



Esophageal disease

A potpourri for clinicians from DDW 2016



From San Diego

to...



San Francisco...

George Triadafilopoulos, MD
Clinical Professor of Medicine
Stanford University School of Medicine

NCSCG Post-DDW meeting

Disclosures

- Consultant to:
- Mederi Therapeutics Inc.
- C2 Therapeutics
- Medtronic
- Endostim

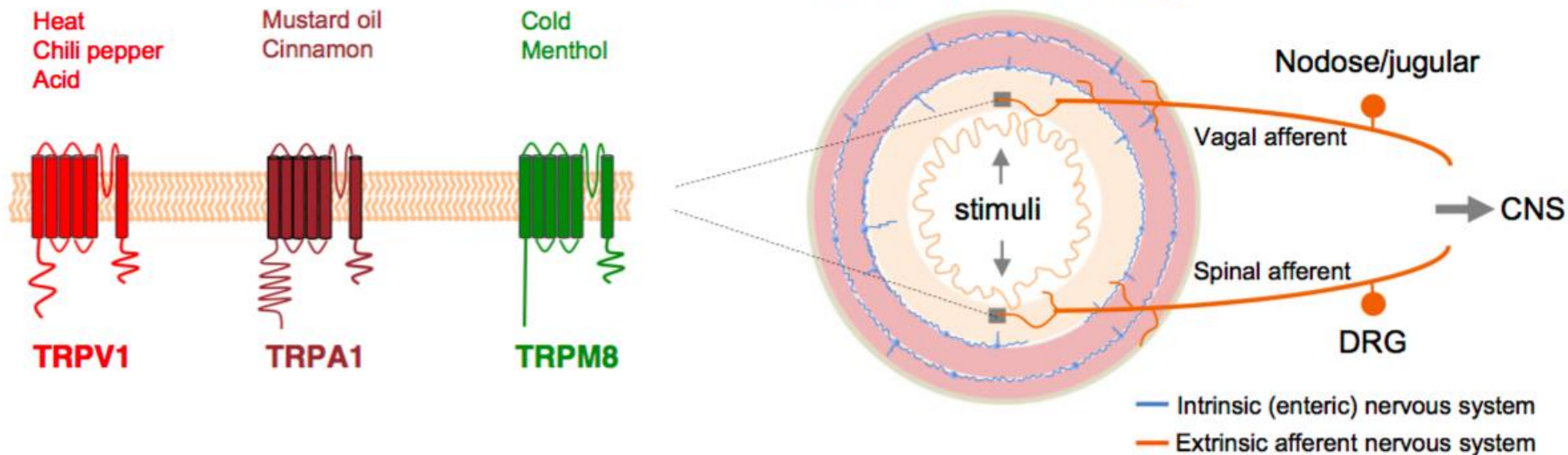


GERD treatment without PPIs



Here, take these, I'd like to see what they do to you...

Transient Receptor Potential (TRP) channels in vagal and spinal afferent nerves in the GI tract



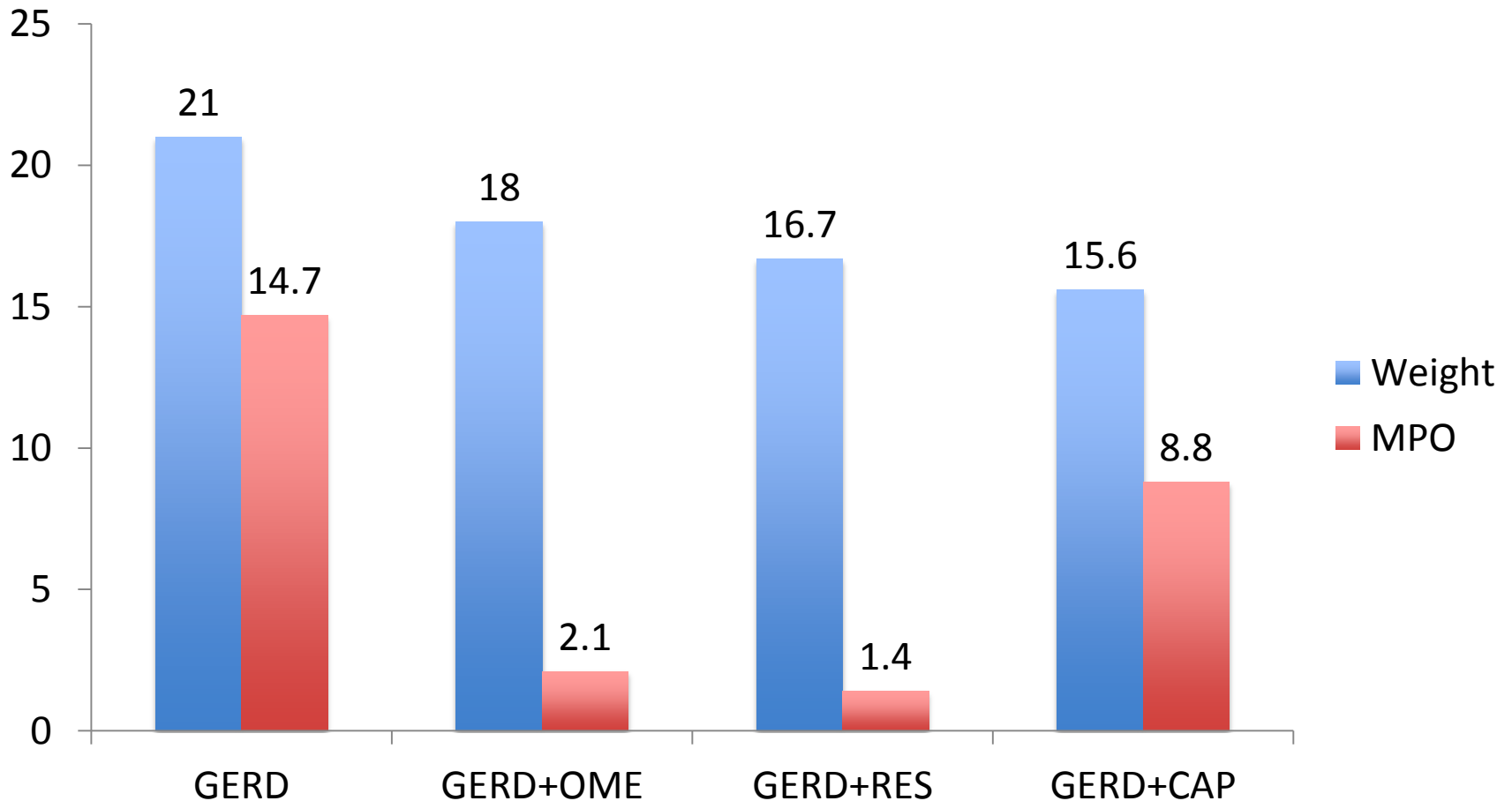
TRPV1 receptors modulate acid induced esophageal inflammation

Silva et al DDW 2016

- Murine model of GERD (Omura 1999)
 - Induces microscopic inflammation but not macroscopic damage
 - Sham and 3 groups
- Inhibition of acid secretion with omeprazole (OME)
- Depletion of capsaicin-sensitive neurons by Resiniferatoxin (RES)
- Treatment with TRPV1 antagonist capsazepin (CAP)

TRPV1 Receptors Modulate Acid Induced Esophageal Inflammation in Surgical Murine Model of Gastro- Esophageal Reflux Disease

Silva et al DDW 2016



Message

Depletion or inhibition of TRPV1 receptors may be a new way to medically treat reflux without affecting acid secretion

Compound development and clinical trials will be needed

Barrett's surveillance



“The best day in the life of a patient with Barrett’s esophagus is when his endoscopist dies...”

Steven Sontag, MD

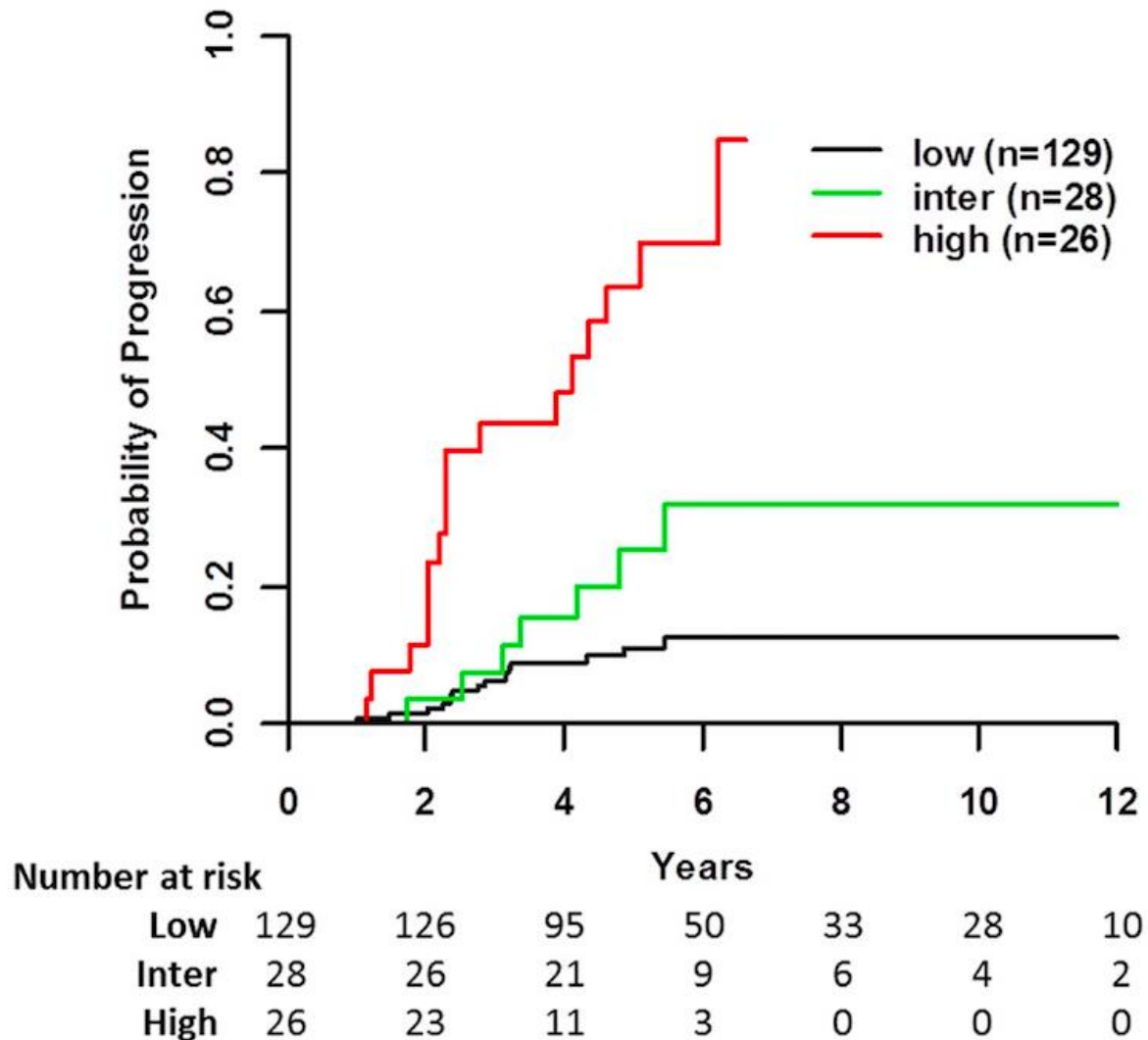
Predicting Barrett's evolution

A Novel Tissue Systems Pathology Test Predicts Progression in Barrett's Esophagus Patients

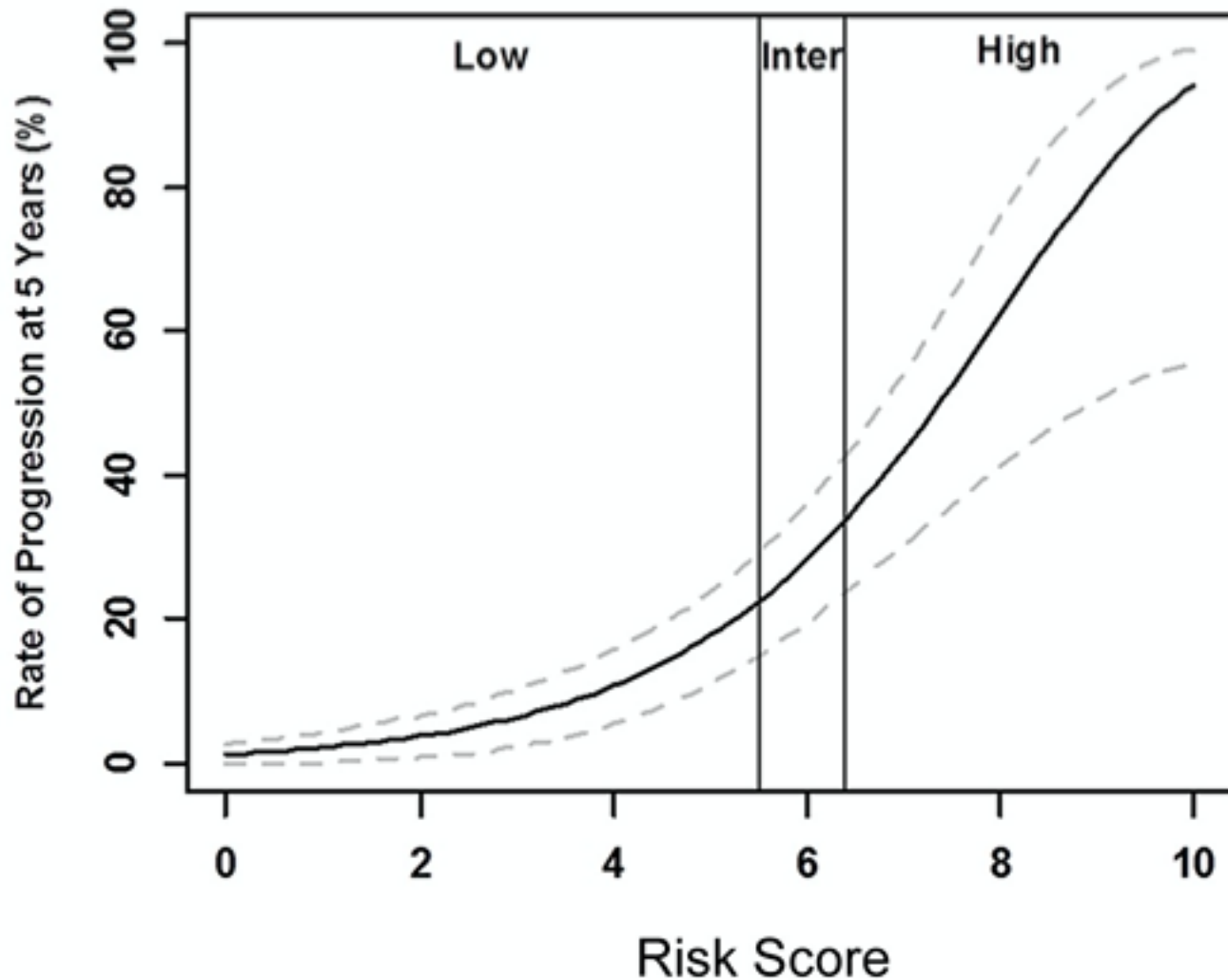
Critchley-Thorne et al. DDW 2016

- An imaging platform that quantifies multiple epithelial, stromal and morphometric variables in baseline BE biopsies
- A candidate panel of 14 biomarkers (p53, p16, AMACR, HER2/neu, K20, CD68, CD45RO, HIF-1alpha, COX-2) was selected, including epithelial and stromal biomarkers known to play a role in carcinogenesis
- Biopsy sections were fluorescently-immunolabeled for the 14 biomarkers, imaged by whole slide fluorescence scanning and analyzed by image analysis software to extract quantitative biomarker/morphometric features.

KM analysis of the probability of progression to HGD/EAC at 5 years in patients classified as low, intermediate and high risk



5-year progression rates as a continuous function of the risk score



Message

This novel tissue systems pathology test predicts progression in BE patients and outperforms standard pathologic diagnosis, segment length, age, gender and p53 overexpression

Prospective validation will be needed

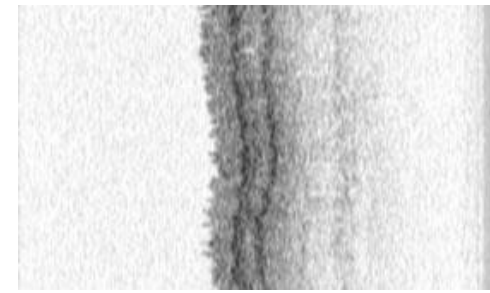


**Nearing the end of screening EGD for
Barrett's esophagus...**



OCT

(Optical Coherence Tomography)

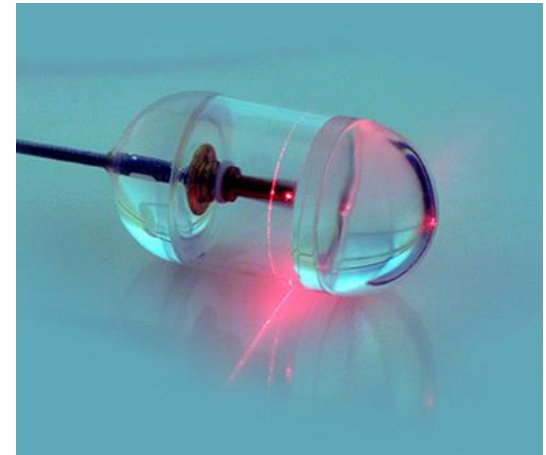
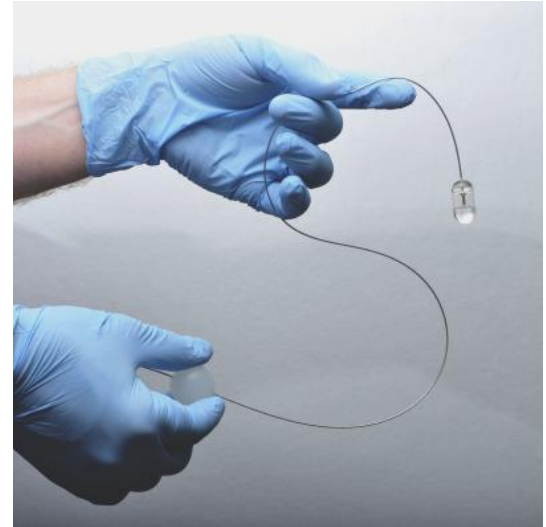


NvisionVLE Imaging System

- Captures images up to 3mm beneath the mucosa at a 7 micron resolution in real time
- Offers a full-field view ($\sim 10,000\text{mm}^2$), vs. a “point” image obtained with confocal microscopy (0.25mm^2)
- Advanced OCT imaging delivers up to 25x higher resolution than EUS

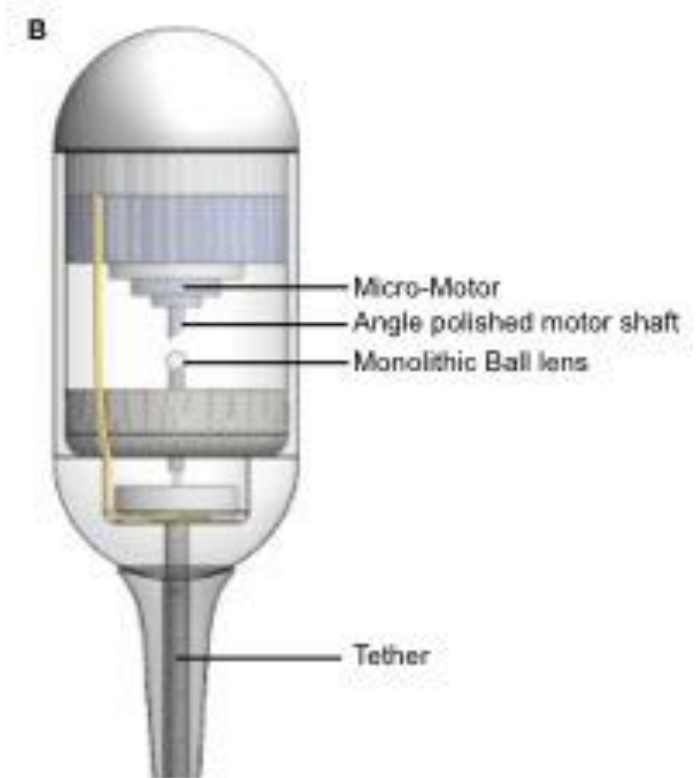
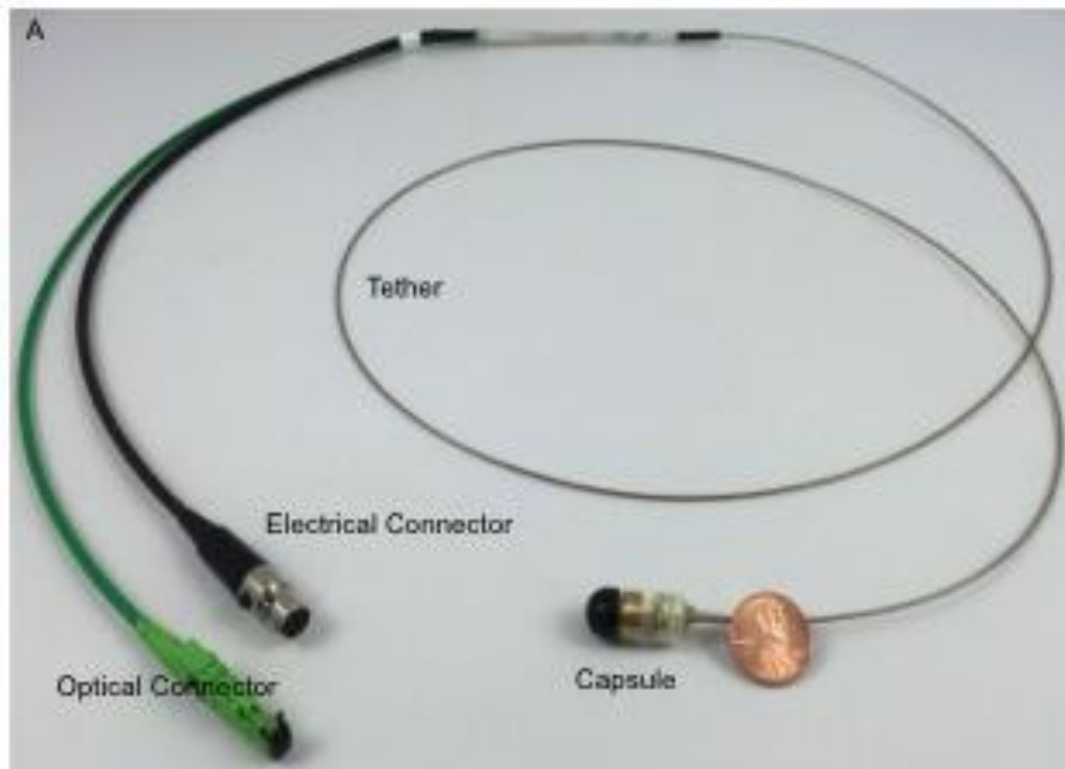
Tethered capsule endomicroscopy (TCE)

- High-resolution cross-sectional (OCT) images of the entire esophagus without sedation
- Screening and surveillance tool for Barrett's esophagus.
- Capabilities of laser cautery via capsule to mark locations as a guide to biopsy/intervention.

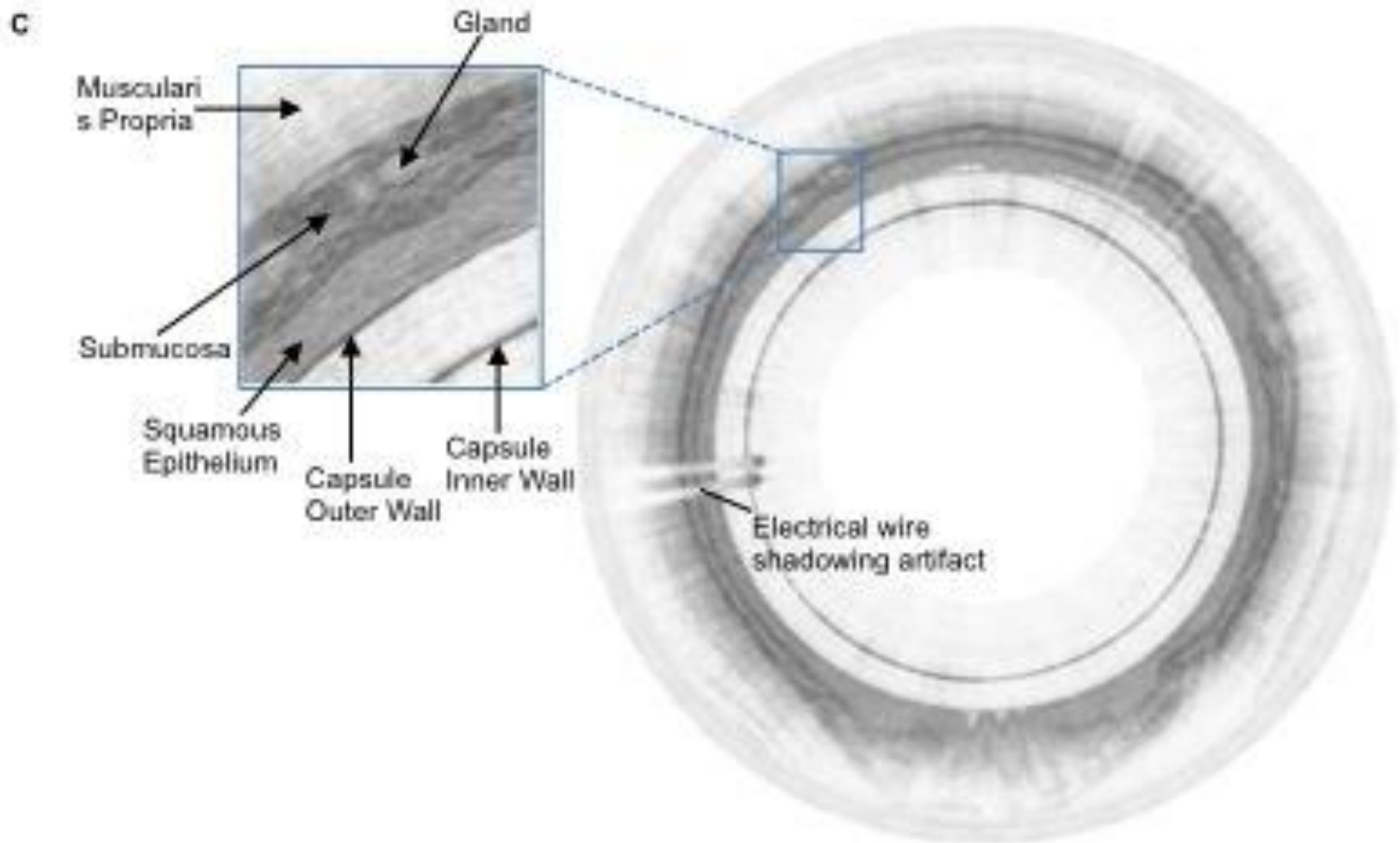


Tethered micro-motor capsule endomicroscopy (TCE)

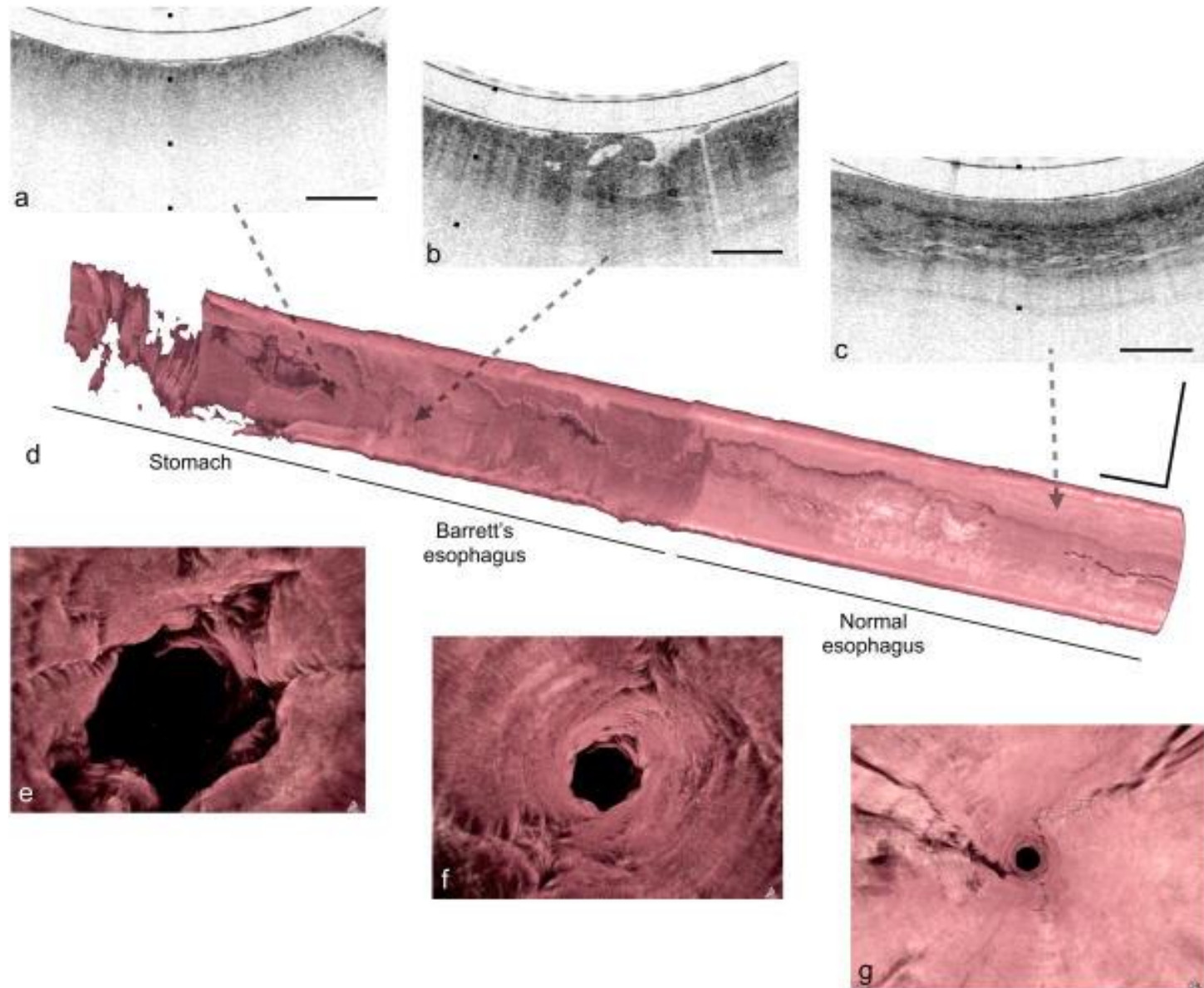
Dong J et al DDW 2016

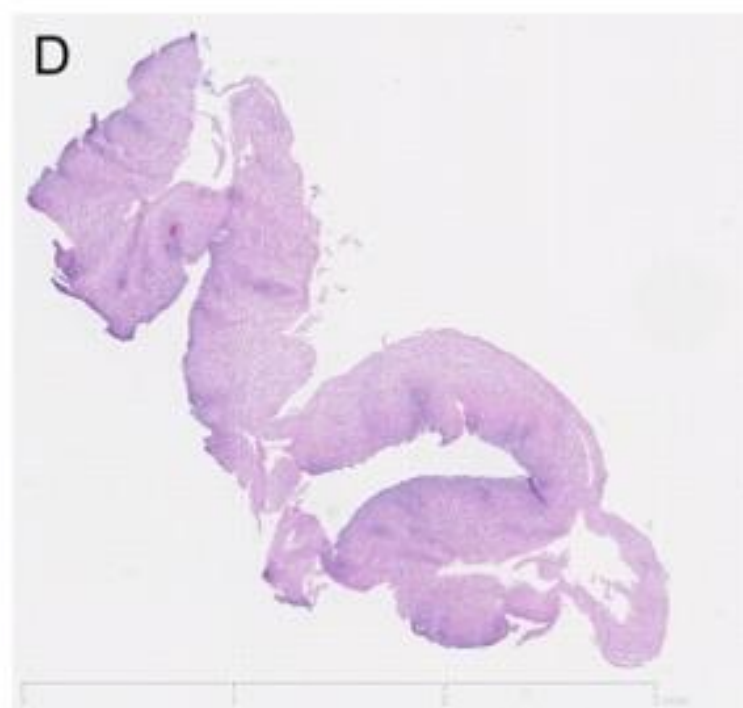
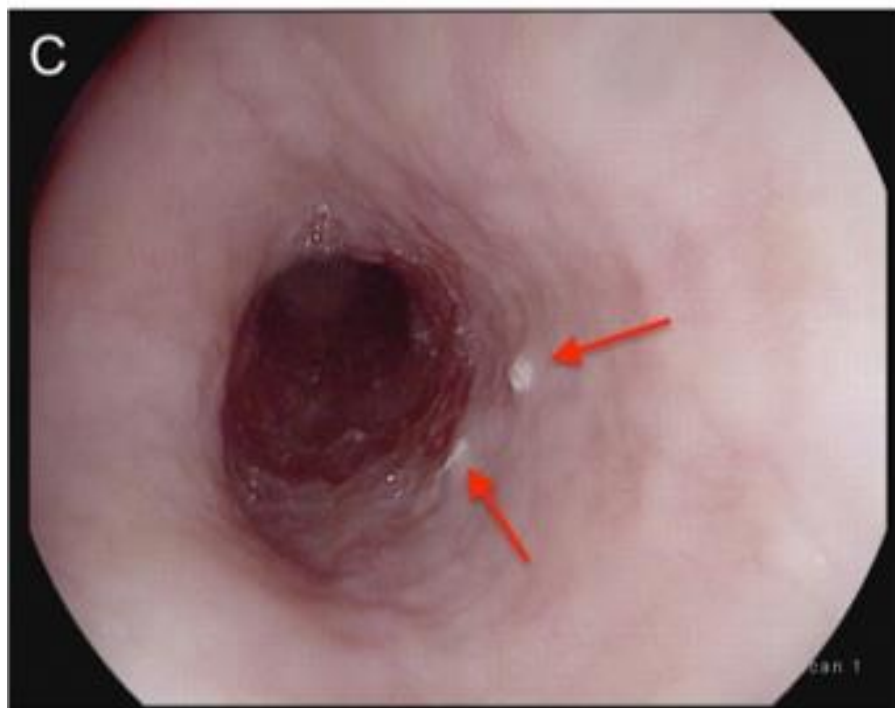
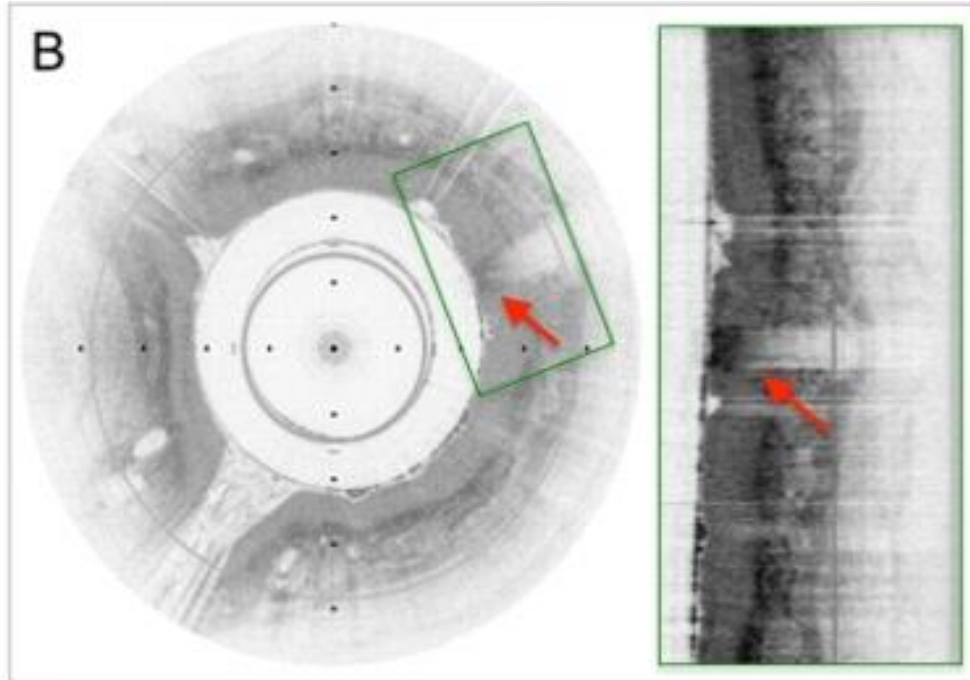
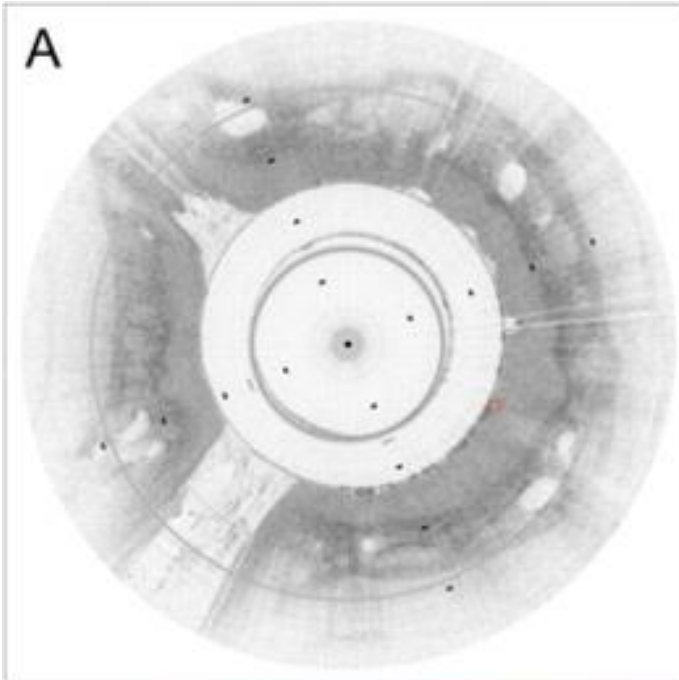


One esophageal circumferential image obtained by the new device from a human subject in vivo



Tethered capsule endomicroscopy (TCE)





2nd gen TCE

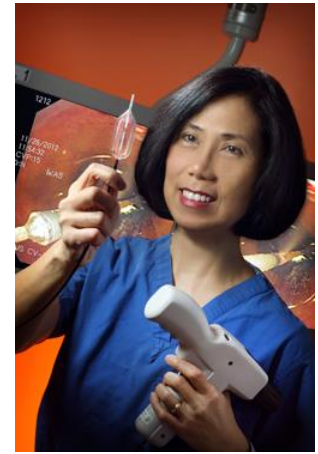
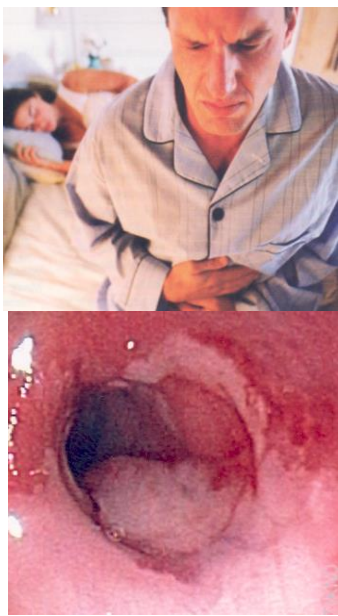
Dong J et al DDW 2016

- 4 healthy subjects enrolled in the tethered micro-motor capsule endomicroscopy study.
- $\frac{3}{4}$ successfully swallowed the capsule.
- High quality microscopic images of the entire esophagus were obtained.
- The entire procedure lasted an average of 3 ± 1 minutes from capsule insertion to removal.
- There were no complications

Message

- In a small number of subjects, motorized TCE was successful and provided high quality images
- TCE may replace BE surveillance, particularly in the post-ablation population, and guide therapy
- Larger trials are needed

Barrett's gadgets



Barrett's esophagus

**Manage
GERD**

**Cancer
prevention**

PPI

Surgery

EMR

Ablation

Esophageal eradication therapy

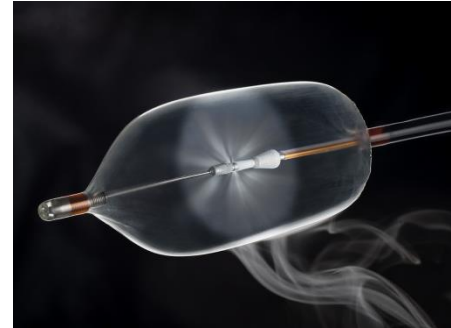
Cryoballoon Treatment

- **Gastroenterologist**
 - Controlled dosing and treatment
- **Patient**
 - Little to no pain
- **Administration**
 - Improved economics



Cryoballoon Platform – Components

- **Catheter**
 - Multiple shapes, sizes, spray
- **Controller**
 - Push button dose control
 - Pressure sensing
- **Cartridge**
 - Nitrous Oxide



The Johns Hopkins cryoballoon trial

Canto M et al DDW2016

- **Coldplay 2** clinical trial – initiated Jan 2015
 - DBE patients enrolled = 35
 - Squamous dysplasia patients = 9
- **Inclusion Criteria**
 - Patients with proven dysplastic BE, any length (limit 22 maximum ablations per session)
 - Patients previously ablated (RFA) for dysplastic BE and ImCA post EMR, with persistent/recurrent dysplasia
 - Patients with any esophageal squamous dysplasia

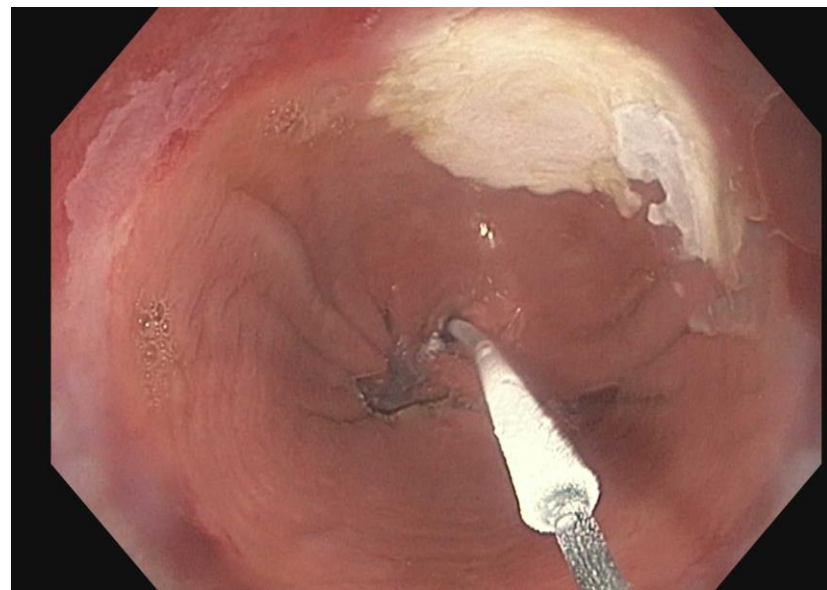
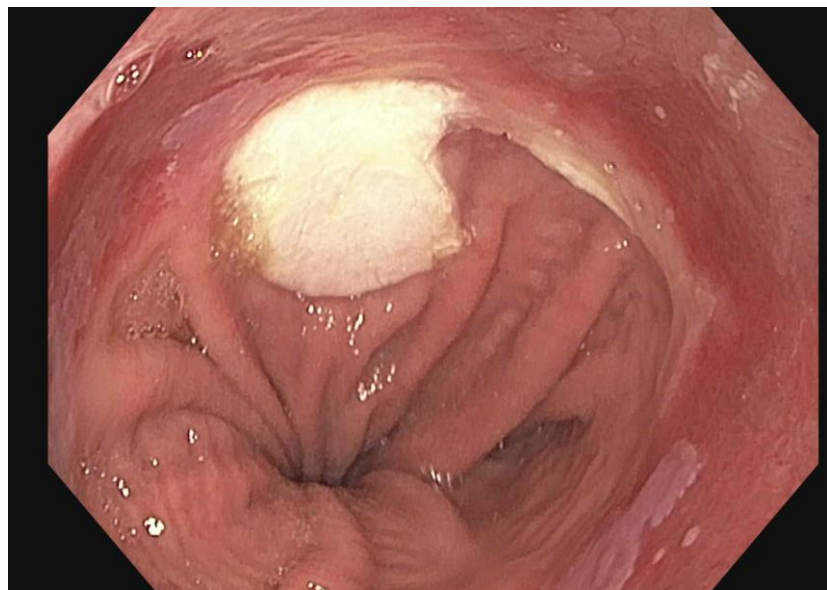
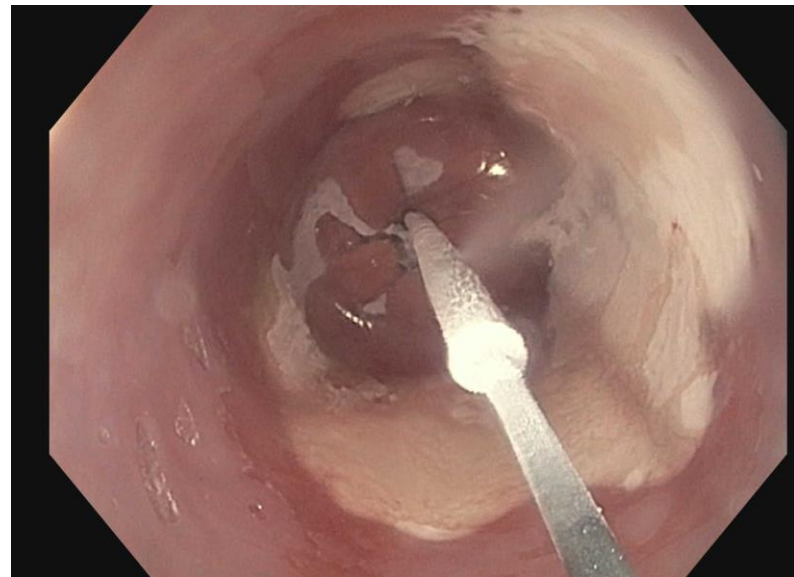
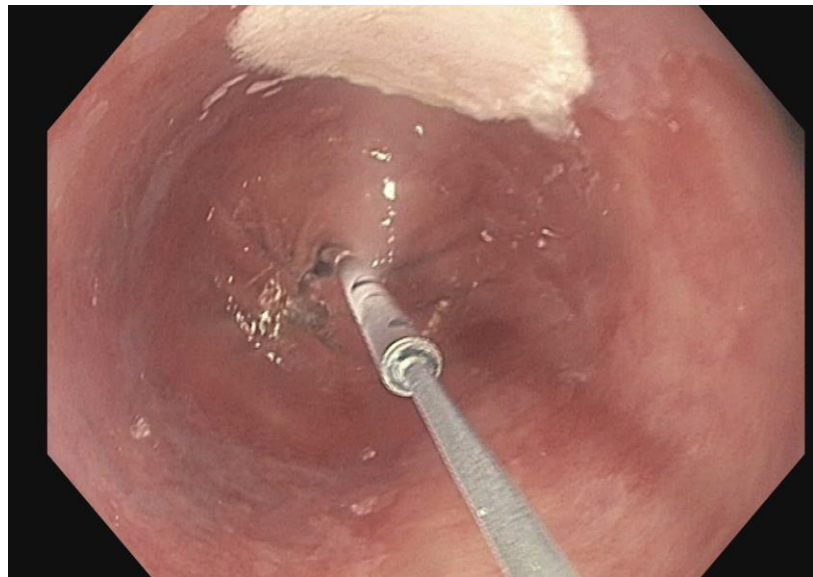
Coldplay 2 in DBE: Patient Characteristics

	Group 1 Tx-Naïve N=23	Group 2 Prev Ablation N=12	Total N=35
Number	10 LGD 11 HGD 2 ImCA	4 LGD 6 HGD 2 ImCA	14 LGD 17 HGD 4 ImCA
BE length	4.1 (1-14)	5.3 (1-14)	4.5 (1-14)
Short < 3	8	6	14
Long 3 to <8	13	2	15
Ultra long >8	2	4	6
Prior RFA	0	12	12 (34%)
Prior EMR	6 (26%)	7(58%)	13 (37%)
Stricture	1(4%)	8(67%)	9 (26%)

Dysplastic BE Prelim Results - 22 Evaluable

	Group 1 Tx-Naïve n=11	Group 2 Prev Ablation n=11	All N=22
CR-D	10 (91%)	11 (100%)	21 (95%)
CR-IM	6 (100%)	6 (86%)	12 (92%)

Mean post procedure pain scores= 2.2 (out of 10)



Esophageal Squamous Neoplasia

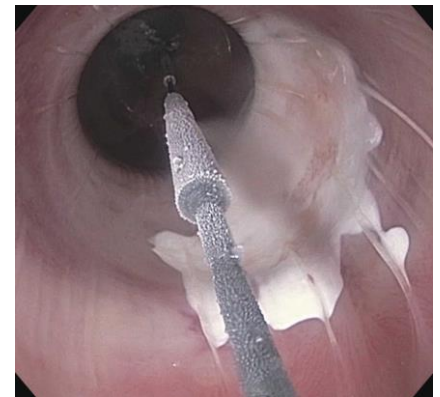
- **Focal disease** (n=7) – median 3.4 ablations (IQR 2-6) – all treated sites negative
- **Circumferential disease** (n=2), 12-13 ablations, each treated with 1-2 more sessions
- Median procedure time 34 min (range 18-57)
- Minor device malfunction in 1, all successful
- No SAE, 1 minor balloon tear
- 5 patients with self-limited pain, no narcotics used
- 2 inflammatory strictures dilated

Efficacy in esophageal squamous neoplasia

Squamous regeneration 100% in all sites treated - no LVLs on at least 1 follow-up biopsy

Pathological CR 100%

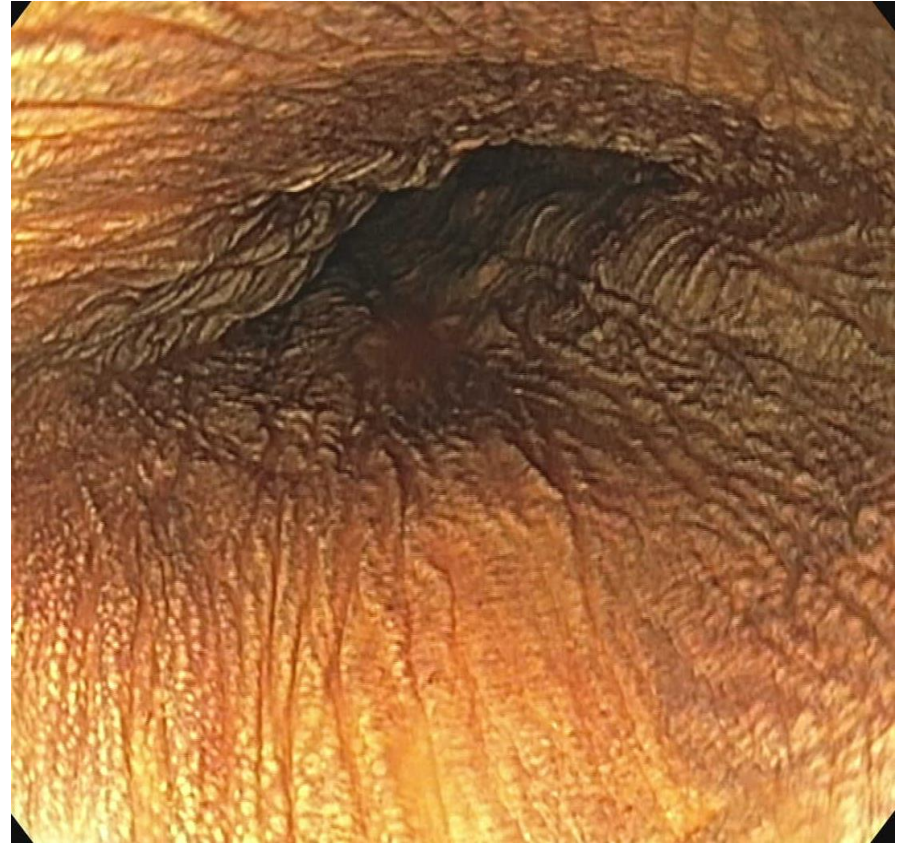
FU mean 165 days (IQR 35-316)



Multifocal Esophageal Squamous HGD



Before



After 2 sessions

Message

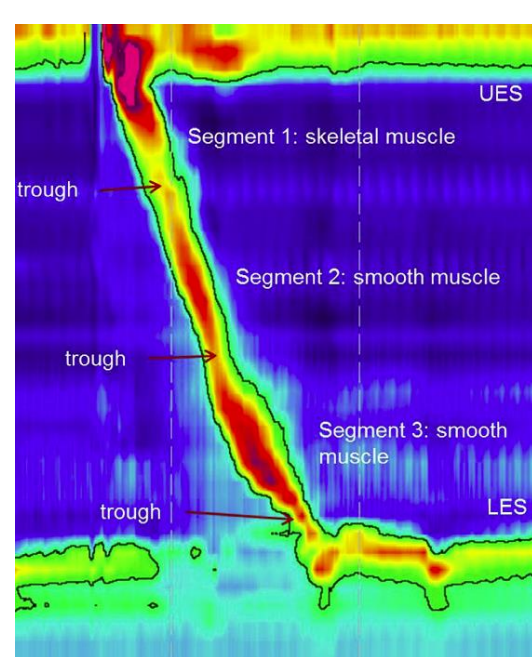
Early experience with multifocal cryoballoon ablation is **safe, effective** and **feasible** for both dysplastic Barrett's esophagus and squamous esophageal dysplasia

RCTs (against sham) will be needed

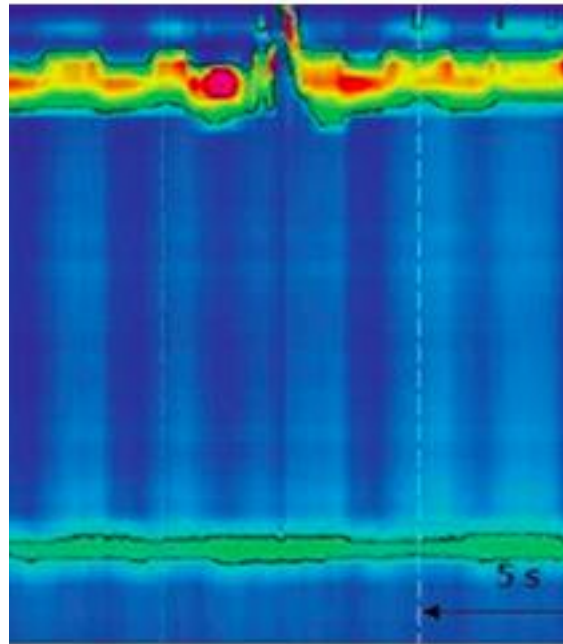
A POEM that led to a revolution...



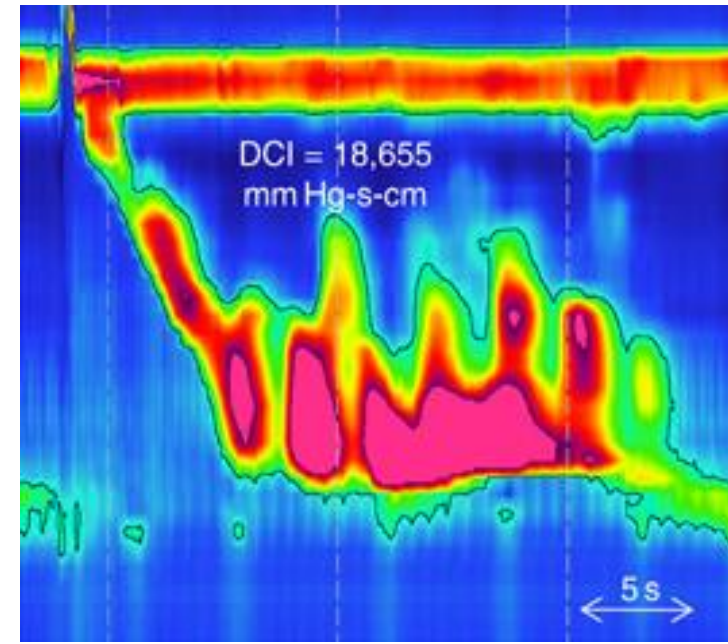
POEM: Endoscopic therapy for achalasia and spastic esophageal disorders (SED)



Normal



Achalasia (Type 1)



Spastic esophageal dysmotility

Primary endpoint: Eckardt Score

Table 1 | Clinical scoring system for achalasia (Eckardt score)

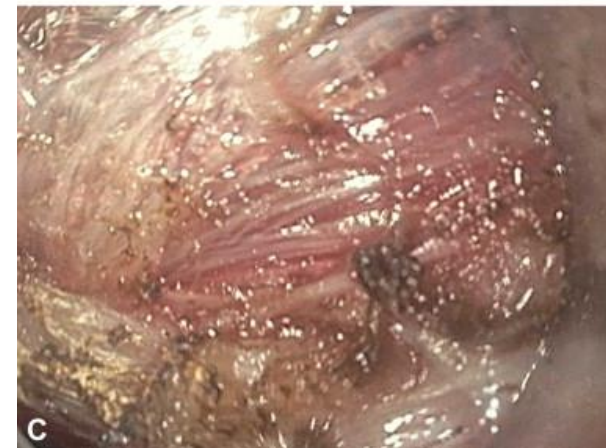
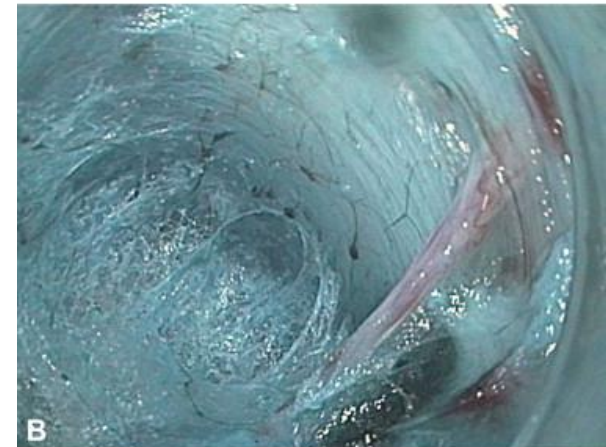
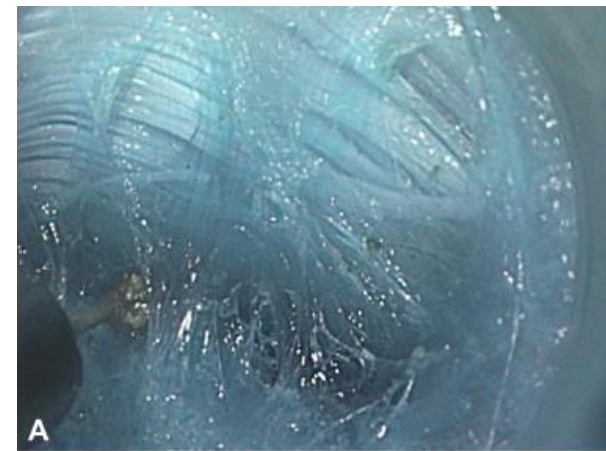
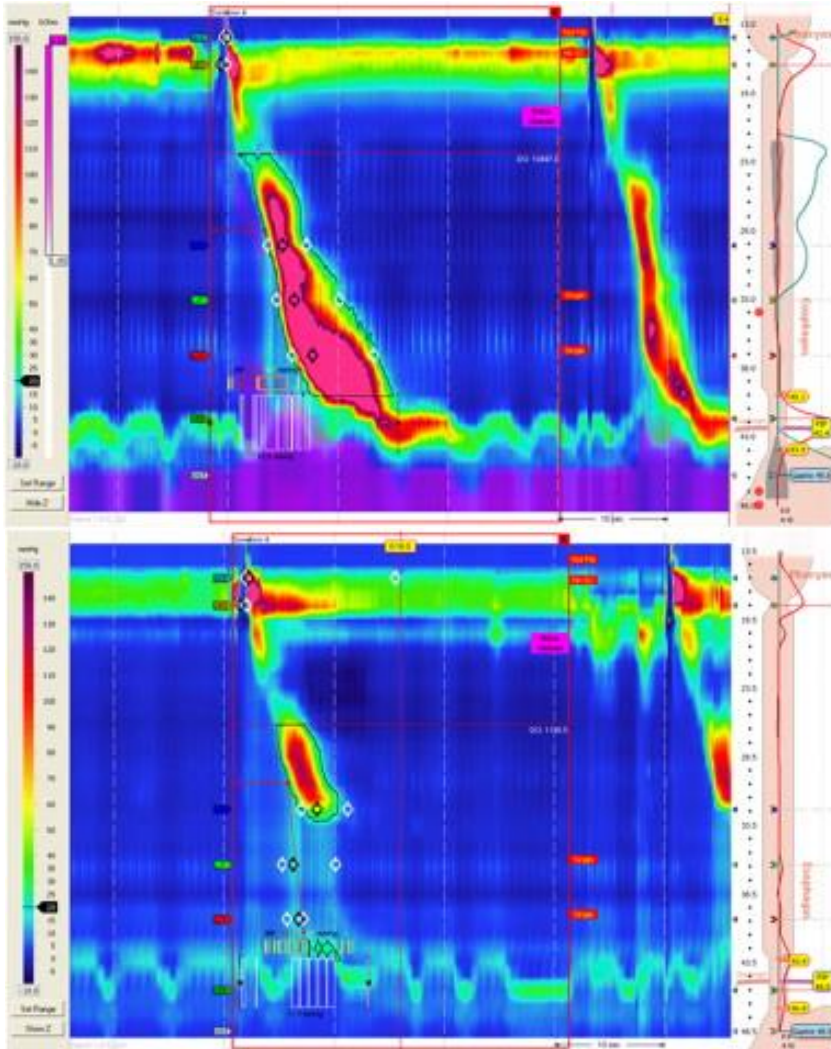
Score	Symptom			
	Weight loss (kg)	Dysphagia	Retrosternal pain	Regurgitation
0	None	None	None	None
1	<5	Occasional	Occasional	Occasional
2	5–10	Daily	Daily	Daily
3	>10	Each meal	Each meal	Each meal

POEM for Achalasia and SED

- 104 patients (mean age 49 yrs, 48 F)
- Achalasia 94, JE 10.
- Mean procedural time of 81 minutes. Not feasible in 1 pt
- Mean myotomy length was 11 cm (esophagus 8.3 and cardia 3.3)
- 16 (12.5%) complications; dealt endoscopically
- **Decrease in Eckardt score** after POEM (7.8 v. 1.7)
- Acid reflux occurred in 68%; median DeMeester 81
- Resolution of manometric abnormalities in all
- Poor symptom correlation

POEM

Chavez et al. DDW 2016



Message

POEM was successfully completed in 99% of cases, even when with extremes of age, previous interventions, or sigmoid esophagus.

Post-POEM GERD occurs in 2/3 of patients and is most commonly **silent**.

Recommend esophageal acid exposure testing in all patients after POEM to avoid long term complications due to acid injury.

Gadgets for GERD...

Symptom relief in GERD



"I think the dosage needs adjusting... I am not nearly as happy as the people in the ads"



PPI therapy

**Complete
response
(no symptoms)**

**Partial response
(breakthrough
symptoms)**

**No response
(no change in
symptoms)**

Refractory Reflux

Therapies for refractory GERD



```
graph TD; A[Therapies for refractory GERD] --> B[Endoscopic therapy]; A --> C[Surgery]; A --> D[Novel therapies]; B --> E[Stretta]; B --> F[TIF]; C --> G[Fundoplication]; C --> H[Gastric bypass];
```

The diagram is a hierarchical flowchart. At the top is a box labeled 'Therapies for refractory GERD'. A line from this box branches into three boxes: 'Endoscopic therapy', 'Surgery', and 'Novel therapies'. From 'Endoscopic therapy', a line branches into 'Stretta' and 'TIF'. From 'Surgery', a line branches into 'Fundoplication' and 'Gastric bypass'. All boxes are light blue with a darker blue shadow on the left side.

Endoscopic
therapy

Surgery

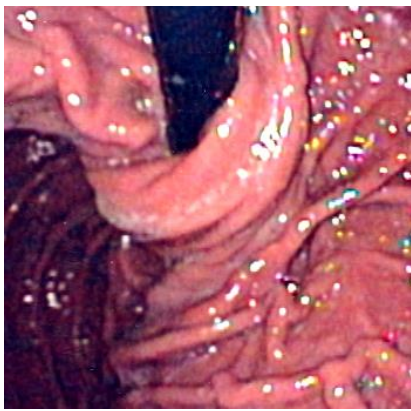
Novel
therapies

Stretta

TIF

Fundoplication

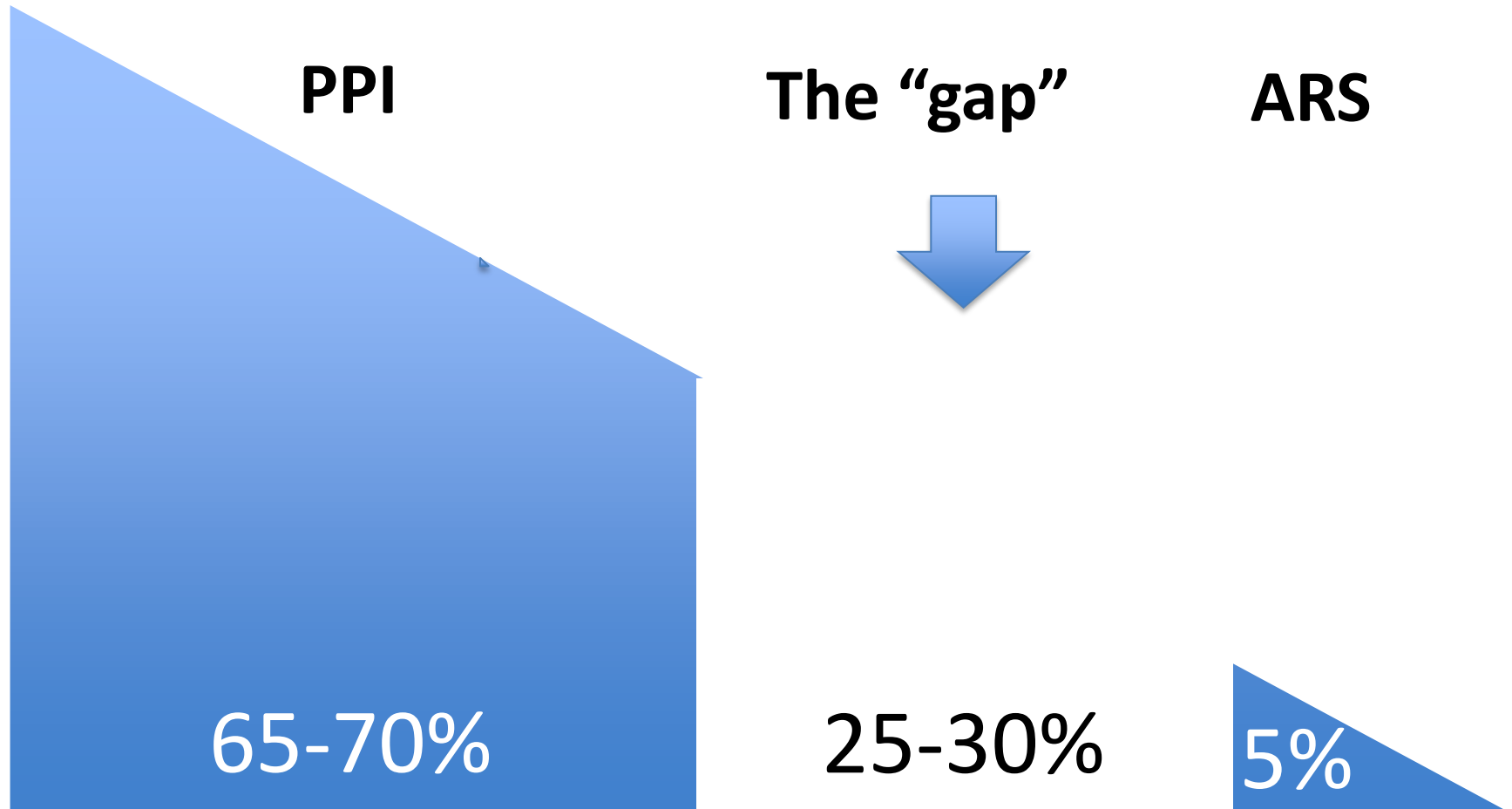
Gastric bypass



Fundoplication

- Should be performed on very carefully selected patients by expert surgeons.
- Community setting results and those of poorly evaluated patients may be inferior
- Long-term (5-12 years) outcomes show new, recurrent or persistent GERD-related symptoms ranging from 2% to 30%.
- 3-10% of these patients with a failed primary surgery undergo a revision.

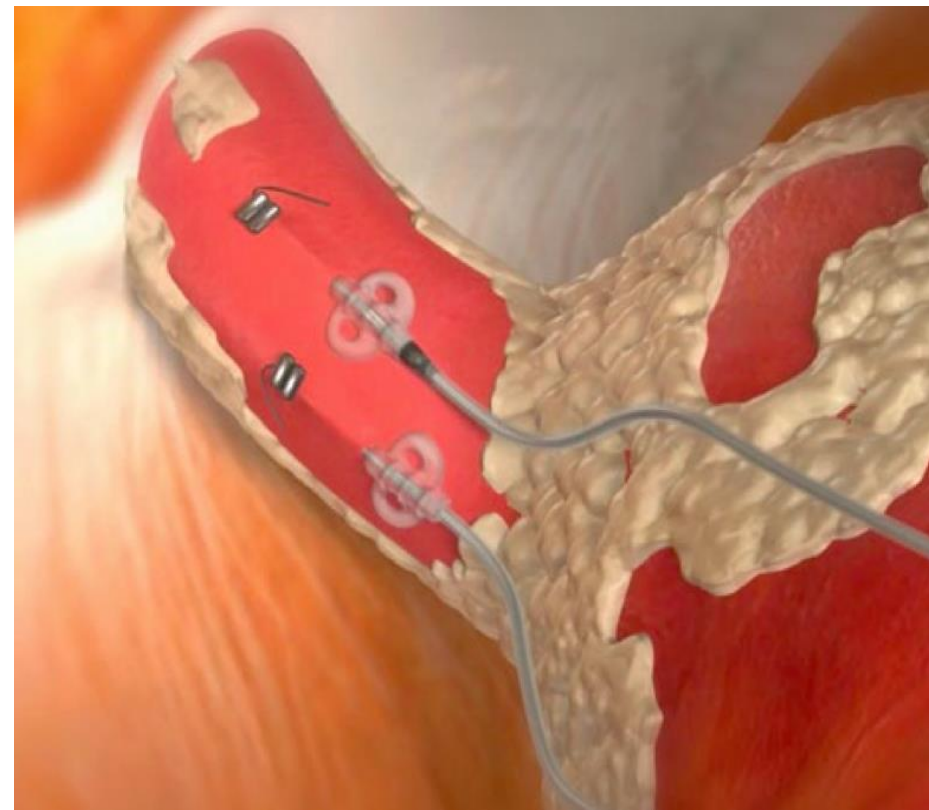
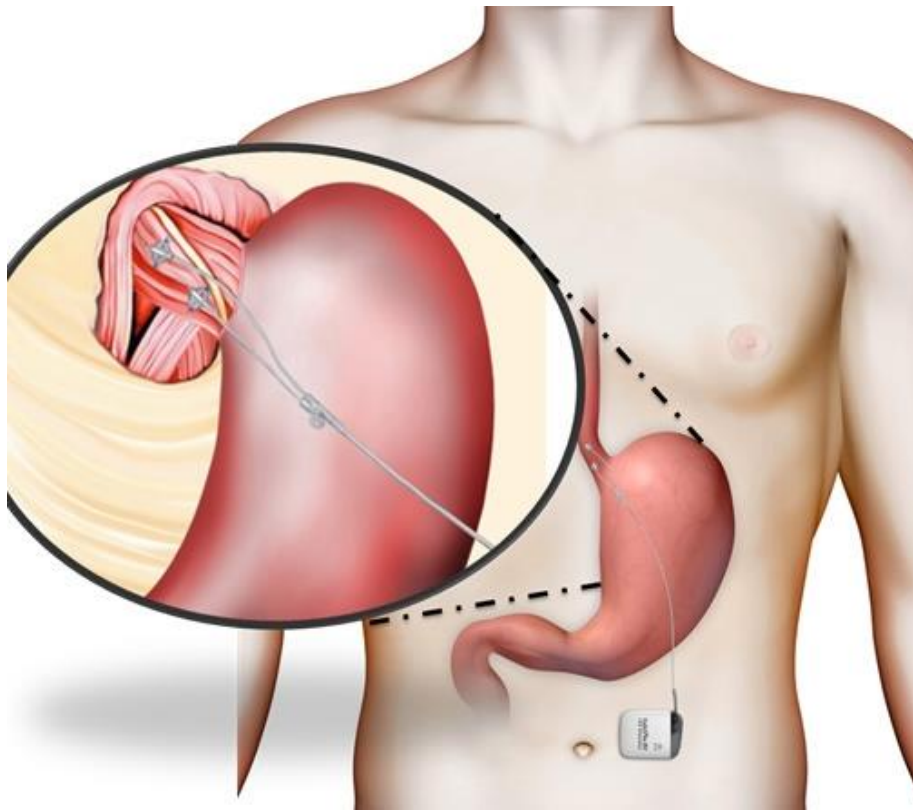
The GERD treatment gap



"Gap": % of patients refractory to PPI not pursuing ARS; ARS: Antireflux surgery

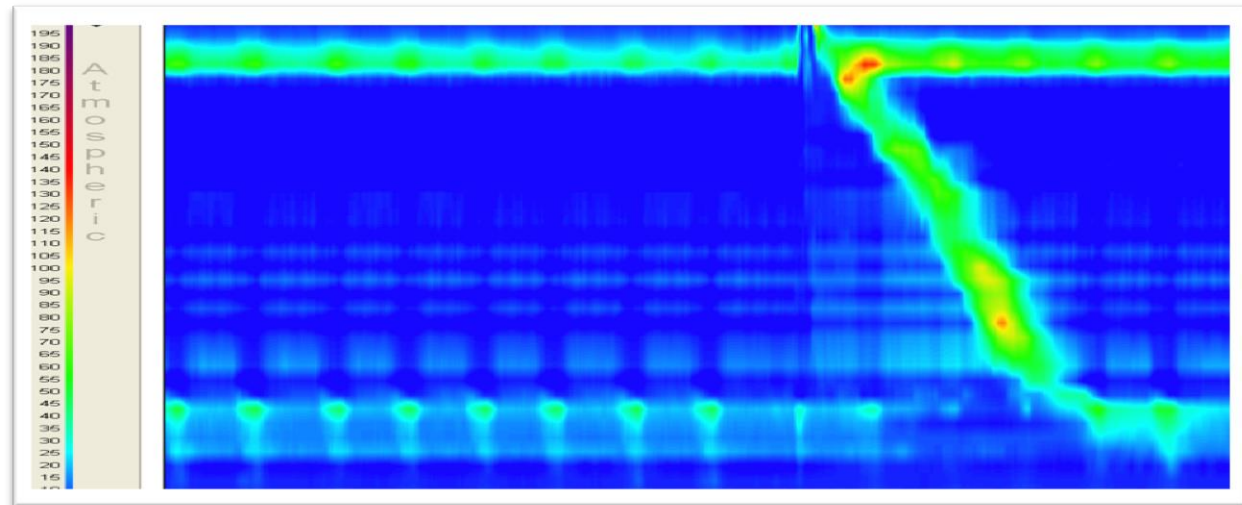
Electrical Stimulation Therapy for GERD

Siersema P, et al. DDW 2016

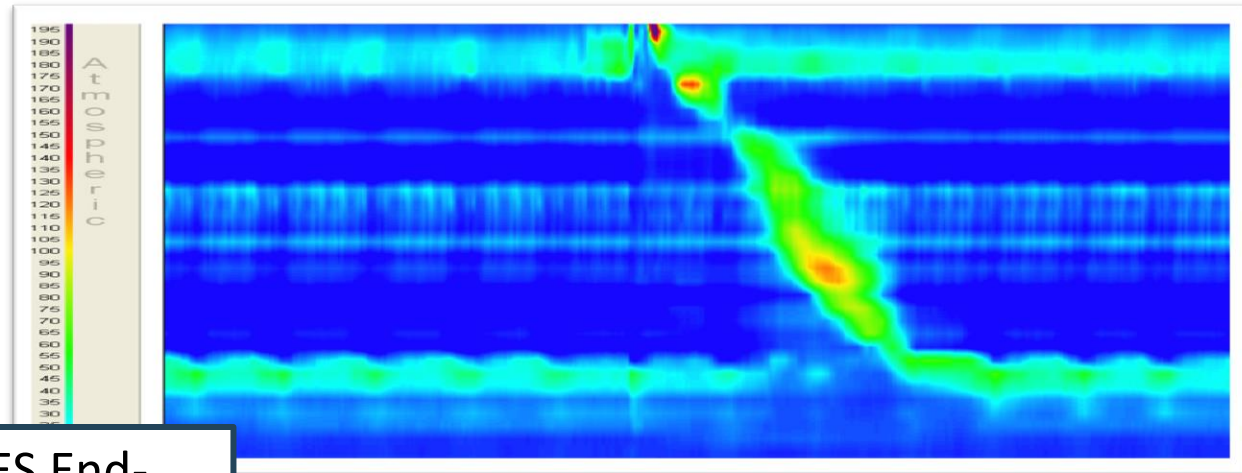


High resolution manometry

Baseline



12 Months on
EndoStim
Therapy



- Enhancement of LES End-Expiratory Pressure
- No Impact on LES Relaxation

Rodriguez et al. Surg Endosc 2013. (27);4:1083-92
Rodriguez et al. Am J Gastro. 2012; 107:S33

Electrical Stimulation Therapy for GERD

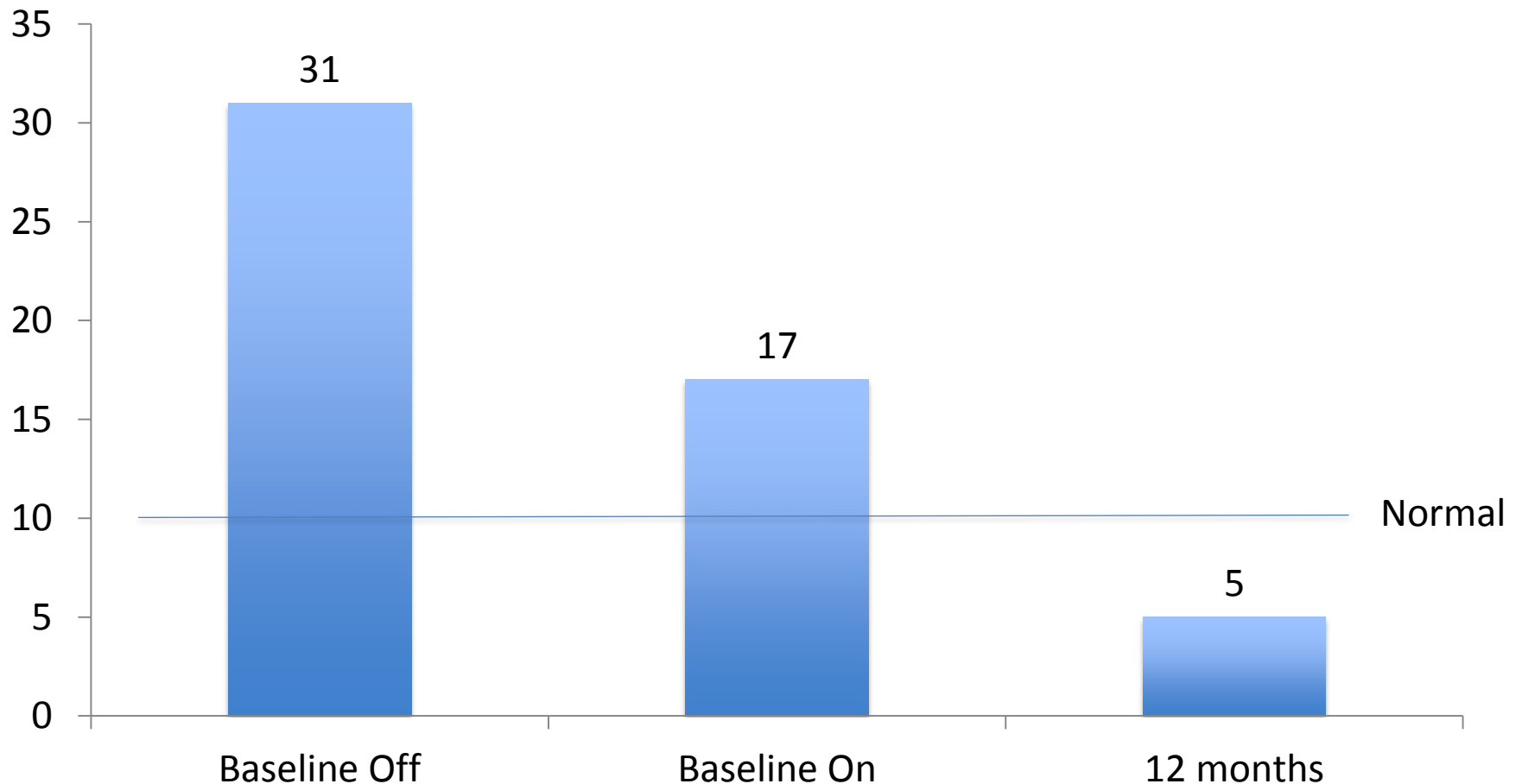
42 patients (median age 51 yr; men=24) were implanted with the LES stimulator. 37 patients completed their 12-month f/u.

81% of patients at 12 months were completely off PPI and 8% reported intermittent PPI use (<50% days with PPI).

Median SF-12 physical health score was 45.5 on-PPI, 38.5 off-PPI at baseline, and 51 at 6 months ($p<0.001$).

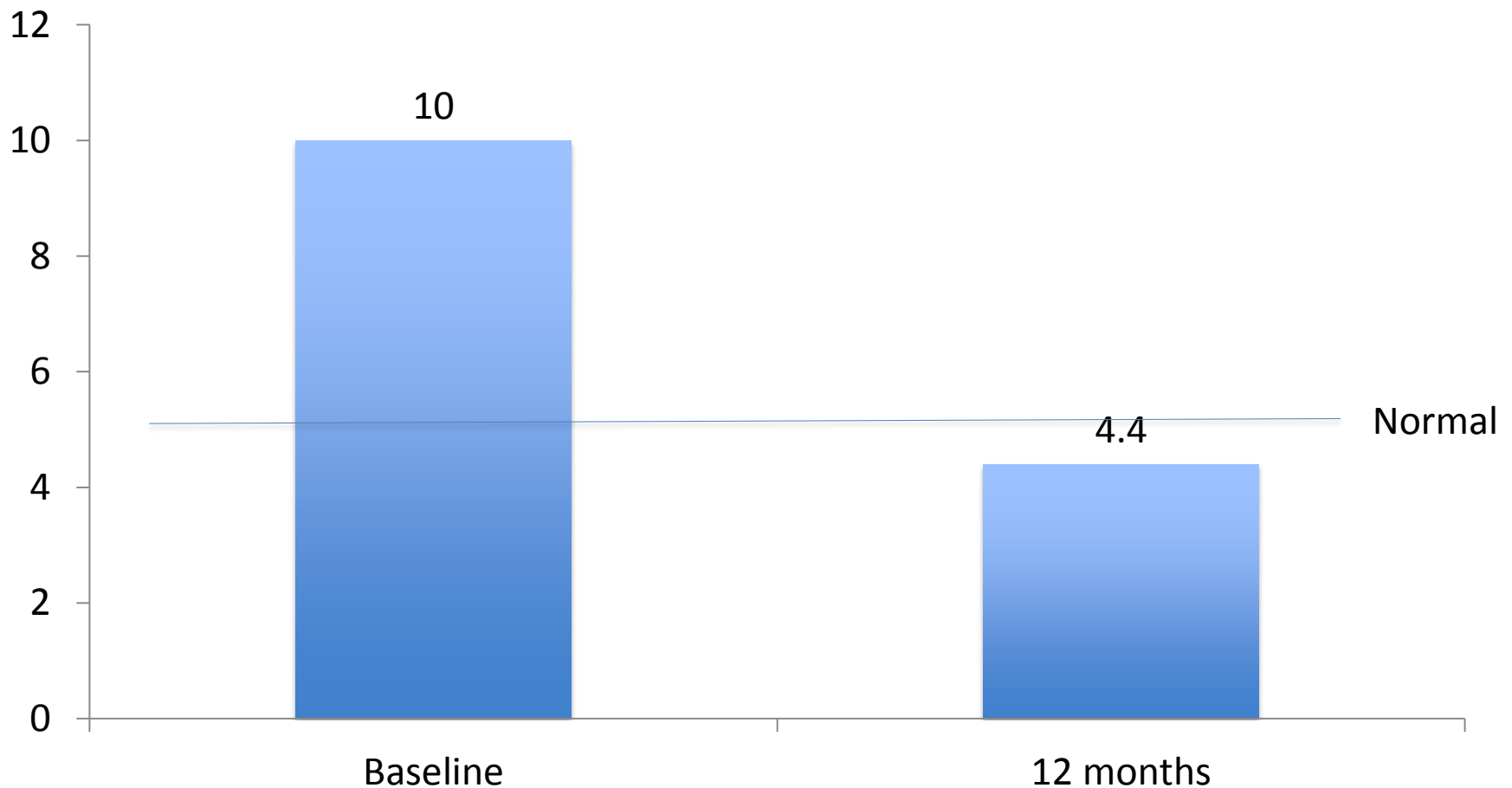
GERD-HRQL scores before and after Endostim

Siersema P, et al. DDW 2016



Esophageal acid exposure

Siersema P, et al. DDW 2016



Important adverse events

Siersema P, et al. DDW 2016

- Two asymptomatic electrode erosions related to the device; both patients reported loss of therapy efficacy and underwent fundoplication during which the device was explanted.
- One procedure-related laparoscopic trocar perforation of the small bowel, successfully repaired laparoscopically.
- An AV nodal reentrant tachycardia, not related to the device or therapy, successfully treated with AV nodal ablation.
- Five instances of dysphagia were reported in 4 patients with a hiatal closure procedure at the time of implant, all resolved without intervention.
- Nausea and pocket pain.

Message

One year open data with Endostim are very encouraging and this simple procedure (+/- hernia repair) may change GERD management

FDA pivotal (sham) trial in the US has been initiated, using pH control as its primary endpoint