National Institute for Health and Care Excellence

Cirrhosis in over 16s: assessment and management (update)

[C] Evidence review for the clinical and cost effectiveness of non-selective beta-blockers for the primary prevention of decompensation in people with compensated cirrhosis

NICE guideline NG50

Evidence reviews underpinning recommendations 1.3.9 to 1.3.11 and research recommendations in the NICE guideline

May 2023

Draft for consultation

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive. All NICE guidance is subject to regular review and may be updated or withdrawn.

Copyright

ISBN: xxx

Contents

1 Non-selective beta-blockers for preventing decompensation in people with cirrhosis 4
1.1 Review question 4
1.1.1 Introduction 4
1.1.2 Summary of the protocol 4
1.1.3 Methods and process 5
1.1.4 Effectiveness evidence 5
1.1.5 Summary of studies included in the effectiveness evidence 7
1.1.6 Summary of the effectiveness evidence 8
1.1.7 Economic evidence 12
1.1.8 Summary of included economic evidence 12
1.1.9 Economic model 12
1.1.10 Unit costs 12
1.1.11 Evidence statements 13
1.1.12 The committee's discussion and interpretation of the evidence 13
1.1.13 Recommendations supported by this evidence review 16
1.1.14 References – included studies 16
Appendices 18
Appendix A – Review protocols 18
Appendix B – Literature search strategies 24
Appendix C – Effectiveness evidence study selection 49
Appendix D – Effectiveness evidence 50
Appendix E – Forest plots 59
Appendix F – GRADE tables 60
Appendix G – Economic evidence study selection 62
Appendix H – Economic evidence tables 63
Appendix I – Health economic model 64
Appendix J – Excluded studies 68
Appendix K– Research recommendations 69

1 Non-selective beta-blockers for preventing decompensation in people with cirrhosis

1.1 Review question

What is the clinical and cost effectiveness of non-selective beta-blockers (NSBBs) for the primary prevention of decompensation in people with compensated cirrhosis?

1.1.1 Introduction

The original guideline NG50 was intended to focus on areas of uncertainty and variability in practice and as such was limited in scope. It did not cover all approaches to the prevention of decompensation. During surveillance, stakeholders highlighted new published research about the use of non-selective beta-blockers for the primary prevention of decompensation (for example, ascites) in people with compensated cirrhosis. This is therefore a new area in which the evidence will be reviewed and in which the committee will consider making recommendations.

1.1.2 Summary of the protocol

Table 1: PICOS inclusion criteria

Population	Inclusion: People aged 16 years and older with compensated cirrhosis. Exclusion: People who have had previous episodes of decompensated cirrhosis.
Interventions	Non-selective beta-blockers (NSBBs): • Nadolol, • Timolol maleate, • Sotalol, • Carvedilol, • Labetalol, • Propranolol. All non-selective beta-blockers (NSBBs) (as class vs placebo/no intervention)
Comparator	• Each other • Placebo/no intervention
Outcomes	**Primary outcomes** (at longest timepoint) • Decompensation (as defined by the study) • Mortality • Quality of life (using a validated scale) **Secondary outcomes** (at longest timepoint)

	• Liver transplant
	• Hospitalisation (including length of hospital stay)
	• Other adverse events
	  ○ Compliance with intervention/discontinuation
	  ○ Infection

Study type	Randomised Controlled Trials

For the full protocol see appendix A.

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.1.3.1 Search methods

The searches for the clinical effectiveness evidence were run on 1st February 2023. The following databases were searched: Central Register of Controlled Trials (Wiley), Cochrane Database of Systematic Reviews (Wiley), Embase (Ovid), Epistemonikos and MEDLINE (Ovid), MEDLINE-in-Process (Ovid), MEDLINE Epub Ahead-of-Print (Ovid). The searches focused on the effectiveness of non-selective beta blockers to prevent decompensation in people with compensated cirrhosis. Full search strategies for each database are provided in appendix B.

The searches for the cost effectiveness evidence were run on 2nd February 2023. The following databases were searched: EconLit (Ovid), Embase (Ovid), INAHTA and MEDLINE (Ovid), MEDLINE-in-Process (Ovid), MEDLINE Epub Ahead-of-Print (Ovid). Full search strategies for each database are provided in appendix B.

A NICE information specialist conducted the searches. The MEDLINE strategy was quality assured by a trained NICE information specialist and all translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the 2015 PRESS Guideline Statement.

1.1.3.2 Protocol deviations

During the sifting for this review question, an individual patient data (IPD) meta-analysis was identified that incorporated unpublished data from authors of the included studies. This meta-analysis is summarised narratively within this review to supplement the data from primary studies.

1.1.4 Effectiveness evidence

1.1.4.1 Included studies

A systematic search carried out to identify potentially relevant studies found 335 references (see appendix B for the literature search strategy).

These 335 references were screened at title and abstract level against the review protocol, with 331 excluded at this level. 10% of references were screened separately by two reviewers with 100% agreement.

The full texts of 4 RCTs and systematic reviews were ordered for closer inspection. 1 of these studies met the criteria specified in the review protocol (appendix A) and 1 IPD meta-analysis was also deemed to be directly relevant and was also included (see 1.1.3.2 protocol deviations). For a summary of the 2 included studies see table 2.

The clinical evidence study selection is presented as a PRISMA diagram in appendix C.

See section 1.1.14 References – included studies for the full references of the included studies.

1.1.4.2 Excluded studies

Details of studies excluded at full text, along with reasons for exclusion are given in appendix J.

1.1.5 Summary of studies included in the effectiveness evidence

Table 2 Summary of studies included in the effectiveness evidence

Study details	Setting/Location	Population	Intervention	Comparison	Risk of bias
Villanueva (2022) N=352 Study type: IPD meta-analysis Follow up time: The mean follow-up in the included RCTs ranged from 13 to 36 months.	Setting: NA Location: NA	Adults with compensated cirrhosis and no history of decompensation. Mean age (IQR): • Intervention: 53 (45 – 60) • Placebo/EVL: 51 (44 – 59)	Carvedilol was administered up to 12.5 mg/day in 2 studies (Tripathi et al 2009; Bhardwaj et al 2017) and up to 25 mg/day in 2 studies (Villanueva 2019; Shah et al 2014)	Endoscopic variceal band ligation (Tripathi et al 2009; Bhardwaj et al 2017) and Placebo (Villanueva 2019; Shah et al al 2014).	Low
Villanueva (2019) N=201 Study type: RCT Follow up time: Mean (SD) follow up (months) -	Setting: Eight hospitals Location: Spain	Patients with cirrhosis aged between 18 and 80 years inclusive, without any previous decompensation of cirrhosis and without high-risk oesophageal varices (i.e. no varices or small varices without red signs). Mean age (SD): • Intervention: 60 (10) • Control: 59 (11)	Propranolol or carvedilol titrated against clinical tolerance. • Mean dose of propranolol per day = 95mg (SD: 81) • Mean dose carvedilol per day = 20mg (SD: 6)	Oral placebo allocated and administered in line with the approach to beta-blocker regimen.	Low

Study details	Setting/Location	Population	Intervention	Comparison	Risk of bias
• Placebo group 37 (16) • Intervention group 36 (16)					

Abbreviations: EVL – endoscopic variceal band ligation

See appendix D for full evidence tables.

1.1.6 Summary of the effectiveness evidence

Table 3 Summary of the effectiveness evidence for decompensation

NSBB compared to placebo for decompensation

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Interpretation of effect
				Risk with	Risk difference with NSBB (95% CI)	
Decompensation or death - NSBB (all) vs placebo	201 (1 study[1]) 36.5 months	⨁⨁⨀⨀ **LOW**[2,3] due to inconsistency, imprecision	**RR 0.6** (0.34 to 1.04)	**267 per 1000**	**107 fewer per 1000** (from 176 fewer to 11 more)	**Could not differentiate**
Decompensation or death - Carvedilol vs placebo	66 (1 study[1]) 36.5 months	⨁⨁⨀⨀ **LOW**[2,3] due to inconsistency, imprecision	**RR 0.33** (0.1 to 1.12)	**273 per 1000**	**183 fewer per 1000** (from 245 fewer to 33 more)	**Could not differentiate**
Decompensation or death - Propranolol vs placebo	135 (1 study[1]) 36.5	⨁⨀⨀⨀ **VERY LOW**[2,4] due to inconsistency, imprecision	**RR 0.73** (0.39 to 1.37)	**265 per 1000**	**71 fewer per 1000** (from 161 fewer to 98 more)	**Could not differentiate**

Decompensation - Decompensation (all)	201 (1 study[1]) 36.5 months	⨁⨁⨀⨀ **LOW**[2,3] due to inconsistency, imprecision	**RR 0.51** (0.27 to 0.95)	**238 per 1000**	**116 fewer per 1000** (from 12 fewer to 173 fewer)	**Favours NSBB**
Decompensation - Decompensated liver resulting in death	36 (1 study[1]) 36.5 months	⨁⨀⨀⨀ **VERY LOW**[2,4] due to inconsistency, imprecision	**RR 0.89** (0.34 to 2.3)	**375 per 1000**	**41 fewer per 1000** (from 248 fewer to 487 more)	**Could not differentiate**

*The basis for the **assumed risk** is the median control group risk across studies. 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; **RR:** Risk 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] Villanueva 2019
[2] Downgraded once because single study
[3] Downgraded once for crossing 1 MID
[4] Downgraded twice for crossing 2 MIDs.

Table 4 Summary of the effectiveness evidence for adverse events

NSBB compared to placebo for adverse events

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Interpretation of effect
				Risk with Control	Risk difference with (95% CI)	
Adverse events - Adverse events - all	201 (1 study[1]) 36.5 months	⨁⨁⨁⨀ **MODERATE**[2] due to inconsistency	**RR 0.96** (0.86 to 1.08)	**871 per 1000**	**35 fewer per 1000** (from 122 fewer to 70 more)	**Could not differentiate**

Adverse events - Adverse events - probably related to treatment	201 (1 study[1]) 36.5 months	⨁⨁⨀⨀ **LOW**[2,3] due to inconsistency, imprecision	**RR 1.31** (0.89 to 1.93)	**297 per 1000**	**92 more per 1000** (from 33 fewer to 276 more)	**Could not differentiate**
Adverse events - Adverse events - very probably related to treatment	201 (1 study[1]) 36.5 months	⨁⨀⨀⨀ **VERY LOW**[2,4] due to inconsistency, imprecision	**RR 1.08** (0.56 to 2.06)	**149 per 1000**	**12 more per 1000** (from 65 fewer to 157 more)	**Could not differentiate**

*The basis for the **assumed risk** is. the median control group risk across studies. 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; **RR:** Risk 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] Villanueva 2019
[2] Downgraded once because single study
[3] Downgraded once for crossing 1 MID
[4] Downgraded twice for crossing 2 MIDs.

1 See appendix F for full GRADE tables.

1.1.6.1 Narrative summary

One study (Villanueva 2022) was not amenable to assessment using GRADE because it was an individual patient data (IPD) meta-analysis, however it was critically appraised using a checklist based on the PRISMA-NMA criteria and was found to be at low risk of bias. The purpose of the meta-analysis was to compare carvedilol to endoscopic variceal band ligation or placebo for the primary prevention of decompensation in adults with compensated cirrhosis. They defined decompensation as the appearance of ascites, gastrointestinal bleeding related to portal hypertension, or overt hepatic encephalopathy.

The authors undertook a competing risk time-to-event meta-analysis using individual patient data IPD obtained by contacting the primary authors of relevant RCTs.

Villanueva et al reviewed125 studies at full text and contacted the authors of relevant studies to request individual patient data. The authors of 4 studies responded. The 4 studies were included in the IPD. They comprised 352 patients with compensated cirrhosis, 181 treated with carvedilol and 171 controls (79 received EVL and 92 placebo). Baseline characteristics were similar between groups in all 4 studies.

The risk of developing decompensation of cirrhosis was lower with carvedilol than in controls (sub-distribution hazard ratio [SHR] 0.506; 95% CI 0.289-0.887; p = 0.017; I2 = 0.0%, Q-statistic-p = 0.880), mainly due to a reduced risk of ascites (SHR 0.491; 95% CI 0.247-0.974; p = 0.042; I2 = 0.0%, Q-statistic-p = 0.384). The risk of death was also lower with carvedilol (SHR 0.417; 95% CI 0.194-0.896; p = 0.025; I2 = 0.0%, Q-statistic-p = 0.989).

The authors conclude that “Long-term carvedilol therapy reduced decompensation of cirrhosis and significantly improved survival in compensated patients with clinically significant portal hypertension. This suggests that screening patients with compensated cirrhosis for CSPH to enable the prompt initiation of carvedilol could improve outcomes.”

1.1.7 Economic evidence

1.1.7.1 Included studies

A search was performed to identify published economic evaluations of relevance to this guideline update. This search retrieved 71 studies. Based on title and abstract screening, all studies were excluded for this question as they did not meet the inclusion criteria.

1.1.7.2 Excluded studies

No studies were examined at full text.

1.1.8 Summary of included economic evidence

No economic studies were included in this review.

1.1.9 Economic model

We conducted an analysis to evaluate the cost savings of NSBBs that could be realised by preventing decompensation of cirrhosis. To be cost saving, NSBBs has to prevent at least one case of decompensation per 79.13 person years. The clinical evidence shows that prophylactic treatment with NSBBs can reduce incidence of decompensation by 116 cases per 1,000 (1 case in every 8.6 people). Based on the clinical evidence, NSBBs appears to be cost saving compared with no active intervention, as the cost savings from averting decompensation and the associated treatment is greater than the cost of providing NSBBs. The full write up of the methods and results is in Appendix I.

Table 5 Health economic evidence profile: non-selective beta blockers (NSBBs) vs placebo for preventing decompensation of cirrhosis

Study type	Applicability	Threshold (cases averted to be cost saving)	Risk reduction in decompensation	Cost saving
Threshold analysis	Directly applicable	1 episode averted per 82.68 person years	1 case in every 8.6 people	Yes

1.1.10 Unit costs

The costs of the drugs and the costs of managing decompensation events included in recommendations for this review question are given below, respectively. For further details about how the cost of decompensation events were calculated, see Appendix I.

Table 6 Unit costs of non-selective beta blockers

Resource	Daily dose	Unit costs	Source
Propranolol (tablets)	80–320 mg	£0.79 for 28 40mg tablets	BNF (accessed Mar 2023)
		£1.57 for 56 80mg tablets	
		£5.88 for 56 160mg tablets	
Propranolol (oral solution)	80–320 mg	£45.84 for 40mg	
		£50.45 for 50mg	
Carvedilol	6.25–12.5 mg	£0.88 for 28 6.25mg tablets	
		£1.25 for 28 12.5mg tablets	

Table 7 Unit costs of managing decompensation events

Decompensation event	Annual cost per person
Treatment costs of managing uncomplicated ascites (moderate and large)	£201
Treatment costs of managing refractory ascites	£20,115

1.1.11 Evidence statements

Effectiveness evidence

- A directly applicable IPD meta-analysis, at low risk of bias containing data from 352 people calculated that carvedilol is associated with a reduced risk of decompensating events (appearance of ascites, gastrointestinal bleeding related to portal hypertension, or overt hepatic encephalopathy) - SHR = 0.506; 95% CI 0.289-0.887 and death SHR = 0.417; 95% CI 0.194-0.896 when compared to placebo or endoscopic variceal band ligation.

Economic evidence

- No published economic studies were identified. A costing analysis based on evidence from the effectiveness review suggests that NSBB may be cost saving for preventing decompensation of cirrhosis.

1.1.12 The committee's discussion and interpretation of the evidence

1.1.12.1. The outcomes that matter most

The committee agreed that the most important outcomes for this question were decompensation, mortality and quality of life. They also noted that it was important to look at the proxy measures for decompensation such as liver transplantation, hospitalisation and infection. Finally adverse events were identified as important to look for and included intervention compliance or discontinuation.

1.1.12.2 The quality of the evidence

The committee considered the evidence from one RCT (Villanueva et al 2019) and in a deviation from the protocol one individual patient data (IPD) meta-analysis (Villanueva et al 2022).The RCT (Villanueva et al 2019) was assessed by outcome using GRADE as being of low to very low quality for outcomes related to decompensation and as being of moderate to very low quality for outcomes related to adverse events (see appendix F). The rationale for downgrading for both outcomes were due to inconsistency, due to the findings only being derived from one study, and imprecision, due to the confidence intervals that bound the effect estimate crossing 1 or 2 minimum important differences (MIDs). The IPD meta-analysis (Villanueva et al 2022) was identified during the initial evidence sift for this review question. Villanueva et al 2022 was assessed and was found to be at low risk of bias. The deviation from protocol, which was on the basis of study type as a non-RCT and on comparator as the study combines data from study arms that considered placebo and endoscopic variceal ligation (EVL). Villanueva et al 2022 was included as Villanueva et al 2022 contacted study authors of 4 RCTs identified through a systematic review, for unpublished decompensation data in compensated patients which was not included in the published papers. This data was deemed directly relevant to this review question and the NICE team felt it would be useful for the committee to consider it in their deliberations. Villanueva et al 2022 was summarised narratively within this review to supplement the data from the initially identified RCT (Villanueva et al 2019).

The committee considered the findings of Villanueva et al 2019 which were equivocal for comparison of non-selective beta-blockers (NSBBs) and placebo for decompensation or death for carvedilol or propranolol individually or when all NSBBs (carvedilol and propranolol) were considered together. There was also equivalence in effect for the comparison of all NSBBs (carvedilol and propranolol) with placebo for decompensated liver resulting in death, and for adverse events. When considering decompensation alone NSBBs (propranolol or carvedilol) were significantly more effective than placebo. The committee considered the findings of the IPD meta-analysis (Villanueva et al 2022) which indicated a significant effect for carvedilol over placebo or EVL for the risk of developing decompensation of cirrhosis, risk of ascites and risk of death.

1.1.12.3 Benefits and harms

The committee acknowledged that based on the evidence and their experience that non-selective beta-blockers (NSBBs) may be an effective treatment option for the primary prevention of decompensation.

The committee discussed NSBB treatment options of carvedilol or propranolol and the lack of current (as of September 2023) UK marketing authorisation for the primary prevention of decompensation for either of those drugs. They also noted that carvedilol is contraindicated in those with ‘clinically significant hepatic dysfunction’. The committee discussed each of these issues based on the evidence presented and their experience, and highlighted that since this recommendation was about the primary prevention of decompensation, the people who would be included in it would not be considered to have clinically significant hepatic impairment. However, they noted that some caution was always needed when prescribing carvedilol to people with cirrhosis, and for that reason people should be started on a much lower dose and the dose titrated up depending on their tolerance.

The committee noted Villanueva et al 2019 recruited people with clinically significant portal hypertension. They noted that in the UK it is uncommon to directly measure portal venous pressure and that the decision about clinically significant portal hypertension was therefore

more likely to be a clinical judgment based on tests like ultrasound, platelet count, presence of oesophageal varices and other factors. They acknowledged that there may be variation in access to equipment for example FibroScan to support this.

The committee noted that as carvedilol and propranolol did not have UK marketing authorisation, prescribing regimens for NSBBs for this indication were not established. The committee agreed that, because propranolol and carvedilol have a greater impact on heart rate and blood pressure in people with cirrhosis, they needed to be used with caution and started at a lower dose that could be titrated upward depending on the persons tolerance. They agreed that dosage regimen set out in the included studies was sensible and was in line with what they had recommended for preventing bleeding of oesophageal varices earlier in this update. Therefore they recommended carvedilol 6.25 mg per day starting dose (Villanueva, 2019, 2022) and for propranolol 40 mg twice a day (Villanueva et al 2019), keeping heart rate above 55 beats per min and systolic blood pressure greater than 90 mm Hg would as an appropriate baseline though they noted this might need to be adjusted based on clinical judgment, for example if the person was very frail.

1.1.12.4 Cost effectiveness and resource use

No recent and relevant published economic studies were identified.

We carried out an analysis to evaluate the cost savings of NSBBs that could be realised by preventing decompensation of cirrhosis in people with clinically significant portal hypertension. The analysis takes into account the annual cost of propranolol and carvedilol, the cost of treating uncomplicated ascites and cost of treating refractory ascites. The analysis focused on the management costs of ascites as opposed to other decompensation events, such as hepatic encephalopathy, because the evidence for the treatment effect of NSBBs was mainly driven by a reduction in ascites. The committee acknowledged that NSBBs may be more cost saving if evidence could support a broader range of decompensated events to be considered in the analysis, as conditions such as hepatic encephalopathy are more expensive to manage.

We estimated that the average cost of treating uncomplicated ascites is about £200, assuming 90% of people would develop moderate ascites and 10% would develop large ascites. People with moderate ascites are treated with a 6-month course of spironolactone while people with large ascites are treated with an average of 2 sessions of large volume paracentesis (LVP) plus human albumin. 10% of people with uncomplicated ascites are assumed to develop refractory ascites. We estimated the annual treatment cost of refractory ascites to be around £20,115. This is based on the assumption that 90% of people are given LVP every 2 weeks in combination with human albumin as per the EASL guidelines, and 10% are treated with transjugular intrahepatic portosystemic shunt (TIPS) according to NICE recommendations.

The committee noted that data on the proportion of people with each grade of ascites and their natural history were sparse, and based the assumption on their experience in the clinical practice. The treatment strategy for ascites is varied and complex, as it depends upon multiple patient factors such as their lifestyle or treatment preferences. As a result, it is challenging to accurately judge the resource utilisation for managing ascites but the committee was content that the costs in our analysis were broadly representative.

The total cost of managing a case of ascites is approximately £2,200, and the average annual cost of NSBBs (namely, propranolol and carvedilol) is approximately £27. Based on these costs, the analysis suggests that NSBBs may be cost saving overall if they prevent at

least 1 episode averted per 82 person years. The evidence indicates that NSBBs can reduce incidence of decompensation by an average of 116 cases per 1,000 (1 case in every 8.6 people). While the outcome of this analysis is compelling enough to support NSBBs given the large cost difference between NSBB drugs and treatment of ascites, the committee noted that this evidence was based on a single study based outside of the UK and subsequently was subject to some degree of uncertainty, and thus elected to make a weak, rather than a strong recommendation to consider the use of NSBBs.

The committee discussed how people with clinically significant portal hypertension would be detected in England. In the PREDESCI trial, people with CSPH were defined by a hepatic venous pressure gradient (HVPG) ≥10 mm Hg. This is considered the gold standard approach, but requires an invasive and often painful procedure in order to measure, and may not be acceptable to a large number of people with cirrhosis. HVPG measurement is done in few liver centres in the UK, and there is not presently the capacity among the interventional radiologists to cope with the increased number of required procedures if this was implemented before giving non-selective beta blockers to these patients and to continue monitoring to estimate dose adjustments. CSPH can alternatively be diagnosed on the basis of clinical features (e.g. ascites, varices) as well as non-invasive methods including liver stiffness (transient elastography, or Fibroscan), serum biomarkers and other imaging. According to current NICE guidelines, these tests should be done as part of diagnosing cirrhosis or are part of ongoing monitoring to detect progression of disease, and so would not constitute any additional resources to implement.

The committee also highlighted that patients receiving non-selective beta blockers to prevent decompensation may not require ongoing monitoring with endoscopy to detect the development of varices, and this would possibly constitute some cost and capacity savings.

1.1.12.5 Other factors the committee took into account

The committee discussed whether the new recommendations might have any impact on health inequalities, and noted that people would have to be compliant with any regime of NSBB to get the full benefit from them. They acknowledged this might be a challenge for some people living with cirrhosis.

1.1.13 Recommendations supported by this evidence review

This evidence review supports recommendations 1.3.9 to 1.3.11 and the research recommendation on preventing decompensation.

1.1.14 References – included studies

1.1.14.1 Effectiveness

Villanueva, Candid, Albillos, Agustin, Genesca, Joan et al. (2019) beta blockers to prevent decompensation of cirrhosis in patients with clinically significant portal hypertension (PREDESCI): a randomised, double-blind, placebo-controlled, multicentre trial. Lancet (London, England) 393(10181): 1597-1608

Villanueva, Candid, Torres, Ferran, Sarin, Shiv Kumar et al. (2022) Carvedilol reduces the risk of decompensation and mortality in patients with compensated cirrhosis in a competing-risk meta-analysis. Journal of hepatology 77(4): 1014-1025

1.1.14.2 Economic

None included.

1.1.14.3 Other references

Mattock, Tripathi, O'Neill, Craig, Tanner, Patch et al. (2021) Economic evaluation of covered stents for transjugular intrahepatic portosystemic stent shunt in patients with variceal bleeding and refractory ascites secondary to cirrhosis. BMJ Open Gastroenterology 8(1): e000641

Solà, E., Solé, C. and Ginès, P. (2016), Management of uninfected and infected ascites in cirrhosis. Liver Int, 36: 109-115.

British National Formulary (2023). Accessed at: https://bnf.nice.org.uk/

Appendices

Appendix A – Review protocols

Review protocol for cirrhosis is in over 16s: assessment and management – primary prevention of decompensation in people with compensated cirrhosis

ID	Field	Content
0.	PROSPERO registration number	CRD42023392940
1.	Review title	The clinical and cost effectiveness of non-selective beta-blockers for the primary prevention of decompensation in people with compensated cirrhosis.
2.	Review question	What is the clinical and cost effectiveness of non-selective beta-blockers (NSBBs) for the primary prevention of decompensation in people with compensated cirrhosis?
3.	Objective	To determine the clinical and cost effectiveness of non-selective beta-blockers (NSBBs) for the primary prevention of decompensation (for example ascites) in people with compensated cirrhosis.
4.	Searches	**Databases** The principal search strategy will be developed in MEDLINE (Ovid interface) and then adapted, as appropriate, for use in the other sources listed, taking into account their size, search functionality and subject coverage. The following databases will be searched: Cochrane Central Register of Controlled Trials (CENTRAL) via Wiley Cochrane Database of Systematic Reviews (CDSR) via Wiley EconLit via Ovid Epistemonikos Embase via Ovid International HTA Database via INAHTA MEDLINE MEDLINE in-process MEDLINE (Epub-Ahead-of-Print) via Ovid **Database search limits** Database functionality will be used, where available, to limit search results to the following: English language studies Studies that involve humans

		Filters to limit results to randomised controlled trials or systematic reviews will be used in relevant databases. Filters to identify economic evidence will also be used in relevant databases. **Other searches** A randomised controlled trial classifier may be used if appropriate The searches will be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion if more than 6 months passes from the original search date. The full search strategies for MEDLINE database will be published in the final review.
5.	Condition or domain being studied	Primary prophylaxis of decompensation in people with compensated cirrhosis.
6.	Population	Inclusion: People aged 16 years and older with compensated cirrhosis. Exclusion: People who have had previous episodes of decompensated cirrhosis.
7.	Intervention/Exposure/Test	• Non-selective beta-blockers (NSBBs) - Nadolol, Timolol maleate, Sotalol, Carvedilol, Labetalol, Propranolol. • Non-selective beta-blockers (NSBBs) (as class vs placebo/no intervention)
8.	Comparator/Reference standard/Confounding factors	• Each other • Placebo/no intervention
9.	Types of study to be included	Randomised controlled trials (RCTs)
10.	Other exclusion criteria	• Other non-comparative study types • Studies not published in English • Pre-prints • Dissertations
11.	Context	The original guideline NG50 was intended to focus on areas of uncertainty and variability in practice and as such was limited in scope. It did not cover all approaches to the prevention of decompensation. During surveillance, stakeholders highlighted new published research about the use of beta-blockers for the primary prevention of decompensation (for example, ascites) in people with compensated

		cirrhosis. This is therefore a new area in which the evidence will be reviewed and in which the committee will consider making recommendations.
12.	Primary outcomes (critical outcomes)	(All at the longest timepoints) • Decompensation (as defined by the study) • Mortality • Quality of life (using a validated scale)
13.	Secondary outcomes (important outcomes)	(All at the longest timepoints) • Liver transplant • Hospitalisation (including length of hospital stay) • Other adverse events • Compliance with intervention/discontinuation • Infection
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). Study investigators may be contacted for missing data where time and resources allow.
15.	Risk of bias (quality) assessment	Risk of bias for RCTs will be assessed using Cochrane Risk of Bias v.2.0 as described in Developing NICE guidelines: the manual.
16.	Strategy for data synthesis	Pairwise meta-analyses will be performed in Cochrane Review Manager V5.3. A pooled relative risk will be calculated for dichotomous outcomes (using the Mantel–Haenszel method) reporting numbers of people having an event. A pooled mean difference will be calculated for continuous outcomes (using the inverse variance method) when the same scale will be used to measure an outcome across different studies. Where different studies presented continuous data measuring the same outcome but using different numerical scales these outcomes will be all converted to the same scale before meta-analysis is conducted on the mean differences. Where outcomes measured the same underlying construct but used different instruments/metrics, data will be analysed using standardised mean differences (SMDs, Hedges' g). Fixed effects models will be fitted unless there is significant statistical heterogeneity in the meta-analysis, defined as $I^2 \geq 50\%$, or where significant

		between study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis, when random effects models will be used instead. Where 10 or more studies are included as part of a single meta-analysis, a funnel plot will be produced to graphically assess the potential for publication bias. GRADE will be used to assess the quality of the outcomes. Outcomes using evidence from RCTs will be rated as high quality initially and downgraded from this point. If data are found for more than four agents (including placebo/no intervention) a network meta-analysis will be considered to inform committee discussions. The decision about whether to undertake an NMA will be based on the sparseness of the data and whether the transitivity assumption is likely to hold given the included studies.
17.	Analysis of sub-groups	Where disaggregation is possible: Age (over/under 65) Severity of underlying condition (Child-Pugh A: 5 to 6 points. Child-Pugh B: 7 to 9 points). Underlying cause of liver disease
18.	Type and method of review	☒ Intervention ☐ Diagnostic ☐ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)
19.	Language	English
20.	Country	England
21.	Anticipated or actual start date	5th January 2023
22.	Anticipated completion date	
23.	Stage of review at time of this submission	**Review stage** / **Started** / **Completed** Preliminary searches Piloting of the study selection process Formal screening of search results against eligibility criteria Data extraction Risk of bias (quality) assessment Data analysis
24.	Named contact	**5a. Named contact**

		NICE Guideline Development Team **5b Named contact e-mail** CirrhosisUpdate@nice.org.uk **5e Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE) Guideline Development Team B.
25.	Review team members	From the NICE Guideline Development Team: Mr Chris Carmona, Technical lead Mr James Jagroo, Senior technical analyst Ms Karen Peploe, Senior technical analyst Ms Lindsay Claxton, Health economics adviser Ms Yuanyuan Zhang, Technical analyst (economics) Mr Wesley Hubbard, Information specialist Ms Nicola Cunliffe, Project manager
26.	Funding sources/sponsor	This systematic review is being completed by the NICE Guideline Development team which is an internal team at NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: www.nice.org.uk.
29.	Other registration details	No other registrations of this protocol.
30.	Reference/URL for published protocol	
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as:

		notifying registered stakeholders of publication publicising the guideline through NICE's newsletter and alerts issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	Compensated cirrhosis Decompensation Beta blockers
33.	Details of existing review of same topic by same authors	Not applicable
34.	Current review status	☒ Ongoing ☒ Completed but not published ☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued
35..	Additional information	This review will be used to update the NICE guideline on Cirrhosis in over 16s: assessment and management
36.	Details of final publication	www.nice.org.uk

1

Appendix B – Literature search strategies

Background and development

Search design and peer review

A NICE information specialist conducted the literature searches for the evidence review. The searches were run on 1st February and 2nd February 2023. This search report is compliant with the requirements of the PRISMA Statement for Reporting Literature Searches in Systematic Reviews (for further details see: Rethlefsen M et al. PRISMA-S. *Systematic Reviews*, 10(1), 39).
The MEDLINE strategy below was quality assured (QA) by a trained NICE information specialist. All translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the Peer Review of Electronic Search Strategies Guideline Statement (for further details see: McGowan J et al. PRESS 2015 Guideline Statement. *Journal of Clinical Epidemiology*, 75, 40-46).
The principal search strategy was developed in MEDLINE (Ovid interface) and adapted, as appropriate, for use in the other sources listed in the protocol, taking into account their size, search functionality and subject coverage.

Review management

The search results were managed in EPPI-Reviewer v5. Duplicates were removed in EPPI-R5 using a two-step process. First, automated deduplication is performed using a high-value algorithm. Second, manual deduplication is used to assess 'low-probability' matches. All decisions made for the review can be accessed via the deduplication history.

Prior work

The population element of the search strategy is based on the standard population search used in the original guideline:
Cirrhosis in over 16s: Assessment and management. Appendix G (2016) NICE guideline 50
Search terms for beta blockers have previously been used in RQ1 of this guideline update.

Limits and restrictions

English language limits were applied in adherence to standard NICE practice and the review protocol.
The limit to remove animal studies in the searches was the standard NICE practice, which has been adapted from: Dickersin K, Scherer R & Lefebvre C. (1994) Systematic Reviews: Identifying relevant studies for systematic reviews. *BMJ*, 309(6964), 1286.

Search filters and classifiers

Clinical searches

- RCT filters:

  - McMaster Therapy – Medline - "best balance of sensitivity and specificity" version.
    Haynes RB et al. (2005) Optimal search strategies for retrieving scientifically strong studies of treatment from Medline: analytical survey. *BMJ*, 330, 1179-1183.

  - McMaster Therapy – Embase "best balance of sensitivity and specificity" version.
    Wong SSL et al. (2006) Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE. Journal of the Medical Library Association, 94(1), 41-47.

- Systematic reviews filters:
  Lee, E. et al. (2012) An optimal search filter for retrieving systematic reviews and meta-analyses. *BMC Medical Research Methodology,* 12(1), 51.

In MEDLINE, the standard NICE modifications were used: pubmed.tw added; systematic review.pt added from MeSH update 2019.

In Embase, the standard NICE modifications were used: pubmed.tw added to line medline.tw.

Cost effectiveness searches

The following search filters were applied to the search strategies in MEDLINE and Embase to identify cost-effectiveness studies:

- Glanville J et al. (2009) Development and Testing of Search Filters to Identify Economic Evaluations in MEDLINE and EMBASE. Alberta: Canadian Agency for Drugs and Technologies in Health (CADTH)
- Hubbard W, Walsh N, Hudson T et al. (2022) Development and validation of paired MEDLINE and Embase search filters for cost-utility studies. BMC Medical Research Methodology 22(1), 310

Key decisions

The population element of the search strategy was based on the previous guideline standard population strategy. The intervention elements of the search were based on the requirements of the review protocol. Relevant free text terms and database subject terms were identified as part of strategy development.
The search strategy was simplified for Epistemonikos to adapt to that databases functionality.

In January 2023 there was a data processing error in Ovid Embase. This error was fixed on 22nd February 2023. Additional results missed during the data processing error in Embase were added to the total search results on 22nd February 2023.

Clinical searches

Main search – Databases

Database	Date searched	Database Platform	Database segment or version	No. of results downloaded
Cochrane Central Register of Controlled Trials (CENTRAL)	01/02/2023	Wiley	Cochrane Database of Systematic Reviews Issue 2 of 12, February 2023	2
Cochrane Database of Systematic Reviews (CDSR)	01/02/2023	Wiley	Cochrane Central Register of Controlled Trials Issue 1 of 12, January 2023	59
Embase	01/02/2023	Ovid	Embase 1974 to 2023 January 31	162 + 6
Epistemonikos	01/02/2023	Epistemonikos	-	156
MEDLINE	01/02/2023	Ovid	Ovid MEDLINE(R) 1946 to January 31, 2023	60
MEDLINE-in-Process	01/02/2023	Ovid	Ovid MEDLINE(R) In-Process & In-Data-Review Citations 1946 to January 31, 2023	0
MEDLINE Epub Ahead-of-Print	01/02/2023	Ovid	Ovid MEDLINE(R) Epub Ahead of Print January 31, 2023	3

Search strategy history

Database name: MEDLINE

1 exp Liver Cirrhosis/ (100414)
2 Fibrosis/ and Liver/ (2175)
3 cirrho*.tw. (99671)
4 ((liver* or hepat* or alcohol* or biliar*) adj4 (fibro* or myxofibro* or cholang* or angiocholit*)).tw. (46927)
5 or/1-4 (159507)
6 (compensat* or decompensat* or asymptomat*).tw. (326140)
7 End Stage Liver Disease/ (4329)
8 Liver Failure/ (7726)

9 ((end* or final* or ultimate*) adj4 (liver* or hepat*) adj4 (diseas* or fail* or d?sfunct* or insufficien* or destruct* or expir* or defect* or disorder* or breakdown* or collaps* or disintegrat* or stag*)).tw. (13038)
10 ((chronic* or continu*) adj4 (liver* or hepat*) adj4 (fail* or destruct* or expir* or breakdown* or collaps* or disintegrat*)).tw. (3895)
11 ((declin* or deteriorat* or failing* or falling* or weaken* or degenerat* or decreas* or diminish*) adj4 (liver* or hepat*) adj4 (function* or activit* or performance*)).tw. (4851)
12 or/6-11 (352402)
13 5 and 12 (17630)
14 exp Adrenergic beta-Antagonists/ (86828)
15 ((beta* or b) adj4 (block* or antagonist* or sympatholy*)).tw. (78319)
16 NSBB*.tw. (116)
17 Nadolol/ (826)
18 (nadolol* or corgard* or solgol* or betadol*).tw. (1169)
19 exp Timolol/ (3849)
20 (timolo* or tiopex* or eysano* or timopt* or timacar* or blocadren* or optimol* or apotimolol* or titol*).tw. (4319)
21 Sotalol/ (2125)
22 (sotalol* or sotacor* or darob* or betacardone* or betades* or betapace* or bonpro* or corsotalol* or gilucor* or rentibloc* or sorine* or sota saar* or sotabeta* or sotacor* or sotahexal* or sotalex* or sotapor* or sotastad* or sotylize* or tachytalol*).tw. (2763)
23 Carvedilol/ (2858)
24 (carvedilol* or dilatrend* or querto* or eucardic* or kredex* or coropres* or coreg or cardiol or carvipress* or dilibloc* or dimitone*).tw. (3778)
25 Labetalol/ (1901)
26 (labetalol* or trandate* or albetol* or apolabetalol* or normodyne* or presolol* or dilevalol* or lamitol* or presdate*).tw. (2128)
27 Propranolol/ (32893)
28 (propranolol* or bedranol* or beta-prograne* or betaprograne* or inderal* or syprol* or rexigen* or dexpropranolol* or dociton* or ob?idan* or anaprilin* or betadren* or arcablock* or authus* or avlocardyl* or beprane* or betadipresan* or betaryl* or cardinol* or ciplar* or corbeta* or deralin* or duranol* or efektolol* or elbrol* or frekven* or hemang?ol* or inderex* or innopran* or ipran* or prandol* or propabloc* or propercuten* or prophylux* or propranur* or sagittol*).tw. (33390)
29 or/14-28 (138356)
30 13 and 29 (286)
31 Animals/ not Humans/ (5054516)
32 30 not 31 (283)
33 limit 32 to english language (257)
34 randomized controlled trial.pt. (585399)
35 randomi?ed.mp. (948313)
36 placebo.mp. (222131)
37 or/34-36 (1005130)
38 (MEDLINE or pubmed).tw. (249179)
39 systematic review.tw. (201926)
40 systematic review.pt. (212259)
41 meta-analysis.pt. (174777)
42 intervention$.ti. (162469)

43 or/38-42 (543493)
44 37 or 43 (1399941)
45 33 and 44 (60)

Database name: MEDLINE-in-Process

1 exp Liver Cirrhosis/ (0)
2 Fibrosis/ and Liver/ (0)
3 cirrho*.tw. (14)
4 ((liver* or hepat* or alcohol* or biliar*) adj4 (fibro* or myxofibro* or cholang* or angiocholit*)).tw. (17)
5 or/1-4 (29)
6 (compensat* or decompensat* or asymptomat*).tw. (71)
7 End Stage Liver Disease/ (0)
8 Liver Failure/ (0)
9 ((end* or final* or ultimate*) adj4 (liver* or hepat*) adj4 (diseas* or fail* or d?sfunct* or insufficien* or destruct* or expir* or defect* or disorder* or breakdown* or collaps* or disintegrat* or stag*)).tw. (3)
10 ((chronic* or continu*) adj4 (liver* or hepat*) adj4 (fail* or destruct* or expir* or breakdown* or collaps* or disintegrat*)).tw. (0)
11 ((declin* or deteriorat* or failing* or falling* or weaken* or degenerat* or decreas* or diminish*) adj4 (liver* or hepat*) adj4 (function* or activit* or performance*)).tw. (0)
12 or/6-11 (74)
13 5 and 12 (2)
14 exp Adrenergic beta-Antagonists/ (0)
15 ((beta* or b) adj4 (block* or antagonist* or sympatholy*)).tw. (6)
16 NSBB*.tw. (0)
17 Nadolol/ (0)
18 (nadolol* or corgard* or solgol* or betadol*).tw. (0)
19 exp Timolol/ (0)
20 (timolo* or tiopex* or eysano* or timopt* or timacar* or blocadren* or optimol* or apotimolol* or titol*).tw. (0)
21 Sotalol/ (0)
22 (sotalol* or sotacor* or darob* or betacardone* or betades* or betapace* or bonpro* or corsotalol* or gilucor* or rentibloc* or sorine* or sota saar* or sotabeta* or sotacor* or sotahexal* or sotalex* or sotapor* or sotastad* or sotylize* or tachytalol*).tw. (0)
23 Carvedilol/ (0)
24 (carvedilol* or dilatrend* or querto* or eucardic* or kredex* or coropres* or coreg or cardiol or carvipress* or dilibloc* or dimitone*).tw. (0)
25 Labetalol/ (0)
26 (labetalol* or trandate* or albetol* or apolabetalol* or normodyne* or presolol* or dilevalol* or lamitol* or presdate*).tw. (0)
27 Propranolol/ (0)
28 (propranolol* or bedranol* or beta-prograne* or betaprograne* or inderal* or syprol* or rexigen* or dexpropranolol* or dociton* or ob?idan* or anaprilin* or betadren* or arcablock* or authus* or avlocardyl* or beprane* or betadipresan* or betaryl* or cardinol* or ciplar* or corbeta* or deralin* or duranol* or efektolol* or elbrol* or frekven* or hemang?ol* or

inderex* or innopran* or ipran* or prandol* or propabloc* or propercuten* or prophylux* or propranur* or sagittol*).tw. (0)
29 or/14-28 (6)
30 13 and 29 (0)
31 Animals/ not Humans/ (0)
32 30 not 31 (0)
33 limit 32 to english language (0)
34 randomized controlled trial.pt. (0)
35 randomi?ed.mp. (190)
36 placebo.mp. (43)
37 or/34-36 (200)
38 (MEDLINE or pubmed).tw. (146)
39 systematic review.tw. (126)
40 systematic review.pt. (2)
41 meta-analysis.pt. (0)
42 intervention$.ti. (61)
43 or/38-42 (236)
44 37 or 43 (377)
45 33 and 44 (0)

Database name: MEDLINE Epub Ahead-of-Print

1 exp Liver Cirrhosis/ (0)
2 Fibrosis/ and Liver/ (0)
3 cirrho*.tw. (1144)
4 ((liver* or hepat* or alcohol* or biliar*) adj4 (fibro* or myxofibro* or cholang* or angiocholit*)).tw. (910)
5 or/1-4 (1857)
6 (compensat* or decompensat* or asymptomat*).tw. (6048)
7 End Stage Liver Disease/ (0)
8 Liver Failure/ (0)
9 ((end* or final* or ultimate*) adj4 (liver* or hepat*) adj4 (diseas* or fail* or d?sfunct* or insufficien* or destruct* or expir* or defect* or disorder* or breakdown* or collaps* or disintegrat* or stag*)).tw. (240)
10 ((chronic* or continu*) adj4 (liver* or hepat*) adj4 (fail* or destruct* or expir* or breakdown* or collaps* or disintegrat*)).tw. (85)
11 ((declin* or deteriorat* or failing* or falling* or weaken* or degenerat* or decreas* or diminish*) adj4 (liver* or hepat*) adj4 (function* or activit* or performance*)).tw. (49)
12 or/6-11 (6339)
13 5 and 12 (332)
14 exp Adrenergic beta-Antagonists/ (0)
15 ((beta* or b) adj4 (block* or antagonist* or sympatholy*)).tw. (618)
16 NSBB*.tw. (7)
17 Nadolol/ (0)
18 (nadolol* or corgard* or solgol* or betadol*).tw. (7)
19 exp Timolol/ (0)
20 (timolo* or tiopex* or eysano* or timopt* or timacar* or blocadren* or optimol* or apotimolol* or titol*).tw. (40)

21 Sotalol/ (0)
22 (sotalol* or sotacor* or darob* or betacardone* or betades* or betapace* or bonpro* or corsotalol* or gilucor* or rentibloc* or sorine* or sota saar* or sotabeta* or sotacor* or sotahexal* or sotalex* or sotapor* or sotastad* or sotylize* or tachytalol*).tw. (31)
23 Carvedilol/ (0)
24 (carvedilol* or dilatrend* or querto* or eucardic* or kredex* or coropres* or coreg or cardiol or carvipress* or dilibloc* or dimitone*).tw. (55)
25 Labetalol/ (0)
26 (labetalol* or trandate* or albetol* or apolabetalol* or normodyne* or presolol* or dilevalol* or lamitol* or presdate*).tw. (14)
27 Propranolol/ (0)
28 (propranolol* or bedranol* or beta-prograne* or betaprograne* or inderal* or syprol* or rexigen* or dexpropranolol* or dociton* or ob?idan* or anaprilin* or betadren* or arcablock* or authus* or avlocardyl* or beprane* or betadipresan* or betaryl* or cardinol* or ciplar* or corbeta* or deralin* or duranol* or efektolol* or elbrol* or frekven* or hemang?ol* or inderex* or innopran* or ipran* or prandol* or propabloc* or propercuten* or prophylux* or propranur* or sagittol*).tw. (131)
29 or/14-28 (809)
30 13 and 29 (10)
31 Animals/ not Humans/ (0)
32 30 not 31 (10)
33 limit 32 to english language (10)
34 randomized controlled trial.pt. (1)
35 randomi?ed.mp. (14469)
36 placebo.mp. (2880)
37 or/34-36 (15381)
38 (MEDLINE or pubmed).tw. (10419)
39 systematic review.tw. (10549)
40 systematic review.pt. (248)
41 meta-analysis.pt. (102)
42 intervention$.ti. (4264)
43 or/38-42 (18421)
44 37 or 43 (29587)
45 33 and 44 (3)

Database name: Embase

1 exp liver cirrhosis/ (185015)
2 fibrosis/ and liver/ (10789)
3 cirrho*.tw. (175053)
4 ((liver* or hepat* or alcohol* or biliar*) adj4 (fibro* or myxofibro* or cholang* or angiocholit*)).tw. (88415)
5 or/1-4 (284601)
6 (compensat* or decompensat* or asymptomat*).tw. (530672)
7 end stage liver disease/ (10473)
8 liver failure/ (45537)

9 ((end* or final* or ultimate*) adj4 (liver* or hepat*) adj4 (diseas* or fail* or d?sfunct* or insufficien* or destruct* or expir* or defect* or disorder* or breakdown* or collaps* or disintegrat* or stag*)).tw. (24651)
10 ((chronic* or continu*) adj4 (liver* or hepat*) adj4 (fail* or destruct* or expir* or breakdown* or collaps* or disintegrat*)).tw. (8641)
11 ((declin* or deteriorat* or failing* or falling* or weaken* or degenerat* or decreas* or diminish*) adj4 (liver* or hepat*) adj4 (function* or activit* or performance*)).tw. (7485)
12 or/6-11 (606272)
13 5 and 12 (47860)
14 exp beta adrenergic receptor blocking agent/ (325175)
15 ((beta* or b) adj4 (block* or antagonist* or sympatholy*)).tw. (114303)
16 NSBB*.tw. (409)
17 nadolol/ (5939)
18 (nadolol* or corgard* or solgol* or betadol*).tw. (2155)
19 timolol maleate/ or timolol/ (14491)
20 (timolo* or tiopex* or eysano* or timopt* or timacar* or blocadren* or optimol* or apotimolol* or titol*).tw. (6811)
21 sotalol/ (14066)
22 (sotalol* or sotacor* or darob* or betacardone* or betades* or betapace* or bonpro* or corsotalol* or gilucor* or rentibloc* or sorine* or sota saar* or sotabeta* or sotacor* or sotahexal* or sotalex* or sotapor* or sotastad* or sotylize* or tachytalol*).tw. (4760)
23 carvedilol/ (17482)
24 (carvedilol* or dilatrend* or querto* or eucardic* or kredex* or coropres* or coreg or cardiol or carvipress* or dilibloc* or dimitone*).tw. (9020)
25 labetalol/ (11778)
26 (labetalol* or trandate* or albetol* or apolabetalol* or normodyne* or presolol* or dilevalol* or lamitol* or presdate*).tw. (4064)
27 propranolol/ (94277)
28 (propranolol* or bedranol* or beta-prograne* or betaprograne* or inderal* or syprol* or rexigen* or dexpropranolol* or dociton* or ob?idan* or anaprilin* or betadren* or arcablock* or authus* or avlocardyl* or beprane* or betadipresan* or betaryl* or cardinol* or ciplar* or corbeta* or deralin* or duranol* or efektolol* or elbrol* or frekven* or hemang?ol* or inderex* or innopran* or ipran* or prandol* or propabloc* or propercuten* or prophylux* or propranur* or sagittol*).tw. (45636)
29 or/14-28 (369732)
30 13 and 29 (1345)
31 nonhuman/ not human/ (5193533)
32 30 not 31 (1329)
33 limit 32 to english language (1270)
34 limit 33 to (conference abstract or conference paper or "conference review") (425)
35 33 not 34 (845)
36 random:.tw. (1901191)
37 placebo:.mp. (512415)
38 double-blind:.tw. (239946)
39 or/36-38 (2174320)
40 (MEDLINE or pubmed).tw. (384348)
41 exp systematic review/ or systematic review.tw. (478844)
42 meta-analysis/ (275889)

43 intervention$.ti. (254136)
44 or/40-43 (919582)
45 39 or 44 (2808946)
46 35 and 45 (162)

Database name: Cochrane Library

#1 MeSH descriptor: [Liver Cirrhosis] explode all trees 3474
#2 MeSH descriptor: [Fibrosis] this term only 1879
#3 MeSH descriptor: [Liver] this term only 3839
#4 #2 and #3 33
#5 (cirrho*):ti,ab,kw 11899
#6 ((liver* or hepat* or alcohol* or biliar*) NEAR/4 (fibro* or myxofibro* or cholang* or angiocholit*)):ti,ab,kw 3680
#7 #1 or #4 or #5 or #6 13895
#8 (compensat* or decompensat* or asymptomat*):ti,ab,kw 24636
#9 MeSH descriptor: [End Stage Liver Disease] this term only 193
#10 MeSH descriptor: [Liver Failure] this term only 291
#11 ((end* or final* or ultimate*) NEAR/4 (liver* or hepat*) NEAR/4 (diseas* or fail* or d?sfunct* or insufficien* or destruct* or expir* or defect* or disorder* or breakdown* or collaps* or disintegrat* or stag*)):ti,ab,kw 1505
#12 ((chronic* or continu*) NEAR/4 (liver* or hepat*) NEAR/4 (fail* or destruct* or expir* or breakdown* or collaps* or disintegrat*)):ti,ab,kw 715
#13 ((declin* or deteriorat* or failing* or falling* or weaken* or degenerat* or decreas* or diminish*) NEAR/4 (liver* or hepat*) NEAR/4 (function* or activit* or performance*)):ti,ab,kw 252
#14 {or #8-#13} 26728
#15 #7 and #14 2727
#16 MeSH descriptor: [Adrenergic beta-Antagonists] explode all trees 5110
#17 ((beta* or b) NEAR/4 (block* or antagonist* or sympatholy*)):ti,ab,kw 16338
#18 (NSBB*):ti,ab,kw 59
#19 MeSH descriptor: [Nadolol] this term only 196
#20 (nadolol* or corgard* or solgol* or betadol*):ti,ab,kw 391
#21 MeSH descriptor: [Timolol] explode all trees 1272
#22 (timolo* or tiopex* or eysano* or timopt* or timacar* or blocadren* or optimol* or apotimolol* or titol*):ti,ab,kw 2408
#23 MeSH descriptor: [Sotalol] this term only 332
#24 (sotalol* or sotacor* or darob* or betacardone* or betades* or betapace* or bonpro* or corsotalol* or gilucor* or rentibloc* or sorine* or sota saar* or sotabeta* or sotacor* or sotahexal* or sotalex* or sotapor* or sotastad* or sotylize* or tachytalol*):ti,ab,kw 636
#25 MeSH descriptor: [Carvedilol] this term only 760
#26 (carvedilol* or querto* or eucardic* or kredex* or coropres* or coreg or cardiol or carvipress* or dilatrend* or dilibloc* or dimitone*):ti,ab,kw 1574
#27 MeSH descriptor: [Labetalol] this term only 438
#28 (labetalol* or trandate* or albetol* or apolabetalol* or normodyne* or presolol* or dilevalol* or lamitol* or presdate*):ti,ab,kw 897
#29 MeSH descriptor: [Propranolol] this term only 3034

#30 (propranolol* or bedranol* or beta-prograne* or betaprograne* or inderal* or syprol* or rexigen* or dexpropranolol* or dociton* or ob?idan* or anaprilin* or betadren* or arcablock* or authus* or avlocardyl* or beprane* or betadipresan* or betaryl* or cardinol* or ciplar* or corbeta* or deralin* or duranol* or efektolol* or elbrol* or frekven* or hemang?ol* or inderex* or innopran* or ipran* or prandol* or propabloc* or propercuten* or prophylux* or propranur* or sagittol*):ti,ab,kw 5381
#31 {or #16-#30} 22799
#32 #15 and #31 124
#33 "conference":pt or (clinicaltrials or trialsearch):so 659511
#34 #32 not #33 61

Database name: Epistemonikos

(title:((title:((title:(cirrho*) OR abstract:(cirrho*)) OR (title:(liver* OR hepat* OR alcohol* OR biliar*) OR abstract:(liver* OR hepat* OR alcohol* OR biliar*)) AND (title:(fibro* OR myxofibro* OR cholang* OR angiocholit*) OR abstract:(fibro* OR myxofibro* OR cholang* OR angiocholit*))) OR abstract:((title:(cirrho*) OR abstract:(cirrho*)) OR (title:(liver* OR hepat* OR alcohol* OR biliar*) OR abstract:(liver* OR hepat* OR alcohol* OR biliar*)) AND (title:(fibro* OR myxofibro* OR cholang* OR angiocholit*) OR abstract:(fibro* OR myxofibro* OR cholang* OR angiocholit*)))) AND (title:((title:(compensat* OR decompensat* OR asymptomat*) OR abstract:(compensat* OR decompensat* OR asymptomat*))) OR abstract:((title:(compensat* OR decompensat* OR asymptomat*) OR abstract:(compensat* OR decompensat* OR asymptomat*))))) OR abstract:((title:((title:(cirrho*) OR abstract:(cirrho*)) OR (title:(liver* OR hepat* OR alcohol* OR biliar*) OR abstract:(liver* OR hepat* OR alcohol* OR biliar*)) AND (title:(fibro* OR myxofibro* OR cholang* OR angiocholit*) OR abstract:(fibro* OR myxofibro* OR cholang* OR angiocholit*))) OR abstract:((title:(cirrho*) OR abstract:(cirrho*)) OR (title:(liver* OR hepat* OR alcohol* OR biliar*) OR abstract:(liver* OR hepat* OR alcohol* OR biliar*)) AND (title:(fibro* OR myxofibro* OR cholang* OR angiocholit*) OR abstract:(fibro* OR myxofibro* OR cholang* OR angiocholit*)))) AND (title:((title:(compensat* OR decompensat* OR asymptomat*) OR abstract:(compensat* OR decompensat* OR asymptomat*))) OR abstract:((title:(compensat* OR decompensat* OR asymptomat*) OR abstract:(compensat* OR decompensat* OR asymptomat*))))) AND (title:((title:(beta* OR b) OR abstract:(beta* OR b)) AND (title:(block* OR antagonist* OR sympatholy*) OR abstract:(block* OR antagonist* OR sympatholy*)) OR (title:(NSBB*) OR abstract:(NSBB*)) OR (title:(nadolol* OR timolo* OR sotalol* OR carvedilol* OR labetalol* OR propranolol*) OR abstract:(nadolol* OR timolo* OR sotalol* OR carvedilol* OR labetalol* OR propranolol*))) OR abstract:((title:(beta* OR b) OR abstract:(beta* OR b)) AND (title:(block* OR antagonist* OR sympatholy*) OR abstract:(block* OR antagonist* OR sympatholy*)) OR (title:(NSBB*) OR abstract:(NSBB*)) OR (title:(nadolol* OR timolo* OR sotalol* OR carvedilol* OR labetalol* OR propranolol*) OR abstract:(nadolol* OR timolo* OR sotalol* OR carvedilol* OR labetalol* OR propranolol*))))

Cost-effectiveness searches

Main search – Databases

Database	Date searched	Database Platform	Database segment or version	No. of results downloaded
EconLit	02/02/2023	Ovid	Econlit 1886 to January 26, 2023	0
Embase	02/02/2023	Ovid	Embase 1974 to 2023 February 01	61 + 5
INAHTA	02/02/2023	INAHTA	-	0
MEDLINE	02/02/2023	Ovid	Ovid MEDLINE(R) 1946 to February 01, 2023	24
MEDLINE-in-Process	02/02/2023	Ovid	Ovid MEDLINE(R) In-Process & In-Data-Review Citations 1946 to February 01, 2023	0
MEDLINE Epub Ahead-of-Print	02/02/2023	Ovid	Ovid MEDLINE(R) Epub Ahead of Print February 01, 2023	0

Search strategy history

Database name: MEDLINE

1 exp Liver Cirrhosis/ (100436)
2 Fibrosis/ and Liver/ (2180)
3 cirrho*.tw. (99682)
4 ((liver* or hepat* or alcohol* or biliar*) adj4 (fibro* or myxofibro* or cholang* or angiocholit*)).tw. (46933)
5 or/1-4 (159529)
6 (compensat* or decompensat* or asymptomat*).tw. (326103)
7 End Stage Liver Disease/ (4325)
8 Liver Failure/ (7726)
9 ((end* or final* or ultimate*) adj4 (liver* or hepat*) adj4 (diseas* or fail* or d?sfunct* or insufficien* or destruct* or expir* or defect* or disorder* or breakdown* or collaps* or disintegrat* or stag*)).tw. (13032)
10 ((chronic* or continu*) adj4 (liver* or hepat*) adj4 (fail* or destruct* or expir* or breakdown* or collaps* or disintegrat*)).tw. (3894)
11 ((declin* or deteriorat* or failing* or falling* or weaken* or degenerat* or decreas* or diminish*) adj4 (liver* or hepat*) adj4 (function* or activit* or performance*)).tw. (4849)
12 or/6-11 (352357)
13 5 and 12 (17632)
14 exp Adrenergic beta-Antagonists/ (86831)
15 ((beta* or b) adj4 (block* or antagonist* or sympatholy*)).tw. (78320)
16 NSBB*.tw. (118)
17 Nadolol/ (826)

18 (nadolol* or corgard* or solgol* or betadol*).tw. (1169)
19 exp Timolol/ (3849)
20 (timolo* or tiopex* or eysano* or timopt* or timacar* or blocadren* or optimol* or apotimolol* or titol*).tw. (4319)
21 Sotalol/ (2125)
22 (sotalol* or sotacor* or darob* or betacardone* or betades* or betapace* or bonpro* or corsotalol* or gilucor* or rentibloc* or sorine* or sota saar* or sotabeta* or sotacor* or sotahexal* or sotalex* or sotapor* or sotastad* or sotylize* or tachytalol*).tw. (2763)
23 Carvedilol/ (2859)
24 (carvedilol* or dilatrend* or querto* or eucardic* or kredex* or coropres* or coreg or cardiol or carvipress* or dilibloc* or dimitone*).tw. (3777)
25 Labetalol/ (1901)
26 (labetalol* or trandate* or albetol* or apolabetalol* or normodyne* or presolol* or dilevalol* or lamitol* or presdate*).tw. (2127)
27 Propranolol/ (32893)
28 (propranolol* or bedranol* or beta-prograne* or betaprograne* or inderal* or syprol* or rexigen* or dexpropranolol* or dociton* or ob?idan* or anaprilin* or betadren* or arcablock* or authus* or avlocardyl* or beprane* or betadipresan* or betaryl* or cardinol* or ciplar* or corbeta* or deralin* or duranol* or efektolol* or elbrol* or frekven* or hemang?ol* or inderex* or innopran* or ipran* or prandol* or propabloc* or propercuten* or prophylux* or propranur* or sagittol*).tw. (33389)
29 or/14-28 (138354)
30 13 and 29 (289)
31 Animals/ not Humans/ (5054524)
32 30 not 31 (286)
33 limit 32 to english language (260)
34 Economics/ (27490)
35 exp "Costs and Cost Analysis"/ (262414)
36 Economics, Dental/ (1920)
37 exp Economics, Hospital/ (25673)
38 exp Economics, Medical/ (14381)
39 Economics, Nursing/ (4013)
40 Economics, Pharmaceutical/ (3093)
41 Budgets/ (11672)
42 exp Models, Economic/ (16176)
43 Markov Chains/ (15891)
44 Monte Carlo Method/ (31897)
45 Decision Trees/ (12049)
46 econom$.tw. (308785)
47 cba.tw. (10445)
48 cea.tw. (23328)
49 cua.tw. (1138)
50 markov$.tw. (22483)
51 (monte adj carlo).tw. (35573)
52 (decision adj3 (tree$ or analys$)).tw. (20144)
53 (cost or costs or costing$ or costly or costed).tw. (569850)
54 (price$ or pricing$).tw. (41156)
55 budget$.tw. (27914)

56 expenditure$.tw. (58836)
57 (value adj3 (money or monetary)).tw. (2645)
58 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (3855)
59 or/34-58 (1124508)
60 "Quality of Life"/ (258476)
61 quality of life.tw. (299445)
62 "Value of Life"/ (5800)
63 Quality-Adjusted Life Years/ (15376)
64 quality adjusted life.tw. (14454)
65 (qaly$ or qald$ or qale$ or qtime$).tw. (11860)
66 disability adjusted life.tw. (4152)
67 daly$.tw. (3684)
68 Health Status Indicators/ (24075)
69 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (26389)
70 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (1558)
71 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (6347)
72 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (33)
73 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (412)
74 (euroqol or euro qol or eq5d or eq 5d).tw. (13248)
75 (qol or hql or hqol or hrqol).tw. (58866)
76 (hye or hyes).tw. (63)
77 health$ year$ equivalent$.tw. (38)
78 utilit$.tw. (214971)
79 (hui or hui1 or hui2 or hui3).tw. (1583)
80 disutili$.tw. (513)
81 rosser.tw. (100)
82 quality of wellbeing.tw. (27)
83 quality of well-being.tw. (431)
84 qwb.tw. (201)
85 willingness to pay.tw. (6644)
86 standard gamble$.tw. (832)
87 time trade off.tw. (1201)
88 time tradeoff.tw. (249)
89 tto.tw. (1120)
90 or/60-89 (616376)
91 Cost-Benefit Analysis/ (91593)
92 Quality-Adjusted Life Years/ (15376)
93 Markov Chains/ (15891)
94 exp Models, Economic/ (16176)
95 cost*.ti. (121834)
96 (cost* adj2 utilit*).tw. (6223)
97 (cost* adj2 (effective* or assess* or evaluat* or analys* or model* or benefit* or threshold* or quality or expens* or saving* or reduc*)).tw. (215733)

98 (economic* adj2 (evaluat* or assess* or analys* or model* or outcome* or benefit* or threshold* or expens* or saving* or reduc*)).tw. (37101)
99 (qualit* adj2 adjust* adj2 life*).tw. (14760)
100 QALY*.tw. (11731)
101 (incremental* adj2 cost*).tw. (14339)
102 ICER.tw. (4695)
103 utilities.tw. (7424)
104 markov*.tw. (22483)
105 (dollar* or USD or cents or pound or pounds or GBP or sterling* or pence or euro or euros or yen or JPY).tw. (45319)
106 ((utility or effective*) adj2 analys*).tw. (20175)
107 (willing* adj2 pay*).tw. (7585)
108 (EQ5D* or EQ-5D*).tw. (10437)
109 ((euroqol or euro-qol or euroquol or euro-quol or eurocol or euro-col) adj3 ("5" or five)).tw. (2803)
110 (european* adj2 quality adj3 ("5" or five)).tw. (531)
111 or/91-110 (401839)
112 59 or 90 or 111 (1682991)
113 33 and 112 (24)

Database name: MEDLINE-in-Process

1 exp Liver Cirrhosis/ (0)
2 Fibrosis/ and Liver/ (0)
3 cirrho*.tw. (15)
4 ((liver* or hepat* or alcohol* or biliar*) adj4 (fibro* or myxofibro* or cholang* or angiocholit*)).tw. (23)
5 or/1-4 (36)
6 (compensat* or decompensat* or asymptomat*).tw. (67)
7 End Stage Liver Disease/ (0)
8 Liver Failure/ (0)
9 ((end* or final* or ultimate*) adj4 (liver* or hepat*) adj4 (diseas* or fail* or d?sfunct* or insufficien* or destruct* or expir* or defect* or disorder* or breakdown* or collaps* or disintegrat* or stag*)).tw. (4)
10 ((chronic* or continu*) adj4 (liver* or hepat*) adj4 (fail* or destruct* or expir* or breakdown* or collaps* or disintegrat*)).tw. (0)
11 ((declin* or deteriorat* or failing* or falling* or weaken* or degenerat* or decreas* or diminish*) adj4 (liver* or hepat*) adj4 (function* or activit* or performance*)).tw. (0)
12 or/6-11 (71)
13 5 and 12 (4)
14 exp Adrenergic beta-Antagonists/ (0)
15 ((beta* or b) adj4 (block* or antagonist* or sympatholy*)).tw. (8)
16 NSBB*.tw. (0)
17 Nadolol/ (0)
18 (nadolol* or corgard* or solgol* or betadol*).tw. (0)
19 exp Timolol/ (0)
20 (timolo* or tiopex* or eysano* or timopt* or timacar* or blocadren* or optimol* or apotimolol* or titol*).tw. (0)

21 Sotalol/ (0)
22 (sotalol* or sotacor* or darob* or betacardone* or betades* or betapace* or bonpro* or corsotalol* or gilucor* or rentibloc* or sorine* or sota saar* or sotabeta* or sotacor* or sotahexal* or sotalex* or sotapor* or sotastad* or sotylize* or tachytalol*).tw. (0)
23 Carvedilol/ (0)
24 (carvedilol* or dilatrend* or querto* or eucardic* or kredex* or coropres* or coreg or cardiol or carvipress* or dilibloc* or dimitone*).tw. (1)
25 Labetalol/ (0)
26 (labetalol* or trandate* or albetol* or apolabetalol* or normodyne* or presolol* or dilevalol* or lamitol* or presdate*).tw. (0)
27 Propranolol/ (0)
28 (propranolol* or bedranol* or beta-prograne* or betaprograne* or inderal* or syprol* or rexigen* or dexpropranolol* or dociton* or ob?idan* or anaprilin* or betadren* or arcablock* or authus* or avlocardyl* or beprane* or betadipresan* or betaryl* or cardinol* or ciplar* or corbeta* or deralin* or duranol* or efektolol* or elbrol* or frekven* or hemang?ol* or inderex* or innopran* or ipran* or prandol* or propabloc* or propercuten* or prophylux* or propranur* or sagittol*).tw. (1)
29 or/14-28 (10)
30 13 and 29 (0)
31 Animals/ not Humans/ (0)
32 30 not 31 (0)
33 limit 32 to english language (0)
34 Economics/ (0)
35 exp "Costs and Cost Analysis"/ (0)
36 Economics, Dental/ (0)
37 exp Economics, Hospital/ (0)
38 exp Economics, Medical/ (0)
39 Economics, Nursing/ (0)
40 Economics, Pharmaceutical/ (0)
41 Budgets/ (0)
42 exp Models, Economic/ (0)
43 Markov Chains/ (0)
44 Monte Carlo Method/ (0)
45 Decision Trees/ (0)
46 econom$.tw. (153)
47 cba.tw. (1)
48 cea.tw. (5)
49 cua.tw. (1)
50 markov$.tw. (15)
51 (monte adj carlo).tw. (17)
52 (decision adj3 (tree$ or analys$)).tw. (17)
53 (cost or costs or costing$ or costly or costed).tw. (221)
54 (price$ or pricing$).tw. (13)
55 budget$.tw. (17)
56 expenditure$.tw. (18)
57 (value adj3 (money or monetary)).tw. (1)
58 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (1)
59 or/34-58 (410)

60 "Quality of Life"/ (0)
61 quality of life.tw. (124)
62 "Value of Life"/ (0)
63 Quality-Adjusted Life Years/ (0)
64 quality adjusted life.tw. (2)
65 (qaly$ or qald$ or qale$ or qtime$).tw. (4)
66 disability adjusted life.tw. (3)
67 daly$.tw. (4)
68 Health Status Indicators/ (0)
69 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (5)
70 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (2)
71 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (1)
72 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (0)
73 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (0)
74 (euroqol or euro qol or eq5d or eq 5d).tw. (6)
75 (qol or hql or hqol or hrqol).tw. (28)
76 (hye or hyes).tw. (0)
77 health$ year$ equivalent$.tw. (0)
78 utilit$.tw. (64)
79 (hui or hui1 or hui2 or hui3).tw. (2)
80 disutili$.tw. (0)
81 rosser.tw. (0)
82 quality of wellbeing.tw. (0)
83 quality of well-being.tw. (0)
84 qwb.tw. (0)
85 willingness to pay.tw. (2)
86 standard gamble$.tw. (0)
87 time trade off.tw. (0)
88 time tradeoff.tw. (0)
89 tto.tw. (0)
90 or/60-89 (196)
91 Cost-Benefit Analysis/ (0)
92 Quality-Adjusted Life Years/ (0)
93 Markov Chains/ (0)
94 exp Models, Economic/ (0)
95 cost*.ti. (31)
96 (cost* adj2 utilit*).tw. (1)
97 (cost* adj2 (effective* or assess* or evaluat* or analys* or model* or benefit* or threshold* or quality or expens* or saving* or reduc*)).tw. (80)
98 (economic* adj2 (evaluat* or assess* or analys* or model* or outcome* or benefit* or threshold* or expens* or saving* or reduc*)).tw. (17)
99 (qualit* adj2 adjust* adj2 life*).tw. (2)
100 QALY*.tw. (4)

101 (incremental* adj2 cost*).tw. (3)
102 ICER.tw. (1)
103 utilities.tw. (5)
104 markov*.tw. (15)
105 (dollar* or USD or cents or pound or pounds or GBP or sterling* or pence or euro or euros or yen or JPY).tw. (10)
106 ((utility or effective*) adj2 analys*).tw. (8)
107 (willing* adj2 pay*).tw. (2)
108 (EQ5D* or EQ-5D*).tw. (4)
109 ((euroqol or euro-qol or euroquol or euro-quol or eurocol or euro-col) adj3 ("5" or five)).tw. (4)
110 (european* adj2 quality adj3 ("5" or five)).tw. (0)
111 or/91-110 (140)
112 59 or 90 or 111 (593)
113 33 and 112 (0)

Database name: MEDLINE Epub Ahead-of-Print

1 exp Liver Cirrhosis/ (0)
2 Fibrosis/ and Liver/ (0)
3 cirrho*.tw. (1149)
4 ((liver* or hepat* or alcohol* or biliar*) adj4 (fibro* or myxofibro* or cholang* or angiocholit*)).tw. (913)
5 or/1-4 (1865)
6 (compensat* or decompensat* or asymptomat*).tw. (6075)
7 End Stage Liver Disease/ (0)
8 Liver Failure/ (0)
9 ((end* or final* or ultimate*) adj4 (liver* or hepat*) adj4 (diseas* or fail* or d?sfunct* or insufficien* or destruct* or expir* or defect* or disorder* or breakdown* or collaps* or disintegrat* or stag*)).tw. (242)
10 ((chronic* or continu*) adj4 (liver* or hepat*) adj4 (fail* or destruct* or expir* or breakdown* or collaps* or disintegrat*)).tw. (85)
11 ((declin* or deteriorat* or failing* or falling* or weaken* or degenerat* or decreas* or diminish*) adj4 (liver* or hepat*) adj4 (function* or activit* or performance*)).tw. (49)
12 or/6-11 (6368)
13 5 and 12 (333)
14 exp Adrenergic beta-Antagonists/ (0)
15 ((beta* or b) adj4 (block* or antagonist* or sympatholy*)).tw. (621)
16 NSBB*.tw. (7)
17 Nadolol/ (0)
18 (nadolol* or corgard* or solgol* or betadol*).tw. (7)
19 exp Timolol/ (0)
20 (timolo* or tiopex* or eysano* or timopt* or timacar* or blocadren* or optimol* or apotimolol* or titol*).tw. (40)
21 Sotalol/ (0)
22 (sotalol* or sotacor* or darob* or betacardone* or betades* or betapace* or bonpro* or corsotalol* or gilucor* or rentibloc* or sorine* or sota saar* or sotabeta* or sotacor* or sotahexal* or sotalex* or sotapor* or sotastad* or sotylize* or tachytalol*).tw. (31)

23 Carvedilol/ (0)
24 (carvedilol* or dilatrend* or querto* or eucardic* or kredex* or coropres* or coreg or cardiol or carvipress* or dilibloc* or dimitone*).tw. (55)
25 Labetalol/ (0)
26 (labetalol* or trandate* or albetol* or apolabetalol* or normodyne* or presolol* or dilevalol* or lamitol* or presdate*).tw. (14)
27 Propranolol/ (0)
28 (propranolol* or bedranol* or beta-prograne* or betaprograne* or inderal* or syprol* or rexigen* or dexpropranolol* or dociton* or ob?idan* or anaprilin* or betadren* or arcablock* or authus* or avlocardyl* or beprane* or betadipresan* or betaryl* or cardinol* or ciplar* or corbeta* or deralin* or duranol* or efektolol* or elbrol* or frekven* or hemang?ol* or inderex* or innopran* or ipran* or prandol* or propabloc* or propercuten* or prophylux* or propranur* or sagittol*).tw. (131)
29 or/14-28 (812)
30 13 and 29 (10)
31 Animals/ not Humans/ (0)
32 30 not 31 (10)
33 limit 32 to english language (10)
34 Economics/ (0)
35 exp "Costs and Cost Analysis"/ (0)
36 Economics, Dental/ (0)
37 exp Economics, Hospital/ (0)
38 exp Economics, Medical/ (0)
39 Economics, Nursing/ (0)
40 Economics, Pharmaceutical/ (0)
41 Budgets/ (0)
42 exp Models, Economic/ (0)
43 Markov Chains/ (0)
44 Monte Carlo Method/ (0)
45 Decision Trees/ (0)
46 econom$.tw. (9433)
47 cba.tw. (67)
48 cea.tw. (280)
49 cua.tw. (22)
50 markov$.tw. (669)
51 (monte adj carlo).tw. (1078)
52 (decision adj3 (tree$ or analys$)).tw. (850)
53 (cost or costs or costing$ or costly or costed).tw. (15486)
54 (price$ or pricing$).tw. (1248)
55 budget$.tw. (652)
56 expenditure$.tw. (1206)
57 (value adj3 (money or monetary)).tw. (91)
58 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (48)
59 or/34-58 (26735)
60 "Quality of Life"/ (0)
61 quality of life.tw. (8657)
62 "Value of Life"/ (0)
63 Quality-Adjusted Life Years/ (0)

64 quality adjusted life.tw. (481)
65 (qaly$ or qald$ or qale$ or qtime$).tw. (407)
66 disability adjusted life.tw. (140)
67 daly$.tw. (126)
68 Health Status Indicators/ (0)
69 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (455)
70 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (51)
71 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (154)
72 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (0)
73 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (6)
74 (euroqol or euro qol or eq5d or eq 5d).tw. (578)
75 (qol or hql or hqol or hrqol).tw. (1741)
76 (hye or hyes).tw. (1)
77 health$ year$ equivalent$.tw. (0)
78 utilit$.tw. (5150)
79 (hui or hui1 or hui2 or hui3).tw. (39)
80 disutili$.tw. (19)
81 rosser.tw. (0)
82 quality of wellbeing.tw. (2)
83 quality of well-being.tw. (8)
84 qwb.tw. (2)
85 willingness to pay.tw. (259)
86 standard gamble$.tw. (6)
87 time trade off.tw. (32)
88 time tradeoff.tw. (0)
89 tto.tw. (34)
90 or/60-89 (14185)
91 Cost-Benefit Analysis/ (0)
92 Quality-Adjusted Life Years/ (0)
93 Markov Chains/ (0)
94 exp Models, Economic/ (0)
95 cost*.ti. (2087)
96 (cost* adj2 utilit*).tw. (255)
97 (cost* adj2 (effective* or assess* or evaluat* or analys* or model* or benefit* or threshold* or quality or expens* or saving* or reduc*)).tw. (5985)
98 (economic* adj2 (evaluat* or assess* or analys* or model* or outcome* or benefit* or threshold* or expens* or saving* or reduc*)).tw. (1226)
99 (qualit* adj2 adjust* adj2 life*).tw. (487)
100 QALY*.tw. (405)
101 (incremental* adj2 cost*).tw. (420)
102 ICER.tw. (185)
103 utilities.tw. (199)
104 markov*.tw. (669)

105 (dollar* or USD or cents or pound or pounds or GBP or sterling* or pence or euro or euros or yen or JPY).tw. (951)
106 ((utility or effective*) adj2 analys*).tw. (644)
107 (willing* adj2 pay*).tw. (282)
108 (EQ5D* or EQ-5D*).tw. (488)
109 ((euroqol or euro-qol or euroquol or euro-quol or eurocol or euro-col) adj3 ("5" or five)).tw. (133)
110 (european* adj2 quality adj3 ("5" or five)).tw. (31)
111 or/91-110 (9494)
112 59 or 90 or 111 (39238)
113 33 and 112 (0)

Database name: Embase

1 exp liver cirrhosis/ (185052)
2 fibrosis/ and liver/ (10789)
3 cirrho*.tw. (175089)
4 ((liver* or hepat* or alcohol* or biliar*) adj4 (fibro* or myxofibro* or cholang* or angiocholit*)).tw. (88438)
5 or/1-4 (284658)
6 (compensat* or decompensat* or asymptomat*).tw. (530791)
7 end stage liver disease/ (10478)
8 liver failure/ (45549)
9 ((end* or final* or ultimate*) adj4 (liver* or hepat*) adj4 (diseas* or fail* or d?sfunct* or insufficien* or destruct* or expir* or defect* or disorder* or breakdown* or collaps* or disintegrat* or stag*)).tw. (24658)
10 ((chronic* or continu*) adj4 (liver* or hepat*) adj4 (fail* or destruct* or expir* or breakdown* or collaps* or disintegrat*)).tw. (8644)
11 ((declin* or deteriorat* or failing* or falling* or weaken* or degenerat* or decreas* or diminish*) adj4 (liver* or hepat*) adj4 (function* or activit* or performance*)).tw. (7485)
12 or/6-11 (606409)
13 5 and 12 (47868)
14 exp beta adrenergic receptor blocking agent/ (325186)
15 ((beta* or b) adj4 (block* or antagonist* or sympatholy*)).tw. (114313)
16 NSBB*.tw. (409)
17 nadolol/ (5939)
18 (nadolol* or corgard* or solgol* or betadol*).tw. (2155)
19 timolol maleate/ or timolol/ (14491)
20 (timolo* or tiopex* or eysano* or timopt* or timacar* or blocadren* or optimol* or apotimolol* or titol*).tw. (6811)
21 sotalol/ (14066)
22 (sotalol* or sotacor* or darob* or betacardone* or betades* or betapace* or bonpro* or corsotalol* or gilucor* or rentibloc* or sorine* or sota saar* or sotabeta* or sotacor* or sotahexal* or sotalex* or sotapor* or sotastad* or sotylize* or tachytalol*).tw. (4760)
23 carvedilol/ (17483)
24 (carvedilol* or dilatrend* or querto* or eucardic* or kredex* or coropres* or coreg or cardiol or carvipress* or dilibloc* or dimitone*).tw. (9021)
25 labetalol/ (11779)

26 (labetalol* or trandate* or albetol* or apolabetalol* or normodyne* or presolol* or dilevalol* or lamitol* or presdate*).tw. (4065)
27 propranolol/ (94278)
28 (propranolol* or bedranol* or beta-prograne* or betaprograne* or inderal* or syprol* or rexigen* or dexpropranolol* or dociton* or ob?idan* or anaprilin* or betadren* or arcablock* or authus* or avlocardyl* or beprane* or betadipresan* or betaryl* or cardinol* or ciplar* or corbeta* or deralin* or duranol* or efektolol* or elbrol* or frekven* or hemang?ol* or inderex* or innopran* or ipran* or prandol* or propabloc* or propercuten* or prophylux* or propranur* or sagittol*).tw. (45637)
29 or/14-28 (369748)
30 13 and 29 (1345)
31 nonhuman/ not human/ (5194717)
32 30 not 31 (1329)
33 limit 32 to english language (1270)
34 limit 33 to (conference abstract or conference paper or "conference review") (425)
35 33 not 34 (845)
36 exp Health Economics/ (995908)
37 exp "Health Care Cost"/ (328195)
38 exp Pharmacoeconomics/ (225097)
39 Monte Carlo Method/ (48634)
40 Decision Tree/ (19897)
41 econom$.tw. (472364)
42 cba.tw. (13922)
43 cea.tw. (40302)
44 cua.tw. (1800)
45 markov$.tw. (38056)
46 (monte adj carlo).tw. (58969)
47 (decision adj3 (tree$ or analys$)).tw. (34889)
48 (cost or costs or costing$ or costly or costed).tw. (954397)
49 (price$ or pricing$).tw. (70210)
50 budget$.tw. (45724)
51 expenditure$.tw. (88154)
52 (value adj3 (money or monetary)).tw. (4158)
53 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (9524)
54 or/36-53 (2158086)
55 "Quality of Life"/ (591524)
56 Quality Adjusted Life Year/ (33982)
57 Quality of Life Index/ (3105)
58 Short Form 36/ (37507)
59 Health Status/ (146786)
60 quality of life.tw. (562684)
61 quality adjusted life.tw. (25554)
62 (qaly$ or qald$ or qale$ or qtime$).tw. (25936)
63 disability adjusted life.tw. (5912)
64 daly$.tw. (5671)
65 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (48607)

66 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (2849)
67 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (11793)
68 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (70)
69 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (507)
70 (euroqol or euro qol or eq5d or eq 5d).tw. (28614)
71 (qol or hql or hqol or hrqol).tw. (125112)
72 (hye or hyes).tw. (161)
73 health$ year$ equivalent$.tw. (41)
74 utilit$.tw. (362050)
75 (hui or hui1 or hui2 or hui3).tw. (2958)
76 disutili$.tw. (1204)
77 rosser.tw. (139)
78 quality of wellbeing.tw. (70)
79 quality of well-being.tw. (556)
80 qwb.tw. (266)
81 willingness to pay.tw. (12280)
82 standard gamble$.tw. (1183)
83 time trade off.tw. (1999)
84 time tradeoff.tw. (316)
85 tto.tw. (2118)
86 or/55-85 (1236500)
87 cost utility analysis/ (11827)
88 quality adjusted life year/ (33982)
89 cost*.ti. (188773)
90 (cost* adj2 utilit*).tw. (12197)
91 (cost* adj2 (effective* or assess* or evaluat* or analys* or model* or benefit* or threshold* or quality or expens* or saving* or reduc*)).tw. (366837)
92 (economic* adj2 (evaluat* or assess* or analys* or model* or outcome* or benefit* or threshold* or expens* or saving* or reduc*)).tw. (63036)
93 (qualit* adj2 adjust* adj2 life*).tw. (26165)
94 QALY*.tw. (25676)
95 (incremental* adj2 cost*).tw. (27457)
96 ICER.tw. (12359)
97 utilities.tw. (14488)
98 markov*.tw. (38056)
99 (dollar* or USD or cents or pound or pounds or GBP or sterling* or pence or euro or euros or yen or JPY).tw. (69082)
100 ((utility or effective*) adj2 analys*).tw. (35986)
101 (willing* adj2 pay*).tw. (13851)
102 (EQ5D* or EQ-5D*).tw. (24214)
103 ((euroqol or euro-qol or euroquol or euro-quol or eurocol or euro-col) adj3 ("5" or five)).tw. (4805)
104 (european* adj2 quality adj3 ("5" or five)).tw. (896)
105 or/87-104 (604498)

106 55 or 86 or 105 (1717942)
107 35 and 106 (61)

Database name: INAHTA

15	#14 AND #10	0
14	#13 OR #12 OR #11	62
13	(NSBB*) OR ("Nadolol"[MH]) OR (nadolol* or corgard* or solgol* or betadol*) OR ("Timolol"[MHE]) OR (timolo* or tiopex* or eysano* or timopt* or timacar* or blocadren* or optimol* or apotimolol* or titol*) OR ("Sotalol"[MH]) OR (sotalol* or sotacor* or darob* or betacardone* or betades* or betapace* or bonpro* or corsotalol* or gilucor* or rentibloc* or sorine* or sota saar* or sotabeta* or sotacor* or sotahexal* or sotalex* or sotapor* or sotastad* or sotylize* or tachytalol*) OR ("Carvedilol"[MH]) OR (carvedilol* or dilatrend* or querto* or eucardic* or kredex* or coropres* or coreg or cardiol or carvipress* or dilibloc* or dimitone*) OR ("Labetalol"[MH]) OR (labetalol* or trandate* or albetol* or apolabetalol* or normodyne* or presolol* or dilevalol* or lamitol* or presdate*) OR ("Propranolol"[MH]) OR (propranolol* or bedranol* or beta-prograne* or betaprograne* or inderal* or syprol* or rexigen* or dexpropranolol* or dociton* or ob?idan* or anaprilin* or betadren* or arcablock* or authus* or avlocardyl* or beprane* or betadipresan* or betaryl* or cardinol* or ciplar* or corbeta* or deralin* or duranol* or efektolol* or elbrol* or frekven* or hemang?ol* or inderex* or innopran* or ipran* or prandol* or propabloc* or propercuten* or prophylux* or propranur* or sagittol*)	27
12	(beta* or b) AND (block* or antagonist* or sympatholy*)	32
11	("Adrenergic beta-Antagonists"[MHE])	8
10	#9 AND #4	31
9	#8 OR #7 OR #6 OR #5	380

8	(declin* or deteriorat* or failing* or falling* or weaken* or degenerat* or decreas* or diminish*) AND (liver* or hepat*) AND (function* or activit* or performance*)	14
7	(chronic* or continu*) AND (liver* or hepat*) AND (fail* or destruct* or expir* or breakdown* or collaps* or disintegrat*)	27
6	(end* or final* or ultimate*) AND (liver* or hepat*) AND (diseas* or fail* or disfunct* or dysfunct* or insufficien* or destruct* or expir* or defect* or disorder* or breakdown* or collaps* or disintegrat* or stag*)	41
5	(compensat* or decompensat* or asymptomat*) OR ("End Stage Liver Disease"[MH]) OR ("Liver Failure"[MH])	321
4	#3 OR #2 OR #1	115
3	(liver* or hepat* or alcohol* or biliar*) AND (fibro* or myxofibro* or cholang* or angiocholit*)	70
2	("Fibrosis"[MH]) AND ("Liver"[MH])	4
1	("Liver Cirrhosis[mhe]") OR (cirrho*)	64

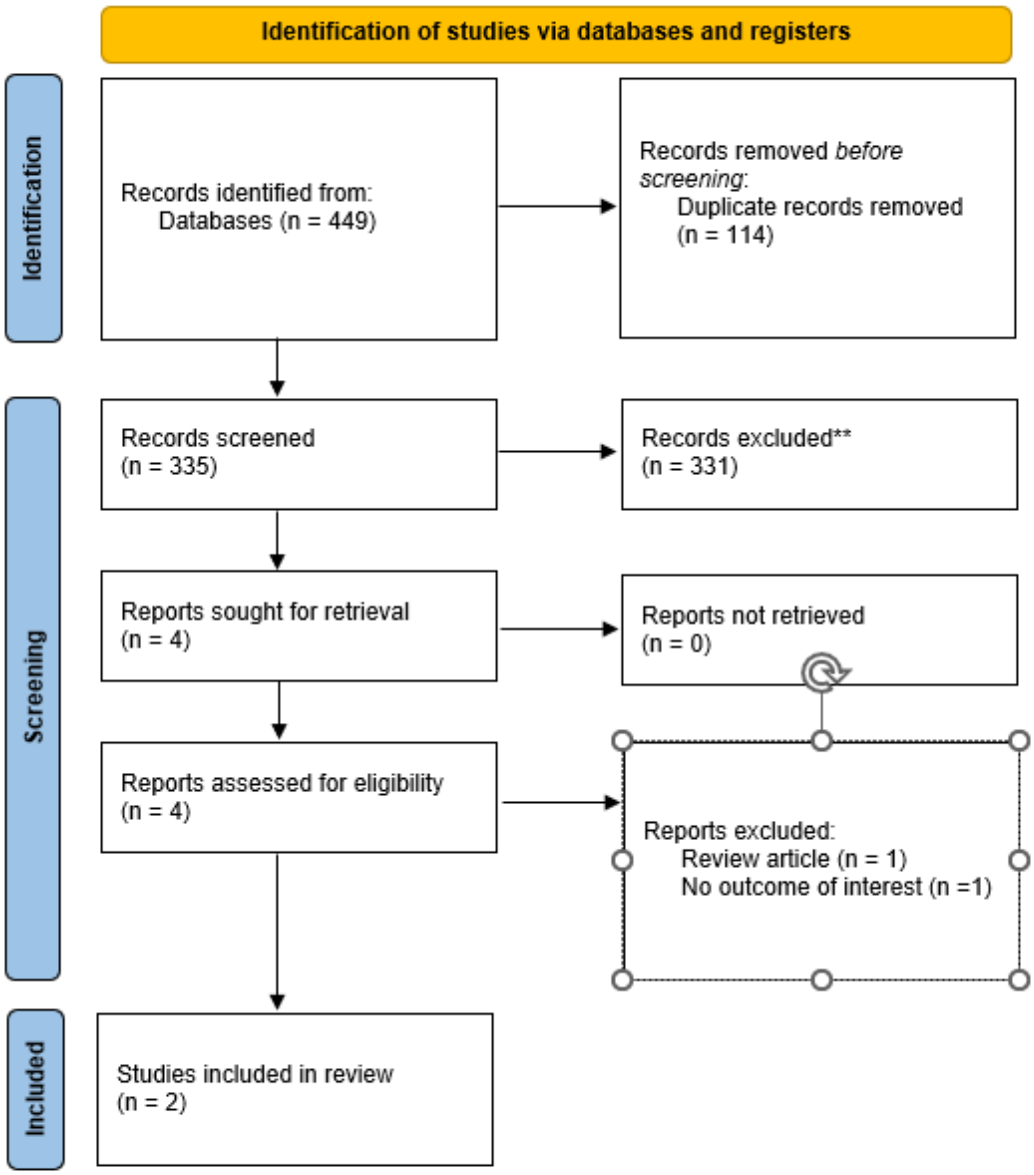
Database name: Econlit

1 cirrho*.tw. (33)
2 ((liver* or hepat* or alcohol* or biliar*) adj4 (fibro* or myxofibro* or cholang* or angiocholit*)).tw. (3)
3 1 or 2 (35)
4 (compensat* or decompensat* or asymptomat*).tw. (20827)
5 ((end* or final* or ultimate*) adj4 (liver* or hepat*) adj4 (diseas* or fail* or d?sfunct* or insufficien* or destruct* or expir* or defect* or disorder* or breakdown* or collaps* or disintegrat* or stag*)).tw. (6)
6 ((chronic* or continu*) adj4 (liver* or hepat*) adj4 (fail* or destruct* or expir* or breakdown* or collaps* or disintegrat*)).tw. (0)
7 ((declin* or deteriorat* or failing* or falling* or weaken* or degenerat* or decreas* or diminish*) adj4 (liver* or hepat*) adj4 (function* or activit* or performance*)).tw. (1)
8 or/4-7 (20832)
9 3 and 8 (8)
10 ((beta* or b) adj4 (block* or antagonist* or sympatholy*)).tw. (40)
11 NSBB*.tw. (0)
12 (nadolol* or corgard* or solgol* or betadol*).tw. (0)
13 (timolo* or tiopex* or eysano* or timopt* or timacar* or blocadren* or optimol* or apotimolol* or titol*).tw. (43)

14 (sotalol* or sotacor* or darob* or betacardone* or betades* or betapace* or bonpro* or corsotalol* or gilucor* or rentibloc* or sorine* or sota saar* or sotabeta* or sotacor* or sotahexal* or sotalex* or sotapor* or sotastad* or sotylize* or tachytalol*).tw. (1)
15 (carvedilol* or dilatrend* or querto* or eucardic* or kredex* or coropres* or coreg or cardiol or carvipress* or dilibloc* or dimitone*).tw. (0)
16 (labetalol* or trandate* or albetol* or apolabetalol* or normodyne* or presolol* or dilevalol* or lamitol* or presdate*).tw. (0)
17 (propranolol* or bedranol* or beta-prograne* or betaprograne* or inderal* or syprol* or rexigen* or dexpropranolol* or dociton* or ob?idan* or anaprilin* or betadren* or arcablock* or authus* or avlocardyl* or beprane* or betadipresan* or betaryl* or cardinol* or ciplar* or corbeta* or deralin* or duranol* or efektolol* or elbrol* or frekven* or hemang?ol* or inderex* or innopran* or ipran* or prandol* or propabloc* or propercuten* or prophylux* or propranur* or sagittol*).tw. (8)
18 or/10-17 (92)
19 9 and 18 (0)

Appendix C – Effectiveness evidence study selection

Figure 1: PRISMA flow chart of study selection



Appendix D – Effectiveness evidence

Villanueva, 2019

Bibliographic Reference	Villanueva, Candid; Albillos, Agustin; Genesca, Joan; Garcia-Pagan, Joan C; Calleja, Jose L; Aracil, Carles; Banares, Rafael; Morillas, Rosa M; Poca, Maria; Penas, Beatriz; Augustin, Salvador; Abraldes, Juan G; Alvarado, Edilmar; Torres, Ferran; Bosch, Jaume; beta blockers to prevent decompensation of cirrhosis in patients with clinically significant portal hypertension (PREDESCI): a randomised, double-blind, placebo-controlled, multicentre trial.; Lancet (London, England); 2019; vol. 393 (no. 10181); 1597-1608

Study details

Trial registration number and/or trial name	PREDESCI trial. Registered on ClinicalTrials.gov, number NCT01059396.
Study type	Randomised controlled trial (RCT)
Study location	Spain
Study setting	Eight hospitals
Study dates	Patients were enrolled from Jan 18, 2010, and July 31, 2013. Follow-up was planned until Oct 31, 2016 but actually ended June 2015.
Sources of funding	This investigator-initiated trial received no commercial support and has been supported by competitive grants from the Instituto de Salud Carlos III (Spanish Ministries of Health and of Economy; EC08/00087, PI10/01552, PI13/02535, PS09/00485, PI14/00876, and PI15/00066).
Inclusion criteria	• >18 and <80 years of age • Cirrhosis • Diagnosed on the basis of previous biopsy or compatible clinical, biochemical, and ultrasonographic findings. Varices were investigated by gastroscopy and absence of ascites by ultrasound (both performed within 3 months pre-randomisation)
Exclusion criteria	• Hepatocellular carcinoma • Contraindications to beta-blocker therapy • Pregnancy • Previous decompensation of cirrhosis • Clinically significant portal hypertension • Portal thrombosis • Baseline bilirubin greater than 3 mg/dL • Platelets less than 30 × 10³

	• International normalised ratio of prothrombin time greater than 2·7 • Renal failure • Comorbidity with life expectancy less than 12 months, contraindication • Previous treatment with β blockers • Anticoagulant treatment • Active antiviral therapy for hepatitis C • Lactation
Intervention(s)	Acute HVPG response to β blockers was evaluated 20 min after intravenous propranolol (0·15 mg/kg). Patients with decreasing HVPG >10% from baseline were considered responders, and receive propranolol. Non-responders were randomly assigned to receive carvedilol. The oral dose of β blockers to be used during the study was individually determined during an open-label titration period. HVPG responders received propranolol starting with 40 mg twice a day increased up to 160 mg twice a day. Non-responders received carvedilol, starting with 6·25 mg/day and increased up to 25 mg/day. The dose was titrated against clinical tolerance, keeping heart rate above 55 beats per min and systolic blood pressure greater than 90 mm Hg, without repeating HVPG measurements. The titration periods lasted up to 3 weeks and patients were randomly assigned once the daily dose of β blocker had been determined. Mean dose of propranolol per day = 95mg (SD: 81) Mean dose carvedilol per day = 20mg (SD: 6)
Comparator	Oral placebo allocated and administered in line with the approach to beta-blocker regimen.
Outcome measures	• Acute, clinically significant bleeding as a result of portal hypertensive gastropathy • Development of ascites • Development of encephalopathy • Death • Decompensation of cirrhosis
Number of participants	201
Duration of follow-up	**Mean (SD) follow up (months) -** • Placebo group 37 (16) • Intervention group 36 (16) **Median (IQR) follow up (months) -** • Placebo group 37 (27–47) • Intervention group 37 (26–47)

Loss to follow-up	44/201 (22%); 25/100 (25%) for beta-blockers and 19/101 (19%) for placebo.
Methods of analysis	Sample size calculation undertaken. Categorical variables were compared with Fisher's exact test and continuous variables with the Student's t test (for paired data within each group). The Wilcoxon rank-sum test was used for skewed or ordinal data. Continuous variables measured repeatedly over time were analysed by the mixed-models repeated measure. Primary and secondary outcomes were analysed as time-to-event variables, considering the stratum according to acute response to β blockers. A competing-risk analysis was predefined considering non-liver related deaths as competing events. Probabilities were estimated with the use of cumulative incidence functions and comparisons relied on Gray's test.

Study arms

Beta-blockers (N = 100)
67 received propranolol; 33 received carvedilol

Placebo (N = 101)
68 received placebo of propranolol; 33 received placebo of carvedilol

Characteristics

Arm-level characteristics

Characteristic	Beta-blockers (N = 100)	Placebo (N = 101)
% Female No of events	n = 41 ; % = 41	n = 37 ; % = 37
Mean age (SD) Mean (SD)	60 (10)	59 (11)
Cause of cirrhosis		
- **Alcohol** Sample size	n = 19 ; % = 19	n = 14 ; % = 14
- **HCV** Sample size	n = 54 ; % = 54	n = 59 ; % = 58
- **Alcohol and HCV** Sample size	n = 9 ; % = 9	n = 8 ; % = 8
- **NASH** Non-alcoholic steatohepatitis Sample size	n = 5 ; % = 5	n = 8 ; % = 8

Characteristic	Beta-blockers (N = 100)	Placebo (N = 101)
- **Others** Not specified Sample size	n = 13 ; % = 13	n = 12 ; % = 12
Child-Pugh class		
- **Class - A**	n = 80 ; % = 80	n = 81 ; % = 80
- **Class - B**	n = 20 ; % = 20	n = 20 ; % = 20

Critical appraisal - GDT Crit App - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low *(Double-blind RCT. Some concerns identified due to the loss to follow-up and withdrawals. An ITT analysis was adopted and considered all those randomised. Loss to follow-up was almost double in the beta-blocker arm (9%) vs the placebo arm (4%). Withdrawals from the study for those randomised to propranolol and carvedilol totalled n=14. Those participants that withdrew continued with the study and their withdrawal was at the 24 month (median) and 28 month (median) point respectively, these participants discontinued treatment/placebo. Combined with the loss to follow-up (not including those who withdrew consent or withdrew due to need to take anti-virials; n=17) totals 21% of the total sample and is a potential source of bias. On review of the study whilst not completely clear missingness/losses-to-follow-up/withdrawals do not appear to be due to the outcomes under investigation.)*
Overall bias and Directness	Overall Directness	Directly applicable

Villanueva, 2022

Bibliographic Reference	Villanueva, Candid; Torres, Ferran; Sarin, Shiv Kumar; Shah, Hasnain Ali; Tripathi, Dhiraj; Brujats, Anna; Rodrigues, Susana G; Bhardwaj, Ankit; Azam, Zahid; Hayes, Peter C; Jindal, Ankur; Abid, Shahab; Alvarado, Edilmar; Bosch, Jaume; Carvedilol-IPD-MA-group and the Baveno Cooperation: an EASL, Consortium; Carvedilol reduces the risk of decompensation and mortality in patients with compensated cirrhosis in a competing-risk meta-analysis.; Journal of hepatology; 2022; vol. 77 (no. 4); 1014-1025

Study details

Trial registration number and/or trial name	Meta-analysis was registered in PROSPERO (CRD42019144786).
Study type	IPD Meta-analysis
Study dates	Comprehensive literature searches were performed in MEDLINE, PubMed, Embase, the Cochrane Collaboration Registry of Controlled Trials and the Cochrane Database of Systematic Reviews. Published studies were searched without language restrictions through February 2020.
Sources of funding	Grants from the Instituto de Salud Carlos III, Spain (EC08/00087, PI10/01552, PI13/02535, PS09/00485, PI14/00876, PI15/00066
Inclusion criteria	• Compensated cirrhosis • Without any previous decompensating event • Small oesophageal varices • Clinically significant portal hypertension • Large oesophageal varices • CSPH confirmed by HVPG

Exclusion criteria	• Authors of papers non-responders
	• Non-randomised or observational studies
	• Studies that only included:
	  ○ decompensated patients
	  ○ patients with non-cirrhotic portal hypertension
	  ○ patients with portal thrombosis or with hepatocellular carcinoma
	  ○ patients with end-stage liver disease
	• Studies treating with agents different to carvedilol (such as classical NSBBs, nitrates or statins) or with transjugular intrahepatic portosystemic shunt or sclerotherapy,
	• Studies with less than 12 months follow up

Intervention(s)	Individuals from RCTs allocating adult patients with cirrhosis to receive carvedilol. Carvedilol was administered up to 12.5 mg/day in 2 studies (Tripathi et al 2009; Bhardwaj et al 2017) and up to 25 mg/day in 2 studies (Villanueva 2019; Shah et al 2014) The mean follow-up in the RCTs included ranged from 13 to 36 months.
Comparator	Individuals from RCTs allocating adult patients with cirrhosis to receive carvedilol or to a control group receiving nospecific therapy or placebo or monotherapy with endoscopic variceal ligation (EVL) in case of high-risk varices.

	EVL (Tripathi et al 2009; Bhardwaj et al 2017) and Placebo (Villanueva 2019; Shah et al 2014).
Outcome measures	• Death • Decompensation of cirrhosis • Overt hepatic hepatorenal syndrome • Ascites • Gastrointestinal bleeding related to portal hypertension • Bleeding • Side effects • Major side effects
Number of participants	352
Duration of follow-up	The mean follow-up in the included RCTs included ranged from 13 to 36 months. Results of IPD meta-analysis presented as rates (in person years).
Loss to follow-up	Not outlined but study outlines that there was "no missing data for primary and secondary outcomes and baseline covariates were described with no imputation". However, the study also outlines that "Carvedilol was withdrawn in 14 patients (8%) due to side effects or non-compliance".
Methods of analysis	Individual patient meta-analysis follows PRISMA–IPD guidelines for protocol registration, trial identification, data collection and integrity, assessment of bias, and sensitivity analyses. Time-to-event data were calculated using the raw data from each study. All analyses used the intention-to-treat principle by including all randomized patients from every single RCT, regardless of receiving the intended treatment. Categorical variables were expressed as frequencies and percentages. Continuous variables were expressed as means with SD or as median and IQR in cases of a non-normal distribution. The treatment effect on the outcomes was estimated using a Cox proportional hazards regression model for competing-risk. In these analyses, the cumulative incidence function of the analysed events were estimated in a competing risk framework in which liver transplantation (LT) was considered a competing event for death, and both LT and death were considered competing events for decompensation and for decompensating events. Sub-distribution hazard ratios (SHRs) and 95% CIs were estimated. The meta-analysis was conducted using a 2-stage procedure, first estimating the risks by study with the inverse probability of treatment weighting (IPTW) competing-risk Cox models and then pooling them using random-effects model (detailed in the supplementary information). A prespecified assessment of the primary outcomes was also conducted, using competing-risk Cox regression models and performing univariate and multivariable analyses, to adjust the effect of treatment for baseline potential confounders. Heterogeneity was evaluated using the I-squared and the Q heterogeneity test.

Additional comments	Villanueva et al 2022 was a individual patient data meta-analysis. It included RCTs (and individual patient data) if it was fully published, if the original data sets were available with information regarding the presence of decompensation of cirrhosis at baseline and if information regarding the development of decompensation of cirrhosis after randomization and regarding death was available or could be obtained. Studies were excluded if they were non-randomized or observational, those including patients with previous bleeding, restricted to decompensated patients, to patients with portal thrombosis or with hepatocellular carcinoma or with end-stage liver disease, those treating with agents different to carvedilol (such as classical NSBBs, nitrates or statins) or with trans-jugular intrahepatic portosystemic shunt or sclerotherapy, those limited to less than 12 months of follow-up and those including patients with non-cirrhotic PH.

Study arms

Carvedilol (N = 181)
The median dose of carvedilol was 12.5 mg/day (IQR, 12.5-18.75).

No active treatment or endoscopic variceal ligation (EVL) (N = 171)
79 received EVL and 92 placebo

Characteristics

Arm-level characteristics

Characteristic	Carvedilol (N = 181)	No active treatment or endoscopic variceal ligation (EVL) (N = 171)
Male Sample size	n = 139 ; % = 77	n = 131 ; % = 77
Age Median (IQR)	53 (45 to 60)	51 (44 to 59)
Cause of cirrhosis		
- **Alcohol** Sample size	n = 51 ; % = 28	n = 39 ; % = 23
- **HCV** Sample size	n = 65	n = 75
- **HBV** Sample size	n = 12	n = 19 ; % = 11

Characteristic	Carvedilol (N = 181)	No active treatment or endoscopic variceal ligation (EVL) (N = 171)
- **Other** Sample size	n = 53 ; % = 29	n = 38 ; % = 22
Child-Pugh class		
- **Class A** Sample size	n = 111 ; % = 61	n = 112 ; % = 65
- **Class B** Sample size	n = 57 ; % = 32	n = 51 ; % = 30
- **Class C** Sample size	n = 13 ; % = 7	n = 8 ; % = 5
Child-Pugh score Median (IQR)	6 (5 to 7)	6 (5 to 7)
MELD score Median (IQR)	8.2 (6.4 to 11)	8.5 (6.9 to 11)
Oesophageal varices Sample size	n = 172 ; % = 95	n = 159 ; % = 93
Large varices Sample size	n = 104 ; % = 57	n = 102 ; % = 60
Red signs on varices Sample size	n = 5 ; % = 57	n = 6 ; % = 3
Gastric varices Sample size	n = 32 ; % = 18	n = 31 ; % = 18
Weight (kg) Median (IQR)	74.2 (66 to 89)	76 (69 to 84.7)
Body mass index Median (IQR)	28.5 (24.7 to 32.2)	26.8 (24.5 to 30.1)

Critical appraisal - GDT Crit App - Assessment of Individual Participant Data Meta-analysis studies

Section	Question	Answer
Overall judgement of study quality	What is the overall judgement of study quality?	High
Overall judgement of study quality	Directness	Directly applicable

Appendix E – Forest plots

No meta-analysis was undertaken for this review.

Appendix F – GRADE tables

Table F1: NSBB vs placebo or no treatment for decompensation

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NSBB	Control	Relative (95% CI)	Absolute	
Decompensation or death - NSBB (all) vs placebo (follow-up mean 36.5 months) <1 favours NSBB											
1	randomised trials[1]	no serious risk of bias	serious[2]	no serious indirectness	serious[3]	none	16/100 (16%)	27/101 (26.7%)	RR 0.6 (0.34 to 1.04)	107 fewer per 1000 (from 176 fewer to 11 more)	⊕⊕OO LOW
Decompensation or death - Carvedilol vs placebo (follow-up mean 36.5 months) <1 favours carvedilol											
1	randomised trials[1]	no serious risk of bias	serious[2]	no serious indirectness	serious[3]	none	3/33 (9.1%)	9/33 (27.3%)	RR 0.33 (0.1 to 1.12)	183 fewer per 1000 (from 245 fewer to 33 more)	⊕⊕OO LOW
Decompensation or death - Propranolol vs placebo (follow-up mean 36.5) <1 favours propranolol											
1	randomised trials[1]	no serious risk of bias	serious[2]	no serious indirectness	very serious[4]	none	13/67 (19.4%)	18/68 (26.5%)	RR 0.73 (0.39 to 1.37)	71 fewer per 1000 (from 161 fewer to 98 more)	⊕OOO VERY LOW
Decompensation - Decompensation (all) (follow-up mean 36.5 months) <1 favours NSBB											
1	randomised trials[1]	no serious risk of bias	serious[2]	no serious indirectness	serious[3]	none	12/100 (12%)	24/101 (23.8%)	RR 0.51 (0.27 to 0.95)	116 fewer per 1000 (from 12 fewer to 173 fewer)	⊕⊕OO LOW
Decompensation - Decompensated liver resulting in death (follow-up mean 36.5 months) <1 favours NSBB											
1	randomised trials[1]	no serious risk of bias	serious[2]	no serious indirectness	very serious[4]	none	4/12 (33.3%)	9/24 (37.5%)	RR 0.89 (0.34 to 2.3)	41 fewer per 1000 (from 248 fewer to 487 more)	⊕OOO VERY LOW

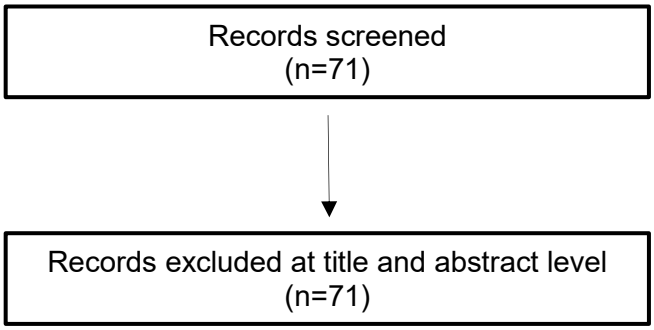
[1] Villanueva 2019
[2] Downgraded once because single study
[3] Downgraded once for crossing 1 MID
[4] Downgraded twice for crossing 2 MIDs.

Table F2: NSBB vs placebo or no treatment for adverse events

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NSBB	Control	Relative (95% CI)	Absolute	
Adverse events - Adverse events - all (follow-up mean 36.5 months) <1 favours NSBB											
1	randomised trials[1]	no serious risk of bias	serious[2]	no serious indirectness	no serious imprecision	none	84/100 (84%)	88/101 (87.1%)	RR 0.96 (0.86 to 1.08)	35 fewer per 1000 (from 122 fewer to 70 more)	⊕⊕⊕O MODERATE
Adverse events - Adverse events - probably related to treatment (follow-up mean 36.5 months) <1 favours NSBB											
1	randomised trials[1]	no serious risk of bias	serious[2]	no serious indirectness	serious[3]	none	39/100 (39%)	30/101 (29.7%)	RR 1.31 (0.89 to 1.93)	92 more per 1000 (from 33 fewer to 276 more)	⊕⊕OO LOW
Adverse events - Adverse events - very probably related to treatment (follow-up mean 36.5 months) <1 favours NSBB											
1	randomised trials[1]	no serious risk of bias	serious[2]	no serious indirectness	very serious[4]	none	16/100 (16%)	15/101 (14.9%)	RR 1.08 (0.56 to 2.06)	12 more per 1000 (from 65 fewer to 157 more)	⊕OOO VERY LOW

[1] Villanueva 2019
[2] Downgraded once because single study
[3] Downgraded once for crossing 1 MID
[4] Downgraded twice for crossing 2 MIDs

Appendix G – Economic evidence study selection



Appendix H – Economic evidence tables

No economic studies were identified.

Appendix I – Health economic model

Model overview

The objective of this analysis is to evaluate the cost savings of non-selective beta-blockers (NSBBs) for the primary prevention of decompensation in people with compensated cirrhosis.

Population

People aged 16 years and older with compensated cirrhosis and no history of decompensated cirrhosis.

Comparators

This analysis compares non-selective beta blockers (NSBBs) with no active intervention. NSBBs included propranolol and carvedilol.

Model structure

We conducted a threshold analysis to evaluate whether NSBBs are more cost saving than the no active intervention for the primary prevention of decompensated cirrhosis. The threshold represents the number of cases of decompensation that NSBBs need to prevent to be cost saving. If the risk reduction of decompensation associated with NSBBs is below the threshold, then the NSBBs will be cost saving. According to the published clinical study PREDESCI, NSBBs shows more clinical benefits in the prevention of developing ascites, therefore our analysis focuses on the ascites only where the strongest clinical evidence lays.

$$Threshold = \frac{Treatment\ cost\ of\ ascites}{Annual\ cost\ of\ NSBBs}$$

Model inputs

We obtained cost inputs and resource utilisation from NHS Cost Collection and published economic studies. Assumptions were applied to the model wherever data were not available. All costs have been inflated to 2019/20 price level using the NHS cost inflation index.

This analysis includes the following costs:

- Annual cost of NSBBs for primary prevention of decompensation,
- Treatment cost of uncomplicated ascites,
- Treatment cost of refractory ascites.

Annual cost of NSBBs

The weighted average annual cost of NSBBs is £26.76, which is calculated based on the proportion of drug usage, mean daily dosage and unit costs of propranolol and carvedilol. The proportion of drug usage and mean daily dosage are identified from the clinical study PREDESCI (Villanueva, 2019).

Table I1: Costs of NSBBs

NSBBs	Proportion of patients	Daily dosage	Unit price per mg	BNF (package size/drug tariff)	Annual cost
Propranolol	76%	95mg	£0.0007	40mg×28 tablets/£0.79	£24.46
Carvedilol	33%	19mg	£0.0036	12.5mg×28 tablets/£1.25	£24.77

Treatment cost of uncomplicated ascites

We identified the treatment costs of uncomplicated ascites from a published cost effectiveness study of people with variceal bleeding and refractory ascites (Mattock, 2021). Using 2019/2020 prices, moderate ascites treated with a 6-month course of spironolactone costs £6.27, while large ascites treated with 2 courses of LVP and human albumin costs £1,673.14. On the basis of discussion with the committee, we assumed 90% of people requiring treatment present with moderate ascites and 10% present with large ascites, giving a weighted treatment cost of £201 per person with ascites.

Table I2: Costs of uncomplicated ascites

Uncomplicated ascites	Proportion	Cost per person
Moderate ascites (spironolactone, 6-month course)	90%	£37.65
Large ascites (LVP + human albumin)*	10%	£1,673.14

*Large ascites has a mean of 2 sessions of LVP + human albumin. This cost includes materials cost, administration cost and hospital stay (either a day case, elective or non-elective, ranging from 1 to 2.8 days)

Treatment cost of refractory ascites

We assumed that 10% of people with uncomplicated ascites can develop refractory ascites, as stated in the previous guideline update (2017). For people who have refractory ascites, we assume that 90% are treated with LVP plus human albumin and 10% are treated with TIPSS. This assumption is in line with clinical guidelines: Baveno (2022) recommends that LVP in combination with human albumin as the 1st line treatment, while NICE recommends that TIPSS is considered. The cost of each treatment strategy is derived from the Mattock (2021) cost effectiveness study. LVP plus human albumin occurring every 14 days costs about £836.57 per session, which amounts to £21,810.53 per year. TIPSS as an elective inpatient procedure costs approximately £4,858.37 a year. The average cost of refractory ascites is estimated to be £20,115 each year.

According to committee's experience, some patients may require LVP sessions every 4 or 6 weeks instead of every 2 weeks. A certain number of people who are not respond to TIPPS will require more LVP sessions whereas people with severe

conditions might need a transplant. Therefore, this cost may represent the highest estimate for treatment of refractory ascites.

Table I3: Costs of refractory ascites

Treatment strategy	Proportion	Annual cost per person
LVP + human albumin	90%	£21,810.53
TIPSS	10%	£4,858.37

Treatment effect

According to the clinical review (2023) conducted by the NICE development team, the risk difference in decompensation between NSBBs and placebo is estimated to be 116 fewer per 1000 (95% confidence interval: from 12 fewer to 173 fewer). This indicates that NSBBs can reduce the incidence of decompensation by an average of 1 case in every 8.6 people.

Results

The total cost of managing ascites is approximately £2,212.73 a year. NSBBs would be cost saving if they can prevent at least 1 case of decompensation per 82.68 person years. The clinical evidence shows that NSBBs reduce incidence of decompensation by an average of 116 cases per 1000 people (1 in every 8.6 people), which is lower than the threshold. Hence, prophylactic treatment with NSBBs is potentially cost saving compared to no active intervention.

Discussion

Principal findings

On the basis of the best available evidence for the effect of NSBBs and assumptions around managing ascites that have been validated by the committee, this analysis shows that prophylactic treatment with NSBBs is highly likely to be a cost saving option compared with no active intervention. The disparity between the cost of NSBBs and the treatment cost of decompensation to some extent reassures this conclusion.

Strengths of the analysis

The resource use and costs associated with the management of ascites stem from Mattock (2021) economic study. This study is directly applicable to the UK clinical setting where inputs have been validated by clinical experts. The clinical evidence incorporated in this model is based upon two sources of evidence (namely, 1 RCT PREDESCI, 1 IPD meta-analysis). The PREDESCI study is the most up-to-date completed trial which demonstrates the clinical benefits of NSBBs over placebo in patients with compensated cirrhosis and clinically significant portal hypertension (CSPH). Therefore, this threshold analysis has utilised the most relevant and latest evidence to inform the decision making while the resource utilisation is representative of the UK clinical practice.

Weakness of the analysis

This analysis potentially underestimates the cost savings of NSBBs in the prevention of decompensation. Currently, this analysis merely takes into account the cost of managing ascites since the PREDESCI trial suggests that the effectiveness of NSBBs is mainly driven by the reduced incidence of ascites as opposed to other signs of decompensation. It is acknowledged that NSBBs could provide greater savings if there are more conclusive evidence to support its effectiveness in a wider range of decompensated events, such as hepatic encephalopathy.

There are some uncertainties around the treatment effect, which was based on a single study and, whilst statistically significant, had a wide confidence interval which crossed the line of the minimally important different. Besides, the clinical evidence is based on the PREDESCI study, a trial conducted in Spain, and it is unclear whether the evidence is generalisable to the UK setting due to differences in clinical management between the healthcare systems. It is also ambiguous that whether PREDESCI study has exaggerated the clinical effectiveness on the prevention of decompensation given the introduction of newly licensed direct-acting antivirals during the trial. All these uncertainties translate to an uncertainty on the extent of the cost savings of NSBBs.

This analysis does not include the costs associated with selecting or diagnosing people with CSPH. As we understood, measuring hepatic venous pressure gradient (HVPG) to diagnose CSPH is invasive and not routinely implemented across UK clinical centres. Alternatively, some non-invasive methods can be adopted to diagnose CSPH. According to current NICE guidelines, these tests should be done as part of diagnosing cirrhosis or are part of ongoing monitoring to detect progression of disease. Hence, there would be no extra costs or resource use associated with people with CSPH.

Conclusions

Prophylactic treatment with NSBBs seems to be a cost saving option compared with no active intervention. Further research with sound evidence would facilitate us to inform the decision makings with more certainties.

Appendix J – Excluded studies

Effectiveness evidence

Study	Reason for exclusion
Gillespie, S.-L., Hanrahan, T.P., Rockey, D.C. et al. (2023) Review article: controversies surrounding the use of carvedilol and other beta blockers in the management of portal hypertension and cirrhosis. Alimentary pharmacology & therapeutics	- Review article but not a systematic review
Groszmann RJ, Garcia-Tsao G, Bosch J et al. (2005) Beta-blockers to prevent gastroesophageal varices in patients with cirrhosis. The New England journal of medicine 353(21): 2254-2261	- Does not report outcome of interest

Economic evidence

All studies were excluded after title and abstract screening, and none were reviewed at full text.

Appendix K– Research recommendations – full details

K1.1 Research recommendation

What is the clinical and cost effectiveness, and acceptability, of non-selective beta-blockers for the primary prevention of decompensation in people with compensated cirrhosis and signs of clinically significant portal hypertension?

K1.1.1 Why this is important

Data from 1 RCT and 1 IPD meta-analysis indicate that propranolol and carvedilol may significantly reduce decompensation in people with cirrhosis. Decompensation is associated with negative outcomes such as bleeding and death.

K1.1.2 Rationale for research recommendation

Importance to 'patients' or the population	Few interventions are known to delay or prevent decompensation of liver cirrhosis.
Relevance to NICE guidance	Further data would enable a stronger recommendation to be made at future updates of this guideline.
Relevance to the NHS	The cost and resource use associated with decompensated cirrhosis are much higher than for compensated cirrhosis. Delaying or preventing decompensation is likely to be highly cost effective.
National priorities	Medium
Current evidence base	1 RCT on carvedilol and propranolol, 1 IPD meta-analysis of carvedilol
Equality considerations	Many people with cirrhosis develop it as a result of problem alcohol use or injection drug use.

K1.1.3 Modified PICO table

Population	People aged 16 years and older with compensated cirrhosis.
Intervention	Non-selective beta-blockers (NSBBs) - Nadolol, Timolol maleate, Sotalol, Carvedilol, Labetalol, Propranolol.
Comparator	Each other Placebo/no intervention
Outcome	• Decompensation (as defined by the study) • Mortality • Quality of life (using a validated scale) • Liver transplant • Hospitalisation (including length of hospital stay) • Other adverse events
Study design	Randomised controlled trials

Timeframe	Long term
Additional information	None