Identification of responders to short-term treatment with Esomeprazole for dyspepsia in primary care

Analysis of a Danish multicenter trial

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AGA Disclosure Statement

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Background

- The response to treatment with proton pump inhibitors (PPI) in primary care patients with acid-related dyspepsia is unpredictable, partly owing to a large placebo response
- In previous studies derived from randomized clinical trials we showed that the PPI response depends on the patient's symptom profile
- Some symptoms are associated with increased PPI response, others with decreased PPI response

- Scand J Gastroenterol. 1998;33:1262-72.
- Am J Gastroenterol. 2000;95:2777-83.

Aim

- To perform a larger study with a comprehensive recording of patient characteristics and symptoms
- To identify symptoms associated with response to PPI
- To improve selection of patients for empirical treatment with PPI
- To develop an easy to use ”pocket chart” to identify responders to PPI

Design

- Double-blind randomized clinical trial of esomeprazole 40 mg daily for 2 weeks versus placebo
- Endpoint: absence of the key complaint (the symptom that prompted the consultation) for the last 24 hours

Criteria of inclusion

- Patients in general practice with symptoms suggestive of acid related disease for which the GP would normally prescribe an acid-inhibiting agent
- Written informed consent
- Age $\geq$ 18 years

Criteria of exclusion

- Symptoms suggestive of Irritable Bowel Syndrome (IBS)
- Any ”alarm” symptoms (significant weight loss, vomiting, dysphagia, hematemesis, melena, fever, jaundice or signs of serious disease)
- Treatment with PPI within the last 2 weeks
- Medications interacting with esomeprazole
- Illness likely to interfere with evaluation of the study results

Recorded variables (1)

- Age
- Gender
- BMI
- Smoking
- Alcohol abuse
- Duration of symptoms
- Intensity of symptoms last 3 days
- Region of pain

Recorded variables (2)

- Key complaint: ordinal scale in 4 grades
- Pain: ordinal scale in 4 grades
- 18 pain characteristics: present or absent
- 13 G-I symptoms: present or absent
- ’Most bothersome symptom’ defined

Statistical Method

- The association of patient characteristics and symptoms with response was studied using **logistic regression analysis**
- **Interaction terms** between therapy (esomeprazole or placebo) and the patient characteristics / symptoms were included in the analysis
- The backward elimination technique of insignificant variables was applied

Details about the method are in: Am J Gastroenterol. 2000;95:2777-83.

Model development and testing

- The study population was divided into a **model sample** (the first 60% included) and a **validation sample** (the last 40%)
- From the model sample we **developed an index** to predict the therapeutic response (the difference between response to esomeprazole and placebo)
- The **validity of the index was tested** in the validation sample.

Results

- 805 patients were included (esomeprazole 410, placebo 395)
- Age (median and range) was 52 (17-90) years
- 45% were males
- The treatment groups were comparable in respect to all descriptive variables

Overall result of trial

- Study endpoint (complete relief of key complaint):
  - Esomeprazole: 68%
  - Placebo: 44%
  - Therapeutic gain: 24%, $p<0.00001$

Results in model sample (N=484)

Variables associated with ↑ PPI response:

- **Significant heartburn** (p=0.01). Correlated with: regurgitation, high BMI, pain quality: burning, etching, sensation of acid
- **Early satiety** (p=0.009). Correlated with: postprandial pain, postprandial fullness

Variables associated with ↓ PPI response:

- **Pain quality: ”dull” (”sensation of stone”)** (p=0.002). Correlated with bloating, constipation, incomplete evacuation
- **Pain releaved by bowel movements** (p=0.03). Correlated with: loose stools, diarrhoea
- **Nausea in women** (p=0.04)

Note: It is important to ask the patient specifically about these symptoms.

Prevalence of the ”therapeutic” variables

Significant heartburn		46%
Early satiety		29%
Pain quality ”dull” (”sensation of stone”)		25%
Pain relieved by bowel movements		13%
Nausea:	males	27%
	females	41%
	(p=0.00003)	

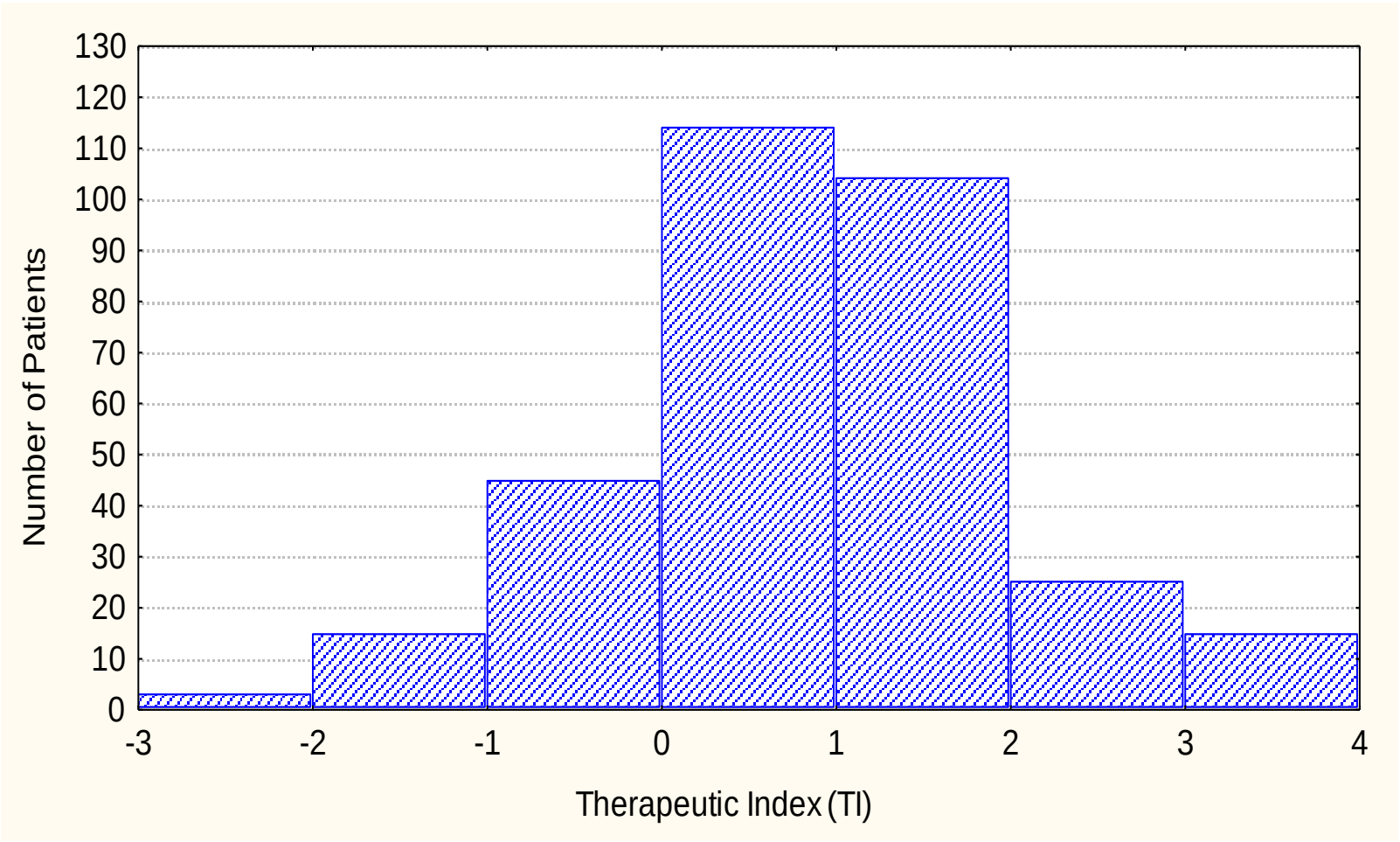
Therapeutic index

	Yes	No	Score
Significant heartburn	+19	+9	
Early satiety	+12	0	
Dull pain quality	-14	0	
Pain relieved by bowel movements	-13	0	
Nausea in women	-9	0	
Therapeutic index =	SUM x 0,1 =		

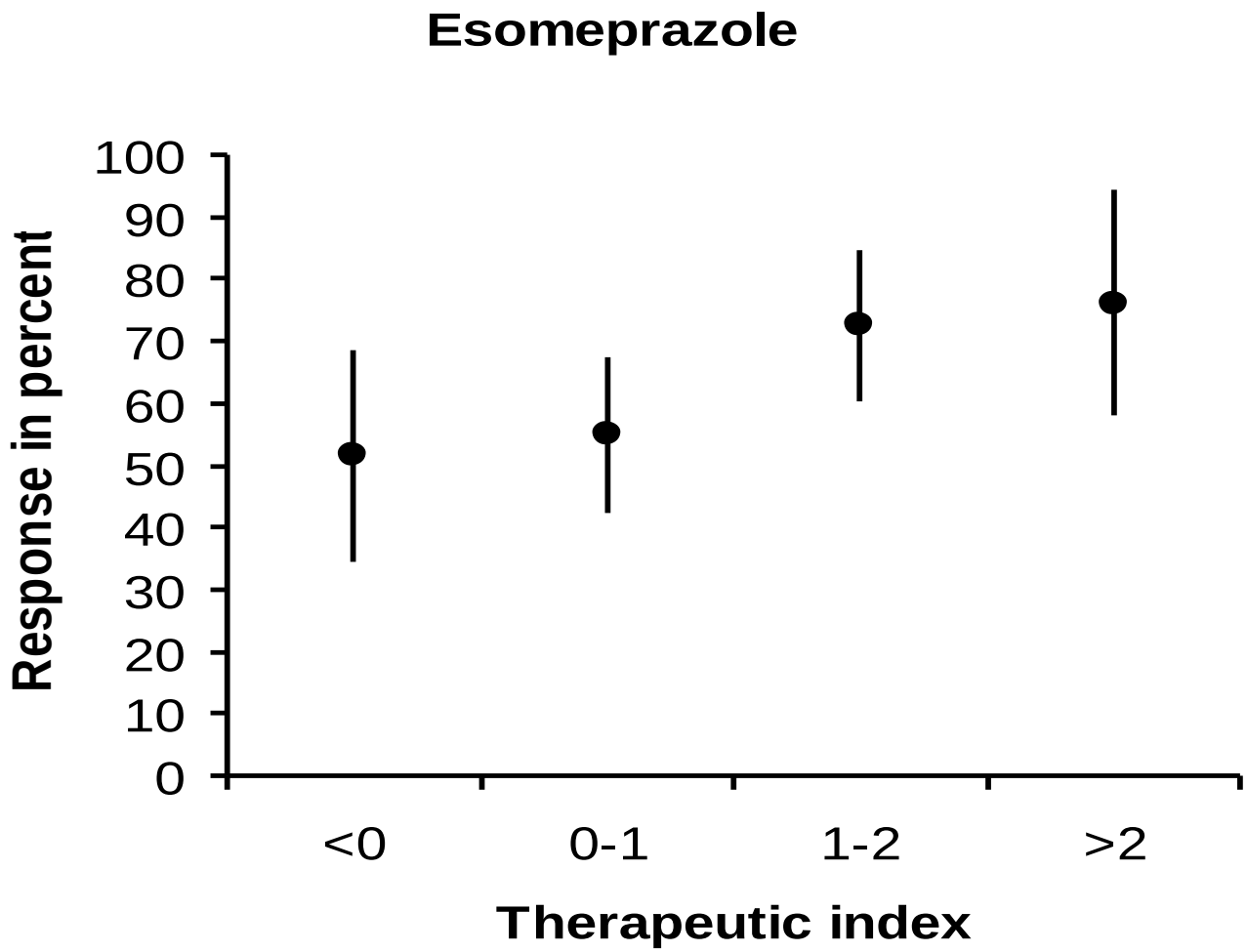
Therapeutic index (example)

	Yes	No	Score
Significant heartburn	+19	+9	+19
Early satiety	+12	0	+12
Dull pain quality	-14	0	-14
Pain relieved by bowel movements	-13	0	0
Nausea in women	-9	0	0
Therapeutic index =		SUM x 0,1 =	17x0.1 = 1.7

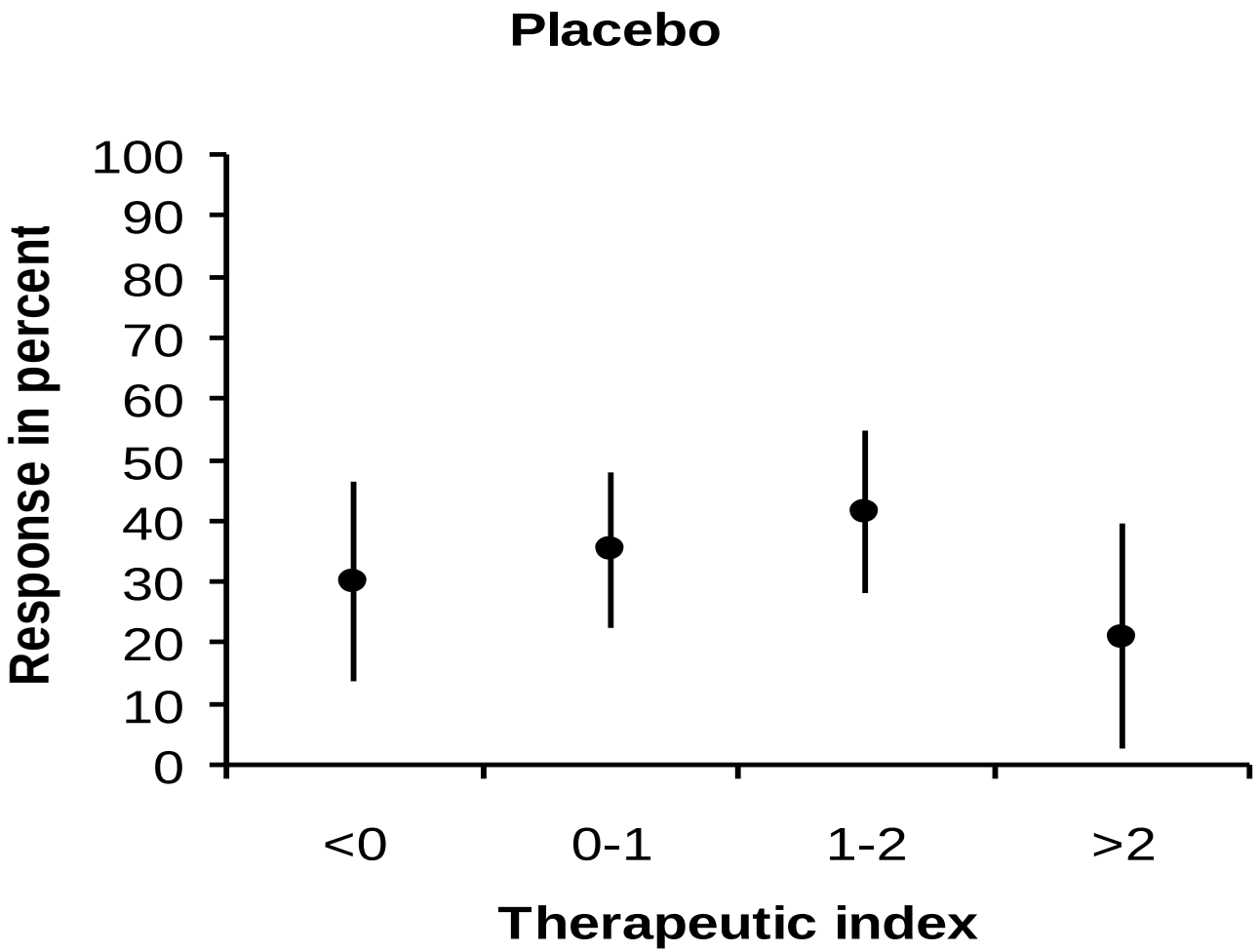
Distribution of therapeutic index in test sample (N=321)



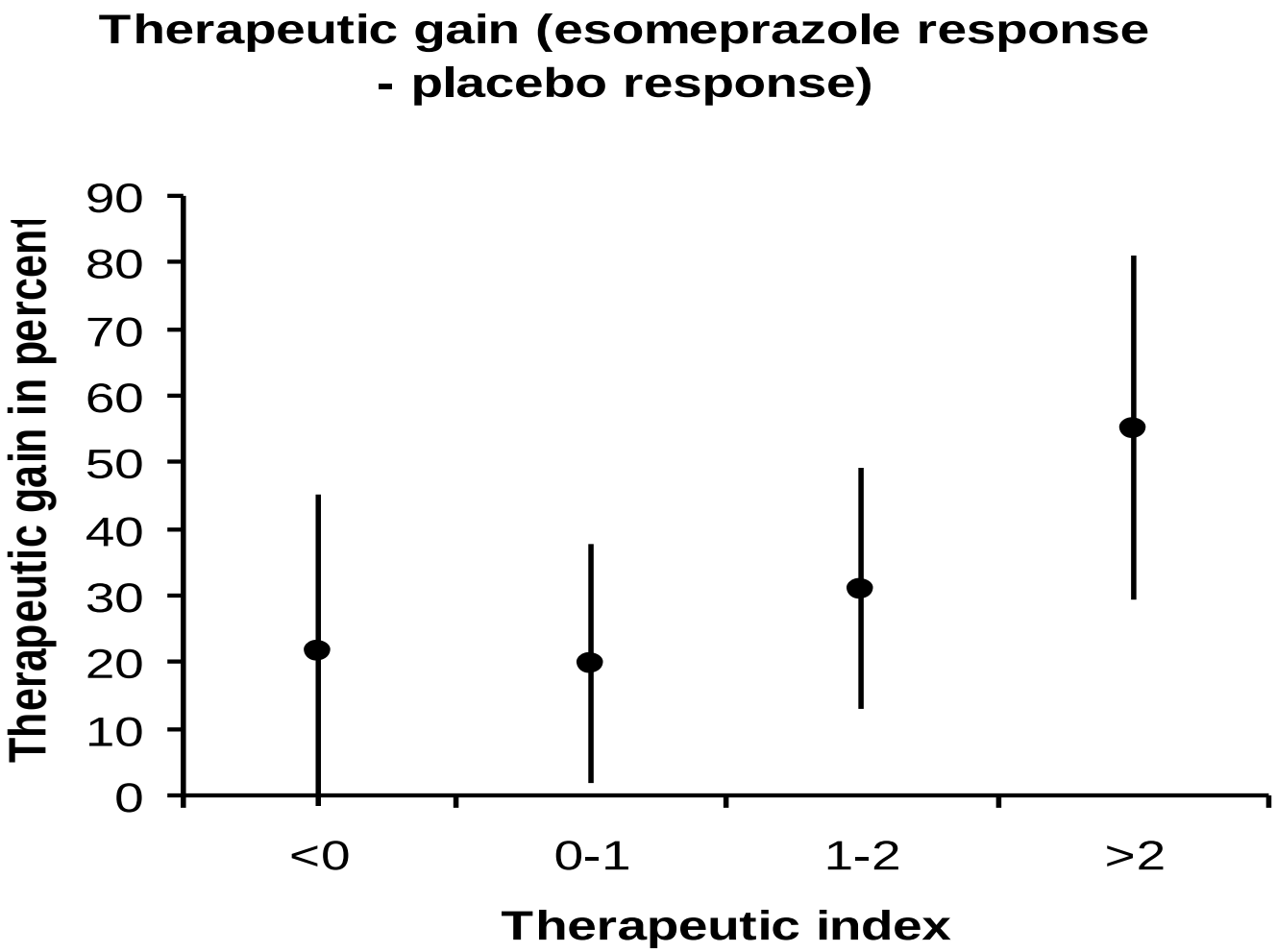
Esomeprazole response by therapeutic index in test sample



Placebo response by therapeutic index in test sample



Therapeutic gain by therapeutic index in test sample (N=321)



Therapeutic index (TI) Interpretation

- TI <1: Low response: Therapeutic gain ~20% (0-40)
- TI 1-2: Intermediary response: Therapeutic gain: ~30% (15-45)
- TI >2: High response: Therapeutic gain ~50% (30-70)

Conclusions:

- In patients with uninvestigated acid-related dyspepsia, responders to PPI therapy can be identified by characteristic symptoms
- Symptoms can predict increased effect or decreased effect of PPI
- A simple pocket chart – validated in independent patients – can predict response to PPI in the individual patient
- The pocket chart provides a simple, practical tool for identifying responders to PPI in dyspepsia in general practice.

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