Heartburn, Acid Reflux, GERD
Preventing the Progression to Esophageal Cancer

Nikolai A. Bildzukewicz, MD
Hoag Digestive Disease Center

Patty & George Hoag Cancer Center
Newport Beach, CA
April 2, 2016
Disclosures

• No financial disclosures
• But I am also a surgeon
  – So the truth will continue
What are the Treatment Options for GERD?
Is This You?
Diet and Lifestyle Modification

- Spicy foods
- Caffeine
- Fatty foods
- Tomato-based
- Fruits
- Chocolate
- Alcohol
- Carbonated beverages
- Large meals
- Medications
Diet and Lifestyle Modification

![Image of ComfortWedge]

“Natural Healing and Sleep Relief”

![Image of AcidRefluxPillow.com]

"When Your Health Needs A Lift"

![Image of BEDZ-UP]

“A Product Designed for Sufferers of ACID REFLUX DISEASE / GERD"

How to Elevate the Head of the Bed

![Image of BED BLOX]

Using Standard Pillow

Using The Prop Up Pillow
The Best Acid Reflux Treatment?
Medications for GERD
Medications

- Work by reducing the amount of acid in the stomach
- Relief can be temporary
- Usually requires escalating doses of medications
- Necessary to change medications
$10 BILLION
Are Patients Satisfied?

- Multicenter RCT
- 5,241 adult patients
- Once daily esomeprazole vs. lansoprazole
  - Healing of esophagitis
  - Resolution of heartburn

Are Patients Satisfied?

Percentage of all pts experiencing breakthrough symptoms while on PPI

- 62% No Breakthrough Symptoms
- 38% Breakthrough Symptoms

How often breakthrough symptoms experienced (among patients with breakthrough symptoms)

<table>
<thead>
<tr>
<th>Frequency of symptoms prior to diagnosis &amp; subsequent PPI use</th>
<th>12</th>
<th>43</th>
<th>19</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 or more times per week</td>
<td>65</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-4 times per week</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 time per week</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less often</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AGA Institute GERD Survey 2008 (n=1064)
Are PPIs Safe?

• FDA Drug Safety Communications about PPIs
  – May 2010: Possible increased risk of fractures of the hip, wrist, and spine
  – March 2011: Low magnesium levels can be associated with long-term use
  – Feb 2012: Clostridium difficile-associated diarrhea can be associated with use
Are PPIs Safe?

Use of Proton Pump Inhibitors and the Risk of Community-Acquired Pneumonia

A Population-Based Case-Control Study

Sinem Ezgi Gulmez, MD, PhD; Anette Holm, MD, PhD; Henrik Frederiksen, MD, PhD; Thøger Gørn Jensen, MD, PhD; Court Pedersen, DMS; Jesper Hallas, DMS

Risk of Community-Acquired Pneumonia and Use of Gastric Acid–Suppressive Drugs

Robert J. F. Lahrer, PhD
Miriam J. M. Sturkenboom, PhD
Robert-Jan Hassing, MSE
Jeanne Biederman, PhD
Bruno H. C. Stricker, MD, PhD
Jan B. M. J. Jansen, MD, PhD

Unexpected Effect of Proton Pump Inhibitors
Elevation of the Cardiovascular Risk Factor Asymmetric Dimethylarginine

Yohannes T. Gebremariam, PhD; Paea LePendu, PhD; Jerry C. Lee, MS;
Daniel A. Erlanson, PhD; Anna Slaviero, PhD; Nigam H. Shah, MBBS, PhD; James Leiper, PhD;
John P. Cooke, MD, PhD

Proton Pump Inhibitor and Histamine 2 Receptor Antagonist Use and Vitamin B₁₂ Deficiency

Jamason R. Lam, MPH; Jennifer L. Schneider, MPH; Wei Zhao, MPH; Douglas A. Corley, MD, PhD

Arch Intern Med. 2007 May 14;167(9):950-5.
JAMA. 2013 Dec 11;310(22):2435-42
Are PPIs Safe?

Proton Pump Inhibitor Usage and the Risk of Myocardial Infarction in the General Population


JAMA Intern Med. 2016 Feb 1;176(2):238-46


Proton pump inhibitors may be linked to dementia risk

Proton Pump Inhibitor Use and the Risk of Chronic Kidney Disease

Benjamin Lazarus, MBBS1,2; Yuan Chen, MS1; Francis P. Wilson, MD, MS3; Yingying Sang, MS1; Alex R. Chang, MD, MS4; Josef Coresh, MD, PhD1,5; Morgan E. Grams, MD, PhD1,5

*hoag*

Hoag Family Cancer Institute

in alliance with

USC Norris Comprehensive Cancer Center

Koch Medicine of USC
Myth: Do Medications Stop Reflux?

- 50 pts with Barrett’s esophagus
- pH studies before and after PPIs
- Patients reflux the SAME amount ON or OFF medications
- Medications mask the symptoms of GERD
- DOES NOT STOP GERD

Median number of refluxes off and on PPI therapy

Myth: Medications Prevent All the Complications Associated with GERD
Medications for GERD

- Work by **reducing** the amount of **acid** in the stomach

- Has **NO** effect on **bile**, **pancreatic enzymes**, **pepsin**, etc.

- Patients **reflux** the **SAME** amount **ON** or **OFF** medications
Medications for GERD

- Do **NOT** restore the barrier to reflux
- The **PROBLEM** is the **VALVE** (LES)
Complications of GERD

Response to Medications

• Esophagitis
• Strictures (helps prevent)
• Loss of muscular strength of the esophagus
• Pulmonary problems
• ENT Problems
• Barrett’s esophagus ??
• Cancer ???
Myth: PPIs for Cancer Prevention?

Langerhen, NEJM 1999
Progression to Esophageal Cancer While On PPI Therapy

A nationwide study of 9,883 newly diagnosed patients with Barrett’s esophagus

No PPI  |  Frequent PPI  |  Daily Use PPI

Median Follow Up
10 Years

Conclusions

- **NO** cancer-protective effects from PPI’s were seen
- “Until future studies can elucidate the association, continuous PPI therapy should be directed at symptom control and **other additional modalities for treatment** should be considered.”

Progression to Esophageal Cancer While On PPI Therapy

A nationwide study of 9,883 newly diagnosed patients with Barrett’s esophagus

Progression of GERD

1. Chronic Injury (GERD)
2. Barrett’s Esophagus
3. Low grade dysplasia
4. High grade dysplasia
5. Cancer
What Restores the Barrier to Reflux?

- **Minimally Invasive Surgery**
  - Laparoscopic Nissen fundoplication
    - “Stomach wrap”
- **Endoscopic treatments**
  - Stretta
  - Endocinch
  - Enteryx
  - Esophyx
  - Medigus
- **Magnetic Sphincter Augmentation**
Nissen Fundoplication

• First described by German surgeon
  – Rudolph Nissen (1956)
• “Gastroplication”
  – Wrapped stomach around lower esophagus
Laparoscopic Nissen Fundoplication

• First performed by Bernard Dallemagne, MD in 1991
• Safe, effective, and durable in experienced hands
• Most common anti-reflux procedure performed today
Minimally Invasive Surgery

Nissen Fundoplication
Minimally Invasive Surgery
Nissen Fundoplication
Minimally Invasive Surgery

Nissen Fundoplication

- Done laparoscopically
- 5 small incisions on the abdomen (<1 inch)
- 1-2 hr procedure
- Overnight stay
- 1-2 weeks off work
Minimally Invasive Surgery
Nissen Fundoplication

- **90% effective in restoring the barrier to reflux**
- Stops reflux of acid, **bile**, pancreatic enzymes, etc.
- Able to **stop all heartburn medications** immediately post-op
- **Decreases** the chance of developing **Barrett’s and esophageal cancer**
Minimally Invasive Surgery
Nissen Fundoplication

Treats the
PROBLEM
Not just the
SYMPTOMS
Down Sides to Nissen?

• **Technically-complicated surgery**
  - 90% success (experienced centers)
  - 50-60% success (community surgeons)

• **Side effects**
  - Difficult to belch or vomit
  - Gas / Bloating
  - Difficulty swallowing (short term)

• **Slow diet advancement**
  - Diet advanced over 4-6 weeks
Endoscopic Methods
The Future of GERD Therapy

• Problem with acid suppression therapy
  – Inability to stop the reflux of gastric juice

• Problem with laparoscopic fundoplication
  – Varying rates of success
  – Potential side effects

• Solution
  – Simple and easy way of augmenting the function of the LES
Another Approach

Restore the Barrier \( \equiv \) Reconstruct the Barrier

- Augment the valve back to normal function
- Preserve normal swallow & belch function
- Maintain normal anatomy
- Minimally-invasive with limited surgery
- Procedural simplification and standardization
LINX Sphincter Augmentation

Mechanical Sphincter Augmentation
Bio-Mechanical Implant

Precise and Consistent Force

Resting Diameter (Highest Force)

Swallow Diameter (Lowest Force)
Magnetic Sphincter Augmentation
LINX Allows Physiologic Function

Closed to Reflux

Normal Peristaltic Pressures
35-80 mmHg

LINX System Dynamic Barrier of ~20 mmHg

Intragastric Pressure
5-10 mmHg

Opens to Swallows, Belching, & Vomiting
Torax Medical has provided valid scientific data that supports the reasonable assurance of safety and effectiveness of the LINX device when used in accordance with the indications for use.

The LINX System is the only available device approved by the FDA to be both safe and effective for the treatment of GERD.
LINX Procedure

- Minimally-invasive (30-45 min)
- No alteration of normal anatomy
- Outpatient
- Resume normal diet post-op
- Allows patients to belch & vomit
- Eliminates or decreases gas & bloating (associated with Nissen)
- Removable
Reduction in Acid Exposure

% TIME pH < 4

**STUDY**

- **FDA PILOT**
  - Centers/Patients: 4/44
  - F/U Range: 4 Years
  - Published Studies: Surgical Endoscopy
- **FDA PIVOTAL**
  - Centers/Patients: 14/100
  - F/U Range: 1-3 Years
  - Published Studies: New England Journal Of Medicine
- **MILAN EXPERIENCE**
  - Centers/Patients: 1/100
  - F/U Range: 1-6 Years
  - Published Studies: Journal American College Of Surgery

Pre-LINX
Post-LINX
Pathologic
GERD-HRQL Questionnaire

<table>
<thead>
<tr>
<th>Scoring Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 = No symptoms</td>
</tr>
<tr>
<td>1 = Symptoms noticeable but not bothersome</td>
</tr>
<tr>
<td>2 = Symptoms noticeable and bothersome but not every day</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Question</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. How bad is your heartburn?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Heartburn when lying down?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Heartburn when standing up?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Heartburn after meals?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Does heartburn change your diet?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Does heartburn wake you from sleep?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Do you have difficulty swallowing?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Do you have bloating or gassy feelings?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Do you have pain with swallowing?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. If you take medication, does this affect your daily life?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. How satisfied are you with your present condition?</td>
<td>Satisfied</td>
<td>Neutral</td>
<td>Dissatisfied</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

GERD-HRQL Total

Long-Term Control of Symptoms

**GERD-HRQL SCORE**

- **Pre-LINX**
- **Post-LINX**

<table>
<thead>
<tr>
<th>STUDY</th>
<th>FDA PILOT</th>
<th>FDA PIVOTAL</th>
<th>MILAN EXPERIENCE</th>
<th>EU REGISTRY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Centers/Patients:</td>
<td>4/44</td>
<td>14/100</td>
<td>1/100</td>
<td>19/249</td>
</tr>
<tr>
<td>F/U Range:</td>
<td>4 Years</td>
<td>1-3 Years</td>
<td>1-6 Years</td>
<td>1 Year</td>
</tr>
<tr>
<td>Published Studies:</td>
<td>Surgical Endoscopy</td>
<td>New England Journal Of Medicine</td>
<td>Journal American College Of Surgery</td>
<td>Pending Publication(1)</td>
</tr>
</tbody>
</table>
Freedom from PPIs

PERCENT OF PATIENTS TAKING ANY PPIs

<table>
<thead>
<tr>
<th>STUDY</th>
<th>FDA PILOT</th>
<th>FDA PIVOTAL</th>
<th>MILAN EXPERIENCE</th>
<th>EU REGISTRY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Centers/Patients:</td>
<td>4/44</td>
<td>14/100</td>
<td>1/100</td>
<td>19/249</td>
</tr>
<tr>
<td>F/U Range:</td>
<td>4 Years</td>
<td>1-3 Years</td>
<td>1-6 Years</td>
<td>1 Year</td>
</tr>
<tr>
<td>Published Studies:</td>
<td>Surgical Endoscopy</td>
<td>New England Journal Of Medicine</td>
<td>Journal American College Of Surgery</td>
<td>Pending Publication(1)</td>
</tr>
</tbody>
</table>
Minimal Side Effects

**ABILITY TO VOMIT AT 4 YEARS**
(% patients reporting)
- 96.5% Yes / No Need
- 1.2% No Response
- 2.3% No

**ABILITY TO BELCH AT 4 YEARS**
(% patients reporting)
- 97.7% Yes / No Need
- 2.3% No

**BLOATING FREQUENCY**
(% patients reporting)
- Baseline: 30.0%
- 1 year: 25.0%
- 2 years: 20.0%
- 3 years: 15.0%
- 4 years: 10.0%

**GAS FREQUENCY**
(% patients reporting)
- Baseline: 40.0%
- 1 year: 35.0%
- 2 years: 30.0%
- 3 years: 25.0%
- 4 years: 20.0%

US Pivotal data on file
Improvement in Regurgitation

Regurgitation Symptoms

Improvement in Dysphagia

# LINX Safety Summary

<table>
<thead>
<tr>
<th></th>
<th>IDE Trials</th>
<th>OUS Commercial</th>
<th>US Commercial</th>
<th>Overall Worldwide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients</td>
<td>144</td>
<td>1073</td>
<td>1689</td>
<td>2906</td>
</tr>
<tr>
<td>Number of Centers</td>
<td>16</td>
<td>50</td>
<td>120</td>
<td>170</td>
</tr>
<tr>
<td>Dilation (reported)</td>
<td>15.3%</td>
<td>3.9%</td>
<td>3.1%</td>
<td>4.0%</td>
</tr>
<tr>
<td>Device Removal²</td>
<td>7.6%</td>
<td>5.1%</td>
<td>2.5%</td>
<td>3.7%</td>
</tr>
<tr>
<td>Erosion</td>
<td>0%</td>
<td>0.56%</td>
<td>0.12%</td>
<td>0.28%</td>
</tr>
<tr>
<td>Migration³ (reported)</td>
<td>0%</td>
<td>0%</td>
<td>0.06%</td>
<td>0.03%</td>
</tr>
</tbody>
</table>

¹Data on file as of May 20th 2015.
²Device Removals include removals for erosion.
³One reported migration not clinically confirmed with no resulting removal or sequel.
• Prospective observational study at Hoag + USC
• 67 LINX patients from 4/2012 to 12/2013
• No intra-op complications
• Average operative time = 60 min
• Average hospital stay = 11 hours
• Median postoperative GERD-HRQL = 4
• 76.9% of LINX patients off of PPIs
• Dysphagia in 79.1% of patients
  – Median time to resolution = 8 wks
  – 8 patients required EGD w/balloon dilatation

Nissen vs. LINX

• Compare Nissen and LINX in patients with similar disease severity
• All patients undergoing Nissen or LINX from 4/2007–10/2013
• 179 patients
  – 117 Nissen and 62 LINX
  – No esophageal stricture
  – Normal motility
  – On PPIs for at least 6 months
  – Objective evidence of GERD

Presented at the 2014 Annual Scientific Session of the Western Surgical Association
Nissen vs. LINX

- 9 preoperative characteristics
  - BMI, duration of GERD, GERD-HRQL, esophagitis grade, hiatal hernia size, Hill grade valve, LPR symptoms, dysphagia, and presence of Barrett’s esophagus
- 51 matched pairs
  - 50 best matches used for analysis (100 total patients)
Nissen vs. LINX

- Preoperative GERD-HRQL for all patients
- Follow up at least 1-year after surgery
  - GERD-HRQL
  - Specific gas/bloating and dysphagia questions
  - Satisfaction questions
  - Chart review for complications and intervention

Presented at the 2014 Annual Scientific Session of the Western Surgical Association
Nissen vs. LINX

GERD-HRQL SCORE

- 50 Nissen
- 50 LINX
- Follow-up at 1 yr

P = 0.34
Nissen vs. LINX

FREEDOM FROM PPIs

- 50 Nissen
- 50 LINX
- Follow-up at 1 yr

FREEDOM FROM PPIs

P = 0.35

Presented at the 2014 Annual Scientific Session of the Western Surgical Association
Nissen vs. LINX

SIDE EFFECTS

- Gas/Bloat: Nissen (p = 0.033), LINX
- Ability to Belch: Nissen (p = 0.033), LINX

Presented at the 2014 Annual Scientific Session of the Western Surgical Association
Hoag + USC Experience

• > 250 total LINX Implants
• 5 removals
  – MRI
  – 2 for persistent GERD
    • 1 converted to Nissen
    • 1 replaced with smaller LINX device (1st in US)
  – Herniated/slipped device (redo LINX)
  – Dysphagia
• 0 erosions
• Success
  – GERD HRQL & PPI elimination = 80-85%

Updated April 1, 2016
LINX Sphincter Augmentation

- Simple
- Safe
- Stops reflux
- Without the side effects of the Nissen
The Role of LINX

LINX importantly expands the options in treating the barrier defect associated with GERD

- Reproducible procedure with a precise mechanism of action
- Minimally-invasive surgical option
- Preserves native anatomy
- Allows physiologic reflux, swallowing, belching, and vomiting
- Does not limit future treatment options
A Better Way to Treat GERD

Early Disease
Medication

Progressive Disease
Sphincter Augmentation

Advanced Disease
Sphincter Reconstruction
GERD - Summary

• GERD is a **serious medical condition**
  – Much more than **heartburn**
  – Leads to **esophagitis, strictures, Barrett’s esophagus** and **cancer** if left untreated

• Medications treat the symptoms (some), **NOT** the problem (valve)

• Medications do **NOT** reduce your risk of developing **Barrett’s esophagus or cancer**
Final Proposal: Stop the Progression
Progression of GERD

1. Chronic Injury (GERD)
2. Barrett’s Esophagus
3. Low grade dysplasia
4. High grade dysplasia
5. Cancer
Final Proposal: Stop the Progression

• **GERD** is a disorder of the sphincter

• A normal sphincter (valve) creates a **barrier** against reflux

• A **weak** sphincter allows reflux of gastric juice

• The problem is the valve!
Fix the Valve
QUESTIONS?

Hoag-USC Digestive Disease Center
Hoag Family Cancer Center, Building 41, 3rd Floor,
Newport Beach, CA
(949) 764-5350
HoagUSCsurgical@hoag.org