Durham University

Bergen 2023

Cytosponge Screening for Barrett's Oesophagus

Stephen Attwood
Durham University
England, United Kingdom

Disclosures

Stephen Attwood has received fees for advisory boards, speaker fees or research management from

AstraZeneca

Dr Falk Pharma

Vifor Pharma

These do not have any influence on the content of this presentation

NICE GUIDELINES 2014
Interventions for gastro-oesophageal reflux disease (GORD)

- Offer people a full-dose PPI for 8 weeks to heal severe oesophagitis, taking into account the person's preference and clinical circumstances (underlying health conditions and possible drug interactions). **[2014]**
- Offer a full-dose PPI long-term as maintenance treatment for people with severe oesophagitis, (person's preference and clinical circumstances tolerability of the PPI), and the acquisition cost of the PPI. **[2014]**
- Do not routinely offer endoscopy to diagnose Barrett's oesophagus, but consider it if the person has GORD. Discuss the person's preferences and their individual risk factors (duration of symptoms, increased frequency of symptoms, previous oesophagitis, hiatus hernia, oesophageal stricture or ulcers, or male gender). **[2014]**

Long term Complications of GORD

- Adenocarcinoma of the Oesophagus
  - For a 40 yr old man with 20 yr history of daily reflux symptoms the risk (odds ratio)of developing oesophageal adenocarcinoma is 44 times the normal population
- 10% of patients with GORD have Barrett's Oesophagus (Intestinal metaplasia) which is a pre malignant epithelial change

Lagergren J et al NEJM 1999

Rising incidence of Adenocarcinoma of Oesophagus

- The rise in incidence of carcinoma of the oesophagus
  - has been continuous for 30 years
  - is all related to adenocarcinioma
  - is inversely related to H Pylori
  - is related to the severity of reflux
  - is associated with the presence of Barrett's oesophagus

Western World: Rising Mortality of Adenocarcinoma of Oesophagus

- Survival within 5 years overall 10%
- Stage related 5 yr survival
  - 1 90%
  - 2 75%
  - 3 15%
  - 4 0%

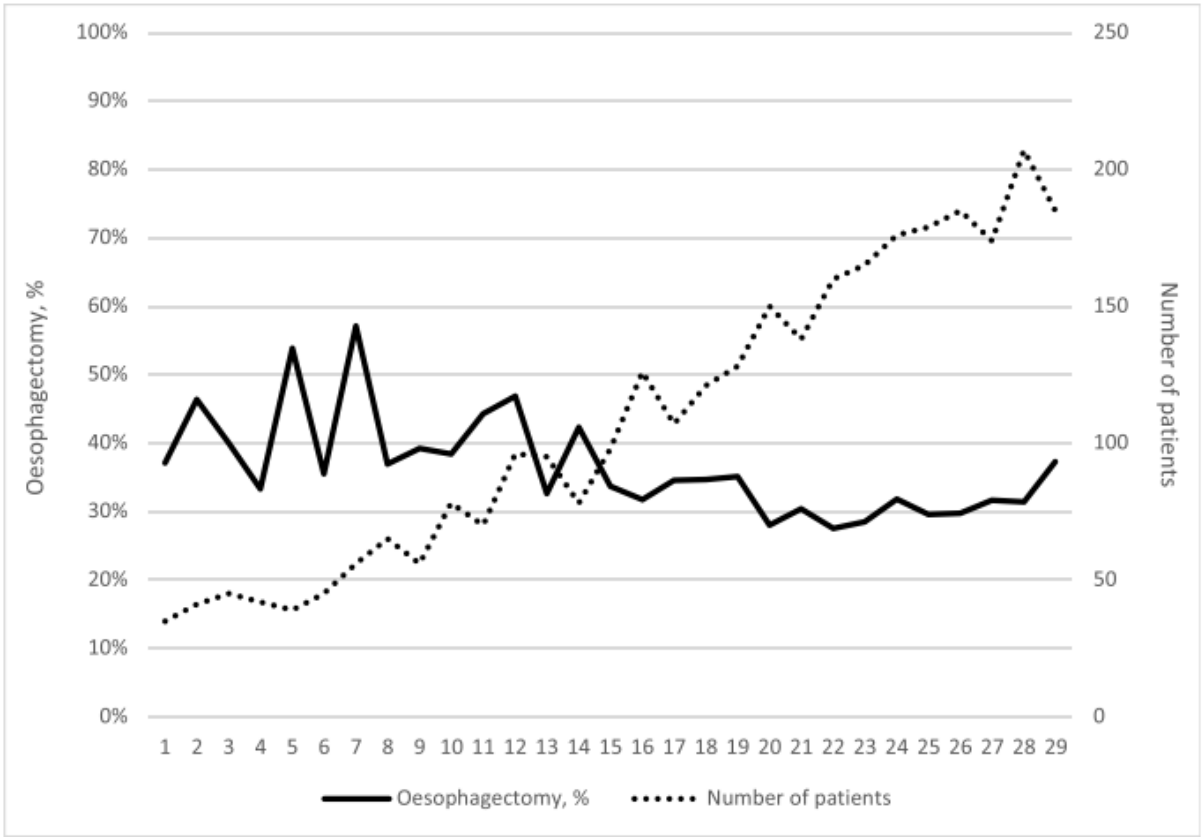
Morgan E et al, Gastroenterology 2022 ; 163: 649-658

Table 2
1-, 3- and 5-year survivals across calendar periods in oesophageal cancer in Finland in 1987–2016,

Calendar period	Oesophageal adenocarcinoma				
	Patients		Survival %		
	Number (%)	Median age	1 year	3 years	5 years
All patients					
1987–1991	202 (6.4)	70.5	33.2	15.8	11.4
1992–1996	300 (9.6)	68	38.7	17.3	13.0
1997–2001	437 (13.9)	68	43.9	19.5	15.1
2002–2006	632 (20.1)	67	46.5	19.3	13.4
2007–2011	818 (26.1)	67	49.9	23.5	17.2
2012–2016	751 (23.9)	67	51.8	27.6	21.5
Surgery					
1987–1991	85 (7.9)	67	48.2	28.2	20.0
1992–1996	124 (11.5)	67	56.5	32.3	24.2
1997–2001	173 (16.1)	66	69.9	39.9	33.5
2002–2006	206 (19.2)	63.5	78.2	47.1	36.4
2007–2011	242 (22.5)	64	86.8	59.1	45.9
2012–2016	244 (22.7)	65	87.3	59.4	49.4
No surgery					
1987–1991	117 (5.7)	72	22.2	6.8	5.1
1992–1996	176 (8.5)	71	26.1	6.8	5.1
1997–2001	264 (12.8)	70	26.9	6.1	3.0
2002–2006	426 (20.6)	69	31.2	5.9	2.3
2007–2011	576 (27.9)	68.5	34.4	8.5	5.2
2012–2016	507 (24.5)	68	34.7	12.2	8.0

Eur J Surg Oncol 2023 in press

a


100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
250
200
150
100
50
0
Oesophagectomy, %
Number of patients
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29
Oesophagectomy, %
Number of patients

b

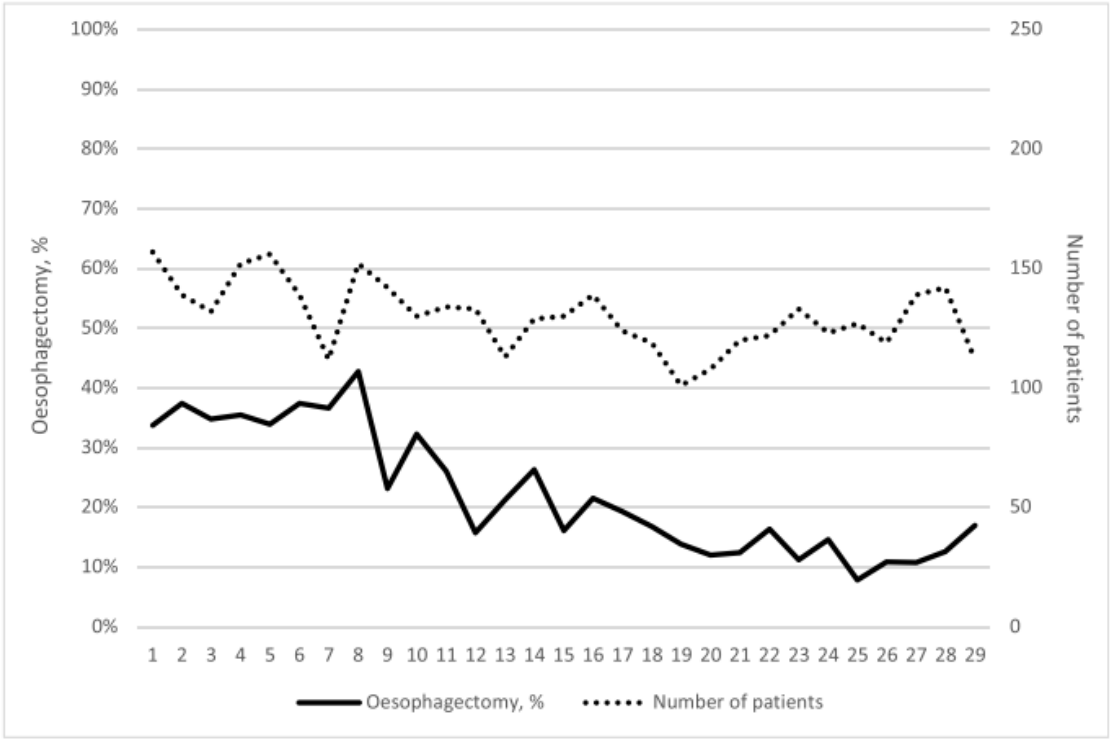


Fig. 1. Proportion of patients undergoing oesophagectomy (solid line) and number of patients (dotted line) diagnosed with oesophageal adenocarcinoma **a**, and oesophageal squamous cell carcinoma **b** in Finland in 1987–2016.

either of the registries. Surgical treatment status was defined based 1987–2001, 2002–2006, 2007–2011, or 2012–2016), age (<50

Strategies to improve outcomes of oesophageal adenocarcinoma

- Improved quality of surgery
- Adding chemo radiation

Small improvements i
5 year survival

- Earlier diagnosis by surveillance of Barrett's oesophagus

Only 10 % of patients with adenoca oesophagus have a previous recognition of Barrett's

- Screening for Barrett's oesophagus

Population screening for Barrett's by endoscopy is cost prohibitive

Challenge to improve outcomes in Oesophageal Adenocarcinoma

- Improve early diagnosis in high risk groups
  - Males > 55 or 60
  - with reflux symptoms
  - Barrett's oesophagus
- Requires identification of the risk in the wider population

Lotus
D9612C00003

CytoSponge : may provide the solution

- An out patient non invasive methodology to assess the lining of the oesophagus
- Developed from screening programmes in China for Squamous carcinoma of the oesophagus
- Adapted for detection of Barrett's Oesophagus and Barrett's dysplasia

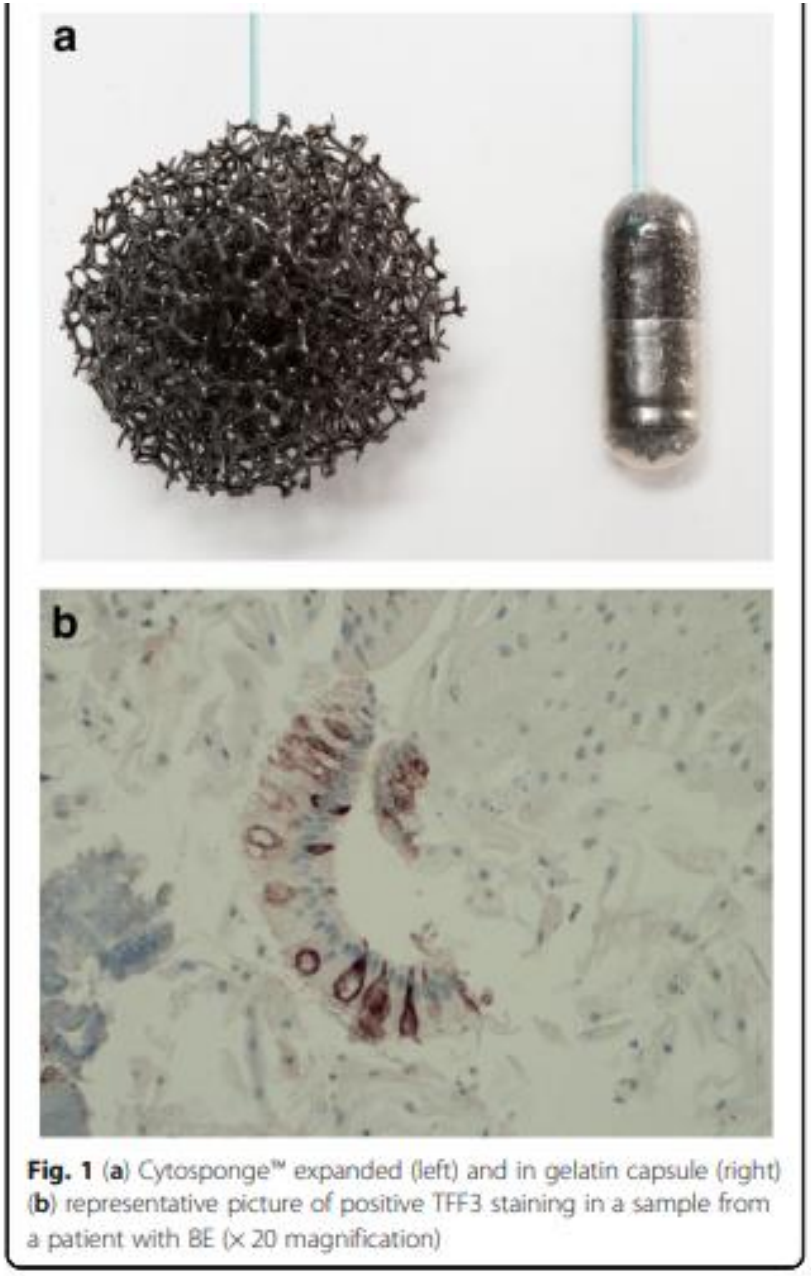


Fig. 1 (**a**) Cytosponge™ expanded (left) and in gelatin capsule (right) (**b**) representative picture of positive TFF3 staining in a sample from a patient with BE (× 20 magnification)

501 cytosponge tests performed in primary care
3% had Barrett's > 1cm median 2cm

TTF-3 staining helps to identify intestinal metaplasia

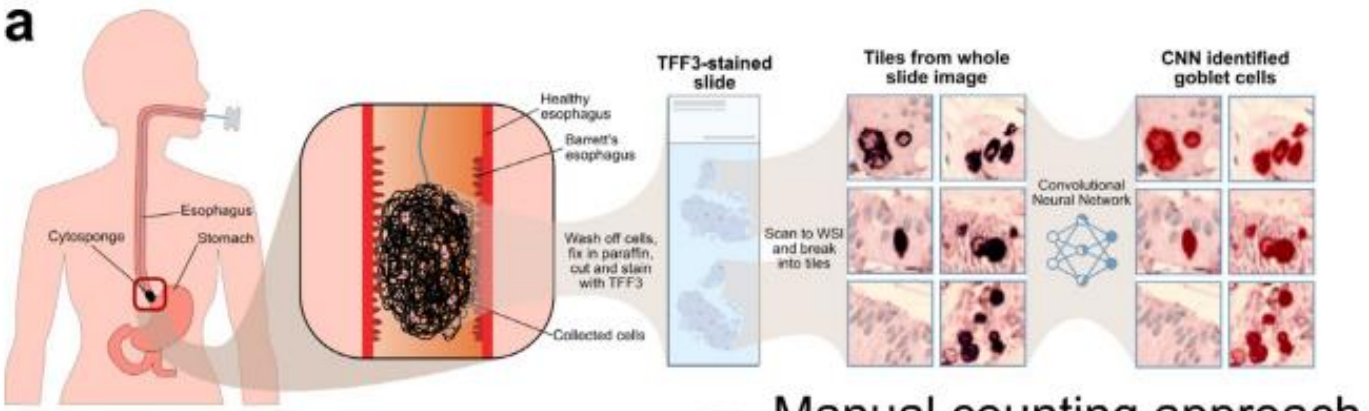
Cytosponge 93% sensitivity for Barrett's 2cm or more
Compared with gastroscopy and biopsy

Kadri SR, Lao-Sirieix P, O'Donovan M, Debiram I, Das M, et al. (2010) Acceptability and accuracy of a non-endoscopic screening test for Barrett's oesophagus in primary care: cohort study. BMJ 341: c4372. pmid:20833740

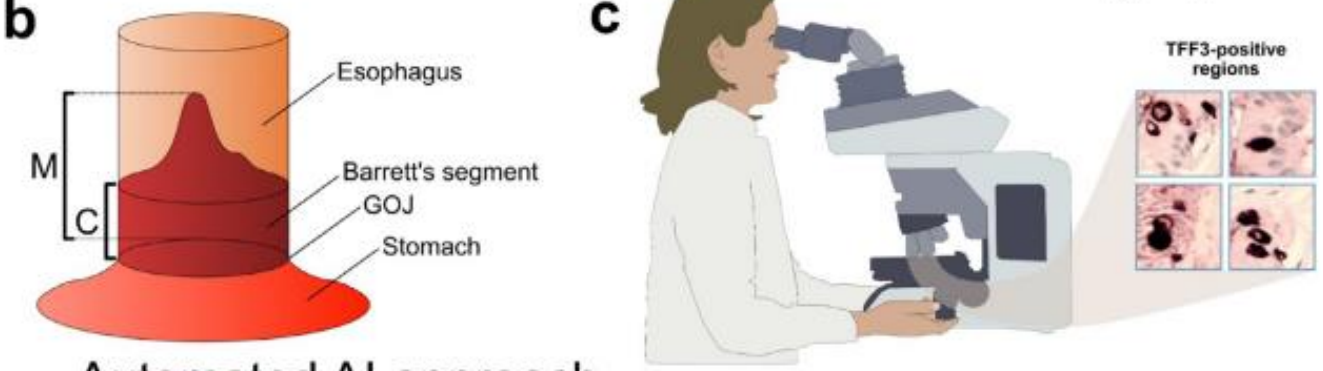
Cytosponge

- Is as effective as Endoscopy to identify Barrett's oesophagus
- Is as effective as Endoscopy to identify dysplasia in Barrett's oesophagus
- Is preferred over Endoscopy for patient comfort and convenience

BEST-1 trial



Manual counting approach



Automated AI approach

d

Training data with CNN-based IM tile counts

Patient	# IM tiles	C length	M length
Training 001	20	5	7
Training 002	55	1	2
Training 003	17	3	6
⋮	⋮	⋮	⋮
Training 527	42	1	5
Training 528	255	3	5
Training 529	7	1	3

Logistic Regression

Test set data with inferred segment length estimates

Patient	BE segment ≥C1 or ≥M3
Test set 001	1
Test set 002	0
Test set 003	0
⋮	⋮
Test set 156	1
Test set 157	0
Test set 158	1

Berman AG et al 2022

eBioMedicine 2022;82: 104160
Published online xxx
https://doi.org/10.1016/j.ebiom.2022.104160

Quantification of TFF3 expression from a non-endoscopic device predicts clinically relevant Barrett's oesophagus by machine learning

Adam G. Berman,[a,1] W. Keith Tan,[b,c,1] Maria O'Donovan,[d,e] Florian Markowetz,[a,2]* and Rebecca C. Fitzgerald [b,c,2]**

Findings Patients with clinically relevant BO had higher mean TFF3 gland count compared to focal IM pathologies (mean difference 4.14; 95% confidence interval, CI 2.76-5.52, $p < 0.001$). The mean class-balanced validation accuracy was 0.84 (95% CI 0.77-0.90), and precision of 0.95 (95% CI 0.87-1.00) for detecting clinically relevant BO. Applying this model on BEST3 showed precision of 0.91 (95% CI 0.85-0.97) for focal IM pathologies with a class-balanced accuracy of 0.77 (95% CI 0.69-0.84). Using this model, 55% of patients (87/158) in BEST3 would fall below the threshold for clinically relevant BO and could avoid gastroscopy, while only missing 5.1% of patients (8/158).

Interpretation Automated Cytosponge-TFF3 gland quantification may enable thresholds to be set to trigger confirmatory gastroscopy to minimize overdiagnosis of focal IM pathologies with very low cancer-associated risk.

eBioMedicine 2022;82: 104160
Published online xxx
https://doi.org/10.1016/j.ebiom.2022.104160

Multicenter Study > Lancet Gastroenterol Hepatol. 2017 Jan;2(1):23-31.
doi: 10.1016/S2468-1253(16)30118-2. Epub 2016 Nov 11.

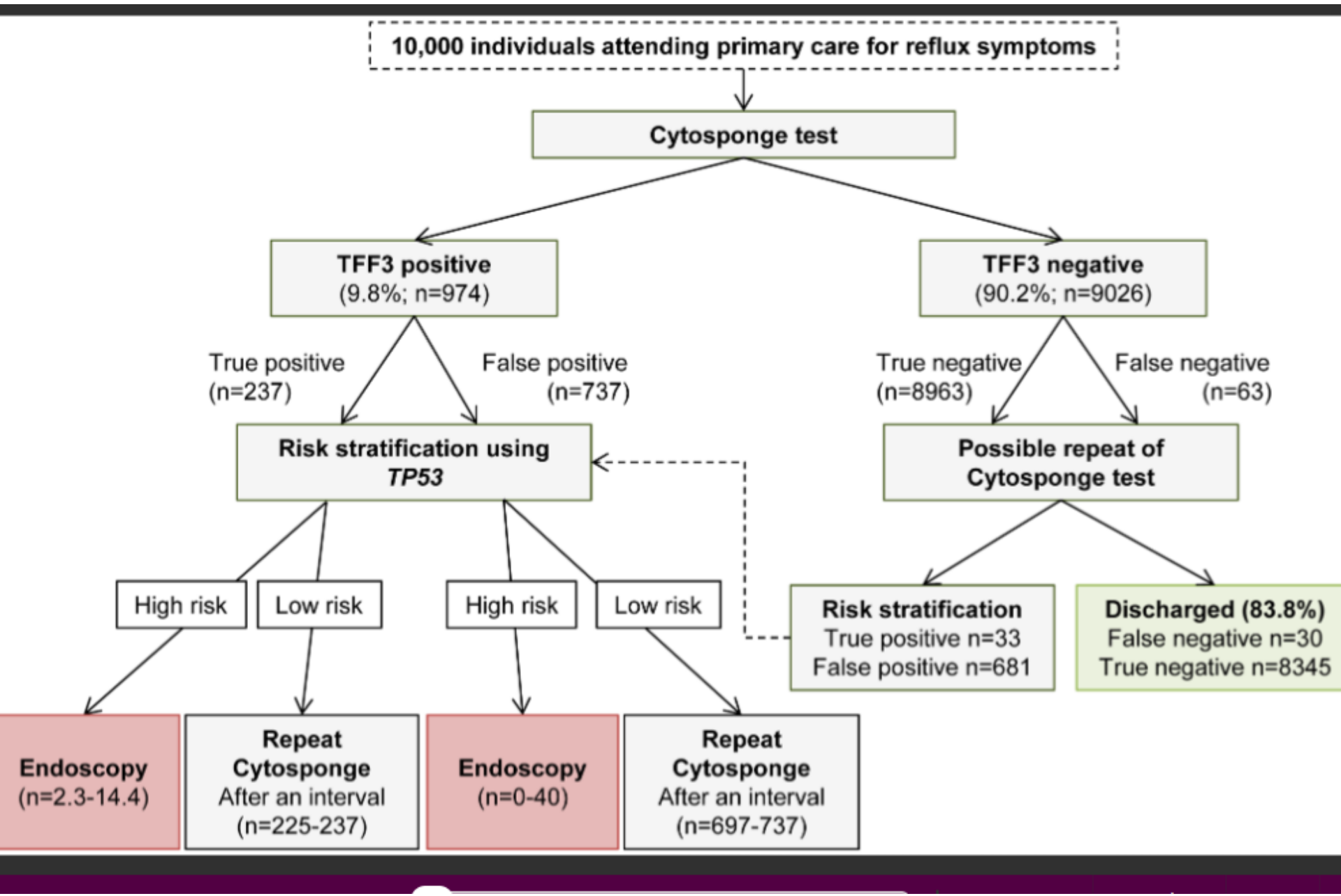
Risk stratification of Barrett's oesophagus using a non-endoscopic sampling method coupled with a biomarker panel: a cohort study

Caryn S Ross-Innes [1], Hamza Chettouh [1], Achilleas Achilleos [1], Nuria Galeano-Dalmau [1], Irene Debiram-Beecham [1], Shona MacRae [1], Petros Fessas [1], Elaine Walker [1], Sibu Varghese [1], Theodore Evan [1], Pierre S Lao-Sirieix [1], Maria O'Donovan [2], Shalini Malhotra [2], Marco Novelli [3], Babett Disep [4], Phillip V Kaye [5], Laurence B Lovat [3], Rehan Haidry [3], Michael Griffin [4], Krish Ragunath [5], Pradeep Bhandari [6], Adam Haycock [7], Danielle Morris [8], Stephen Attwood [9], Anjan Dhar [10], Colin Rees [11], Matt D Rutter [12], Richard Ostler [13], Benoit Aigret [13], Peter D Sasieni [13], Rebecca C Fitzgerald [14]; BEST2 study group

Affiliations Expand

Methods: In this multicentre cohort study (BEST2), patients with Barrett's oesophagus underwent the Cytosponge test before their surveillance endoscopy. We collected clinical and demographic data and tested Cytosponge samples for a molecular biomarker panel including three protein biomarkers (P53, c-Myc, and Aurora kinase A), two methylation markers (MYOD1 and RUNX3), glandular atypia, and TP53 mutation status. We used a multivariable logistic regression model to compute the conditional

Best- 2 Lancet Gastro-Hep 2017



Ross-Innes et al 2015 Plos med

CytoSponge Best-2 study

In the discovery cohort, a model with high classification accuracy consisted of glandular atypia, P53 abnormality, and Aurora kinase A positivity, and the interaction of age, waist-to-hip ratio, and length of the Barrett's oesophagus segment.

162 (35%) of 468 of patients fell into the low-risk category and the probability of being a true non-dysplastic patient was 100% (99% CI 96-100) and the probability of having high-grade dysplasia or intramucosal adenocarcinoma was 0% (0-4).

238 (51%) of participants were classified as of moderate risk; the probability of having high-grade dysplasia was 14% (9-21).

58 (12%) of participants were classified as high-risk; the probability of having non-dysplastic endoscopic biopsies was 13% (5-27), whereas the probability of having high-grade dysplasia or intramucosal adenocarcinoma was 87% (73-95).

Conclusion

A combination of biomarker assays from a single Cytosponge sample can be used to determine a group of patients at low risk of progression, for whom endoscopy could be avoided. This strategy could help to avoid overdiagnosis and overtreatment in patients with Barrett's oesophagus.

Best- 2 Lancet Gastro-Hep 2017

STUDY PROTOCOL Open Access

Barrett's oESophagus trial 3 (BEST3): study protocol for a randomised controlled trial comparing the Cytosponge-TFF3 test with usual care to facilitate the diagnosis of oesophageal pre-cancer in primary care patients with chronic acid reflux

Judith Offman[1], Beth Muldrew[2], Maria O'Donovan[3], Irene Debiram-Beecham[4], Francesca Pesola[1], Irene Kaimi[2], Samuel G. Smith[5], Ashley Wilson[2], Zohrah Khan[2], Pierre Lao-Sirieix[6], Benoit Aigret[2], Fiona M. Walter[7], Greg Rubin[8], Steve Morris[9], Christopher Jackson[10], Peter Sasieni[1,2], Rebecca C. Fitzgerald[4*] and on behalf of the BEST3 Trial team

Best – 3 Offman et al BMC Cancer 2018: 18; 784.

Methods

Design

This is a pragmatic multi-site cluster randomised controlled trial where approximately 120 general practices will be randomised 1:1 to either the intervention or control arm (Fig. 2). Anonymised data will be collected from eligible patients in both arms at baseline and 1 year post entry into the study. Patients will be informed about being entered into BEST3 data collection by letter. Patients in the intervention arm will receive an invitation for a Cytosponge™-TFF3 test in their general practice. Patients with a positive TFF3 test will receive an invitation for an upper gastro-intestinal (GI) endoscopy at their local hospital-based endoscopy clinic to test for BE. In addition to the TFF3-positive patients, 10% of the patients in each arm (who have not had an endoscopy since the start of the trial) will be randomly selected to be invited for an endoscopy at approximately 12 months.

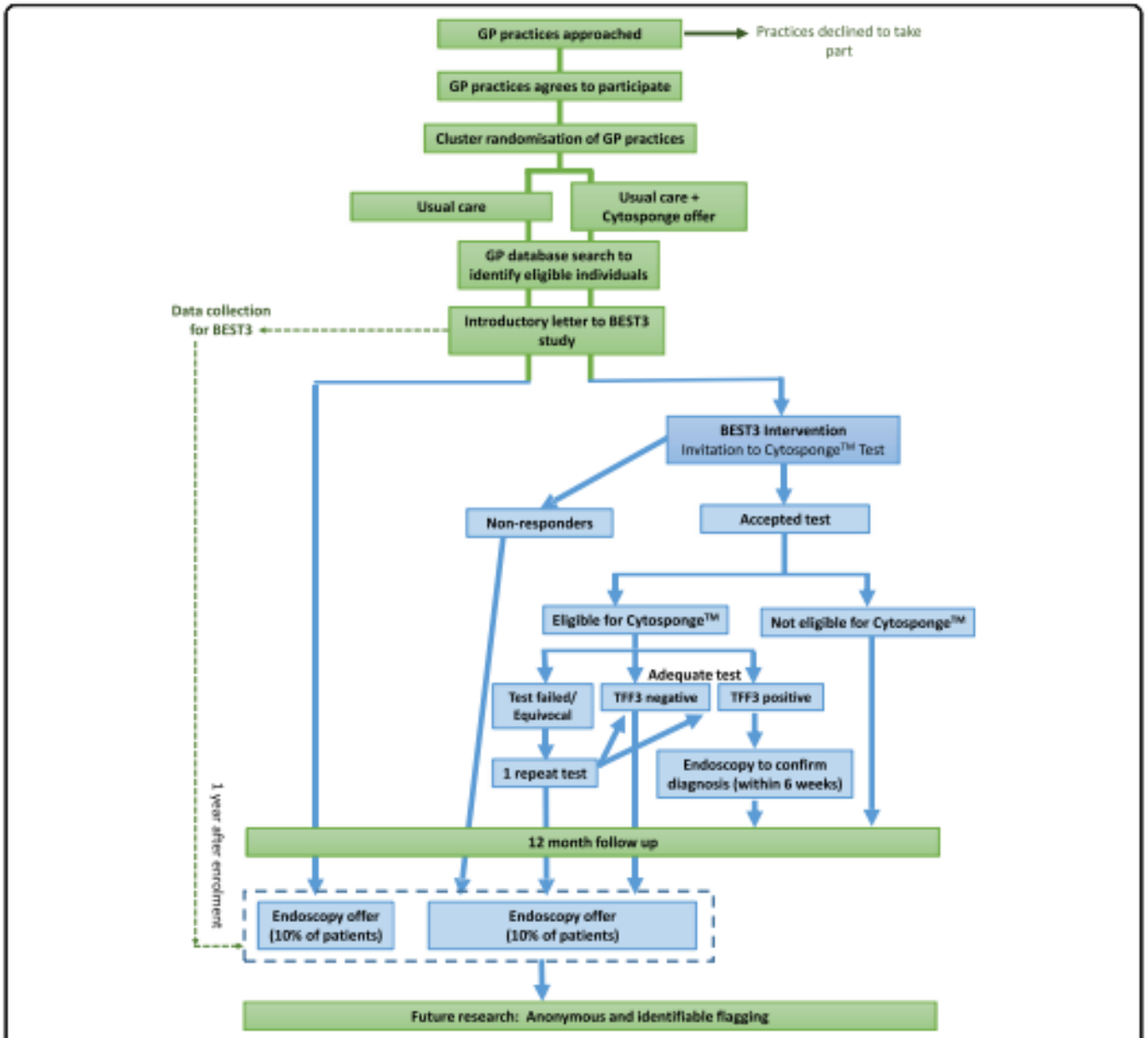


Fig. 2 BEST3 trial design overview showing both BEST3 anonymous data collection steps (green) and intervention, Cytosponge™-TFF3 test or upper GI endoscopy related procedures (blue)

Cytosponge-trefoil factor 3 versus usual care to identify Barrett's oesophagus in a primary care setting: a multicentre, pragmatic, randomised controlled trial

Rebecca C Fitzgerald, Massimiliano di Pietro, Maria O'Donovan, Roberta Maroni, Beth Muldrew, Irene Debiram-Beecham, Marcel Gehrung, Judith Offman, Monika Tripathi, Samuel G Smith, Benoit Aigret, Fiona M Walter, Greg Rubin, on behalf of the BEST3 Trial team, Peter Sasieni*

Lancet 2020; 396: 333–44

	Usual care group (n=6388)	Intervention group (n=6834)	Absolute difference in rates per 1000 person-years (95% CI)	Overall rate ratio (95% CI); p value	Adjusted rate ratios (95% CI); p value		
					Cluster randomised group	Patient-level randomised group	Overall*
Number of participants diagnosed with Barrett's oesophagus	13 (<1%)	140 (2%)†	..	..	..	..	..
Follow-up, person-years	6579	6952	..	..	..	..	..
Rate of Barrett's oesophagus, per 1000 person-years	2·0	20·2‡	18·3 (14·8–21·8)	10·2 (5·8–18·1)	10·0 (5·0–20·0); p<0·0001	12·0 (4·3–33·2); p<0·0001	10·6 (6·0–18·8); p<0·0001

Data are n (%), unless otherwise specified. *Overall adjusted rate ratio is a combined rate ratio of the two randomisation groups (cluster randomisation and individual patient-level randomisation) and accounts for clustering. †Number of participants diagnosed with Barrett's oesophagus in the intervention group includes all participants who were offered the Cytosponge procedure. ‡The rate of Barrett's oesophagus in the intervention group was calculated as the weighted average of the rate in the first 4 months of follow-up and the rate in the following months, with a weight ratio of 1:2.

Table 2: **Barrett's oesophagus diagnoses in the usual care group compared with the intervention group**

	Usual care group (n=6388)	Intervention group		
		Underwent the Cytosponge procedure (n=1750)	Did not undergo the Cytosponge procedure (n=5084)	Overall (n=6834)
Grade of dysplastic Barrett's oesophagus				
No dysplasia	13	116	13	129
Indefinite	0	7	0	7
Low-grade	0	1	0	1
High-grade	0	3	0	3
Total	13	127	13	140
Oesophago-gastric cancer stage				
I	0	4	1	5
II	1	0	0	0
III	1	0	0	0
IV	1	0	2	2
Total number of participants with Barrett's oesophagus, cancer, or both	16	131	16	147

Table 3: **Number of individuals with Barrett's oesophagus in the usual care group and intervention group with or without cancer, by grade of dysplasia and cancer stage**

Lancet 2020; 396: 333–44

Lancet Oncol. 2022 Feb; 23(2): 270–278.
doi: 10.1016/S1470-2045(21)00667-7

PMCID: PMC8803607
PMID: 35030332

Use of a Cytosponge biomarker panel to prioritise endoscopic Barrett's oesophagus surveillance: a cross-sectional study followed by a real-world prospective pilot

Nastazja Dagny Pilonis, MD,[a,†] Sarah Killcoyne, PhD,[a,†] W Keith Tan, MD,[a] Maria O'Donovan, MD,[a,b] Shalini Malhotra, MD,[a,b] Monika Tripathi, MD,[a,b] Ahmad Miremadi, MD,[a,b] Irene Debiram-Beecham, RN,[a] Tara Evans, RN,[a] Rosemary Phillips, MD,[c] Danielle L Morris, MD,[d] Craig Vickery, MD,[e] Jon Harrison, MD,[f] Massimiliano di Pietro, MD,[a] Jacobo Ortiz-Fernandez-Sordo, MD,[g] Rehan Haidry, MD,[g] Abigail Kerridge, BSc,[a] Peter D Sasieni, Prof, PhD,[h] and Rebecca C Fitzgerald, Prof, MD[a,*]

The prevalence of high-grade dysplasia or cancer determined endoscopic biopsy was

17% (92 of 557 patients) in the training cohort

10% (35 of 344) in the validation cohort.

high risk, atypia or p53 overexpression or both on Cytosponge;

moderate risk, defined by age, sex, and segment length;

low risk, defined as Cytosponge-negative and no clinical risk factors.

The risk of high-grade dysplasia or intramucosal cancer in the high-risk group was 52% (68 of 132 patients) in the training cohort and 41% (31 of 75) in the validation cohort, compared with 2% (five of 210) and 1% (two of 185) in the low-risk group, respectively.

In the real-world setting, Cytosponge results prospectively identified 39 (17%) of 223 patients as high risk (atypia or p53 overexpression, or both) requiring endoscopy, among whom the positive predictive value was 31% (12 of 39 patients) for high-grade dysplasia or

BMJ Open

Patient-reported experiences and views on the Cytosponge test: a mixed-methods analysis from the BEST3 trial

Roberta Maroni [1], Jessica Barnes,[1] Judith Offman,[2] Fiona Scheibl,[3] Samuel G Smith,[4] Irene Debiram-Beecham,[5] Jo Waller [2], Peter Sasieni [1,2] Rebecca C Fitzgerald,[5,6] Greg Rubin [7], BEST3 Consortium,[8] Fiona M Walter [9,10]

Cytosponge appointment (N=1750).

Results 1488 patients successfully swallowing the Cytosponge completed the follow-up questionnaires, while 30 were interviewed, including some with an unsuccessful swallow.

Overall, participants were satisfied with the Cytosponge test. Several items showed positive ratings, in particular convenience and accessibility, staff's interpersonal skills and perceived technical competence. The most

The perceived risk of OAC increased following the Cytosponge appointment ($p<0.001$). Moreover, interviews suggested that some participants had trouble conceptualising risk and did not understand the relationships between test results, gastro-oesophageal reflux and risk of Barrett's oesophagus and OAC.

Conclusions When delivered during a trial in primary care, the Cytosponge is well accepted and causes little anxiety.

Safety

The safety of the Cytosponge-TFF3 device has been evaluated previously in a systematic review[25] of 2672 procedures done across four different studies in the UK, the USA, and Australia. In this review,[25] 2334 (97%) of 2418 patients swallowed the device successfully and there were two adverse events associated with the device; one was a detachment and one was a self-limiting pharyngeal bleed. These results are similar to those of our trial. The proactive telephone call to patients 7–14 days after they underwent the procedure also allowed us to collect data on side-effects. We found that 63 (4%) of 1654 participants had a sore throat after the procedure, indicating that patients should be told that they might experience this adverse event after the procedure.

Barrett's oesophagus once found

- Improve maintenance therapy with high dose ppi therapy and aspirin ?
- Consider anti reflux surgery – insufficient evidence for cancer prevention
- Surveillance endoscopy – low yield (0.5% per annum) and high cost
- Repeated cytosponge in "at risk" determined Intervals for early dysplasia detection
- Therapy of early stage cancer with Endoscopic mucosal resection +/- Ablation (RFA)

Dis Esophagus. 2022 Nov 15;35(11):doac026. doi: 10.1093/dote/doac026.

Laparoscopic total fundoplication is superior to medical treatment for reducing the cancer risk in Barrett's esophagus: a long-term analysis

S Szachnowicz [1], A F Duarte [1], A Nasi [1], J R M da Rocha [1], F B Seguro [1], E T Bianchi [1], F Tustumi [1], E G H de Moura [2], R A A Sallum [1], I Cecconello [1]

laparoscopic Nissen fundoplication. The groups were compared using propensity score matching paired by Barrett's esophagus length. A total of 398 patients met inclusion criteria. There were 207 patients in the omeprazole group (Group A) and 191 in the total fundoplication group (Group B). After applying the propensity score matching paired by Barrett's esophagus length, the groups were 180 (Group A) and 190 (Group B). Median follow-up was 80 months. Group B was significantly superior for controlling GERD symptoms. Group B was more efficient than Group A in promoting Barrett's esophagus regression or blocking its progression. Group B was more efficient than Group A in preventing the development of dysplasia and cancer. Logistic regression was performed for the outcomes of adenocarcinoma and dysplasia. Age and body mass index were used as covariates in the logistic regression models. Even after regression analysis, Group B was still superior to Group A to prevent esophageal adenocarcinoma or dysplasia transformation (odds ratio [OR]: 0.51; 95% confidence interval [CI]: 0.27-0.97, for adenocarcinoma or any dysplasia; and OR: 0.26; 95% CI: 0.08-0.81, for adenocarcinoma or high-grade dysplasia). Surgical treatment is superior to medical management, allowing for better symptom control, less need for reflux medication use, higher regression rate of the columnar epithelium and intestinal metaplasia, and lower risk for progression to dysplasia and cancer.

NICE GUIDELINES 2014
Interventions for gastro-oesophageal reflux disease (GORD)

- Offer people a full-dose PPI for 8 weeks to heal severe oesophagitis, taking into account the person's preference and clinical circumstances (underlying health conditions and possible drug interactions). **[2014]**
- Offer a full-dose PPI long-term as maintenance treatment for people with severe oesophagitis, (person's preference and clinical circumstances tolerability of the PPI), and the acquisition cost of the PPI. **[2014]**
- Do not routinely offer endoscopy to diagnose Barrett's oesophagus, but consider it if the person has GORD. Discuss the person's preferences and their individual risk factors (duration of symptoms, increased frequency of symptoms, previous oesophagitis, hiatus hernia, oesophageal stricture or ulcers, or male gender). **[2014]**

Putative PPI Side effects
clinically relevant

- Clostridia difficile infection (colitis) - OR x 3
- Campylobacter pylori - OR x 5
- Bacterial peritonitis in advanced cirrhosis OR x 12

Maes LM et al Therapeutic Advances in Drug Safety 2017; 8: 273-297

Putative PPI Side effects – confounding variables ?

- Community acquired pneumonia
- Osteoporosis – hip, vertebral #s
- Kidney – acute injury, chronic disease
- Dementia, Alzheimer's disease
- Vit B12 deficiency

Maes LM et al Therapeutic Advances in Drug Safety 2017; 8: 273-297

AP&T Alimentary Pharmacology and Therapeutics

Long-term safety of proton pump inhibitor therapy assessed under controlled, randomised clinical trial conditions: data from the SOPRAN and LOTUS studies

S. E. Attwood*, C. Ell†, J.P. Galmiche§, R. Fiocca¶, J. G. Hatlebakk**, B. Hasselgren††, G. Långström††, M. Jahreskog††, S. Eklund††, T. Lind†† & L. Lundell‡‡

2015; 41: 1162-74

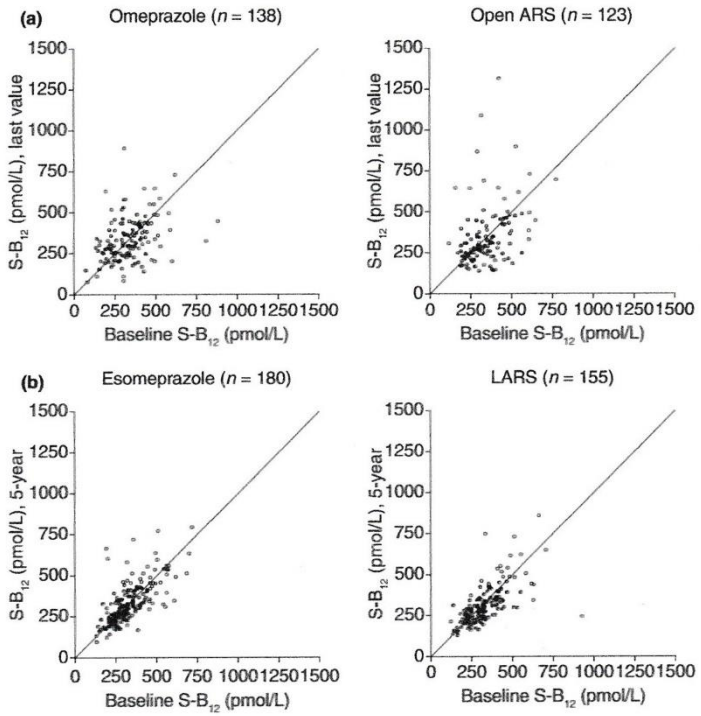


Figure 2 | Serum levels of vitamin B_{12} in individual patients treated with a proton pump inhibitor (omeprazole or esomeprazole) or anti-reflux surgery (open ARS or laparoscopic ARS [LARS]) in (a) the SOPRAN study (baseline vs. last value) and (b) the LOTUS study (baseline vs. 5 years). Diagonal line indicates 'no change'.

Calcium
Fractures
Liver enzymes
Creatinine
=

Pneumonia
Gastroenteritis
>

Følsomhet

Fracture risk
Lotus trial – PPi vs Surgery x 7 years follow up

2,103 patient years of follow up

Surgery	PPI
7	1

Surgery patients suffered more fractures during outdoor activities – QoL questionaires suggested that patients following surgery were more active than those with persistent regurgitation

Esomeprazole and aspirin in Barrett's oesophagus (AspECT): a randomised factorial trial

Janusz A Z Jankowski, John de Caestecker, Sharon B Love, Gavin Reilly, Peter Watson, Scott Sanders, Yeng Ang, Danielle Morris, Pradeep Bhandari, Stephen Attwood, Krish Ragunath, Bashir Rameh, Grant Fullarton, Art Tucker, Ian Penman, Colin Rodgers, James Neale, Claire Brooks, Adelyn Wise, Stephen Jones, Nicholas Church, Michael Gibbons, David Johnston, Kishor Vaidya, Mark Anderson, Sherzad Balata, Gareth Davies, William Dickey, Andrew Goddard, Cathryn Edwards, Stephen Gore, Chris Haigh, Timothy Harding, Peter Isaacs, Lucina Jackson, Thomas Lee, Peik Loon Lim, Christopher Macdonald, Philip Mairs, James McLoughlin, David Monk, Andrew Murdock, Iain Murray, Sean Preston, Stirling Pugh, Howard Smart, Ashraf Soliman, John Todd, Graham Turner, Joy Worthington, Rebecca Harrison, Hugh Barr, Paul Moayyedi

Summary

Background Oesophageal adenocarcinoma is the sixth most common cause of cancer death worldwide and Barrett's oesophagus is the biggest risk factor. We aimed to evaluate the efficacy of high-dose esomeprazole proton-pump inhibitor (PPI) and aspirin for improving outcomes in patients with Barrett's oesophagus.

Methods The Aspirin and Esomeprazole Chemoprevention in Barrett's metaplasia Trial had a 2×2 factorial design and was done at 84 centres in the UK and one in Canada. Patients with Barrett's oesophagus of 1 cm or more were randomised 1:1:1:1 using a computer-generated schedule held in a central trials unit to receive high-dose (40 mg twice-daily) or low-dose (20 mg once-daily) PPI, with or without aspirin (300 mg per day in the UK, 325 mg per day in Canada) for at least 8 years, in an unblinded manner. Reporting pathologists were masked to treatment allocation. The primary composite endpoint was time to all-cause mortality, oesophageal adenocarcinoma, or high-grade dysplasia, which was analysed with accelerated failure time modelling adjusted for minimisation factors (age, Barrett's oesophagus length, intestinal metaplasia) in all patients in the intention-to-treat population. This trial is registered with EudraCT, number 2004-003836-77.

Findings Between March 10, 2005, and March 1, 2009, 2557 patients were recruited. 705 patients were assigned to low-dose PPI and no aspirin, 704 to high-dose PPI and no aspirin, 571 to low-dose PPI and aspirin, and 577 to high-dose PPI and aspirin. Median follow-up and treatment duration was 8·9 years (IQR 8·2–9·8), and we collected 20 095 follow-up years and 99·9% of planned data. 313 primary events occurred. High-dose PPI (139 events in 1270 patients) was superior to low-dose PPI (174 events in 1265 patients; time ratio [TR] 1·27, 95% CI 1·01–1·58, p=0·038). Aspirin (127 events in 1138 patients) was not significantly better than no aspirin (154 events in 1142 patients; TR 1·24, 0·98–1·57, p=0·068). If patients using non-steroidal anti-inflammatory drugs were censored at the time of first use, aspirin was significantly better than no aspirin (TR 1·29, 1·01–1·66, p=0·043; n=2236). Combining high-dose PPI with aspirin had the strongest effect compared with low-dose PPI without aspirin (TR 1·59, 1·14–2·23, p=0·0068). The numbers needed to treat were 34 for PPI and 43 for aspirin. Only 28 (1%) participants reported study-treatment-related serious adverse events.

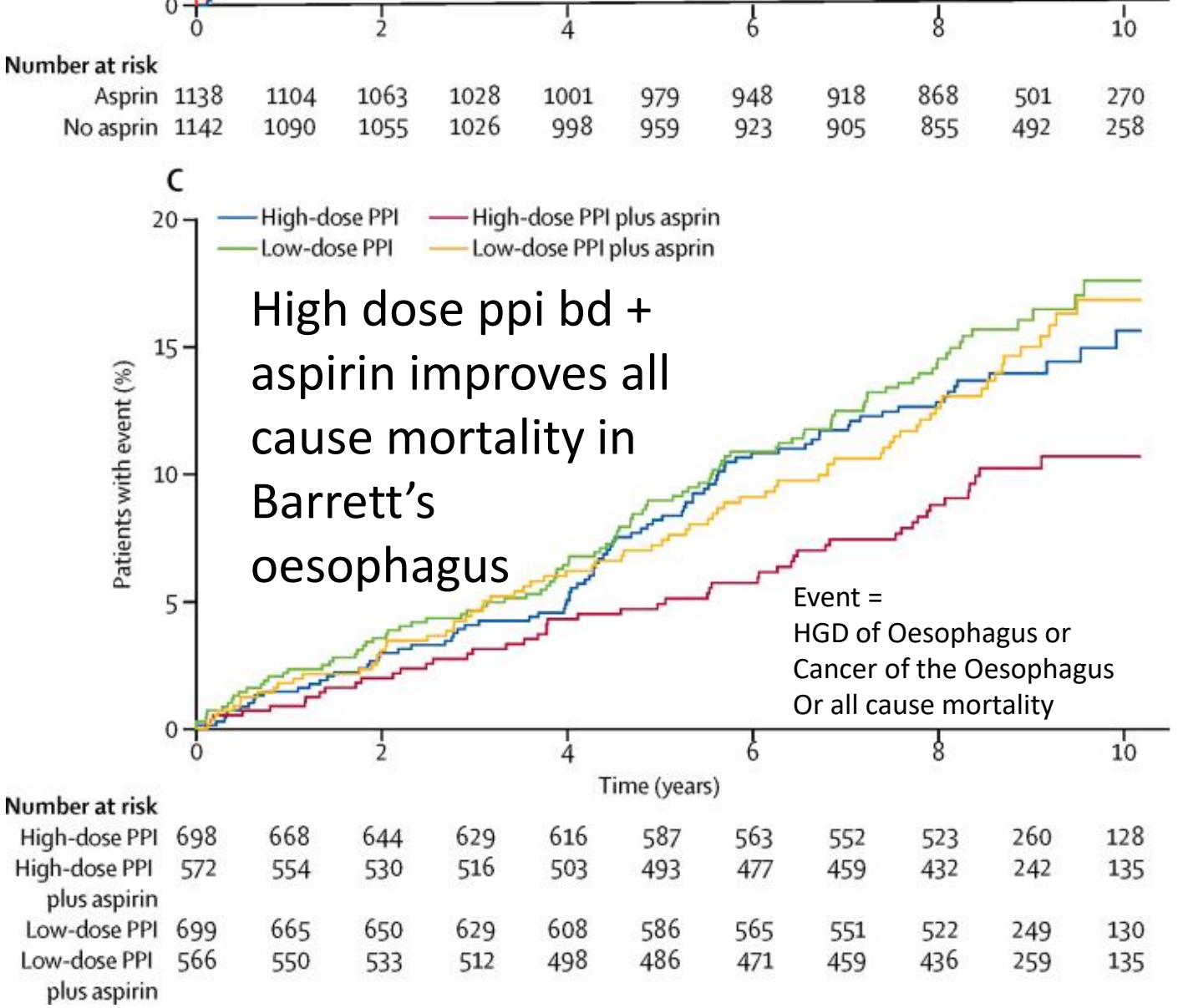
Interpretation High-dose PPI and aspirin chemoprevention therapy, especially in combination, significantly and safely improved outcomes in patients with Barrett's oesophagus.

Factorial design 2,500 patients	No aspirin	Aspirin 300mg
Low dose ppi	705	571
High dose ppi	709	577

Follow up 9 years

Findings Between March 10, 2005, and March 1, 2009, 2557 patients were recruited. 705 patients were assigned to low-dose PPI and no aspirin, 704 to high-dose PPI and no aspirin, 571 to low-dose PPI and aspirin, and 577 to high-dose PPI and aspirin. Median follow-up and treatment duration was 8·9 years (IQR 8·2–9·8), and we collected 20 095 follow-up years and 99·9% of planned data. 313 primary events occurred. High-dose PPI (139 events in 1270 patients) was superior to low-dose PPI (174 events in 1265 patients; time ratio [TR] 1·27, 95% CI 1·01–1·58, p=0·038). Aspirin (127 events in 1138 patients) was not significantly better than no aspirin (154 events in 1142 patients; TR 1·24, 0·98–1·57, p=0·068). If patients using non-steroidal anti-inflammatory drugs were censored at the time of first use, aspirin was significantly better than no aspirin (TR 1·29, 1·01–1·66, p=0·043; n=2236). Combining high-dose PPI with aspirin had the strongest effect compared with low-dose PPI without aspirin (TR 1·59, 1·14–2·23, p=0·0068). The numbers needed to treat were 34 for PPI and 43 for aspirin. Only 28 (1%) participants reported study-treatment-related serious adverse events.

Interpretation High-dose PPI and aspirin chemoprevention therapy, especially in combination, significantly and safely improved outcomes in patients with Barrett's oesophagus.



	High-dose PPI *vs* low-dose PPI					Aspirin *vs* no aspirin				
	Total number of patients in analysis	Events/patients on high-dose PPI	Events/patients on low-dose PPI	Time ratio (95% CI)	p value	Total number of patients in analysis	Events/patients on aspirin	Events/patients not on aspirin	Time ratio (95% CI)	p value
All-cause mortality	2535	79/1270	105/1265	1·36 (1·01–1·82)	0·039	2280	73/1138	90/1142	1·25 (0·92–1·70)	0·16
Oesophageal adenocarcinoma	2535	40/1270	41/1265	1·04 (0·67–1·61)	0·86	2280	35/1138	35/1142	1·02 (0·64–1·64)	0·92
High-grade dysplasia	2535	44/1270	59/1265	1·36 (0·92–2·02)	0·12	2280	37/1138	55/1142	1·51 (1·00–2·29)	0·053
Cause-specific mortality	2535	8/1270	12/1265	1·55 (0·63–3·80)	0·34	2280	8/1138	8/1142	1·01 (0·38–2·69)	0·98
Composite endpoint, men only	2022	118/1010	148/1012	1·26 (0·99–1·61)	0·06	1796	105/896	130/900	1·26 (0·98–1·64)	0·07
Composite endpoint, women only	513	21/260	26/253	1·27 (0·72–2·27)	0·41	484	22/242	24/242	1·13 (0·63–2·02)	0·69

Table 2 shows the results of the secondary analyses.
High-dose PPI decreased all-cause mortality compared with low-dose PPI.

The largest difference was in the comparison of combined aspirin and high-dose PPI (52 events in 572 participants) with low-dose PPI and no aspirin (99 events in 699 participants; TR 1·59, 95% CI 1·14–2·23, p=0·0068).

For high-grade dysplasia (the precursor lesion to oesophageal adenocarcinoma), the comparison of aspirin versus no aspirin gave a TR of 1·51 (95% CI 1·00–2·29, p=0·053).

Aspect trial – Jankowski JAZ et al
The Lancet 2018; 392 (10145), 400-408

Prevention of cancer of the oesophagus by Aspirin or high dose ppi

NNT

- 43 patients would need to be treated with aspirin to prevent one event (95% CI 20–250).

- 34 (18–333) for high-dose PPI— 34 patients would need to be treated with high-dose PPI instead of low-dose PPI to prevent one event.

Aspect trial – Jankowski JAZ et al
The Lancet 2018; 392 (10145), 400-408

Future Improvement in Oesophageal Cancer Mortality

- Likely to come from early diagnosis
- Best achieved through Cytosponge screening
- Risk managed endoscopic surveillance
- Interventions at stage 1 disease – endoscopic and less frequently surgical

Conclusion

- The use of Cytosponge is valid
- to identify Barrett's oesophagus in symptomatic refluxers
- to stratify those who would benefit from increased levels of surveillance endoscopy
- to identify patients who would benefit from interventions that reduce the risk of invasive cancer
  - Medical acid suppression + aspirin
  - Anti reflux surgery
- To improve the stage of cancer diagnosis, increase those who can be treated with endoscopic therapy for cancer
- Yet to be proven that overall survival of oesophageal cancer mortality is achieved

Thank you

- Acknowledgements

- Professor Rebecca Fitzgerald and the BEST team based at Cambridge University and Collaborators in the UK performed all of these studies on the Cytosponge