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Efficacy and safety of proton pump inhibitors for stress ulcer prophylaxis in critically ill patients: a systematic review and meta-analysis of randomized trials

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日期：2017年4月11日

Abstract

Background: The relative efficacy and safety of proton pump inhibitors (PPIs) compared to histamine-2-receptor antagonists (H2RAs) should guide their use in reducing bleeding risk in the critically ill.

Methods: We searched the Cochrane library, MEDLINE, EMBASE, ACPJC, clinical trials registries, and conference proceedings through November 2015 without language or publication date restrictions. Only randomized controlled trials (RCTs) of PPIs vs H2RAs for stress ulcer prophylaxis in critically ill adults for clinically important bleeding, overt gastrointestinal (GI) bleeding, nosocomial pneumonia, mortality, ICU length of stay and *Clostridium difficile* infection were included. We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess our confidence in the evidence for each outcome.

Results: In 19 trials enrolling 2117 patients, PPIs were more effective than H2RAs in reducing the risk of clinically important GI bleeding (RR 0.39; 95 % CI 0.21, 0.71; $P = 0.002$; $I^2 = 0$ %, moderate confidence) and overt GI bleeding (RR 0.48; 95 % CI 0.34, 0.66; $P < 0.0001$; $I^2 = 3$ %, moderate confidence). PPI use did not significantly affect risk of pneumonia (RR 1.12; 95 % CI 0.86, 1.46; $P = 0.39$; $I^2 = 2$ %, low confidence), mortality (RR 1.05; 95 % CI 0.87, 1.27; $P = 0.61$; $I^2 = 0$ %, moderate confidence), or ICU length of stay (mean difference (MD), –0.38 days; 95 % CI –1.49, 0.74; $P = 0.51$; $I^2 = 30$ %, low confidence). No RCT reported Clostridium difficile infection.

Conclusions: PPIs were superior to H2RAs in preventing clinically important and overt GI bleeding, without significantly increasing the risk of pneumonia or mortality. Their impact on Clostridium difficile infection is yet to be determined.

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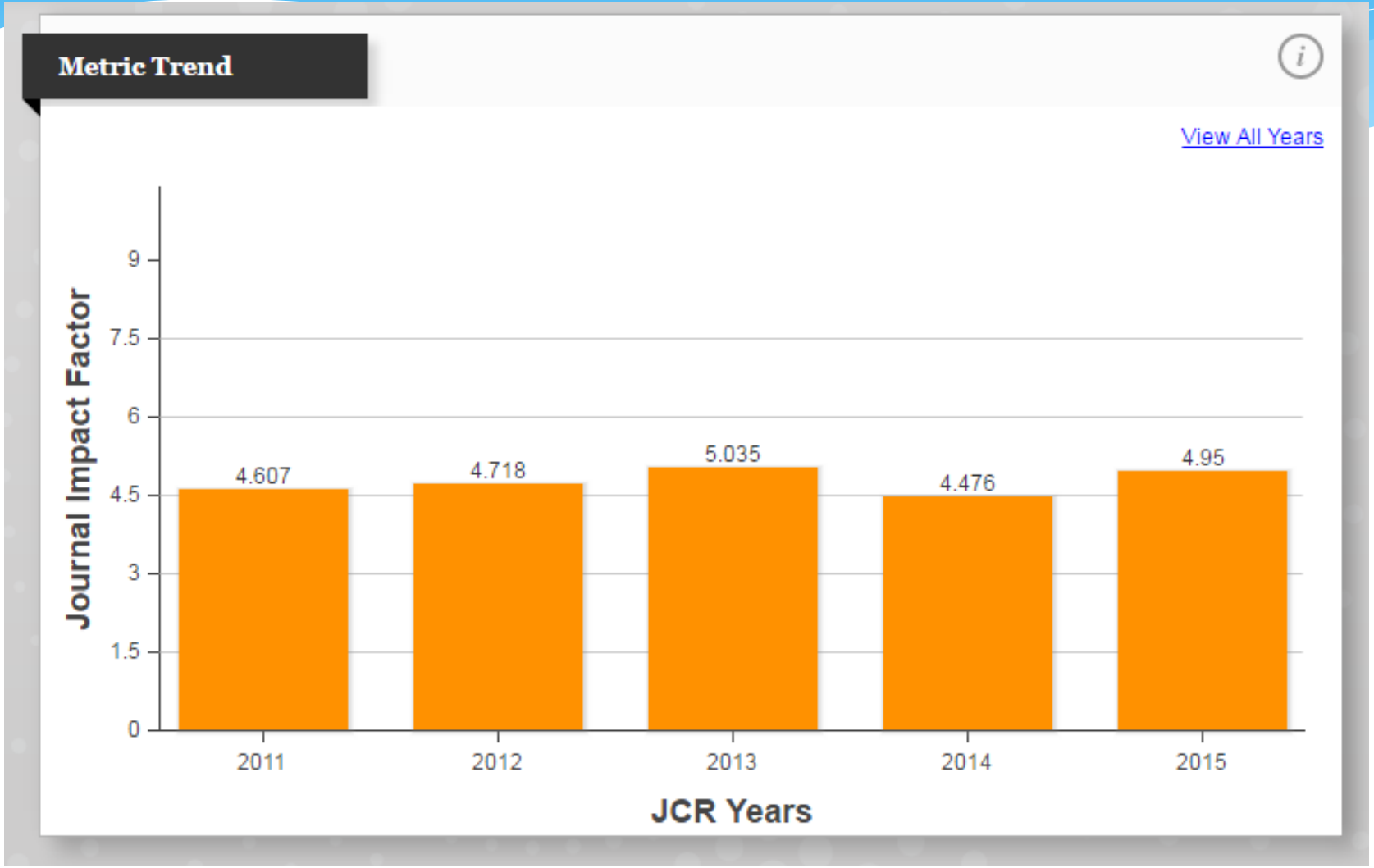

Background

* Stress ulcers typically occur in the gastric body, esophagus, or duodenum, sometimes resulting in gastrointestinal (GI) bleeding. Earlier studies reported overt GI bleeding in 5 to 25 % of critically ill patients.

Shuman RB, Schuster DP, Zuckerman GR. Prophylactic therapy for stress ulcer bleeding: a reappraisal. Ann Intern Med. 1987;106(4):562 – 7.
Mutlu GM, Mutlu EA, Factor P. GI complications in patients receiving mechanical ventilation. Chest. 2001;119(4):1222 – 41

Background

* RCTs have investigated different classes of medication for stress ulcer prophylaxis.

* A meta-analysis of 29 RCTs showed that prophylaxis with either protonpump inhibitors (PPIs) or histamine-2-receptor antagonists (H2RAs) was associated with lower risk of overt GI bleeding compared to placebo or no prophylaxis.

Krag M, et al. Intensive Care Med. 2014;40(1):11 – 22.

Background

* PPIs, more potent at increasing gastric pH than H2RAs and maintaining gastric pH between 3.5 and 5.0,may minimize the risk of gastric mucosal injury.

* Of four meta-analyses comparing PPIs to H2RAs, three suggested that PPIs are superior to H2RAs and one did not.

Lin PC, Crit Care Med. 2010;38(4):1197 – 205.

Background

* In terms of the relative impact of PPIs and H2RAs,adverse effects are also a concern.

* A recent large retrospective observational study suggested PPI versus H2RA use in critically ill patients was associated with higher risks of pneumonia and Clostridium difficile infection compared to H2RA.

MacLaren R, JAMA Intern Med. 2014;174(4):564 – 74.

步驟 1：系統性文獻回顧探討的問題為何？

* 研究族群／問題 (Population/ Problem)：
  critically ill patients in ICU

* 介入措施 (Intervention)：proton pump inhibitors
  either parenteral or enteral, regardless of the dose, frequency, or duration

* 比較 (Comparison)： H2RAs

* 結果 (Outcomes)：
  clinically important GI bleeding; overt upper GI bleeding
  nosocomial pneumonia, mortality, ICU length of stay
  and Clostridium difficile infection

步驟2：系統性文獻回顧的品質如何？（FAITH）

F - 研究是否找到 (Find) 所有的相關證據？	
最好的狀況是？	**我可以在哪裡找到這些資訊？**
良好的文獻搜尋至少應包括二個主要的資料庫(如：Medline, Cochrane 考科藍實證醫學資料庫, EMBASE 等)，並且加上文獻引用檢索(參考文獻中相關研究、Web of Science, Scopus 或 Google Scholar)、試驗登錄資料等。文獻搜尋應不只限於英文，並且應同時使用 MeSH 字串及一般檢索詞彙(text words)。	在文章的**方法(Methods)**章節，可以找到詳細搜尋策略的說明，包括使用的名詞，**結果(Results)**章節中可以找到本篇系統性文獻回顧評估的摘要及全文文獻數目、文獻納入與排除的數量及原因。資料可能會以圖表或 PRISMA 的流程圖呈現。

Search strategy

Searched MEDLINE, EMBASE, Cochrane Library, ACPJC, and International Clinical Trial Registry Platform (ICTRP) from March 2012 through November 2015. Eligible articles without language or publication date restrictions. We conducted an electronic search of conference proceedings via a website provided by McMaster University (http://library.mcmaster.ca/articles/proceedingsfirst).

步驟2：系統性文獻回顧的品質如何？(FAITH)

F—研究是否找到(Find)所有的相關證據？

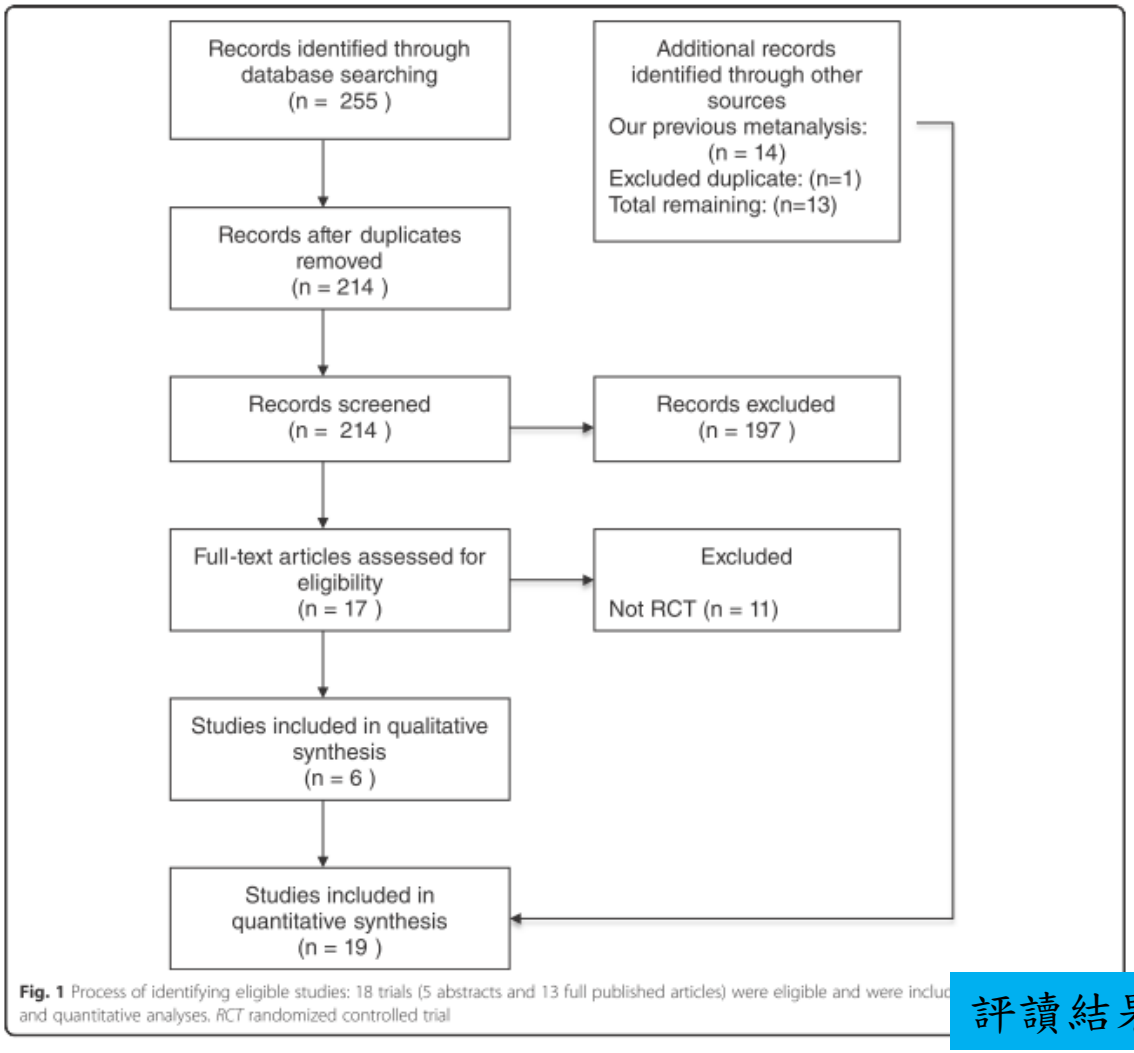

Fig. 1 Process of identifying eligible studies: 18 trials (5 abstracts and 13 full published articles) were eligible and were inclu
and quantitative analyses. *RCT* randomized controlled trial

評讀結果: ■是 否 不清楚

步驟 2：系統性文獻回顧的品質如何？(FAITH)

A-文獻是否經過嚴格評讀 (Appraisal)?

Risk of bias assessment

Two reviewers (FA and EB) independently examined eligible trials for risk of bias using the Cochrane Collaboration tool [27]. For each included trial, we judged articles as having low, unclear, or high risk of bias for the domains of adequate sequence generation, allocation sequence concealment, blinding for objective outcomes, incomplete outcome data, selective outcome reporting, and for other bias. The overall risk of bias for each trial included was categorized as low if the risk of bias was low in all domains, unclear if the risk of bias was unclear in at least one domain and with no high risk of bias domain, or high if the risk of bias was high in at least one domain. We resolved disagreements by discussion and consensus.

e-Table 6: Risk of Bias assessment of the included trials using Cochrane Risk of Bias tool.

Author	Sequence Generation	Allocation Concealment	Blinding	Incomplete Outcome Data	Selective Reporting Bias	Free of Other Bias	Overall Risk of Bias
Conrad et al	Low	Low	Low	Low	Low	Low	Low
Azevedo et al	Low	Low	High	Low	Low	Low	High
Hata et al	Low	High	High	Low	Low	Low	High
Kantorova et al	Low	Low	Low	Low	Low	Low	Low
Kotlyanskaya et al	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Levy et al	Low	Low	High	Low	Low	Low	High
Pan et al	Unclear	Unclear	High	Low	Unclear	Low	High
Phillips et al	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Powell et al	Low	Unclear	Low	Low	Low	Low	Unclear
Risaliti et al	Low	Unclear	Unclear	Low	Unclear	Low	Unclear
Solouki et al	Low	Low	Low	Low	Low	Low	Low
Somberg et al	Low	Low	High	Low	Low	Low	High
Fink et al	Unclear	Unclear	High	Unclear	Unclear	Unclear	High
Bashar et al	Low	Low	Unclear	High	High	Unclear	High
Lee et al	Low	Low	High	Low	Unclear	Unclear	High
Liu et al	Low	Low	High	High	Low	Unclear	High
Fogas et al	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Wee et al	High	High	High	High	Unclear	Unclear	High
Bhanot et al	Unclear	Unclear	Unclear	Unclear			

評讀結果: ■是　否　不清楚

Table 1 Characteristics of trials included

Table 1 Characteristics of trials included

Author	Population	Interventions	Definition of GI bleeding	Definition of pneumonia	Funding
Conrad [35] USA ($n = 359$)	MV patients with risk factors Age (mean) 55.6 years Male 59 % APACHE II (mean) 23.7	Omeprazole 40 mg IV twice daily loading, then 40 mg daily ($n = 178$) Cimetidine 300 mg IV bolus, then infusion at 50 mg/h ($n = 181$)	(1) Bright red blood not clearing after tube adjustment and lavage (2) 8 h of persistent coffee grounds material with aspirates every 2 h not clearing with lavage or (3) Persistent coffee grounds material over 2–4 h on day 3–14 in 3 consecutive aspirates not clearing with lavage	USFDA	Pharmaceutical
Azevedo [36] Brazil ($n = 108$)	Critically ill patients with risk factors Age (mean) 56.7 years Male 52 % APAHE (mean) 55.3	Omeprazole 40 mg IV twice daily ($n = 38$) Ranitidine 150 mg/ Sucralfate 1 g PO fo ($n = 32$)	Overt bleeding	CDC criteria	NR
Hata [37] Japan ($n = 210$)	Cardiac surgery patients Age (mean) 64.5 years Male 73 % APACHE II NR	Rabeprazole 10 mg ($n = 70$) Ranitidine 300 mg ($n = 70$) Teprenone 150 mg ($n = 70$)			
Kantorova [38] Czech Republic ($n = 287$)	Surgical ICU with risk factors Age (mean) 47 years Male 67 % APACHE II (mean) 18.4	Omeprazole 40 mg ($n = 72$) Famotidine 40 mg ($n = 71$) Sucralfate 1 g PO fo ($n = 69$) Placebo ($n = 75$)			
Kotlyanskaya [31] Abstract USA ($n = 66$)	MV patients. Age 71.2 years Male NR APACHE II 27.6	Lansoprazole (suspe ($n = 22$) Lansoprazole (table Ranitidine ($n = 21$) frequency not repo			
Levy [39] USA ($n = 67$)	Medical and surgical ICU patients with risk factors. Age 57.1 years Male 55 % APACHE II 18.9	Omeprazole 40 mg ($n = 32$) Ranitidine 50 mg IV 150 mg IV daily (n =			
Pan [40] China ($n = 30$)	Severe pancreatitis Age 48 years Male 45 % APACHE II 12.2	Rabeprazole 20 mg ($n = 20$) Famotidine 40 mg ($n = 10$)			

Definition of GI bleeding
(1) Bright red blood not clearing after tube adjustment and lavage
(2) 8 h of persistent coffee grounds material with aspirates every 2 h not clearing with lavage or
(3) Persistent coffee grounds
material over 2 – 4 h on day 3 – 14 in 3 consecutive aspirates not clearing with lavage

Overt bleeding with one of the following:
(1) Drop in SBP >20 mmHg or rise in HR >20 beats/min within 24 h not explained by other causes
(2) Drop in hemoglobin >2 g/dL not explained by other causes

Table 1 Characteristics of trials included

Table 1 Characteristics of trials included *(Continued)*

Phillips [32] Abstract USA ($n = 58$)	MV patients with risk factors Age NR Male NR APACHE II NR	Omeprazole 40 mg PO, then 20 mg PO daily ($n = 33$) Ranitidine 50 mg IV loading, then 150–200 mg/day infusion ($n = 25$)	No clear definition	NR	NR
Powell [41] UK ($n = 41$)	Cardiac surgery Age 56.5 years Male 86 % APACHE II NR	Omeprazole 80 mg IV bolus, then 40 mg IV bolus three times daily ($n = 10$) Omeprazole 80 mg IV bolus then 40 mg IV infusion three times daily ($n = 10$) Ranitidine 50 mg IV three times daily ($n = 11$) Placebo ($n = 10$)	Overt bleeding	NA	Academic
Risaliti [42] Italy ($n = 28$)	Surgical ICU Age 61.5 years Male 64 % APACHE II NR	Omeprazole 40 mg IV daily, then 20 mg PO daily ($n = 14$) Ranitidine 150 mg IV daily, then 300 mg PO daily ($n = 14$)	No clear definition	NA	NR
Solouki [43] Iran ($n = 129$)	MV patients with other risk factors. Age 50.8 years Male 52 % APACHE II NR	Omeprazole 20 mg PO twice daily ($n = 61$) Ranitidine 50 mg IV twice daily ($n = 68$)	Overt bleeding associated with one of the following: (1) 20 mmHg decrease in SBP or DBP within 24 h or 20 beat/min increase in HR or postural drop by 10 mmHg in SBP (2) 2 g/dL decrease in Hb or 6 % decrease in Hct within 24 h (3) Lack of increase in Hb after two units of packed cells	New infiltrate and two of the following: (1) Fever ≥38.3 °C (2) WBC $>10 \times 10^9$/L (3) Pus in ETT aspirate	NR
Somberg [34] USA ($n = 202$)	Medical and surgical ICU patients with risk factors Age 42 years Male 74 % APACHE II 15.2	Pantoprazole 40 mg IV daily ($n = 32$) Pantoprazole 40 mg IV twice daily ($n = 38$) Pantoprazole 80 mg IV daily ($n = 23$) Pantoprazole 80 mg IV twice daily ($n = 39$) Pantoprazole 80 mg IV three times daily ($n = 35$) Cimetidine 300 mg IV bolus, then 50 mg/h infusion ($n = 35$)	(1) Hematemesis or bright red blood in gastric aspirate that did not clear after tube adjustment and 10-min lavage (2) Persistent coffee ground material for 8 h that did not clear with lavage, or accompanied by 5 % decrease in Hct (3) Decrease in Hct requiring ≥1 transfusions in the absence of obvious source or (4) Melena or hematochizia	Radiological changes	Pharmaceutical
Fink [33] Abstract USA ($n = 189$)	Adult critically ill patients Age NR Male NR APACHE II 15	Pantoprazole 40 mg IV daily, 40 mg IV twice daily, 80 mg IV daily, or 80 mg IV twice daily ($n = 158$); Cimetidine IV 300 mg bolus, then 50 mg/h infusion ($n = 31$)	No clear definition	NA	NR

Table 1 Characteristics of trials included

Table 1 Characteristics of trials included *(Continued)*

Bashar [21] Iran ($n = 120$)	MV trauma patients, APACHE II < 25 Age 40.15 Male 7 % APACHE II 15.2	Pantoprazole 40 mg IV daily then 40 mg PO daily when enteral feeds started ($n = 60$) Ranitidine 50 mg IV three times daily while NPO then 150 mg PO daily when enteral feeds started ($n = 60$)	No clear definition	Clinical Pulmonary Infection Score (CPIS)	NR
Lee [23] Taiwan ($n = 60$)	Neurosurgical ICU Age 57.7 years Male 60 % APACHE II 17.1	Esomeprazole 40 mg PO daily for 7 days ($n = 30$) Famotidine 20 mg IV twice daily for 7 days ($n = 30$)	Overt bleeding, or decreased hemoglobin level >2 g/dL and lesions on endoscopy	>48 h of ventilation and 3 or more of: (1) Persistent (>48 h) or new infiltrate (2) Positive sputum smear (3) Fever >38.3 °C (4) WBC $>12 \times 10^9$/L	Academic
Liu [24] China ($n = 165$)	Neurosurgical ICU with ICH Age NA Male 65 (58 %) APACHE II NR	Omeprazole 40 mg IV twice daily ($n = 58$) Cimetidine 300 mg IV four times daily ($n = 54$) Placebo ($n = 53$)	Overt bleeding that requires transfusion, with or without hemodynamic instability	NR	Academic
Fogas [22] Abstract Hungary ($n = 79$)	MV patients Age 69.5 Male 61 % APACHE II 27	PPI ($n = 38$) H2RA ($n = 41$) No molecule, route, dose or frequency described	No clear definition	Leukocytosis, elevated procalcitonin, fever, purulent ETT secretion, positive ETT microbiology, new/increased infiltrate	NR
Wee [20] Abstract USA (n =129)	Critically ill patients with risk factors Age median 72 Male NR APACHE II 22	Pantoprazole 40 mg IV daily ($n = 68$) Famotidine 20 mg IV twice daily ($n = 61$)	Overt bleeding with any of the following: (1) Decrease in SBP by >20 mmHg (2) Decrease in MAP to <65 mmHg 3. Decrease in Hb >2 g/dL and need for >1 unit of blood	NA	NR
Bhanot [38] Abstract India ($n = 150$)	Mechanically ventilated, critically ill.	Omeprazole 40 mg PO daily ($n = 50$) Ranitidine 50 mg IV four times daily ($n = 50$) Sucralfate 1 gm PO four times daily ($n = 50$)	NR	NR	NR

Description of populations, settings, interventions, outcomes and funding sources. *APACHE* Acute Physiology and Chronic Health Evaluation, *MV* mechanically ventilated, *NR* not reported, *GI* gastrointestinal, *IV* intravenous, *PO* oral, *hb* hemoglobin, *USFDA* US Food and Drug Agency, *SBP* systolic blood pressure, *HR* heart rate, *ETT* endotracheal tube, *WBC* white blood cells, *BAL*, bronchiolar lavage, *CFU* colony-forming units, *DBP* diastolic blood pressure, *Hct* hematocrit, *PPI* proton pump inhibitor, *H2RA* histamine-2-receptor antagonist, *MAP* mean arterial pressure, *CDC* Center of disease control, *NG* nasogastric, *NA* not applicable

步驟 2：系統性文獻回顧的品質如何？(FAITH)

I-是否只納入 (included) 具良好效度的文章?

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最好的狀況是？	**我可以在哪裡找到這些資訊？**
僅進行文獻判讀是不足夠，系統性文獻回顧只納入至少要有一項研究結果是極小偏誤的試驗。	在文章的**方法**章節，可以找到文章評估的方式，以及是由誰完成評估的，在**結果**章節則會提供審查者意見一致性的程度。

Study selection

Studies were eligible if: (1) the study design was an RCT; (2) the population involved adult critically ill patients in the ICU; (3) the intervention group received a PPI (either parenteral or enteral), regardless of the dose, frequency, or duration; (4) the control group received an H2RA, either parenteral or enteral, regardless of the dose, frequency, or duration; and (5) the outcomes included all or any of the following: clinically im GI bleeding; overt upper GI bleeding; pneumoni tality, ICU length of stay, and/or *Clostridium* infection.

Risk of bias assessment

Using the Cochrane risk of bias tool, three trials were judged to be at low risk of bias, and for six trials the risk of bias was unclear (Additional file 1: Table S6). We could not evaluate the risk of bias in six trials published as abstracts [20, 23, 32–34, 38]. In total, 10 trials were judged to be at high risk of bias, primarily due to lack of or inappropriate blinding.

I—是否只納入(included)具良好效度的文章？

Table 2 Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) evidence profile

Quality assessment						Patients, number		Effect		Quality
Studies, number	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PPIs	H2RAs	Relative (95 % CI)	Absolute (95 % CI)	
Clinically important bleeding										
14	Serious[a]	Not serious	Not serious	Not serious[b]	None	13/986 (1.3 %)	39/693 (5.6 %)	RR 0.39 (0.21, 0.71)	15 fewer per 1000 (7–20 fewer)	Moderate[a,b]
Overt upper gastrointestinal bleeding										
17	Serious[a]	Not serious[c]	Not serious	Not serious	None	53/1102 (4.8 %)	118/795 (14.8 %)	RR 0.48 (0.34, 0.66)	26 fewer per 1000 (17–33 fewer)	Moderate[a,c]
Nosocomial pneumonia										
13	Serious[a]	Not serious[d]	Not serious	Serious[e]	None	119/862 (13.8 %)	92/709 (13.0 %)	RR 1.12 (0.86, 1.46)	16 more per 1000 (18 fewer to 60 more)	Low[a,d,e]
Mortality										
11	Not serious[f]	Not serious	Not serious	Serious[e]	None	151/874 (17.3 %)	120/614 (19.5 %)	RR 1.05 (0.87, 1.27)	10 more per 1000 (25 fewer to 53 more)	Moderate[e,f]
ICU length of stay										
7	Serious[g]	Not serious	Not serious	Serious[h]	None	371	373	-	MD 0.58 days fewer (2.03 fewer to 0.86 more)	Low[g,h]

The Guideline Development Tool was used to summarize the quality of evidence for individual outcomes based on five main domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias. *PPI* proton pump inhibitor, *H2RA* histamine-2-receptor antagonist, *MD* mean difference, *RR* relative risk. [a]We downgraded by one level, for risk of bias; most studies were unblinded. [b]Although the total number of events was small, we did not downgrade for imprecision. [c]Significant inconsistency was not present ($I^2 = 6$ %). [d]Significant inconsistency was not present ($I^2 = 4$ %). [e]We downgraded by one level for imprecision; the confidence interval contains significant benefit and harm. [f]We did not downgrade for risk of bias because mortality is an objective outcome that is less likely to be affected by lack of blinding in clinical trials. [g]We downgraded by one level for risk of bias. [h]We downgraded by one level for imprecision; the confidence interval contained significant benefit and harm

評讀結果: ■是　否　不清楚

步驟 2：系統性文獻回顧的品質如何？(FAITH)

T—作者是否以表格和圖表「總結」(total up) 試驗結果？

T - 作者是否以表格和圖表「總結」(total up) 試驗結果？	
最好的狀況是？	**我可以在哪裡找到這些資訊？**
應該用至少 1 個摘要表格呈現所納入的試驗結果，若結果相近，可針對結果進行統合分析(meta-analysis)，並以「森林圖」(forest plot)呈現研究結果，最好再加上異質性分析（見後文）。	在文章的**結果**章節，可以找到摘要的圖表，以及作者對系統性文獻回顧結果的解釋。

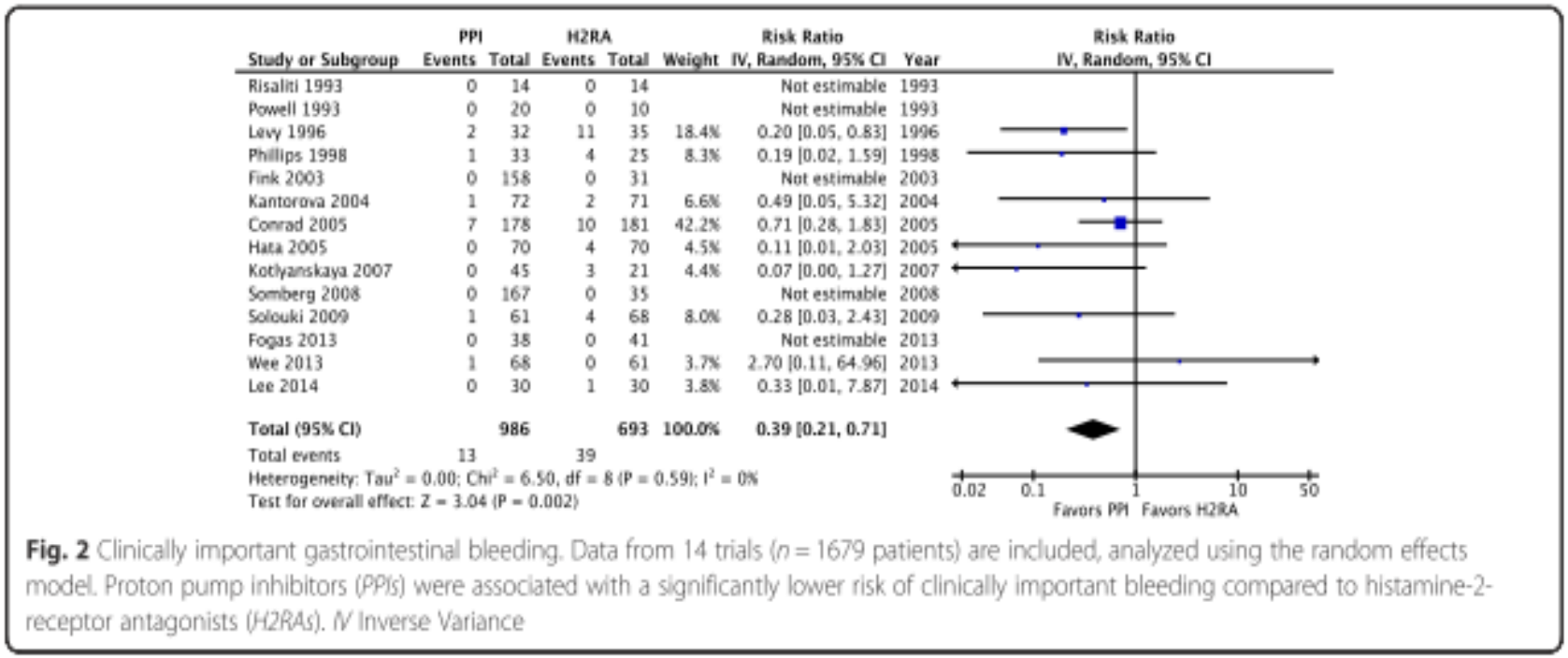

Fig. 2 Clinically important gastrointestinal bleeding. Data from 14 trials ($n = 1679$ patients) are included, analyzed using the random effects model. Proton pump inhibitors (*PPIs*) were associated with a significantly lower risk of clinically important bleeding compared to histamine-2-receptor antagonists (*H2RAs*). *IV* Inverse Variance

步驟2：系統性文獻回顧的品質如何？(FAITH)

T—作者是否以表格和圖表「總結」(total up)試驗結果？

Study or Subgroup	PPI Events	PPI Total	H2RA Events	H2RA Total	Weight	Risk Ratio IV, Random, 95% CI	Year
Risaliti 1993	0	14	0	14		Not estimable	1993
Powell 1993	0	20	0	10		Not estimable	1993
Levy 1996	2	32	11	35	5.2%	0.20 [0.05, 0.83]	1996
Phillips 1998	1	33	4	25	2.4%	0.19 [0.02, 1.59]	1998
De Azevedo 2000	0	38	4	38	1.3%	0.11 [0.01, 1.99]	2000
Fink 2003	0	158	0	31		Not estimable	2003
Kantorova 2004	1	72	2	71	1.9%	0.49 [0.05, 5.32]	2004
Pan 2004	0	20	1	10	1.1%	0.17 [0.01, 3.94]	2004
Conrad 2005	34	178	58	181	57.0%	0.60 [0.41, 0.86]	2005
Hata 2005	0	70	4	70	1.3%	0.11 [0.01, 2.03]	2005
Kotlyanskaya 2007	0	45	3	21	1.3%	0.07 [0.00, 1.27]	2007
Somberg 2008	0	167	0	35		Not estimable	2008
Solouki 2009	3	61	14	68	7.3%	0.24 [0.07, 0.79]	2009
Wee 2013	3	68	1	61	2.1%	2.69 [0.29, 25.19]	2013
Liu 2013	9	58	15	54	18.1%	0.56 [0.27, 1.17]	2013
Fogas 2013	0	38	0	41		Not estimable	2013
Lee 2014	0	30	1	30	1.1%	0.33 [0.01, 7.87]	2014
Total (95% CI)		**1102**		**795**	**100.0%**	**0.48 [0.34, 0.66]**	
Total events	53		118				

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 11.35$, df = 11 (P = 0.41); $I^2 = 3\%$

Test for overall effect: Z = 4.41 (P < 0.0001)

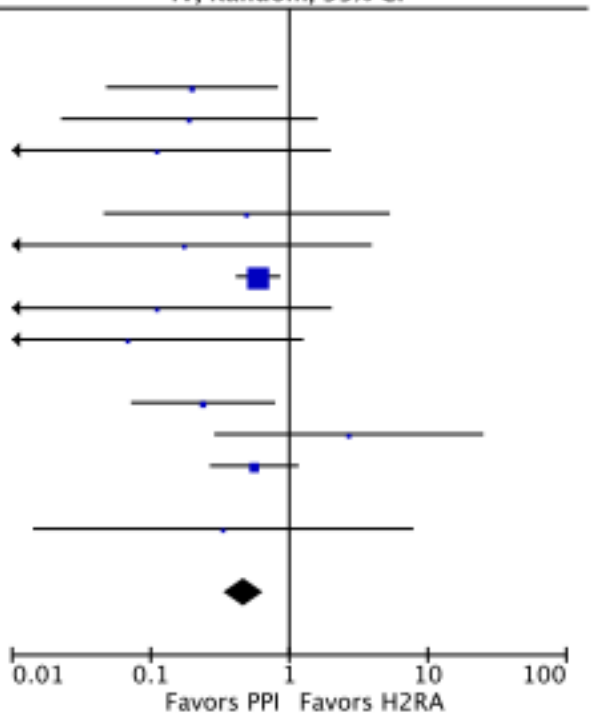

Fig. 3 Overt upper gastrointestinal bleeding. Data from 17 trials ($n = 1897$ patients) are included, analyzed using the random effects model. Proton pump inhibitors (*PPIs*) were associated with a significantly lower risk of overt bleeding compared to histamine-2-receptor antagonists (*H2RAs*). *IV* Inverse Variance

步驟 2：系統性文獻回顧的品質如何？(FAITH)

T—作者是否以表格和圖表「總結」(total up) 試驗結果？

Study or Subgroup	PPI Events	PPI Total	H2RA Events	H2RA Total	Weight	Risk Ratio IV, Random, 95% CI	Year
Levy 1996	1	32	5	35	1.6%	0.22 [0.03, 1.77]	1996
Phillips 1998	6	33	4	25	5.1%	1.14 [0.36, 3.60]	1998
De Azevedo 2000	5	38	4	38	4.5%	1.25 [0.36, 4.30]	2000
Kantorova 2004	8	72	7	71	7.4%	1.13 [0.43, 2.94]	2004
Conrad 2005	20	178	17	181	17.6%	1.20 [0.65, 2.21]	2005
Kotlyanskaya 2007	2	45	4	21	2.6%	0.23 [0.05, 1.17]	2007
Somberg 2008	16	167	3	35	4.9%	1.12 [0.34, 3.63]	2008
Solouki 2009	8	61	6	68	6.8%	1.49 [0.55, 4.04]	2009
Bhanot 2010	11	50	13	50	13.6%	0.85 [0.42, 1.71]	2010
Bashar 2013	18	60	6	60	9.3%	3.00 [1.28, 7.03]	2012
Fogas 2013	9	38	10	41	10.9%	0.97 [0.44, 2.13]	2013
Liu 2013	14	58	12	54	14.6%	1.09 [0.55, 2.14]	2013
Lee 2014	1	30	1	30	0.9%	1.00 [0.07, 15.26]	2014
Total (95% CI)		**862**		**709**	**100.0%**	**1.12 [0.86, 1.46]**	
Total events	119		92				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 12.24$, df = 12 (P = 0.43); $I^2 = 2\%$

Test for overall effect: Z = 0.86 (P = 0.39)

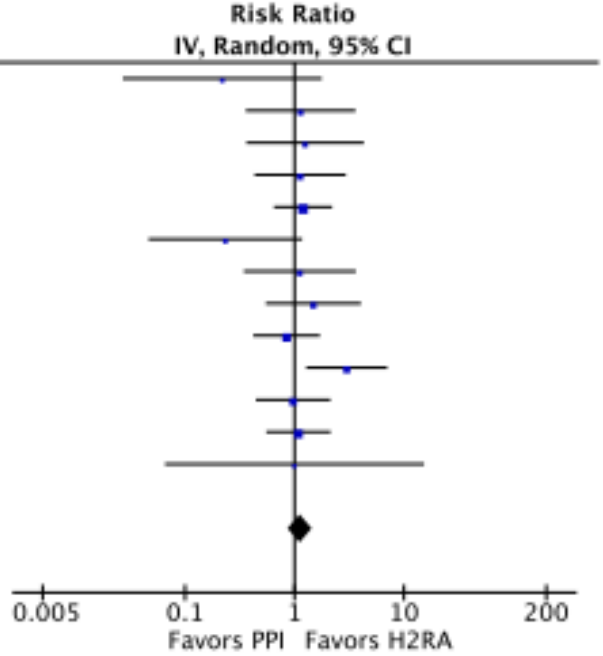

Fig. 4 Pneumonia outcome. Data from 12 trials ($n = 1471$ patients) were included, analyzed using the random effects model. The risk of pneumonia was similar in both groups. *PPI* proton pump inhibitor, *H2RA* histamine-2-receptor antagonist. *IV* Inverse Variance

評讀結果:■是　否　不清楚

步驟 2：系統性文獻回顧的品質如何？(FAITH)

H－試驗的結果是否相近－異質性 (Heterogeneity)？

H - 試驗的結果是否相近 - 異質性 (Heterogeneity)？	
最好的狀況是？	**我可以在哪裡找到這些資訊？**
在理想情況下，各個試驗的結果應相近或具同質性，若具有異質性，作者應評估差異是否顯著(卡方檢定)。根據每篇個別研究中不同的 PICO 及研究方法，探討造成異質性的原因。	在文章的**結果**章節，可以找到研究結果是否具異質性，及造成異質性可能的原因探討。森林圖中可以找到異質性的卡方檢定結果。

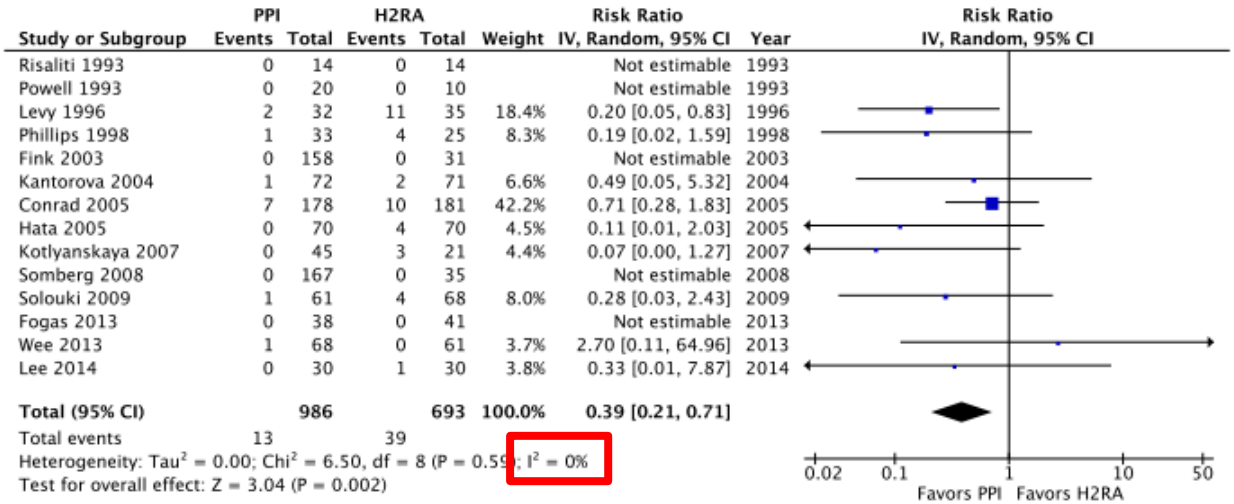

Fig. 2 Clinically important gastrointestinal bleeding. Data from 14 trials ($n = 1679$ patients) are included, analyzed using the random effects model. Proton pump inhibitors (*PPIs*) were associated with a significantly lower risk of clinically important bleeding compared to histamine-2-receptor antagonists (*H2RAs*). *IV* Inverse Variance

步驟 2：系統性文獻回顧的品質如何？(FAITH)

H－試驗的結果是否相近－異質性 (Heterogeneity)？

Study or Subgroup	PPI Events	PPI Total	H2RA Events	H2RA Total	Weight	Risk Ratio IV, Random, 95% CI	Year
Risaliti 1993	0	14	0	14		Not estimable	1993
Powell 1993	0	20	0	10		Not estimable	1993
Levy 1996	2	32	11	35	5.2%	0.20 [0.05, 0.83]	1996
Phillips 1998	1	33	4	25	2.4%	0.19 [0.02, 1.59]	1998
De Azevedo 2000	0	38	4	38	1.3%	0.11 [0.01, 1.99]	2000
Fink 2003	0	158	0	31		Not estimable	2003
Kantorova 2004	1	72	2	71	1.9%	0.49 [0.05, 5.32]	2004
Pan 2004	0	20	1	10	1.1%	0.17 [0.01, 3.94]	2004
Conrad 2005	34	178	58	181	57.0%	0.60 [0.41, 0.86]	2005
Hata 2005	0	70	4	70	1.3%	0.11 [0.01, 2.03]	2005
Kotlyanskaya 2007	0	45	3	21	1.3%	0.07 [0.00, 1.27]	2007
Somberg 2008	0	167	0	35		Not estimable	2008
Solouki 2009	3	61	14	68	7.3%	0.24 [0.07, 0.79]	2009
Wee 2013	3	68	1	61	2.1%	2.69 [0.29, 25.19]	2013
Liu 2013	9	58	15	54	18.1%	0.56 [0.27, 1.17]	2013
Fogas 2013	0	38	0	41		Not estimable	2013
Lee 2014	0	30	1	30	1.1%	0.33 [0.01, 7.87]	2014
Total (95% CI)		**1102**		**795**	**100.0%**	**0.48 [0.34, 0.66]**	
Total events	53		118				

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 11.35$, df = 11 (P = 0.41); $I^2 = 3\%$

Test for overall effect: Z = 4.41 (P < 0.0001)

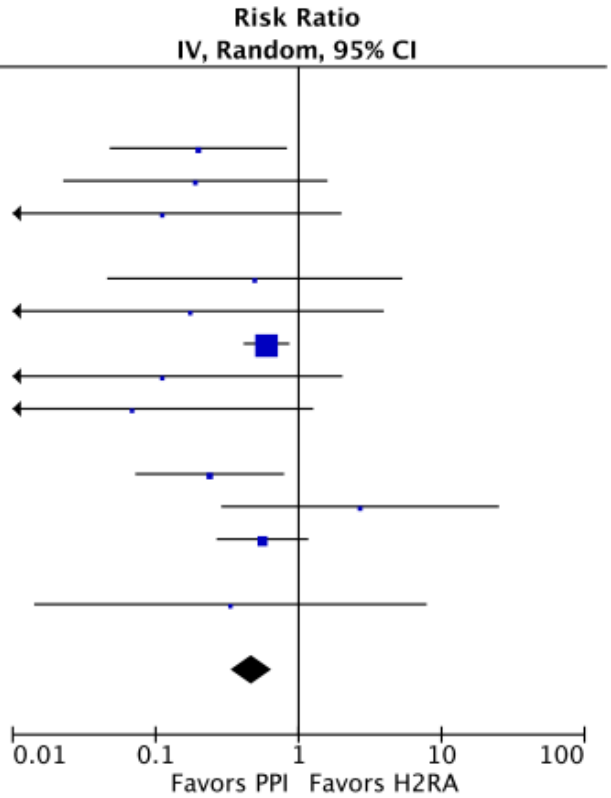

Fig. 3 Overt upper gastrointestinal bleeding. Data from 17 trials ($n = 1897$ patients) are included, analyzed using the random effects model. Proton pump inhibitors (*PPIs*) were associated with a significantly lower risk of overt bleeding compared to histamine-2-receptor antagonists (*H2RAs*). *IV* Inverse Variance

步驟 2：系統性文獻回顧的品質如何？(FAITH)

H－試驗的結果是否相近－異質性 (Heterogeneity)？

Study or Subgroup	PPI Events	PPI Total	H2RA Events	H2RA Total	Weight	Risk Ratio IV, Random, 95% CI	Year
Levy 1996	1	32	5	35	1.6%	0.22 [0.03, 1.77]	1996
Phillips 1998	6	33	4	25	5.1%	1.14 [0.36, 3.60]	1998
De Azevedo 2000	5	38	4	38	4.5%	1.25 [0.36, 4.30]	2000
Kantorova 2004	8	72	7	71	7.4%	1.13 [0.43, 2.94]	2004
Conrad 2005	20	178	17	181	17.6%	1.20 [0.65, 2.21]	2005
Kotlyanskaya 2007	2	45	4	21	2.6%	0.23 [0.05, 1.17]	2007
Somberg 2008	16	167	3	35	4.9%	1.12 [0.34, 3.63]	2008
Solouki 2009	8	61	6	68	6.8%	1.49 [0.55, 4.04]	2009
Bhanot 2010	11	50	13	50	13.6%	0.85 [0.42, 1.71]	2010
Bashar 2013	18	60	6	60	9.3%	3.00 [1.28, 7.03]	2012
Fogas 2013	9	38	10	41	10.9%	0.97 [0.44, 2.13]	2013
Liu 2013	14	58	12	54	14.6%	1.09 [0.55, 2.14]	2013
Lee 2014	1	30	1	30	0.9%	1.00 [0.07, 15.26]	2014
Total (95% CI)		**862**		**709**	**100.0%**	**1.12 [0.86, 1.46]**	
Total events	119		92				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 12.24$, df = 12 (P = 0.43); $I^2 = 2\%$

Test for overall effect: Z = 0.86 (P = 0.39)

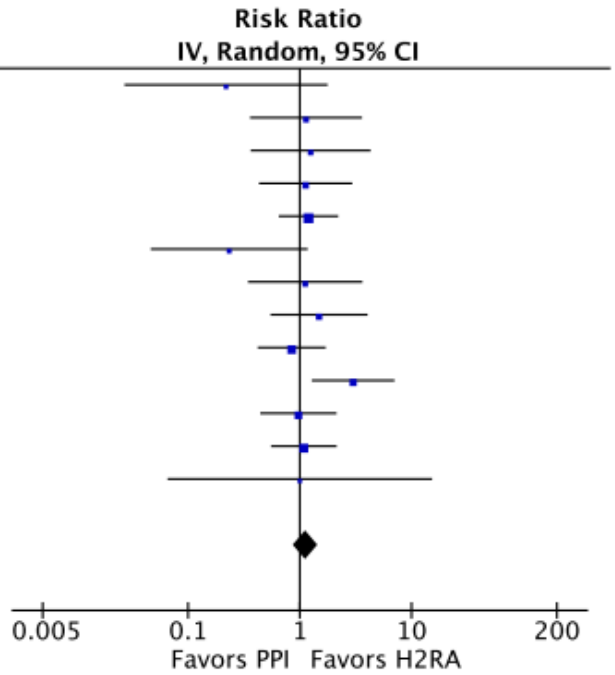

Fig. 4 Pneumonia outcome. Data from 12 trials ($n = 1471$ patients) were included, analyzed using the random effects model. The risk of pneumonia was similar in both groups. *PPI* proton pump inhibitor, *H2RA* histamine-2-receptor antagonist. *IV* Inverse Variance

Main outcomes

- A total of 14 trials enrolling 1679 patients reported clinically important GI bleeding PPI use was associated with lower risk of clinically important GI bleeding compared to H2RAs (RR 0.39; 95 % CI 0.21, 0.71; P = 0.002; I^2 = 0 %; moderate confidence).
- Using an assumed control event rate of 3 %, the number needed to treat (NNT) was 55 (95 % CI 42, 115).
- Seventeen trials enrolling 1897 patients reported overt GI bleeding Prophylaxis with PPI was associated with a lower risk of overt GI bleeding compared to H2RA (RR 0.48; 95 % CI 0.34, 0.66; P < 0.0001; I^2 = 3 %, moderate confidence).
- The NNT to prevent GI bleeding was 37 (95 % CI 29, 59) for an assumed control event rate of 5 %

Publication bias

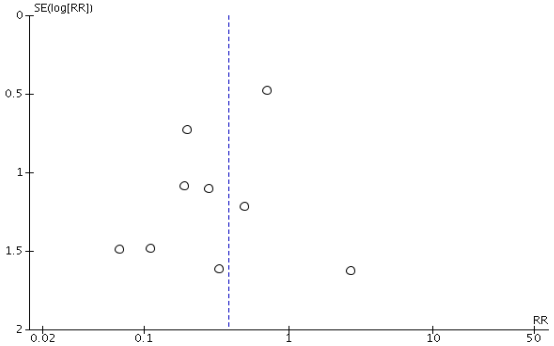

Figure 8: Funnel Plot for Clinically Important Bleeding Outcome

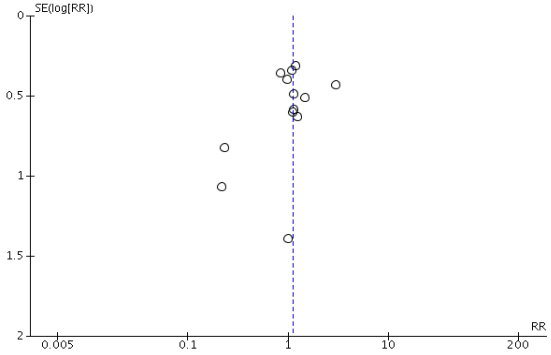

Figure 9: Funnel plot for pneumonia outcome

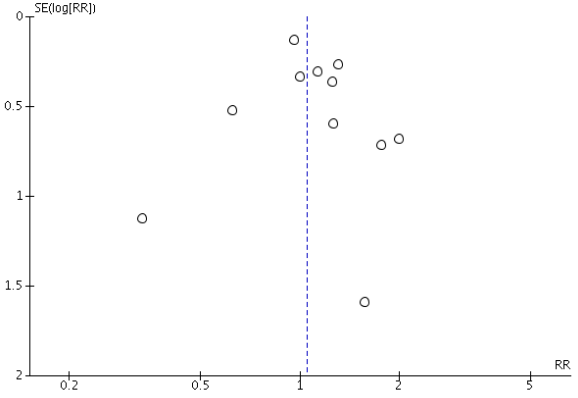

Figure 10: Funnel plot for ICU mortality outcome

Discussion the clinical application

IV Proton pump inhibitors for stress ulcer bleeding prophylaxis in case of ICU and MV

Agree or Not ??


THANK
YOU!