GERD와 NSAID 궤양의 long-term management

성균관대학교 내과 이준행
GERD의 long-term management
Modern diagnosis of GERD: the Lyon Consensus

C Prakash Gyawali,1 Peter J Kahrilas,2 Edoardo Savarino,3 Frank Zerbib,4 Francois Mion,5,6,7 André J P M Smout,8 Michael Vaezi,9 Daniel Sifrim,10 Mark R Fox,11,12 Marcelo F Vela,13 Radu Tutuian,14 Jan Tack,15 Albert J Bredenoord,8 John Pandolfino,2 Sabine Roman5,6,7

ABSTRACT
Clinical history, questionnaire data and response to antisecretory therapy are insufficient to make a conclusive diagnosis of GERD in isolation, but are of value in determining need for further investigation. Conclusive evidence for reflux on oesophageal testing include advanced grade erosive oesophagitis (LA grades C and D), long-segment Barrett’s mucosa or peptic strictures on endoscopy or distal oesophageal acid exposure time (AET) >6% on ambulatory pH or pH-impedance monitoring. A normal endoscopy does not exclude GERD, but provides supportive evidence refuting GERD in conjunction with distal AET <4% and <40 reflux episodes on pH-impedance monitoring off proton pump inhibitors. Reflux-symptom association on ambulatory

peristalsis.5 GERD symptoms, however, have multiple potential determinants including the number of reflux episodes, the proximal extent to which the refluxate migrates, the acidity of the refluxate, oesophageal hypersensitivity and cognitive hypervigilance. Consequently, depending on the clinical context, the defining features of GERD can be pathology, physiology or symptomatology. In this paradigm, oesophageal testing is often undertaken to define optimal management, be that PPI therapy, antireflux surgery (ARS) or cognitive behavioural therapy.

The aim of the GERD consensus process was to determine modern indications for oesophageal testing in GERD, and as an extension to that aim,
Interpretation of esophageal test results in the context of GERD

ENDOSCOPY
- LA grades C&D esophagitis
- Long segment Barrett’s mucosa
- Peptic esophageal stricture

pH or pH-IMPEDANCE
- AET > 6%

HRM

CONCLUSIVE EVIDENCE FOR PATHOLOGIC REFUX
- LA grades C&D esophagitis
- Long segment Barrett’s mucosa
- Peptic esophageal stricture

BORDERLINE OR INCONCLUSIVE EVIDENCE
- LA grades A&B esophagitis

AET 4-6%
- Reflux episodes 40-80

ADJUNCTIVE OR SUPPORTIVE EVIDENCE
- Histopathology (score)
- Electron microscopy (DIS)
- Low mucosal impedance

Reflux-symptom association
- Reflux episodes > 80
- Low MNBI
- Low PSPWI

EVIDENCE AGAINST PATHOLOGIC REFUX
- AET < 4%
- Reflux episodes < 40

Hypotensive EGJ
- Hiatus hernia
- Esophageal hypomotility
Borderline or inconclusive of GERD

- Asymptomatic reflux esophagitis, LA A
분명히 HRM는 필요하지 않습니다.
GERD is increasing in Korea

Fig. 1. Summary of epidemiology of gastroesophageal reflux disease in Korea.
Prevalence of GERD in health checkup

Erosive esophagitis

Reflux symptoms

7%

3%

7%

83%
Ablation 후 PPI 드시면서 속이 쓰리지 않았다고 너무 좋아했던 환자

■ 진료계획

출혈은 없었습니다. 정소 속이 쓰렸는데 내시경 소작을 후 약 먹는 동안에는 전하 쓰리지 않았다.

감감한 첨생질: 1년 후 재검

[투약] 필요시 드세요

Pantoprazole 20mg I T 1회/AM 56일

[검사]

Eosophagegastro-duodenoscopy (-tisiran)

■ 밀그림 및 비자

입도 위

분류: 미량성 위식도유출성
비강성 

비약물치료: 하층문자, 운동

[약, 약], 약 [약], 지방

위산백내거: 1일 1일

위산방성제: 

 penetration

다시 1일 (약, 상) 

다시 1일 (약, 상) 

다시 1일 (약, 상)
PPI (not H₂RA) Treatment of GERD
Treatment goals of GERD

• Relief of symptom(s): the most important goal
• Healing of esophagitis
• Prevention of complication
• Prevention of recurrence
Guidelines for the Treatment of Gastroesophageal Reflux Disease

Jun Haeng Lee, Yu Kyung Cho¹, Seong Woo Jeon², Jie Hyun Kim³, Nawayng Kim⁴, Joon Seong Lee⁵, Young-Tae Bak⁶ and The Korean Society of Neurogastroenterology and Motility

Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, The Catholic University of Korea⁴, Seoul, Kyungpook National University School of Medicine², Daegu, Yonsei University College of Medicine³, Seoul, Seoul National University Bundang Hospital, Seoul National University College of Medicine⁴, Seongnam, Institute for Digestive Research, Soonchunhyang University College of Medicine⁵, Seoul, Department of Internal Medicine, Korea University College of Medicine⁶, Seoul, Korea

Gastroesophageal reflux disease (GERD) is defined as a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications. In the last decade, GERD has been increasing in Korea. Seventeen consensus statements for the treatment of GERD were developed using the modified Delphi approach. Acid suppression treatments, such as proton pump inhibitors (PPIs), histamine-2 receptor antagonists and antacids are effective in the control of GERD-related symptoms. Among them, PPIs are the most effective medication. Standard dose PPI is recommended as the initial treatment of erosive esophagitis (for 8 weeks) and non-erosive reflux disease (at least for 4 weeks). Long-term continuous PPI or on-demand therapy is required for the majority of GERD patients after the initial treatment. Anti-reflux surgery can be considered in well selected patients. Prokinetic agents and mucosal protective drugs have limited roles. Twice daily PPI therapy can be tried to control extra-esophageal symptoms of GERD. For symptomatic patients with Barrett’s esophagus, long-term treatment with PPI is required. Further studies are strongly needed to develop better treatment strategies for Korean patients with GERD.

(Korean J Gastroenterol 2011;57:57-66)

Key Words: Gastroesophageal reflux disease; Treatment; Guideline
Impaired mucosal defence

Impaired LES (smoking, fat, alcohol)
- transient LOS relaxations
- basal tone

Bile and pancreatic enzymes

Bile reflux

oesophageal clearance of acid (lying flat, alcohol, coffee)

Hiatus hernia

acid output (smoking, coffee)

intragastric pressure (obesity, lying flat)

gastric emptying (fat)

Complex pathophysiology
Symptoms suggestive of GERD (burning retrosternal pain responding to antacids) Alarm symptoms?

NO

Antacids and simple antireflux measures (eg, raising bed, weight loss, avoidance of precipitating foods and drug)

Symptoms persist, Nocturnal predominance

PPI

Symptoms persist or recur

No/mild esophagitis

PPI low dose

Maintain for 3 months

Symptoms remit

Reduce to half dose

Symptoms persist and/or nocturnal

PPI full dose

Maintain for 3 months

Symptoms remit

Maintain for 3 months

Persistence of symptoms

Symptoms controlled

4 weeks, then stop

No symptoms

No further investigation

Other diagnoses

Manage as appropriate

PPI therapy for 1 year, age <40 years and/or lifestyle reasons

Increase dose

Long-term medical therapy (with episodic attempts to reduce the dose)

Persistant/recurrerent

Symptoms

Asymptomatic

Maintain for 3 months: Discontinue medication

Laparoscopic fundoplication

Surgery

Resection

Barrett’s esophagus

Diagnostic EGD

Symptoms persist or recur

Mod/severe esophagitis or troublesome symptoms

PPI full dose

Maintain for 3 months

Symptoms remit

Maintain for 3 months

Symptoms persistent and/or nocturnal

PPI full dose and prokinetic

Maintain for 3 months

Surveillance programme

No dysplasia

Low grade

Surveillance at 1 year

No dysplasia

Dysplasia

Low grade

High grade

High-grade PPI for 3 months, then repeat biopsy

Low grade

High grade

Manage as appropriate

H2 blocker

Complex treatment algorithm

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PPI full dose
Simple clinical treatment option

P P I
PPI dosage can be individualized

- Acid inhibition (%)
- PPI dosage (mg)

- Non-erosive GERD
- Maintenance of erosive esophagitis
- Erosive esophagitis

Step down from 20 mg/day
Why PPI is superior to H2RA?

• Factors for successful acid suppression
  – Degree of acid suppression (pH < 4)
  – Time of acid suppression during 24 hours
  – Duration of treatment

![Graph showing the percentage of patients healed after 8 weeks against the duration of intragastric pH > 4 in hours.](Bell. Gut 1992;33:118-124)
Meta-analysis: Healing Rate

- Placebo: 28.2%
- Sucralfate: 39.2%
- Cisapride: 37.9%
- H2-blocker: 51.9%
- PPIs: 83.6%

Chiba. Gastroenterology 1997;112:1798-1810
Meta-analysis: Relief of Heartburn

Chiba. Gastroenterology 1997;112:1798-1810
Rapid tolerance of $H_2$RA

Long-term Tx of GERD
Need for long-term maintenance of GERD

- Even if you stop the medicine and feel pain, this is not simply an unusual thing, but rather an underlying issue.
- This disease is not a disease that is treated, but rather a disease that is managed. Similar to diabetes being treated and not cured, and high blood pressure not being treated, this disease also does not aim for treatment.
- Well managed and symptomless is the best state of life.
- Long-term maintenance is necessary.
EE와 NERD에서 다른 방법이 선택되고 있다

위식도 역류질환의 초 치료 및 유지치료에 관한 온라인 설문조사: 전국 2, 3차 의료기관 소화기내과 전문의를 대상으로

수진·김상균*·정현채*·송인성*·김주성

Fig. 1. Medication of choice for maintenance therapy in mild and severe gastroesophageal reflux disease. GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor; H$_2$RA, H$_2$ receptor antagonist.

Fig. 2. Maintenance strategy of choice for mild and severe gastroesophageal reflux disease. EE, erosive esophagitis; NERD, non-erosive reflux disease.
On demand therapy는 어떻게?

• The recurrence of your determining symptom at a level which you judge as incompatible with your well-being should lead to the start of the treatment.

• The disappearance of this symptom for 48 h should lead to discontinuation of the treatment.
내시경적 치유율은 on demand 중인 환자 보다 매일 PPI 복용자에서 우수하다

Figure 2. Kaplan–Meier estimates of proportions of patients in endoscopic remission during 6 months of maintenance treatment with esomeprazole 20 mg once daily (—) or on-demand (•••••••).
On demand therapy may not be enough for healing esophageal mucosal breaks.
On demand 치료받는 환자는 일주일에 1-3 회 정도의 half dose PPI를 사용한다

♠ On-demand therapy with rabeprazole 10 mg provides an alternative to continuous therapy in patients with mild to moderate gastro-esophageal reflux disease suffering from frequent symptomatic relapses
Initial PPI treatment for 4 – 8 weeks

Uninvestigated, mild EE or NERD

PPI on demand

Unsatisfactory response

Severe EE, frequent attacks or slow PPI response

PPI maintenance
Threshold therapy는 무엇인가?

- For 'threshold' therapy, patients gradually increase the interval between medications (for example, to every second or third day) as long as symptoms do not recur.
- The patient titrates the medication down to a frequency that still maintains adequate control of symptoms.
- This is different from on-demand therapy where each time the patient waits for recurrence of symptoms.

Lifestyle modifications
- only for selected patients

• Grade B: **Weight loss** should be advised for overweight or obese patients with esophageal GERD syndromes.

• Grade B: **Elevation of the head of the bed** for selected patients who are troubled with heartburn or regurgitation when recumbent. Other lifestyle modifications, including avoiding late meals, avoiding specific foods, or avoiding specific activities should be tailored to the circumstances of the individual patient.

• Grade Insuff: Broadly advocating lifestyle changes for all (as opposed to selected) patients with GERD.

*AGA position statement.* Gastroenterology 2008;135:1383-1391
Laparoscopic treatment of GERD
- Lotus trial final results

![Graph showing patients in remission over years after randomization with results for Esomeprazole and LARS, and number of patients at risk for each treatment.]

Log-rank $P = .048$

<table>
<thead>
<tr>
<th>Years After Randomization</th>
<th>Esomeprazole</th>
<th>LARS</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>266</td>
<td>288</td>
</tr>
<tr>
<td>1</td>
<td>228</td>
<td>231</td>
</tr>
<tr>
<td>2</td>
<td>217</td>
<td>216</td>
</tr>
<tr>
<td>3</td>
<td>205</td>
<td>202</td>
</tr>
<tr>
<td>4</td>
<td>199</td>
<td>192</td>
</tr>
<tr>
<td>5</td>
<td>181</td>
<td>168</td>
</tr>
</tbody>
</table>

Galmiche. JAMA 2011;305:1969-77
이준행의 환자 설명서 (1/2)

• 위식도역류질환(GERD)은 하부식도조임근(LES)의 구조적 혹은 기능적 이상으로 위액이 역류하는 질환입니다. 속쓰림, 가슴쓰림, 신물, 흉통 등 다양한 증상이 발생할 수 있습니다. 내시경은 정상일 수 있습니다. 하부식도조임근 이상을 근본적으로 고치기 어렵기 때문에 치료보다는 관리한다는 입장으로 접근해야 합니다. 약을 쓰면 증세가 좋아지고 끊으면 재발하는 그런 병입니다.
• 체중감량, 적절한 운동이 필요하고 야식, 과식, 지방식을 줄이십시오. 담배와 탄산음료도 좋지 않습니다. 약은 하루 한알 아침 식전에 복용하는 위산억제제(PPI)가 표준입니다. 증상이 좋아지면 약을 줄이거나 끊고 필요시만 쓰시면 됩니다. 이틀이나 삼일에 한번 절반용량의 위산억제제를 장기 복용하는 분들이 많습니다.

http://endotoday.com/manual/sulmyung.html#GERD
위산분비 억제제 개발의 역사

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
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<tbody>
<tr>
<td><strong>H₂RA</strong></td>
<td>• Cimetidine, Ranitidine, Famotidine, Nizatidine, Roxatidine</td>
</tr>
<tr>
<td><strong>1st PPI</strong></td>
<td>• Omeprazole, Lansoprazole, Pantoprazole</td>
</tr>
<tr>
<td><strong>2nd PPI</strong></td>
<td>• Rabeprazole, Esomeprazole, Dexlansoprazole, Ilaprazole</td>
</tr>
<tr>
<td><strong>P-CAB</strong></td>
<td>• Revaprazan, Vonoprazan, Tegoprazan</td>
</tr>
</tbody>
</table>
Randomised phase 3 trial: tegoprazan, a novel potassium-competitive acid blocker, vs. esomeprazole in patients with erosive oesophagitis

Kwang Jae Lee1 | Byoung Kwan Son2 | Gwang Ha Kim3 | Hye-Kyung Jung2 | Hwoon-Yong Jung2 | Il-Kwun Chung4 | In-Kyung Sung2 | Jin Il Kim2 | Jong Hyeok Kim5 | Joon Seong Lee2 | Joong Goo Kwon6 | Jung Ho Park2 | Kyu Chan Huh7 | Kyung Sik Park6 | Moo-In Park3 | Nayoung Kim8 | Oh Young Lee2 | Sam Ryong Jee3 | Sang Kil Lee2 | Sei Jin Youn9 | Sung Kook Kim6 | Soo Teik Lee10 | Su Jin Hong11 | Suck Chei Choi12 | Tae Nyeun Kim6 | Young Hoon Youn2 | Hyo Ju Park2 | Min Ja Kang2 | Chi Hye Park2 | Bong Tae Kim2 | Sangjun Youn2 | Geun Seog Song2 | Poong-Lyul Rhee2
## TABLE 2  Healing rates (%) of erosive oesophagitis up to

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Week 8 PPS</th>
<th>Week 4 PPS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% Patients healed</td>
<td>Difference from esomeprazole</td>
</tr>
<tr>
<td>Tegoprazan 50 mg</td>
<td>98.9</td>
<td>0.1</td>
</tr>
<tr>
<td>Tegoprazan 100 mg</td>
<td>98.9</td>
<td>0.0</td>
</tr>
<tr>
<td>Esomeprazole 40 mg</td>
<td>98.9</td>
<td></td>
</tr>
<tr>
<td>ITT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tegoprazan 50 mg</td>
<td>96.0</td>
<td>3.0</td>
</tr>
<tr>
<td>Tegoprazan 100 mg</td>
<td>95.1</td>
<td>2.2</td>
</tr>
<tr>
<td>Esomeprazole 40 mg</td>
<td>92.9</td>
<td></td>
</tr>
</tbody>
</table>

Lee KJ. Aliment Pharmacol Ther 2019
### TABLE 3 Mean RDQ symptom scores at baseline, week 4 and 8 (per protocol set)

<table>
<thead>
<tr>
<th>Mean RDQ</th>
<th>Tegoprazan 50 mg (n = 92)</th>
<th>Tegoprazan 100 mg (n = 91)</th>
<th>Esomeprazole 40 mg (n = 88)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Week 4</td>
<td>Week 8</td>
</tr>
<tr>
<td>Major symptom</td>
<td>2.00</td>
<td>0.58</td>
<td>0.58</td>
</tr>
<tr>
<td>Heartburn</td>
<td>1.76</td>
<td>0.53</td>
<td>0.56</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>1.43</td>
<td>0.41</td>
<td>0.40</td>
</tr>
<tr>
<td>Regurgitation</td>
<td>2.24</td>
<td>0.62</td>
<td>0.60</td>
</tr>
<tr>
<td>Frequency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major symptom</td>
<td>2.02</td>
<td>0.88</td>
<td>0.87</td>
</tr>
<tr>
<td>Heartburn</td>
<td>1.75</td>
<td>0.79</td>
<td>0.79</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>1.54</td>
<td>0.52</td>
<td>0.51</td>
</tr>
<tr>
<td>Regurgitation</td>
<td>2.29</td>
<td>0.97</td>
<td>0.95</td>
</tr>
</tbody>
</table>

RDQ, Reflux Disease Questionnaire.
강력한 위산 분비 억제의 영향을 주시해야 

![Diagram showing the impact of PPIs on various conditions including structural and functional changes in the gastric mucosa, acute kidney injury, chronic kidney disease, dementia, gastrointestinal malignancies, cardiovascular events, negative effect on clopidogrel, pneumonia, hypomagnesaemia, hypocalcaemia, osteoporosis, bone fractures, enteric infections, SIBO, Clostridium difficile infection, and vitamin B₁₂ deficiency.]

Nature Reviews | Gastroenterology & Hepatology
Prothrombotic | Prostacyclin Inhibition (COX-2 mediated) | More GI side toxicity

Less GI side effect | Thromboxane Inhibition (COX-1 mediated) | Anti-thrombotic

Rofecoxib | Diclofenac | Ibuprofen | ASA
Celecoxib | Naproxen
Etoricoxib | Lumiracoxib
Vonoprazan is a problem for hypergastrinemia.
**Product Information**

<table>
<thead>
<tr>
<th>제품(성분)</th>
<th>에소원 정(Esomeprazole 20/40mg)</th>
</tr>
</thead>
</table>
| 효능·효과 | 1. 위식도 역류질환(GERD)  
2. 헬리코박터필로리 박멸을 위한 항생제 병용요법  
3. NSAIDs에 의한 궤양(지속적인 NSAIDs 투여가 필요한 환자)  
4. 촨링거-엘리슨 증후군의 치료  
5. 유지 요법 |

<table>
<thead>
<tr>
<th>용법·용량</th>
<th></th>
<th>ERD</th>
<th>NERD</th>
<th>H.Pylori</th>
<th>NSAIDs</th>
<th>촨링거</th>
<th>유지요법</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>기간</td>
<td>4주/8주</td>
<td>4주</td>
<td>1주</td>
<td>4주</td>
<td>8주</td>
<td>4주</td>
</tr>
<tr>
<td></td>
<td>횟수/d</td>
<td>1회</td>
<td>1회</td>
<td>2회</td>
<td>1회</td>
<td>2회</td>
<td>1회</td>
</tr>
<tr>
<td></td>
<td>용량</td>
<td>40mg</td>
<td>20mg</td>
<td>20mg</td>
<td>20mg</td>
<td>40mg</td>
<td>40mg</td>
</tr>
</tbody>
</table>

| 보험약가 | 20mg: 768원/Tab.  
40mg: 1,078원/Tab. |

<table>
<thead>
<tr>
<th>특장점</th>
<th></th>
</tr>
</thead>
</table>
| ▪ 빠른 증상 개선효과  
▪ 강력한 위산분비 억제 효과 | ▪ 강력한 증상 개선 효과  
▪ 낮은 약물 상호 작용 |
Summary: a personal approach

http://endotoday.com
NSAID 궤양의 long-term management

성균관대학교 내과 이준행
What is NSAID?

Nonsteroidal Anti-Inflammatory Drug
Numerous Side effects And Indispensable Drug
Modified Lanza score

Grade 0
No erosion

Grade 2
3-5 erosions

Grade 3
Two areas

Grade 5
Ulcer
아스피린 2일 드신 후 급성 복통
Abdominal pain
- 5 days after taking NSAID
DU Bleeding (F/72)
- on aspirin + clopidogrel
Meloxicam 쓰시던 분의 동시 궤양
PCI 후 aspirin, ticagrelor $\rightarrow$ 3주 후 출혈
$\rightarrow$ PPI add. 다시 약을 써서 $\rightarrow$ 2주 후 재출혈

PCI 3주 후 첫 출혈

2주 후 재출혈
Primary closure due to BGU perforation

- aspirin과 clopidogrel 드시던 분의 갑작스런 천공
There is no plateau.

MUCOSA Trial\(^1\)

<table>
<thead>
<tr>
<th>NSAIDs (n=4439)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probability of upper GI complication</td>
</tr>
<tr>
<td>Month</td>
</tr>
<tr>
<td>0.15</td>
</tr>
<tr>
<td>0.12</td>
</tr>
<tr>
<td>0.10</td>
</tr>
<tr>
<td>0.09</td>
</tr>
<tr>
<td>0.08</td>
</tr>
<tr>
<td>0.07</td>
</tr>
<tr>
<td>0.06</td>
</tr>
<tr>
<td>0.05</td>
</tr>
<tr>
<td>0.04</td>
</tr>
<tr>
<td>0.03</td>
</tr>
<tr>
<td>0.02</td>
</tr>
<tr>
<td>0.01</td>
</tr>
<tr>
<td>0.00</td>
</tr>
</tbody>
</table>

VIGOR Trial\(^2\)

<table>
<thead>
<tr>
<th>Naproxen (n=4029)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative incidence</td>
</tr>
<tr>
<td>Month</td>
</tr>
<tr>
<td>0.025</td>
</tr>
<tr>
<td>0.05</td>
</tr>
<tr>
<td>0.075</td>
</tr>
<tr>
<td>0.10</td>
</tr>
<tr>
<td>0.125</td>
</tr>
<tr>
<td>0.15</td>
</tr>
</tbody>
</table>

2. FDA Arthritis Advisory Committee; February 8, 2001; Gaithersburg
Most patients are asymptomatic.

* Bleeding, perforation, and gastric outlet obstruction


Prior complicated ulcer
Use of multiple NSAIDs (including aspirin)
High-dose of NSAIDs
Anticoagulant therapy
Prior uncomplicated ulcer
Age > 70 years
H. pylori infection
Glucocorticoid therapy

Risk factors for ulcer complications induced by NSAIDs
There is no safe NSAID.

<table>
<thead>
<tr>
<th>Individual NSAID</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-use</td>
<td>Reference</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>1.0 (0.4 to 2.1)</td>
</tr>
<tr>
<td>Aceclofenac</td>
<td>2.6 (1.5 to 4.6)</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>3.1 (2.3 to 4.2)</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>4.1 (3.1 to 5.3)</td>
</tr>
<tr>
<td>Naproxen</td>
<td>7.3 (4.7 to 11.4)</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>8.6 (2.5 to 29.2)</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>9.0 (3.9 to 20.7)</td>
</tr>
<tr>
<td>Meloxicam</td>
<td>9.8 (4.0 to 23.8)</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>14.4 (5.2 to 39.9)</td>
</tr>
</tbody>
</table>
GI risk factors in Korean OA patients

<table>
<thead>
<tr>
<th>GI risk factors</th>
<th>Percent of cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Need for long-term NSAID use</td>
<td>79</td>
</tr>
<tr>
<td>Age over 65 yr</td>
<td>54</td>
</tr>
<tr>
<td>Comorbid disease (cardiovascular, renal, liver, diabetes, hypertension)</td>
<td>46</td>
</tr>
<tr>
<td>High dose of NSAID use</td>
<td>43</td>
</tr>
<tr>
<td>History of GI symptom</td>
<td>36</td>
</tr>
<tr>
<td>Aspirin use</td>
<td>15</td>
</tr>
<tr>
<td>Heavy smoking habit</td>
<td>14</td>
</tr>
<tr>
<td>Heavy drinking habit</td>
<td>13</td>
</tr>
<tr>
<td>History of steroid use</td>
<td>8</td>
</tr>
<tr>
<td>Currently poor health status</td>
<td>8</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>6</td>
</tr>
<tr>
<td>Previous hospitalization history due to Gl events</td>
<td>6</td>
</tr>
<tr>
<td>Selective serotonin reuptake inhibitor (SSRI) use</td>
<td>4</td>
</tr>
<tr>
<td><em>Helicobactor pylori</em> infection</td>
<td>4</td>
</tr>
<tr>
<td>Anticoagulant use</td>
<td>2</td>
</tr>
</tbody>
</table>
• We used the Manitoba Population Health Research Data Repository to perform a population-based matched case-control analysis

Table 4. ORs and P Values for Comparisons Between Gastroprotective Strategies for Upper GI Complications Secondary to Peptic Ulcer Disease

<table>
<thead>
<tr>
<th>Treatment(Assessment Level)</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>nsNSAID + low-dose misoprostol (0.61)</td>
<td>0.81 (0.48–1.38)</td>
<td>&gt; .20</td>
</tr>
<tr>
<td>nsNSAID + PPI (0.50)</td>
<td>0.74 (0.55–1.00)</td>
<td>= .050</td>
</tr>
<tr>
<td>COX-2 inhibitor alone (0.46)</td>
<td>0.91 (0.55–1.50)</td>
<td>&gt; .20</td>
</tr>
<tr>
<td>nsNSAID + PPI + low-dose misoprostol (0.29)</td>
<td>0.46 (0.18–1.21)</td>
<td>= .117</td>
</tr>
<tr>
<td>COX-2 inhibitor + PPI (0.23)</td>
<td>0.58 (0.21–1.60)</td>
<td>&gt; .20</td>
</tr>
<tr>
<td>nsNSAID + low-dose misoprostol</td>
<td>0.63 (0.25–1.60)</td>
<td>&gt; .20</td>
</tr>
<tr>
<td>nsNSAID + PPI</td>
<td>0.49 (0.25–0.82)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>COX-2 inhibitor alone</td>
<td>0.50 (0.34–0.73)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>nsNSAID + PPI + low-dose misoprostol</td>
<td>0.79 (0.29–2.09)</td>
<td>&gt; .20</td>
</tr>
<tr>
<td>COX-2 inhibitor + PPI</td>
<td>0.37 (0.23–0.57)</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

NOTE. ORs for relative risk reduction versus nsNSAID users alone shown in parentheses.

* Differences are statistically significant.
• Dyspepsia: change of the medication, dose reduction, empirical treatment with H₂RA or PPI
• *H. pylori* infection: eradication treatment in patients with risk factor(s)
• Active ulcer (NSAID discontinued): H₂RA or PPI
• Active ulcer (NSAID continued): PPI
• Prophylactic therapy: misoprostol, PPI, COX-2 selective agent

Cumulative rate of ulcer development
- Venous study

Placebo: 20.4%
Esomeprazole 20 mg: 5.3%
Esomeprazole 40 mg: 4.7%

Scheiman et al. Am J Gastroenterol 2006;101:701-710
Esomeprazole vs famotidine
- Prevention of UGI bleeding in ACS of AMI

The study was terminated, and the patients were prescribed open-label PPI for their safety.
PPI + COX-2 — the best method for upper GI tract complication prevention

Number at risk
Celecoxib with esomeprazole 137 136 136 136 136 135 135 135 135
Celecoxib with placebo 136 132 130 127 125 124 123 122

Chan. Lancet 2007;369:1621-1626
# Risk groups and recommendations

<table>
<thead>
<tr>
<th>Low GI risk</th>
<th>High GI risk</th>
<th>Very high GI risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not on aspirin</td>
<td>nsNSAID</td>
<td>nsNSAID + PPI/misoprostol</td>
</tr>
<tr>
<td>On aspirin</td>
<td>Naproxen</td>
<td>Naproxen + PPI/misoprostol</td>
</tr>
</tbody>
</table>

Celecoxib alone 만으로는 부족할 수 있다.
- 궤양 출혈 병력이 있는 환자에서 celecoxib 사용하고 melena
NSAID ulcer 환자에게 드리는 말씀

혹시 다음에 다른 이유로 아스피린이나 소염진통제를 드실 일이 있으시면 الان 의사에게 "과거에 소염진통제 먹고 위궤양 생겼던 적이 있다"고 말씀해 주세요. 그러면 소염제와 함께 궤양약을 처방받게 되실 것입니다. 재발을 막기 위해서 중요하니까 잊지 마세요.
Concurrent NSAID, PPI use tapers over long term

BY DENISE NAPOLI
IMNG Medical News

Among chronic nonsteroidal anti-inflammatory drug patients at high risk for a gastrointestinal bleeding, only two-thirds continue to be prescribed a proton pump inhibitor after 2 years.

Moreover, patients whose PPI prescriptions were discontinued were significantly more likely to experience a GI adverse event, compared with patients who had continuous NSAID and PPI coprescription, wrote Dr. Isabelle Le Ray and colleagues. The report was published in the May issue of Clinical Gastroenterology and Hepatology.

Dr. Le Ray, of the Centre Hospitalier Universitaire de Dijon, France, and colleagues looked at records from the Longitudinal Patient Database, which collects data from a representative sample of 1,200 general practitioners in France.

Specifically, Dr. Le Ray focused on high-risk patients within the database who received a ten- year probability of still having an active PPI prescription fell to 0.77 (95% confidence interval, 0.75-0.79).

By 2 years, that likelihood fell to 0.68 (95% CI, 0.66-0.70).

The authors then looked at the presence of GI adverse events in this cohort. They found that 379 patients experienced an event, with patients who were not persistently prescribed a PPI at significantly higher risk, compared with patients whose PPI prescriptions never lapsed (odds ratio 1.45; 95% CI, 1.06-2.09, P = .02).

“Absolute risk reduction associated with a continuous prescription of PPI with NSAIDs, in at-risk patients, was 3.2%,” wrote the authors.

According to the researchers, factors associated with discontinuing a PPI included change from a given NSAID to a COX-2 inhibitor (multivariate hazard ratio for PPI discontinuation, 2.50; 95% CI, 1.91-3.28), despite the fact that “international guidelines recommend coprescription of a PPI for at-risk patients, even when using a COX-2 selective

Factors increasing the risk for upper GI complications in NSAID users include older age (greater than 60-75 years); prior upper GI complications or symptomatic ulcers; and concurrent use of aspirin, other antithrombotics, or corticosteroids. If patients cannot be switched to a non-NSAID analgesic, strategies recommended to decrease GI risk include PPI (or misoprostol), cotherapy or substitution of a COX-2 selective NSAID. Patients at very high risk (e.g., recent ulcer bleeding) should receive a COX-2 selective NSAID plus PPI (or misoprostol).

However, multiple observational studies demonstrate that most NSAID users with GI risk factors do not receive protective therapy. Importantly, adherence to a PPI more than 80% of the time is associated with significantly fewer upper GI clinical events than adherence less than 80% and less than 20% of the time.

The study by Le Ray et al. looks at a group of NSAID users in whom a decision to provide a PPI prescription has been made. Co-therapy was stopped in
Aspirin-associated ulcer로 PPI 장기복용 권하였으나 PPI 끊고 aspirin 쓰면서 재출혈
Management of rheumatoid arthritis
- a multidisciplinary approach
집으로 가져가는 메세지

• GERD의 증상은 PPI와 같은 강력한 위산분비억제제로 잘 조절된다. 그러나 잦은 증상 재발이 문제이다. 개별화된 적절한 장기유지요법으로 삶의 질을 유지할 수 있다.

• NSAID 관련 위장관 질환의 일차 예방 및 이차예방을 위하여 PPI의 역할은 중요하다. Plateau가 없으므로 장기 치료가 중요하다.