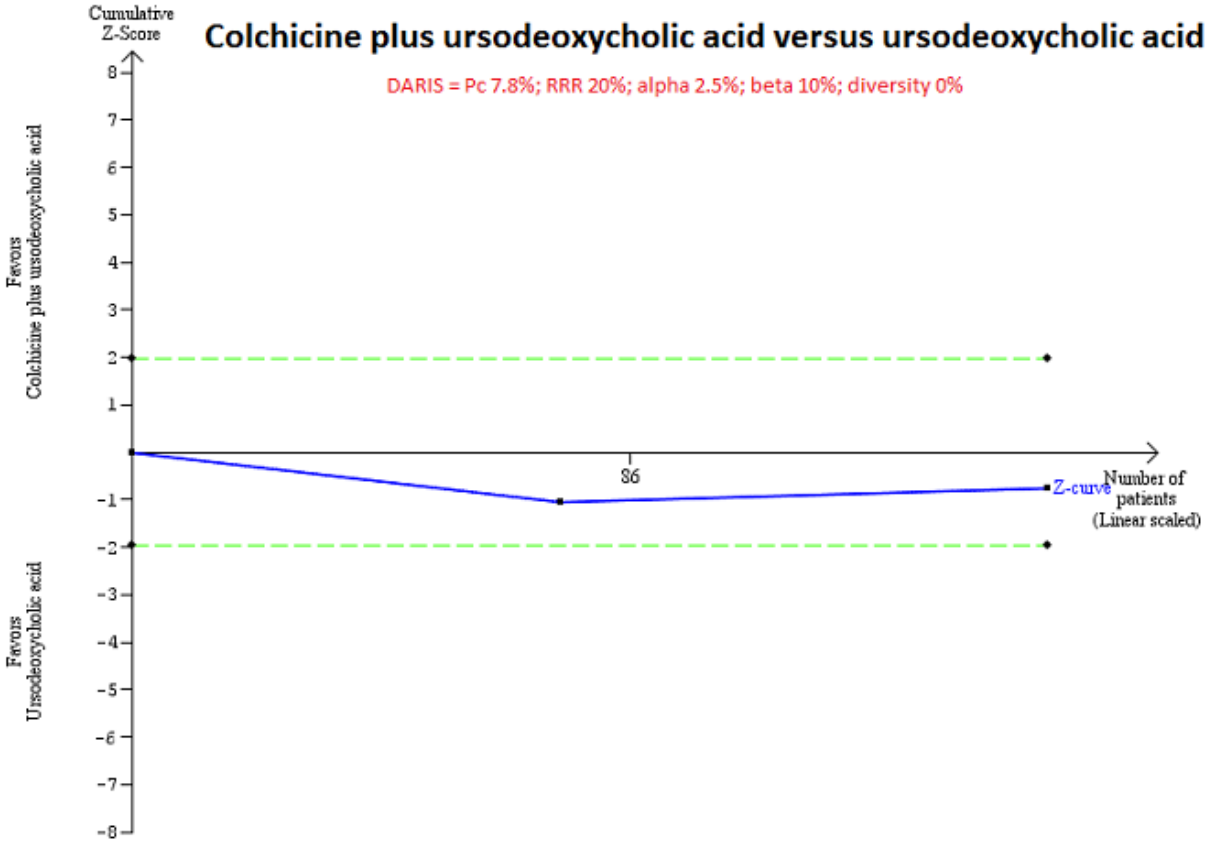


Figure 6. Trial Sequential Analysis of mortality at maximal follow-up: colchicine plus UDCA versus UDCA. Based on an alpha error of 2.5%, power of 90% (beta error of 10%), a relative risk reduction (RRR) of 20%, a control group proportion observed in the trials (Pc = 7.8%), and diversity observed in the analyses (0%), the accrued sample size (160 participants) was only a small fraction of the diversity adjusted required information size (DARIS) (13,316); therefore, the trial sequential monitoring boundaries were not drawn. The Z-curve (blue line) did not cross the conventional boundaries (green dotted line). This indicates that there is a high risk of random errors in both this comparison.



DISCUSSION

Summary of main results

We included 74 trials (5902 participants) in this review, and included 4274 participants from 46 trials in one or more outcomes in this review. We did not perform the planned network meta-analysis because there was no closed loop (i.e. outcomes for which direct and indirect estimates were available to allow us estimation of inconsistency). Therefore, we reported only the direct comparisons. We reported the results from frequentist meta-analysis only as it is more familiar to people.

Although mortality at maximal follow-up was lower in people who received azathioprine versus no intervention, there was no evidence of any reduction in mortality by any intervention, either at less than one year or between one and five years. However, this evidence is unreliable because the Christensen 1985 trial excluded a large proportion of participants (25%) (i.e. only 185/224 participants were included in the meta-analysis). The Trial Sequential Analysis showed that only a small proportion of the required information size was reached and the risk of random errors was high. In addition to the risk of systematic errors and random errors, the proportion of people who died was high (71.3%) in the no intervention group of the Christensen 1985 trial compared to the other trials (the overall mortality at maximal follow-up was 20.8%). Although this difference could be due to the shorter follow-up periods in some of the other trials, the mortality observed in this trial was much higher than that observed in the other trials with similar or longer follow-up such as Epstein 1979; Hendrickse 1999; and Papatheodoridis 2002. The general care of people with cirrhosis is likely to have improved since the 1980s and it is unlikely to be as high as that mortality observed in Christensen 1985. This is another reason why there is no need to recommend azathioprine routinely in people with primary biliary cholangitis.

There was no evidence of a decrease in liver transplantation, decompensated liver disease, or cirrhosis in any of the interventions compared with no intervention. However, several interventions increased the number of people with, and total number of, adverse events. Although the Trial Sequential Analysis revealed that only a small proportion of the required information size was reached, the risk of random errors was high. Thus, concluding that there were more adverse events in some of these comparisons is only of academic interest because none of the interventions appeared to result in clinical benefit.

However, it has to be pointed out that the periods of follow-up in the trials were sufficiently long to identify any differences in clinical outcomes because primary biliary cholangitis is a slowly progressive disease. Trials with sufficient follow-up (e.g. five or 10 years) are required to detect any differences in clinically important outcomes.

Overall completeness and applicability of evidence

The trials included symptomatic and asymptomatic primary biliary cholangitis, AMA-positive and AMA-negative primary biliary cholangitis, treatment-naive people, and people regardless of the treatments that they had received previously. However, majority of the trials excluded people with advanced liver cirrhosis and primary biliary cholangitis in people with other liver diseases. Therefore, this review is applicable to people with primary biliary cholangitis without advanced liver cirrhosis or with coexisting other liver diseases.

Quality of the evidence

The overall quality of evidence was very low for all the outcomes. The major reasons for this were the high risk of bias in the trials, in particular, exclusion of participants from the analysis after randomisation, small sample size, and imprecision. Overall, there were serious concerns about whether the effect estimates observed were the true effect estimates.

Potential biases in the review process

We followed the guidance of the *Cochrane Handbook for Systematic Reviews of Interventions* with two review authors independently selecting trials and extracting data (Higgins 2011). We performed a thorough search of the literature. However, the search period includes the premandatory trial registration era and it is possible that some trials on treatments that were not effective or were harmful were not reported at all.

We excluded studies which compared variations in the different treatments. Hence, this review does not provide information on whether one variation is better than another.

We only included randomised clinical trials which are known to focus mostly on benefits and do not collect and report harms in a detailed manner. Therefore, we might have missed a large number of studies that addressed the reporting of harms. Accordingly, this review is biased towards benefits ignoring harms. We did not search for interventions and trials registered at regulatory authorities (e.g. US Food and Drug Administration; European Medicines Agency, etc.). This may have overlooked trials and as such trials usually are unpublished, the lack of inclusion of such trials may make our comparisons look more advantageous than they really are. However, this is of academic interest only because there is no evidence of benefit of any treatment in people with primary biliary cholangitis (i.e. there is no reason to suggest that any of the treatments should be used in routine clinical practice regardless of the adverse event profile of the intervention).

We planned to perform a network meta-analysis. However, it was not possible to assess whether the potential effect modifiers were similar across different comparisons. Performing a network meta-analysis in this scenario can be misleading. Therefore, we did not perform the network meta-analysis, and assessed the comparative benefits and harms of different interventions using standard Cochrane methodology.

Agreements and disagreements with other studies or reviews

We identified three network meta-analyses on this topic (Zhu 2015a; Zhu 2015b; Zhu 2015c). We disagreed with the authors of these reviews that UDCA in combination with corticosteroids or methotrexate are effective interventions in the treatment of primary biliary cholangitis. The disagreements were probably due to considering mortality and liver transplantation separately in this review compared to Zhu 2015a and Zhu 2015b and only including evidence prior to cross-over in our review. In particular, the cross-over was not true cross-over where the interventions were swapped but all the participants belonging to the 'no intervention' were switched over to the intervention. Therefore, it was not possible to obtain the effect estimate adjusted for intra-participant correlation either. It should be also noted that the decision to switch the no intervention to intervention was based on improvement of some laboratory parameters which are invalidated surrogate outcomes. This can only be considered as observational evidence. We disagree with current EASL and AASLD guideline recommendations that UDCA should be used for the management of primary biliary cholangitis (EASL 2009; Lindor 2009). Again, these recommendations were based on observational evidence and invalidated surrogate outcomes (Gluud 2007).

We agreed with several systematic reviews that showed that none of the interventions are effective in improving survival or other major clinical outcomes such as cirrhosis or liver transplantation (Giljaca 2010; Rudic 2012a; Rudic 2012b; Yin 2015; Zhang 2015).

AUTHORS' CONCLUSIONS

Implications for practice

Based on very low quality evidence, there is currently no evidence that any intervention is beneficial for primary biliary cholangitis.

Implications for research

Randomised clinical trials need to be conducted and reported according to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) statement (Chan 2013) and the CONSORT statement (Schulz 2010). Future randomised clinical trials ought to be adequately powered, performed in people who are generally seen in the clinic rather than in highly selected participants, employ blinding, avoid post-randomisation dropouts or planned cross-overs, should have sufficient follow-up period (e.g. five to 10 years or more), and use clinically important outcomes such as mortality, health-related quality of life, cirrhosis, decompensated cirrhosis, and liver transplantation.

ACKNOWLEDGEMENTS

We thank the Cochrane Comparing of Multiple Interventions Methods Group and the Cochrane Hepato-Biliary for their support and advice.

Peer reviewers: Frederik Nevens, Belgium; Annarosa Floreani, Italy.
Contact editor: Christian Gluud, Denmark.
Sign-off editor: Christian Gluud, Denmark.

Cochrane Review Group funding acknowledgement: the Danish State is the largest single funder of the Cochrane Hepato-Biliary Group through its investment in The Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen University Hospital, Denmark.

Disclaimer: the views and opinions expressed in this review are those of the review authors and do not necessarily reflect those of the Danish State or The Copenhagen Trial Unit.

REFERENCES

References to studies included in this review

Almasio 2000 *{published data only}*

Almasio P, Provenzano G, Battezzati PM, Podda M, Todros L, Rosina F, et al. The Italian multi-centre randomized controlled trial of UDCA vs colchicine plus UDCA in symptomatic primary biliary cholangitis. *Hepatology* 1994;**20**(4 (Pt 2)):73.

* Almasio PL, Floreani A, Chiaramonte M, Provenzano G, Battezzati P, Crosignani A, et al. Multicentre randomized placebo-controlled trial of UDCA with or without colchicine in symptomatic primary biliary cholangitis. *Alimentary Pharmacology & Therapeutics* 2000;**14**(12):1645-52.

Battezzati PM, Zuin M, Crosignani A, Allocca M, Invernizzi P, Selmi C, et al. Ten-year combination treatment with colchicine and UDCA for primary biliary cholangitis: a double-blind, placebo-controlled trial on symptomatic patients. *Alimentary Pharmacology & Therapeutics* 2001;**15**(9):1427-34.

Podda M, Almasio P, Battezzati PM, Crosignani A. Long-term effect of the administration of UDCA alone or with colchicine in patients with primary biliary cholangitis: a double-blind multicentre study. 68th Falk Symposium; 1992 Oct 12-14; Basel, Switzerland. 1993:310-5.

Angulo 1999a *{published data only}*

Angulo P, Dickson ER, Therneau TM, Jorgensen RA, Smith C, DeSotel CK, et al. Comparison of three doses of UDCA in the treatment of primary biliary cholangitis: a randomized trial. *Journal of Hepatology* 1999;**30**(5):830-5.

Arora 1990 *{published data only}*

* Arora R, Batta AK, Salen G, O'Brien C, Senior JR. Effect of ursodiol on bile acid conjugation in patients with primary biliary cholangitis. *Hepatology* 1990;**12**(4 (Pt 2)):994.

Batta AK, Arora R, Salen G, Katz S. UDCA improves liver function and reduces serum and urinary endogenous bile acids in primary biliary cholangitis. *Hepatology* 1988;**8**(5):1221.

Batta AK, Arora R, Salen G, O'Brien C, Senior JR. Effect or ursodiol on biliary bile acid composition and conjugation in patients with primary biliary cholangitis. *Gastroenterology* 1990;**98**(2 (Pt 2)):A567.

Askari 2010 *{published data only}*

Askari F, Innis D, Dick RB, Hou GQ, Marrero J, Greenson J, et al. Treatment of primary biliary cholangitis with tetrathiomolybdate: results of a double-blind trial. *Translational Research* 2010;**155**(3):123-30.

Battezzati 1993 *{published data only}*

Anonymous. UDCA (UDCA) for symptomatic primary biliary cholangitis (PBC): a double-blind multicenter trial. *Journal of Hepatology* 1989;**9**(Suppl 1):S44.

* Battezzati PM, Podda M, Bianchi FB, Naccarato R, Orlandi F, Surrenti C, et al. UDCA for symptomatic primary biliary cholangitis. Preliminary analysis of a double-blind multicenter trial. Italian multicenter group for the study of UDCA in PBC. *Journal of Hepatology* 1993;**17**(3):332-8.

Podda M, Battezzati PM, Crosignani A, Bianchi FB, Fusconi M, Chiaramonte M, et al. UDCA (UDCA) for symptomatic primary biliary cholangitis (PBC): a double-blind multicenter trial. *Hepatology* 1989;**10**(4):639.

Bobadilla 1994 *{published data only}*

Bobadilla J, Vargas F, Dehesa M, Zapata L, Kaplan M, Nava R, et al. Colchicine and ursodiol in the treatment of primary biliary cholangitis. *Hepatology* 1994;**20**(4 (Pt 2)):332a.

Bodenheimer 1988 *{published data only}*

* Bodenheimer H Jr, Schaffner F, Pezzullo J. Evaluation of colchicine therapy in primary biliary cholangitis. *Gastroenterology* 1988;**95**(1):124-9.

Bodenheimer H, Schaffner F, Pezzullo J. A randomized double-blind controlled trial of colchicine in primary biliary cholangitis. *Hepatology* 1985;**5**(5):968.

Bodenheimer H, Schaffner F, Pezzullo J. Colchicine therapy in primary biliary cholangitis. *Hepatology* 1986;**6**(5):1172.

Zifroni A, Schaffner F. Long-term follow-up of patients with primary biliary cholangitis on colchicine therapy. *Hepatology* 1991;**14**(6):990-3.

Bowlus 2014 *{published data only}*

Bowlus CL, Pockros PJ, Drenth J, Floreani A, Vincent C, Luketic VA, et al. Obeticholic acid in PBC patients: the utility of titration based on therapeutic response and tolerability. *Hepatology* 2014;**60**:353a.

Cash 2013 *{published data only}*

Cash WJ, O'Neill S, O'Donnell ME, McCance DR, Young IS, McEneny J, et al. Randomized controlled trial assessing the effect of simvastatin in primary biliary cholangitis. *Liver International* 2013;**33**(8):1166-74.

Christensen 1985 *{published data only}*

* Christensen E, Neuberger J, Crowe J. Beneficial effect of azathioprine and prediction of prognosis in primary biliary cholangitis. Final results of an international trial. *Gastroenterology* 1985;**89**(5):1084-91.

Christensen E, Neuberger J, Crowe J, Popper H, Portmann B, Deniach D, et al. Azathioprine in primary biliary cholangitis: late results of an international trial. *Liver* 1984;**4**(1):81.

Christensen E, Neuberger J, Crowe J, Popper H, Portmann B, Doniach D, et al. Azathioprine in primary biliary cholangitis: late results of an international trial. *Gut* 1983;**24**(10):A995-6.

Crowe J, Christensen E, Smith M. Azathioprine in primary biliary cholangitis: a preliminary report of an international trial. *Gastroenterology* 1980;**78**(5 I):1005-10.

Combes 1995a *{published data only}*

Carithers RL, Luketic VA, Peters M, Zetterman RK, Garcia-Tsao G, Munoz SJ. Extended follow-up of patients in the US multicenter trial of UDCA for primary biliary cholangitis. *Gastroenterology* 1996;**110**(Suppl 4):A1163.

* Combes B, Carithers RL Jr, Maddrey WC, Lin D, McDonald MF, Wheeler DE, et al. A randomized, double-blind, placebo-controlled trial of UDCA in primary biliary cholangitis. *Hepatology* 1995;**22**(3):759-66.

Combes B, Carithers RL Jr, Maddrey WC, Munoz S, Garcia-Tsao G, et al. Biliary bile acids in primary biliary cholangitis: effect of UDCA. *Hepatology* 1999;**29**(6):1649-54.

Combes B, Carithers RL Jr, McDonald MF, Maddrey WC, Munoz SJ, Boyer JL, et al. UDCA therapy in patients with primary biliary cholangitis. *Hepatology* 1991;**14**(4 (Pt 2)):91a.

Combes B, Carithers RL, Maddrey WC, Munoz SJ, McDonald MF, Garcia-Tsao G. A randomized, double-blind, placebo-controlled trial of UDCA in primary biliary cholangitis. 68th Falk Symposium; 1992 Oct 12-14; Basel, Switzerland. 1993:289-91.

Combes B, Carithers RL, Maddrey WC, Munoz SJ, McDonald MF, Garcia-Tsao G, et al. A randomized, double-blind, placebo-controlled trial of UDCA (UDCA) in primary biliary cholangitis. *Hepatology* 1993;**18**(4 (Pt 2)):175a.

Combes B, Markin RS, Wheeler DE, Rubin R, West AB, Mills AS, et al. The effect of UDCA on the florid duct lesion of primary biliary cholangitis. *Hepatology* 1999;**30**(3):602-5.

Combes 2005 *{published data only}*

Combes B, Emerson SS, Flye NL. The primary biliary cholangitis (PBC) ursodiol (UDCA) plus methotrexate (MTX) or its placebo study (PUMPS) - a multicenter randomized trial. *Hepatology* 2003;**38**(4):210A-1A.

* Combes B, Emerson SS, Flye NL, Munoz SJ, Luketic VA, Mayo MJ, et al. Methotrexate (MTX) plus UDCA (UDCA) in the treatment of primary biliary cholangitis. *Hepatology* 2005;**42**(5):1184-93.

Munoz S, Carithers R, Emerson SS, Flye N, Kowdley K, Combes B. Absence of pulmonary toxicity in primary biliary cholangitis (PBC) treated with methotrexate and ursodiol. *Hepatology* 1998;**28**(Suppl 4):392a.

NCT00004784. Phase III randomized study of ursodiol with vs without methotrexate for primary biliary cholangitis. clinicaltrials.gov/ct2/show/NCT00004784 (date first received: 24 February 2000).

Dickson 1985 *{published data only}*

Deering TB, Dickson ER, Fleming CR. Effect of D penicillamine on copper retention in patients with primary biliary cholangitis. *Gastroenterology* 1977;**72**(6):1208-12.

Dickson ER. The syndrome of primary biliary cholangitis. *Journal of Rheumatology - Supplement* 1981;**7**:121-3.

Dickson ER, Fleming CR, Geall MG. A double blind controlled study using D-penicillamine in chronic cholangiolitic hepatitis (primary biliary cholangitis). *Gastroenterology* 1977;**72**(5 II):A-26.

* Dickson ER, Fleming TR, Wiesner RH. Trial of penicillamine in advanced primary biliary cholangitis. *New England Journal of Medicine* 1985;**312**(16):1011-5.

Dickson ER, Wiesner RH, Baldus WP, Fleming CR, Ludwig JL. D-penicillamine improves survival and retards histologic progression in primary biliary-cirrhosis. *Gastroenterology* 1982;**82**(5 Part 2):1225.

Fleming CR, Ludwig J, Dickson ER. Asymptomatic primary biliary cholangitis. Presentation, histology, and results with D-penicillamine. *Mayo Clinic Proceedings* 1978;**53**(9):587-93.

Locke GR 3rd, Therneau TM, Ludwig J, Dickson ER, Lindor KD. Time course of histological progression in primary biliary cholangitis. *Hepatology* 1996;**23**(1):52-6.

Powell FC, Rogers RS, Dickson ER. Primary biliary cholangitis and lichen planus. *Journal of the American Academy of Dermatology* 1983;**9**(4):540-5.

Epstein 1979 *{published data only}*

Epstein G, De Williers D, Jain S, Potter BJ, Thomas HC, Sherlock S. Effect of penicillamine on immune complexes and immunoglobulins in primary biliary cholangitis (PBC). *Gut* 1978;**19**(Suppl 3):A994.

Epstein O, Cook D, Jain S, Sherlick S. D-Penicillamine in primary biliary cholangitis (PBC) - an untested (and untestable?) treatment. *Gut* 1984;**25**:A1134.

Epstein O, Cook DG, Jain S, McIntyre N, Sherlock S. D-Penicillamine and clinical-trials in PBC. *Hepatology* 1984;**4**(5):1032.

Epstein O, Cook DG, Jain S, Sherlock S. D-Penicillamine in PBC - an untested (and untestable?) treatment. *Journal of Hepatology* 1985;**1**(Suppl 1):S49.

* Epstein O, De Villiers D, Jain S. Reduction of immune complexes and immunoglobulins induced by D-penicillamine in primary biliary cholangitis. *New England Journal of Medicine* 1979;**300**(6):274-8.

Epstein O, Jain S, Lee RG. D-Penicillamine treatment improves survival in primary biliary cholangitis. *Lancet* 1981;**1**(8233):1275-7.

Epstein O, Jain S, Lee RG, Cook DG, Boss AM, Scheuer PJ, et al. D-Penicillamine treatment improves survival in primary biliary-cirrhosis. *Gut* 1981;**22**(5):A433-A.

Jain S, McGee JD, Scheuer PJ, Samourian S, Sherlock S. A controlled trial of D-penicillamine therapy in primary biliary cholangitis and chronic active hepatitis. *Digestion* 1976;**14**:523.

Jain S, Scheuer PJ, Samourian S. A controlled trial of D-penicillamine therapy in primary biliary cholangitis. *Lancet* 1977;**1**(8016):831-4.

Jain S, Scheur PJ, Samourian S, McGee JD, Sherlock S. A controlled trial of D-penicillamine therapy in primary biliary cholangitis. *Gut* 1976;**17**(Suppl 2):822.

Eriksson 1997 *{published data only}*

Eriksson LS, Olsson R, Glauman H, Prytz H, Befrits H, Lindgren S, et al. UDCA (UDCA) in patients with primary biliary cholangitis (PBC): results of a two-year randomized placebo-controlled study (abstract). *Scandinavian Journal of Gastroenterology* 1995;**30**(Suppl 209):35.

* Eriksson LS, Olsson R, Glauman H, Prytz H, Befrits R, Ryden BO, et al. UDCA treatment in patients with primary biliary cholangitis. A Swedish multicentre, double-blind, randomized controlled study. *Scandinavian Journal of Gastroenterology* 1997;**32**(2):179-86.

Ferri 1993 *{published data only}*

Ferri F, Bernocchi P, Fedeli S. [Taurodeoxycholic acid in the treatment of primary biliary cholangitis. A controlled study in comparison to UDCA]. *Clinica Terapeutica* 1993;**143**(4):321-6.

Gao 2012 *{published data only}*

Gao LX, Zhang FC, Wang L, Zhang X, Liu B. The clinical observation of different therapeutic strategies in combined primary biliary cholangitis and Sjogren syndrome. *Chung-Hua Nei Ko Tsa Chih* 2012;**51**(11):851-4.

Goddard 1994 *{published data only}*

Goddard C, Smith A, Hunt L, Halder T, Hillier V, Rowan B, et al. Surrogate markers of response in a trial of UDCA (UDCA) and colchicine in primary biliary cholangitis (PBC). *Gut* 1995;**36**(Suppl 1):A30.

* Goddard CJR, Hunt L, Smith A, Followfield G, Rowan B, Warnes TW. A trial of UDCA (UDCA) and colchicine in primary biliary cholangitis (PBC). *Hepatology* 1994;**20**(4 (Pt 2)):151a.

Gonzalezkoch 1997 *{published data only}*

Gonzalezkoch A, Brahm J, Antezana C, Smok G, Cumsille MA. The combination of UDCA and methotrexate for primary biliary cholangitis is not better than UDCA alone. *Journal of Hepatology* 1997;**27**(1):143-9.

Heathcote 1976 *{published data only}*

* Heathcote J, Ross A, Sherlock S. A prospective controlled trial of azathioprine in primary biliary cholangitis. *Gastroenterology* 1976;**70**(5 PT.1):656-60.

Ross A, Sherlock S. A controlled trial of azathioprine in primary biliary cholangitis. *Gut* 1971;**12**(2):770.

Ross A, Sherlock S. A trial of azathioprine in primary biliary cholangitis. *Gut* 1970;**11**(12):1058.

Heathcote 1994 *{published data only}*

* Heathcote EJ, Cauch-Dudek K, Walker V, Bailey RJ, Blendis LM, Ghent CN, et al. The Canadian multicenter double-blind randomized controlled trial of UDCA in primary biliary cholangitis. *Hepatology* 1994;**19**(5):1149-56.

Heathcote EJL, Cauch K, Walker V, Bailey RJ, Blendis LM, Ghent CN, et al. The Canadian multicenter double-blind randomized controlled trial of UDCA in primary biliary-cirrhosis. *Hepatology* 1992;**16**(4):A91.

Heathcote EJL, Cauch K, Walker V, Blendis LM, Pappas SC, Wanless IR. A double-blind randomized controlled multicentre trial of UDCA in primary biliary cholangitis: results from a 1991 interim analysis. 68th Falk Symposium; 1992 Oct 12-14; Basel, Switzerland. 1993:294-8.

Neuman MG, Cameron RG, Haber JA, Katz GG, Blendis LM. An electron microscopic and morphometric study of ursodeoxycholic effect in primary biliary cholangitis. *Liver* 2002;**22**(3):235-44.

Neuman MG, Cameron RG, Shear NH, Blendis LM. Electron microscopic study on antifibrotic effects of ursodeoxycholate treatment in primary biliary cholangitis. *Bile Acids and Cholestasis* 1999;**108**:254-69.

Worobetz LJ, Cauch-Dudek K, Heathcote EJ. The effect of UDCA (UDCA) on anti-mitochondrial antibody (AMA) titre in primary biliary cholangitis (PBC). *Gastroenterology* 1995;**108**(4 Suppl 3):A1200.

Hendrickse 1999 *{published data only}*

Giaffer MH, Hendrickse M, Soomoro I, Triger DR, Underwood JCE, Gleeson D. Low-dose methotrexate in treatment of primary biliary cholangitis. *Gut* 1995;**36**(Suppl 1):A30.

Hendrickse M, Rigney E, Giaffer MH, Soomoro I, Triger DR, Underwood JC, et al. Low-dose methotrexate in primary biliary cholangitis: long-term results of a placebo-controlled trial. *Hepatology* 1997;**26**(4):479.

* Hendrickse MT, Rigney E, Giaffer MH, Soomro I, Triger DR, Underwood JC, et al. Low-dose methotrexate is ineffective in primary biliary cholangitis: long-term results of a placebo-controlled trial. *Gastroenterology* 1999;**117**(2):400-7.

Hirschfield 2015 *{published data only}*

Hirschfield G, Kowdley K, Mason A, Luketic V, Gordon S, Vincent C, et al. Long-term (LT) therapy of a farnesoid X receptor (FXR) agonist obeticholic acid (OCA) maintains biochemical response in primary biliary cholangitis (PBC). *Journal of Hepatology* 2012;**56**:S372.

* Hirschfield GM, Mason A, Luketic V, Lindor K, Gordon SC, Mayo M, et al. Efficacy of obeticholic acid in patients with primary biliary cholangitis and inadequate response to UDCA. *Gastroenterology* 2015;**148**(4):751-61.e8.

Luketic V, Gordon SG, Vincent C, Chapman R, Mayo M, Kowdley K, et al. The FXR agonist obeticholic acid improves a transplant free survival-proven biochemical response criterion in placebo controlled primary biliary cholangitis studies. *Journal of Hepatology* 2014;**60**(1 (Suppl 1)):S193-4.

Luketic VA, Invernizzi P, Trauner M, Regula J, Mazzella G, Strasser SI, et al. Efficacy of obeticholic acid in primary biliary

cholangitis as assessed by response criteria associated with clinical outcome: a poise analysis. *Hepatology* 2014;**60**:355a-6a.

Marschall H, Luketic VA, Mason AL, Lindor KD, Hirschfield GM, Gordon SC, et al. The farnesoid X receptor (FXR) agonist obeticholic acid (INT-747, 6α-ethyl chenodeoxycholic acid) in combination with UDCA (UDCA) increases plasma FGF-19 concentrations but not bile acid concentration or profile in primary biliary cholangitis (PBC). *Hepatology* 2010;**52**(Suppl S1):355a.

Mason AL, Lindor KD, Bacon BR, Vincent C, Neuberger JM, Wasilenko ST. Multi-center, double blind, randomized controlled trial of zidovudine and lamivudine (Combivir) therapy for patients with primary biliary cholangitis. *Hepatology* 2007;**46**(4):264A.

Hoofnagle 1986 *{published data only}*

* Hoofnagle JH, Davis GL, Schafer DF, Peters M, Avigan MI, Pappas SC, et al. Randomized trial of chlorambucil for primary biliary cholangitis. *Gastroenterology* 1986;**91**(6):1327-34.

Hoofnagle JH, Davis GL, Schafer DF, Peters MG, Avigan MI, Hanson RG, et al. Randomized trial of chlorambucil for primary biliary-cirrhosis. *Hepatology* 1984;**4**(5):1062.

Hosonuma 2015 *{published data only}*

* Hosonuma K, Sato K, Yamazaki Y, Yanagisawa M, Hashizume H, Horiguchi N, et al. A prospective randomized controlled study of long-term combination therapy using UDCA and bezafibrate in patients with primary biliary cholangitis and dyslipidaemia. *American Journal of Gastroenterology* 2015;**110**(3):423-31.

Sato K, Hosonuma K, Yamazaki Y, Yanagisawa M, Hashizume H, Horiguchi N, et al. Long-term prognosis of combination therapy with UDCA and bezafibrate for primary biliary cholangitis: a prospective, multicenter, randomized controlled study. *Hepatology International* 2014;**8**(1 (Suppl 1)):S15.

Ikeda 1996 *{published data only}*

Ikeda T, Tozuka S, Noguchi O, Kobayashi F, Sakamoto S, Marumo F, et al. Effects of additional administration of colchicine in UDCA-treated patients with primary biliary cholangitis: a prospective randomized study. *Journal of Hepatology* 1996;**24**(1):88-94.

Iwasaki 2008a *{published data only}*

Iwasaki S, Ohira H, Nishiguchi S, Zeniya M, Kaneko S, Onji M, et al. The efficacy of UDCA and bezafibrate combination therapy for primary biliary cholangitis: a prospective, multicenter study. *Hepatology Research* 2008;**38**(6):557-64.

Iwasaki 2008b *{published data only}*

Iwasaki S, Ohira H, Nishiguchi S, Zeniya M, Kaneko S, Onji M, et al. The efficacy of UDCA and bezafibrate combination therapy for primary biliary cholangitis: a prospective, multicenter study. *Hepatology Research* 2008;**38**(6):557-64.

Kanda 2003 *{published data only}*

Kanda T, Yokosuka O, Imazeki F, Saisho H. Bezafibrate treatment: a new medical approach for PBC patients?. *Journal of Gastroenterology* 2003;**38**(6):573-8.

Kaplan 1986 *{published data only}*

Johnston DE, Kaplan MM, Miller KB, Connors CM, Milford EL. Histocompatibility antigens in primary biliary cholangitis. *American Journal of Gastroenterology* 1987;**82**(11):1127-9.

Kaplan MM, Alling DW, Wolfe HJ, Zimmerman HJ. Colchicine is effective in the treatment of primary biliary cholangitis. *Hepatology* 1985;**5**(5):967.

Kaplan MM, Alling DW, Zimmerman HJ, Wolfe HJ, Sepersky RA, Hirsch GE, et al. A prospective trial of colchicine for primary biliary cholangitis. (abstract). *Acta Gastroenterologica Belgica* 1987;**50**(3):382.

* Kaplan MM, Alling DW, Zimmerman HJ, Wolfe HJ, Sepersky RA, Hirsch GS, et al. A prospective trial of colchicine for primary biliary cholangitis. *New England Journal of Medicine* 1986;**315**(23):1448-54.

Miller LC, Kaplan MM. Serum interleukin-2 and tumor necrosis factor-alpha in primary biliary cholangitis: decrease by colchicine and relationship to HLA-DR4. *American Journal of Gastroenterology* 1992;**87**(4):465-70.

Kaplan 1999 *{published data only}*

Kaplan M, Schmid C, McKusick A, Provenzale D, Sharma A, Sepe T. Double blind trial of methotrexate (MTX) versus colchicine (COLCH) in primary biliary cholangitis (PBC). *Hepatology* 1993;**18**(4 (Pt 2)):176a.

Kaplan MM, Dickstein G, Schmid C. Methotrexate (MTX) improves histology in primary biliary cholangitis (PBC). *Hepatology* 1994;**20**(4 (Pt 2)):152a.

* Kaplan MM, Schmid C, Provenzale D, Sharma A, Dickstein G, McKusick A. A prospective trial of colchicine and methotrexate in the treatment of primary biliary cholangitis. *Gastroenterology* 1999;**117**(5):1173-80.

Miller LC, Sharma A, McKusick AF, Tassoni JP, Dinarello CA, Kaplan MM. Synthesis of interleukin-1 beta in primary biliary cholangitis: relationship to treatment with methotrexate or colchicine and disease progression. *Hepatology* 1995;**22**(2):518-24.

NCT00004748. Phase III randomized, double-blind, placebo-controlled study of low-dose oral methotrexate vs colchicine for primary biliary cholangitis. www.clinicaltrials.gov/ct2/show/NCT00004748 Date first received: 24 February 2000.

Sharma A, Provenzale D, McKusick A, Kaplan MM. Interstitial pneumonitis after low-dose methotrexate therapy in primary biliary cholangitis. *Gastroenterology* 1994;**107**(1):266-70.

Kowdley 2011 *{published data only}*

Kowdley K, Jones D, Luketic V, Chapman R, Burroughs A, Hirschfield G, et al. An international study evaluating the

farnesoid X receptor agonist obeticholic acid as monotherapy in PBC. *Journal of Hepatology* 2011;**54**:S13.

Kurihara 2000 *{published data only}*

Kurihara T, Niimi A, Maeda A, Shigemoto M, Yamashita K. Bezafibrate in the treatment of primary biliary cholangitis: comparison with UDCA. *American Journal of Gastroenterology* 2000;**95**(10):2990-2.

Leuschner 1989 *{published data only}*

Guldutuna S, Leuschner U, Imhof M, Zimmer G. Treatment of chronic active hepatitis and primary biliary cholangitis with UDCA. *Zeitschrift Fur Gastroenterologie* 1992;**30 Suppl 1**:49-54.

Leuschner U, Fischer H, Guldutuna S, Kurtz W, Gatzen M, Hellstern A. Does UDCA (UDCA) influence cell membrane architecture in patients with primary biliary cholangitis (PBC)?. *Gastroenterology* 1989;**96**(5 (Pt 2)):A621.

Leuschner U, Fischer H, Hubner K. [UDCA in the treatment of primary biliary cholangitis: results of a controlled study]. *Zeitschrift fur Gastroenterologie - Verhandlungsband* 1989;**24**:133.

* Leuschner U, Fischer H, Kurtz W, Guldutuna S, Hubner K, Hellstern A, et al. UDCA in primary biliary cholangitis: results of a controlled double-blind trial. *Gastroenterology* 1989;**97**(5):1268-74.

Leuschner U, Fisher H, Hübner K, Güldütuna S, Gatzen M, Hellstern A. UDCA (UDCA) treatment of primary biliary cholangitis: clinical and histological results of a controlled study. *52nd Falk Symposium; 1988 Jun 9-11; Freiburg, Germany* 1989;**41**:355-8.

Leuschner 1999 *{published data only}*

Leuschner M, Maier KP, Schlichting J, Strahl R, Herrmann G, Dahm HH, et al. Combination of UDCA (UDCA) with budesonide (BUD) is superior to UDCA-mono-therapy in primary biliary cholangitis (PBC). *Journal of Hepatology* 1999;**30**(Suppl 1):57.

Leuschner M, Maier KP, Schlichting J, Strahl R, Herrmann G, Dahm HH, et al. UDCA (UDCA) and budesonide (BUD) in the treatment of primary biliary cholangitis (PBC): a prospective double-blind trial. *Hepatology* 1999;**30**(4):471a.

Leuschner M, Maier KP, Schlichting J, Strahl R, Herrmann G, Dahm HH, et al. [UDCA (UDCA)-placebo versus UDCA-budesonide by primary biliary cholangitis (PBC). A double-blind study]. *Zeitschrift fur Gastroenterologie* 1999;**37**(9):897.

* Leuschner M, Maier KP, Schlichting J, Strahl S, Herrmann G, Dahm HH, et al. Oral budesonide and UDCA for treatment of primary biliary cholangitis: results of a prospective double-blind trial. *Gastroenterology* 1999;**117**(4):918-25.

Liberopoulos 2010 *{published data only}*

Liberopoulos EN, Florentin M, Elisaf MS, Mikhailidis DP, Tsianos E. Fenofibrate in primary biliary cholangitis: a pilot study. *Open Cardiovascular Medicine Journal* 2010;**4**:120-6.

Lim 1994 *{published data only}*

Lim AG, Jazrawi RP, Maxwell JD, Northfield TC. UDCA (UDCA) improves hepatic excretion in primary biliary cholangitis (PBC). *Gut* 1994;**35**(S5):S11.

* Lim AG, Jazrawi RP, Petroni ML, Pereira S, Maxwell JD, Northfield TC. T-lymphocyte activation in primary biliary cholangitis: effects of UDCA. *Falk Symposium XIII International Bile Acid Meeting* 1994;**80**:147.

Lindor 1994 *{published data only}*

Balan V, Dickson ER, Jorgensen RA, Lindor KD. Effect of UDCA on serum lipids of patients with primary biliary cholangitis. *Mayo Clinic Proceedings* 1994;**69**(10):923-9.

Batts KP, Jorgensen RA, Dickson ER, Hofmann AF, Rossi SS, Ludwig J, et al. The effects of UDCA on hepatic inflammation and histologic stage in patients with primary biliary cholangitis. *Hepatology* 1993;**18**(4 (Pt 2)):175a.

Batts KP, Jorgensen RA, Dickson ER, Lindor KD. Effects of UDCA on hepatic inflammation and histological stage in patients with primary biliary cholangitis. *American Journal of Gastroenterology* 1996;**91**(11):2314-7.

Dickson ER, Lindor KD, Baldus WP, Jorgensen RA, Ludwig J, Murtaugh PA. Ursodiol is effective therapy for patients with primary biliary cholangitis. 68th Falk Symposium; 1992 Oct 12-14; Basel, Switzerland. 1993:292-3.

Jorgensen RA, Dickson ER, Hofmann AF, Rossi SS, Lindor KD. Characterisation of patients with a complete biochemical response to UDCA. *Gut* 1995;**36**(6):935-8.

Lacerda MA, Lindor KD, Jorgensen RA, Rossi SS, Hofmann AF, Salen GR, et al. Dissimilar patterns of serum and biliary bile-acids in primary biliary-cirrhosis (PBC) patients treated with UDCA (UDCA). *Hepatology* 1993;**18**(4):A174.

Laurin JM, DeSotel CK, Jorgensen RA, Dickson ER, Lindor KD. The natural history of abdominal pain associated with primary biliary cholangitis. *American Journal of Gastroenterology* 1994;**89**(10):1840-3.

Lindor KD, Baldus WP, Jorgensen RA, Ludwig J, Murtaugh PA, Dickson ER. UDCA (UDCA) is beneficial therapy for patients with primary biliary cholangitis (PBC). *Hepatology* 1992;**16**(2 (Pt 2)):91a.

* Lindor KD, Dickson ER, Baldus WP, Jorgensen RA, Ludwig J, Murtaugh PA, et al. UDCA in the treatment of primary biliary cholangitis. *Gastroenterology* 1994;**106**(5):1284-90.

Lindor KD, Janes CH, Crippin JS, Jorgensen RA, Dickson ER. Bone disease in primary biliary cholangitis: does UDCA make a difference?. *Hepatology* 1995;**21**(2):389-92.

Lindor KD, Jorgensen RA, Dickson ER. UDCA delays the onset of esophageal varices in primary biliary cholangitis. *Hepatology* 1995;**22**(4 (Pt 2)):125a.

Lindor KD, Jorgensen RA, Therneau TM, Malinchoc M, Dickson ER. UDCA delays the onset of esophageal varices

in primary biliary cholangitis. *Mayo Clinic Proceedings* 1997;**72**(12):1137-40.

Lindor KD, Lacerda MA, Jorgensen RA, DeSotel CK, Batta AK, Salen G, et al. Relationship between biliary and serum bile acids and response to UDCA in patients with primary biliary cholangitis. *American Journal of Gastroenterology* 1998;**93**(9):1498-504.

Siegel JL, Jorgensen R, Angulo P, Lindor KD. Treatment with UDCA is associated with weight gain in patients with primary biliary cholangitis. *Journal of Clinical Gastroenterology* 2003;**37**(2):183-5.

Zukowski TH, Jorgensen RA, Dickson ER, Lindor KD. Autoimmune conditions associated with primary biliary cholangitis: response to UDCA therapy. *American Journal of Gastroenterology* 1998;**93**(6):958-61.

Lindor 1997 *{published data only}*

Lindor KD, Jorgensen R, Therneau TM, Smith C, Mahoney DW, Dickson ER. Comparison of three different doses of UDCA in the treatment of primary biliary cholangitis: a randomized trial. *Hepatology* 1997;**26**(4):1240.

Lombard 1993 *{published data only}*

Guanabens N, Pares A, Navasa M, Martinez de Osaba MJ, Hernandez ME, Munoz J, et al. Cyclosporin a increases the biochemical markers of bone remodeling in primary biliary cholangitis. *Journal of Hepatology* 1994;**21**(1):24-8.

Guañabens N, Parés A, Navasa M, Rivera F, Muñoz J, Rodés J. Influence of cyclosporin a in bone metabolism in primary biliary cholangitis. *Revista Española de Reumatología* 1990;**17**(Suppl 1):14-5.

* Lombard M, Portmann B, Neuberger J, Williams R, Tygstrup N, Ranek L, et al. Cyclosporin a treatment in primary biliary cholangitis: results of a long-term placebo controlled trial. *Gastroenterology* 1993;**104**(2):519-26.

Lombard M, Portmann BP, Tygstrup N, Ranek L, Larsen HR, Trepo C, et al. Cyclosporin a in primary biliary cholangitis: results of a long-term placebo controlled trial and effect on survival. *Hepatology* 1990;**12**(4 (Pt 2)):872.

Ma 2016 *{published data only}*

Ma H, Zeng M, Han Y, Yan H, Tang H, Sheng J, et al. A multicenter, randomized, double-blind trial comparing the efficacy and safety of TUDCA and UDCA in Chinese patients with primary biliary cholangitis. *Medicine* 2016;**95**(47):e5391.

Macklon 1982 *{published data only}*

Bassendine M, Macklon A, Mulcahy R, James O. Controlled trial of high and low dose D-penicillamine (DP) in primary biliary cholangitis (PBC): results at three years. *Gut* 1982;**23**:A909.

* Macklon AF, Bassendine MF, James OFW. Controlled trial of D-penicillamine in primary biliary cholangitis: incidence of side effects and relation to dose. *Hepatology* 1982;**2**(1):166.

Manzillo 1993a *{published data only}*

Manzillo G, Piccinino F, Surrenti C, Frezza M, Grazie C. Double-blind, placebo-controlled study with parenteral and oral S-adenosyl-L-methionine (SAMe) in primary biliary cholangitis. *II United European Gastroenterology Week* 1993:A337.

Manzillo 1993b *{published data only}*

Manzillo G, Piccinino F, Surrenti C, Frezza M, Grazie C. Double-blind, placebo-controlled study with parenteral and oral S-adenosyl-L-methionine (SAMe) in primary biliary cholangitis. *II United European Gastroenterology Week* 1993:A337.

Mason 2008 *{published data only}*

Mason A, Luketic V, Lindor K, Hirschfield G, Gordon S, Mayo M. Farnesoid-x receptor agonists: a new class of drugs for the treatment of PBC? An international study evaluating the addition of INT-747 to UDCA. *Journal of Hepatology* 2010;**52**(Suppl 1):S1-S2.

* Mason AL, Lindor KD, Bacon BR, Vincent C, Neuberger JM, Vvasilenko ST. Clinical trial: randomized controlled study of zidovudine and lamivudine for patients with primary biliary cholangitis stabilized on ursodiol. *Alimentary Pharmacology & Therapeutics* 2008;**28**(7):886-94.

Matloff 1982 *{published data only}*

Matloff D, Resnick R, Alpert E, Kaplan M. D-Penicillamine does not alter the course of primary biliary cholangitis. *Clinical Research* 1979;**27**:579A.

* Matloff DS, Alpert E, Resnick RH, Kaplan MM. A prospective trial of D-penicillamine in primary biliary cholangitis. *New England Journal of Medicine* 1982;**306**(6):319-26.

Mayo 2015 *{published data only}*

Mayo MJ, Wigg AJ, Roberts SK, Arnold H, Hassanein TI, Leggett BA, et al. NGM282, a novel variant of FGF-19, demonstrates biologic activity in primary biliary cholangitis patients with an incomplete response to UDCA: results of a phase 2 multicenter, randomized, double blinded, placebo controlled trial. *Hepatology* 2015;**62**:263A-4A.

Mazzarella 2002 *{published data only}*

Enrico R, Federica B, Andrea L, Patrizia S, Roda A, Mazzella G. Treatment of early (I-II stage) primary biliary cholangitis (PBC): high versus standard UDCA doses after 15 years follow-up. A randomized open controlled trial. *Hepatology* 2011;**54**(4 (Suppl)):1209a.

Mazzarella G, Azzolini F, Casanova S, Giovanelli S, Ferrara F, Liva S, et al. Standard vs high dose UDCA in PBC: efficacy on liver function tests and histology after six years of treatment in a randomised controlled trial. *Gastroenterology* 2002;**123**(1):66.

McCormick 1994 *{published data only}*

McCormick PA, Scott F, Epstein O, Burroughs AK, Scheuer PJ, McIntyre N. Thalidomide as therapy for primary biliary cholangitis: a double-blind placebo controlled pilot study. *Journal of Hepatology* 1994;**21**(4):496-9.

Minuk 1988 *{published data only}*

Hanley DA, Ayer LM, Gundberg CM, Minuk GY. Parameters of calcium metabolism during a pilot study of cyclosporin a in patients with symptomatic primary biliary cholangitis. *Clinical & Investigative Medicine - Medecine Clinique et Experimentale* 1991;**14**(4):282-7.

Minuk G, Bohme C, Burgess E, Hershfield N, Kelly J, Shaffer E, et al. A prospective, double-blind, randomized, controlled trial of cyclosporine a in primary biliary-cirrhosis. *Hepatology* 1987;**7**(5):1119.

Minuk G, Bohme C, Burgess E, Hershfield N, Kelly J, Shaffer E, et al. A prospective, randomized, placebo-controlled study of cyclosporine a in primary biliary-cirrhosis. *Clinical and Investigative Medicine - Medecine Clinique et Experimentale* 1987;**10**(4):B131.

* Minuk GY, Bohme CE, Burgess E, Hershfield NB, Kelly JK, Shaffer EA, et al. Pilot study of cyclosporin a in patients with symptomatic primary biliary cholangitis. *Gastroenterology* 1988;**95**(5):1356-63.

Parsons HG, Thirsk JE, Frohlich J, Dias V, Minuk GY. Effect of cyclosporin a on serum lipids in primary biliary cholangitis patients. *Clinical & Investigative Medicine - Medecine Clinique et Experimentale* 1989;**12**(6):386-91.

Mitchison 1989 *{published data only}*

* Mitchison HC, Bassendine MF, Malcolm AJ, Watson AJ, Record CO, James OF. A pilot, double-blind, controlled 1-year trial of prednisolone treatment in primary biliary cholangitis: hepatic improvement but greater bone loss. *Hepatology* 1989;**10**(4):420-9.

Mitchison HC, Bassendine MF, Watson AJ, Record CO, James OFW. Double blind placebo-controlled trial of prednisolone treatment in primary biliary cholangitis (PBC): a 3 year update. *Journal of Hepatology* 1989;**9**(1):P4.

Mitchison HC, Palmer JM, Bassendine MF, Watson AJ, Record CO, James OF. A controlled trial of prednisolone treatment in primary biliary cholangitis. Three-year results. *Journal of Hepatology* 1992;**15**(3):336-44.

Mitchison HC, Watson AJ, Bassendine MF, Record CO, James OFW. A pilot double blind controlled trial of prednisolone treatment in primary biliary cholangitis (PBC). *Journal of Hepatology* 1986;**3**(Suppl 1):S28.

Mitchison 1993 *{published data only}*

Buuren HR, Schalm SW. Beneficial effect of malotilate on primary biliary cholangitis (PBC): results of a multicentre controlled trial. *Journal of Hepatology* 1989;**9**(Suppl 1):S28.

* Mitchison HC, Mutimer DJ, James OFW, Triger DR, Moller B, Hopf U, et al. The results of a randomized double blind controlled trial evaluating malotilate in primary biliary cholangitis. *Journal of Hepatology* 1993;**17**(2):227-35.

Nakai 2000 *{published data only}*

* Nakai S, Masaki T, Kurokohchi K, Deguchi A, Nishioka M. Combination therapy of bezafibrate and UDCA in primary biliary cholangitis: a preliminary study. *American Journal of Gastroenterology* 2000;**95**(1):326-7.

Nakai S, Masaki T, Morita T, Deguchi A, Nishioka M. The effect of bezafibrate in patients with primary biliary cholangitis. *Hepatology* 1999;**30**(4 Suppl):566a.

Neuberger 1985 *{published data only}*

Neuberger J, Christensen E, Popper H, Portmann B, Caballeri J, Rodes J, et al. D-Penicillamine in primary biliary cholangitis: preliminary results of an international trial. *Gut* 1983;**24**(10):A968.

Neuberger J, Christensen E, Popper H, Portmann B, Caballeri J, Rodes J, et al. D-Penicillamine in primary biliary cholangitis: preliminary results of an international trial. *Liver* 1984;**4**(1):74.

* Neuberger J, Christensen E, Portmann B, Caballeria J, Rodes J, Ranek L, et al. Double blind controlled trial of D-penicillamine in patients with primary biliary cholangitis. *Gut* 1985;**26**(2):114-9.

Nevens 2016 *{published data only}*

Andreone P, Mazzella G, Invernizzi P, Floreani A, Picaro LA, Adorini L. Efficacy and safety of obeticholic acid in patients with primary biliary cirrhosis: an analysis of the Italian patients from a phase 3, randomized, placebo controlled study. *Digestive and Liver Disease* 2016;**48**:e81.

Andreone P, Mazzella G, Strasser SI, Bowlus CL, Invernizzi P, Drenth J, et al. The FXR agonist obeticholic acid (OCA) improves liver biochemistry parameters correlated with clinical benefit across a range of patient characteristics. *Hepatology* 2014;**60**:360a.

Hirschfield GM, Floreani A, Trivedi PJ, Pencek R, Liberman A, Marmon T, et al. Long-term effect of obeticholic acid on transient elastography and AST to platelet ratio index in patients with PBC. *Hepatology* 2017;**64**(1 Suppl S1):110A-1A.

Mayo M, Kremer AE, Beuers U, Marmon T, Hooshmand-Rad R, Pencek R, et al. Mitigation of pruritus during obeticholic acid treatment in patients with primary biliary cirrhosis: strategies and successes. *Gastroenterology* 2016;**150**(4 Suppl):S1072.

Nevens F, Andreone P, Mazzella G, Strasser S, Bowlus C, Invernizzi P, et al. The first primary biliary cholangitis (PBC) phase 3 trial in two decades-an international study of the FXR agonist obeticholic acid in PBC patients. *Journal of Hepatology* 2014;**60**(1 Suppl 1):S525-6.

* Nevens F, Andreone P, Mazzella G, Strasser SI, Bowlus C, Invernizzi P, et al. A placebo-controlled trial of obeticholic acid in primary biliary cholangitis. *New England Journal of Medicine* 2016;**375**(7):631-43.

Nevens F, Andreone P, Mazzella G, Strasser SI, Bowlus CL, Invernizzi P, et al. An international phase 3 study of the FXR agonist obeticholic acid in PBC patients: effects on markers of cholestasis associated with clinical outcomes and hepatocellular damage. *Hepatology* 2014;**60**:347a-8a.

Pares A, Pencek R, Peters Y, Marmon T, MacConell L, Adorini L, et al. FXR agonism with obeticholic acid may attenuate bone

mineral density decrease in subjects with primary biliary cirrhosis. *Journal of hepatology* 2015;**62**:S786.

Pencek R, Lutz K, Marmon T, MacConell L. Evaluation of the posology of obeticholic acid (OCA) in patients with PBC. *Hepatology* 2015;**62**:525a-6a.

Peters Y, Hooshmand-Rad R, Pencek R, Owens-Grillo J, Marmon T, MacConell L, et al. Long-term safety of OCA in patients with PBC. *Hepatology* 2015;**62**:530a.

Peters Y, Hooshmand-Rad R, Pencek R, Owens-Grillo J, Marmon T, Macconell L, et al. Long-term safety of obeticholic acid in patients with primary biliary cirrhosis. *Digestive and Liver Disease* 2016;**48**:e117-8.

Pockros PJ, Reddy KG, Owens-Grillo J, Marmon T, MacConell L. Efficacy of obeticholic acid in patients with primary biliary cholangitis and renal impairment. *Hepatology* 2017;**64**(1 Suppl S1):205A.

Trauner M, Nevens F, Andreone P, Mazzella G, Strasser SI, Bowlus CL, et al. Sustained improvement in the markers of cholestasis in an open label long term safety extension study of obeticholic acid in primary biliary cirrhosis patients. *Hepatology* 2015;**62**:511a-2a.

Vierling JM, Hirschfield GM, Jones D, Groszmann RJ, Kowdley KV, Pencek R, et al. Efficacy of obeticholic acid treatment in patients with primary biliary cholangitis with cirrhosis. *Hepatology* 2017;**64**(1 Suppl S1):187A.

Oka 1990 *{published data only}*

* Oka H, Toda G, Ikeda Y, Hashimoto N, Hasumura Y, Kamimura T, et al. A multi-center double-blind controlled trial of UDCA for primary biliary cholangitis. *Gastroenterologia Japonica* 1990;**25**(6):774-80.

Toda G, Oka H, Hasumura Y, Kamimura T, Ohat Y, Tsuji T, et al. A multicenter double-blind controlled trial of UDCA for primary biliary cholangitis in Japan. *XI International Bile Acid Meeting Bile Acids as Therapeutic Agents - From Basic Science to Clinical Practice* 1990:76.

Papatheodoridis 2002 *{published data only}*

Hadziyannis S. Long-term treatment of primary biliary cholangitis with UDCA: the third year of a controlled trial. *XI International Bile Acid Meeting Bile Acids as Therapeutic Agents - From Basic Science to Clinical Practice* 1990:57-8.

Hadziyannis S, Hadziyannis E. A randomised controlled trial of UDCA (UDCA) in primary biliary cholangitis (PBC). *Hepatology* 1988;**8**(5):1421.

Hadziyannis S, Hadziyannis E, Lianidou E, Makris A. Long-term treatment of primary biliary cholangitis with UDCA: the third year of a controlled trial. *Bile Acids as Therapeutic Agents From Basic Science to Clinical Practice Falk Symposium 58* 1990:287-96.

Hadziyannis SJ, Hadziyannis ES, Makris A. A randomized controlled trial of UDCA (UDCA) in primary biliary cholangitis (PBC). *European Journal of Clinical Investigation* 1989;**19**(Pt 2):A15.

Hadziyannis SJ, Hadziyannis ES, Makris A. A randomized controlled trial of UDCA (UDCA) in primary biliary cholangitis (PBC). *Hepatology* 1989;**10**(4):580.

Papatheodoridis GV, Deutsch M, Hadziyannis E, Tzakou A, Hadzivannis SJ. Ursodeoxycholic-acid for primary biliary cholangitis: final results of a 12-year prospective, randomised, controlled trial. *Journal of Hepatology* 2000;**32**:40.

* Papatheodoridis GV, Hadziyannis ES, Deutsch M, Hadziyannis SJ. UDCA for primary biliary cholangitis: final results of a 12-year, prospective, randomized, controlled trial. *American Journal of Gastroenterology* 2002;**97**(8):2063-70.

Pares 2000 *{published data only}*

Pares A. Long-term treatment of primary biliary cholangitis with UDCA: results of a randomized, double-blind, placebo-controlled trial. *Journal of Hepatology* 1997;**26**(Suppl 1):S166.

Pares A, Caballeria L, Bruguera M, Rodes J. Factors influencing historical progression of early primary biliary cholangitis effect of UDCA (abstract). *Journal of Hepatology* 2001;**34**(1):189-90.

Pares A, Caballeria L, Rodes J. Long-term UDCA treatment delays progression of mild primary biliary cholangitis (abstract). *Journal of Hepatology* 2001;**34**(1):187-8.

* Pares A, Caballeria L, Rodes J, Bruguera M, Rodrigo L, Garcia-Plaza A, et al. Long-term effects of UDCA in primary biliary cholangitis: results of a double-blind controlled multicentric trial. UDCA-cooperative group from the Spanish Association for the Study of the Liver. *Journal of Hepatology* 2000;**32**(4):561-6.

Poupon 1991a *{published data only}*

Calmus Y, Poupon R. UDCA (UDCA) in the treatment of chronic cholestatic diseases. *Biochimie* 1991;**73**(10):1335-8.

Huet PM, Huet J, Hotte S. Long term effect of UDCA (UDCA) on hepatic function and portal hypertension in primary biliary cholangitis (PBC). *Hepatology* 1994;**20**(4 (Pt 2)):202a.

Huet PM, Willems B, Huet J, Poupon R. Effects of UDCA (UDCA) on hepatic function and portal hypertension in primary biliary cholangitis (PBC). *Hepatology* 1990;**12**(4 (Pt 2)):907.

Poupon R, Chazouilleres O, Balkau B, Poupon RE. Clinical and biochemical expression of the histopathological lesions of primary biliary cholangitis. UDCA-PBC Group. *Journal of Hepatology* 1999;**30**(3):408-12.

* Poupon RE, Balkau B, Eschwege E, Poupon R. A multicenter, controlled trial of ursodiol for the treatment of primary biliary cholangitis. *New England Journal of Medicine* 1991;**324**(22):1548-54.

Poupon RE, Balkau B, Guechot J, Heintzmann F. Predictive factors in UDCA-treated patients with primary biliary cholangitis: role of serum markers of connective tissue. *Hepatology* 1994;**19**(3):635-40.

Poupon RE, Balkau B, Poupon R. Beneficial effect of UDCA (UDCA) in primary biliary cholangitis (PBC) final results of the French Canadian trial. *Hepatology* 1990;**12**(4 (Pt 2)):872.

Poupon RE, Chretien Y, Balkau B, Niard AM, Poupon R. Ursodeoxycholic therapy for primary biliary cholangitis: a four year controlled study. *Hepatology* 1992;**16**(2 (Pt 2)):91a.

Poupon RE, Chretien Y, Poupon R, Paumgartner G. Serum bile acids in primary biliary cholangitis: effect of UDCA therapy. *Hepatology* 1993;**17**(4):599-604.

Poupon RE, Eschwege E, Poupon R. UDCA for the treatment of primary biliary cholangitis. Interim analysis of a double-blind multicentre randomized trial. The UDCA-PBC Study Group. *Journal of Hepatology* 1990;**11**(1):16-21.

Poupon RE, Ouguerram K, Chretien Y, Verneau C, Eschwege E, Magot T, et al. Cholesterol-lowering effect of UDCA in patients with primary biliary cholangitis. *Hepatology* 1993;**17**(4):577-82.

Poupon RE, Ouguerram K, Chretien Y, Verneau C, Eschwege E, Magot T, et al. [Hypocholesterolemic properties of UDCA in patients with primary biliary cholangitis]. *Medecine & Chirurgie Digestives* 1995;**24**(3):163-4.

Poupon RE, Poupon R. UDCA (UDCA) for treatment of primary biliary cholangitis (PBC): interim analysis of a double-blind multicenter randomized trial. *Hepatology* 1989;**10**(4):639.

Poupon 1996 *{published data only}*

Huet P, Willems B, Huet J, Poupon R. Effects of UDCA (UDCA) on hepatic function and portal hypertension in primary biliary cholangitis (PBC). *XII International Bile Acid Meeting Bile Acids and the Hepatobiliary System from Basic Science to Clinical Practice Falk Symposium No 68* 1992:118.

Huet PM, Huet J, Deslauriers J. Long-term UDCA (UDCA) and colchicine (C) treatment in primary biliary cholangitis (PBC): effect on hepatic function and portal hypertension. *Canadian Journal of Gastroenterology* 1996;**10**(Suppl A):S47.

Huet PM, Huet J, Poupon RE, Deslauriers J. The combination of UDCA (UDCA) and colchicine (C) for patients with primary biliary cholangitis (PBC): effect on hepatic function and portal hypertension. *Hepatology* 1996;**23**(1):I-49.

* Poupon RE, Huet PM, Poupon R, Bonnand AM, Nhieu JT, Zafrani ES. A randomized trial comparing colchicine and UDCA combination to UDCA in primary biliary cholangitis. UDCA-PBC Study Group. *Hepatology* 1996;**24**(5):1098-103.

Poupon RE, Niard AM, Huet PM, Miguet JP, Mathieuchandelier C, Doffoel M, et al. A randomized trial comparing the combination UDCA (UDCA) and colchicine to UDCA alone in primary biliary-cirrhosis. *Hepatology* 1994;**20**(4):A151.

Raedsch 1993 *{published data only}*

Raedsch R, Stiehl A, Walker S, Rudi J, Schlenker T, Gerteis C. Controlled study on the effects of a combined colchicine plus UDCA treatment in primary biliary cholangitis. 68th Falk Symposium; 1992 Oct 12-14; Basel, Switzerland. 1993:303-9.

Raedsch R, Stiehl A, Walker S, Scherrmann JM, Kommerell B. [Combined colchicine plus UDCA-treatment of primary biliary cholangitis: results of a placebo-controlled double-blind study]. *Zeitschrift Fur Gastroenterologie* 1992;**30**(Suppl 1):55-7.

Raedsch R, Stiehl A, Walker S, Theilmann L, Kommerell B. Effects of UDCA and colchicine plus UDCA in primary biliary cholangitis: a double-blind pilot study. *Bile Acids as Therapeutic Agents From Basic Science to Clinical Practice Falk Symposium 58* 1991, (36):301-4.

Raedsch R, Stiehl A, Walker S, Theilmann L, Kommerell B. Influence of UDCA and URSO plus colchicine on primary biliary cholangitis: a double-blind controlled pilot study. *Klinische Wochenschrift* 1991;**69**(Suppl 23):84.

Rautiainen 2005 *{published data only}*

Rautiainen H, Farkkila M, Neuvonen M, Sane T, Karvonen AL, Nurm H, et al. Pharmacokinetics and bone effects of budesonide in primary biliary cholangitis. *Alimentary Pharmacology & Therapeutics* 2006;**24**(11-12):1545-52.

* Rautiainen H, Karkkainen P, Karvonen AL, Nurmi H, Pikkarainen P, Nuutinen H, et al. Budesonide combined with UDCA to improve liver histology in primary biliary cholangitis: a three-year randomized trial. *Hepatology* 2005;**41**(4):747-52.

Senior 1991 *{published data only}*

O'Brien CB, Senior JR, Sternlieb JM, Sample M, Saul SM, Arora R. Ursodiol treatment of primary biliary cholangitis. *Gastroenterology* 1990;**98**(2 (Pt 2)):A617.

* Senior JR, O'Brien C. Mortality risk indices as outcome measures of the effectiveness of UDCA treatment of cholestatic liver diseases. *Bile Acids as Therapeutic Agents From Basic Science to Clinical Practice Falk Symposium 58* 1991:273-85.

Senior JR, O'Brien CB, Dickson ER. Effect of oral ursodiol treatment on the predicted probability of mortality in primary biliary cholangitis. *Hepatology* 1990;**12**(2):438.

Smart 1990 *{published data only}*

Smart HL, Cann PA, Thuluvath PJ, Triger DR. A double blind placebo controlled study of antioxidants in primary biliary cholangitis (PBC). *Gut* 1990;**31**(10):A1184.

Steenbergen 1994 *{published data only}*

Steenbergen W, Sciot R, Eycken P, Desmet V, Fevery J. Combined treatment with methotrexate and UDCA in primary biliary cholangitis (PBC). *Journal of Hepatology* 1994;**21**(Suppl 1):S89.

* Steenbergen W, Sciot R, Eyken P, Desmet V, Fevery J. Methotrexate alone or in combination with UDCA as possible treatment in primary biliary cholangitis. *Cholestatic Liver diseases: New Strategies for Prevention and Treatment of Hepatobiliary and Cholestatic Liver Diseases Falk Symposium 75* 1994:246-54.

Van Steenbergen W, Sciot R, Van Eyken P, Desmet V, Fevery J. Combined treatment with methotrexate and UDCA in non-cirrhotic primary biliary cholangitis. *Acta Clinica Belgica* 1996;**51**(1):8-18.

Taal 1983 *{published data only}*

Taal BG, Schalm SW. Prednisone plus D-penicillamine, D-penicillamine and placebo compared in primary biliary-cirrhosis syndrome. *Gastroenterology* 1981;**80**(5 Part 2):1351.

Taal BG, Schalm SW, Kate FWJ. Double-blind controlled study of penicillamine in primary biliary cholangitis: dose-dependent effects. *Nederlands Tijdschrift voor Geneeskunde* 1982;**126**(12):547.

* Taal BG, Schalm SW, Ten Kate FW, Van Berge Henegouwen GP, Brandt KH. Low therapeutic value of D-penicillamine in a short-term prospective trial in primary biliary cholangitis. *Liver* 1983;**3**(6):345-52.

Triger 1980 *{published data only}*

Triger DR, Manifold IH, Cloke P, Underwood JCE. D-Penicillamine in primary biliary cholangitis: two year results of a single centre, doubled-blind controlled trial. *Gut* 1980;**21**(10):A919-20.

Turner 1994 *{published data only}*

Myszor M, Turner I, Mitshison H, Bennett M, Burt AD, James OFW. No symptomatic or histological benefit from UDCA treatment in PBC after 1 year controlled pilot study. *Hepatology* 1990;**12**(2):415.

* Turner IB, Myszor M, Mitchison HC, Bennett MK, Burt AD, James OF. A two year controlled trial examining the effectiveness of UDCA in primary biliary cholangitis. *Journal of Gastroenterology & Hepatology* 1994;**9**(2):162-8.

Ueno 2005 *{published data only}*

Ueno Y, Moritoki Y, Kanno N, Fukushima K, Yamagiwa Y, Kogure T, et al. Randomized double blind control trial of reverse transcriptase inhibitor for the treatment of UDCA-resistant PBC. *Gastroenterology* 2005;**128**(4):A775-A.

Van Hoogstraten 1998 *{published data only}*

Hoogstraten HJF, Smet MBM, Renooij W, Hop WCJ, Berge-Henegouwen GP, Schalm SW. A randomized controlled trial evaluating therapy with UDCA in daily doses of 10 mg/kg versus 20 mg/kg in primary biliary cholangitis. *European Journal of Gastroenterology & Hepatology* 1998;**10**(12):A7.

* Van Hoogstraten HJF, De Smet MBM, Renooij W, Breed JGS, Engels L, Den Ouden-Muller JW, et al. A randomized trial in primary biliary cholangitis comparing UDCA in daily doses of either 10 mg/kg or 20 mg/kg. *Alimentary Pharmacology & Therapeutics* 1998;**12**(10):965-71.

Van Hoogstraten HJF, De Smet MBM, Renooij W, Hop WCJ, Van Buuren HR, VanBerge-Henegouwen GP. A randomized controlled trial evaluating therapy with UDCA in daily doses of 10 mg/kg versus 20 mg/kg in primary biliary cholangitis. *Gastroenterology* 1998;**114**(4):A1358-A.

Warnes 1987 *{published data only}*

Warnes T, Babbs C, Smith A, Lee F, Haboubi NY, Johnson PJ, et al. A controlled trial of colchicine in primary biliary cholangitis (PBC). *Journal of Hepatology* 1985;**1**(Suppl 2):S348.

Warnes TW, Goddard CJR, Smith A, Rowan BP, Hunt L. Liver function and prognosis in primary biliary cholangitis: 'sharp' and 'blunt' tests and the influence of colchicine treatment on survival. *Hepatology* 1996;**23**(1):I-82.

Warnes TW, Smith A, Lee F, Haboubi NY, Johnson PJ, Hunt L. A controlled trial of colchicine in primary biliary cholangitis. *Hepatology* 1984;**4**(5):1022.

* Warnes TW, Smith A, Lee FI, Haboubi NY, Johnson PJ, Hunt L. A controlled trial of colchicine in primary biliary cholangitis. Trial design and preliminary report. *Journal of Hepatology* 1987;**5**(1):1-7.

Wiesner 1990 *{published data only}*

Wiesner RH, Dickson ER, Lindor KD, Jørgensen R, LaRusso NF, Baldus W. A controlled clinical trial evaluating cyclosporin in the treatment of primary biliary cholangitis: a preliminary report. *Hepatology* 1987;**7**(5):1025.

* Wiesner RH, Ludwig J, Lindor KD, Jorgensen RA, Baldus WP, Homburger HA, et al. A controlled trial of cyclosporine in the treatment of primary biliary cholangitis. *New England Journal of Medicine* 1990;**322**(20):1419-24.

Wolfhagen 1998 *{published data only}*

Hoogstraten H, Wolfhagen FHJ, Berge Henegouwen GP, Schalm SW, Kate FJW, Hop WCJ, et al. Combined bile acid-immunosuppressive therapy for primary biliary cholangitis. Results of a 1-year multi centre, placebo controlled trial. *European Journal of Gastroenterology & Hepatology* 1996;**8**(Suppl 12):A 41.

Lim AG, Wolfhagen FH, Verma A, Van Buuren HR, Jazrawi RP, Levy JH, et al. Soluble intercellular adhesion molecule-1 in primary biliary cholangitis: effect of UDCA and immunosuppressive therapy. *European Journal of Gastroenterology & Hepatology* 1997;**9**(2):155-61.

Lim AG, Wolfhagen FHJ, Verma A, Buuren HR, Jazrawi RP, Levy JH, et al. Soluble intercellular adhesion molecule 1 in primary biliary cholangitis: effect of UDCA and immunosuppressive therapy. *Hepatology* 1995;**22**(4 (Pt 2)):124a.

Lim AG, Wolfhagen FHJ, Verma A, Buuren HR, Jazrawi RP, Northfield TC. Soluble intercellular adhesion molecule-1 in primary biliary cholangitis: effect of UDCA, prednisone and azathioprine. *Falk Symposium Bile Acids and Immunology* 1995;**86**:9.

Lim AG, Wolfhagen FHJ, Verma A, Jazrawi RP, Bururen HR, Levy JH, et al. Combination UDCA and immunosuppressive therapy for the treatment of primary biliary cholangitis. *Gut* 1995;**37**(Suppl 2):A27.

Van Hoogstraten HJF, Wolfhagen FHJ, Henegouwen GPB, Schalm SW, tenKate FJW, Hop WCJ. Combined bile acid - immunosuppressive therapy for primary biliary cholangitis. Results of a 1-year multi centre, placebo controlled trial. *Hepatology* 1996;**24**(4 Suppl):167.

Wolfhagen FHJ, Buuren HR, Berge Henegouwen GP, Hattum J, Ouden JW, Kerbert MJ, et al. A randomized placebo-controlled trial with prednisone/azathioprine in addition to UDCA in primary biliary cholangitis. *Journal of Hepatology* 1994;**21**(Suppl 1):S49.

Wolfhagen FHJ, Buuren HR, Berge-Henegouwen GP, Hattum J, Ouden JW, Kerbert MJ. Prednisone/azathioprine treatment in primary biliary cholangitis (PBC) a randomized, placebo-controlled trial. *Netherlands Journal of Surgery* 1995;**46**:A10.

Wolfhagen FHJ, Lim AG, Verma A, Buuren HR, Jazrawi RP, Northfield TC, et al. Soluble ICAM-1 in primary biliary cholangitis (PBC) during combined treatment with UDCA, prednisone and azathioprine. *Netherlands Journal of Surgery* 1995;**47**:A29-30.

* Wolfhagen FHJ, Van Hoogstraten HJF, Van Buuren HR, Van Berge-Henegouwen GP, Ten Kate FJW, Hop WCJ, et al. Triple therapy with UDCA, prednisone and azathioprine in primary biliary cholangitis: A 1-year randomized, placebo-controlled study. *Journal of Hepatology* 1998;**29**(5):736-42.

Yokomori 2001 *{published data only}*

Yokomori H, Oda M, Ishii H. Effects of UDCA and colestilan versus UDCA alone on serum bile acids and pruritus: a randomized, open-label study. *Current Therapeutic Research - Clinical and Experimental* 2001;**62**(3):221-9.

References to studies excluded from this review

Angulo 1999b *{published data only}*

Angulo P, Batts KP, Therneau TM, Jorgensen RA, Dickson ER, Lindor KD. Long-term UDCA delays histological progression in primary biliary cholangitis. *Hepatology* 1999;**29**(3):644-7.

Angulo 1999c *{published data only}*

Angulo P, Lindor KD, Therneau TM, Jorgensen RA, Malinchoc M, Kamath PS, et al. Utilization of the Mayo risk score in patients with primary biliary cholangitis receiving UDCA. *Liver* 1999;**19**(2):115-21.

Angulo 2002 *{published data only}*

Angulo P, Petz JL, Jorgensen RA, Lindor KD. A randomized, cross-over study evaluating single- and multiple-daily dosage schedules of UDCA in primary biliary cholangitis. *Gastroenterology* 2002;**122**(4):A629.

Attili 1994 *{published data only}*

Attili AF, Rusticali A, Varriale M, Carli L, Repice AM, Callea F. Effect of UDCA on serum enzymes and liver histology in patients with chronic active hepatitis - a 12 month double-blind, placebo-controlled trial. *Journal of Hepatology* 1994;**20**(3):315-20.

Avezov 2004a *{published data only}*

Avezov SA, Mansurova F. [Efficacy of combined use of UDCA and heptral in the treatment of primary biliary cholangitis]. *Klinicheskaia Meditsina* 2004;**82**(2):46-9.

Avezov 2004b *{published data only}*

Avezov SA, Mansurov F. [Efficacy of combined administration of UDCA and hepthral in the treatment of primary biliary cholangitis]. *Klinicheskaia Meditsina* 2004;**82**(3):55-8.

Bach 2003 *{published data only}*

Bach N, Bodian C, Bodenheimer H, Croen E, Berk PD, Thung SN, et al. Methotrexate therapy for primary biliary cholangitis. *American Journal of Gastroenterology* 2003;**98**(1):187-93.

Batta 1989 *{published data only}*

Batta AK, Salen G, Arora R, Shefer S, Tint GS, Abroon J, et al. Effect of UDCA on bile acid metabolism in primary biliary cholangitis. *Hepatology* 1989;**10**(4):414-9.

Beukers 1988 *{published data only}*

Beukers R, Schalm SW. Effect of cyclosporine and cyclosporine plus prednisone in primary biliary cholangitis. *Transplantation Proceedings* 1988;**20**(3 Suppl 4):340-3.

Blanche 1994 *{published data only}*

Blanche P, Sicard D. Methotrexate for polymyositis associated with primary biliary cholangitis. *Clinical & Experimental Rheumatology* 1994;**12**(6):694.

Bonis 2006 *{published data only}*

Bonis PA, Kaplan M. Methotrexate for treatment of primary biliary cholangitis. *Hepatology* 2006;**43**(3):632; author reply 633.

Borum 1990 *{published data only}*

Borum M, Fromm H. UDCA in the treatment of primary biliary cholangitis: first controlled data. *Hepatology* 1990;**12**(1):172-3.

Bray 1991 *{published data only}*

Bray GP, Padova C, Tredger JM, Williams R. A comparison of S-adenosylmethionine (SAMe), rifampicin (R) and UDCA (UDCA) in primary biliary cholangitis (PBC): interim results. *Journal of Hepatology* 1991;**13**(Suppl 2):S101.

Carbone 2016 *{published data only}*

Carbone M, Jones D, Mells GF, Pencek R, Marmon T, Shapiro D. Predicted risk of end stage liver disease with continued standard of care and subsequent addition of obeticholic acid in patients with PBC. *Hepatology* 2016;**63 (1 Suppl 1)**:184A-5A.

Chazouilleres 1995 *{published data only}*

Chazouilleres O, Legendre C, StMaur P, Ismail PR, Poupon R. Histological course of primary biliary cholangitis (PBC) treated with UDCA (UDCA). *Hepatology* 1995;**22**(4 (Pt 2)):125a.

Christensen 1986 *{published data only}*

Christensen E, Neuberger J, Crowe J, Portmann B, Williams R, Altman DG, et al. Azathioprine and prognosis in primary biliary cholangitis. *Gastroenterology* 1986;**90**(2):508-9.

Combes 1989 *{published data only}*

Combes B. Prednisolone for primary biliary cholangitis - good news, bad news. *Hepatology* 1989;**10**(4):511-3.

Combes 2004 *{published data only}*

Combes B, Luketic VA, Peters MG, Zetterman RK, Garcia-Tsao G, Munoz SJ, et al. Prolonged follow-up of patients in the U.S. Multicenter trial of UDCA for primary biliary cholangitis. *American Journal of Gastroenterology* 2004;**99**(2):264-8.

Combes 2005b *{published data only}*

Combes B. Reflections on therapeutic trials in primary biliary cholangitis. *Hepatology* 2005;**42**(5):1009.

Copaci 2001 *{published data only}*

Copaci I, Micu L, Cojocaru L. UDCA and methotrexate for primary biliary cholangitis. *Journal of Hepatology* 2001;**34**(1):59.

Corpechot 2000 *{published data only}*

Corpechot C, Carrat F, Bonnand AM, Poupon RE, Poupon R. The effect of UDCA therapy on liver fibrosis progression in primary biliary cholangitis. *Hepatology* 2000;**32**(6):1196-9.

Corpechot 2001 *{published data only}*

Corpechot C, Carrat F, Bonnand AM, Poupon RE, Poupon R. The effect of UDCA therapy on liver fibrosis progression in primary biliary cholangitis. *European Journal of Gastroenterology & Hepatology* 2001;**13**(1):90.

Crosignani 1996a *{published data only}*

Crosignani A, Larghi A, Invernizzi P, Battezzati PM, DeValle G, Zuin M, et al. Tauroursodeoxycholic and UDCAs for the treatment of primary biliary cholangitis: a crossover study. *Hepatology* 1996;**23**(1):P111.

Crosignani 1996b *{published data only}*

Crosignani A, Battezzati PM, Setchell KDR, Invernizzi P, Covini G, Zuin M, et al. TauroUDCA for treatment of primary biliary cholangitis - a dose-response study. *Digestive Diseases and Sciences* 1996;**41**(4):809-15.

Degott 1999 *{published data only}*

Degott C, Zafrani ES, Callard P, Balkau B, Poupon RE, Poupon R. Histopathological study of primary biliary cholangitis and the effect of UDCA treatment on histology progression. *Hepatology* 1999;**29**(4):1007-12.

De la Mora 1994 *{published data only}*

De la Mora G, Bobadilla J, Romero P, Rodríguez-Leal G, Morán S, Kershenobich D, et al. Does treatment with UDCA (UDCA) really diminish cholesterol serum levels in primary biliary cholangitis (PBC)?. *Hepatology* 1994;**19**:571.

Dickson 1991 *{published data only}*

Dickson ER, Lindor KD. Beneficial effects of UDCA in an open trial of patients with primary biliary cholangitis. *Bile Acids as Therapeutic Agents From Basic Science to Clinical Practice Falk Symposium 58* 1991, (32):271-2.

Emond 1996 *{published data only}*

Emond M, Carithers RL, Luketic VA, Peters M, Zetterman RK, Garcia-Tsao G. Does UDCA improve survival in patients with primary biliary cholangitis? Comparison of outcome in the US multicenter trial to expected survival using the Mayo Clinic prognostic model. *Hepatology* 1996;**24**(4 (Pt 2)):168a.

Fischer 1967 *{published data only}*

Fischer JA, Schmid M. Treatment of primary biliary cholangitis with azathioprine. *Lancet* 1967;**1**(7487):421-4.

Golovanova 2010 *{published data only}*

Golovanova EV, Khomeriki SG, Petrakov AV, Serova TI. Budesonide in treatment of patients with cross primary biliary cholangitis and autoimmune hepatitis. *Eksperimental'Naia i Klinicheskaia Gastroenterologiia* 2010, (8):113-7.

Heathcote 1993 *{published data only}*

Heathcote EJL, Cauch K, Walker V, Blendism LM, Ghent CN, Pappas SC. A four-year follow-up study of UDCA therapy for primary biliary cholangitis. *Gastroenterology* 1993;**104**(4 (Pt 2)):A914.

Heathcote 1995 *{published data only}*

Heathcote EJ, Lindor KD, Poupon R, Cauchdudek K, Dickson ER, Trout R, et al. Combined analysis of French, American and Canadian randomized controlled trials of UDCA therapy in primary biliary cholangitis. *Gastroenterology* 1995;**108**(4 Suppl 3):A1082.

Hirschfield 2011 *{published data only}*

Hirschfield GM, Mason AL, Gordon SC, Luketic VA, Mayo M, Vincent C, et al. A long term safety extension trial of the farnesoid x receptor (FXR) agonist obeticholic acid (OCA) and UDCA in primary biliary cholangitis (PBC). *Hepatology* 2011;**54**(S1):429a.

Hishon 1982 *{published data only}*

Hishon S, Tobin G, Ciclitira PJ. A clinical trial of levamisole in primary biliary cholangitis. *Postgraduate Medical Journal* 1982;**58**(685):701-3.

Howat 1966 *{published data only}*

Howat HT, Ralston AJ, Varley H, Wilson JA. The late results of long-term treatment of primary biliary cholangitis by corticosteroids. *Revue Internationale d' Hepatologie* 1966;**16**(2):227-38.

Hwang 1993 *{published data only}*

Hwang SJ, Chan CY, Lee SD, Wu JC, Tsay SH, Lo KJ. UDCA in the treatment of primary biliary cholangitis: a short-term, randomized, double-blind controlled, cross-over study with long-term follow up. *Journal of Gastroenterology & Hepatology* 1993;**8**(3):217-23.

Invernizzi 1996 *{published data only}*

Invernizzi A, Setchell DDR, Crosignani A, Larghi A, Battezzatti PM, O'Connell N, et al. Comparison between tauroursodeoxycholic and UDCAs in patients with primary biliary cholangitis: a cross over study. *Hepatology* 1996;**24**(4 (Pt 2)):168a.

Invernizzi 2015 *{published data only}*

Invernizzi P, Pencek R, Marmon T, MacConell L, Shapiro D. Integrated efficacy summary for obeticholic acid in subjects with primary biliary cholangitis. *Journal of Hepatology* 2015;**62**:S778.

Itakura 2004 *{published data only}*

Itakura J, Izumi N, Nishimura Y, Inoue K, Ueda K, Nakanishi H, et al. Prospective randomized crossover trial of combination

therapy with bezafibrate and UDCA for primary biliary cholangitis. *Hepatology Research* 2004;**29**(4):216-22.

Jazrawi 1999 *{published data only}*

Jazrawi RP, Verma A, Ahmed HA, Northfield TC. Effect of UDCA on cholestatic features and complications of primary biliary cholangitis. *Bile Acids and Cholestasis* 1999;**108**:231-46.

Jones 2006 *{published data only}*

Jones DE, Bhala N, Newton JL. Reflections on therapeutic trials in primary biliary cholangitis: a quality of life oriented counter-view. *Hepatology* 2006;**43**(3):633; Author reply 634.

Jorgensen 2002 *{published data only}*

Jorgensen R, Angulo P, Dickson ER, Lindor KD. Results of long-term ursodiol treatment for patients with primary biliary cholangitis. *American Journal of Gastroenterology* 2002;**97**(10):2647-50.

Joshi 2002 *{published data only}*

Joshi S, Cauch-Dudek K, Wanless IR, Lindor KD, Jorgensen R, Batts K, et al. Primary biliary cholangitis with additional features of autoimmune hepatitis: response to therapy with UDCA. *Hepatology* 2002;**35**(2):409-13.

Kaplan 1993 *{published data only}*

Kaplan MM. New strategies needed for treatment of primary biliary cholangitis?. *Gastroenterology* 1993;**104**(2):651-3.

Kaplan 1998 *{published data only}*

Kaplan M. Primary biliary cholangitis. *Lancet* 1998;**351**(9097):216.

Kaplan 2004 *{published data only}*

Kaplan MM, Cheng S, Price LL, Bonis PA. A randomized controlled trial of colchicine plus ursodiol versus methotrexate plus ursodiol in primary biliary cholangitis: ten-year results. *Hepatology* 2004;**39**(4):915-23.

Kaplan 2009 *{published data only}*

Kaplan MM, Poupon R. Treatment with immunosuppressives in patients with primary biliary cholangitis who fail to respond to ursodiol. *Hepatology* 2009;**50**(2):652.

Kisand 1996 *{published data only}*

Kisand KE, Karvonen AL, Vuoristo M, Farkkila M, Lehtola J, Inkovaara J, et al. UDCA treatment lowers the serum level of antibodies against pyruvate dehydrogenase and influences their inhibitory capacity for the enzyme complex in patients with primary biliary cholangitis. *Journal of Molecular Medicine* 1996;**74**(5):269-72.

Kisand 1998 *{published data only}*

Kisand KE, Kisand KV, Karvonen AL, Vuoristo M, Mattila J, Makinen J, et al. Antibodies to pyruvate dehydrogenase in primary biliary cholangitis: correlation with histology. *APMIS* 1998;**106**(9):884-92.

Kowdley 2014a *{published data only}*

Kowdley K, Hirschfield G, Chapman R, Vincent C, Jones D, Pares A, et al. Long-term treatment of primary biliary cholangitis with the FXR agonist obeticholic acid shows durable efficacy. *Journal of Hepatology* 2014;**60**(1 Suppl 1):S192-3.

Kowdley 2014b *{published data only}*

Kowdley KV, Pencek R, Marmon T, Shapiro D, Hooshmand-Rad R. FXR agonist obeticholic acid: sustained improvement in markers of cholestasis and long-term safety in patients with primary biliary cholangitis through 4 years. *Hepatology* 2014;**60**:361a.

Kowdley 2015 *{published data only}*

Kowdley KV, Shah H, Mason A, Luketic VA, Pencek R, Marmon T, et al. Long-term safety and efficacy of obeticholic acid treatment in primary biliary cirrhosis after more than 4 years of treatment. *Hepatology* 2015;**62**:521a-2a.

Kugler 1991 *{published data only}*

Kugler CF, Fleig WE. [Placebo-controlled double-blind study of cyclosporin a in primary biliary cholangitis]. *Zeitschrift Fur Gastroenterologie* 1991;**29**(12):663-4.

Kurihara 2002 *{published data only}*

Kurihara T, Maeda A, Shigemoto M, Yamashita K, Hashimoto E. Investigation into the efficacy of bezafibrate against primary biliary cholangitis, with histological references from cases receiving long term monotherapy. *American Journal of Gastroenterology* 2002;**97**(1):212-4.

Lampe 1972 *{published data only}*

Lampe K, Hudepohl M, Schopen RD. [Immunosuppressive therapy of chronic aggressive hepatitis and primary biliary cholangitis]. *Medizinische Klinik* 1972;**67**(15):527-34.

Larghi 1997 *{published data only}*

Larghi A, Crosignani A, Battezzati PM, De Valle G, Allocca M, Invernizzi P, et al. Ursodeoxycholic and tauro-UDCAs for the treatment of primary biliary cholangitis: a pilot crossover study. *Alimentary Pharmacology & Therapeutics* 1997;**11**(2):409-14.

Lee 2003 *{published data only}*

Lee YM, Kaplan MM. Efficacy of colchicine in patients with primary biliary cholangitis poorly responsive to ursodiol and methotrexate. *American Journal of Gastroenterology* 2003;**98**(1):205-8.

Leung 2010 *{published data only}*

Leung J, Bonder A, Sasson M, Bonis P, Kaplan M. 19-year follow-up of patients in a double-blind trial of colchicine plus ursodiol versus methotrexate plus ursodiol in the treatment of primary biliary cholangitis. *Gastroenterology* 2010;**1**:S218.

Leung 2011 *{published data only}*

Leung J, Bonis PA, Kaplan MM. Colchicine or methotrexate, with ursodiol, are effective after 20 years in a subset of patients with primary biliary cholangitis. *Clinical Gastroenterology & Hepatology* 2011;**9**(9):776-80.

Leuschner 1990 *{published data only}*

Leuschner U, Güldütuna S, Fischer H, Hellstern A, Hübner K. UDCA in the treatment of primary biliary cholangitis:

the Frankfurt experience. *Strategies for the treatment of hepatobiliary diseases Falk symposium 53* 1990, (9):83-90.

Leuschner 1993a *{published data only}*

Leuschner M, Güldütuna S, Imhof M, Bhati S, You T, Leuschner U. UDCA therapy in primary biliary cholangitis. *68th Falk Symposium; 1992 Oct 12-14; Basel, Switzerland* 1993:299-302.

Leuschner 1993b *{published data only}*

Leuschner M, Guldutuna S, Benjaminov A, Hubner K, Leuschner U. Interim evaluation of a prospective double-blind trial of UDCA (UDCA) versus UDCA plus prednisolone in primary biliary cholangitis (PBC). *Gastroenterology* 1993;**104**(4):A938.

Leuschner 1996a *{published data only}*

Leuschner M, Guldutuna S, You T, Hubner K, Bhatti S, Leuschner U. UDCA and prednisolone versus UDCA and placebo in the treatment of early stages of primary biliary cholangitis. *Journal of Hepatology* 1996;**25**(1):49-57.

Leuschner 1996b *{published data only}*

Leuschner M, Guldutuna S, Hubner K, You T, Leuschner U. UDCA (UDCA) and prednisolone in the treatment of primary biliary cholangitis (PBC). Results of a controlled double-blind trial. *Gastroenterology* 1996;**110**(4):A1250.

Leuschner 1997 *{published data only}*

Leuschner U, Maier KP, Guldutuna S, Parte-Peterhans S, Leuschner M. UDCA in combination with prednisolone or budesonide in the therapy of primary biliary cholangitis. *Bile Acids in Hepatobiliary Diseases: Basic Research and Clinical Application* 1997;**93**:299-302.

Leuschner 1998 *{published data only}*

Leuschner U, Maier P, Schitling J, Strahl R, Herrmann G, Leuschner M. UDCA and budesonide in the treatment of primary biliary cholangitis. *XV International Bile Acid Meeting Bile Acids and Cholestasis Vol* 1998;**Falk Symposium 108**:60-1.

Levy 2004 *{published data only}*

Levy C, Angulo P. UDCA and long-term survival in primary biliary cholangitis. *American Journal of Gastroenterology* 2004;**99**(2):269-70.

Licinio 2015 *{published data only}*

Licinio R, Facciorusso A, Castellaneta NM, Di Leo A. Combination therapy of UDCA and bezafibrate in patients with primary biliary cholangitis: the end of the steroid era in autoimmune liver diseases?. *American Journal of Gastroenterology* 2015;**110**(7):1086.

Lim 2000 *{published data only}*

Lim AG, Jazrawi RP, Ahmed HA, Northfield TC. UDCA - an immunomodulator in primary biliary cholangitis?. *Bile Acids in Hepatobiliary Disease* 2000;**110B**:30-5.

Lindor 1994a *{published data only}*

Lindor KD, Jorgensen RA, Anderson ML, Gores GJ, Baldus WP, Dickson ER. The combination of UDCA (UDCA) and methotrexate (MTX) for patients with primary biliary cholangitis (PBC): the results of a pilot study. *Hepatology* 1994;**20**(4 (Pt 2)):202.

Lindor 1995a *{published data only}*

Lindor KD, Therneau TM, Jorgensen RA, Malinochoc M, Dickson ER. Effects of UDCA (UDCA) on survival in patients with primary biliary-cirrhosis (PBC). *Gastroenterology* 1995;**108**(4 Suppl 3):A1111.

Lindor 1995b *{published data only}*

Lindor KD, Dickson ER, Jorgensen RA, Anderson ML, Wiesner RH, Gores GJ, et al. The combination of UDCA and methotrexate for patients with primary biliary cholangitis: the results of a pilot study. *Hepatology* 1995;**22**(4 I):1158-62.

Lindor 1995c *{published data only}*

Lindor K. Long-term experience with UDCA for patients with primary biliary cholangitis and primary sclerosing cholangitis. *International Falk Workshop Bile Acids in Liver Diseases* 1995:141-5.

Lindor 1996 *{published data only}*

Lindor KD, Therneau TM, Jorgensen RA, Malinchoc M, Dickson ER. Effects of UDCA on survival in patients with primary biliary cholangitis. *Gastroenterology* 1996;**110**(5):1515-8.

Lindor 2000 *{published data only}*

Lindor KD, Poupon R, Poupon R, Heathcote EJ, Therneau T. UDCA for primary biliary cholangitis. *Lancet* 2000;**355**(9204):657-8.

Lindor 2005 *{published data only}*

Lindor KD. Dose effect of UDCA used in the treatment of primary biliary cholangitis and primary sclerosing cholangitis. *Bile Acid Biology and Its Therapeutic Implications* 2005;**141**:225-9.

Lindor 2007 *{published data only}*

Lindor K. UDCA for the treatment of primary biliary cholangitis. *New England Journal of Medicine* 2007;**357**(15):1524-9.

Lytvyak 2015 *{published data only}*

Lytvyak E, Montano-Loza AJ, Saxinger L, Mason A. Combination anti-retroviral therapy provides reduction in human betaretrovirus load and durable biochemical responses in patients with primary biliary cholangitis. *Hepatology* 2015;**62**:528A.

Lytvyak 2016 *{published data only}*

Lytvyak E, Montano-Loza AJ, Mason AL. Combination antiretroviral studies for patients with primary biliary cirrhosis. *World Journal of Gastroenterology* 2016;**22**(1):349-60.

Miettinen 1993 *{published data only}*

Miettinen TA, Farkkila M, Vuoristo M, Karvonen AL, Leino R, Lehtola J. Improvement of serum noncholesterol sterols may indicate retarded progression of primary biliary cholangitis (PBC) in a randomized placebo controlled two-year trial with colchicine and UDCA. *Gastroenterology* 1993;**104**(4 (Pt 2)):A954.

Miettinen 1995 *{published data only}*

Miettinen TA, Farkkila M, Vuoristo M, Karvonen AL, Leino R, Lehtola J, et al. Serum cholestanol, cholesterol precursors, and plant sterols during placebo-controlled treatment of

primary biliary cholangitis with UDCA or colchicine. *Hepatology* 1995;**21**(5):1261-8.

Muntoni 2010 *{published data only}*

Muntoni S, Rojkind M, Muntoni S. Colchicine reduces procollagen III and increases pseudocholinesterase in chronic liver disease. *World Journal of Gastroenterology* 2010;**16**(23):2889-94.

Nikolaidis 2006 *{published data only}*

Nikolaidis N, Kountouras J, Giouleme O, Tzarou V, Chatzizisi O, Patsiaoura K, et al. Colchicine treatment of liver fibrosis. *Hepato-Gastroenterology* 2006;**53**(68):281-5.

Ohmoto 2001 *{published data only}*

Ohmoto K, Mitsui Y, Yamamoto S. Effect of bezafibrate in primary biliary cholangitis: a pilot study. *Liver* 2001;**21**(3):223-4.

Ohmoto 2006 *{published data only}*

Ohmoto K, Yoshioka N, Yamamoto S. Long-term effect of bezafibrate on parameters of hepatic fibrosis in primary biliary cholangitis. *Journal of Gastroenterology* 2006;**41**(5):502-3.

Pan 2013 *{published data only}*

Pan XL, Zhao L, Li L, Li AH, Ye J, Yang L, et al. Efficacy and safety of TUDCA in the treatment of liver cirrhosis: a double-blind randomized controlled trial. *Journal of Huazhong University of Science and Technology-Medical Sciences* 2013;**33**(2):189-94.

Pares 2009 *{published data only}*

Pares A. Excellent long-term survival in patients with primary biliary cholangitis treated with UDCA. *Bile Acid Biology and Therapeutic Actions* 2009;**165**:259-69.

Podda 1989 *{published data only}*

Podda M, Ghezzi C, Battezzati PM, Bertolini E, Crosignani A, Petroni ML, et al. Effect of different doses of UDCA in chronic liver disease. *Digestive Diseases & Sciences* 1989;**34**(12 Suppl):59S-65S.

Poupon 1989 *{published data only}*

Poupon R, Poupon R, the UDCA-PBCG. UDCA for primary biliary cholangitis. International Lugano Symposium on Biliary Physiology and Diseases: Strategies for the Treatment of Hepatobiliary Diseases Falk Symposium No 53 1989, issue 22.

Poupon 1990 *{published data only}*

Poupon R, Poupon R, The UDCA-PBCG. UDCA in the treatment of primary biliary cholangitis. Strategies for the treatment of hepatobiliary diseases. *Falk Symposium 53* 1990:79-81.

Poupon 1991b *{published data only}*

Poupon RE, Balkau B, Eschwege E, Poupon R, Kaplan MM. A multicenter, controlled trial of ursodiol for the treatment of primary biliary cholangitis. *Annals of Internal Medicine* 1991;**115**(6 Suppl 2):48.

Poupon 1994 *{published data only}*

Poupon RE, Poupon R, Balkau B. Ursodiol for the long-term treatment of primary biliary cholangitis. The UDCA-PBC study group. *New England Journal of Medicine* 1994;**330**(19):1342-7.

Poupon 1997 *{published data only}*

Poupon RE, Lindor KD, CauchDudek K, Dickson ER, Poupon R, Heathcote EJ. Combined analysis of randomized controlled trials of UDCA in primary biliary cholangitis. *Gastroenterology* 1997;**113**(3):884-90.

Poupon 1999 *{published data only}*

Poupon RE, Bonnand AM, Chretien Y, Poupon R. Ten-year survival in UDCA-treated patients with primary biliary cholangitis. The UDCA-PBC study group. *Hepatology* 1999;**29**(6):1668-71.

Poupon 2003 *{published data only}*

Poupon RE, Lindor KD, Pares A, Chazouilleres O, Poupon R, Heathcote EJ. Combined analysis of the effect of treatment with UDCA on histologic progression in primary biliary cholangitis. *Journal of Hepatology* 2003;**39**(1):12-6.

Raedsch 1989 *{published data only}*

Raedsch R, Stiehl A, Hopf U, Moller B. [Effect of UDCA treatment on primary biliary cholangitis]. *Zeitschrift fur Gastroenterologie - Verhandlungsband* 1989;**24**:125-7.

Reed 1982 *{published data only}*

Reed M. Penicillamine therapy 'encouraging' in primary biliary cholangitis study. *JAMA* 1982;**248**(1):11-2.

Robson 1994 *{published data only}*

Robson SC, Neuberger JM, Williams R. The influence of cyclosporine a therapy on sex hormone levels in pre- and post-menopausal women with primary biliary cholangitis. *Journal of Hepatology* 1994;**21**(3):412-6.

Roda 2002 *{published data only}*

Roda E, Azzaroli F, Nigro G, Piazza F, Jaboli F, Ferrara F, et al. Improved liver tests and greater biliary enrichment with high dose UDCA in early stage primary biliary cholangitis. *Digestive & Liver Disease* 2002;**34**(7):523-7.

Savolainen 1983 *{published data only}*

Savolainen ER, Miettinen TA, Pikkarainen P, Salaspuro MP, Kivirikko KI. Enzymes of collagen synthesis and type III procollagen aminopropeptide in the evaluation of D-penicillamine and medroxyprogesterone treatments of primary biliary cholangitis. *Gut* 1983;**24**(2):136-42.

Schaffner 1982 *{published data only}*

Schaffner F, Sternlieb I, Sachs H. A 2 dose level randomized double-blind controlled trial of penicillamine in primary biliary cholangitis - the 1st 2 years. *Hepatology* 1982;**2**(5):714.

Setchell 1994 *{published data only}*

Setchell KDR, Rodrigues C, Podda M, Crosignani A. TauroUDCA (TUDCA) appears more effective than UDCA at displacing hydrophobic bile acids from the bile acid pool of patients with primary biliary cholangitis (PBC). *Hepatology* 1994;**20**(4 (Pt 2)):150a.

Setchell 1996 *{published data only}*

Setchell KDR, Rodrigues CMP, Podda M, Crosignani A. Metabolism of orally administered TUDCA in patients with primary biliary cholangitis. *Gut* 1996;**38**(3):439-46.

Stellaard 1979 *{published data only}*

Stellaard F, Bolt MG, Boyer JL, Klein PD. Phenobarbital treatment in primary biliary cholangitis. Differences in bile acid composition between responders and nonresponders. *Journal of Laboratory & Clinical Medicine* 1979;**94**(6):853-61.

Taal 1985 *{published data only}*

Taal BG, Schalm SW. Cryoglobulins in primary biliary cholangitis: prevalence and modulation by immunosuppressive therapy. *Zeitschrift Fur Gastroenterologie* 1985;**23**(5):228-34.

Tang 2008 *{published data only}*

Tang HH, Chen YJ, Tong GD, Zhou DQ, He JS, Zhou XZ, et al. [Efficacy of UDCA combined with Tongdan Decoction in treatment of patients with primary biliary cholangitis]. *World Chinese Journal of Digestology* 2008;**16**(13):1417-24.

Tong 2012 *{published data only}*

Tong GD, Tang HH, Wei CS, Chen YJ, He JS, Zhou XZ, et al. Efficacy of UDCA combined with Tongdan Decoction on immunological indices and histopathological changes in primary biliary cholangitis patients. *Chinese Journal of Integrative Medicine* 2012;**18**(1):16-22.

Verma 1999 *{published data only}*

Verma A, Jazrawi RP, Ahmed HA, Davis T, Bland JM, Benson M, et al. Optimum dose of UDCA in primary biliary cholangitis. *European Journal of Gastroenterology & Hepatology* 1999;**11**(10):1069-76.

Verma 2000 *{published data only}*

Verma A, Jazrawi RP, Ahmed HA, Northfield TC. The optimum dose of UDCA in primary biliary cholangitis. *Bile Acids in Hepatobiliary Disease* 2000;**110B**:25-9.

Vogel 1988 *{published data only}*

Vogel W, Kathrein H, Judmaier G, Braunsteiner H. Deterioration of primary biliary cholangitis during treatment with UDCA. *Lancet* 1988;**1**(8595):1163.

Vuoristo 1995 *{published data only}*

Vuoristo M, Farkkila M, Karvonen AL, Leino R, Lehtola J, Makinen J, et al. A placebo-controlled trial of primary biliary cholangitis treatment with colchicine and UDCA. *Gastroenterology* 1995;**108**(5):1470-8.

Vuoristo 1997 *{published data only}*

Vuoristo M, Farkkila M, Gylling H, Karvonen AL, Leino R, Lehtola J, et al. Expression and therapeutic response related to apolipoprotein e polymorphism in primary biliary cholangitis. *Journal of Hepatology* 1997;**27**(1):136-42.

Wiesner 1994 *{published data only}*

Wiesner RH. Progression of primary biliary cholangitis on UDCA. *Gastroenterology* 1994;**106**(2):555.

Wolfhagen 1995 *{published data only}*

Wolfhagen FH, Van Buuren HR, Schalm SW, Ten Kate FJ, Van Hattum J, Eskens FA, et al. Can UDCA induce disease remission in primary biliary cholangitis? The Dutch Multicentre PBC Study Group. *Journal of Hepatology* 1995;**22**(3):381.

Yan 2007 *{published data only}*

Yan G, Erik C, Gluud C. The long-term beneficial effects of UDCA in primary biliary cholangitis are highly questionable. *American Journal of Gastroenterology* 2007;**102**(2):464-5.

Yano 2002 *{published data only}*

Yano K, Kato H, Morita S, Takahara O, Ishibashi H, Furukawa R. Is bezafibrate histologically effective for primary biliary cholangitis?. *American Journal of Gastroenterology* 2002;**97**(4):1075-7.

Zuin 1991 *{published data only}*

Zuin M, Grandinetti G, Camisasca M, Boga E, Ravizza L, Molteni P. A comparison of cholestyramine and diethylaminoethyl-dextran for the treatment of hyperlipidemia and pruritus of primary biliary cholangitis. *Current Therapeutic Research, Clinical and Experimental* 1991;**49**(4):659-65.

References to studies awaiting assessment

O'Brian 1990 *{published data only}*

O'Brian C, Senior J, Sternlieb J, Saul S. Caution: not all patients with primary biliary cholangitis may successfully be treated by ursodiol. *Second International Meeting on Pathochemistry, Pathophysiology and Pathomechanisms of the Biliary System and New Strategies for the Treatment of Hepato-biliary Diseases* 1990:208.

Zaman 2006 *{published data only}*

Zaman A. Methotrexate in combination with UDCA is ineffective in the treatment of primary biliary cholangitis: commentary. *Evidence-Based Gastroenterology* 2006;**7**(1):21-2.

References to ongoing studies

ChiCTR-IPR-16008935 *{unpublished data only}*

Biochemical Response of PBC-AIH Overlap Syndrome Induced by Ursodeoxycholic Acid Only or Combination Therapy of Immunosuppressive Agents. Ongoing study Not stated..

EUCTR2015-002698-39-GB *{unpublished data only}*

A 12-Week, Double-Blind, Randomized, Placebo-Controlled, Phase 2 Study to Evaluate the Effects of Two Doses of MBX-8025 in Subjects with Primary Biliary Cirrhosis (PBC) and an Inadequate Response to Ursodeoxycholic Acid (UDCA).. Ongoing study Not stated..

NCT02308111 *{published and unpublished data}*

Lindor K, Hansen B, Pencek R, Hooshmand-Rad R, Marmon T, MacConell L, et al. A phase 3b, double blind, placebo controlled study evaluating the effect of obeticholic acid on clinical outcomes in subjects with primary biliary cholangitis at elevated risk of progression to liver transplant or death. *Journal of Hepatology* 2015;**62**:S850-1.

NCT02701166 *{unpublished data only}*

The Effect of Bezafibrate on Cholestatic Itch. Ongoing study February 2016..

NCT02823353 *{unpublished data only}*

Fenofibrate in Combination with Ursodeoxycholic Acid in Primary Biliary Cirrhosis: a Randomized Control Study. Ongoing study January 2016..

NCT02823366 *{unpublished data only}*

Fenofibrate for Patients with Primary Biliary Cirrhosis who had an Inadequate Response to Ursodeoxycholic Acid. Ongoing study January 2016..

NCT02937012 *{unpublished data only}*

Efficacy and Security of Bezafibrate in Patients with Primary Biliary Cirrhosis without Biochemical Response to Ursodeoxycholic Acid: a Randomized, Double-blind, Placebo-controlled Trial. Ongoing study October 2016..

NCT02943447 *{unpublished data only}*

A Phase 2, Randomized, Double-Blind, Placebo Controlled Study Evaluating the Safety, Tolerability, and Efficacy of GS-9674 in Subjects with Primary Biliary Cholangitis without Cirrhosis. Ongoing study December 2016..

NCT02965911 *{unpublished data only}*

A Randomized Controlled Clinical Trial on the Efficacy and Safety of Fenofibrate Combined with Ursodeoxycholic Acid in PBC Patients with an Incomplete Biochemical Response to UDCA. Ongoing study January 2016..

Additional references

Baldursdottir 2012

Baldursdottir TR, Bergmann OM, Jonasson JG, Ludviksson BR, Axelsson TA, Bjornsson ES. The epidemiology and natural history of primary biliary cholangitis: a nationwide population-based study. *European Journal of Gastroenterology and Hepatology* 2012;**24**(7):824-30.

Bergasa 2000

Bergasa NV, Mehlman JK, Jones EA. Pruritus and fatigue in primary biliary cholangitis. *Bailliere's Best Practice & Research: Clinical Gastroenterology* 2000;**14**(4):643-55.

Boberg 1998

Boberg KM, Aadland E, Jahnsen J, Raknerud N, Stiris M, Bell H. Incidence and prevalence of primary biliary cholangitis, primary sclerosing cholangitis, and autoimmune hepatitis in a Norwegian population. *Scandinavian Journal of Gastroenterology* 1998;**33**(1):99-103.

Boonstra 2014

Boonstra K, Kunst AE, Stadhouders PH, Tuynman HA, Poen AC, Van Nieuwkerk KM, et al. Rising incidence and prevalence of primary biliary cholangitis: a large population-based study. *Liver International* 2014;**34**(6):e31-8.

Chaimani 2012

Chaimani A, Salanti G. Using network meta-analysis to evaluate the existence of small-study effects in a network of interventions. *Research Synthesis Methods* 2012;**3**(2):161-76.

Chaimani 2013

Chaimani A, Higgins JP, Mavridis D, Spyridonos P, Salanti G. Graphical tools for network meta-analysis in STATA. *PLoS One* 2013;**8**(10):e76654.

Chan 2013

Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gotzsche PC, Krleza-Jeric K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Annals of Internal Medicine* 2013;**158**(3):200-7.

Del Re 2013

Del Re AC, Spielmans GI, Flückiger C, Wampold BE. Efficacy of new generation antidepressants: differences seem illusory. *PLoS One* 2013;**8**(6):e63509.

DeMets 1987

DeMets DL. Methods for combining randomized clinical trials: strengths and limitations. *Statistics in Medicine* 1987;**6**(3):341-50.

DerSimonian 1986

DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clinical Trials* 1986;**7**(3):177-88.

Dias 2010

Dias S, Welton NJ, Caldwell DM, Ades AE. Checking consistency in mixed treatment comparison meta-analysis. *Statistics in Medicine* 2010;**29**(7-8):932-44.

Dias 2012a

Dias S, Sutton AJ, Welton NJ, Ades AE. NICE DSU Technical Support Document 3: heterogeneity: subgroups, meta-regression, bias and bias-adjustment, September 2011 (last updated April 2012). www.nicedsu.org.uk/TSD3%20Heterogeneity.final%20report.08.05.12.pdf (accessed 27 March 2014).

Dias 2012b

Dias S, Welton NJ, Sutton AJ, Ades AE. NICE DSU Technical Support Document 1: introduction to evidence synthesis for decision making, April 2011 (last updated April 2012). www.nicedsu.org.uk/TSD1%20Introduction.final.08.05.12.pdf (accessed 27 March 2014).

Dias 2014a

Dias S, Welton NJ, Sutton AJ, Ades AE. NICE DSU Technical Support Document 2: a generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials, August 2011 (last updated April 2014). www.nicedsu.org.uk/TSD2%20General%20meta%20analysis%20corrected%2015April2014.pdf (accessed 8 October 2014).

Dias 2014b

Dias S, Welton NJ, Sutton AJ, Caldwell DM, Lu G, Ades AE. NICE DSU Technical Support Document 4: inconsistency in

networks of evidence based on randomised controlled trials, May 2011 (last updated April 2014). www.nicedsu.org.uk/TSD4%20Inconsistency.final.15April2014.pdf (accessed 8 October 2014).

Dronamraju 2010

Dronamraju D, Odin J, Bach N. Primary biliary cholangitis: environmental risk factors. *Disease Markers* 2010;**29**(6):323-8.

EASL 2009

European Association for the Study of the Liver. EASL clinical practice guidelines: management of cholestatic liver diseases. *Journal of Hepatology* 2009;**51**(2):237-67.

Egger 1997

Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ (Clinical Research Ed.)* 1997;**315**(7109):629-34.

EuroQol 2014

EuroQol. About EQ-5D, 2014. www.euroqol.org/about-eq-5d.html (accessed 8 October 2014).

Floreani 2011

Floreani A, Caroli D, Variola A, Rizzotto ER, Antoniazzi S, Chiaramonte M, et al. A 35-year follow-up of a large cohort of patients with primary biliary cholangitis seen at a single centre. *Liver International* 2011;**31**(3):361-8.

Gershwin 2005

Gershwin ME, Selmi C, Worman HJ, Gold EB, Watnik M, Utts J, et al. Risk factors and comorbidities in primary biliary cholangitis: a controlled interview-based study of 1032 patients. *Hepatology* 2005;**42**(5):1194-202.

Giljaca 2010

Giljaca V, Poropat G, Stimac D, Gluud C. Methotrexate for primary biliary cholangitis. *Cochrane Database of Systematic Reviews* 2010, Issue 5. [DOI: 10.1002/14651858.CD004385.pub3]

Gluud 2007

Gluud C, Brok J, Gong Y, Koretz RL. Hepatology may have problems with putative surrogate outcome measures. *Journal of hepatology* 2007;**46**(4):734-42. [PUBMED: 17316871]

Gluud 2017

Gluud C, Nikolova D, Klingenberg SL. Cochrane Hepato-Biliary Group. About The Cochrane Collaboration (Cochrane Review Groups (CRGs)) 2017, Issue 2. Art. No.: LIVER.

Gong 2004a

Gong Y, Gluud C. Colchicine for primary biliary cholangitis. *Cochrane Database of Systematic Reviews* 2004, Issue 2. [DOI: 10.1002/14651858.CD004481.pub2]

Gong 2004b

Gong Y, Klingenberg SL, Gluud C. D-Penicillamine for primary biliary cholangitis. *Cochrane Database of Systematic Reviews* 2004, Issue 4. [DOI: 10.1002/14651858.CD004789.pub2]

Gong 2007a

Gong Y, Christensen E, Gluud C. Azathioprine for primary biliary cholangitis. *Cochrane Database of Systematic Reviews* 2007, Issue 3. [DOI: 10.1002/14651858.CD006000.pub2]

Gong 2007b

Gong Y, Christensen E, Gluud C. Cyclosporin A for primary biliary cholangitis. *Cochrane Database of Systematic Reviews* 2007, Issue 3. [DOI: 10.1002/14651858.CD005526.pub2]

Guanabens 2013

Guanabens N, Monegal A, Cerda D, Muxi A, Gifre L, Peris P, et al. Randomized trial comparing monthly ibandronate and weekly alendronate for osteoporosis in patients with primary biliary cholangitis. *Hepatology* 2013;**58**(6):2070-8.

Guyatt 2011

Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction - GRADE evidence profiles and summary of findings tables. *Journal of Clinical Epidemiology* 2011;**64**(4):383-94.

Higgins 2011

Higgins JPT, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Higgins 2012

Higgins JPT, Jackson D, Barrett JK, Lu G, Ades AE, White IR. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. *Research Synthesis Methods* 2012;**3**(2):98-110.

ICH-GCP 1997

International Conference on Harmonisation Expert Working Group. International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use. ICH harmonised tripartite guideline. Guideline for good clinical practice CFR & ICH Guidelines. Vol. **1**, Pennsylvania: Barnett International/PAREXEL, 1997.

Jakobsen 2014

Jakobsen JC, Wetterslev J, Winkel P, Lange T, Gluud C. Thresholds for statistical and clinical significance in systematic reviews with meta-analytic methods. *BMC Medical Research Methodology* 2014;**14**(1):120.

Jones 1999

Jones EA, Ten Kate FJ, Ter Borg F, Houben M, Reesink HW, Chamuleau RA. Combination therapy with mycophenolate mofetil and UDCA for primary biliary cholangitis. *European Journal of Gastroenterology & Hepatology* 1999;**11**(10):1165-9.

Kim 2000

Kim WR, Lindor KD, Locke GR 3rd, Therneau TM, Homburger HA, Batts KP, et al. Epidemiology and natural history of primary biliary cholangitis in a US community. *Gastroenterology* 2000;**119**(6):1631-6.

Kjaergard 2001

Kjaergard LL, Villumsen J, Gluud C. Reported methodologic quality and discrepancies between large and small randomized trials in meta-analyses. *Annals of Internal Medicine* 2001;**135**(11):982-9.

Lammert 2013

Lammert C, Nguyen DL, Juran BD, Schlicht E, Larson JJ, Atkinson EJ, et al. Questionnaire based assessment of risk factors for primary biliary cholangitis. *Digestive and Liver Disease* 2013;**45**(7):589-94.

Lazaridis 2007

Lazaridis KN, Talwalkar JA. Clinical epidemiology of primary biliary cholangitis: incidence, prevalence, and impact of therapy. *Journal of Clinical Gastroenterology* 2007;**41**(5):494-500.

Leung 2005

Leung PS, Coppel RL, Gershwin ME. Etiology of primary biliary cholangitis: the search for the culprit. *Seminars in Liver Disease* 2005;**25**(3):327-36.

Li Wei 2012

Li Wei X, Yan X, Shi Chun R, Zhang Ai P. Chlorambucil for patients with primary biliary cirrhosis. *Cochrane Database of Systematic Reviews* 2012, Issue 9. [DOI: 10.1002/14651858.CD008714.pub2]

Lindor 2009

Lindor KD, Gershwin ME, Poupon R, Kaplan M, Bergasa NV, Heathcote EJ, et al. Primary biliary cholangitis. *Hepatology* 2009;**50**(1):291-308.

Lu 2006

Lu G, Ades AE. Assessing evidence inconsistency in mixed treatment comparisons. *Journal of the American Statistical Association* 2006;**101**(474):447-59.

Lundh 2017

Lundh A, Sismondo S, Lexchin J, Busuioc OA, Bero L. Industry sponsorship and research outcome. *Cochrane Database of Systematic Reviews* 2017, Issue 2. [DOI: 10.1002/14651858.MR000033.pub3]

Macaskill 2001

Macaskill P, Walter SD, Irwig L. A comparison of methods to detect publication bias in meta-analysis. *Statistics in Medicine* 2001;**20**(4):641-54.

Metcalf 1997

Metcalf JV, Bhopal RS, Gray J, Howel D, James OF. Incidence and prevalence of primary biliary cholangitis in the city of Newcastle upon Tyne, England. *International Journal of Epidemiology* 1997;**26**(4):830-6.

Mills 2012

Mills EJ, Ioannidis JP, Thorlund K, Schünemann HJ, Puhan MA, Guyatt GH. How to use an article reporting a multiple treatment comparison meta-analysis. *JAMA* 2012;**308**(12):1246-53.

Moher 1998

Moher D, Pham B, Jones A, Cook DJ, Jadad AR, Moher M, et al. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses?. *Lancet* 1998;**352**(9128):609-13.

Myers 2009

Myers RP, Shaheen AA, Fong A, Burak KW, Wan A, Swain MG, et al. Epidemiology and natural history of primary biliary cholangitis in a Canadian health region: a population-based study. *Hepatology* 2009;**50**(6):1884-92.

NCBI 2014

NCBI. Liver cirrhosis, biliary, 2014. www.ncbi.nlm.nih.gov/mesh/68008105 (accessed 19 October 2014).

Newell 1992

Newell DJ. Intention-to-treat analysis: implications for quantitative and qualitative research. *International Journal of Epidemiology* 1992;**21**(5):837-41.

OpenBUGS 3.2.3 [Computer program]

Members of OpenBUGS Project Management Group. OpenBUGS. Version 3.2.3. Members of OpenBUGS Project Management Group, 2014.

Ormarsdottir 2004

Ormarsdottir S, Mallmin H, Naessen T, Petren-Mallmin M, Broome U, Hultcrantz R, et al. An open, randomized, controlled study of transdermal hormone replacement therapy on the rate of bone loss in primary biliary cholangitis. *Journal of Internal Medicine* 2004;**256**(1):63-9.

Parikh-Patel 2001

Parikh-Patel A, Gold EB, Worman H, Krivy KE, Gershwin ME. Risk factors for primary biliary cholangitis in a cohort of patients from the United States. *Hepatology* 2001;**33**(1):16-21.

Paumgartner 2002

Paumgartner G, Beuers U. UDCA in cholestatic liver disease: mechanisms of action and therapeutic use revisited. *Hepatology* 2002;**36**(3):525-31.

Perez 2009

Perez MJ, Briz O. Bile-acid-induced cell injury and protection. *World Journal of Gastroenterology* 2009;**15**(14):1677-89.

Pla 2007

Pla X, Vergara M, Gil M, Dalmau B, Cistero B, Bella RM, et al. Incidence, prevalence and clinical course of primary biliary cholangitis in a Spanish community. *European Journal of Gastroenterology and Hepatology* 2007;**19**(10):859-64.

Prince 2005

Prince M, Christensen E, Gluud C. Glucocorticosteroids for primary biliary cholangitis. *Cochrane Database of Systematic Reviews* 2005, Issue 2. [DOI: 10.1002/14651858.CD003778.pub2]

Prince 2010

Prince MI, Ducker SJ, James OF. Case-control studies of risk factors for primary biliary cholangitis in two United Kingdom populations. *Gut* 2010;**59**(4):508-12.

Puhan 2014

Puhan MA, Schünemann HJ, Murad MH, Li T, Brignardello-Petersen R, Singh JA, et al. A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. *BMJ (Clinical Research Ed.)* 2014;**349**:g5630.

Rautiainen 2007

Rautiainen H, Salomaa V, Niemela S, Karvonen AL, Nurmi H, Isoniemi H, et al. Prevalence and incidence of primary biliary cholangitis are increasing in Finland. *Scandinavian Journal of Gastroenterology* 2007;**42**(11):1347-53.

RevMan 2014 [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Royle 2003

Royle P, Milne R. Literature searching for randomized controlled trials used in Cochrane reviews: rapid versus exhaustive searches. *International Journal of Technology Assessment in Health Care* 2003;**19**(4):591-603.

Rudic 2011a

Rudic JS, Giljaca V, Krstic MN, Bjelakovic G, Gluud C. Bisphosphonates for osteoporosis in primary biliary cholangitis. *Cochrane Database of Systematic Reviews* 2011, Issue 12. [DOI: 10.1002/14651858.CD009144.pub2]

Rudic 2011b

Rudic JS, Poropat G, Krstic MN, Bjelakovic G, Gluud C. Hormone replacement for osteoporosis in women with primary biliary cholangitis. *Cochrane Database of Systematic Reviews* 2011, Issue 12. [DOI: 10.1002/14651858.CD009146.pub2]

Rudic 2012a

Rudic JS, Poropat G, Krstic MN, Bjelakovic G, Gluud C. Ursodeoxycholic acid for primary biliary cirrhosis. *Cochrane Database of Systematic Reviews* 2012, Issue 12. [DOI: 10.1002/14651858.CD000551.pub3]

Rudic 2012b

Rudic JS Poropat G, Krstic MN, Bjelakovic G, Gluud C. Bezafibrate for primary biliary cirrhosis. *Cochrane Database of Systematic Reviews* 2012, Issue 1. [DOI: 10.1002/14651858.CD009145.pub2]

Salanti 2011

Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *Journal of Clinical Epidemiology* 2011;**64**(2):163-71.

Salanti 2012

Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. *Research Synthesis Methods* 2012;**3**(2):80-97.

Savović 2012a

Savović J, Jones HE, Altman DG, Harris RJ, Jüni P, Pildal J, et al. Influence of reported study design characteristics on intervention effect estimates from randomized controlled trials: combined analysis of meta-epidemiological studies. *Health Technology Assessment* 2012;**16**(35):1-82.

Savović 2012b

Savović J, Jones HE, Altman DG, Harris RJ, Jüni P, Pildal J, et al. Influence of reported study design characteristics on intervention effect estimates from randomized controlled trials. *Annals of Internal Medicine* 2012;**157**(6):429-38.

Schulz 1995

Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995;**273**(5):408-12.

Schulz 2010

Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ (Clinical Research Ed.)* 2010;**340**:c332.

Selmi 2010

Selmi C, Gershwin ME. The etiology mystery in primary biliary cholangitis. *Digestive Diseases* 2010;**28**(1):105-15.

Severini 1993

Severini TA. Bayesian interval estimates which are also confidence intervals. *Journal of the Royal Statistical Society. Series B (Methodological)* 1993;**55**(2):533-40.

Song 2008

Song M, Song Z, Barve S, Zhang J, Chen T, Liu M, et al. Tetrathiomolybdate protects against bile duct ligation-induced cholestatic liver injury and fibrosis. *Journal of Pharmacology and Experimental Therapeutics* 2008;**325**(2):409-16.

Sood 2004

Sood S, Gow PJ, Christie JM, Angus PW. Epidemiology of primary biliary cholangitis in Victoria, Australia: high prevalence in migrant populations. *Gastroenterology* 2004;**127**(2):470-5.

Stata/SE 14.2 [Computer program]

StataCorp LP. Stata/SE 14.2 for Windows[64-bit x86-64]. Version 14. College Station: StataCorp LP, 2017.

Talwalkar 2005

Talwalkar JA, Angulo P, Keach JC, Petz JL, Jorgensen RA, Lindor KD. Mycophenolate mofetil for the treatment of primary biliary cholangitis in patients with an incomplete response to UDCA. *Journal of Clinical Gastroenterology* 2005;**39**(2):168-71.

Talwalkar 2006

Talwalkar JA, Donlinger JJ, Gossard AA, Keach JC, Jorgensen RA, Petz JC, et al. Fluoxetine for the treatment of fatigue in primary biliary cholangitis: a randomized, double-blind controlled trial. *Digestive Diseases and Sciences* 2006;**51**(11):1985-91.

Ter Borg 2004

Ter Borg PC, Van Os E, Van den Broek WW, Hansen BE, Van Buuren HR. Fluvoxamine for fatigue in primary biliary cholangitis and primary sclerosing cholangitis: a randomised controlled trial [ISRCTN88246634]. *BMC Gastroenterology* 2004;**4**:13.

Thorlund 2011

Thorlund K, Engstrøm J, Wetterslev J, Brok J, Imberger G, Gluud C. User manual for Trial Sequential Analysis (TSA). Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen, Denmark. Available from www.ctu.dk/tsa 2011:1-115.

Thorlund 2012

Thorlund K, Mills EJ. Sample size and power considerations in network meta-analysis. *Systematic Reviews* 2012;**1**:41.

TSA 2011 [Computer program]

Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen. TSA version 0.9. Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen, 2011.

Turner 2012

Turner RM, Davey J, Clarke MJ, Thompson SG, Higgins JP. Predicting the extent of heterogeneity in meta-analysis, using empirical data from the Cochrane Database of Systematic Reviews. *International Journal of Epidemiology* 2012;**41**(3):818-27.

Van Valkenhoef 2012

Van Valkenhoef G, Lu G, De Brock B, Hillege H, Ades AE, Welton NJ. Automating network meta-analysis. *Research Synthesis Methods* 2012;**3**(4):285-99.

Ware 2014

Ware JE. SF-36® health survey update, 2014. www.sf-36.org/tools/sf36.shtml (accessed on 8 October 2014).

Wetterslev 2008

Wetterslev J, Thorlund K, Brok J, Gluud C. Trial Sequential Analysis may establish when firm evidence is reached in cumulative meta-analysis. *Journal of Clinical Epidemiology* 2008;**61**(1):64-75.

Wetterslev 2017

Wetterslev J, Jakobsen JC, Gluud C. Trial Sequential Analysis in systematic reviews with meta-analysis. *BMC Medical Research Methodology* 2017;**17**(1):39.

Wood 2008

Wood L, Egger M, Gluud LL, Schulz KF, Jüni P, Altman DG, et al. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. *BMJ (Clinical Research Ed.)* 2008;**336**(7644):601-5.

Yin 2015

Yin Q, Li J, Xia Y, Zhang R, Wang J, Lu W, et al. Systematic review and meta-analysis: bezafibrate in patients with primary biliary cholangitis. *Drug Design, Development and Therapy* 2015;**9**:5407-19.

Zhang 2015

Zhang Y, Li S, He L, Wang F, Chen K, Li J, et al. Combination therapy of fenofibrate and UDCA in patients with primary biliary cholangitis who respond incompletely to UDCA monotherapy: a meta-analysis. *Drug Design, Development and Therapy* 2015;**9**:2757-66.

Zhu 2015a

Zhu GQ, Huang S, Huang GQ, Wang LR, Lin YQ, Wu YM, et al. Optimal drug regimens for primary biliary cholangitis: a systematic review and network meta-analysis. *Oncotarget* 2015;**6**(27):24533-49.

Zhu 2015b

Zhu GQ, Shi KQ, Huang S, Huang GQ, Lin YQ, Zhou ZR, et al. Network meta-analysis of randomized controlled trials: efficacy and safety of UDCA-based therapies in primary biliary cholangitis. *Medicine* 2015;**94**(11):e609.

Zhu 2015c

Zhu GQ, Shi KQ, Huang GQ, Wang LR, Lin YQ, Braddock M, et al. A network meta-analysis of the efficacy and side effects of UDCA-based therapies for primary sclerosing cholangitis. *Oncotarget* 2015;**6**(29):26757-69.

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Almasio 2000

Methods	Randomised clinical trial.
Participants	Country: Italy. Number randomised: 90.

Almasio 2000 *(Continued)*

	Post-randomisation dropouts: 6 (6.7%). Revised sample size: 84. Mean age: 54 years. Females: 81 (96.4%). Symptomatic participants: 84 (100%). AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): not stated. Inclusion criteria • Symptom status: symptomatic participants only. • AMA status: not stated. • Response status: not stated. Exclusion criteria • People with biliary obstruction. • Anticipated requirement for liver transplantation in 1 year. • Pregnancy. • Aged < 18 years or > 70 years. • Coexisting liver disease. • Anticipated life expectancy < 3 years.
Interventions	Participants were randomly assigned to 2 groups. Group 1: UDCA (low) + colchicine (n = 42). Further details: UDCA: 250 mg BD for 3 years + colchicine: 1 mg/day for 3 years. Group 2: UDCA (low) (n = 42). Further details: UDCA: 250 mg BD for 3 years.
Outcomes	Mortality, decompensated liver disease.
Notes	Reasons for post-randomisation dropouts: adverse effects and low compliance.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Colchicine, 1 mg daily, or an indistinguishable placebo were randomly assigned to patients according to a computer-generated list developed separately for each centre".
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was performed by a central study unit…".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: identical placebo used and authors stated double-blind.

Almasio 2000 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: identical placebo used and authors stated double-blind.
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation dropouts.
Selective reporting (reporting bias)	High risk	Comment: adverse events not reported.
For-profit bias	Low risk	Comment: no money received for the trial; the drug was provided by Abc Farmaceutici S.p.a (author's reply).
Other bias	Low risk	Comment: no other bias noted.

Angulo 1999a

Methods	Randomised clinical trial.
Participants	Country: USA. Number randomised: 155. Post-randomisation dropouts: not stated. Revised sample size: 155. Mean age: 53 years. Females: 130 (83.9%). Symptomatic participants: not stated. AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): all participants followed up for 12 months. Inclusion criteria • Symptom status: symptomatic and asymptomatic participants. • AMA status: not stated. • Response status: not stated. Exclusion criteria • People with decompensated cirrhosis. • Hepatocellular carcinoma. • Concomitant immunosuppressive regimen. • Other major diseases unrelated to primary biliary cholangitis. • Alcohol abuse. • Low compliance.
Interventions	Participants were randomly assigned to 3 groups. Group 1: UDCA (low) (n = 52).

Angulo 1999a *(Continued)*

	Further details: UDCA: 5 mg/kg/day to 7 mg/kg/day; duration: 1 to 2 years. Group 2: UDCA (moderate) (n = 49). Further details: UDCA: 13 mg/kg/day to 15 mg/kg/day; duration: 1 to 2 years. Group 3: UDCA (high) (n = 54). Further details: UDCA: 23 mg/kg/day to 25 mg/kg/day; duration: 1 to 2 years.
Outcomes	Mortality, adverse events, liver transplantation.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was carried out separately for each of the eight strata with a computer-generated, blocked, randomized drug assignment schedule".
Allocation concealment (selection bias)	Low risk	Quote: "Patients were randomized by a statistician (D.W.M.), and the drug was provided by a pharmacist who was not involved in the patient's clinical evaluation or follow-up".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The patients, physicians, nurses, and study coordinator were unaware throughout the study which dose was being administered. To assure blindness patients received the same number of tablets by mixing UDCA-tablets with placebo-tablets in a ratio defined by their assigned dose; therefore, the number of tablets taken per day according to the body weight was exactly the same regardless of the dose assigned". Comment: identical placebo used and authors stated double-blind.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: identical placebo used and authors stated double-blind.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: unclear whether all participants randomised were included in the analysis.
Selective reporting (reporting bias)	Low risk	Comment: mortality and morbidity reported.
For-profit bias	Unclear risk	Comment: information not available.
Other bias	Low risk	Comment: no other risk of bias.

Arora 1990

Methods	Randomised clinical trial.
Participants	Country: USA. Number randomised: 9. Post-randomisation dropouts: not stated.

Arora 1990 *(Continued)*

	Revised sample size: 9. Mean age: not stated. Females: not stated. Symptomatic participants: 9 (100%). AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): all participants followed up for 5 months. Inclusion criteria • Symptom status: symptomatic participants only. • AMA status: not stated. • Response status: not stated.
Interventions	Participants were randomly assigned to 2 groups. Group 1: UDCA (low) (n = 5). Further details: UDCA: 10 mg/kg/day for 5 months. Group 2: placebo (n = 4).
Outcomes	None of the outcomes of interest reported.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: placebo used and authors stated double blind; however, unclear whether identical placebo used.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: placebo used and authors stated double blind; however, unclear whether identical placebo used.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available.
Selective reporting (reporting bias)	High risk	Comment: neither mortality nor adverse events reported.
For-profit bias	Unclear risk	Comment: information not available.

Arora 1990 *(Continued)*

Other bias	Low risk	Comment: no other risk of bias.

Askari 2010

Methods	Randomised clinical trial.
Participants	Country: USA. Number randomised: 28. Post-randomisation dropouts: 0 (0%). Revised sample size: 28. Mean age: 54 years. Females: 26 (92.9%). Symptomatic participants: not stated. AMA positive: 27 (96.4%). Responders: not stated. Mean follow-up period (for all groups): not stated. Inclusion criteria • Symptom status: symptomatic and asymptomatic participants. • AMA status: AMA-positive and AMA-negative participants. • Response status: not stated. Exclusion criteria • Did not take UDCA in the previous 3 months. • Decompensated cirrhosis. • Required renal dialysis. • Pregnant or nursing. • Had a serious illness of other types such as uncontrolled congestive heart failure, severe diabetic neuropathy, severe pulmonary disease, advanced cancer, etc.
Interventions	Participants were randomly assigned to 2 groups. Group 1: tetrathiomolybdate (n = 13). Further details: tetrathiomolybdate: 10 mg/day to 120 mg/day based on serum ceruloplasmin levels; duration: not stated. Group 2: placebo (n = 15).
Outcomes	None of the outcomes of interest reported.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Askari 2010 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "The patients were assigned to the placebo arm or the tetrathiomolybdate arm using a table of random numbers".
Allocation concealment (selection bias)	Low risk	Quote: "Central allocation by pharmacy" (author's reply).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: identical placebo used and authors stated double-blind.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: identical placebo used and authors stated double-blind.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "There were not post-randomisation drop-outs" (author's reply).
Selective reporting (reporting bias)	High risk	Comment: neither mortality nor adverse events reported.
For-profit bias	Low risk	Quote: "Supported by Grant FD-02590-02 from the U.S. Food and Drug Administration's Orphan Products Office, the General Clinical Research Center of the University of Michigan Hospitals, Grant MO1- RR000042 from the National Institutes of Health, and Grant Ul1- RR024986 Clinical and Translational Science Awards".
Other bias	High risk	Comment: unclear whether the participants continued to take UDCA in both groups.

Battezzati 1993

Methods	Randomised clinical trial.
Participants	Country: Italy. Number randomised: 88. Post-randomisation dropouts: 2 (2.3%). Revised sample size: 86. Mean age: 55 years. Females: 78 (90.7%). Symptomatic participants: 86 (100%). AMA positive: 77 (89.5%). Responders: not stated. Mean follow-up period (for all groups): minimum 6 months. Inclusion criteria • Symptom status: symptomatic participants only. • AMA status: AMA-positive and AMA-negative participants.

Battezzati 1993 *(Continued)*

- Response status: not stated.

Exclusion criteria

- Serum bilirubin levels > 10 mg/dL.
- Decompensated liver disease.
- Evidence of malignancy.
- Alcohol abuse.

Interventions	Participants were randomly assigned to 2 groups. Group 1: UDCA (low) (n = 42). Further details: UDCA: 250 mg BD for 6 months. Group 2: placebo (n = 44).
Outcomes	None of the outcomes of interest reported.
Notes	Reasons for post-randomisation dropouts: lost to follow-up.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization of treatment assignments was performed separately for each centre: patients were consecutively given indistinguishable medications, which had been assigned by the central pharmacy according to a computer- generated list. UDCA and an identical-appearing placebo were obtained through the courtesy of ABC Farmaceutici, Torino, Italy".
Allocation concealment (selection bias)	Low risk	Quote: "Randomization of treatment assignments was performed separately for each centre: patients were consecutively given indistinguishable medications, which had been assigned by the central pharmacy according to a computer- generated list. UDCA and an identical-appearing placebo were obtained through the courtesy of ABC Farmaceutici, Torino, Italy".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Randomization of treatment assignments was performed separately for each centre: patients were consecutively given indistinguishable medications, which had been assigned by the central pharmacy according to a computer- generated list. UDCA and an identical-appearing placebo were obtained through the courtesy of ABC Farmaceutici, Torino, Italy".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Randomization of treatment assignments was performed separately for each centre: patients were consecutively given indistinguishable medications, which had been assigned by the central pharmacy according to a computer- generated list. UDCA and an identical-appearing placebo were obtained through the courtesy of ABC Farmaceutici, Torino, Italy".
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation dropouts.
Selective reporting (reporting bias)	High risk	Comment: neither mortality nor adverse events reported.
For-profit bias	Unclear risk	Comment: information not available.
Other bias	Low risk	Comment: no other risk of bias.

Bobadilla 1994

Methods	Randomised clinical trial.
Participants	Country: Mexico. Number randomised: 40. Post-randomisation dropouts: not stated. Revised sample size: 40. Mean age: not stated. Females: not stated. Symptomatic participants: not stated. AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): all participants followed up for 12 months. Inclusion criteria • Symptom status: not stated. • AMA status: not stated. • Response status: not stated.
Interventions	Participants were randomly assigned to 2 groups. Group 1: UDCA (moderate) + colchicine (n = 21). Further details: UDCA: 13 mg/kg/day to 15 mg/kg/day for 1 year + colchicine: 1 mg/day for 5 days in a week for 1 year. Group 2: placebo (n = 19).
Outcomes	None of the outcomes of interest reported.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: although placebo used in double-blind trial, unclear whether the placebo was identical.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: although placebo used in double-blind trial, unclear whether the placebo was identical.

Bobadilla 1994 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available.
Selective reporting (reporting bias)	High risk	Comment: neither mortality nor adverse events reported.
For-profit bias	Unclear risk	Comment: information not available.
Other bias	Low risk	Comment: no other source of bias.

Bodenheimer 1988

Methods	Randomised clinical trial.
Participants	Country: USA. Number randomised: 57. Post-randomisation dropouts: 10 (17.5%). Revised sample size: 47. Mean age: 52 years. Females: not stated. Symptomatic participants: 45 (95.7%). AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): 33 months. Inclusion criteria • Symptom status: symptomatic and asymptomatic participants. • AMA status: AMA-positive and AMA-negative participants. • Response status: not stated.
Interventions	Participants were randomly assigned to 2 groups. Group 1: colchicine (n = 28). Further details: colchicine: 0.6 mg BD orally for 5 years. Group 2: placebo (n = 29).
Outcomes	None of the outcomes of interest reported.
Notes	Reasons for post-randomisation dropouts: non-compliance.

Risk of bias

Bias	Authors' judgement	Support for judgement

Bodenheimer 1988 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The design of our trial was that of a double-blind, randomized evaluation of colchicine (0.6 mg) twice daily compared with an identically appearing placebo".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The design of our trial was that of a double-blind, randomized evaluation of colchicine (0.6 mg) twice daily compared with an identically appearing placebo".
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation dropouts.
Selective reporting (reporting bias)	High risk	Comment: neither mortality nor adverse events reported.
For-profit bias	High risk	Quote: "The colchicine and placebo tablets were prepared and generously supplied by Eli Lilly and Company, Indianapolis, Ind".
Other bias	Low risk	Comment: no other source of bias.

Bowlus 2014

Methods	Randomised clinical trial.
Participants	Country: multicentric; international. Number randomised: 216. Post-randomisation dropouts: not stated. Revised sample size: 216. Mean age: 56 years. Females: 197 (91.2%). Symptomatic participants: not stated. AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): all participants followed up for 12 months. Inclusion criteria • Symptom status: not stated. • AMA status: not stated. • Response status: not stated.
Interventions	Participants were randomly assigned to 3 groups.

Bowlus 2014 *(Continued)*

	Group 1: obeticholic acid (low) (n = 73). Further details: obeticholic acid (low): 5 mg orally for 12 months; frequency not stated. Group 2: obeticholic acid (low) (n = 73). Further details: obeticholic acid (low): 10 mg orally for 12 months; frequency not stated. Group 3: placebo (n = 70).
Outcomes	None of the outcomes of interest reported.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: although placebo was used in double-blind trial, unclear whether the placebo was identical.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: although placebo was used in double-blind trial, unclear whether the placebo was identical.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available.
Selective reporting (reporting bias)	High risk	Comment: neither mortality nor adverse events reported.
For-profit bias	High risk	Comment: Several authors had advised pharmaceutical companies or were employees of pharmaceutical company.
Other bias	Low risk	Comment: no other source of bias.

Cash 2013

Methods	Randomised clinical trial.
Participants	Country: UK. Number randomised: 21. Post-randomisation dropouts: 8 (38.1%). Revised sample size: 13. Mean age: 55 years.

Cash 2013 *(Continued)*

	Females: not stated. Symptomatic participants: not stated. AMA positive: 13 (100%). Responders: not stated. Mean follow-up period (for all groups): all participants followed up for 12 months. Inclusion criteria • Symptom status: not stated. • AMA status: AMA-positive participants only. • Response status: not stated. Exclusion criteria • Aged < 19 years or > 76 years. • Cholesterol < 5 mmol/L. • Known hypertension. • Diabetes mellitus. • History of cardiovascular disease. • Already prescribed lipid-lowering agents or hormonal preparations. • Pregnancy.
Interventions	Participants were randomly assigned to 2 groups. Group 1: simvastatin (n = 7). Further details: simvastatin: 20 mg/day orally for 12 months. Group 2: placebo (n = 6).
Outcomes	None of the outcomes of interest reported.
Notes	Reasons for post-randomisation dropouts: adverse effects.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Low risk	Quote: "Patient treatment randomization and allocation was performed independently by the Department of Research Pharmacology in the Royal Victoria Hospital at the initial baseline visit".
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "The patients were blinded but the healthcare providers were not" (author's reply).
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "Outcome assessors were not blinded" (author's reply).
Incomplete outcome data (attrition bias)	High risk	Comment: there were post-randomisation dropouts.

Cash 2013 *(Continued)*
All outcomes

Selective reporting (reporting bias)	High risk	Comment: neither mortality nor adverse events reported.
For-profit bias	Low risk	Quote: "Financial support: The Royal Victoria Hospital Liver Support Group".
Other bias	High risk	Quote: "Patients were allowed to continue previous prescriptions for primary biliary cholangitis. It was not clear whether this was balanced across groups".

Christensen 1985

Methods	Randomised clinical trial.
Participants	Country: multicentric; international. Number randomised: 248. Post-randomisation dropouts: 63 (25.4%). Revised sample size: 185. Mean age: 55 years. Females: not stated. Symptomatic participants: not stated. AMA positive: not stated. Mean follow-up period (for all groups): minimum 63 months. Inclusion criteria • Symptom status: not stated. • AMA status: AMA-positive and AMA-negative participants. • Response status: not stated. Exclusion criteria • No antimetabolites in the previous 6 months.
Interventions	Participants were randomly assigned to 2 groups. Group 1: azathioprine (n = 98). Further details: azathioprine: escalating doses up to a maximum of 100 mg/day; duration: not stated. Group 2: placebo (n = 87).
Outcomes	Mortality.
Notes	Reasons for post-randomisation dropouts: lost to follow-up.

Risk of bias

Bias	Authors' judgement	Support for judgement

Christensen 1985 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Quote: "Patients were randomized to azathioprine or placebo separately for each centre and for each sex by the sealed envelope technique". Comment: further details of sealed envelope technique were not available.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: identical placebo used and authors stated double-blind.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: identical placebo used and authors stated double-blind.
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation dropouts.
Selective reporting (reporting bias)	High risk	Comment: adverse events not reported.
For-profit bias	High risk	Quote: "This work was also supported by the Wellcome Foundation. J.N. was supported by Ciba-Geigy Ltd".
Other bias	Low risk	Comment: no other source of bias.

Combes 1995a

Methods	Randomised clinical trial.
Participants	Country: USA. Number randomised: 151. Post-randomisation dropouts: 0 (0%). Revised sample size: 151. Mean age: 49 years. Females: 134 (88.7%). Symptomatic participants: not stated. AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): all participants followed up for 24 months. Inclusion criteria • Symptom status: not stated. • AMA status: AMA-positive and AMA-negative participants. • Response status: not stated.

Combes 1995a *(Continued)*

	Other exclusion criteria • Recurrent bleeds from oesophagogastric varices, spontaneous encephalopathy, or diuretic-resistant ascites. • Serum bilirubin ≥ 20 mg/dL. • Pregnancy. • Aged < 19 years. • Findings of other causes of liver disease.
Interventions	Participants were randomly assigned to 2 groups. Group 1: UDCA (moderate) (n = 77). Further details: UDCA: 10 mg/kg/day to 12 mg/kg/day for 2 years. Group 2: placebo (n = 74).
Outcomes	Decompensated liver disease.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: identical placebo used in double-blind trial.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: identical placebo used in double-blind trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no post-randomisation dropouts.
Selective reporting (reporting bias)	High risk	Comment: neither mortality nor adverse events reported.
For-profit bias	High risk	Quote: "Supported in part by a research grant from Ciba-Geigy".
Other bias	Low risk	Comment: no other risk of bias.

Combes 2005

Methods	Randomised clinical trial.
Participants	Country: USA.

Combes 2005 *(Continued)*

	Number randomised: 265. Post-randomisation dropouts: 0 (0%). Revised sample size: 265. Mean age: 51 years. Females: 245 (92.5%). Symptomatic participants: not stated. AMA positive: 265 (100%). Responders: not stated. Median follow-up period (for all groups): 91 months. Inclusion criteria • Symptom status: symptomatic and asymptomatic participants. • AMA status: AMA-positive participants only. • Response status: not stated. Exclusion criteria • People with advanced biliary cirrhosis. • People with decompensated cirrhosis. • Aged < 19 years or > 69 years. • History of alcohol abuse. • Pregnant or unwilling to use contraception. • Use of immunosuppressive agents. • Renal or pulmonary dysfunction.
Interventions	Participants were randomly assigned to 2 groups. Group 1: UDCA (moderate) + methotrexate (n = 132). Further details: UDCA: 15 mg/kg/day for 2 years + methotrexate: 2.5 mg orally once a week. Group 2: UDCA (moderate) (n = 133). Further details: UDCA: 15 mg/kg/day for 2 years.
Outcomes	Mortality, liver transplantation, decompensated liver disease.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias)	Unclear risk	Comment: placebo used in this double-blind trial; however, the authors did not state whether the placebo was identical.

Combes 2005 *(Continued)*
All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: placebo used in this double-blind trial; however, the authors did not state whether the placebo was identical.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no post-randomisation dropouts.
Selective reporting (reporting bias)	High risk	Comment: adverse events not reported.
For-profit bias	High risk	Quote: "By provision of UDCA by Ciba-Geigy Corporation, and subsequently Novartis; by provision of methotrexate and its placebo by Lederle Laboratories, and subsequently Wyeth-Ayerst Laboratories".
Other bias	Low risk	Comment: no other source of bias.

Dickson 1985

Methods	Randomised clinical trial.
Participants	Country: USA. Number randomised: 309. Post-randomisation dropouts: 82 (26.5%). Revised sample size: 227. Mean age: not stated. Females: 200 (88.1%). Symptomatic participants: 182 (80.2%). AMA positive: not stated. Responders: not stated. Median follow-up period (for all groups): 60 months. Inclusion criteria • Symptom status: symptomatic and asymptomatic participants. • AMA status: not stated. • Response status: not stated. Exclusion criteria • People with severe hepatitis. • Evidence of inflammatory bowel disease. • Malignant condition other than skin cancer. • Evidence of prior or present extrahepatic obstruction. • Use of cholestatic or hepatotoxic drugs. • Excessive alcohol intake. • Presence of hepatitis B antigen.

Dickson 1985 *(Continued)*

Interventions	Participants were randomly assigned to 2 groups. Group 1: D-penicillamine (n = 111). Further details: D-penicillamine: 1000 mg/day; duration: not stated. Group 2: placebo (n = 116).
Outcomes	Adverse events.
Notes	Reasons for post-randomisation dropouts: histological stages < 3; alcoholism.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned to drug or placebo groups according to a table of random numbers".
Allocation concealment (selection bias)	Low risk	Quote: "Penicillamine and placebo (furnished to us through the courtesy of Merck Sharp and Dohme, West Point, Pa.) were dispensed in identical yellow capsules by a central pharmacist".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: identical placebo used in double-blind trial.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: identical placebo used in double-blind trial.
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation dropouts.
Selective reporting (reporting bias)	High risk	Comment: mortality not reported.
For-profit bias	High risk	Quote: "Penicillamine and placebo (furnished to us through the courtesy of Merck Sharp and Dohme, West Point, Pa.) were dispensed in identical yellow capsules by a central pharmacist".
Other bias	High risk	Comment: authors presented the results of only a subgroup of participants without explaining the reason for this.

Epstein 1979

Methods	Randomised clinical trial.
Participants	Country: UK. Number randomised: 98. Post-randomisation dropouts: not stated. Revised sample size: 98.

Epstein 1979 *(Continued)*

	Mean age: not stated. Females: not stated. Symptomatic participants: not stated. AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): mean: 66 months. Inclusion criteria • Symptom status: not stated. • AMA status: not stated. • Response status: not stated.
Interventions	Participants were randomly assigned to 2 groups. Group 1: D-penicillamine (n = 61). Further details: D-penicillamine: 600 mg/day to 900 mg/day for 12 months. Group 2: placebo (n = 37).
Outcomes	Mortality.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "The original double-blind design of the trial was discontinued after a year because both major and minor side effects identified treated patients".
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "The original double-blind design of the trial was discontinued after a year because both major and minor side effects identified treated patients".
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available.
Selective reporting (reporting bias)	High risk	Comment: adverse events not reported.
For-profit bias	Unclear risk	Comment: information not available.
Other bias	Low risk	Comment: no other source of bias.

Eriksson 1997

Methods	Randomised clinical trial.
Participants	Country: Sweden. Number randomised: 116. Post-randomisation dropouts: 15 (12.9%). Revised sample size: 101. Mean age: 57 years. Females: 99 (98%). Symptomatic participants: 39 (38.6%). AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): all participants followed up for 24 months. Inclusion criteria • Symptom status: symptomatic and asymptomatic participants. • AMA status: not stated. • Response status: not stated. Exclusion criteria • People with severe end-stage liver disease. • Pregnancy. • Alcohol or drug abuse.
Interventions	Participants were randomly assigned to 2 groups. Group 1: UDCA (low) (n = 60). Further details: UDCA: 500 mg/day for 24 months. Group 2: placebo (n = 56).
Outcomes	Liver transplantation.
Notes	Reasons for post-randomisation dropouts: adverse effects, alcoholic hepatitis, liver transplantation, death.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias)	Unclear risk	Comment: placebo used in this double-blind trial; however, the authors did not state whether the placebo was identical.

Eriksson 1997 *(Continued)*
All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: placebo used in this double-blind trial; however, the authors did not state whether the placebo was identical.
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation dropouts.
Selective reporting (reporting bias)	High risk	Comment: neither mortality nor adverse events reported.
For-profit bias	High risk	Quote: "We acknowledge the financial support from Meda AB, Searle AB, and the Swedish Medical Research Council (03x-4793)".
Other bias	Low risk	Comment: no other source of bias.

Ferri 1993

Methods	Randomised clinical trial.
Participants	Country: Italy. Number randomised: 30. Post-randomisation dropouts: 0 (0%). Revised sample size: 30. Mean age: 53 years. Females: 27 (90%). Symptomatic participants: not stated. AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): all participants followed up for 6 months. Inclusion criteria • Symptom status: not stated. • AMA status: not stated. • Response status: not stated. Exclusion criteria • People with decompensated cirrhosis. • Extrahepatic biliary obstruction. • Severe kidney or heart disease. • Neoplasms. • Pregnancy or breastfeeding. • Excessive alcohol consumption.
Interventions	Participants were randomly assigned to 2 groups.

Ferri 1993 *(Continued)*

	Group 1: TUDCA (moderate) (n = 15). Further details: TUDCA: 13 mg/day to 15 mg/day for 6 months. Group 2: UDCA (moderate) (n = 15). Further details: UDCA: 13 mg/day to 15 mg/day for 6 months.
Outcomes	Adverse events.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: adverse events, the only outcome of interest reported in this study were available from all randomised participants.
Selective reporting (reporting bias)	High risk	Comment: mortality not reported.
For-profit bias	Unclear risk	Comment: information not available.
Other bias	Low risk	Comment: no other source of bias.

Gao 2012

Methods	Randomised clinical trial.
Participants	Country: China. Number randomised: 79. Post-randomisation dropouts: not stated. Revised sample size: 79. Mean age: 53 years. Females: 77 (97.5%).

Gao 2012 *(Continued)*

	Symptomatic participants: not stated. AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): not stated. Inclusion criteria • Symptom status: not stated. • AMA status: not stated. • Response status: not stated. Other inclusion criteria • Only people with Sjogren's syndrome were included. Exclusion criteria • People with decompensated cirrhosis. • Aged > 70 years. • Other autoimmune diseases.
Interventions	Participants were randomly assigned to 3 groups. Group 1: UDCA (moderate) (n = 29). Further details: UDCA: 13 mg/kg/day to 15 mg/kg/day; duration: not stated. Group 2: UDCA (moderate) + glucocorticosteroids (n = 37). Further details: UDCA: 13 mg/kg/day to 15 mg/kg/day; duration: not stated + prednisolone: 7.5 mg/day; duration: not stated. Group 3: UDCA (moderate) + azathioprine (n = 13). Further details: UDCA: 13 mg/kg/day to 15 mg/kg/day; duration: not stated + azathioprine: 1 mg/kg/day; duration: not stated.
Outcomes	Adverse events, decompensated liver disease.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information not available.
Blinding of outcome assessment (detection bias)	Unclear risk	Comment: information not available.

Gao 2012 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available.
Selective reporting (reporting bias)	High risk	Comment: mortality not reported.
For-profit bias	Unclear risk	Comment: information not available.
Other bias	Low risk	Comment: no other source of bias.

Goddard 1994

Methods	Randomised clinical trial.
Participants	Country: UK. Number randomised: 57. Post-randomisation dropouts: not stated. Revised sample size: 57. Mean age: not stated. Females: not stated. Symptomatic participants: 30 (52.6%). AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): 15 months. Inclusion criteria • Symptom status: symptomatic and asymptomatic participants. • AMA status: not stated. • Response status: not stated.
Interventions	Participants were randomly assigned to 4 groups. Group 1: UDCA (low) (n = not stated). Further details: UDCA: 10 mg/kg/day; duration: not stated. Group 2: colchicine (n = not stated). Further details: colchicine: 1 mg/day; duration: not stated. Group 3: UDCA (low) + colchicine (n = not stated). Further details: UDCA: 10 mg/kg/day; duration: not stated + colchicine: 1 mg/day; duration: not stated. Group 4: placebo (n = not stated).
Outcomes	None of the outcomes of interest reported.

Goddard 1994 *(Continued)*

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: placebo used; however, the authors did not mention blinding.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: placebo used; however, the authors did not mention blinding.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available.
Selective reporting (reporting bias)	High risk	Comment: neither mortality nor adverse events reported.
For-profit bias	Unclear risk	Comment: information not available.
Other bias	Low risk	Comment: no other source of bias.

Gonzalezkoch 1997

Methods	Randomised clinical trial.
Participants	Country: Chile. Number randomised: 25. Post-randomisation dropouts: not stated. Revised sample size: 25. Mean age: 50 years. Females: 25 (100%). Symptomatic participants: not stated. AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): all participants followed up for 11 months. Inclusion criteria • Symptom status: not stated.

Gonzalezkoch 1997 *(Continued)*

- AMA status: not stated.
- Response status: not stated.

Exclusion criteria

- Other concomitant liver or biliary diseases.
- Decompensated cirrhosis.
- Presence of other serious diseases (e.g. diabetes mellitus, chronic renal insufficiency).
- Need to use additional medications.
- Pregnancy.
- Any pharmacological therapy during the previous 6 months.

Interventions	Participants were randomly assigned to 2 groups. Group 1: UDCA (low) + methotrexate (n = 13). Further details: UDCA: 250 mg BD for 48 weeks + methotrexate: 10 mg/week given over 48 hours each week for 48 months. Group 2: UDCA (low) (n = 12). Further details: UDCA: 250 mg BD for 48 weeks.
Outcomes	Mortality, adverse events.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Low risk	Quote: "A physician who was blinded to the treatment, followed them up clinically, evaluated clinical symptoms, adverse side effects, complications and compliance".
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: placebo used in this double-blind trial; however, the authors did not state whether the placebo was identical.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: placebo used in this double-blind trial; however, the authors did not state whether the placebo was identical.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available.
Selective reporting (reporting bias)	Low risk	Comment: mortality and morbidity reported.
For-profit bias	Unclear risk	Comment: information not available.
Other bias	Low risk	Comment: no other source of bias.

Heathcote 1976

Methods	Randomised clinical trial.
Participants	Country: UK. Number randomised: 45. Post-randomisation dropouts: 6 (13.3%). Revised sample size: 39. Mean age: 51 years. Females: not stated. Symptomatic participants: 39 (100%). AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): not stated. Inclusion criteria • Symptom status: symptomatic participants only. • AMA status: not stated. • Response status: not stated. Exclusion criteria • Established cirrhosis or liver failure. • Presence of oesophageal varices. • Recurrent suppurative infections. • Treatment with other immunosuppressants.
Interventions	Participants were randomly assigned to 2 groups. Group 1: azathioprine (n = 19). Further details: azathioprine: 2 mg/kg; frequency and duration: not stated. Group 2: control (n = 20).
Outcomes	Mortality, cirrhosis.
Notes	Reasons for post-randomisation dropouts: adverse events, wrong diagnosis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Quote: "Patients were randomly allocated to the treatment or control group, using the sealed envelope technique". Comment: further details of sealed envelope technique not available.

Heathcote 1976 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "No placebo was given to the control patients".
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "No placebo was given to the control patients".
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation dropouts.
Selective reporting (reporting bias)	High risk	Comment: adverse events not reported.
For-profit bias	Low risk	Quote: "This work was supported by the Medical Research Council and the Ingram Fund".
Other bias	Low risk	Comment: no other source of bias.

Heathcote 1994

Methods	Randomised clinical trial.
Participants	Country: Canada. Number randomised: 222. Post-randomisation dropouts: not stated. Revised sample size: 222. Mean age: 56 years. Females: 206 (92.8%). Symptomatic participants: not stated. AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): all participants followed up for 24 months. Inclusion criteria • Symptom status: symptomatic and asymptomatic participants. • AMA status: not stated. • Response status: not stated. Exclusion criteria • Aged < 18 years. • On transplant list. • Needed to take enzyme-inducing drugs. • Pregnant. • Other medical illnesses with anticipated life expectancy < 5 years.

Heathcote 1994 *(Continued)*

Interventions	Participants were randomly assigned to 2 groups. Group 1: UDCA (moderate) (n = 111). Further details: UDCA: 14 mg/kg/day for 2 years. Group 2: placebo (n = 111).
Outcomes	Mortality, liver transplantation.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was done separately at each centre by the study pharmacist using consecutive identification numbers, and patients were stratified according to whether they were symptomatic or asymptomatic".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Once informed consent was obtained from the patients, double-blind randomization to UDCA or an identical placebo (1 : 1) was conducted".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Once informed consent was obtained from the patients, double-blind randomization to UDCA or an identical placebo (1 : 1) was conducted".
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: unclear whether the authors have reported the outcomes on all randomised participants.
Selective reporting (reporting bias)	High risk	Comment: adverse events not reported.
For-profit bias	High risk	Quote: "Study medications kindly provided by Interfalk Canada and Jouveinal Inc., Quebec, Canada".
Other bias	Low risk	Comment: no other source of bias.

Hendrickse 1999

Methods	Randomised clinical trial.
Participants	Country: UK. Number randomised: 60. Post-randomisation dropouts: not stated. Revised sample size: 60. Mean age: 57 years.

Hendrickse 1999 *(Continued)*

	Females: 55 (91.7%). Symptomatic participants: 57 (95%). AMA positive: 51 (85%). Responders: not stated. Mean follow-up period (for all groups): minimum 68 months. Inclusion criteria • Symptom status: symptomatic and asymptomatic participants. • AMA status: AMA-positive and AMA-negative participants. • Response status: not stated. Exclusion criteria • Advanced liver disease. • Continuing or recent alcohol abuse. • Immunosuppressive drugs in the previous 6 months. • Contemplation of pregnancy. • Haematological abnormalities. • Other serious medical illness that might cause liver dysfunction or limit life expectancy.
Interventions	Participants were randomly assigned to 2 groups. Group 1: methotrexate (n = 30). Further details: methotrexate: 2.5 mg 3 times weekly for 6 years. Group 2: placebo (n = 30). Further details: placebo: 3 times weekly for 6 years.
Outcomes	Mortality, liver transplantation.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomized in groups of 10 by a random-number technique, operated by the hospital pharmacy, to receive 2.5 mg MTX [methotrexate] or identical placebo tablets, both supplied by Lederle Laboratories, on Friday, Saturday, and Sunday of each week for up to 6 years".
Allocation concealment (selection bias)	Low risk	Quote: "Patients were randomized in groups of 10 by a random-number technique, operated by the hospital pharmacy, to receive 2.5 mg MTX or identical placebo tablets, both supplied by Lederle Laboratories, on Friday, Saturday, and Sunday of each week for up to 6 years".
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: placebo used in this double-blind trial; however, the authors did not state whether the placebo was identical.
Blinding of outcome assessment (detection bias)	Unclear risk	Comment: placebo used in this double-blind trial; however, the authors did not state whether the placebo was identical.

Hendrickse 1999 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available.
Selective reporting (reporting bias)	High risk	Comment: neither mortality nor morbidity reported.
For-profit bias	Unclear risk	Comment: information not available.
Other bias	Low risk	Comment: no other source of bias.

Hirschfield 2015

Methods	Randomised clinical trial.
Participants	Country: multicentric; international. Number randomised: 165. Post-randomisation dropouts: 0 (0%). Revised sample size: 165. Mean age: 55 years. Females: 157 (95.2%). Symptomatic participants: not stated. AMA positive: 134 (81.2%). Responders: 0 (0%). Mean follow-up period (for all groups): all participants followed up for 3 months. Inclusion criteria • Symptom status: not stated. • AMA status: AMA-positive and AMA-negative participants. • Response status: non-responders only. Exclusion criteria • Advanced liver disease or decompensated liver disease. • Immunosuppressive drugs in the previous 3 months. • Other concomitant liver diseases.
Interventions	Participants were randomly assigned to 3 groups. Group 1: obeticholic acid (low) (n = 38). Further details: obeticholic acid (low): 10 mg for 85 days; frequency not stated. Group 2: obeticholic acid (moderate) (n = 48). Further details: obeticholic acid (moderate): 25 mg for 85 days; frequency not stated. Group 3: obeticholic acid (high) (n = 41).

Hirschfield 2015 *(Continued)*

	Further details: obeticholic acid (high): 50 mg for 85 days; frequency not stated. Group 4: placebo (n = 38).
Outcomes	Adverse events.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The computerized randomization schedule used a block size of 4 at each center".
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: identical placebo used in this double-blind trial.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: identical placebo used in this double-blind trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no post-randomisation dropouts.
Selective reporting (reporting bias)	High risk	Comment: mortality not reported.
For-profit bias	Unclear risk	Comment: information not available.
Other bias	High risk	Quote: "Patients received varying doses of UDCA".

Hoofnagle 1986

Methods	Randomised clinical trial.
Participants	Country: multicentric; international. Number randomised: 24. Post-randomisation dropouts: 0 (0%). Revised sample size: 24. Mean age: 47 years. Females: 23 (95.8%). Symptomatic participants: 24 (100%). AMA positive: 22 (91.7%).

Hoofnagle 1986 *(Continued)*

	Responders: not stated. Mean follow-up period (for all groups): 52 months. Inclusion criteria • Symptom status: symptomatic participants only. • AMA status: AMA-positive and AMA-negative participants. • Response status: not stated. Exclusion criteria • Advanced liver disease or decompensated liver disease.
Interventions	Participants were randomly assigned to 2 groups. Group 1: chlorambucil (n = 13). Further details: chlorambucil: 2 mg OD; duration: not stated. Group 2: control (n = 11).
Outcomes	Mortality, adverse events.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomized by random numbers (generated by pharmacy) to either chlorambucil or no therapy. Pre-computer age. They were kept in envelopes" (author's reply).
Allocation concealment (selection bias)	Low risk	Quote: "Patients were randomized by random numbers (generated by pharmacy) to either chlorambucil or no therapy. Pre-computer age. They were kept in envelopes" (author's reply).
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Not a blinded study" (author's reply).
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "The outcomes were not blinded" (author's reply).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no post-randomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: mortality and morbidity reported.
For-profit bias	Low risk	Quote: "The study was funded by the NIH intramural program" (author's reply).
Other bias	Low risk	Comment: no other source of bias.

Hosonuma 2015

Methods	Randomised clinical trial.
Participants	Country: Japan. Number randomised: 27. Post-randomisation dropouts: 0 (0%). Revised sample size: 27. Mean age: 64 years. Females: 22 (81.5%). Symptomatic participants: not stated. AMA positive: not stated. Responders: 0 (0%). Mean follow-up period (for all groups): minimum: 96 months. Inclusion criteria • Symptom status: not stated. • AMA status: not stated. • Response status: non-responders only. Other inclusion criteria • People with dyslipidaemia. Exclusion criteria • Other liver diseases, e.g. alcoholic liver disease. • Obstructive biliary disease.
Interventions	Participants were randomly assigned to 2 groups. Group 1: UDCA (moderate) + bezafibrate (n = 13). Further details: UDCA: 12 mg/kg/day to 15 mg/kg/day; duration: not stated + bezafibrate: 400 mg/day; duration: not stated. Group 2: UDCA (moderate) (n = 14). Further details: UDCA: 12 mg/kg/day to 15 mg/kg/day; duration: not stated.
Outcomes	Mortality, adverse events, liver transplantation.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Sealed opaque envelopes" (author's reply).
Allocation concealment (selection bias)	Low risk	Quote: "These patients were randomly allocated to treatment with either UDCA alone (the UDCA group) or with the combination therapy (the UDCA+BF

Hosonuma 2015 *(Continued)*

		[bezafibrate] group), according to sequential sealed envelopes in blocks of four to ensure equal randomization for the duration of the study".
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "However, our study was an unblinded, open trial and was therefore not free from bias".
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "However, our study was an unblinded, open trial and was therefore not free from bias".
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no post-randomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: mortality and adverse events reported.
For-profit bias	Low risk	Quote: "This study was supported by the authors' own research funds".
Other bias	Low risk	Comment: no other source of bias.

Ikeda 1996

Methods	Randomised clinical trial.
Participants	Country: Japan. Number randomised: 22. Post-randomisation dropouts: 0 (0%). Revised sample size: 22. Mean age: 61 years. Females: 19 (86.4%). Symptomatic participants: 7 (31.8%). AMA positive: 22 (100%). Responders: not stated. Mean follow-up period (for all groups): all participants followed up for 24 months. Inclusion criteria • Symptom status: symptomatic and asymptomatic participants. • AMA status: AMA-positive participants only. • Response status: not stated. Exclusion criteria • Other liver diseases. • No immunosuppressants or hepatotoxic drugs in the previous 6 months. • Alcohol or drug abuse.

Ikeda 1996 *(Continued)*

Interventions	Participants were randomly assigned to 2 groups. Group 1: UDCA (moderate) + colchicine (n = 10). Further details: UDCA: 9 mg/kg/day to 15 mg/kg/day for 2 years + colchicine: 1 mg/day for 2 years. Group 2: UDCA (moderate) (n = 12). Further details: UDCA: 9 mg/kg/day to 15 mg/kg/day for 2 years.
Outcomes	Adverse events.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no post-randomisation dropouts.
Selective reporting (reporting bias)	High risk	Comment: mortality not reported.
For-profit bias	Unclear risk	Quote: "Part of the present study was supported by a grant from the Intractable Liver Diseases Research Committee, the Ministry of Health and Welfare, Japan". Comment: unclear how the remaining part of the funds were obtained.
Other bias	High risk	Comment: dose range for UDCA was very wide.

Iwasaki 2008a

Methods	Randomised clinical trial.
Participants	Country: Japan. Number randomised: 45. Post-randomisation dropouts: not stated.

Iwasaki 2008a *(Continued)*

	Revised sample size: 45. Mean age: 56 years. Females: 37 (82.2%). Symptomatic participants: not stated. AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): all participants followed up for 12 months. Inclusion criteria • Symptom status: not stated. • AMA status: not stated. • Response status: not stated. Exclusion criteria • Cirrhosis. • Advanced liver disease or decompensated cirrhosis. • Renal insufficiency. • Malignancy. • Pregnancy. • Aged < 19 years.
Interventions	Participants were randomly assigned to 2 groups. Group 1: bezafibrate (n = 20). Further details: bezafibrate: 400 mg/day for 52 weeks. Group 2: UDCA (low) (n = 25). Further details: UDCA: 600 mg/day for 52 weeks.
Outcomes	None of the outcomes of interest reported.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Low risk	Quote: "Consecutive patients from these hospitals were randomized centrally at the Kanagawa Dental University and were enrolled into the study if they met the following criteria".
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "A randomized, open study design was used because there was no suitable placebo for bezafibrate available".
Blinding of outcome assessment (detection bias)	High risk	Quote: "A randomized, open study design was used because there was no suitable placebo for bezafibrate available".

Iwasaki 2008a *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available.
Selective reporting (reporting bias)	High risk	Comment: neither mortality nor adverse events reported.
For-profit bias	Low risk	Quote: "The Ministry of Health, Labour and Welfare of Japan supported this study from 2002 to 2004 with a Health Science Research Grant on a Specific Disease (Study of Intractable Liver Diseases) to chief scientist Gotaro Toda".
Other bias	Low risk	Comment: no other bias.

Iwasaki 2008b

Methods	Randomised clinical trial.
Participants	Country: Japan. Number randomised: 22. Post-randomisation dropouts: not stated. Revised sample size: 22. Mean age: 54 years. Females: 19 (86.4%). Symptomatic participants: not stated. AMA positive: not stated. Responders: 0 (0%). Mean follow-up period (for all groups): all participants followed up for 12 months. Inclusion criteria • Symptom status: not stated. • AMA status: not stated. • Response status: non-responders only. Exclusion criteria • Cirrhosis. • Advanced liver disease or decompensated cirrhosis. • Renal insufficiency. • Malignancy. • Pregnancy. • Aged < 19 years.
Interventions	Participants were randomly assigned to 2 groups. Group 1: UDCA (low) + bezafibrate (n = 10). Further details: UDCA: 600 mg/day for 52 weeks + bezafibrate: 400 mg/day for 52 weeks.

Iwasaki 2008b *(Continued)*

	Group 2: UDCA (low) (n = 12). Further details: UDCA: 600 mg/day for 52 weeks.
Outcomes	None of the outcomes of interest reported.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Low risk	Quote: "Consecutive patients from these hospitals were randomized centrally at the Kanagawa Dental University and were enrolled into the study if they met the following criteria".
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "A randomized, open study design was used because there was no suitable placebo for bezafibrate available".
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "A randomized, open study design was used because there was no suitable placebo for bezafibrate available".
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available.
Selective reporting (reporting bias)	High risk	Comment: neither mortality nor adverse events reported.
For-profit bias	Low risk	Quote: "The Ministry of Health, Labour and Welfare of Japan supported this study from 2002 to 2004 with a Health Science Research Grant on a Specific Disease (Study of Intractable Liver Diseases) to chief scientist Gotaro Toda".
Other bias	Low risk	Comment: no other bias.

Kanda 2003

Methods	Randomised clinical trial.
Participants	Country: Japan. Number randomised: 22. Post-randomisation dropouts: 0 (0%). Revised sample size: 22. Mean age: 56 years. Females: 19 (86.4%). Symptomatic participants: not stated.

Kanda 2003 *(Continued)*

	AMA positive: not stated. Responders: 0 (0%). Mean follow-up period (for all groups): minimum 7 months. Inclusion criteria • Symptom status: not stated. • AMA status: not stated. • Response status: non-responders only. Other inclusion criteria • Treatment with UDCA for ≥ 6 months prior the study. • Prior compliance with UDCA therapy. Exclusion criteria • Other chronic liver diseases or decompensated liver disease. • Previous colchicine, corticosteroid, or immunosuppressive treatment. • Thyroid or renal dysfunction.
Interventions	Participants were randomly assigned to 2 groups. Group 1: UDCA (low) + bezafibrate (n = 11). Further details: UDCA: 600 mg/day for 6 months + bezafibrate: 400 mg/day for 52 weeks. Group 2: UDCA (low) (n = 11). Further details: UDCA: 600 mg/day for 6 months.
Outcomes	Adverse events.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no post-randomisation dropouts.

Kanda 2003 *(Continued)*

Selective reporting (reporting bias)	High risk	Comment: mortality was not reported.
For-profit bias	Unclear risk	Comment: information not available.
Other bias	Low risk	Comment: no other bias.

Kaplan 1986

Methods	Randomised clinical trial.
Participants	Country: USA. Number randomised: 60. Post-randomisation dropouts: 3 (5%). Revised sample size: 57. Mean age: not stated. Females: 57 (100%). Symptomatic participants: 45 (78.9%). AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): all participants followed up for 24 months. Inclusion criteria • Symptom status: symptomatic and asymptomatic participants. • AMA status: AMA-positive and AMA-negative participants. • Response status: not stated. Exclusion criteria • Concomitant debilitating cardiovascular illness. • End-stage cirrhosis.
Interventions	Participants were randomly assigned to 2 groups. Group 1: colchicine (n = 28). Further details: colchicine: 0.6 mg BD for ≥ 2 years. Group 2: placebo (n = 29).
Outcomes	Mortality.
Notes	Reasons for post-randomisation dropouts: adverse effects, despondent about treatment.

Risk of bias

Bias	Authors' judgement	Support for judgement

Kaplan 1986 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: authors stated that this was a double-blind trial and used a placebo; however, they did not state whether the placebo was identical.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: authors stated that this was a double-blind trial and used a placebo; however, they did not state whether the placebo was identical.
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation dropouts.
Selective reporting (reporting bias)	High risk	Comment: adverse events not reported.
For-profit bias	Unclear risk	Comment: information not available.
Other bias	Low risk	Comment: no other bias.

Kaplan 1999

Methods	Randomised clinical trial.
Participants	Country: USA. Number randomised: 87. Post-randomisation dropouts: 2 (2.3%). Revised sample size: 85. Mean age: 51 years. Females: 82 (96.5%). Symptomatic participants: 71 (83.5%). AMA positive: 77 (90.6%). Responders: not stated. Mean follow-up period (for all groups): minimum 24 months. Inclusion criteria • Symptom status: symptomatic and asymptomatic participants. • AMA status: AMA-positive and AMA-negative participants. • Response status: not stated. Exclusion criteria • End-stage liver failure.

Kaplan 1999 *(Continued)*

- History of alcohol abuse.
- Administration of drugs associated with chronic liver disease.
- Contemplation of pregnancy.
- Other serious medical illnesses such as renal or heart disease that may cause liver dysfunction or shorten life expectancy.
- Hypersplenism.

Interventions	Participants were randomly assigned to 2 groups. Group 1: colchicine (n = 43). Further details: colchicine: 0.6 mg BD for 2 years. Group 2: methotrexate (n = 42). Further details: methotrexate: 15 mg/week orally.
Outcomes	None of the outcomes of interest reported.
Notes	Reasons for post-randomisation dropouts: withdrawal from study.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Both the patients and investigators were blinded to the treatment assignments".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Both the patients and investigators were blinded to the treatment assignments". Comment: authors stated that this was a double-blind trial and used a placebo; however, they did not state whether the placebo was identical.
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation dropouts.
Selective reporting (reporting bias)	High risk	Comment: neither mortality nor adverse events reported.
For-profit bias	Unclear risk	Comment: information not available.
Other bias	Low risk	Comment: no other bias.

Kowdley 2011

Methods	Randomised clinical trial.

Kowdley 2011 *(Continued)*

Participants	Country: multicentric; international. Number randomised: 59. Post-randomisation dropouts: not stated. Revised sample size: 59. Mean age: 55 years. Females: 50 (84.7%). Symptomatic participants: not stated. AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): not stated. Inclusion criteria • Symptom status: not stated. • AMA status: not stated. • Response status: not stated.
Interventions	Participants were randomly assigned to 3 groups. Group 1: obeticholic acid (low) (n = 20). Further details: obeticholic acid (low): 10 mg OD for 12 weeks. Group 2: obeticholic acid (high) (n = 16). Further details: obeticholic acid (high): 50 mg OD for 12 weeks. Group 3: placebo (n = 23).
Outcomes	None of the outcomes of interest reported.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: although this was a double-blind trial and placebo was used, unclear whether the placebo was identical.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: although this was a double-blind trial and placebo was used, unclear whether the placebo was identical.

Kowdley 2011 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available.
Selective reporting (reporting bias)	High risk	Comment: neither mortality nor adverse events reported.
For-profit bias	High risk	Comment: some of the coauthors were from the pharmaceutical industry.
Other bias	Low risk	Comment: no other source of bias.

Kurihara 2000

Methods	Randomised clinical trial.
Participants	Country: Japan. Number randomised: 24. Post-randomisation dropouts: not stated. Revised sample size: 24. Mean age: 60 years. Females: 23 (95.8%). Symptomatic participants: not stated. AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): not stated. Inclusion criteria • Symptom status: not stated. • AMA status: not stated. • Response status: not stated. Exclusion criteria • Cirrhosis. • Advanced liver disease or decompensated cirrhosis. • Renal insufficiency. • Malignancy. • Pregnancy. • Aged < 19 years of age.
Interventions	Participants were randomly assigned to 2 groups. Group 1: bezafibrate (n = 12). Further details: bezafibrate: 400 mg/day for 1 year. Group 2: UDCA (low) (n = 12). Further details: UDCA: 600 mg/day for 1 year.

Kurihara 2000 *(Continued)*

Outcomes	Adverse events.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available.
Selective reporting (reporting bias)	High risk	Comment: mortality not reported.
For-profit bias	Unclear risk	Comment: information not available.
Other bias	Low risk	Comment: no other bias.

Leuschner 1989

Methods	Randomised clinical trial.
Participants	Country: Germany. Number randomised: 20. Post-randomisation dropouts: 2 (10%). Revised sample size: 18. Mean age: not stated. Females: 18 (100%). Symptomatic participants: not stated. AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): all participants followed up for 12 months.

Leuschner 1989 *(Continued)*

	Inclusion criteria • Symptom status: not stated. • AMA status: not stated. • Response status: not stated. Exclusion criteria • Decompensated liver cirrhosis. • Chronic pancreatitis. • Taking immunosuppressive drugs, glucocorticosteroids, or sex hormones. • Taking other drugs for treatment of liver diseases or known to cause hepatotoxicity.
Interventions	Participants were randomly assigned to 2 groups. Group 1: UDCA (low) (n = 10). Further details: UDCA: 10 mg/kg/day for 9 months. Group 2: placebo (n = 8).
Outcomes	Mortality, adverse events.
Notes	Reasons for post-randomisation dropouts: not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: although placebo was used in this double-blind trial, unclear whether identical placebo used.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: although placebo was used in this double-blind trial, unclear whether identical placebo used.
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: mortality and morbidity reported.
For-profit bias	Unclear risk	Comment: information not available.
Other bias	Low risk	Comment: no other source of bias.

Leuschner 1999

Methods	Randomised clinical trial.
Participants	Country: Germany. Number randomised: 40. Post-randomisation dropouts: 1 (2.5%). Revised sample size: 39. Mean age: 58 years. Females: 37 (94.9%). Symptomatic participants: not stated. AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): all participants followed up for 24 months. Inclusion criteria • Symptom status: not stated. • AMA status: not stated. • Response status: not stated. Exclusion criteria • Decompensated liver cirrhosis. • Diabetes mellitus. • Glaucoma. • Previous history of duodenal or gastric ulcer. • Pregnancy. • Hypertension.
Interventions	Participants were randomly assigned to 2 groups. Group 1: UDCA (moderate) + corticosteroids (n = 20). Further details: UDCA: 10 mg/kg/day to 15 mg/kg/day for 2 years + budesonide: 3 mg 3 times daily for 2 years. Group 2: UDCA (moderate) (n = 19).
Outcomes	None of the outcomes of interest reported.
Notes	Reasons for post-randomisation dropouts: personal reasons.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Complete randomization was done according to Rancode + (version 3.1; IDV-Co., Marsaglia and Bray, Gauting, Germany)".
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.

Leuschner 1999 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: although placebo was used in this double-blind trial, unclear whether identical placebo used.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: although placebo was used in this double-blind trial, unclear whether identical placebo used.
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation dropouts.
Selective reporting (reporting bias)	High risk	Comment: neither mortality nor adverse events reported.
For-profit bias	High risk	Quote: "UDCA, budesonide, and placebo were provided by Dr. Falk Pharma GmbH (Freiburg, Germany)".
Other bias	Low risk	Comment: no other source of bias.

Liberopoulos 2010

Methods	Randomised clinical trial.
Participants	Country: Greece. Number randomised: 10. Post-randomisation dropouts: not stated. Revised sample size: 10. Mean age: 57 years. Females: 8 (80%). Symptomatic participants: not stated. AMA positive: not stated. Responders: 0 (0%). Mean follow-up period (for all groups): not stated. Inclusion criteria • Symptom status: not stated. • AMA status: not stated. • Response status: non-responders only. Exclusion criteria • Cardiovascular disease. • Diabetes mellitus. • Cancer. • Renal disease. • Hypothyroidism.

Liberopoulos 2010 *(Continued)*

- Recent lipid-lowering agent use.
- Agents that affect lipid metabolism.

Interventions	Participants were randomly assigned to 2 groups. Group 1: UDCA (low) + fenofibrate (n = 6). Further details: UDCA: 600 mg/day for 8 weeks + fenofibrate: 200 mg/day for 8 weeks. Group 2: UDCA (low) (n = 4). Further details: UDCA: 600 mg/day for 8 weeks.
Outcomes	None of the outcomes of interest reported.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Continue open-label UDCA".
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "Continue open-label UDCA".
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available.
Selective reporting (reporting bias)	High risk	Comment: neither mortality nor adverse events reported.
For-profit bias	Unclear risk	Quote: "This study was conducted independently; no company or institution supported it financially. Some of the authors have given talks, attended conferences and participated in trials and advisory boards sponsored by various pharmaceutical companies". Comment: unclear whether the authors were in the advisory board of related pharmaceutical companies.
Other bias	Low risk	Comment: no other source of bias.

Lim 1994

Methods	Randomised clinical trial.
Participants	Country: UK.

Lim 1994 *(Continued)*

	Number randomised: 32. Post-randomisation dropouts: not stated. Revised sample size: 32. Mean age: not stated. Females: not stated. Symptomatic participants: not stated. AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): not stated. Inclusion criteria • Symptom status: not stated. • AMA status: not stated. • Response status: not stated.
Interventions	Participants were randomly assigned to 2 groups. Group 1: UDCA (moderate) (n = not stated). Further details: UDCA: 10 mg/kg/day to 12 mg/kg/day; duration: not stated. Group 2: placebo (n = not stated).
Outcomes	None of the outcomes of interest reported.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: although a placebo was used in this double-blind trial, unclear whether the placebo was identical.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: although a placebo was used in this double-blind trial, unclear whether the placebo was identical.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available.
Selective reporting (reporting bias)	High risk	Comment: neither mortality nor adverse events reported.

Lim 1994 *(Continued)*

For-profit bias	Unclear risk	Comment: information not available.
Other bias	Low risk	Comment: no other source of bias.

Lindor 1994

Methods	Randomised clinical trial.
Participants	Country: USA. Number randomised: 180. Post-randomisation dropouts: 10 (5.6%). Revised sample size: 170. Mean age: 53 years. Females: 160 (94.1%). Symptomatic participants: not stated. AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): all participants followed up for 24 months. Inclusion criteria • Symptom status: symptomatic and asymptomatic participants. • AMA status: not stated. • Response status: not stated. Exclusion criteria • People with decompensated cirrhosis. • Hepatocellular carcinoma. • Concomitant immunosuppressive regimen. • Other major diseases unrelated to primary biliary cholangitis. • Alcohol abuse. • Low compliance. • Recurrent variceal haemorrhage, intractable ascites, spontaneous encephalopathy.
Interventions	Participants were randomly assigned to 2 groups. Group 1: UDCA (moderate) (n = 86). Further details: UDCA: 13 mg/kg/day to 15 mg/kg/day; duration: not stated. Group 2: placebo (n = 84).
Outcomes	Mortality, adverse events, liver transplantation.
Notes	Reasons for post-randomisation dropouts: not stated.
Risk of bias	

Lindor 1994 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The patients, physicians, nurses, and study coordinators were blinded as to whether active drug or placebo was being administered".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The patients, physicians, nurses, and study coordinators were blinded as to whether active drug or placebo was being administered".
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: mortality and morbidity reported.
For-profit bias	High risk	Quote: "Supported by Falk Pharma and Interfalk".
Other bias	Low risk	Comment: no other risk of bias.

Lindor 1997

Methods	Randomised clinical trial.
Participants	Country: USA. Number randomised: 150. Post-randomisation dropouts: not stated. Revised sample size: 150. Mean age: not stated. Females: not stated. Symptomatic participants: not stated. AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): all participants followed up for 12 months. Inclusion criteria • Symptom status: not stated. • AMA status: AMA positive participants only. • Response status: not stated.

Lindor 1997 *(Continued)*

Interventions	Participants were randomly assigned to 3 groups. Group 1: UDCA (low) (n = not stated). Further details: UDCA: 5 mg/kg/day to 7 mg/kg/day; duration: not stated. Group 2: UDCA (moderate) (n = not stated). Further details: UDCA: 13 mg/kg/day to 15 mg/kg/day; duration: not stated. Group 3: UDCA (high) (n = not stated). Further details: UDCA: 22 mg/kg/day to 25 mg/kg/day; duration: not stated.
Outcomes	None of the outcomes of interest reported.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available.
Selective reporting (reporting bias)	High risk	Comment: neither mortality nor adverse events reported.
For-profit bias	Unclear risk	Comment: information not available.
Other bias	Low risk	Comment: no other risk of bias.

Lombard 1993

Methods	Randomised clinical trial.
Participants	Country: multicentric; international. Number randomised: 349. Post-randomisation dropouts: 0 (0%).

Lombard 1993 *(Continued)*

	Revised sample size: 349. Mean age: 54 years. Females: 298 (85.4%). Symptomatic participants: not stated. AMA positive: not stated. Responders: not stated. Median follow-up period (for all groups): 31 months. Inclusion criteria • Symptom status: not stated. • AMA status: AMA-positive and AMA-negative participants. • Response status: not stated. Exclusion criteria • Significant renal impairment. • Serious non-hepatic or malignant disease limiting life expectancy. • Inability to attend for regular follow-up. • Consideration for a liver transplant.
Interventions	Participants were randomly assigned to 2 groups. Group 1: ciclosporin (n = 176). Further details: ciclosporin: 3 mg/kg/day to maintain levels at 150 ng/mL by polyclonal radioimmunoassay or 75 ng/mL by monoclonal radioimmunoassay. Group 2: placebo (n = 173).
Outcomes	Mortality, adverse events, liver transplantation.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Quote: "Sealed envelopes" (author's reply).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: identical placebo used in this double-blind trial.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: identical placebo used in this double-blind trial.
Incomplete outcome data (attrition bias)	Low risk	Comment: no post-randomisation dropouts.

Lombard 1993 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Low risk	Comment: mortality and morbidity reported.
For-profit bias	High risk	Quote: "The authors are grateful to Sandoz Pharmaceuticals, Basle, Switzerland and their international sub-offices for supplying Sandimmune and placebo for this study and for their support throughout. The authors are grateful to Sandoz Pharmaceuticals, Basle, Zerland and their international sub-offices for supplying Sandimmune and placebo for this study and for their support throughout".
Other bias	Low risk	Comment: no other source of bias.

Ma 2016

Methods	Randomised clinical trial.
Participants	Country: China. Number randomised: 199. Post-randomisation dropouts: 8 (4.0%). Revised sample size: 191. Mean age: 51 years. Females: 167 (83.9%). Symptomatic participants: 38 (19.9%). AMA positive: 187 (97.9%). Responders: not stated. Mean follow-up period (for all groups): all participants: 6 months. Inclusion criteria • Symptom status: symptomatic and asymptomatic participants. • AMA status: AMA-positive and AMA-negative participants. • Response status: not stated. Exclusion criteria • Advanced or decompensated liver disease. • Pregnancy or breastfeeding. • Other causes of liver diseases. • Serious comorbidities.
Interventions	Participants were randomly assigned to 2 groups. Group 1: UDCA (moderate) (n = 66). Further details: UDCA: 250 mg 3 times daily for 24 weeks. Group 2: TUDCA (moderate) (n = 125). Further details: TUDCA: 250 mg 3 times daily for 24 weeks.

Ma 2016 *(Continued)*

Outcomes	Adverse events.
Notes	Reason for drop-outs: not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A centralized telecommunication-based interactive voice response system was used for patient randomization after patient eligibility was determined through clinical and laboratory screening assessments".
Allocation concealment (selection bias)	Low risk	Quote: "A centralized telecommunication-based interactive voice response system was used for patient randomization after patient eligibility was determined through clinical and laboratory screening assessments".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: identical placebo used in this double-blind trial.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: identical placebo used in this double-blind trial.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: unclear whether all participants were included in the analysis.
Selective reporting (reporting bias)	High risk	Comment: mortality not reported.
For-profit bias	High risk	Quote: "This study was sponsored by the Beijing Trendful Kangjian Medical Information Consulting Co., Ltd. and the Major Science and Technology Special Project of China Twelfth Five-year Plan (2012ZX10002003). Registration Number: NCT01829698".
Other bias	Low risk	Comment: no other source of bias.

Macklon 1982

Methods	Randomised clinical trial.
Participants	Country: UK. Number randomised: 60. Post-randomisation dropouts: 0 (0%). Revised sample size: 60. Mean age: not stated. Females: not stated. Symptomatic participants: not stated. AMA positive: not stated.

Macklon 1982 *(Continued)*

	Responders: not stated. Mean follow-up period (for all groups): 37 months. Inclusion criteria • Symptom status: not stated. • AMA status: not stated. • Response status: not stated.
Interventions	Participants were randomly assigned to 2 groups. Group 1: D-penicillamine (n = 41). Further details: D-penicillamine: 250 mg/day or 1 g/day; duration: not stated. Group 2: placebo (n = 19).
Outcomes	Mortality, adverse events.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: although placebo was used, there is no mention of blinding.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: although placebo was used, there is no mention of blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no post-randomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: mortality and morbidity reported.
For-profit bias	Unclear risk	Comment: information not available.
Other bias	Low risk	Comment: no other bias.

Manzillo 1993a

Methods	Randomised clinical trial.
Participants	Country: Italy.

Manzillo 1993a *(Continued)*

	Number randomised: 32. Post-randomisation dropouts: not stated. Revised sample size: 32. Mean age: not stated. Females: not stated. Symptomatic participants: not stated. AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): all participants followed up for 1 month. Inclusion criteria • Symptom status: not stated. • AMA status: not stated. • Response status: not stated.
Interventions	Participants were randomly assigned to 2 groups. Group 1: SAMe (n = 16). Further details: SAMe: 800 mg/day IV for 2 weeks. Group 2: placebo (n = 16).
Outcomes	None of the outcomes of interest reported.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: although placebo was used, there was no mention of blinding.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: although placebo was used, there was no mention of blinding.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available.
Selective reporting (reporting bias)	High risk	Comment: neither mortality nor adverse events reported.

Manzillo 1993a *(Continued)*

For-profit bias	Unclear risk	Comment: information not available.
Other bias	Low risk	Comment: no other bias.

Manzillo 1993b

Methods	Randomised clinical trial.
Participants	Country: Italy. Number randomised: 6. Post-randomisation dropouts: not stated. Revised sample size: 6. Mean age: not stated. Females: not stated. Symptomatic participants: not stated. AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): all participants followed up for 2 months. Inclusion criteria • Symptom status: not stated. • AMA status: not stated. • Response status: not stated.
Interventions	Participants were randomly assigned to 2 groups. Group 1: SAMe (n = 3). Further details: SAMe: 1600 mg/day orally for 8 weeks. Group 2: placebo (n = 3).
Outcomes	None of the outcomes of interest reported.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias)	Unclear risk	Comment: although placebo was used, there was no mention of blinding.

Manzillo 1993b *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: although placebo was used, there was no mention of blinding.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available.
Selective reporting (reporting bias)	High risk	Comment: neither mortality nor adverse events reported.
For-profit bias	Unclear risk	Comment: information not available.
Other bias	Low risk	Comment: no other bias.

Mason 2008

Methods	Randomised clinical trial.
Participants	Country: multicentric; international. Number randomised: 59. Post-randomisation dropouts: 0 (0%). Revised sample size: 59. Mean age: 56 years. Females: 58 (98.3%). Symptomatic participants: not stated. AMA positive: 59 (100%). Responders: 0 (0%). Mean follow-up period (for all groups): all participants followed up for 6 months. Inclusion criteria • Symptom status: not stated. • AMA status: AMA-positive participants only. • Response status: non-responders only. Other exclusion criteria • Advanced or decompensated liver disease. • Use of immunosuppressants or anti-inflammatory drugs in previous 3 months. • Significant renal impairment. • Excessive alcohol consumption. • Pregnant, breastfeeding, or not using contraceptives in sexually active women of child-bearing age.
Interventions	Participants were randomly assigned to 2 groups. Group 1: lamivudine + zidovudine + UDCA (moderate) (n = 30).

Mason 2008 *(Continued)*

	Further details: lamivudine: 150 mg BD for 6 months + zidovudine: 300 mg BD for 6 months + UDCA: 13 mg/kg/day to 15 mg/kg/day for 6 months. Group 2: UDCA (moderate) (n = 29). Further details: UDCA: 13 mg/kg/day to 15 mg/kg/day for 6 months.
Outcomes	Adverse events.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was performed centrally at the University of Alberta by a dynamic randomization" (author's reply).
Allocation concealment (selection bias)	Low risk	Quote: "Sealed opaque envelopes" (author's reply).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Dilan Clinical Packaging Ltd (Mississauga, ON, Canada) coded samples ensuring that the investigators and patients were blinded to the treatment".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Dilan Clinical Packaging Ltd (Mississauga, ON, Canada) coded samples ensuring that the investigators and patients were blinded to the treatment".
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available.
Selective reporting (reporting bias)	High risk	Comment: mortality not reported.
For-profit bias	High risk	Quote: "This study was funded in full by GlaxoSmithKline and Axcan Pharma".
Other bias	Low risk	Comment: no other bias.

Matloff 1982

Methods	Randomised clinical trial.
Participants	Country: USA. Number randomised: 52. Post-randomisation dropouts: 0 (0%). Revised sample size: 52. Mean age: 52 years. Females: 48 (92.3%). Symptomatic participants: not stated.

Matloff 1982 *(Continued)*

	AMA positive: 42 (80.8%). Responders: not stated. Mean follow-up period (for all groups): minimum 24 months. Inclusion criteria • Symptom status: not stated. • AMA status: AMA-positive and AMA-negative participants. • Response status: not stated.
Interventions	Participants were randomly assigned to 2 groups. Group 1: D-penicillamine (n = 26). Further details: D-penicillamine: 1 g/day; duration: not stated. Group 2: placebo (n = 26).
Outcomes	Mortality, adverse events.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: although placebo was used in this double-blind trial, there was no mention about identical placebo.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: although placebo was used in this double-blind trial, there was no mention about identical placebo.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no post-randomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: mortality and morbidity reported.
For-profit bias	High risk	Quote: "We are indebted to Merck, Sharp and Dohme Research Laboratories for providing the D-penicillamine and placebo tablets".
Other bias	Low risk	Comment: no other bias.

Mayo 2015

Methods	Randomised clinical trial.
Participants	Country: multicentric; international. Number randomised: 45. Post-randomisation dropouts: 3 (6.7%). Revised sample size: 42. Mean age: 56 years. Females: 38 (90.5%). Symptomatic participants: not stated. AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): not stated. Inclusion criteria • Symptom status: not stated. • AMA status: not stated. • Response status: not stated.
Interventions	Participants were randomly assigned to 2 groups. Group 1: NGM282 (n = 27). Further details: NGM282: 0.3 mg/day or 3 mg/day SC for 28 days. Group 2: placebo (n = 15).
Outcomes	None of the outcomes of interest reported.
Notes	Reasons for post-randomisation dropouts: not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: although placebo was used in this double-blind trial, unclear whether the placebo was identical.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: although placebo was used in this double-blind trial, unclear whether the placebo was identical.
Incomplete outcome data (attrition bias)	High risk	Comment: there were post-randomisation dropouts.

Mayo 2015 *(Continued)*
All outcomes

Selective reporting (reporting bias)	High risk	Comment: neither mortality nor adverse events reported.
For-profit bias	High risk	Quote: "Grant/Research Support: Intercept, Salix, NGM, Lumena, Gilead".
Other bias	Low risk	Comment: no other bias.

Mazzarella 2002

Methods	Randomised clinical trial.
Participants	Country: Italy. Number randomised: 42. Post-randomisation dropouts: not stated. Revised sample size: 42. Mean age: not stated. Females: 37 (88.1%). Symptomatic participants: not stated. AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): all participants followed up for 72 months. Inclusion criteria • Symptom status: not stated. • AMA status: not stated. • Response status: not stated.
Interventions	Participants were randomly assigned to 2 groups. Group 1: UDCA (high) (n = 21). Further details: UDCA (high): 30 mg/kg/day for 6 years. Group 2: UDCA (moderate) (n = 21). Further details: UDCA (moderate): 10.5 mg/kg/day for 6 years.
Outcomes	None of the outcomes of interest reported.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.

Mazzarella 2002 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available.
Selective reporting (reporting bias)	High risk	Comment: neither mortality nor adverse events reported.
For-profit bias	Unclear risk	Comment: information not available.
Other bias	Low risk	Comment: no other bias.

McCormick 1994

Methods	Randomised clinical trial.
Participants	Country: UK. Number randomised: 18. Post-randomisation dropouts: 0 (0%). Revised sample size: 18. Mean age: 60 years. Females: 14 (77.8%). Symptomatic participants: not stated. AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): not stated. Inclusion criteria • Symptom status: not stated. • AMA status: not stated. • Response status: not stated. Exclusion criteria • Premenopausal or unsterilised women.
Interventions	Participants were randomly assigned to 2 groups.

McCormick 1994 *(Continued)*

	Group 1: thalidomide (n = 10). Further details: thalidomide: 100 mg/day for 6 months. Group 2: placebo (n = 8).
Outcomes	None of the outcomes of interest reported.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: identical placebo used in double-blind trial.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: identical placebo used in double-blind trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no post-randomisation dropouts.
Selective reporting (reporting bias)	High risk	Comment: neither mortality nor adverse events reported.
For-profit bias	High risk	Quote: "Thalidomide and identical placebo tablets were supplied by Penn Pharmaceuticals Ltd".
Other bias	Low risk	Comment: no other bias.

Minuk 1988

Methods	Randomised clinical trial.
Participants	Country: Canada. Number randomised: 12. Post-randomisation dropouts: 0 (0%). Revised sample size: 12. Mean age: 55 years. Females: 11 (91.7%). Symptomatic participants: not stated.

Minuk 1988 *(Continued)*

	AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): not stated. Inclusion criteria • Symptom status: not stated. • AMA status: not stated. • Response status: not stated.
Interventions	Participants were randomly assigned to 2 groups. Group 1: ciclosporin (n = 6). Further details: ciclosporin: maintain serum radioimmunoassay dosage between 100 ng/mL and 200 ng/mL for 12 months. Group 2: placebo (n = 6).
Outcomes	Mortality, adverse events.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Quote: "…patients were randomized by sealed envelope to receive either cyclosporin A or placebo". Comment: further details of the sealed envelope method not available.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: identical placebo used in this double-blind trial.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: although a placebo was used, there was no mention about blinding.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: although a placebo was used, there was no mention about blinding.
Selective reporting (reporting bias)	Low risk	Comment: mortality and morbidity reported.
For-profit bias	High risk	Comment: the drugs were provided by the pharmaceutical company.
Other bias	Low risk	Comment: no other bias.

Mitchison 1989

Methods	Randomised clinical trial.
Participants	Country: UK. Number randomised: 36. Post-randomisation dropouts: 0 (0%). Revised sample size: 36. Mean age: 55 years. Females: 33 (91.7%). Symptomatic participants: 35 (97.2%). AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): all participants followed up for 36 months. Inclusion criteria • Symptom status: symptomatic and asymptomatic participants. • AMA status: not stated. • Response status: not stated. Exclusion criteria • Aged > 70 years. • Treatment for primary biliary cirrhosis in the preceding 4 months. • Early liver disease.
Interventions	Participants were randomly assigned to 2 groups. Group 1: glucocorticosteroids (n = 19). Further details: prednisolone: 10 mg/day for 36 months (loading dose was used). Group 2: placebo (n = 17).
Outcomes	Mortality.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were paired according to the presence or absence of cirrhosis, their age by decade, menopausal status (for women) and their serum bilirubin (greater or less than 30 µmoles per litre)". Comment: minimisation used.
Allocation concealment (selection bias)	Low risk	Quote: "Patients were paired according to the presence or absence of cirrhosis, their age by decade, menopausal status (for women) and their serum bilirubin (greater or less than 30 µmoles per litre)". Comment: minimisation used.

Mitchison 1989 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Study was double-blind for the first year, single blind thereafter (patients were blinded)".
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "Study was double-blind for the first year, single blind thereafter (patients were blinded)".
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no post-randomisation dropouts.
Selective reporting (reporting bias)	High risk	Comment: adverse events not reported.
For-profit bias	Unclear risk	Comment: information not available.
Other bias	Low risk	Comment: no other bias.

Mitchison 1993

Methods	Randomised clinical trial.
Participants	Country: multicentric; international. Number randomised: 104. Post-randomisation dropouts: 3 (2.9%). Revised sample size: 101. Mean age: 54 years. Females: 93 (92.1%). Symptomatic participants: 101 (100%). AMA positive: not stated. Responders: not stated. Median follow-up period (for all groups): 25 months. Inclusion criteria • Symptom status: symptomatic participants only. • AMA status: not stated. • Response status: not stated. Exclusion criteria • Aged > 65 years. • Immunosuppressive drugs in the preceding 6 months. • Advanced liver disease or decompensated liver disease.
Interventions	Participants were randomly assigned to 2 groups. Group 1: malotilate (n = 52).

Mitchison 1993 *(Continued)*

	Further details: malotilate: 500 mg 3 times daily; mean duration: 23 months. Group 2: placebo (n = 49).
Outcomes	Mortality, adverse events.
Notes	Reasons for post-randomisation dropouts: elementary data not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Random sequence was generated by the trial statistician with tables with random numbers" (author's reply).
Allocation concealment (selection bias)	Low risk	Quote: "Sequentially numbered identical containers" (author's reply).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Both patients and doctors were unaware of the nature of the tablets". Comment: placebo used to achieve blinding.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Both patients and doctors were unaware of the nature of the tablets". Comment: placebo used to achieve blinding.
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: mortality and morbidity reported.
For-profit bias	High risk	Quote: "The study was supported in part by Zyma S.A., Nyon, Switzerland, and by Nihon Nohyaku, Tokyo, Japan".
Other bias	Low risk	Comment: no other source of bias.

Nakai 2000

Methods	Randomised clinical trial.
Participants	Country: Japan. Number randomised: 23. Post-randomisation dropouts: not stated. Revised sample size: 23. Mean age: 57 years. Females: not stated. Symptomatic participants: not stated. AMA positive: not stated.

Nakai 2000 *(Continued)*

	Responders: not stated. Mean follow-up period (for all groups): all participants followed up for 12 months. Inclusion criteria • Symptom status: not stated. • AMA status: not stated. • Response status: not stated.
Interventions	Participants were randomly assigned to 2 groups. Group 1: UDCA (low) + bezafibrate (n = 13). Further details: UDCA: 600 mg/day; duration: not stated + bezafibrate: 400 mg/day; duration: not stated. Group 2: UDCA (low) (n = 10). Further details: UDCA: 600 mg/day; duration: not stated.
Outcomes	None of the outcomes of interest reported.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available.
Selective reporting (reporting bias)	High risk	Comment: neither mortality nor adverse events reported.
For-profit bias	Low risk	Quote: "This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture of Japan".
Other bias	Low risk	Comment: no other source of bias.

Neuberger 1985

Methods	Randomised clinical trial.
Participants	Country: multicentric; international. Number randomised: 189. Post-randomisation dropouts: not stated. Revised sample size: 189. Mean age: not stated. Females: 174 (92.1%). Symptomatic participants: 172 (91%). AMA positive: 163 (86.2%). Responders: not stated. Mean follow-up period (for all groups): not stated. Inclusion criteria • Symptom status: symptomatic and asymptomatic participants. • AMA status: AMA-positive and AMA-negative participants. • Response status: not stated. Exclusion criteria • Taking azathioprine in the previous 6 months.
Interventions	Participants were randomly assigned to 2 groups. Group 1: D-penicillamine (n = 98). Further details: D-penicillamine: 1200 mg/day; duration: not stated. Group 2: placebo (n = 91).
Outcomes	Mortality, liver transplantation.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Low risk	Quote: "Opaque sealed envelopes" (author's reply).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double blind trial, identical appearing placebo" (author's reply).
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Assessors were blinded, identical placebo" (author's reply).

Neuberger 1985 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available.
Selective reporting (reporting bias)	High risk	Comment: adverse events not reported.
For-profit bias	Unclear risk	Quote: "Not pharmaceutical funding" (author's reply).
Other bias	Low risk	Comment: no other source of bias.

Nevens 2016

Methods	Randomised clinical trial.
Participants	Country: multicentric; international. Number randomised: 217. Post-randomisation dropouts: 1. Revised sample size: 216. Mean age: 56 years. Females: 196 (90.7%). Symptomatic participants: not stated. AMA positive: not stated. Responders: 0 (0%). Mean follow-up period (for all groups): all participants followed up for 12 months. Inclusion criteria • Symptom status: not stated. • AMA status: not stated. • Response status: non-responders only. • Aged > 18 years. • Alkaline phosphatase level ≥ 1.67 times the upper limit of the normal range or an abnormal total bilirubin level < 2 times the upper limit of the normal range.
Interventions	Participants were randomly assigned to 2 groups. Group 1: obeticholic acid (low) + UDCA (moderate) (n = 143). Further details: obeticholic acid: 5 mg to 10 mg for 1 year + UDCA: 13 mg/kg/day to 15 mg/kg/day for 1 year. Group 2: UDCA (moderate) (n = 73). Further details: UDCA: 13 mg/kg/day to 15 mg/kg/day for 1 year.
Outcomes	Mortality, adverse events.

Nevens 2016 *(Continued)*

Notes	Reasons for post-randomisation dropouts: withdrawal from study.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "On a predefined randomization code (generated by the Sponsor or designee) using an IWRS".
Allocation concealment (selection bias)	Low risk	Quote: "The randomization number will be recorded in the CRF and will serve for patient identification and for assignment of appropriate study medication and bottle number(s) by the IWRS".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: identical placebo used and authors stated double-blind.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: identical placebo used and authors stated double-blind.
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: mortality and morbidity reported.
For-profit bias	High risk	Quote: "Supported by Intercept Pharmaceuticals". Comment: trial funded by industrial sources which might benefit by the nature of the results.
Other bias	Low risk	Comment: no other source of bias.

Oka 1990

Methods	Randomised clinical trial.
Participants	Country: Japan. Number randomised: 52. Post-randomisation dropouts: 7 (13.5%). Revised sample size: 45. Mean age: 59 years. Females: 41 (91.1%). Symptomatic participants: 17 (37.8%). AMA positive: 41 (91.1%). Responders: not stated. Mean follow-up period (for all groups): not stated.

Oka 1990 *(Continued)*

	Inclusion criteria • Symptom status: symptomatic and asymptomatic participants. • AMA status: AMA-positive and AMA-negative participants. • Response status: not stated. Exclusion criteria • Advanced liver disease or decompensated liver disease. • Pregnancy. • Complications from illnesses other than primary biliary cholangitis. • Use of treatment for primary biliary cholangitis within the past 3 months.
Interventions	Participants were randomly assigned to 2 groups. Group 1: UDCA (low) (n = 22). Further details: UDCA: 600 mg/day for 24 weeks. Group 2: placebo (n = 23).
Outcomes	None of the outcomes of interest reported.
Notes	Reasons for post-randomisation dropouts: worsening liver disease, lack of compliance.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Low risk	Quote: "The patients were allocated to two groups, a UDCA group and a placebo group, by a single monitor according to a randomization scheme in which the number of patients allocated to two groups tended to be equal".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: identical placebo used in this double-blind trial.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: identical placebo used in this double-blind trial.
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation dropouts.
Selective reporting (reporting bias)	High risk	Comment: neither mortality nor adverse events reported.
For-profit bias	High risk	Quote: "UDCA and placebo tablets were generously furnished by Tokyo Tanabe Pharmaceutical Company".
Other bias	Low risk	Comment: no other source of bias.

Papatheodoridis 2002

Methods	Randomised clinical trial.
Participants	Country: Greece. Number randomised: 92. Post-randomisation dropouts: 6 (6.5%). Revised sample size: 86. Mean age: 54 years. Females: 77 (89.5%). Symptomatic participants: 86 (100%). AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): 89 months. Inclusion criteria • Symptom status: symptomatic participants only. • AMA status: not stated. • Response status: not stated. Exclusion criteria • Extrahepatic biliary obstruction. • Other liver diseases. • Aged > 70 years. • Immunosuppression within previous 12 months. • Advanced or decompensated liver disease.
Interventions	Participants were randomly assigned to 2 groups. Group 1: UDCA (moderate) (n = 43). Further details: UDCA: 12 mg/kg//day to 15 mg/kg//day for ≥ 2 years. Group 2: control (n = 43).
Outcomes	Mortality, liver transplantation, decompensated liver disease.
Notes	Reasons for post-randomisation dropouts: not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was carried out by serially numbered sealed envelopes containing random table numbers 14 patients crossed over from placebo to UDCA".
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was carried out by serially numbered sealed envelopes containing random table numbers 14 patients crossed over from placebo to UDCA".

Papatheodoridis 2002 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Patients and healthcare providers were not blinded" (author's reply).
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "The outcome assessors were not blinded" (author's reply).
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation dropouts in the initial report.
Selective reporting (reporting bias)	High risk	Comment: adverse events not reported.
For-profit bias	High risk	Quote: "Support for this work was provided during the first 2 years of the study by a research grant the pharmaceutical company Galenica Hellas and by the Greek Ministry of Health and Welfare".
Other bias	High risk	Comment: 14 participants crossed over from placebo to UDCA.

Pares 2000

Methods	Randomised clinical trial.
Participants	Country: Spain. Number randomised: 192. Post-randomisation dropouts: 0 (0%). Revised sample size: 192. Mean age: 54 years. Females: 179 (93.2%). Symptomatic participants: not stated. AMA positive: 172 (89.6%). Responders: not stated. Median follow-up period (for all groups): 41 months. Inclusion criteria • Symptom status: not stated. • AMA status: AMA-positive and AMA-negative participants. • Response status: not stated. Exclusion criteria • Aged > 72 years. • Immunosuppression within previous 6 months. • Life expectancy < 6 months. • Pregnancy. • Drug addiction.

Pares 2000 *(Continued)*

	• Other liver diseases.
Interventions	Participants were randomly assigned to 2 groups. Group 1: UDCA (moderate) (n = 99). Further details: UDCA 14 mg/kg/day to 16 mg/kg/day; duration: 25 to 73 months. Group 2: placebo (n = 93).
Outcomes	Mortality, adverse events.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: identical placebo used in this double-blind trial.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: identical placebo used in this double-blind trial.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: unclear whether all participants were included in the analysis.
Selective reporting (reporting bias)	Low risk	Comment: mortality and morbidity reported.
For-profit bias	High risk	Quote: "We are indebted to Zambon S. A., Laboratorio Farmaceutico for supplying the UDCA and placebo capsules, and for the invaluable administrative support".
Other bias	Low risk	Comment: no other risk of bias.

Poupon 1991a

Methods	Randomised clinical trial.
Participants	Country: France. Number randomised: 149. Post-randomisation dropouts: 3 (2%). Revised sample size: 146.

Poupon 1991a *(Continued)*

	Mean age: 56 years. Females: 134 (91.8%). Symptomatic participants: not stated. AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): not stated. Inclusion criteria • Symptom status: not stated. • AMA status: not stated. • Response status: not stated. Exclusion criteria • Received any of the following drugs during the previous 6 months: ursodiol, azathioprine, chlorambucil, colchicine, corticosteroids, D-penicillamine, and ciclosporin. • Serum bilirubin concentration > 150 µmol/L. • Serum albumin concentration < 25 g/L. • Past or active gastrointestinal bleeding from oesophageal varices. • Evidence of past or present extrahepatic obstruction of the bile ducts. • Excessive alcohol consumption (> 50 g/day). • Positive test for hepatitis B surface antigen.
Interventions	Participants were randomly assigned to 2 groups. Group 1: UDCA (moderate) (n = 73). Further details: UDCA: 13 mg/kg/day to 15 mg/kg/day for 2 years. Group 2: placebo (n = 73).
Outcomes	None of the outcomes of interest reported.
Notes	Reasons for post-randomisation dropouts: bilirubin > 300 µmol/L, ascites, other coexisting disease.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: identical placebo used in this double-blind trial.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: identical placebo used in this double-blind trial.

Poupon 1991a *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation dropouts.
Selective reporting (reporting bias)	High risk	Comment: neither mortality nor adverse events reported.
For-profit bias	High risk	Quote: "This work was supported in part by Synthélabo-Recherche and in Canada by Jouveinal and Interfalk".
Other bias	Low risk	Comment: no other source of bias.

Poupon 1996

Methods	Randomised clinical trial.
Participants	Country: France. Number randomised: 74. Post-randomisation dropouts: not stated. Revised sample size: 74. Mean age: 54 years. Females: 63 (85.1%). Symptomatic participants: not stated. AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): all participants followed up for 24 months. Inclusion criteria • Symptom status: not stated. • AMA status: not stated. • Response status: not stated. Exclusion criteria • Received any of the following drugs during the previous 6 months: ursodiol, azathioprine, chlorambucil, colchicine, corticosteroids, D-penicillamine, and ciclosporin. • Serum bilirubin concentration > 150 µmol/L. • Serum albumin concentration < 25 g/L. • Past or active gastrointestinal bleeding from oesophageal varices. • Evidence of past or present extrahepatic obstruction of the bile ducts. • Excessive alcohol consumption (> 50 g/day). • Other identified causes of liver or biliary diseases. • Aged ≥ 75 years.
Interventions	Participants were randomly assigned to 2 groups. Group 1: UDCA (moderate) + colchicine (n = 37).

Poupon 1996 *(Continued)*

	Further details: UDCA: 13 mg/kg/day to 15 mg/kg/day for 2 years + colchicine: 1 mg/day for 5 days in a week for 2 years. Group 2: UDCA (moderate) (n = 37). Further details: UDCA: 13 mg/kg/day to 15 mg/kg/day for 2 years.
Outcomes	Mortality, adverse events.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: identical placebo used in this double-blind trial.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: identical placebo used in this double-blind trial.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: unclear whether all randomised participants were included for analysis.
Selective reporting (reporting bias)	Low risk	Comment: mortality and morbidity reported.
For-profit bias	High risk	Quote: "Supported in part by Laboratoires Houde (France) and Jouveinal (Canada)".
Other bias	Low risk	Comment: no other source of bias.

Raedsch 1993

Methods	Randomised clinical trial.
Participants	Country: Germany. Number randomised: 28. Post-randomisation dropouts: 8 (28.6%). Revised sample size: 20. Mean age: 54 years. Females: 20 (100%).

Raedsch 1993 *(Continued)*

	Symptomatic participants: not stated. AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): all participants followed up for 24 months. Inclusion criteria • Symptom status: not stated. • AMA status: not stated. • Response status: not stated.
Interventions	Participants were randomly assigned to 2 groups. Group 1: UDCA (moderate) + colchicine (n = 8). Further details: UDCA: 10 mg/kg/day to 12 mg/kg/day for 24 months + colchicine: 1 mg/day for 24 months. Group 2: UDCA (moderate) (n = 12). Further details: UDCA: 10 mg/kg/day to 12 mg/kg/day for 24 months.
Outcomes	Adverse events.
Notes	Reasons for post-randomisation dropouts: adverse events, lost to follow-up.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: although a placebo used in this double-blind trial, unclear whether the placebo was identical.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: although a placebo used in this double-blind trial, unclear whether the placebo was identical.
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation dropouts.
Selective reporting (reporting bias)	High risk	Comment: mortality not reported.
For-profit bias	Unclear risk	Comment: information not available.
Other bias	Low risk	Comment: no other source of bias.

Rautiainen 2005

Methods	Randomised clinical trial.
Participants	Country: Finland. Number randomised: 77. Post-randomisation dropouts: 8 (10.4%). Revised sample size: 69. Mean age: 53 years. Females: 60 (87%). Symptomatic participants: not stated. AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): all participants followed up for 36 months. Inclusion criteria • Symptom status: not stated. • AMA status: not stated. • Response status: not stated. Exclusion criteria • Aged < 18 years or > 70 years. • Pregnancy or inadequate contraceptive use. • Systemic immunosuppressive use. • Other liver diseases. • Cirrhosis.
Interventions	Participants were randomly assigned to 2 groups. Group 1: UDCA (moderate) + glucocorticosteroids (n = 37). Further details: UDCA: 15 mg/kg/day for 3 years + budesonide: 6 mg/day for 3 years. Group 2: UDCA (moderate) (n = 32). Further details: UDCA: 15 mg/kg/day for 3 years.
Outcomes	Adverse events.
Notes	Reasons for post-randomisation dropouts: adverse effects, death, refused follow-up biopsy.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Quote: "Randomization was done centrally at Helsinki University Hospital with sealed envelopes in a block of 10".

Rautiainen 2005 *(Continued)*

		Comment: further details of sealed envelope technique not available.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Study design was randomized but open because placebo for budesonide was not available for us".
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "Study design was randomized but open because placebo for budesonide was not available for us".
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation dropouts.
Selective reporting (reporting bias)	High risk	Comment: mortality not reported.
For-profit bias	High risk	Quote: "Medication was supplied free of charge by AstraZeneca Finland (budesonide, Entocort) and Leiras Finland (UDCA, Adursal)".
Other bias	Low risk	Comment: no other source of bias.

Senior 1991

Methods	Randomised clinical trial.
Participants	Country: USA. Number randomised: 20. Post-randomisation dropouts: 1 (5%). Revised sample size: 19. Mean age: not stated. Females: not stated. Symptomatic participants: not stated. AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): all participants followed up for 18 months. Inclusion criteria • Symptom status: not stated. • AMA status: not stated. • Response status: not stated.
Interventions	Participants were randomly assigned to 2 groups. Group 1: UDCA (low) (n = 9). Further details: UDCA (low): 8 mg/kg/day to 12 mg/kg/day for 6 months.

Senior 1991 *(Continued)*

	Group 2: placebo (n = 10).
Outcomes	None of the outcomes of interest reported.
Notes	Reasons for post-randomisation dropouts: had coexisting gallstones.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: although a placebo used in this double-blind trial, unclear whether the placebo was identical.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: although a placebo used in this double-blind trial, unclear whether the placebo was identical.
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation dropouts.
Selective reporting (reporting bias)	High risk	Comment: neither mortality nor adverse events reported.
For-profit bias	High risk	Quote: "and ursodiol supplies provided by Ciba-Geigy Corporation".
Other bias	Low risk	Comment: no other source of bias.

Smart 1990

Methods	Randomised clinical trial.
Participants	Country: UK. Number randomised: 20. Post-randomisation dropouts: not stated. Revised sample size: 20. Mean age: not stated. Females: not stated. Symptomatic participants: not stated. AMA positive: not stated. Responders: not stated.

Smart 1990 *(Continued)*

	Mean follow-up period (for all groups): not stated. Inclusion criteria • Symptom status: not stated. • AMA status: not stated. • Response status: not stated.
Interventions	Participants were randomly assigned to 2 groups. Group 1: antioxidants (n = not stated). Further details: antioxidant: cocktail of vitamin E 100 mg, zinc 135 mg, and selenium 100 µg daily; duration: not stated. Group 2: placebo (n = not stated).
Outcomes	None of the outcomes of interest reported.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: although a placebo was used, no mention of blinding made.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: although a placebo was used, no mention of blinding made.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available.
Selective reporting (reporting bias)	High risk	Comment: neither mortality nor adverse events reported.
For-profit bias	Unclear risk	Comment: information not available.
Other bias	Low risk	Comment: no other source of bias.

Steenbergen 1994

Methods	Randomised clinical trial.
Participants	Country: Belgium.

Steenbergen 1994 *(Continued)*

Number randomised: 14.

Post-randomisation dropouts: not stated.

Revised sample size: 14.

Mean age: 51 years.

Females: 12 (85.7%).

Symptomatic participants: not stated.

AMA positive: 13 (92.9%).

Responders: not stated.

Mean follow-up period (for all groups): all participants followed up for 24 months.

Inclusion criteria

- Symptom status: not stated.
- AMA status: AMA-positive and AMA-negative participants.
- Response status: not stated.

Exclusion criteria

- Presence of cirrhosis.
- Excessive alcohol consumption.
- Other viral diseases.
- Mental disorders.
- Pregnancy.
- Chronic infection.

Interventions	Participants were randomly assigned to 2 groups. Group 1: UDCA (low) + methotrexate (n = 8). Further details: UDCA: 500 mg/day; duration: not stated + methotrexate: 15 mg/week; duration: not stated. Group 2: control (n = 6).
Outcomes	None of the outcomes of interest reported.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Using a random number table…".
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information not available.

Steenbergen 1994 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available.
Selective reporting (reporting bias)	High risk	Comment: neither mortality nor adverse events reported.
For-profit bias	Unclear risk	Comment: information not available.
Other bias	Low risk	Comment: no other source of bias.

Taal 1983

Methods	Randomised clinical trial.
Participants	Country: Netherlands. Number randomised: 24. Post-randomisation dropouts: not stated. Revised sample size: 24. Mean age: 49 years. Females: 23 (95.8%). Symptomatic participants: 24 (100%). AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): all participants followed up for 18 months. Inclusion criteria • Symptom status: symptomatic participants only. • AMA status: not stated. • Response status: not stated. Exclusion criteria • Advanced or decompensated liver disease. • Use of cholestatic drug in the previous 6 months. • Associated inflammatory bowel disease. • Neoplasm within last 5 years. • Pregnancy.
Interventions	Participants were randomly assigned to 2 groups. Group 1: D-penicillamine (n = 11). Further details: D-penicillamine: 250 mg/day to 1000 mg/day (escalating dose) and then 500 mg/day: total duration: 1 year.

Taal 1983 *(Continued)*

	Group 2: placebo (n = 13).
Outcomes	Mortality, adverse events, decompensated liver disease.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: identical placebo used in this double-blind trial.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: identical placebo used in this double-blind trial.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available.
Selective reporting (reporting bias)	Low risk	Comment: mortality and adverse events reported.
For-profit bias	Unclear risk	Comment: information not available.
Other bias	Low risk	Comment: no other source of bias.

Triger 1980

Methods	Randomised clinical trial.
Participants	Country: UK. Number randomised: 35. Post-randomisation dropouts: not stated. Revised sample size: 35. Mean age: not stated. Females: not stated. Symptomatic participants: not stated. AMA positive: not stated. Responders: not stated.

Triger 1980 *(Continued)*

	Mean follow-up period (for all groups): not stated. Inclusion criteria • Symptom status: not stated. • AMA status: not stated. • Response status: not stated.
Interventions	Participants were randomly assigned to 2 groups. Group 1: D-penicillamine (n = not stated). Further details: D-penicillamine: 250 mg to 875 mg (escalating dose). Group 2: placebo (n = not stated).
Outcomes	Mortality.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: in this double-blind trial, unclear whether the placebo was identical to active treatment.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: in this double-blind trial, unclear whether the placebo was identical to active treatment.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available.
Selective reporting (reporting bias)	High risk	Comment: adverse events not reported.
For-profit bias	High risk	Quote: "The UDCA and placebo tablets were generously donated by Thames Laboratories, Wrexham, Wales".
Other bias	Low risk	Comment: no other source of bias.

Turner 1994

Methods	Randomised clinical trial.
Participants	Country: UK.

Turner 1994 *(Continued)*

	Number randomised: 46. Post-randomisation dropouts: 0 (0%). Revised sample size: 46. Mean age: 58 years. Females: 44 (95.7%). Symptomatic participants: not stated. AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): all participants followed up for 24 months. Inclusion criteria • Symptom status: not stated. • AMA status: not stated. • Response status: not stated.
Interventions	Participants were randomly assigned to 2 groups. Group 1: UDCA (low) (n = 22). Further details: UDCA: 10 mg/kg/day for 2 years. Group 2: placebo (n = 24).
Outcomes	Mortality, liver transplantation, cirrhosis.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: identical placebo used in this double-blind trial.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: identical placebo used in this double-blind trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no post-randomisation dropouts.
Selective reporting (reporting bias)	High risk	Comment: adverse events not reported.

Turner 1994 *(Continued)*

For-profit bias	Unclear risk	Comment: information not available.
Other bias	Low risk	Comment: no other source of bias.

Ueno 2005

Methods	Randomised clinical trial.
Participants	Country: Japan. Number randomised: 20. Post-randomisation dropouts: not stated. Revised sample size: 20. Mean age: not stated. Females: 16 (80%). Symptomatic participants: not stated. AMA positive: not stated. Responders: 0 (0%). Mean follow-up period (for all groups): not stated. Inclusion criteria • Symptom status: not stated. • AMA status: not stated. • Response status: non-responders only Exclusion criteria • Aged < 20 years or > 70 years. • History of antiretroviral or steroid treatment. • Renal dysfunction. • Other causes of liver damage.
Interventions	Participants were randomly assigned to 2 groups. Group 1: lamivudine (n = not stated). Further details: lamivudine: 100 mg/day for 3 months. Group 2: placebo (n = not stated).
Outcomes	None of the outcomes of interest reported.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.

Ueno 2005 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: identical placebo used in this double-blind trial.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: identical placebo used in this double-blind trial.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available.
Selective reporting (reporting bias)	High risk	Comment: neither mortality nor adverse events reported.
For-profit bias	Unclear risk	Comment: information not available.
Other bias	Low risk	Comment: no other source of bias.

Van Hoogstraten 1998

Methods	Randomised clinical trial.
Participants	Country: Netherlands. Number randomised: 61. Post-randomisation dropouts: 2 (3.3%). Revised sample size: 59. Mean age: 57 years. Females: 55 (93.2%). Symptomatic participants: not stated. AMA positive: not stated. Responders: 0 (0%). Mean follow-up period (for all groups): not stated. Inclusion criteria • Symptom status: not stated. • AMA status: not stated. • Response status: non-responders only. Exclusion criteria • Decompensated liver disease.
Interventions	Participants were randomly assigned to 2 groups.

Van Hoogstraten 1998 *(Continued)*

	Group 1: UDCA (low) (n = 32). Further details: UDCA (low): 10 mg/kg/day for 6 months. Group 2: UDCA (moderate) (n = 27). Further details: UDCA (moderate): 20 mg/kg/day for 6 months.
Outcomes	Adverse events.
Notes	Reasons for post-randomisation dropouts: developed liver failure, lost to follow-up.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Tables with random numbers" (author's reply).
Allocation concealment (selection bias)	Low risk	Quote: "Opaque closed envelopes" (author's reply).
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "randomised open controlled trial".
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "randomised open controlled trial".
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available.
Selective reporting (reporting bias)	High risk	Comment: mortality not reported.
For-profit bias	High risk	Quote: "This study was supported in part by Zambon Nederland BV, Amersfoort, the Netherlands".
Other bias	Low risk	Comment: no other source of bias.

Warnes 1987

Methods	Randomised clinical trial.
Participants	Country: UK. Number randomised: 64. Post-randomisation dropouts: not stated. Revised sample size: 64. Mean age: not stated. Females: not stated.

Warnes 1987 *(Continued)*

	Symptomatic participants: not stated. AMA positive: 64 (100%). Responders: not stated. Median follow-up period (for all groups): 19 months. Inclusion criteria • Symptom status: not stated. • AMA status: AMA-positive participants only. • Response status: not stated.
Interventions	Participants were randomly assigned to 2 groups. Group 1: colchicine (n = 34). Further details: colchicine: 0.5 mg BD; duration: not stated. Group 2: placebo (n = 30).
Outcomes	Mortality, adverse events.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "To ensure that treatment groups were comparable, patients were stratified according to serum bilirubin level at entry (A, < 19/µmol/1; B, 20-34/µmol/L; C, 35-102/µmol/L; D, >102/µmol/1). The first patient in any pair was allocated by the staff pharmacist to the treatment or placebo group by reference to random tables. The pair was completed when another patient, in the same bilirubin group and with an age within 5 years of the first patient, was entered into the study. The second member of the pair was allocated to the alternative treatment group. The study was double-blind". Comment: minimisation method used.
Allocation concealment (selection bias)	Low risk	Quote: "To ensure that treatment groups were comparable, patients were stratified according to serum bilirubin level at entry (A, < 19/µmol/1; B, 20-34/µmol/L; C, 35-102/µmol/L; D, >102/µmol/1). The first patient in any pair was allocated by the staff pharmacist to the treatment or placebo group by reference to random tables. The pair was completed when another patient, in the same bilirubin group and with an age within 5 years of the first patient, was entered into the study. The second member of the pair was allocated to the alternative treatment group. The study was double-blind". Comment: minimisation method used.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: identical placebo used in this double-blind trial.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: identical placebo used in this double-blind trial.
Incomplete outcome data (attrition bias)	Unclear risk	Comment: information not available.

Warnes 1987 *(Continued)*

All outcomes

Selective reporting (reporting bias)	Low risk	Comment: mortality and morbidity reported.
For-profit bias	Unclear risk	Comment: information not available.
Other bias	Low risk	Comment: no other source of bias.

Wiesner 1990

Methods	Randomised clinical trial.
Participants	Country: USA. Number randomised: 40. Post-randomisation dropouts: 11 (27.5%). Revised sample size: 29. Mean age: 46 years. Females: 28 (96.6%). Symptomatic participants: not stated. AMA positive: not stated. Responders: not stated. Median follow-up period (for all groups): 35 months. Inclusion criteria • Symptom status: not stated. • AMA status: not stated. • Response status: not stated. Exclusion criteria • Cirrhosis or advanced liver disease. • Renal dysfunction. • Uncontrolled hypertension. • Neoplastic disease. • Skin cancer. • Previous immunosuppressive therapy. • Other liver diseases.
Interventions	Participants were randomly assigned to 2 groups. Group 1: ciclosporin (n = 19). Further details: ciclosporin: 4 mg/kg/day. Group 2: placebo (n = 10).
Outcomes	Mortality, adverse events, liver transplantation.

Wiesner 1990 *(Continued)*

Notes	Reasons for post-randomisation dropouts: follow-up < 1 year.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: identical placebo used in this double-blind trial.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: identical placebo used in this double-blind trial.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available.
Selective reporting (reporting bias)	Low risk	Comment: mortality and morbidity reported.
For-profit bias	High risk	Quote: "Supported by a grant from Sandoz and by the Mayo foundation".
Other bias	Low risk	Comment: no other source of bias.

Wolfhagen 1998

Methods	Randomised clinical trial.
Participants	Country: Netherlands. Number randomised: 50. Post-randomisation dropouts: not stated. Revised sample size: 50. Mean age: 52 years. Females: 45 (90%). Symptomatic participants: not stated. AMA positive: not stated. Responders: 0 (0%). Mean follow-up period (for all groups): all participants followed up for 12 months. Inclusion criteria • Symptom status: not stated.

Wolfhagen 1998 *(Continued)*

- AMA status: not stated.
- Response status: non-responders only.

Exclusion criteria

- Advanced or decompensated liver disease.
- Alcohol abuse.
- Other causes of liver disease.

Interventions	Participants were randomly assigned to 2 groups. Group 1: UDCA (moderate) + azathioprine + glucocorticosteroids (n = 26). Further details: UDCA: 10 mg/kg/day for 6 months + azathioprine: 50 mg/day for 6 months + prednisolone: 10 mg/day for 6 months. Group 2: UDCA (moderate) (n = 24). Further details: UDCA: 10 mg/kg/day for 6 months.
Outcomes	Adverse events, cirrhosis.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Tables with random numbers" (author's reply).
Allocation concealment (selection bias)	Low risk	Quote: "Opaque closed envelopes" (author's reply).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: identical placebo used in this double-blind trial.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: identical placebo used in this double-blind trial.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available.
Selective reporting (reporting bias)	High risk	Comment: mortality not reported.
For-profit bias	High risk	Quote: "Supported by…Zambon Nederland B.v. and Glaxo Wellcome Research and Development Ltd".
Other bias	Low risk	Comment: no other source of bias.

Yokomori 2001

Methods	Randomised clinical trial.
Participants	Country: Japan. Number randomised: 11. Post-randomisation dropouts: not stated. Revised sample size: 11. Mean age: 54 years. Females: 9 (81.8%). Symptomatic participants: 11 (100%). AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): not stated. Inclusion criteria • Symptom status: symptomatic participants only. • AMA status: not stated. • Response status: not stated. Exclusion criteria • Advanced or decompensated liver disease. • Pregnancy. • Treatment with immunosuppressants or other drugs that interfere with bile secretion. • Severe complications other than primary biliary cholangitis.
Interventions	Participants were randomly assigned to 2 groups. Group 1: UDCA (low) + colestilan (n = 5). Further details: UDCA: 600 mg/day for 8 weeks + colestilan: 6.42 mg/day for 4 weeks. Group 2: UDCA (low) (n = 6). Further details: UDCA: 600 mg/day for 8 weeks.
Outcomes	Adverse events.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias)	High risk	Quote: "open-label".

Yokomori 2001 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "open-label".
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available.
Selective reporting (reporting bias)	High risk	Comment: mortality not reported.
For-profit bias	Unclear risk	Comment: information not available.
Other bias	Low risk	Comment: no other source of bias.

AMA: antimitochondrial antibody; BD: twice daily; IV: intravenous; OD: once daily; SAMe: S-adenosyl methionine; SC: subcutaneous; TUDCA: taurodeoxycholic acid; UDCA: ursodeoxycholic acid.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Angulo 1999b	Long-term follow-up of participants included in an included trial (Lindor 1994), but the randomisation was not maintained.
Angulo 1999c	Long-term follow-up of participants included in an included trial (Lindor 1994), but the randomisation was not maintained.
Angulo 2002	Comparison of different administration schedules of the same dose of UDCA.
Attili 1994	Not in people with primary biliary cholangitis.
Avezov 2004a	Not a randomised clinical trial.
Avezov 2004b	Not a randomised clinical trial.
Bach 2003	Not a randomised clinical trial.
Batta 1989	Not a randomised clinical trial.
Beukers 1988	Not a randomised clinical trial.
Blanche 1994	Not a randomised clinical trial.
Bonis 2006	Not a randomised clinical trial.
Borum 1990	Not a primary study (editorial).
Bray 1991	Cross-over RCT; no results presented before cross-over.
Carbone 2016	Long-term follow-up of Nevens 2016, but excluded because randomisation not maintained.
Chazouilleres 1995	Not a randomised clinical trial.

Study	Reason for exclusion
Christensen 1986	Not a primary study (letter to editor).
Combes 1989	Not a primary study (editorial).
Combes 2004	Not a primary study (editorial).
Combes 2005b	Long-term follow-up of participants in an included RCT (Combes 1995a); however, all participants received the intervention after the end of the initial study.
Copaci 2001	Not a randomised clinical trial.
Corpechot 2000	Long-term follow-up of an included trial (Poupon 1991a); however, all participants received the active intervention at the end of the trial period.
Corpechot 2001	Not a primary study (editorial).
Crosignani 1996a	Cross-over RCT; no outcomes of interest reported before cross-over.
Crosignani 1996b	In this RCT of different doses of TUDCA, participants who were intolerant to the drug were replaced. This affected the randomisation.
De la Mora 1994	No separate data on people who were randomised (included non-randomised participants in the results).
Degott 1999	Long-term follow-up of an included trial (Poupon 1991a); however, all participants received the active intervention at the end of the trial period.
Dickson 1991	No separate data on people who were randomised (included non-randomised participants in the results).
Emond 1996	Long-term follow-up of an included trial (Combes 1995a); however, all participants received the active intervention at the end of the trial period.
Fischer 1967	Not a randomised clinical trial.
Golovanova 2010	Not a randomised clinical trial.
Heathcote 1993	Not a randomised clinical trial.
Heathcote 1995	Not a primary study.
Hirschfield 2011	Not a randomised clinical trial.
Hishon 1982	Not a randomised clinical trial.
Howat 1966	Not a randomised clinical trial.
Hwang 1993	Cross-over RCT; none of the outcomes of interest reported prior to cross-over.
Invernizzi 1996	Cross-over RCT, no results presented before cross-over.
Invernizzi 2015	Not a primary study.
Itakura 2004	Not a primary study.

Study	Reason for exclusion
Jazrawi 1999	Not a randomised clinical trial.
Jones 2006	Not a primary study (letter to editor).
Jorgensen 2002	Long-term follow-up of an included trial (Lindor 1994); however, all participants received the active intervention at the end of the trial period.
Joshi 2002	Not a primary study.
Kaplan 1993	Not a primary study (editorial).
Kaplan 1998	Not a primary study (letter to editor).
Kaplan 2004	Long-term follow-up of an included trial (Kaplan 1999), but the treatment was changed at the completion of the RCT.
Kaplan 2009	Not a primary study (letter to editor).
Kisand 1996	Quasi-randomised study (allocation by case numbers).
Kisand 1998	Quasi-randomised study (allocation by case numbers).
Kowdley 2014a	Not a randomised clinical trial.
Kowdley 2014b	Not a randomised clinical trial.
Kowdley 2015	Long-term follow-up of Kowdley 2011, but excluded because randomisation was not maintained.
Kugler 1991	Not a primary study (commentary).
Kurihara 2002	Not a randomised clinical trial.
Lampe 1972	Not a randomised clinical trial.
Larghi 1997	Cross-over RCT; no results presented before cross-over.
Lee 2003	Not a randomised clinical trial.
Leung 2010	Long-term follow-up of a subgroup of participants in an included trial (Kaplan 1999), where additional interventions were added after completion of the trial period.
Leung 2011	Long-term follow-up of a subgroup of participants in an included trial (Kaplan 1999), where additional interventions were added after completion of the trial period.
Leuschner 1990	Not a primary study (review).
Leuschner 1993a	Not a primary study (review).
Leuschner 1993b	Quasi-randomised study (allocation by alternation).
Leuschner 1996a	Quasi-randomised study (allocation by alternation).
Leuschner 1996b	Quasi-randomised study (allocation by alternation).
Leuschner 1997	Not a primary study (review).

Study	Reason for exclusion
Leuschner 1998	Not a primary study (review).
Levy 2004	Not a primary study (editorial).
Licinio 2015	Not a primary study (letter to editor).
Lim 2000	Not a randomised clinical trial.
Lindor 1994a	Not a randomised clinical trial
Lindor 1995a	Long-term follow-up an included RCT (Lindor 1994); however, all participants received the intervention after the completion of the RCT.
Lindor 1995b	Not a randomised clinical trial.
Lindor 1995c	Not a primary study (review).
Lindor 1996	Long-term follow-up an included RCT (Lindor 1994); however, all participants received the intervention after the completion of the RCT.
Lindor 2000	Not a primary study (letter to editor).
Lindor 2005	Not a primary study (review).
Lindor 2007	Not a primary study (review).
Lytvyak 2015	Cross-over RCT; no outcomes reported prior to cross-over.
Lytvyak 2016	Not a randomised clinical trial
Miettinen 1993	Quasi-randomised study (allocation by case numbers).
Miettinen 1995	Quasi-randomised study (allocation by case numbers).
Muntoni 2010	Only 4 participants in this trial had primary biliary cholangitis and separate data not available for these 4 participants.
Nikolaidis 2006	Only 5 participants had primary biliary cholangitis and only 1 of them received placebo. Separate data not available on these participants.
Ohmoto 2001	Not a randomised clinical trial.
Ohmoto 2006	Not a randomised clinical trial.
Pan 2013	Only 5 participants had primary biliary cholangitis. Separate data not available for these participants.
Pares 2009	Not a randomised clinical trial.
Podda 1989	Cross-over study of different doses of UDCA; outcomes not reported at the end of first treatment.
Poupon 1989	Not a primary study (review).
Poupon 1990	Not a primary study (review).

Study	Reason for exclusion
Poupon 1991b	Not a primary study (commentary).
Poupon 1994	Long-term follow-up of an included trial (Poupon 1991a); however, all participants received the active intervention at the end of the trial period.
Poupon 1997	Not a primary study.
Poupon 1999	Not a randomised clinical trial.
Poupon 2003	Not a primary study.
Raedsch 1989	Not a randomised clinical trial.
Reed 1982	Not a primary study (editorial).
Robson 1994	Not a randomised clinical trial.
Roda 2002	Not a randomised clinical trial.
Savolainen 1983	Unclear whether this was a randomised clinical trial.
Schaffner 1982	Comparison of 2 doses of D-penicillamine with no other treatment as comparator.
Setchell 1994	In this RCT of different doses of TUDCA, participants who were intolerant to the drug were replaced. This affected the randomisation.
Setchell 1996	In this RCT of different doses of TUDCA, participants who were intolerant to the drug were replaced. This affected the randomisation.
Stellaard 1979	Not a randomised clinical trial.
Taal 1985	Not a randomised clinical trial.
Tang 2008	Not a pharmacological agent.
Tong 2012	Not a pharmacological agent.
Verma 1999	Cross-over RCT; no results presented before cross-over.
Verma 2000	Not a primary study (review).
Vogel 1988	Not a randomised clinical trial.
Vuoristo 1995	Quasi-randomised study (allocation by case numbers).
Vuoristo 1997	Quasi-randomised study (allocation by case numbers).
Wiesner 1994	Not a randomised clinical trial.
Wolfhagen 1995	Not a randomised clinical trial.
Yan 2007	Not a primary study (letter to editor).
Yano 2002	Not a randomised clinical trial.

Study	Reason for exclusion
Zuin 1991	Symptomatic treatment of dyslipidaemia associated with primary biliary cholangitis.

TUDCA: taurodeoxycholic acid; UDCA: ursodeoxycholic acid.

Characteristics of studies awaiting assessment *[ordered by study ID]*

O'Brian 1990

Methods	Full text not available.
Participants	
Interventions	
Outcomes	
Notes	

Zaman 2006

Methods	Full text not available.
Participants	
Interventions	
Outcomes	
Notes	

Characteristics of ongoing studies *[ordered by study ID]*

ChiCTR-IPR-16008935

Trial name or title	Biochemical Response of PBC-AIH Overlap Syndrome Induced by Ursodeoxycholic Acid Only or Combination Therapy of Immunosuppressive Agents
Methods	Randomised parallel clinical trial
Participants	People with primary biliary cholangitis and autoimmune hepatitis overlap syndrome.
Interventions	Group 1: UDCA + immunosuppression Further details: not provided. Group 2: UDCA. Further details: not provided.
Outcomes	Adverse events
Starting date	Not stated.

ChiCTR-IPR-16008935 *(Continued)*

Contact information	yangli_hx@scu.edu.cn
Notes	Status: recruiting.

EUCTR2015-002698-39-GB

Trial name or title	A 12-Week, Double-Blind, Randomized, Placebo-Controlled, Phase 2 Study to Evaluate the Effects of Two Doses of MBX-8025 in Subjects with Primary Biliary Cirrhosis (PBC) and an Inadequate Response to Ursodeoxycholic Acid (UDCA).
Methods	Randomised, placebo-controlled, double-blind clinical trial.
Participants	People with primary biliary cholangitis (non-responders).
Interventions	Group 1: MBX-8025. Further details: not provided. Group 2: placebo.
Outcomes	None of the outcomes of interest for this review measured in this trial.
Starting date	Not stated.
Contact information	KRosemark@cymabay.com
Notes	Status: recruiting.

NCT02308111

Trial name or title	A Phase 3b, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study Evaluating the Effect of Obeticholic Acid on Clinical Outcomes in Patients With Primary Biliary Cirrhosis
Methods	Phase 3, double-blind, randomised, placebo-controlled, multicentre study.
Participants	People with primary biliary cholangitis.
Interventions	Group 1: obeticholic acid. Further details: obeticholic acid 5 mg to 10 mg tablets once daily for the duration of the study based on tolerability at 3 months. Group 2: placebo. Further details: 1 tablet daily for the remainder of the study.
Outcomes	Mortality, liver transplantation, liver decompensation, hepatocellular carcinoma.
Starting date	December 2014.
Contact information	dshapiro@interceptpharma.com
Notes	Status: recruiting.

NCT02701166

Trial name or title	The Effect of Bezafibrate on Cholestatic Itch
Methods	Double-blind, randomised, placebo-controlled clinical trial.
Participants	People with primary biliary cholangitis.
Interventions	Group 1: bezafibrate. Further details: bezafibrate 400 mg/day. Group 2: placebo.
Outcomes	None of the outcomes of interest for this review are measured in this trial.
Starting date	February 2016.
Contact information	u.h.beuers@amc.uva.nl
Notes	Status: recruiting.

NCT02823353

Trial name or title	Fenofibrate in Combination with Ursodeoxycholic Acid in Primary Biliary Cirrhosis: a Randomized Control Study
Methods	Phase 3, open-label, randomised clinical trial.
Participants	People with primary biliary cholangitis.
Interventions	Group 1: UDCA + fenofibrate. Further details: not provided. Group 2: UDCA. Further details: not provided.
Outcomes	None of the outcomes of interest for this review are measured in this trial.
Starting date	January 2016.
Contact information	hanying@fmmu.edu.cn
Notes	Status: recruiting.

NCT02823366

Trial name or title	Fenofibrate for Patients with Primary Biliary Cirrhosis who had an Inadequate Response to Ursodeoxycholic Acid
Methods	Phase 3, open-label, randomised clinical trial.

NCT02823366 *(Continued)*

Participants	People with primary biliary cholangitis.
Interventions	Group 1: UDCA + fenofibrate Further details: not provided. Group 2: UDCA. Further details: not provided.
Outcomes	None of the outcomes of interest for this review measured in this trial.
Starting date	January 2016.
Contact information	hanying@fmmu.edu.cn
Notes	Status: recruiting. May be the same as NCT02823353.

NCT02937012

Trial name or title	Efficacy and Security of Bezafibrate in Patients with Primary Biliary Cirrhosis without Biochemical Response to Ursodeoxycholic Acid: a Randomized, Double-blind, Placebo-controlled Trial
Methods	Randomised, double-blind, placebo-controlled clinical trial.
Participants	People with primary biliary cholangitis (non-responders).
Interventions	Group 1: UDCA + bezafibrate. Further details: bezafibrate 200 mg capsule every 12 hours + UDCA 13 mg/kg/day to 15 mg/kg/day for 12 months. Group 2: UDCA + placebo. Further details: placebo capsule (for bezafibrate 200 mg capsule) every 12 hours + UDCA 13 mg/kg/day to 15 mg/kg/day for 12 months.
Outcomes	Quality of life.
Starting date	October 2016.
Contact information	ericlopezmendez@yahoo.com.mx sergio_sg@hotmail.com
Notes	Status: recruiting.

NCT02943447

Trial name or title	A Phase 2, Randomized, Double-Blind, Placebo Controlled Study Evaluating the Safety, Tolerability, and Efficacy of GS-9674 in Subjects with Primary Biliary Cholangitis without Cirrhosis
Methods	Randomised, double-blind, placebo-controlled clinical trial.

NCT02943447 *(Continued)*

Participants	People with primary biliary cholangitis.
Interventions	Group 1: GS-9674. Further details: GS-9674 30 mg for 12 weeks. Group 2: placebo.
Outcomes	Adverse events.
Starting date	December 2016.
Contact information	GS-US-427-4024@Gilead.com
Notes	Status: recruiting.

NCT02965911

Trial name or title	A Randomized Controlled Clinical Trial on the Efficacy and Safety of Fenofibrate Combined with Ursodeoxycholic Acid in PBC Patients with an Incomplete Biochemical Response to UDCA
Methods	Open-label, randomised clinical trial.
Participants	People with primary biliary cholangitis.
Interventions	Group 1: fenofibrate + UDCA. Further details: UDCA 13 mg/kg/day to 15 mg/kg/day + fenofibrate 200 mg once daily for 12 months. Group 2: UDCA. Further details: UDCA 13 mg/kg/day to 15 mg/kg/day.
Outcomes	None of the outcomes of interest for this review measured in this trial.
Starting date	January 2016.
Contact information	zszou302@163.com
Notes	Status: recruiting.

UDCA: ursodeoxycholic acid.

DATA AND ANALYSES

Comparison 1. Main analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality at maximal follow-up	28		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Azathioprine versus no intervention	2	224	Odds Ratio (M-H, Fixed, 95% CI)	0.56 [0.32, 0.98]
1.2 Chlorambucil versus no intervention	1	24	Odds Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 3.28]
1.3 Colchicine versus no intervention	2	122	Odds Ratio (M-H, Fixed, 95% CI)	0.77 [0.32, 1.85]
1.4 Cyclosporin versus no intervention	3	390	Odds Ratio (M-H, Fixed, 95% CI)	0.88 [0.51, 1.50]
1.5 D-Penicillamine versus no intervention	5	423	Odds Ratio (M-H, Fixed, 95% CI)	0.90 [0.57, 1.44]
1.6 Glucocorticosteroids versus no intervention	1	36	Odds Ratio (M-H, Fixed, 95% CI)	0.64 [0.14, 2.92]
1.7 Malotilate versus no intervention	1	101	Odds Ratio (M-H, Fixed, 95% CI)	2.0 [0.47, 8.48]
1.8 Methotrexate versus no intervention	1	60	Odds Ratio (M-H, Fixed, 95% CI)	8.83 [1.01, 76.96]
1.9 UDCA versus no intervention	6	734	Odds Ratio (M-H, Fixed, 95% CI)	0.99 [0.60, 1.64]
1.10 Bezafibrate plus UDCA versus UDCA	1	27	Odds Ratio (M-H, Fixed, 95% CI)	9.67 [0.45, 207.78]
1.11 Colchicine plus UDCA versus UDCA	2	158	Odds Ratio (M-H, Fixed, 95% CI)	1.84 [0.38, 8.91]
1.12 Methotrexate plus UDCA versus UDCA	2	290	Odds Ratio (M-H, Fixed, 95% CI)	1.17 [0.55, 2.51]
1.13 Obeticholic acid plus UDCA versus UDCA	1	216	Odds Ratio (M-H, Fixed, 95% CI)	1.55 [0.06, 38.46]
2 Mortality (< 1 year)	8		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Azathioprine versus no intervention	1	39	Odds Ratio (M-H, Fixed, 95% CI)	0.58 [0.16, 2.10]
2.2 Colchicine versus no intervention	1	64	Odds Ratio (M-H, Fixed, 95% CI)	0.86 [0.22, 3.33]
2.3 Cyclosporin versus no intervention	1	12	Odds Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 3.63]
2.4 D-Penicillamine versus no intervention	1	189	Odds Ratio (M-H, Fixed, 95% CI)	0.71 [0.35, 1.42]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.5 Ursodeoxycholic acid (UDCA) versus no intervention	1	18	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.6 Colchicine plus UDCA versus UDCA	1	84	Odds Ratio (M-H, Fixed, 95% CI)	1.0 [0.13, 7.45]
2.7 Methotrexate plus UDCA versus UDCA	1	25	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.8 Obeticholic acid plus UDCA versus UDCA	1	216	Odds Ratio (M-H, Fixed, 95% CI)	1.55 [0.06, 38.46]
3 Mortality (1 to 5 years)	20		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Azathioprine versus no intervention	1	185	Odds Ratio (M-H, Fixed, 95% CI)	0.56 [0.30, 1.04]
3.2 Chlorambucil versus no intervention	1	24	Odds Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 3.28]
3.3 Colchicine versus no intervention	1	58	Odds Ratio (M-H, Fixed, 95% CI)	0.71 [0.22, 2.25]
3.4 Cyclosporin versus no intervention	2	378	Odds Ratio (M-H, Fixed, 95% CI)	0.94 [0.54, 1.64]
3.5 D-Penicillamine versus no intervention	4	234	Odds Ratio (M-H, Fixed, 95% CI)	1.10 [0.59, 2.08]
3.6 Glucocorticosteroids versus no intervention	1	36	Odds Ratio (M-H, Fixed, 95% CI)	0.64 [0.14, 2.92]
3.7 Malotilate versus no intervention	1	101	Odds Ratio (M-H, Fixed, 95% CI)	2.0 [0.47, 8.48]
3.8 Methotrexate versus no intervention	1	60	Odds Ratio (M-H, Fixed, 95% CI)	8.83 [1.01, 76.96]
3.9 UDCA versus no intervention	5	716	Odds Ratio (M-H, Fixed, 95% CI)	0.99 [0.60, 1.64]
3.10 Bezafibrate plus UDCA versus UDCA	1	27	Odds Ratio (M-H, Fixed, 95% CI)	9.67 [0.45, 207.78]
3.11 Colchicine plus UDCA versus UDCA	1	74	Odds Ratio (M-H, Fixed, 95% CI)	5.28 [0.24, 113.87]
3.12 Methotrexate plus UDCA versus UDCA	1	265	Odds Ratio (M-H, Fixed, 95% CI)	1.17 [0.55, 2.51]
4 Serious adverse events (proportion)	11		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only

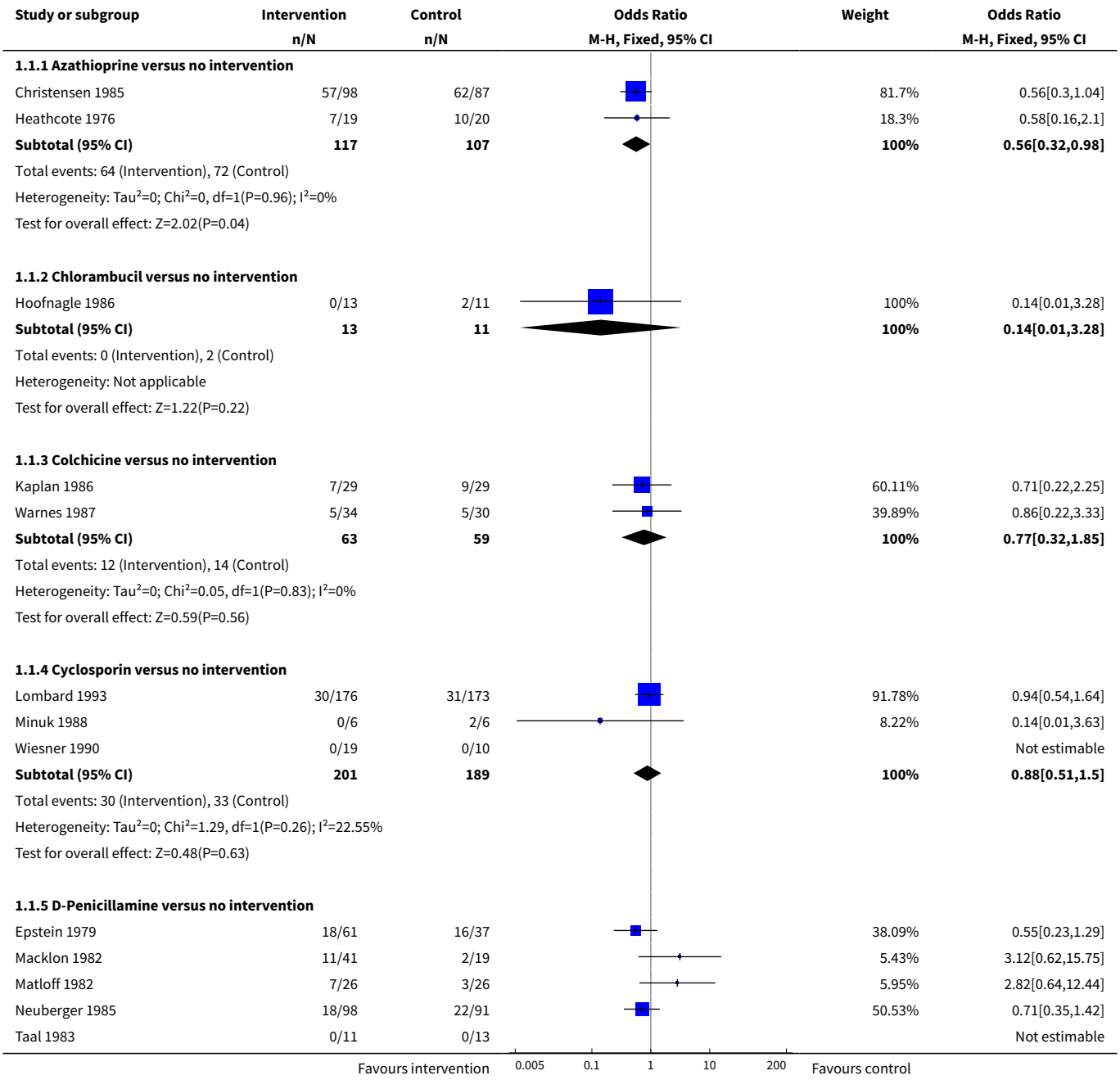
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Colchicine versus no intervention	1	64	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 D-Penicillamine versus no intervention	1	52	Odds Ratio (M-H, Fixed, 95% CI)	28.77 [1.57, 526.67]
4.3 Obeticholic acid versus no intervention	1	165	Odds Ratio (M-H, Fixed, 95% CI)	1.83 [0.21, 15.73]
4.4 UDCA versus no intervention	3	380	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.5 UDCA versus bezafibrate	1	24	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.6 Bezafibrate plus UDCA versus UDCA	1	22	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.7 Colchicine plus UDCA versus UDCA	1	74	Odds Ratio (M-H, Fixed, 95% CI)	3.08 [0.12, 78.14]
4.8 Lamivudine plus zidovudine plus UDCA versus UDCA	1	59	Odds Ratio (M-H, Fixed, 95% CI)	0.47 [0.04, 5.43]
4.9 Obeticholic acid plus UDCA versus UDCA	1	216	Odds Ratio (M-H, Fixed, 95% CI)	3.58 [1.02, 12.51]
5 Serious adverse events (number of events)	1		Rate Ratio (Fixed, 95% CI)	Subtotals only
5.1 Obeticholic acid plus UDCA versus UDCA	1	216	Rate Ratio (Fixed, 95% CI)	1.66 [0.75, 3.66]
6 Adverse events (proportion)	19		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Cyclosporin versus no intervention	3	390	Odds Ratio (M-H, Fixed, 95% CI)	3.04 [1.98, 4.68]
6.2 D-Penicillamine versus no intervention	2	287	Odds Ratio (M-H, Fixed, 95% CI)	4.51 [2.56, 7.93]
6.3 Malotilate versus no intervention	1	101	Odds Ratio (M-H, Fixed, 95% CI)	11.43 [1.40, 93.04]
6.4 Obeticholic acid versus no intervention	1	165	Odds Ratio (M-H, Fixed, 95% CI)	4.58 [1.31, 15.95]
6.5 UDCA versus no intervention	3	380	Odds Ratio (M-H, Fixed, 95% CI)	1.45 [0.50, 4.25]
6.6 Azathioprine plus UDCA versus UDCA	1	42	Odds Ratio (M-H, Fixed, 95% CI)	19.67 [0.94, 413.50]

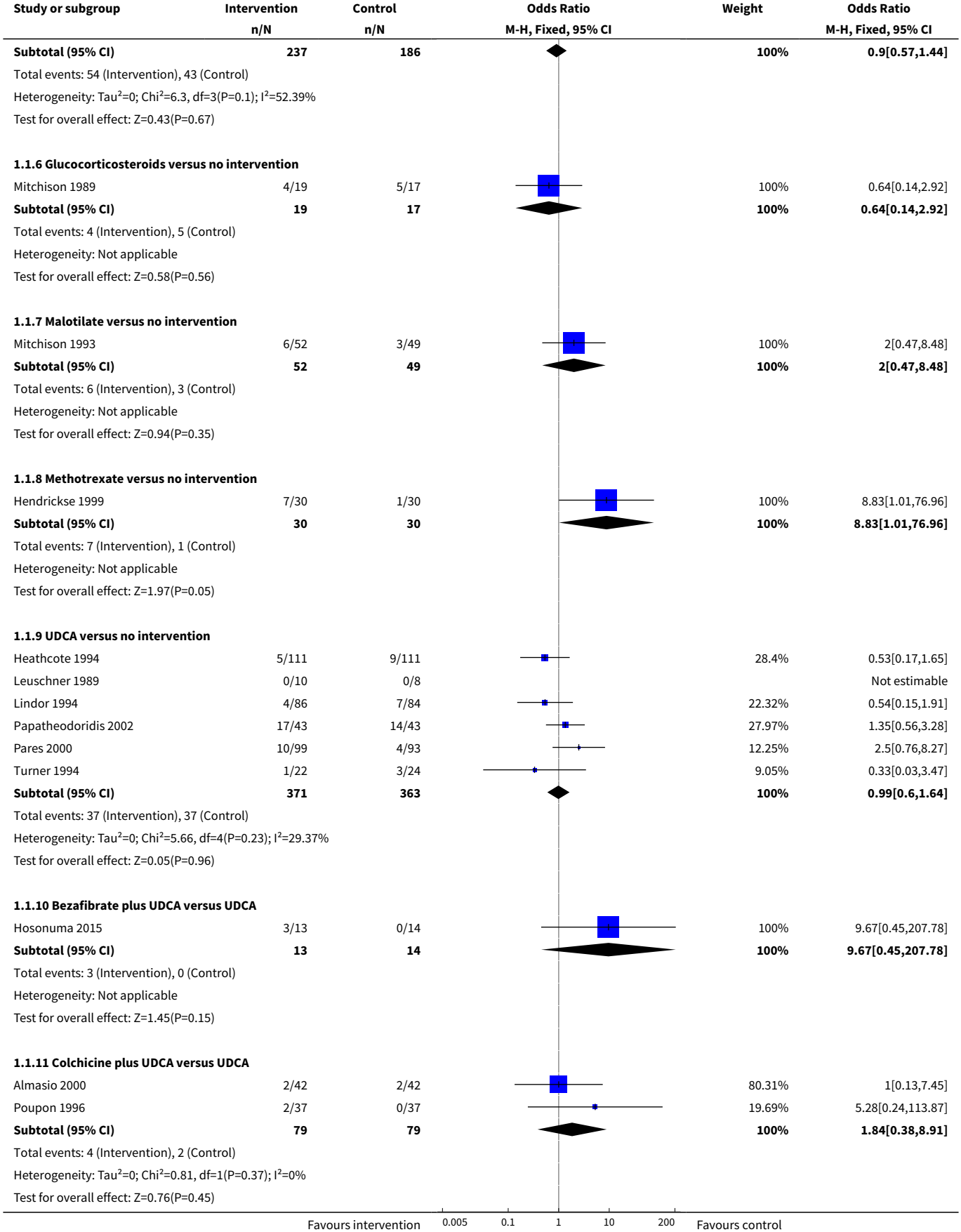
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.7 Bezafibrate versus UDCA	1	24	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.8 Bezafibrate plus UDCA versus UDCA	1	22	Odds Ratio (M-H, Fixed, 95% CI)	3.29 [0.12, 89.81]
6.9 Colchicine plus UDCA versus UDCA	2	42	Odds Ratio (M-H, Fixed, 95% CI)	6.20 [0.63, 60.80]
6.10 Colestilan plus UDCA versus UDCA	1	11	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.11 Glucocorticosteroids plus UDCA versus UDCA	2	135	Odds Ratio (M-H, Fixed, 95% CI)	5.54 [1.35, 22.84]
6.12 Methotrexate plus UDCA versus UDCA	1	25	Odds Ratio (M-H, Fixed, 95% CI)	115.0 [4.98, 2657.48]
6.13 TauroUDCA versus UDCA	1	30	Odds Ratio (M-H, Fixed, 95% CI)	21.0 [2.16, 204.61]
6.14 Glucocorticosteroids plus UDCA versus azathioprine plus UDCA	1	50	Odds Ratio (M-H, Fixed, 95% CI)	0.40 [0.08, 2.12]
7 Adverse events (number)	14		Rate Ratio (Random, 95% CI)	Subtotals only
7.1 Chlorambucil versus no intervention	1	24	Rate Ratio (Random, 95% CI)	3.67 [1.04, 12.87]
7.2 Cyclosporin versus no intervention	3	390	Rate Ratio (Random, 95% CI)	2.58 [1.26, 5.31]
7.3 D-Penicillamine versus no intervention	3	303	Rate Ratio (Random, 95% CI)	2.99 [1.04, 8.63]
7.4 Malotilate versus no intervention	1	101	Rate Ratio (Random, 95% CI)	6.13 [1.38, 27.14]
7.5 Obeticholic acid versus no intervention	1	76	Rate Ratio (Random, 95% CI)	1.41 [1.13, 1.75]
7.6 Azathioprine plus glucocorticosteroids plus UDCA versus UDCA	1	50	Rate Ratio (Random, 95% CI)	1.32 [0.88, 1.97]
7.7 Bezafibrate plus UDCA versus UDCA	1	29	Rate Ratio (Random, 95% CI)	11.79 [0.65, 213.14]
7.8 Colchicine plus UDCA versus UDCA	1	24	Rate Ratio (Random, 95% CI)	5.91 [0.28, 123.08]
7.9 Methotrexate plus UDCA versus UDCA	1	27	Rate Ratio (Random, 95% CI)	30.64 [1.84, 510.76]
7.10 TauroUDCA versus UDCA	1	191	Rate Ratio (Random, 95% CI)	1.17 [0.81, 1.71]

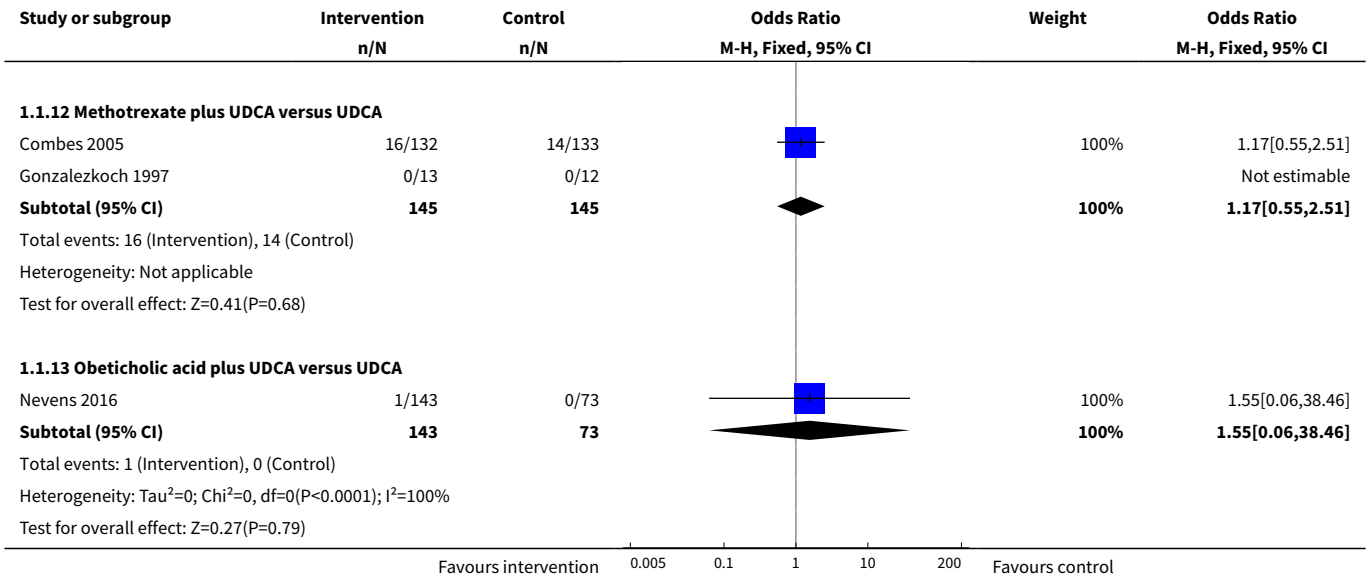
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8 Liver transplantation	11		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 Cyclosporin versus no intervention	2	378	Odds Ratio (M-H, Fixed, 95% CI)	0.86 [0.43, 1.72]
8.2 D-Penicillamine versus no intervention	1	189	Odds Ratio (M-H, Fixed, 95% CI)	0.93 [0.06, 15.05]
8.3 Methotrexate versus no intervention	1	60	Odds Ratio (M-H, Fixed, 95% CI)	0.17 [0.02, 1.58]
8.4 UDCA versus no intervention	5	640	Odds Ratio (M-H, Fixed, 95% CI)	0.90 [0.48, 1.68]
8.5 Bezafibrate plus UDCA versus UDCA	1	27	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.6 Methotrexate plus UDCA versus UDCA	1	265	Odds Ratio (M-H, Fixed, 95% CI)	0.70 [0.35, 1.39]
9 Decompensated liver disease	7		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 D-Penicillamine versus no active treatment	1	24	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.2 UDCA versus no intervention	2	237	Odds Ratio (M-H, Fixed, 95% CI)	1.60 [0.86, 2.98]
9.3 Azathioprine plus UDCA versus UDCA	1	42	Odds Ratio (M-H, Fixed, 95% CI)	0.52 [0.05, 5.18]
9.4 Colchicine plus UDCA versus UDCA	1	84	Odds Ratio (M-H, Fixed, 95% CI)	0.21 [0.04, 1.07]
9.5 Glucocorticosteroids plus UDCA versus UDCA	1	66	Odds Ratio (M-H, Fixed, 95% CI)	0.55 [0.11, 2.69]
9.6 Methotrexate plus UDCA versus UDCA	1	265	Odds Ratio (M-H, Fixed, 95% CI)	1.34 [0.77, 2.33]
9.7 Obeticholic acid plus UDCA versus UDCA	1	216	Odds Ratio (M-H, Fixed, 95% CI)	1.55 [0.06, 38.46]
9.8 Glucocorticosteroids plus UDCA versus azathioprine plus UDCA	1	50	Odds Ratio (M-H, Fixed, 95% CI)	1.06 [0.10, 11.18]
10 Cirrhosis	3		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 Azathioprine versus no intervention	1	31	Odds Ratio (M-H, Fixed, 95% CI)	0.79 [0.18, 3.41]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.2 UDCA versus no intervention	1	22	Odds Ratio (M-H, Fixed, 95% CI)	0.15 [0.01, 1.53]
10.3 Azathioprine plus glucocorticosteroids plus UDCA versus UDCA	1	50	Odds Ratio (M-H, Fixed, 95% CI)	0.28 [0.03, 2.90]

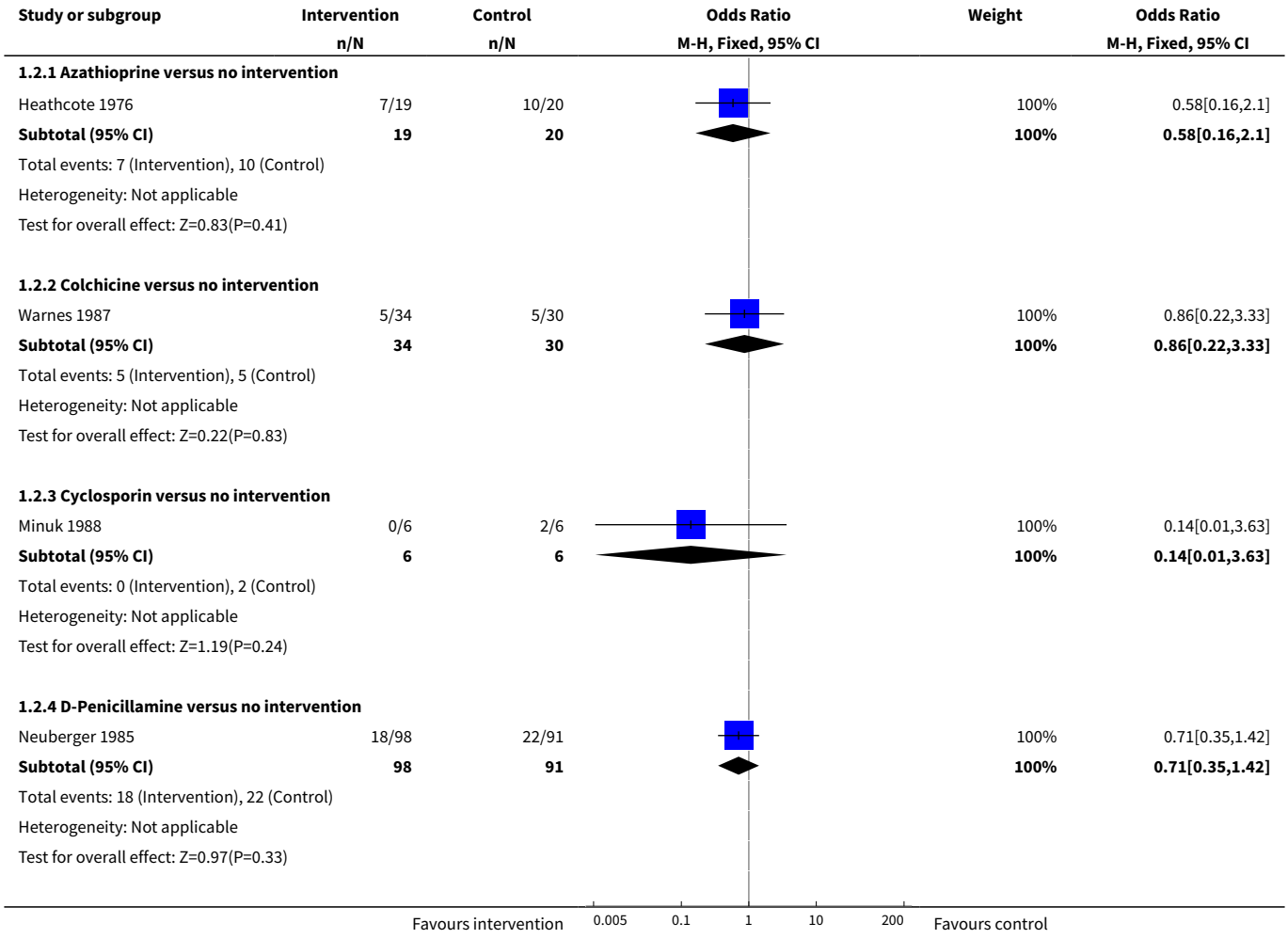
Analysis 1.1. Comparison 1 Main analysis, Outcome 1 Mortality at maximal follow-up.

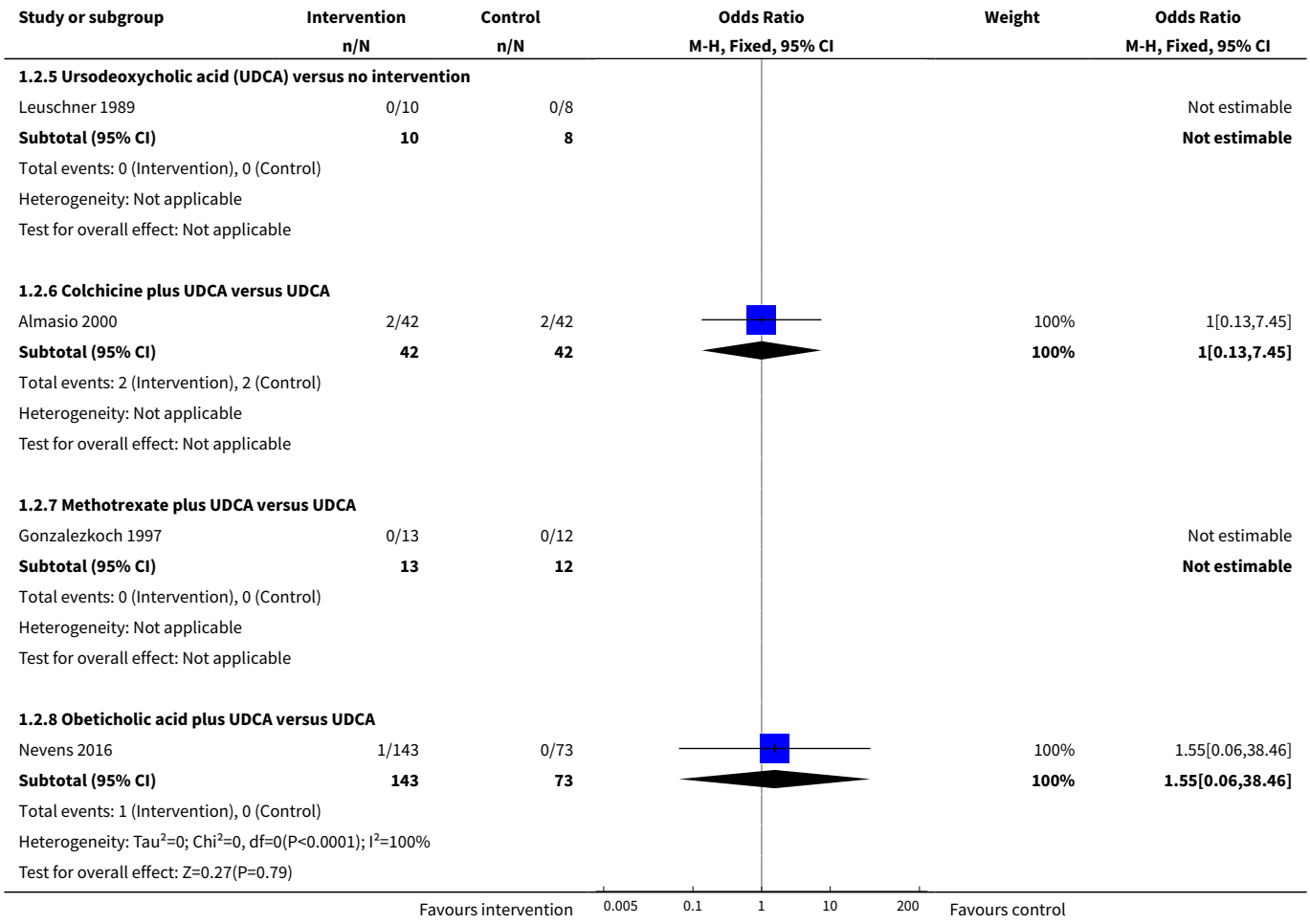




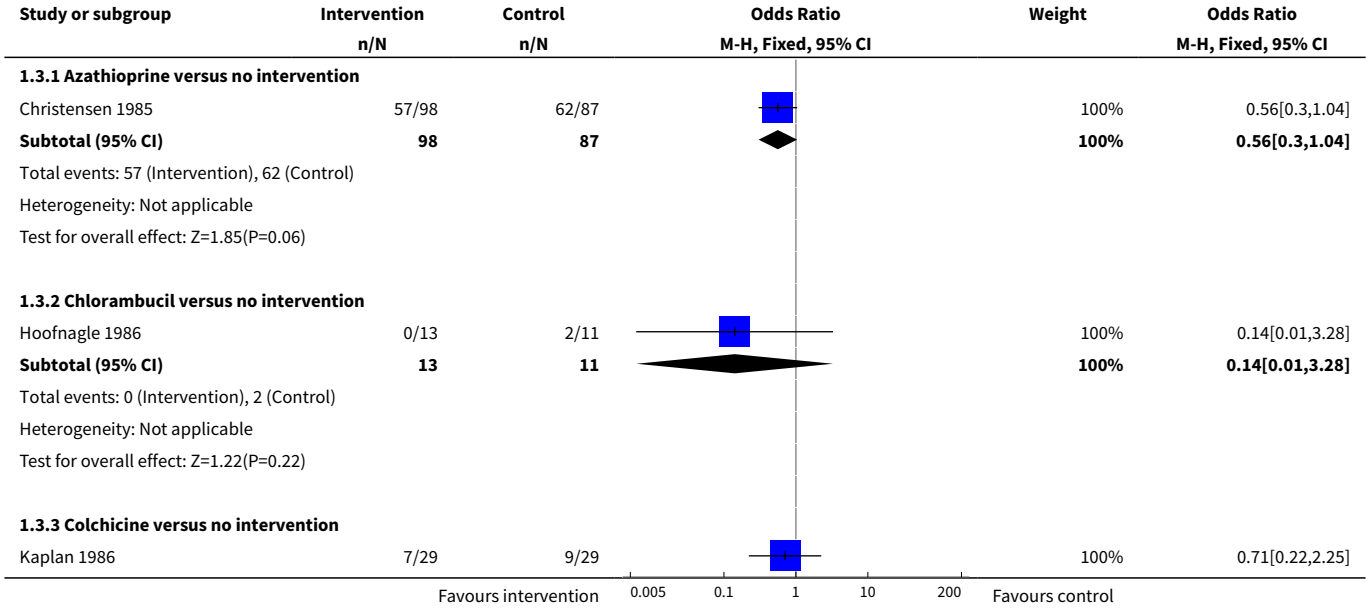


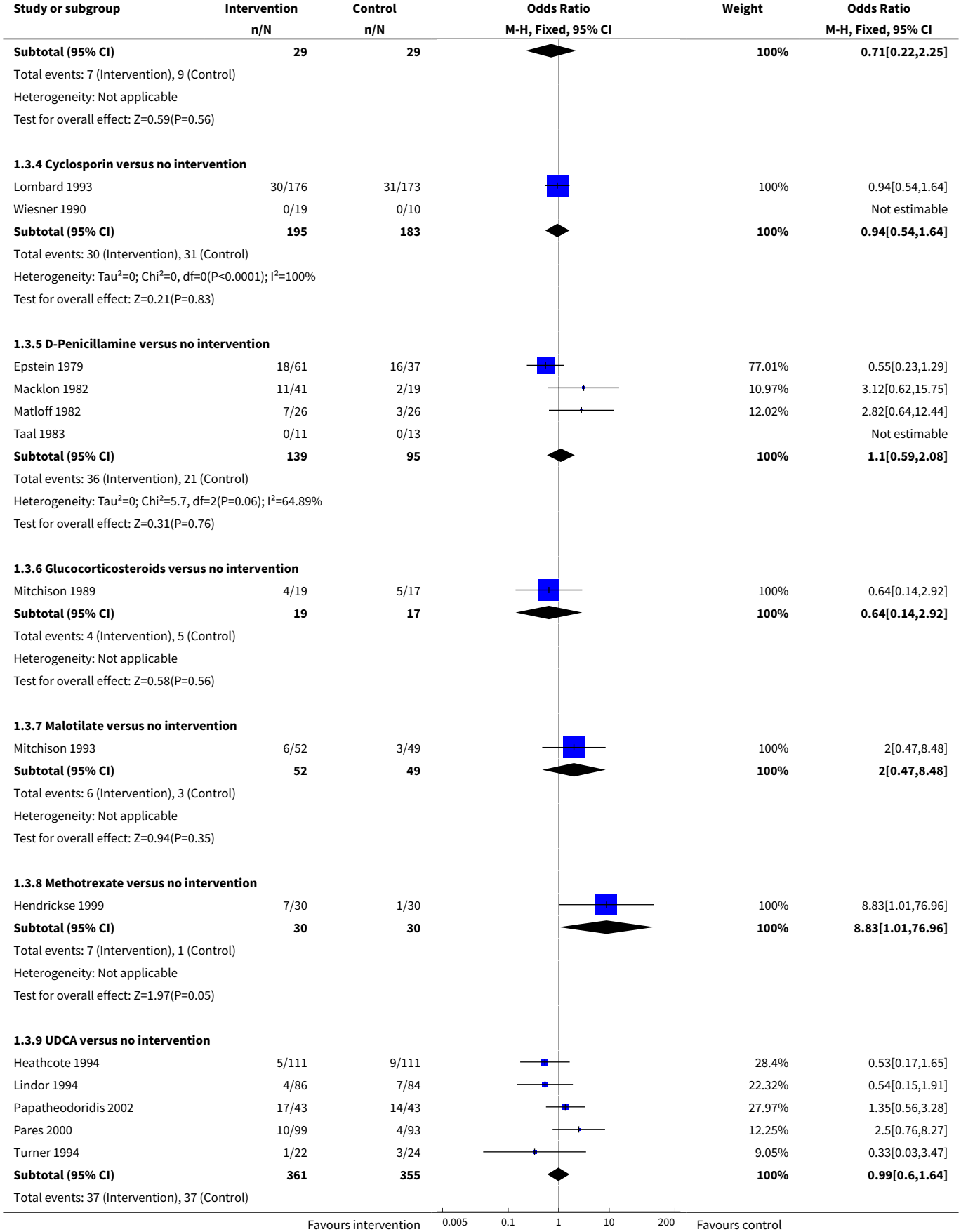
Analysis 1.2. Comparison 1 Main analysis, Outcome 2 Mortality (< 1 year).

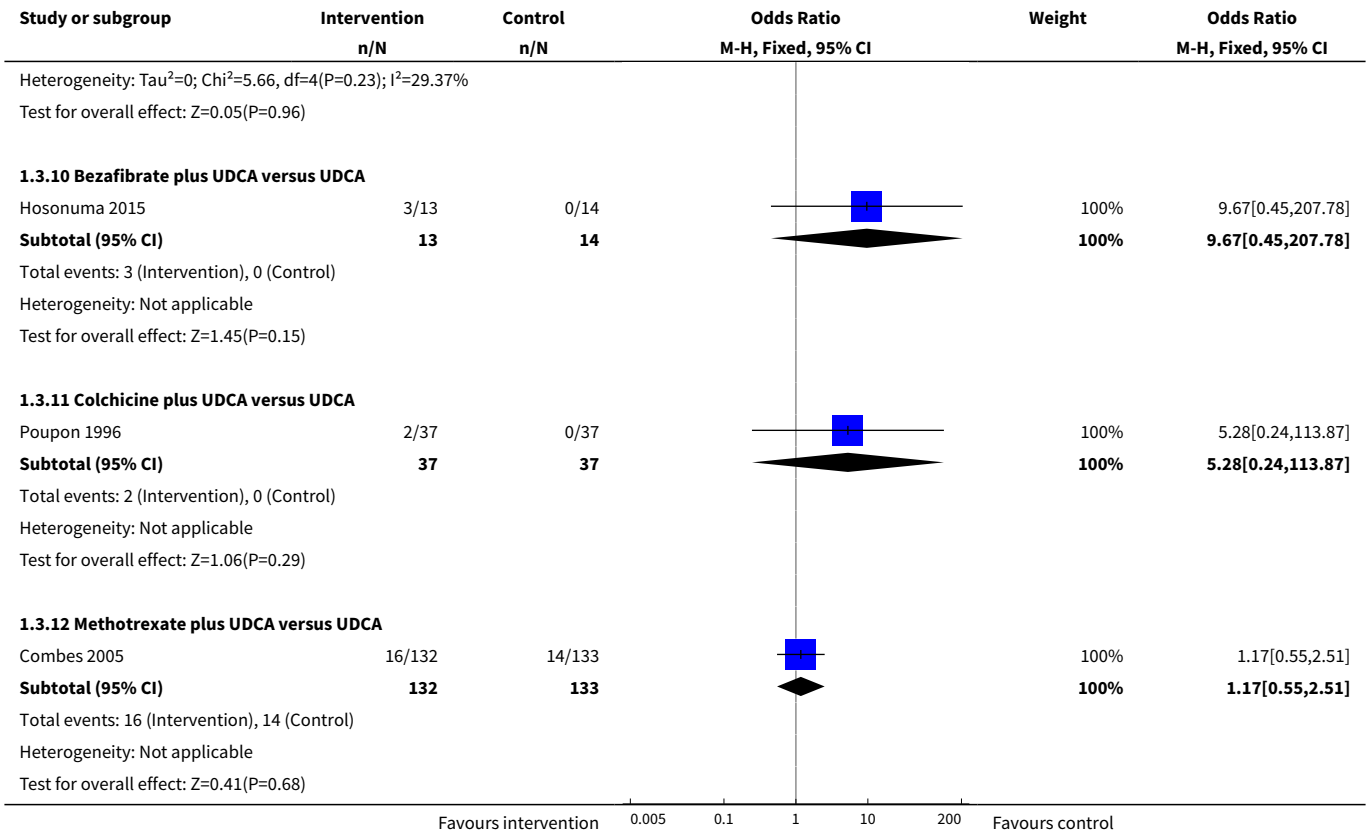




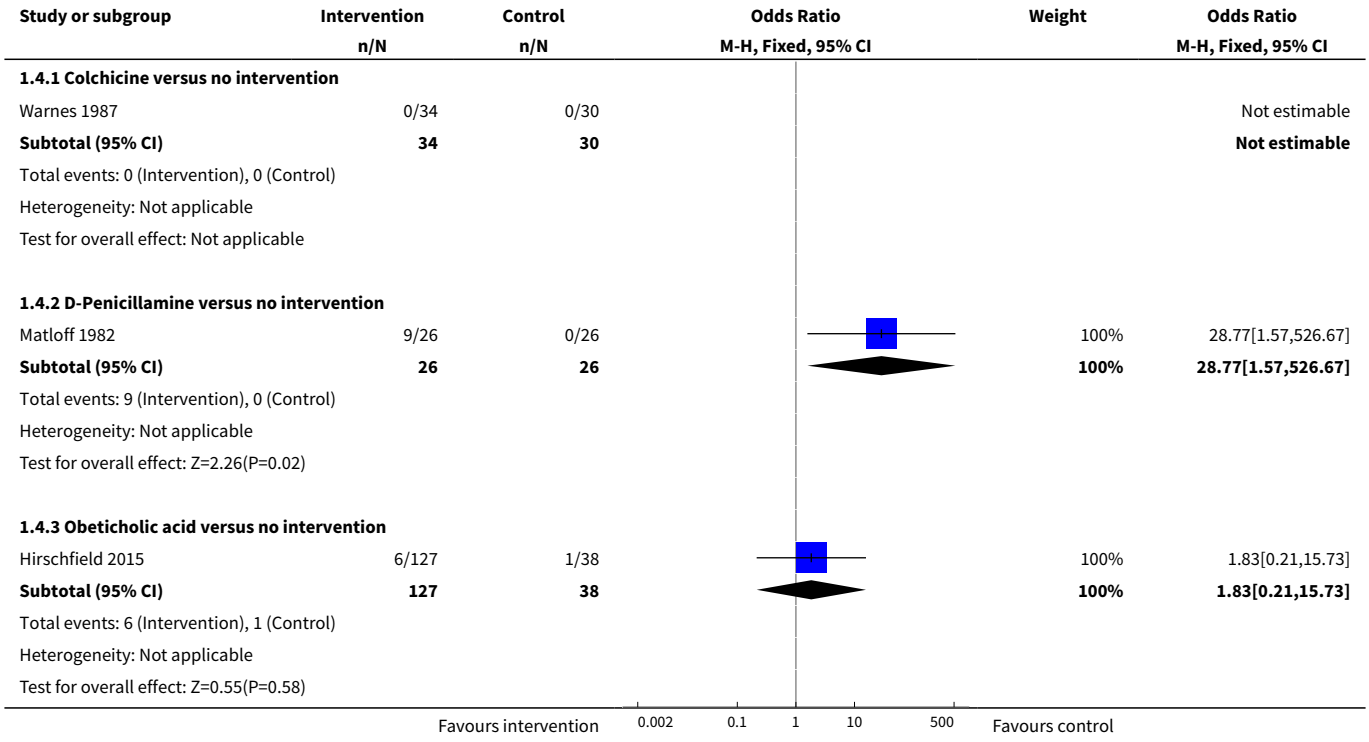
Analysis 1.3. Comparison 1 Main analysis, Outcome 3 Mortality (1 to 5 years).

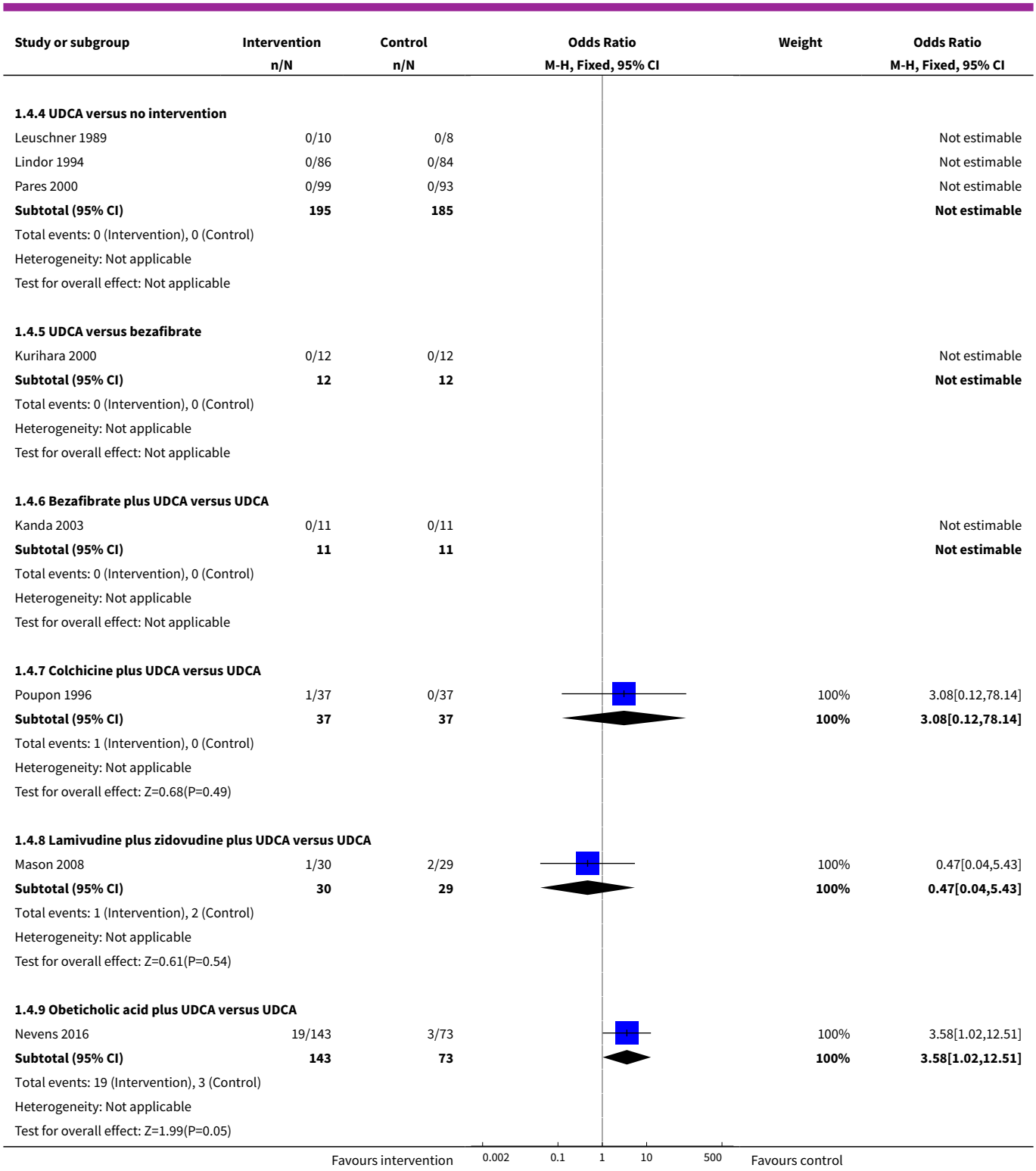






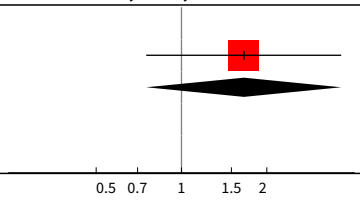
Analysis 1.4. Comparison 1 Main analysis, Outcome 4 Serious adverse events (proportion).





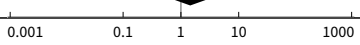
Analysis 1.5. Comparison 1 Main analysis, Outcome 5 Serious adverse events (number of events).

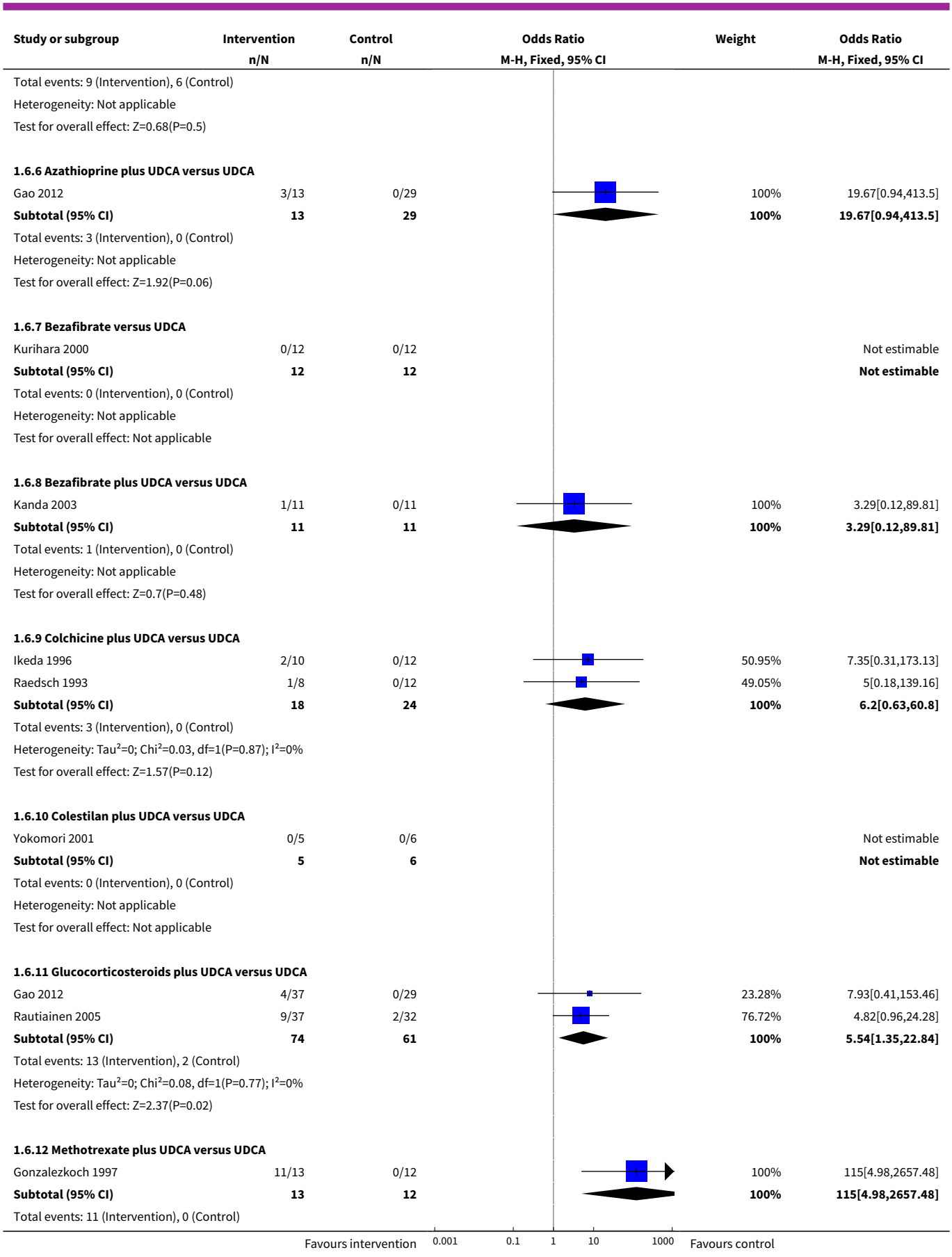
Study or subgroup	Inter-vention N	Control N	log[Rate Ratio] (SE)	Rate Ratio IV, Fixed, 95% CI	Weight	Rate Ratio IV, Fixed, 95% CI
1.5.1 Obeticholic acid plus UDCA versus UDCA						
Nevens 2016	73	143	0.5 (0.404)		100%	1.66[0.75,3.66]
Subtotal (95% CI)					**100%**	**1.66[0.75,3.66]**
Heterogeneity: Not applicable						
Test for overall effect: Z=1.25(P=0.21)						

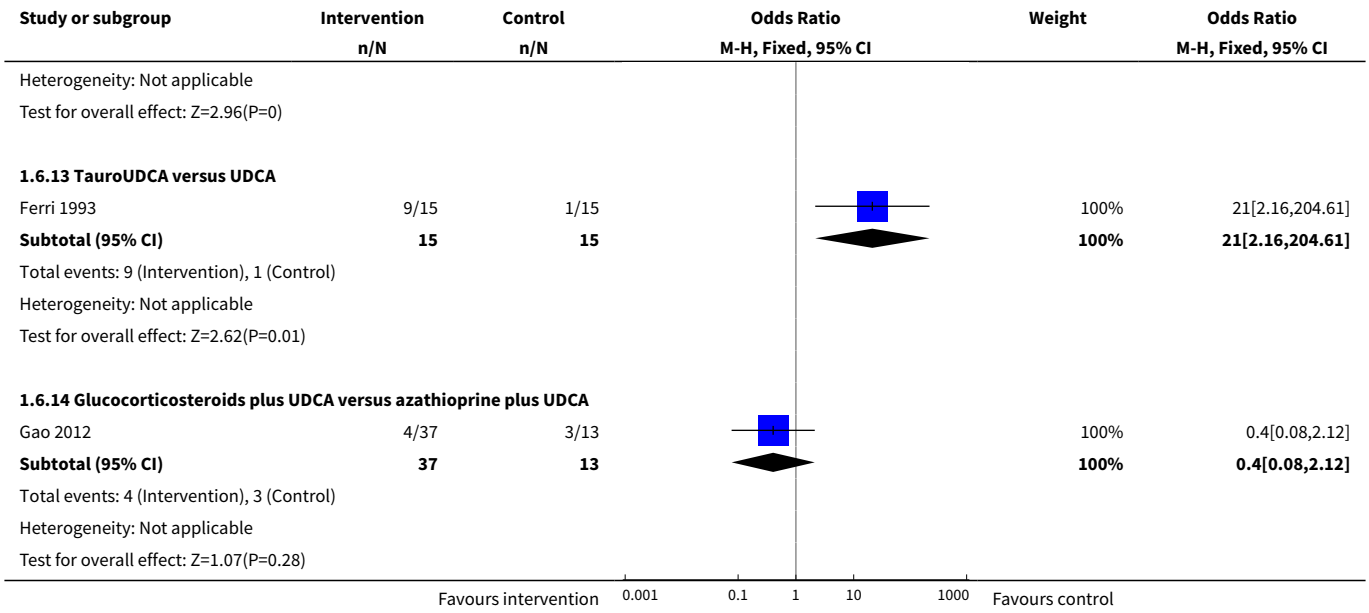


Analysis 1.6. Comparison 1 Main analysis, Outcome 6 Adverse events (proportion).

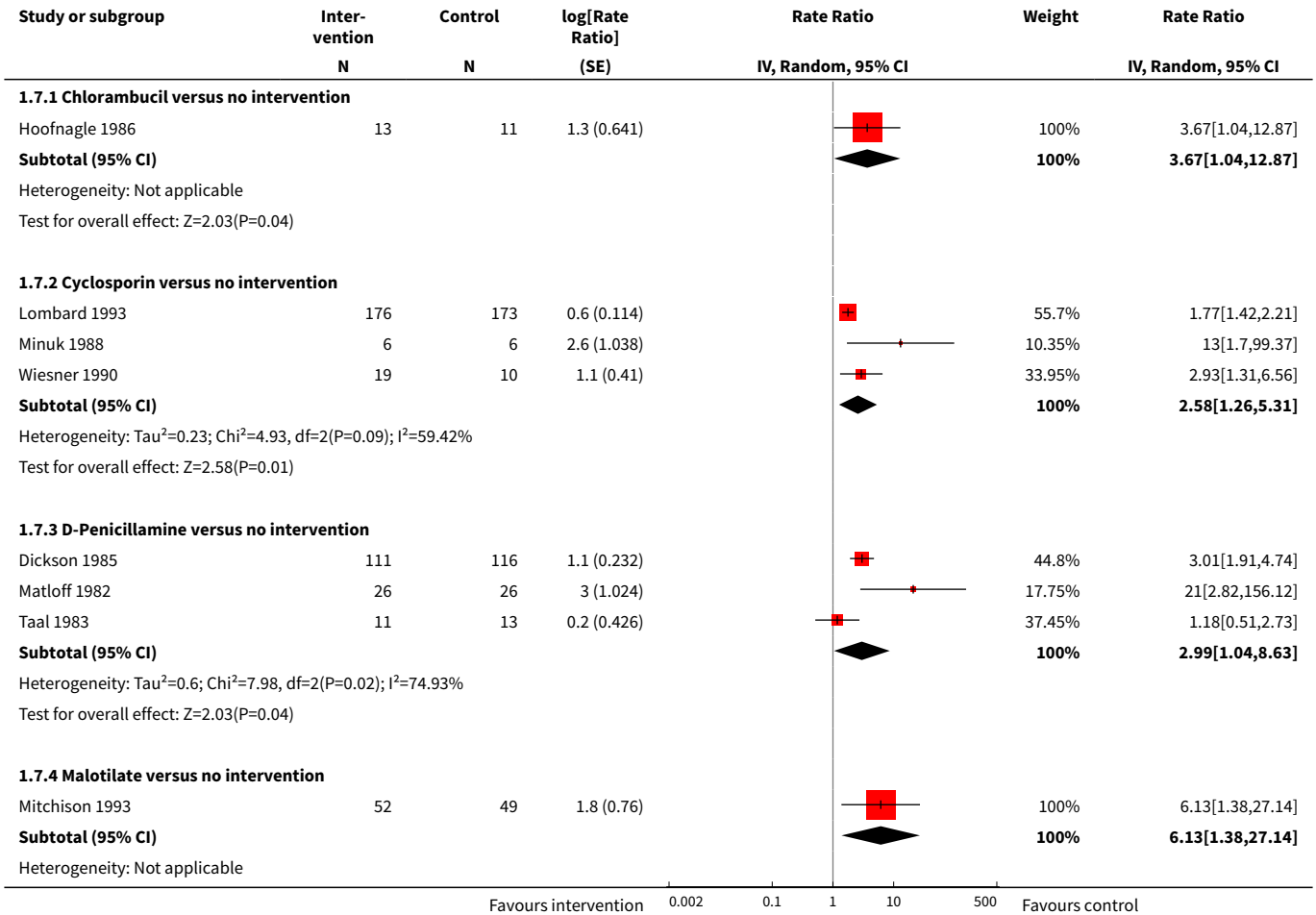
Study or subgroup	Intervention n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
1.6.1 Cyclosporin versus no intervention					
Lombard 1993	133/176	91/173		93.78%	2.79[1.77,4.39]
Minuk 1988	6/6	1/6		0.45%	47.67[1.6,1422.69]
Wiesner 1990	15/19	5/10		5.77%	3.75[0.71,19.71]
Subtotal (95% CI)	**201**	**189**		**100%**	**3.04[1.98,4.68]**
Total events: 154 (Intervention), 97 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.73, df=2(P=0.26); I^2=26.62%					
Test for overall effect: Z=5.07(P<0.0001)					
1.6.2 D-Penicillamine versus no intervention					
Dickson 1985	59/111	25/116		95.75%	4.13[2.32,7.37]
Macklon 1982	10/41	0/19		4.25%	13[0.72,234.55]
Subtotal (95% CI)	**152**	**135**		**100%**	**4.51[2.56,7.93]**
Total events: 69 (Intervention), 25 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.6, df=1(P=0.44); I^2=0%					
Test for overall effect: Z=5.22(P<0.0001)					
1.6.3 Malotilate versus no intervention					
Mitchison 1993	10/52	1/49		100%	11.43[1.4,93.04]
Subtotal (95% CI)	**52**	**49**		**100%**	**11.43[1.4,93.04]**
Total events: 10 (Intervention), 1 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.28(P=0.02)					
1.6.4 Obeticholic acid versus no intervention					
Hirschfield 2015	122/127	32/38		100%	4.58[1.31,15.95]
Subtotal (95% CI)	**127**	**38**		**100%**	**4.58[1.31,15.95]**
Total events: 122 (Intervention), 32 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.39(P=0.02)					
1.6.5 UDCA versus no intervention					
Leuschner 1989	0/10	0/8			Not estimable
Lindor 1994	0/86	0/84			Not estimable
Pares 2000	9/99	6/93		100%	1.45[0.5,4.25]
Subtotal (95% CI)	**195**	**185**		**100%**	**1.45[0.5,4.25]**

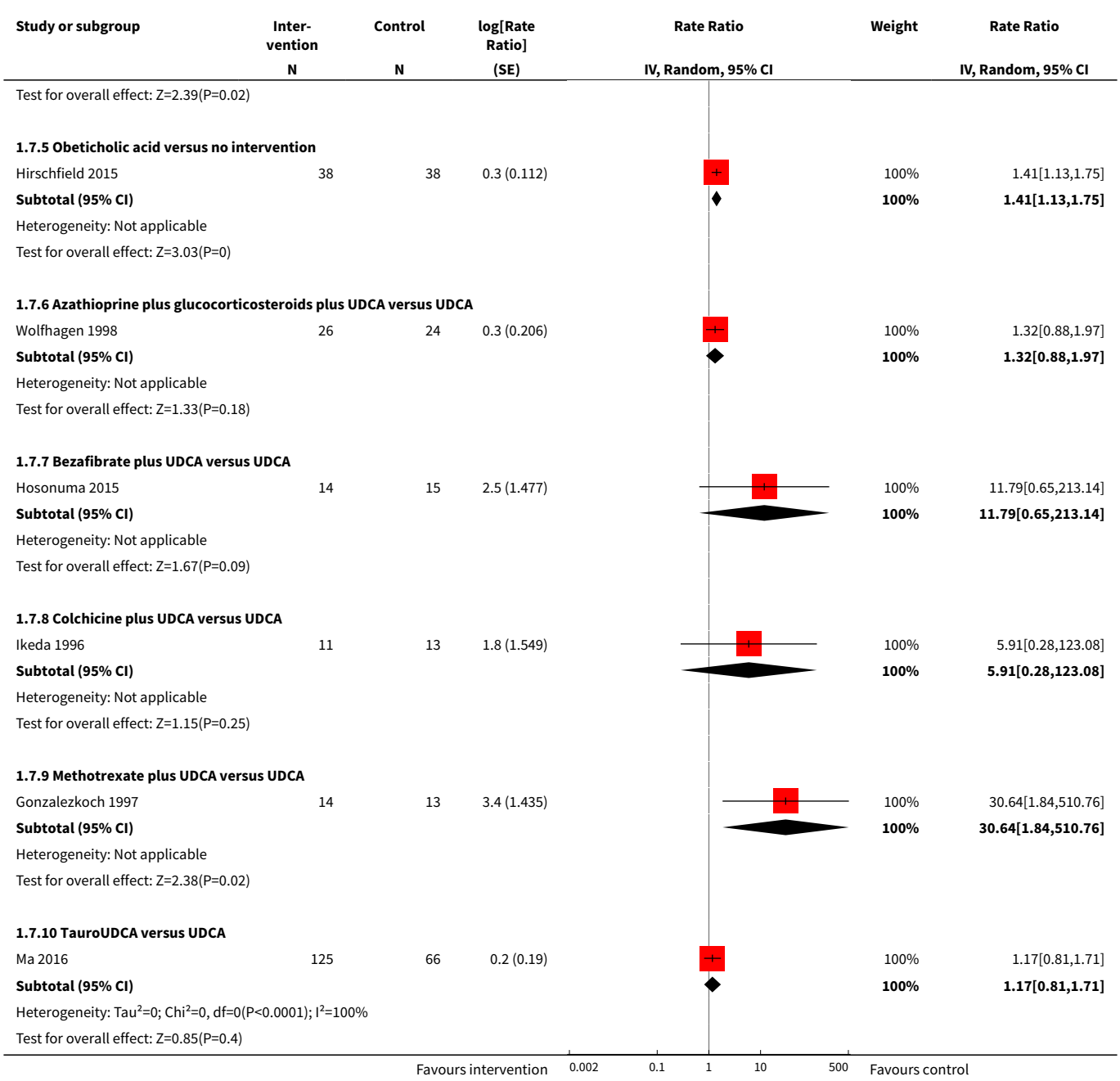




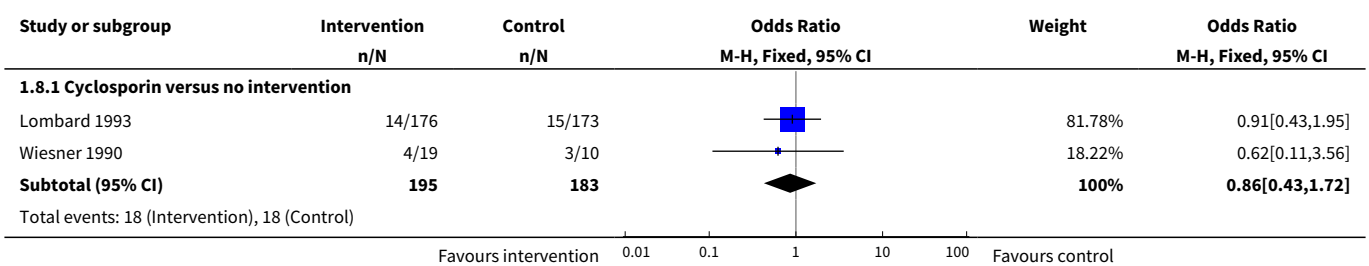


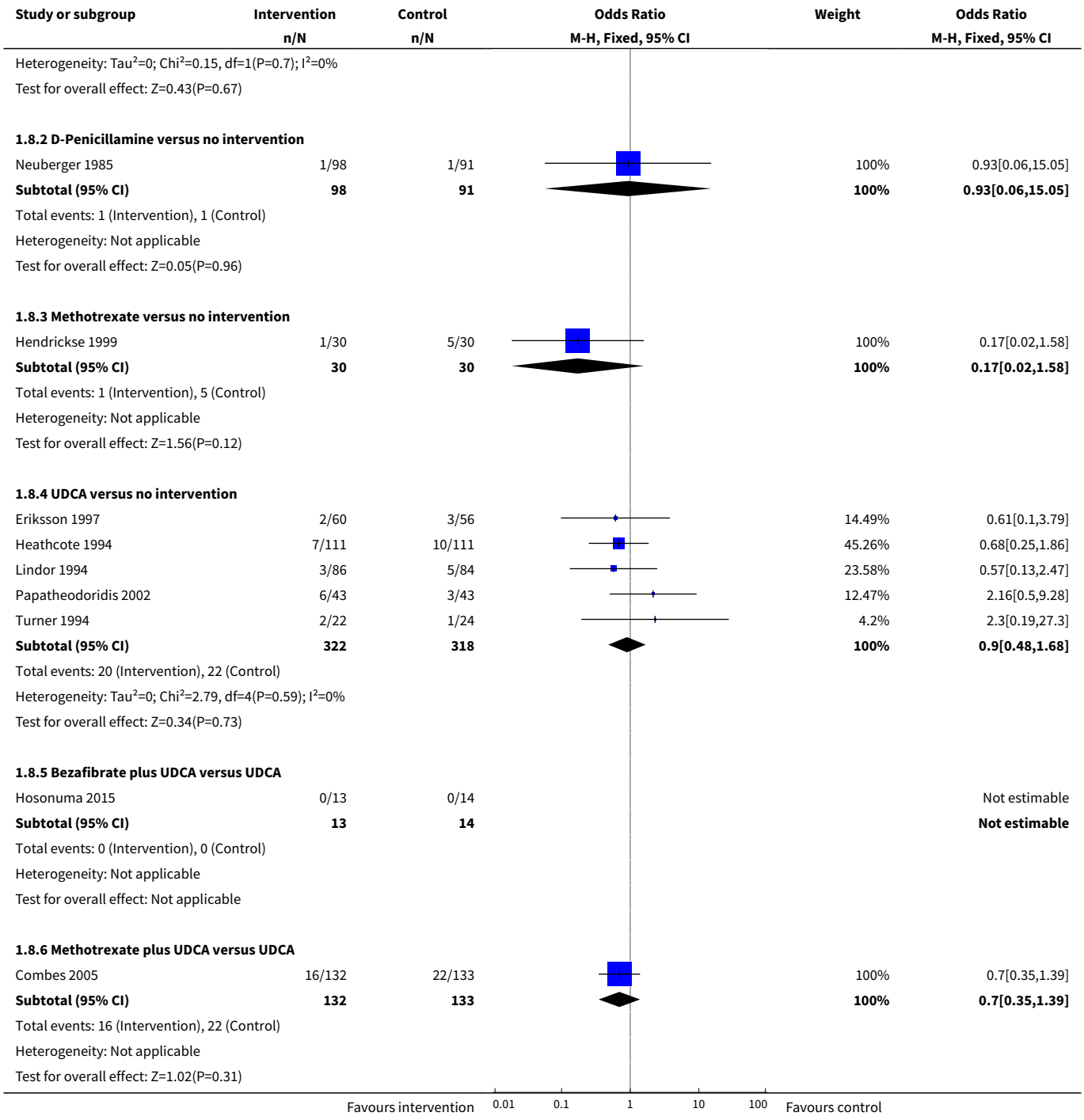
Analysis 1.7. Comparison 1 Main analysis, Outcome 7 Adverse events (number).



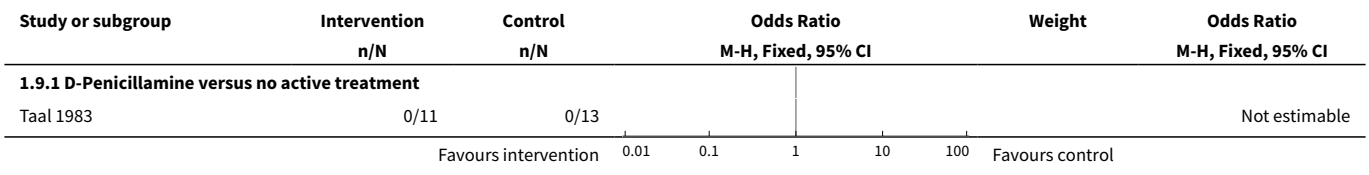


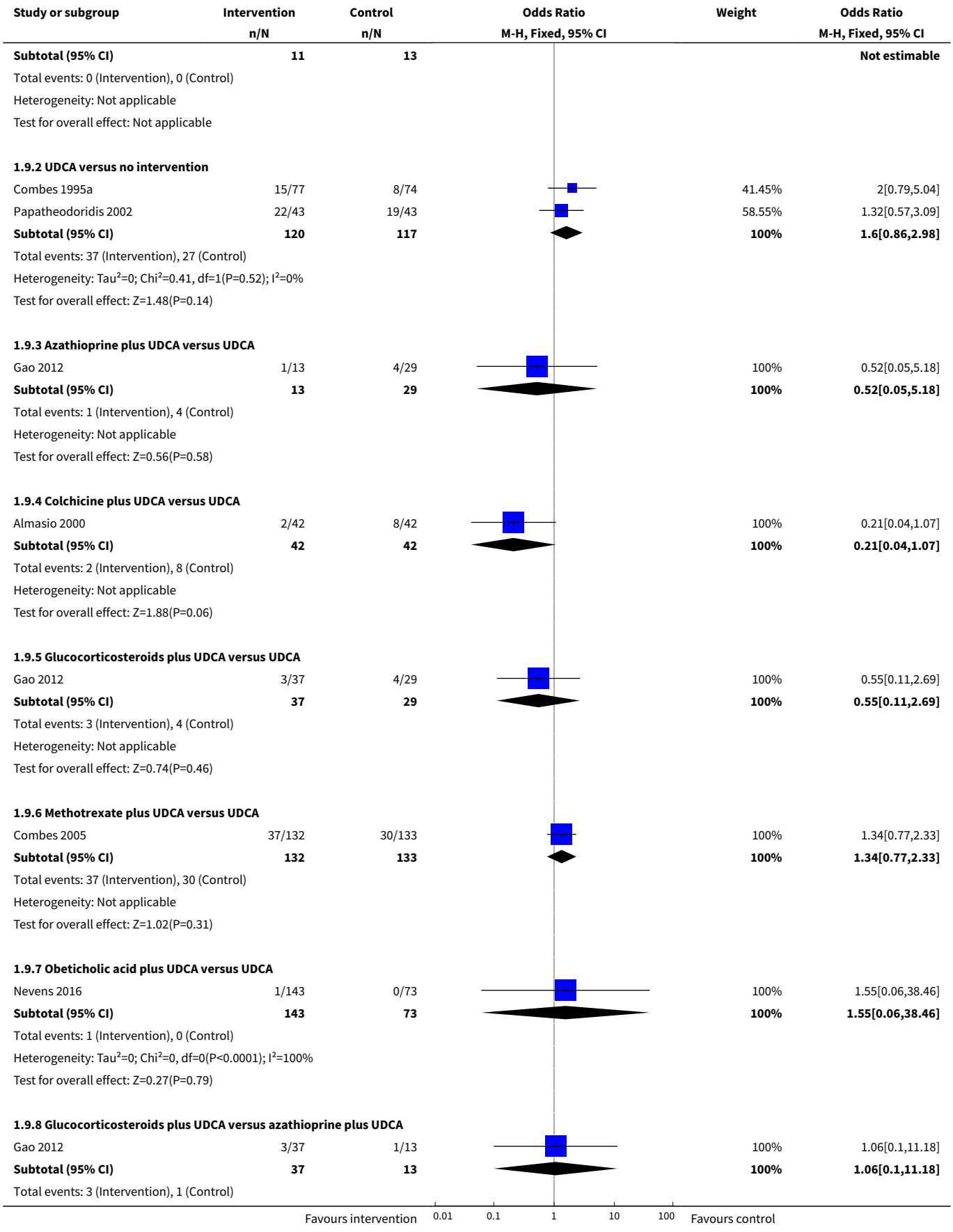
Analysis 1.8. Comparison 1 Main analysis, Outcome 8 Liver transplantation.

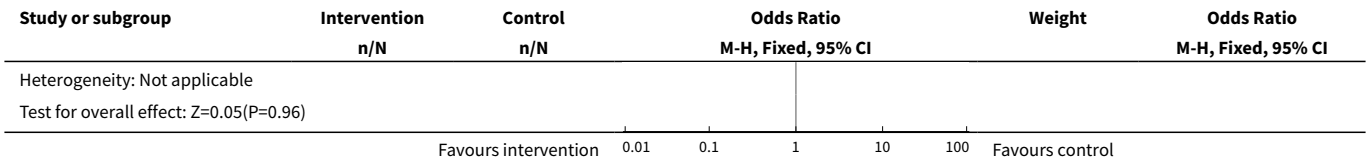




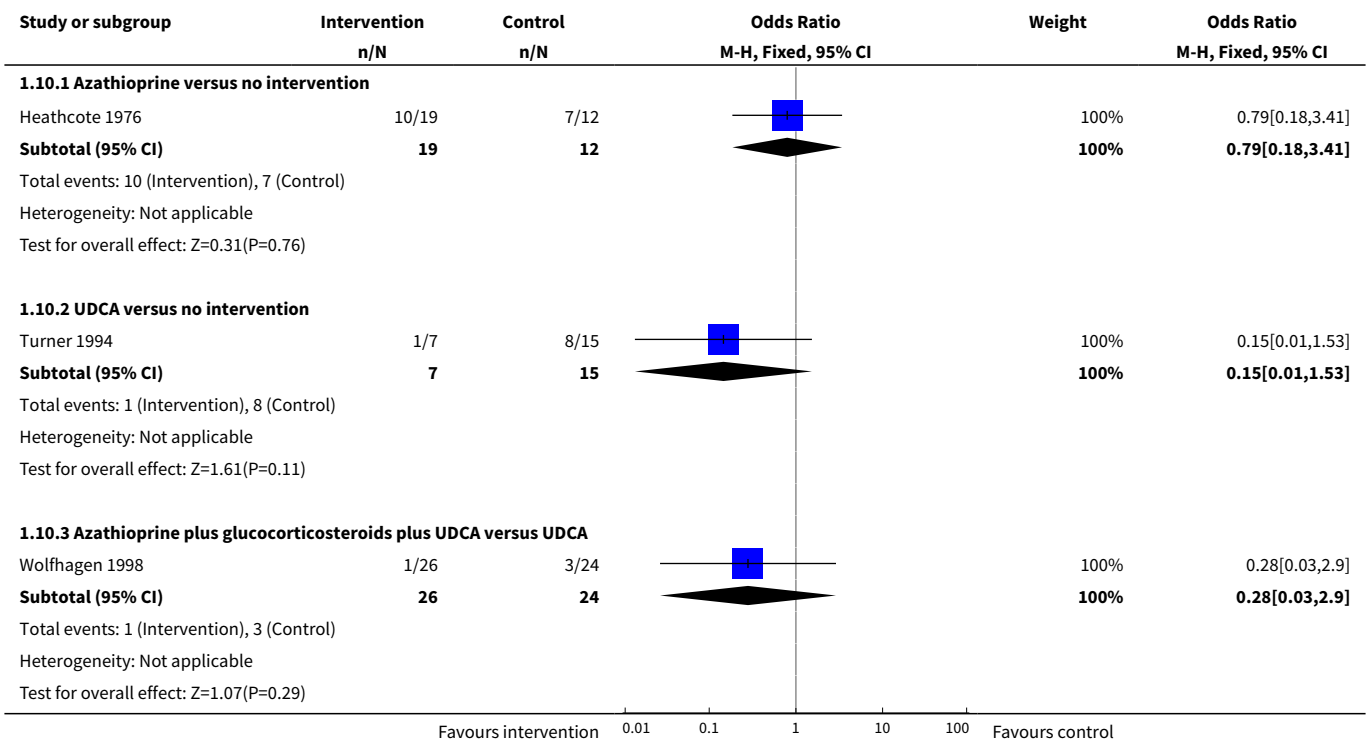
Analysis 1.9. Comparison 1 Main analysis, Outcome 9 Decompensated liver disease.







Analysis 1.10. Comparison 1 Main analysis, Outcome 10 Cirrhosis.



Comparison 2. Stratified by dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality at maximal follow-up	29		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Azathioprine versus no intervention	2	224	Odds Ratio (M-H, Fixed, 95% CI)	0.56 [0.32, 0.98]
1.2 Chlorambucil versus no intervention	1	24	Odds Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 3.28]
1.3 Colchicine versus no intervention	2	122	Odds Ratio (M-H, Fixed, 95% CI)	0.77 [0.32, 1.85]
1.4 Cyclosporin versus no intervention	3	390	Odds Ratio (M-H, Fixed, 95% CI)	0.88 [0.51, 1.50]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.5 D-Penicillamine versus no intervention	5	423	Odds Ratio (M-H, Fixed, 95% CI)	0.90 [0.57, 1.44]
1.6 Glucocorticosteroids versus no intervention	1	36	Odds Ratio (M-H, Fixed, 95% CI)	0.64 [0.14, 2.92]
1.7 Malotilate versus no intervention	1	101	Odds Ratio (M-H, Fixed, 95% CI)	2.0 [0.47, 8.48]
1.8 Methotrexate versus no intervention	1	60	Odds Ratio (M-H, Fixed, 95% CI)	8.83 [1.01, 76.96]
1.9 UDCA (low) versus no intervention	2	64	Odds Ratio (M-H, Fixed, 95% CI)	0.33 [0.03, 3.47]
1.10 UDCA (moderate) versus no intervention	4	670	Odds Ratio (M-H, Fixed, 95% CI)	1.05 [0.62, 1.77]
1.11 UDCA (low) versus UDCA (high)	1	106	Odds Ratio (M-H, Fixed, 95% CI)	1.04 [0.06, 17.06]
1.12 UDCA (moderate) versus UDCA (high)	1	103	Odds Ratio (M-H, Fixed, 95% CI)	0.36 [0.01, 9.05]
1.13 UDCA (low) plus colchicine versus UDCA (low)	1	84	Odds Ratio (M-H, Fixed, 95% CI)	1.0 [0.13, 7.45]
1.14 UDCA (low) plus methotrexate versus UDCA (low)	1	25	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.15 UDCA (moderate) versus UDCA (low)	1	101	Odds Ratio (M-H, Fixed, 95% CI)	0.35 [0.01, 8.72]
1.16 Bezafibrate plus UDCA (moderate) versus UDCA (moderate)	1	27	Odds Ratio (M-H, Fixed, 95% CI)	9.67 [0.45, 207.78]
1.17 Colchicine plus UDCA (moderate) versus UDCA (moderate)	1	74	Odds Ratio (M-H, Fixed, 95% CI)	5.28 [0.24, 113.87]
1.18 Methotrexate plus UDCA (moderate) versus UDCA (moderate)	1	265	Odds Ratio (M-H, Fixed, 95% CI)	1.17 [0.55, 2.51]
1.19 Obeticholic acid (low) plus UDCA (moderate) versus UDCA (moderate)	1	216	Odds Ratio (M-H, Fixed, 95% CI)	1.55 [0.06, 38.46]
2 Mortality (< 1 year)	9		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Azathioprine versus no intervention	1	39	Odds Ratio (M-H, Fixed, 95% CI)	0.58 [0.16, 2.10]
2.2 Colchicine versus no intervention	1	64	Odds Ratio (M-H, Fixed, 95% CI)	0.86 [0.22, 3.33]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.3 Cyclosporin versus no intervention	1	12	Odds Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 3.63]
2.4 D-Penicillamine versus no intervention	1	189	Odds Ratio (M-H, Fixed, 95% CI)	0.71 [0.35, 1.42]
2.5 UDCA (low) versus no intervention	1	18	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.6 UDCA (low) versus UDCA (high)	1	106	Odds Ratio (M-H, Fixed, 95% CI)	1.04 [0.06, 17.06]
2.7 UDCA (moderate) versus UDCA (high)	1	103	Odds Ratio (M-H, Fixed, 95% CI)	0.36 [0.01, 9.05]
2.8 Obeticholic acid (low) plus UDCA (moderate) versus UDCA (moderate)	1	216	Odds Ratio (M-H, Fixed, 95% CI)	1.55 [0.06, 38.46]
2.9 UDCA (low) plus colchicine versus UDCA (low)	1	84	Odds Ratio (M-H, Fixed, 95% CI)	1.0 [0.13, 7.45]
2.10 UDCA (low) plus methotrexate versus UDCA (low)	1	25	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.11 UDCA (moderate) versus UDCA (low)	1	101	Odds Ratio (M-H, Fixed, 95% CI)	0.35 [0.01, 8.72]
3 Mortality (1 to 5 years)	20		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Azathioprine versus no intervention	1	185	Odds Ratio (M-H, Fixed, 95% CI)	0.56 [0.30, 1.04]
3.2 Chlorambucil versus no intervention	1	24	Odds Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 3.28]
3.3 Colchicine versus no intervention	1	58	Odds Ratio (M-H, Fixed, 95% CI)	0.71 [0.22, 2.25]
3.4 Cyclosporin versus no intervention	2	378	Odds Ratio (M-H, Fixed, 95% CI)	0.94 [0.54, 1.64]
3.5 D-Penicillamine versus no intervention	4	234	Odds Ratio (M-H, Fixed, 95% CI)	1.10 [0.59, 2.08]
3.6 Glucocorticosteroids versus no intervention	1	36	Odds Ratio (M-H, Fixed, 95% CI)	0.64 [0.14, 2.92]
3.7 Malotilate versus no intervention	1	101	Odds Ratio (M-H, Fixed, 95% CI)	2.0 [0.47, 8.48]
3.8 Methotrexate versus no intervention	1	60	Odds Ratio (M-H, Fixed, 95% CI)	8.83 [1.01, 76.96]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.9 UDCA (low) versus no intervention	1	46	Odds Ratio (M-H, Fixed, 95% CI)	0.33 [0.03, 3.47]
3.10 UDCA (moderate) versus no intervention	4	670	Odds Ratio (M-H, Fixed, 95% CI)	1.05 [0.62, 1.77]
3.11 Bezafibrate plus UDCA (moderate) versus UDCA (moderate)	1	27	Odds Ratio (M-H, Fixed, 95% CI)	9.67 [0.45, 207.78]
3.12 Colchicine plus UDCA (moderate) versus UDCA (moderate)	1	74	Odds Ratio (M-H, Fixed, 95% CI)	5.28 [0.24, 113.87]
3.13 Methotrexate plus UDCA (moderate) versus UDCA (moderate)	1	265	Odds Ratio (M-H, Fixed, 95% CI)	1.17 [0.55, 2.51]
4 Serious adverse events (proportion)	12		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Colchicine versus no intervention	1	64	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 D-Penicillamine versus no intervention	1	52	Odds Ratio (M-H, Fixed, 95% CI)	28.77 [1.57, 526.67]
4.3 Obeticholic acid (high) versus no intervention	1	79	Odds Ratio (M-H, Fixed, 95% CI)	5.14 [0.57, 46.17]
4.4 Obeticholic acid (low) versus no intervention	1	76	Odds Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 8.22]
4.5 Obeticholic acid (moderate) versus no intervention	1	86	Odds Ratio (M-H, Fixed, 95% CI)	0.79 [0.05, 13.01]
4.6 UDCA (low) versus no intervention	1	18	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.7 UDCA (moderate) versus no intervention	2	362	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.8 UDCA (low) versus bezafibrate	1	24	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.9 Obeticholic acid (low) versus obeticholic acid (high)	1	79	Odds Ratio (M-H, Fixed, 95% CI)	0.09 [0.00, 1.61]
4.10 Obeticholic acid (moderate) versus obeticholic acid (high)	1	89	Odds Ratio (M-H, Fixed, 95% CI)	0.15 [0.02, 1.37]
4.11 Obeticholic acid (moderate) versus obeticholic acid (low)	1	86	Odds Ratio (M-H, Fixed, 95% CI)	2.43 [0.10, 61.39]
4.12 Lamivudine plus zidovudine plus UDCA (moderate) versus UDCA (moderate)	1	59	Odds Ratio (M-H, Fixed, 95% CI)	0.47 [0.04, 5.43]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.13 UDCA (moderate) versus obeticholic acid (low) plus UDCA (moderate)	1	216	Odds Ratio (M-H, Fixed, 95% CI)	0.28 [0.08, 0.98]
4.14 Bezafibrate plus UDCA (low) versus UDCA (low)	1	22	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.15 UDCA (moderate) versus UDCA (low)	1	59	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.16 Colchicine plus UDCA (moderate) versus UDCA (moderate)	1	74	Odds Ratio (M-H, Fixed, 95% CI)	3.08 [0.12, 78.14]
5 Serious adverse events (number of events)	1		Rate Ratio (Fixed, 95% CI)	Subtotals only
5.1 Obeticholic acid (low) plus UDCA (moderate) versus UDCA (moderate)	1		Rate Ratio (Fixed, 95% CI)	1.66 [0.75, 3.66]
6 Adverse events (proportion)	20		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Cyclosporin versus no intervention	3	390	Odds Ratio (M-H, Fixed, 95% CI)	3.04 [1.98, 4.68]
6.2 D-Penicillamine versus no intervention	2	287	Odds Ratio (M-H, Fixed, 95% CI)	4.51 [2.56, 7.93]
6.3 Malotilate versus no intervention	1	101	Odds Ratio (M-H, Fixed, 95% CI)	11.43 [1.40, 93.04]
6.4 Obeticholic acid (high) versus no intervention	1	79	Odds Ratio (M-H, Fixed, 95% CI)	16.6 [0.90, 305.59]
6.5 Obeticholic acid (low) versus no intervention	1	76	Odds Ratio (M-H, Fixed, 95% CI)	1.59 [0.41, 6.17]
6.6 Obeticholic acid (moderate) versus no intervention	1	86	Odds Ratio (M-H, Fixed, 95% CI)	8.81 [1.01, 76.73]
6.7 UDCA (low) versus no intervention	1	18	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.8 UDCA (moderate) versus no intervention	2	362	Odds Ratio (M-H, Fixed, 95% CI)	1.45 [0.50, 4.25]
6.9 Glucocorticosteroids plus UDCA (moderate) versus azathioprine plus UDCA (moderate)	1	50	Odds Ratio (M-H, Fixed, 95% CI)	0.40 [0.08, 2.12]
6.10 UDCA (low) versus bezafibrate	1	24	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.11 Obeticholic acid (low) versus obeticholic acid (high)	1	79	Odds Ratio (M-H, Fixed, 95% CI)	0.09 [0.00, 1.78]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.12 Obeticholic acid (moderate) versus obeticholic acid (high)	1	89	Odds Ratio (M-H, Fixed, 95% CI)	0.38 [0.02, 9.62]
6.13 Obeticholic acid (moderate) versus obeticholic acid (low)	1	86	Odds Ratio (M-H, Fixed, 95% CI)	5.53 [0.59, 51.70]
6.14 Bezafibrate plus UDCA (low) versus UDCA (low)	1	22	Odds Ratio (M-H, Fixed, 95% CI)	3.29 [0.12, 89.81]
6.15 Colestilan plus UDCA (low) versus UDCA (low)	1	11	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.16 Methotrexate plus UDCA (low) versus UDCA (low)	1	25	Odds Ratio (M-H, Fixed, 95% CI)	115.0 [4.98, 2657.48]
6.17 UDCA (moderate) versus UDCA (low)	1	59	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.18 Azathioprine plus UDCA (moderate) versus UDCA (moderate)	1	42	Odds Ratio (M-H, Fixed, 95% CI)	19.67 [0.94, 413.50]
6.19 Colchicine plus UDCA (moderate) versus UDCA (moderate)	2	42	Odds Ratio (M-H, Fixed, 95% CI)	6.20 [0.63, 60.80]
6.20 Glucocorticosteroids plus UDCA (moderate) versus UDCA (moderate)	2	135	Odds Ratio (M-H, Fixed, 95% CI)	5.54 [1.35, 22.84]
6.21 TauroUDCA (moderate) versus UDCA (moderate)	1	30	Odds Ratio (M-H, Fixed, 95% CI)	21.0 [2.16, 204.61]
7 Adverse events (number)	15		Rate Ratio (Fixed, 95% CI)	Subtotals only
7.1 Chlorambucil versus no intervention	1		Rate Ratio (Fixed, 95% CI)	3.67 [1.04, 12.87]
7.2 Cyclosporin versus no intervention	3		Rate Ratio (Fixed, 95% CI)	1.87 [1.51, 2.32]
7.3 D-Penicillamine versus no intervention	3		Rate Ratio (Fixed, 95% CI)	2.64 [1.78, 3.91]
7.4 Malotilate versus no intervention	1		Rate Ratio (Fixed, 95% CI)	6.13 [1.38, 27.14]
7.5 Obeticholic acid (high) versus no intervention	1		Rate Ratio (Fixed, 95% CI)	1.91 [1.50, 2.44]
7.6 Obeticholic acid (low) versus no intervention	1		Rate Ratio (Fixed, 95% CI)	1.05 [0.80, 1.39]
7.7 Obeticholic acid (moderate) versus no intervention	1		Rate Ratio (Fixed, 95% CI)	1.25 [0.97, 1.62]
7.8 Obeticholic acid (low) versus obeticholic acid (high)	1		Rate Ratio (Fixed, 95% CI)	0.55 [0.43, 0.70]
7.9 Obeticholic acid (moderate) versus obeticholic acid (high)	1		Rate Ratio (Fixed, 95% CI)	0.66 [0.53, 0.81]

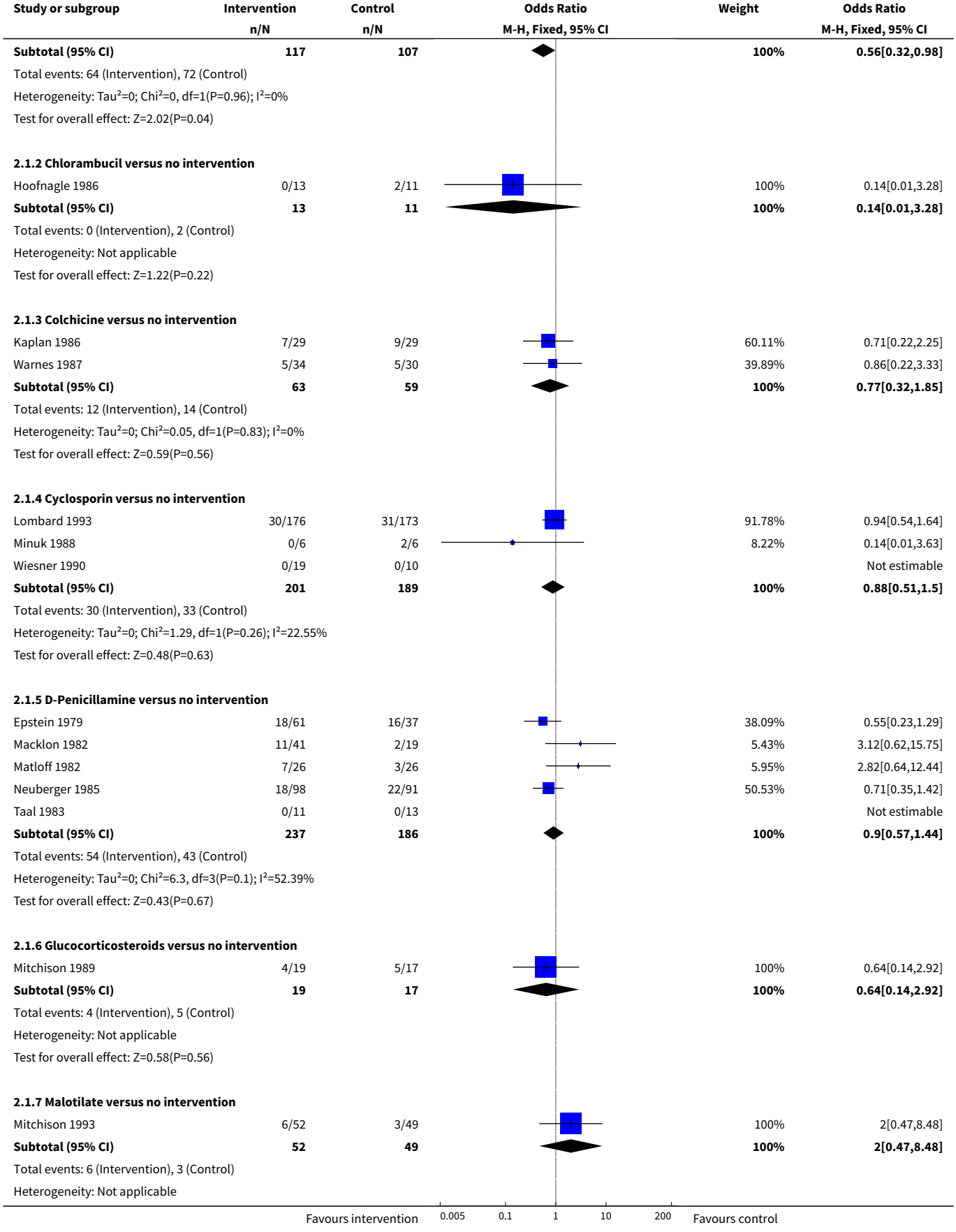
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.10 Obeticholic acid (moderate) versus obeticholic acid (low)	1		Rate Ratio (Fixed, 95% CI)	1.19 [0.93, 1.53]
7.11 UDCA (low) versus UDCA (high)	1		Rate Ratio (Fixed, 95% CI)	2.08 [0.78, 5.53]
7.12 UDCA (moderate) versus UDCA (high)	1		Rate Ratio (Fixed, 95% CI)	0.73 [0.21, 2.60]
7.13 UDCA (low) plus methotrexate versus UDCA (low)	1		Rate Ratio (Fixed, 95% CI)	30.64 [1.84, 510.76]
7.14 UDCA (moderate) versus UDCA (low)	1		Rate Ratio (Fixed, 95% CI)	0.35 [0.11, 1.10]
7.15 Azathioprine plus glucocorticosteroids plus UDCA (moderate) versus UDCA (moderate)	1		Rate Ratio (Fixed, 95% CI)	1.32 [0.88, 1.97]
7.16 Bezafibrate plus UDCA (moderate) versus UDCA (moderate)	1		Rate Ratio (Fixed, 95% CI)	11.79 [0.65, 213.14]
7.17 Colchicine plus UDCA (moderate) versus UDCA (moderate)	1		Rate Ratio (Fixed, 95% CI)	5.91 [0.28, 123.08]
7.18 TauroUDCA (moderate) versus UDCA (moderate)	1		Rate Ratio (Fixed, 95% CI)	1.17 [0.81, 1.71]
8 Liver transplantation	12		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 Cyclosporin versus no intervention	2	378	Odds Ratio (M-H, Fixed, 95% CI)	0.86 [0.43, 1.72]
8.2 D-Penicillamine versus no intervention	1	189	Odds Ratio (M-H, Fixed, 95% CI)	0.93 [0.06, 15.05]
8.3 Methotrexate versus no intervention	1	60	Odds Ratio (M-H, Fixed, 95% CI)	0.17 [0.02, 1.58]
8.4 UDCA (low) versus no intervention	2	162	Odds Ratio (M-H, Fixed, 95% CI)	0.99 [0.24, 4.06]
8.5 UDCA (moderate) versus no intervention	3	478	Odds Ratio (M-H, Fixed, 95% CI)	0.88 [0.44, 1.76]
8.6 UDCA (low) versus UDCA (high)	1	106	Odds Ratio (M-H, Fixed, 95% CI)	3.17 [0.13, 79.71]
8.7 UDCA (moderate) versus UDCA (high)	1	103	Odds Ratio (M-H, Fixed, 95% CI)	3.37 [0.13, 84.70]
8.8 UDCA (moderate) versus UDCA (low)	1	101	Odds Ratio (M-H, Fixed, 95% CI)	1.06 [0.06, 17.47]
8.9 Bezafibrate plus UDCA (moderate) versus UDCA (moderate)	1	27	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

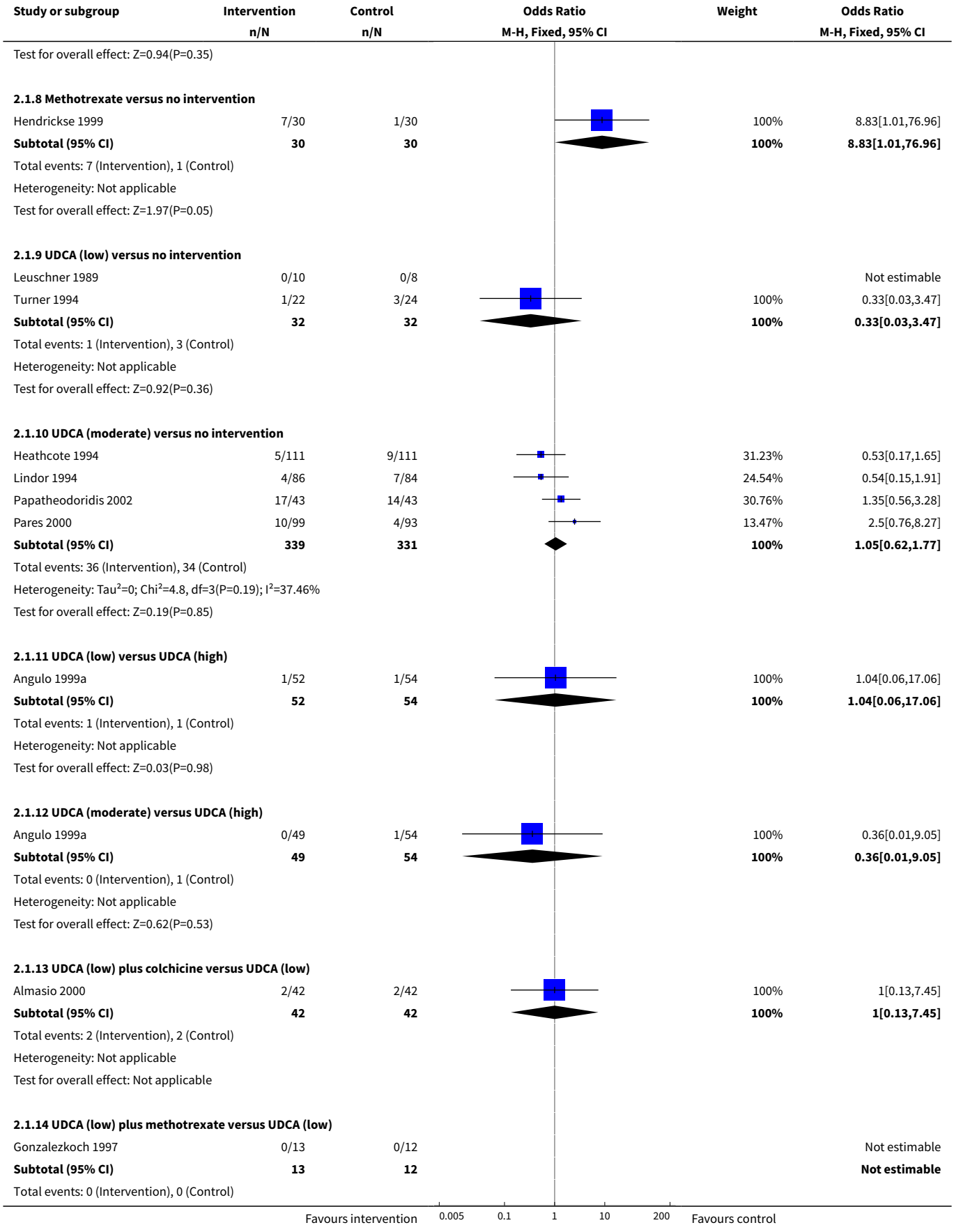
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.10 Methotrexate plus UDCA (moderate) versus UDCA (moderate)	1	265	Odds Ratio (M-H, Fixed, 95% CI)	0.70 [0.35, 1.39]
9 Decompensated liver disease	7		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 D-Penicillamine versus no intervention	1	24	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.2 UDCA (moderate) versus no intervention	2	351	Odds Ratio (M-H, Fixed, 95% CI)	1.33 [0.84, 2.12]
9.3 Obeticholic acid (low) plus UDCA (moderate) versus UDCA (moderate)	1	216	Odds Ratio (M-H, Fixed, 95% CI)	1.55 [0.06, 38.46]
9.4 UDCA (low) plus colchicine versus UDCA (low)	1	84	Odds Ratio (M-H, Fixed, 95% CI)	0.21 [0.04, 1.07]
9.5 Azathioprine plus UDCA (moderate) versus UDCA (moderate)	1	42	Odds Ratio (M-H, Fixed, 95% CI)	0.52 [0.05, 5.18]
9.6 Glucocorticosteroids plus UDCA (moderate) versus UDCA (moderate)	1	66	Odds Ratio (M-H, Fixed, 95% CI)	0.55 [0.11, 2.69]
9.7 Methotrexate plus UDCA (moderate) versus UDCA (moderate)	1	151	Odds Ratio (M-H, Fixed, 95% CI)	2.00 [0.79, 5.04]
9.8 Glucocorticosteroids plus UDCA (moderate) versus azathioprine plus UDCA (moderate)	1	50	Odds Ratio (M-H, Fixed, 95% CI)	1.06 [0.10, 11.18]
10 Cirrhosis	3		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 Azathioprine versus no intervention	1	31	Odds Ratio (M-H, Fixed, 95% CI)	0.79 [0.18, 3.41]
10.2 UDCA (low) versus no intervention	1	22	Odds Ratio (M-H, Fixed, 95% CI)	0.15 [0.01, 1.53]
10.3 Azathioprine plus glucocorticosteroids plus UDCA (moderate) versus UDCA (moderate)	1	50	Odds Ratio (M-H, Fixed, 95% CI)	0.28 [0.03, 2.90]

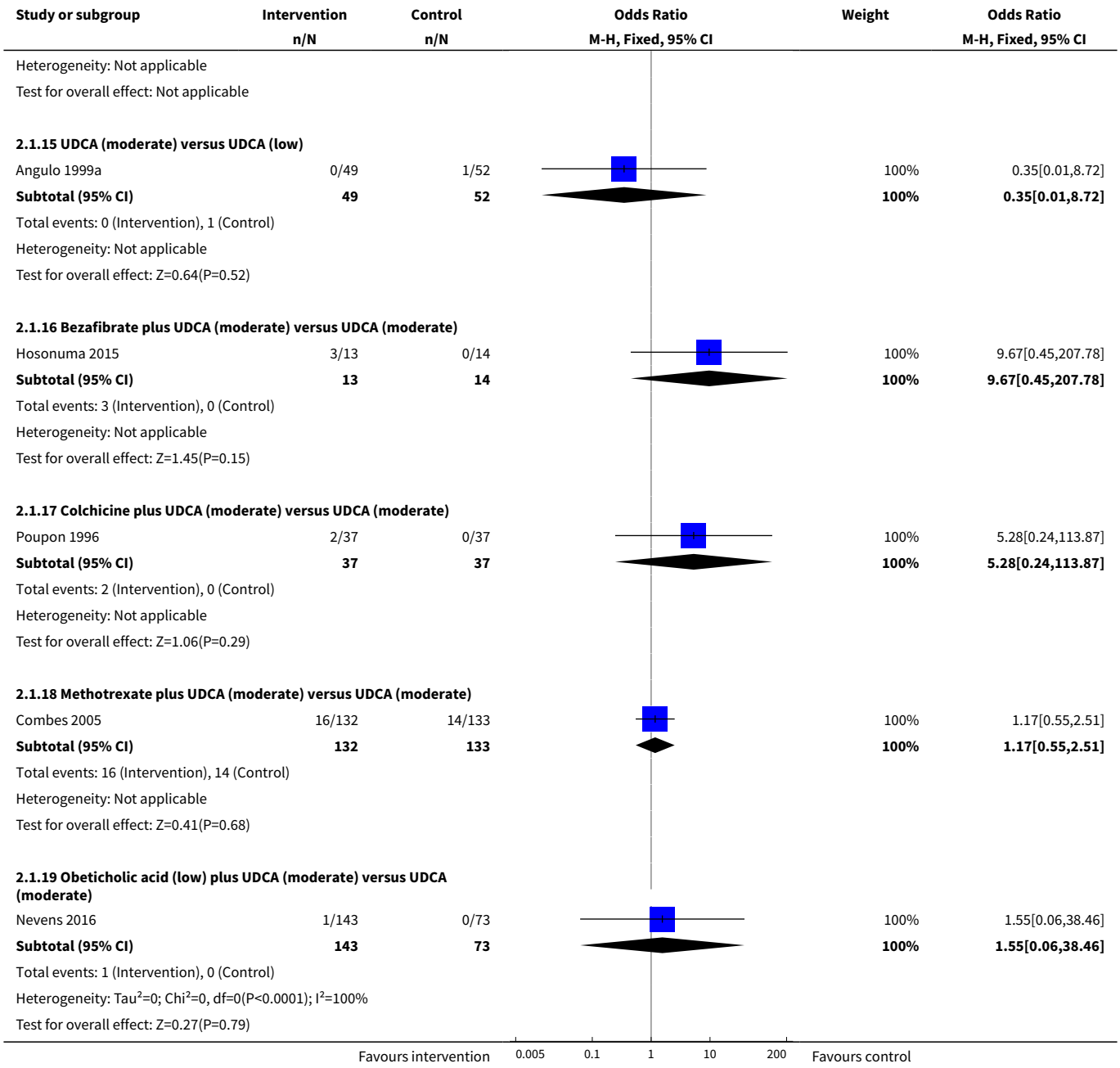
Analysis 2.1. Comparison 2 Stratified by dose, Outcome 1 Mortality at maximal follow-up.

Study or subgroup	Intervention n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
2.1.1 Azathioprine versus no intervention					
Christensen 1985	57/98	62/87		81.7%	0.56[0.3,1.04]
Heathcote 1976	7/19	10/20		18.3%	0.58[0.16,2.1]

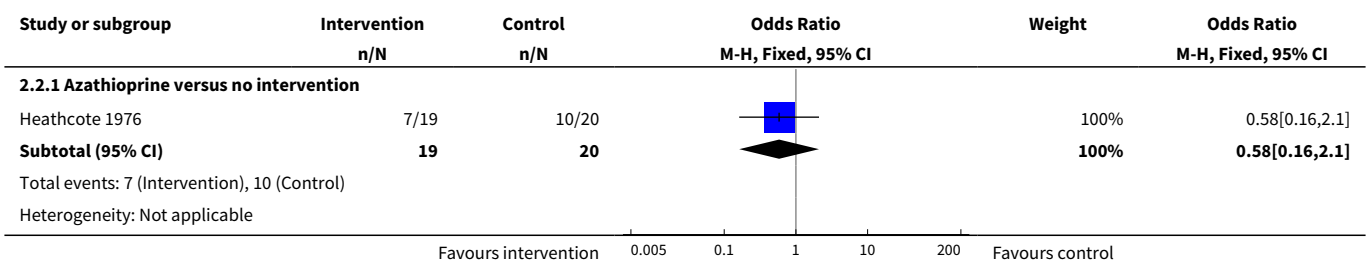
Favours intervention — Favours control

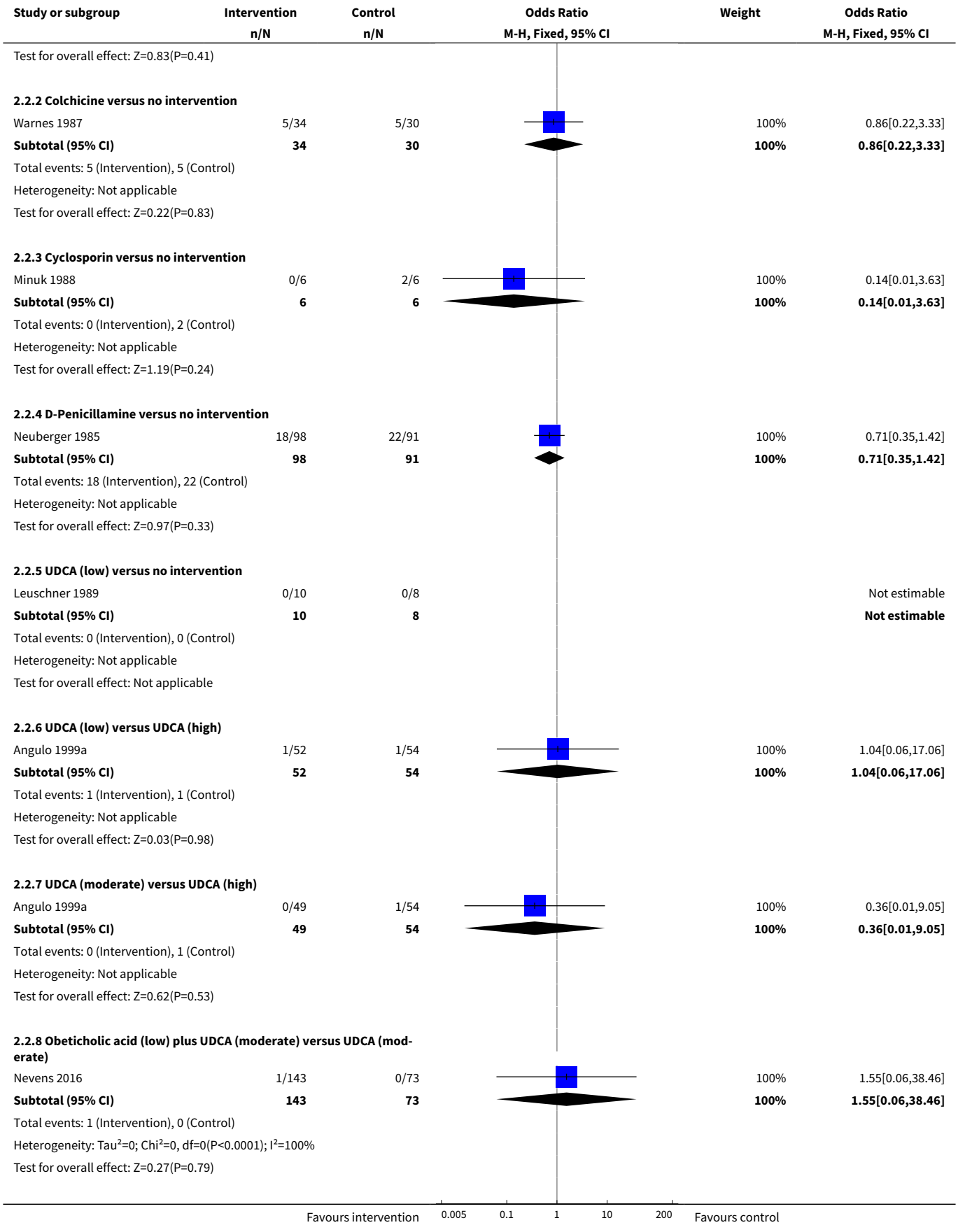


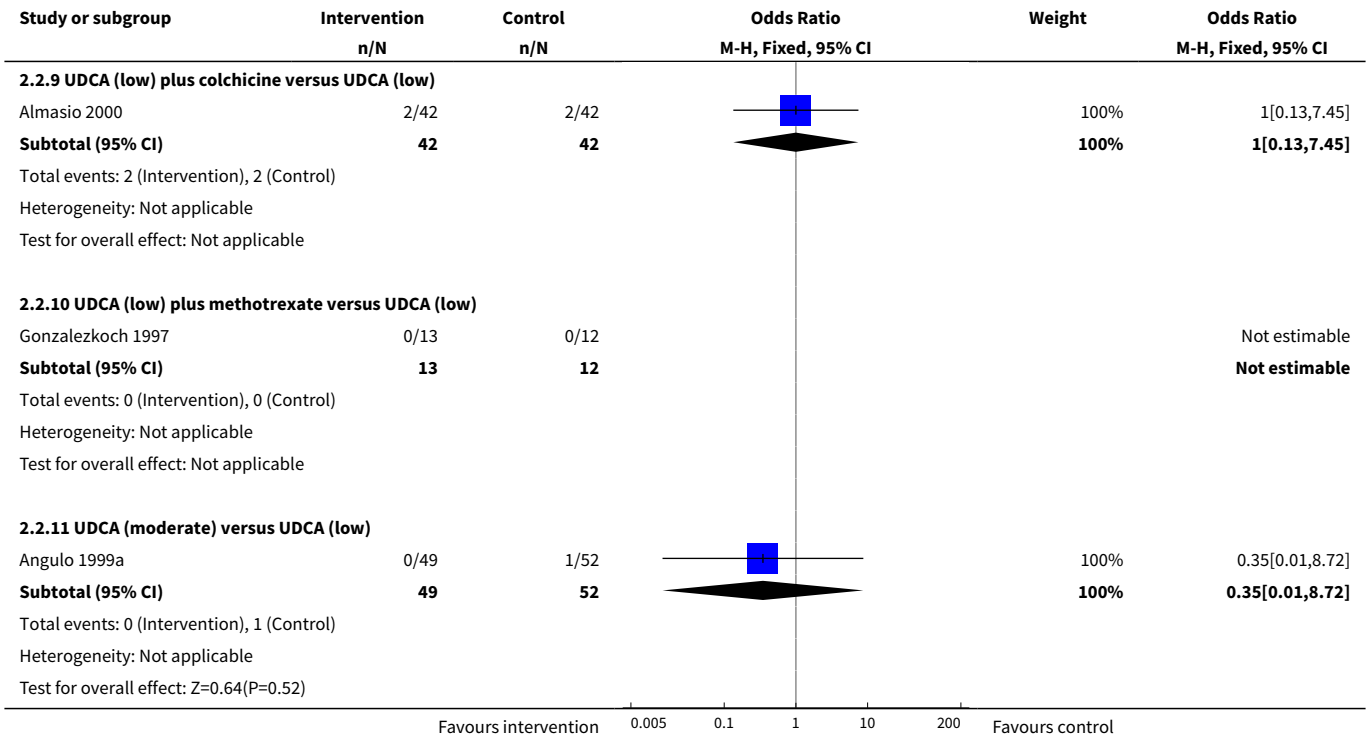




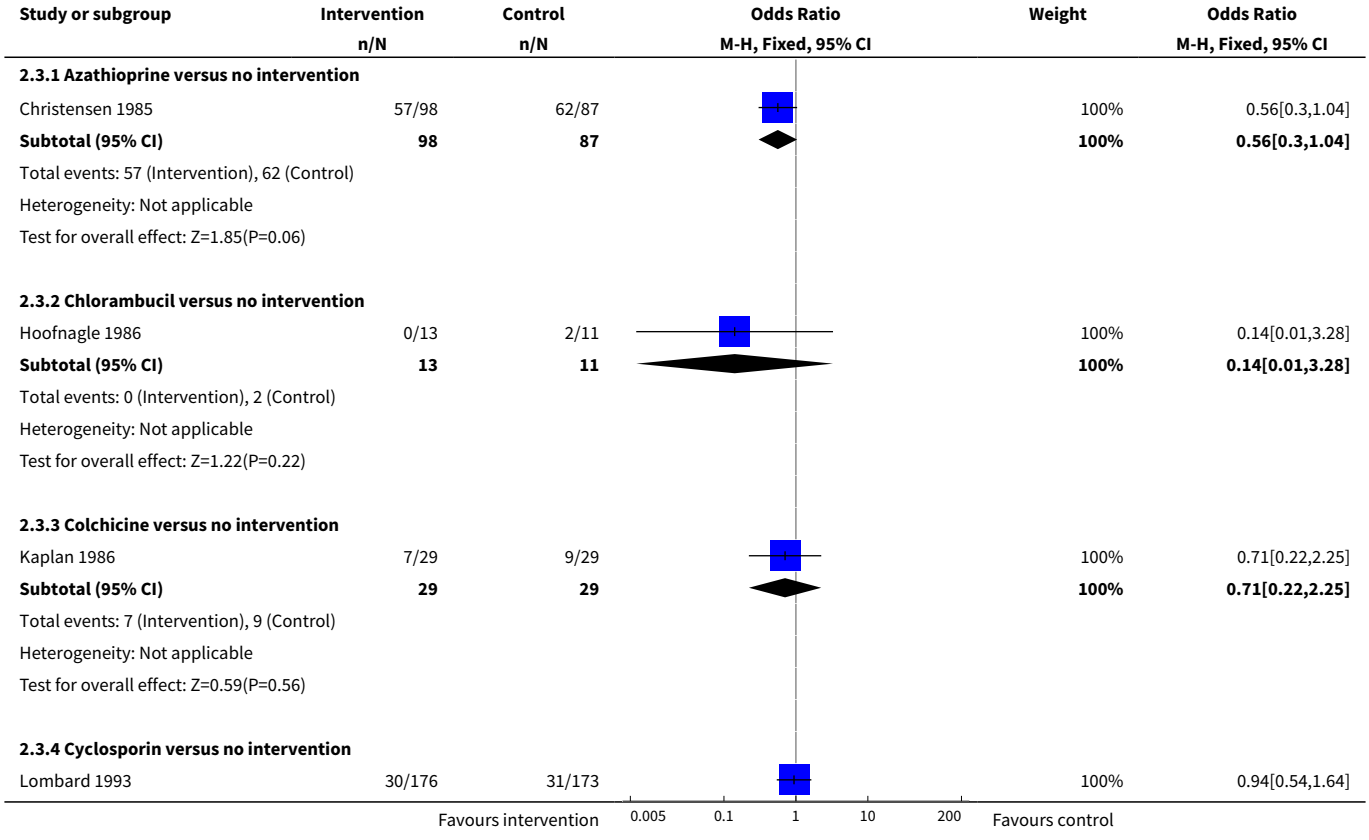
Analysis 2.2. Comparison 2 Stratified by dose, Outcome 2 Mortality (< 1 year).

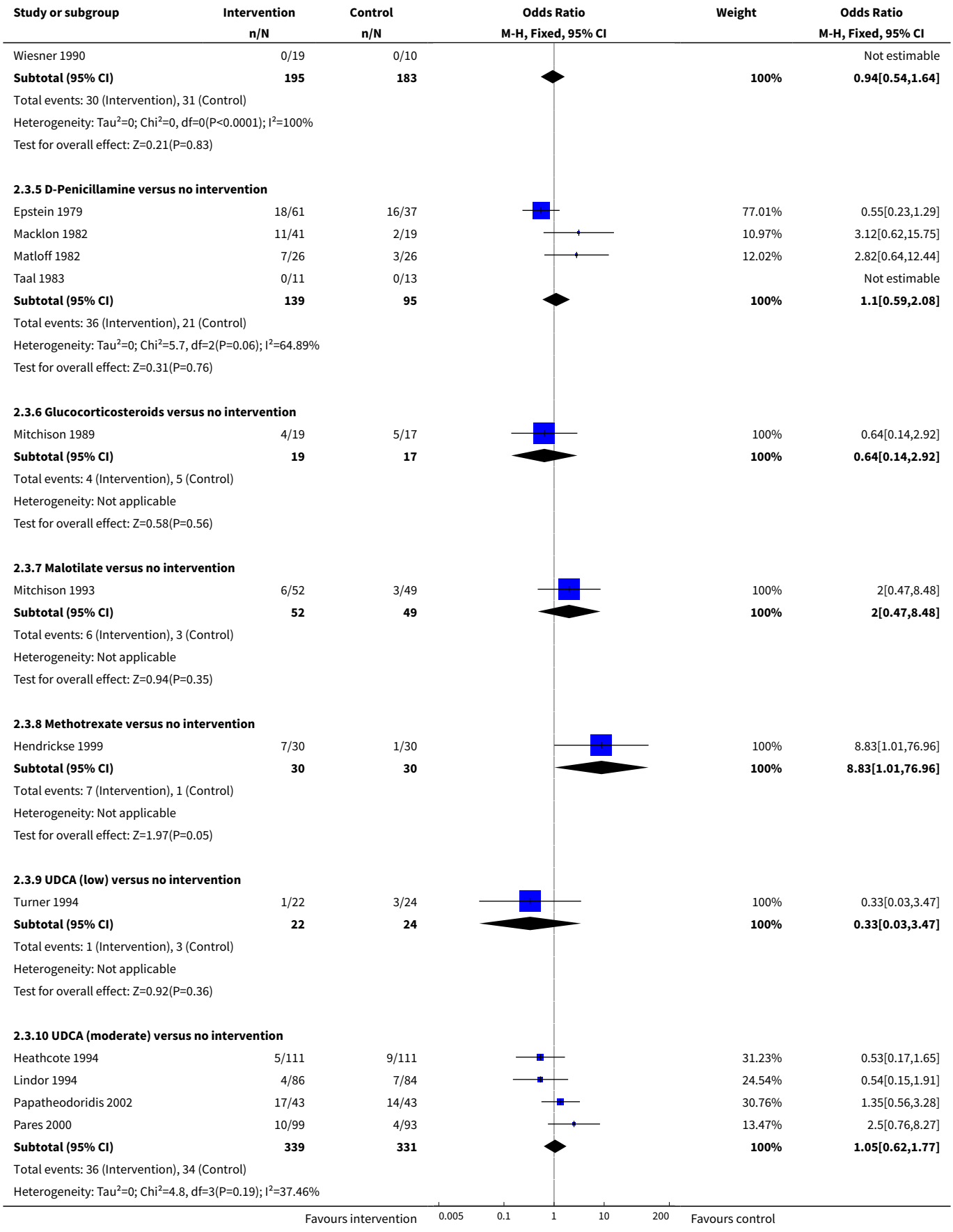


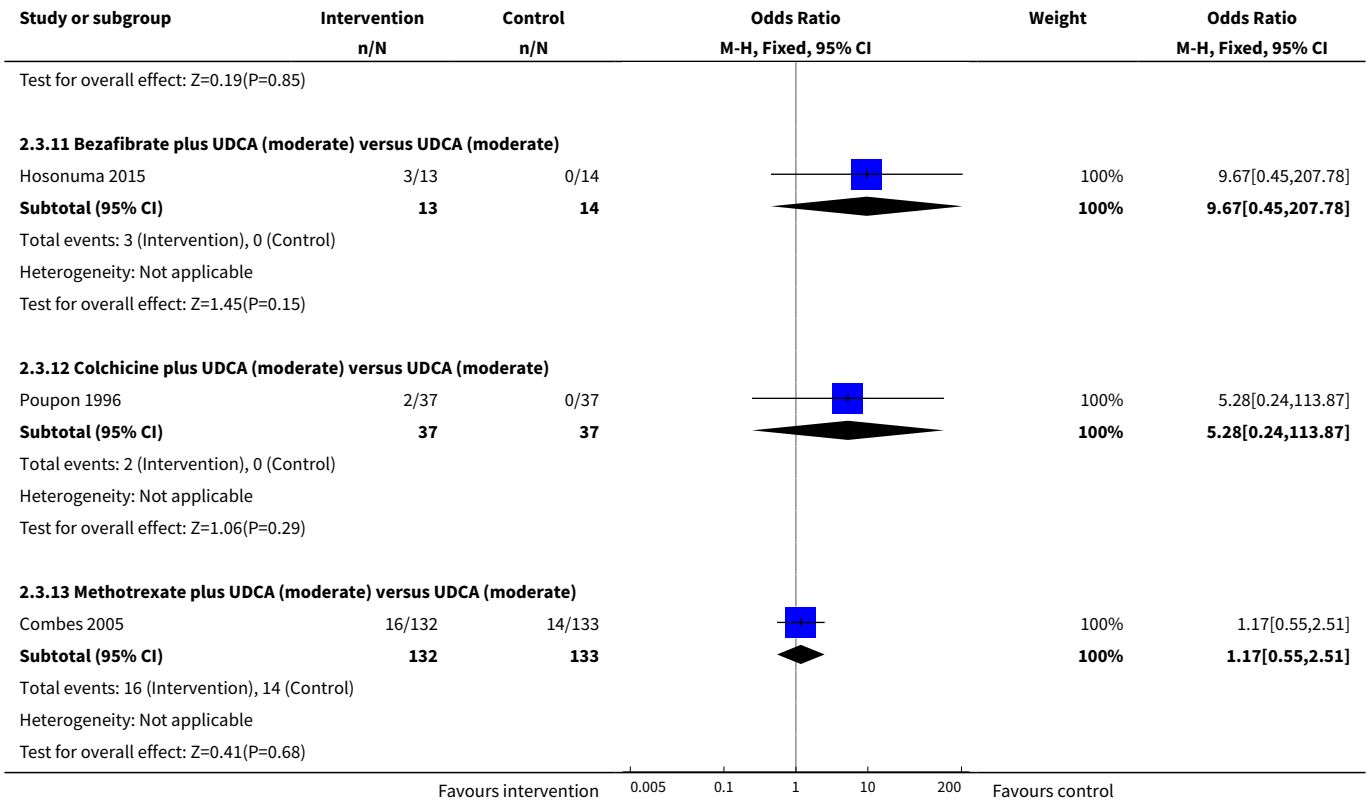




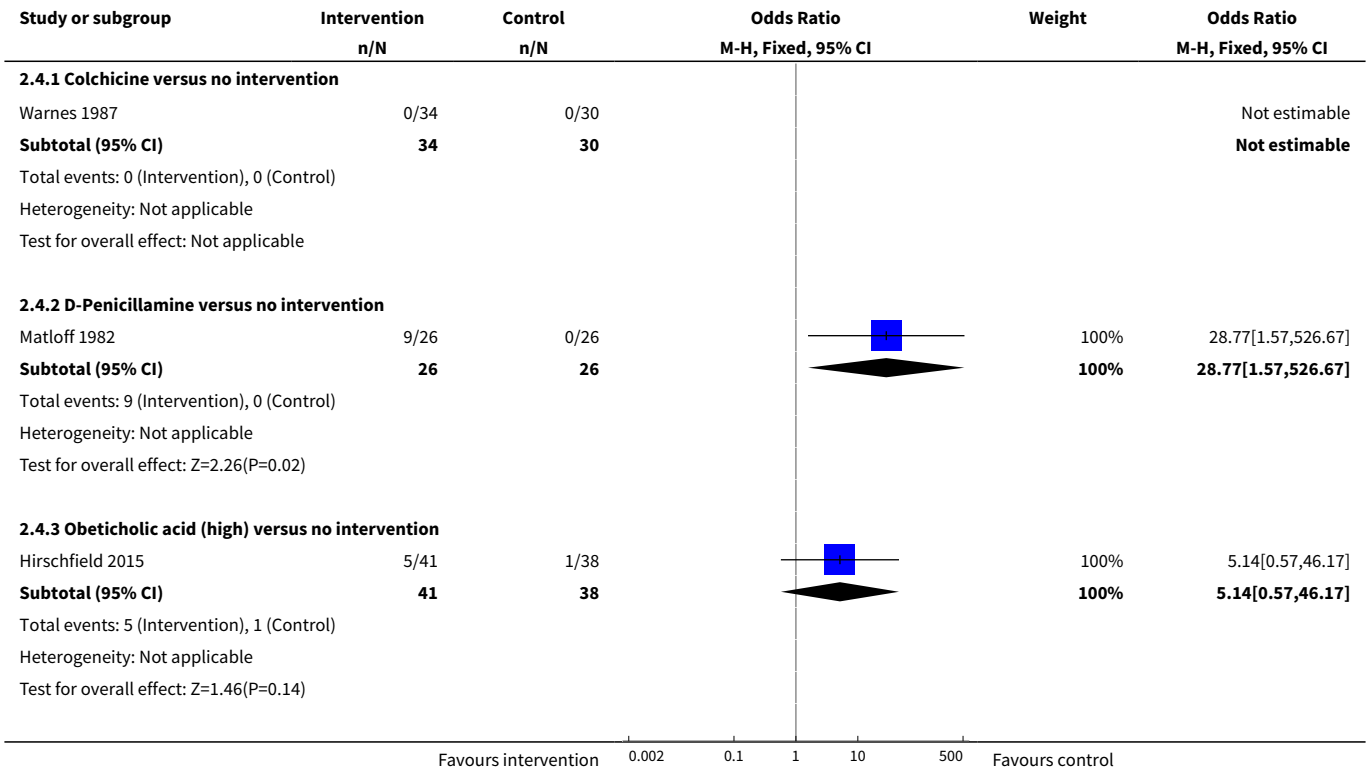
Analysis 2.3. Comparison 2 Stratified by dose, Outcome 3 Mortality (1 to 5 years).

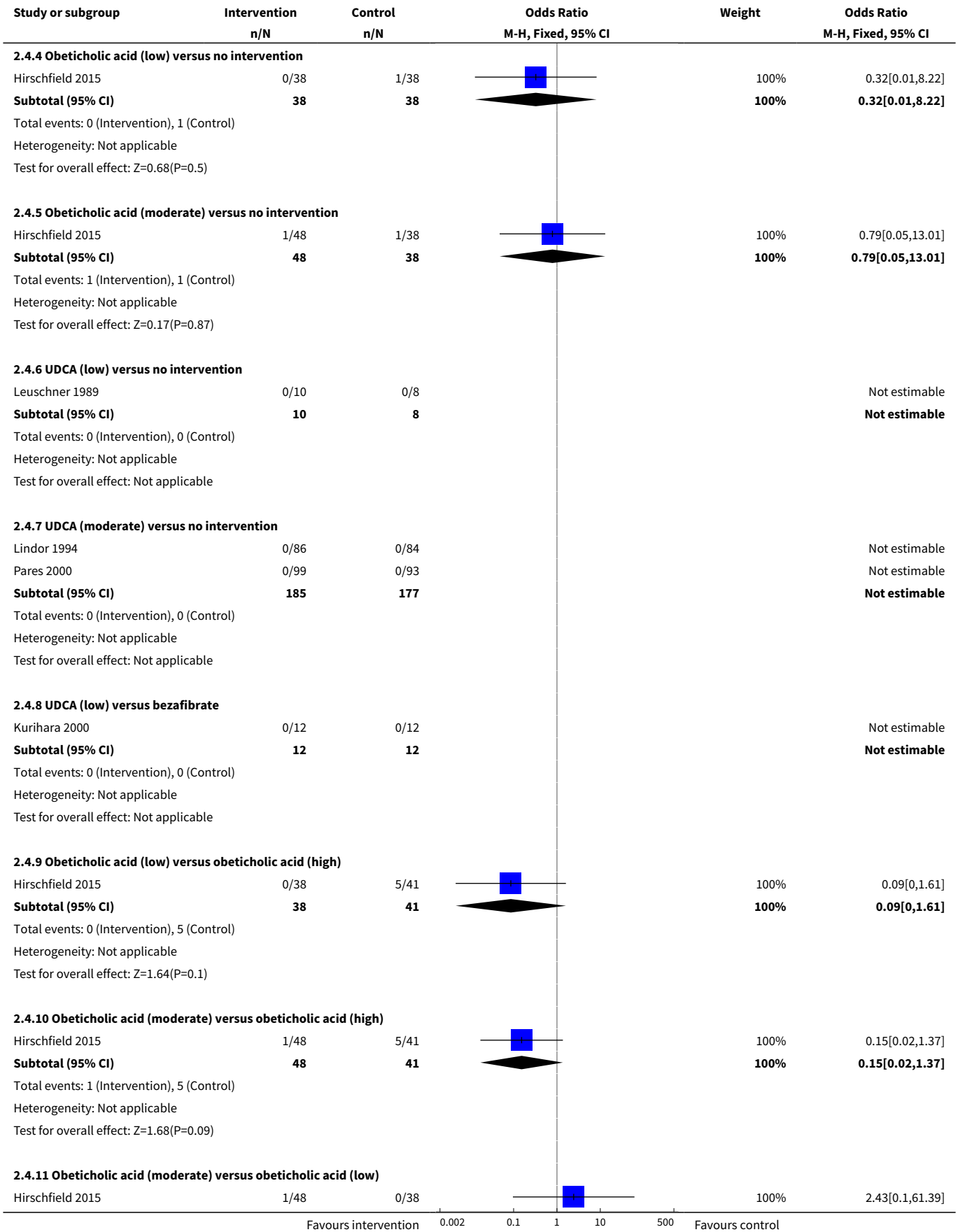


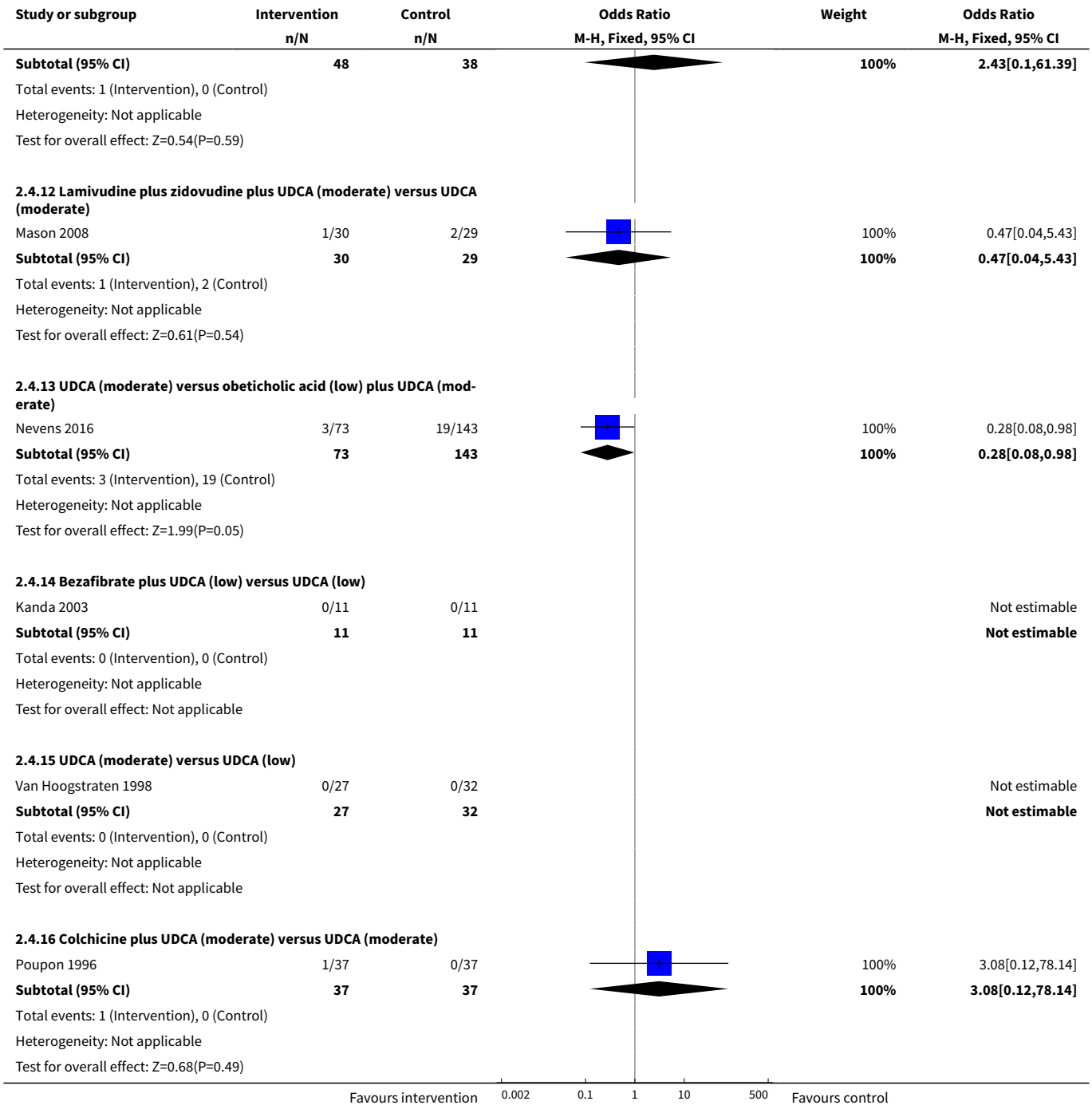




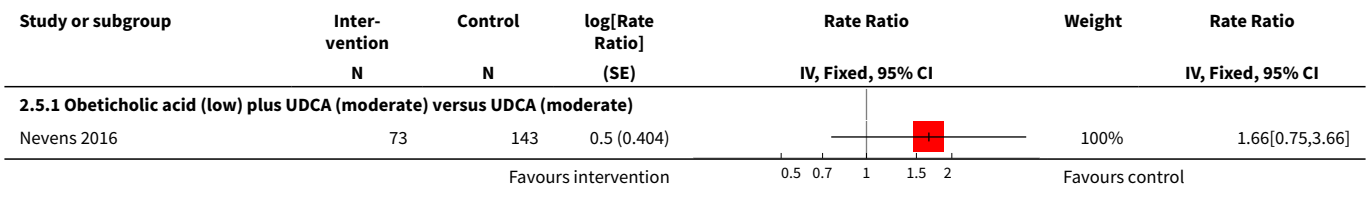
Analysis 2.4. Comparison 2 Stratified by dose, Outcome 4 Serious adverse events (proportion).







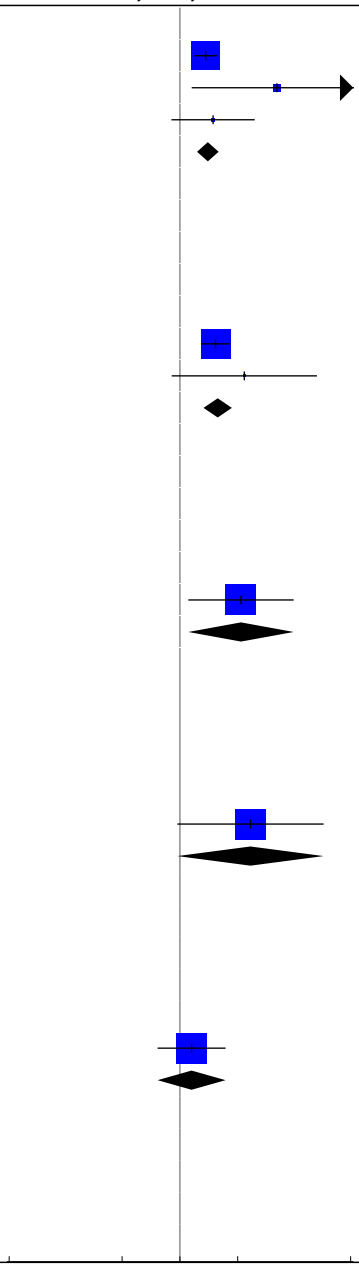
Analysis 2.5. Comparison 2 Stratified by dose, Outcome 5 Serious adverse events (number of events).

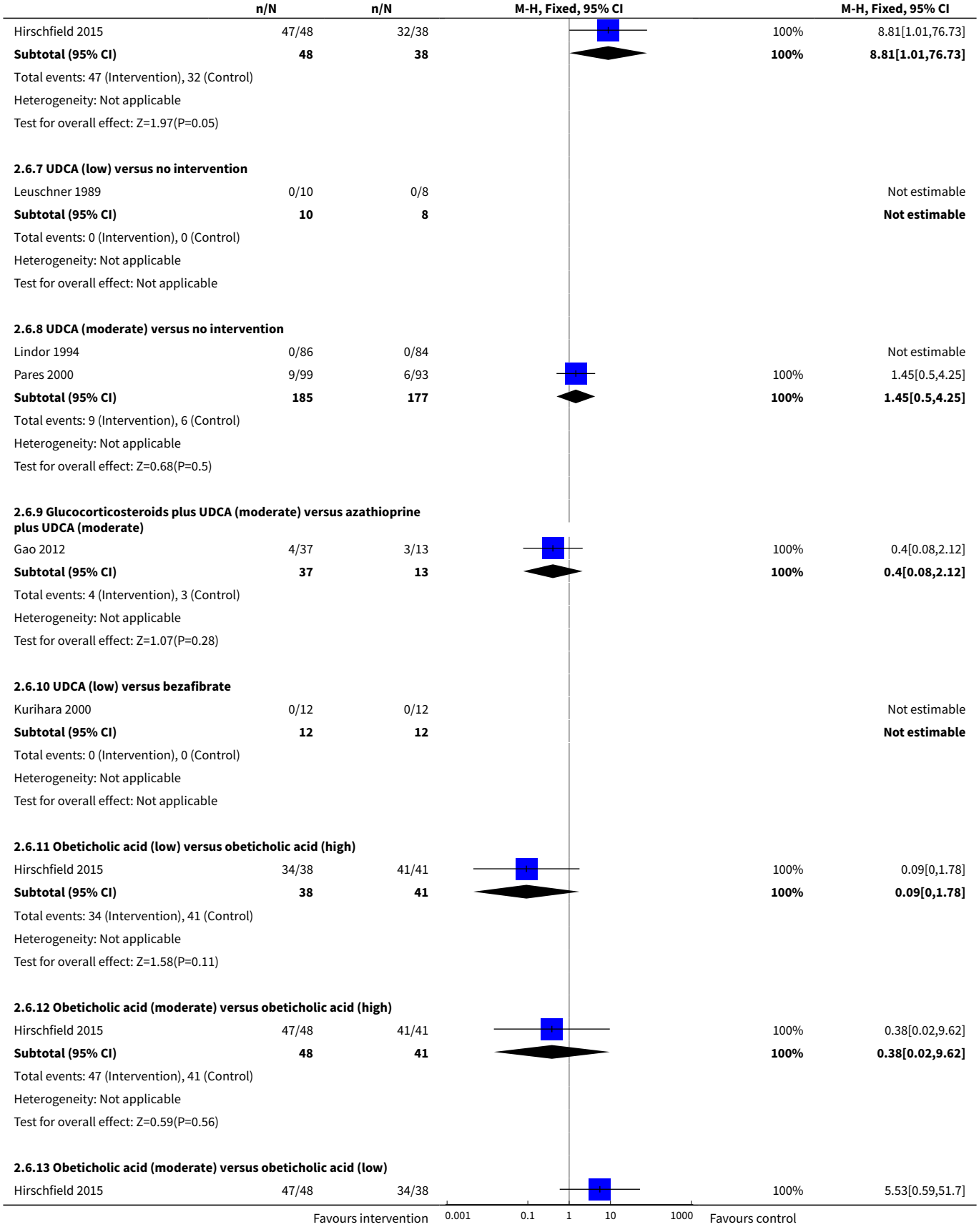


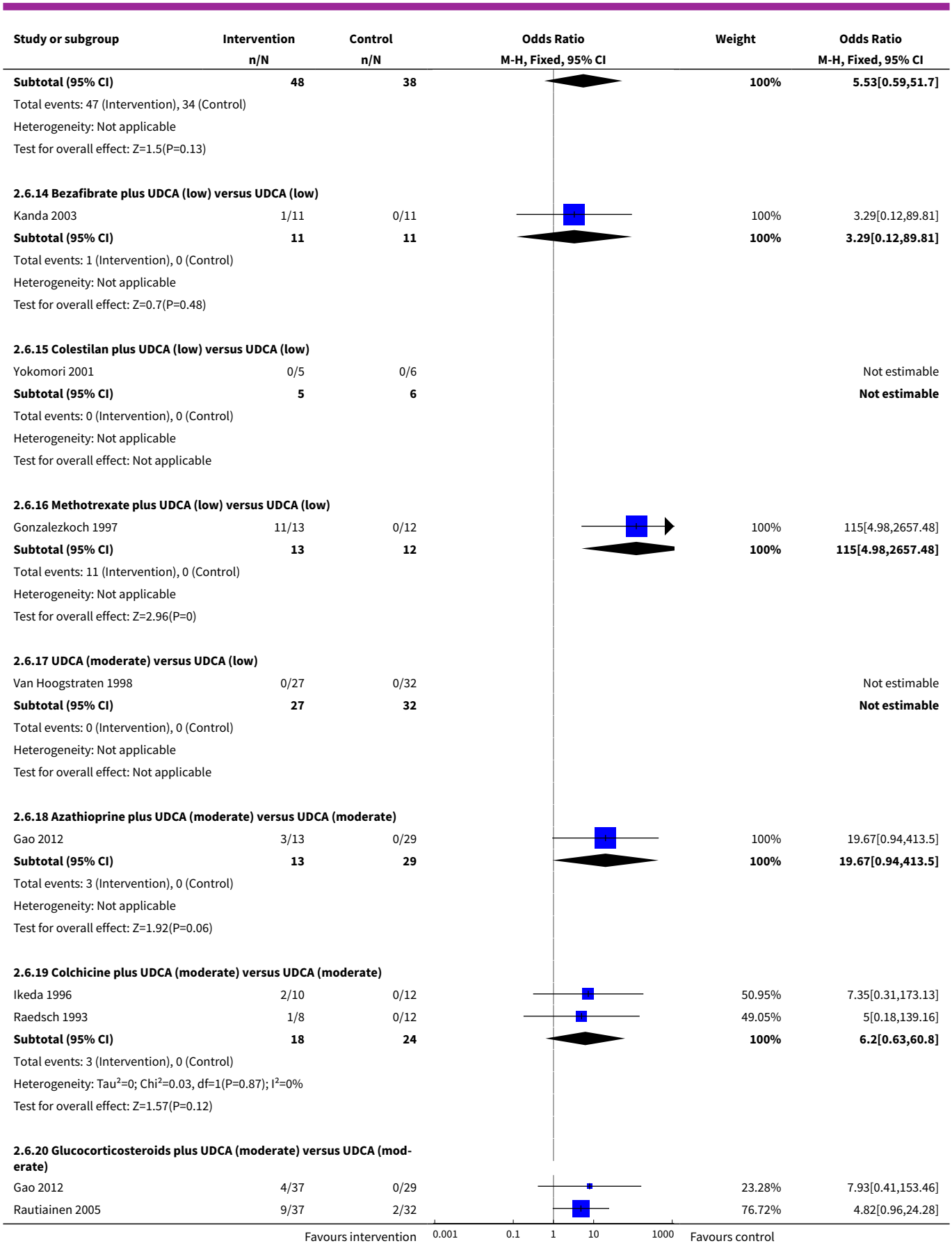
Study or subgroup	Inter-vention N	Control N	log[Rate Ratio] (SE)	Rate Ratio IV, Fixed, 95% CI	Weight	Rate Ratio IV, Fixed, 95% CI
Subtotal (95% CI)					**100%**	**1.66[0.75,3.66]**
Heterogeneity: Not applicable						
Test for overall effect: Z=1.25(P=0.21)						

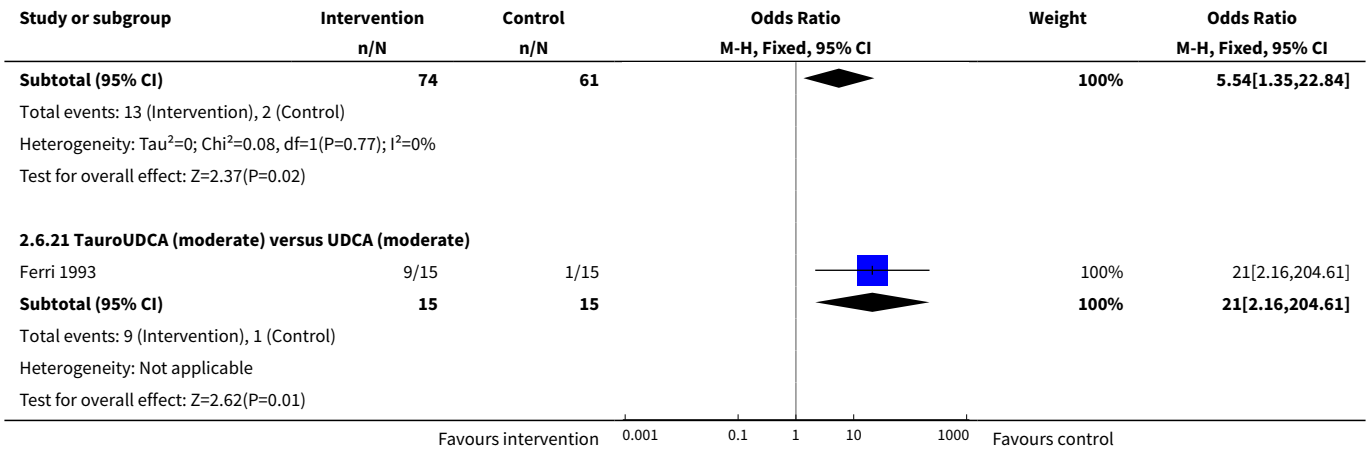
Analysis 2.6. Comparison 2 Stratified by dose, Outcome 6 Adverse events (proportion).

Study or subgroup	Intervention n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
2.6.1 Cyclosporin versus no intervention					
Lombard 1993	133/176	91/173		93.78%	2.79[1.77,4.39]
Minuk 1988	6/6	1/6		0.45%	47.67[1.6,1422.69]
Wiesner 1990	15/19	5/10		5.77%	3.75[0.71,19.71]
Subtotal (95% CI)	**201**	**189**		**100%**	**3.04[1.98,4.68]**
Total events: 154 (Intervention), 97 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.73, df=2(P=0.26); I^2=26.62%					
Test for overall effect: Z=5.07(P<0.0001)					
2.6.2 D-Penicillamine versus no intervention					
Dickson 1985	59/111	25/116		95.75%	4.13[2.32,7.37]
Macklon 1982	10/41	0/19		4.25%	13[0.72,234.55]
Subtotal (95% CI)	**152**	**135**		**100%**	**4.51[2.56,7.93]**
Total events: 69 (Intervention), 25 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.6, df=1(P=0.44); I^2=0%					
Test for overall effect: Z=5.22(P<0.0001)					
2.6.3 Malotilate versus no intervention					
Mitchison 1993	10/52	1/49		100%	11.43[1.4,93.04]
Subtotal (95% CI)	**52**	**49**		**100%**	**11.43[1.4,93.04]**
Total events: 10 (Intervention), 1 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.28(P=0.02)					
2.6.4 Obeticholic acid (high) versus no intervention					
Hirschfield 2015	41/41	32/38		100%	16.6[0.9,305.59]
Subtotal (95% CI)	**41**	**38**		**100%**	**16.6[0.9,305.59]**
Total events: 41 (Intervention), 32 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.89(P=0.06)					
2.6.5 Obeticholic acid (low) versus no intervention					
Hirschfield 2015	34/38	32/38		100%	1.59[0.41,6.17]
Subtotal (95% CI)	**38**	**38**		**100%**	**1.59[0.41,6.17]**
Total events: 34 (Intervention), 32 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.67(P=0.5)					
2.6.6 Obeticholic acid (moderate) versus no intervention					

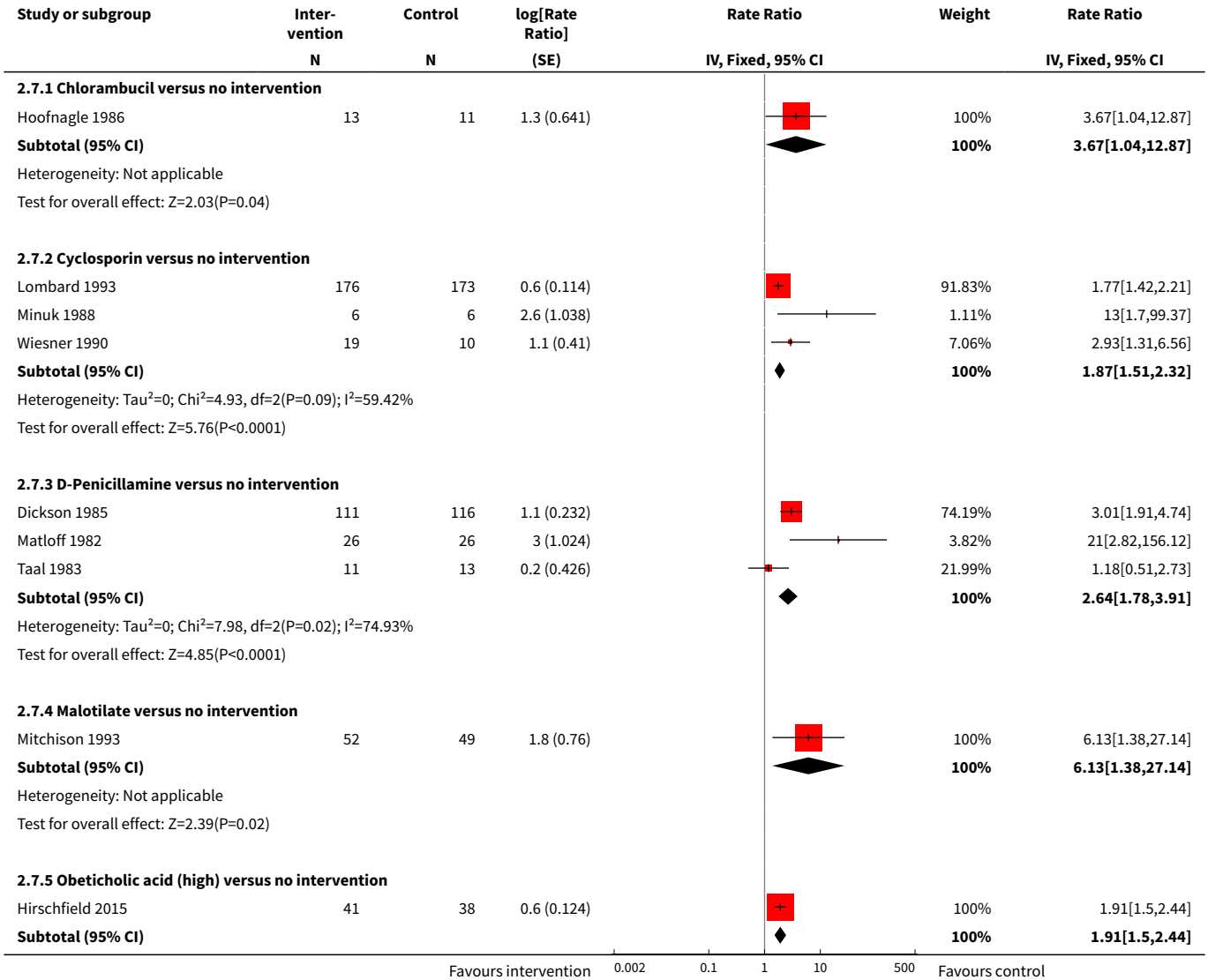




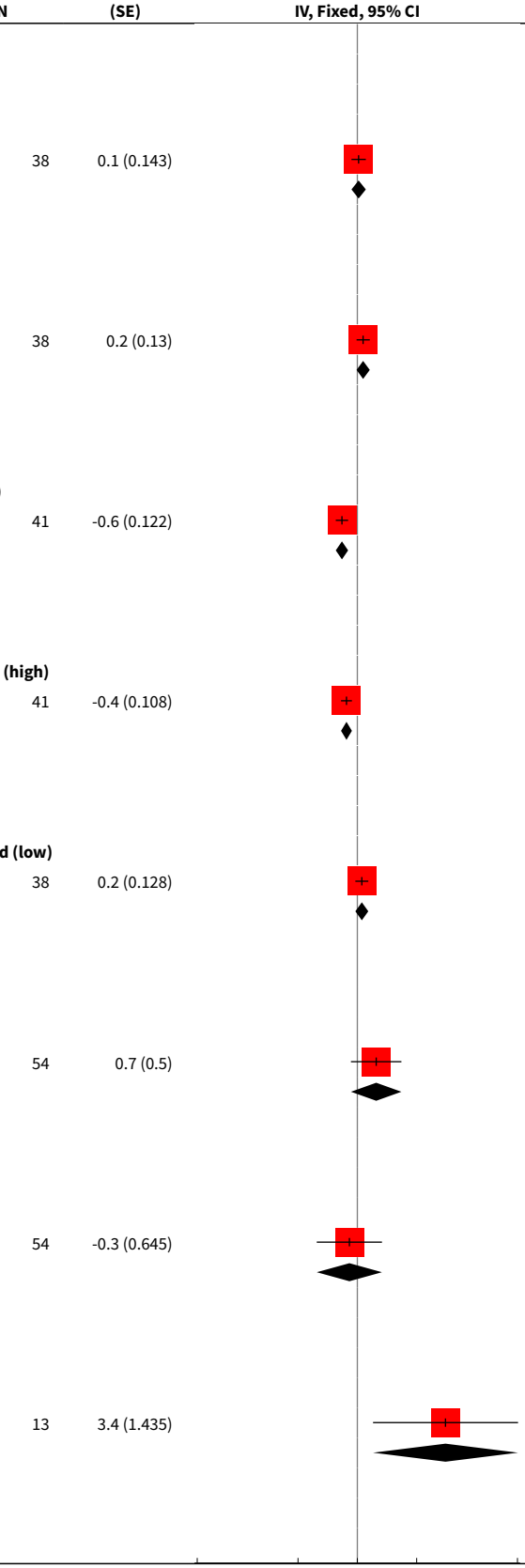


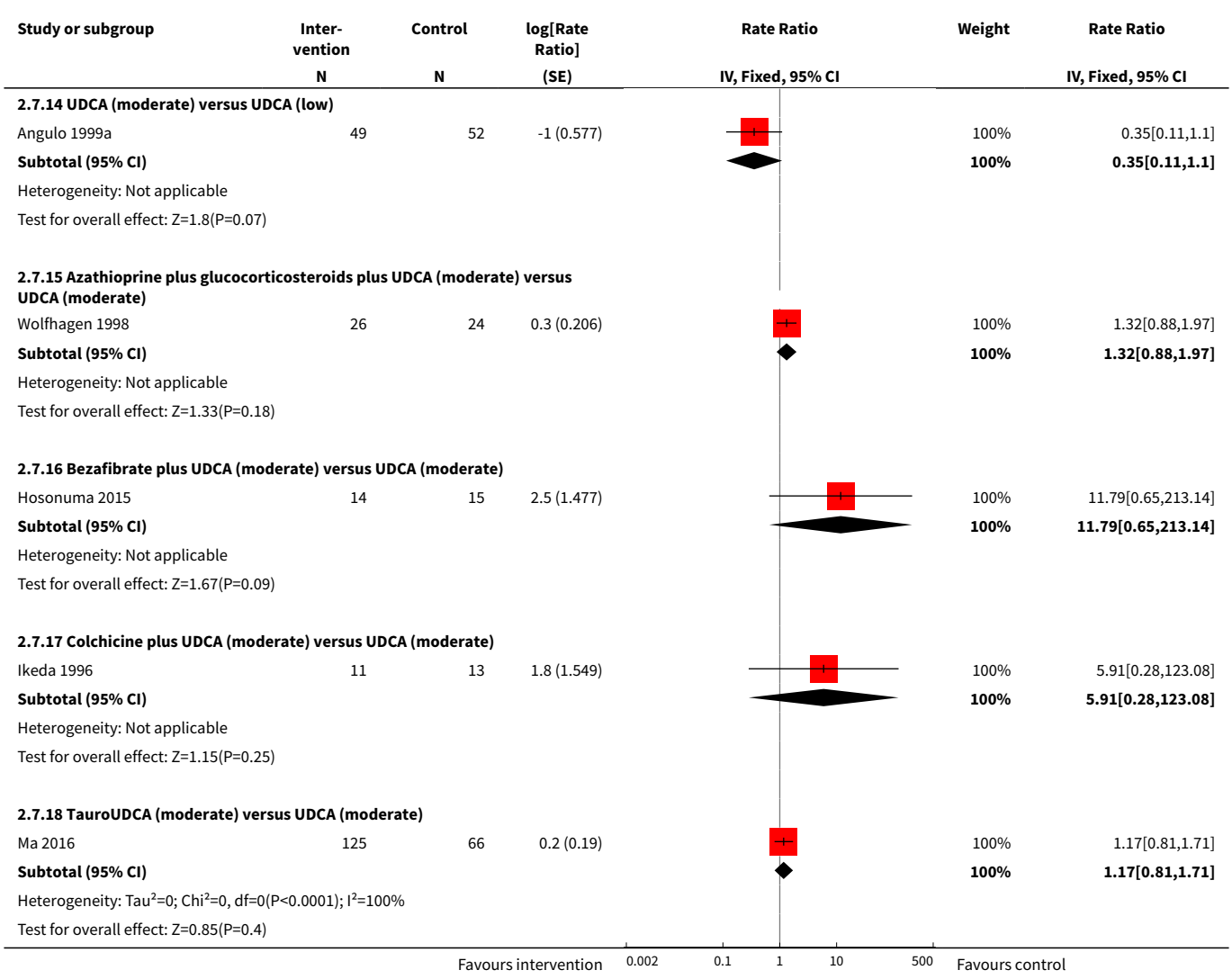


Analysis 2.7. Comparison 2 Stratified by dose, Outcome 7 Adverse events (number).

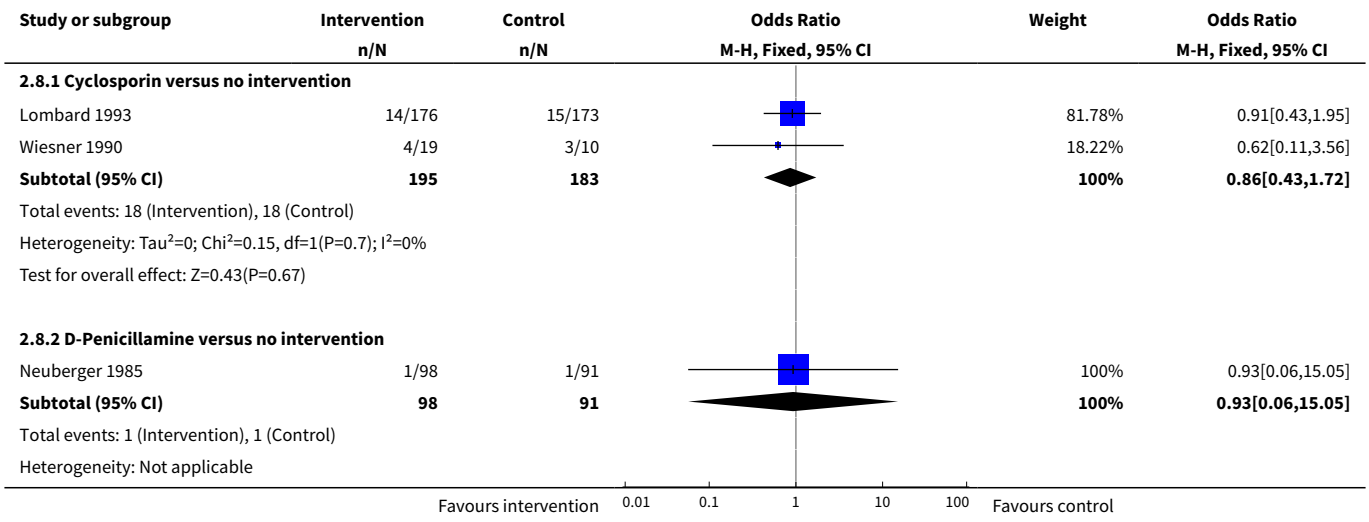


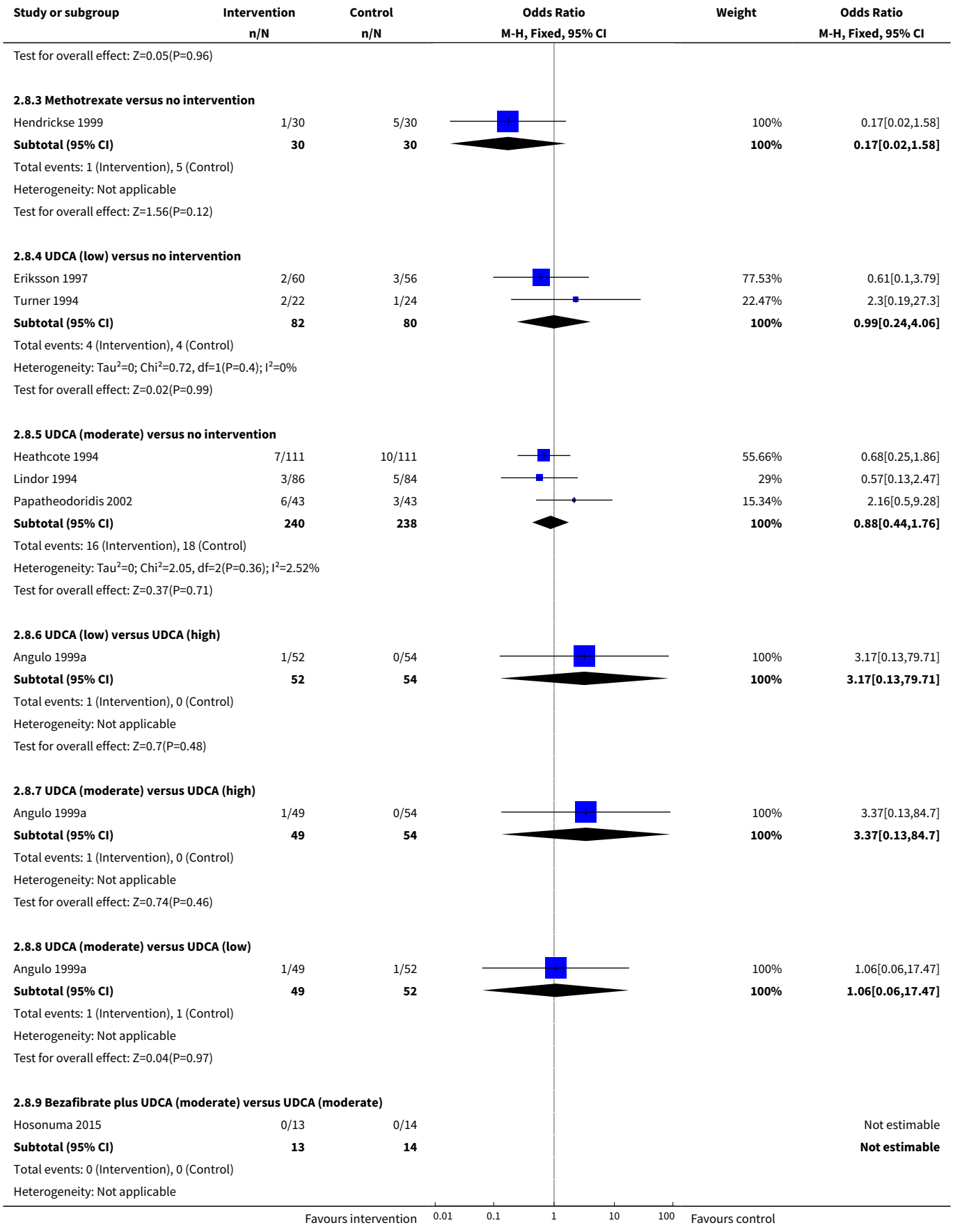
Study or subgroup	Inter-vention N	Control N	log[Rate Ratio] (SE)	Rate Ratio IV, Fixed, 95% CI	Weight	Rate Ratio IV, Fixed, 95% CI
Heterogeneity: Not applicable						
Test for overall effect: Z=5.21(P<0.0001)						
2.7.6 Obeticholic acid (low) versus no intervention						
Hirschfield 2015	38	38	0.1 (0.143)		100%	1.05[0.8,1.39]
Subtotal (95% CI)					**100%**	**1.05[0.8,1.39]**
Heterogeneity: Not applicable						
Test for overall effect: Z=0.36(P=0.72)						
2.7.7 Obeticholic acid (moderate) versus no intervention						
Hirschfield 2015	48	38	0.2 (0.13)		100%	1.25[0.97,1.62]
Subtotal (95% CI)					**100%**	**1.25[0.97,1.62]**
Heterogeneity: Not applicable						
Test for overall effect: Z=1.73(P=0.08)						
2.7.8 Obeticholic acid (low) versus obeticholic acid (high)						
Hirschfield 2015	38	41	-0.6 (0.122)		100%	0.55[0.43,0.7]
Subtotal (95% CI)					**100%**	**0.55[0.43,0.7]**
Heterogeneity: Not applicable						
Test for overall effect: Z=4.88(P<0.0001)						
2.7.9 Obeticholic acid (moderate) versus obeticholic acid (high)						
Hirschfield 2015	48	41	-0.4 (0.108)		100%	0.66[0.53,0.81]
Subtotal (95% CI)					**100%**	**0.66[0.53,0.81]**
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%						
Test for overall effect: Z=3.91(P<0.0001)						
2.7.10 Obeticholic acid (moderate) versus obeticholic acid (low)						
Hirschfield 2015	48	38	0.2 (0.128)		100%	1.19[0.93,1.53]
Subtotal (95% CI)					**100%**	**1.19[0.93,1.53]**
Heterogeneity: Not applicable						
Test for overall effect: Z=1.36(P=0.17)						
2.7.11 UDCA (low) versus UDCA (high)						
Angulo 1999a	52	54	0.7 (0.5)		100%	2.08[0.78,5.53]
Subtotal (95% CI)					**100%**	**2.08[0.78,5.53]**
Heterogeneity: Not applicable						
Test for overall effect: Z=1.46(P=0.14)						
2.7.12 UDCA (moderate) versus UDCA (high)						
Angulo 1999a	49	54	-0.3 (0.645)		100%	0.73[0.21,2.6]
Subtotal (95% CI)					**100%**	**0.73[0.21,2.6]**
Heterogeneity: Not applicable						
Test for overall effect: Z=0.48(P=0.63)						
2.7.13 UDCA (low) plus methotrexate versus UDCA (low)						
Gonzalezkoch 1997	14	13	3.4 (1.435)		100%	30.64[1.84,510.76]
Subtotal (95% CI)					**100%**	**30.64[1.84,510.76]**
Heterogeneity: Not applicable						
Test for overall effect: Z=2.38(P=0.02)						

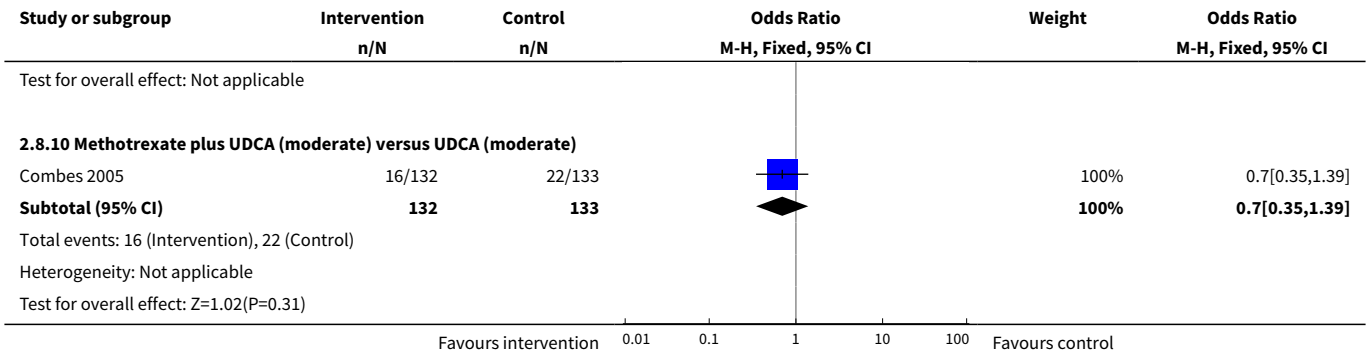




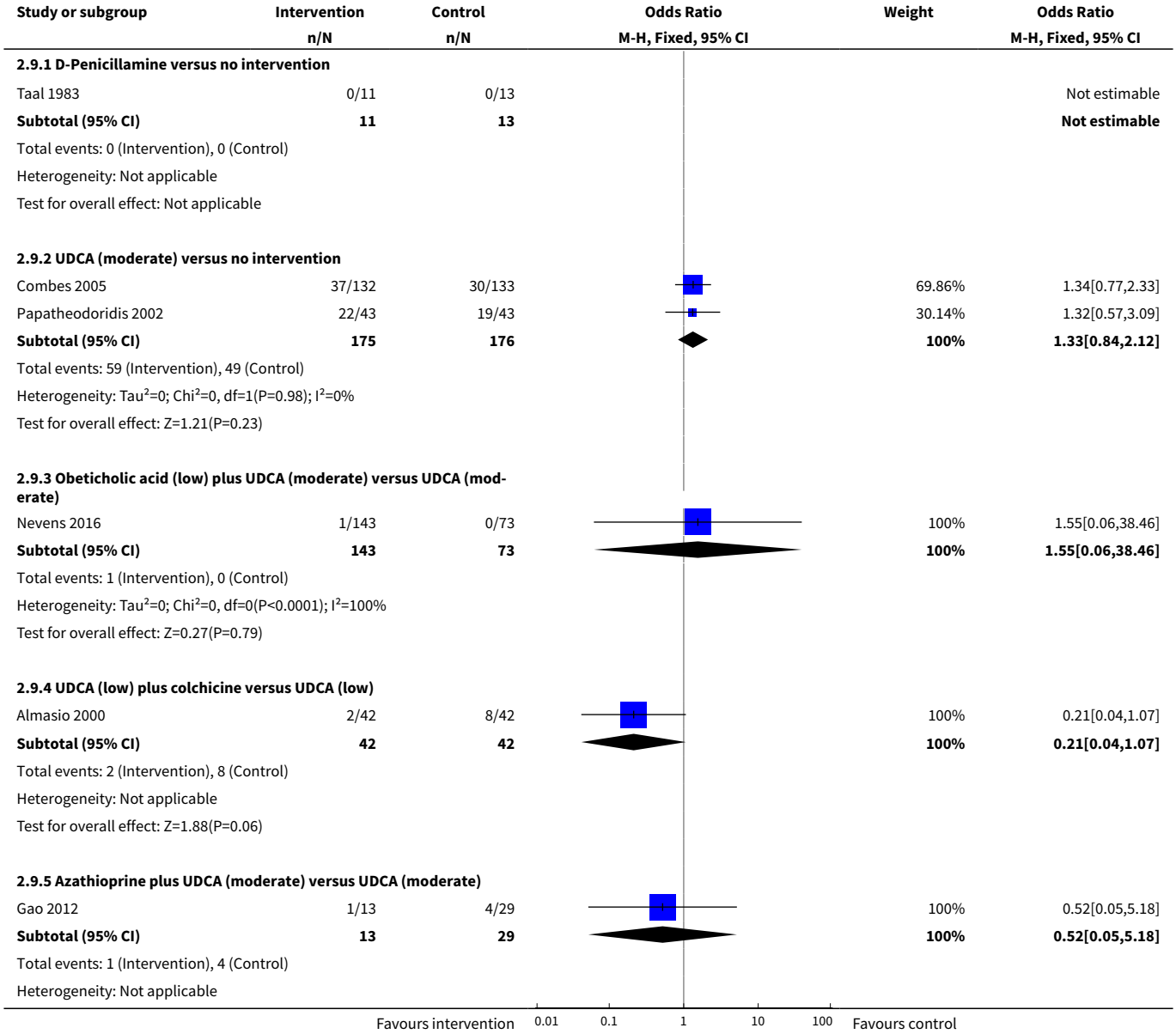
Analysis 2.8. Comparison 2 Stratified by dose, Outcome 8 Liver transplantation.

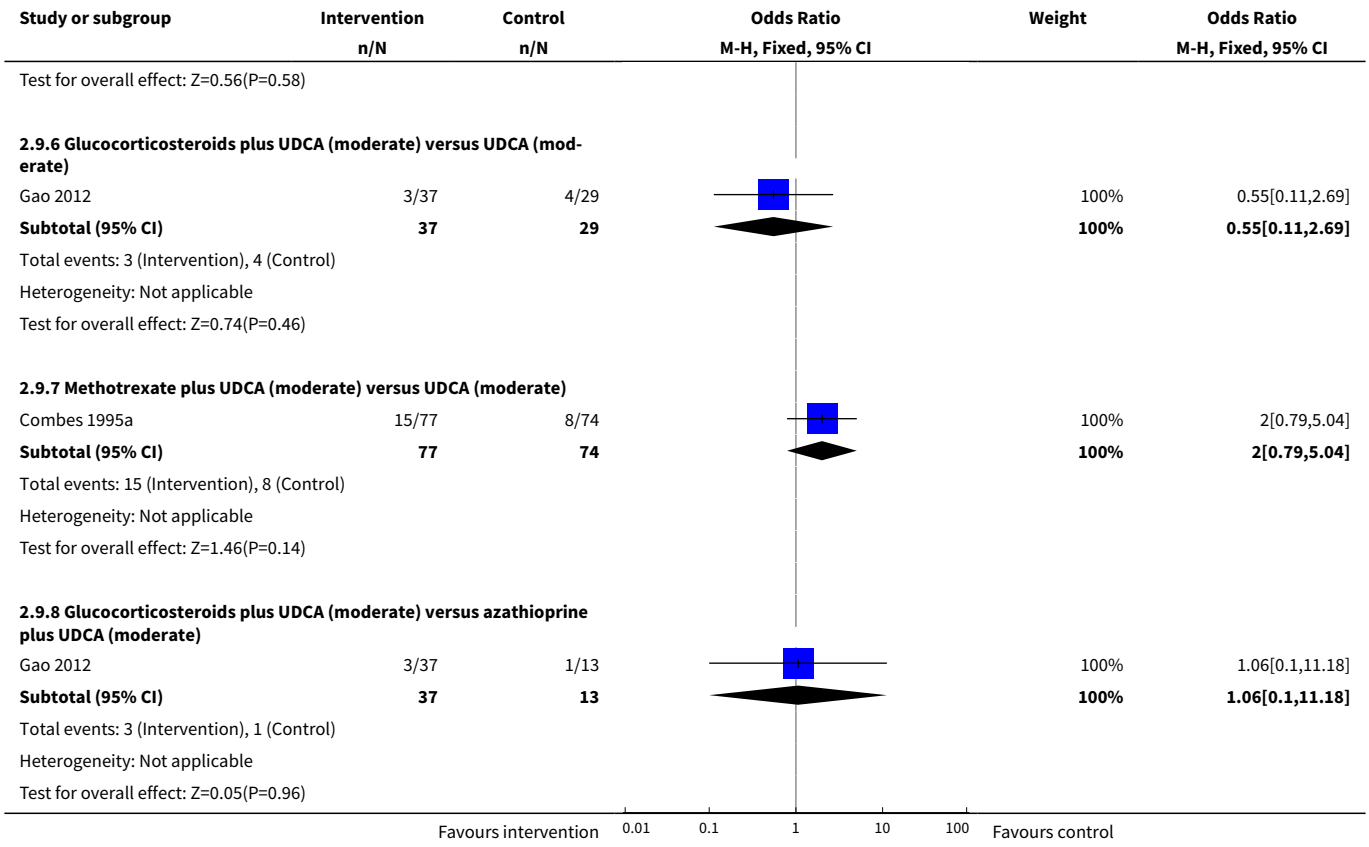




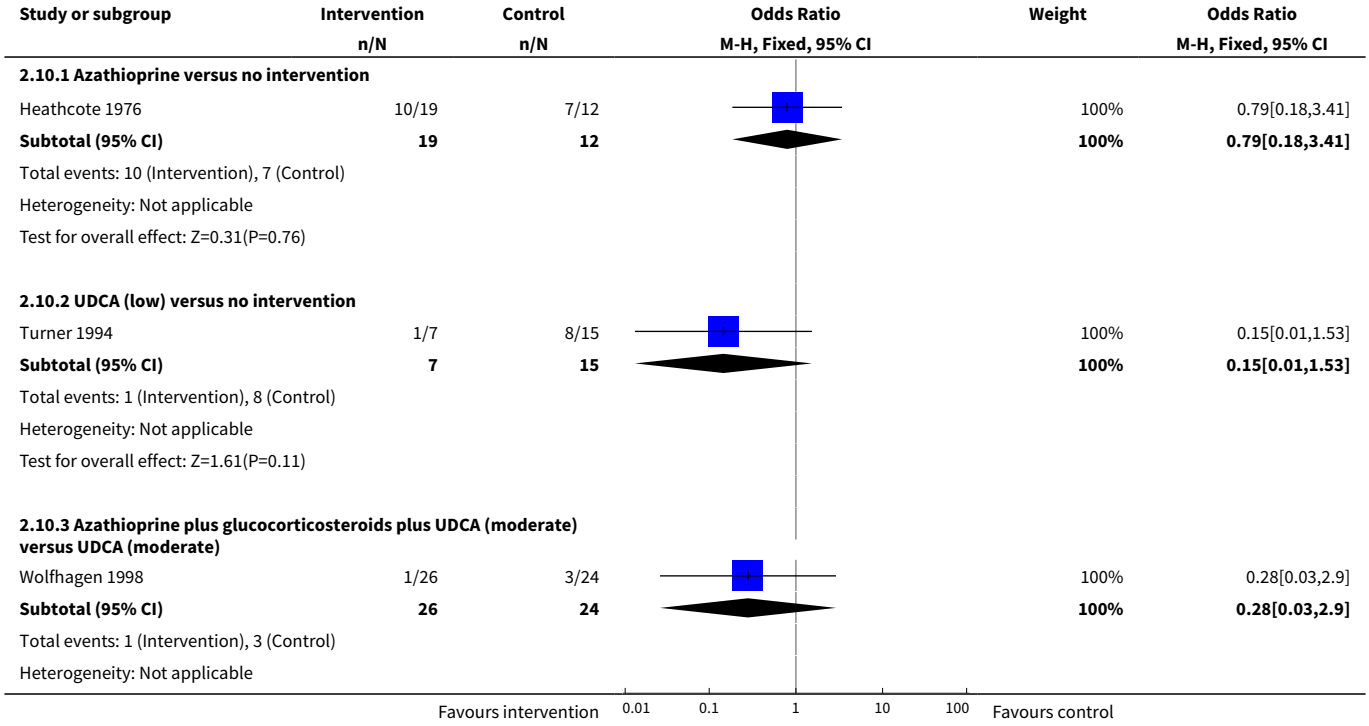


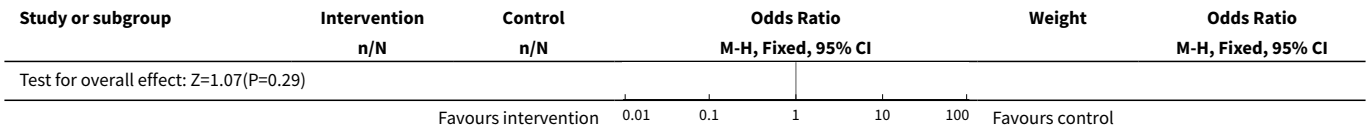
Analysis 2.9. Comparison 2 Stratified by dose, Outcome 9 Decompensated liver disease.





Analysis 2.10. Comparison 2 Stratified by dose, Outcome 10 Cirrhosis.





ADDITIONAL TABLES

Table 1. Characteristics of included studies arranged by comparison

Study name	No participants randomised	Post-randomisation dropouts	No participants for whom outcome was reported	Intervention(s)	Control	Mean follow-up period (months)
Smart 1990	20	Not stated	20	Antioxidants	No intervention	Not stated
Christensen 1985	248	63	185	Azathioprine	No intervention	63
Heathcote 1976	45	6	39	Azathioprine	No intervention	Not stated
Hoofnagle 1986	24	0	24	Chlorambucil	No intervention	52
Bodenheimer 1988	57	10	47	Colchicine	No intervention	33
Kaplan 1986	60	3	57	Colchicine	No intervention	24
Warnes 1987	64	Not stated	64*	Colchicine	No intervention	19 (median)
Bobadilla 1994	40	Not stated	40	Colchicine + UDCA	No intervention	12
Lombard 1993	349	0	349	Ciclosporin	No intervention	31 (median)
Minuk 1988	12	0	12	Ciclosporin	No intervention	Not stated
Wiesner 1990	40	11	29	Ciclosporin	No intervention	35 (median)
Dickson 1985	309	82	227	D-Penicillamine	No intervention	60 (median)
Epstein 1979	98	Not stated	98	D-Penicillamine	No intervention	66
Macklon 1982	60	0	60	D-Penicillamine	No intervention	37
Matloff 1982	52	0	52	D-Penicillamine	No intervention	24
Neuberger 1985	189	Not stated	189	D-Penicillamine	No intervention	Not stated
Taal 1983	24	Not stated	24	D-Penicillamine	No intervention	18
Triger 1980	35	Not stated	35	D-Penicillamine	No intervention	Not stated

Table 1. Characteristics of included studies arranged by comparison *(Continued)*

Mitchison 1989	36	0	36	Glucocorticosteroids	No intervention	36
Ueno 2005	20	Not stated	20	Lamivudine	No intervention	Not stated
Mitchison 1993	104	3	101	Malotilate	No intervention	25 (median)
Hendrickse 1999	60	Not stated	60	Methotrexate	No intervention	68
Steenbergen 1994	14	Not stated	14	Methotrexate + UDCA	No intervention	24
Mayo 2015	45	3	42	NGM282	No intervention	Not stated
Bowlus 2014	216	Not stated	216	Obeticholic acid	No intervention	12
Hirschfield 2015	165	0	165	Obeticholic acid	No intervention	3
Kowdley 2014a	59	Not stated	59	Obeticholic acid	No intervention	Not stated
Manzillo 1993a	32	Not stated	32	S-Adenosyl methionine	No intervention	1
Manzillo 1993b	6	Not stated	6	S-Adenosyl methionine	No intervention	2
Cash 2013	21	8	13	Simvastatin	No intervention	12
Askari 2010	28	0	28	Tetrathiomolybdate	No intervention	Not stated
McCormick 1994	18	0	18	Thalidomide	No intervention	Not stated
Arora 1990	9	Not stated	9	UDCA	No intervention	5
Battezzati 1993	88	2	86	UDCA	No intervention	6
Combes 1995a	151	0	151	UDCA	No intervention	24
Eriksson 1997	116	15	101	UDCA	No intervention	24
Heathcote 1994	222	Not stated	222	UDCA	No intervention	24
Leuschner 1989	20	0	18	UDCA	No intervention	12
Lim 1994	32	Not stated	32	UDCA	No intervention	Not stated
Lindor 1994	180	10	170	UDCA	No intervention	24
Oka 1990	52	7	45	UDCA	No intervention	Not stated
Papatheodoridis 2002	92	6	86	UDCA	No intervention	89
Pares 2000	192	0	192	UDCA	No intervention	41 (median)
Poupon 1991a	149	3	146	UDCA	No intervention	Not stated
Senior 1991	20	1	19	UDCA	No intervention	18

Table 1. Characteristics of included studies arranged by comparison *(Continued)*

Turner 1994	46	0	46	UDCA	No intervention	24
Goddard 1994	57	Not stated	57	Intervention 1: UDCA Intervention 2: colchicine Intervention 3: colchicine + UDCA	No intervention	15
Wolfhagen 1998	50	Not stated	50	Azathioprine + glucocorticosteroids + UDCA	UDCA	12
Iwasaki 2008a	45	Not stated	45	Bezafibrate	UDCA	12
Kurihara 2000	24	Not stated	24	Bezafibrate	UDCA	Not stated
Hosonuma 2015	27	0	27	Bezafibrate + UDCA	UDCA	96
Iwasaki 2008b	22	Not stated	22	Bezafibrate + UDCA	UDCA	12
Kanda 2003	22	0	22	Bezafibrate + UDCA	UDCA	7
Nakai 2000	23	Not stated	23	Bezafibrate + UDCA	UDCA	12
Almasio 2000	90	6	84	Colchicine + UDCA	UDCA	Not stated
Ikeda 1996	22	0	22	Colchicine + UDCA	UDCA	24
Poupon 1996	74	Not stated	74	Colchicine + UDCA	UDCA	24
Raedsch 1993	28	8	20	Colchicine + UDCA	UDCA	24
Yokomori 2001	11	Not stated	11	Colestilan + UDCA	UDCA	Not stated
Liberopoulos 2010	10	Not stated	10	Fenofibrate + UDCA	UDCA	Not stated
Leuschner 1999	40	0	39	Glucocorticosteroids + UDCA	UDCA	24
Rautiainen 2005	77	8	69	Glucocorticosteroids + UDCA	UDCA	36
Gao 2012	79	Not stated	79	Intervention 1: glucocorticosteroids + UDCA Intervention 2: azathioprine + UDCA	UDCA	Not stated
Mason 2008	59	0	59	Lamivudine + zidovudine + UDCA	UDCA	6
Combes 2005	265	0	265	Methotrexate + UDCA	UDCA	91 (median)
Gonzalezkoch 1997	25	Not stated	25	Methotrexate + UDCA	UDCA	11
Nevens 2016	217	Not stated	216	Obeticholic acid + UDCA	UDCA	12
Ferri 1993	30	0	30	TUDCA	UDCA	6

Table 1. Characteristics of included studies arranged by comparison *(Continued)*

Ma 2016	199	8	191	TUDCA	UDCA	6
Kaplan 1999	87	2	85	Colchicine	Methotrexate	24
Comparison of doses						
Lindor 1997	150	Not stated	150	Intervention 1: UDCA (high) Intervention 2: UDCA (moderate)	UDCA (low)	12
Angulo 1999a	155	Not stated	155	Intervention 1: UDCA (high) Intervention 2: UDCA (moderate)	UDCA (low)	12
Van Hoogstraten 1998	61	2	59	UDCA (moderate)	UDCA (low)	Not stated
Mazzarella 2002	42	Not stated	42	UDCA (high)	UDCA (moderate)	72

TUDCA: taurodeoxycholic acid; UDCA: ursodeoxycholic acid.

Table 2. Risk of bias arranged according to comparisons

Name of studies	Intervention(s)	Control	Random sequence generation	Allocation concealment	Blinding of participants and health professionals	Blinding of outcome assessors	Missing outcome bias	Selective outcome reporting	For-profit bias	Other bias
Smart 1990	Antioxidants	No intervention	Unclear	Unclear	Unclear	Unclear	Unclear	High	Unclear	Low
Christensen 1985	Azathioprine	No intervention	Unclear	Unclear	Low	Low	High	High	High	Low
Heathcote 1976	Azathioprine	No intervention	Unclear	Unclear	High	High	High	High	Low	Low
Hoofnagle 1986	Chlorambucil	No intervention	Low	Low	High	High	Low	Low	Low	Low
Bodenheimer 1988	Colchicine	No intervention	Unclear	Unclear	Low	Low	High	High	High	Low
Kaplan 1986	Colchicine	No intervention	Unclear	Unclear	Unclear	Unclear	High	High	Unclear	Low
Warnes 1987	Colchicine	No intervention	Low	Low	Low	Low	Unclear	Low	Unclear	Low
Bobadilla 1994	Colchicine + UDCA	No intervention	Unclear	Unclear	Unclear	Unclear	Unclear	High	Unclear	Low
Lombard 1993	Ciclosporin	No intervention	Unclear	Unclear	Low	Low	Low	Low	High	Low
Minuk 1988	Ciclosporin	No intervention	Unclear	Unclear	Low	Unclear	Unclear	Low	High	Low
Wiesner 1990	Ciclosporin	No intervention	Unclear	Unclear	Low	Low	Unclear	Low	High	Low
Dickson 1985	D-Penicillamine	No intervention	Low	Low	Low	Low	High	High	High	High
Epstein 1979	D-Penicillamine	No intervention	Unclear	Unclear	High	High	Unclear	High	Unclear	Low
Macklon 1982	D-Penicillamine	No intervention	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear	Low
Matloff 1982	D-Penicillamine	No intervention	Unclear	Unclear	Unclear	Unclear	Low	Low	High	Low
Neuberger 1985	D-Penicillamine	No intervention	Unclear	Low	Low	Low	Unclear	High	Unclear	Low
Taal 1983	D-Penicillamine	No intervention	Unclear	Unclear	Low	Low	Unclear	Low	Unclear	Low

Table 2. Risk of bias arranged according to comparisons *(Continued)*

Triger 1980	D-Penicillamine	No intervention	Unclear	Unclear	Unclear	Unclear	Unclear	High	High	Low
Mitchison 1989	Glucocorticosteroids	No intervention	Low	Low	High	High	Low	High	Unclear	Low
Ueno 2005	Lamivudine	No intervention	Unclear	Unclear	Low	Low	Unclear	High	Unclear	Low
Mitchison 1993	Malotilate	No intervention	Low	Low	Low	Low	High	Low	High	Low
Hendrickse 1999	Methotrexate	No intervention	Low	Low	Unclear	Unclear	Unclear	High	Unclear	Low
Steenbergen 1994	Methotrexate + UDCA	No intervention	Low	Unclear	Unclear	Unclear	Unclear	High	Unclear	Low
Mayo 2015	NGM282	No intervention	Unclear	Unclear	Unclear	Unclear	High	High	High	Low
Bowlus 2014	Obeticholic acid	No intervention	Unclear	Unclear	Unclear	Unclear	Unclear	High	High	Low
Hirschfield 2015	Obeticholic acid	No intervention	Low	Unclear	Low	Low	Low	High	Unclear	High
Kowdley 2011	Obeticholic acid	No intervention	Unclear	Unclear	Unclear	Unclear	Unclear	High	High	Low
Manzillo 1993a	S-Adenosyl methionine	No intervention	Unclear	Unclear	Unclear	Unclear	Unclear	High	Unclear	Low
Manzillo 1993b	S-Adenosyl methionine	No intervention	Unclear	Unclear	Unclear	Unclear	Unclear	High	Unclear	Low
Cash 2013	Simvastatin	No intervention	Unclear	Low	High	High	High	High	Low	High
Askari 2010	Tetrathiomolybdate	No intervention	Low	Low	Low	Low	Low	High	Low	High
McCormick 1994	Thalidomide	No intervention	Unclear	Unclear	Low	Low	Low	High	High	Low
Arora 1990	UDCA	No intervention	Unclear	Unclear	Unclear	Unclear	Unclear	High	Unclear	Low
Battezzati 1993	UDCA	No intervention	Low	Low	Low	Low	High	High	Unclear	Low
Combes 1995a	UDCA	No intervention	Unclear	Unclear	Low	Low	Low	High	High	Low
Eriksson 1997	UDCA	No intervention	Unclear	Unclear	Unclear	Unclear	High	High	High	Low

Table 2. Risk of bias arranged according to comparisons *(Continued)*

Heathcote 1994	UDCA	No intervention	Unclear	Low	Low	Low	Unclear	High	High	Low
Leuschner 1989	UDCA	No intervention	Unclear	Unclear	Unclear	Unclear	High	Low	Unclear	Low
Lim 1994	UDCA	No intervention	Unclear	Unclear	Unclear	Unclear	Unclear	High	Unclear	Low
Lindor 1994	UDCA	No intervention	Unclear	Unclear	Low	Low	High	Low	High	Low
Oka 1990	UDCA	No intervention	Unclear	Low	Low	Low	High	High	High	Low
Papatheodoridis 2002	UDCA	No intervention	Low	Low	High	High	High	High	High	High
Pares 2000	UDCA	No intervention	Unclear	Unclear	Low	Low	Unclear	Low	High	Low
Poupon 1991a	UDCA	No intervention	Unclear	Unclear	Low	Low	High	High	High	Low
Senior 1991	UDCA	No intervention	Unclear	Unclear	Unclear	Unclear	High	High	High	Low
Turner 1994	UDCA	No intervention	Unclear	Unclear	Low	Low	Low	High	Unclear	Low
Goddard 1994	Intervention 1: UDCA Intervention 2: colchicine Intervention 3: colchicine + UDCA	No intervention	Unclear	Unclear	Unclear	Unclear	Unclear	High	Unclear	Low
Wolfhagen 1998	Azathioprine + glucocorticosteroids + UDCA	UDCA	Low	Low	Low	Low	Unclear	High	High	Low
Iwasaki 2008a	Bezafibrate	UDCA	Unclear	Low	High	High	Unclear	High	Low	Low
Kurihara 2000	Bezafibrate	UDCA	Unclear	Unclear	Unclear	Unclear	Unclear	High	Unclear	Low
Hosonuma 2015	Bezafibrate + UDCA	UDCA	Low	Low	High	High	Low	Low	Low	Low
Iwasaki 2008b	Bezafibrate + UDCA	UDCA	Unclear	Low	High	High	Unclear	High	Low	Low
Kanda 2003	Bezafibrate + UDCA	UDCA	Unclear	Unclear	Unclear	Unclear	Low	High	Unclear	Low

Table 2. Risk of bias arranged according to comparisons *(Continued)*

Nakai 2000	Bezafibrate + UDCA	UDCA	Unclear	Unclear	Unclear	Unclear	Unclear	High	Low	Low
Almasio 2000	Colchicine + UDCA	UDCA	Low	Low	Low	Low	High	High	Low	Low
Ikeda 1996	Colchicine + UDCA	UDCA	Unclear	Unclear	Unclear	Unclear	Low	High	Unclear	High
Poupon 1996	Colchicine + UDCA	UDCA	Unclear	Unclear	Low	Low	Unclear	Low	High	Low
Raedsch 1993	Colchicine + UDCA	UDCA	Unclear	Unclear	Unclear	Unclear	High	High	Unclear	Low
Yokomori 2001	Colestilan + UDCA	UDCA	Unclear	Unclear	High	High	Unclear	High	Unclear	Low
Liberopoulos 2010	Fenofibrate + UDCA	UDCA	Unclear	Unclear	High	High	Unclear	High	Unclear	Low
Leuschner 1999	Glucocorticosteroids + UDCA	UDCA	Low	Unclear	Unclear	Unclear	High	High	High	Low
Rautiainen 2005	Glucocorticosteroids + UDCA	UDCA	Unclear	Unclear	High	High	High	High	High	Low
Gao 2012	Glucocorticosteroids + UDCA Azathioprine + UDCA	UDCA	Unclear	Unclear	Unclear	Unclear	Unclear	High	Unclear	Low
Mason 2008	Lamivudine + zidovudine + UDCA	UDCA	Low	Low	Low	Low	Unclear	High	High	Low
Combes 2005	Methotrexate + UDCA	UDCA	Unclear	Unclear	Unclear	Unclear	Low	High	High	Low
Gonzalezkoch 1997	Methotrexate + UDCA	UDCA	Unclear	Low	Unclear	Unclear	Unclear	Low	Unclear	Low
Nevens 2016	Obeticholic acid + UDCA	UDCA	Low	Low	Low	Low	High	Low	High	Low
Ferri 1993	TUDCA	UDCA	Unclear	Unclear	Unclear	Unclear	Low	High	Unclear	Low
Ma 2016	TUDCA	UDCA	Low	Low	Low	Low	Unclear	High	High	Low
Kaplan 1999	Colchicine	Methotrexate	Unclear	Unclear	Low	Low	High	High	Unclear	Low

Table 2. Risk of bias arranged according to comparisons *(Continued)*

Comparison of doses

Lindor 1997	Intervention 1: UDCA (high) Intervention 2: UDCA (moderate)	UDCA (low)	Unclear	Unclear	Unclear	Unclear	Unclear	High	Unclear	Low
Angulo 1999a	Intervention 1: UDCA (high) Intervention 2: UDCA (moderate)	UDCA (low)	Low	Low	Low	Low	Unclear	Low	Unclear	Low
Van Hoogstraten 1998	UDCA (moderate)	UDCA (low)	Low	Low	High	High	Unclear	High	High	Low
Mazzarella 2002	UDCA (high)	UDCA (moderate)	Unclear	Unclear	Unclear	Unclear	Unclear	High	Unclear	Low

TUDCA: taurodeoxycholic acid; UDCA: ursodeoxycholic acid.

APPENDICES

Appendix 1. Methods for network meta-analysis if we find this is possible in future

Measures of treatment effect

Relative treatment effects

For dichotomous variables (e.g. proportion of participants with serious adverse events or any adverse events), we will calculate the odds ratio with 95% credible interval (or Bayesian confidence interval) (Severini 1993). For continuous variables (e.g. quality of life reported on the same scale), we will calculate the mean difference with 95% credible interval. We will use standardised mean difference values with 95% credible interval for quality of life if included trials use different scales. For count outcomes (e.g. number of adverse events and serious adverse events), we will calculate the rate ratio with 95% credible interval. For time-to-event data (e.g. mortality at maximal follow-up), we will calculate hazard ratio with 95% credible interval.

Relative ranking

We will estimate the ranking probabilities for all treatments of being at each possible rank for each intervention. Then, we will obtain the surface under the cumulative ranking curve (SUCRA) (cumulative probability) and rankogram (Salanti 2011; Chaimani 2013).

Unit of analysis issues

We will collect data for all trial treatment groups that meet the inclusion criteria. The codes for analysis, that we will use, accounts for the correlation between the effect sizes from trials with more than two groups.

Assessment of heterogeneity

We will assess clinical and methodological heterogeneity by carefully examining the characteristics and design of included trials. We will assess the presence of clinical heterogeneity by comparing effect estimates under different categories of potential effect modifiers. Different study designs and risk of bias may contribute to methodological heterogeneity.

We will assess the statistical heterogeneity by comparing the results of the fixed-effect model meta-analysis and the random-effects model meta-analysis, between-study standard deviation (tau^2 and comparing this with values reported in the study of the distribution of between-study heterogeneity (Turner 2012)), and by calculating the I^2 statistic (using Stata/SE 14.2). If we identify substantial heterogeneity, clinical, methodological, or statistical, we will explore and address heterogeneity in a subgroup analysis (see 'Subgroup analysis and investigation of heterogeneity for network meta-analysis' section).

Assessment of transitivity across treatment comparisons

We will evaluate the plausibility of transitivity assumption (the assumption that the participants included in the different studies with different immunosuppressive regimens can be considered to be a part of a multi-arm randomised clinical trial and could potentially have been randomised to any of the treatments) (Salanti 2012). In other words, any participant that meets the inclusion criteria is, in principle, equally likely to be randomised to any of the above eligible interventions. If there was any concern that the clinical safety and effectiveness are dependent upon the effect modifiers, we will not perform a network meta-analysis on all participant subgroups.

Assessment of reporting biases

For the network meta-analysis, we will judge the reporting bias by the completeness of the search (i.e. searching various databases and including conference abstracts), as we do not currently find any meaningful order to perform a comparison-adjusted funnel plot as suggested by Chaimani 2012. However, if we find any meaningful order, for example, the control group used depended upon the year of conduct of the trial, we will use comparison-adjusted funnel plot as suggested by Chaimani 2012.

Data synthesis

Methods for indirect and mixed comparisons

We will conduct network meta-analyses to compare multiple interventions simultaneously for each of the primary and secondary outcomes. Network meta-analysis combines direct evidence within trials and indirect evidence across trials (Mills 2012). We will obtain a network plot to ensure that the trials were connected by treatments using Stata/SE 14.2 (Chaimani 2013). We will exclude any trials that were not connected to the network. We will conduct a Bayesian network meta-analysis using the Markov chain Monte Carlo method in OpenBUGS 3.2.3 as per the guidance from the National Institute for Health and Care Excellence (NICE) Decision Support Unit (DSU) documents (Dias 2014a). We will model the treatment contrast (i.e. log odds ratio for binary outcomes, mean difference or standardised mean difference for continuous outcomes, log rate ratio for count outcomes, and log hazard ratio for time-to-event outcomes) for any two interventions ('functional parameters') as a function of comparisons between each individual intervention and an arbitrarily selected reference group ('basic parameters') (Lu 2006) using appropriate likelihood functions and links. We will use binomial likelihood and logit link for binary outcomes, Poisson likelihood and log link for count outcomes, binomial likelihood and complementary log-log link for time-to-event outcomes, and normal likelihood and identity link for continuous outcomes. We will perform a fixed-effect model and random-

effects model for the network meta-analysis. We will report both models for comparison with the reference group in a forest plot. For pairwise comparison, we will report the fixed-effect model if the two models report similar results; otherwise, we will report the more conservative model.

We will use a hierarchical Bayesian model using three different initial values using codes provided by NICE DSU (Dias 2014a). We will use a normal distribution with large variance (10,000) for treatment effect priors (vague or flat priors). For the random-effects model, we will use a prior distributed uniformly (limits: 0 to 5) for between-trial standard deviation but assume similar between-trial standard deviation across treatment comparisons (Dias 2014a). We will use a 'burn-in' of 5000 simulations, check for convergence visually, and run the models for another 10,000 simulations to obtain effect estimates. If we do not obtain convergence, we will increase the number of simulations for 'burn-in'. If we do not obtain convergence still, we will use alternate initial values and priors using methods suggested by Van Valkenhoef 2012. We will also estimate the probability that each intervention ranks at one of the possible positions using the NICE DSU codes (Dias 2014a).

Assessment of inconsistency

We will assess inconsistency (statistical evidence of the violation of transitivity assumption) by fitting both an inconsistency model and a consistency model. We will use the inconsistency models used in the NICE DSU manual, as we plan to use a common between-study deviation for the comparisons (Dias 2014b). In addition, we will use the design-by-treatment full interaction model (Higgins 2012) and IF (inconsistency factor) plots (Chaimani 2013) to assess inconsistency. In the presence of inconsistency, we will assess whether the inconsistency is because of clinical or methodological heterogeneity by performing separate analyses for each of the different subgroups mentioned in the ‘Subgroup analysis and investigation of heterogeneity for network meta-analysis’ section.

If there was evidence of inconsistency, we will identify areas in the network where substantial inconsistency might be present in terms of clinical and methodological diversities between trials and, when appropriate, limit network meta-analysis to a more compatible subset of trials.

Direct comparison

We will perform the direct comparisons using the same codes and the same technical details.

Sample size calculations

To control for the risk of random errors, we will interpret the information with caution when the accrued sample size in the network meta-analysis (i.e. across all treatment comparisons) is less than the required sample size (required information size). For calculation of the required information size, see Appendix 3.

Subgroup analysis and investigation of heterogeneity for network meta-analysis

We will assess the differences in the effect estimates between the subgroups listed in Subgroup analysis' and 'Investigation of heterogeneity' sections using meta-regression with the help of the OpenBUGS code (Dias 2012a) if we include a sufficient number of trials. We will use the potential modifiers as study level co-variates for meta-regression. We will calculate a single common interaction term (Dias 2012a). If the 95% credible intervals of the interaction term do not overlap zero, we will consider this as evidence of difference in subgroups.

Presentation of results

We will present the effect estimates with 95% credible interval for each pairwise comparisons calculated from the direct comparisons and network meta-analysis. We will also present the cumulative probability of the treatment ranks (i.e. the probability that the treatment is within the top two, the probability that the treatment is within the top three, etc.) in graphs (SUCRA) (Salanti 2011). We will also plot the probability that each treatment is best, second best, third best, etc. for each of the different outcomes (rankograms), which are generally considered more informative (Salanti 2011; Dias 2012b).

We will present the 'Summary of findings' tables for mortality. In the 'Summary of findings', we will follow the approach suggested by Puhan and colleagues (Puhan 2014). First, we will calculate the direct and indirect effect estimates and 95% credible intervals using the node-splitting approach (Dias 2010), that is calculate the direct estimate for each comparison by including only trials in which there was direct comparison of treatments and the indirect estimate for each comparison by excluding the trials in which there was direct comparison of treatments. Then we will rate the quality of direct and indirect effect estimates using GRADE which takes into account the risk of bias, inconsistency, directness of evidence, imprecision, and publication bias (Guyatt 2011). Then, we will present the estimates of the network meta-analysis and rated the quality of network meta-analysis effect estimates as the best quality of evidence between the direct and indirect estimates (Puhan 2014). In addition, in the same table, we will present illustrations and information on the number of trials and participants as per the standard 'Summary of findings' table.

Appendix 2. Search strategies

Database	Time span	Search strategy
Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley)	Issue 2, 2017.	#1 MeSH descriptor: [Liver Cirrhosis, Biliary] explode all trees #2 (primary biliary cholangitis or PBC) #3 #1 or #2
MEDLINE (OvidSP)	January 1947 to February 2017.	1. exp Liver Cirrhosis, Biliary/ 2. (primary biliary cholangitis or PBC).ti,ab. 3. 1 or 2 4. randomized controlled trial.pt. 5. controlled clinical trial.pt. 6. randomized.ab. 7. placebo.ab. 8. drug therapy.fs. 9. randomly.ab. 10. trial.ab. 11. groups.ab. 12. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 13. exp animals/ not humans.sh. 14. 12 not 13 15. 3 and 14
Embase (OvidSP)	January 1974 to February 2017.	1. exp primary biliary cholangitis/ 2. (primary biliary cholangitis or PBC).ti,ab. 3. 1 or 2 4. exp crossover-procedure/ or exp double-blind procedure/ or exp randomized controlled trial/ or single-blind procedure/ 5. (((((random* or factorial* or crossover* or cross over* or cross-over* or placebo* or double*) adj blind*) or single*) adj blind*) or assign* or allocat* or volunteer*).af. 6. 4 or 5 7. 3 and 6
Science Citation Index Expanded (Web of Knowledge)	January 1945 to February 2017.	#1 TS=(primary biliary cholangitis or PBC) #2 TS=(random* OR rct* OR crossover OR masked OR blind* OR placebo* OR meta-analysis OR systematic review* OR meta-analys*) #3 #1 AND #2
World Health Organization International Clinical Trials Registry	February 2017.	Condition: "primary biliary cholangitis" or PBC

(Continued) Platform Search Portal (apps.who.int/trialsearch/Default.aspx)		
ClinicalTrials.gov	February 2017.	Interventional Studies | "primary biliary cholangitis" OR PBC | Phase 2, 3, 4

Appendix 3. Sample size calculation

The five-year mortality in people with primary biliary cholangitis is 20% (Kim 2000). The required information size based on a control group proportion of 20%, a relative risk reduction of 20% in the intervention group, type I error of 5%, and type II error of 20% is 2894 participants. Network analyses are more prone to the risk of random errors than direct comparisons (Del Re 2013). Accordingly, a greater sample size is required in indirect comparisons than direct comparisons (Thorlund 2012). The power and precision in indirect comparisons depends upon various factors, such as the number of participants included under each comparison and the heterogeneity between the trials (Thorlund 2012). If there is no heterogeneity across the trials, the sample size in indirect comparisons would be equivalent to the sample size in direct comparisons. The effective indirect sample size can be calculated using the number of participants included in each direct comparison (Thorlund 2012). For example, a sample size of 2500 participants in the direct comparison A versus C (n_{AC}) and a sample size of 7500 participants in the direct comparison B versus C (n_{BC}) results in an effective indirect sample size of 1876 participants. However, in the presence of heterogeneity within the comparisons, the sample size required is higher. In the above scenario, for an I^2 statistic for each of the comparisons A versus C (I_{AC}^2) and B versus C (I_{BC}^2) of 25%, the effective indirect sample size is 1407 participants. For an I^2 statistic for each of the comparisons A versus C and B versus C of 50%, the effective indirect sample size is 938 participants (Thorlund 2012). If there were only three groups and the sample size in the trials is more than the required information size, we planned to calculate the effective indirect sample size using the following generic formula (Thorlund 2012):

$((n_{AC} \times (1 - I_{AC}^2)) \times (n_{BC} \times (1 - I_{BC}^2))/((n_{AC} \times (1 - I_{AC}^2)) + (n_{BC} \times (1 - I_{BC}^2))$.

There is currently no method to calculate the effective indirect sample size for a network analysis involving more than three intervention groups.

WHAT'S NEW

Date	Event	Description
12 April 2017	Amended	The Cochrane Central Editorial Unit requested removal of the 'attempted network meta-analysis' phrase from the end of the review title, as this further description of the review might create confusion in the reader. Although we followed the planned methodology for network meta-analysis, it was not possible to assess whether the potential effect modifiers were similar across different comparisons. Therefore, we did not perform the network meta-analysis and instead assessed the comparative benefits and harms of different interventions using standard Cochrane methodology.

CONTRIBUTIONS OF AUTHORS

FS identified the trials, extracted the data for half the trials, and completed the characteristics tables.
KG identified the trials, extracted the data, performed the analysis, and wrote the review.
LHE extracted the data for half the trials.
ET, BD, and DT critically commented on the review.

DECLARATIONS OF INTEREST

This report is independent research funded by the National Institute for Health Research (NIHR Cochrane Programme Grants, 13/89/03 - Evidence-based diagnosis and management of upper digestive, hepato-biliary, and pancreatic disorders). The views expressed in this publication are those of the review authors and not necessarily those of the National Health System (NHS), the NIHR, or the Department of Health.

FS has no financial disclosures.
KG has no financial disclosures.
LHE has no financial disclosures.
ET has participated in advisory boards for Astra Zeneca and ViiV healthcare.
BD has no financial disclosures.
DT was funded by Astellas for his attendance at the International Liver Transplantation Society meeting in 2014. He received GBP 25,000 from Boston Scientific to fund a clinical research fellow in 2013.

SOURCES OF SUPPORT

Internal sources

- University College London, UK.

External sources

- National Institute for Health Research, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- It was not possible to assess whether the potential effect modifiers were similar across different comparisons. Therefore, we did not perform the network meta-analysis and assessed the comparative benefits and harms of different interventions using standard Cochrane methodology. The methodology that we plan to use if we conduct a network meta-analysis in the future is available in Appendix 1.
- We performed Trial Sequential Analysis in addition to conventional method of assessing the risk of random errors using P values.

NOTES

There is considerable overlap between the 'Methods' of this review and those of several other reviews written by the same group of authors.

INDEX TERMS

Medical Subject Headings (MeSH)

Azathioprine [adverse effects] [therapeutic use]; Chenodeoxycholic Acid [adverse effects] [analogs & derivatives] [therapeutic use]; Cholagogues and Choleretics [adverse effects] [therapeutic use]; Cholangitis [*drug therapy] [immunology] [mortality]; Chronic Disease; Colchicine [adverse effects] [therapeutic use]; Cyclosporine [adverse effects] [therapeutic use]; Immunosuppressive Agents [adverse effects] [therapeutic use]; Methotrexate [adverse effects] [therapeutic use]; Mitochondria [immunology]; Network Meta-Analysis; Penicillamine [adverse effects] [therapeutic use]; Quality of Life; Randomized Controlled Trials as Topic; Ursodeoxycholic Acid [adverse effects] [therapeutic use]

MeSH check words

Humans