

胃食道反流疾病的西醫藥治療

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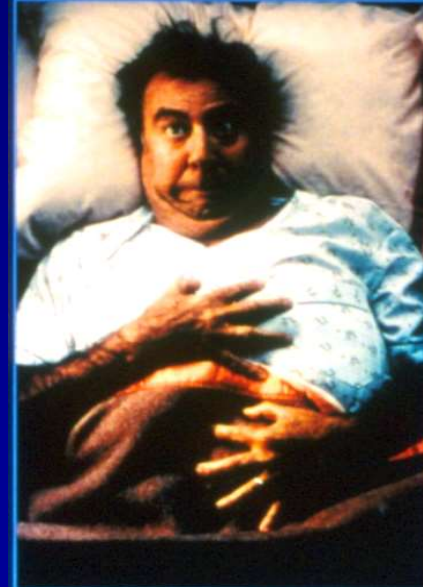
臨床醫學副教授

胃食道反流疾病 (GERD)

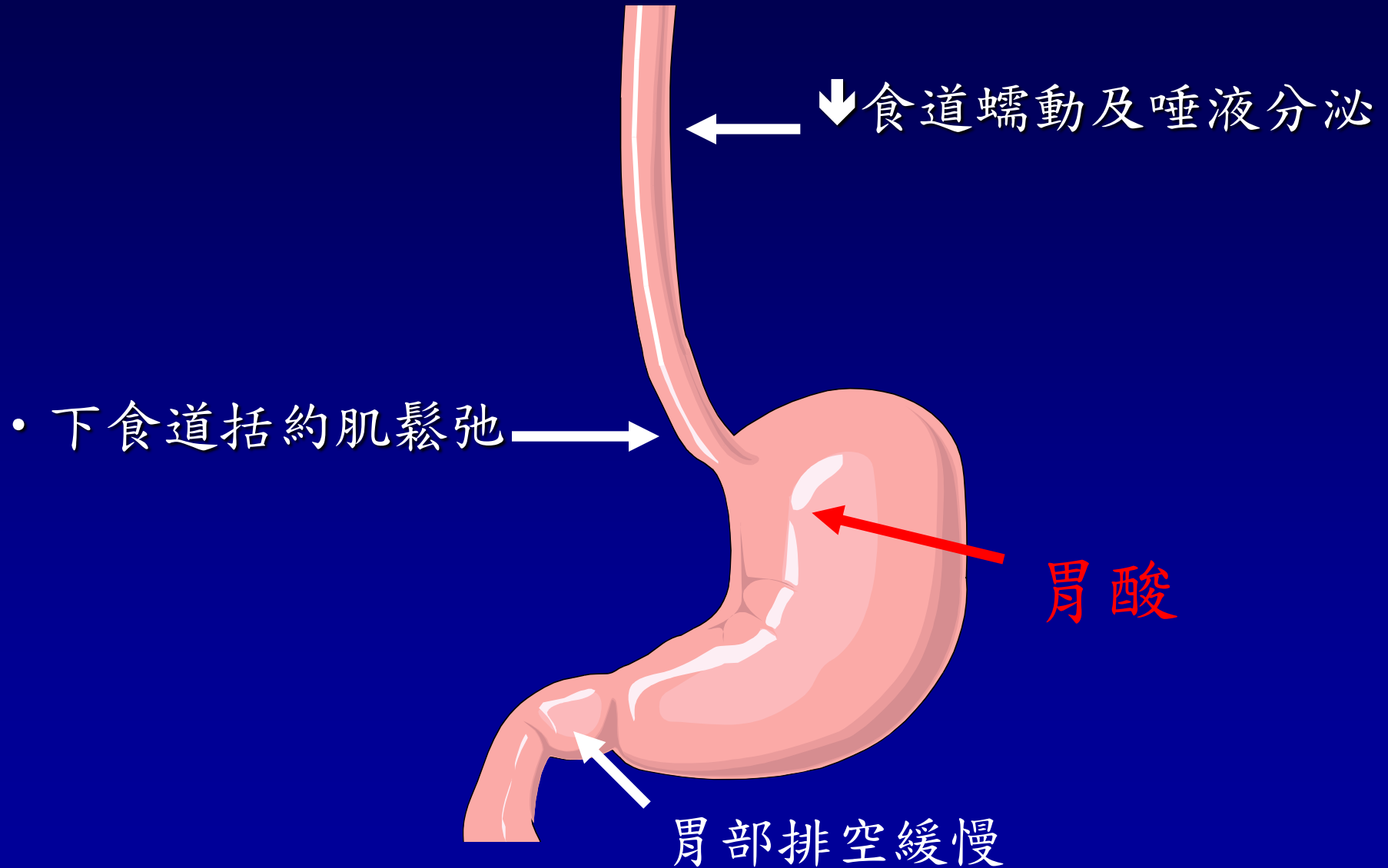


1. 併發症

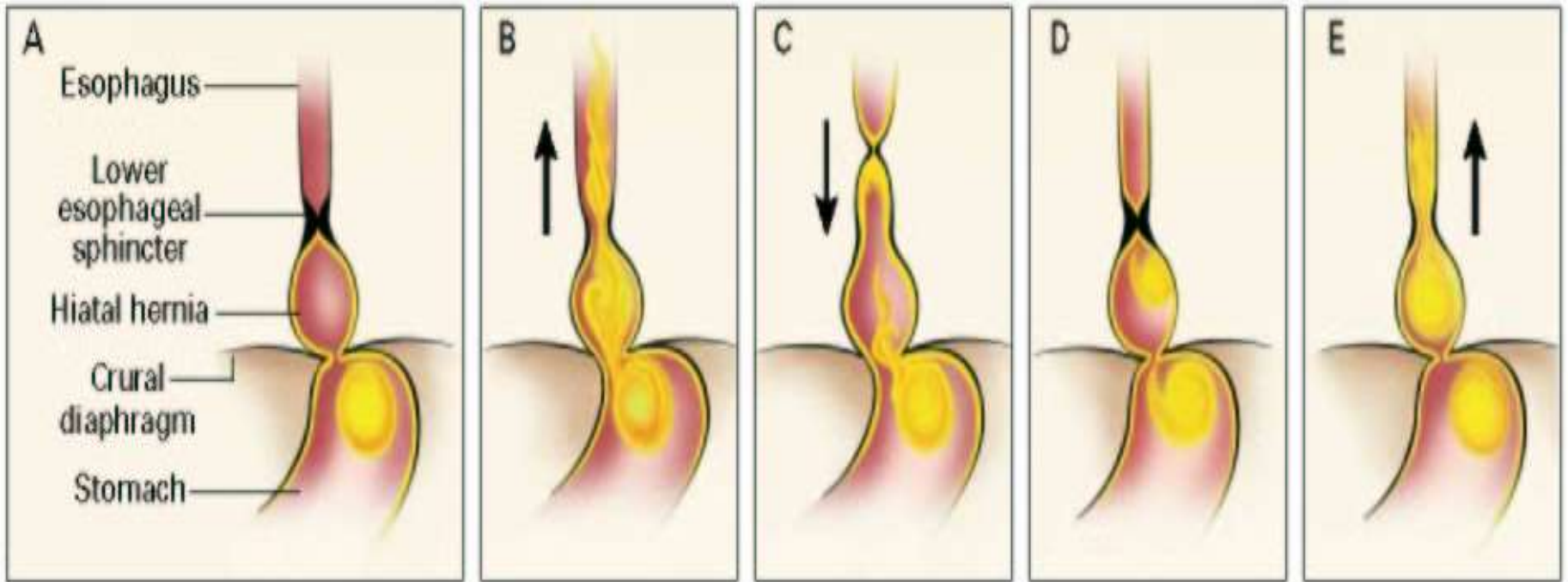
2. 令人困擾的症狀



胃酸倒流的原理



Hiatus hernia results in more reflux episodes and ↑ esophageal acid exposure

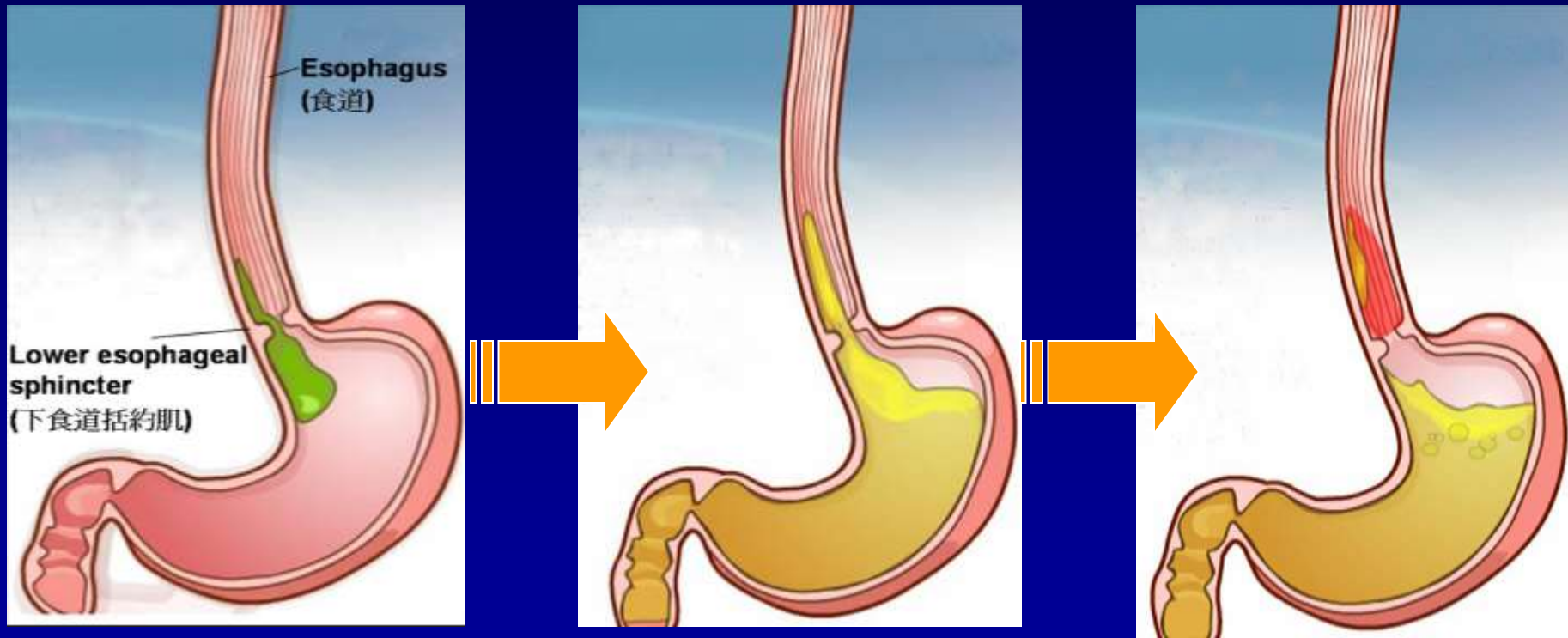


食管裂孔疝

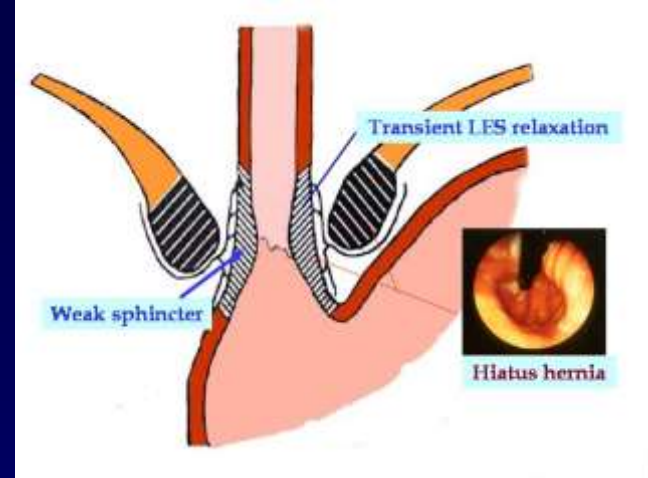
Figure 4. Mechanism of Reflux Due to Hiatal Hernia.

A hiatal hernia is an acquired herniation of part of the stomach through the diaphragm (Panel A). After an episode of reflux (Panel B), an esophageal peristaltic contraction clears the bolus of acid from the esophagus (Panel C) into the hiatal hernia (Panel D). Subsequently, swallowing-induced relaxation of the lower esophageal sphincter results in reflux of acid from the hernial sac into the esophagus (Panel E). This sequence can be repeated several times and results in markedly prolonged clearance of acid.

胃食道反流性疾病的原理



括約肌「失守」



- 連接我們食道與胃部的肌肉貴門叫下食道括約肌，專責防止胃內食物及胃酸倒流入食道，如果下食道括約肌鬆弛，就會令到胃酸倒流入食道。
- 而食道的黏膜十分脆弱，若長久受到胃酸刺激會令食道發炎、潰瘍、出血、及出現一種癌前病變的情況（巴洛氏食道）。
- 巴洛氏食道是指一些病人的正常食道細胞被不正常的細胞取代了，而巴洛氏食道與食道癌有密切關係。

胃酸倒流引致的食道炎

Grade A



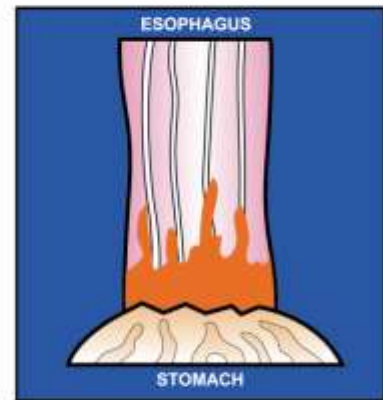
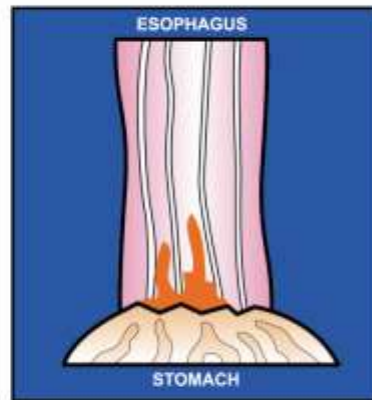
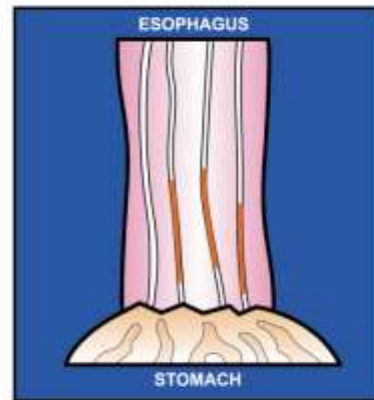
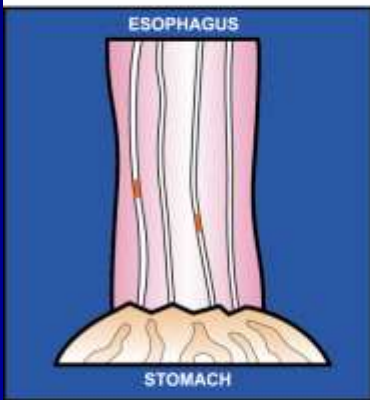
Grade B



Grade C

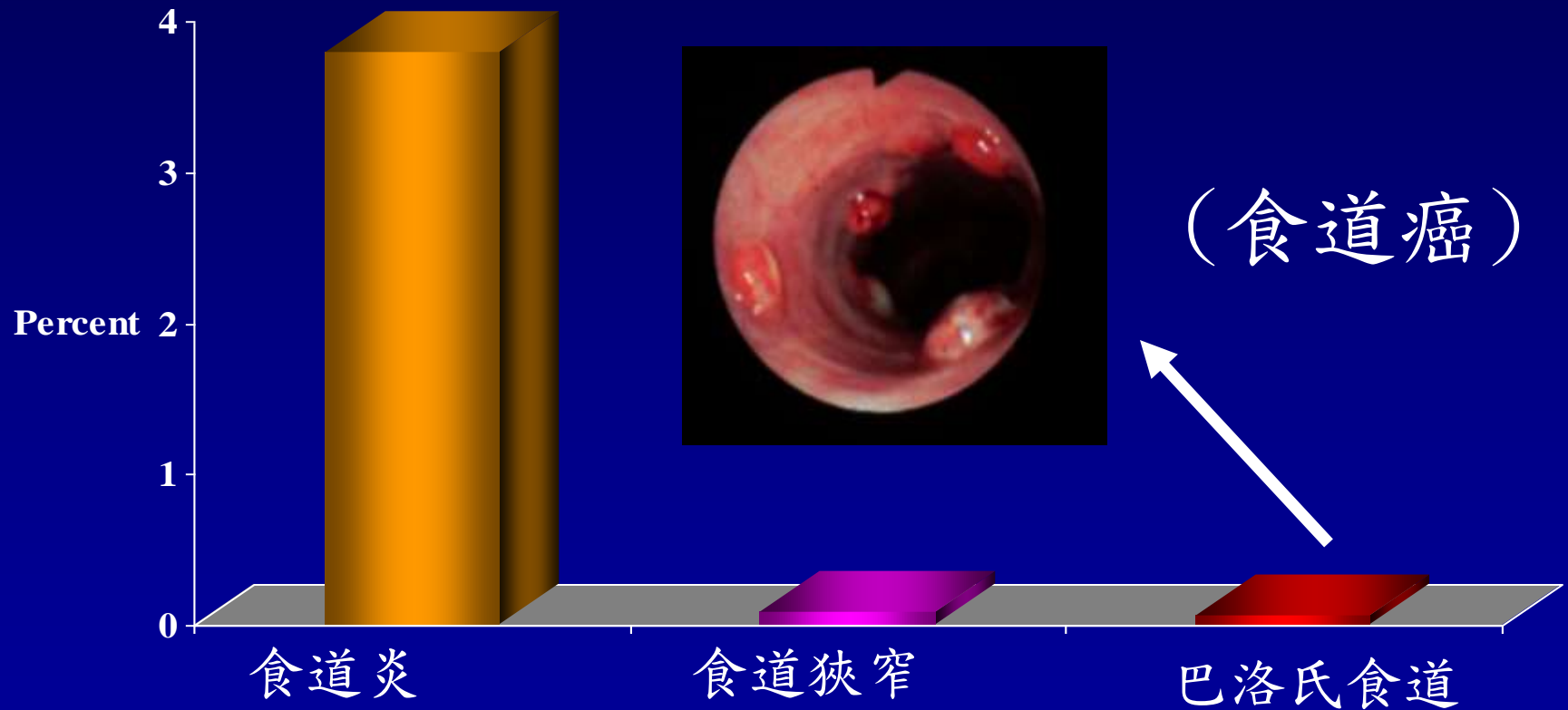


Grade D



LA Classification Scale

於四年半內，在香港瑪麗醫院之統計中，
有16,606位患者進行內窺鏡測試



胃食道反流疾病之典型徵狀

- 胸口灼痛
- 胃酸倒流
- 噯氣
- 有胃酸的感覺

一般來說，胃酸倒流入食道情況以睡覺時比日間嚴重，原因是地心吸力關係，令我們平臥在床上時胃酸更容易倒流入食道。



胃食道反流疾病之非典型徵狀

- 非心臟病胸口痛
- 慢性咳嗽 / 哮喘
- 聲嘶

警號之徵狀

體重下降，吞嚥困難，吞嚥時感到疼痛，
嘔血，窒息感覺

➔ 需要盡快施行內視鏡檢查

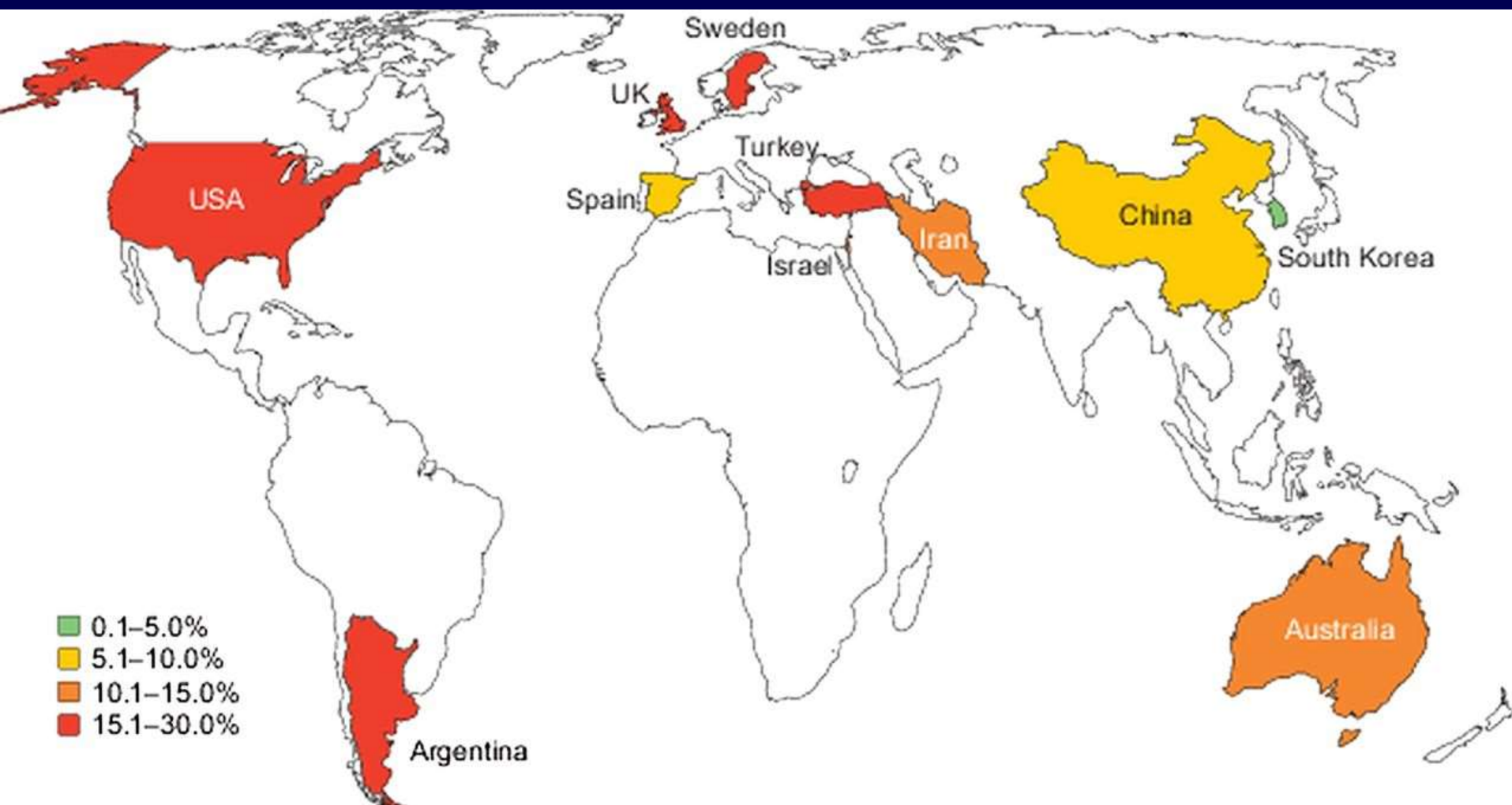


高危人士

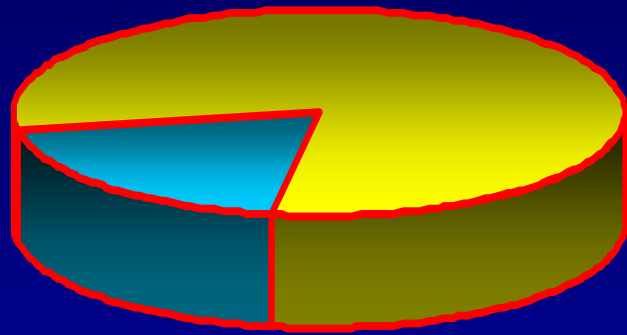


- 暴飲暴食、喝過多咖啡及食太辣食物者；
- 妊娠婦女及過度肥胖人士；
- 常吃宵夜之人士；
- 吸煙、酗酒之人。

Weekly symptoms of heartburn / acid regurgitation 2013



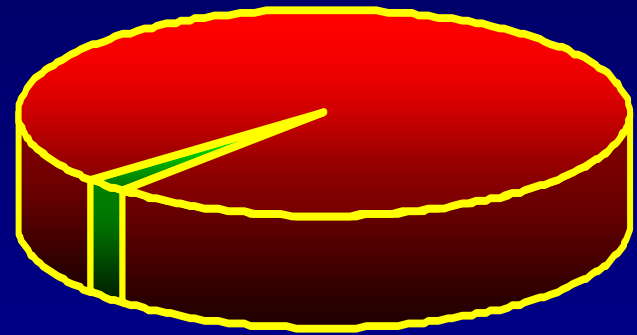
每星期受胸口灼痛 / 胃酸倒流的症狀影響



19.8%

美國

Locke et al. 1997

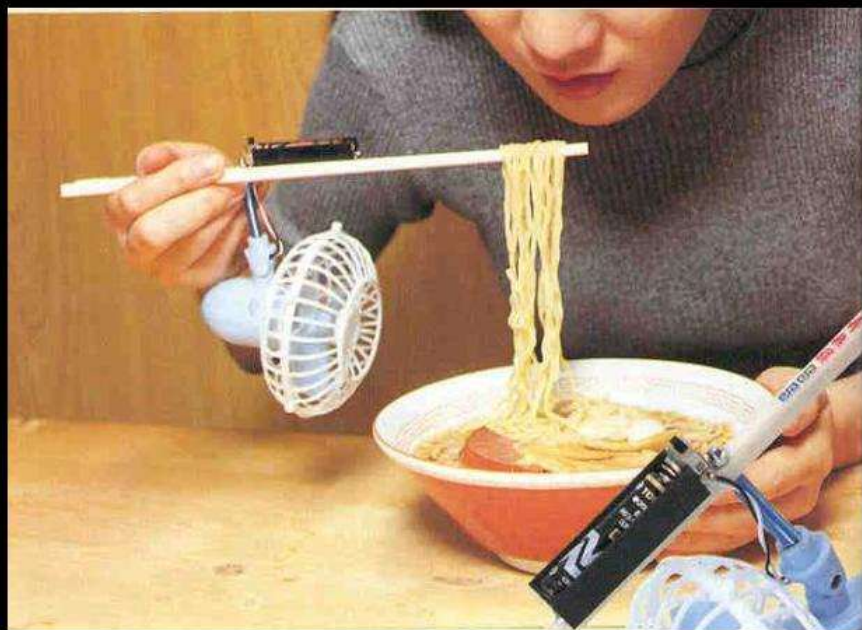


2.5%

香港

Wong WM, et al. 2003

飲食習慣 - 東方與西方



Prevalence of GERD

(胃食道反流疾病的流程度)

2011年香港的總人口 - 700萬人

每星期均有一次受胃食道

反流疾病的症狀影響 - 266,000

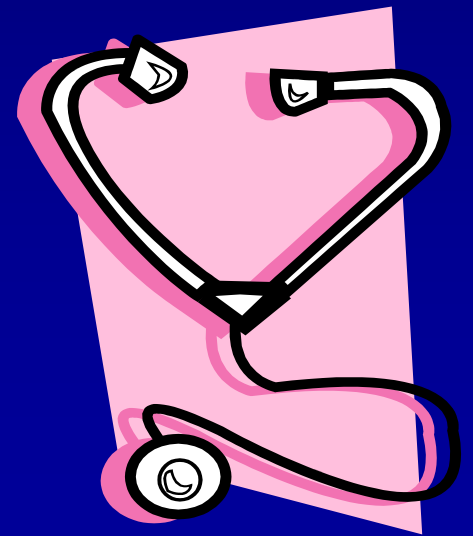
每月均有一次受胃食道

反流疾病的症狀影響 - 854,000

Wong WM APT 2004;20:803-12, Wong WM APT 2003:18:595-604.

**V Tan, J Clin Gastroenterol 2015 Mar 6 [Epub ahead of print]*

診斷方法



內視鏡檢查





內視鏡檢查



- 對診斷食道炎非常有用。
- 大部份患有胃食道反流病之病者在內視鏡檢查中無發現患上食道炎。
- 內視鏡檢查是一種介入和昂貴的檢查，而且在檢查中會有少許不舒適。



食道測壓計



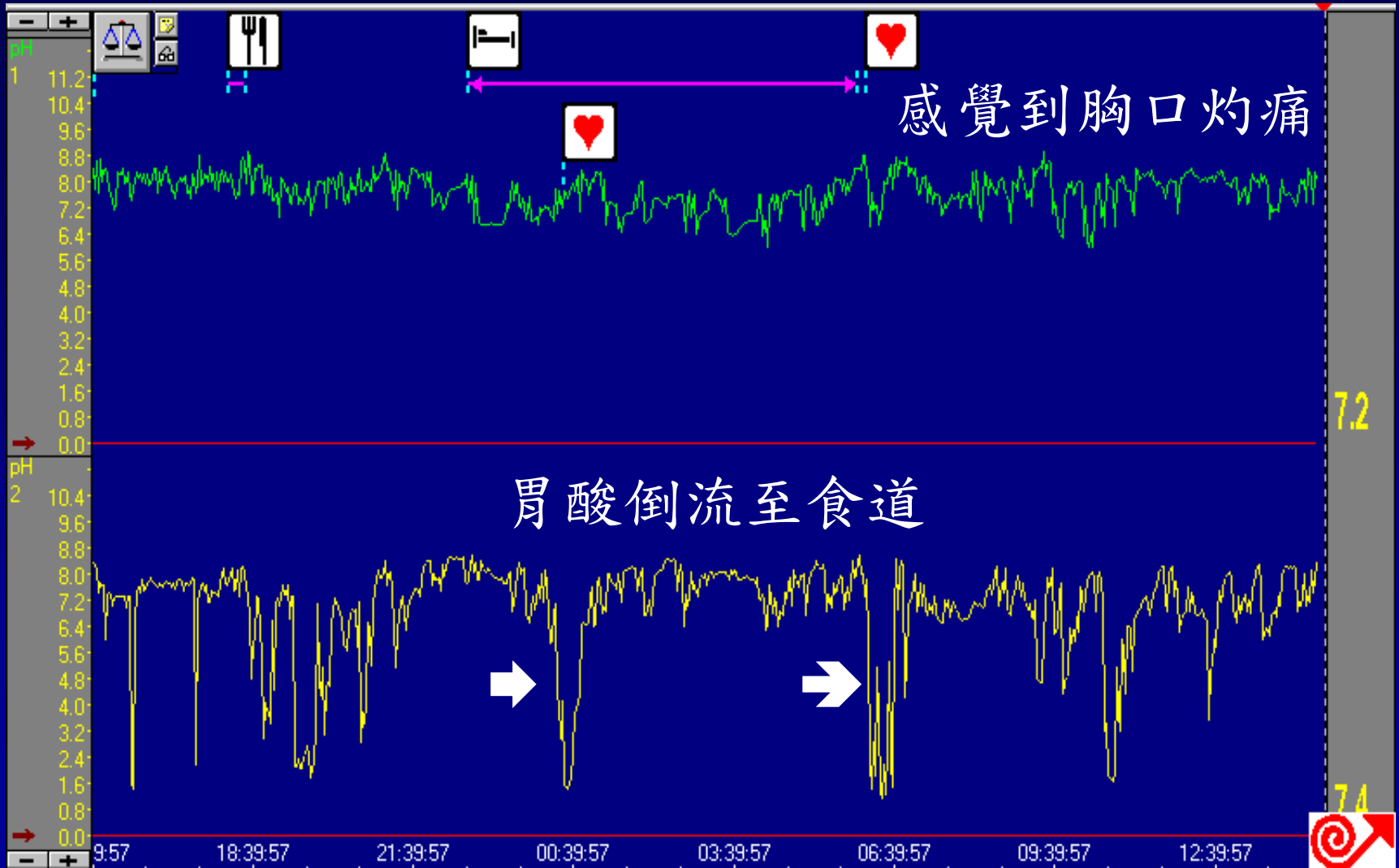
24小時活動胃酸監測儀



食道下端測到的酸鹼
值小於4.0，即表示有
胃酸倒流至食道

探測酸鹼度之膠導管

24小時活動胃酸監測儀





24小時活動胃酸 監測儀

接受檢查者不可以淋浴
及防礙睡眠

鼻導管測試時會引致不適

Bravo酸鹼度測量系統

RF遙控測量術



無喉管的酸鹼度
測量系統

- 如傳呼機大小之接收器
- 接受檢查者可以淋浴及不防礙睡眠


無線之膠囊

Bravo酸鹼度測量系統

酸鹼度膠囊與接收器



- 酸鹼度膠囊會將測到的資料傳送到一個像傳呼機大小之接收器內
- 此方法可免除用鼻導管測試時所引起之不舒適



膠囊放送系統

真空抽吸器

接收器

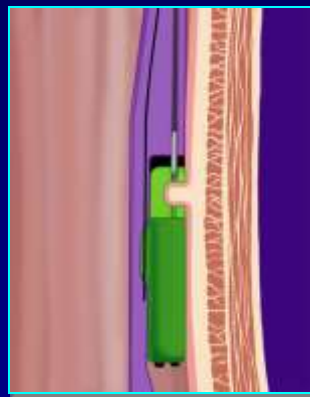
Bravo酸鹼度測量系統

Capsule Attachment



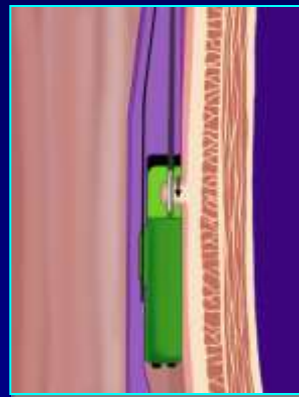
Step 1

**Position Bravo
Capsule**



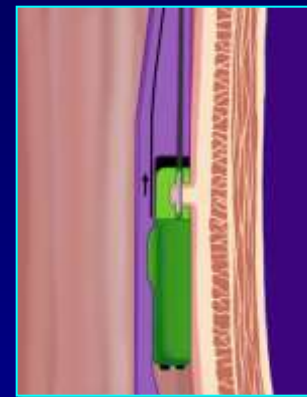
Step 2

**Apply
Suction**



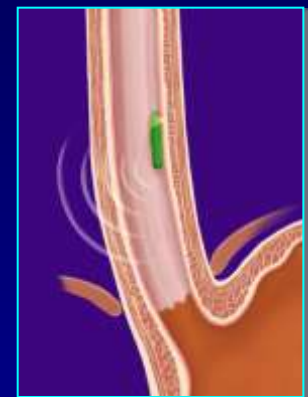
Step 3

Advance Pin



Step 4

**Release
Capsule**



Step 5

**Begin pH
Recording**

Bravo無線酸鹼度膠囊



膠囊之長
度為2.6cm

Bravo膠囊

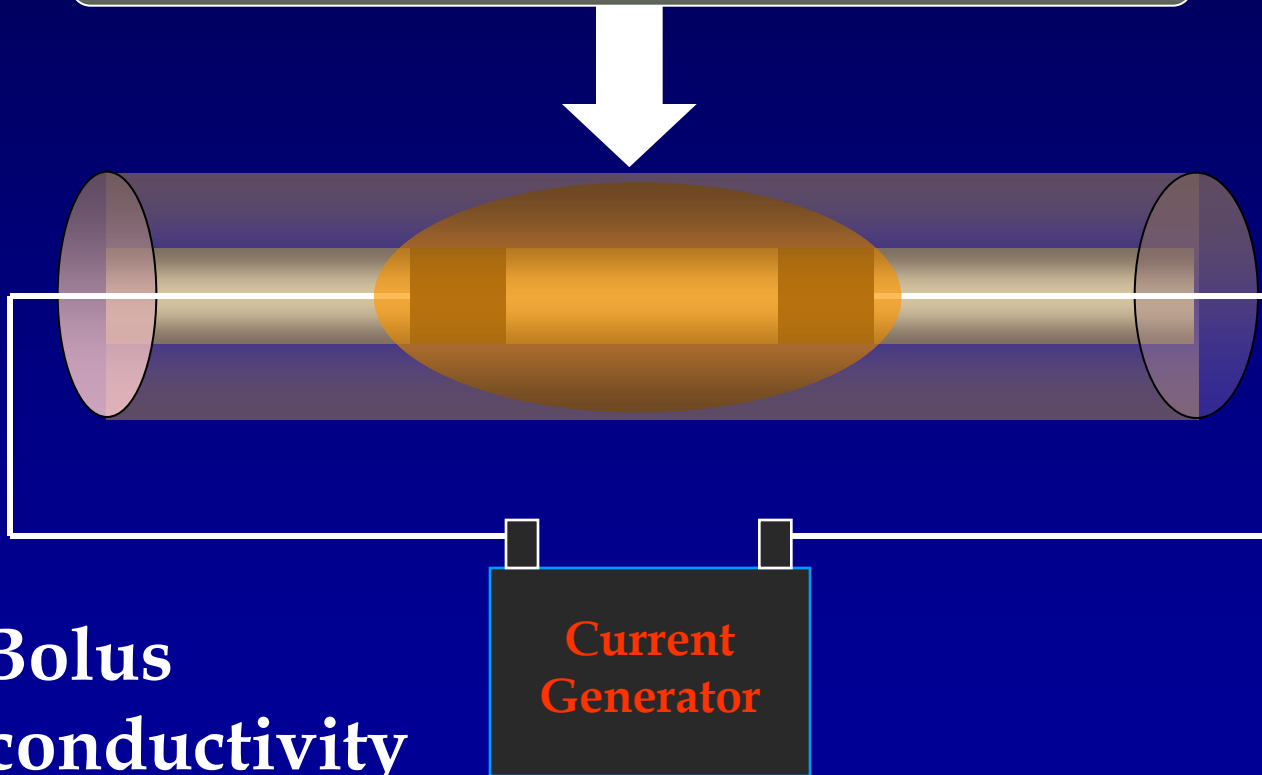
患者進行BRAVO
膠囊安裝



Impedance Technology Fundamentals

電阻抗監測系統

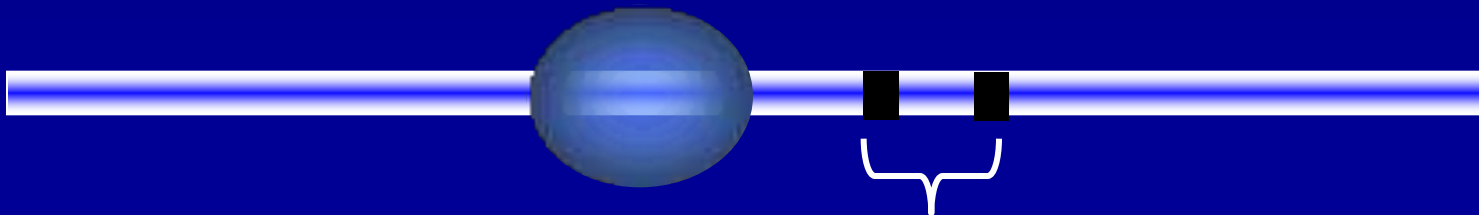
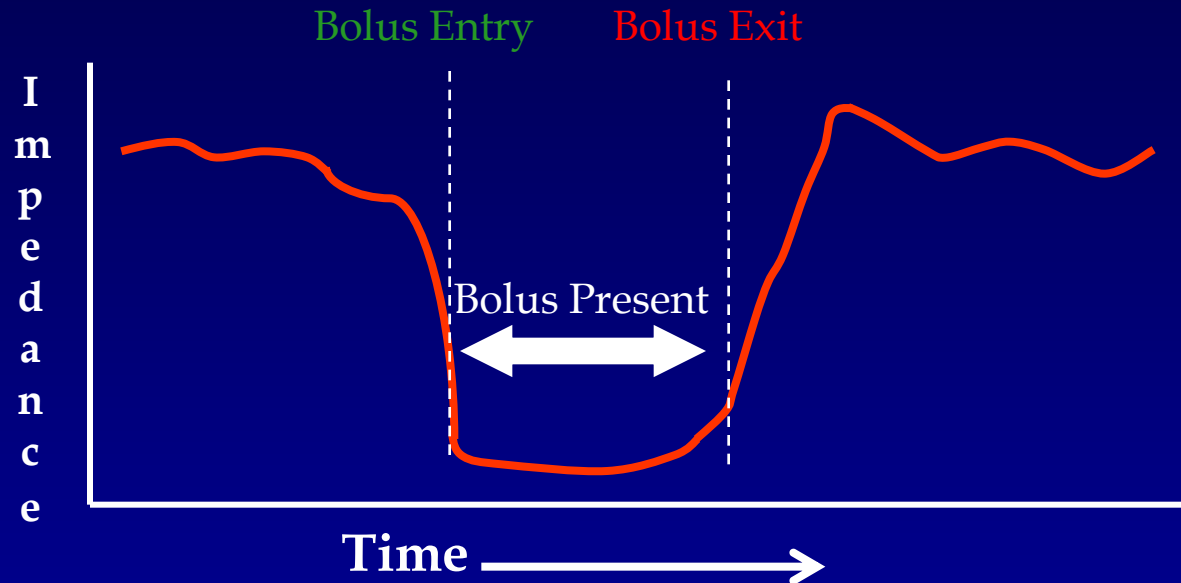
Bolus Spanning Impedance Contacts



Food Bolus
High conductivity
Low impedance

Impedance Technology Fundamentals

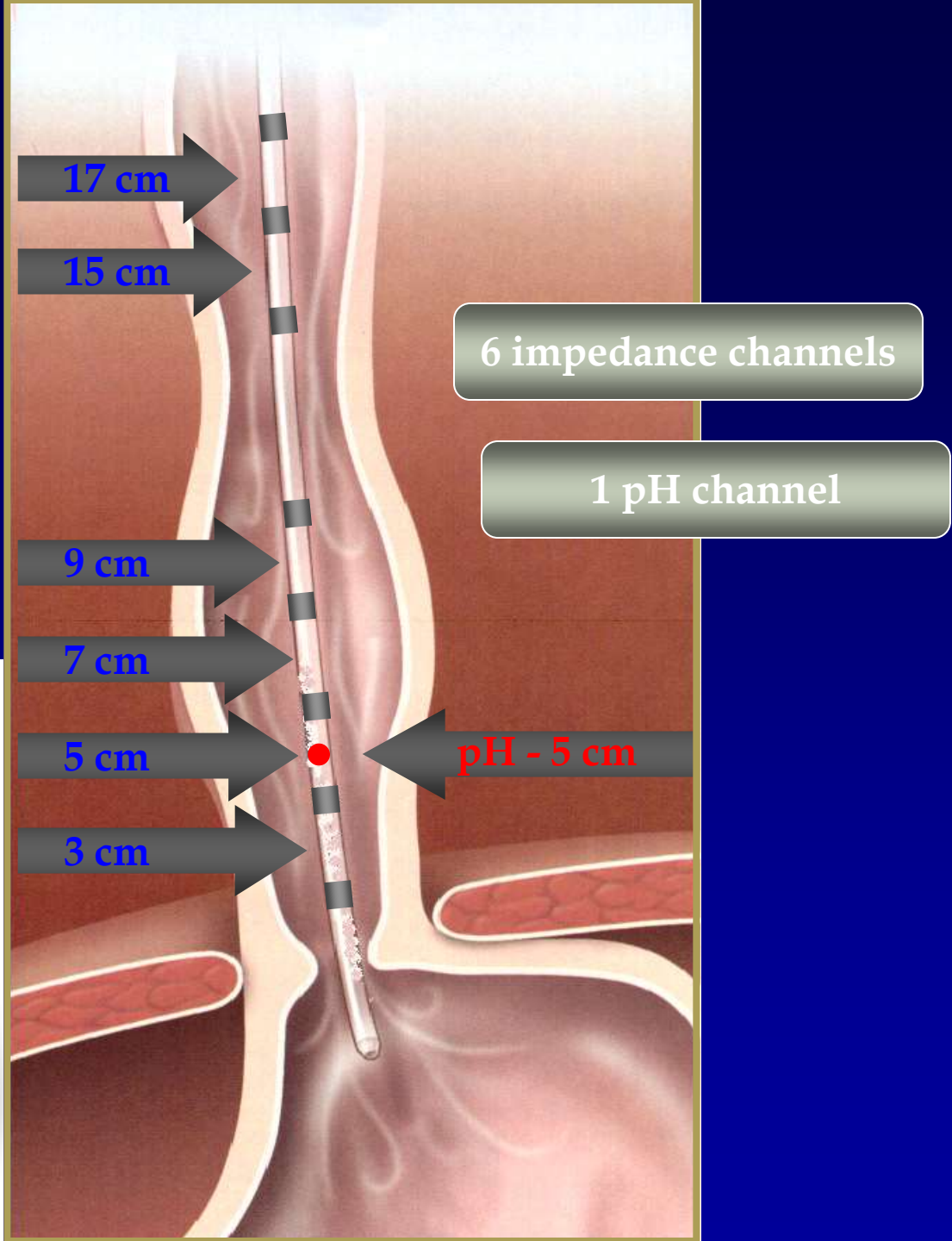
電阻抗監測系統



Impedance Contacts

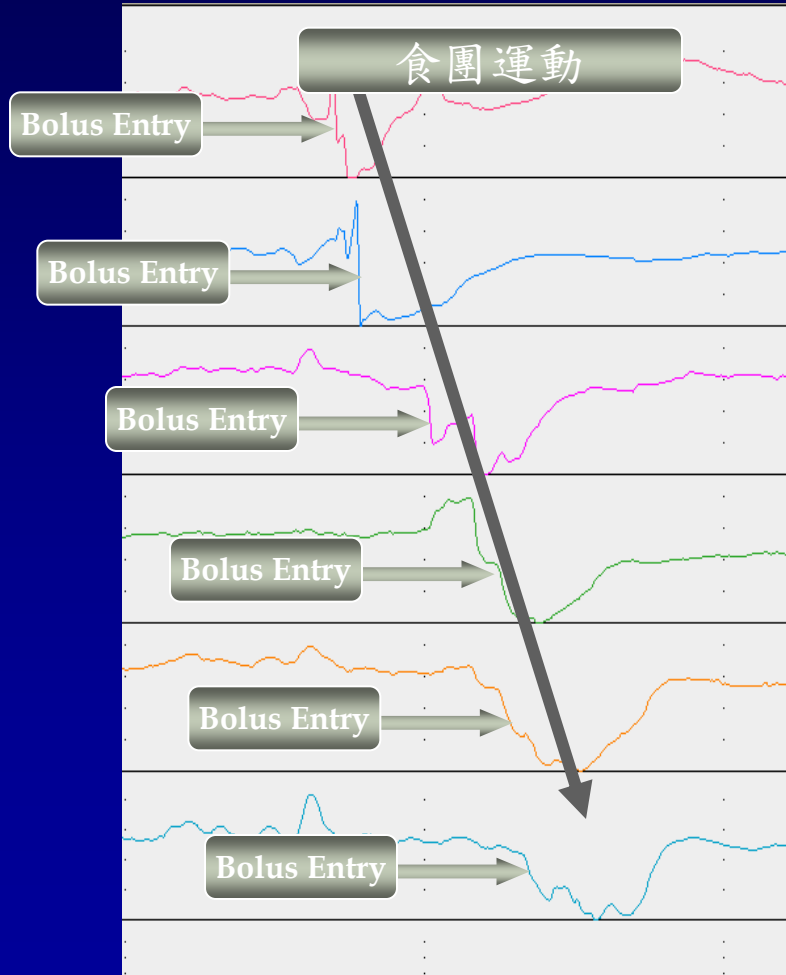
Impedance -pH Catheter

聯合多通道腔內
電阻抗及酸鹼度
測量系統

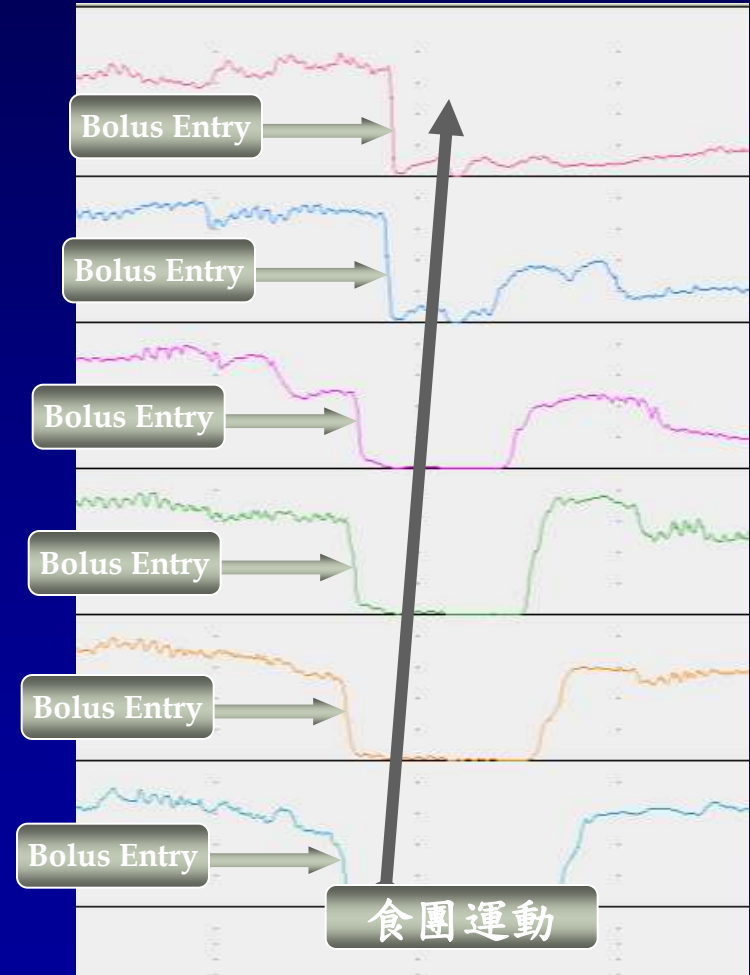


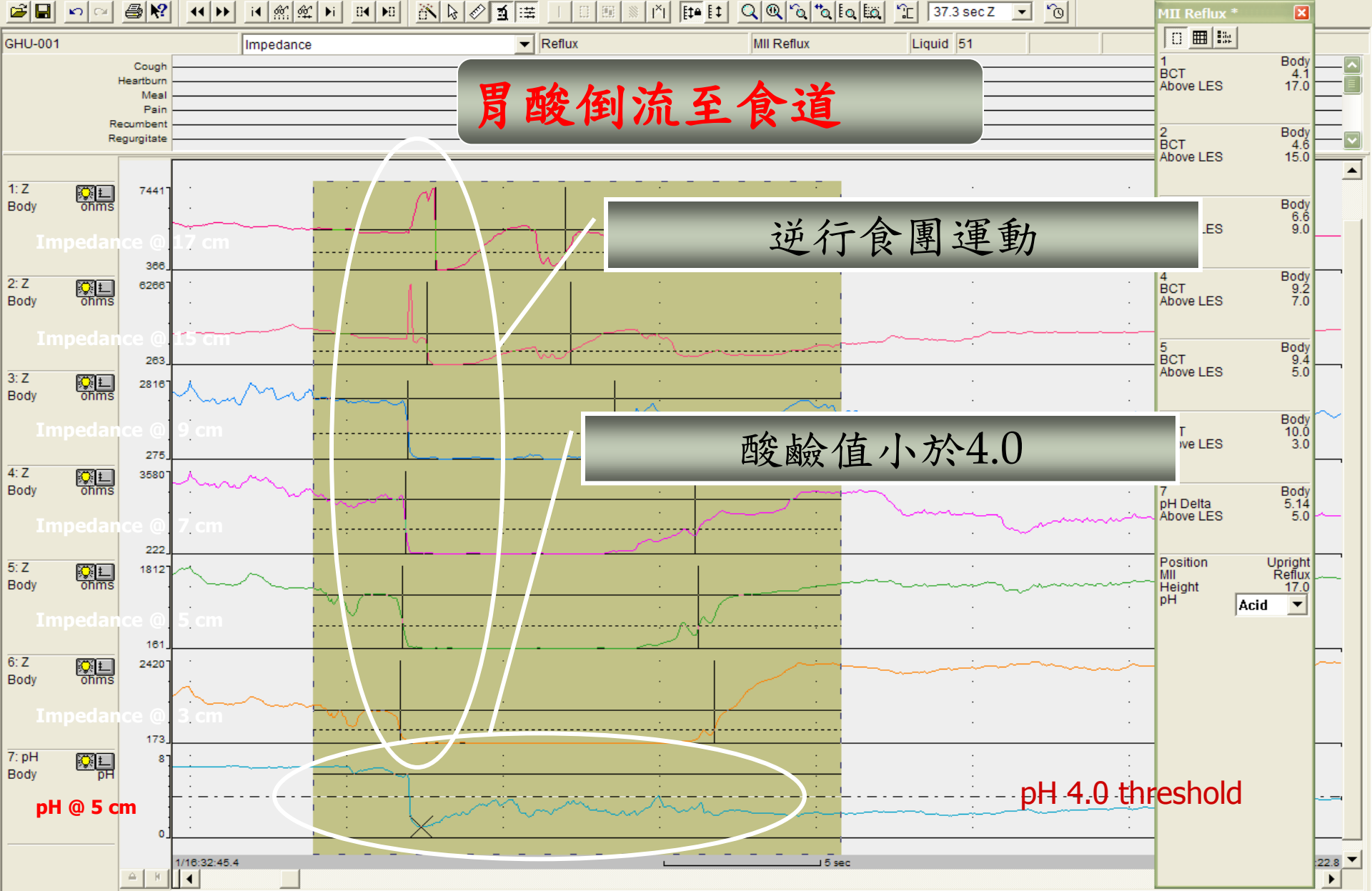
電阻抗監測系統

吞咽



反流





胃酸倒流至食道

逆行食團運動

酸鹼值小於4.0

pH 4.0 threshold

pH @ 5 cm

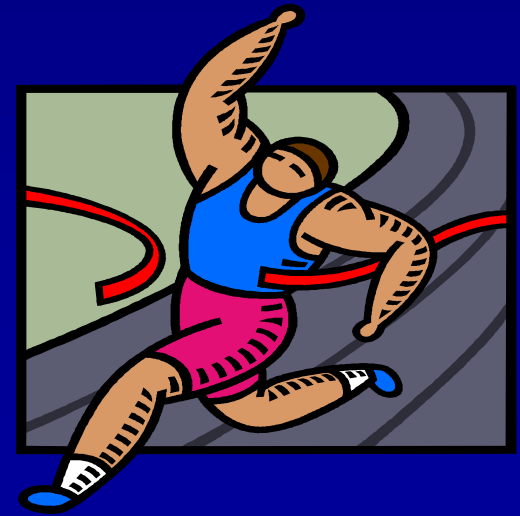
治療方法

胃食道反流疾病之治療方法

- 改變生活習慣
- 胃動力促進劑
- 制酸劑
- H₂受體抗制劑
- 質子泵抑制劑 (PPI)
- 外科手術

保持良好的生活習慣

- 少食多餐，每餐不要吃得過飽，保持正常體重，肥胖者以運動減肥。
- 避免吃油炸、肥膩及辛辣的食物或酸性飲品，如檸檬、番茄、薄荷、洋蔥及蒜、咖啡、濃茶、巧克力、吸煙及酗酒。
- 進餐後勿立即睡覺，勿平臥或彎曲身體，若平躺睡覺時可將頭及胸部墊高一些。
- 睡前4小時勿進食及戒宵夜習慣。

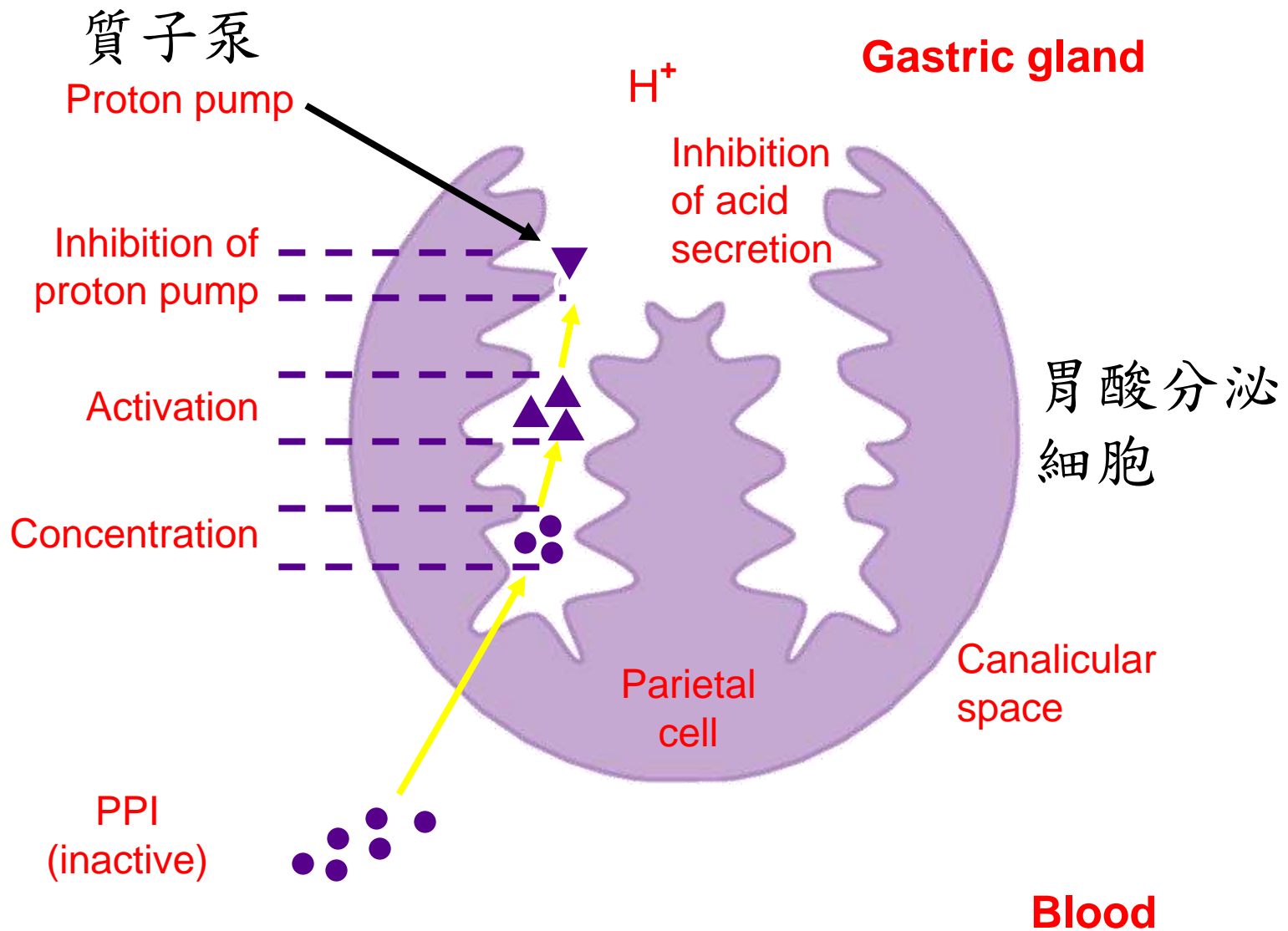


制酸劑

制酸劑不能有效治療
中度或嚴重胃食道反流疾病之病人

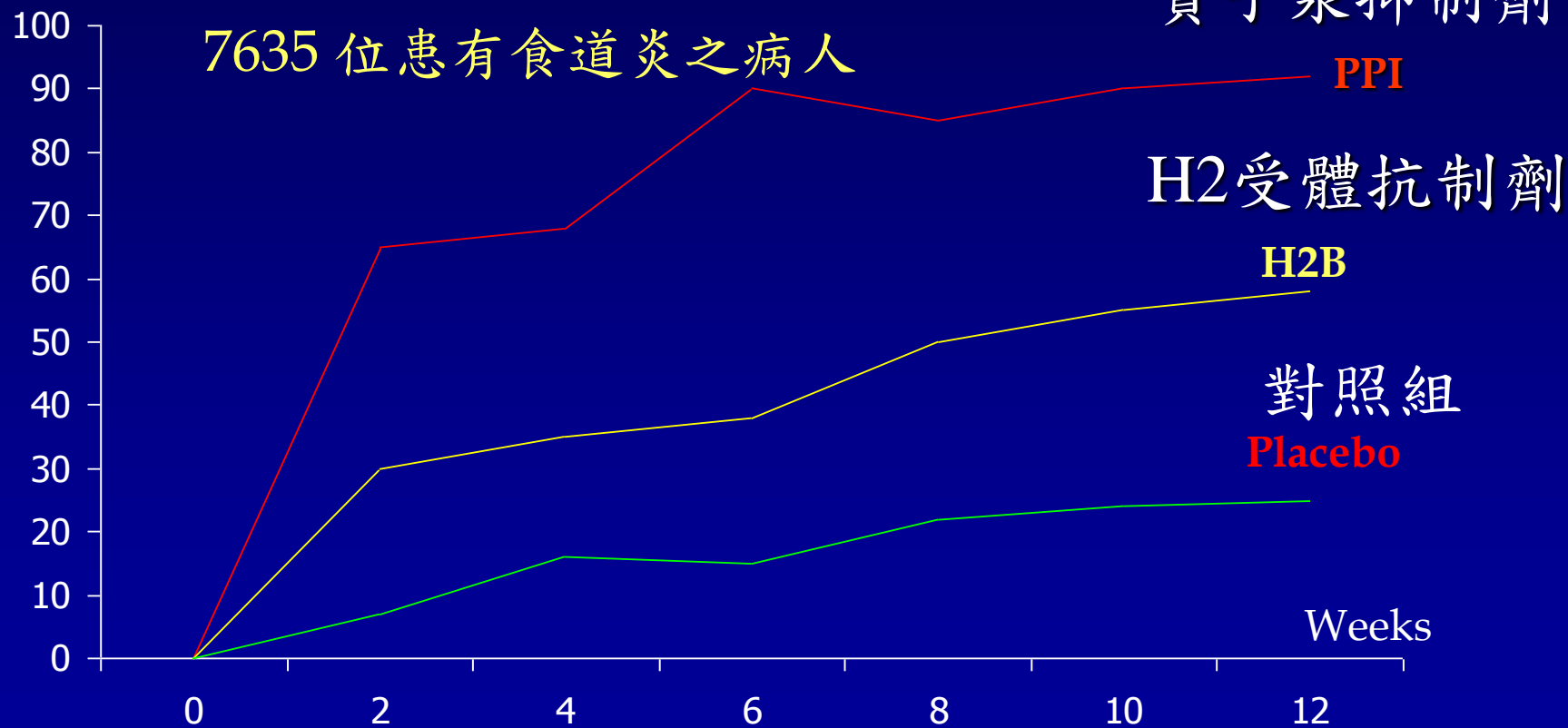


質子泵抑制劑



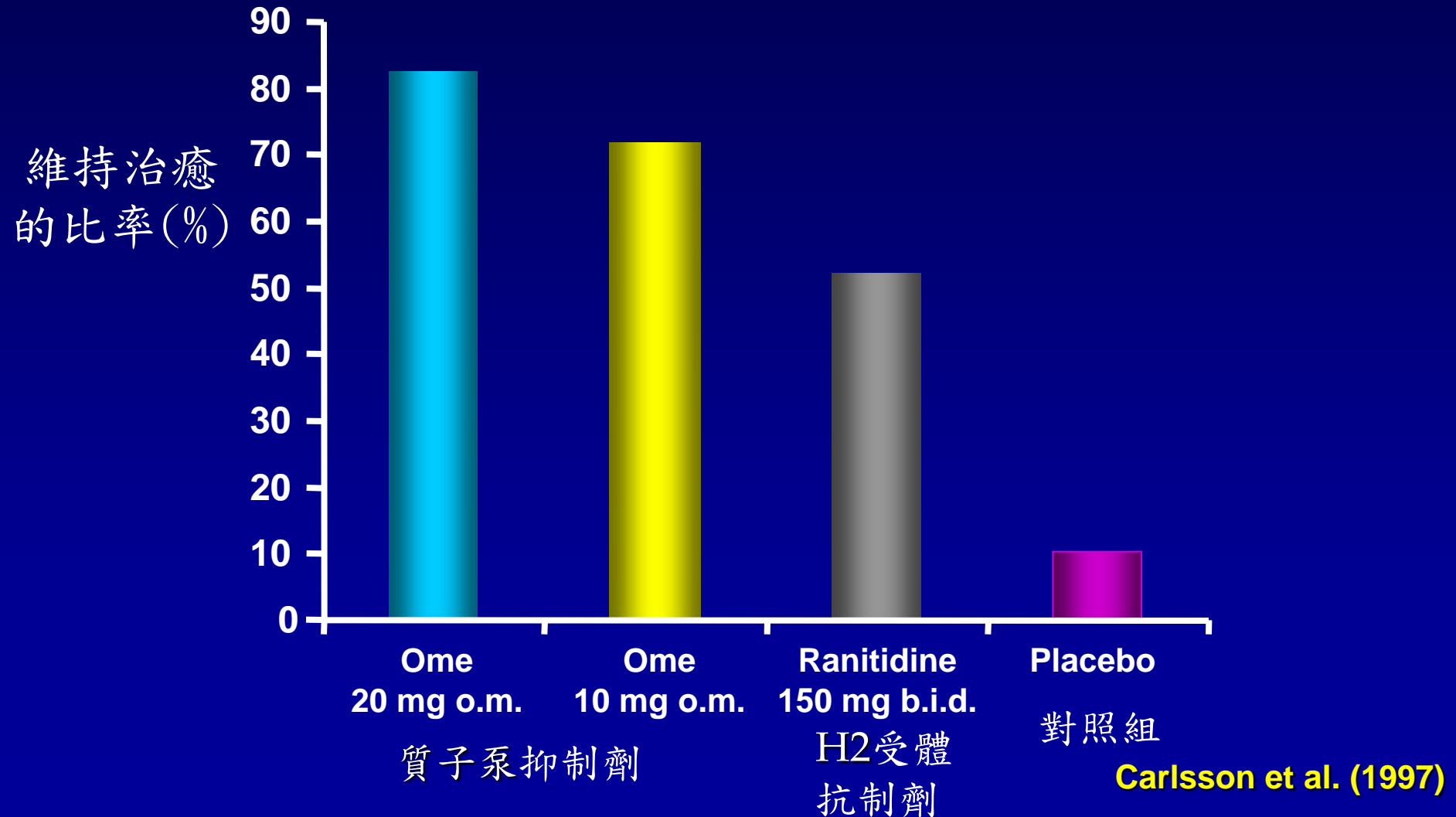
質子泵抑制劑為最有效治療 食道炎之藥物

累積治愈率 (%)



Chiba. Gastroenterology 1997

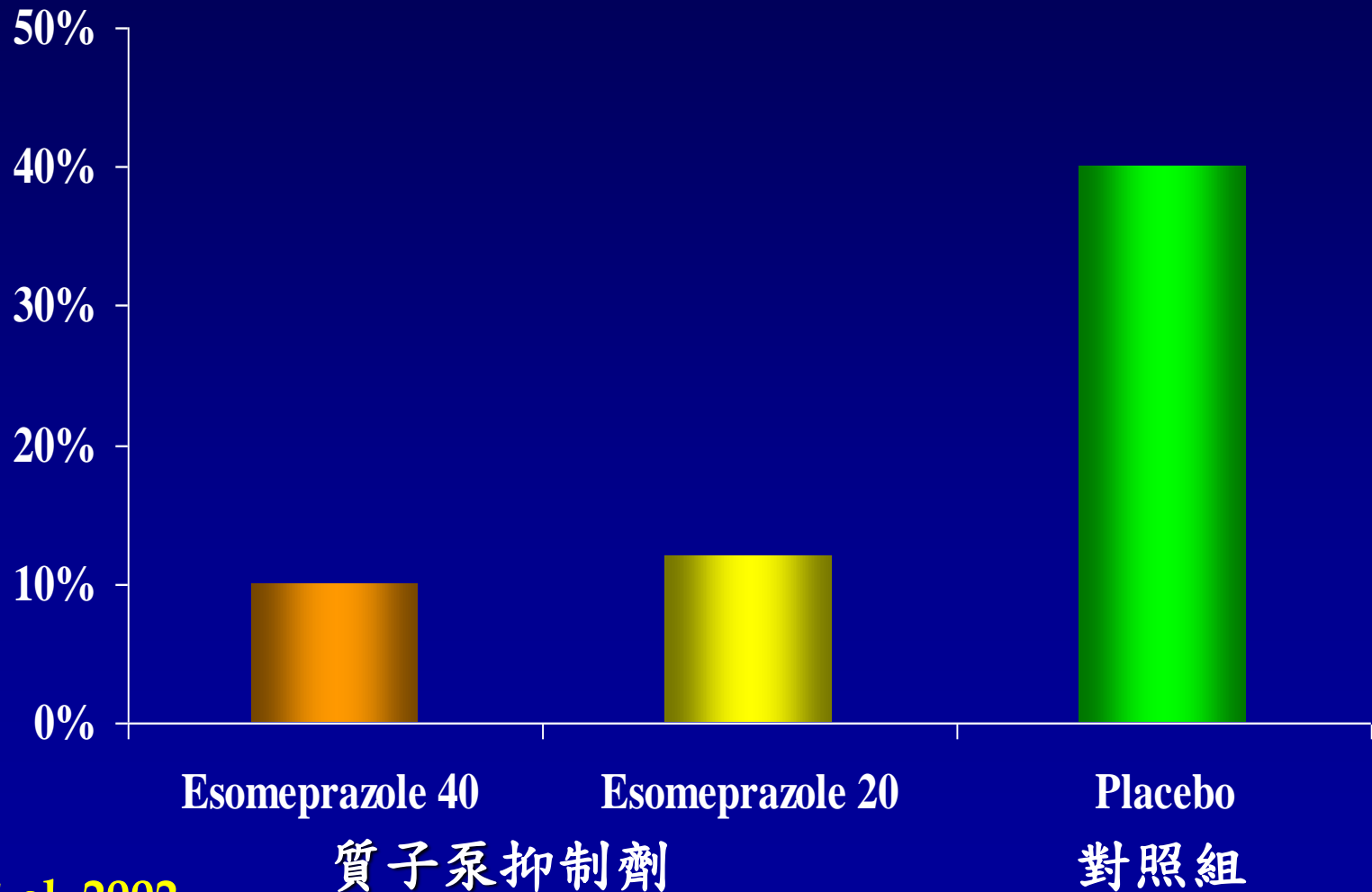
質子泵抑制劑為最好之維持劑



質子泵抑制劑

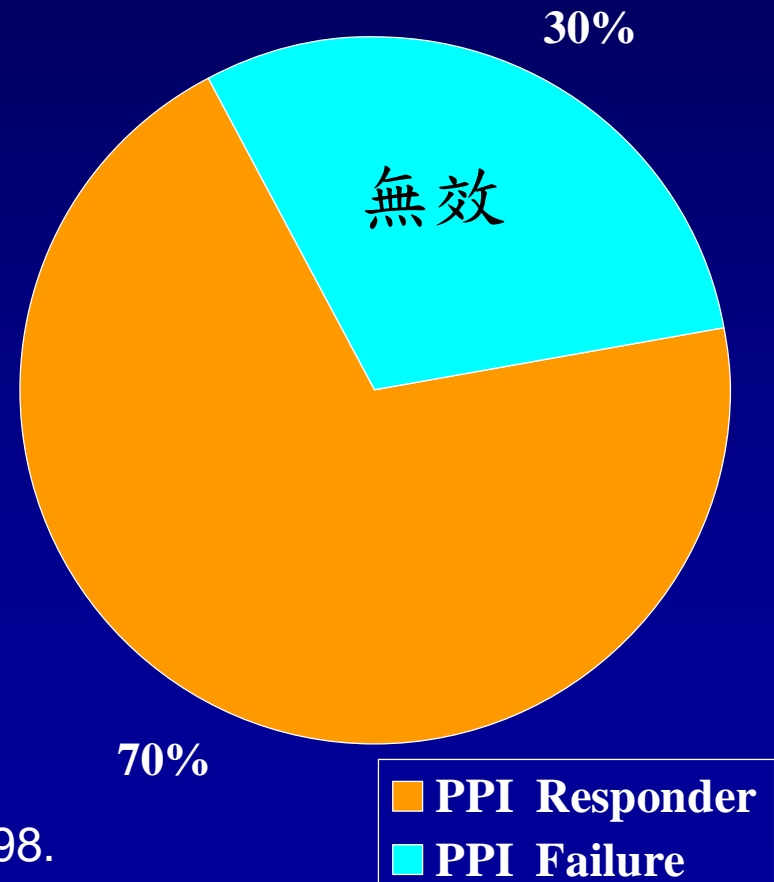
— 按需要服用治療法

維持治療
的比率

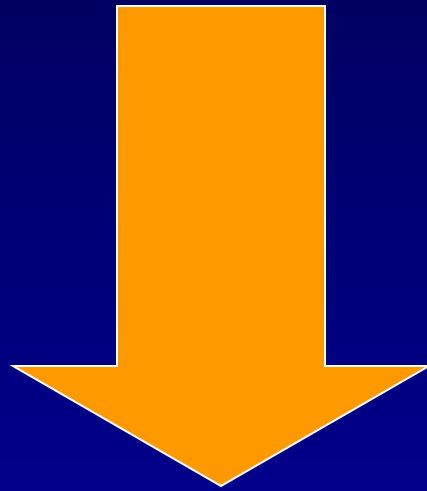


質子泵抑制劑 – 治療無效?

每日服用一次質子泵抑制劑, 而病徵持續的機會是
多少呢?



每日服用一次質子泵抑制劑，
而患者病徵持續

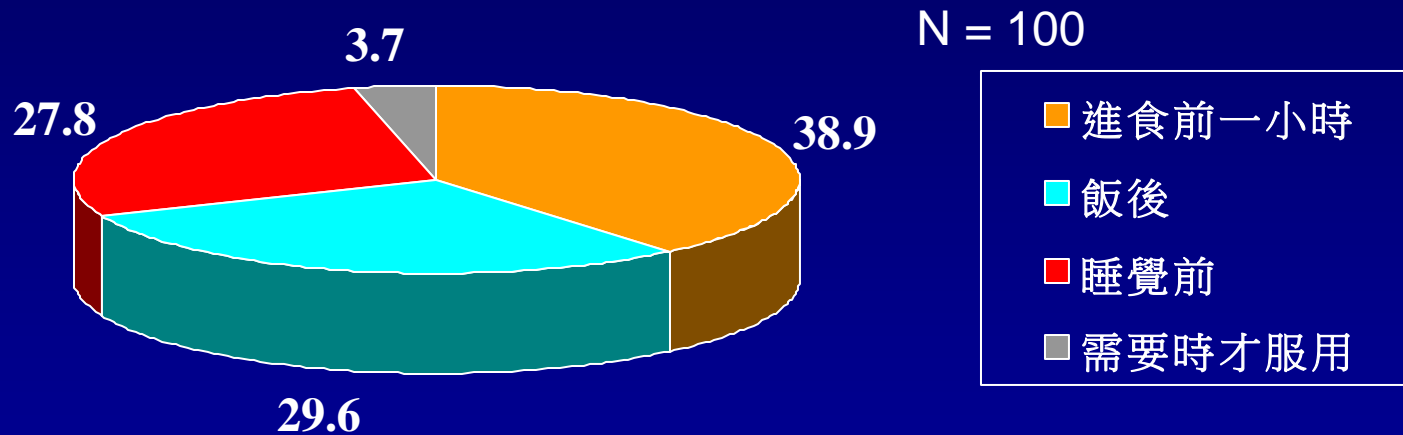


依從服藥的指引

(在服用初期是有效的)

治療胃食道反流疾病

— 不依從服藥指引是非常普遍的



十二指腸反流

腸道敏感

非胃酸性
反流

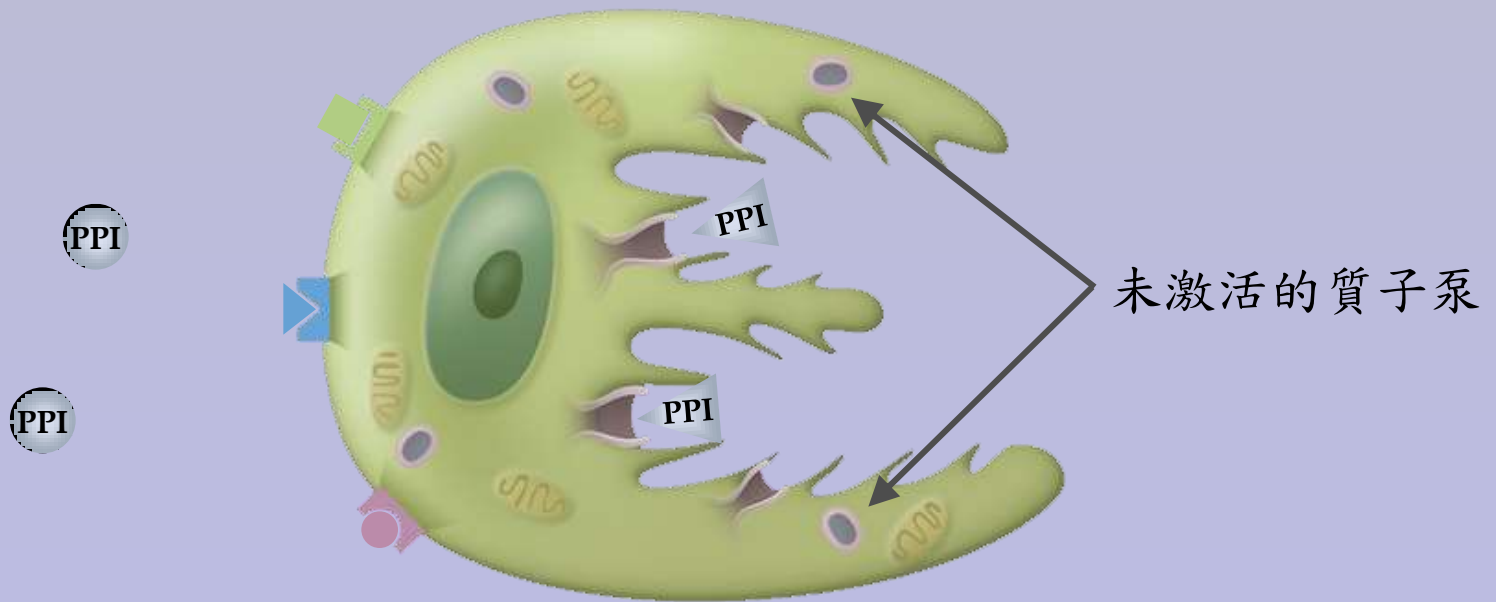


其他胃腸動力
問題
-胃排空緩慢
-心理作用

治療無效，應該甚辨？

質子泵抑制劑只能夠抑制活躍的質子泵

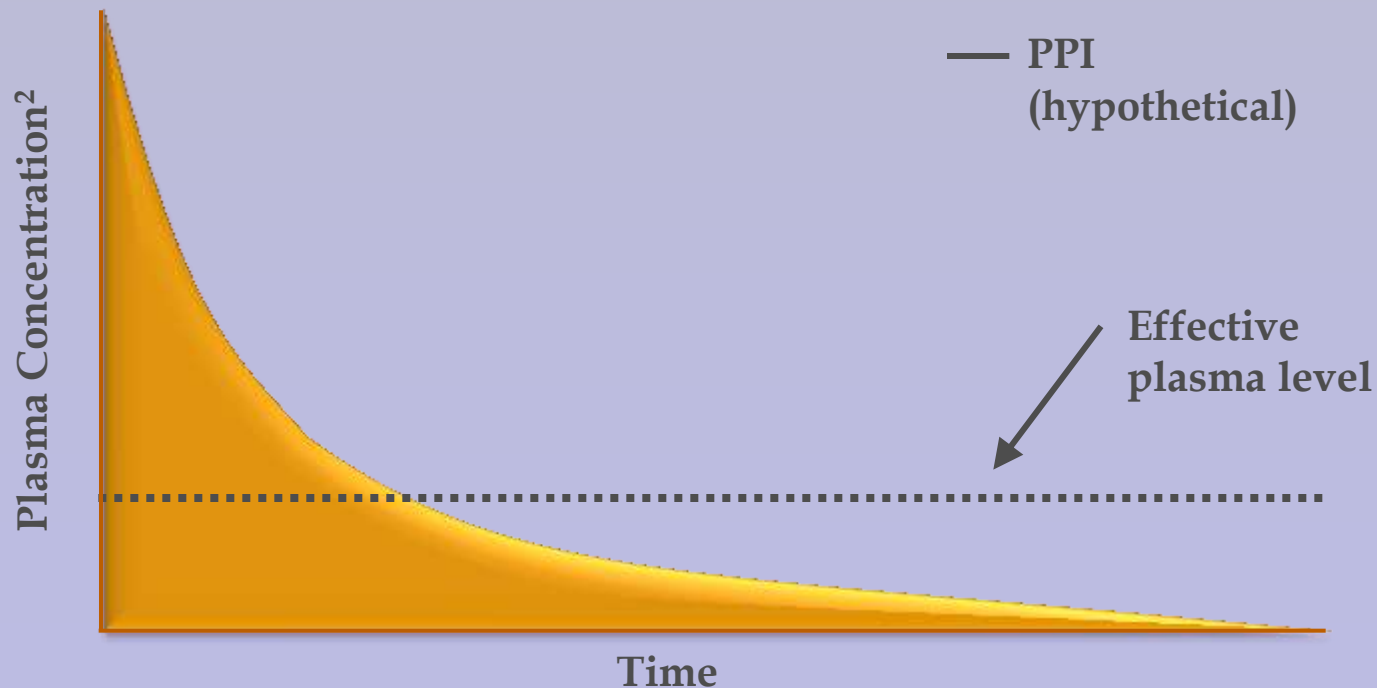
PPIs only bind to active proton pumps¹



1. Del Valle J et al. Acid peptic disorders. In: Yamada et al, eds. *Textbook of Gastroenterology*. 4th ed. Philadelphia, Pa: Lippincott Williams and Wilkins; 2003:1321-1376.

質子泵抑制劑的藥物半衰期 ~1-2 Hours¹

Any proton pumps activated after PPI concentrations fall below effective plasma levels may not be inhibited¹



1. Sachs G. *Pharmacotherapy*. 1997;17:22-37.
2. Brenner GM. Pharmacokinetics. In: Brenner GM. *Pharmacology*. 1st ed. Philadelphia, PA: WB Saunders Co; 2000:9-25.

服用一個劑量的質子泵抑制劑 - 1/4質子泵仍有製造胃酸的能力

AT LEAST

25%

OF ACID PRODUCTION CAPACITY MAY
NOT BE SHUT DOWN BY A PPI DOSE¹⁻³

- PPIs only inhibit active proton pumps
- Not all proton pumps are active at any given time ¹⁻³

1. Blair JA et al. *J Clin Invest.* 1987;79:582-587.

2. Sachs G. *Pharmacotherapy.* 1997;17:22-37.

3. Del Valle J et al. Acid peptic disorders. In: Yamada T et al, eds. *Textbook of Gastroenterology.* 4th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2003:1321-1376.

American Gastroenterological Association (AGA) Survey

1064 GERD patients

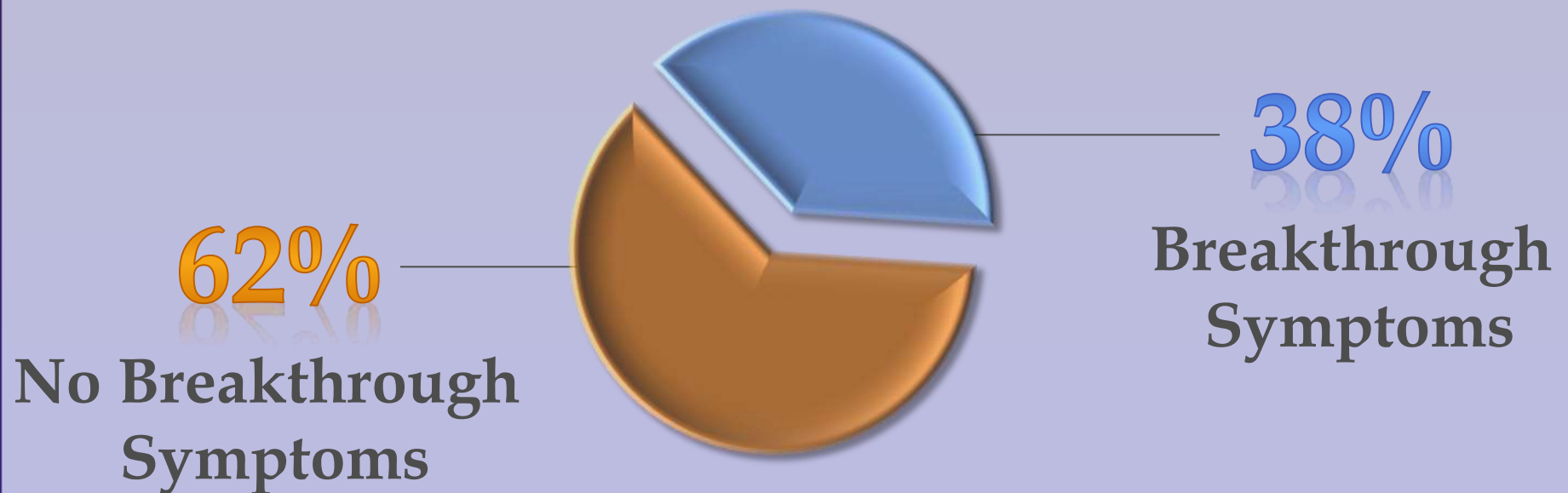
- Physician-made diagnosis of GERD
- Receiving once-daily PPI for ≥ 3 months

10-min online patient survey designed to assess

- Symptom control
- Use of over-the-counter (OTC) remedies
- Physician-patient dialogue about GERD

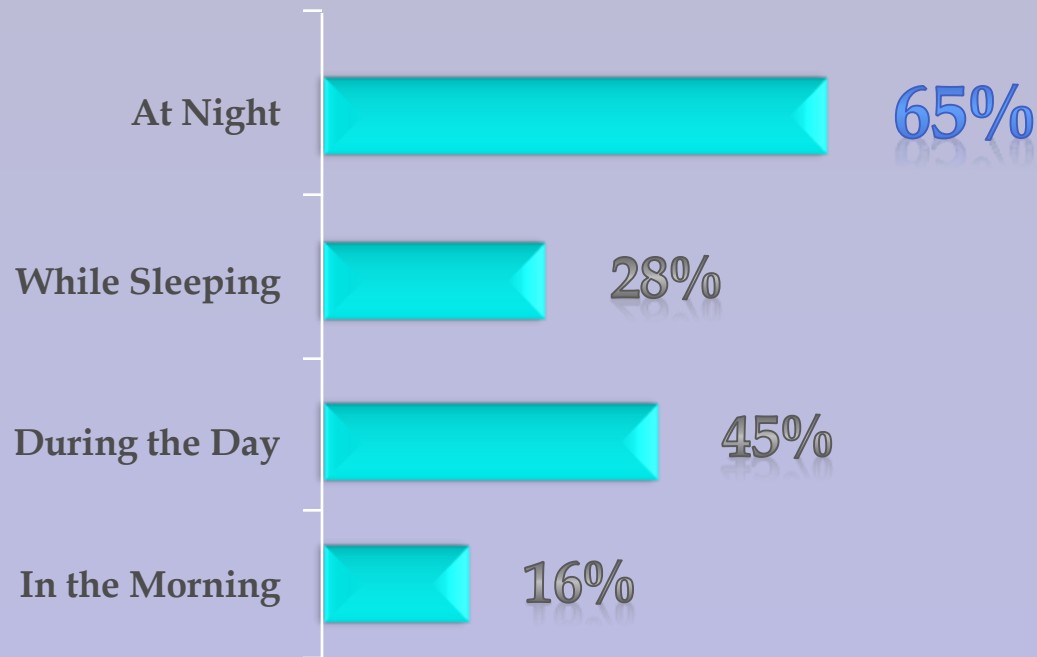
Nearly 40% of Patients on Once-Daily PPI Therapy Have Breakthrough Symptoms

Patient-Reported Symptoms on Once-Daily PPI Therapy (N=1064)



Breakthrough Symptoms Are Often Experienced at Night

Most Patients With Breakthrough Symptoms Experience Them at Night



56% of Patients With Breakthrough Symptoms Use Adjunctive OTC Medications

Additional Medications Used to Manage Breakthrough Symptoms

49% OTC

7% OTC

現時的質子泵抑制劑的限制 -

1. 需要餐前30至60分鐘服用
2. 很多時候都需要服用兩次
3. 半衰期很短

OTC products mentioned: Alka-Seltzer®, Maalox®, Mylanta®, Pepcid® Complete®, Pepto-Bismol®, Rolaids®, TUMS®.

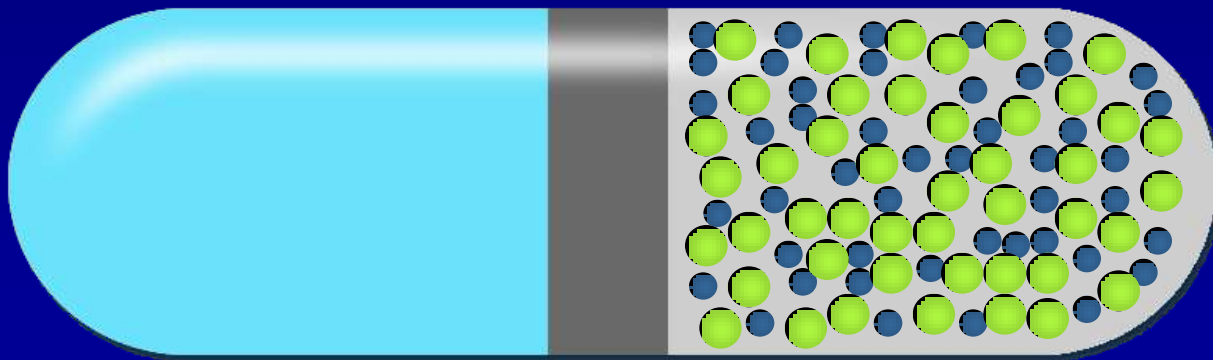
*OTC acid reducer includes OTC acid reduction agents, OTC H₂RAs, and OTC PPIs.

American Gastroenterological Association. *GERD Patient Study: Patients and Their Medications*. Harris Interactive Inc; 2008.

Dexlansoprazole Consists of a Dual Delayed Release™ (DDR) Formulation

右蘭索拉唑緩釋膠囊

- Dexlansoprazole is the R-enantiomer of lansoprazole
- 一種具有雙重緩釋效果的質子泵抑制劑，有兩種獨立的藥物釋放方式。

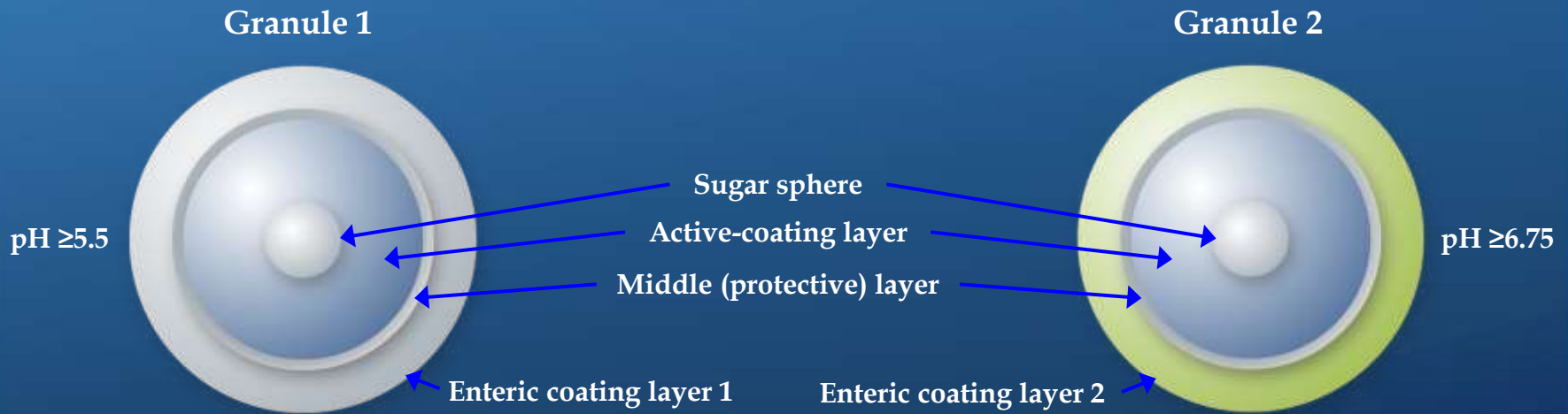


Artistic rendition. Not an actual representation of granules.

DEXILANT (雙重緩釋效果的質子泵抑制劑)

DDR formulation of DEXILANT allows each type of granule to release medication at different pH levels¹

The Enteric Coating of Each Type of Granule Dissolves at a Different pH in the GI Tract^{1,2}



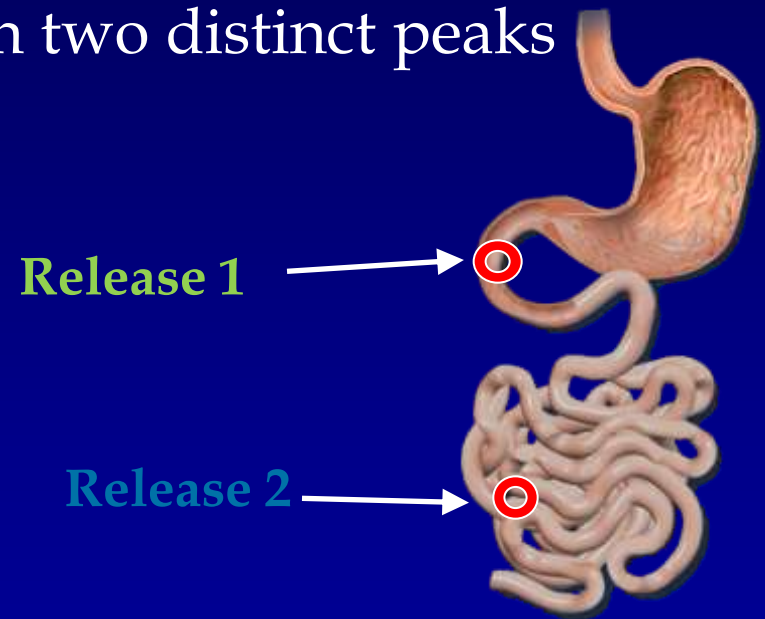
GI=gastrointestinal.

Artistic rendition of granules.

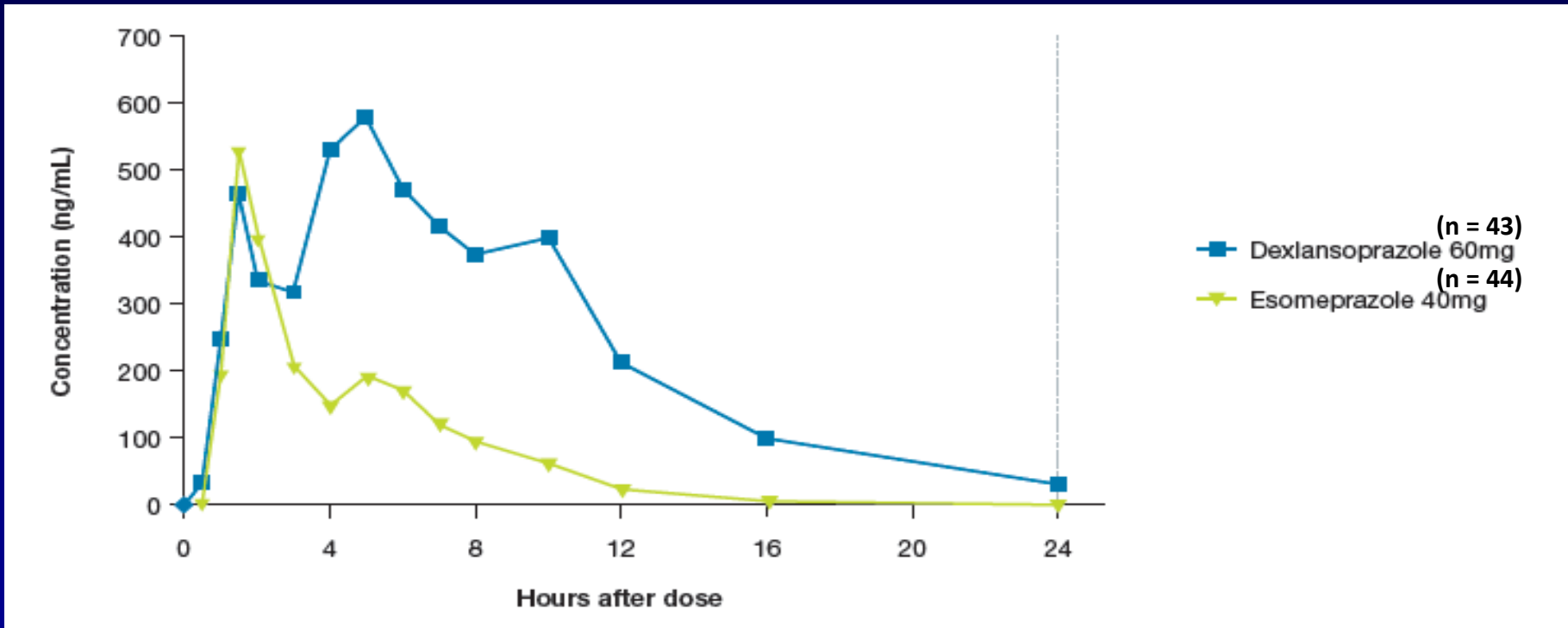
1. DEXILANT Package Insert.
2. Vakily M et al. *Curr Med Res Opin.* 2009;25:627-638.

一種具有雙重緩釋效果的質子泵抑制劑， 有兩種獨立的藥物釋放方式。

- The DDR formulation results in a plasma concentration-time profile with two distinct peaks
- ❖ Granule 1 comprises 25% of total dose and is released at pH 5.5 within 2 hours of dosing²
- ❖ Granule 2 comprises 75% of total dose and is released at pH 6.75 several hours after dosing



Dexlansoprazole maintains high plasma concentrations longer than esomeprazole

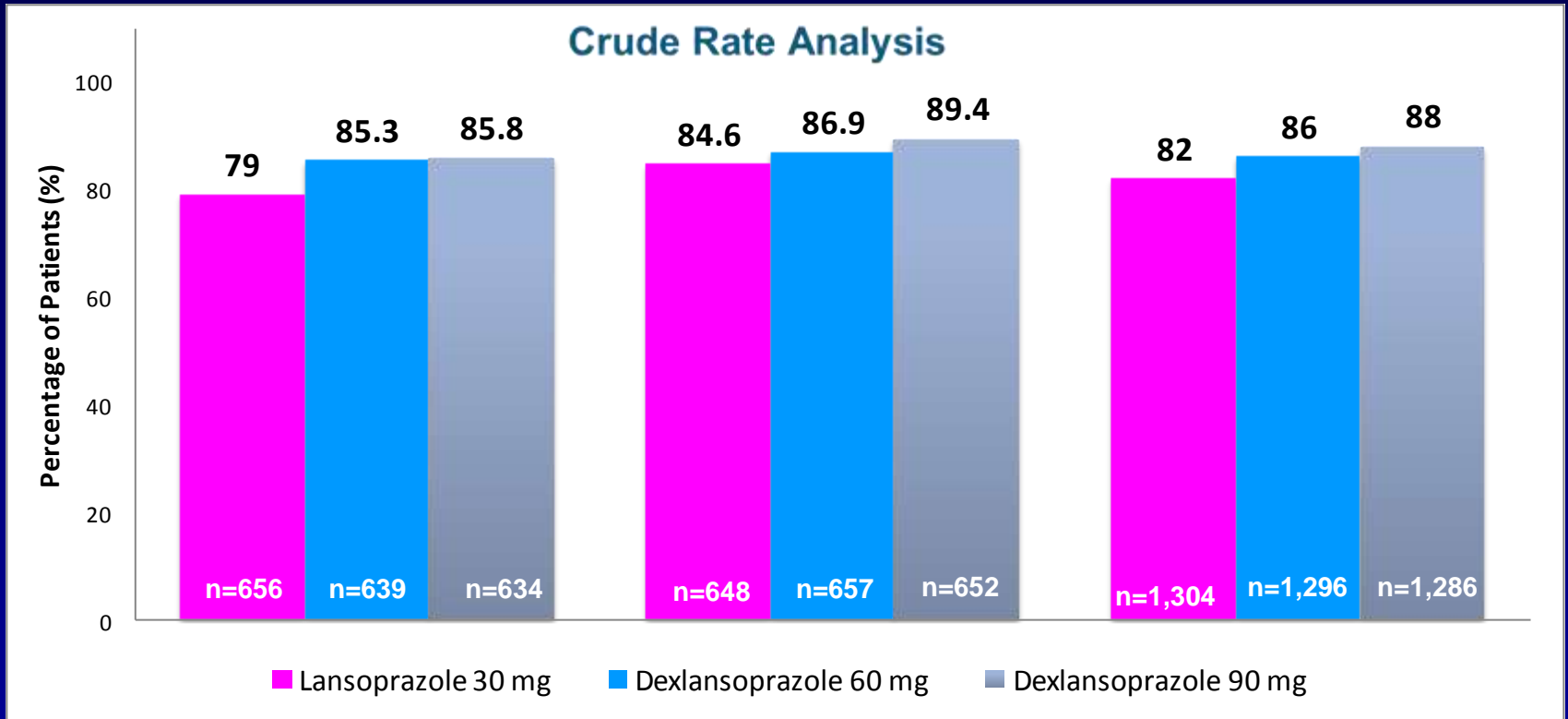


DDR formulation allows dexlansoprazole to have:

- 10% increase in duration with pH>4 compared with esomeprazole

Dexilant (右蘭索拉唑緩釋膠囊)

八星期內的食道炎治愈率



	Study 1				Study 2				Combined			
Life Table Analysis												
Healing (%)	86	92	92		92	93	95		89	93*	94*	
n	684	673	665		672	685	680		1,356	1,358	1,345	

$P < 0.05$ after adjusting for the number of doses compared. Pairwise treatment comparisons performed with Cochran-Mantel-Haenszel test for crude rate analysis and with log-rank tests for life table analysis.

對食道炎病徵的控制 - 燒心感, 火燒心

Dexlansoprazole 30 mg Provided 96% Heartburn-Free 24-Hour Periods in a 6-Month Study

Median Percentage of 24-Hour Heartburn-Free Periods of the Maintenance of Healed EE Study – Overall Treatment¹



Potassium-competitive acid blockers (P-CABs) 鉀離子競爭性胃酸抑制劑

- ◆ Block gastric H^+ / K^+ -ATPase by reversible and K^+ - competitive ionic binding.
- ◆ Rapid onset of anti-secretory effect.
- ◆ Maximal antisecretory effect may be seen after first dose.

鉀離子競爭性胃酸抑制劑 與質子泵抑制劑之比較

P-CABs

鉀離子競爭性胃酸抑制劑

Acts directly on the H/K ATPase

Superconcentration in parietal cell acid space (**100,000** fold of plasma)

Binds **competitively** to the K-binding site of H/K ATPase

Duration of effect related to half-life of drug in plasma

Full effect from the **first dose**

PPIs

質子泵抑制劑

Prodrug

Concentrate in parietal cell acid space (**1,000** fold of plasma)

Binds **covalently** to H/K ATPase

Duration of effect related to the half-life of the Sulphenamide-enzyme complex

Full effect after **repeated doses**

鉀離子競爭性胃酸抑制劑

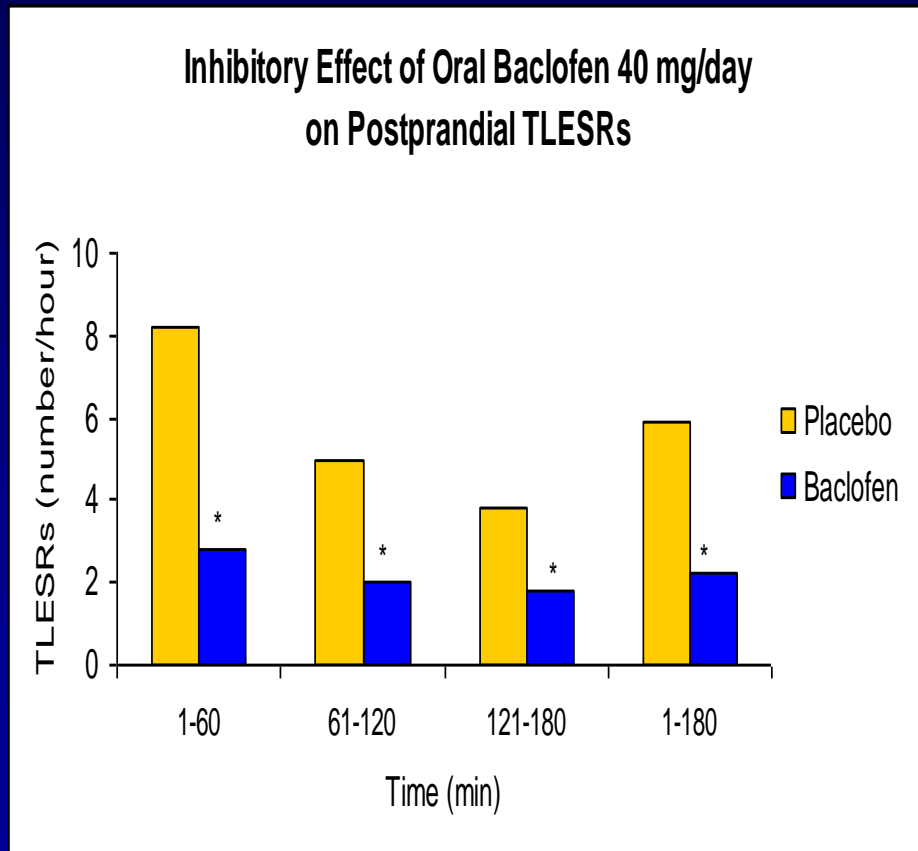
- ◆ Revaprazan (Revanex) 鹽酸瑞伐拉贊, Licensed in South Korea (Yuhan).



- ◆ Vonaprazan 沃諾拉贊 Licensed in Japan.
Phase III study of Vonaprazan 20mg vs Lansoprazole 30mg once daily in the treatment of patients With Erosive Esophagitis in China (Jan, 2017).

Baclofen 巴氣芬 - For Non-Acidic Reflux 弱酸反流

- GABA-B agonists.
- Reduces TLESR.
- Mild gastrokinetic.
- 40-50% reduction in TLESR rate.
- Improve GERD symptoms.
- Start with 10mg at bed time.
- Can increase up to 20mg tid.
- Watch for neurological side effects – hypotonia, drowsiness

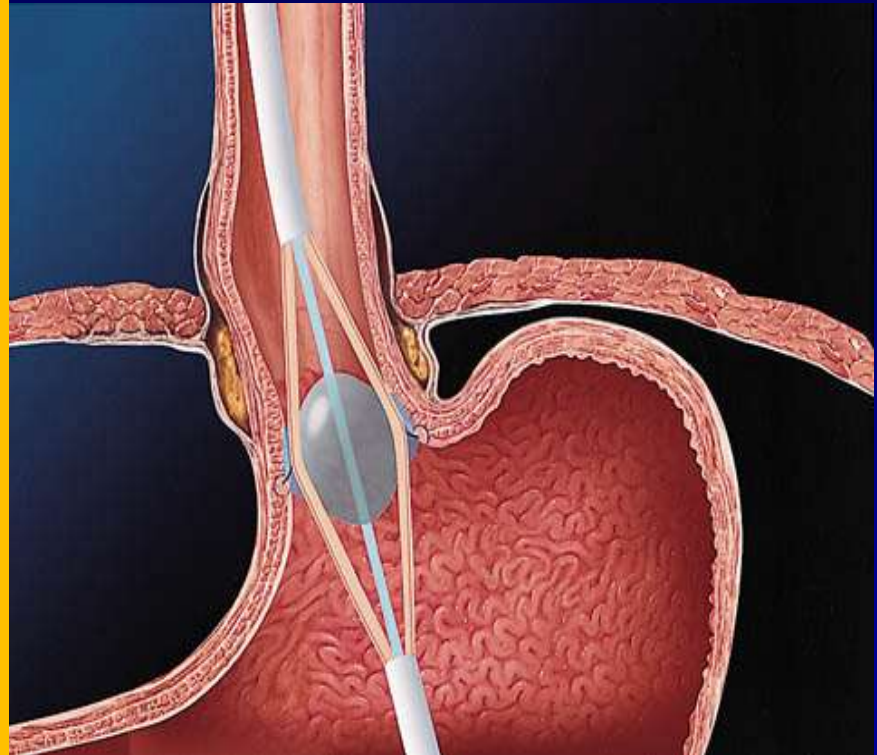


The Stretta Technique

非燒蝕射頻能量

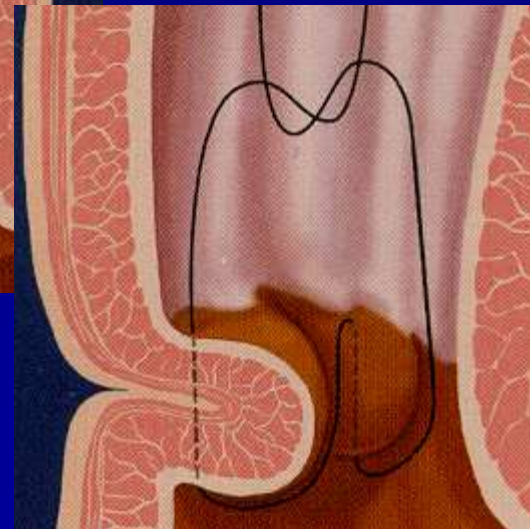
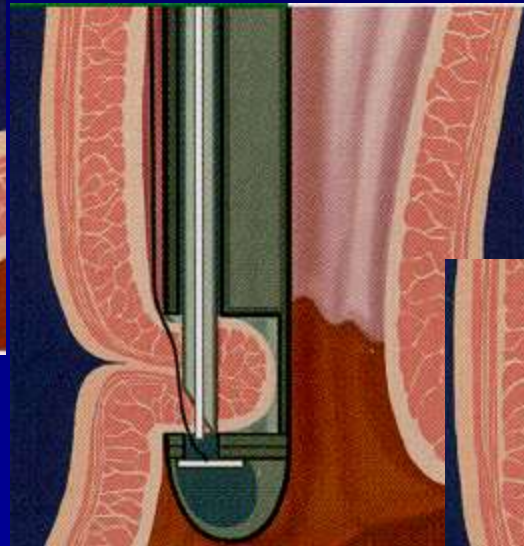
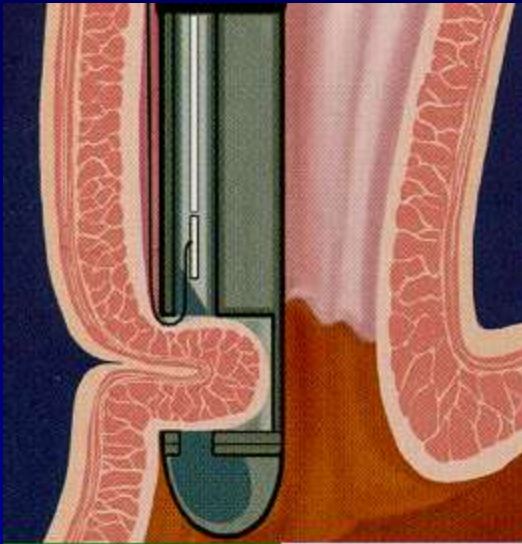
Apply radiofrequency energy delivery to the distal oesophagus -> decrease esophageal sensitivity to acid.

Improvement of esophageal symptoms, decrease in PPI use, but no effect on esophageal acid exposure.



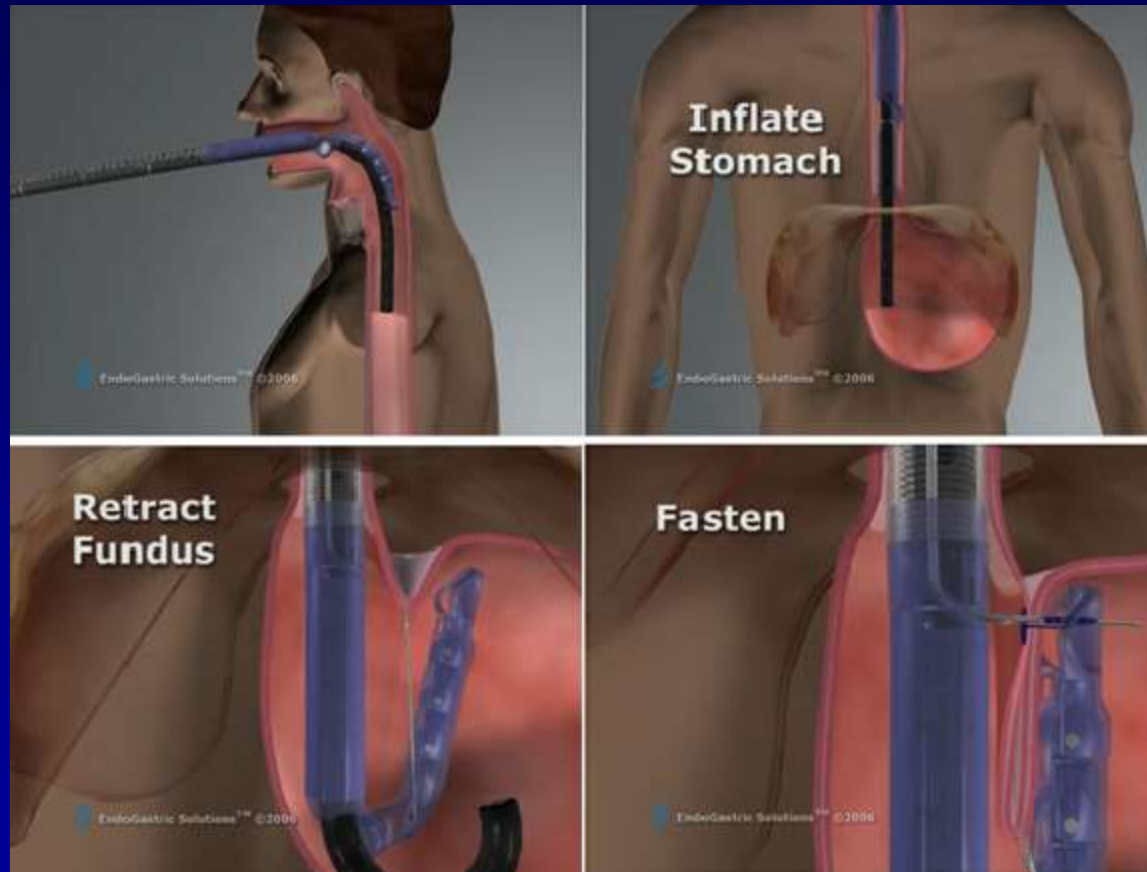
Utley et al. GIE 2000

內窺鏡結紮



Martinez-Serna et al. GIE 2000

內窺鏡結紮





LINX™ Reflux Management System

磁環系統

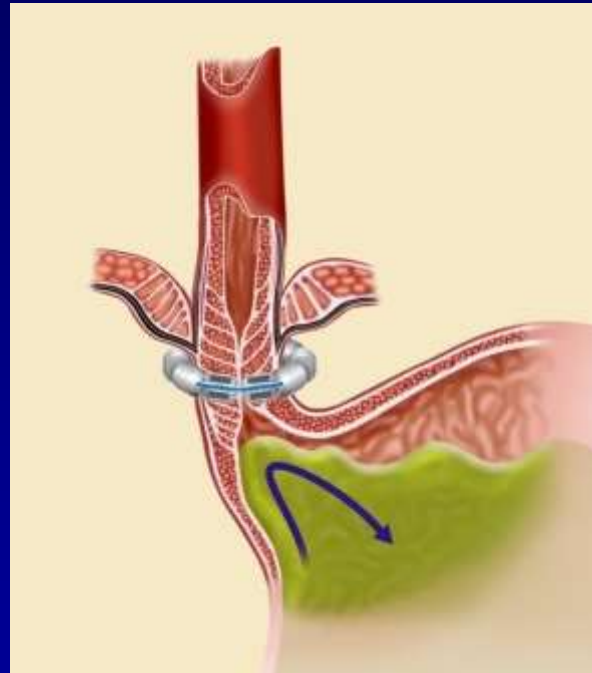
LINX consists of magnetic beads that are connected by titanium links that allow the beads to open during a swallow or belch. The force of magnetic attraction exerts forces to strengthen the LES.



LINX™ Reflux Management System

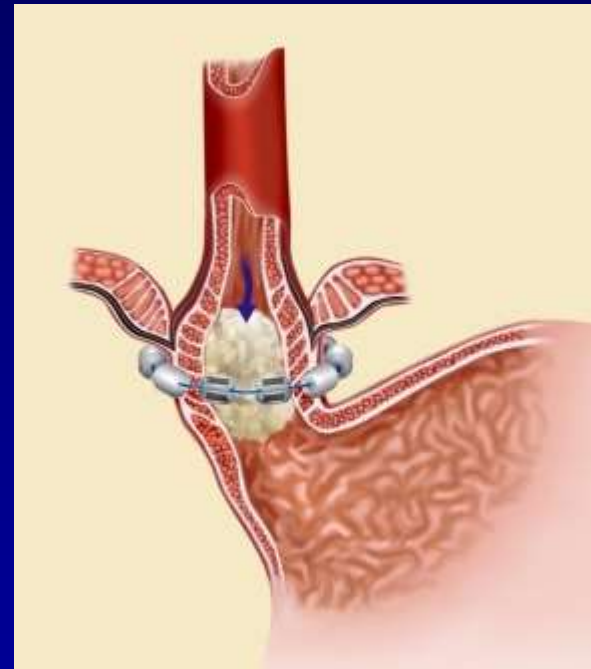
磁環系統

Reinforces the LES restoring the barrier function



Highest Magnetic Resistance

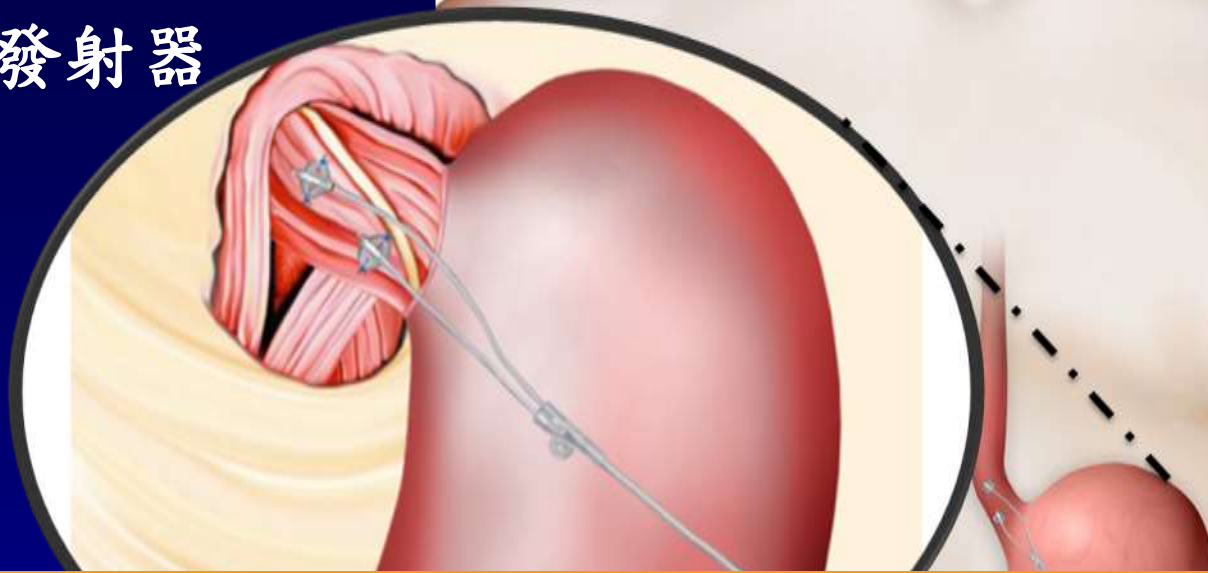
Expands during swallow allowing food to enter stomach



Lowest Magnetic Resistance

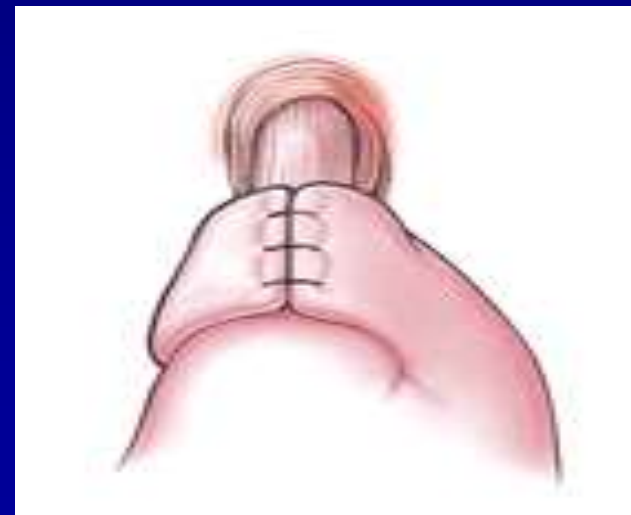
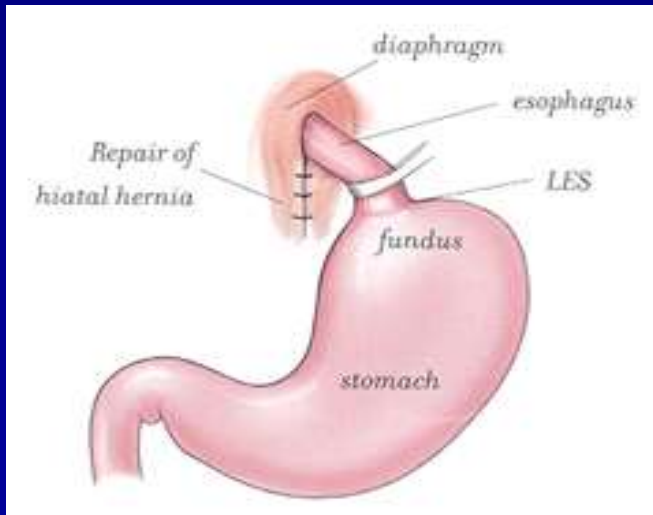
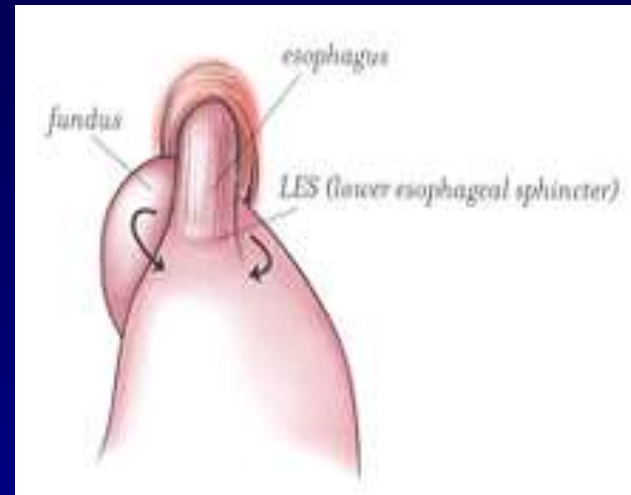
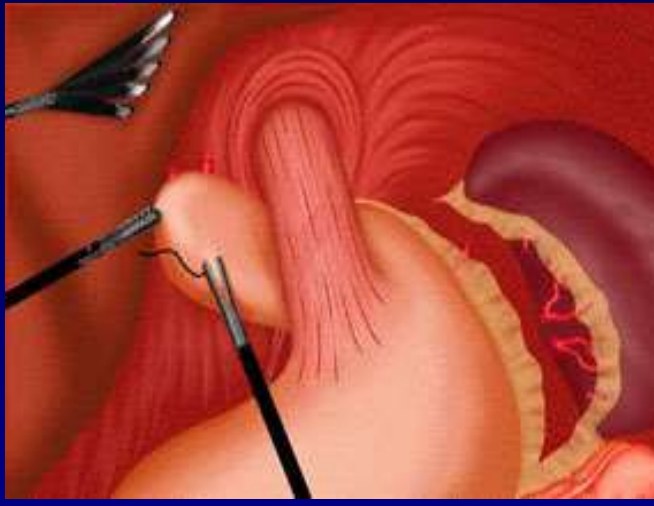
EndoStim Implant

植入式脈衝發射器



The EndoStim system automatically delivers tiny electronic pulses from the implanted pulse generator to the weak LES muscle. The pulses stimulate the muscle to function as a healthy LES, opening for swallowing, belching, and other normal behaviors, but remaining closed at other times.

外科手術



結論 Conclusions

- ◆ GERD is a growing problem in Asia.

胃食道反流疾病在亞洲的流行情度遠低於西方國家，但有上升的趨勢。

- ◆ New diagnostic modality available.

現時有新的診斷方法。

- ◆ PPIs are currently the optimal medical therapy.

質子泵抑制劑是最有效的藥物。

- ◆ Newer PPI / P-CABS and new endoscopic techniques potentially promising.

在不久將來，新的藥物和手術為治療胃食道反流疾病帶來新的希望。