



三軍總醫院 *Tri-Service General Hospital*



E*vidence*-**B***ased* **M***edicine*

實證醫學

Medical Center

High-Quality Medical Service





臨床場景

Clinical Scenario

全三總

全

照護

Wholehearted
Holistic Care

77歲的李奶奶，有風濕性關節炎、胃潰瘍病史，去年因為急性冠心症接受心導管介入，放置兩支塗藥支架，術後開始使用雙重抗血小板藥品治療，心臟科醫師知道李奶奶有胃潰瘍病史，因此建議使用質子幫浦阻斷劑預防腸胃道出血。

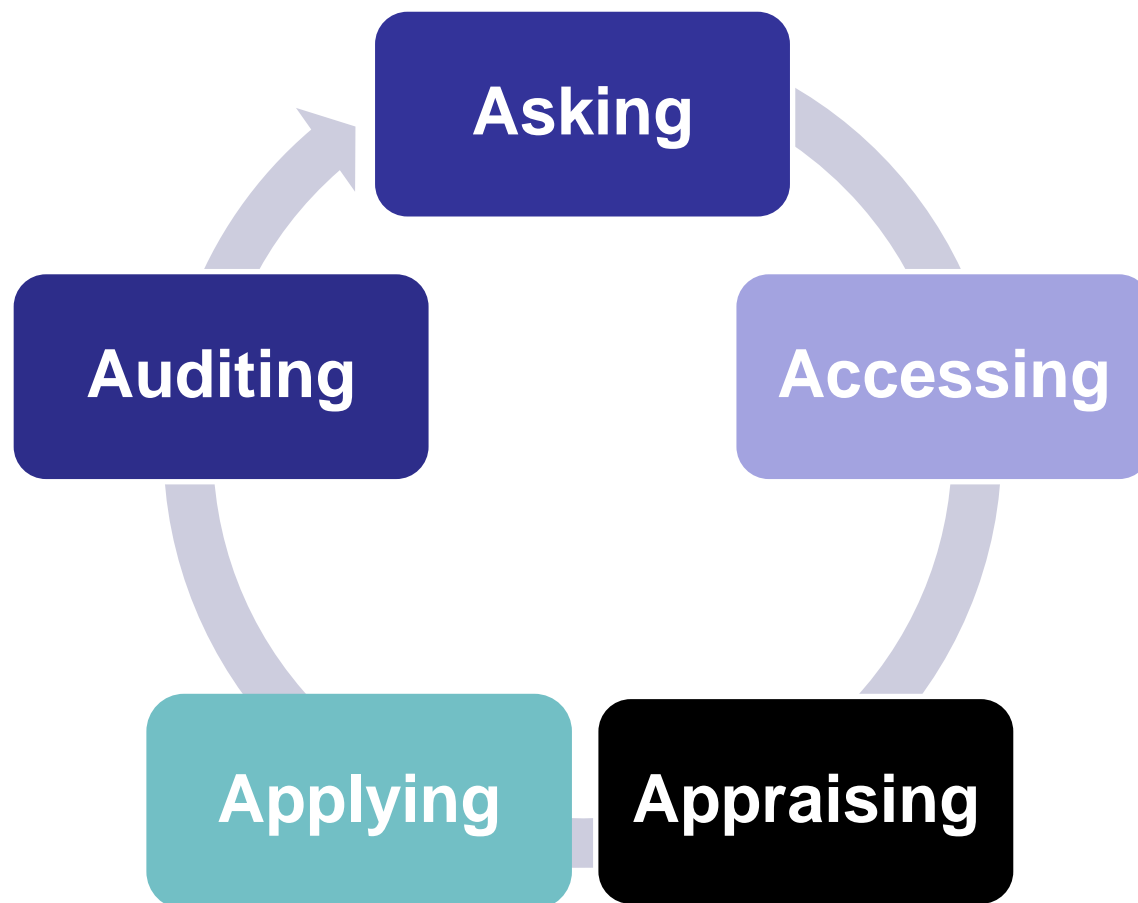
一次回診時，李奶奶問到長期使用質子幫浦阻斷劑可能的副作用，她聽朋友說，新聞上說這些藥可能增加骨質疏鬆症風險，甚至是骨折，請問這是真的嗎？會增加多少風險？

另外，李奶奶已經使用雙重抗血小板藥品超過一年了，還需要繼續吃下去嗎？繼續吃下去的好處有大於風險嗎？





5-Step Evidence-Based Medicine Process (5A)





Step 1. Asking answerable clinical question

病患主要問題：

有胃潰瘍病史的年長女性，接受心導管合併塗藥支架置放後，長期使用氫離子幫浦阻斷劑是否會增加骨質疏鬆症風險？





背景資訊

Background

Knowledge



1. **Gastric ulcer** occurring in the stomach proximal to the distal antrum and prepyloric region. It occurs mostly by *H. pylori* infection and the ingestion of **NSAIDs** (eg. aspirin).
2. **PPIs are effective** for treatment of **all acid-related disorders**. They are effective in treating and preventing NSAIDs and *H. pylori* infection related peptic ulcer.
3. The 3 main concerns of long-term **safety** of PPIs include, prolonged hypochlorhydria, hypergastrinemia, and gastric atrophy.
4. **Hypochlorhydria** is of concern since it may predispose to **infections** and **malabsorption**





臨床問題

Asking

提出可以回答的臨床問題



Key Word



Synonym 1

PICO 1

P	77 y/o female with gastric ulcer	Old age with peptic ulcer
I	Proton pump inhibitor	PPI
C	Without Proton pump inhibitor	Without PPI
O	Osteoporosis	Bone fracture



這是一個 治療型 診斷型 預後型 傷害型問題



臨床問題

Asking

提出可以回答的臨床問題



Key Word



Synonym 1

PICO 2

P

77 y/o female with CAD
post stenting

Patient with
coronary stent

I

Aspirin and clopidogrel

Dual anti-platelet

C

Without
aspirin and clopidogrel

Without dual
anti-platelet

O

recurrence of
coronary disease

Coronary artery
re-stenosis



這是一個 治療型 診斷型 預後型 傷害型問題





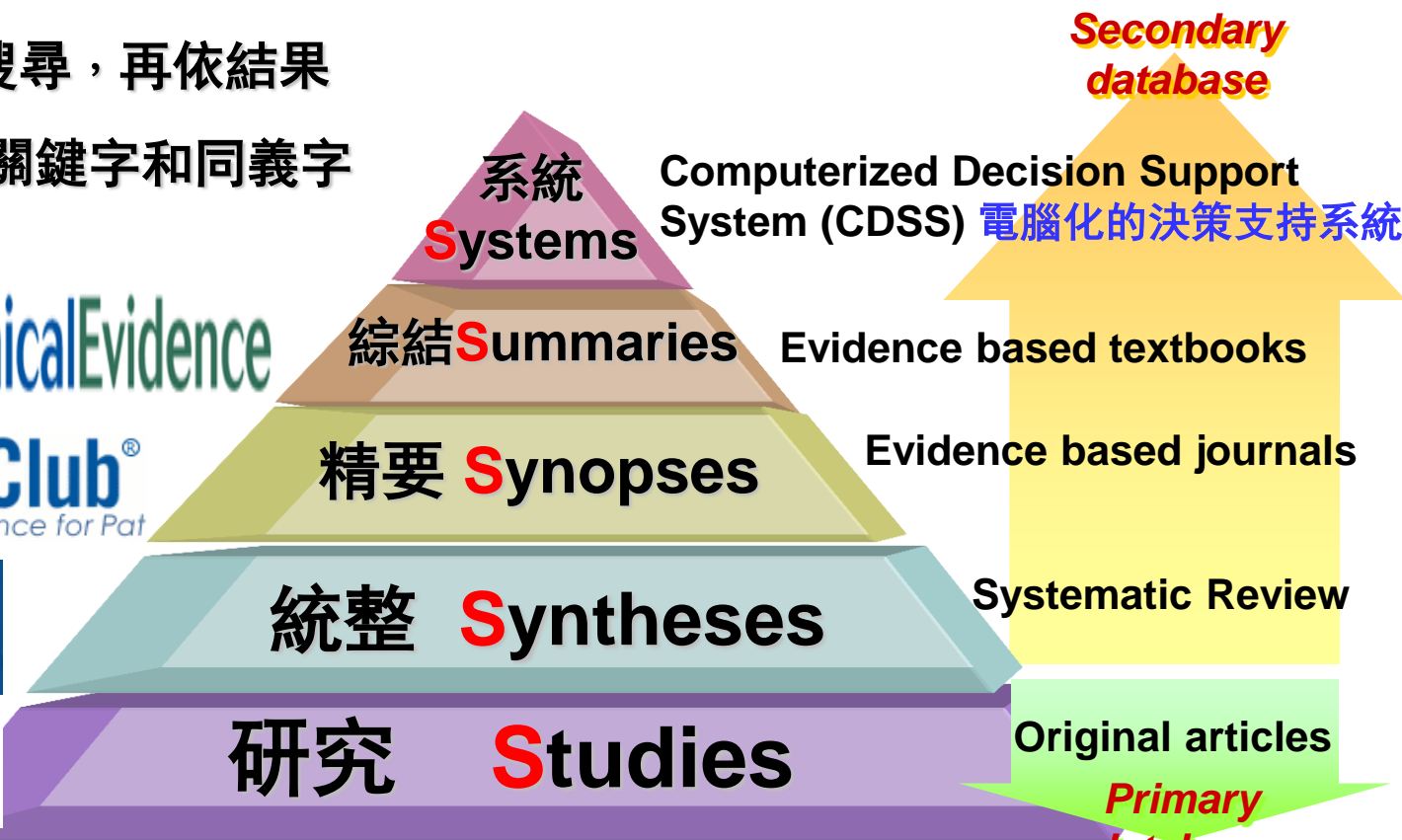
Step 2. Tracking down the best evidence



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



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

Brian Haynes, R Evid Based Med 2006;11:162-164





檢索策略

我們的「檢索策略」為「同步搜尋，依序評讀」

搜尋符合臨床問題的
系統性綜論 (SR)

尋獲

嚴格評讀
↓
做出結論並
提供建議

未尋獲

搜尋符合臨床問題的
隨機分派研究 (RCT)

尋獲

嚴格評讀
↓
做出結論並
提供建議

未尋獲

搜尋符合臨床問題的
非隨機分派研究
↓

*如果這項治療於人種間可能存在顯著差異，我們進一步搜尋亞洲文獻

檢索



Secondary Database



Proton pump inhibitor and fracture [Contents](#) | [Patient Education](#)

Search Results for "Proton pump inhibitor and fracture"

- All
- Adult
- Pediatric
- Patient
- Graphics

Overview and comparison of the proton pump inhibitors for the treatment of acid-related disorders

... risk of **fractures** associated with PPI use . The 11 studies included 1,084,560 patients with 62,210 PPI users, 71,339 patients with hip **fractures**, 161,179 patients with any-site **fractures**,... percent for **lansoprazole** at two and four weeks, respectively, while the corresponding figures for the H2-antagonists were 40 and 75 percent. **Pantoprazole** and **rabeprazole** have also demonstrated...

- [Hip fracture and calcium malabsorption](#)
- [Summary and recommendations](#)

Drugs that affect bone metabolism

... in the risk of **fracture**, whereas other drugs appear to improve BMD and decrease the risk of **fracture**. In observational studies, commonly used medications, such as **proton pump inhibitors** (PPIs), antidepressants ...

- [Proton pump inhibitors](#)
- [Summary](#)

[Omeprazole: Pediatric drug information](#)

[Pantoprazole: Drug information](#)

[Lansoprazole: Pediatric drug information](#)

1篇符合PICO





Conclusion

Secondary Database

The more important clinical question is whether PPIs affect fracture risk. In meta-analyses of case-control and cohort studies, the risk of hip, spine, and any-site fractures was modestly but significantly increased in patients taking PPIs (RRs 1.30, 1.56, and 1.16, respectively) [55-58]. In some studies [57,59], but not another [60], the risk was highest in long-term users of high-dose PPI therapy. In one analysis, the risk was confined to patients with at least one other risk factor for hip fracture [61], and in another, to current or former smokers [57].

The largest prospective cohort study (the WHI Study) did not find an association between PPI use and hip fracture (HR 1.00, 95% CI 0.71-1.40) [62]. However, PPI use was associated with an increased risk of clinical vertebral (HR 1.47, 95% CI 1.18-1.82), wrist, and total fractures. There was a smaller number of hip fracture events compared with wrist, clinical spine, or total fractures. The lower number of events, combined with the fact that PPI users were more likely than nonusers to be taking hormone therapy, may have reduced the ability of the study to detect an increased risk of hip fracture in PPI users.





THE COCHRANE LIBRARY

Independent high-quality evidence for health care decision making

from The Cochrane Collaboration




Cochrane Database of Systematic Reviews : Issue 2 of 12, February 2017

Issue updated daily throughout month

There is 1 result from 9737 records for your search on 'Proton pump inhibitor and fracture in Title, Abstract, Keywords in Cochran

Sort by

Select all | [Export all](#) | [Export selected](#)

-  Medical versus surgical treatment for refractory or recurrent peptic ulcer
Kurinchi Selvan Gurusamy and Elena Pallari
Online Publication Date: March 2016

[Review](#)

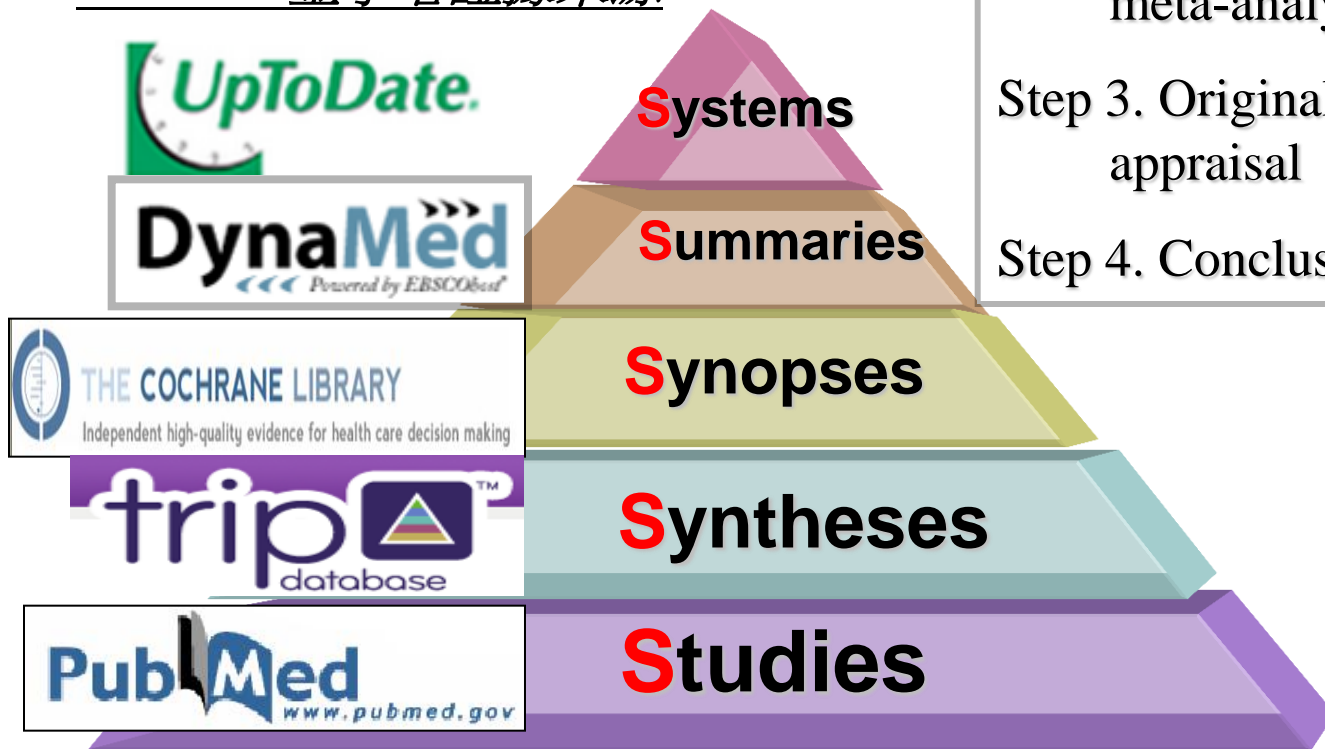
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0篇符合PICO



檢索策略

‘5S” 金字塔證據來源



Step 1. Background review from evidence base journal

Step 2. Systemic review articles and meta-analysis

Step 3. Original articles with critical appraisal

Step 4. Conclusion

Secondary database

Primary database

PubMed Proton pump inhibitor and fracture

Create RSS Create alert Advanced

Format: Summary Sort by: Most Recent

Send to

Search results

Items: 1 to 20 of 26

<< First < Prev Page 1 of 2 Next > Last >>

Filters activated: Systematic Reviews. [Clear all](#) to show 242 items.

[Proton-pump inhibitors adverse effects: a review of the evidence and position statement by the](#)

1. [Sociedad Española de Patología Digestiva](#)

de la Coba Ortiz C, Argüelles Arias F, Martín de Argila de Prados C, Júdez Gutiérrez J, Linares Rodríguez A, Ortega Alonso A, Rodríguez de Santiago E, Rodríguez-Téllez M, Vera Mendoza MI, Aguilera Castro L, Álvarez Sánchez Á, Andrade Bellido RJ, Bao Pérez F, Castro Fernández M, Giganto Tomé F.

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Rev Med Suisse. 2015 Sep 9;11(485):1665-71. Review. French.

PMID: 26540997

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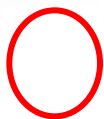
Osteoporos Int. 2016 Jan;27(1):339-47.

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共26篇，符合PICO: 11篇





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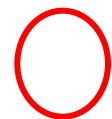
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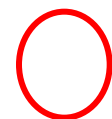
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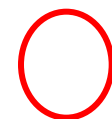
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搜尋到的文章



資料庫	文章總數	符合 PICO
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Cochrane Library	1	0
PubMed.gov	26	11





Critical Appraisal



Osteoporos Int (2016) 27:339–347

DOI 10.1007/s00198-015-3365-x

ORIGINAL ARTICLE

Proton-pump inhibitors and risk of fractures: an update meta-analysis

B. Zhou¹ · Y. Huang¹ · H. Li¹ · W. Sun¹ · J. Liu¹

這篇文獻的「納入理由」

- 臨床適用性高
- 發表年份較新
- 有全文可供評讀





What question (PICO) did the systematic review address?	
What is best?	Where do I find the information?
The <u>main question being addressed should be clearly stated</u> . The exposure, such as a therapy or diagnostic test, and the outcome(s) of interest will often be expressed in terms of a simple relationship.	The Title, Abstract or final paragraph of the Introduction should clearly state the question. If you still cannot ascertain what the focused question is after reading these sections, search for another paper!
This paper: Yes <input type="checkbox"/> No <input type="checkbox"/> Unclear <input type="checkbox"/>	
Comment:	





Proton-pump inhibitors and risk of fractures: an update meta-analysis

Subsequently, several observational including prospective studies have been performed regarding the association of PPI use and fracture risk. Large numbers of incident cases may enhance the statistical power of meta-analysis to assess the relationship between exposure and outcome risk. Therefore, we undertook this update meta-analysis to further clarify the association between PPI use and fracture risk.





F - Is it unlikely that important, relevant studies were missed? ↻	
What is best? ↻	Where do I find the information? ↻
The starting point for comprehensive search for all relevant studies is the major bibliographic databases (e.g., Medline, Cochrane, EMBASE, <u>etc</u>) but should also include a search of reference lists from relevant studies, and contact with experts, particularly to inquire about unpublished studies. The search should not be limited to English language only. The search strategy should include both MESH terms and text words. ↻	The Methods section should describe the search strategy, including the terms used, in some detail. The Results section will outline the number of titles and abstracts reviewed, the number of full-text studies retrieved, and the number of studies excluded together with the reasons for exclusion. This information may be presented in a figure or flow chart. ↻
This paper: Yes <input type="checkbox"/> No <input type="checkbox"/> Unclear <input type="checkbox"/> ↻	
Comment: ↻	





Search strategy



We performed a systematic literature search to February 2015 in PubMed without restrictions using the broad free-text and indexing search terms: proton pump inhibitor and fracture. Moreover, we also hand-searched reference lists from retrieved articles, reviews, and meta-analysis papers to identify additional relevant studies. This meta-analysis we conducted





A - Were the criteria used to select articles for inclusion appropriate?	
What is best?	Where do I find the information?
The inclusion or exclusion of studies in a systematic review should be clearly defined a priori. The eligibility criteria used should specify the patients, interventions or exposures and outcomes of interest. In many cases the type of study design will also be a key component of the eligibility criteria.	The Methods section should describe in detail the inclusion and exclusion criteria. Normally, this will include the study design.
This paper: Yes <input type="checkbox"/> No <input type="checkbox"/> Unclear <input type="checkbox"/>	
Comment:	



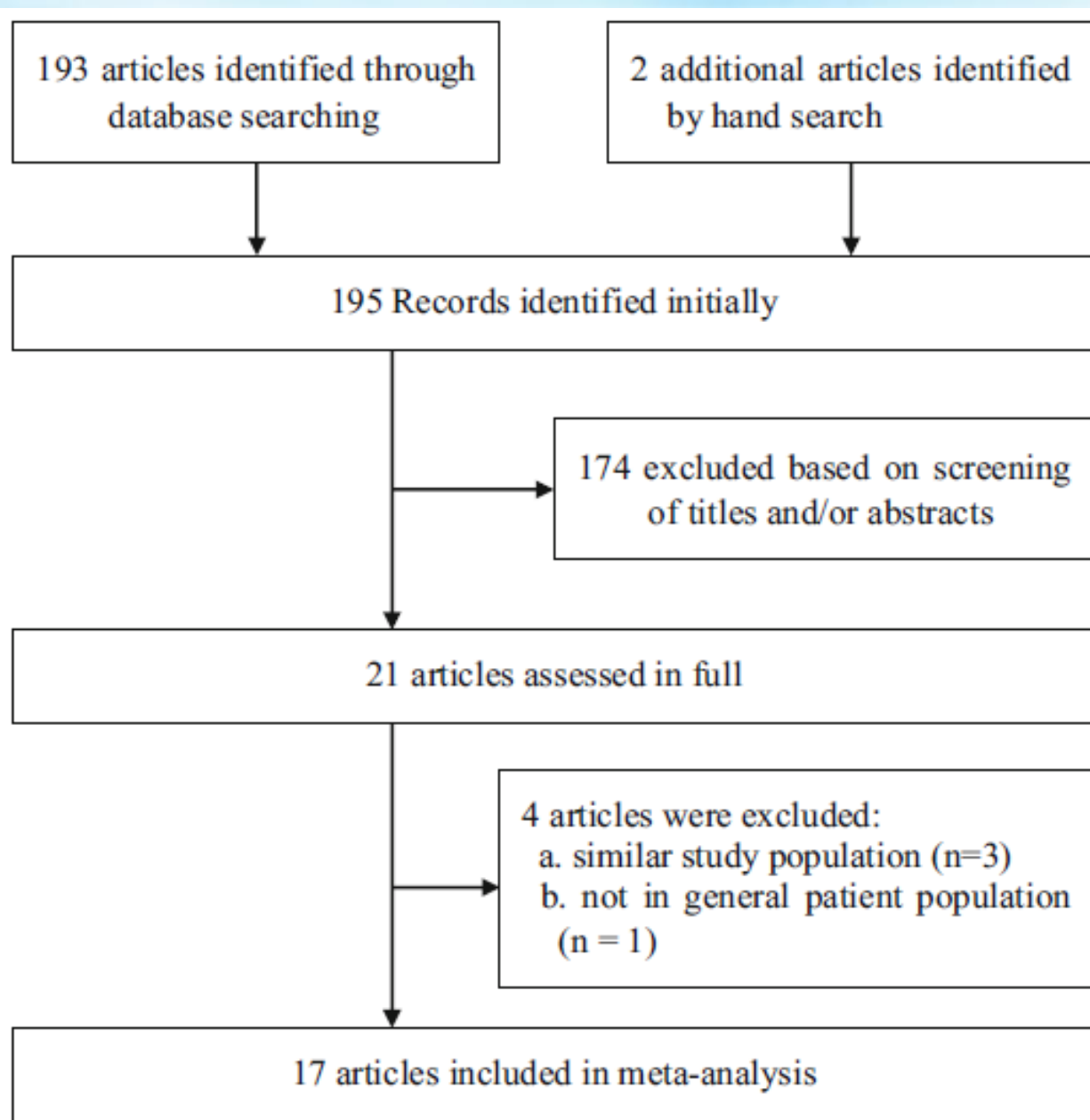


Eligibility criteria



- Studies were included in our meta-analysis if they met the following criteria:
 - (1) The study had a **cohort** and **case control** design,
 - (2) The exposure of interest was PPI use
 - (3) The outcome of interest was fracture
 - (4) The relative risk (RR) estimates (approximated by the odds ratio [OR] estimates for case-control studies) with corresponding 95 % confidence interval (CI) were provided.







A - Were the included studies sufficiently valid for the type of question asked?	
What is best?	Where do I find the information?
The article should describe how the quality of each study was assessed using predetermined quality criteria appropriate to the type of clinical question (e.g., randomization, blinding and completeness of follow-up)	The Methods section should describe the assessment of quality and the criteria used. The Results section should provide information on the quality of the individual studies.
This paper: Yes <input type="checkbox"/> No <input type="checkbox"/> Unclear <input type="checkbox"/>	
Comment:	





Table 2 Methodological quality of included cohort studies and case-control studies based on the Newcastle-Ottawa Scale

Cohort studies	Selection Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome of interest was not present at start of study	Comparability control for important factor or additional factor	Outcome Assessment of outcome	Follow-up long enough for outcomes to occur ^a	Adequacy of follow-up of cohort	Total score
Yu, 2008 [19]	*b	*	*	*	**	*	*		8
Roux, 2009 [20]	*	*		*	**	*	*	*	8
Gray, 2010 [22]	*	*		*	**	*	*	*	8
Khalili, 2012 [25]		*		*	**		*	*	6
Fraser, 2013 [26]	*	*	*	*	**	*	*	*	9
Moberg, 2014 [28]	*	*		*	**	*	*		7
Lewis, 2014 [30]	*	*		*	**		*		6
Ding, 2014 [31]	*	*		*	**		*	*	7
Case-control studies	Adequate definition of cases	Representativeness of cases	Selection of controls	Definition of controls	Comparability control for important factor or additional factor	Exposure Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-response rate	Total score
Yang, 2006 [16]		*	*	*	**		*		6
Vestergaard, 2006 [17]		*	*	*	**		*		6
Targownik, 2008 [18]	*	*	*	*	**		*		7
Corley, 2010 [21]	*	*	*	*	**		*		7
Chiu, 2010 [23]		*	*	*	**		*		6
Pouwels, 2011 [24]		*	*	*	**		*		6
Reyes, 2013 [27]		*	*	*	**		*		6
Soriano, 2014 [29]	*	*	*	*	**		*		7
Adams, 2014 [32]	*	*	*	*	**		*		7

- The quality of studies was assessed using the **nine-star Newcastle-Ottawa scale (NOS)**. The NOS is a quality assessment tool for non-randomized study. This scale includes major three perspectives of evaluation: selection (0–4 stars), comparability (0–2 stars), and exposure between the case group and control group (0–3 stars). A total score of 3 or less was considered poor, 4–6 was considered moderate, and 7–9 was deemed high quality.





■ T - Were the results similar from study to study? ↴

What is best? ↴	Where do I find the information? ↴
Ideally, the results of the different studies should be similar or homogeneous. If heterogeneity exists the authors may estimate whether the differences are significant (chi-square test). Possible reasons for the heterogeneity should be explored. ↴	The Results section should state whether the results are heterogeneous and discuss possible reasons. The forest plot should show the results of the chi-square test for heterogeneity and if discuss reasons for heterogeneity, if present. ↴
This paper: Yes <input type="checkbox"/> No <input type="checkbox"/> Unclear <input type="checkbox"/> ↴ Comment: ↴	





Possible reasons for the heterogeneity

To explore the heterogeneity among studies of PPI use and hip fracture risk, we performed stratified analyses.

After **limiting the meta-analysis to cohort studies**, a moderate increase in hip fracture risk was still found without evidence of study heterogeneity [RR=1.24, 95 % CI 1.06–1.45; p=0.263, I²=22.7 %]



**Table 3** Summary risk estimates

Stratification group	References	RR (95 % CI)		Heterogeneity test		
				<i>Q</i>	<i>P</i> value	<i>I</i> ² (%) ^a
Hip	[16–19, 21–27, 29, 31, 32]	1.26	1.16 to 1.36	49.85	<0.001	71.9
Geographic region						
Europe	[16, 17, 24, 27, 29]	1.28	1.11 to 1.47	26.30	<0.001	84.8
USA	[19, 21, 22, 25, 31, 32]	1.21	1.10 to 1.34	13.03	0.043	53.9
Other	[18, 23, 26]	1.54	0.95 to 2.51	9.98	0.007	80.0
Study type						
Cohort	[19, 22, 25, 26, 31]	1.24	1.06 to 1.45	6.47	0.263	22.7
Case-control	[16–18, 21, 23, 24, 27, 29, 32]	1.27	1.15 to 1.39	43.22	<0.001	81.5
Study quality						
<7	[16, 17, 23–25, 27]	1.39	1.26 to 1.54	10.08	0.073	50.4
≥7	[18, 19, 21, 22, 26, 29, 31, 32]	1.16	1.06 to 1.27	19.35	0.013	58.7
Adjust for calcium intake						
No	[17, 18, 21, 23, 24, 26, 27, 31, 32]	1.28	1.17 to 1.41	24.32	0.002	67.1
Yes	[16, 19, 22, 25, 29]	1.20	1.01 to 1.41	24.37	<0.001	79.5
Sex						
Male	[19, 29, 32]	1.11	1.04 to 1.19	1.84	0.399	0
Female	[19, 22, 25, 29]	1.14	0.98 to 1.33	6.66	0.084	54.9
Duration of PPI use						
<1 year	[17, 21–25, 29, 32]	1.25	1.14 to 1.37	18.03	0.012	61.2
>1 year	[16–18, 21–25, 29, 32]	1.27	1.16 to 1.38	34.65	<0.001	74.0
Any site	[17–20, 22, 26, 28, 30, 31]	1.33	1.15 to 1.54	66.07	<0.001	86.4
Spine	[17, 20, 22, 31]	1.58	1.38 to 1.82	2.38	0.498	0





What were the results? ↴

How are the results presented? ↴

A systematic review provides a summary of the data from the results of a number of individual studies. If the results of the individual studies are similar, a statistical method (called meta-analysis) is used to combine the results from the individual studies and an overall summary estimate is calculated. The meta-analysis gives weighted values to each of the individual studies according to their size. The individual results of the studies need to be expressed in a standard way, such as relative risk, odds ratio or mean difference between the groups. Results are traditionally displayed in a figure, like the one below, called a **forest plot**. ↴



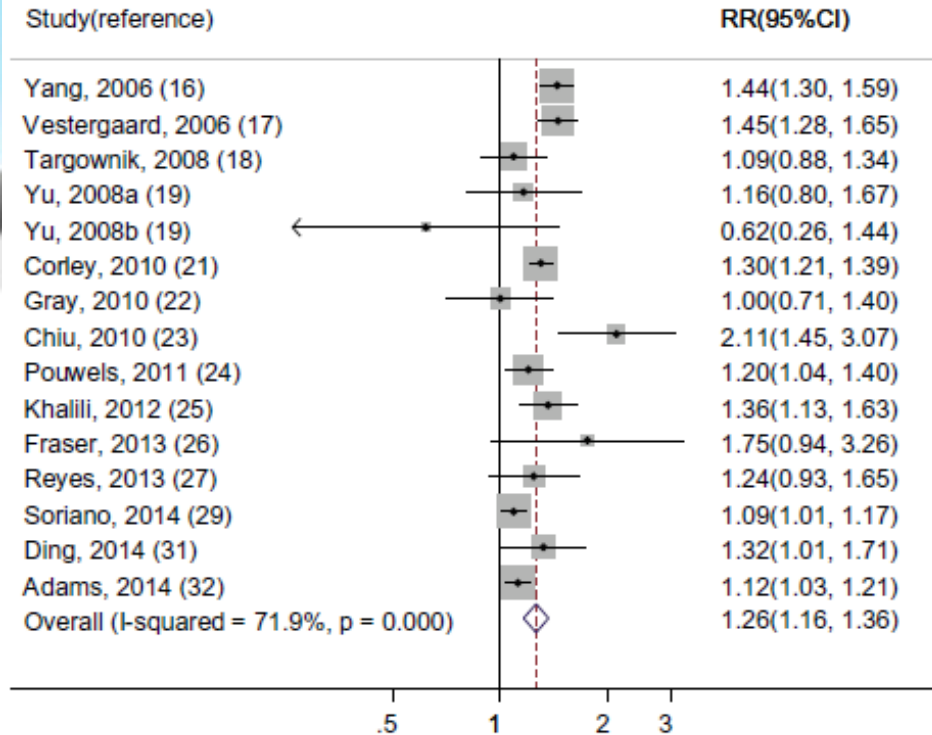


Fig. 2 Pooled risk estimate of hip fracture associated with PPI use.

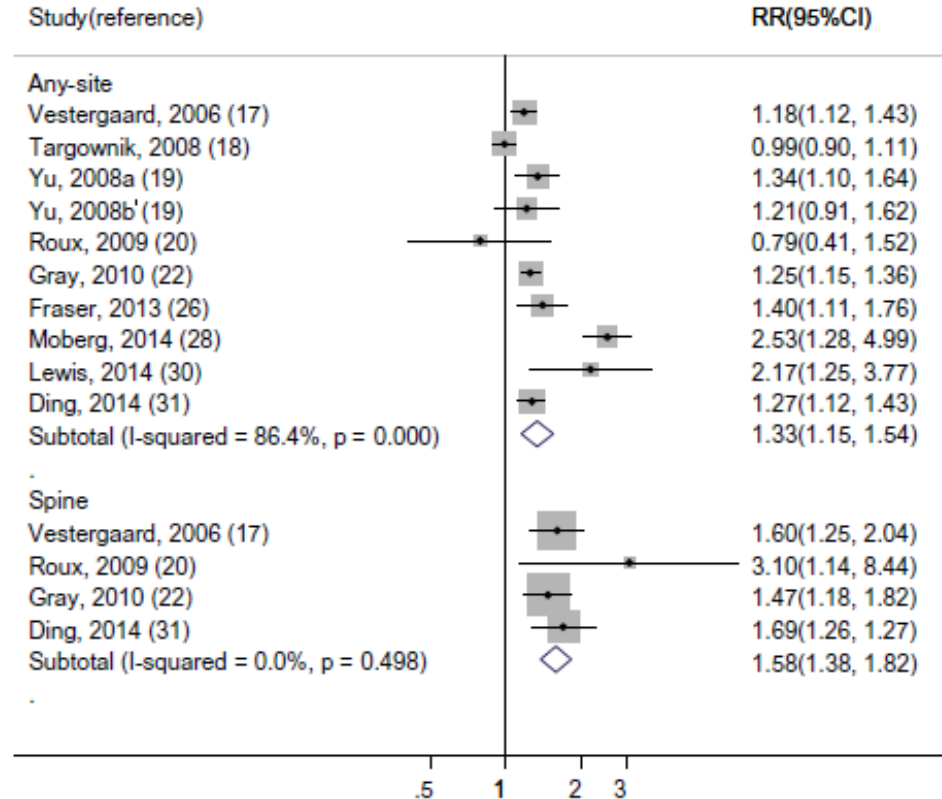


Fig. 3 Pooled risk estimate of spine and all-site fracture associated with PPI use. *Squares* indicate study-specific risk estimates (the size of the

This updated meta-analysis of observational studies showed that PPI use could modestly increase the risk of hip, spine, and any-site fracture.

Oxford center 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)
How common is the problem?	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
Is this diagnostic or monitoring test accurate? (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
What will happen if we do not add a therapy? (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
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or <i>n</i> -of-1 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
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, <i>n</i> -of-1 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
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or <i>n</i> -of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non-randomized controlled cohort/follow-up study**		



Level I



臨床回覆

- 李奶奶您好，根據您的疑問，長期使用氫離子幫浦阻斷劑可能造成骨質疏鬆及骨折的風險；經過實證醫學方法搜尋統整國內外最新的資料庫及文獻，目前證據顯示出該藥物**會增加**骨質疏鬆及骨折的危險性。
- 至於會**增加**多少，對於身體每個部位的骨折風險各不相同，和個人身體狀況也有相關，普遍來說是多了**至少2成**的風險性。以上是相關的文獻考證結果，提供給您參考。





THANK YOU FOR YOUR ATTENTION!

