

Supplementary data 3

Search strategy (beta-blockers studies)

The following databases were searched for the available data up to February 17th, 2022: Embase, Cochrane Library, Medline and Scopus. A search strategy was developed in consultation with a librarian at the University of Alberta. In Medline, the final search strategy included the following heading liver cirrhosis and searched title and keywords using terms (liver cirrhosis) or (Cirrho*). The results from searches in subject heading and titles and keywords were combined using the function of (OR) to generate a collection of articles related to liver cirrhosis (referred as collection A). Hepatic venous pressure gradient was searched with the following heading, title and keywords using terms (hepatic venous pressure gradient) or (hepatic venous pressure gradients) or (HVPG) or (HVPGs) or (HVPG*). The results from searches in subjective heading, title and keywords were combined using the (OR) function to generate a collection of articles related to hepatic venous pressure gradient (referred as collection B). Beta blockers was searched with the following heading, title and keyword using terms (propranolol) or (propranolol) or (carvedilol) or (nadolol) or (beta blocker*) or (adrenergic beta antagonist*) or (beta adrenergic block*). The results from searches in subjective heading, title and keywords were combined using the (OR) function to generate a collection of articles related to beta blocker (referred as collection C). Collection A and collection B and collection C were combined using the (AND) function to generate a collection of articles related to liver cirrhosis and beta blockers and hepatic venous pressure gradient. This collection was also combined with randomized clinical trials only using the (AND) function to generate a collection of randomized clinical trials of liver cirrhosis and beta blocker and hepatic venous pressure gradient. This search strategy was translated to Embase, Cochrane Library and Scopus. Please refer to the individual database below for details of search strategies.

Search Strategy 2 (beta blockers studies)

This systematic review searched for available data to quantify the heterogeneous effect of different NSBBs on portal hypertension in patients with cirrhosis. Articles were screened using the inclusion and exclusion criteria. Additional articles were included after the search was completed.

Search term 1: Liver Cirrhosis/ or cirrho*

Search term 2: HVPG or HVPGs or HVPG* or hepatic venous pressure gradient* or hvpg* or

hepatic venous pressure gradients

Search term 3: propranolol or propanolol or nadolol or carvedilol or beta blocker* or adrenergic beta-antagonist* or beta adrenergic block*

Databases: Embase, Cochrane Library, Medline, and Scopus.

Scopus

(TITLE-ABS-KEY (cirrho*) AND TITLE-ABS-KEY (hvpg OR hvpgs OR (hepatic AND venous AND pressure AND gradient*) OR (portal AND pressure*)) AND TITLE-ABS-KEY (propranolol OR propanolol OR nadolol OR carvedilol OR (beta AND blocker*) OR (adrenergic AND beta-antagonist*) OR (beta AND adrenergic AND block*))) AND TITLE-ABS-KEY ({Clinical-trial} OR {controlled-trial} OR randomi* OR randomly OR (random W/4 (allocat* OR distribut* OR assign*)) OR {placebo} OR {trial} OR {groups} OR {subgroups}) OR TITLE (rct)

Embase

Simplified version

1. Liver Cirrhosis/ or cirrho*
2. (propranolol or propanolol or nadolol or carvedilol or beta blocker* or adrenergic beta-antagonist* or beta adrenergic block*)
3. (HVPG or HVPGs or HVPG* or hepatic venous pressure gradient* or hvpg* or hepatic venous pressure gradients)
4. 1 and 2 and 3
5. RCT was applied to 4

Detailed version:

1. Randomized controlled trial/ or Controlled clinical study/ or randomization/ or intermethod comparison/ or double blind procedure/ or human experiment/
2. (random\$ or placebo or (open adj label) or ((double or single or doubly or singly) adj (blind or blinded or blindly)) or parallel group\$1 or crossover or cross over or ((assign\$ or match or matched or allocation) adj5 (alternate or group\$1 or intervention\$1 or patient\$1 or subject\$1 or participant\$1)) or assigned or allocated or (controlled adj7 (study or design or trial)) or volunteer or volunteers)
3. (compare or compared or comparison or trial)
4. evaluated or evaluate or evaluating or assessed or assess) and (compare or compared

or comparing or comparison)

5. or/1-4
6. (random\$ adj sampl\$ adj7 (cross section\$ or questionnaire\$1 or survey\$ or database\$1)).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.)
7. Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group\$1.ti,ab.)
8. (((case adj control\$) and random\$) not randomi?ed controlled).ti,ab.
9. (Systematic review not (trial or study)).ti.
10. (nonrandom\$ not random\$).ti,ab.
11. Random field\$.ti,ab.
12. (random cluster adj3 sampl\$).ti,ab.
13. (review.ab. and review.pt.) not trial.ti.
14. "we searched".ab. and (review.ti. or review.pt.)
15. update review.ab.
16. (databases adj4 searched).ab.
17. (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset\$1).ti. and animal experiment/
18. Animal experiment/ not (human experiment/ or human/)
19. or/6-18
20. 5 not 19
21. exp Liver Cirrhosis/ or cirrho*.mp.
22. (propranolol or propanolol or nadolol or carvedilol or beta blocker* or adrenergic beta-antagonist* or beta adrenergic block*).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word]
23. (HVPG or HVPGs or HVPG* or hepatic venous pressure gradient* or hvpg* or hepatic venous pressure gradients).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population

supplementary concept word, anatomy supplementary concept word]

24. 21 and 22 and 23

25. 20 and 24

Medline:

detailed version of the search for RCT

1. randomized controlled trial.pt.

2. clinical trial.pt.

3. Randomi?ed.ti,ab.

4. Placebo.ti,ab.

5. Dt.fs.

6. Randomly.ti,ab.

7. Trial.ti,ab.

8. Groups.ti,ab.

9. or/1-8

10. animals/

11. humans/

12. 10 not (10 and 11)

13. 9 not 12

14. exp Liver Cirrhosis/ or cirrho*.mp.

15. (propranolol or propanolol or nadolol or carvedilol or beta blocker* or adrenergic beta-antagonist* or beta adrenergic block*).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word]

16. (HVPG or HVPGs or HVPG* or hepatic venous pressure gradient* or hvpg* or hepatic venous pressure gradients).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word]

17. 14 and 15 and 16

18. 13 and 17

simplified version of the search for RCT

1. exp Liver Cirrhosis/ or cirrho*.mp.
2. (HVPG or HVPGs or hepatic venous pressure gradient* or portal pressure*).mp.
[mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word]
3. (propranolol or propanolol or nadolol or carvedilol or beta blocker* or adrenergic beta-antagonist* or beta adrenergic block*).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word]
4. 1 and 2 and 3
5. Applying RCT to 4

Cochrane Library:

Search from Feb 2022 was not saved in my account.

ID	Search
#1	Liver Cirrhosis or cirrho*:ti,ab,kw AND HVPG or HVPGs or HVPG* or hepatic venous pressure gradient* or hvpg* or hepatic venous pressure gradients:ti,ab,kw AND propranolol or propanolol or nadolol or carvedilol or beta blocker* or adrenergic beta-antagonist* or beta adrenergic block*:ti,ab,kw (Word variations have been searched)

Trials for #1 were exported for selected citation.

Study selection and data extraction

Study selection process was carried out in the Covidence platform. Two independent reviewers (MA and JGA) screened the articles by titles and abstract using the inclusion/exclusion criteria.

Discrepancies were resolved by consensus. Full text reviews and data extraction were completed by two independent reviewers (MA and JGA) and discrepancies were resolved by consensus. Summary of the study selection can be found in the figure 1 below.

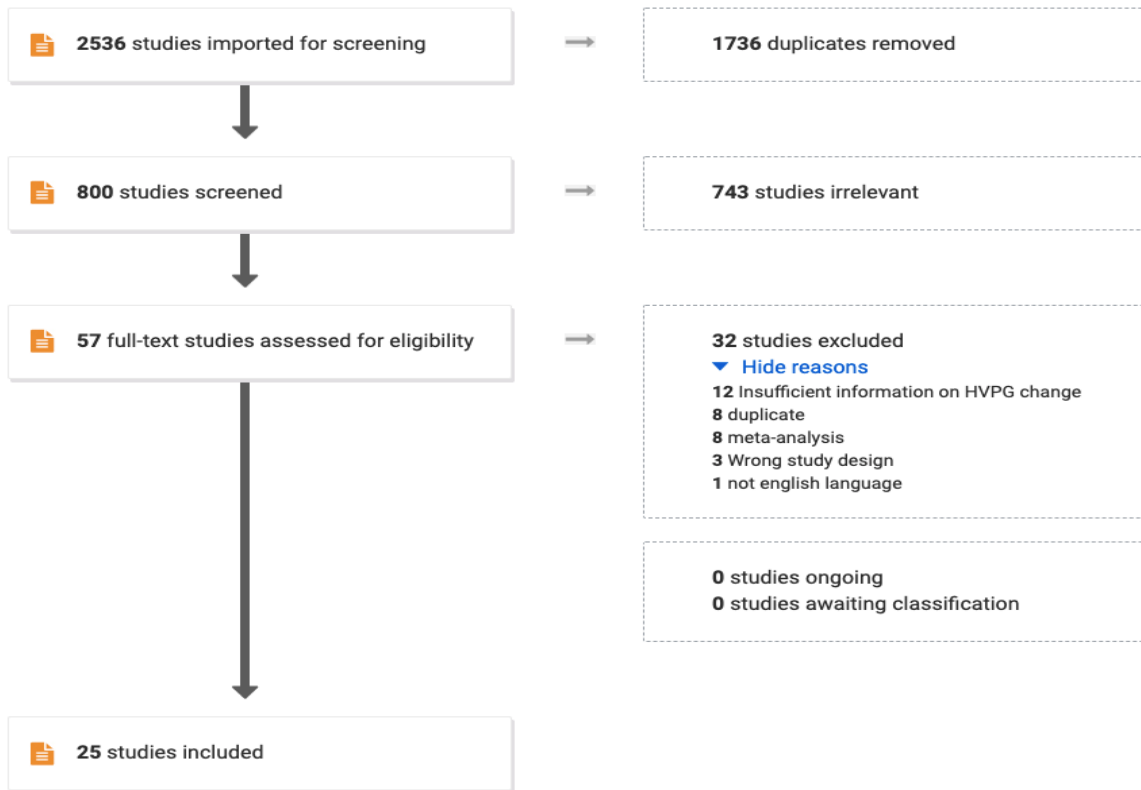


Figure 1: Summary of study selection

Statins studies

We used our previously published systematic search to identify randomized controlled trials comparing the effect of statins with placebo on portal pressure ¹. We updated the systematic search with the same strategy up to July 2022, without identifying additional eligible new studies.

Quality analysis

Table 1 illustrates the quality assessment of each included randomized controlled trial (RCT). The quality assessment was conducted using the Cochrane Risk of Bias Tool, and details of the tool can be found in the reference included².

References:

1. Sung S, Al-Karaghoul M, Kalainy S, Cabrera Garcia L, Abraldes JG. A systematic review on pharmacokinetics, cardiovascular outcomes and safety profiles of statins in cirrhosis. *BMC Gastroenterol* 2021;21(1):120.
2. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011 Oct 18;343:d592