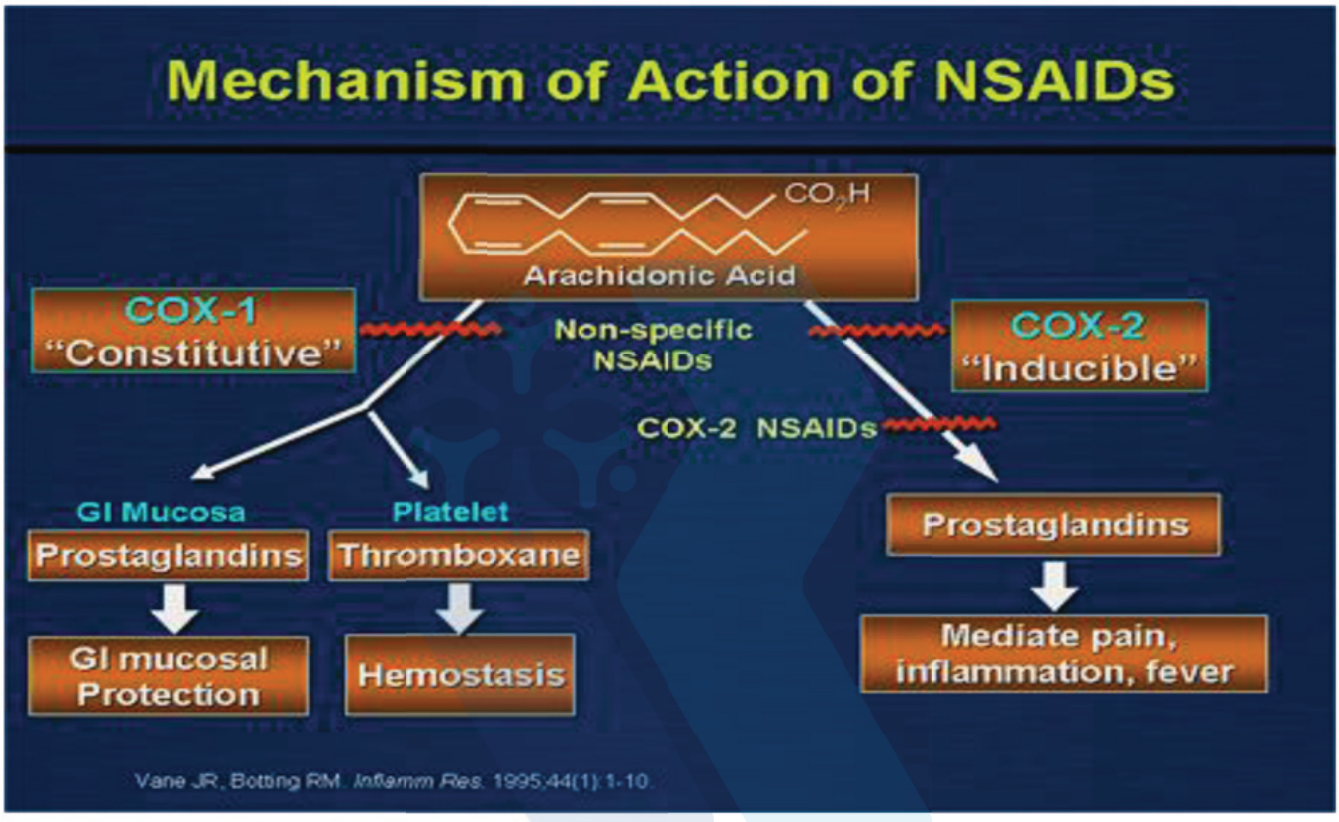
DỰ PHÒNG TỔN THƯƠNG ĐƯỜNG TIÊU HÓA DO NSAIDS

PGS.TS.BS BÙI HỮU HOÀNG
Phó Chủ tịch - Hội Y Học TP.HCM
Ban Chuyên gia – Bệnh viện ĐH Y Dược TP.HCM



Phân loại NSAIDS

NSAID
Non steroidal anti-inflammatory Drugs

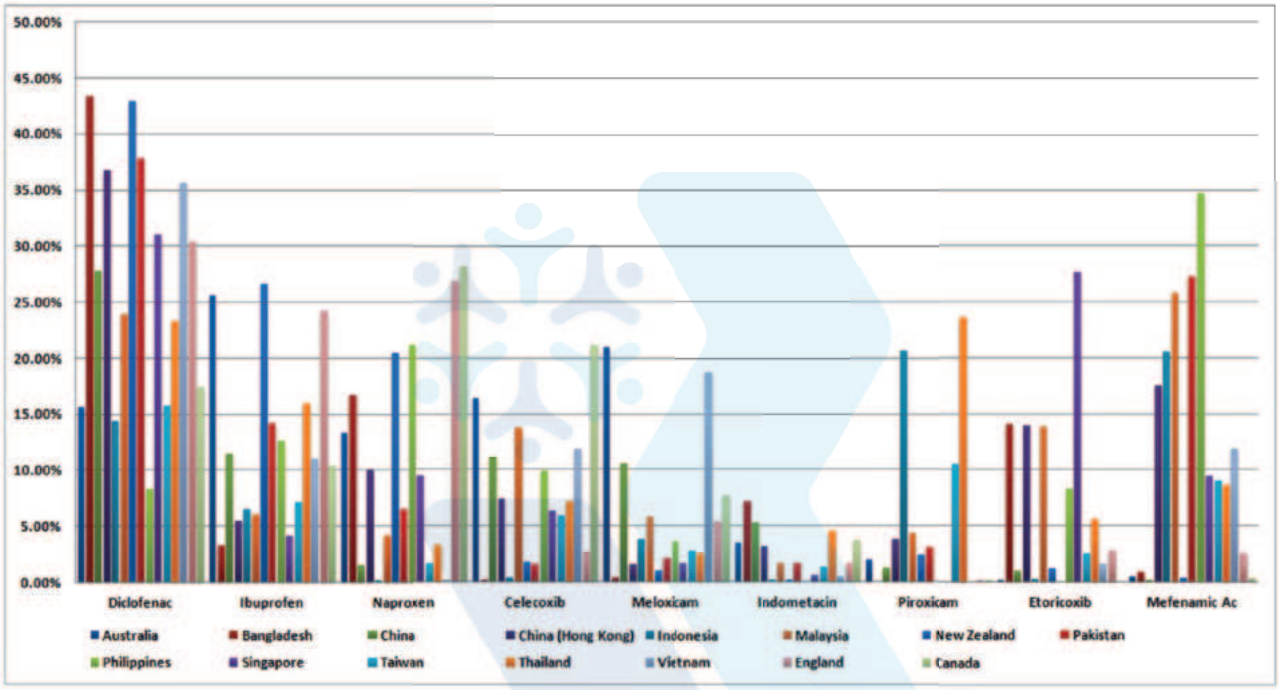
- Non-Selective COX Inhibitor
- Preferential COX_2 Inhibitor — Nimesulide, Diclofenac, Aceclofenac, Meloxicam, Etodolac
- Selective COX_2 Inhibitor — Celecoxib, Etoricoxib, Parecoxib
- Analgesic-Antipyretic with poor Anti-inflammatory Action

Category	Example
Salicylates	Aspirin
Propionic acid derivative	Ibuproprofen, Naproxen, Ketoprofen, Flurbiprofen
Fenamate	Mephenmic acid
Enolic acid derivative	Piroxicam, Tenoxicam
Acetic acid derivative	Ketorolac, Indomethacin, Nabumetone
Pyrazolone derivative	Phenylbutazone, Oxyphenbutazone

Example
Paracetamol (Acetaminophen)
Metamizol, Propiphenazone
Nefopam

Courtesy of Hamza Baig

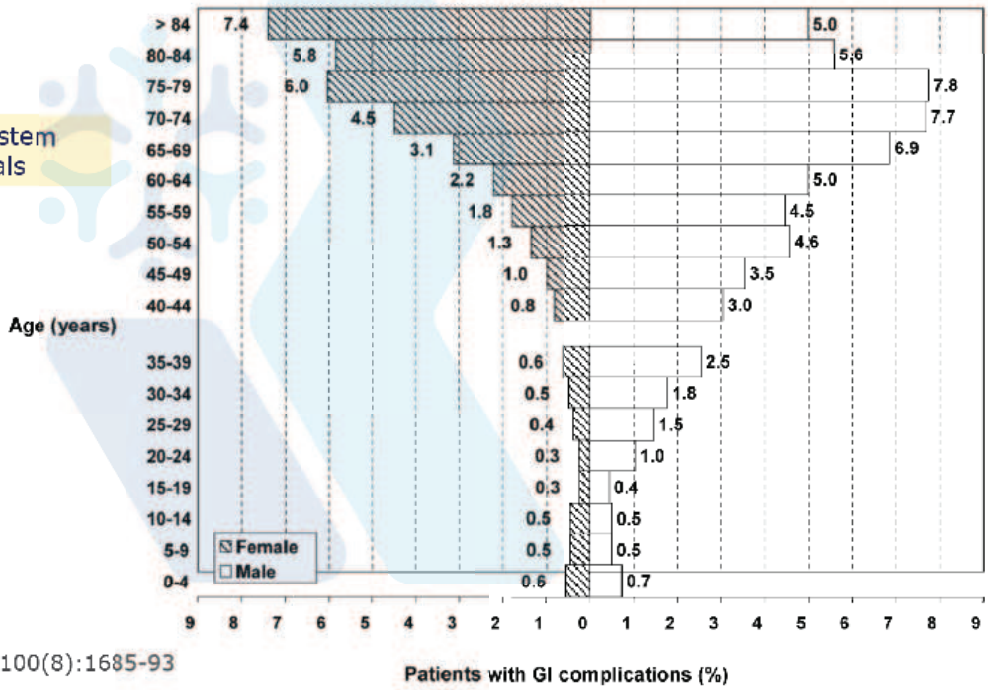
Mức độ tiêu thụ NSAIDS trên thế giới



PLoS Med. 2013;10(2):e1001388

Biến chứng tiêu hóa phân bố theo tuổi và giới

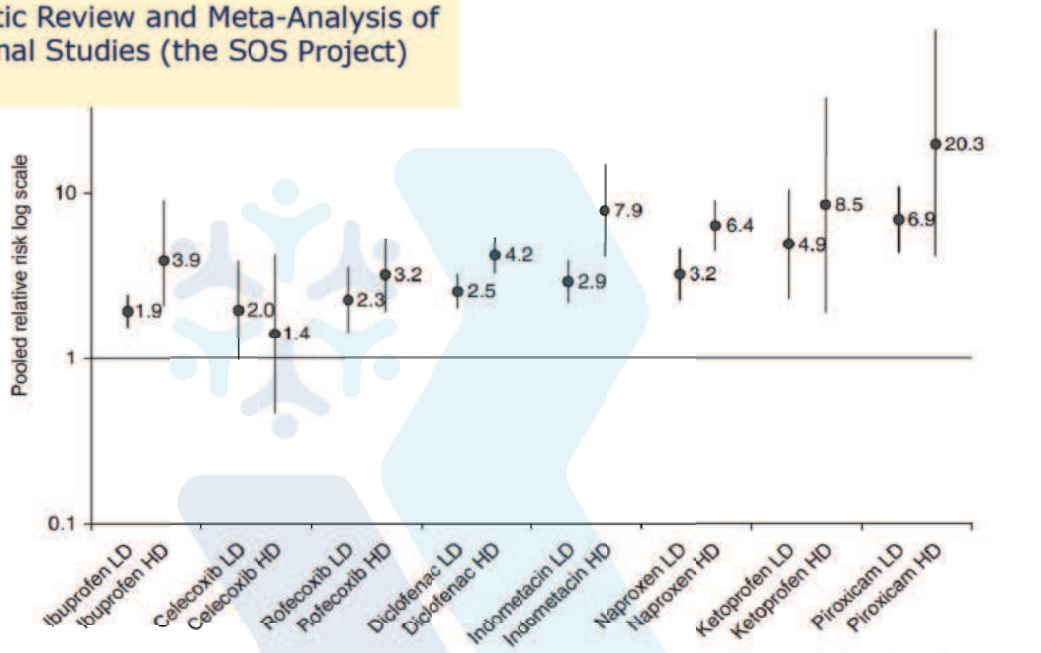
- Spanish National Health System
- Study 1: 26 general hospitals



Am J Gastroenterol. 2005 Aug;100(8):1685-93

Biến chứng tiêu hóa của các loại NSAIDS theo liều

A Systematic Review and Meta-Analysis of Observational Studies (the SOS Project)
N = 28



Drug Saf. 2012 Dec 1;35(12):1127-46

Tử vong và nhập viện liên quan NSAIDS

- Spanish National Health System
- Study 2: 197 general hospitals

Table 2. Distribution of Hospitalization and Mortality Due to GI Bleeding and Perforation by Main Diagnosis (Study 2)

Description	% of All GI Events	Mean Hospital Stay (Days)	Mortality Rate (%)
Gastric ulcer bleeding	21.3	8.36	3.3
Duodenal ulcer bleeding	23.1	7.53	3.5
Peptic ulcer bleeding	1.1	8.55	5.3
Gastrojejunal ulcer	0.8	9.51	3.4
Nonbleeding peptic lesion events	13.2	6.62	1.6
Unspecified GI bleeding	27.5	7.40	9.9
GI perforation	2.1	17.40	30.3
Rectal bleeding	6.5	6.90	5.3
Small-bowel diverticuli with bleeding	0.1	11.60	8.5
Small-bowel diverticulitis with bleeding	<0.1	16.20	13.3
Colonic diverticuli with bleeding	3.5	8.60	1.1
Colonic diverticulitis with bleeding	0.8	10.50	6.8

Am J Gastroenterol. 2005 Aug;100(8):1685-93

NSAIDS và biến chứng trên tiêu hóa

- Phân tích gộp
- 280 thử nghiệm NSAIDs vs placebo (n = 124.513)
- 474 thử nghiệm so sánh các loại NSAIDs (n = 229.296)

NSAID	Upper GI bleed		Any upper GI complication (obstruction, perforation, or bleed)	
	Rate ratio (95 % CI)[a]	*P* value	Rate ratio (95 % CI)[a]	*P* value
Coxib	2.22 (1.64–4.23)[b]	0.0014	1.81 (1.17–2.81)[b]	0.0070
Diclofenac	2.20 (1.06–4.54)[c]	0.0051	1.89 (1.16–3.09)[c]	0.0106
Ibuprofen	3.63 (1.09–12.12)[c]	0.0059	3.97 (2.22–17.10)[c]	<0.0001
Naproxen	5.49 (2.74–10.99)[c]	<0.0001	4.22 (2.71–6.56)[c]	<0.0001

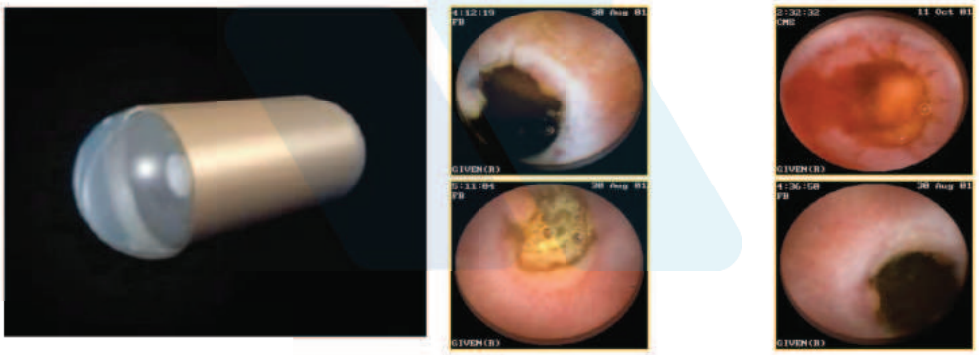
CI confidence interval, *GI* gastrointestinal, *NSAID* non-steroidal anti-inflammatory drug

[a] Rate ratio versus placebo [b] Direct evidence [c] Adjusted rate versus placebo

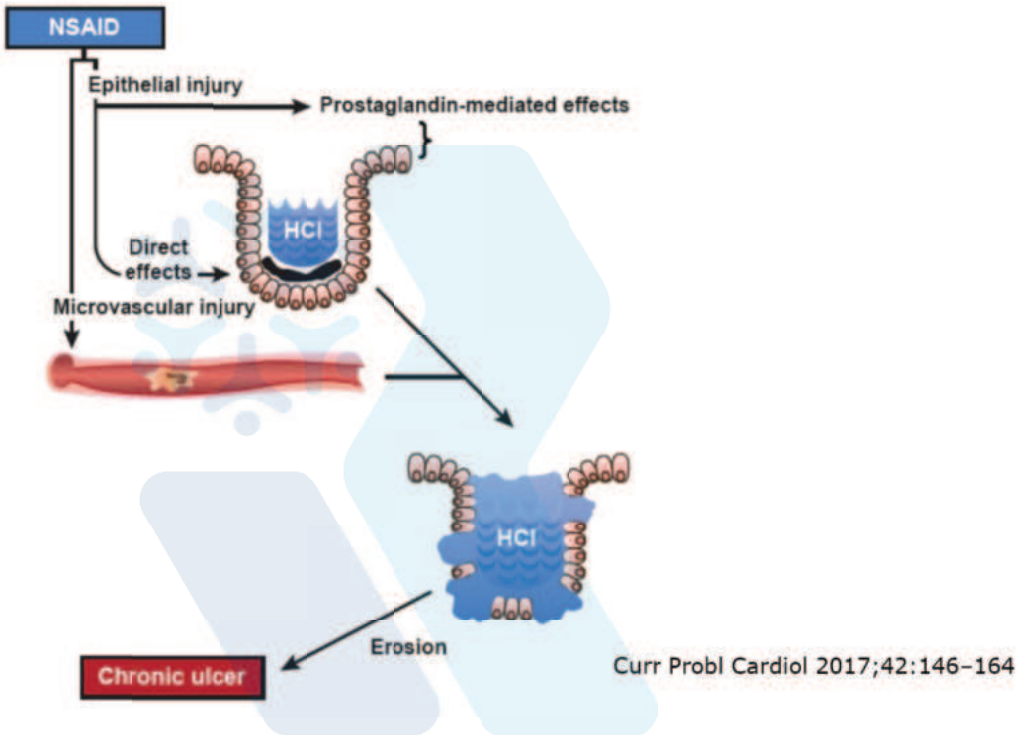
Lancet 2013; 382:769–79

NSAIDS và Xuất huyết tiêu hóa dưới

- ≥ 1/5 trường hợp sử dụng NSAID có liên quan XHTH dưới và giảm Hb do các tổn thương viêm trợt/ loét đường tiêu hóa dưới
- Các dữ liệu được ghi nhận nhờ phương pháp nội soi viên nang
- Nếu không dùng aspirin, thuốc ức chế chọn lọc COX-2 ít gây XHTH dưới hơn các NSAID cổ điển
- PPI hầu như không có tác dụng trên XHTH dưới do NSAID



Cơ chế tác động NSAID/ASA trên ống tiêu hóa



Curr Probl Cardiol 2017;42:146–164

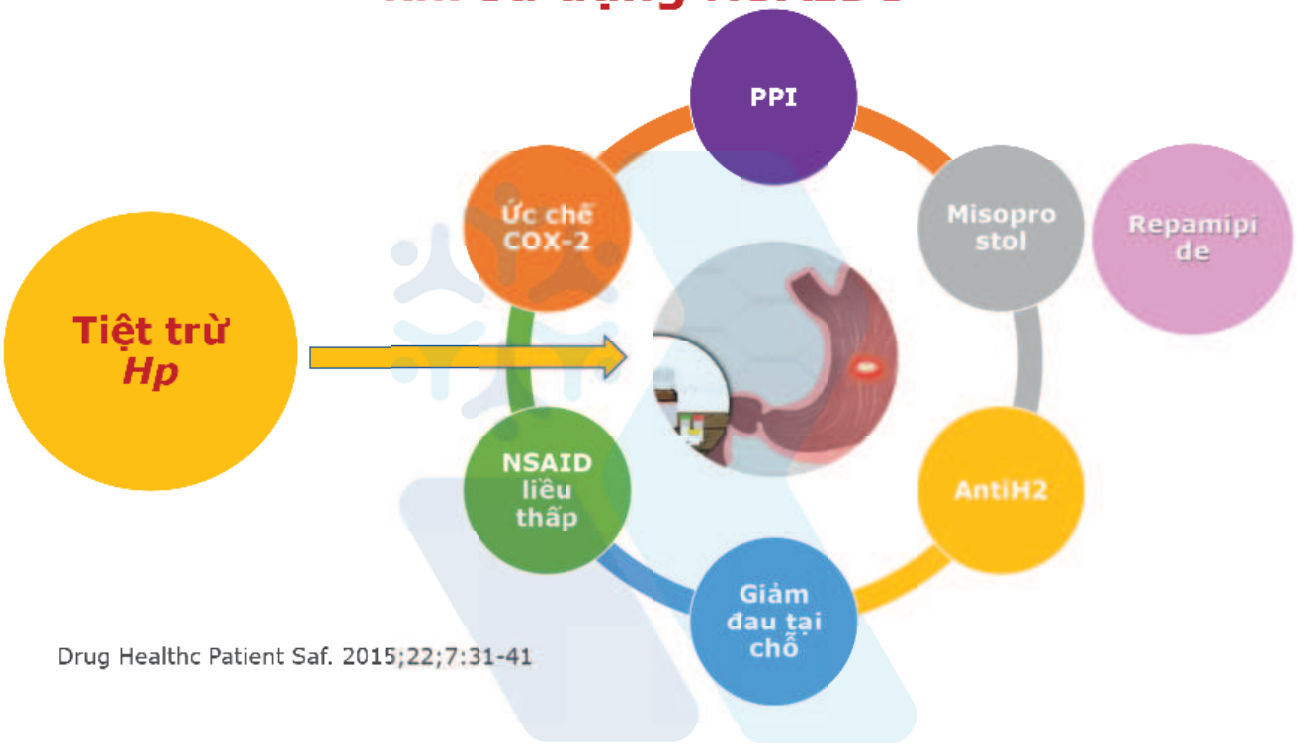
Yếu tố nguy cơ biến chứng tiêu hóa khi sử dụng NSAIDS

Risk factors

- Age 60 years and above
- Dyspepsia history
- Current high dose of NSAID
- Multiple NSAID therapy
- Concomitant use of ASA
- Uncomplicated peptic ulcer history
- Concomitant use of corticosteroids
- Concomitant use of oral anticoagulants
- Peptic ulcer bleeding
- *Helicobacter pylori* infection
- Cigarette smoking
- Alcohol use
- Chronic debilitating disorders, especially cardiovascular disease

Journal of Pain Research 2018:11

Dự phòng biến chứng tiêu hóa khi sử dụng NSAIDS



Drug Healthc Patient Saf. 2015;22;7:31-41

Hiệu quả của Misoprostol so với giả dược

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Gastric ulcers - 4 - 11 week studies	8	2033	Risk Ratio (M-H, Fixed, 95% CI)	0.17 [0.09, 0.31]
2 Duodenal ulcers - 4 - 11 week studies	6	1546	Risk Ratio (M-H, Fixed, 95% CI)	0.30 [0.14, 0.62]
3 Total ulcers - 4 - 11 week studies	4	1323	Risk Ratio (M-H, Fixed, 95% CI)	0.24 [0.14, 0.42]
4 Gastric ulcers - 12 weeks or longer studies	11	3641	Risk Ratio (M-H, Random, 95% CI)	0.26 [0.17, 0.39]
5 Duodenal ulcers - 12 weeks or longer studies	8	2785	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.22, 0.81]
6 Total endoscopic ulcers - 12 weeks or longer studies	6	1791	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.20, 0.59]
7 Total endoscopic ulcers Chan 2001 removed - 12 weeks or longer studies	5	1701	Risk Ratio (M-H, Fixed, 95% CI)	0.28 [0.20, 0.38]
8 Clinical ulcers - 12 weeks or longer studies	2	9276	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.27, 0.87]

Cochrane Database Syst Rev. 2002;(4):CD002296

Bất lợi khi sử dụng Misoprostol

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Nausea	6	11021	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [1.07, 1.48]
2 Dyspepsia	7	10634	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.95, 1.36]
3 Constipation	2	9199	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.38, 1.06]
4 Diarrhea	10	11793	Risk Ratio (M-H, Fixed, 95% CI)	2.36 [2.01, 2.77]
5 Abdominal pain	6	11098	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [1.20, 1.55]
6 Flatulence	3	9638	Risk Ratio (M-H, Random, 95% CI)	2.46 [0.91, 6.65]
7 Vomiting	2	9525	Risk Ratio (M-H, Random, 95% CI)	1.62 [0.36, 7.31]
8 Drop-outs due to side-effects	12	12146	Risk Ratio (M-H, Fixed, 95% CI)	1.41 [1.31, 1.51]
9 Drop-outs overall	15	13239	Risk Ratio (M-H, Random, 95% CI)	1.44 [1.11, 1.86]

Cochrane Database Syst Rev. 2002;(4):CD002296

Comparison of Prevention of NSAID-Induced Gastrointestinal Complications by Rebamipide and Misoprostol: A Randomized, Multicenter, Controlled Trial—STORM STUDY

Effect of rebamipide on endoscopic appearance of NSAID-induced gastric mucosal injury in high-risk subjects

	Rebamipide n = 151 (%)	Misoprostol n = 154 (%)	OR(95%CI)	*p* value
Gastric ulcer	5 (3.3)	2 (1.3)	0.38 (0.05–1.81)	0.2574
Duodenal ulcer	1 (0.7)	4 (2.6)	3.99 (0.58–78.68)	0.2174
Peptic ulcer	6 (4.0)	6 (3.9)	0.97 (0.30–3.19)	0.9723

J. Clin. Biochem. Nutr. 2007;40:148–155

Comparison of Prevention of NSAID-Induced Gastrointestinal Complications by Rebamipide and Misoprostol: A Randomized, Multicenter, Controlled Trial—STORM STUDY

Cumulative incidences of dyspeptic and abdominal symptoms determined from patients diaries

Number of dyspeptic and abdominal symptoms	Rebamipide (%)	Misoprostol (%)	*p* value
Diarrhea	4 (1.9)	43 (21.2)	<.0001
Low abdominal pain	16 (7.7)	30 (14.8)	0.0228
Low abdominal symptoms	20	73	<.0001
Nausea	20 (9.7)	20 (9.9)	n.s.
Bloating	21 (10.1)	42 (20.7)	0.0029
Satiety	19 (9.2)	18 (8.9)	n.s.
Fullness	21 (10.1)	32 (15.8)	n.s.
Vomiting	5 (2.4)	9 (4.4)	n.s.
Epigastric pain	28 (13.5)	40 (19.7)	n.s.
Acid regurgitation	11 (5.3)	11 (5.4)	n.s.
Total dyspeptic symptoms	125	172	0.0509
Total	145	245	0.0083

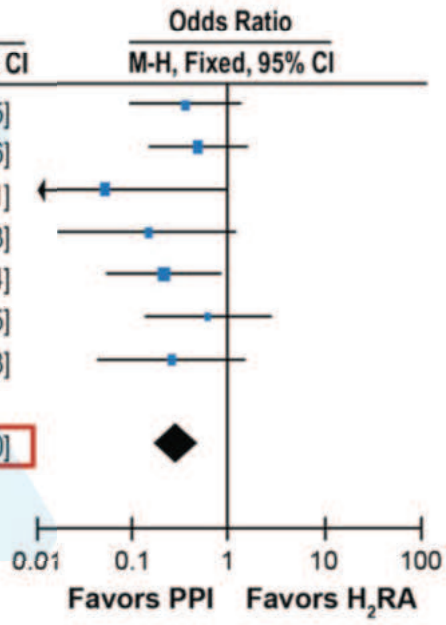
J. Clin. Biochem. Nutr. 2007;40:148–155

Hiệu quả AntiH2 so với PPI

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Guo M 2009	5	42	6	22	13.8%	0.36 [0.10, 1.35]
Hu L 2012	5	50	9	48	16.5%	0.48 [0.15, 1.56]
Ng 2010	0	65	8	65	16.8%	0.05 [0.00, 0.91]
Ng 2012	1	163	6	148	12.5%	0.15 [0.02, 1.23]
Sun RR 2012	3	40	11	40	20.3%	0.21 [0.05, 0.84]
Wang J 2012	3	43	5	46	9.0%	0.61 [0.14, 2.75]
Wang YP 2012	2	23	6	22	11.2%	0.25 [0.05, 1.43]
Total (95% CI)		**426**		**391**	**100.0%**	0.28 [0.16, 0.50]
Total events	19		51			

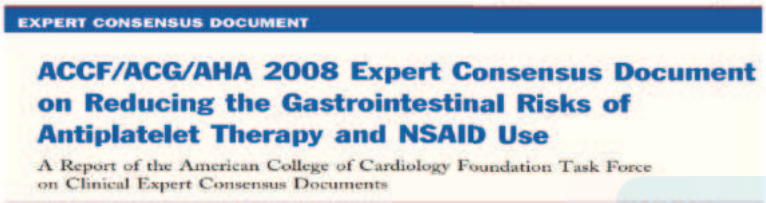
Heterogeneity: Chi² = 3.84, df = 6 (*P*=0.70); I² = 0%

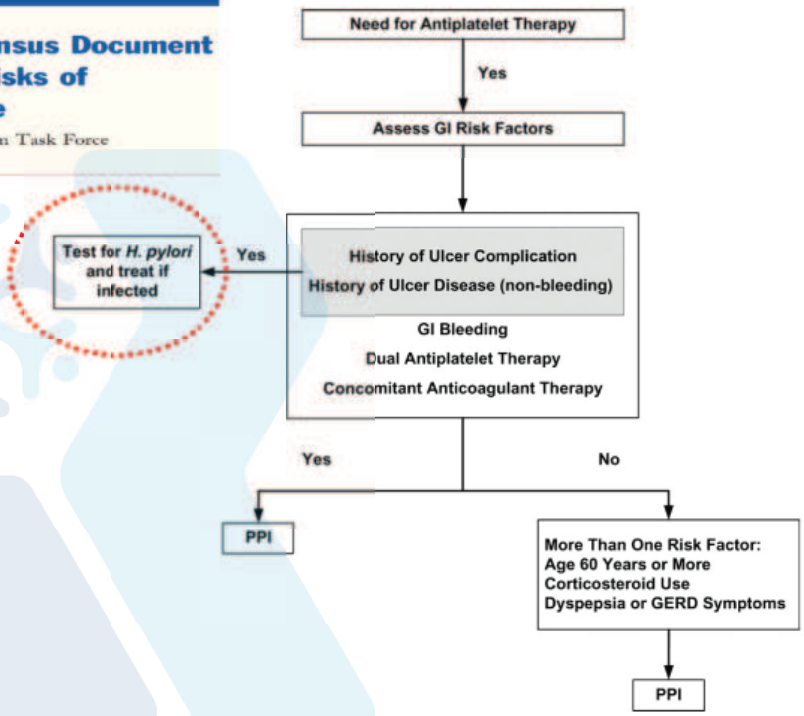
Test for overall effect: Z = 4.39 (*P*<0.0001)



Curr Probl Cardiol 2017;42:146–164

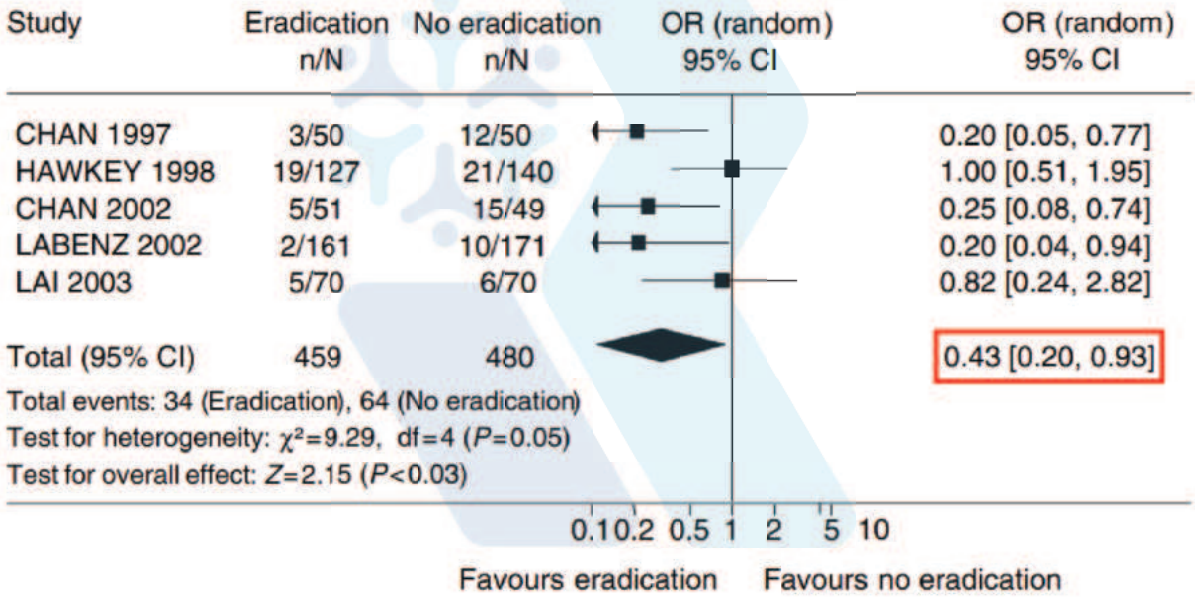
Tiệt trừ *H.pylori*





JACC 2008;52(18):1502–17

Hiệu quả của Tiệt trừ *H.pylori* so với không tiệt trừ *H.pylori* trong dự phòng biến chứng của NSAIDS



Aliment Pharmacol Ther 2005;21: 1411–1418

AGA CLINICAL PRACTICE UPDATE: EXPERT REVIEWS

Bằng chứng lợi ích lâu dài của PPIs

Potential adverse effect	Types of studies	Threats to validity	Overall quality of evidence
GERD with esophagitis or stricture	• Observational • RCT	• Generalizability to patients with non-severe esophagitis • Absence of long-term data	Moderate to high
GERD without esophagitis or stricture	• Observational • RCT	• Generalizability to patients with relatively mild symptoms • Absence of long-term data • Absence of objective outcome data	Moderate
Barrett's esophagus with GERD	• Observational • RCT	• Indirect evidence extrapolated from GERD • Absence of long-term data	Moderate to high
Barrett's esophagus without GERD	• Observational	• Inconsistent results • Modest effect size	Low
NSAID bleeding prophylaxis	• Observational • RCT	• Generalizability to patients at lower baseline risk for bleeding • Absence of long-term data	High

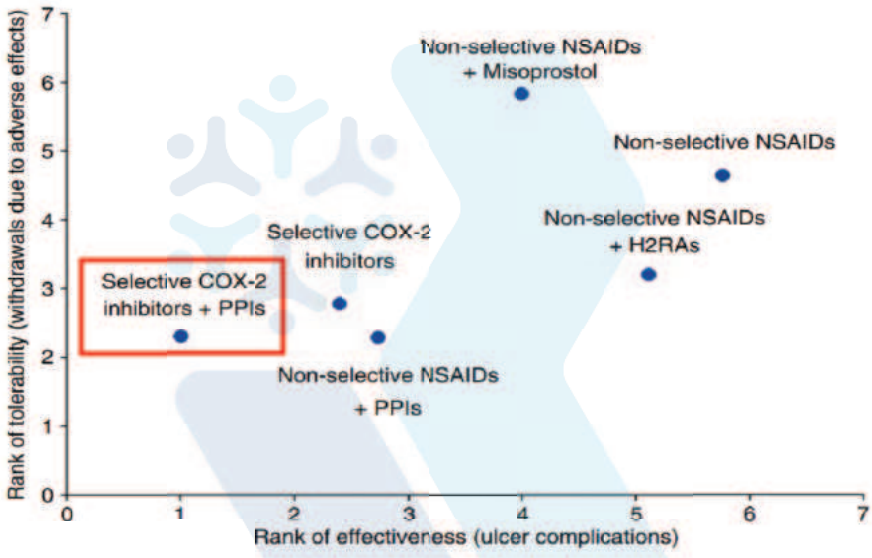
Gastroenterology 2017;152:706–715

Yếu tố ủng hộ PPIs ngắn hạn và lâu dài cho BN dùng NSAID

- Age > 70 years
- Prior ulcer
- History of ulcer complications, especially bleeding
- NSAIDs at high doses/multiple agents or in combination with other drugs (steroids, selective serotonin re-uptake inhibitors, warfarin)
- Aspirin use, even at low dosage in elderly patients, or combined with other drugs (NSAIDs, steroids, anticoagulants, clopidogrel)
- Ticlopidine or clopidogrel use in patients at high risk (see above)
- Acute NSAIDs use in patients taking chronically anticoagulant drugs of any type

Int J Clin Pract 2012;66(6):582–591

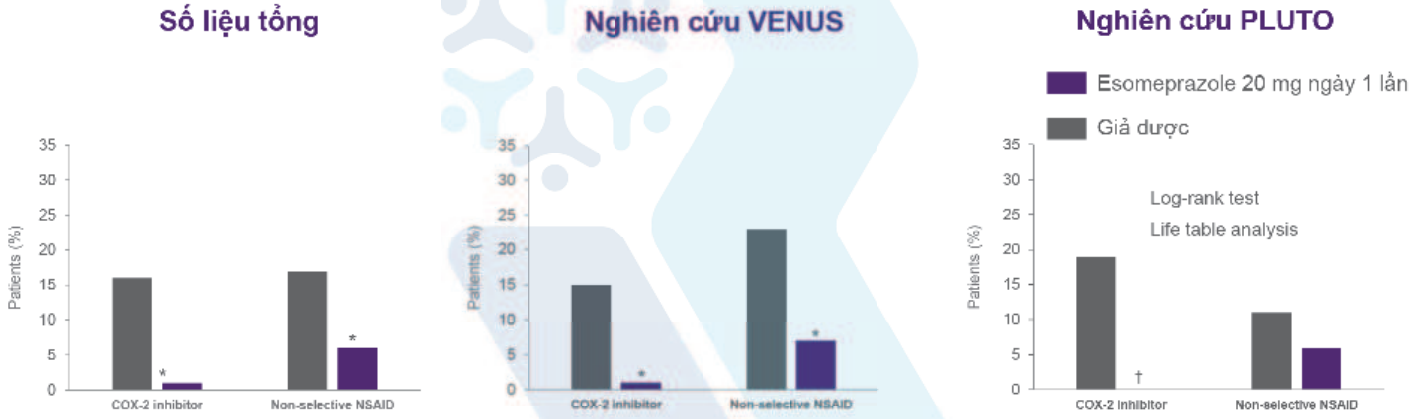
Systematic review with network meta-analysis: comparative effectiveness and safety of strategies for preventing NSAID-associated gastrointestinal toxicity



Aliment Pharmacol Ther 2016; 43: 1262–1275

Sử dụng NSAIDS kèm esomeprazole làm giảm tỉ lệ phát triển thành loét dạ dày – tá tràng[1]

Tỉ lệ cộng dồn trong 6 tháng [1]

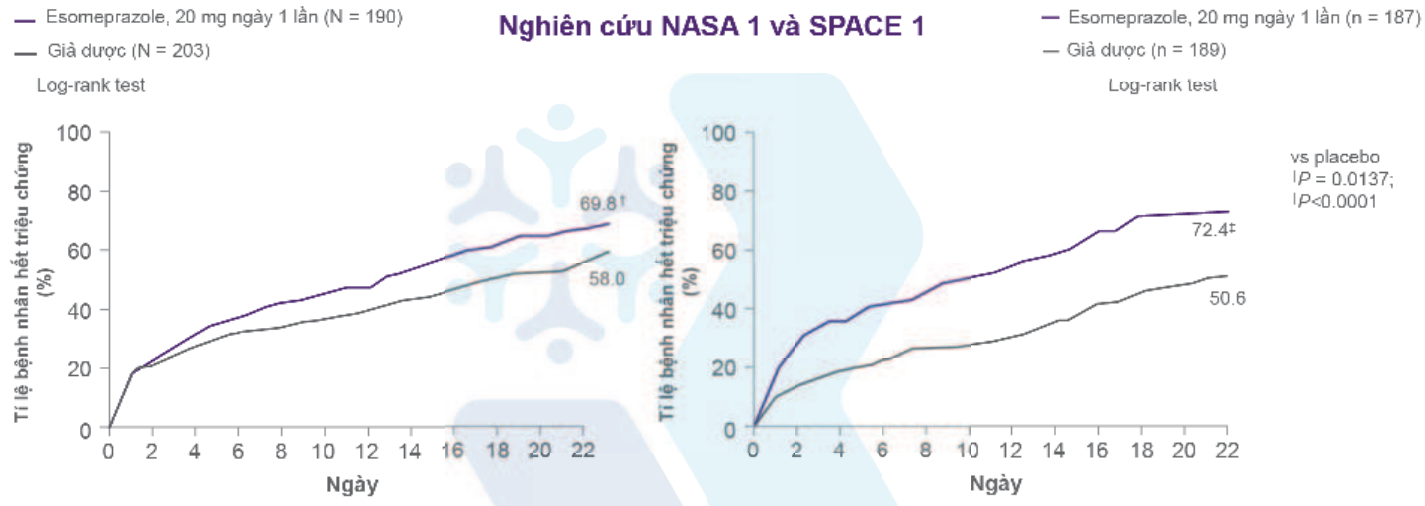


Cumulative proportion of patients developing a gastric ulcer (GU) or duodenal ulcer (DU) at 6 months, split by non-steroidal anti-inflammatory drug (NSAID) type for the (A) pooled study data, (B) VENUS study, and the (c) PLUTO study, based on life table estimates, intent-to-treat population, *P<0.001, †P = 0.03, versus placebo (log rank test). 95% confidence intervals are shown.

Adapted from Scheiman JM, et al, 2006.

COX = cyclooxygenase; NSAID = nonsteroidal anti-inflammatory drug; PLUTO = precutaneous shunting in lower urinary tract obstruction study
An analysis of two studies Venus study (N = 844) and Pluto (N = 585) in At Risk Patients using Non Selective NSAIDs and COX2 Inhibitors
1. Scheiman JM, Yeomans ND, Talley NJ et al. Prevention of ulcers by esomeprazole in at risk patients using non selective NSAIDs and COX-2 inhibitors. *Am J Gastroenterol* 2006; 101(4): 701-710

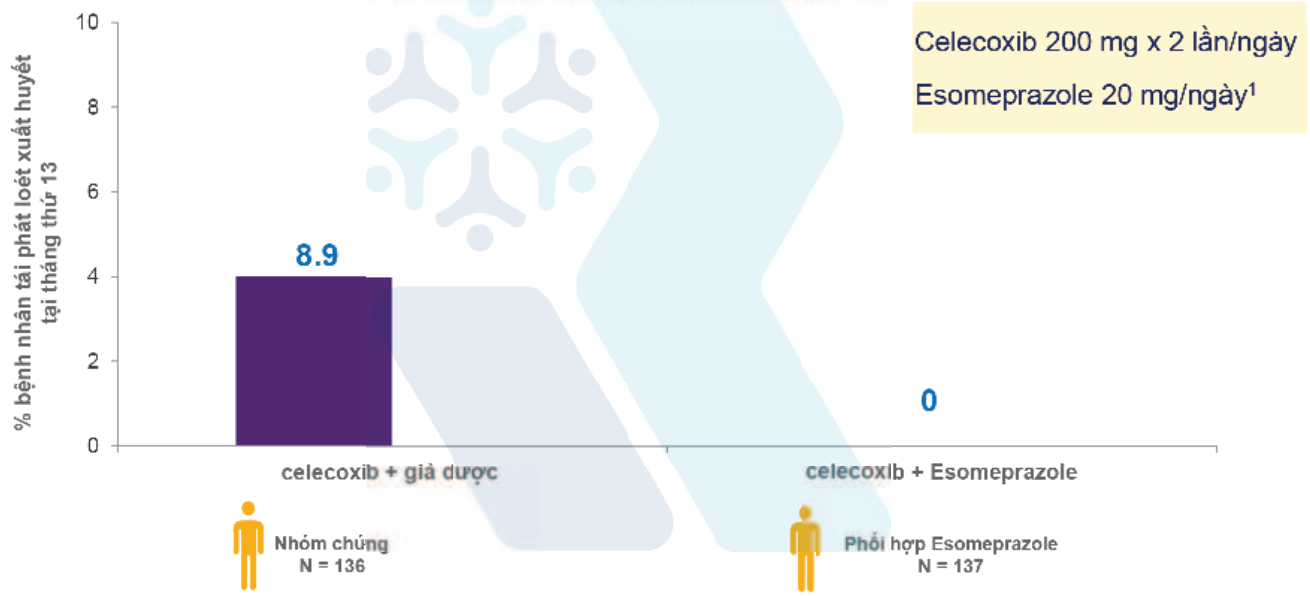
Esomeprazole cải thiện triệu chứng rõ rệt ở bệnh nhân loét tiêu hóa trên do sử dụng NSAID chọn lọc COX-2[1]



Adapted from Hawkey CJ, et al, 2005.

COX = cyclooxygenase; NSAID = nonsteroidal anti-inflammatory drug
*Defined as any 7 consecutive days with a diary assessment of 'none' or 'minimal', but with up to 2 days rated as 'mild' during the 7-day period
1. Hawkey C, Talley NJ, Yeomans ND, et al. Improvements with esomeprazole in patients with upper gastrointestinal symptoms taking non-steroidal antiinflammatory drugs, including selective COX-2 inhibitors. *Am J Gastroenterol* 2005;100(5):1020-1036

Esomeprazole kèm Celecoxib làm giảm rõ rệt nguy cơ tái phát loét xuất huyết trong thời gian dài[1]



Adapted from Chan FK, et al, 2007.

A randomised, double-blind 12 months trial of 273 patients who were taking non-selective NSAIDs for arthritis, enrolled after their ulcers had healed and a histological test for Helicobacter pylori was negative.

1. Chan FK, Wong VW, Suen BY, et al. Combination of a cyclo-oxygenase-2 inhibitor and a proton-pump inhibitor for prevention of recurrent ulcer bleeding in patients at very high risk: a double-blind, randomised trial. Lancet. 2007; 369(9573): 1621-1626.

Hướng dẫn điều trị NSAIDS lâu dài dựa vào nguy cơ tiêu hóa và tim mạch

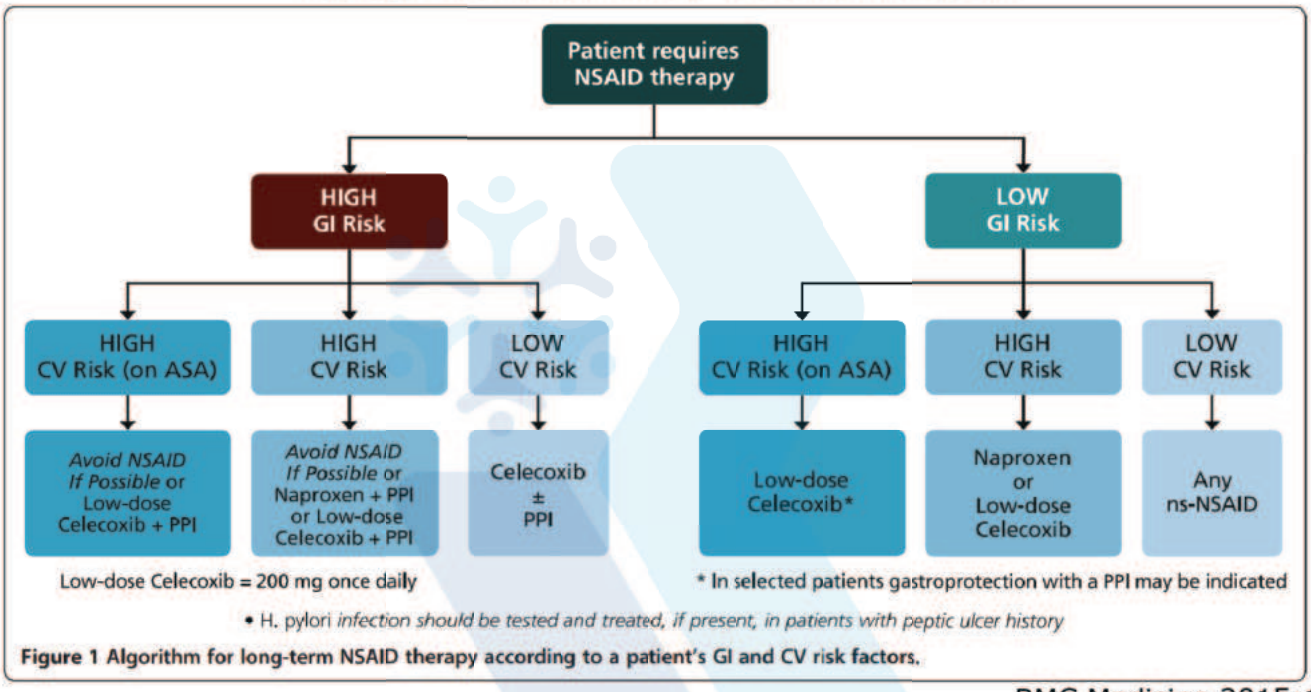
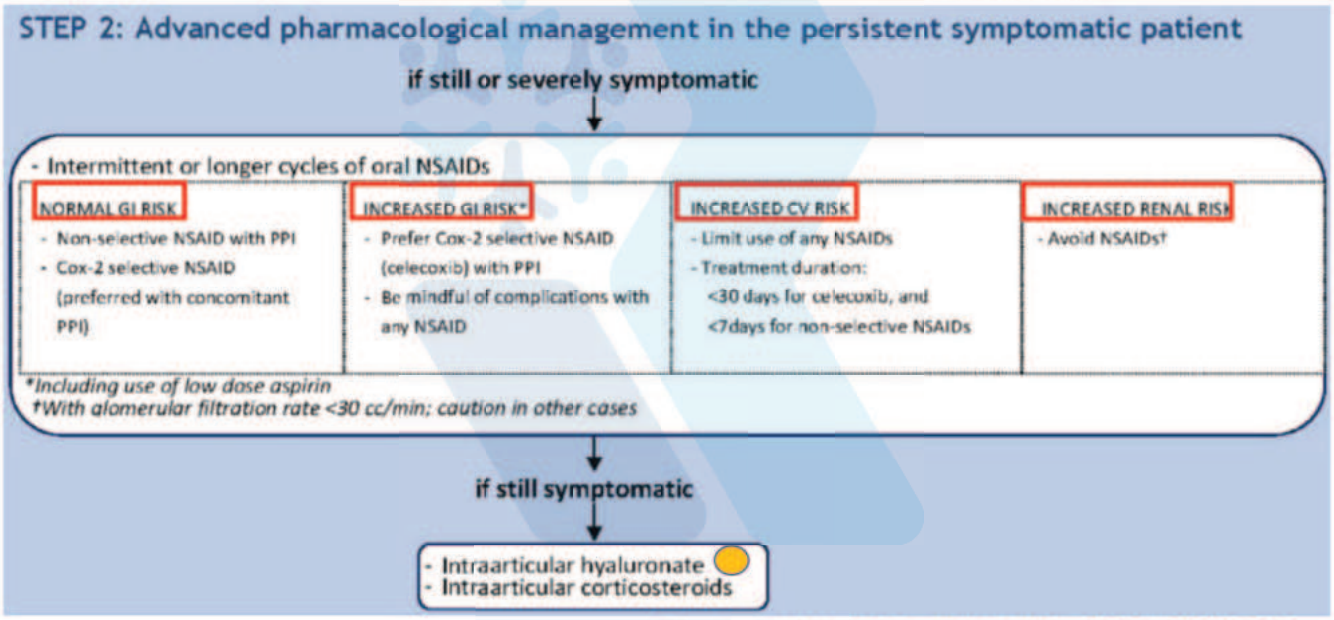


Figure 1 Algorithm for long-term NSAID therapy according to a patient's GI and CV risk factors.

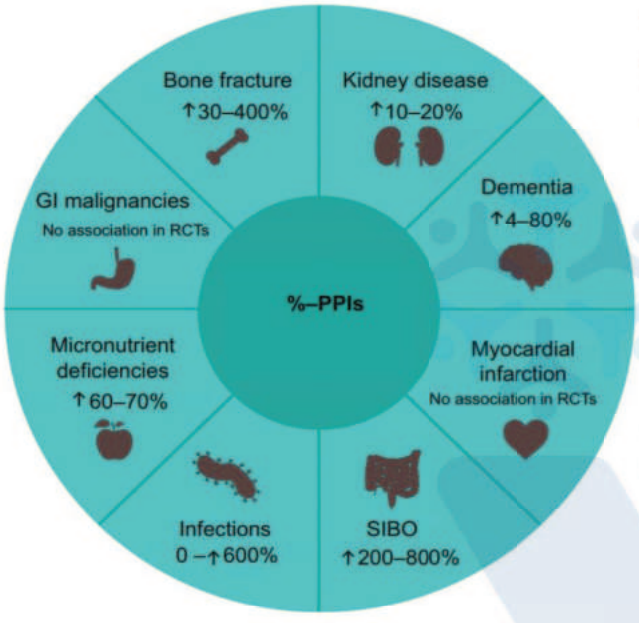
BMC Medicine 2015;13:55

An updated algorithm recommendation for the management of knee osteoarthritis from the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO)



Seminars in Arthritis and Rheumatism 2019;49:337-350

Tác dụng bất lợi của PPIs lâu dài



Gastroenterology 2017;152:706–715

Summary of Evidence for Potential PPI-Associated Adverse Effects

Potential adverse effect	Types of studies	Threats to validity	Overall quality of evidence
Kidney disease	• Observational only	• Modest effect size • Residual confounding would bias towards harm • Absence of dose-response effect	Very low
Dementia	• Observational only	• Modest effect size • Residual confounding would bias towards harm	Very low
Bone fracture	• Observational only	• Inconsistent results • Modest effect size • Residual confounding would bias towards harm	Low or very low
Myocardial infarction	• Observational • RCT	• Results differ between RCTs and observational studies • Secondary analysis of RCT data • Modest effect size • Residual confounding would bias towards harm	Very low
Small intestinal bacterial overgrowth	• Observational • Crossover	• Sparse data • Residual confounding would bias towards harm • Protopathic bias	Low
Spontaneous bacterial peritonitis	• Observational only	• Modest effect size • Residual confounding would bias towards harm	Very low
Clostridium difficile infection	• Observational only	• Modest effect size • Residual confounding would bias towards harm	Low
Pneumonia	• Observational • RCT	• Results differ between RCTs and observational studies • Secondary analysis of RCT data • Modest effect size • Absence of dose-response effect • Residual confounding would bias towards harm • Protopathic bias	Very low
Micronutrient deficiencies	• Observational only	• Inconsistent results • Modest effect size • Absence of dose-response effect • Residual confounding would bias towards harm	Low or very low
Gastrointestinal malignancies	• Observational • RCT	• Results differ between RCTs and observational studies • RCTs use surrogate outcomes • Modest effect size • Residual confounding would bias towards harm • Confounding by indication and protopathic bias	Very low

NOTE. Assessments regarding the quality of evidence are based on the methodology of the GRADE Working Group (see inset).[77]

Kết luận

- NSAIDS là thuốc giảm đau kháng viêm được sử dụng phổ biến nhất
- Biến chứng tổn thương tiêu hóa rất thường gặp, có nguy cơ tử vong do xuất huyết tiêu hóa
- Xem xét đánh giá yếu tố nguy cơ trước khi sử dụng NSAIDS
- Dự phòng bất lợi do NSAIDS:
  - PPI
  - Tìm và tiệt trừ *H.pylori*
  - NSAIDS chọn lọc COX-2
  - Biện pháp thay thế
- Cân nhắc chỉ định và liều thuốc phù hợp.