

# 跨領域討論 實證醫學報告

外科部



# 臨床情境

- 李先生54男性，170公分、94公斤體重呈現中年發福體態，雖120公分腰圍但也不改其長時間坐沙發看電視吃個不停。最近經多次測量血壓都超過160/110mmHg；抽血健檢三酸甘油脂340mg/dl，空腹血糖150mg/dl、且健康檢查發現有膽結石。針對以上檢查結果，醫師除了建議生活型態調整(包含飲食控制、運動、減重)以外，立刻開始藥物治療高血壓、高血脂；雖血壓血脂有受到控制，但體重似乎沒什麼進展。他看到一些新研究顯示有些降血糖藥物似乎對減重效果不錯，好像滿適合食慾很好吃不停的他。台灣衛服部核准liraglutide成分的Saxenda膳纖達用於自費體重減輕需求。
- 李先生提出疑問：他的膽結石會因為使用Saxenda膳纖達而增加發作風險嗎？



# 背景資料

## Glucagon-like peptide 1 (GLP-1)

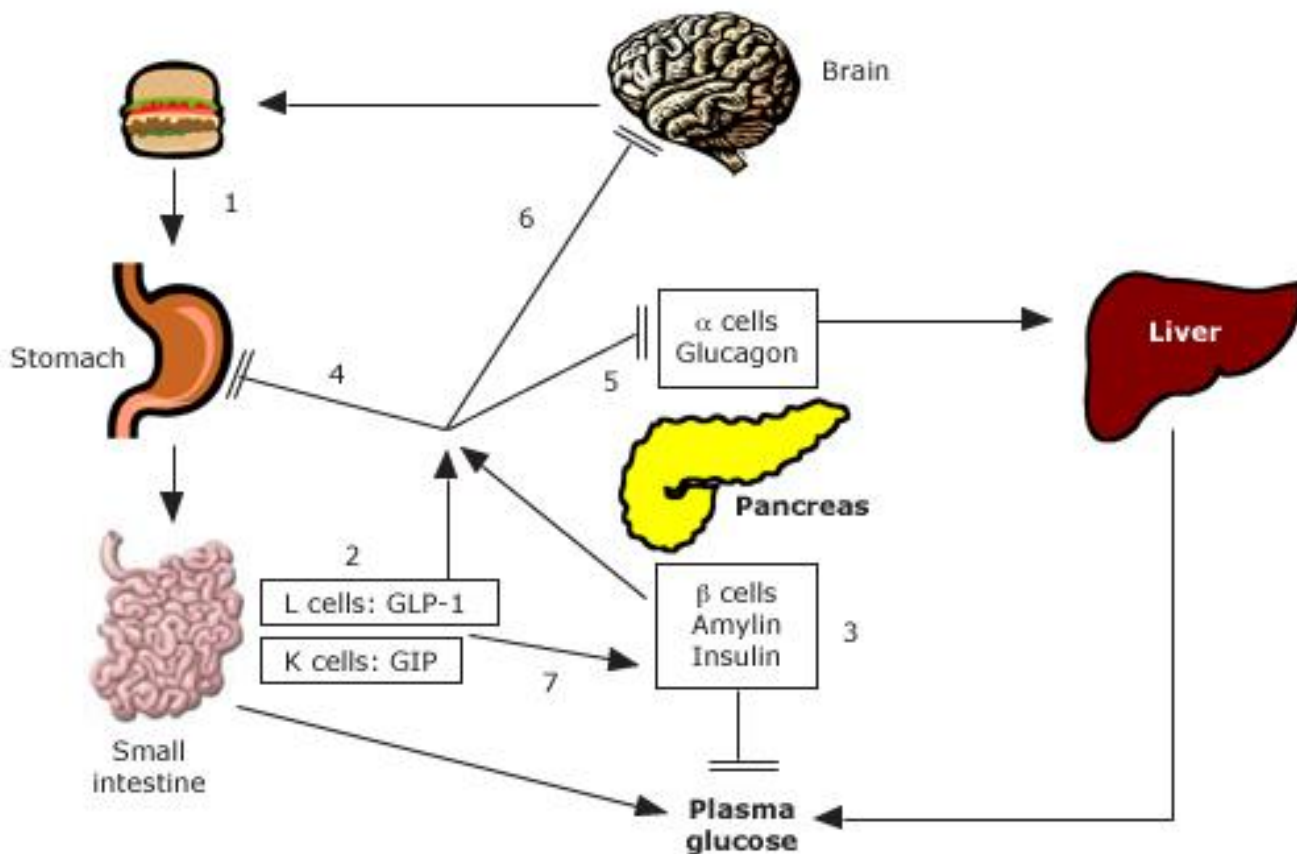
- Produced from the proglucagon gene in L cells of the small intestine
- Main effect by stimulating glucose-dependent insulin release from the pancreatic islets
- GLP-1 receptor expressed in pancreatic beta cells, pancreatic ducts, gastric mucosa, kidney, lung, heart, skin, immune cells, and the hypothalamus





# 背景資料

## Glucagon-like peptide 1 (GLP-1)





## 背景資料

# Glucagon-like peptide 1 (GLP-1)

- Clinical outcomes
  - reduce glycated hemoglobin(1 to 1.5 percentage)
  - modest weight loss (approximately 2 to 3 kg)
  - reducing cardiovascular disease



## 背景資料

# Glucagon-like peptide 1 (GLP-1)

- Adverse effects
  - nausea, vomiting, and diarrhea
  - acute pancreatitis or cholecystitis
  - hypersensitivity reactions
  - risk of hypoglycemia is small





# 臨床問題

體重過重的病人，在以GLP-1類的Liraglutide治療時，會增加膽結石發作風險嗎？

P	I	C	O
Overweight OR Obesity	Liraglutide OR Glucagon-like peptide-1 receptor agonist	Placebo	Gall stone OR Gallbladder disease



這是一個



治療型



診斷型



預後型



傷害型問題



# 檢索策略

先以” P & I”搜尋，再依結果  
調整納入關鍵字和同義字

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綜結 Summaries

精要 Synopses

統整 Syntheses

研究 Studies

Secondary  
database

Primary  
database

THE COCHRANE LIBRARY  
Independent high-quality evidence for health care decision making

PubMed.gov

Embase

The "5S" levels of organisation of evidence  
from healthcare research





### Secondary Database



### Primary Database



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13 results

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選擇「systematic review」的文章

1 result

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選擇「5年內」之文章

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2 results



2 results

Page 1 of 1

Filters applied: Systematic Review. Clear all

- 1 Association of **Glucagon-Like Peptide-1 Receptor Agonist** Use With Risk of **Gallbladder** and Biliary **Diseases**: A Systematic Review and Meta-analysis of Randomized Clinical Trials.

Cite  
Share

He L, Wang J, Ping F, Yang N, Huang J, Li Y, Xu L, Li W, Zhang H.

JAMA Intern Med. 2022 May 1;182(5):513-519. doi: 10.1001/jamainternmed.2022.0338.

PMID: 35344001

IMPORTANCE: **Glucagon-like peptide-1 receptor agonists** (GLP-1 RAs) have been widely recommended for glucose control and cardiovascular risk reduction in patients with type 2 diabetes, and more recently, for weight loss. However, the ...

- 2 Dipeptidyl peptidase-4 inhibitors and **gallbladder** or biliary **disease** in type 2 diabetes: systematic review and pairwise and network meta-analysis of randomised controlled trials.

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He L, Wang J, Ping F, Yang N, Huang J, Li W, Xu L, Zhang H, Li Y.

BMJ. 2022 Jun 28;377:e068882. doi: 10.1136/bmj-2021-068882.

PMID: 35764326 **Free PMC article.**

ELIGIBILITY CRITERIA: Randomised controlled trials of adult patients with type 2 diabetes who received



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1    Association of **Glucagon-Like Peptide-1 Receptor Agonist** Use with Risk of Gallbladder and Biliary Diseases: A Systematic Review and Meta-analysis of Randomized Clinical Trials

He L., Wang J., Ping F., Yang N., Huang J., Li Y., Xu L., Li W., Zhang H.  
*JAMA Internal Medicine* 2022 182:5 (513-519)

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2    Dipeptidyl peptidase-4 inhibitors and gallbladder or biliary disease in type 2 diabetes: systematic review and pairwise and network meta-analysis of randomised controlled trials

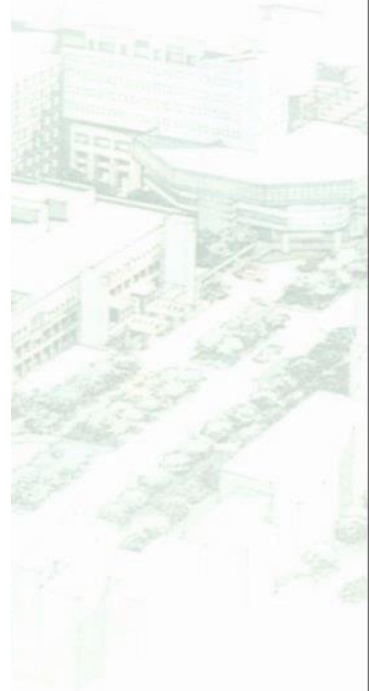
He L., Wang J., Ping F., Yang N., Huang J., Li W., Xu L., Zhang H., Li Y.  
*The BMJ* 2022 Article Number e068882

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# 各資料庫收納結果



三個資料庫(Cochrane、PubMed、Embase)搜尋符合PICO之文章為兩篇：

May,  
2022

**Association of Glucagon-Like Peptide-1 Receptor Agonist Use With Risk of Gallbladder and Biliary Diseases: A Systematic Review and Meta-analysis of Randomized Clinical Trials**

June,  
2022

**Dipeptidyl peptidase-4 inhibitors and gallbladder or biliary disease in type 2 diabetes: systematic review and pairwise and network meta-analysis of randomised controlled trials**



### Secondary Database



### Primary Database



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選擇「systematic review」之文章

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1 result

2 results

2 results

選擇「符合臨床問題」之文章

0 results

**1 result**

**1 result**



# 嚴格評讀



Meta-Analysis > JAMA Intern Med. 2022 May 1;182(5):513-519.

doi: 10.1001/jamainternmed.2022.0338.

## Association of Glucagon-Like Peptide-1 Receptor Agonist Use With Risk of Gallbladder and Biliary Diseases: A Systematic Review and Meta-analysis of Randomized Clinical Trials

Liyun He<sup>1</sup>, Jialu Wang<sup>1</sup>, Fan Ping<sup>1</sup>, Na Yang<sup>1</sup>, Jingyue Huang<sup>1</sup>, Yuxiu Li<sup>1</sup>, Lingling Xu<sup>1</sup>, Wei Li<sup>1</sup>, Huabing Zhang<sup>1</sup>

Affiliations + expand

PMID: 35344001 PMCID: PMC8961394 (available on 2023-03-28)

DOI: 10.1001/jamainternmed.2022.0338

這篇文獻「納入理由」



符合臨床問題



較完整的文獻納入



系統性回顧與統合分析



發表年份最新



有全文可供評讀





# 嚴格評讀

# CASP

Critical Appraisal  
Skills Programme



## CASP Systematic Review Checklist

**CASP Checklist:** 10 questions to help you make sense of a **Systematic Review**

**How to use this appraisal tool:** Three broad issues need to be considered when appraising a systematic review study:

- Are the results of the study valid? (Section A)
- What are the results? (Section B)
- Will the results help locally? (Section C)



## Critical Appraisal Are the results of the review valid?

**Did the review address a clearly focused question?**

此回顧是否問了一個清楚、明確的臨床問題？

**Yes**

Key point

**Question** What is the association of glucagon-like peptide-1 receptor agonist (GLP-1 RAs) use with the risk of gallbladder or biliary diseases?

Abstract

**Objective** To evaluate the association of GLP-1 RA treatment with gallbladder and biliary diseases and to explore risk factors for these associations.



## Critical Appraisal Are the results of the review valid?

**Did the authors look for the right type of papers?**

**Yes**

作者是否收納適當的研究類型？

### Study Selection

Two reviewers (H.L.Y., Z.H.B.) independently searched for randomized clinical trials of GLP-1 RA medications (albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide, or semaglutide) that also reported adverse events of gallbladder or biliary diseases according to predefined inclusion and exclusion criteria available in eTable 1 in the Supplement. Eligible studies were identified and selected by 2 reviewers (H.L.Y., W.J.L.) who screened titles, abstracts, and citations, and evaluated full-text records. Disagreements were resolved through discussions with other team members.





## Critical Appraisal Is it worth continuing?

**Do you think all the important, relevant studies were included?**

**重要、相關的研究是否皆被納入？**

**Yes**

### Data Sources and Searches

The literature search was conducted of MEDLINE (via PubMed), Cochrane Library, EMBASE, and Web of Science, from inception to June 30, 2021, with no language restrictions (details are available in eMethods 1 in the Supplement).

The search was supplemented by screening the reference lists of relevant systematic reviews and manually searching for gray literature on clinical trial registries.



## Critical Appraisal Is it worth continuing?

**Did the review's authors do enough to assess the quality of the included studies?**  
作者是否有評估收納研究的品質？

**Yes**

The risk of bias in each of the studies included was assessed independently by 3 reviewers (H.L.Y., Z.H.B., W.J.L.) using the revised Cochrane risk-of-bias tool for randomized clinical trials.<sup>13</sup> Disagreements were resolved by discussion with other team members.



# Critical Appraisal Is it worth continuing?

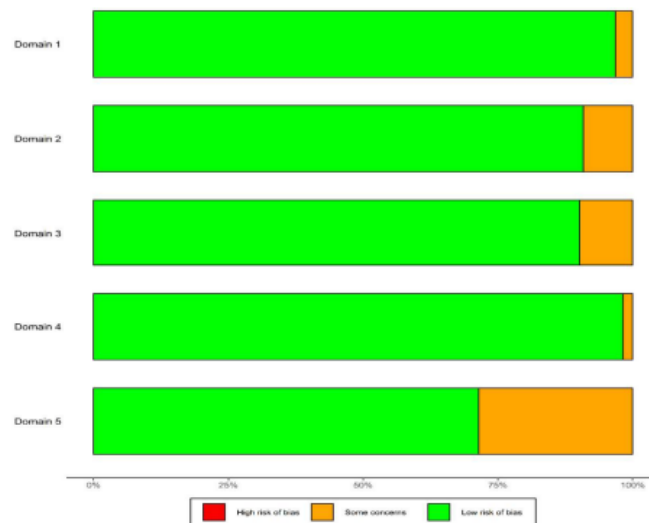
If the results of the review have been combined, was it reasonable to do so?

作者是否有把各個研究的結果合併起來 這樣的合併是合理的嗎？

Yes

eFigure 1. Summary of risks of bias of all included studies

Notes: Domain 1: Risk of bias arising from randomization process Domain 2: Risk of bias due to deviations from intended interventions Domain 3: Risk of bias due to missing outcome data. Domain 4: Risk of bias in outcome measurements. Domain 5: Risk of bias in the selection of reported results.







# Critical Appraisal What are the results?

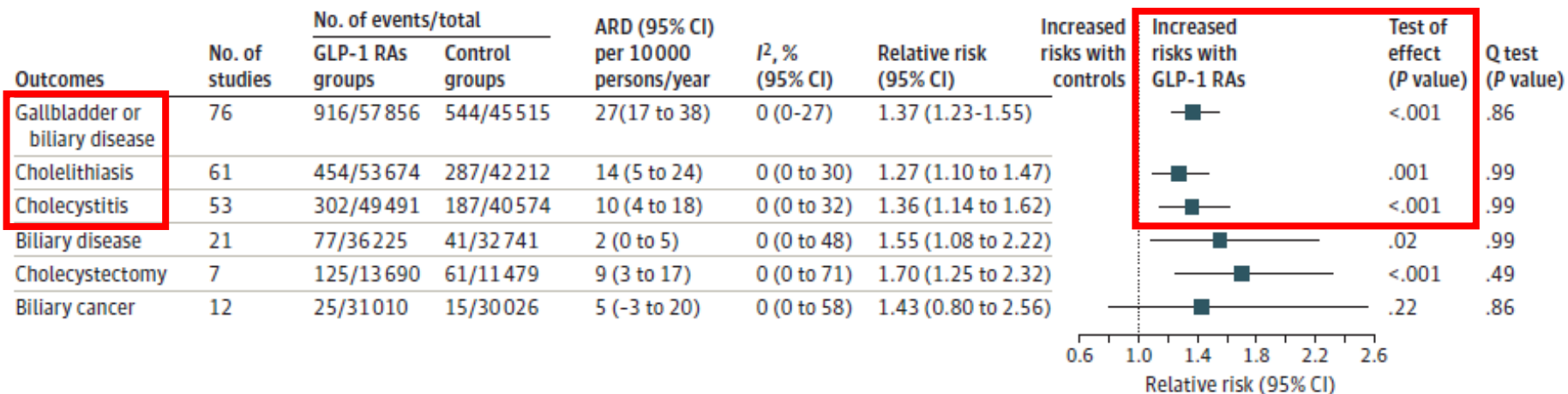
## What are the overall results of the review?

## How precise are the results?

## 這篇回顧呈現了什麼結果？結果精準嗎？

### Gallbladder or biliary disease/ cholelithiasis/ cholecystitis:

Figure 2. Risks of Cholelithiasis, Cholecystitis, and Biliary Diseases in Patients Randomized to GLP-1 RA Treatment Compared With Controls in All Trials



ARD denotes the absolute risk difference and GLP-1 RA, glucagon-like peptide-1 receptor agonist.

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# Critical Appraisal What are the results?

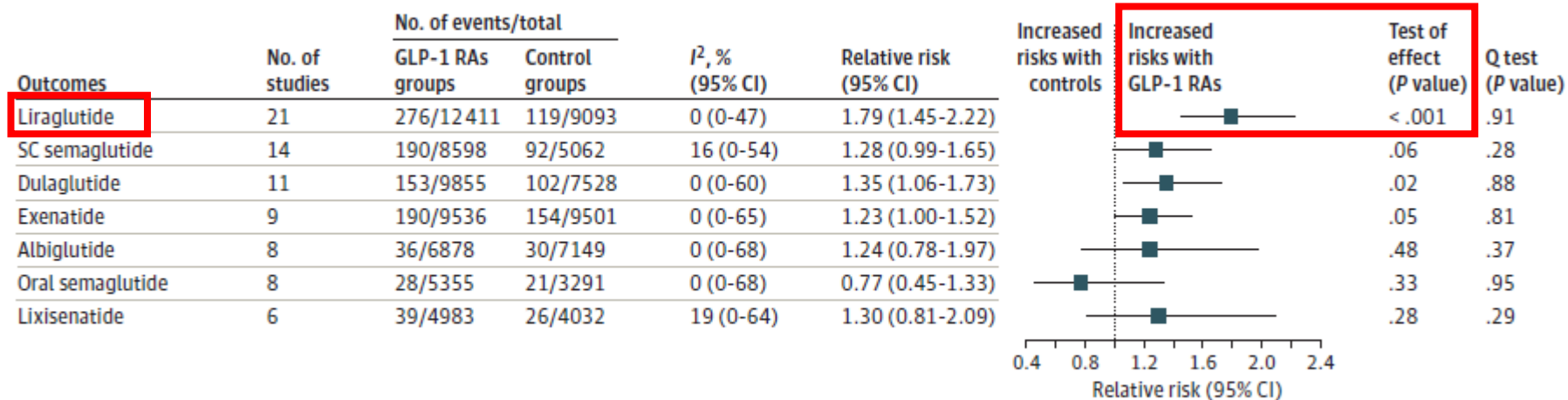
## What are the overall results of the review?

## How precise are the results?

## 這篇回顧呈現了什麼結果？結果精準嗎？

### Liraglutide with risks of gallbladder or biliary disease:

Figure 3. Risks of Gallbladder or Biliary Diseases Associated With Individual GLP-1 RA Drugs



GLP-1 RA indicates glucagon-like peptide-1 receptor agonist; and SC, subcutaneous.

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# Critical Appraisal Will the results help locally?

## Can the results be applied to the local population?

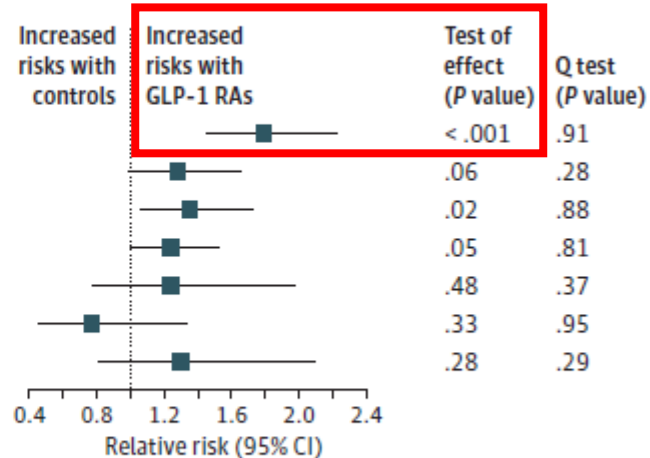
**Yes**

## 此研究是否可應用到你的病患？

### Liraglutide with risks of gallbladder or biliary disease:

Figure 3. Risks of Gallbladder or Biliary Diseases Associated With Individual GLP-1 RA Drugs

Outcomes	No. of studies	No. of events/total		I <sup>2</sup> , % (95% CI)	Relative risk (95% CI)
		GLP-1 RAs groups	Control groups		
Liraglutide	21	276/12411	119/9093	0 (0-47)	1.79 (1.45-2.22)
SC semaglutide	14	190/8598	92/5062	16 (0-54)	1.28 (0.99-1.65)
Dulaglutide	11	153/9855	102/7528	0 (0-60)	1.35 (1.06-1.73)
Exenatide	9	190/9536	154/9501	0 (0-65)	1.23 (1.00-1.52)
Albiglutide	8	36/6878	30/7149	0 (0-68)	1.24 (0.78-1.97)
Oral semaglutide	8	28/5355	21/3291	0 (0-68)	0.77 (0.45-1.33)
Lixisenatide	6	39/4983	26/4032	19 (0-64)	1.30 (0.81-2.09)



GLP-1 RA indicates glucagon-like peptide-1 receptor agonist; and SC, subcutaneous.

**有顯著差異且精確**





# Critical Appraisal Will the results help locally?

## Can the results be applied to the local population?

Yes

## 此研究是否可應用到你的病患？

Table. Factors and Risks of Gallbladder or Biliary Diseases in 76 Randomized Clinical Trials of GLP-1 RA Drug Use

Factor	No. of patients	No. of trials	Relative risks (95% CI)	Heterogeneity		P value for interaction <sup>a</sup>
				I <sup>2</sup> %	P value	
Treatment						
Dose <sup>b</sup>						
High	61 962	54	1.56 (1.36-1.78)	0	.99	.006
Low	16 952	33	0.99 (0.74-1.33)	0	.67	
Duration, wk						
≤26	13 401	24	0.79 (0.48-1.31)	0	.97	.03
>26	90 417	53	1.40 (1.26-1.56)	0	.64	
Indication <sup>c</sup>						
Weight loss	11 282	13	2.29 (1.64-3.18)	0	.85	<.001
T2D/other	92 090	63	1.27 (1.14-1.43)	0	.94	
Baseline BMI <sup>d</sup>						
High	25 275	33	1.49 (1.20-1.84)	0	.50	.36
Low	77 530	42	1.33 (1.18-1.50)	0	.89	
Type of control						
Placebo	80 281	45	1.41 (1.26-1.58)	0	.83	.08
Active comparator	25 433	36	1.03 (0.74-1.44)	0	.93	

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**Critical Appraisal** Will the results help locally?

**Were all important outcomes considered?  
是否所有重要的臨床結果都被考量到？**

**Yes**

**Primary outcome: gallbladder or biliary diseases, including gallbladder disorders and biliary-related events**

**Secondary outcomes: 3 subcategories of gallbladder and biliary diseases, including bile duct obstruction, stenosis, and stone; biliary colic, cyst, and fistula; biliary tract cancer; cholecystectomy, cholecystitis, and cholelithiasis; and cholangitis.**



## **Critical Appraisal** Will the results help locally?

**Are the benefits worth the harms and costs?**

這些好處隨之而來的傷害和花費是否值得？

**Can't  
tell**

文章內沒有討論成本效益。





# Level of Evidence

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
<b>How common is the problem?</b>	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
<b>Is this diagnostic or monitoring test accurate?</b> (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
<b>What will happen if we do not add a therapy?</b> (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
<b>Does this intervention help?</b> (Treatment Benefits)	Systematic review of randomized trials or <i>n-of-1</i> trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
<b>What are the COMMON harms?</b> (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, <i>n-of-1</i> trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
<b>What are the RARE harms?</b> (Treatment Harms)	Systematic review of randomized trials or <i>n-of-1</i> trial	Randomized trial or (exceptionally) observational study with dramatic effect			
<b>Is this (early detection) test worthwhile?</b> (Screening)	Systematic review of randomized trials	Randomized trial	Non-randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

\* Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.

\*\* As always, a systematic review is generally better than an individual study.

此問題為治療性問題，我們評讀了一篇Systemic review and Meta-analysis，故屬於level 1的證據等級



CEBM





## 臨床回覆

- 李先生您好，經過我們團隊縝密的實證搜尋後，根據目前研究結果顯示，在肥胖之患者，長期使用並高劑量Saxena膳纖達，和未使用之病患相比，在**膽道疾病**上似乎有**增加**的趨勢。
- 因此依您對此藥物時，建議您持續門診追蹤膽結石之變化，並在日常生活中觀察自身症狀。



- 經由實證醫學作為輔佐，討論出病人治療偏好，評估利弊及費用資源，共享治療決策





Thanks for your listening

