106 EBM競賽

Feb 16th, 2017

江永貞
蔡育倫
張家瑜

Clinical Scenario

77歲的林奶奶，有風濕性關節炎，胃潰瘍病史，去年因急性冠心症接受心導管介入，放置兩隻塗藥支架，術後開始使用抗血小板藥品治療，心臟科醫師知道林奶奶有胃潰瘍病史，因此建議使用PPI預防腸胃道出血。

病人考量的問題

1.長期使用質子幫浦阻斷劑(PPI)可能增加骨質疏鬆風險，甚至骨折，這是真的嗎? 會增加多少風險?

2.已使用雙抗血小板藥品超過一年，還需要繼續吃下去嗎?

THE EBM PROCESS :

STEP 1 :

Ask a clinical question in PICO format

PICO-1：Key words(Mesh Term)and Synonym

Key search term				
PICO	**Key words**	**Synonyms**	**Mesh terms**	
Patient/Problem	Old women	**Postmenopausal women/ use anti-platelet drug**	Old women	
Intervention	Use Proton pump inhibitor (PPI)		Use Proton pump inhibitor (PPI)	
Compare	Don't use PPI		Don't use PPI	
Outcome	**fracture**		**fracture**	
Filter & limits	2012-2017 有全文 英文、中文 SR-> RCT-> cohort study			

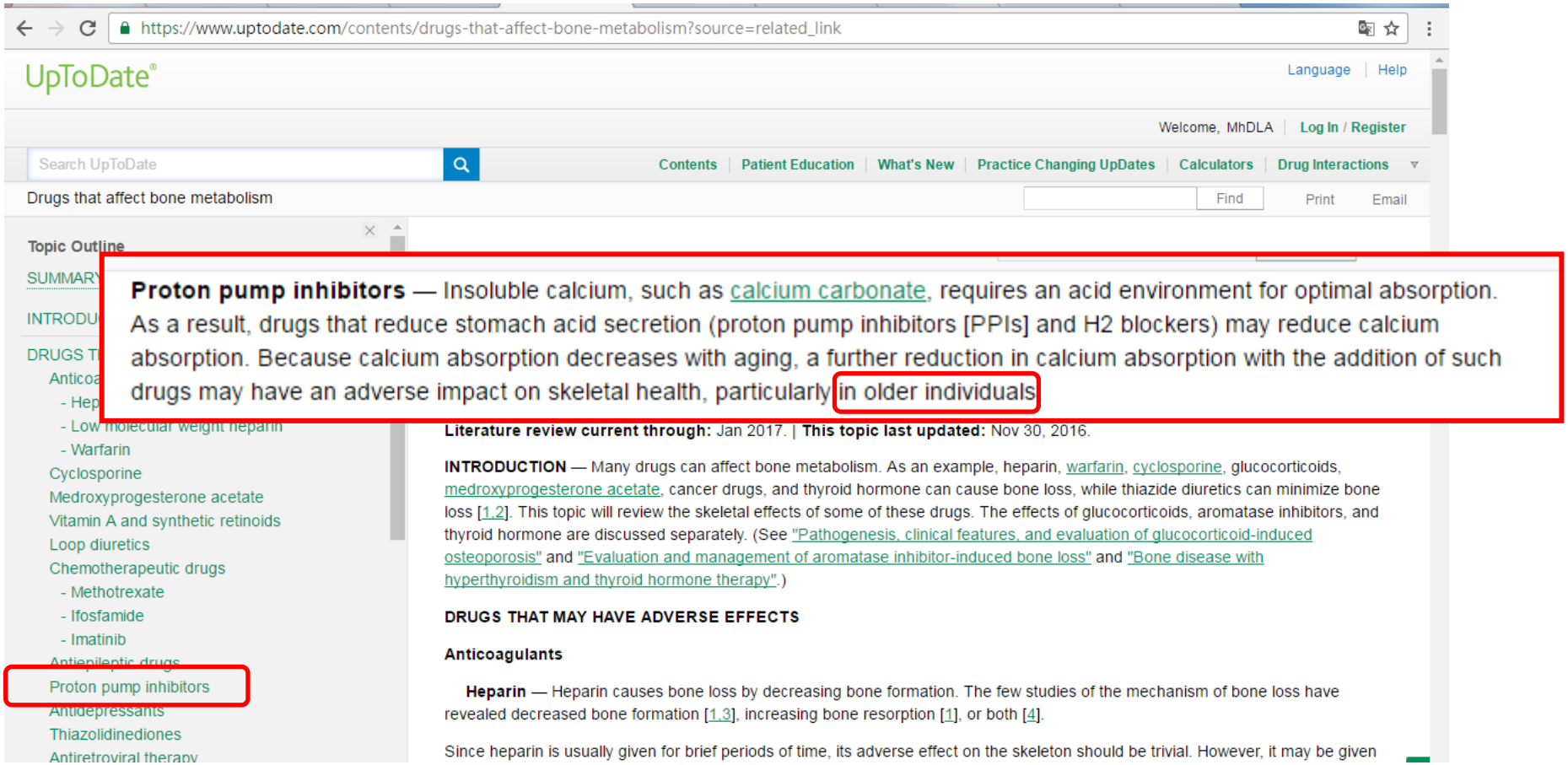
這是一個 ◯治療型 ◯診斷型 ✓預後型 ◯傷害型問題

PICO-2 : Key words(Mesh Term)and Synonym

Key search term				
PICO	MeSH		Synonyms	
Patient/Problem	Old women		**Postmenopausal women/ use anti-platelet drug**	
Intervention	Use **anti-platelet drug**			
Compare	Stop to use **anti-platelet drug**			
Outcome	AMI的發生			

團隊選用PICO-1

背景資訊



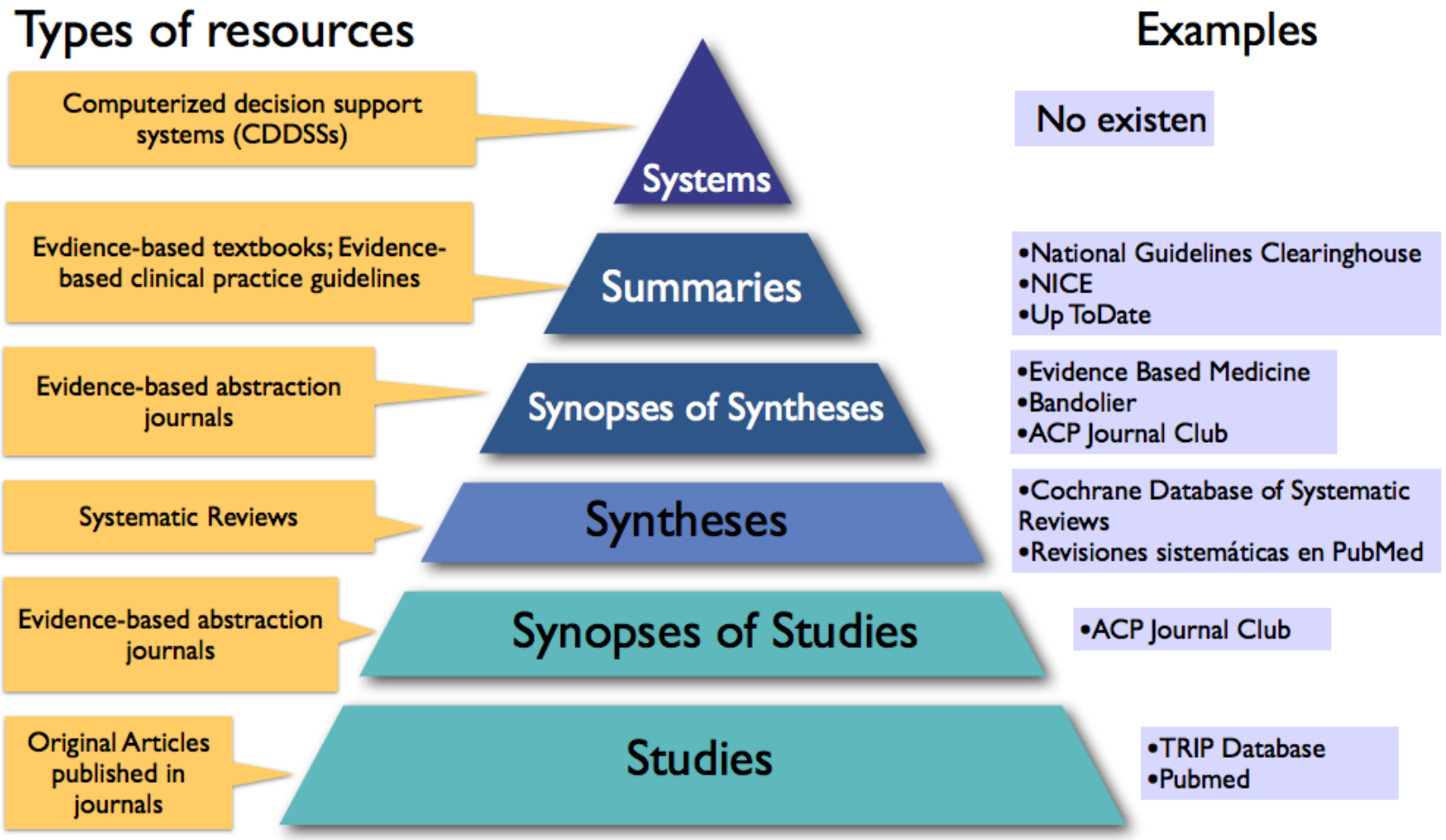
The more important clinical question is whether PPIs affect fracture risk. In meta-analyses of case-control and

THE EBM PROCESS :

STEP 2 :

Search for the most relevant best evidence

"6 S" Hierarchy of Preappraised Evidence



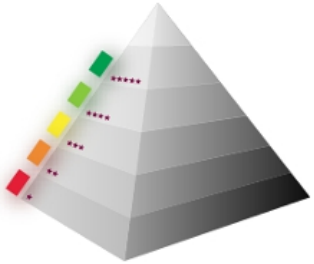
{DiCenso et al., 2009, Ann Intern Med, 151, JC3-2, JC3-3}

Home | Search | My Profile | My Alerts | Hit Parade | Vital Links | External Links Contact | Help | About | Sign Out

ACCESSSS
Federated Search

History
women and PPI and osteoporosis
Search
Advanced Options

Current PLUS Database: Physician
Resource Portal: None
Add your Institution Change



6S model explained
Criteria for articles in PLUS

- **Summaries ★★★★★**
  - UpToDate
  - DynaMed
  - Best Practice
  - EBM Guidelines
- **Synopses of Syntheses ★★★★☆**
  - ACP Journal Club (via PLUS)
- **Syntheses ★★★☆☆**
  - PLUS Syntheses
- **Synopses of Studies ★★☆☆☆**
  - ACP Journal Club (via PLUS)
- **Studies ★☆☆☆☆**
  - PLUS Studies
- **Non-Appraised ☆☆☆☆☆**
  - PubMed CQ
  - PubMed

Summaries ★★★★★

UpToDate
Overview and comparison of the proton pump inhibitors for the treatment of acid-related disorders
Drugs that affect bone metabolism
More Results (52)

DynaMed
Osteoporosis causes and risk factors
Alendronate
More Results (17)

EBM Guidelines
Hypocalcaemia, hypoparathyroidism and vitamin D deficiency

Syntheses ★★★☆☆

PLUS Syntheses
Use of acid-suppressive drugs and risk of fracture: a meta-analysis of observational studies. *(Systematic Review)*

Synopses of Studies ★★☆☆☆

ACP Journal Club (selected via PLUS)
Proton-pump inhibitors were associated with reduced effectiveness of alendronate for preventing hip fractures

Studies (pre-appraised by these criteria) ★☆☆☆☆

PLUS Studies
Proton pump inhibitor use and the antifracture efficacy of alendronate. *(Original Study)*
Proton pump inhibitor use, hip fracture, and change in bone mineral density in postmenopausal women: results from the Women's Health Initiative. *(Original Study)*

Below this bar you must do your own critical appraisal. (and can use these criteria if you wish)

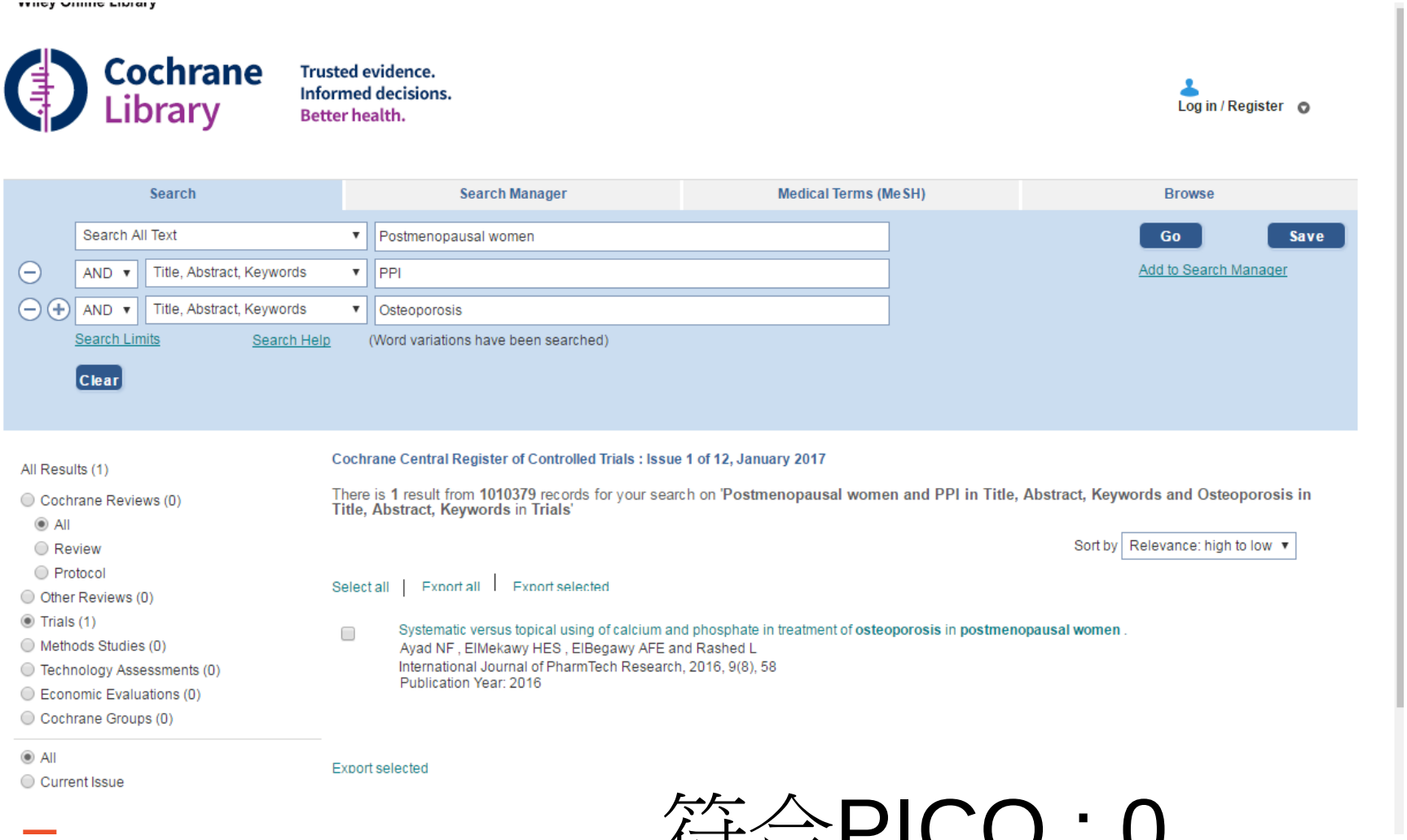
PubMed Clinical Queries

These results are yielded from your search term combined with Search Filters which are a modified version of our PubMed Clinical Queries.

Systematic Reviews
Network-Based Meta-Analyses of Associations of Multiple Gene Expression Profiles with Bone Mineral Density Variations in Women.

Therapy

搜尋畫面



符合PICO : 0

NCBI Resources How To Sign in to NCBI

PubMed Clinical Queries

Results of searches on this page are limited to specific clinical research areas. For comprehensive searches, use PubMed directly.

postmenopausal women use PPI Search

Clinical Study Categories

Category: Therapy

Scope: Broad

Results: 5 of 9

Identification of crucial genes related to postmenopausal osteoporosis using gene expression profiling.
Ma M, Chen X, Lu L, Yuan F, Zeng W, Luo S, Yin F, Cai J.
Aging Clin Exp Res. 2016 Dec; 28(6):1067-1074. Epub 2015 Dec 16.

The effect of dose and type of proton pump inhibitor use on risk of fractures and osteoporosis treatment in older Australian women: A prospective cohort study.
van der Hoorn MM, Tett SE, de Vries OJ, Dobson AJ, Peeters GM.
Bone. 2015 Dec; 81:675-82. Epub 2015 Aug 28.

Acid-suppressive medications and risk of fracture: an updated meta-analysis.
Cai D, Feng W, Jiang Q.
Int J Clin Exp Med. 2015 Jun 15; 8(6):8893-904. Epub 2015 Jun 15.

Use of proton pump inhibitors (PPI) and history of earlier fracture are independent risk factors for fracture in postmenopausal women. The WHILA study.
Moberg LM, Nilsson PM, Samsioe G, Borgfeldt C.
Maturitas. 2014 Aug; 78(4):310-5. Epub 2014 Jun 2.

Long-term proton pump inhibitor therapy and falls and fractures in elderly women: a prospective cohort study.
Lewis JR, Barre D, Zhu K, Ivey KL, Lim EM, Hughes J, Prince RL.
J Bone Miner Res. 2014 Nov; 29(11):2489-97.

See all (9)

This column displays citations filtered to a specific clinical study category and scope. These search filters were developed by

Systematic Reviews

Results: 1 of 1

Acid-suppressive medications and risk of fracture: an updated meta-analysis.
Cai D, Feng W, Jiang Q.
Int J Clin Exp Med. 2015 Jun 15; 8(6):8893-904. Epub 2015 Jun 15.

See all (1)

This column displays citations for systematic reviews, meta-analyses, reviews of clinical trials, evidence-based medicine, consensus development conferences, and guidelines. See filter information or additional related sources.

Medical Genetics

Topic: All

Results: 1 of 1

Identification of crucial genes related to postmenopausal osteoporosis using gene expression profiling.
Ma M, Chen X, Lu L, Yuan F, Zeng W, Luo S, Yin F, Cai J.
Aging Clin Exp Res. 2016 Dec; 28(6):1067-1074. Epub 2015 Dec 16.

See all (1)

This column displays citations pertaining to topics in medical genetics. See more filter information.

符合PICO：1

醫藥衛生（原：醫學與生命科學） (5)

年代

2013年以後 (1)
2012 (3)
2010 (1)

出版品名稱

內科學誌 (1)
台北市醫師公會會刊 (1)
家庭醫學與基層醫療 (1)
臺灣臨床藥學雜誌 (1)
臺灣醫界 (1)

指標期刊

地區

台灣 (5)

語言 清除條件

繁體中文 (5)

每頁 10 筆

共 5 筆，1 - 5 筆

共 1 頁 1

書目匯出 加入追蹤 加入購物車 相關程度最高

1 氫離子幫浦阻斷劑（PPI）藥物之比較
莊宗憲 ；
家庭醫學與基層醫療 27卷2期 (2012/02) , 52-58
加入追蹤 全文下載

2 氫離子幫浦阻斷劑在使用非類固醇消炎止痛藥與阿斯匹靈患者的胃保護角色
羅景全 ；
台北市醫師公會會刊 58卷3期 (2014/03) , 40-43
加入追蹤 全文下載

3 急性冠心症病人併用clopidogrel與氫離子幫浦阻斷劑的可能不良影響
張育霖 ；
臺灣醫界 55卷2期 (2012/02) , 59-60
加入追蹤 全文下載

4 氫離子幫浦阻斷劑之比較與其同療效藥品替代可行性之探討
黎燕鶯(Yen-Ying Lee) ；林攸美(You-Meei Lin) ；沈宛真(Wan-Chen Shen) ；陳香吟(Hsiang-Yin Chen) ；
臺灣臨床藥學雜誌 20卷3期 (2012/09) , 221-233
氫離子幫浦阻斷劑 ；同療效藥品替代 ；proton pump inhibitors ；therapeutic interchange
預覽摘要 加入追蹤 全文下載

5 胃食道逆流疾病之處置現況
廖思嘉(Szu-Chia Liao) ；葉宏仁(Hong-Zen Yeh) ；柯忠旺(Chung-Wang Ko) ；連漢仲(Han-Chung Lien) ；張繼森(Chi-Sen Chang) ；
內科學誌 21卷6期 (2010/12) , 481-[illegible]
胃食道逆流疾病 ；逆流性食道炎 ；巴雷氏食道 ；Gastroesophageal reflux disease ；Reflux esophagitis ；Barrett's esophagus
10.6314/JIMT.2010.21(6).01
預覽摘要 | 被引用次數 (3) 加入追蹤 全文下載

符合PICO：2

搜尋總結果

資料庫	搜尋篇數	符合PICO數
DynaMed Powered by EBSCOhost	Total: 100	2
ACP Journal Club® The Best New Evidence for Patient Care℠	Total: 6	0
THE COCHRANE LIBRARY Independent high-quality evidence for health care	Total:1	0
PubMed Clinical Queries	Total: 11	1
airiti Library 華藝線上圖書館 (CEPS中文電子期刊資料庫暨平台服務+CETD中文碩博士論文	Total: 13	2

納入評讀的文章

Original Article

Acid-suppressive medications and risk of fracture: an updated meta-analysis

Dawei Cai[1], Wan Feng[2], Qing Jiang[1]

[1]Department of Orthopedics, Drum Tower Hospital, Nanjing University Medical School, No. 321 Zhongshan Road, Nanjing, China; [2]Nanjing University Medical School, Nanjing, People's Republic of China

Received March 13, 2015; Accepted May 20, 2015; Epub June 15, 2015; Published June 30, 2015

	本篇研究的內容	我們設計的PICO
P	Adults women	☑ Yes
I	Use PPI	☑ Yes
C	Fellow up	☑ Yes
O	fracture	☑ Yes

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)
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 *n*-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, *n*-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 *n*-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**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

THE EBM PROCESS :

StEP 3 :

Critical appraise the evidence

1.Did the review address a clearly focused question?
本題目是否有清楚描述主題

■是	□否	□不清楚

To obtain a better understanding of associations between acid-suppressive medications and fracture risk, we updated previous meta-analysis with data from new observational studies published in the past two years. With more studies included, we were able to examine the effect of acid-suppressive drugs on the risk of fracture at various fracture sites (any, hip, spine and wrist fracture) and evaluate the association among postmenopausal women. Additionally, large prospective studies with relatively long follow-up enabled us to explore whether duration of exposure affected the risk of fracture.

能夠清楚描述本文的主題，在於了解**acid-suppressive藥物與骨折**的相關性。此外還特別針對**停經後婦女族群**進行討論與分析。

2. Did the authors look for the right type of papers
作者所搜尋的文章是否正確?

■是	□否	□不清楚

Data extraction was independently conducted by 2 investigators. Inconsistencies were resolved by discussion and referring back to the original citation.

由兩位獨立的審查者，進行摘要的評讀，若有認知出入的情況下，會由第三位審查者進行審核。

3.Do you think all the important, relevant studies were included?
其他重要相關的文章是否被納入?

☐是	☐否	■不清楚

We systematically searched the Pubmed and Embase database for relevant publications. Following key words were used: "proton pump inhibitor", "PPI", histamine receptor antagonist", "H_2RA", "cimetidine", "lansoprazole", "omeprazole", "pantoprazole" and "fracture", "bone density", "osteoporosis".

Studies were included if they satisfied the following criteria: 1. Cohort study or case-control study reported association between acid-suppressive medications and fracture risk. 2. Human studies. 3. Providing a measure of RR, OR or HR and 95%CI. 4. The risk estimates should be at least controlled for one cofounder. 5. Risk of fracture was an outcome.

Case-reports or reviews without providing risk estimates were excluded. One study was removed because the results were reported in the earlier publication. We did not include studies that reported bone mineral density alterations as outcome.

作者僅搜尋電子資料庫，應可以再查詢已經登記的相關研究或是相關研究重要的國際會議紀錄或發表。

4.Did the review's authors do enough to assess the quality of the included studies?

如何評值文章的品質?

☐是	☐否	■不清楚

Table 1. Case-control and cohort studies on the association between acid-suppressing medication and fracture risk

source	country	Study design	Gender (% female)	Study population	Mean age (year)	Duration of follow-up (year)	Fracture site
Yang 2006	UK	Nested Case-control	79.9%	13556 cases 1353386 controls	77	1987-2003	hip
Corley 2010	USA	Case-control	65%	33752 cases 130471 controls	69.4% older Than 70	1995-2007	hip
Reyes 2013	Spain	Case-control	76.9%	358 cases 698 controls	82	2007-2010	hip
Adam 2014	USA	Case-control	0%	6774 cases 6774 controls	69% older Than 70	1997-2006	hip
Gray 2010	USA	cohort	100%	161806 women 119084 nonusers 2731 PPI users 7952 H_2RA users	50-79	7.8	Spine Hip wrist
Pouwels 2011	Netherland	Case-control	72.7%	6763 cases 26341 controls	75	1991-2002	hip
Targownik 2008	Canada	cohort	70.2%	15792 cases 47289 controls	More than 50	1996-2004	Hip Vertebra wrist
Vestergaard 2006	Denmark	Case-control	51.8%	124655 cases 373962 controls	43.44	NA	Hip Spine wrist
Kaye 2008	UK	Nested case-control	71.6%	1098 cases 10923 controls	50.79	1995-2005	hip
Yu 2008	USA	cohort	SOF: 100% MrOS: 0%	F: 234 PPI users 519 H_2RA users 4574 controls M: 487 PPI users 335 H_2RA users 4920 controls	F: 79 M: 74	NA	Hip Non-spine
Chiu 2010	Taiwan	Case-control	57.94%	1241 cases 1241 controls	74	NA	hip
Raux 2008	Europe	cohort	100%	61 PPI users 1150 nonusers	55-79	Patients received 1999-2001	spine
Fraser 2013	Canada	cohort	69.39%	261 PPI users			
De Varies 2009	UK	cohort	55.8%	234144 PPI users 0 non-users 166793 H_2RA users 0 nonusers	PPI users 62 H_2RA 61	PPI: 3.5 H_2ra: 6.3	Hip Spine Any
Moberg 2014	Sweden	cohort	100%	47 users 2724 nonusers	56.4	1995-2012	any
Khalili 2012	USA	cohort	100%	74558 nonusers 5341 user	67	2000-2008	hip
Soriano 2014	USA	Case-control		10958 cases 20000 controls	40-89	2000-2008	hip
Grisso 1997	USA	Case-control	0%	355 cases 402 controls	Older than 45	1991-1993	hip

僅詳細列出18篇文章的內容與重要結果，未提及是否有針對文章的品質進行把關與評值。

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

文章結論被合併的過程是否合理

☐是	☐否	■不清楚

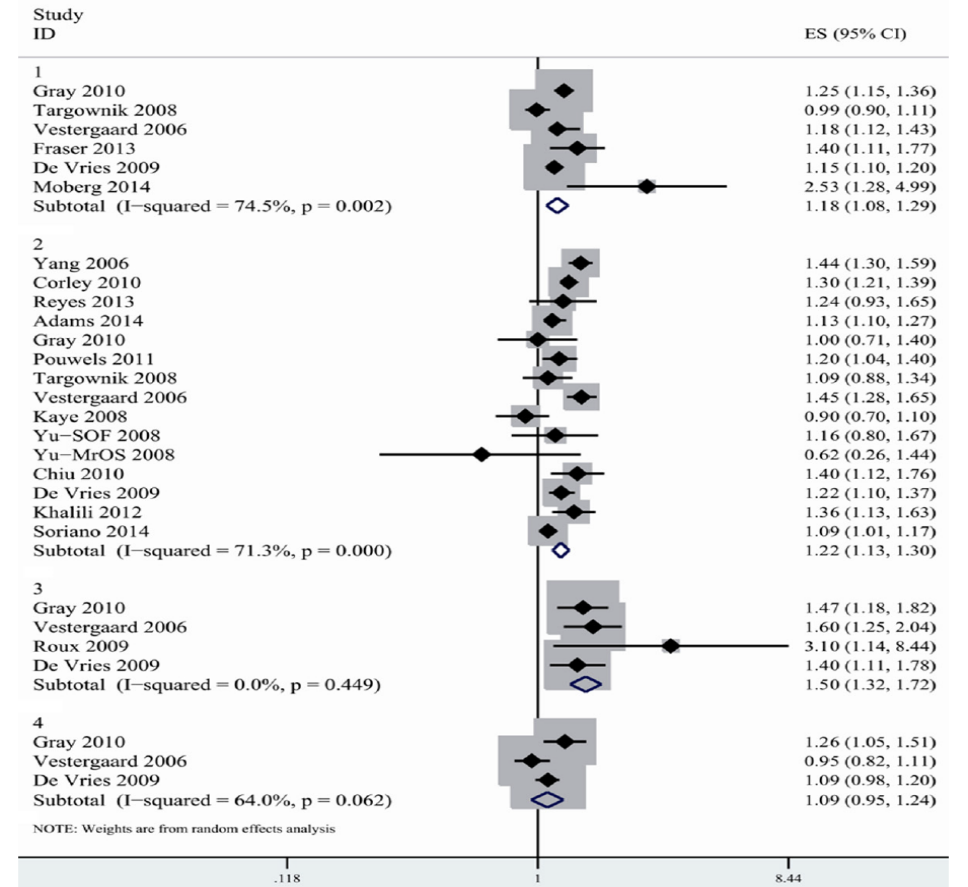


Figure 1. Combined random-effects estimates of RR and 95% CI for the association between fracture risk and PPI use. 1. Any fracture. 2. Hip fracture. 3. Spine fracture. 4. Wrist fracture.

本文納入的18篇文章中，其一質性偏高，I^2 =0-74.5%，P<0.01，雖有使用統計方式矯正，但未說明為何不將異質性高的文章屏除。

6.What are the overall results of the review?
本回顧的重要結論為何

■是	□否	□不清楚

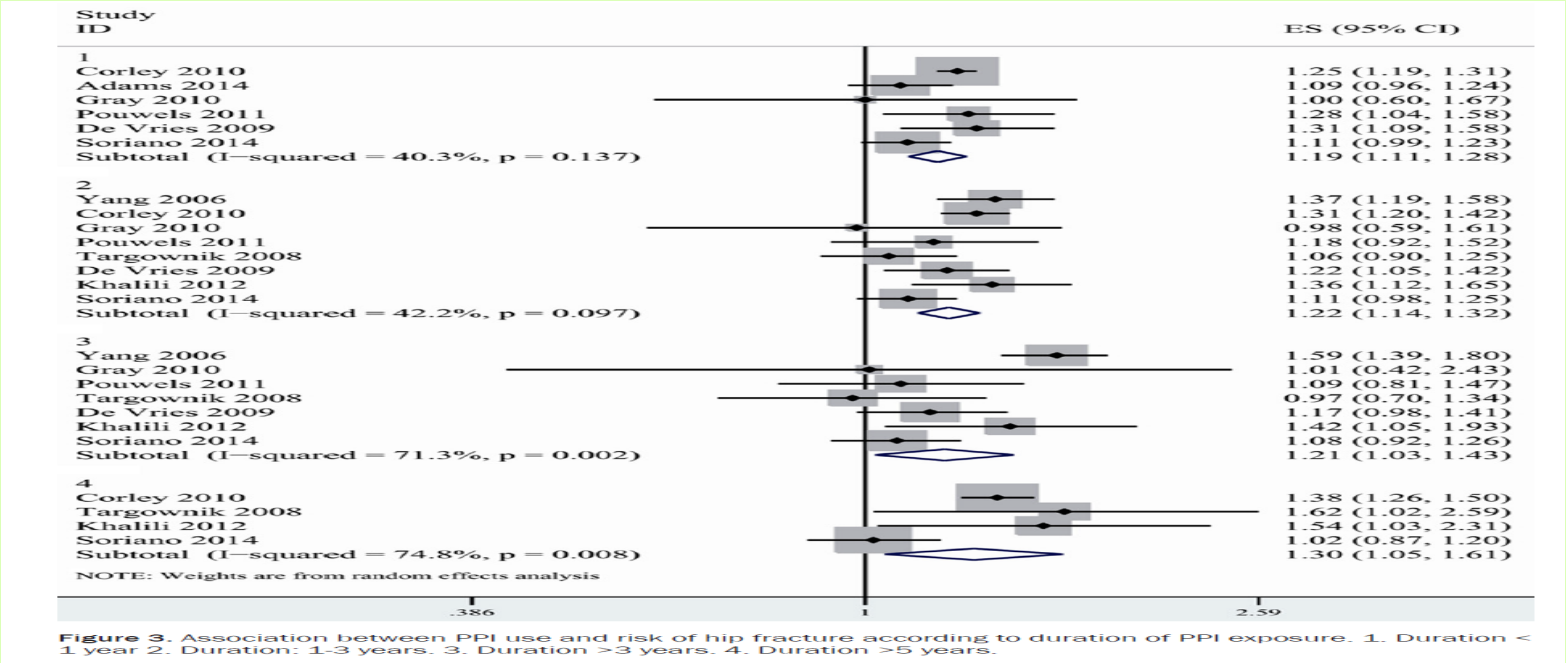


Figure 3. Association between PPI use and risk of hip fracture according to duration of PPI exposure. 1. Duration < 1 year 2. Duration: 1-3 years. 3. Duration >3 years. 4. Duration >5 years.

在18篇的corhot-study中，呈現重要的結論使用PPI藥物造成骨折的危險性其RR:1.216, 95% CI: 1.134-1.304，達統計上顯著差異。

7.How precise are the results?
如何呈現結果

■是	□否	□不清楚

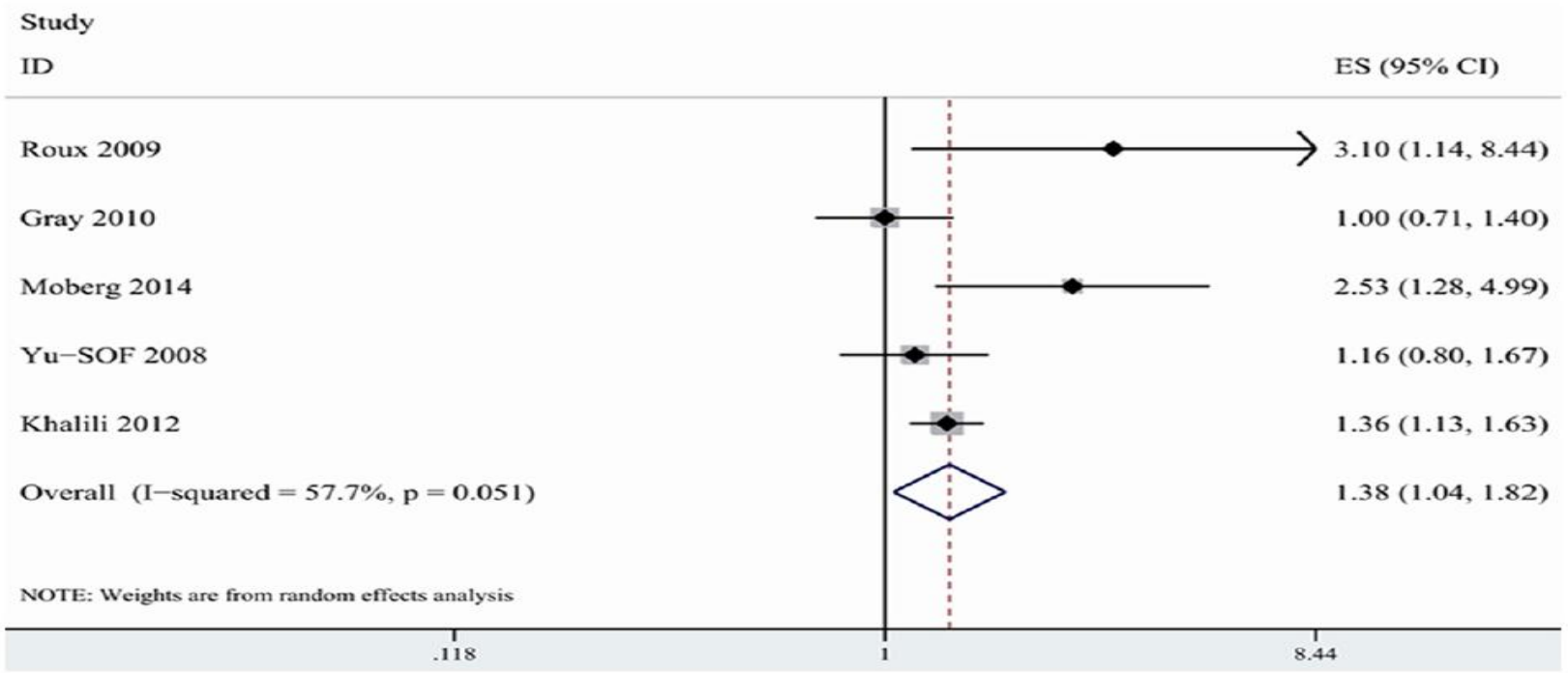


Figure 4. Association between PPI use and risk of hip fracture among postmenopausal women.

此外，針對停經婦女進行Subgroup分析RR :1.376, 95% CI: 1.043-1.816，I2=57.7%亦達統計上顯著差異

8. Can the results be applied to the local population?

是否可以應用在病人身上?

■是	□否	□不清楚

研究結果顯示提供acid-suppressive medications 會增加病人發生骨折的危險，尤其是hip骨折

9.Were all important outcomes considered?
是否重要的結果都被提及?

■是	□否	□不清楚

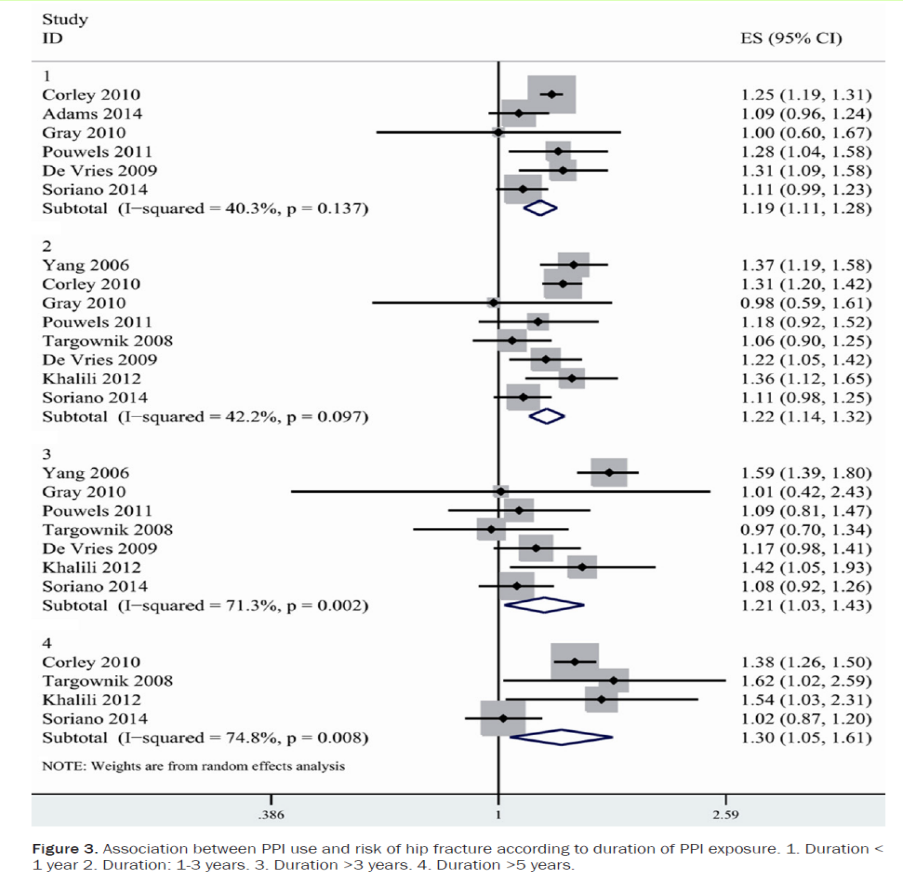


Figure 3. Association between PPI use and risk of hip fracture according to duration of PPI exposure. 1. Duration < 1 year 2. Duration: 1-3 years. 3. Duration >3 years. 4. Duration >5 years.

追蹤1年、1-3年、>3年、>5年等結果均有如實呈現

10.Are the benefits worth the harms and costs?
對個案的利弊為何?

■是	□否	□不清楚

研究結果顯示提供acid-suppressive medications 會增加病人發生骨折的危險，尤其是hip骨折。但若是沒有提供相關制酸劑，會早成病人有潰瘍情況，因此還是建議使用，但可使用其他預防措施防止骨質疏鬆及骨折。

THE EBM PROCESS :

StEP 4 :

Evidence application :

According to clinical expertise & patient preferences

副本

檔　號：
保存年限：

行政院衛生署　公告

受文者：行政院衛生署食品藥物管理局(藥品及新興生技藥品組)

發文日期：中華民國100年11月3日
發文字號：署授食字第1001406870號
附件：

主旨：公告氫離子幫浦抑制劑（proton pump inhibitors，PPIs）藥品仿單加刊警語相關事宜。

依據：藥事法第四十八條、第七十五條及第八十條

公告事項：

一、依據文獻指出，氫離子幫浦抑制劑（proton pump inhibitors，PPIs）藥品長期使用時，具有導致低血鎂之風險，經本署再評估該類藥品之風險與臨床效益後，該類藥品仿單應加刊下列內容：

(一)「警語」：

低血鎂：

1、曾有通報案件顯示，當長期使用PPI類成分藥品（至少使用3個月，大部分在使用1年以上），可能出現罕見低血鎂之不良反應，可能無症狀或嚴重之不良反應症狀，包括手足抽搐、心律不整、癲癇發作等。大部分出現低血鎂之病人需要補充鎂離子予以治療，並停止使用PPI類成分藥品。

2、針對使用PPI類成分藥品之病人，如將長期使用、併用digoxin或其他可能造成低血鎂之藥品（如利尿

食品藥物管理局提醒：使用抗凝血藥品clopidogrel應謹慎評估病患肝臟酵素CYP2C19之代謝活性 (發布日期2010-03-18)

美國 FDA近期發布抗凝血藥品 clopidogrel之用藥資訊，要求抗凝血藥品 clopidogrel之仿單，應以加框警語（ Boxed Warning），說明該藥品使用於肝臟酵素 CYP2C19代謝活性較低之病患，其藥品療效會降低，並建議醫療人員考慮使用其他抗凝血藥品或調整劑量。

經查，衛生署核准含有 clopidogrel成分製劑之藥品許可證有 15 張，所核准之適應症為「降低近期發生中風、心肌梗塞或周邊動脈血管疾病的粥狀動脈硬化病人之粥狀動脈栓塞事件 (如 :心肌梗塞、中風或其他因血管病變引起的死亡)的發生。與 ASPIRIN併用降低非 ST段上升之急性冠心症 (不穩定性心絞痛和非 Q波型心肌梗塞)病人（包括經皮冠狀動脈介入性治療後放置支架的患者）之粥狀動脈栓塞事件。與 ASPIRIN併用可用於以內科治療的 ST段上升之急性心肌梗塞病人。」。衛生署曾於 98年 11月 19日發布新聞稿提醒醫療人員「氫離子幫浦抑制劑」（ Proton pump inhibitors, PPIs）不宜與抗凝血藥品 Clopidogrel合併使用，並發布公告要求所有含有 Clopidogrel成分藥品仿單都必須加刊「病人併用 clopidogrel與氫離子幫浦抑制劑（ Proton pump inhibitors, PPIs） 可能會增加心血管血栓與心血管疾病再發風險。因此，除非必要否則應避免合併使用該二類藥品。倘若臨床醫療需併用該二種藥品時，亦應經臨床醫師審慎評估病人之風險效益。」。

關於 Clopidogrel使用於肝臟酵素 CYP2C19代謝活性較低者之風險，衛生署食品藥物管理局將函請各相關醫藥學團體，提醒醫師為病人處方含 Clopidogrel成分之藥品時，應謹慎評估病患肝臟酵素 CYP2C19代謝活性。同時，儘速蒐集國、內外相關安全資訊，評估是否加註警語。

食品藥物管理局已建立藥物安全資訊主動監控機制，除有藥物不良反應通報系統之外，對於安全有關訊息，隨時進行瞭解，以保障民眾之用藥安

臨床應用

- **政策因素**

  人員教育政策、醫療照護政策

- **倫理考量**

「行善原則」、「不傷害原則」、「自主原則」

- **經濟因素**

  目前台灣Betaine/Polihexanide沖洗液並無列入健保給付項

  目，需仰賴家屬自費給付，使得沖洗液在傷口護理上受到限制。

倫理原則

行善
- 對病人最有利的！

自主
- 尊重病人自主意願

公平
- 只要疾病相關皆可接受治療

不傷害
- 在正確的使用方法下使用，不會造成副作用。

✓ 安全性 (bleeding)

✓ 有效性 (mortality / re-infarction)

✓ 經濟性 (cost-effectiveness)

✓ 以病人為中心 (coagulation monitoring)

臨床回覆
~給病人/家屬貼心的建議~

Thank you for your attention.