How I Do It: Optimal Use of IL-23 Monoclonal Antibodies for IBD

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Disclosures

- Advisor/Consultant: Abbvie, Abivax, Astra Zeneca, BMS, Eli Lilly, Janssen, Merck,Pfizer, Prometheus biosciences, Sphyre, Takeda

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Risankizumab

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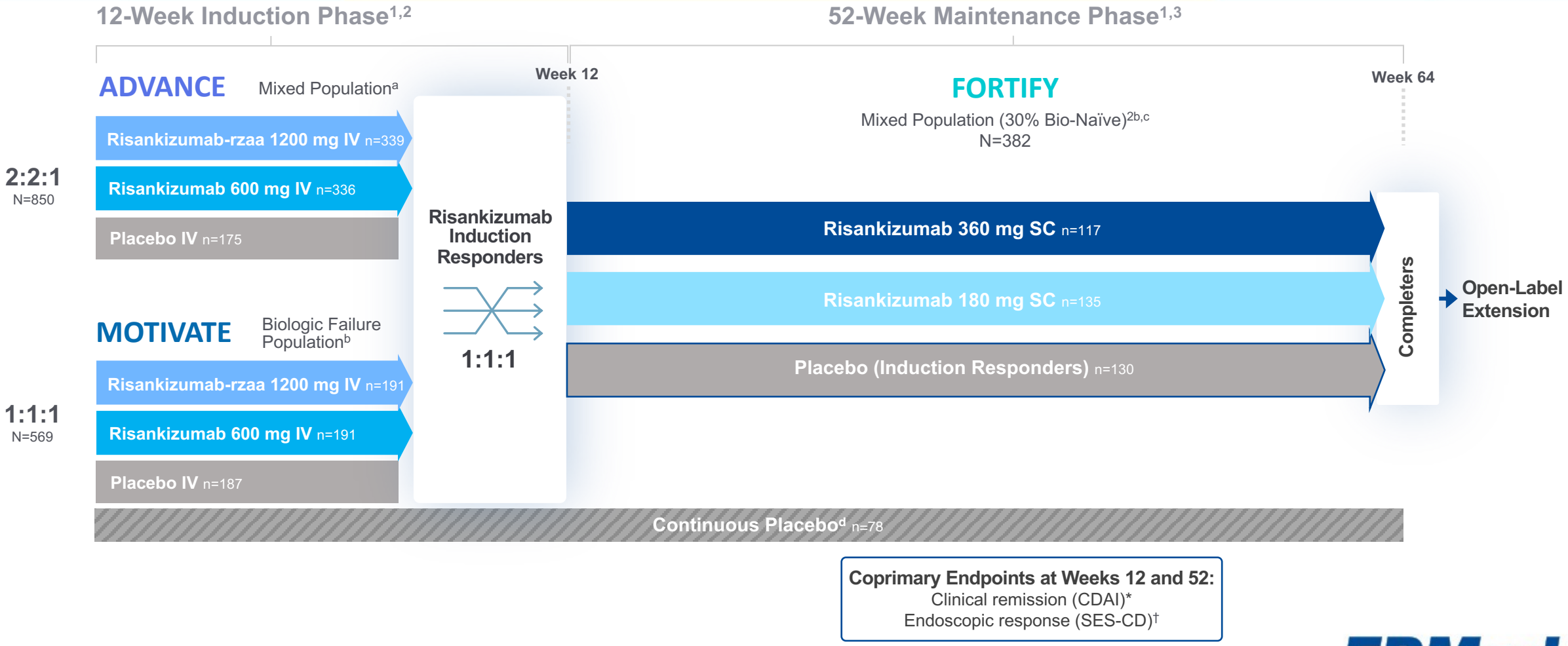
Risankizumab Phase 3 Crohn's Program Study Design[1]



1. D'Haens G, et al. *Lancet*. 2022;399:2015-2030; 2. Ferrante M, et al. *Lancet*. 2022;399:2031-2046.

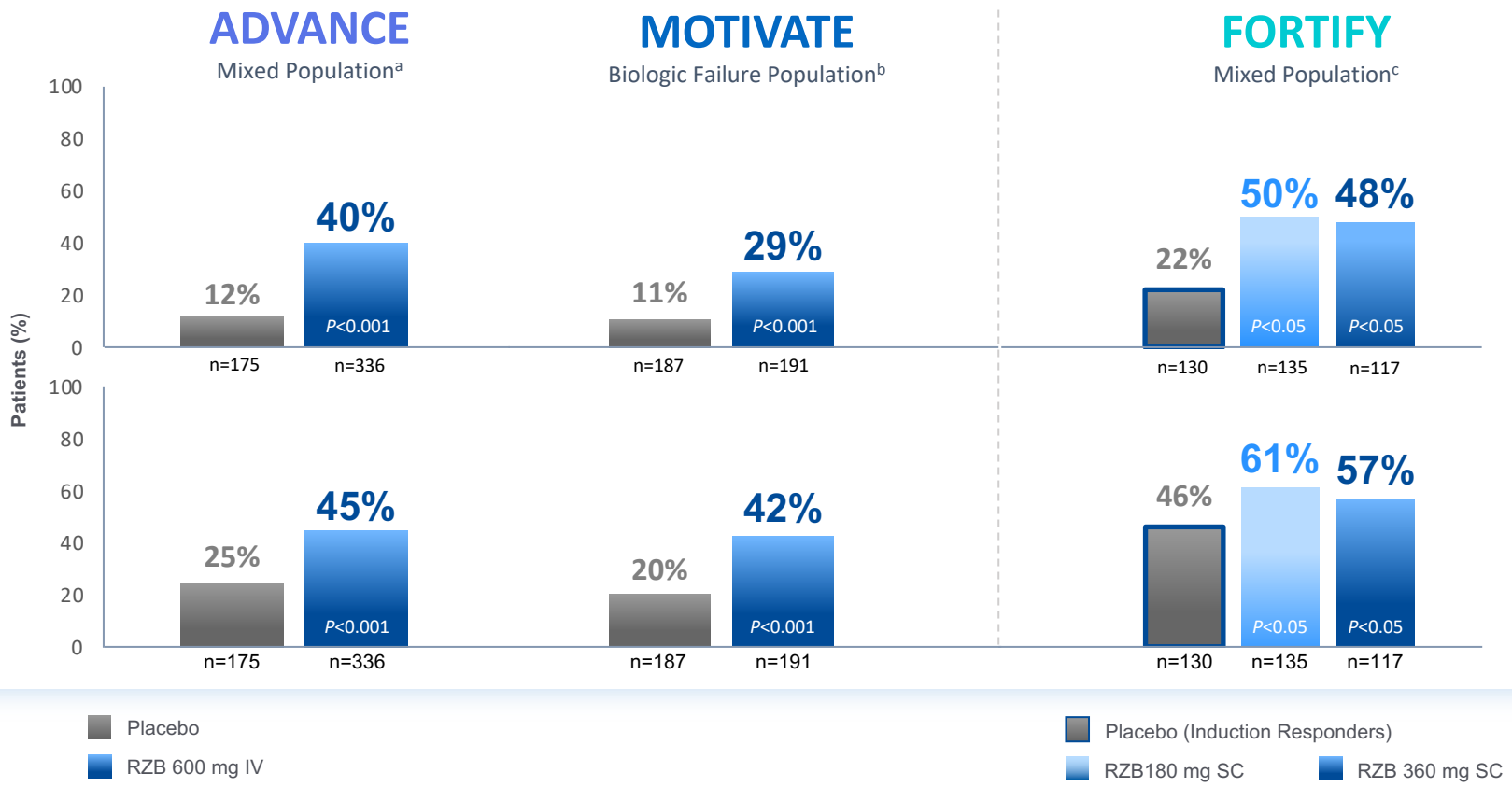
Risankizumab for CD: Phase 3 Placebo Controlled Trial

INDUCTION[2] (WEEK 12) | **MAINTENANCE[2] (WEEK 52)**

Coprimary Endpoints

Endoscopic Response
(decrease in SES-CD >50% from baseline)*

Clinical Remission
(CDAI <150)



1. D'Haens G, et al. *Lancet*. 2022;399:2015-2030; 2. Ferrante M, et al. *Lancet*. 2022;399:2031-2046.

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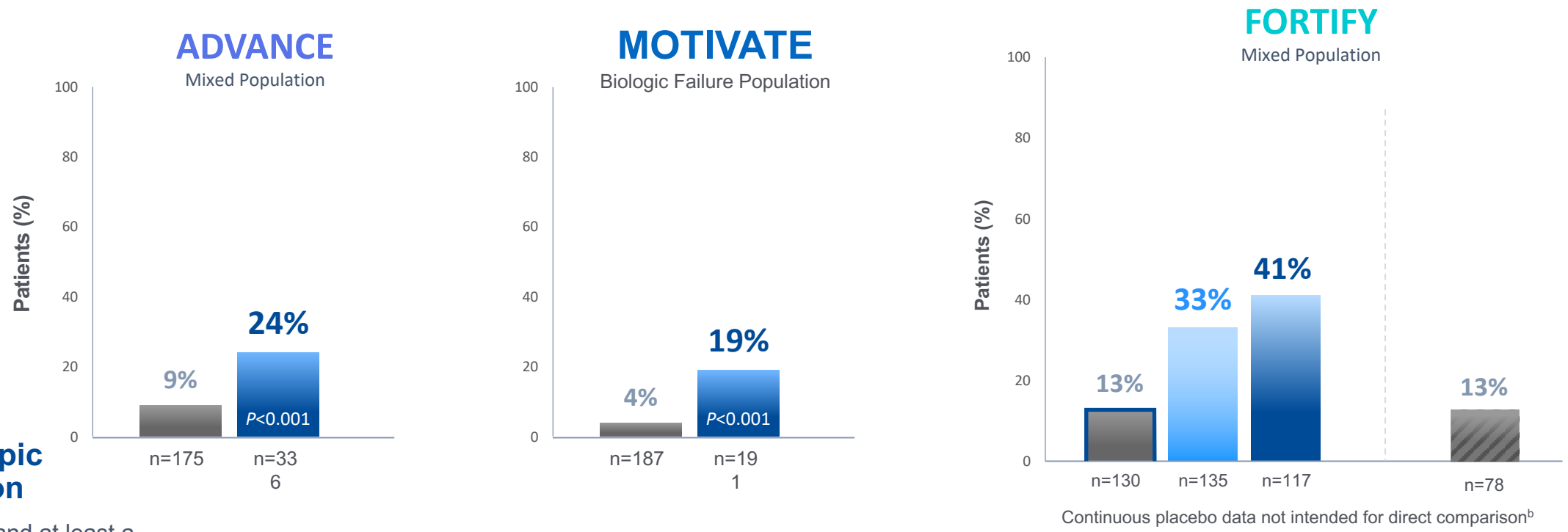
Endoscopic Remission Week 12 and Week 64

RANKED SECONDARY ENDPOINT



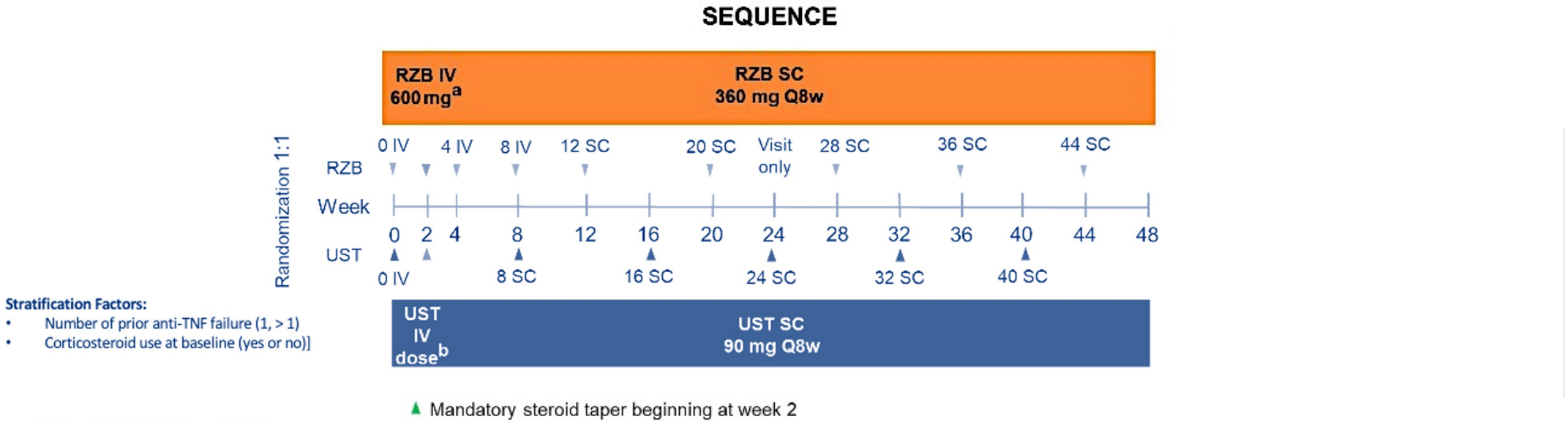
Continuous placebo data not intended for direct comparison[b]

Endoscopic Remission

SES-CD ≤4 and at least a 2-point reduction vs baseline and no subscore >1 in any individual variable[a]

1. D'Haens G, et al. *Lancet*. 2022;399:2015-2030; 2. Ferrante M, et al. *Lancet*. 2022;399:2031-2046.

Phase 3b Head-to-Head SEQUENCE Study in Crohn's Disease



Key Eligibility Criteria

Moderate to severe CD

- CDAI 220-450
- Average daily SF ≥4 and/or average daily APS ≥2
- SES-CD, excluding the narrowing component, ≥6 (≥4 for isolated ileal disease), as scored by the site Investigator and confirmed by a central reader

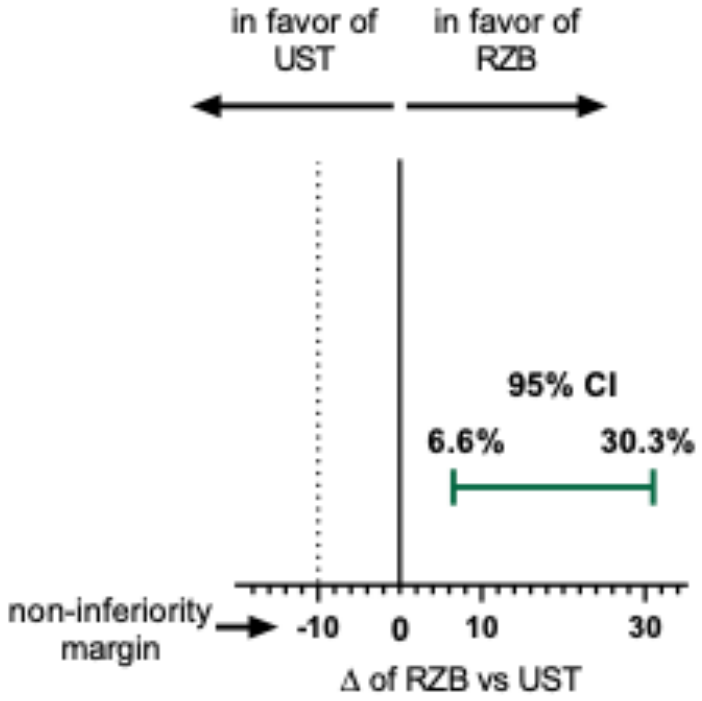
Prior failure of ≥1anti-TNF therapies

- Prior biologic therapy that could potentially influence the therapeutic impact on CD was exclusionary, including vedolizumab

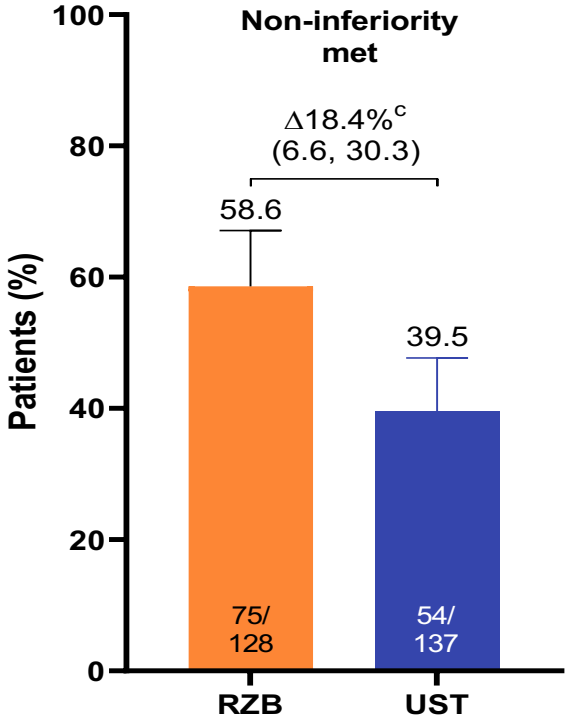
Peyrin-Biroulet L, et al. Presented at UEGW. October 2023. LB01.

RZB Demonstrated Non-inferiority to UST for Wk24 Clinical Remission and Superiority to UST for Wk48 Endoscopic Remission

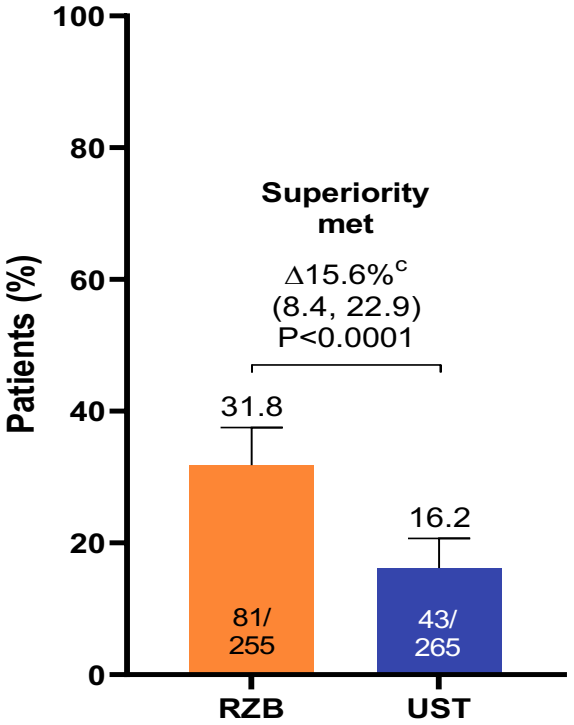
CDAI Clinical Remission Week 24 (ITT)



CDAI Clinical Remission Week 24 (ITT)



Endoscopic Remission Week 48 (ITT)



CDAI clinical remission: CDAI < 150

Endoscopic remission: SES-CD ≤ 4 and at least a 2-point reduction versus BL and no subscore > 1 in any individual variable, as scored by a central reviewer

Peyrin-Biroulet L, et al. Presented at UEGW. October 2023. LB01.

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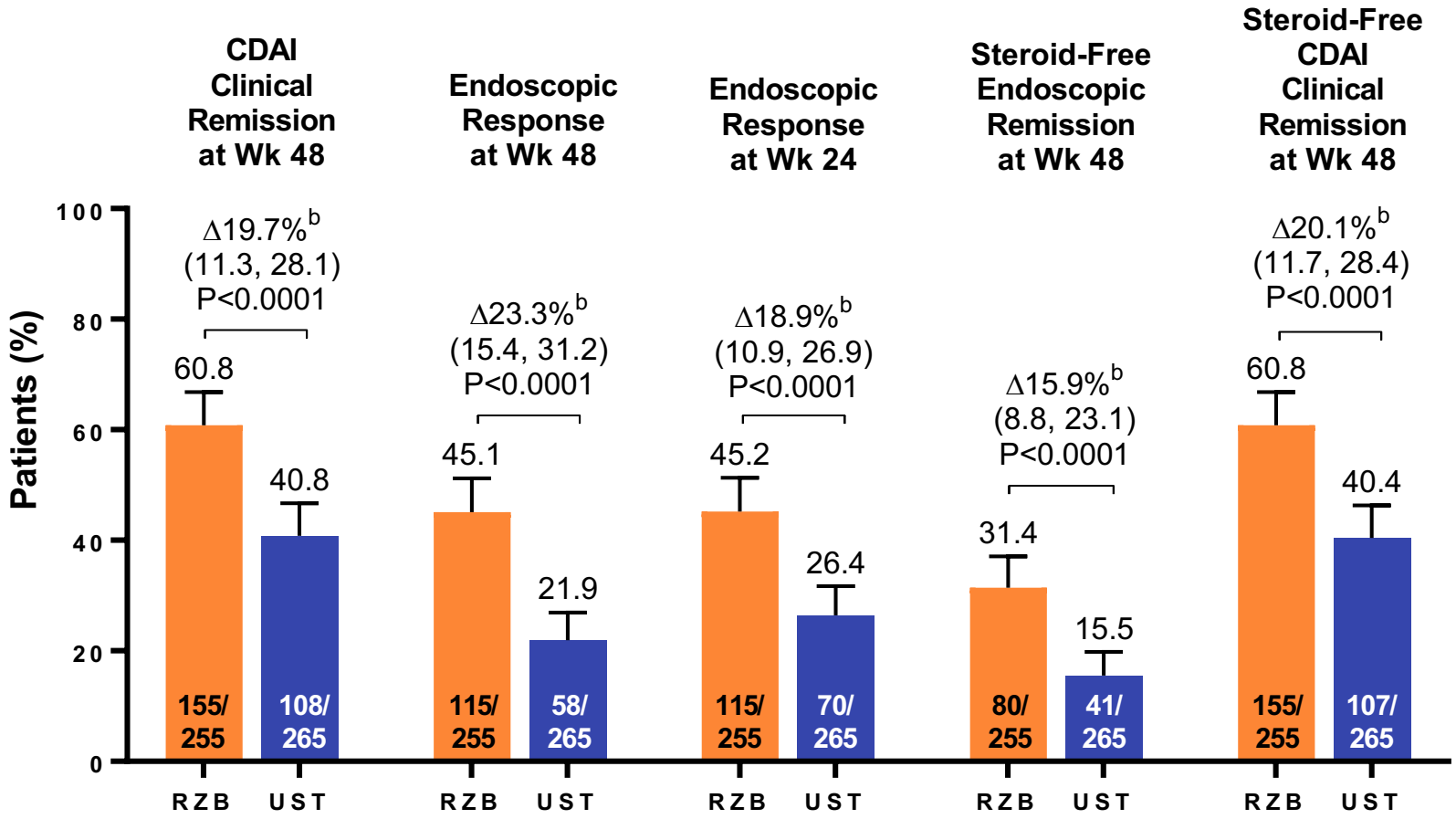
RZB Demonstrated Superiority to UST for ALL Secondary Endpoints



Superiority met for all endpoints

CDAI clinical remission: CDAI < 150
Endoscopic response: Decrease in SES-CD > 50% from BL (or for subjects with isolated ileal disease and a baseline SES-CD of 4, at least a 2-point reduction from baseline), as scored by central reviewer
Endoscopic remission: SES-CD ≤ 4 and at least a 2-pt reduction versus BL and no subscore > 1 in any individual variable, as scored by a central reviewer
Steroid-free: Patient not receiving steroids at the corresponding visit
Peyrin-Biroulet L, et al. Presented at UEGW. October 2023. LB01.

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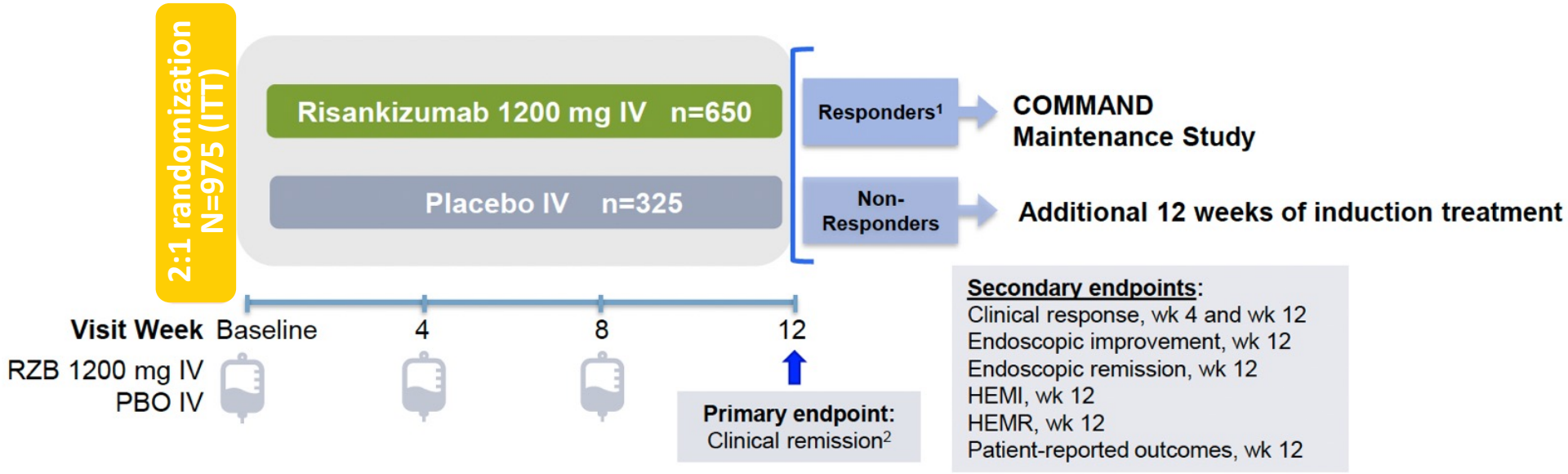
Risankizumab UC Phase 3 INSPIRE Induction Study

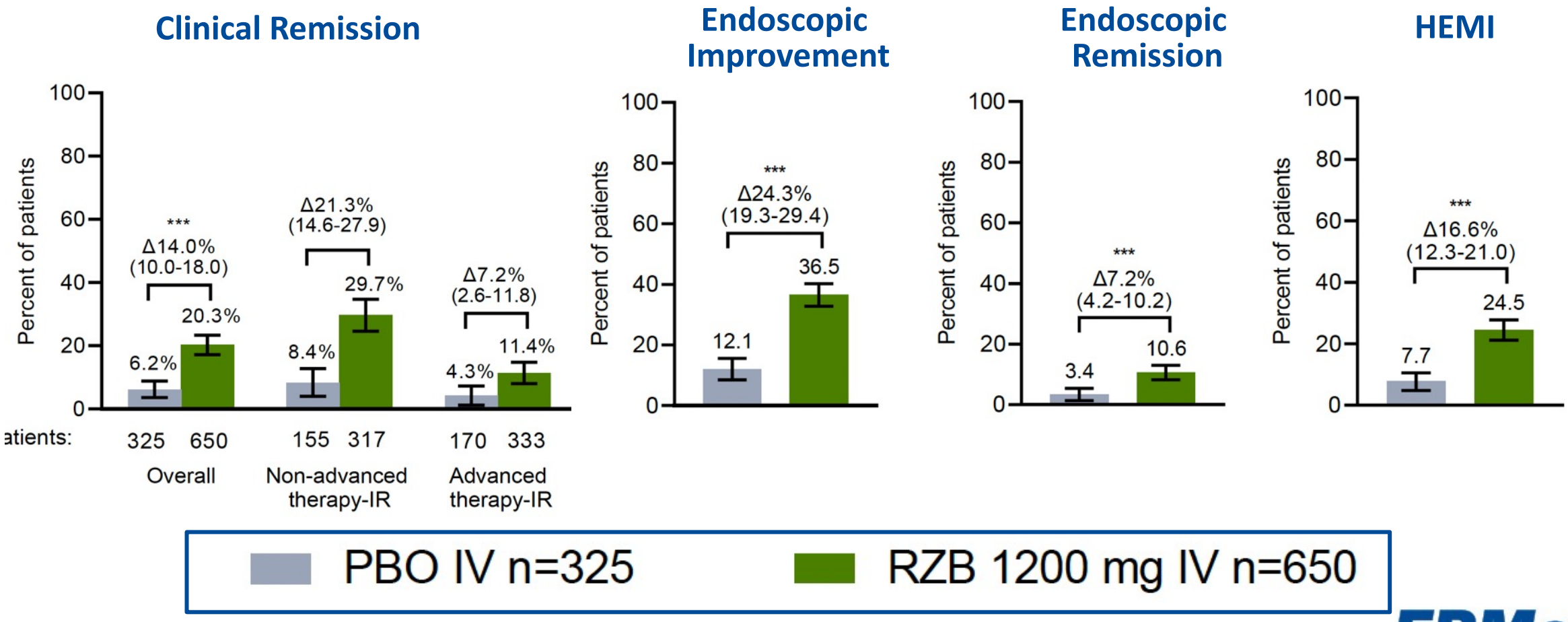


Key Inclusion Criteria:

- 18 to 80 years of age
- **Moderately to severely active UC:** Adapted Mayo score of 5–9 and endoscopic subscore of 2–3 (central review) with biopsy-confirmed diagnosis at least 3 months prior to baseline
- **Intolerance or inadequate response to conventional (non-advanced) and/or advanced therapies** (biologics, JAK inhibitors, and S1P receptor modulators)
- No prior exposure to ustekinumab or IL-23 inhibitors was permitted

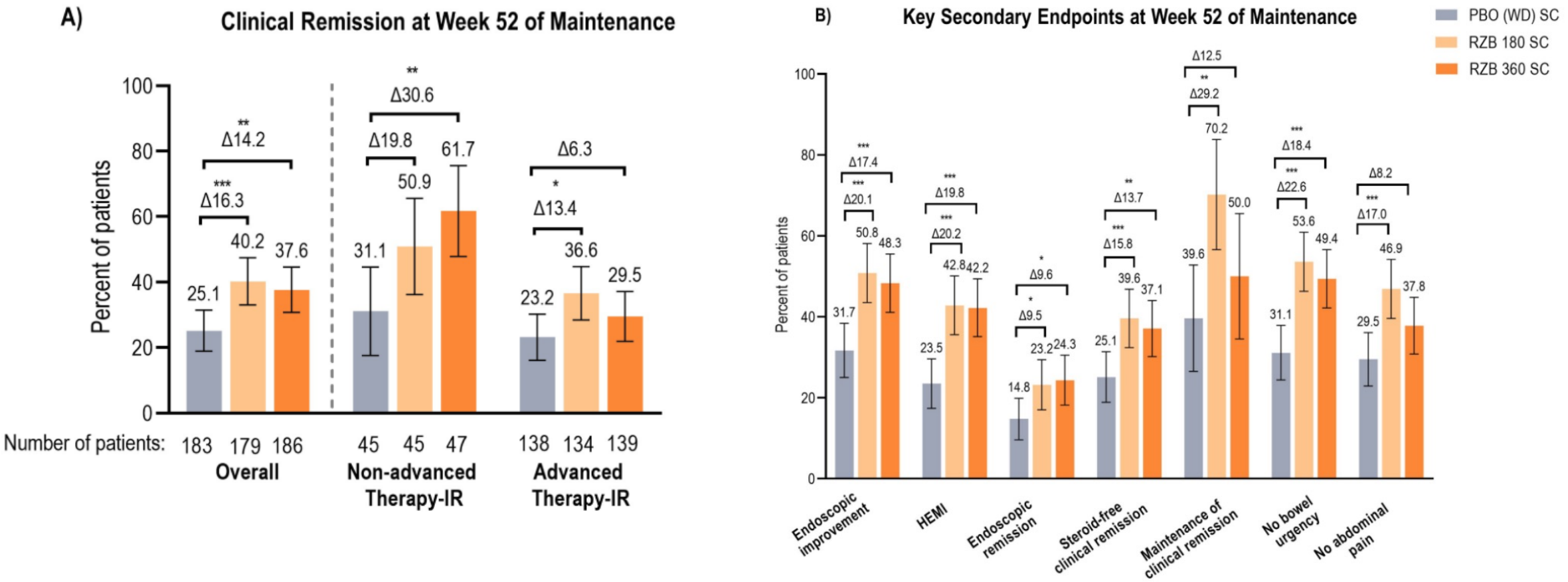
Louis E, et al. Presented at UEGW. October 2023. OP021.

RZB Superior to Placebo for Wk12 Clinical, Endoscopic, and Histologic Endpoints



Louis E, et al. Presented at UEGW. October 2023. OP021.

Efficacy of Risankizumab Maintenance UC COMMAND Study: Rerandomized Placebo Withdrawal Design



Schreiber S, et al. Presented at ECCO 2024. OP06.

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Safety of Risankizumab Maintenance UC COMMAND Study

Table 1. Treatment-Emergent Adverse Events Among Safety Population Through Week 52[a]

E/100 PY	PBO (WD) SC n = 196; PY = 174.9	RZB 180 mg SC n = 193; PY = 185.4	RZB 360 mg SC n = 195; PY = 173.5
Any AE:	399 (228.1)	399 (215.2)	406 (234.0)
AE related to COVID-19	28 (16.0)	21 (11.3)	29 (16.7)
AE with reasonable possibility of being *drug related*[b]	75 (42.9)	85 (45.9)	61 (35.2)
Severe AE	14 (8.0)	3 (1.6)	7 (4.0)
Serious AE	20 (11.4)	11 (5.9)	11 (6.3)
AE leading to discontinuation of study drug	4 (2.3)	5 (2.7)	5 (2.9)
All deaths	0	0	1 (0.6)[c]
Serious infections[d]	4 (2.3)	2 (1.1)	1 (0.6)
Infusion/Injection site reactions[e]	3 (1.7)	14 (7.6)	10 (5.8)

AE, adverse event; COVID-19, coronavirus disease 2019; E, events; patient-years; PBO, placebo; RZB, risankizumab; SC, subcutaneous; WD, withdrawal

[a]The safety population included all patients who clinically responded to IV RZB at 12 or 24 weeks, were randomised to COMMAND at maintenance week 0, and received at least one dose of study drug during 52-week maintenance period.
[b]As assessed by the investigator.
[c]One death was reported in the RZB360 arm in a patient diagnosed with colon adenocarcinoma, which was retrospectively found in the screening biopsy tissue.
[d]Serious infections in risankizumab-treated patients included COVID-19, COVID-19 pneumonia, abscess limb, and pneumonia.
[e]All infusion/injection site reaction events were nonserious and did not lead to study discontinuation.

Schreiber S, et al. Presented at ECCO 2024. OP06.

Mirikizumab

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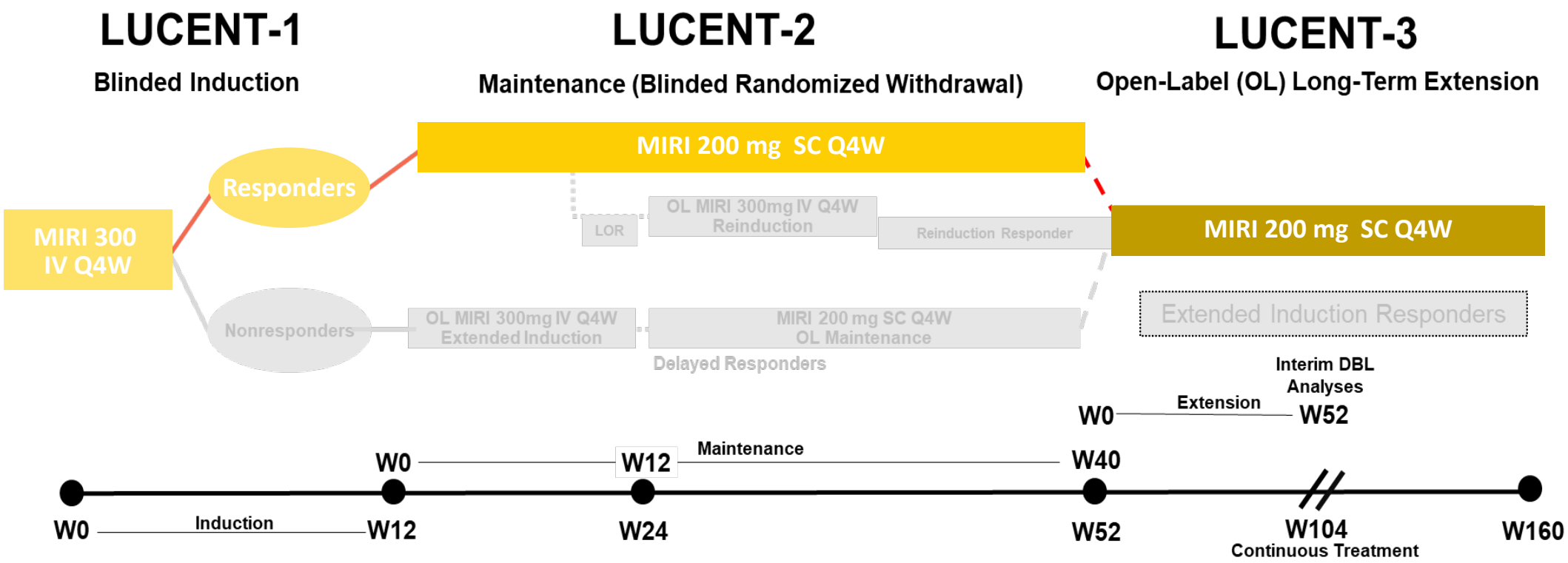
LUCENT UC Phase 3 Program



Sands BE, et al. Presented at UEG 2023. S848.

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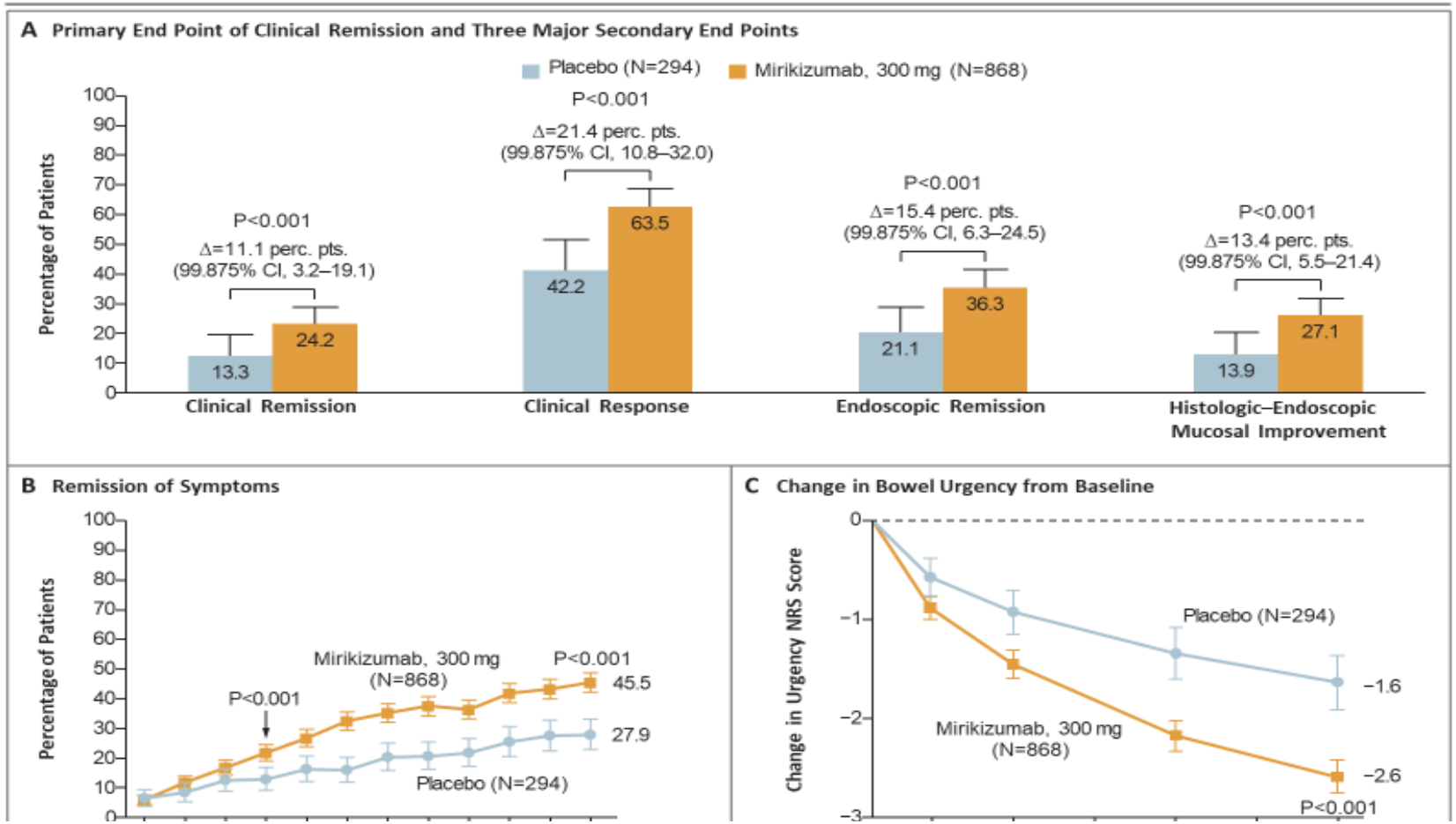
Mirikizumab is Safe and Effective in Inducing Clinical Remission in Moderate-to-Severe UC: LUCENT 1



D'Haens G, et al. *N Engl J Med.* 2023;388:2444-2455.

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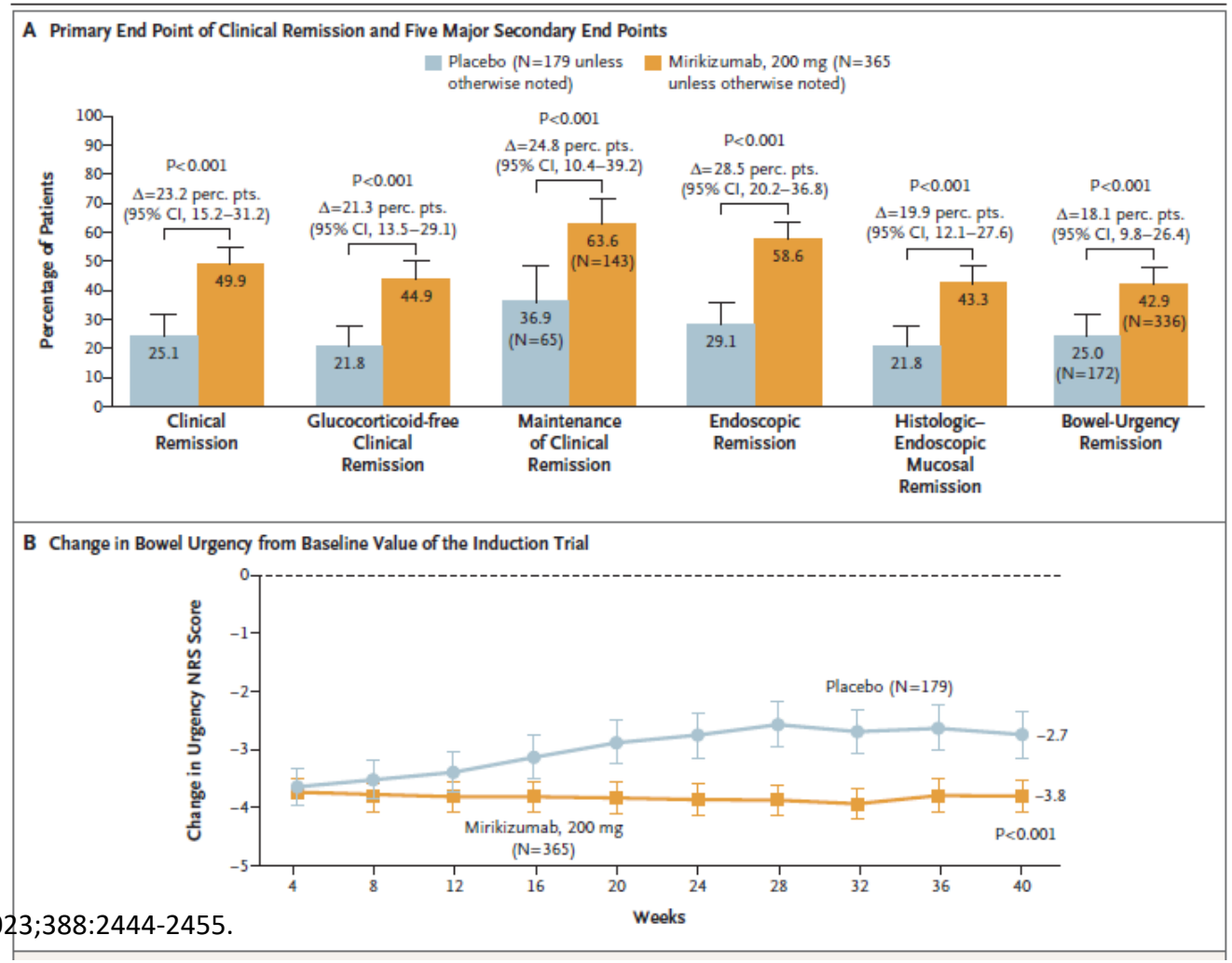
Mirikizumab is Safe and Effective in Maintaining Clinical Remission in Moderate-to-Severe UC: LUCENT 2



D'Haens G, et al. *N Engl J Med.* 2023;388:2444-2455.

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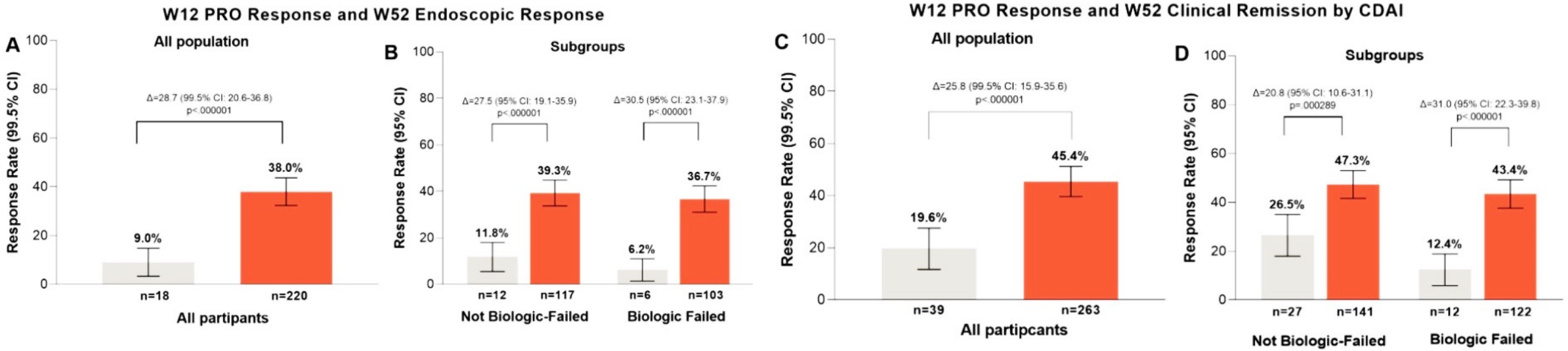
Primary Efficacy and Safety of Mirikizumab CD-Vivid-1 Phase 3 Treat Straight Through Trial



Ferrante M, et al. Presented at ECCO 2024. OP05.

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Primary Efficacy and Safety of Mirikizumab CD-Vivid-1 Phase 3 Treat Straight Through Trial

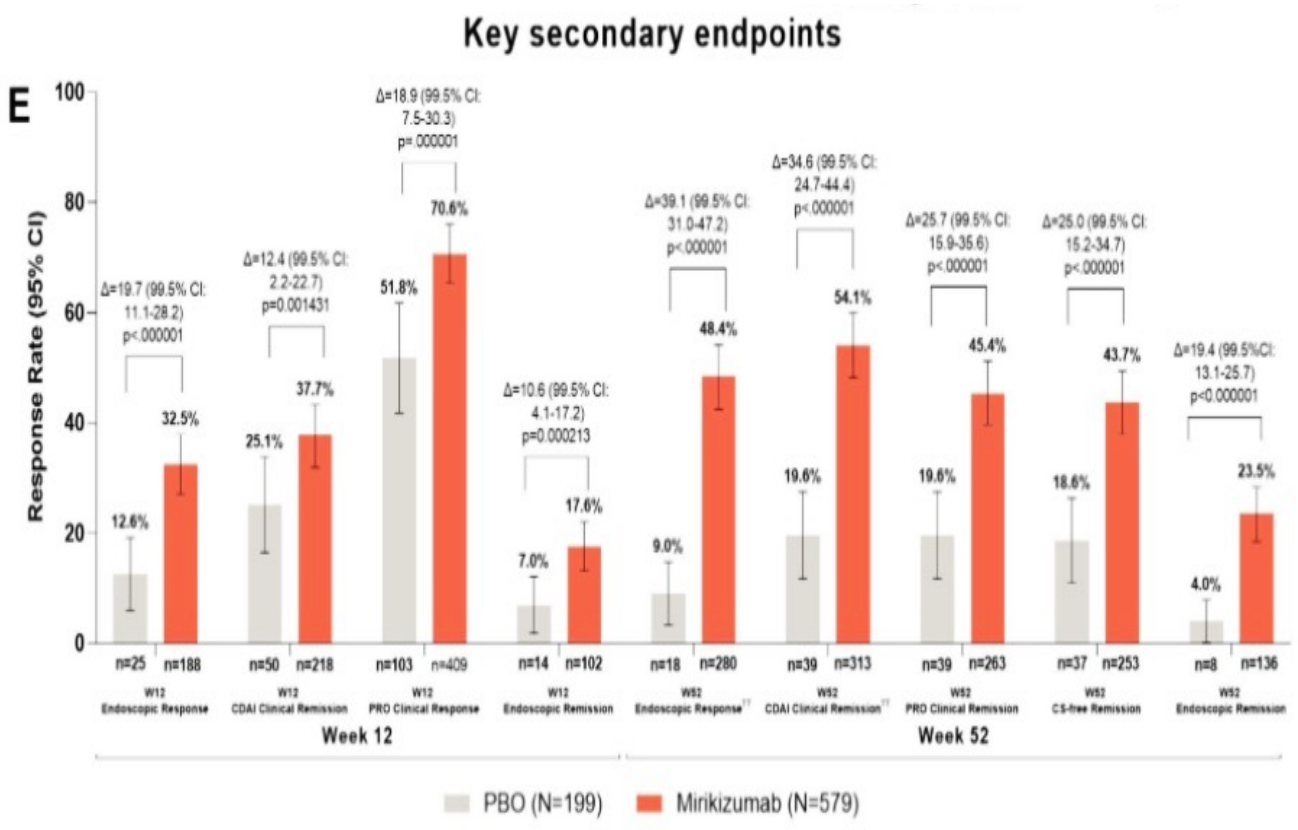

Table 1. Safety Outcomes up to W52.		
	Treatment groups	
	PBO N=211 PYE=119.5	Miri N=630 PYE=593.6
TEAE, n (%) [EAIR]	154 (73.0) [291.8]	495 (78.6) [201.9]
Most common TEAEs[a], n (%) [EAIR]		
COVID-19	29 (13.7) [26.4]	104 (16.5) [19.3]
Anaemia	14 (6.6) [12.2]	42 (6.7) [7.4]
Arthralgia	11 (5.2) [9.6]	41 (6.5) [7.2]
Headache	9 (4.3) [7.8]	41 (6.5) [7.2]
Upper respiratory tract infection	9 (4.3) [7.8]	38 (6.0) [6.7]
Nasopharyngitis	9 (4.3) [7.7]	36 (5.7) [6.3]
Diarrhoea	10 (4.7) [8.6]	35 (5.6) [6.1]
AEs of interest, n (%) [EAIR]		
Infections: (All)	73 (34.6) [81.3]	261 (41.4) [59.7]
Serious Infections:	6 (2.8) [5.1]	14 (2.2) [2.4]
Opportunistic[b] Infections:	0 (0.0) [0]	7 (1.1) [1.2]
Injection-site reaction	8 (3.8) [10.4]	66 (10.5) [15.3]
Cerebrocardiovascular events	2 (0.9) [1.7]	3 (0.5) [0.5]
Major adverse cardiac event	1 (0.5) [0.8]	0 (0.0) [0]
Malignancies[c]	1 (0.5) [0.8]	2 (0.3) [0.3]
Suicide/self-injury[d]	0 (0.0) [0]	2 (0.3) [0.3]
Hepatic event	9 (4.3) [7.8]	39 (6.2) [6.8]
SAE, n (%) [EAIR]	36 (17.1) [32.5]	65 (10.3) [11.5]
Discontinuation due to AE, n (%) [EAIR]	20 (9.5) [17.1]	32 (5.1) [5.4]

Ferrante M, et al. Presented at ECCO 2024. OP05.

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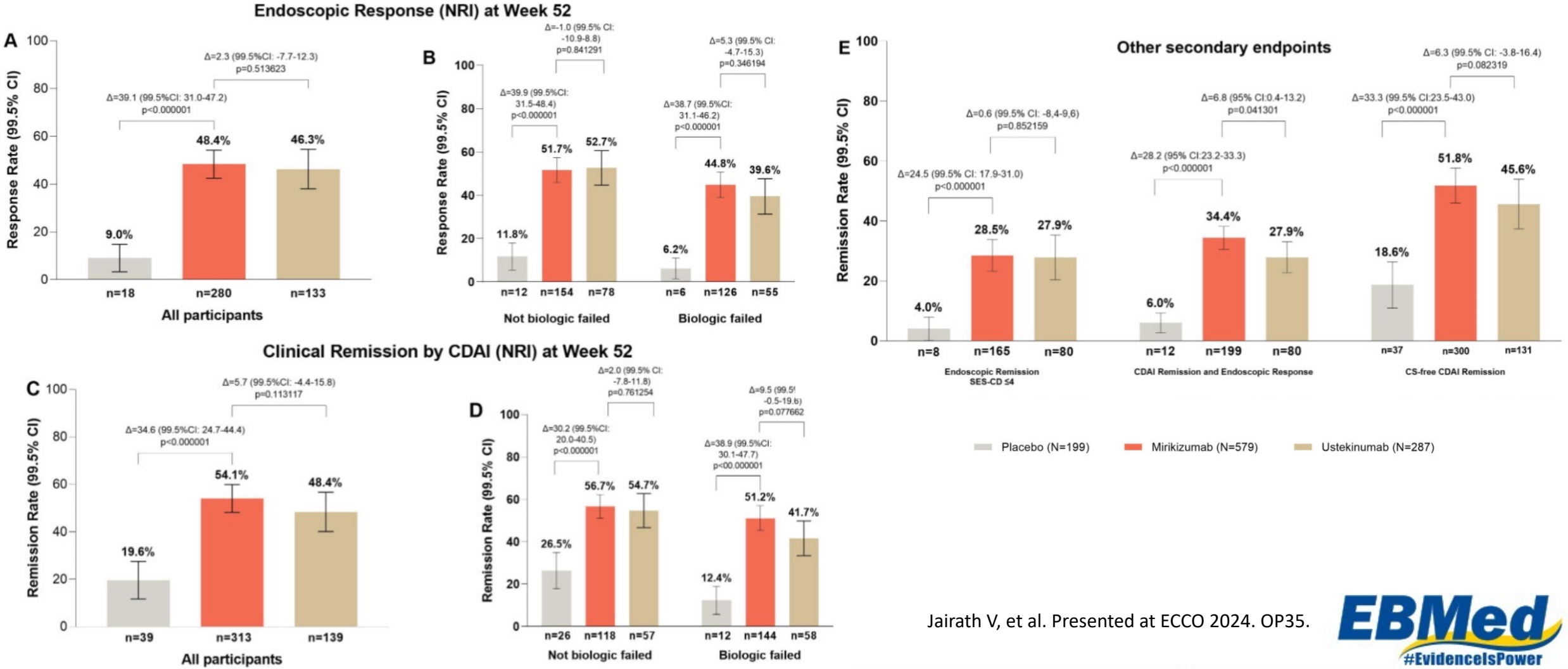
Mirikizumab Non-Inferior to Ustekinumab for Clinical Remission but Not Superior for Endo Response in CD Vivid-1 TST Phase 3 Study: Superior to Placebo



Jairath V, et al. Presented at ECCO 2024. OP35.

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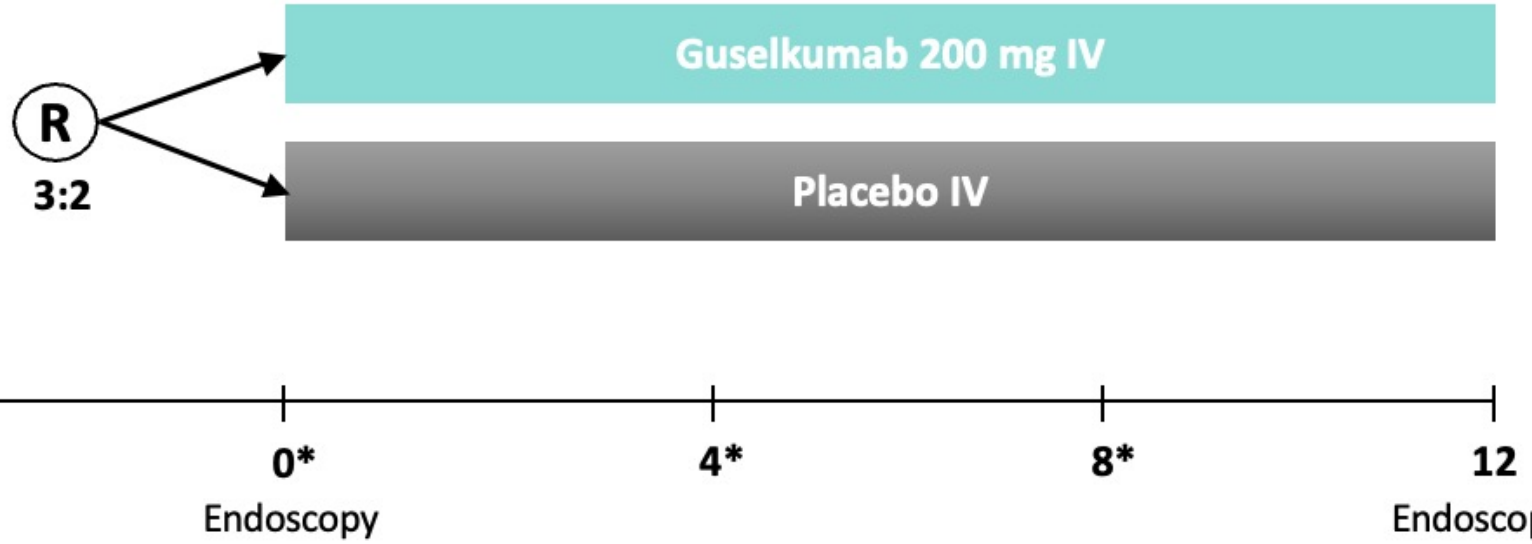
Guselkumab

Phase 3 QUASAR UC Guselkumab Induction Study

Target patient population:

- 18 years of age or older
- Moderately to severely active UC, defined as baseline modified Mayo score of 5 to 9 with a Mayo rectal bleeding subscore ≥1 and a Mayo endoscopy subscore ≥2 based on central review

Note: Concomitant conventional immunosuppressants, oral 5-aminosalicylic compounds, and corticosteroids up to 20 mg/day of prednisone (or equivalent) were permitted

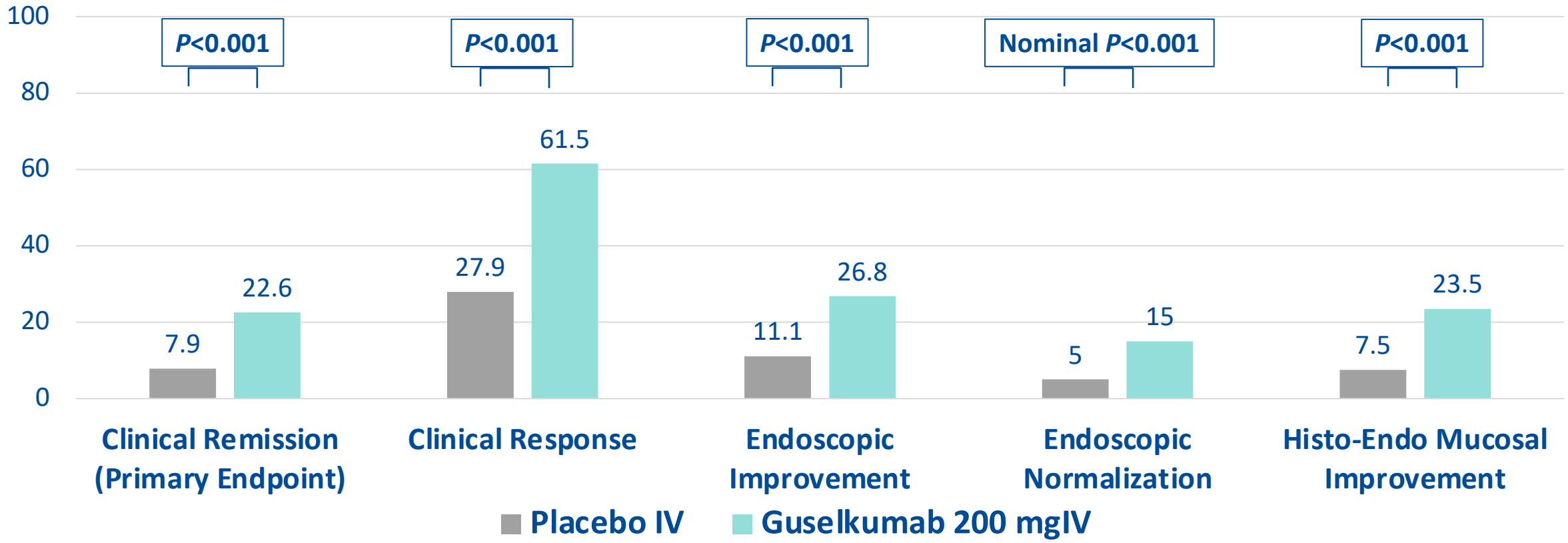


R = Randomization stratified by history of inadequate response or intolerance to advanced therapy, region, and concomitant use of corticosteroids at baseline

* = Study treatment (Guselkumab IV or Placebo IV) administration

Peyrin-Biroulet L, et al. Presented at UEGW 2023. OP039.

GUS 200 mg IV Achieved Significant Improvement in Clinical & Histo-endoscopic Outcomes at Wk12 for Moderate-to-Severe UC



- No new safety signal through Week 12

Peyrin-Biroulet L, et al. Presented at UEGW 2023. OP039.

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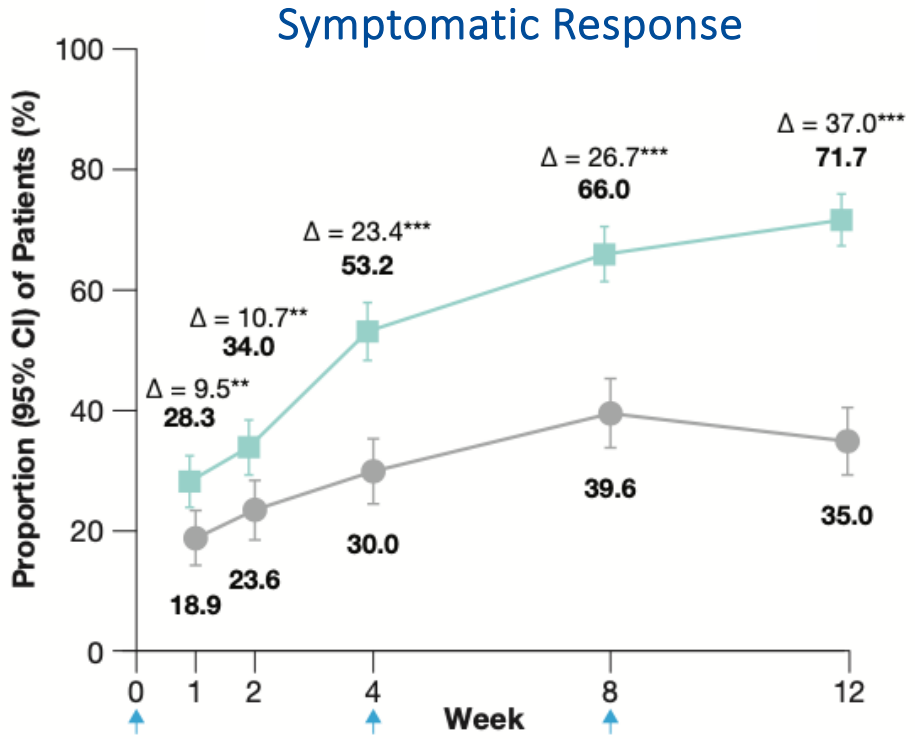
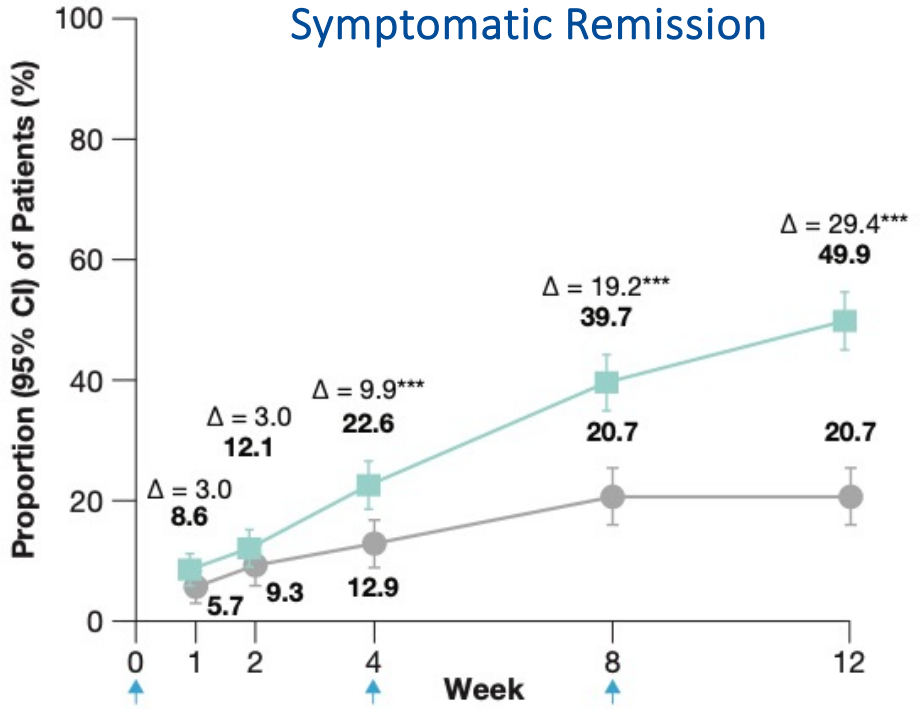
Symptomatic Improvement as Early as Wk1 with Guselkumab Induction in Moderate-to-Severely Active UC





- **In patients with moderately to severely active UC, guselkumab 200 mg IV induction was effective in improving symptoms as early as 1 week after the first dose**
- **Symptomatic improvements continued to increase through Week 12 with guselkumab treatment**

Lichtenstein GR, et al. Presented at UEGW 2023. MP082.

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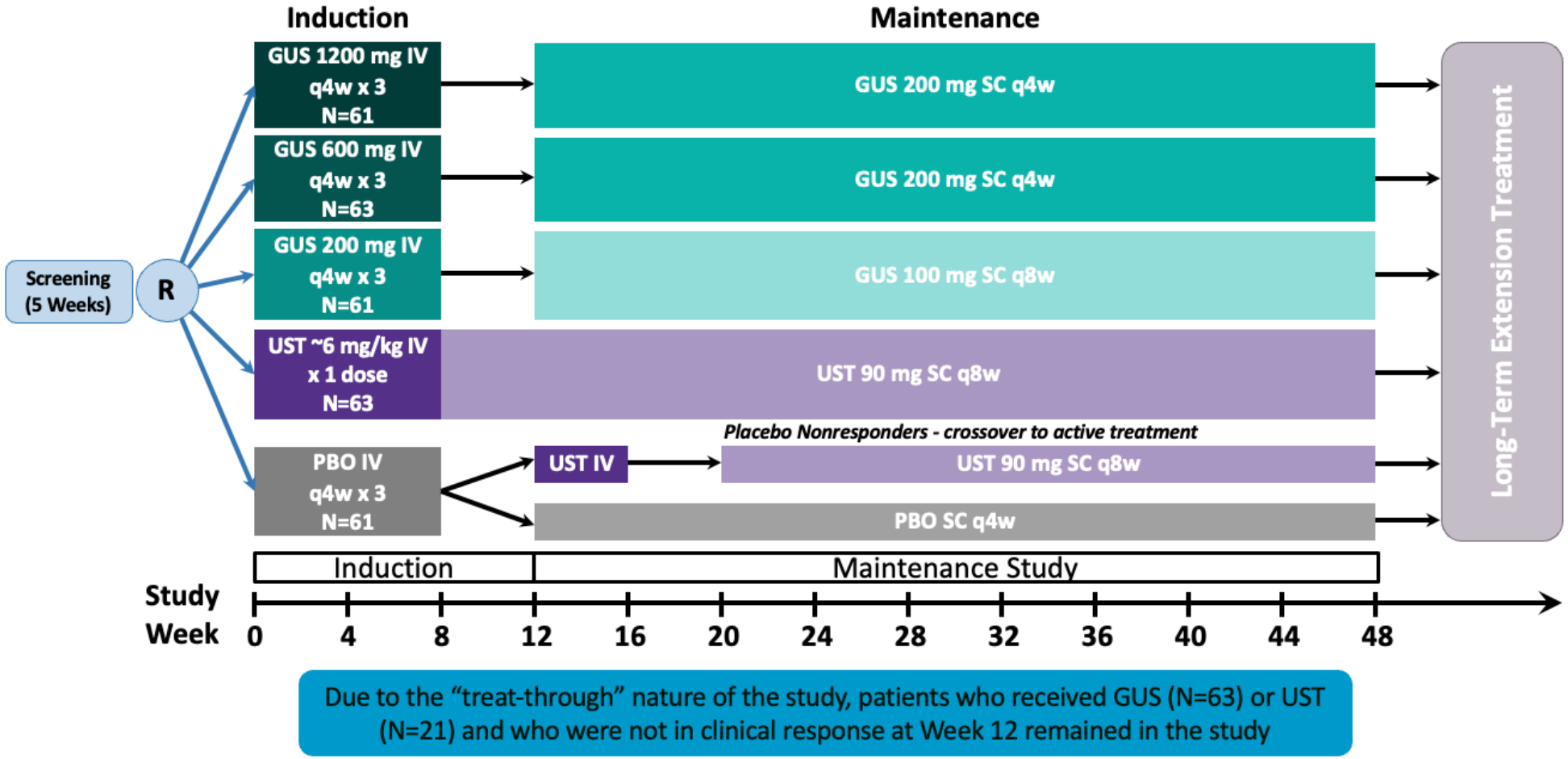
Phase 2b GALAXI 1 CD Guselkumab: Treat-Through Design



Due to the "treat-through" nature of the study, patients who received GUS (N=63) or UST (N=21) and who were not in clinical response at Week 12 remained in the study

Sandborn WJ, et al. *Gastroenterology*. 2022;162:1650-1664.e8

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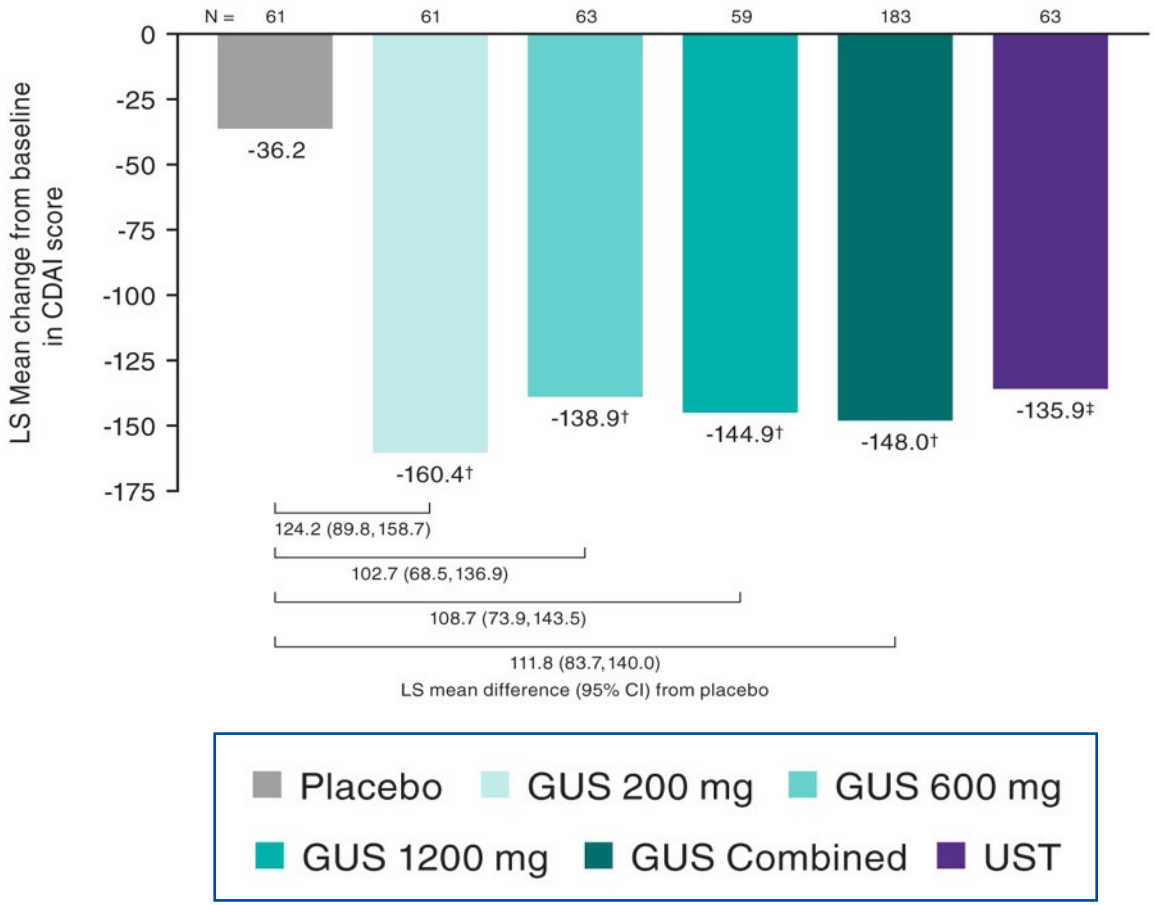
Guselkumab for the Treatment of Crohn's Disease: Induction Results From the Phase 2b GALAXI-1 Study

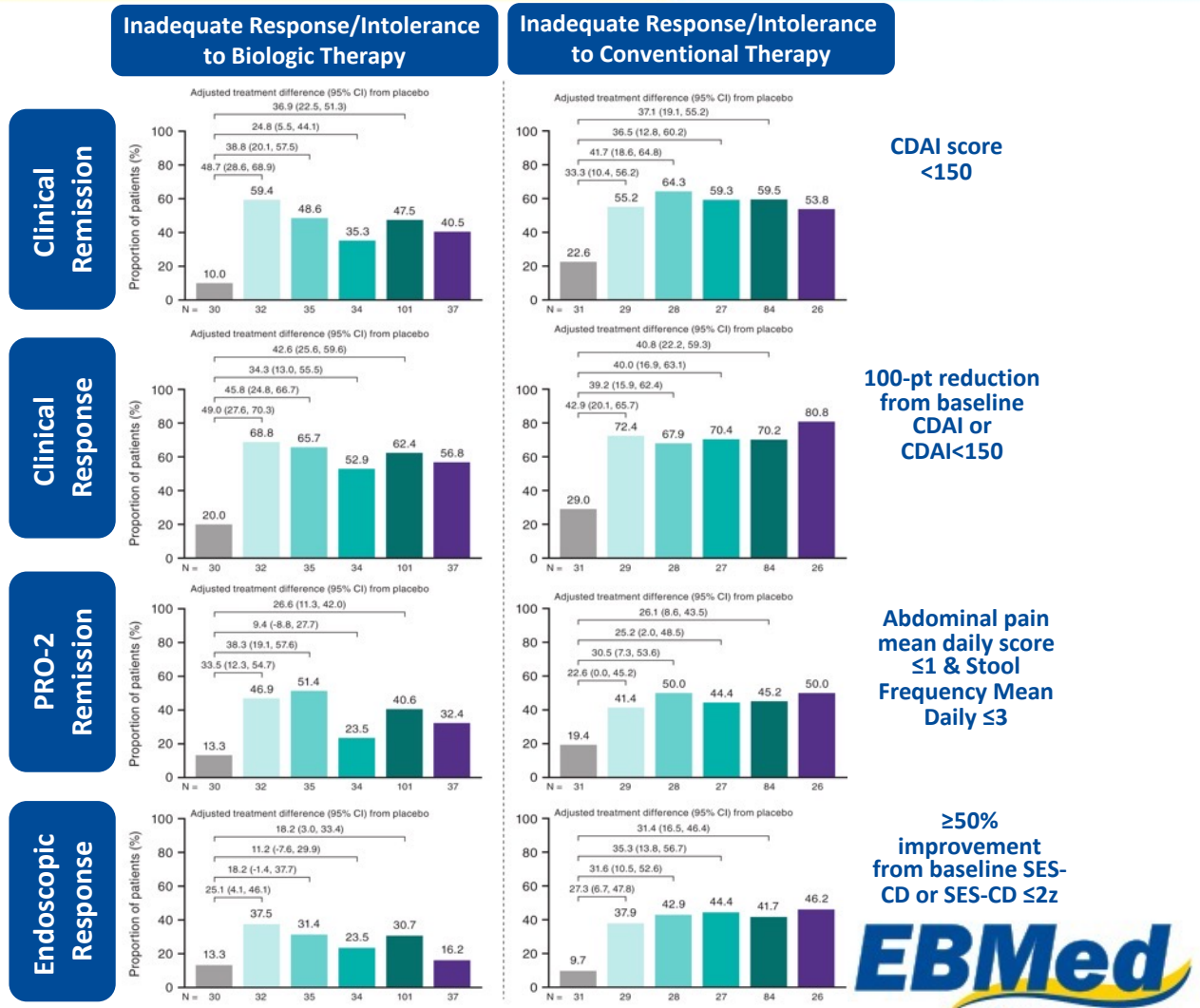
Change from Baseline CDAI Score



† p-value <.05 for GUS vs placebo

‡ Nominal p-value <.05 from post hoc analysis of UST vs placebo

Sandborn WJ, et al. *Gastroenterology* 2022;162:1650-1664.



Guselkumab Maintenance (W48) in CD Achieves Corticosteroid-Free Remission: Phase 2b GALAXI 1 Study

W48 Outcomes, n (%)	200mg IV q4w → 100mg SC q8w n=61	600mg IV q4w → 200mg SC q4w n=63	1200mg IV q4Ww → 200mg SC q4w n=61	UST 6mg/kg IV → 90mg q8w n=63
CDAI clinical remission (<150)	39 (64%)	46 (73%)	35 (57%)	37 (59%)
Corticosteroid-free clinical remission (<150)	36 (59%)	45 (71%)	34 (56%)	37 (59%)

Afzali A, et al. Presented at DDW 2023. Tu1707.

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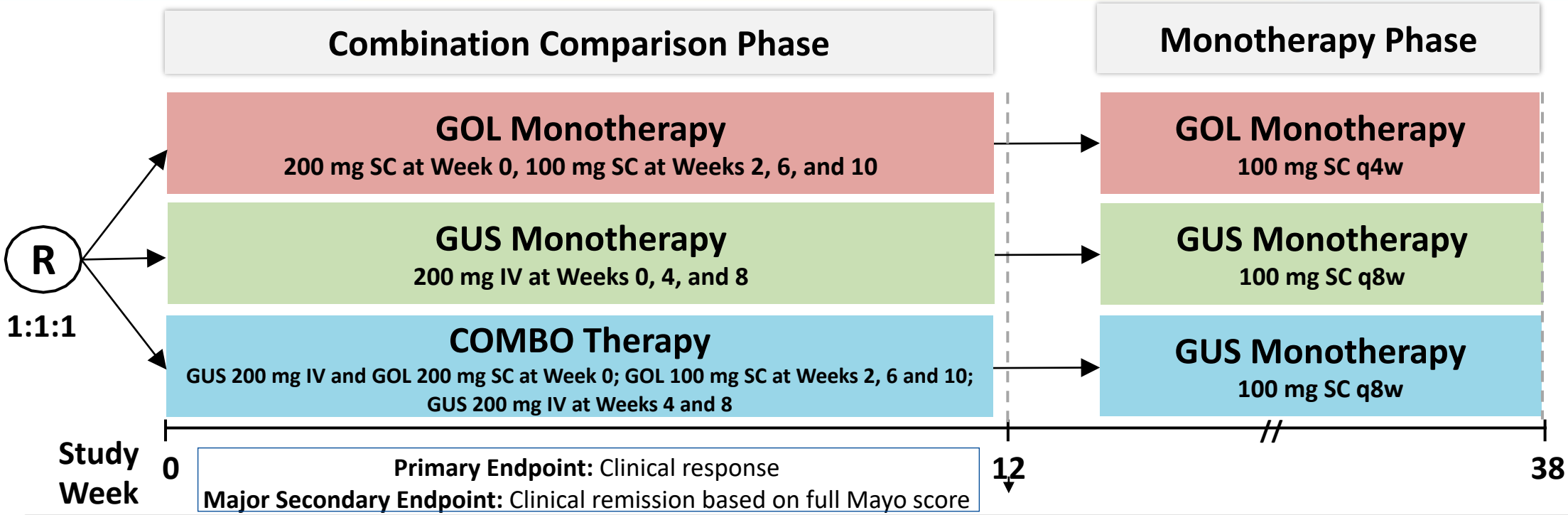
VEGA: GUS + GOL vs GUS vs GOL in Moderate to Severely Active Ulcerative Colitis



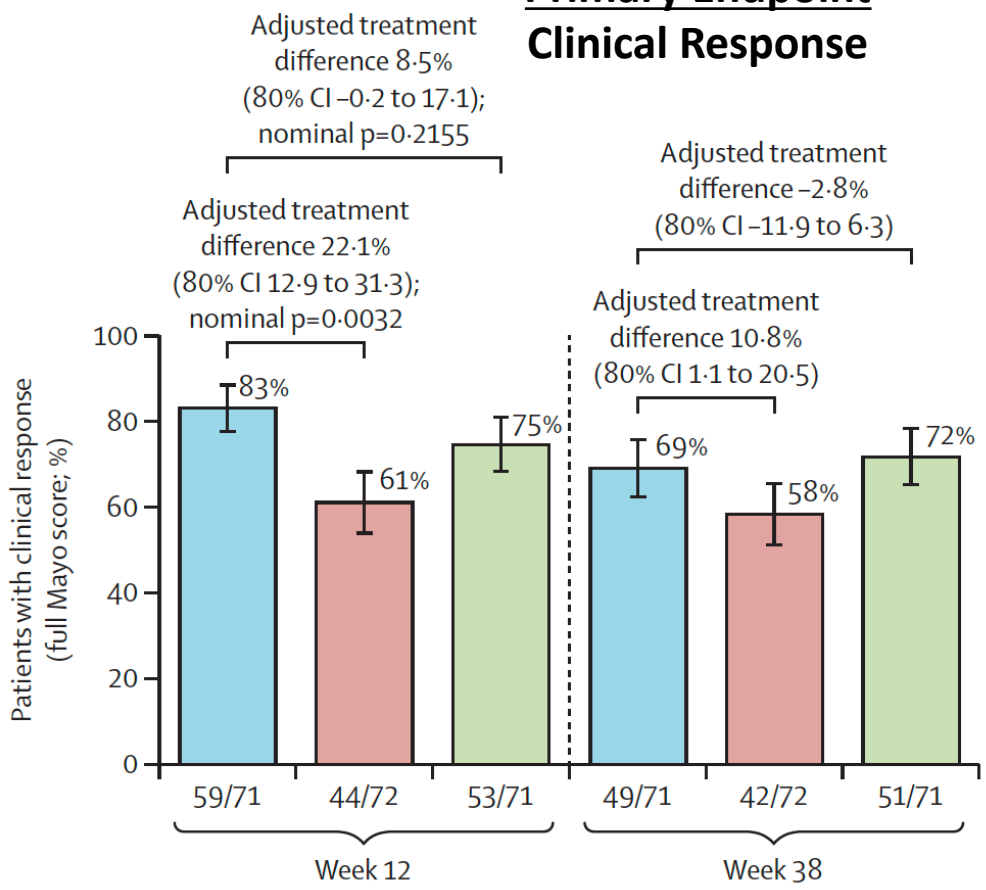
Patient Population

- Moderately-to-severely active UC (Mayo score 6-12, inclusive, and an endoscopy subscore ≥2 by central review)
- Naïve to TNFα antagonists and have had an inadequate response or intolerance to conventional therapy (immunosuppressants [AZA, 6-MP] and/or corticosteroids)
- Immunosuppressants must have been discontinued prior to randomization
- Corticosteroids up to a dose of prednisone (or equivalent) of 20 mg/day permitted with mandatory tapering beginning at Week 6

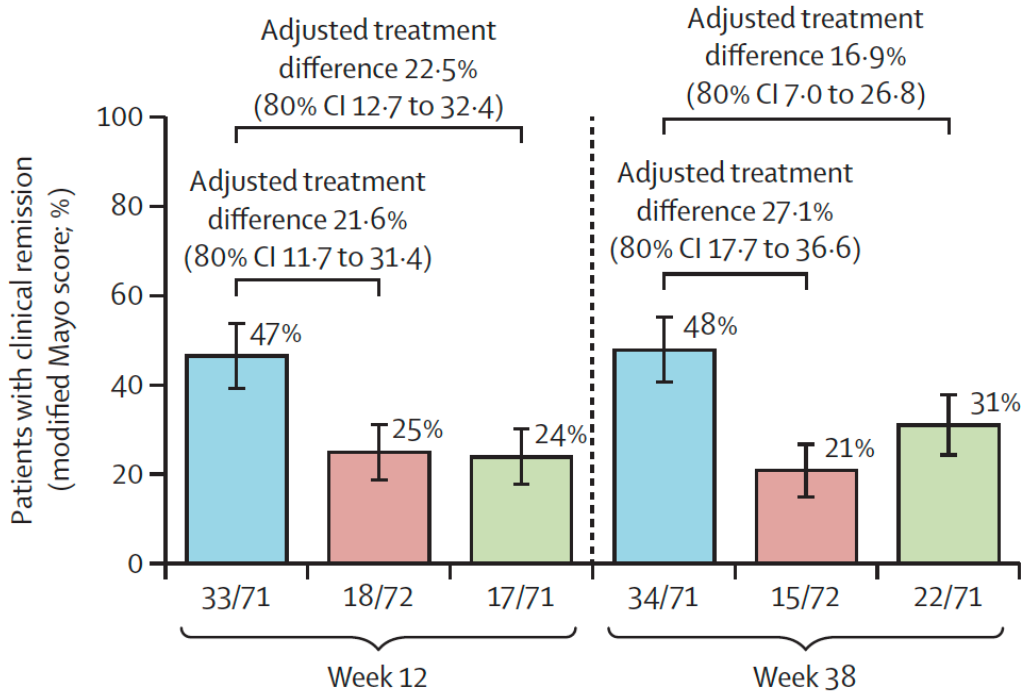
Feagan BG, et al. *Lancet Gastroenterol Hepatol*. 2023;8:307-320.

Guselkumab Plus Golimumab vs Guselkumab or Golimumab Monotherapy in Moderate to Severe UC

Primary Endpoint
Clinical Response



Major Secondary Endpoints
Clinical Remission (Modified Mayo Score)



Combination therapy | Golimumab monotherapy | Guselkumab monotherapy

Feagan BG, et al. *Lancet Gastroenterol Hepatol*. 2023;8:307-320.

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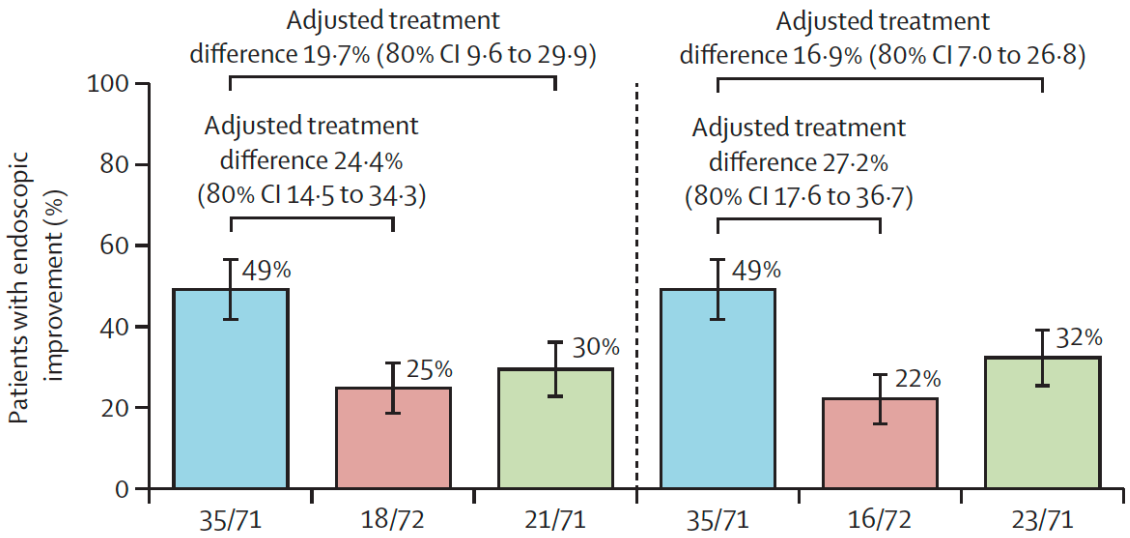
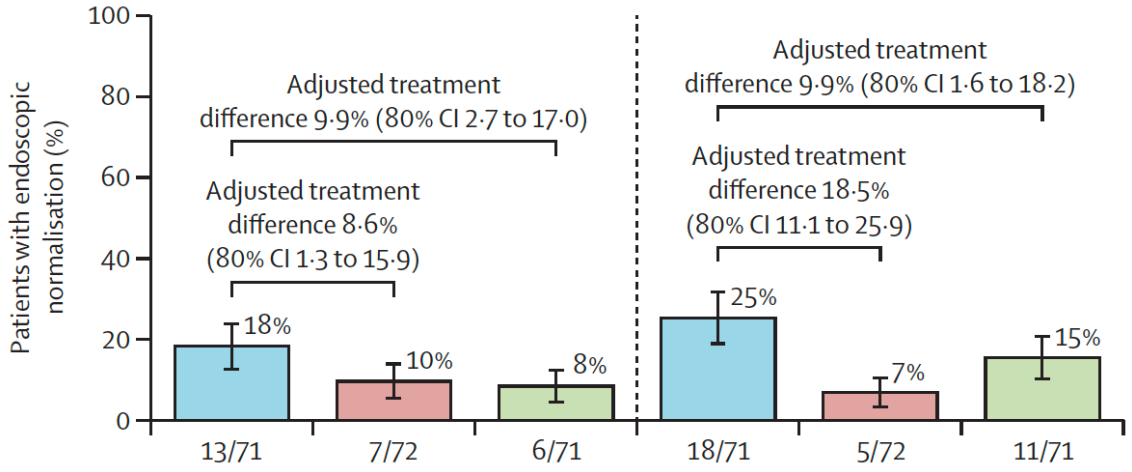
Guselkumab Plus Golimumab vs Guselkumab or Golimumab Monotherapy in Moderate to Severe UC

Major Secondary Endpoints

Endoscopic Improvement



Endoscopic Normalization



Combination therapy | Golimumab monotherapy | Guselkumab monotherapy

Feagan BG, et al. *Lancet Gastroenterol Hepatol*. 2023;8:307-320.

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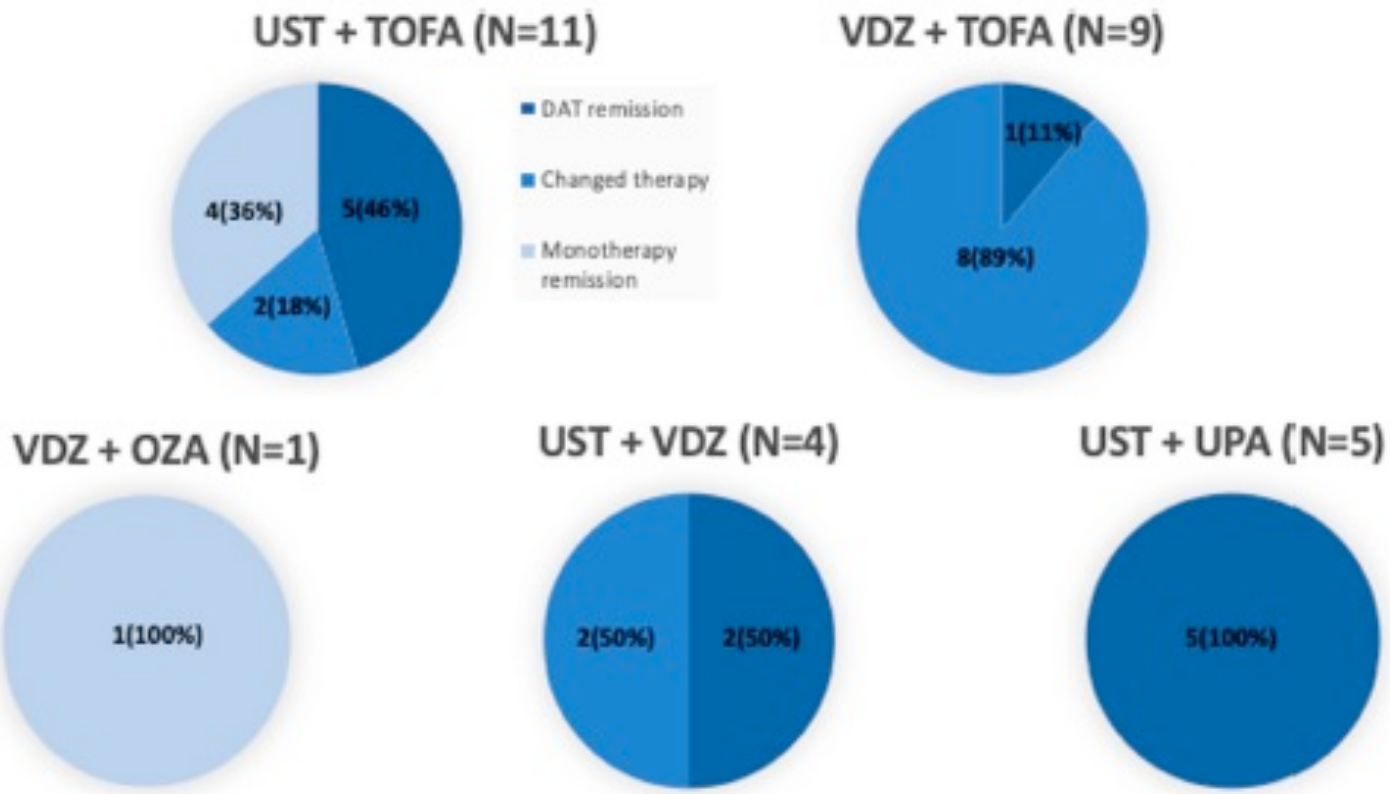
The Role of IL-23 as Platform Drug



Keller A, et al. *Dig Dis Sci*. Published online March 23, 2024.

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Summary: The IL-23 Revolution

- Risankizumab approved for CD and SEQUENCE demonstrated superior to UST
- Risankizumab UC Awaiting Approval: Induction dose 1200MG vs 600MG for CD
- Mirikizumab approved for UC and await CD approval as shown superiority to placebo and same safety as UC
- Mirikizumab not superior to ustekinumab as it relates to endoscopic outcomes in CD
- Guselkumab: Induction Data for UC shows superiority and await Maintenance Data
- Guselkumab CD awaiting Phase 3 induction and Maintenance Data
- Combination IL-23 with TNF or JAK 1 promising as future combination therapy

Treat to Target: Endoscopic & *Histologic* Remission

Bincy P. Abraham, MD, MS, AGAF, FACG, FASGE
Professor of Clinical Medicine- Weill Cornell
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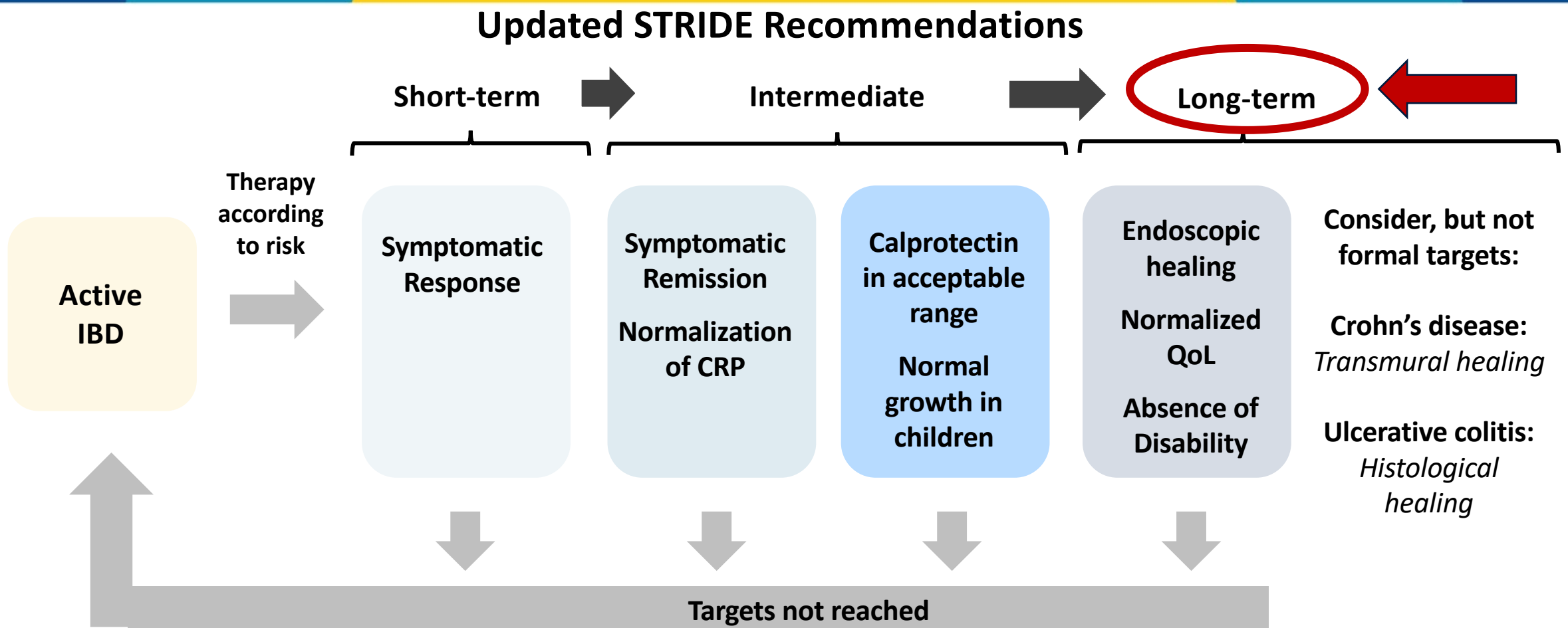
Adjunct Professor of Medicine– Texas A&M School of Medicine
@IBD_Houston

Treating to Target in IBD



STRIDE = Selecting Therapeutic Targets in Inflammatory Bowel Disease Initiative

Turner D, et al. *Gastroenterology* 2021;160:1570-1583.

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Treat to Target Update in UC: A Systematic Review

	STRIDE Consensus Targets	Accumulating Evidence	Optimized Targets
Clinical Targets and PROs	Resolution of rectal bleeding and normalization of bowel habits should be the target. Monitor every 3 months until symptom resolution and every 6 months thereafter.	Discrepancy between symptom normalization and endoscopic activity.	Validated PRO scores and tools/technologies for PRO reporting.
Endoscopic Targets	Absence of ulceration is the target (minimum score of 1). Assessments should be done every 3-6 months after start of therapy.	Utility of UCEIS and modified Mayo scores. More stringent endoscopic resolution associated with better outcomes (Mayo score = 0).	Validated UCEIS and Mayo scores. Mayo score = 0
Histological Targets	Not recommended as a target because of insufficient evidence.	Histological healing associated with endoscopic healing and can predict long-term outcomes.	Validated histological index. Nancy and Robarts scores as promising potential tools in clinical practice and clinical trials

Ungaro R, et al. *Am J Gastroenterol*. 2019;114:874-883.

ACG Guidelines

Table 2. Summary and strength of GRADED recommendations for the management of ulcerative colitis

Diagnosis, assessment, and prognosis of ulcerative colitis
1. We recommend stool testing to rule out *Clostridioides difficile* in patients suspected of having UC (strong recommendation, very low quality of evidence).
2. We recommend against serologic antibody testing to establish or rule out a diagnosis of UC (strong recommendation, very low quality of evidence).
3. We recommend against serologic antibody testing to determine the prognosis of UC (strong recommendation, very low quality of evidence).
Goals for managing patients with ulcerative colitis
4. We suggest treating patients with UC to achieve mucosal healing (defined as resolution of inflammatory changes (Mayo endoscopic subscore 0 or 1)) to increase the likelihood of sustained steroid-free remission and prevent hospitalizations and surgery (conditional recommendation, low quality of evidence).
5. We suggest FC as a surrogate for endoscopy when endoscopy is not feasible or available to assess for mucosal healing (conditional recommendation, very low quality of evidence).

Rubin DT, et al. *Am J Gastroenterol*. 2019;114:384-413.

IOIBD Stride II Updated Guidelines

Endoscopic and transmural assessment		
7. **Endoscopic healing is a long-term target.** Consider changing treatment if this target has not been achieved.	8.7	87
8. Assessment of endoscopic healing can be achieved by sigmoidoscopy or colonoscopy. When not feasible, alternatives in CD can be capsule endoscopy or balloon enteroscopy.	8.3	86
9. Endoscopic healing should be measured by: **a)** CD: SES-CD <3 points or absence of ulcerations (e.g. SES-CD ulceration subscores = 0) b) UC: Mayo endoscopic subscore = 0 points, or UCEIS ≤1 points	8.5	85
10. Histologic remission is not a treatment-target in either CD or UC. Nonetheless, in UC it could be used as an adjunct to endoscopic remission to represent a deeper level of healing.	7.7	80
11. Transmural healing (assessed by CTE, MRE, or bowel ultrasound) is not a treatment-target in either CD or UC. Nonetheless, in CD it should be used as an adjunct to endoscopic remission to represent a deeper level of healing.	7.5	77

Turner D, et al. *Gastroenterology*. 2021;160:1570-1583.

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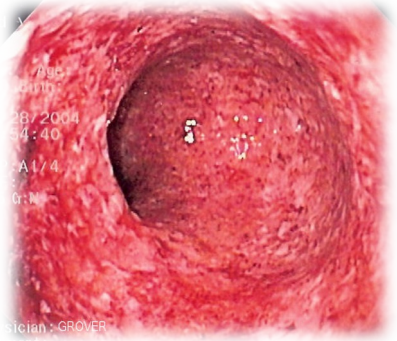
Goals of Therapy in IBD

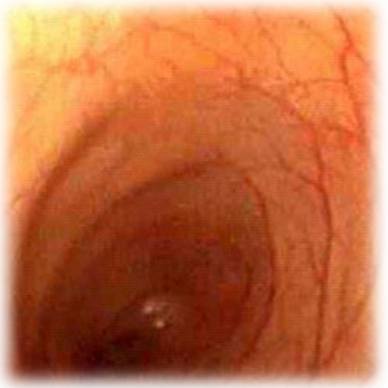
Clinical Remission

- Lack of Symptoms
- Improved Quality of Life



Endoscopic Remission

- Reduce Hospitalizations & Surgery
- Delay of Clinical Relapse



Histologic Healing

- Reduce Dysplasia/ Cancer risk

Allez M, et al. *Am J Gastroenterol*. 2002;97:947-953; Frøslie KF, et al. *Gastroenterology*. 2007;133:412-422.

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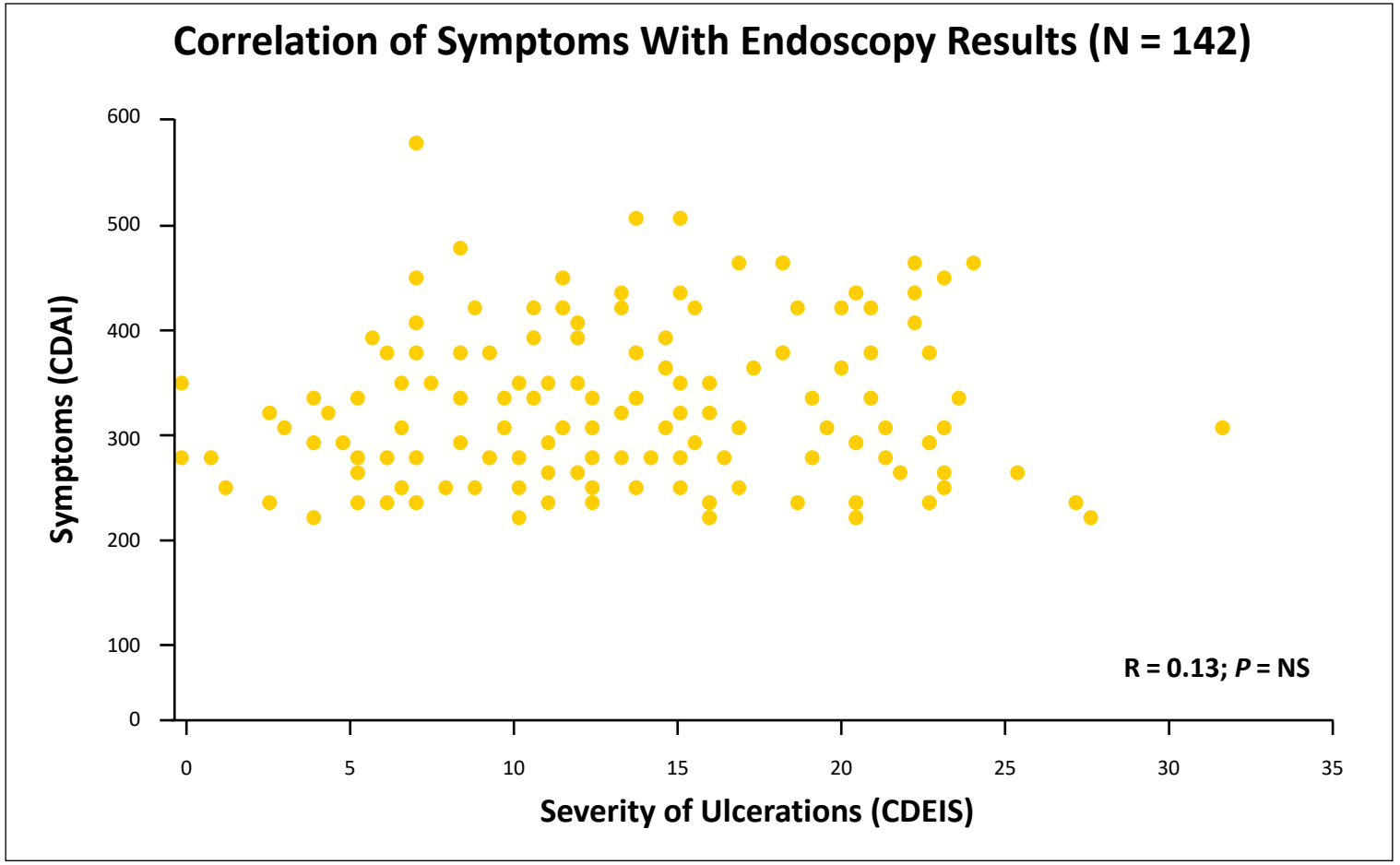
Symptoms Do Not Correlate With Inflammation!



Modigliani R, et al. *Gastroenterology*. 1990;98:811-818.

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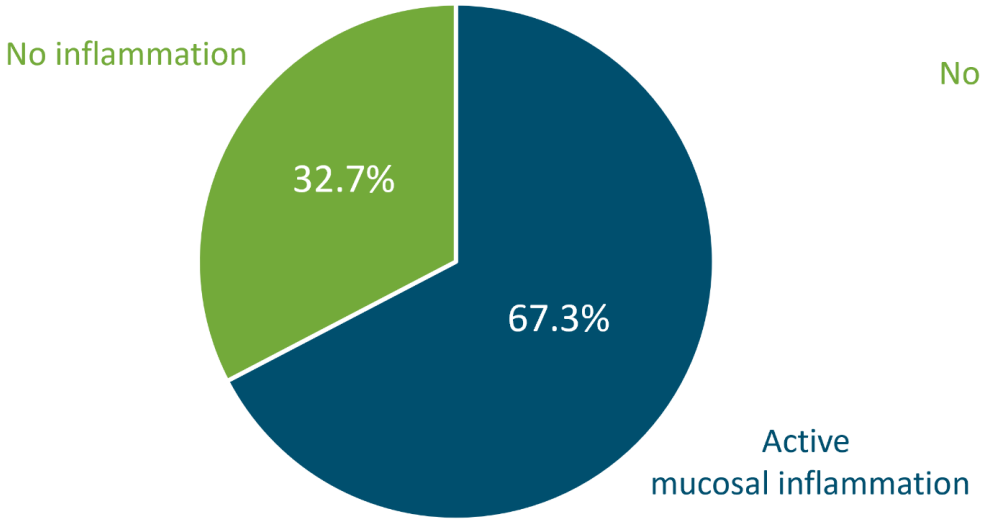
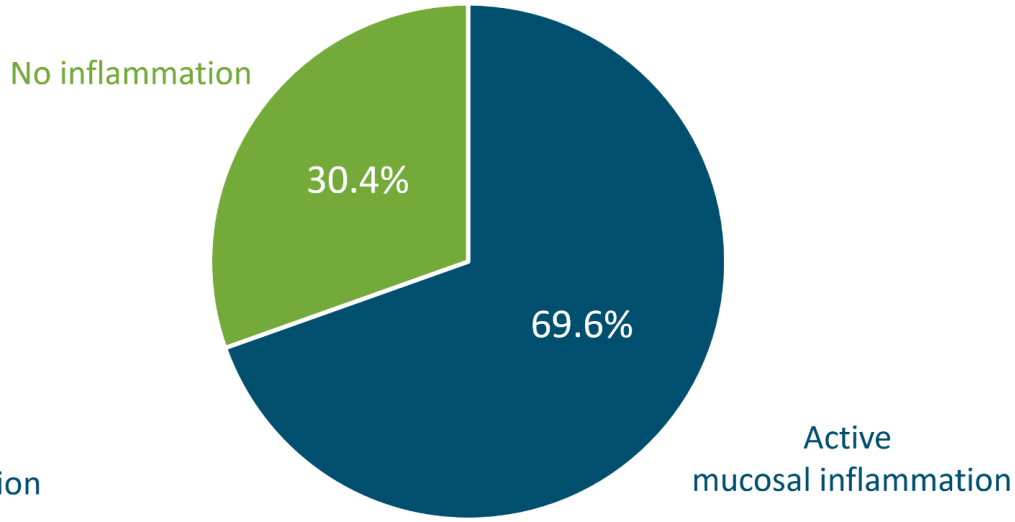
Importance of Mucosal Evaluation

A 3-year longitudinal study from the Netherlands identified UC (n=98) and CD patients (n=46) who underwent a surveillance colonoscopy* between 2001 and 2003 and found:

UC Patients in Clinical Remission (n=98)



CD Patients in Clinical Remission (n=46)



CD = Crohn's disease; IBD = inflammatory bowel disease; UC = ulcerative colitis.

Baars JE, et al. *Inflamm Bowel Dis*. 2012;18:1634-1640.

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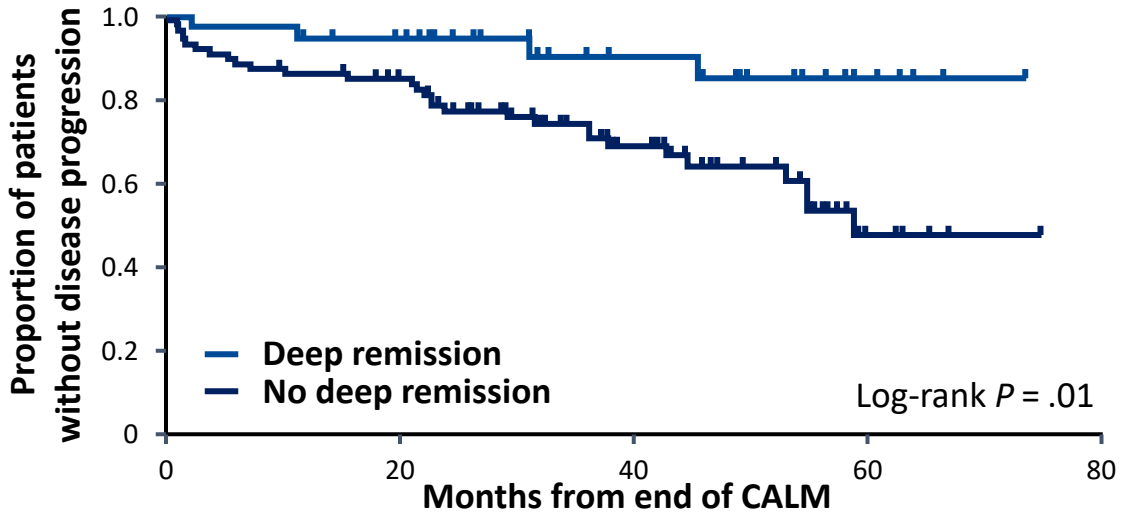
CALM Follow-up: Impact of Induction of Deep Remission on Disease Progression in CD

Kaplan-Meier Estimates of CD Disease Progression Based on Deep Remission at 1 Year



CD patients achieving endoscopic or deep remission after 1 year of tight control are less likely to have disease progression over a median of 3 years
(Disease Progression: new internal fistula/abscess, stricture, perianal fistula/abscess, CD hospitalization, or CD surgery**)**

Ungaro RC, et al. *Gastroenterology*. 2020;159:139-147.

JOHNS HOPKINS
MEDICINE

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FAKE NEWS

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Key Considerations:
Weigh Benefits & Risks Based on Disease Severity

UC: Poor prognostic factors

- Age <40 years
- Extensive colitis
- Severe endoscopic disease (Mayo endoscopic subscore 3, UCEIS ≥7)
- Hospitalization for colitis
- Elevated CRP levels
- Low serum albumin levels

CD Poor prognostic factors

- Young age
- Initial extensive bowel involvement
- Perianal or severe rectal disease
- Penetrating or stenosing at diagnosis
- ***Only 20% to 30% of CD patients will have an indolent course**

Advanced Therapies Cost Effective to Prevent Complications!

D'Amico F, et al. *J Clin Med*. 2023;12:3094.

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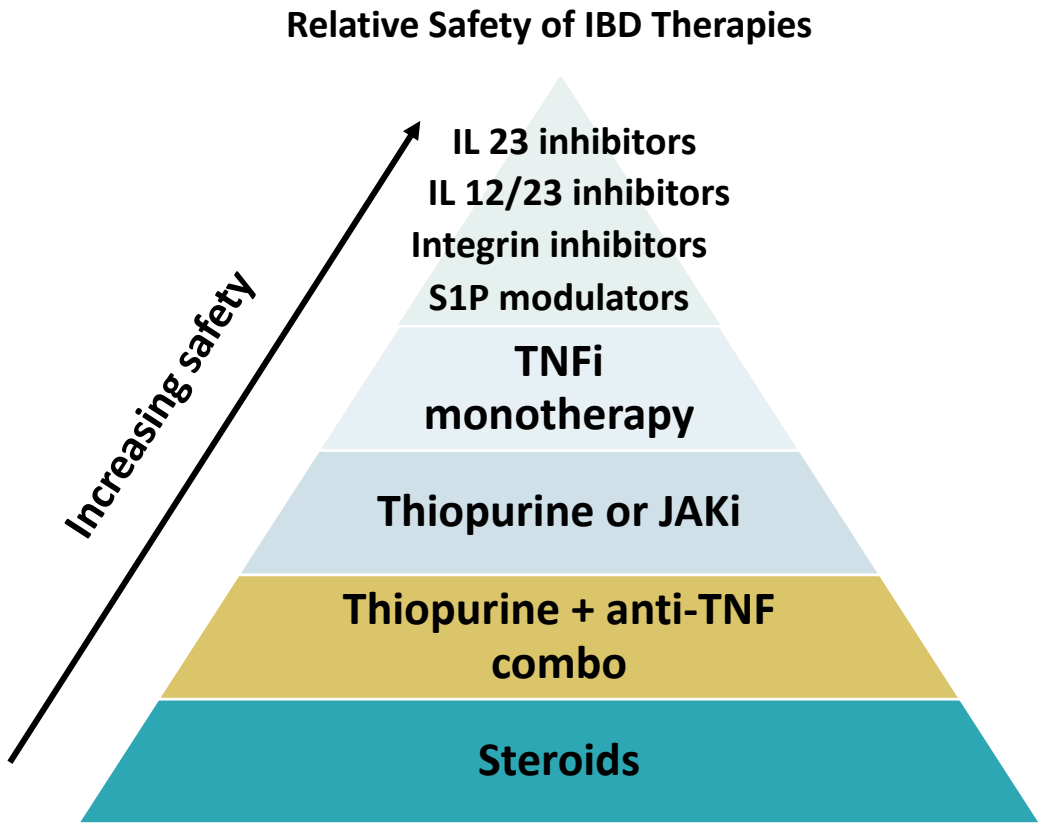
Safety Considerations of Advanced IBD Therapies



Infection Risks can be reduced with:

- **Pre-treatment screening for latent infections**
- **Vaccinations**

64 RCTs of adult patients with IBD

22 RCTs / 12,196 patients with CD

32 RCTs / 22,000 patients with UC

Use of biologic and small molecule therapies had no significant impact on the risk of MACEs during induction and maintenance periods**

FDA Online Label Repository. Available at: https://labels.fda.gov. Accessed 7/8/2021. Figure modified from Click B, Regueiro M. *Inflamm Bowel Dis.* 2019;5:831-842.
Olivera PA, et al. *Aliment Pharmacol Ther*. 2023;57:1231-1248; Shehab M, et al. *Expert Rev Gastroenterol Hepatol*. 2023:10;1-9.

EBMed #EvidenceIsPower

Summary: Treating to Target

- Determine disease severity to guide IBD management: Assess early for poor prognostic risk factors for more aggressive disease
- Goals include endoscopic as well as PRO remission
- “Silent” inflammation is associated with disease-related complications
- CALM: those in deep remission were less likely to progress over next 3 years!
- Strategically monitor for mucosal healing with biomarkers/ imaging/ colonoscopy to prevent complications.

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Aline Charabaty, MD, FACG, AGAF @DCharabaty · Jul 21, 2018

Clinical challenges in #IBD @IBDMD JF Colombel: **#T2T** treat to target: treat early to prevent disease complications, monitor frequently by using objective markers and adjust treatment accordingly

What is treat to target (T2T)?

Aim	Concept	Strategy	Additional principles
To avoid development of serious complications and disability in patients with chronic conditions	Treating to a pre-defined treatment target that is associated with optimal long-term outcomes (goal-oriented approach)	Ongoing and regular monitoring of the target and/or surrogate marker, with optimisation of treatment when the target is not met	All components – target, treatment and monitoring – are tailored to the needs of the individual patient De-escalation of therapy may be considered when treatment goals are achieved

A T2T approach involves pre-defining a treatment target, in consultation with the patient, continuously monitoring disease activity, and modifying treatment until the target is reached

Bouguen G, et al. Clin Gastroenterol Hepatol 2015;13:1042–50; McCloskey EV, et al. Int J Clin Rheumatol 2015;10:1–4

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Aline Charabaty, MD, FACG, AGAF @DCharabaty · Oct 19, 2019 ···

Great summary of our **#T2T** & #IBD monitoring convo @EdwardLoftus2 by our #IBDAlgorithmMaster @DrMalSimons : Be CALM and carry on or push on ? @JeanFredericCo1 @moss_md @waqqasafif @ibdnaik @FITWITMD @fudmanMD @nahlaassam5 @HorstIBDDoc @NFuIBD @QueirozNataliaF @RajaAtreya @sqabbasi

IBD/CD Treat to Target and Monitoring Concepts

Active Disease

Early Intervention is Key

Assessing Response to Therapy

T2T: Individualized target to patient → Choose + Adjust therapy to reach target year one

GOAL TARGETs:
CLINICAL Remission
(Assess Post-induction + Q3-6months)
BIOLOGIC Remission
(Assess post-induction+ Q3-6months)
ENDOSCOPIC Remission
(Assess 6-12months post-induction)

What is Our "Target"?

- Be #CALM & Carry on?

Tight Control→ Escalate if FCP> 250 or CRP>5mg/L or symptoms

Clinical Management → Escalate if symptoms

Escalation: ADL 40 Qowk->40 qwk->40mg qwk+IMM

- Mucosal Healing = Absence of deep ulcers

-> TC: ↓CD-hospitalization &↑ MH at 1 yr

-> No Difference TC vs CM beyond 1 yr

- ? Advantages of escalating therapy for mild asymptomatic residual disease (aphthous ulcers; FCP 150-250)
- Complete MH can be difficult to achieve
- Follow FCP/CRP trend, adjust therapy if ↑

#MondayNightIBD @EdwardLoftus2
#IBDAlgorithm @DrMalSimons

On the Horizon:

- Proactive TDM: what's the target level during maintenance ?
- Use SBUS to monitor response
- Role of histologic remission?

Always bring it back to the Patient!

Remember! Tests may not correlate with symptoms

- #PatientExperience #IBDPoll: > 50% still feel poorly despite inactive disease on tests
- Other Targets to include: Systemic symptoms, Extraintestinal manifestations, Quality of life, Emotional and social health, Decrease financial toxicity

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@Dcharabaty #T2T

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Aline Charabaty, MD, FACG, AGAF @DCharabaty · May 22, 2019

#IBD #DDW19 : Treat to target **#T2T** got a step further (or deeper?): beyond endoscopic healing, normalization of histology is associated with ⬇️ risk of flare in #UlcerativeColitis

> **Waqqas Afif, MD** @waqqasafif · May 22, 2019
>
> Replying to @waqqasafif
>
> 4/4 UC histology: Complete normalization of histology associated with a reduced risk of relapse. Architectural changes and chronic inflammatory infiltrates associated with >risk of relapse. Histology will be an important target of therapy in the future in UC. #IBDupdate #DDW19

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IBD: Treat to Clinical (and Reasonable) Response

Aline Charabaty, MD, FACG, AGAF
Associate Professor of Clinical Medicine
Johns Hopkins School of Medicine
Clinical Director of the IBD Center
Johns Hopkins-Sibley Memorial Hospital, Washington DC

Twitter/X or IG: @DCharabaty

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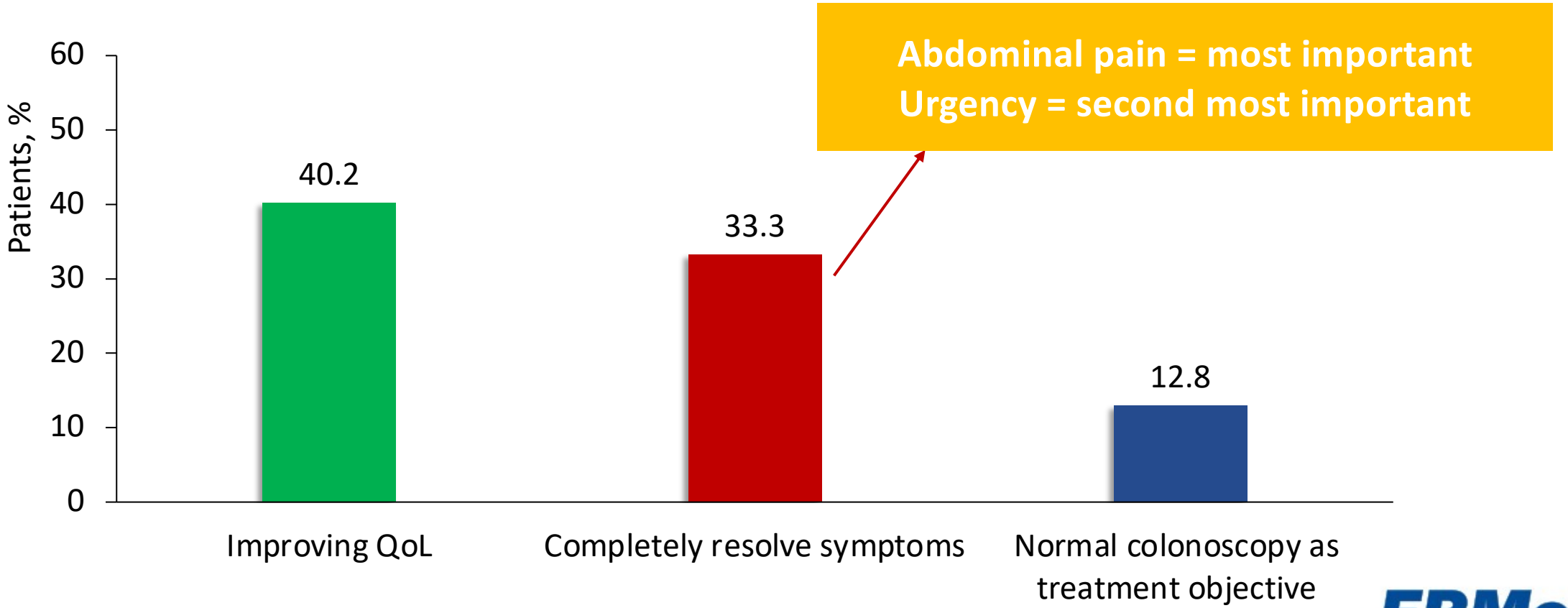
STRIDE II is Gold — But What about Patients' Goals?

Barcelona study: 117 outpatients with CD or UC



Casellas F, et al. *Dig Liver Dis*. 2017;49(2):152-156.

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Treat to Reasonable/Clinical Response

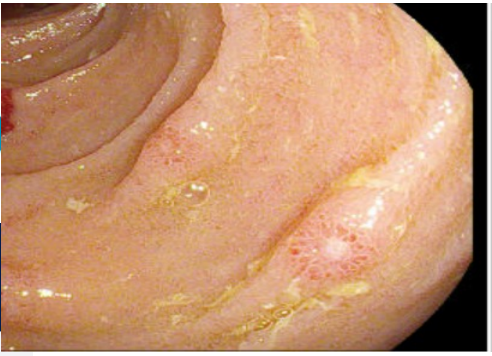
- How often can we achieve endo/mucosal healing with current therapies
- Is the next therapy more effective than prior therapies and risk of Cycling through biologics and small molecules
- Do new MOA or combination biologics better at breaking the therapeutic ceiling ?
- How effective are current therapies in preventing disease progression / complication ?
- When perfection is the enemy of good : cycling through effective therapies

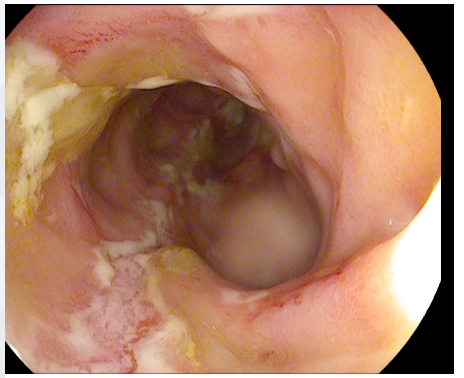
Crohn's Disease Endo Assessment: Simple Endoscopic Score SES-CD

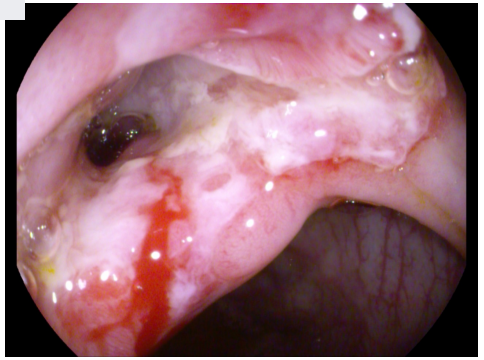
	Simple endoscopic score			
Variable	**0**	**1**	**2**	**3**
Size of ulcers	None	Aphthous ulcers	Large ulcers	Very large ulcers
Diameter of ulcers	None	0.1–0.5 cm	0.5–2 cm	>2 cm
Ulcerated surface	None	<10%	10–30%	>30%
Affected surface	Unaffected segment	<50%	50–75%	>75%
Narrow-ings	None	Single, can be passed	Multiple, can be passed	Cannot be passed

Modified from Daperno M, et al.[6]

Score	Decoding
0 - 2	remission
3 - 6	mild endoscopic activity
7 - 15	moderate endoscopic activity
> 15	severe endoscopic activity







Score calculated for EACH segment : ileum, right colon, transverse, left colon and rectum- total added

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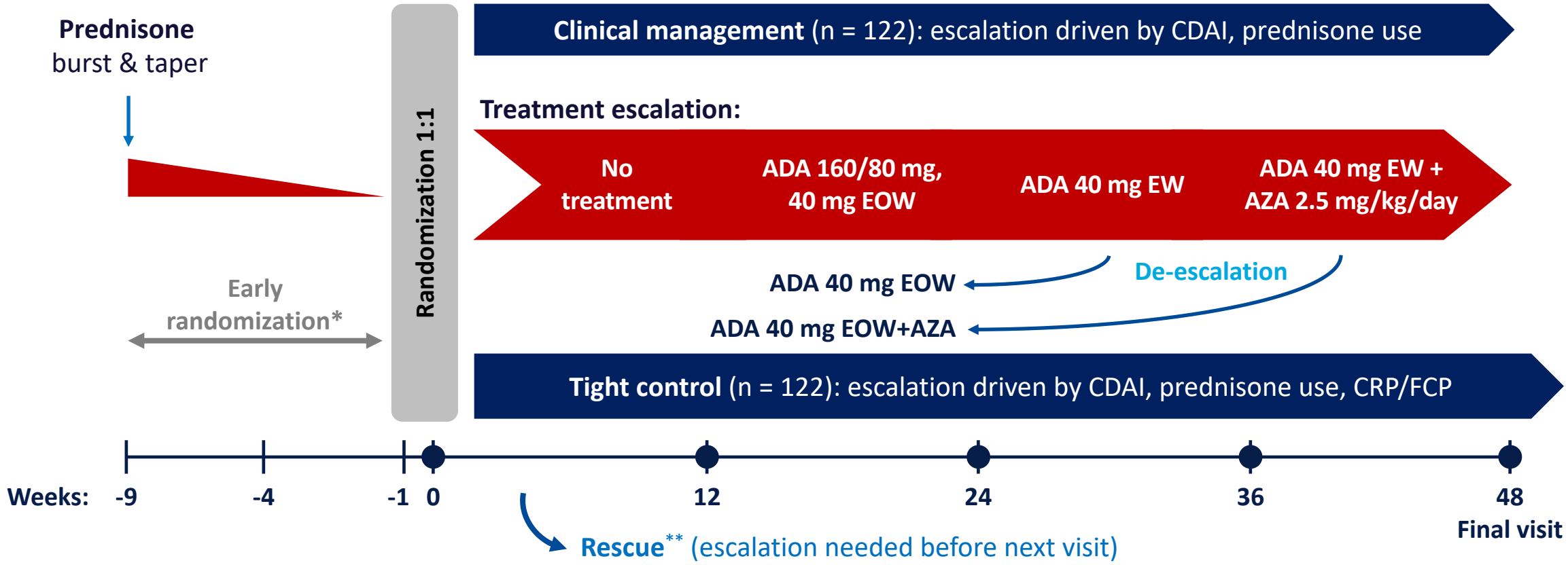
CALM: Clinical vs T2T/Tight Control in CD

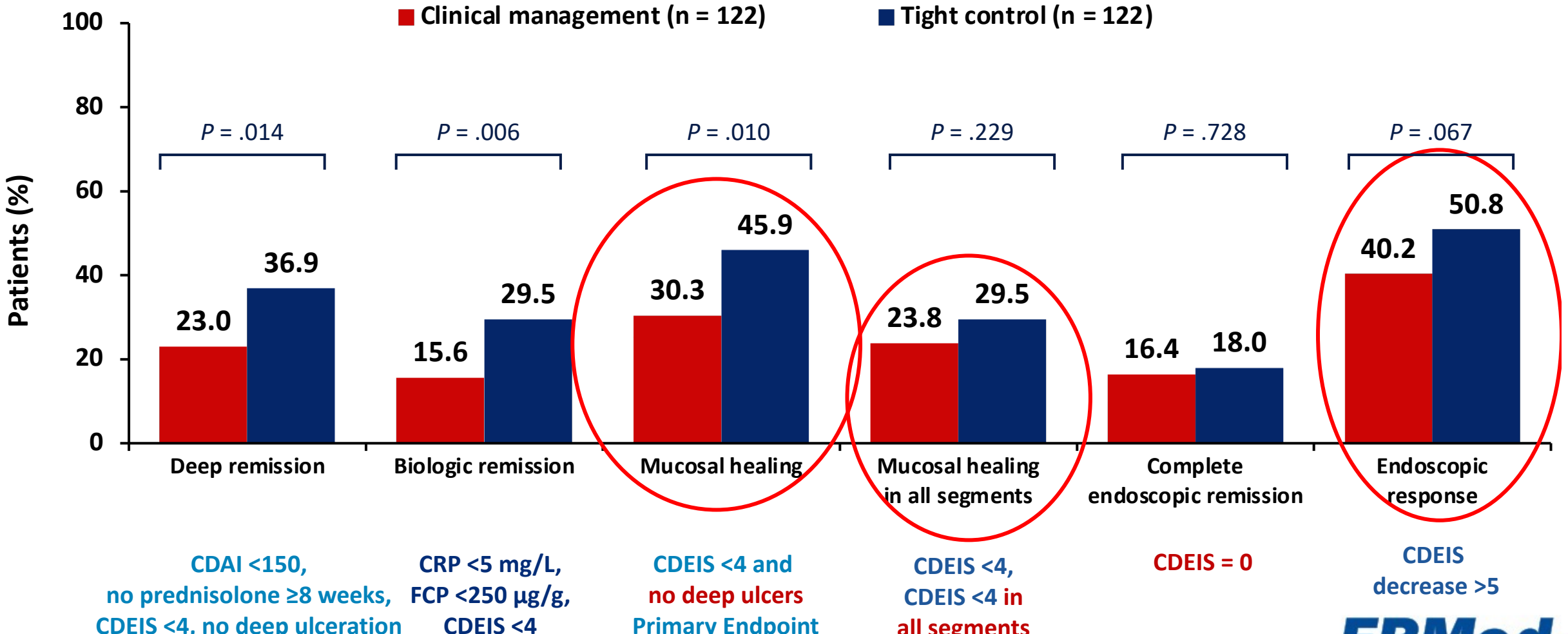


FCP ≥ 250 µg/g
CRP ≥ 5 mg/L
CDAI > 200 in clinical management group ; CDAI ≥ 150 in tight control

AZA, azathioprine; EOW, every other week; EW, every week; FCP, fecal calprotectin.

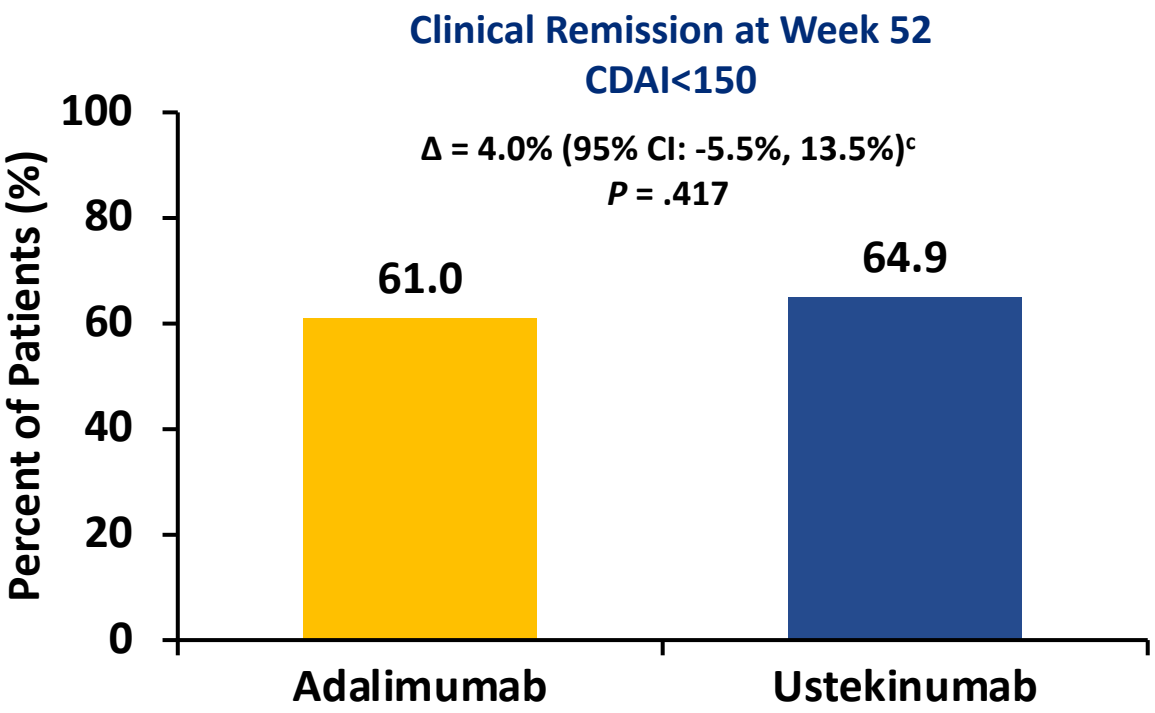
Colombel JF, et al. *Lancet.* 2017;390:2779-2789.

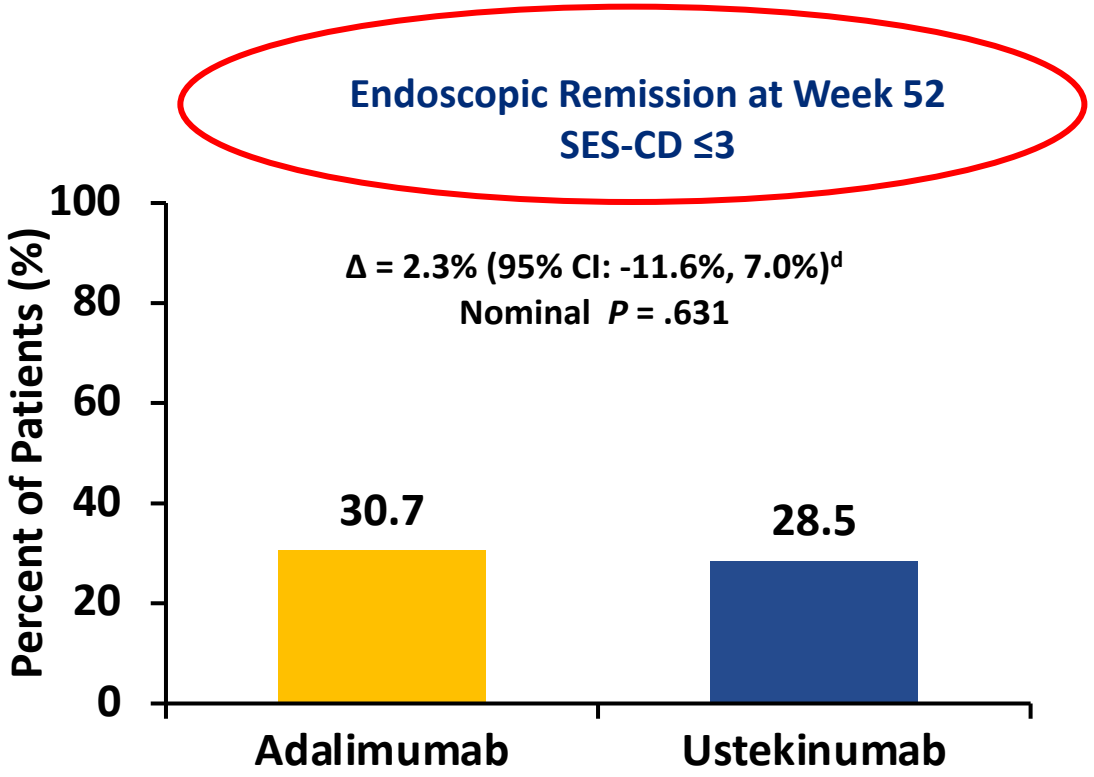
CALM: Even a T2T Strategy With Effective Therapies Lead to Endo Response < 50% of Patients



Colombel JF, et al. *Lancet*. 2017;390:2779–89.

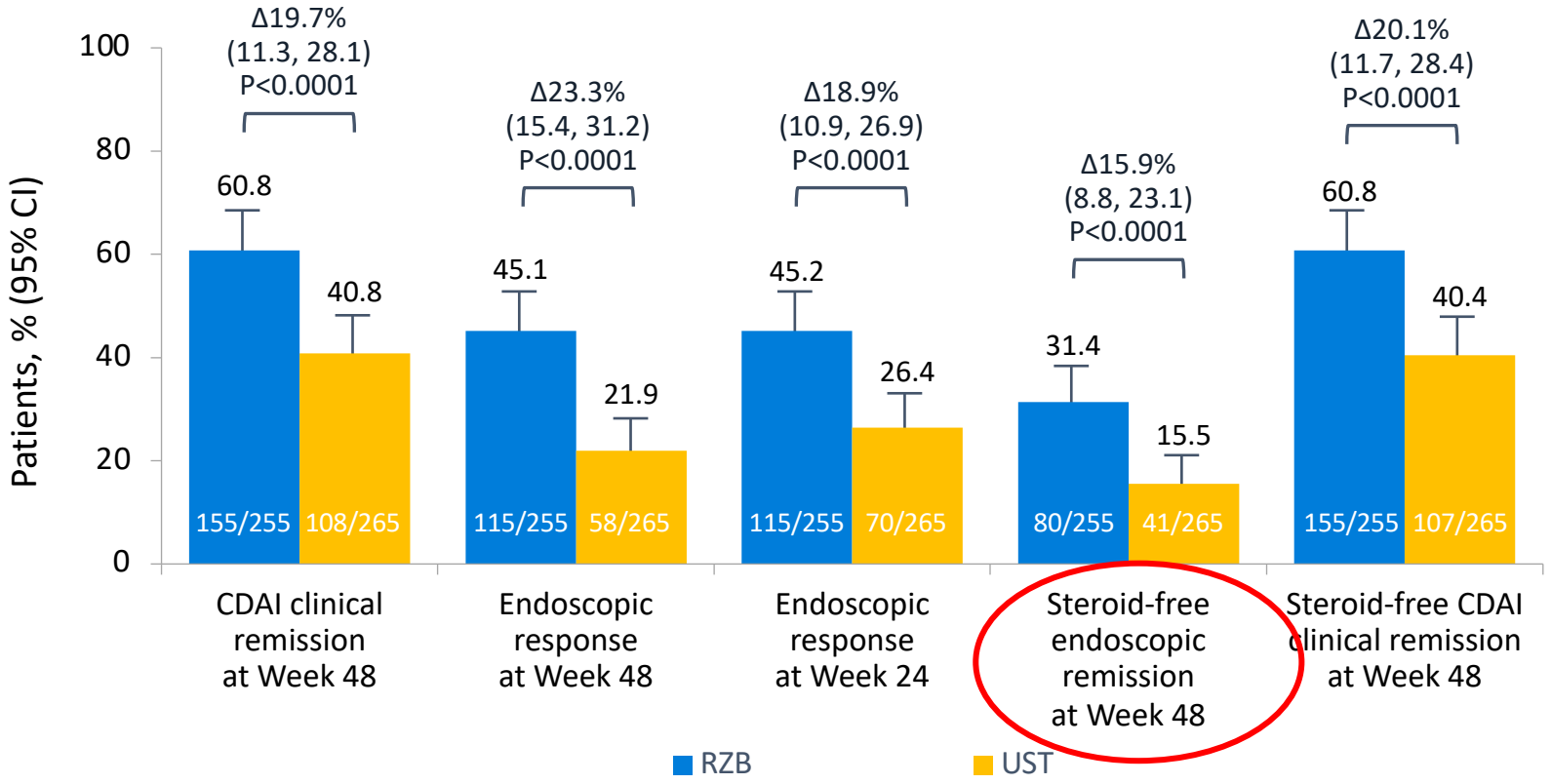
SEAVUE: H2H Trial in Bio-Naïve CD: Efficacy of ADAL vs UST





NOTE: Because primary endpoint was not met, formal testing of major secondary endpoints was not performed.
a. Patients who had a prohibited CD-related surgery, had prohibited concomitant medication changes, or discontinued study agent due to lack of efficacy or due to an adverse event indicated to be of worsening CD prior to the designated analysis timepoint are considered not to be in clinical remission, regardless of their CDAI score; b. Patients who had insufficient data to calculate the CDAI score at the designated analysis timepoint are considered not to be in clinical remission; c. The confidence intervals were based on the Wald statistic with Mantel-Haenszel weight.
Sands BE, et al. Late Breaking Abstract 775d. Digestive Disease Week. 2021.

SEQUENCE: RISA vs UST in TNFi Exposed CD: Secondary Endpoints



Demographic summary

- Mean age: ~38 years
- Mean disease duration: ~9 years
- Mean SES-CD: ~14
- Mean FCal >1000 mg/kg
- ~1/4 of patients had failed >1 anti-TNF
- Disease location:
  - Ileal (17%)
  - Colonic (40%)
  - Ileocolonic (43%)

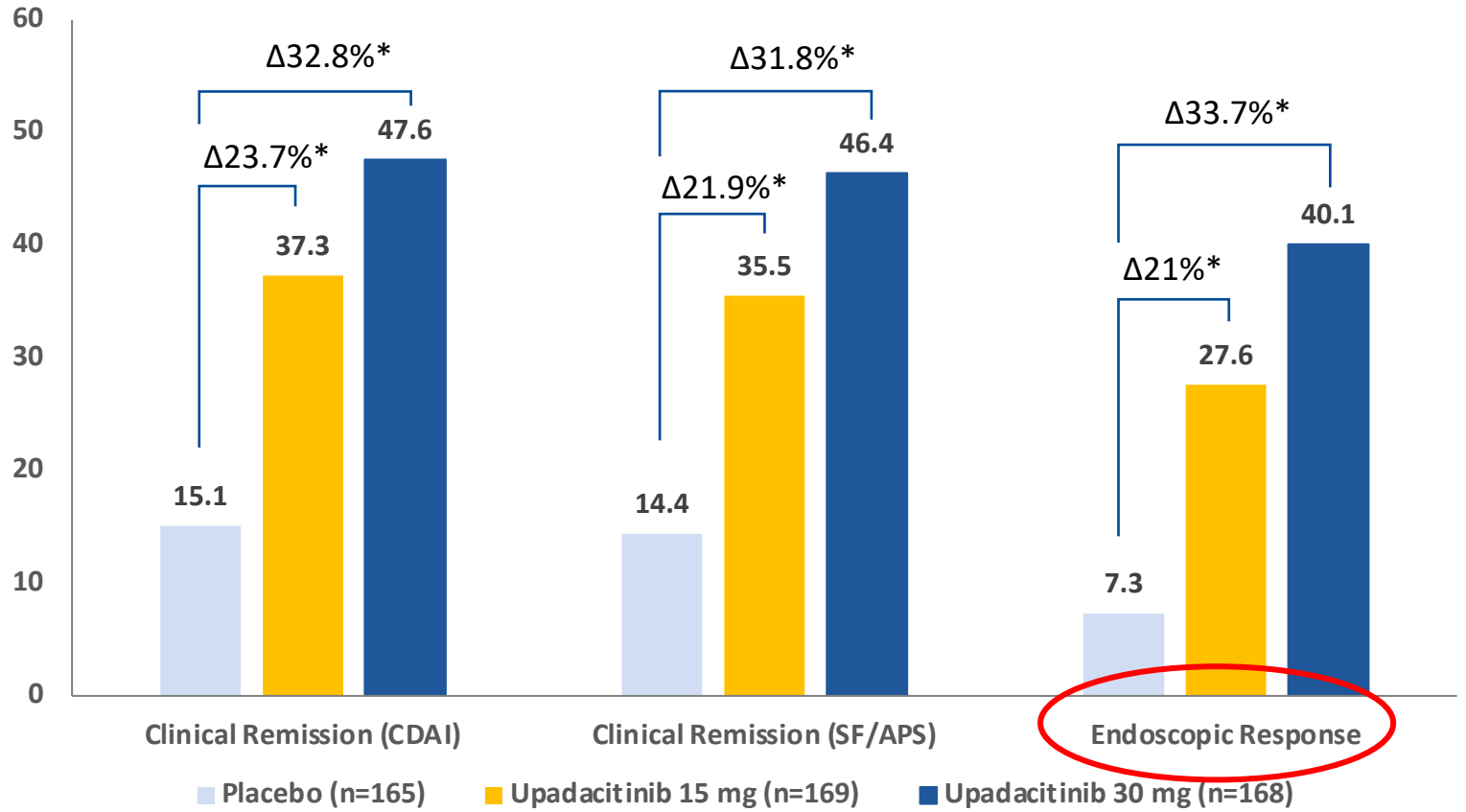
Analysis stratified for biologic exposure and corticosteroid exposure

AE, adverse event; CDAI, Crohn's disease activity index; RZB, risankizumab; TEAE, treatment-emergent adverse event; UST, ustekinumab.

Peyrin-Biroulet L, et al. UEGW 2023. Abstract LB01

U-ENDURE: Upadacitinib in Mod-Severe (Bio-exposed) Crohn's Disease
Maintenance week 52

Efficacy at Week 52



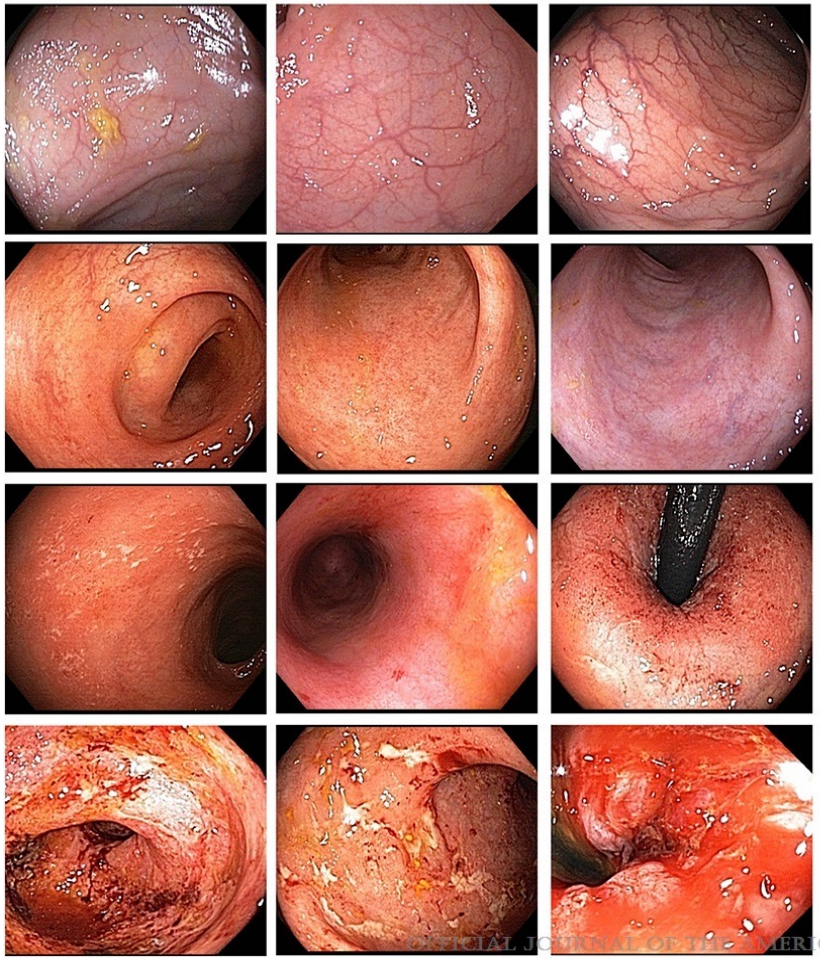
Endoscopic response defined as:

- Decrease in SES-CD >50% from baseline,
- or decrease of at least 2 points if baseline score of 4 and isolated ileal disease

*p<0.001

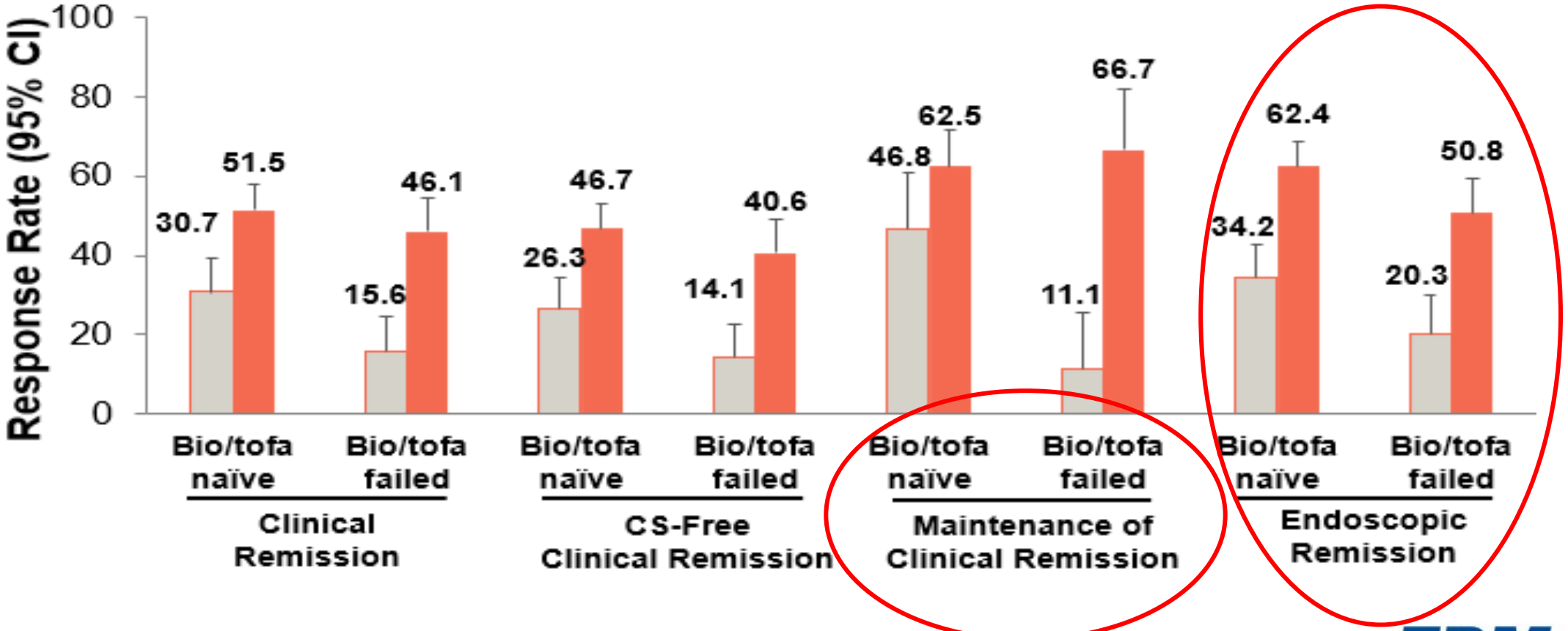
Loftus EV, et al. *N Engl J Med*. 2023;388:1966-1980.

Endoscopic Assessment of UC Disease Activity

Endoscopic Assessment of Disease Activity	UCEIS Score	Mayo Score	Endoscopic Features
	0	0	Normal
	1-3	1	Erythema, decreased vascular pattern, mild friability
	4-6	2	Marked erythema, absent vascular pattern, friability, erosions
	7-8	3	Spontaneous bleeding, ulceration

Rubin DT, et al. *J Gastroenterol*. 2019;114:384-413; Images courtesy David T. Rubin, MD.

Lucent2: Miri in UC by Prior Therapy Exposure



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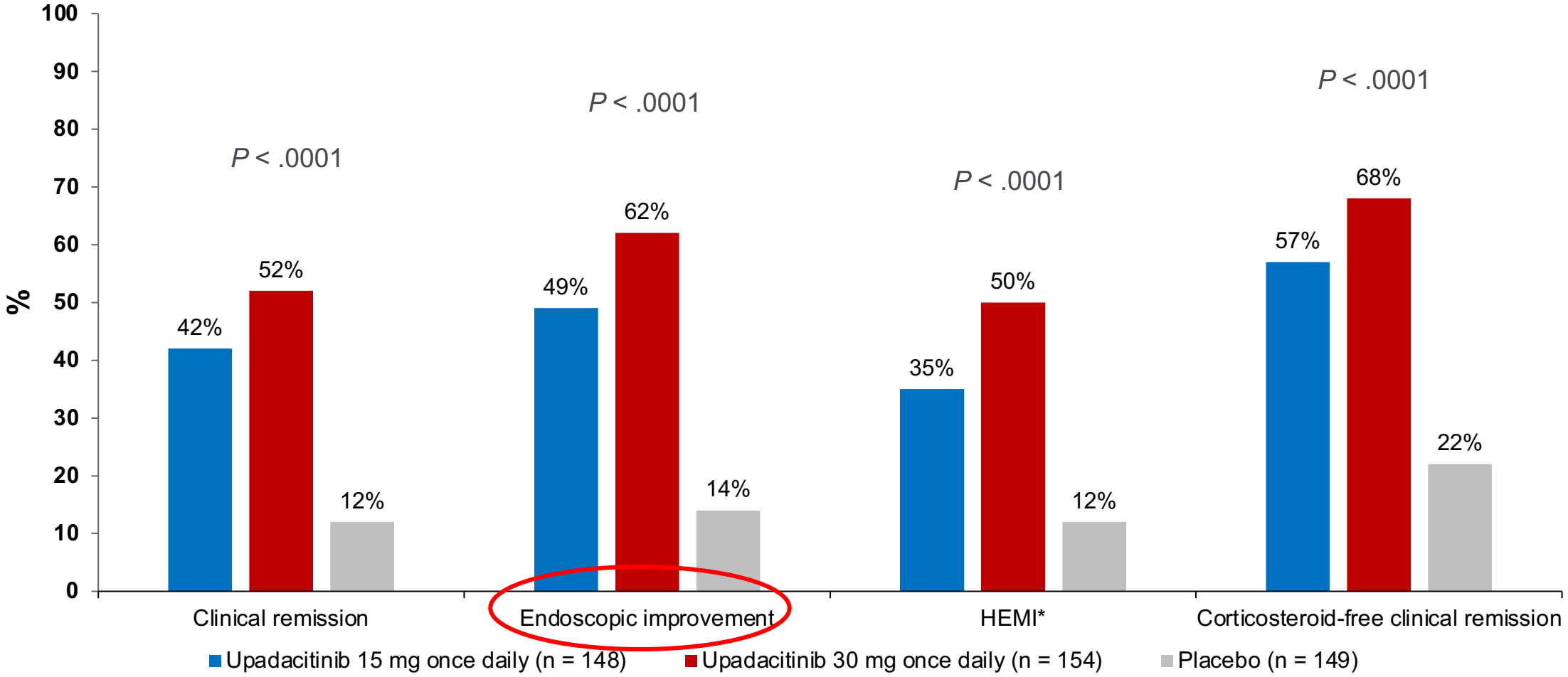
UPA Maintenance Therapy in UC: Week 52
U-ACHIEVE Maintenance



*HEMI defined as an endoscopic subscore of ≤1 without friability and Geboes score ≤ 3.1.

Danese S, et al. *Lancet*. 2022;399:2113-2128.

Endo improvement: Endo Mayo score 0 or 1 w/o friability

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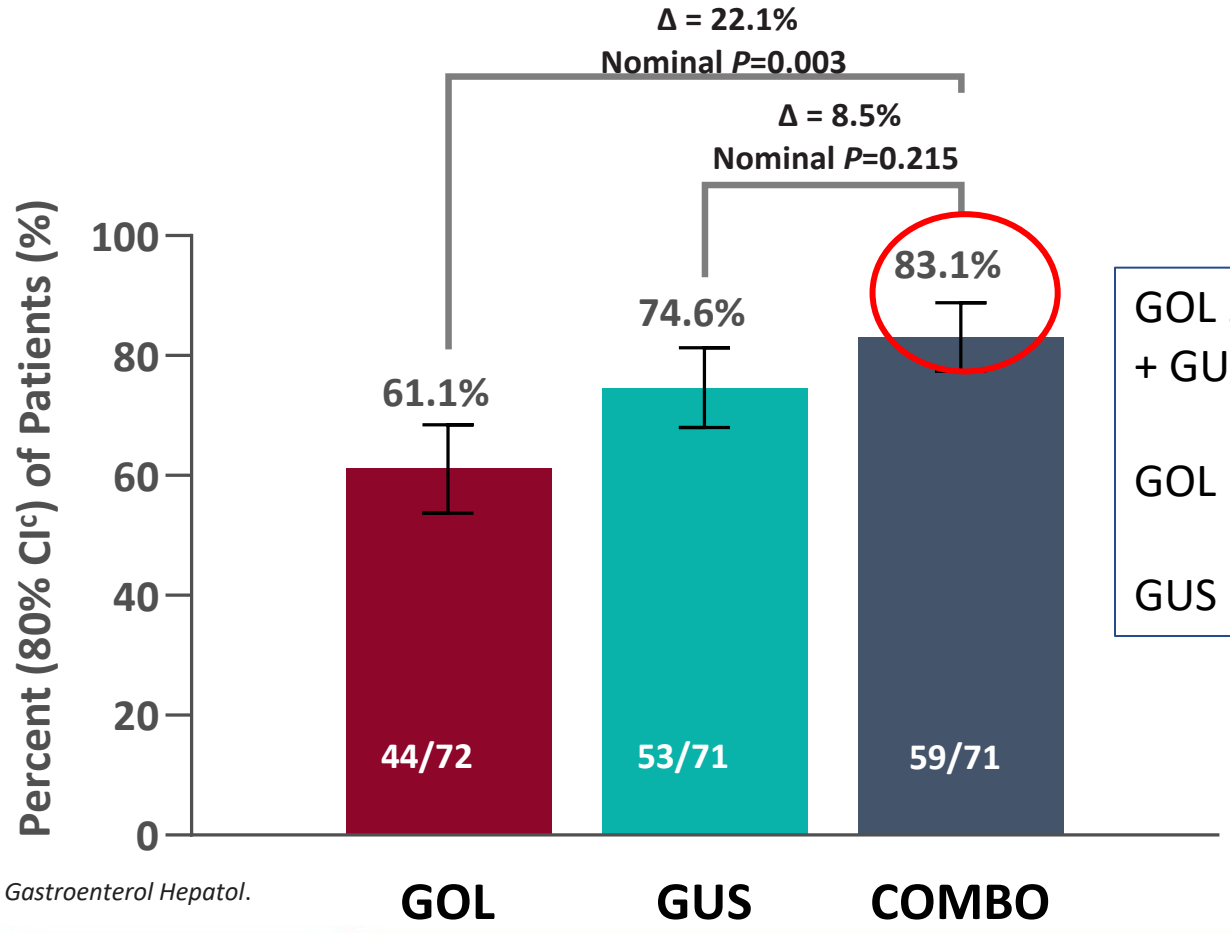
How about if we start with combo therapy in Bio-naive UC: Golimumab + Guselkumab in Bio-Naïve UC: VEGA Study: Results at Week 12

Clinical Response: Decrease from Baseline in the Mayo Score ≥30% and ≥3 Points with Either a Decrease in Rectal Bleeding Subscore ≥1 or a Rectal Bleeding Subscore of 0 or 1



GOL 200mg SQ wk0, 100mg SQ wk2 then q4wks
+ GUS 200mg IV 0,4,8 → GUS 100mg q8wks

GOL mono SQ:200mg wk0, 100mg wk2 → 100mg q4wks

GUS mono: IV 200mg wk0,4,8 →100mg SQ q8wks

Feagan BG, et al. *Lancet Gastroenterol Hepatol*. 2023;8:307-320.

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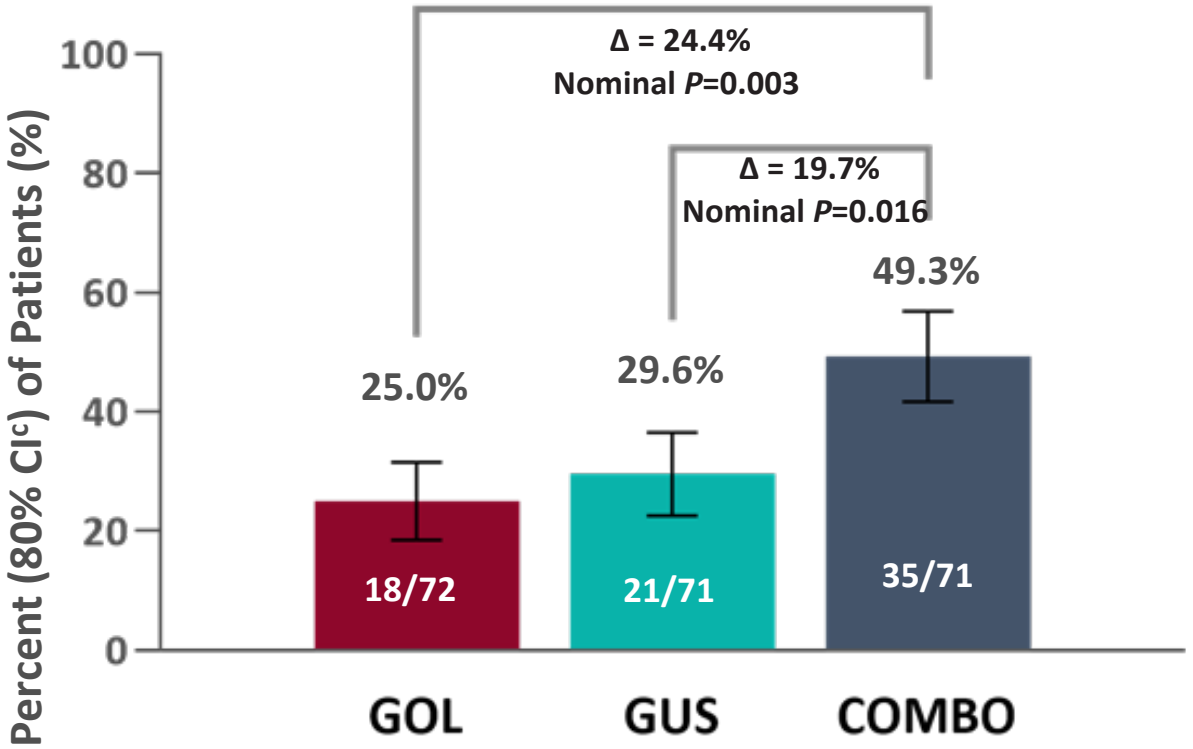
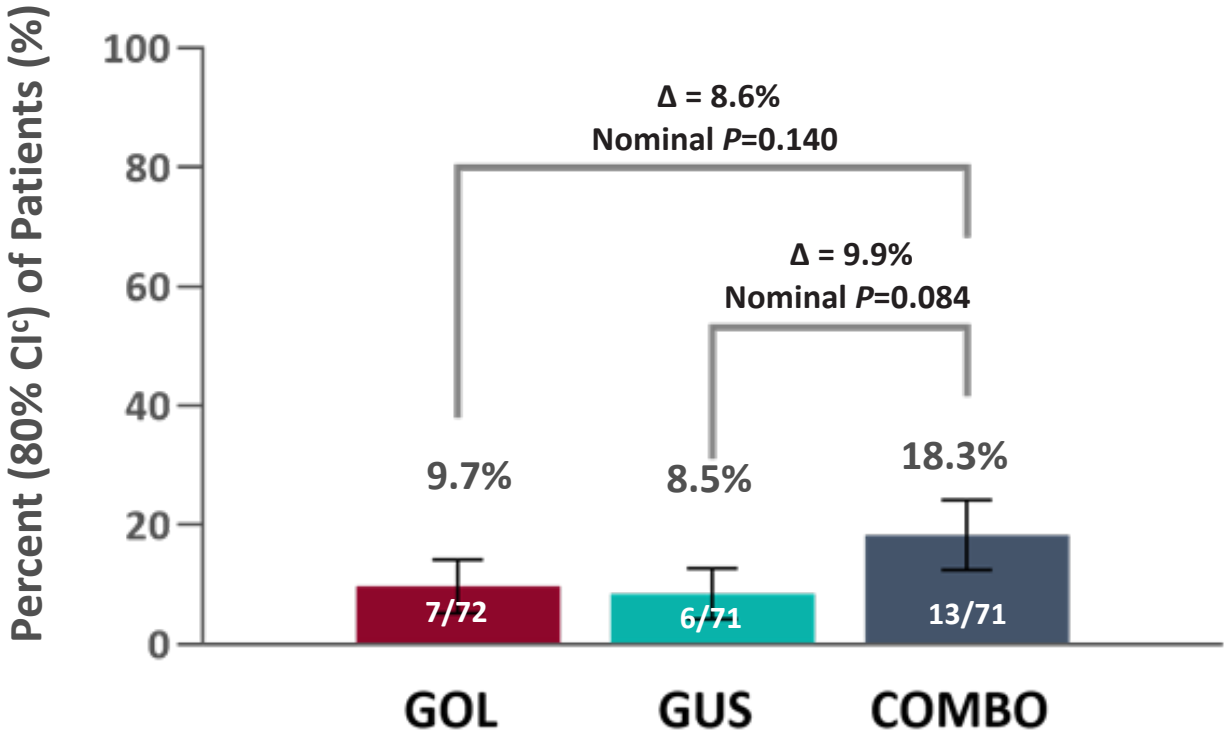
UC: Combination Biologic Golimumab (TNFi)+Guselkumab (IL23): VEGA Study: Results at Week 12

Endoscopic Improvement: Endoscopy Subscore of 0 or 1 with No Friability Present on the Endoscopy



Endoscopic Normalization: Endoscopy Subscore of 0 with No Friability Present on the Endoscopy



Sands BE, et al. ECCO 2022.

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How I Do It:
When Patient Is in Clinical Remission but Endo Active

- Is the endoscopic activity significantly improved: decrease in score, less segments with disease
- Is the endo appearance stable on follow-up
- What is the patient risk of disease progression / complications (eg risk of colon CA in UC-PSC)
- What is the risk/benefit profile of the current therapy in the specific patient (eg elderly, co-morbidities)
- Is this the first treatment or #4!
- Monitor for progression (FCP, c-scope)
- In there room for improvement on current therapy
  - Check drug levels if available
  - Optimize current therapy
  - Add on: topicals, mesalamine, IMM

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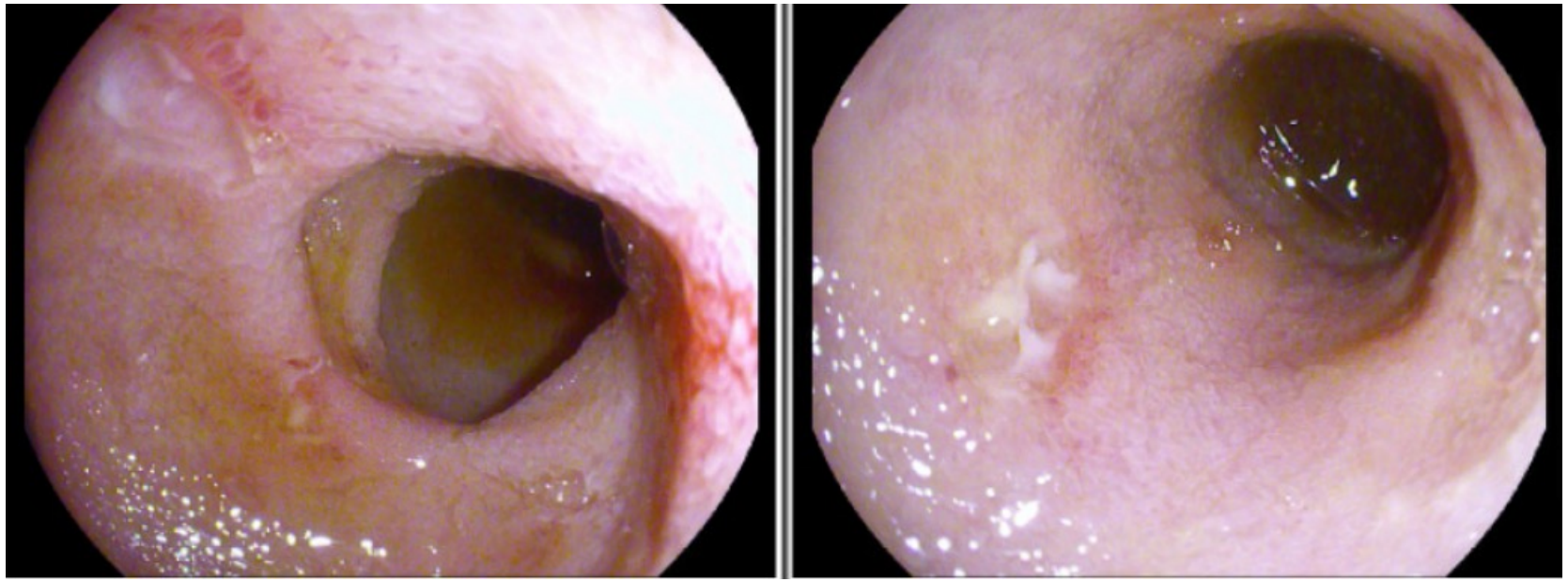
Case 1

- 50 y/o male with Crohn's ileitis, presented with abdominal pain, some weight loss, and peripheral joint pains
- CLN : ileitis and started on Ustekinumab
- Clinical remission x 5 years and he recently moved to DC
- Labs: H/H, B12 normal. FeSat borderline low 18% (nm in male 20-50%)

Case 1



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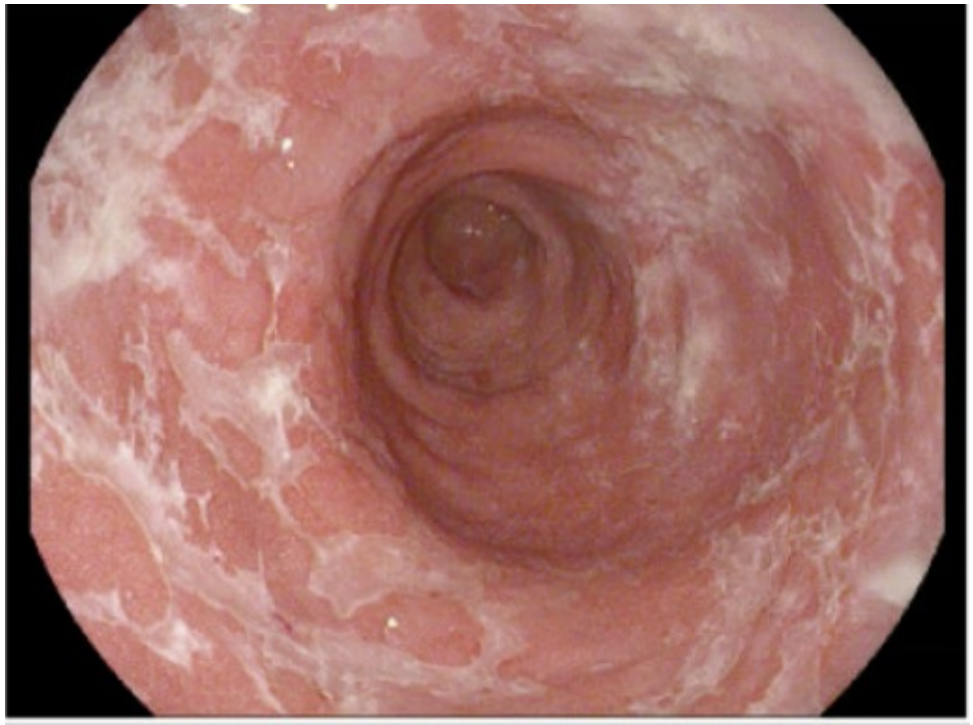
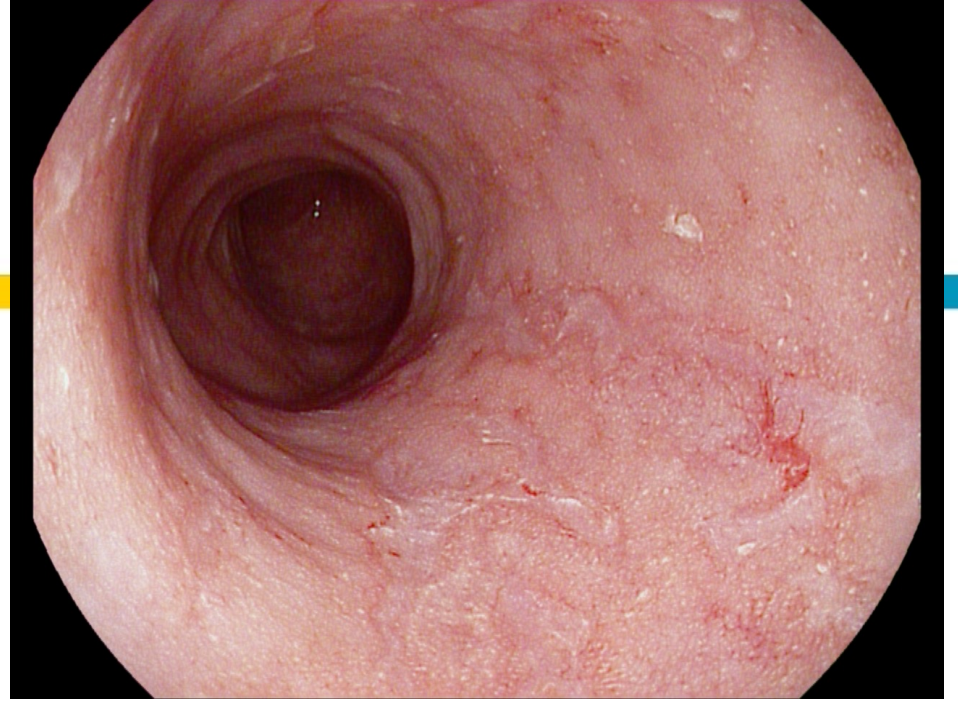
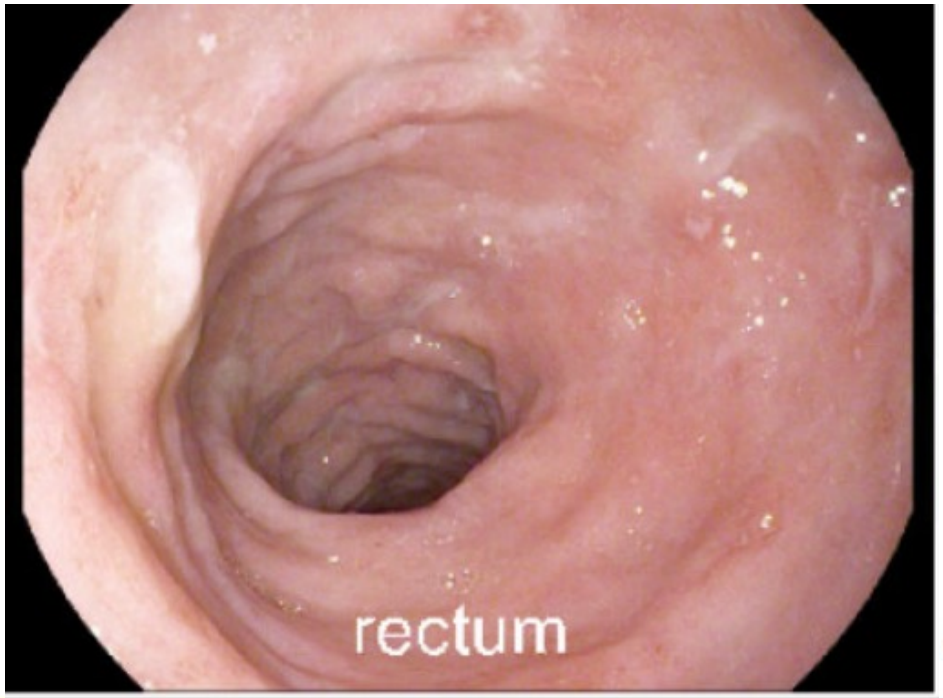
Case 2

- 24 year old dx of Crohn's colitis involving most of the colon
- Weight loss, abdo pain diarrhea, some blood in stool
- Did well on IFX, LOR with ATI
- Started UST, did well x 2 years, then re-flared, c-scope severe colitis, unable to taper off prednisone
- Started ADAL a year ago, colonoscopy repeated at one year

Case 2







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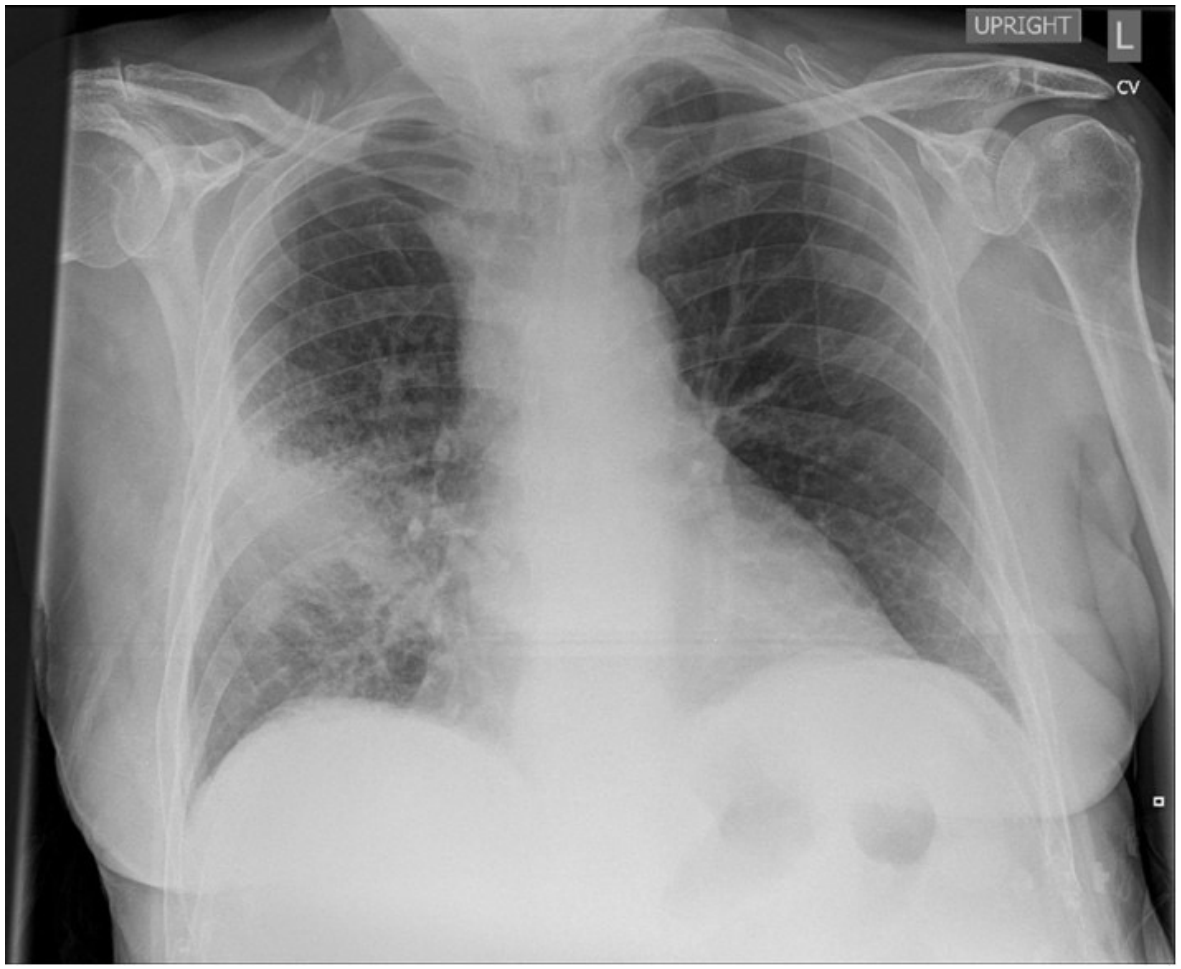
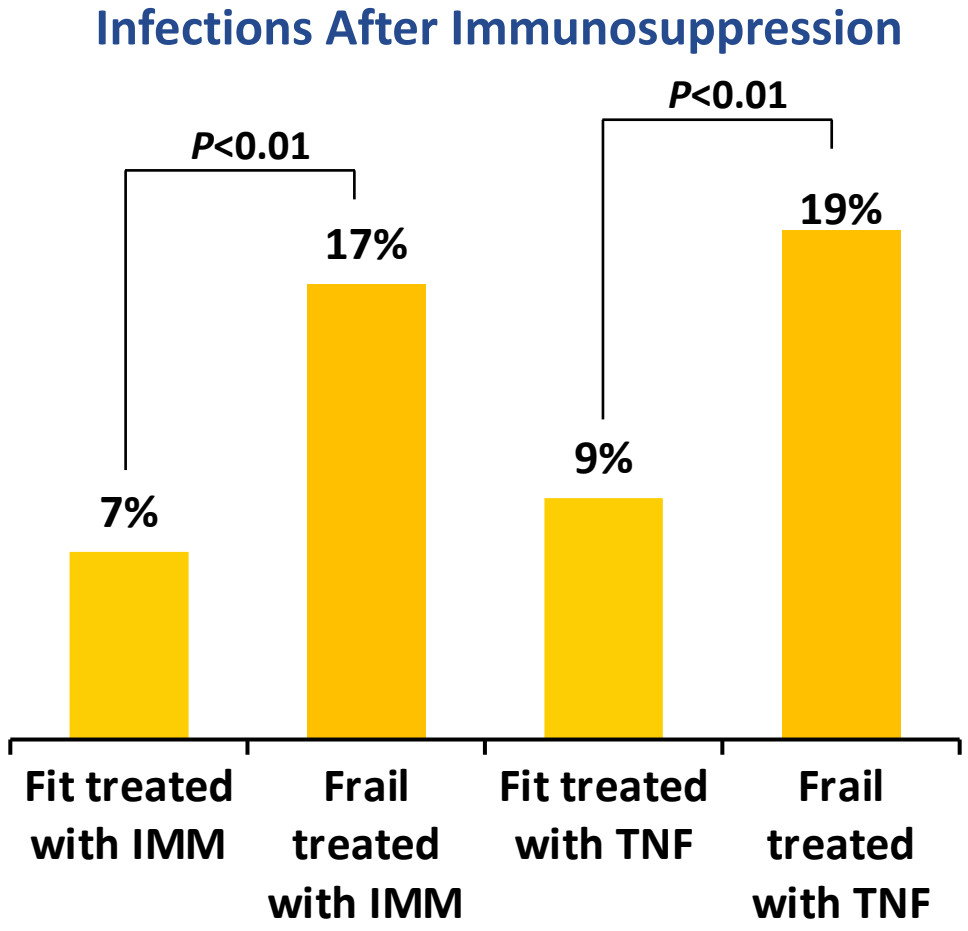
Case 3

- 72 y/o M, with long standing UC pancolitis in remission on AZA
- Stopped AZA because of several squamous cell CA of the skin and recurrent sinus infections
- Flare with bloody diarrhea x4-5/day and urgency/incontinence
- Started Vedolizumab and now diarrhea resolved, but occ blood streaks and urgency
  - Mostly manageable , patient takes 2 Imodium before going out

- Colonoscopy: Persistent rectosigmoid disease, Mayo endo subscore 1

Frailty as a Risk Factor for Infection With IS





Kochar B, et al. *Gastroenterology.* 2020;158:2104-2111.

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Network Creation and Mentorship is Your Professional Net Worth

Jennifer Christie, MD, FASGE, AGAF
President, American Society for Gastrointestinal Endoscopy
Professor of Medicine
Division Director for Gastroenterology and Hepatology
University of Colorado School of Medicine

Great GI Debates April 2024

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WISE AND SUCCESSFUL PEOPLE ARE ALWAYS IN A POSITION TO MAXIMIZE RESOURCES, BECAUSE THEY NEVER STOP CULTIVATING RELATIONSHIPS.

“RELATIONSHIPS MATTER”

-Sent by Mr. Sylvester
Emory University Hospital Concierge

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Network Creation is Similar to Net Worth Creation

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Our Objectives for This Talk:

1. Understand why networking and mentorship is important to career success.
2. Identify good networking and mentorship practices.
3. Create an Elevator Pitch.
4. Discuss the “Do’s and Don’ts”.

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Why Network? It's Everything!

- Direct correlation with career satisfaction as well as salary growth rate
- More beneficial for career success than single mentor relationship alone
- Impact of mentor relationship and mentee success is mediated by networking behaviors
- Exchange ideas and create opportunities
- Growth in self confidence

1. Wolff HG and Moser K. *J Appl Psychol*. 2009;94:196-206; 2. Blickle G, et al. *J Vocat Behav*. 2009;74:181-189; 3. ForbesWoman.com. March 2019.

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Why the Minoritized and Women Individuals May Find Networking More Difficult

1. Traditionally left out of the powerful networking circle
2. Likes Attract
3. Separate spheres dynamic
4. Fear of “Using People”
5. Limited Time

Forbes.com. Apr 2016; Lopes S. EllevateNetwork.com.

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Networking Ugh!
"I'm an Introvert"

- Ask and listen
- Do some research in advance
- Plan what you might say
- Have an Exit Strategy: "Stick and Move"
- Preserve your energy

Pollard M, et al. *The Introvert's Edge to Networking*. Harper Leadership. January 19, 2021.

Networking Venues Are Everywhere

- School of Medicine, Departmental, and Hospital Committees
- Grand rounds

Institutional

Regional Meetings/ Conferences

- Attend Small Group Discussions
- Opening receptions
- Attend monthly local meetings

National Meetings (ANMS, DDW, ACG, AASLD)

- Seminars
- Focused Receptions
- Luncheons

Professional GI Societies

- Specific committee request
- Attend business meeting
- Volunteer to serve on abstract review committee

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Digital Connections

- Social Media (SoMe)
  - Online communities with professional societies
  - Easily Accessible
  - Informal Communication
  - Knowledge quickly distributed
  - Tags: @GITwitter, #NeuroGI, @ANMSociety, #motility, @scrubsandheels

doximity

twitter

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5 Tips for Networking and Building Lasting Relationships

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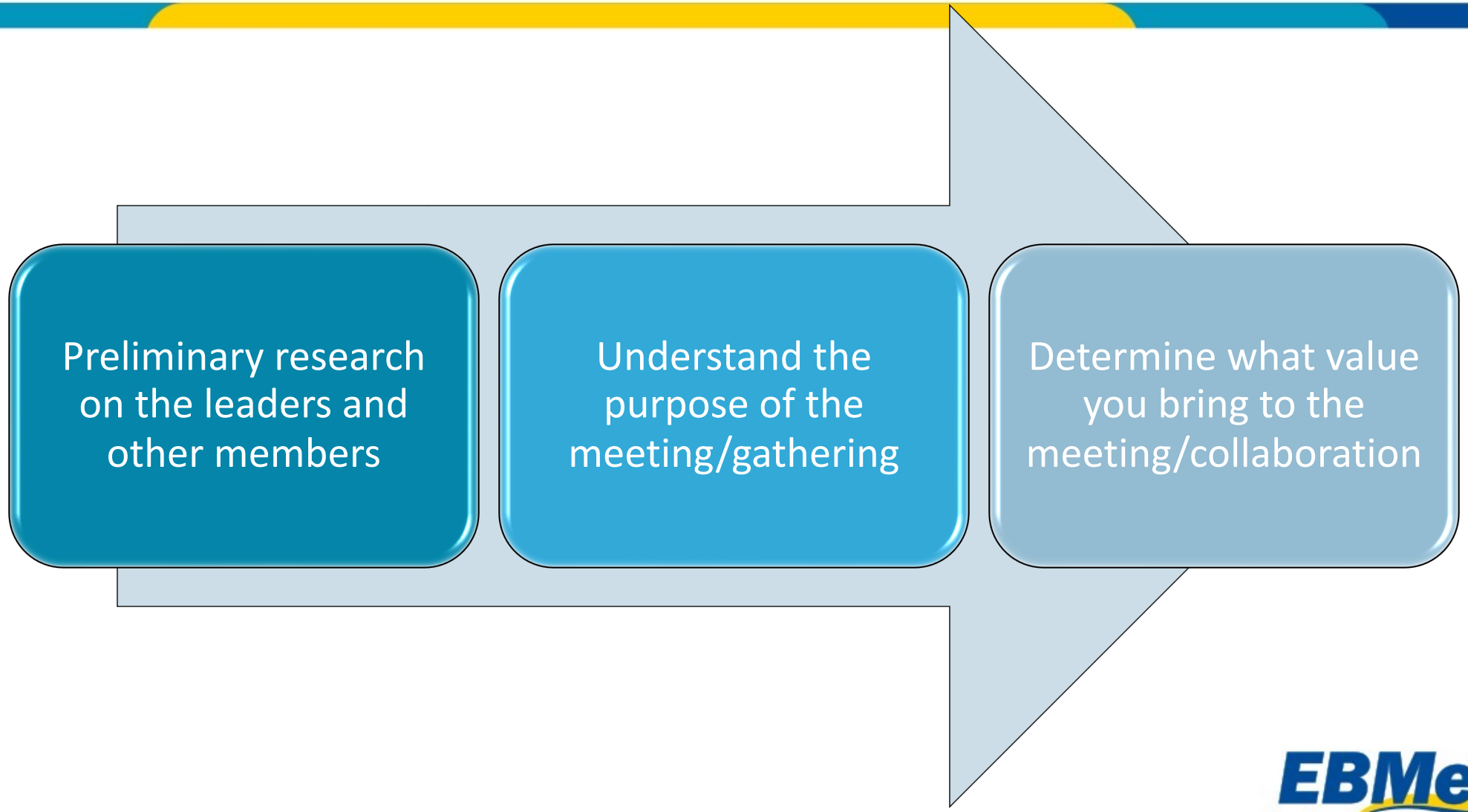
Tip #1: Know the Person or Group



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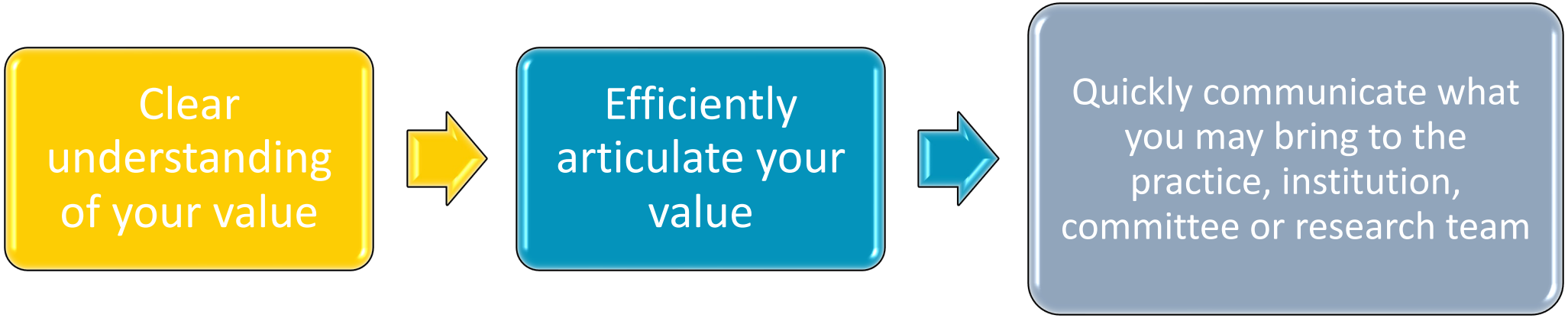
Tip #2: Create an Elevator Pitch



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Tip #3: Ask Open-ended Questions

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Tip #4: Authenticity

- Be real
- Be consistent
- Share your goals and work with enthusiasm
- Know your limits
- Builds and maintains lasting relationships

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Tip #5: Follow-up Efficiently

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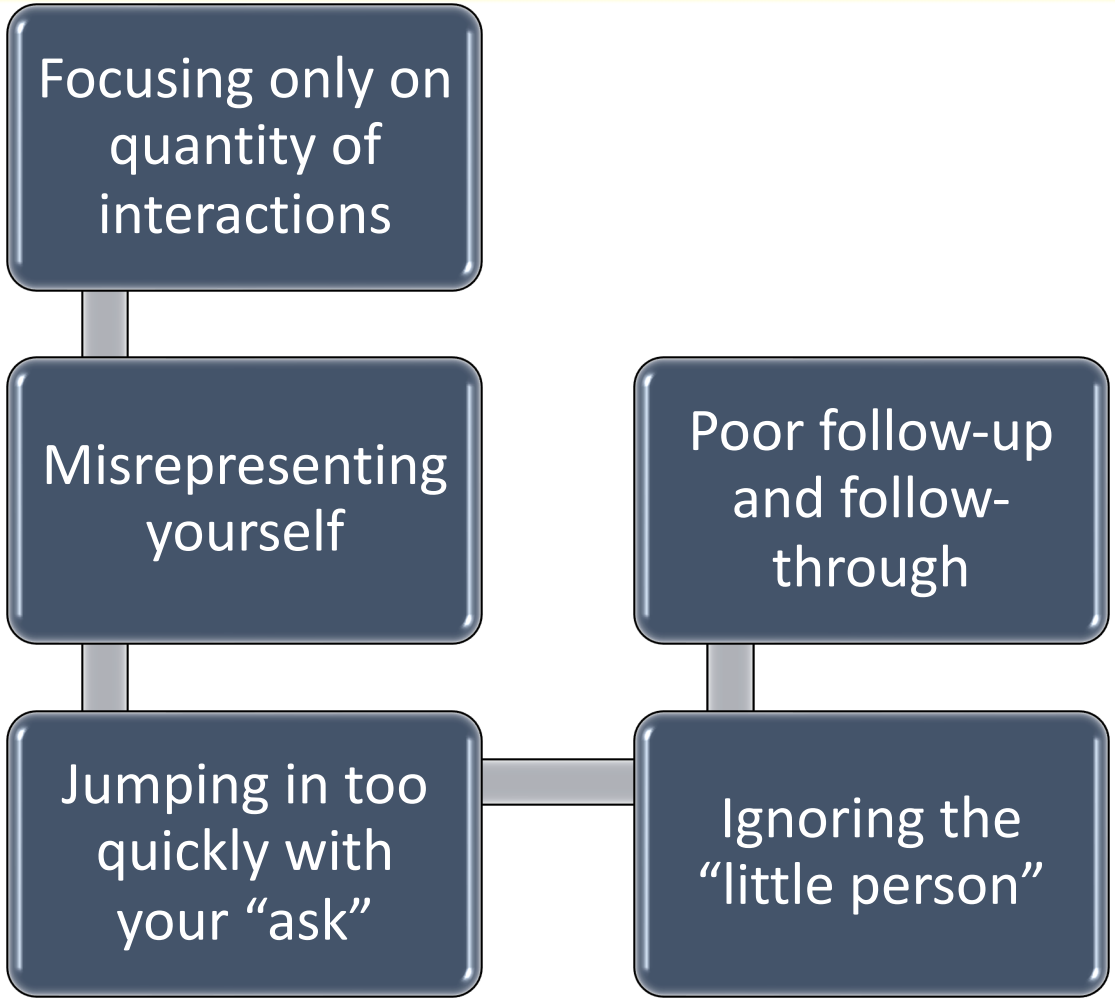
Networking Pitfalls



Clements S. BusinessKnowHow.com. 2016.

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Why Mentoring is Important

Mentor

In Academic Medicine correlated with:

- Career choice
- Skill Building
- Career satisfaction, longevity
- Networking
- Career advancement
- ↑ productivity (publications, funding, flourishing clinical practice)

Mentee

Sambunjak D, et al. *JAMA*. 2006;296:1103-1115.

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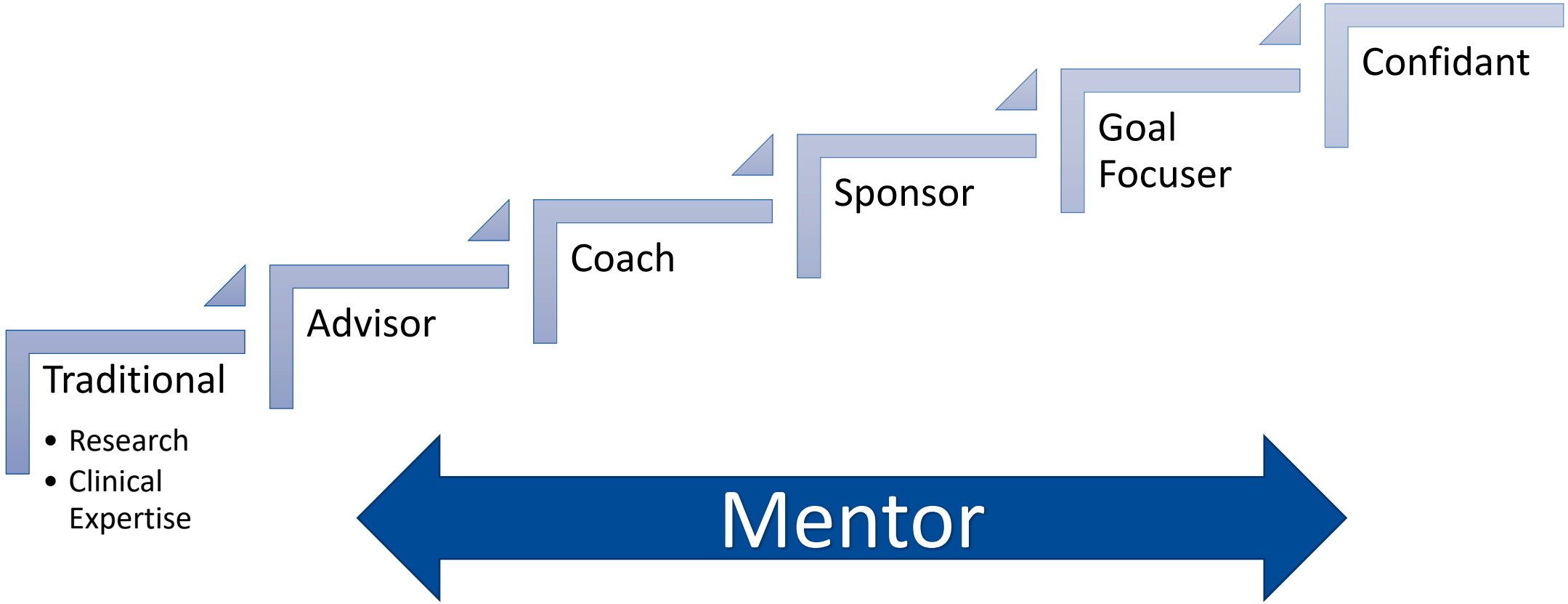
There are Multiple Mentor Styles



McBurney EI. *Clin Dermatol*. 2015;33:257-260.

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Strategic Mentoring

Mentor

Be thoughtful about your role/style
Suggest not instruct
Follow-up/Accountability
Awareness of implicit bias

Mentee

Choosing the “Right” Mentor
Prepare for the ask
Be specific about your ask
Follow-up/Accountability

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Effective Mentor-Mentee Relationship

- **Align Expectations**
  - Shared understanding of what each person expects from the relationship
  - Create Time-lines and Set Goals
- **Active communication**
  - Active listening
  - Reflective listening
  - Summarizing
  - Open-ended questions
  - Probing
  - Confrontation

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Effective Communication Builds Trust

- Honest and Effective Feedback
- Respect each other's boundaries

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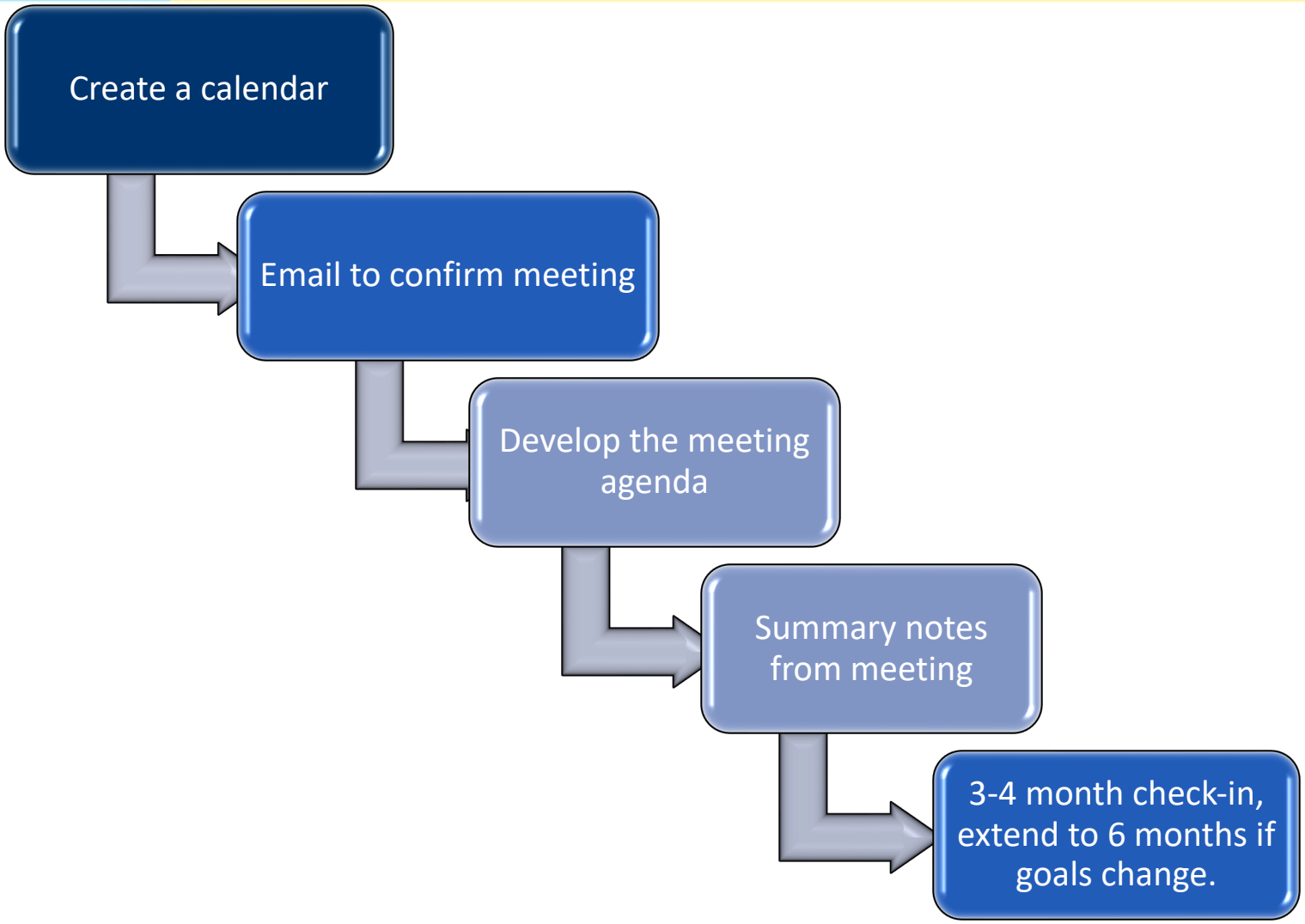
Mentees: Managing your mentor



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Pitfalls and Opportunities

- Misinterpret the mentee's potential.
- Be mindful of individual differences (sex, gender, race/ethnicity, religion, sexual orientation) and attempt to learn about each other's experiences.
- Inappropriate praise or criticism.
- Disregard for the mentee's opinions, other types of unethical and, rarely, immoral behavior.
- Impose your career goals on your mentee.
- Transitioning to another mentor who is more appropriate for the stage of your career.
- Peer Mentoring

Holmes DR Jr, et al. *Circulation*. 2010;121:336-340.

“If you want to go fast, go alone.
If you want to go far, go with others.”

-African Proverb

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6. The Introvert's Edge to Networking: Work the Room. Leverage Social Media. Develop Powerful Connection. HarperCollins Leadership. Matthew Poland with Derek Lewis 2021.
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8. Valerie Vaughn, MD, MSc, et al. Mentee Missteps: Tales From the Academic Trenches. JAMA, 2017;317(5)
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How I Do It: Management of Pouchitis

Maia Kayal, MD MS
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New York, New York

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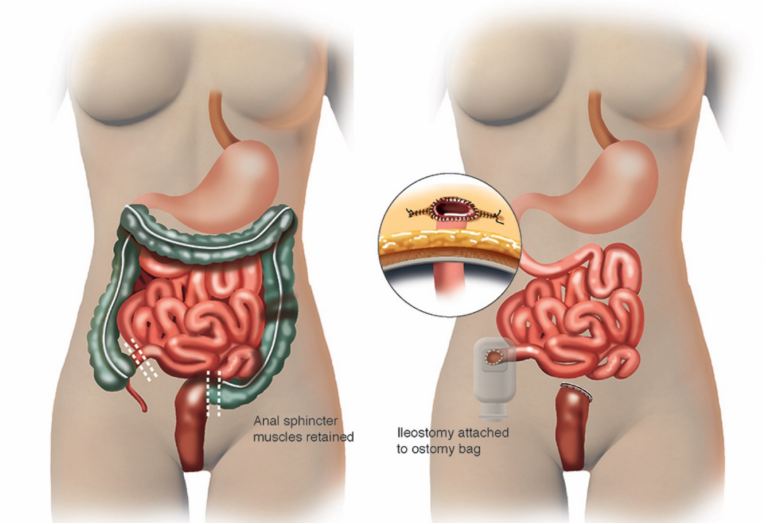
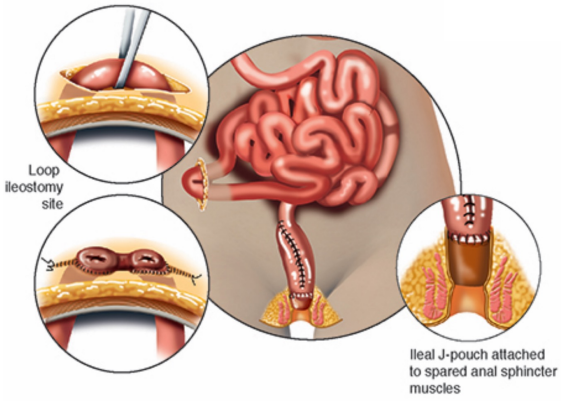
Proctocolectomy with Ileal Pouch Anal Anastomosis

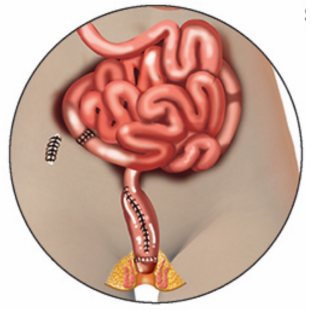
Stage 1



Stage 2



Stage 3



The three stage TPC with IPAA is the optimal staged method to reduce post-operative complications

Plietz, Kayal et al. Dis Colon Rectum. 2021

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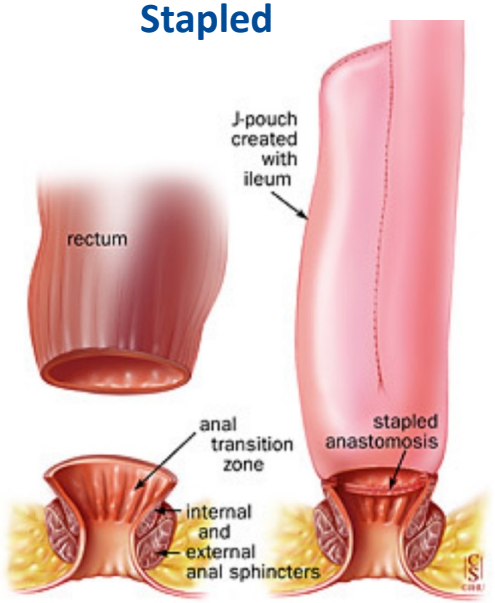
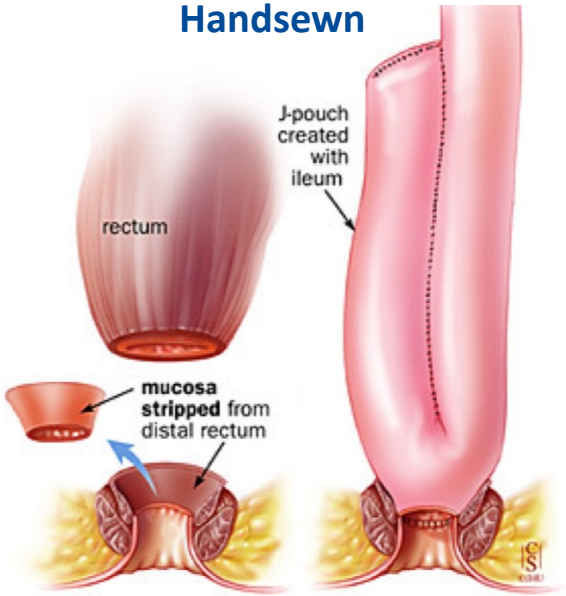
Types of Pouch-Anal Anastomoses

- Stapled anastomosis
  - Requires residual 1-2 cm rectal cuff
  - Better quality of life with less nocturnal seepage, incontinence, pad use
- Handsewn anastomosis
  - Performed with rectal mucosectomy
  - Eliminates risk of cuffitis, anal transition zone cancer

Stapled



Handsewn



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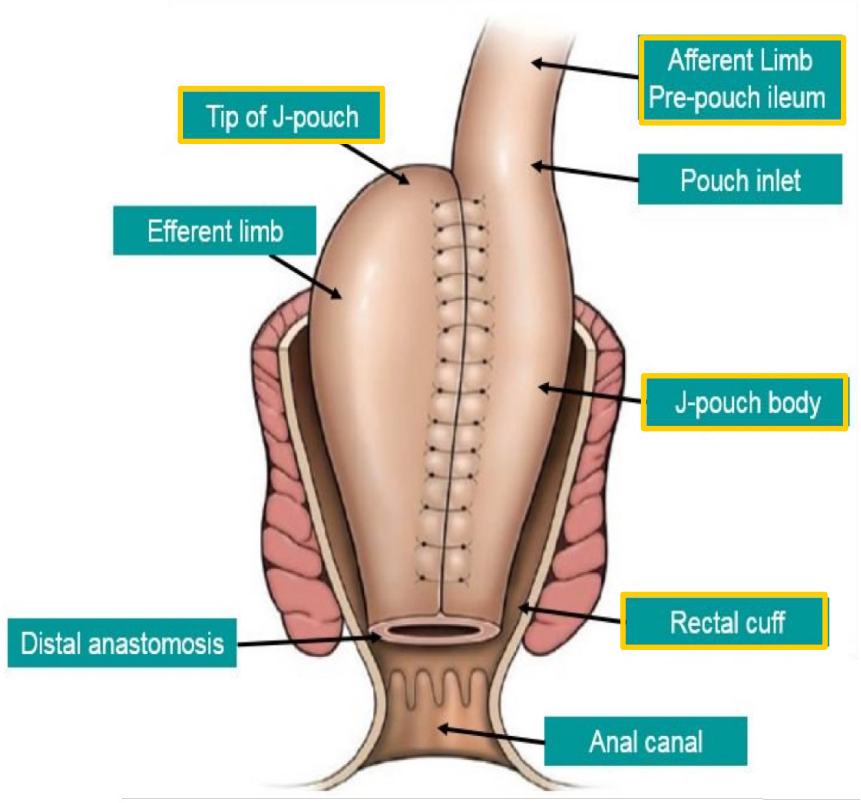
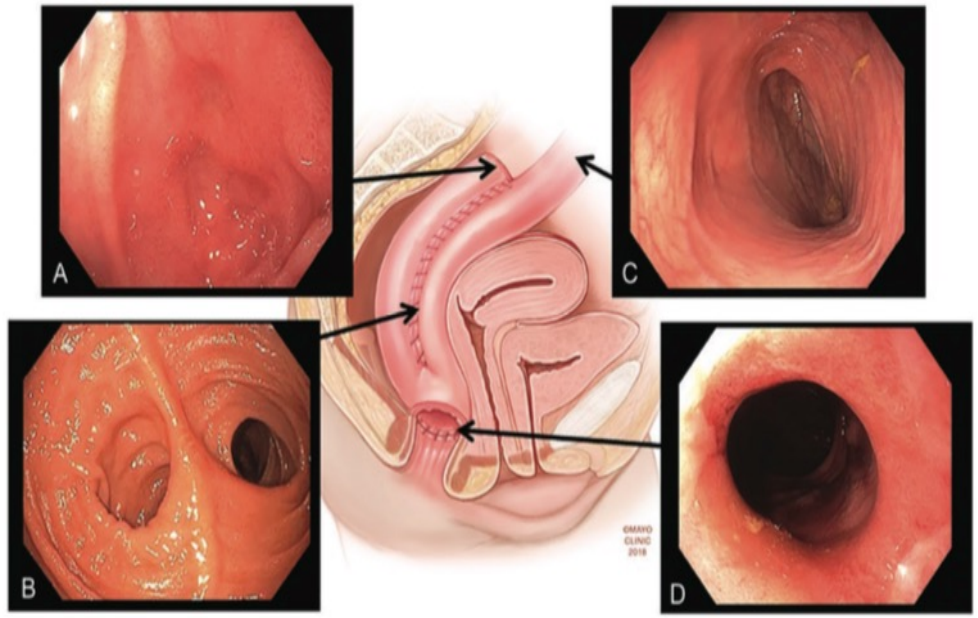
Pouch Anatomical Landmarks





Quinn et al. Inflamm Bowel Dis. 2018

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Short Term Outcomes

- **1-2 weeks post-op**
  - Many liquid bowel movements (> 10) within 24 hours
  - Minimal urgency

- **3-6 months post-op**
  - 6-8 thick (toothpaste like) bowel movements within 24 hours
  - No urgency
  - Excellent continence
    - 5-10% night time seepage requiring pad

Quinn KP et al. Am J Gastro 2020

Long Term Outcomes

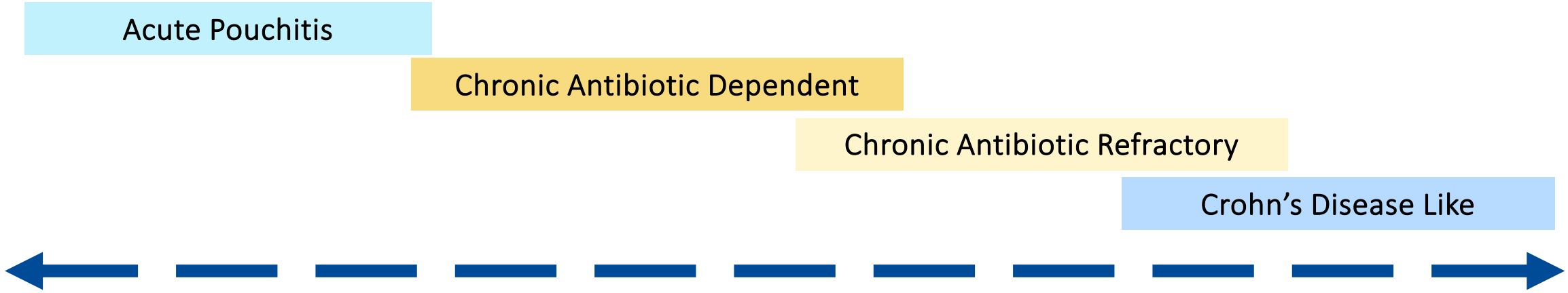
- **Positive:**
  - Complete continence in 50-75% of patients
  - Improved quality of life
    - 97% of patients said they would recommend IPAA

- **Negative:**
  - Infertility rate 40% in women after open RPC with IPAA
    - Rates are likely lower in the modern age of laparoscopic surgery
  - Pouchitis

Quinn KP et al. Am J Gastro 2020
Fazio VW et al. Ann Surg. 2013

Pouchitis

- Acute pouchitis occurs in up to **80%** of patients with UC
- Approximately **60%** of patients develop at least one recurrence after the first episode of pouchitis, and up to **20%** of patients develop chronic pouchitis



Lightner et al. Inflamm Bowel Dis. 2017

Pouchitis Phenotypes

- **Acute Pouchitis AP**
  - Symptoms <4 weeks, respond to 2-4 week course of antibiotics
- **Chronic antibiotic dependent pouchitis CADP**
  - Frequent (>4/year) episodes of pouchitis or persistent symptoms that require continuous antibiotics
- **Chronic antibiotic refractory pouchitis CARP**
  - Persistent symptoms, objective inflammation unresponsive to 4 weeks of antibiotics
- **Crohn's disease-like pouch inflammation CDLPI**
  - Inflammatory: pouchitis and pre-pouch ileitis
  - Fibrostenotic: stricturing of pre-pouch ileum, proximal small bowel
  - Fistulizing: fistulae involving pouch, perineum, proximal small bowel

Quinn et al. Am J Gastroenterol. 2020
Shen et al. Lancet Gastroenterol Hepatol. 2021

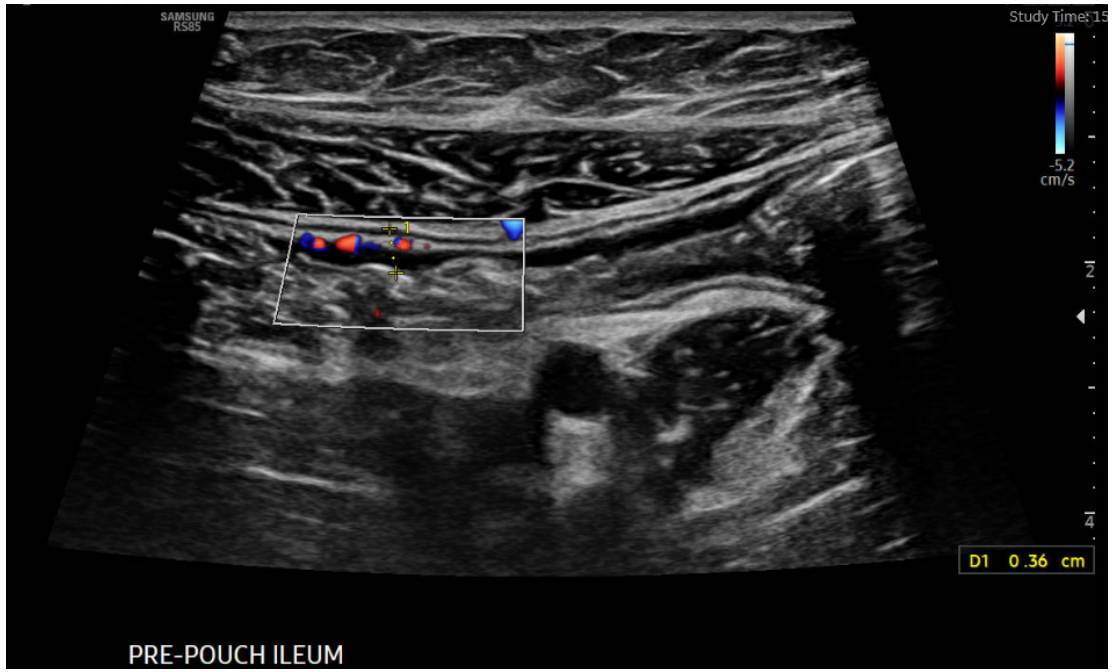
Pouchitis Disease Activity Index

Criteria	Score
Clinical	
• Stool frequency (# BMs > post-op usual)	0-2
• Rectal bleeding (Absent/present daily)	0-1
• Fecal urgency (None/occasional/usual)	0-2
• Fever (Absent/present)	0-1
Endoscopy	
• Edema	1
• Granularity	1
• Friability	1
• Loss of vascular pattern	1
• Mucous exudates	1
• Ulceration	1
Histology	
• PMN infiltration mild / moderate / severe	1-3
• Ulceration (<25% / 25% - 50% / >50%)	1-3

PDAI score ≥ 7 indicates pouchitis, score < 7 indicates remission

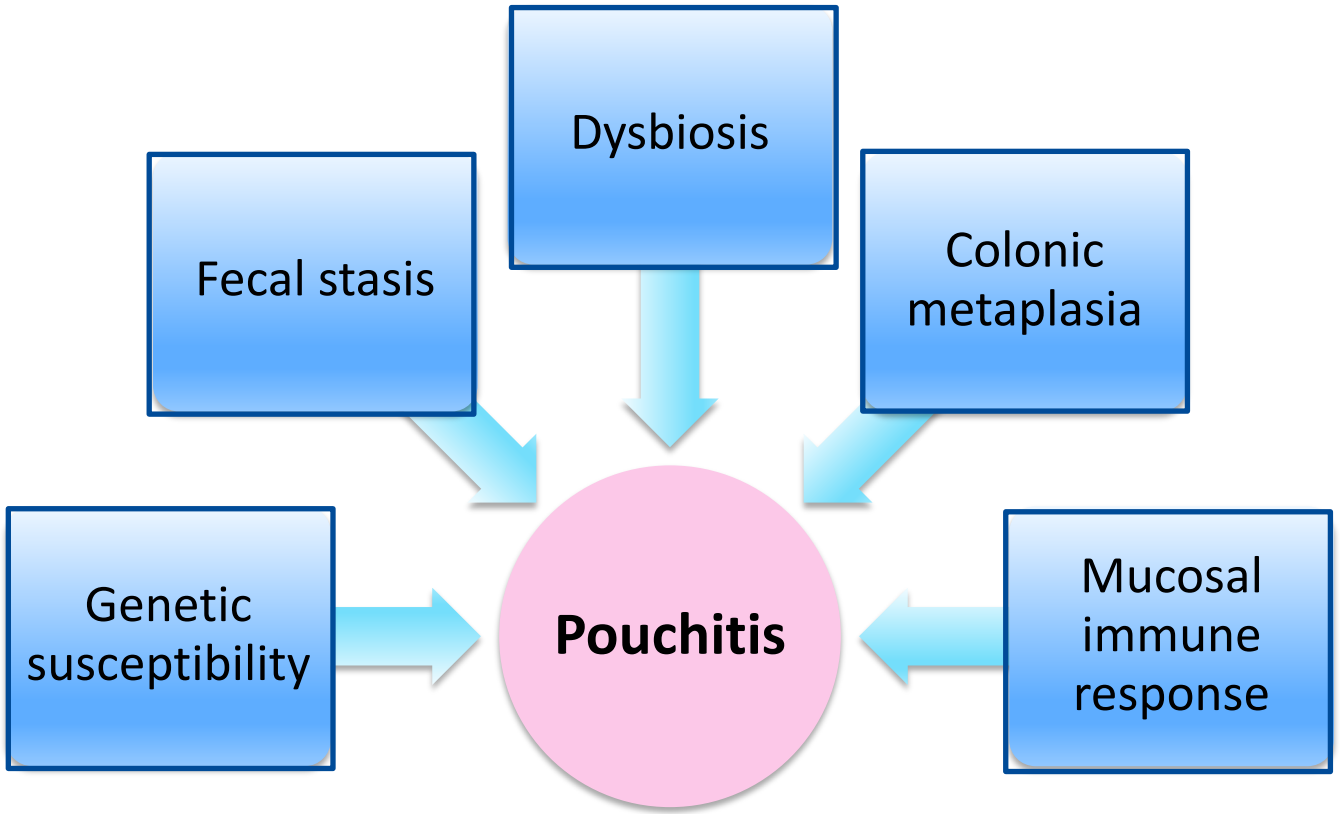
Intestinal Ultrasound for Diagnosis of Pouchitis

- IUS is accurate and complementary to calprotectin to diagnose pouchitis and pre-pouch ileitis
  - Pouch wall thickness of ≥4 mm was 87% specific in diagnosing pouchitis
  - IUS had good utility [AUC: 0.78] in diagnosing moderate-severe pre-pouch ileitis



Ardalan et al. J Crohn's Colitis. 2022

Pathogenesis of Pouchitis



Landy et al. Inflamm Bowel Dis. 2012
Batista et al. Inflamm Bowel Dis. 2014

Management of Acute Pouchitis

First line therapy
Ciprofloxacin or metronidazole for 2 weeks

↓ Relapse

Relapse (1st)
4 weeks of ciprofloxacin (+/- metronidazole)

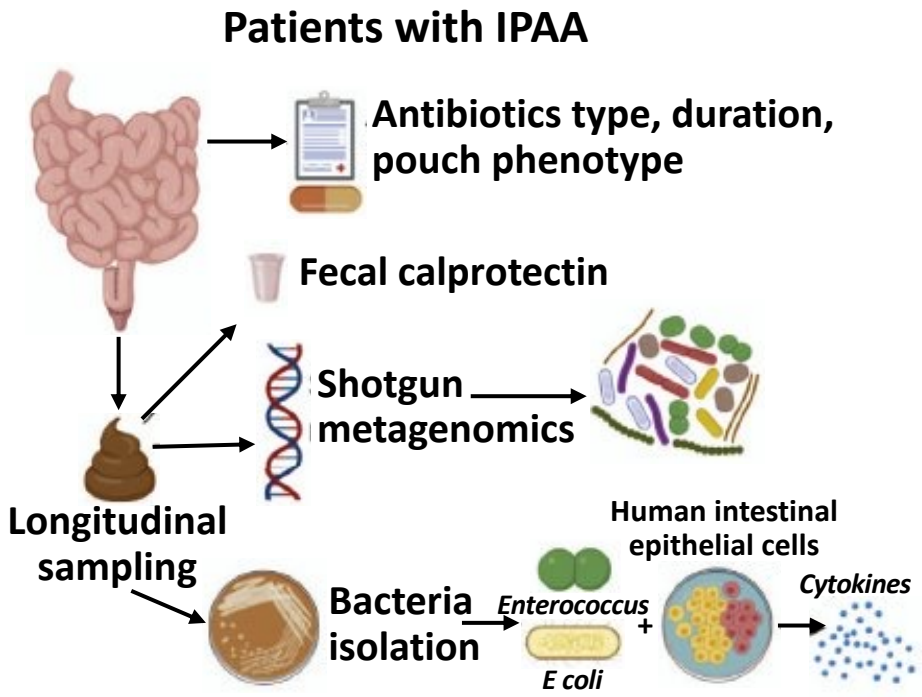
↓ Relapse

Multiple relapses (>4)
Chronic ciprofloxacin or metronidazole at lowest possible dose, tinidazole, rifaximin, vancomycin

Approximately **80%** of patients reach remission after one antibiotic course
Up to **60%** of patients may have a recurrence

Nguyen N, et al. Cochrane Database Syst Rev. 2019.
Shen B, et al. Inflamm Bowel Dis. 2001.

Antibiotics Effect on Pouch Microbiome



Outcomes of antibiotic therapy	Abx+	Abx–
• Clinical flare	↓	↑
• Fecal calprotectin	↓	↑
• Microbiome diversity	↓	↑
• Resistant bacteria	↑	↓
• Mobile resistance genes	↑	↓
• Virulence genes	↓	↑
• Bacterial density	↓	↑
• Proinflammatory bacteria	↓	↑
• Commensal species	↓	↑

Antibiotics reduce proinflammatory disease-associated bacteria

Dubinsky V et al. Gastroenterol. 2020.

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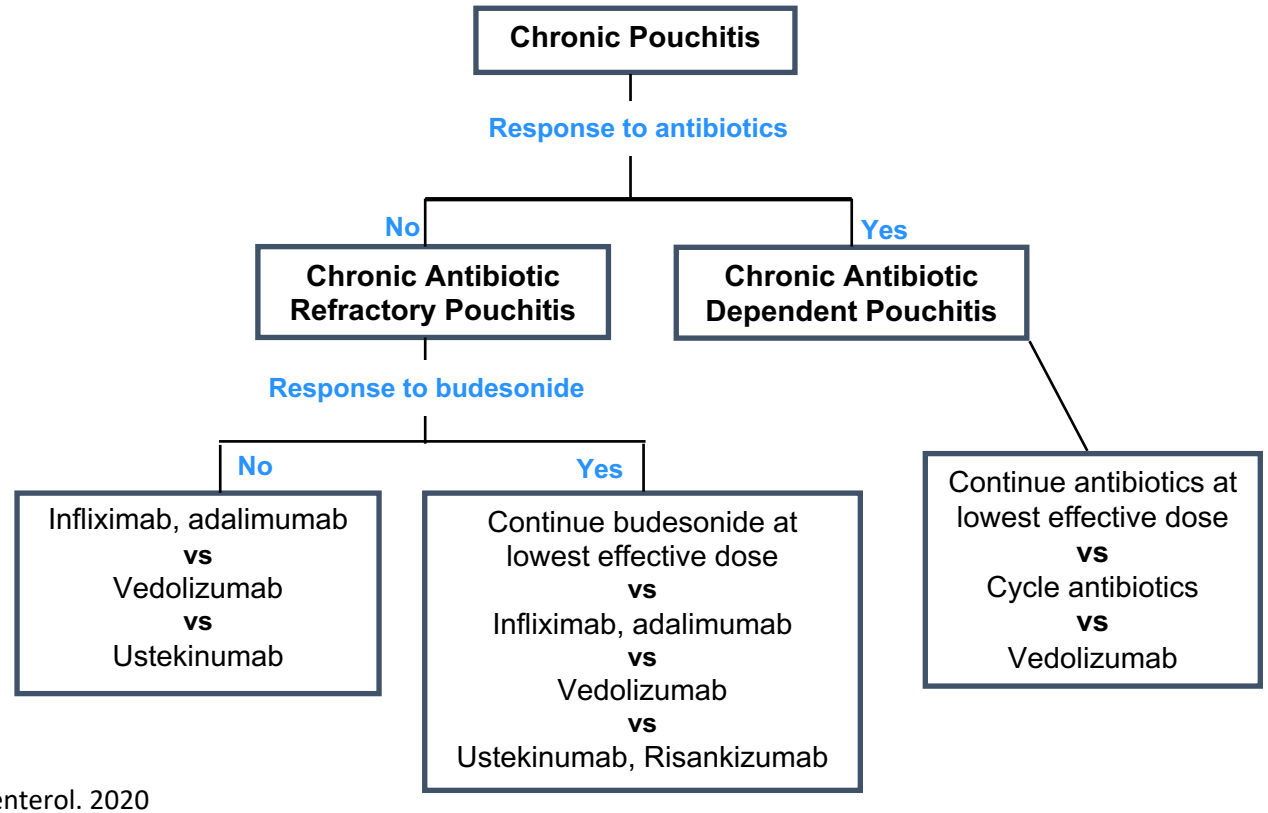
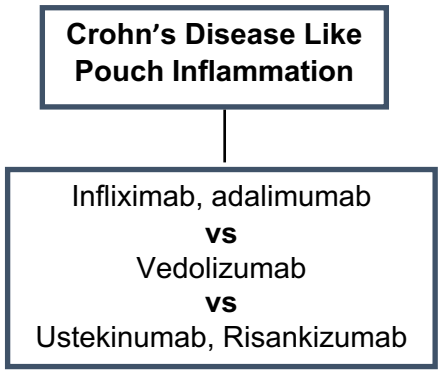
Management of Chronic Pouchitis

- Budesonide: remission rates 40-60%
- Anti-TNF agents, ustekinumab, vedolizumab, tofacitinib: remission rates 30-60%





- Optimize early
- Avoid recycling of pre-colectomy biologics

Quinn et al. Am J Gastroenterol. 2020
Kayal et al. Curr Res Pharmacol Drug Discov. 2022.

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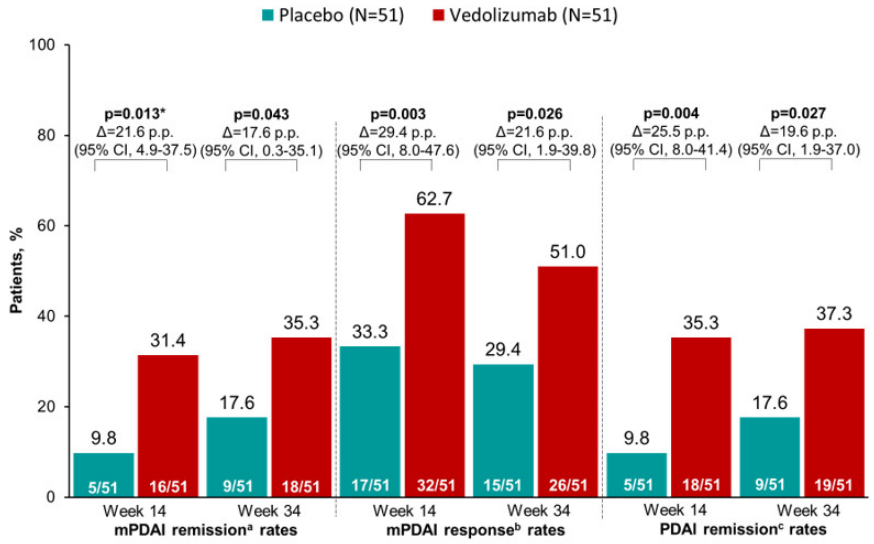
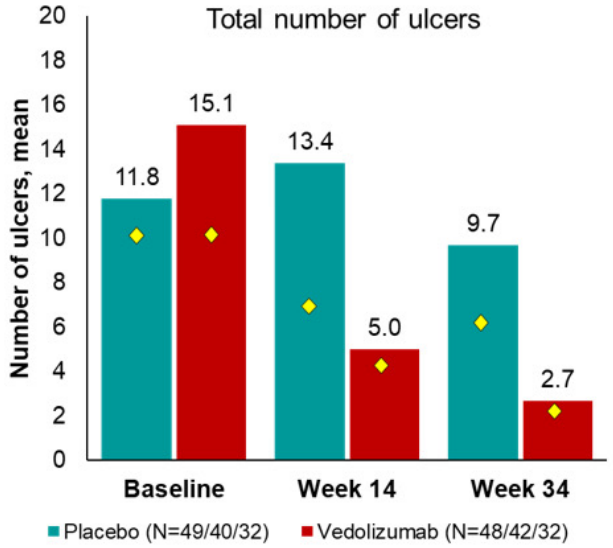
Vedolizumab is Effective in Chronic Pouchitis

- First randomized, double-blind, placebo-controlled trial of vedolizumab in patients with chronic pouchitis, N=102
- Significant differences in favor of vedolizumab over placebo in mPDAI remission rates, mPDAI response rates, and PDAI remission rates
- Greater reduction in number of endoscopic ulcers from baseline for vedolizumab over placebo at weeks 14 and 34





Travis S et al. N Engl J Med. 2023

Vedolizumab Achieves Mucosal Healing in Chronic Pouchitis

More patients treated with vedolizumab achieved reduction in ulcerated surface area, complete absence of ulceration/erosions and SES-CD remission

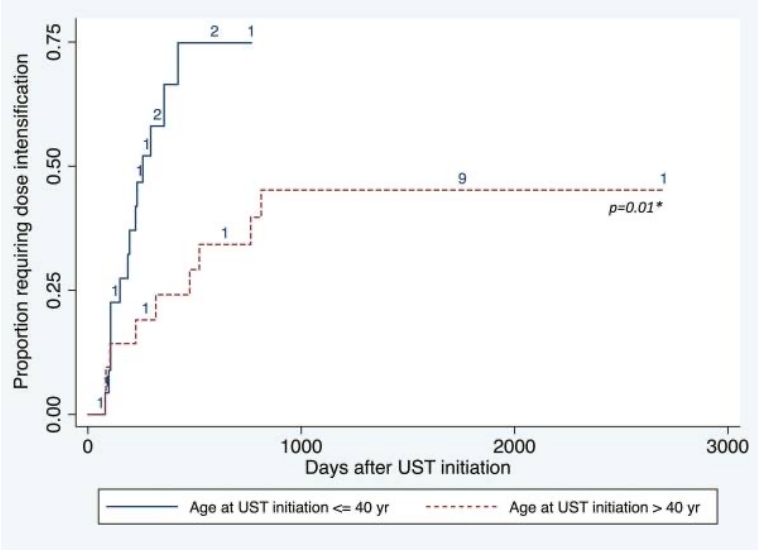
	Baseline		Week 14		Week 34	
	VDZ	PBO	VDZ	PBO	VDZ	PBO
Mean (SD) total number of ulcers/erosions	n=48 15.1 (16.4)	n=49 11.8 (11.3)	n=42 5.0 (4.9)	n=40 13.4 (18.4)	n=32 2.7 (3.2)	n=32 9.7 (13.8)
Number of patients with reduction from baseline in ulcerated surface area, n (%)	–	–	n=42 22 (52.4)	n=40 8 (20.0)	n=32 17 (53.1)	n=31 4 (12.9)
Number of patients with zero ulcers/erosions, n (%)	n=48 2 (4.2)	n=49 4 (8.2)	n=42 10 (23.8)	n=40 3 (7.5)	n=32 11 (34.4)	n=32 5 (15.6)
Number of patients with SES-CD remission (SES-CD ≤2), n (%)	n=48 1 (2.1)	n=49 4 (8.2)	n=42 10 (23.8)	n=40 3 (7.5)	n=32 11 (34.4)	n=32 5 (15.6)
Number of patients with mucosal healing*, n (%)	n=48 0 (0)	n=49 2 (4.1)	n=42 7 (16.7)	n=40 1 (2.5)	n=32 6 (18.8)	n=32 4 (12.5)

These effects of vedolizumab in the pouch mucosa are consistent with those observed in the wider patient population with IBD

Jairath et al. ECCO. 2023

Ustekinumab Dose Optimization Recaptures Response

- Retrospective, single center study of patients with chronic pouchitis prescribed ustekinumab:
  - 80.4% had clinical response 8-16 weeks after ustekinumab initiation
  - 50.0% underwent dose intensification after a median of 223 days
  - 63.6% had clinical response 8 to 16 weeks after dose intensification



Dalal et al. Inflamm Bowel Dis. 2022

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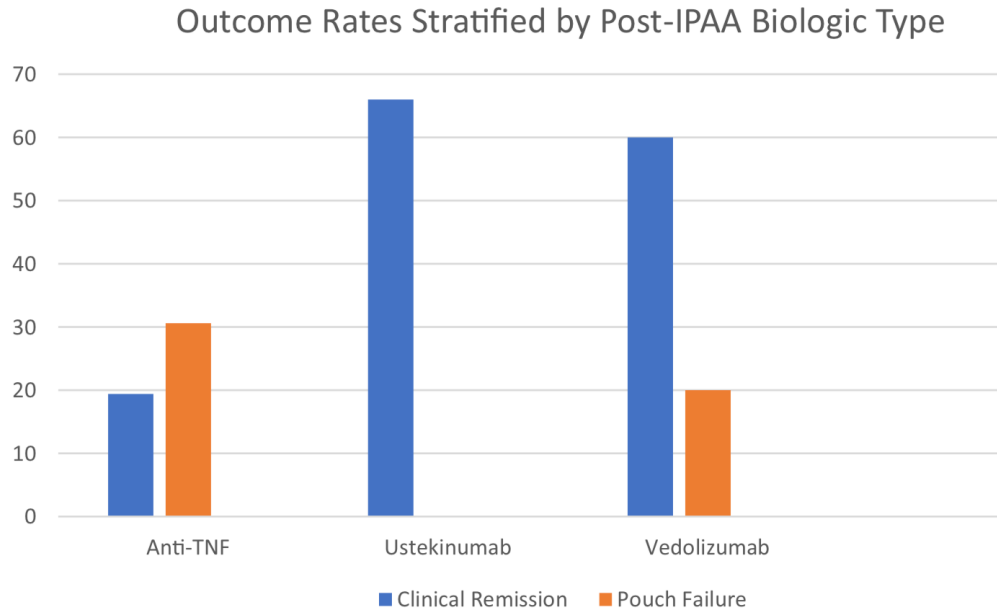
Recycling of Pre-Colectomy Anti-TNF Agents in Chronic Pouch Inflammation is Associated with Treatment Failure

- Retrospective study, N=83 patients on biologic therapy for chronic pouch inflammation, N=57 on anti-TNF agents
- Patients exposed to anti-TNF agents pre-colectomy and post-IPAA were less likely to experience clinical remission and more likely to have pouch failure



Kayal et al. Clin Gastroenterol Hepatol. 2020

EBMed #EvidenceIsPower

Treatment Targets

Clinical Remission

Endoscopic Improvement

Calprotectin Reduction

Insufficient data to support endoscopic, histologic or biomarker remission as treatment targets

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Not All Pouch Symptoms Are Due to Pouchitis

Symptoms :
Incontinence, bloating, abdominal cramping, hematochezia, incomplete evacuation, pelvic pain

Surgical Complications
<12 months post-op

- **Anastomotic leak**
- **Pelvic sepsis**
- **Pouch fistula**

Functional Disorders

- **Dyssynergic defecation**
- **Irritable pouch syndrome**
- **Fecal incontinence**

Cuffitis

- **Symptoms similar to proctitis**

MRE, MR pelvis, anorectal manometry, MR defecography, laparoscopy

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Conclusions

- Pouchitis is the most common long term complication after IPAA
  - Not all pouch disorders are pouchitis!

- Chronic pouch inflammation occurs in up to 20% of patients
  - Chronic antibiotic dependent or refractory
  - Crohn's disease like pouch inflammation

- Vedolizumab is the first biologic to show efficacy in chronic antibiotic refractory pouchitis in a RCT

CASE STUDY

What's First Line in UC Pancolitis?

Case Presenter: Priscila Santiago, MD

Moderator: Samir Shah, MD

Panel: Aja McCutchen, MD and Joshua Novak, MD

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A 24 yo Female With Bloody Diarrhea

- Presented to PCP 1 week ago with new onset of diarrhea in the last month, progressed to up to 10 BMs/day, Bristol stool 7, mostly with blood and mucus, significant urgency.
- + Cramps, tenesmus, nighttime symptoms.
- + Decreased energy levels, 5 lbs weight loss.
- No hospitalization.

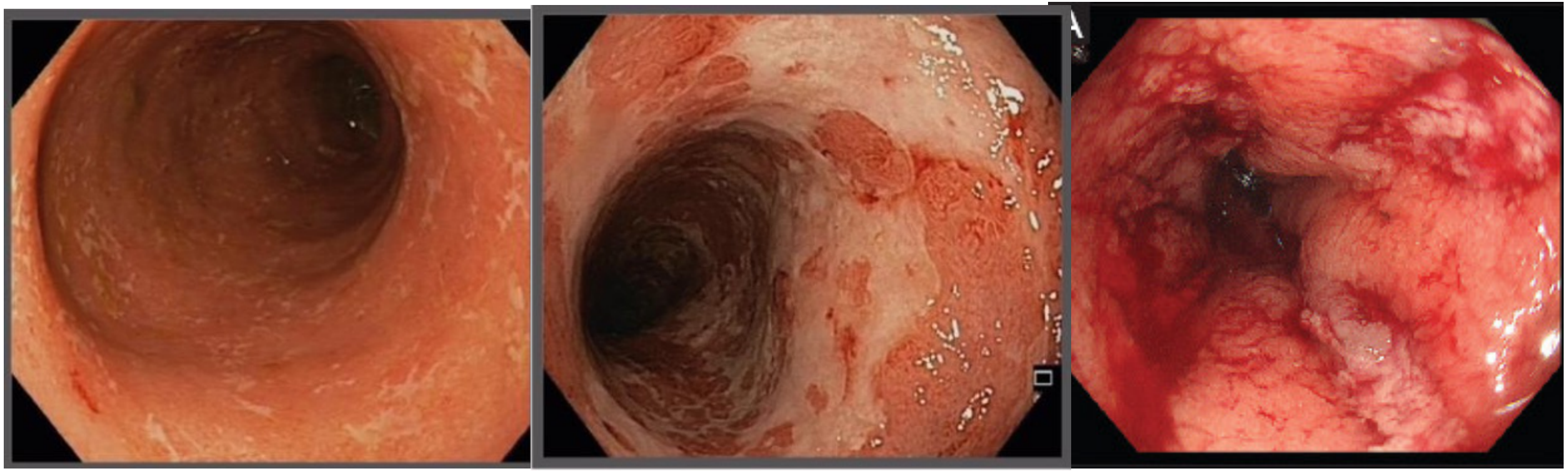
- No tobacco or NSAIDs. No recent travel or sick contacts.
- No other PMH. No abdominal surgeries.
- Meds: oral contraceptive.
- No family history of IBD or CRC.
- Married, no kids.

Diagnostic Evaluation

LABS:

- WBC 7, Hgb 11, Ferritin 20, Iron sat 15%
- Normal liver tests. Albumin 3.9.
- CRP 25
- Fecal calprotectin 1,500
- Negative stool pathogen panel

Colonoscopy



Biopsies: chronic active severe inflammation. No CMV.

Komeda Y, et al. *Ann Gastroenterol*. 2023;36:97-102.

Case Continues…

- Diagnosed with severe pancolonic UC
- Treated with prednisone 40 mg x 1wk – and received a taper
- Comes to see you in GI clinic:
  - 5 BMs per day (Type 6), **no** blood, but still with mucus, cramps.
  - CRP 10. Negative viral hepatitis panel. Normal Quantiferon Gold.

- She has seen TV commercials about upadacitinib and she is interested to know if that would be an option for her.

Questions

1. Given that patient had clinical response to oral steroids, what would be your first choice for an advanced medical therapy?

2. What do you tell her about upadacitinib candidacy?
   - How would you counsel her about the side effect profile? Any special concerns for a young female patient?

3. What if the patient had **mild to moderate** pancolonic disease on index colonoscopy? Would you consider other initial therapies, like an S1P modulator?

Increased Ostomy Output in Crohn's Disease with Short Bowel Syndrome

Rahul S. Dalal, MD, MPH

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Case

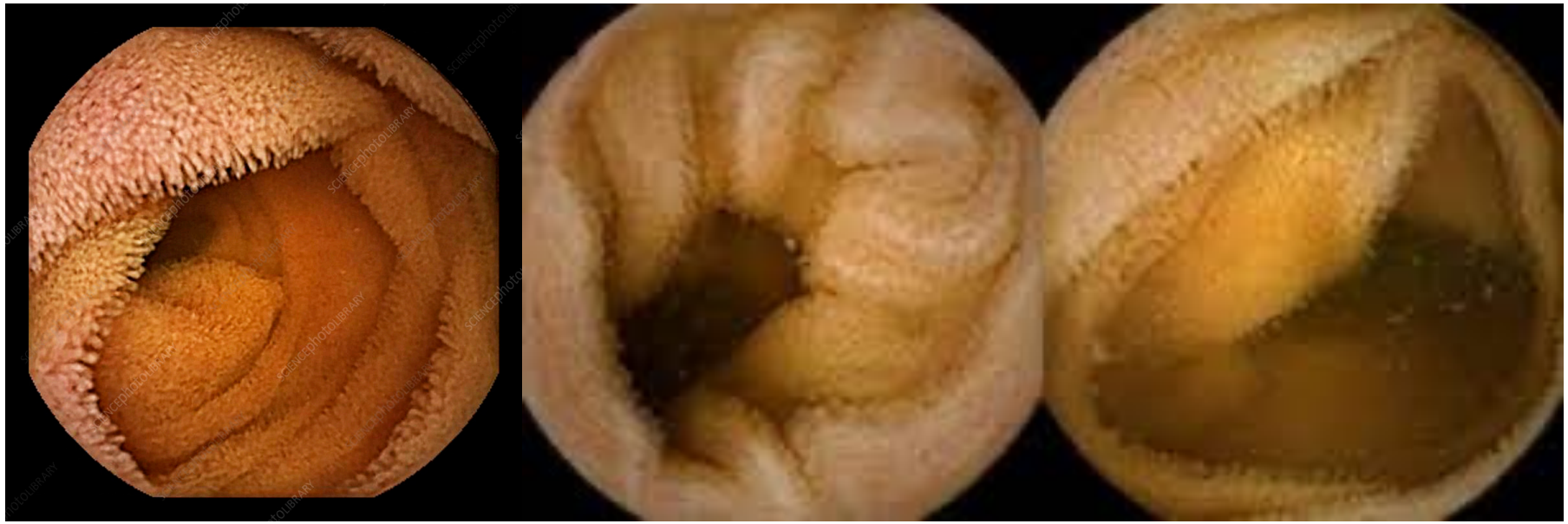
- A 57 year-old female with history of stricturing Crohn's disease of ileum and colon with subtotal colectomy/end ileostomy and 3 small bowel resections undergoes an additional ileal resection for an incarcerated peristomal hernia. The remaining small bowel is 140 cm in length.

- Prior advanced therapies include infliximab, adalimumab + 6-mercaptopurine, and upadacitinib. Post-operatively, she is started on risankizumab.

- Over the next 3 months, she is hospitalized twice for dehydration and hypomagnesemia/hypokalemia. Ostomy output exceeds 2L/24 hours despite maximizing her oral anti-diarrheal regimen. BMI is 17.

What are your next steps in evaluation?

- EGD and ileoscopy are unrevealing. Secretory diarrhea workup is negative. She undergoes a successful patency capsule followed by video capsule (representative images below):



- At 4-month follow-up, she requires weekly IV fluids and electrolyte repletion. BMI is now 15.

- She is started on parenteral nutrition (PN) due to worsening of ostomy output with trials of oral and enteral nutrition.

- A trial of octreotide results in no improvement.

What is your next step in therapy?

What are your treatment goals?

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- Tedaglutide is started at 0.05 mg/kg daily.

- After 24 weeks, she is able to take some nutrition orally and PN requirements have decreased by 50%. She still requires IV fluids and electrolytes monthly.

- After 72 weeks, she is off of PN and on an oral diet. IV fluids and electrolytes are required rarely.

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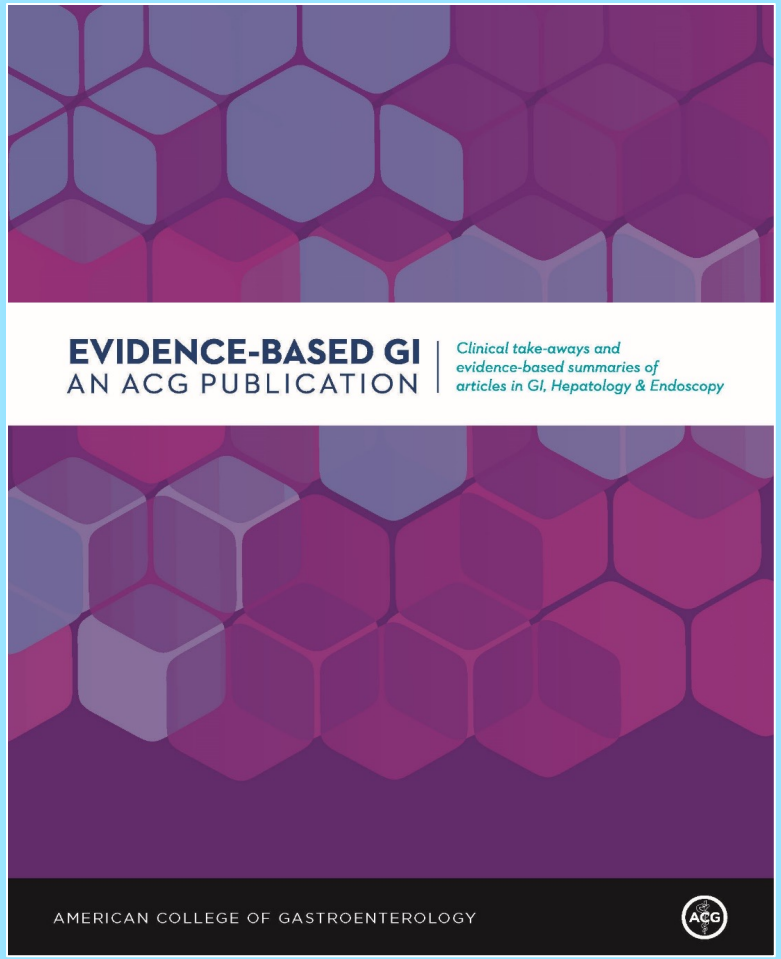

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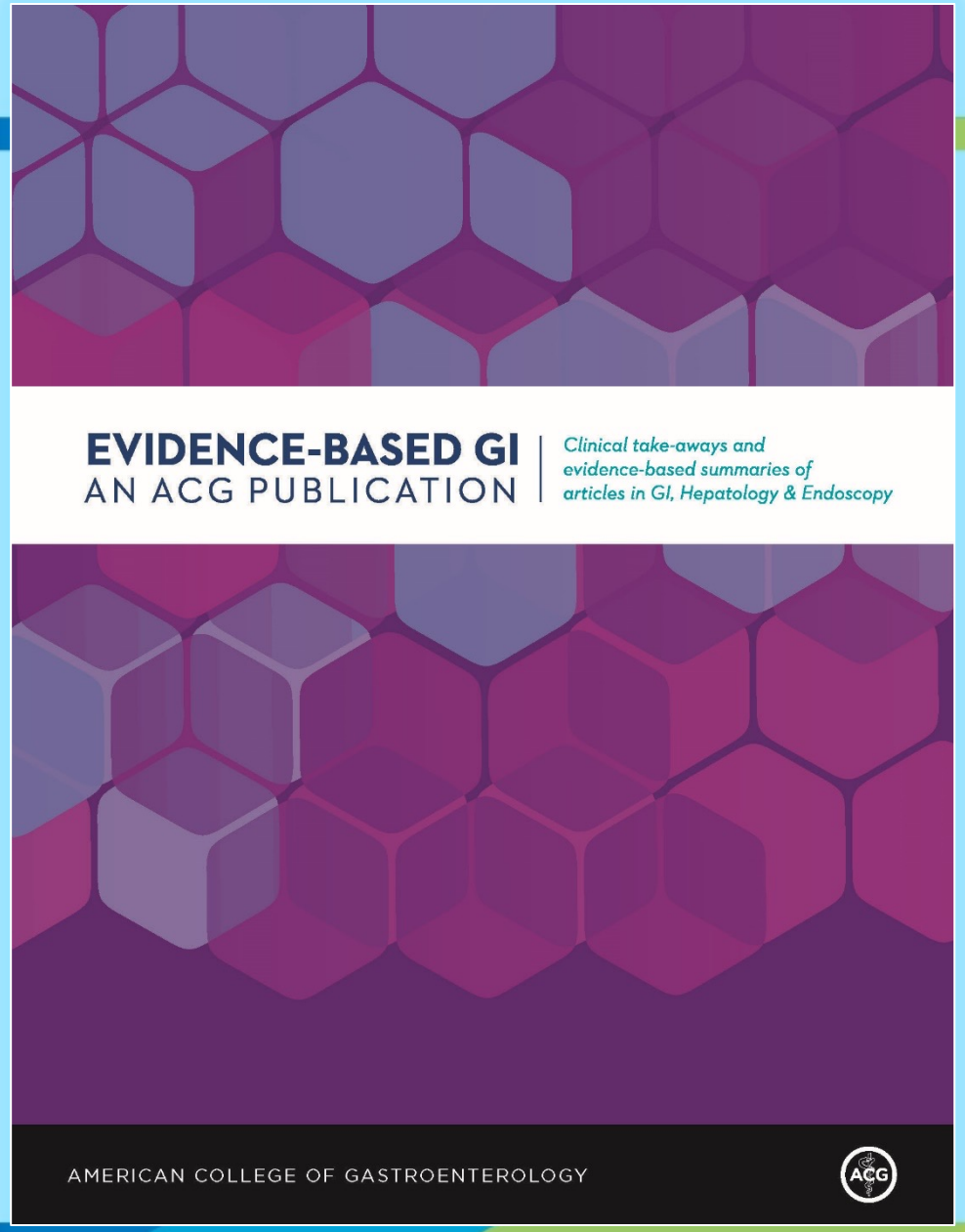
American College of. New issue of Evidenced-Based GI - Each issue is available on the ACG website. Log in with your A... Jul 12



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Upadacitinib Is Effective for the Induction and Maintenance of Moderate-to-Severe Crohn's Disease

Rahul Dalal, MD, MPH; Jessica Allegretti, MD, MPH

Listen to the audio summary

In two 12-week, double-blind, placebo-controlled randomized control trials of moderate-to-severe Crohn's disease patients, upadacitinib 45 mg daily was more effective than placebo at inducing clinical remission: 50% vs 29% in U-EXCEL, and 39% vs 21% in U-EXCEED. In a 52-week, double-blind, placebo-controlled randomized control trial, upadacitinib 30 mg and upadacitinib 15 mg daily was more effective than placebo at maintaining clinical remission: 48% vs 37% vs 15%, respectively.

Summarizing Loftus EV Jr, Panés J, Lacerda AP, Peyrin-Biroulet L, et al. Upadacitinib Induction and Maintenance Therapy for Crohn's Disease. N Engl J Med. 2023 May 25;388(21):1966-1980. doi:

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Best of Evidence-Based GI: Esophageal Disorders

Moderator: Swathi Eluri MD

Panel: Felice Schnoll-Sussman, MD, MSc and Prakash Gyawali, MD, MRCP

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Non-Erosive GERD Does Not Lead to an Increased Risk of Esophageal Adenocarcinoma: A Nordic Population Based Cohort Study

Swathi Eluri, MD, MSCR

Senior Associate Consultant, Mayo Clinic Florida, Jacksonville, FL; Adjunct Assistant Professor of Medicine, University of North Carolina School of Medicine, Chapel Hill, NC

This summary reviews: Holmberg D, Giola S, von Euler-Chelpin M, et al. Non-erosive gastro-oesophageal reflux disease and incidence of oesophageal adenocarcinoma in three Nordic countries: population based cohort study. BMJ 2023;382:e076017

Tweetorial Provided by:

Kuntal Bhowmick, MD

@KBhowmick92

PGY-3, Brown University

Dr. Eluri and Dr. Bhowmick have no conflicts of interest.

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Importance

"Non-Erosive GERD Does Not Lead to an Increased Risk of Esophageal Adenocarcinoma: A Nordic Population Based Cohort Study"
This summary reviews Holmberg D, Giola S, von Euler-Chelpin M, et al. *BMJ.* 2023;382:e076017.

"Doc, how sure are you that I don't need anymore cancer screening?"

How likely are patients with GERD to develop esophageal adenocarcinoma after a normal screening endoscopy?

Untreated gastroesophageal reflux disease (GERD), a prevalent chronic condition, is a major risk factor for erosive esophagitis, Barrett's esophagus, and esophageal adenocarcinoma, prompting screening endoscopy in those at risk. However, many GERD patients do not have erosive disease.

ACG Guidelines: "We suggest against repeat screening in patients who have undergone an initial negative screening examination by endoscopy."

Quality of Evidence: Low

The evidence for these guidelines are based off a maximum of 6 years of follow-up.

The study by Holmberg et al. bridges an important gap in the literature with over 30 years of follow-up data.

"Hm."

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Definitions & Endpoints

"Non-Erosive GERD Does Not Lead to an Increased Risk of Esophageal Adenocarcinoma: A Nordic Population Based Cohort Study"
This summary reviews Holmberg D, Giola S, von Euler-Chelpin M, et al. *BMJ.* 2023;382:e076017.

Definitions

GERD – At least weekly symptoms of troublesome heartburn or regurgitation.
Erosive GERD – GERD diagnosis with endoscopic features of esophagitis.
Non-Erosive GERD – GERD diagnosis with a normal endoscopy.

Question

Are patients with non-erosive GERD at an increased risk of developing esophageal adenocarcinoma?

End Point

Incidence of esophageal adenocarcinoma
Identified by coding data.

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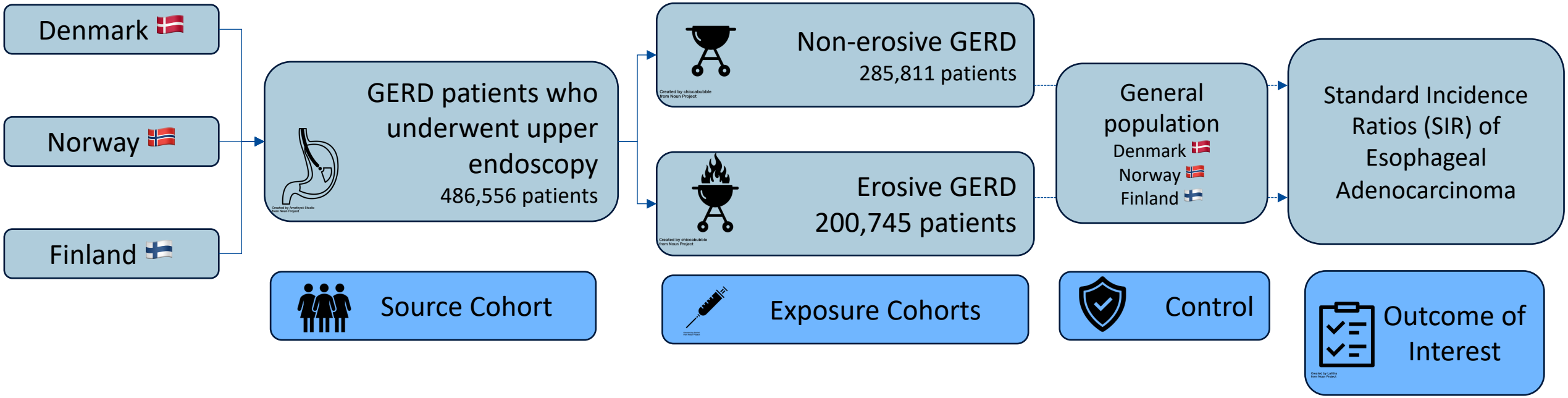
Study Design

"Non-Erosive GERD Does Not Lead to an Increased Risk of Esophageal Adenocarcinoma: A Nordic Population Based Cohort Study"
This summary reviews Holmberg D, Giola S, von Euler-Chelpin M, et al. *BMJ.* 2023;382:e076017.



Observational

Population-based

1/1/1987 — 12/31/2019

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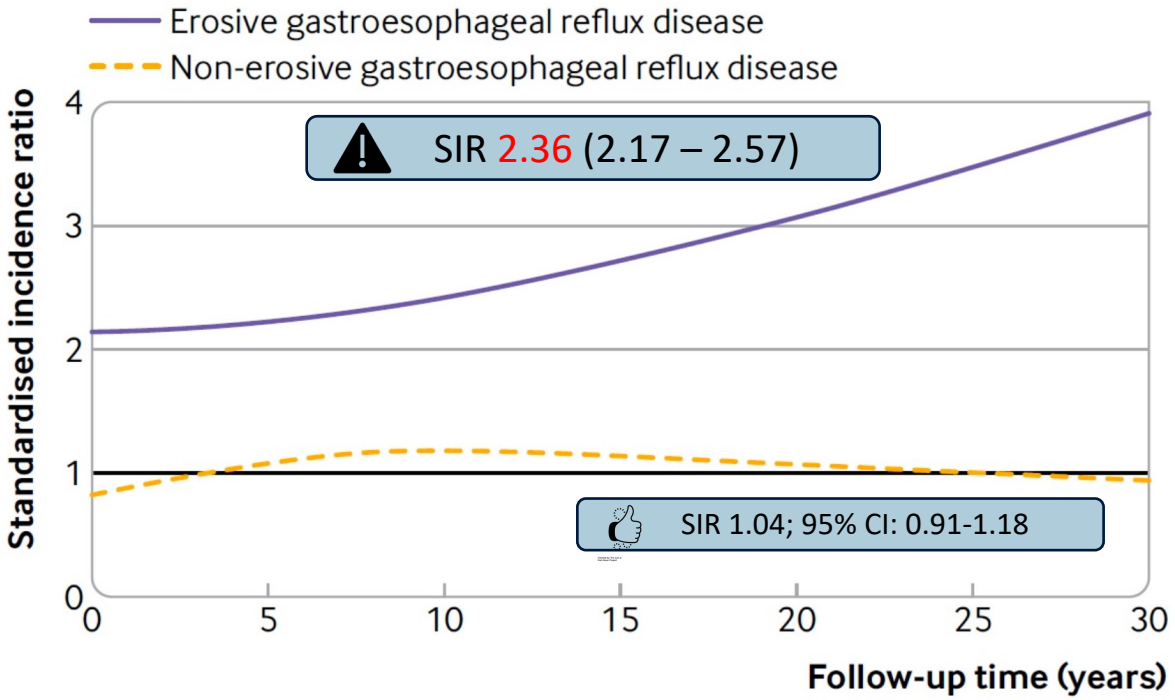
Results

"Non-Erosive GERD Does Not Lead to an Increased Risk of Esophageal Adenocarcinoma: A Nordic Population Based Cohort Study"
This summary reviews Holmberg D, Giola S, von Euler-Chelpin M, et al. *BMJ.* 2023;382:e076017.



Subgroup	SIR for Non-Erosive GERD	SIR for Erosive GERD
1-4 years follow-up	0.86 (0.67 - 1.09)	⚠ 2.14 (1.82 - 2.51)
15-31 years follow-up	1.07 (0.65 - 1.65)	⚠ 2.73 (2.15 - 3.42)
Women	⚠ 1.38 (1.08 - 1.73)	⚠ 2.82 (2.31 - 3.41)

Patients with non-erosive GERD carried similar risk for esophageal cancer to that of the general population, even at longer follow-up intervals.

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Caution

“Non-Erosive GERD Does Not Lead to an Increased Risk of Esophageal Adenocarcinoma: A Nordic Population Based Cohort Study”
This summary reviews Holmberg D, Giola S, von Euler-Chelpin M, et al. *BMJ.* 2023;382:e076017.

Limited medication data

Unclear if patients were on proton pump inhibitor (PPI) therapy, raising several questions.

Created by Ken Messenger from Noun Project

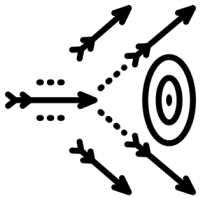
Did erosive GERD cohort develop cancer despite adequate PPI therapy?

Did non-erosive GERD have adequate symptom control that prevented cancer development?

Non-erosive GERD or functional heartburn?

Created by Ji Sub Jeong from Noun Project

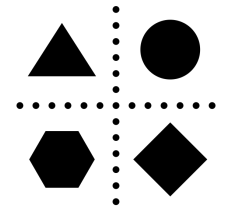
GERD was diagnosed by ICD code. How many patients in the non-erosive “GERD” cohort had true GERD or functional heartburn?



Created by WEBTECHOPS LLP from Noun Project

Misclassification bias?

Did any cases of healed erosive GERD get categorized to the non-erosive GERD cohort because of a normal endoscopy?



Created by Bold Yellow from Noun Project

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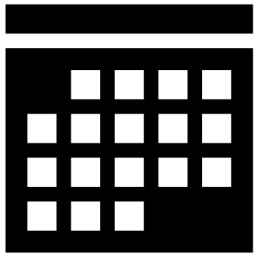
Questions

1. What is your practice for follow-up of non-erosive GERD?

2. If symptoms are not well-controlled, how do you differentiate true gastro-esophageal reflux from functional heartburn? Another EGD? More acid suppression? Esophageal manometry, Bravo, etc.?

My Practice

"Non-Erosive GERD Does Not Lead to an Increased Risk of Esophageal Adenocarcinoma: A Nordic Population Based Cohort Study"
This summary reviews Holmberg D, Giola S, von Euler-Chelpin M, et al. *BMJ.* 2023;382:e076017.



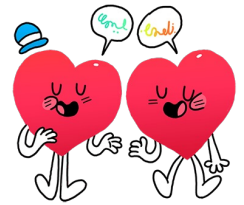
My Practice: Follow Non-erosive GERD Clinically

Maintain annual follow-up with non-erosive GERD.

This otherwise excellent study was unable to tell us the impact of symptom control on esophageal cancer risk in non-erosive GERD.

If symptoms are well-controlled, do not re-screen.

Ensure appropriately treating GERD or functional heartburn.



This study reinforces the ACG guideline recommendation with robust, long-term data:

"We suggest against repeat screening in patients who have undergone an initial negative screening examination by endoscopy."

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Vonoprazan, a Potassium-Competitive Acid Blocker, Is Superior to Lansoprazole for Managing Erosive Esophagitis

Dr. Philip Schoenfeld
Editor-in-Chief
Editor-in-Chief

Philip Schoenfeld, MD, MSEd, MSc (Epi)

Chief (Emeritus), Gastroenterology Section, John D. Dingell VA Medical Center, Detroit, MI

Tweetorial provided by:

Romy Chamoun, MD
@RomyChamoun

EBGI Ambassador

PGY-3, Lankenau Medical

Conflict of Interest: Dr. Schoenfeld reports being an advisory board member and consultant for Phathom Pharmaceuticals. Dr. Chamoun reports no conflicts of interest.

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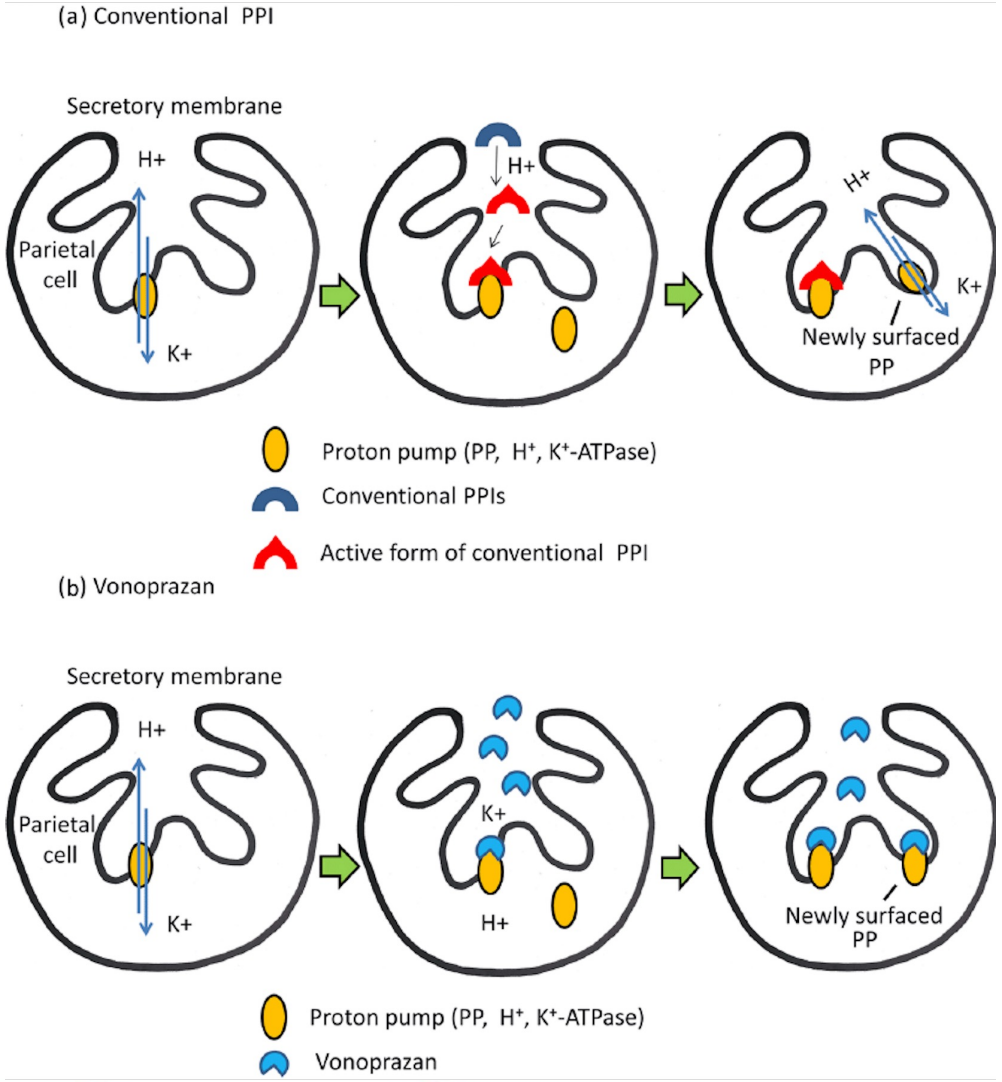
Adapted from:
Akazawa Y, et al. Vonoprazan-based therapy for *Helicobacter pylori* eradication: experience and clinical evidence. *Therap Adv Gastroenterol*. 2016;9:845-852.



Conventional PPIs are
- unstable in canaliculi
- rapidly degraded
- not able to inhibit new proton pumps (PPs) that surface after administration of the drug.

→ require a few days to reach their maximum effect

Vonoprazan, a potassium-competitive acid blocker acts differently:

✓does not require acid activation
✓rapidly absorbed in the small intestine
✓binding to H+/K+-ATPase in a K+-competitive manner
✓more stable than conventional PPIs in the canaliculi

→ fast and stable inhibition of gastric acid secretion

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Adapted from:
Laine L, et al. Vonoprazan Versus Lansoprazole for Healing and Maintenance of Healing of Erosive Esophagitis: A Randomized Trial. *Gastroenterology*. 2023;164:61-71.

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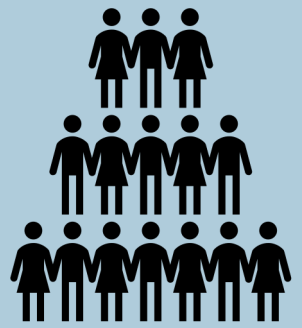

≥ 18 years old + Erosive esophagitis on endoscopy

Active *Helicobacter pylori* infection & Barrett's esophagus.

Randomized Controlled trial

Vonoprazan 20 mg daily

Endoscopy to assess healing was performed at 2 weeks and 8 weeks

Lansoprazole 30 mg daily

who achieved healing were re-randomized 1:1:1 to V 20, V10 or L15

Vonoprazan 20 mg daily

Vonoprazan 10 mg daily

Lansoprazole 15 mg daily

Tx X 24 weeks, followed by repeat upper endoscopy.

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Adapted from:
Laine L, et al. Vonoprazan Versus Lansoprazole for Healing and Maintenance of Healing of Erosive Esophagitis: A Randomized Trial. *Gastroenterology*. 2023;164:61-71.

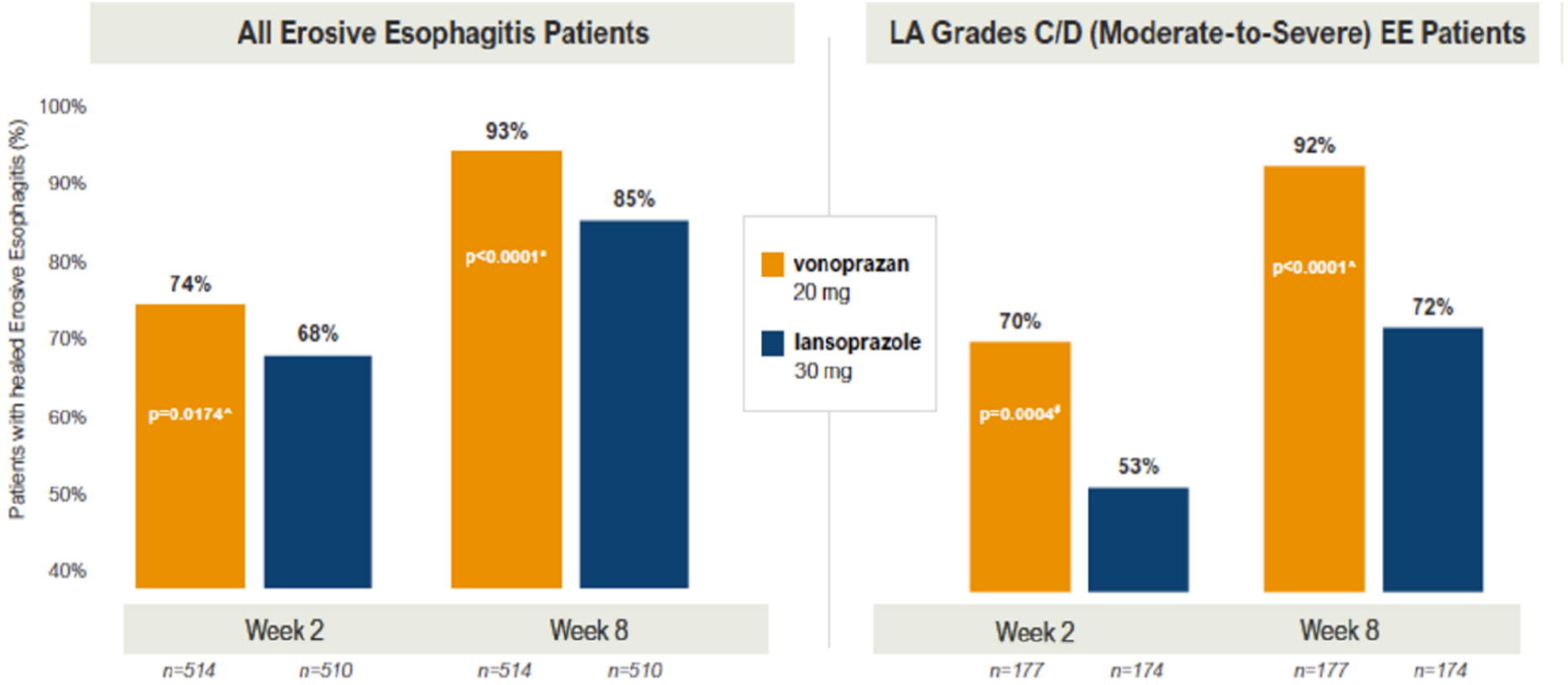

Figure 1. Healing of erosive esophagitis.

LA, Los Angeles

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Adapted from:
Laine L, et al. Vonoprazan Versus Lansoprazole for Healing and Maintenance of Healing of Erosive Esophagitis: A Randomized Trial. *Gastroenterology*. 2023;164:61-71.

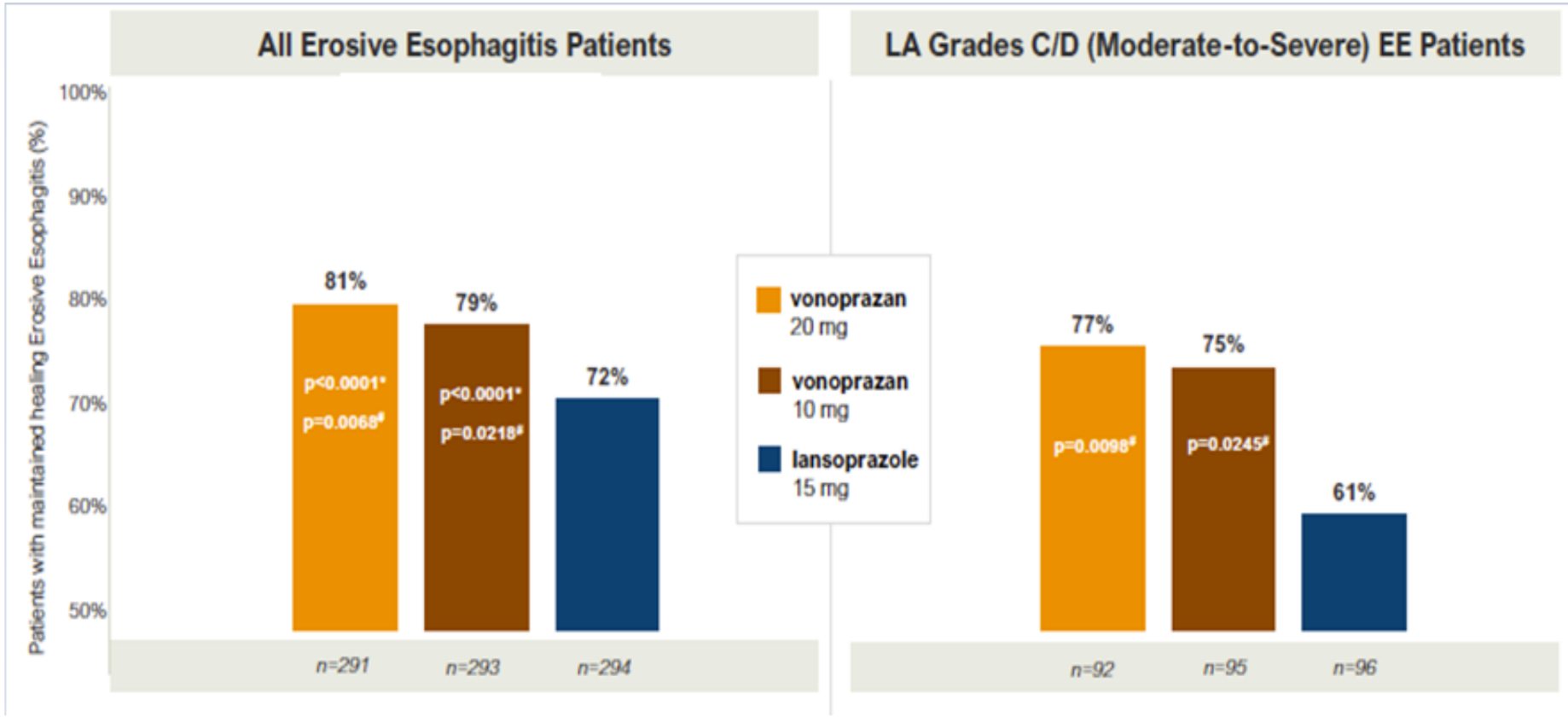

Figure 2. Maintenance of healing erosive esophagitis.

EE, erosive esophagitis

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Questions

1. When are you likely to use vonoprazan for erosive esophagitis?

2. If GERD symptoms recur, but healed esophagitis on repeat EGD, then what is your preferred treatment approach?

STEP-UP Treatment for Eosinophilic Esophagitis (EoE)

Joan Chen, MD MS
Clinical Associate Professor of Medicine
Division of Gastroenterology & Hepatology
University of Michigan

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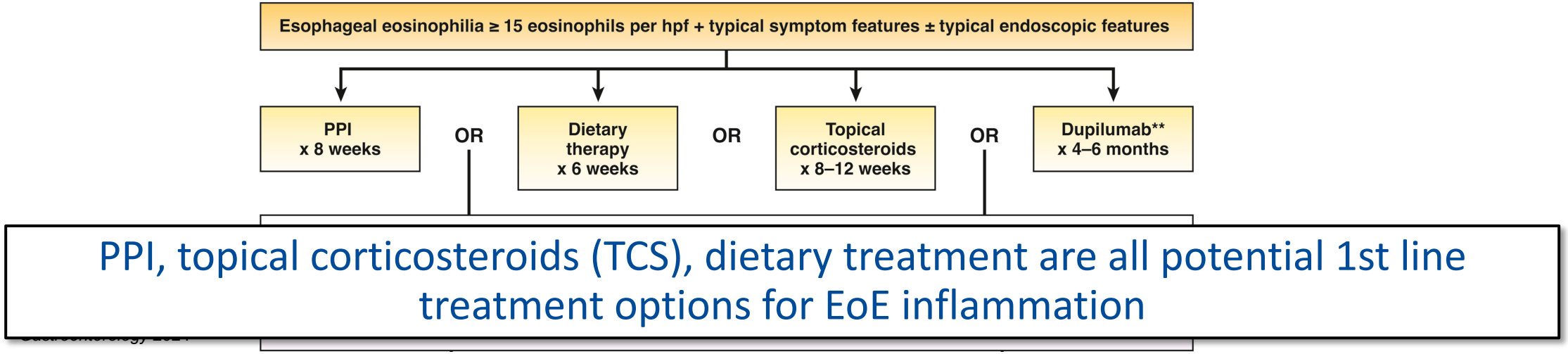
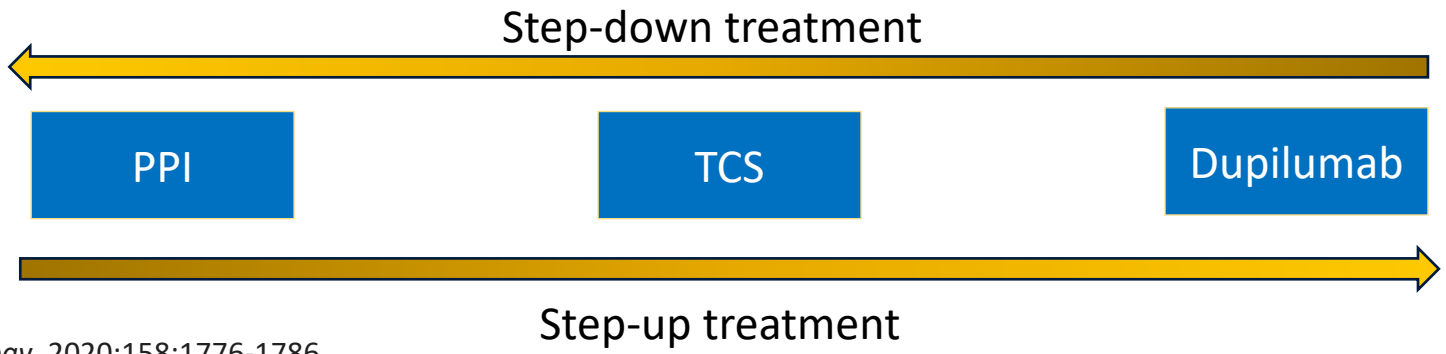
Current EoE Treatment Guideline



PPI, topical corticosteroids (TCS), dietary treatment are all potential 1st line treatment options for EoE inflammation



Hirano I, et al. *Gastroenterology*. 2020;158:1776-1786.

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STEP-UP Therapy for EoE

Why try PPI first?

- It is effective
  - Data on PPI in EoE
  - Comparative data on PPI vs. TCS
- It is safe with long-term data available
- Other considerations

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Efficacy of PPI in EoE

Efficacy of Proton Pump Inhibitor Drugs for Inducing Clinical and Histologic Remission in Patients With Symptomatic Esophageal Eosinophilia: A Systematic Review and Meta-Analysis

Alfredo J. Lucendo,* Ángel Arias,‡ and Javier Molina-Infante§

Clinical Gastroenterology and Hepatology 2016;14:13–22

- 33 studies (11 prospective) with 619 EoE patients included.
- PPI led to a clinical response in 60.8% (95% confidence interval, 48.38%–72.2%; I^2=80.2) and histologic remission in 50.5% (95% confidence interval, 42.2%–58.7%; I^2=67.5) of patients.

Efficacy of proton pump inhibitor therapy for eosinophilic oesophagitis in 630 patients: results from the EoE connect registry

Laserna-Mendieta & the EUREOS EoE CONNECT Research group, Aliment Pharmacol Ther. 2020;52:798–807

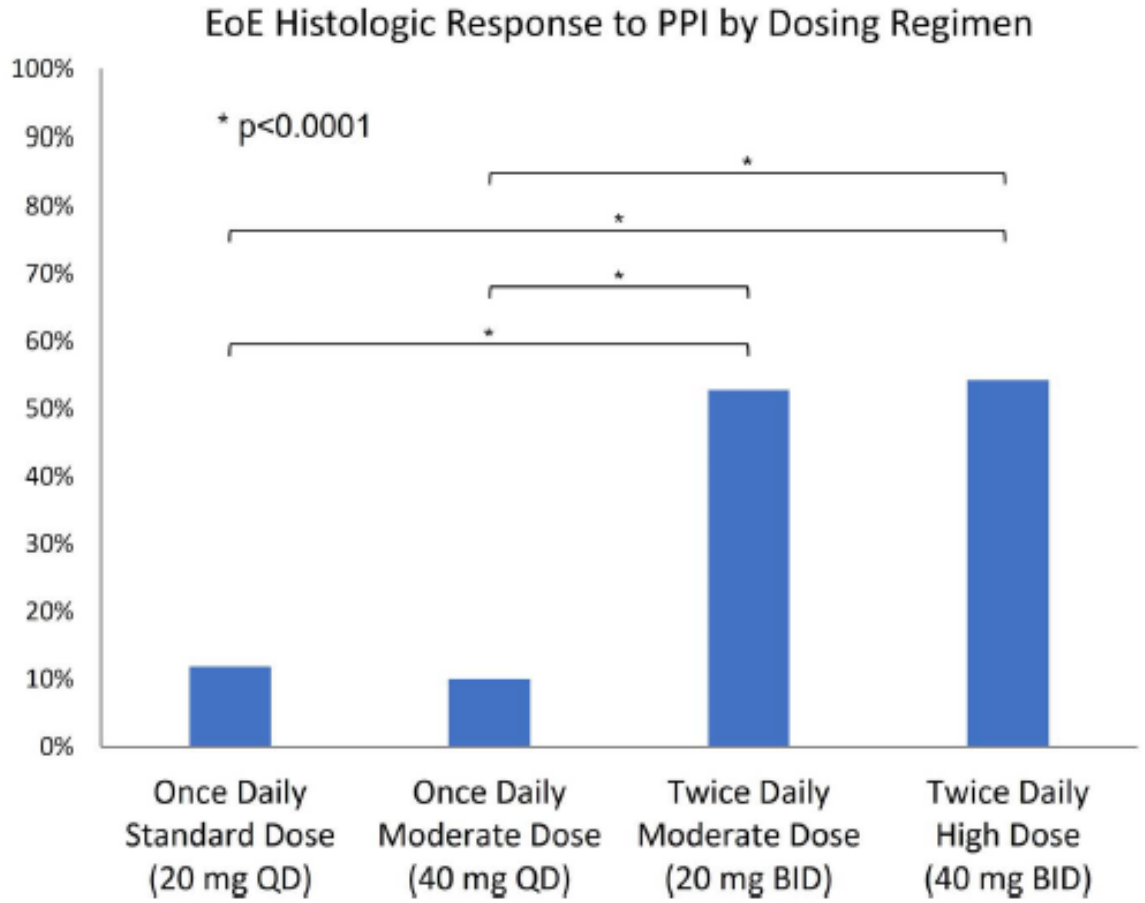
- PPI therapy reduced eos <15 eos/hpf in 48.8% of patients, with 37.9% of patients achieving deep histological (<5 eos/hpf) remission.
- PPI therapy induced symptomatic improvement in 71.0% of patients
- Clinico-histological remission was achieved in 48.9%

Efficacy of PPI in EoE

Efficacy of proton pump inhibitor therapy fo oesophagitis in 630 patients: results from th registry

Laserna-Mendieta & the EUREOS EoE CON

- Likelihood of clinico-histological remission was grea dose PPI (51% vs 36%; p=.027; OR 1.85).
- PPI treatment length >10-12 weeks provided highe rate increased from 50.4% to 65.2% when treatmer



Twice-Daily Proton Pump Inhibitor Induces Higher Remission Rate in Eosinophilic Esophagitis Than Once-Daily Regimen Regardless of Total Daily Dose

Muftah M, et al, *Am J Gastroenterol* 2024;00:1-5

- Retrospecitve analysis of 305 patients with newly diagnosed EoE on PPI treatment.
- Twice-daily PPI is associated with higher EoE histologic response rates than once-daily PPI (optimal PPI induction regimen: 20mg omeprazole BID or equivalent)

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PPI vs. Topical Steroid in EoE

Systematic review with network meta-analysis: comparative effectiveness of topical steroids vs. PPIs for the treatment of the spectrum of eosinophilic oesophagitis

S. Lipka*, A. Kumar†, B. Miladinovic† & J. E. Richter‡

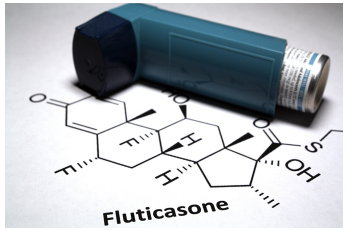
Aliment Pharmacol Ther. 2016;43:663-73

- SUCRA ranking probability indicated that PPI had the highest probability of being the best treatment for achieving histological remission and mean change in eosinophils (PPI>budesonide>fluticasone). None of the comparison indicated a statistically significant difference.

RCT

Nexium 40mg QD

vs.



Fluticasone 440mcg BID x8 weeks

Moawad F, et al. *Am J Gastroenterol*. 2013;108:366-372.

- 42 patients randomized
- No difference in histologic response between groups (19 vs 33%, p=0.484)
- Symptoms improved after esomeprazole but not fluticasone

Peterson K, et al. *Dig Dis Sci*. 2010;55:1313-1319.

- 30 patients randomized
- No significant difference in improvement in dysphagia score or histologic response between arms.

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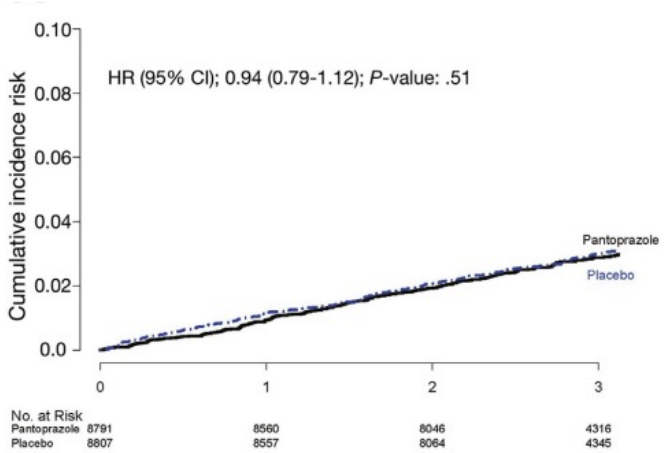
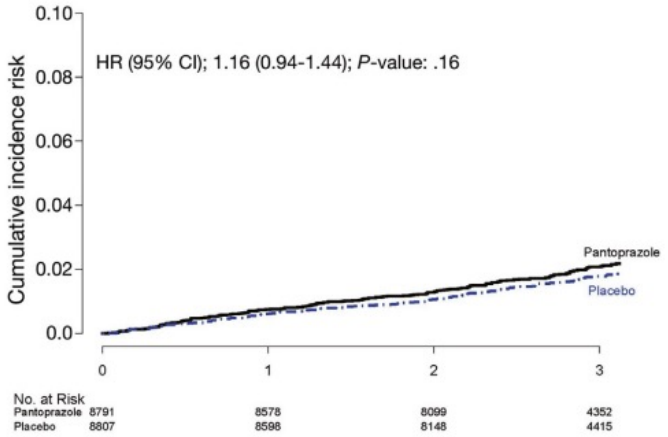
PPI Safety in a Large, Multi-Year Randomized Trial

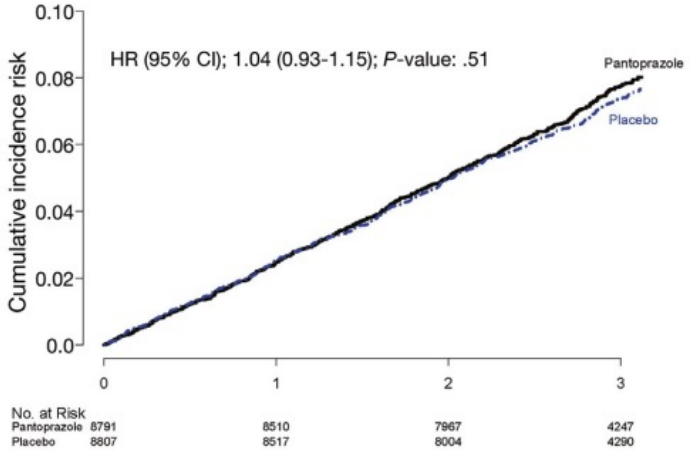
Myocardial infarction



Stroke



CV death, MI, stroke



Long term AEs were similar in pantoprazole vs. placebo arms of a randomized trial with 53,000 patient years of follow-up.

Moayyedi P, et al. *Gastroenterology*. 2019;157:682-691.e2.

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PPIs Were Associated With an Increased Risk of Enteric Infections

Outcome	Incident events, n (%)		OR (95% CI)	*P* value
	Pantoprazole 40 mg/day n=6947	Placebo n=6868		
Gastric atrophy	10 (0.1)	24 (0.2)	0.71 (0.31-1.59)	0.40
C difficile	5 (<0.1)	2 (<0.1)	2.48 (0.48-12.8)	0.28
Other enteric infection	**60 (0.9)**	**42 (0.6)**	**1.42 (0.95-2.10)**	**0.08**
Chronic kidney disease	104 (1.5)	98 (1.4)	1.05 (0.80-1.39)	0.73
Dementia	24 (0.3)	22 (0.3)	1.08 (0.60-1.93)	0.80
Pneumonia	203 (2.9)	185 (2.7)	1.09 (0.89-1.33)	0.41
Fracture	136 (2.0)	150 (2.2)	0.89 (0.71-1.13)	0.35
COPD	94 (1.4)	83 (1.2)	1.12 (0.83-1.51)	0.45
Diabetes mellitus	393 (5.7)	423 (6.2)	0.91 (0.79-1.05)	0.21

- A statistically significant increased risk of enteric infections in those allocated to PPI was found (though this became non-significant after excluding those permanently discontinued PPI or placebo)
- Number needed to harm was >300 with 3 years of PPI use

Moayyedi P, et al. *Gastroenterology.* 2019;157:682-691.

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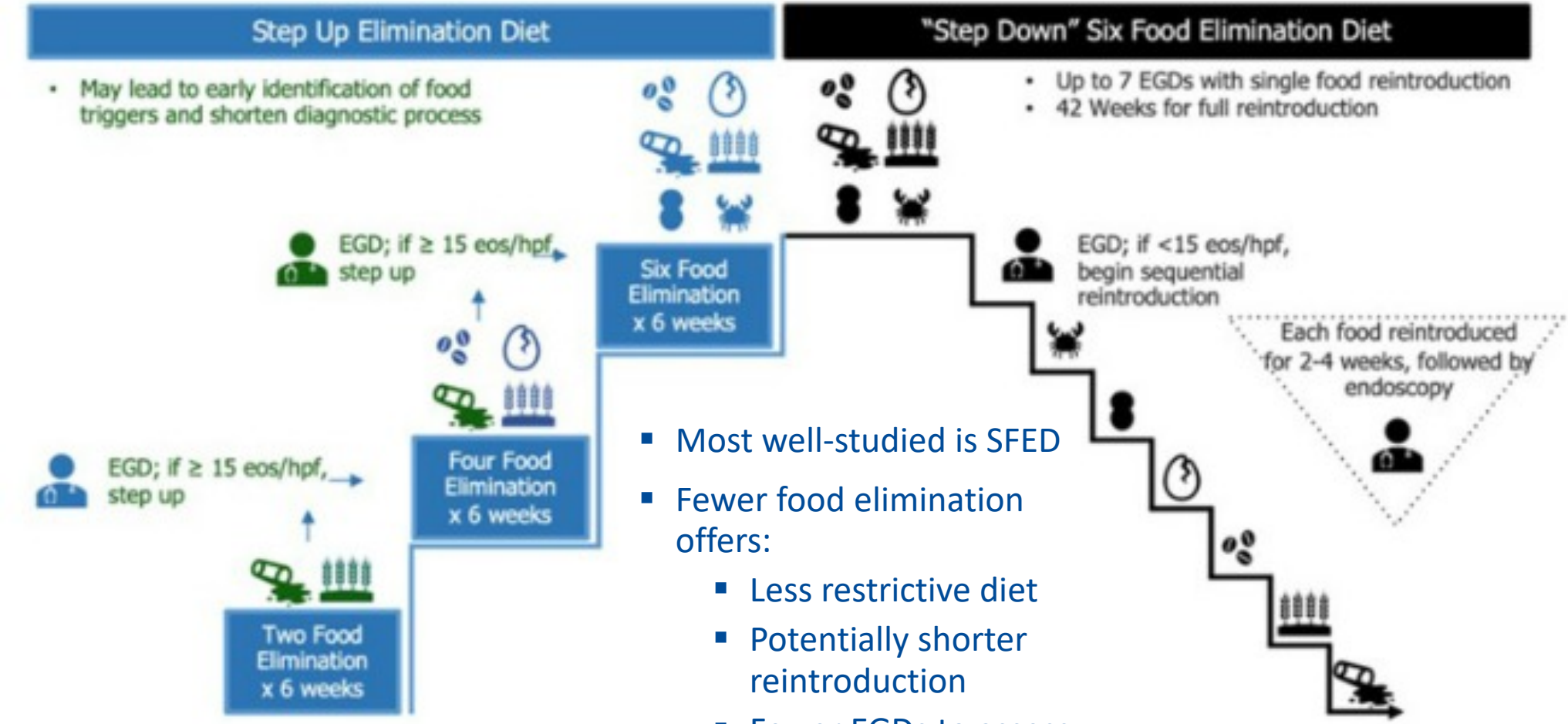
Other Considerations

- Ease of starting the medication (widely available)
- Ease of use
- Least costly
- Treat GERD and EoE concurrently
- Limited data on biologics or TCS safety

Step-up vs. Step-down Elimination Diet



- Most well-studied is SFED
- Fewer food elimination offers:
  - Less restrictive diet
  - Potentially shorter reintroduction
  - Fewer EGDs to assess response

Peterson K, et al. *Gastroenterology*. 2024;166:382-395.

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Single Food (Animal Milk) vs. SFED

129 patients randomly assigned (1:1)

Phase 1

67 assigned to 1FED

2 discontinued (insurance and unknown)

62 assigned to 6FED

3 discontinued (2 unwilling to continue 1 non-compliant)

Phase 2

21 patients without histologic remission after 1FED opted for 6FED

1 discontinued (insurance)

11 patients without histologic remission after 6FED opted for topical swallowed fluticasone propionate

2 discontinued (1 removed by investigator 1 suicidal ideation)

Results:

	1FED (n=67)	6FED (n=62)	P value
Partial remission: <15 eos/hpf	23 (34%; 23-46)	25 (40%; 28-53)	0.58
Partial remission: ≤10 eos/hpf	20 (30%; 19-41)	23 (37%; 25-49)	0.46
Partial remission: ≤6 eos/hpf	12 (18%; 9-27)	20 (32%; 21-44)	0.069
Complete remission: ≤1 eos/hpf	4 (6%; 0-12)	12 (19%; 10-29)	0.031

- 43% of patients without histologic response to 1FED who proceeded to 6FED reached histologic remission.
- 82% of patients without histologic response to 6FED who proceeded to fluticasone reached histologic remission.

Kliewer K, et al. *Lancet Gastroenterol Hepatol.* 2023;8:408-421

Single Food (Animal Milk) vs. SFED

	1FED (n=67)			6FED (n=62)			6FED vs 1FED	
	Baseline	Week 6	Change from baseline to week 6	Baseline	Week 6	Change from baseline to week 6	Change difference (95% CI)	p value
Peak eosinophil count, eos/hpf	50·3 (42·2 to 60·0)	20·8 (15·0 to 28·9)	0·41 (0·29 to 0·57)	38·4 (32·8 to 44·9)	10·9 (7·3 to 16·5)	0·29 (0·20 to 0·43)	0·72 (0·43 to 1·20)	0·21
EoEHSS total	0·83 (0·77 to 0·90)	0·68 (0·60 to 0·76)	−0·15 (−0·25 to −0·06)	0·81 (0·74 to 0·88)	0·58 (0·50 to 0·65)	−0·23 (−0·32 to −0·14)	−0·08 (−0·21 to 0·05)	0·23
EoEHSS grade	0·43 (0·39 to 0·47)	0·34 (0·30 to 0·38)	−0·09 (−0·14 to −0·04)	0·42 (0·39 to 0·46)	0·30 (0·26 to 0·33)	−0·13 (−0·17 to −0·08)	−0·04 (−0·11 to 0·03)	0·26
EoEHSS stage	0·39 (0·36 to 0·42)	0·33 (0·29 to 0·37)	−0·06 (−0·11 to −0·01)	0·39 (0·35 to 0·42)	0·28 (0·24 to 0·32)	−0·11 (−0·15 to −0·06)	−0·04 (−0·11 to 0·02)	0·21
EREFS total	3·7 (3·3 to 4·2)	3·0 (2·5 to 3·4)	−0·6 (−1·0 to −0·2)	4·2 (3·7 to 4·7)	2·8 (2·3 to 3·3)	−1·0 (−1·5 to −0·4)	−0·4 (−1·1 to 0·3)	0·28
EEsAI total	29·3 (24·5 to 34·2)	26·1 (21·3 to 30·9)	−3·0 (−7·2 to 1·2)	30·1 (25·4 to 34·7)	21·7 (17·5 to 25·9)	−8·2 (−12·6 to −3·8)	−5·2 (−11·2 to 0·8)	0·091
EoE-QoL-A total	68·9 (65·0 to 72·7)	67·1 (62·7 to 71·5)	−0·9 (−3·5 to 1·6)	64·2 (59·9 to 68·6)	63·9 (59·7 to 68·1)	−0·3 (−3·3 to 2·7)	0·6 (−3·3 to 4·5)	0·76
PROMIS GH physical health T-score	49·4 (48·0 to 50·9)	50·8 (49·3 to 52·2)	1·3 (0·4 to 2·2)	50·6 (48·8 to 52·4)	52·2 (50·7 to 53·8)	1·6 (0·5 to 2·8)	0·4 (−1·0 to 1·7)	0·61
PROMIS GH mental health T-score	50·0 (48·4 to 51·5)	51·6 (50·0 to 53·2)	1·5 (0·4 to 2·7)	51·7 (49·8 to 53·5)	52·5 (50·6 to 54·4)	1·1 (−0·3 to 2·5)	−0·4 (−2·2 to 1·3)	0·62

P value
0.58
0.46
0.069
0.031

Kliewer K, et al. *Lancet Gastroenterol Hepatol.* 2023;8:408-421

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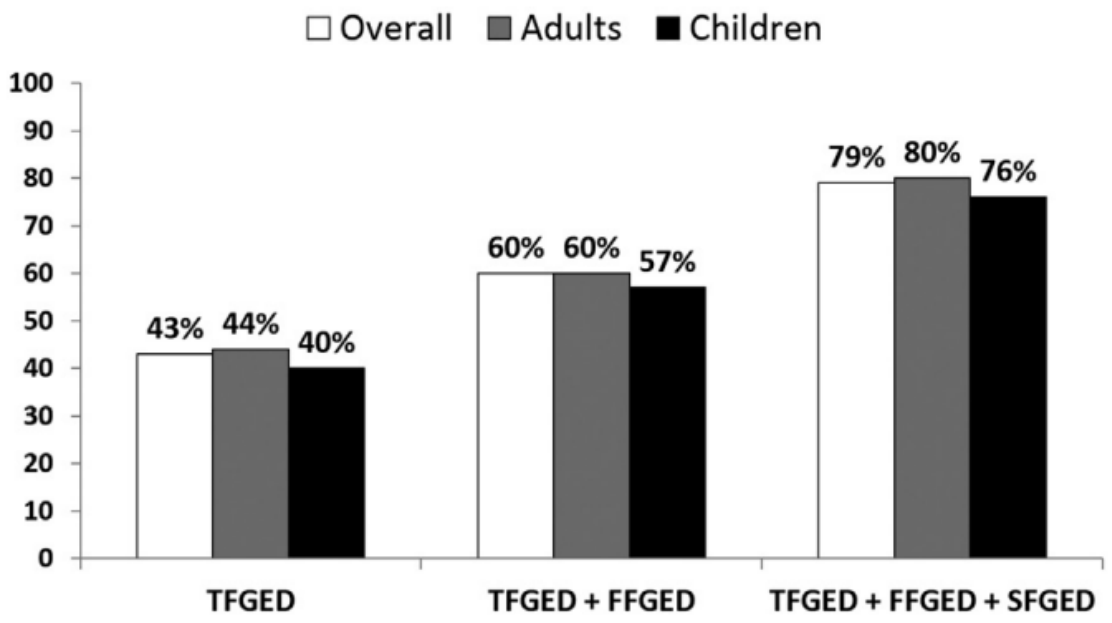
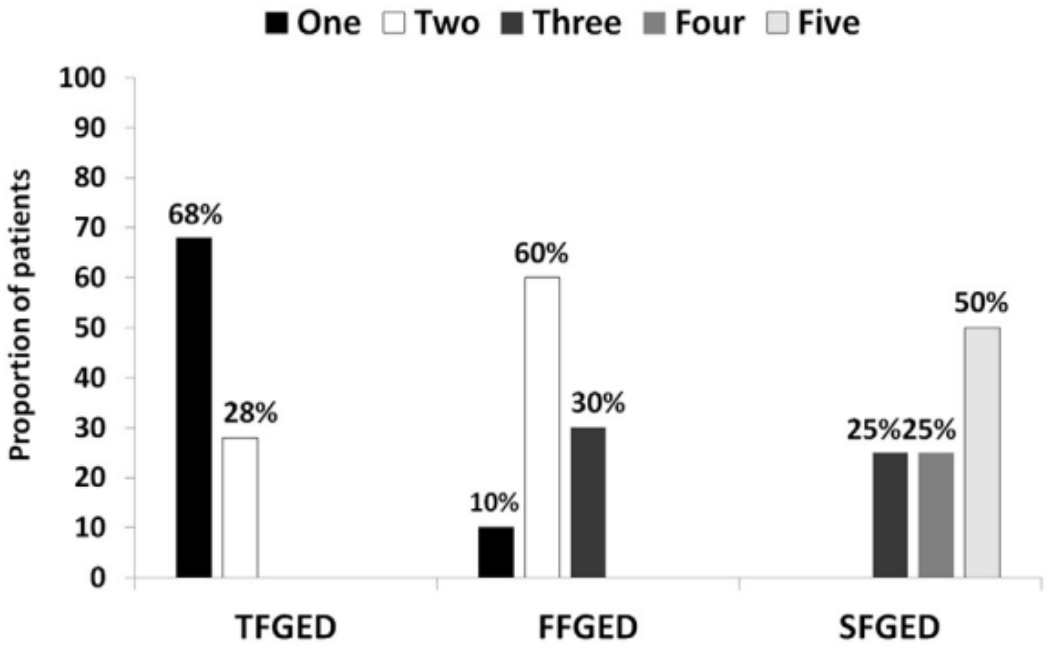
2-4-6 Food Elimination Diet





Step-up 2-4-6 or 2-4 strategies might save 20% and 30% of endoscopic procedures and diagnostic process time, respectively, compared to SFED (top-down approach).

Molina-Infante J, et al. *J Allergy Clin Immunol*. 2018;141:1365-1372.

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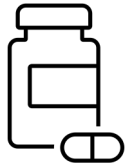
Other Considerations

- Patient preference and personal situations
- Availability of specialized dietitians
- Individual patient history and comorbidity/nutritional status
- Other food allergies
- EoE disease severity

Summary: STEP UP THERAPY



PPI trial upfront → topical corticosteroid → biologics

- PPIs are effective
- Easy & safe (with long-term data available)

Single or TFED → FFED → SFED

- Effective
- Ease of less restrictive diet
- Potentially fewer scopes, shorter reintroduction phase

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Debate: Top-Down Treatment for Eosinophilic Esophagitis (EoE)

April 20, 2024

Joy Chang, MD MS

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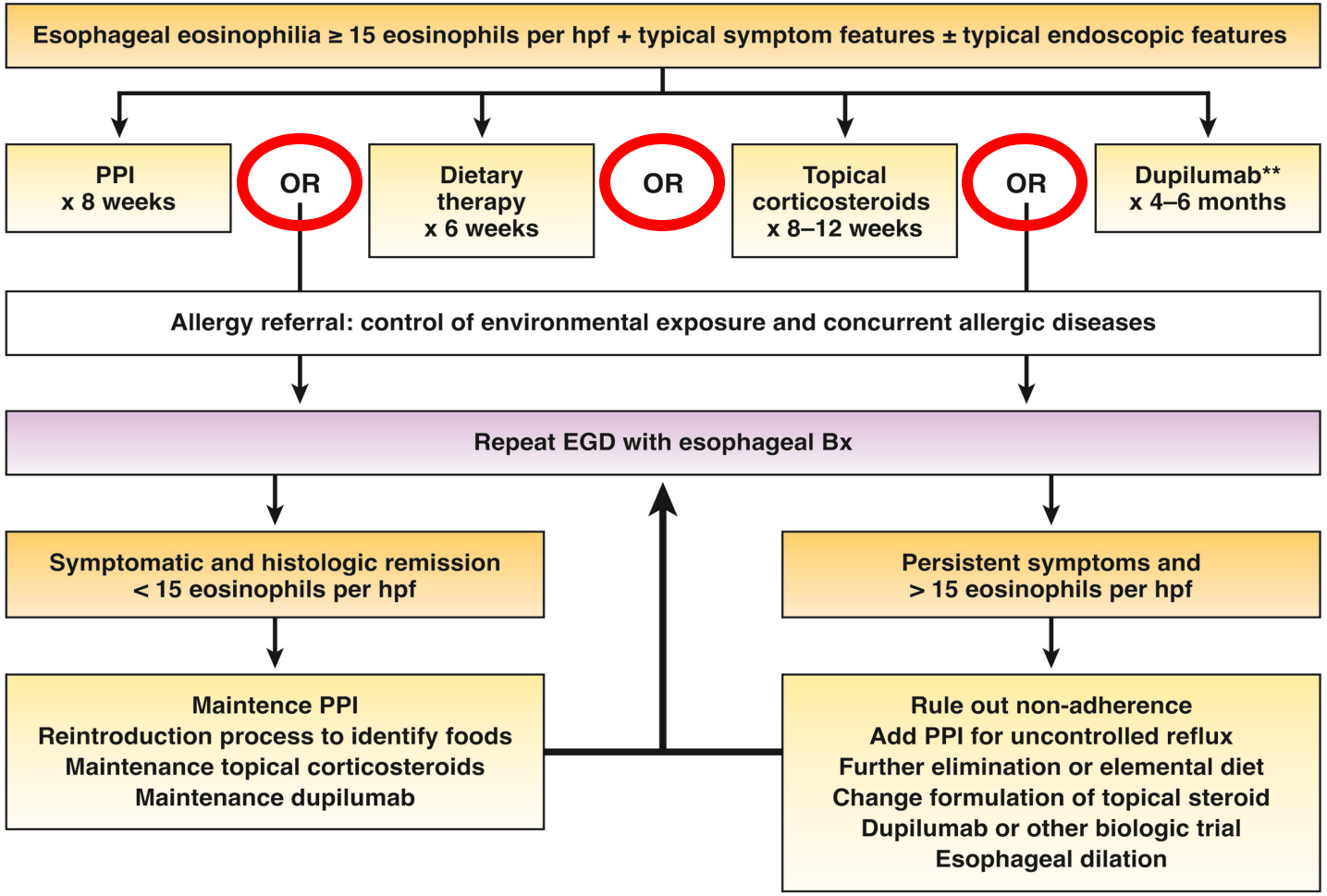
Proposed EoE Treatment Algorithm



Peterson K, et al. *Gastroenterology*. 2024;166:382-395.

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Ideal Management Strategy?

- No studies to date comparing the efficacy of medications versus diet as maintenance therapy.

- Medications **OR** diet are recommended as first-line treatments.
  - PPI
  - Topical corticosteroids
  - Dietary therapy
  - ?Biologics

Ideal Management Strategy?

- No rsus die
- Me ts.
  -
  -
  -
  -

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AGA Guidelines: Management of Eosinophilic Esophagitis Topical Corticosteroids

Recommendation	Strength of recommendation	Quality of evidence
1. Recommendation: In patients with symptomatic esophageal eosinophilia, the AGA/JTF suggests using proton pump inhibition over no treatment.	Conditional	Very low quality
2. In patients with EoE, the AGA/JTF recommends topical glucocorticosteroids over no treatment.	Strong	Moderate
3. In patients with EoE, the AGA/JTF suggests topical glucocorticosteroids rather than oral glucocorticosteroids.	Conditional	Moderate
4. In patients with EoE, the AGA/JTF suggests using elemental diet over no treatment.	Conditional	Moderate
Comment: Patients who put a higher value on avoiding the challenges of adherence to an elemental diet and the prolonged process of dietary reintroduction may reasonably decline this treatment option.		
5. In patients with EoE, the AGA/JTF suggests using an empiric, 6-food elimination diet over no treatment.	Conditional	Low
Comment: Patients who put a higher value on avoiding the challenges of adherence to diet involving elimination of multiple common food staples and the prolonged process of dietary reintroduction may reasonably decline this treatment option.		

Hirano I, et al. *Gastroenterology*. 2020;158:1776-1786.

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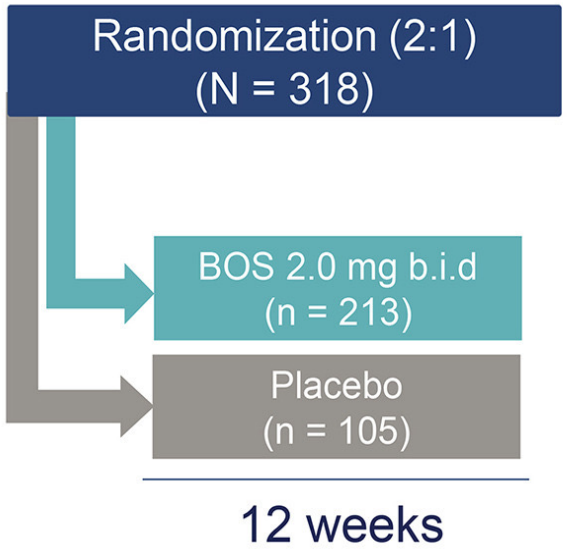
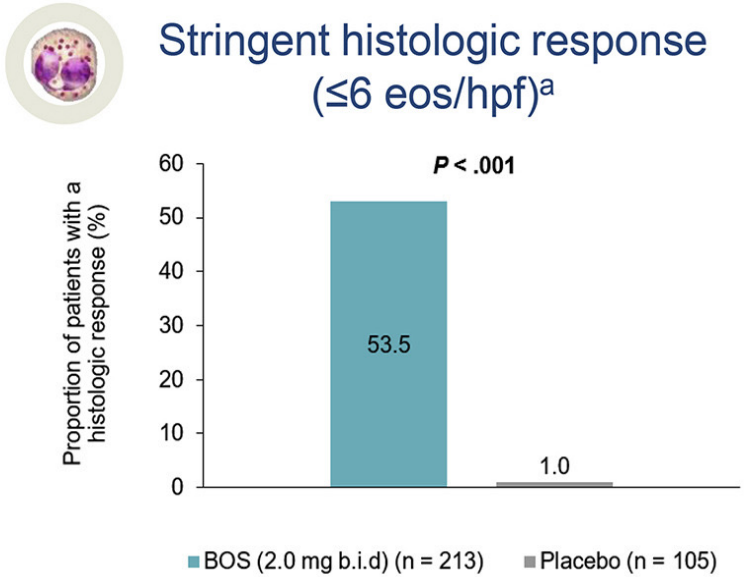
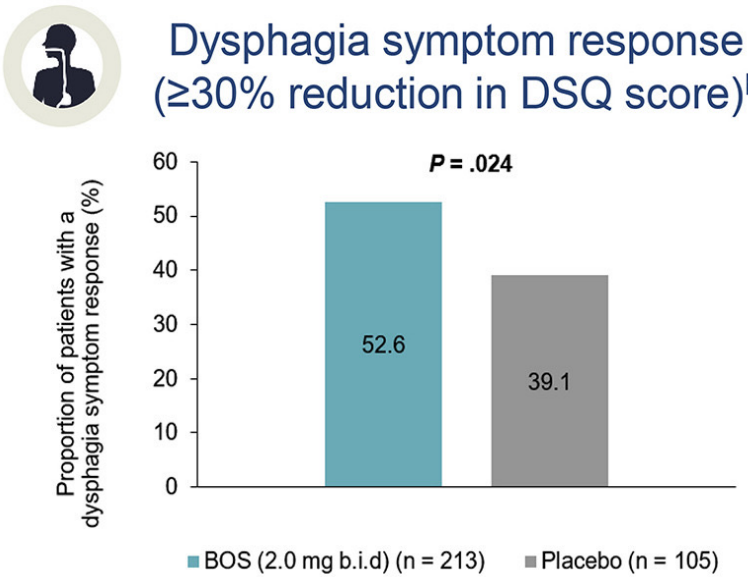
Budesonide Oral Suspension

Patients with eosinophilic esophagitis and dysphagia (11–55 years old) were randomized 2:1 to receive either **budesonide oral suspension (BOS)** or placebo







b.i.d. twice daily; DSQ, Dysphagia Symptom Questionnaire; eos/hpf, eosinophils/high-power field
[a]Stringent histologic response defined as ≤6 eos/hpf at week 12 of therapy; [b]Dysphagia symptom response defined as ≥30% reduction in DSQ score at week 12 of therapy

Clinical Gastroenterology and Hepatology

February 9, 2024: FDA-approved in the US for 12 weeks of treatment in adult and pediatric patients 11 years of age and older with EoE

Hirano I, et al. *Clin Gastroenterol Hepatol*. 2022;20:525-534.e10.

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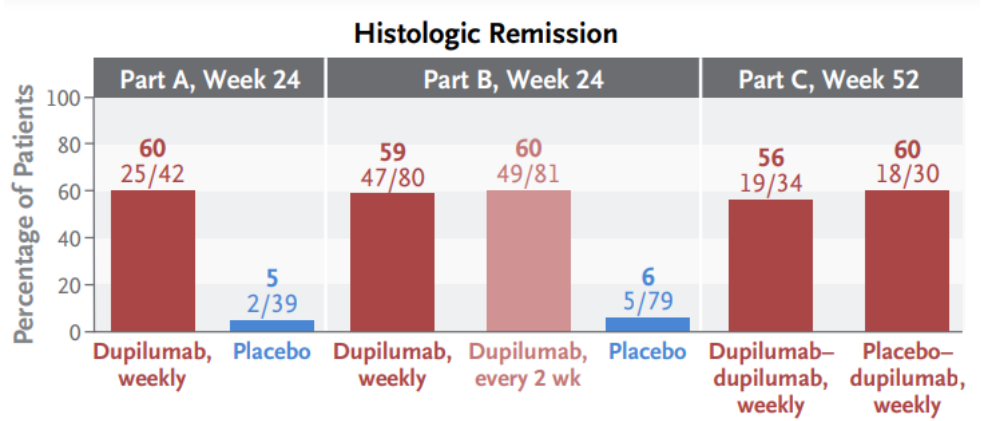
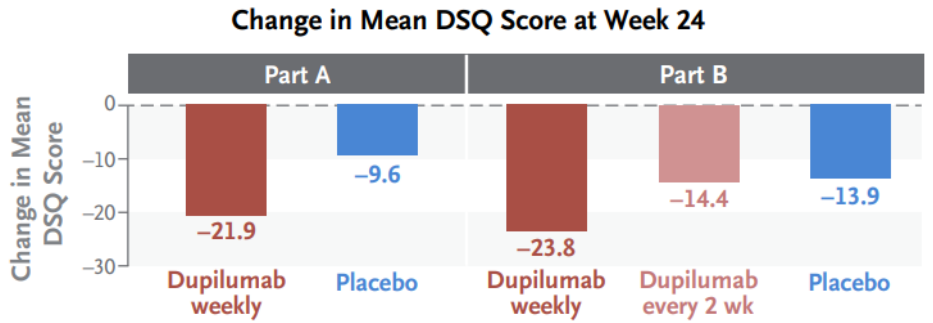
Dupilumab in EoE

- Monoclonal antibody against IL-4Rα (involved in IL4, IL13 signaling)
  - Type 2 inflammatory pathway: IL-4 and IL-13 promote recruitment of eosinophils, fibroblast proliferation



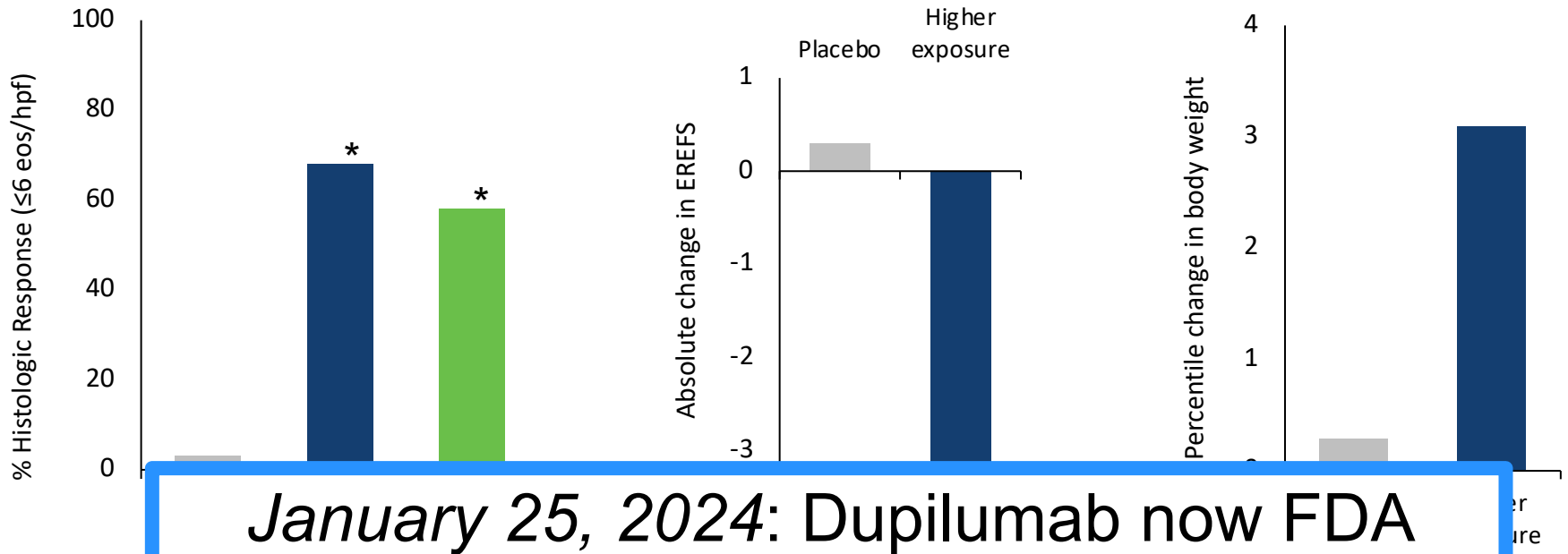


- First FDA-approved medication for EoE, May 2022
  - 300mg weekly subcutaneous injection
- Uncertainties: Balancing pros/cons, who is the "right patient," long-term safety, cost barriers

Hirano I, et al. *Gastroenterology*. 2020;158:1776-1786; Dellon ES, et al. *N Engl J Med*. 2022;387:2317-2330; Rothenberg ME, et al. *Lancet Gastroenterol Hepatol.* 2023;8:990-1004.

Dupilumab in EoE - Children

- Phase 3 RCT of pediatric patients aged 1-11yo (n=102)
- Randomized 1:1:1 (higher dose, lower dose, placebo) for 16 weeks



January 25, 2024: Dupilumab now FDA approved for children ages 1 year and older

Chehade M, et al. UEGW 2022; Chehade M, et al. DDW 2023.

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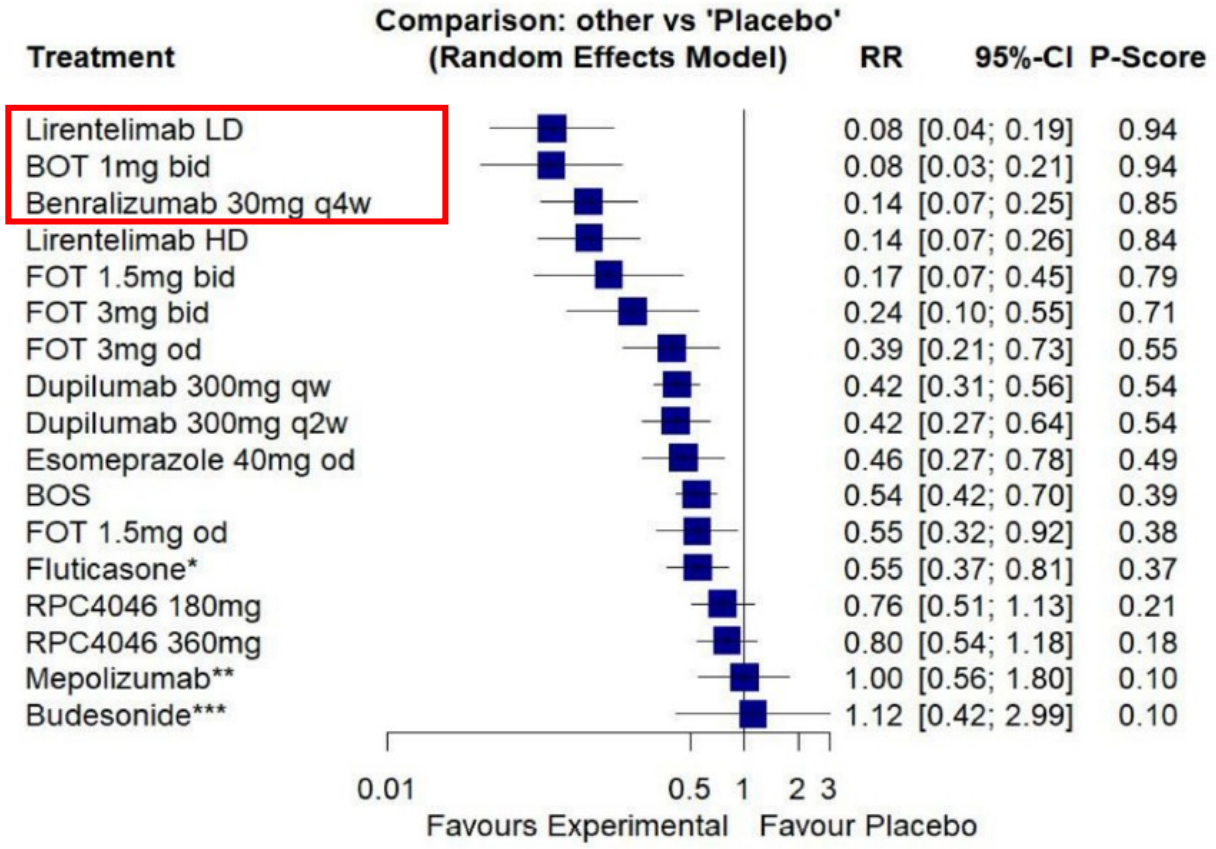
Table 1. Selected Demographic and Clinical Characteristics of the Patients at Baseline (Full Analysis Set).*

Characteristic	Part A			Part B			
	Dupilumab, 300 mg weekly (N=42)	Placebo (N=39)	Total (N=81)	Dupilumab, 300 mg weekly (N=80)	Dupilumab, 300 mg every 2 wk (N=81)	Placebo (N=79)	Total (N=240)
Age — yr	33.9±15.53	28.8±12.53	31.5±14.31	28.7±13.72	27.8±13.21	27.9±12.56	28.1±13.12
Female sex — no. (%)	14 (33)	18 (46)	32 (40)	30 (38)	36 (44)	21 (27)	87 (36)
Duration of eosinophilic esophagitis — yr†	5.23±4.18	4.77±4.55	5.01±4.34	5.89±4.66	5.92±5.18	4.88±4.48	5.57±4.79
Previous use of topical glucocorticoids for eosinophilic esophagitis — no. (%)	29 (69)	31 (79)	60 (74)	55 (69)	65 (80)	56 (71)	176 (73)
Refractory to previous therapy — no. (% of patients with previous use)	23 (79)	21 (68)	44 (73)	32 (58)	38 (58)	34 (61)	104 (59)
Inadequate response to or unacceptable side effects from previous therapy or current contraindication — no. (%)‡	—	—	—	38 (48)	41 (51)	39 (49)	118 (49)
History of esophageal dilation — no. (%)	18 (43)	17 (44)	35 (43)	26 (32)	26 (32)	33 (42)	85 (35)
Food elimination diet at screening — no. (%)	17 (40)	16 (41)	33 (41)	31 (39)	29 (36)	29 (37)	89 (37)
Presence of concurrent type 2 inflammatory disease — no. (%)	33 (79)	35 (90)	68 (84)	71 (89)	74 (91)	69 (87)	214 (89)
Allergic rhinitis	26 (62)	22 (56)	48 (59)	48 (60)	49 (60)	52 (66)	149 (62)
Food allergy	19 (45)	17 (44)	36 (44)	46 (58)	42 (52)	41 (52)	129 (54)
Asthma	10 (24)	15 (38)	25 (31)	32 (40)	31 (38)	27 (34)	90 (38)
Atopic dermatitis	6 (14)	9 (23)	15 (19)	12 (15)	17 (21)	19 (24)	48 (20)
DSQ score§	32.2±12.66	35.1±12.11	33.6±12.41	38.4±10.70	35.6±12.24	36.1±10.55	36.7±11.22
EREFS score¶	6.5±3.20	6.0±2.38	6.3±2.83	6.8±2.96	7.5±3.14	7.2±3.34	7.2±3.15
EoE-HSS grade score‖	1.26±0.41	1.32±0.47	1.29±0.44	1.31±0.39	1.25±0.37	1.23±0.40	1.26±0.39
EoE-HSS stage score‖	1.30±0.33	1.38±0.40	1.34±0.37	1.29±0.32	1.25±0.32	1.22±0.36	1.25±0.34
Peak eosinophil count per high-power field**	82.6±41.02	96.5±54.69	89.3±48.29	89.2±46.67	87.7±49.37	84.3±41.20	87.1±45.76
Median blood peripheral eosinophils (IQR) — IU/ml	430 (260–600)	450 (270–680)	440 (270–610)	420 (280–520)	380 (250–510)	430 (270–530)	400 (270–520)
Median IgE (IQR) — IU/ml	110 (51–463)	100 (47–294)	107 (50–306)	134 (48–302)	134 (47–362)	126 (52–416)	134 (48–330)

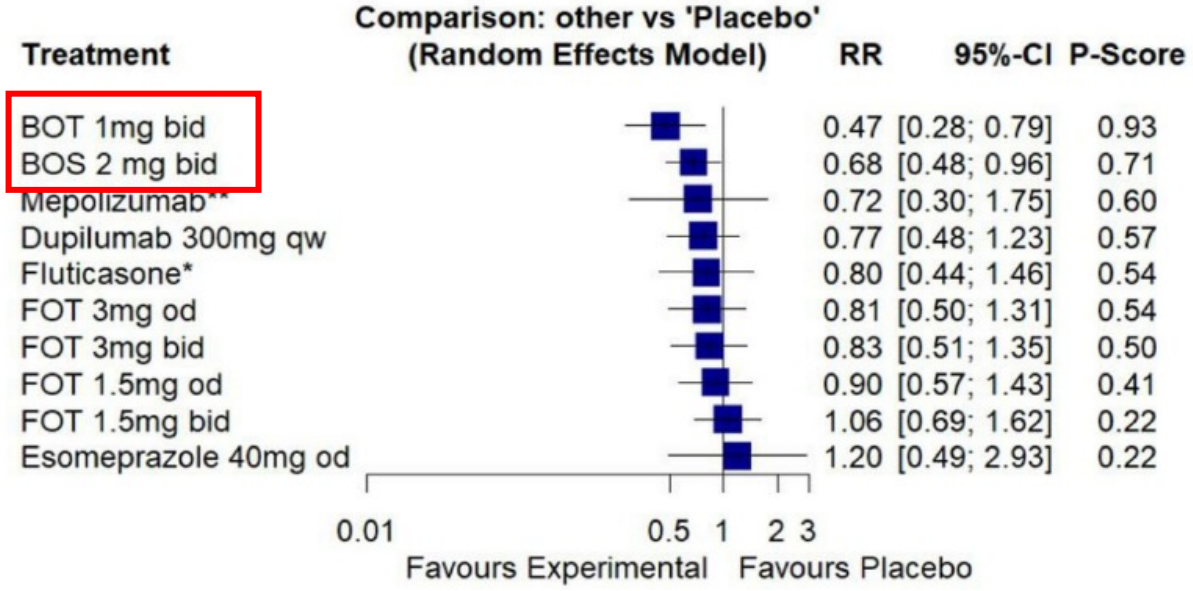
Dellon ES, et al. *N Engl J Med*. 2022;387:2317-2330.

Comparing Pharmacologic Options

Histologic Remission (≤6 eos/hpf)



Symptomatic Remission



Visaggi P, et al, Oesophagus. 2023.

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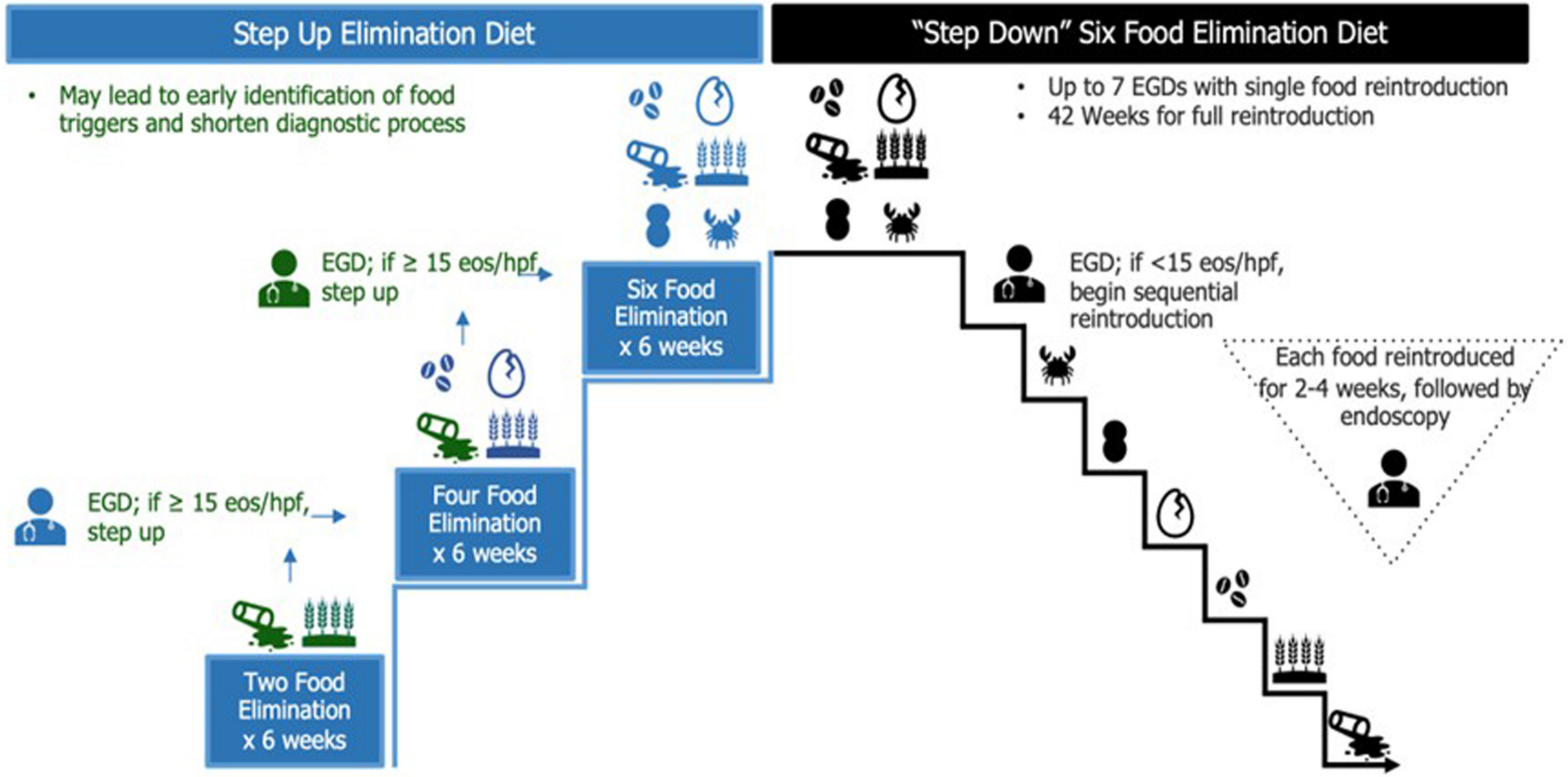
Dietary Therapy: Step-up or Down?



Peterson K, et al. *Gastroenterology*. 2024;166:382-395.

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AGA Guidelines: Management of Eosinophilic Esophagitis Dietary Therapy

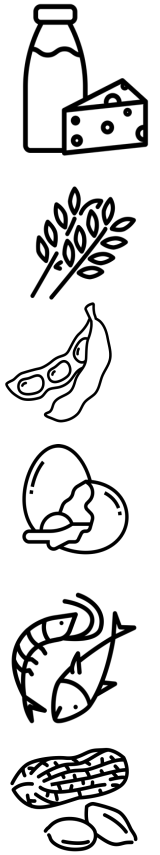
Recommendation	Strength of recommendation	Quality of evidence
1. Recommendation: In patients with symptomatic esophageal eosinophilia, the AGA/JTF suggests using proton pump inhibition over no treatment.	Conditional	Very low quality
2. In patients with EoE, the AGA/JTF recommends topical glucocorticosteroids over no treatment.	Strong	Moderate
3. In patients with EoE, the AGA/JTF suggests topical glucocorticosteroids rather than oral glucocorticosteroids.	Conditional	Moderate
4. In patients with EoE, the AGA/JTF suggests using elemental diet over no treatment.	Conditional	Moderate
Comment: Patients who put a higher value on avoiding the challenges of adherence to an elemental diet and the prolonged process of dietary reintroduction may reasonably decline this treatment option.		
5. In patients with EoE, the AGA/JTF suggests using an empiric, 6-food elimination diet over no treatment.	Conditional	Low
Comment: Patients who put a higher value on avoiding the challenges of adherence to diet involving elimination of multiple common food staples and the prolonged process of dietary reintroduction may reasonably decline this treatment option.		

Hirano I, et al. *Gastroenterology*. 2020;158:1776-1786.

EBMed #EvidenceIsPower

Six Food Elimination Diet

- Most well studied of the empiric elimination diets
  - Proposed in 2006
- Previously highest histologic remission rate for empiric elimination diets

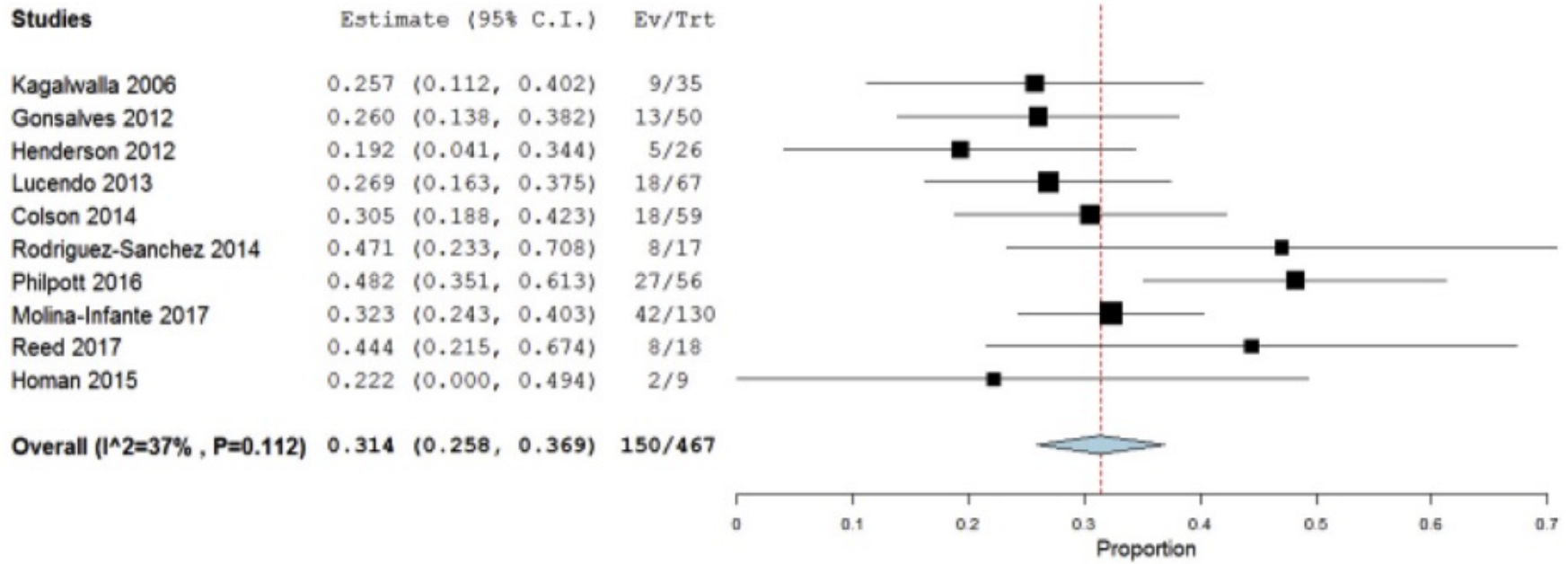


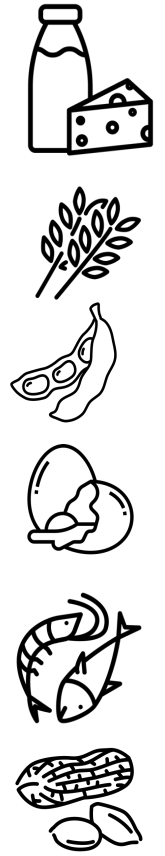
Hirano I, et al. *Gastroenterology*. 2020;158:1776-1786; Rank MA, et al. *Gastroenterology*. 2020;158:1789-1810.e15

Six Food Elimination Diet

- Most well studied of the empiric elimination diets
  - Proposed in 2006
- Prev
  elim

Forest plot for not achieving histologic remission





Histologic response of 68%

Hirano I, et al. *Gastroenterology*. 2020;158:1776-1786; Rank MA, et al. *Gastroenterology*. 2020;158:1789-1810.e15

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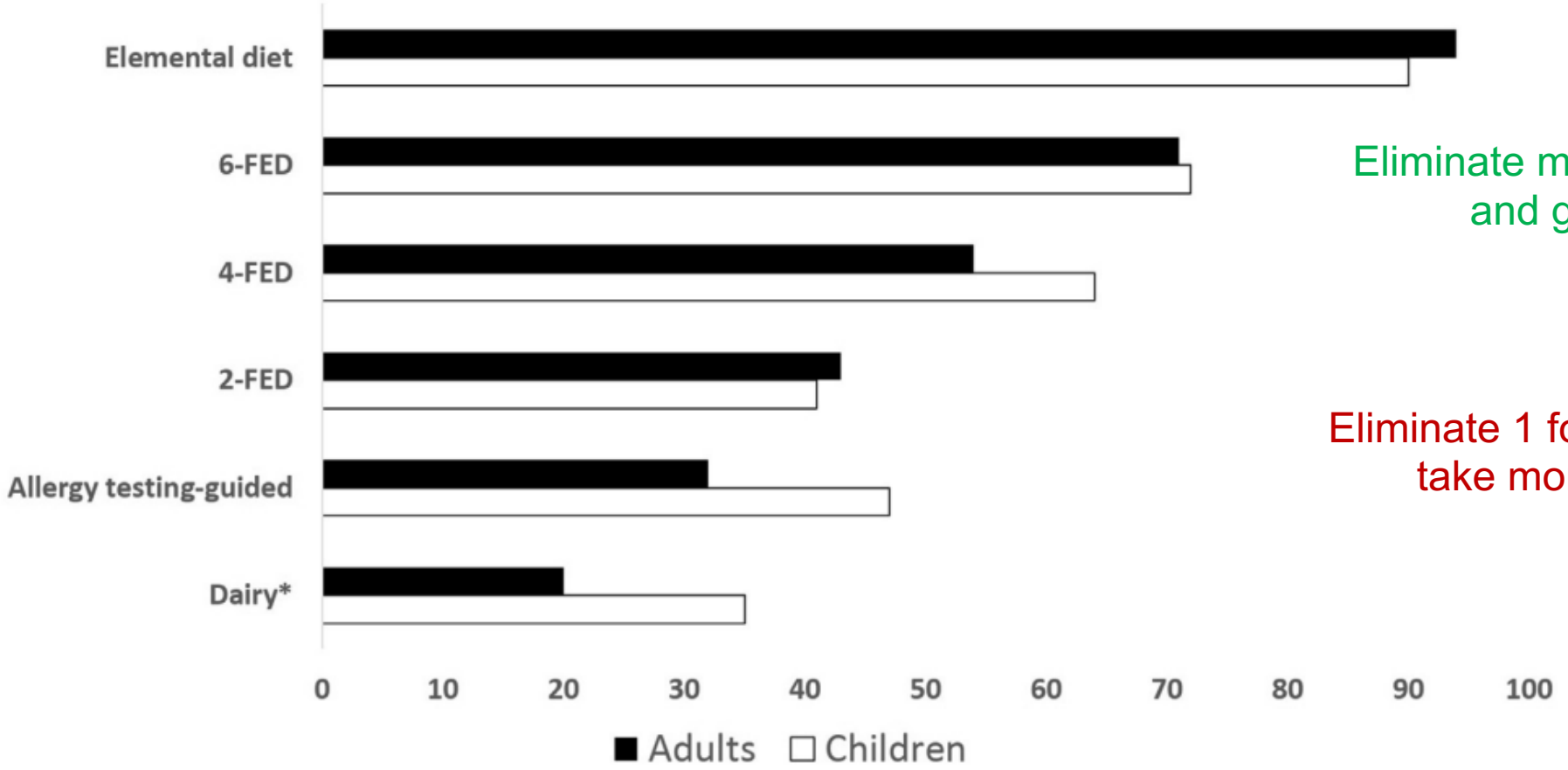
Comparing EoE Diet Therapies in Adults and Children



Eliminate many, then reintroduce and gain foods back

Eliminate 1 food, then gradually take more foods away

Molina-Infante J, Lucendo AJ. *J Allergy Clin Immunol*. 2018;142:41-47.

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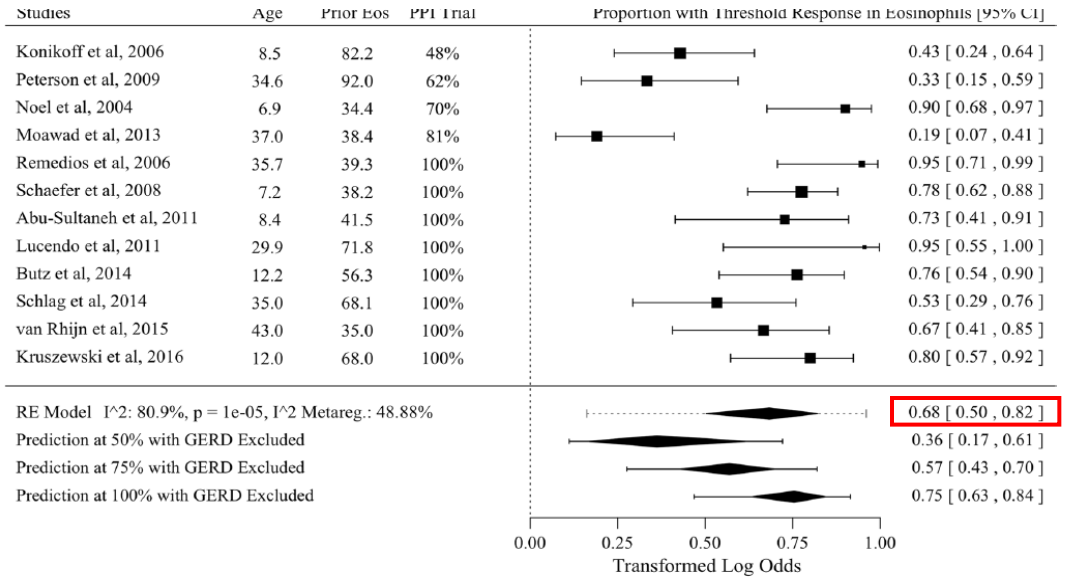
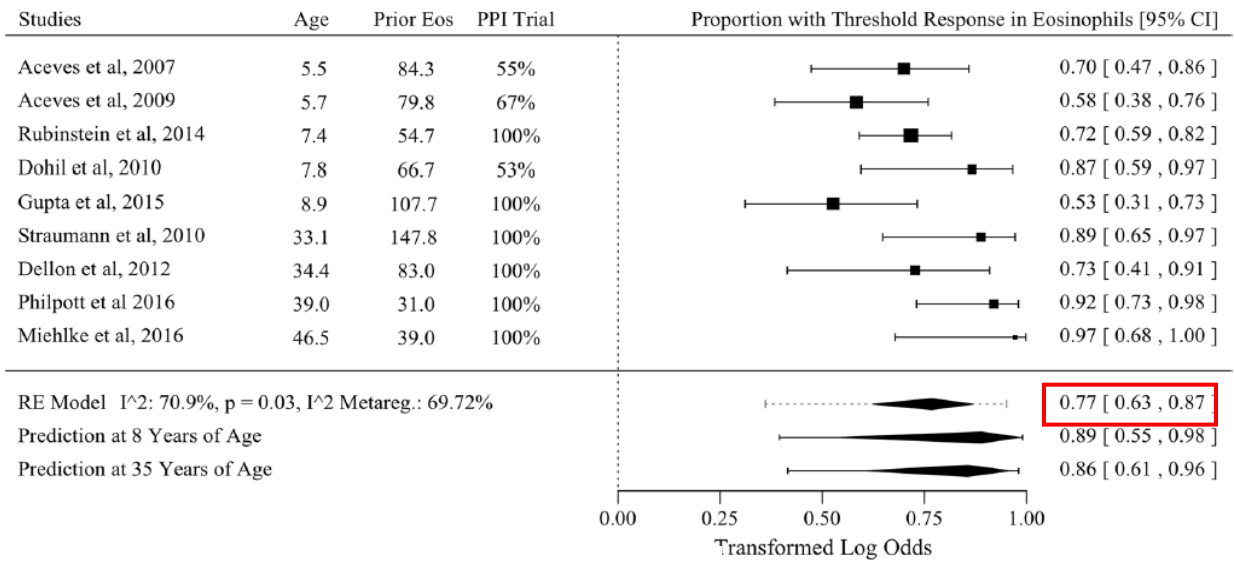
Six-Food Elimination Diet and Topical Steroids are Effective

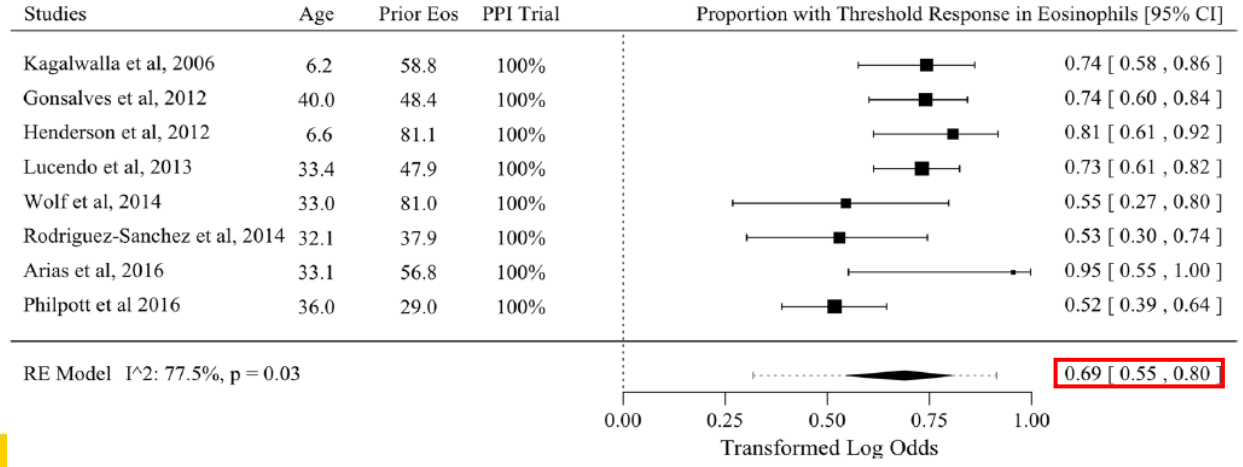
Topical Fluticasone



Topical Budesonide



6-food Elimination Diet



Cotton CC, et al *Dig Dis Sci*. 2017;62:2408-2420.

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Consider Patients' Preferences

- Adolescents/college age
- Adults who do not want to do diet or unable to adhere (costs, lifestyle, extra endoscopies)
- Already restrictive diet, at risk for malnutrition
- Diet non-responders
- No dietitian/nutrition expertise/support

- Infants/young children (with parent)
- Highly selected adolescents/college age
- Motivated adults (want to avoid medications, "root cause")
- Steroid non-responders
- Have dietitian/nutrition expertise/support

Dellon ES. *Gastroenterology*. 2020;159:20-25.

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Summary: Go Big or Go Home

- Biologics and topical corticosteroids
  - FDA approved!
  - Very effective
  - Convenient
  - Good safety profile

- Six Food Elimination Diet
  - Most well studied, most evidence
  - Most inclusive of potential food triggers
  - “Get back” (vs “taking away”) psychology

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Advancing DEI in the GI Workforce in 2024

Sandra Quezada, MD, MS, AGAF

Professor of Medicine, Division of Gastroenterology and Hepatology
Associate Dean for Admissions
Associate Dean for Faculty Diversity and Inclusion
University of Maryland School of Medicine

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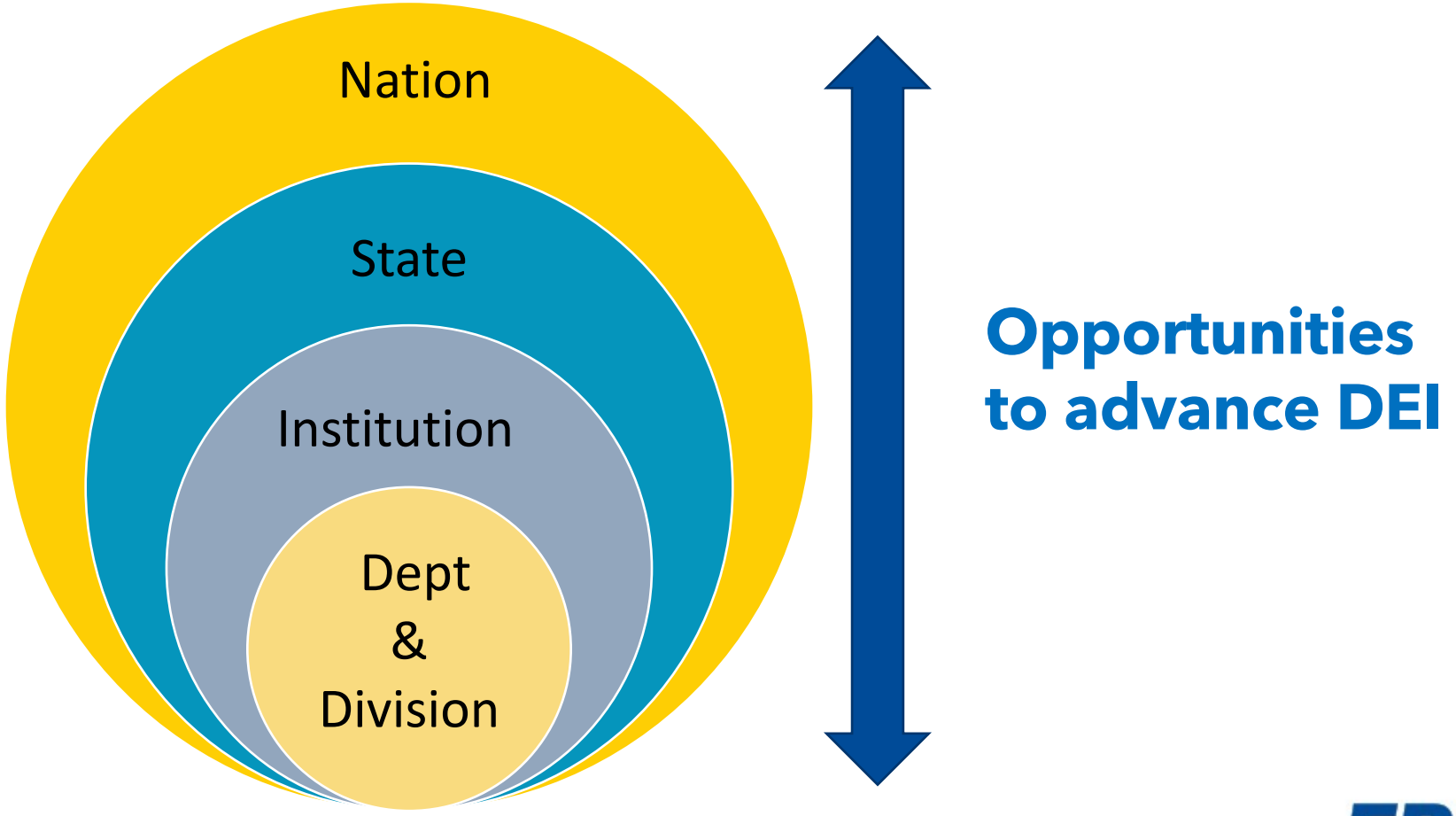
Advancing DEI in GI



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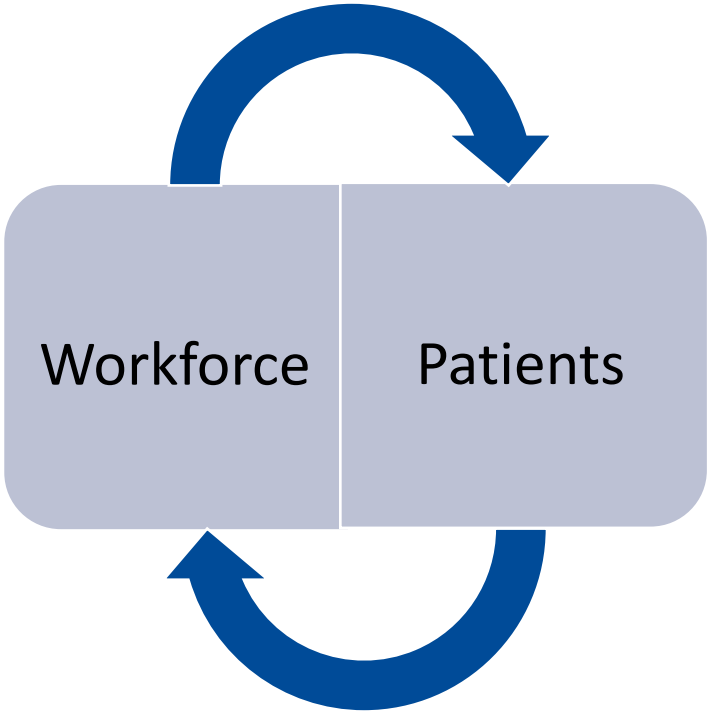
Advancing DEI in GI

- D = Diversity
- E = Equity
- I = Inclusion
- Workforce ≠ Patients



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JAMA Network Open

Original Investigation | Equity, Diversity, and Inclusion

Black Representation in the Primary Care Physician Workforce and Its Association With Population Life Expectancy and Mortality Rates in the US

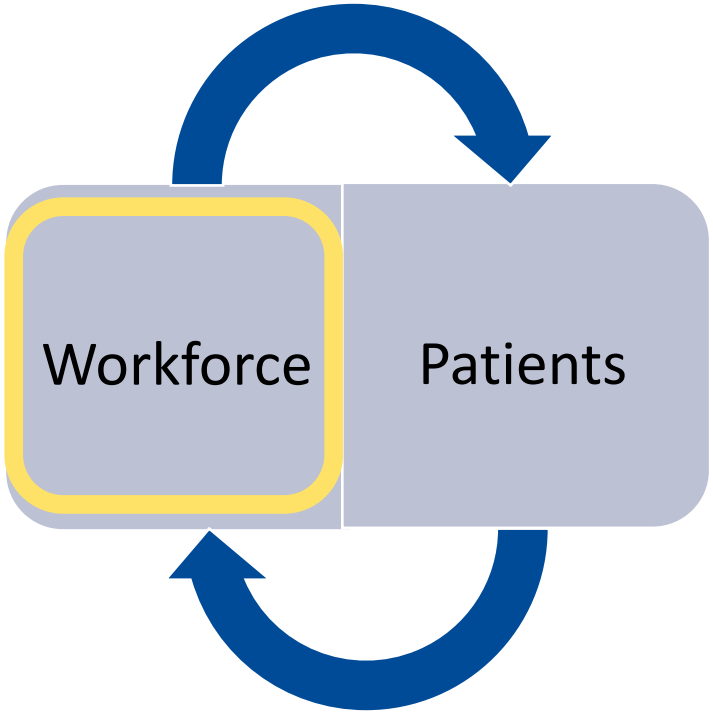
John E. Snyder, MD, MS, MPH; Rachel D. Upton, PhD; Thomas C. Hassett, PhD; Hyunjung Lee, PhD, MS, MPP, MBA; Zakia Nouri, MA; Michael Dill, MAPP

- "Greater Black workforce representation was associated with higher life expectancy and was inversely associated with all-cause Black mortality and mortality rate disparities between Black and White individuals."

Snyder JE, et al. *JAMA Netw Open*. 2023;6:e236687.

Advancing DEI in GI

- D = Diversity
- E = Equity
- I = Inclusion
- Workforce ≠ Patients



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GI Workforce Diversity

18% Women	•54% Women in US
4.4% AA	•13% AA in US
6.7% Latinos	•19% Latinos in US

Association of American Medical Colleges. Physician Specialty Data Report: Active Physicians by Sex and Specialty. 2021. Available at: https://www.aamc.org/data-reports/workforce/data/active-physicians-sex-specialty-2021; Association of American Medical Colleges. Active physicians who identified as Hispanic (Alone or With Any Race). 2021. Available at: https://www.aamc.org/data-reports/workforce/data/active-physicians-hispanic-alone-or-any-race-2021.

GI Workforce Equity

- Leadership
  - Program Directors
  - Division Chiefs
  - Society Presidents and Board representation
- Awards & Recognition
  - Speakers/panels
  - Advisory boards
- Salary and Promotion Equity
  - Grants, editorial boards, pubs…

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GI Workforce Inclusion

- ABGH (Association of Black Gastroenterologists and Hepatologists)
- Rainbows in Gastro
- Women in Endoscopy
- Scrubs and Heels
- Society-sponsored affinity and special interest groups

GI Workforce Equity – and Inclusion!!

- Leadership
  - Program Directors
  - Division Chiefs
  - Society Presidents and Board representation
- Awards & Recognition
  - Speakers/panels
  - Advisory boards
- Salary and Promotion Equity

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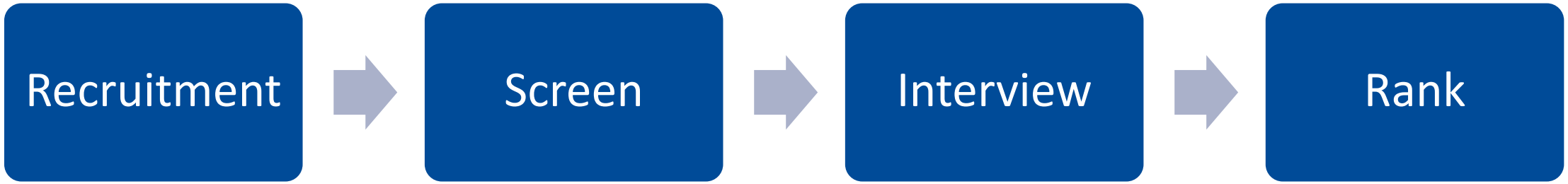
Strategies to Advance Diversity in GI Workforce

- Workforce → Fellows



Medical School Admissions – Multi-pronged Approach to Mitigate Bias

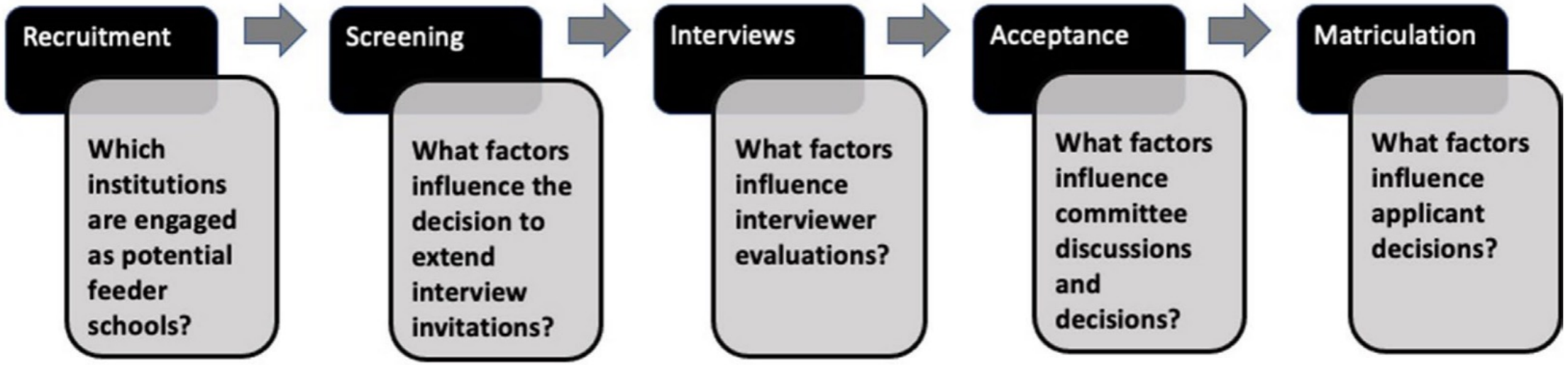


FIGURE 1 Opportunities for bias in the medical school admissions are present at every step of the process. They include unconscious bias, as well as systemic racism, that effect URM students

Robinett K, Kareem R, Reavis K, Quezada S. *Med Educ*. 2021;55:1376-1382.

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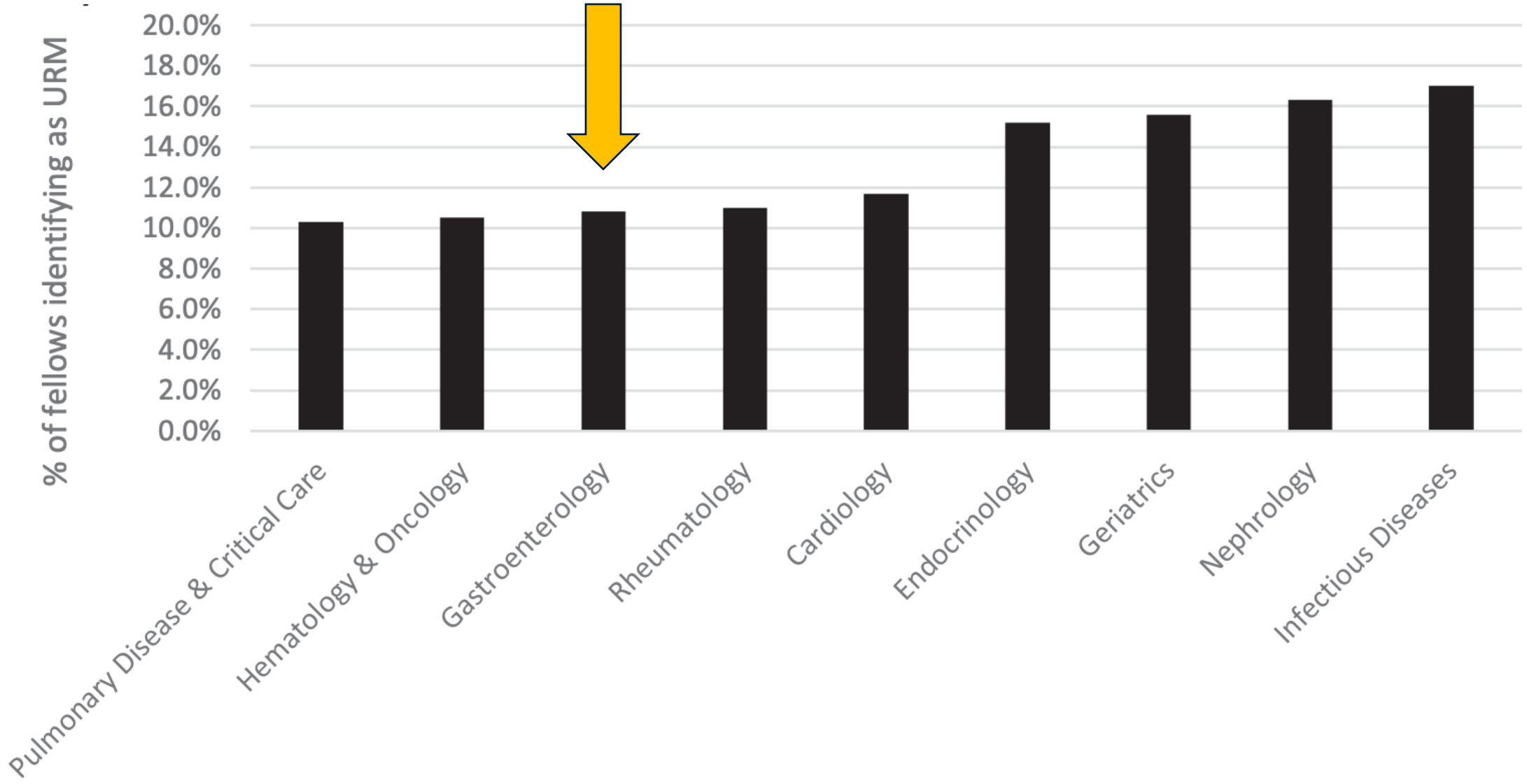

Cryer B, Quezada S, Culpepper-Morgan JA, et al. *Gastroenterology*. 2022;163:800-805.

EBMed
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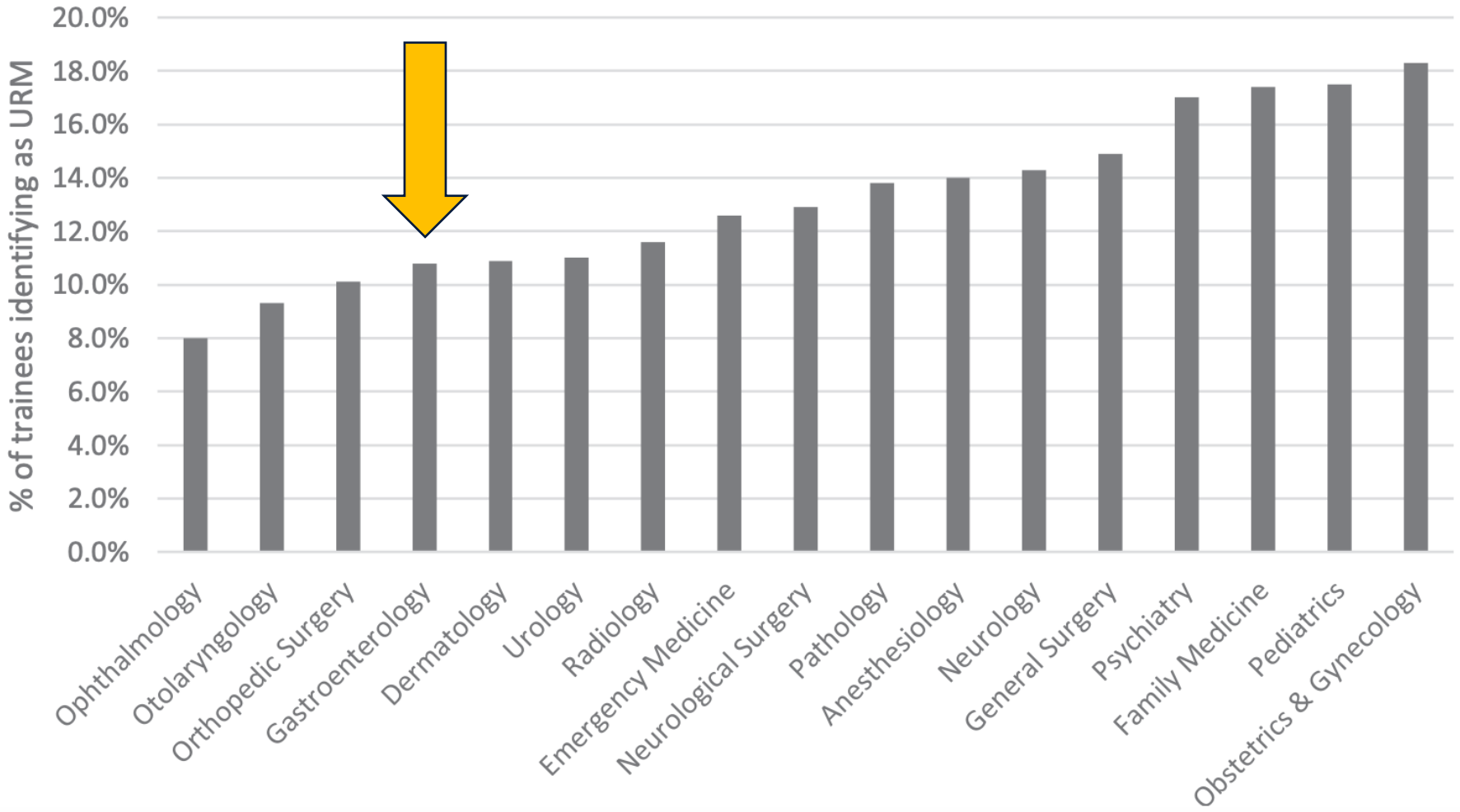

Figure 3. Percentages of URMs that have matriculated into (*A*) IM subspecialties and (*B*) all medical residencies in comparison with GI fellowship programs. Fiscal Year 2019–2020 data.

Cryer B, Quezada S, Culpepper-Morgan JA, et al. *Gastroenterology*. 2022;163:800-805.

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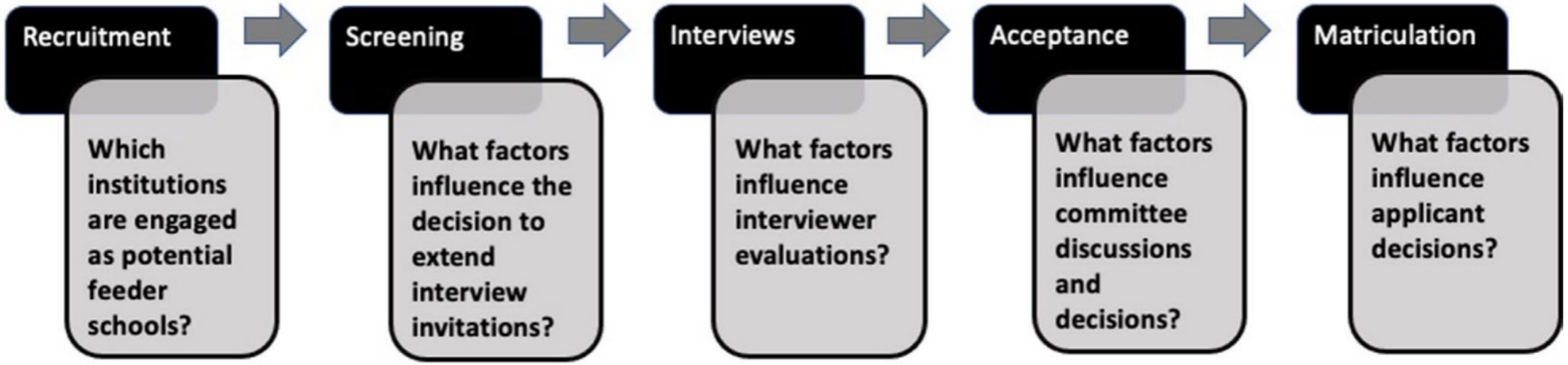
Medical School Admissions – Multi-pronged Approach to Mitigate Bias



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Standardized Test Scores Do Not Predict Success in Medicine

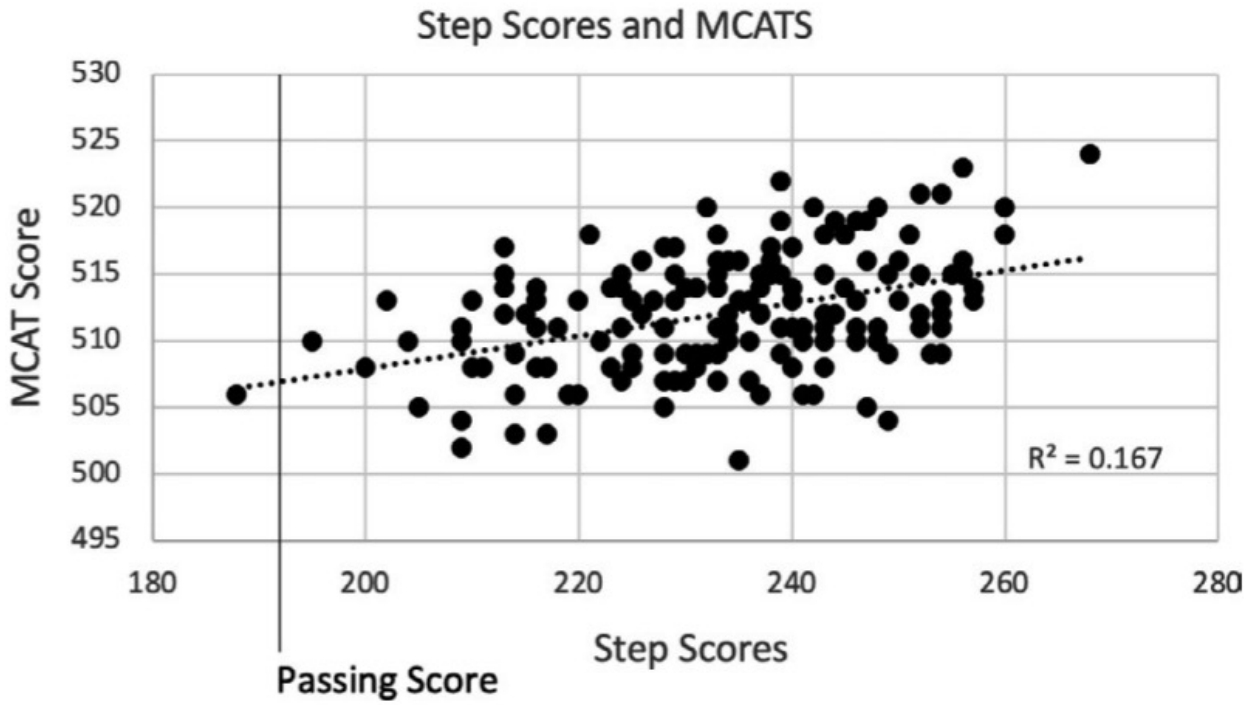

FIGURE 2 Internal study demonstrated a weak correlation between applicant MCAT scores and USMLE Step 1 scores

Robinett K, Kareem R, Reavis K, Quezada S. *Med Educ*. 2021;55:1376-1382.

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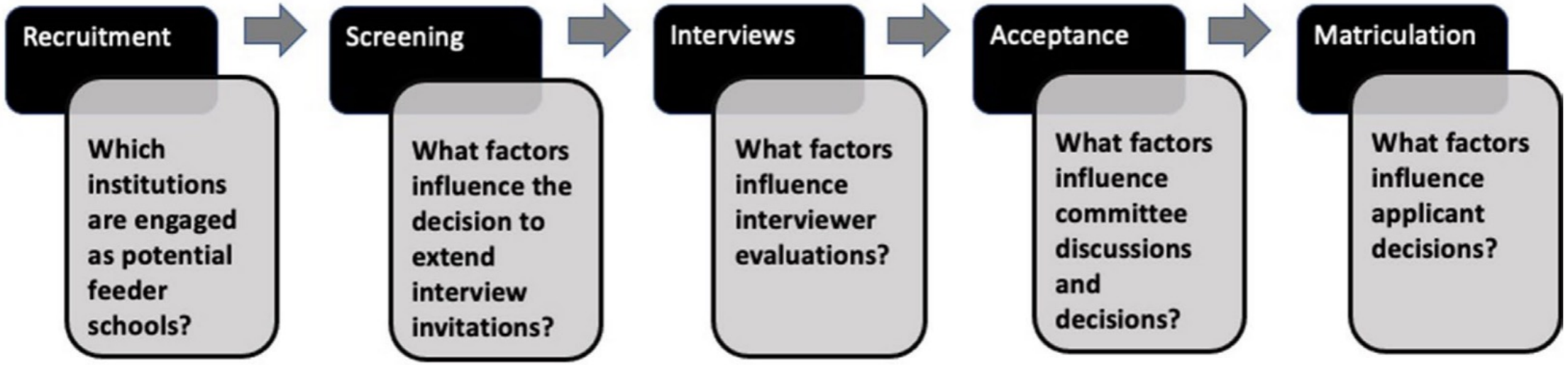
Medical School Admissions – Multi-pronged Approach to Mitigate Bias



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Strategies to Advance Diversity in GI Workforce

- Representation on interview and selection committee
- Implicit bias training for interviewers and selection committee
- Onboarding connections with affinity groups

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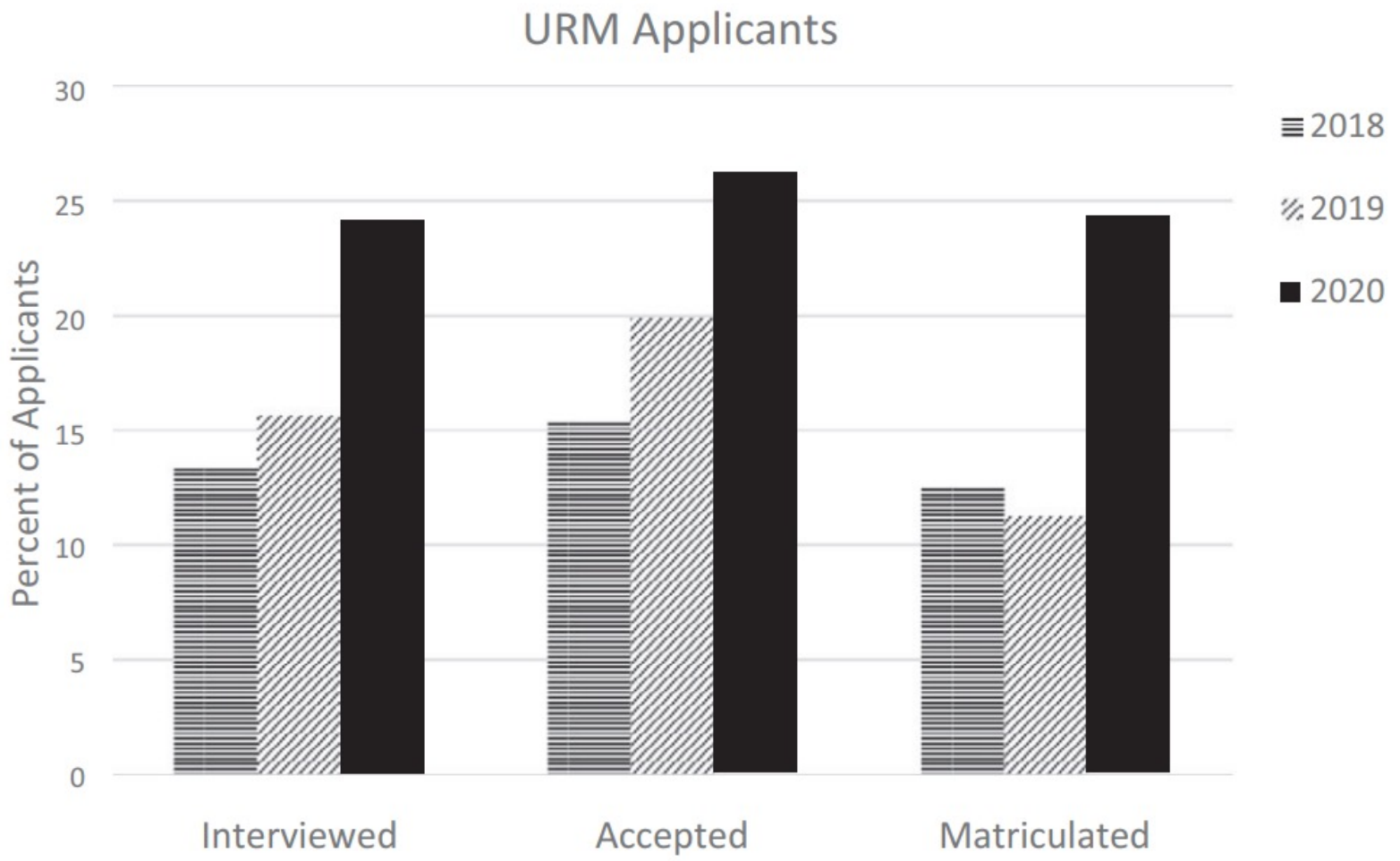

FIGURE 3 Percent of URM applicants interviewed, accepted, and matriculated from 2018-2020 by application cycle

Robinett K, Kareem R, Reavis K, Quezada S. *Med Educ*. 2021;55:1376-1382.

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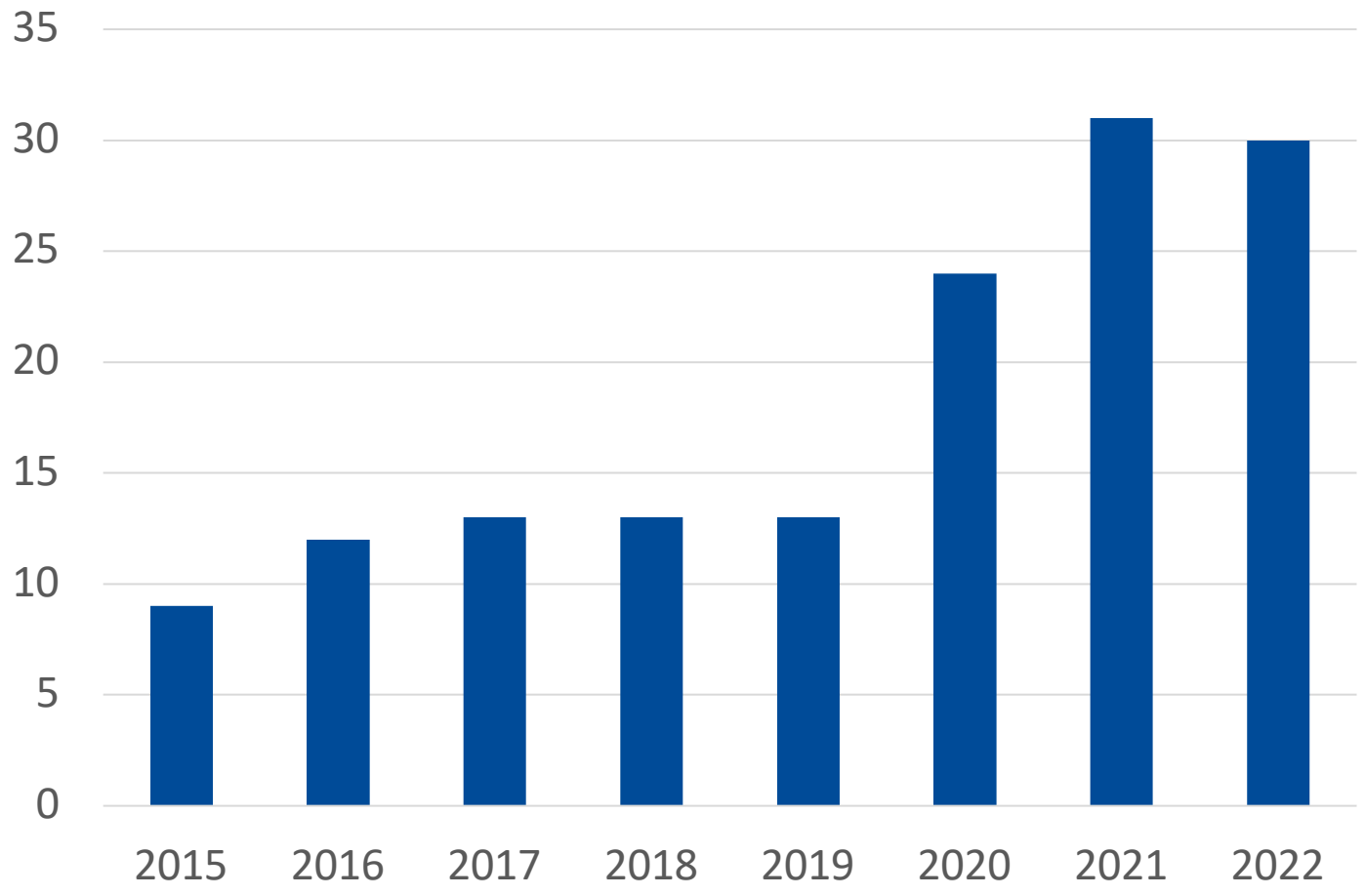
SOM % Underrepresented in Medicine in First Year Class



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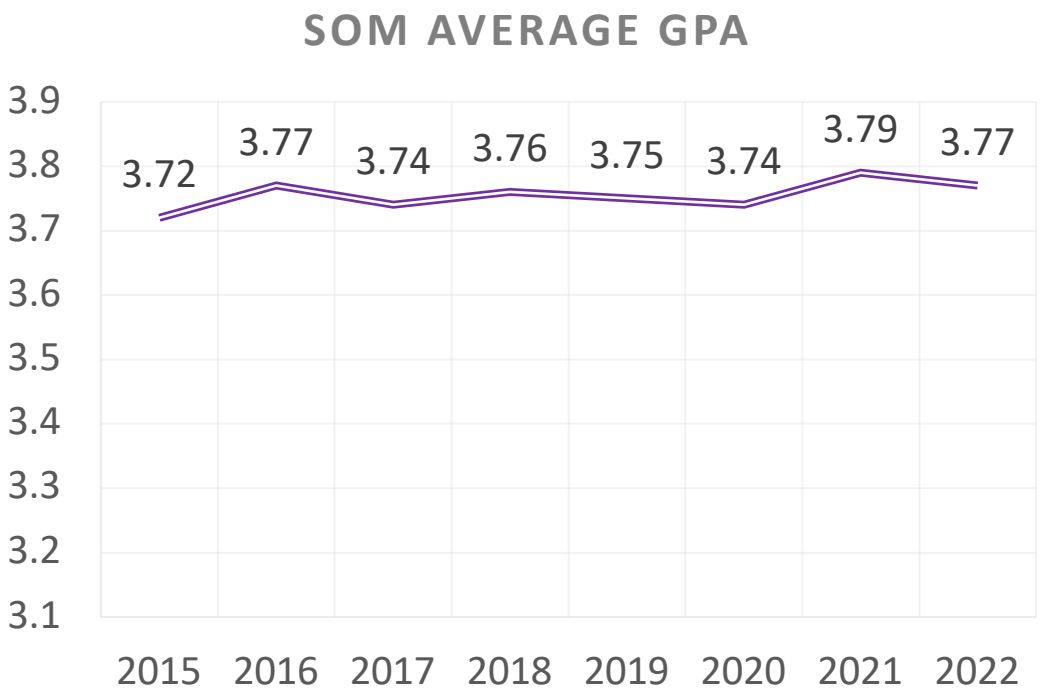
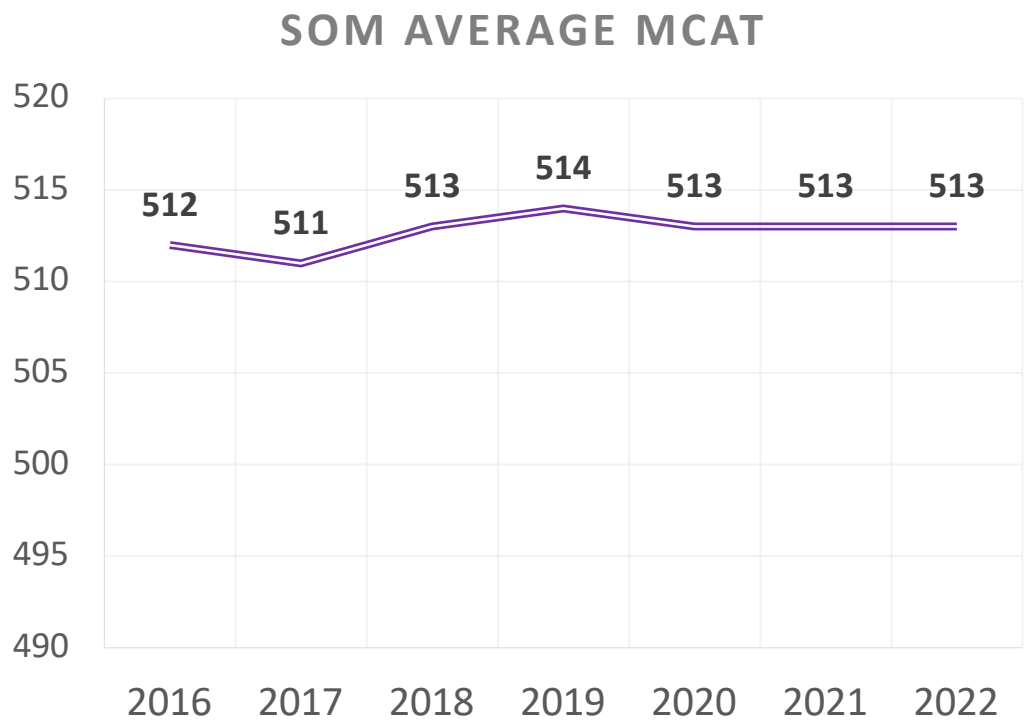
Consistent MCAT & GPA Averages





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UNIVERSITY of MARYLAND
SCHOOL OF MEDICINE

More stats on incoming class..

- 62% Students of Color
- 19% LGBTQ+ identifying
- 16% Disadvantaged status
- 62% women
- 71% in-state
- 58 colleges and universities
- Age range 19-32

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Strategies to Advance Diversity in GI Workforce

Workforce → Faculty Recruitment

- Representation and training of interviewers and selection committees
- Be aware of gendered language
- Standardize evaluation criteria and discussion
- Include opportunities to connect with individuals or groups with affinity

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Strategies to Advance Diversity in GI Workforce

Workforce → Faculty Recruitment

Table 1. Academic Development Areas in Which URMs Struggle

1. Lack of knowledge about how to become an investigator
2. Lack of exposure to role models (ie, inspiration)
3. Lack of mentorship
4. Lack of sponsorship from mentors
5. Lack of visibility within both the AGA and their institution for general leadership opportunities, not just leadership opportunities in the URM space
6. Lack of programs within their home institution for leadership training
7. Lack of support for pursuit of a career and personal identity as a physician-scientist

Data are derived from the AGA survey of URM GI fellows and early career gastroenterologists (5 years for fewer since completion of gastroenterology training).

Cryer B, Quezada S, Culpepper-Morgan JA, et al. *Gastroenterology*. 2022;163:800-805.

Strategies to Advance Diversity in GI Workforce

- Interviewers and selection committee closely resembles the group you will recruit - train them to recognize and address biases
- Broaden your pool by broadening who you recruit/advertise to
  - SNMA, LMSA, SACNAS, AAMC, DDW, ACG, AASLD
- Align application review criteria with your mission and goals
- Connect applicants with potential future allies, collaborators, community
- Continue connection and support for trainees and faculty after recruitment!!
  - Affinity groups, events, salary and promotion equity, recognition and visibility

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Listen To Me If You Want To Appropriately Treat IBS-C: Prescription (Aka FDA Approved) Treatments Are The Way To Go

Darren M. Brenner, MD, AGAF, FACG, RFF
Professor of Medicine and Surgery
Director—Northwestern Neurogastromotility and Functional Bowel Programs
Northwestern University Feinberg School of Medicine

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Fact: Baha Is Amazing….

MD, MSc, FACG, AGAF
Clinical Professor of Medicine
Director of Motility
ANMS Education Chair
Overall good person and friend

But She Is LYING To You!!

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Fact: Baha

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Rome III/IV & Everything Before Diagnostic Criteria for IBS

Recurrent abdominal pain or discomfort at least 3 days per month over the last 3 months associated with 2 or more of the following:

Recurrent abdominal pain on average at least 1 day per week in the last 3 months associated with 2 or more of the following:

Longstreth GF, et al. *Gastroenterology.* 2006;130:1480-1491; Lacy BE, et al. *Gastroenterology.* 2016;150:1393-1407.

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Rome III/IV & Everything Before Diagnostic Criteria for IBS

Recurrent abdominal pain or discomfort at least 3 days per month over the last 3 months associated with 2 or more of the following:

Recurrent a … ek in the last 3 mont…

PAIN OR DISCOMFORT

Longstreth GF, et al. *Gastroenterology.* 2006;130:1480-1491; Lacy BE, et al. *Gastroenterology.* 2016;150:1393-1407.

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Can I Improve Abdominal Symptoms (Pain, Discomfort, Bloating) In Constipation?

Therapeutic Class (OTC)	Improve Bowel Symptoms	Improve Abdominal Symptoms
Osmotic Laxatives	YES	NO
Stimulant Laxatives	YES	NO
Soluble Fiber	**YES**	**YES**
Saline (Mg) Laxatives	YES	NO
Stool Softeners	??	No
Therapeutic Class (Prescription)		
Secretagogues (Plecanatide, Linaclotide, Lubiprostone)	YES	YES
Retainagogues (Tenapanor)	YES	YES

THP: OTCs Fail To Treat The Cardinal Symptoms of IBS

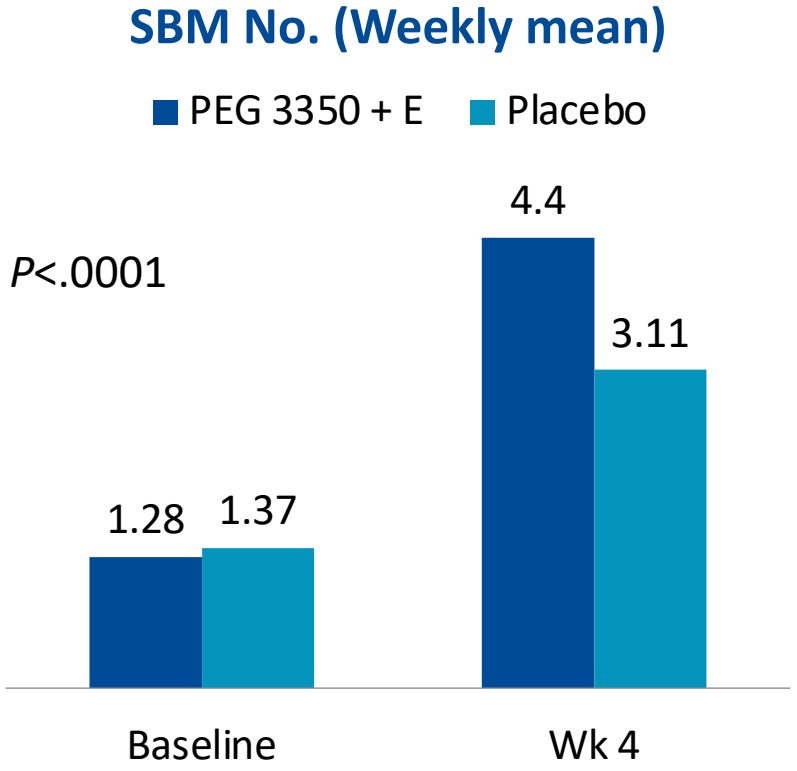
Rao SSC and Brenner DM. *Am J Gastroenterol*. 2021;116:1156-1181; Sayuk GS, et al. *Am J Gastroenterol*. 2022;117:S6-S13.

Rao SSC and Brenner DM. AJG 2021;116(6):1156-1181.
Sayuk GS, Waldman SA, Brenner DM. AJG 2022;117:S6-13.

Case In Point: PEG 3350 for IBS-C 👎👎👎😪

- RCT of PEG 3350 + E vs Placebo
- Primary endpoint
  - No. SBMs/week in Wk 4
- PEG 3350 + E significantly improved SBMs, stool consistency, and straining vs placebo (*P*<.0001)
  - PEG 3350 + E significantly improved abdominal pain from baseline (*P*<.005)
  - *No difference* observed compared to placebo
  - Some experience increased gas/bloating
- AGA recommendation:

> Although PEG has been shown to improve symptoms of constipation, larger high-quality studies are clearly needed to adequately evaluate the efficacy of PEG in patients with IBS-C in whom abdominal pain is a more predominant symptom.



THP: PEG Fails To Treat The Cardinal Symptoms of IBS & May Make Worse

Chapman RW, et al. *Am J Gastroenterol*. 2013;108:1508-1515; Chang L, et al. *Gastroenterology*. 2022;163:118-136.

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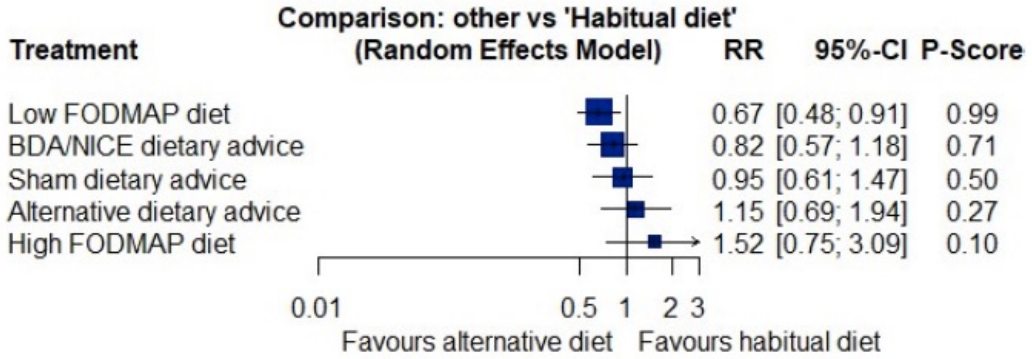
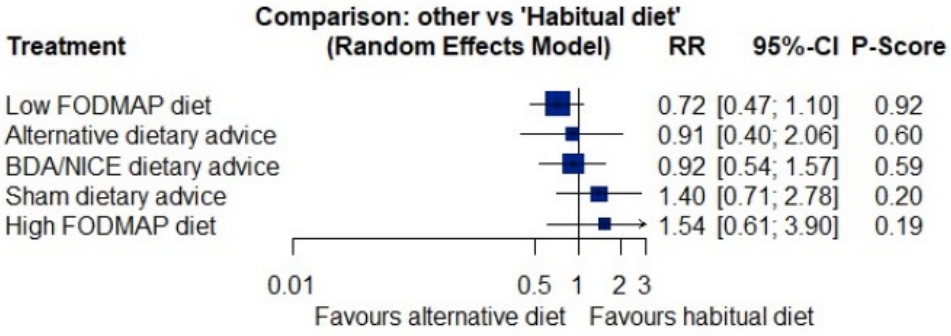
Is FODMAP Avoidance Really That Good Especially in IBS-C?

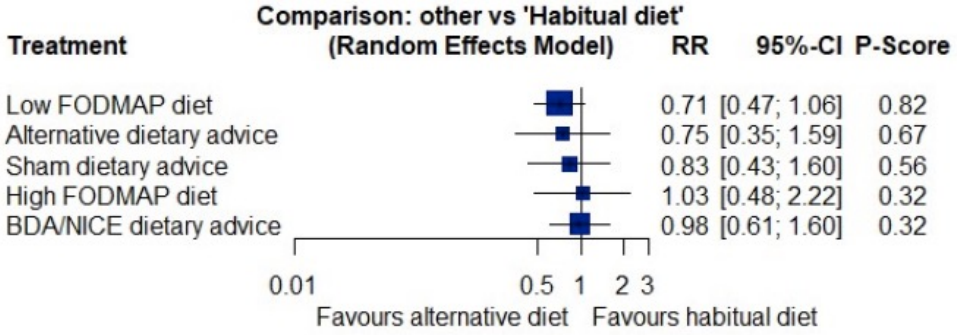
Global Symptoms



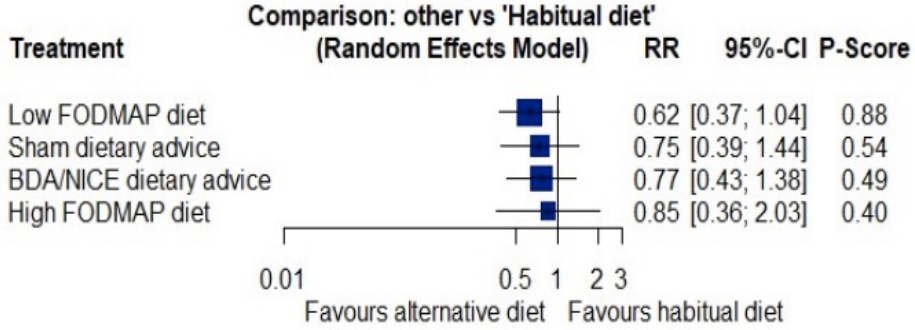
Abdominal Pain



Bloating



Bowel Habits



Limitations: Elimination phase, 7/13 not recruit IBS-C/M, all recs via RD

Black CJ, et al. *Gut*. 2022;71:1117-1126.

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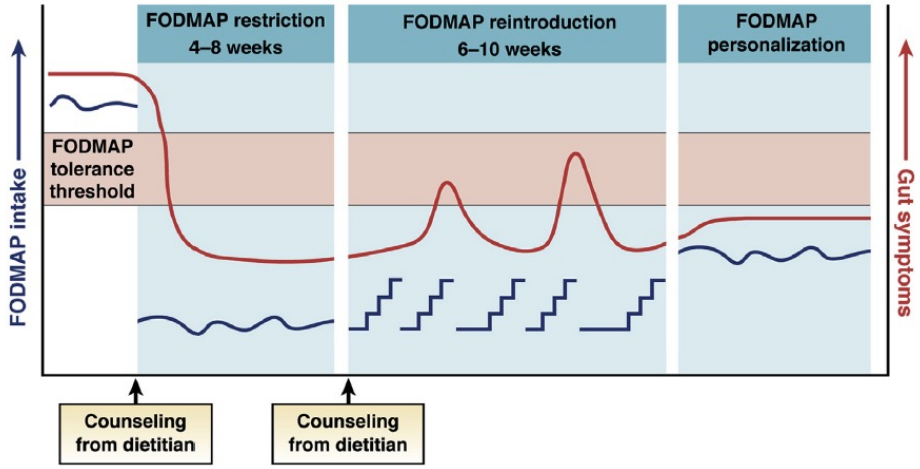
Low FODMAPs: The Traditional Approach Be Difficult & Dangerous



Concerns/Complications:

- Never leave elimination phase
- Alternations in gut microbiome
  - Decreased *Bifidobacter*
- Disordered Eating
- Vitamin/micronutrient deficiency? (Riboflavin, Thiamine, Fe?)
- IBS: D>M ? ? ? *CCC*
- Any better than standard dietary advice?

Low FODMAP Dietary Food Lists are Often Discordant

Ann R. McMeans, MS, RD[1],
Kristi L. King, MPH, RD[2] and
Bruno P. Chumpitazi, MD, MPH, FACG[2]

doi:10.1038/ajg.2016.593

In summary, we found that three readily available US-based low FODMAP food lists are often discordant with respect to the foods that are listed (lack of overlap in >50%). When the same foods are listed on more than one list, there is generally good agreement, though there are a sizable number of foods (>20%) with recommendations that are in disagreement. It should be noted that none of the lists provide guidance on how to combine foods of varying FODMAP content. Further evaluation of low FODMAP food lists (in conjunction with efforts to build global FODMAP content databases from which these lists may derive) are needed to identify those which are most accurate and effective within an educational program.

Chey WD, et al. *Gastroenterology*. 2021;160:47-62; Hill P, et al. *Gastroenterol Hepatol (N Y).* 2017;13:36-45; Eswaran SL, et al. Abstract Su576. DDW 2021; Van Den Houte K, et al. Abstract 381 DDW 2021; O'Keeffe M, et al. *Neurogastroenterol Motil*. 2018;30:10.1111/nmo.13154; Eswaran S, et al. *J Acad Nutr Diet*. 2020;120:641-649; McMeans AR, et al. *Am J Gastroenterol*. 2017;112:655-656; Bellini M, et al. *Nutrients*. 2020;12:2360; McMeans AR, et al. *Am J Gastroenterol*. 2017;112:655-656.

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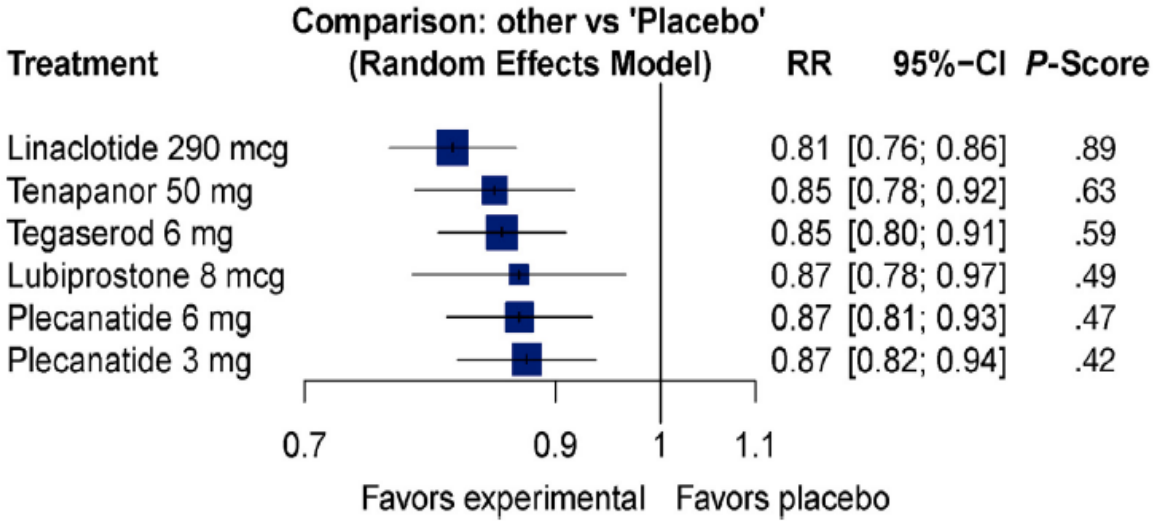
Real Science: All FDA Approved Treatments Better Than Placebo

- SR/Network MA RCTs: Therapies for IBS-C; N=14
- Defined as RR of failure to achieve FDA guidance endpoint
- All more effective than PBO
- Linaclotide 290 mcg most effective but also most side-effects
- Indirect comparison: Non-inferiority between Tx

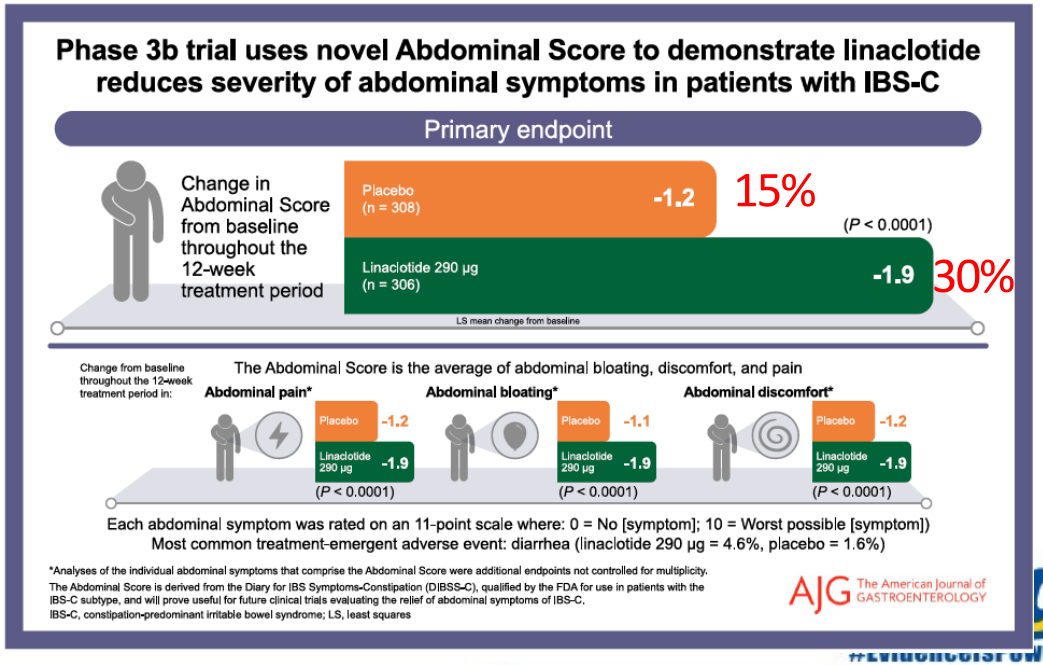
Overall FDA Responder



And They Improve Abdominal Symptoms (And Baha Knows This Too)

Efficacy of Linaclotide in Reducing Abdominal Symptoms of Bloating, Discomfort, and Pain: A Phase 3B Trial Using a Novel Abdominal Scoring System

Lin Chang, MD[1], Brian E. Lacy, MD, PhD[2], Baha Moshiree, MD, MSc[3], Amy Kassebaum, PA-C, MMS, RD[4], Jessica L. Abel, MPH[5], Jennifer Hanlon, MPH[6], Wilmin Bartolini, PhD[7], Ramesh Boinpally, PhD[5], Wieslaw Bochenek, MD[8], Susan M. Fox, PhD[5], Madhuja Mallick, PhD[5], Ken Tripp, PhD[6,9], Nicholas Omniewski, MPH[7], Elizabeth Shea, PhD[7] and Niels Borgstein, MD[6]



Black CJ, et al. *Clin Gastroenterol Hepatol*. 2020;18:1238-1239.e1; Chang L, et al. *Am J Gastroe*
P1597. ACG 2023.

Real Science: All FDA Approved Treatments Better Than Placebo

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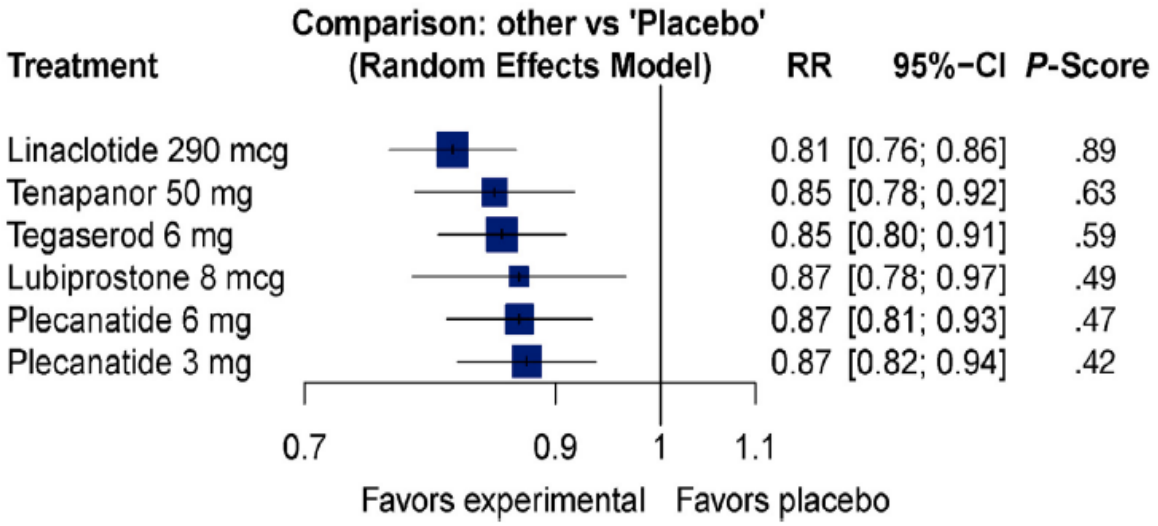
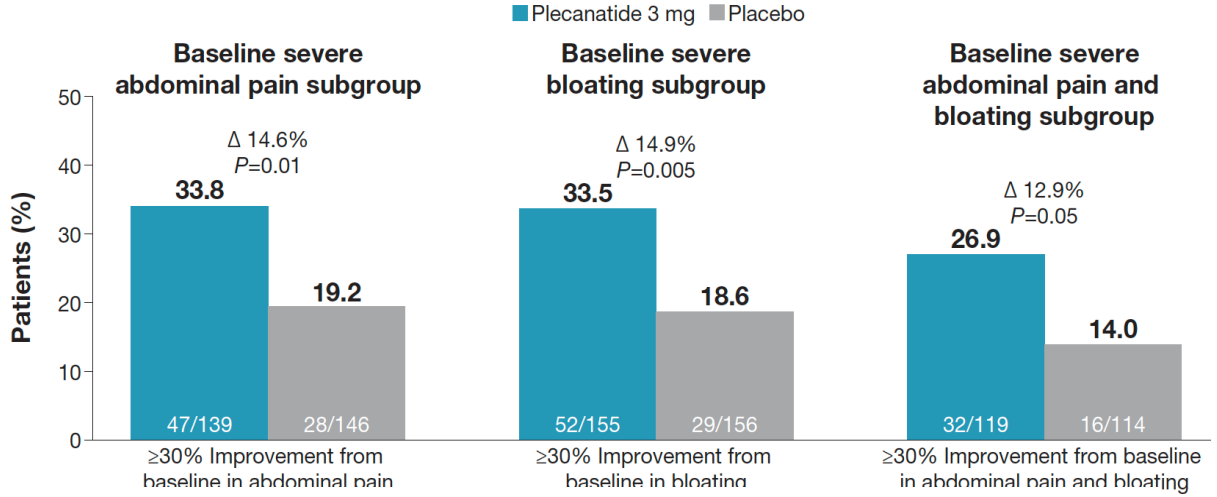


And They Improve Abdominal Symptoms (And Baha Knows This Too)

Efficacy of Linaclotide in Reducing Abdominal Symptoms of Bloating, Discomfort, and Pain: A Phase 3B Trial Using a Novel Abdominal Scoring System

Figure. Percentage of Patients With ≥30% Improvement From Baseline in Severe Abdominal Pain, Bloating, or Both at Week 12, by Subgroup



American College of Gastroenterology Annual Scientific Meeting & Postgraduate Course (ACG 2023); October 20–25, 2023; Vancouver, Canada

Each abdominal symptom was rated on an 11-point scale where: 0 = No [symptom]; 10 = Worst possible [symptom])
Most common treatment-emergent adverse event: diarrhea (linaclotide 290 µg = 4.6%, placebo = 1.6%)

*Analyses of the individual abdominal symptoms that comprise the Abdominal Score were additional endpoints not controlled for multiplicity.
The Abdominal Score is derived from the Diary for IBS Symptoms-Constipation (DIBSS-C), qualified by the FDA for use in patients with the IBS-C subtype, and will prove useful for future clinical trials evaluating the relief of abdominal symptoms of IBS-C.
IBS-C, constipation-predominant irritable bowel syndrome; LS, least squares

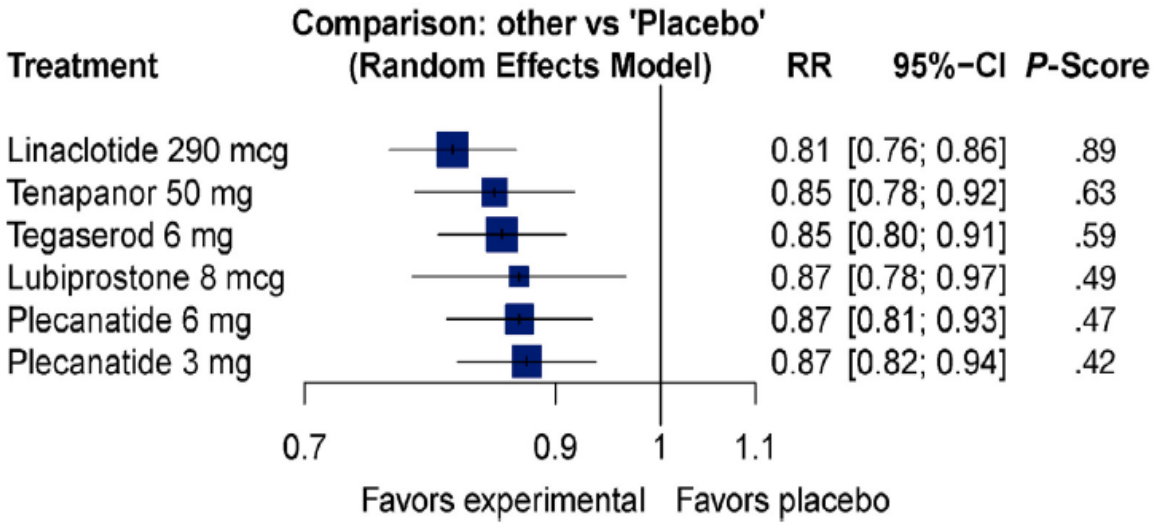
AJG The American Journal of GASTROENTEROLOGY

Black CJ, et al. *Clin Gastroenterol Hepatol*. 2020;18:1238-1239.e1; Chang L, et al. *Am J Gastroe*
P1597. ACG 2023.

Real Science: All FDA Approved Treatments Better Than Placebo

- SR/Network MA RCTs: Therapies for IBS-C; N=14
- Defined as RR of failure to achieve FDA guidance endpoint
- All more effective than PBO
- Linaclotide 290 mcg most effective but also most side-effects
- Indirect comparison: Non-inferiority between Tx

Overall FDA Responder



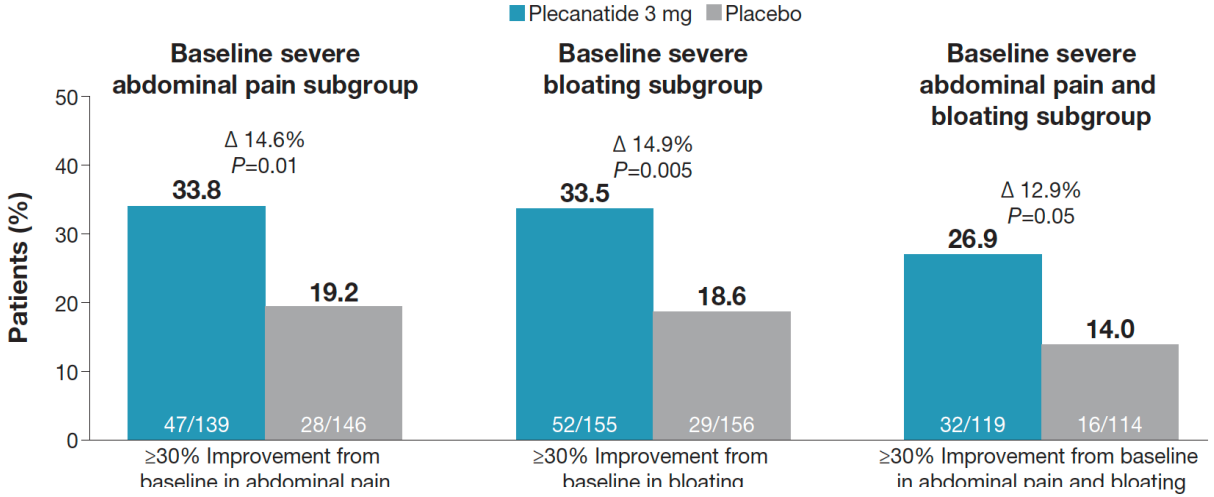
And They Improve Abdominal Symptoms (And Baha Knows This Too)

POSTER NUMBER B0261

Plecanatide Improves Severe Abdominal Pain and Severe Bloating in Individuals With Irritable Bowel Syndrome With Constipation: A Pooled Analysis of Two Phase 3 Trials

Gregory S. Sayuk, MD, MPH[1]; Reena V. Chokshi, MD[2]; Adam P. Laitman, MD[3]; Christopher Allen, MS[3]; Darren M. Brenner, MD[4]
[1]Washington University School of Medicine, St. Louis, MO, USA; [2]Baylor College of Medicine, Houston, TX, USA; [3]Salix Pharmaceuticals, Inc., Bridgewater, NJ, USA; [4]Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Figure. Percentage of Patients With ≥30% Improvement From Baseline in Severe Abdominal Pain, Bloating, or Both at Week 12, by Subgroup



American College of Gastroenterology Annual Scientific Meeting & Postgraduate Course (ACG 2023); October 20–25, 2023; Vancouver, Canada

American College of Gastroenterology (ACG) 2022 Annual Scientific Meeting • October 21–26, 2022 • Charlotte, NC

Each abdominal symptom was rated on an 11-point scale where: 0 = No [symptom]; 10 = Worst possible [symptom])
Most common treatment-emergent adverse event: diarrhea (linaclotide 290 µg = 4.6%, placebo = 1.6%)

*Analyses of the individual abdominal symptoms that comprise the Abdominal Score were additional endpoints not controlled for multiplicity.
The Abdominal Score is derived from the Diary for IBS Symptoms-Constipation (DIBSS-C), qualified by the FDA for use in patients with the IBS-C subtype, and will prove useful for future clinical trials evaluating the relief of abdominal symptoms of IBS-C.
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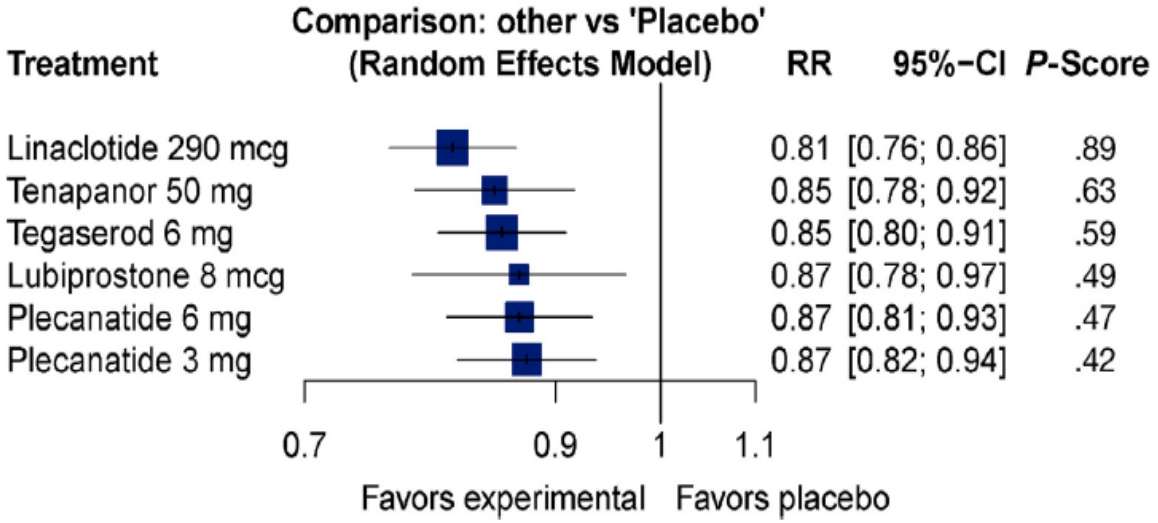
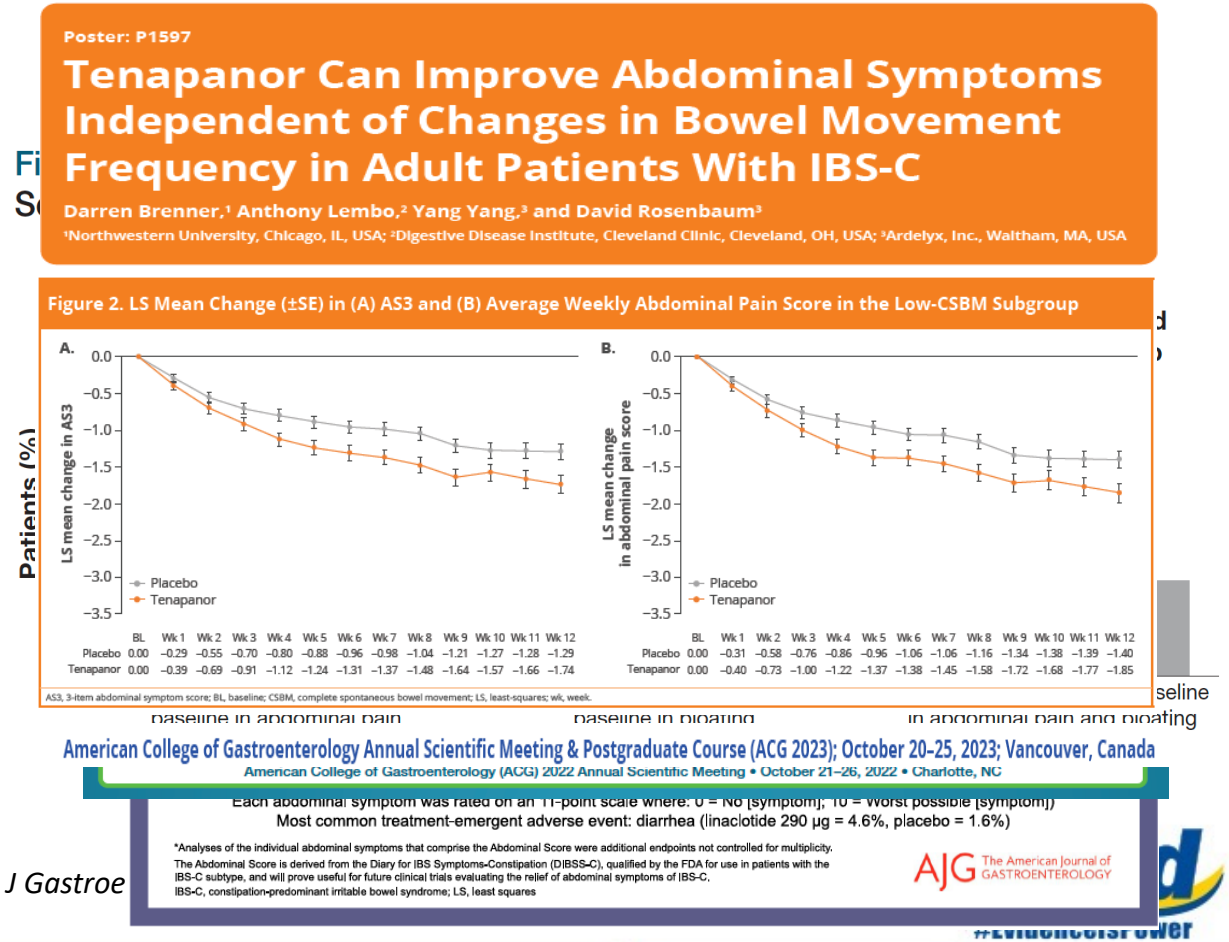
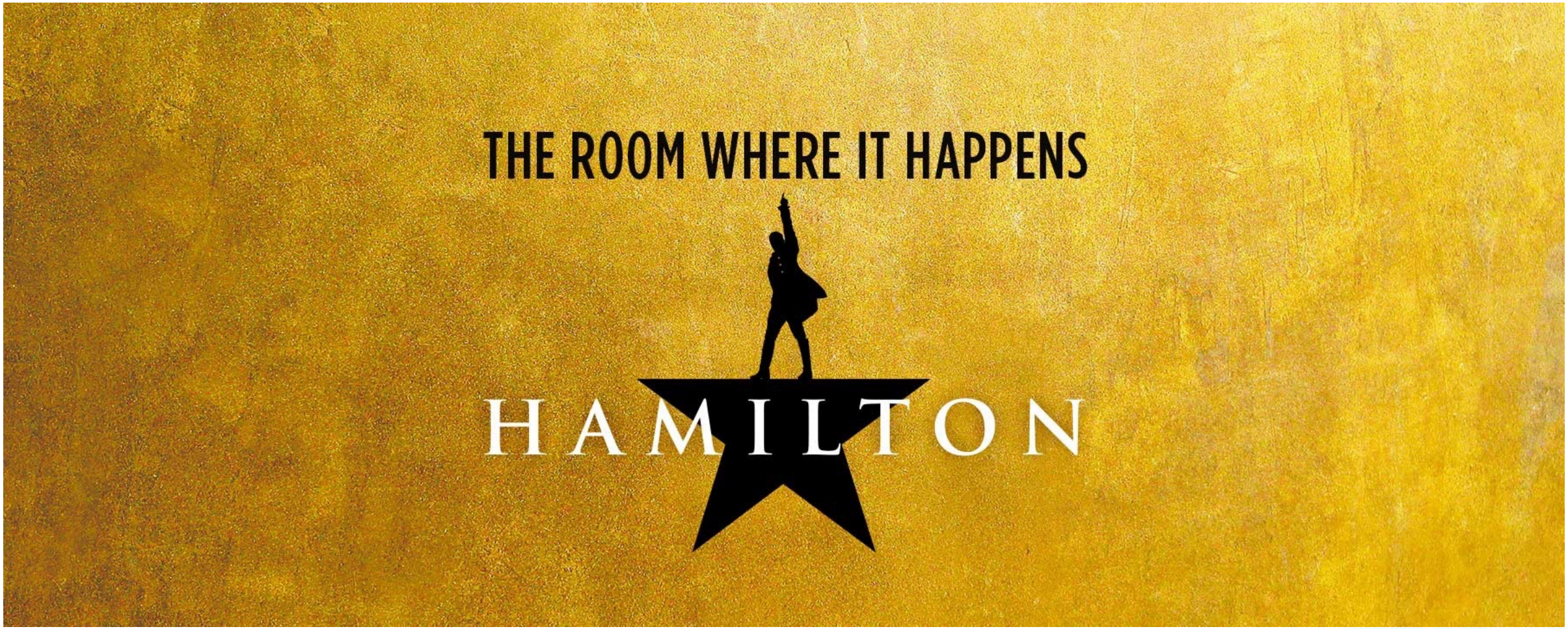


And They Improve Abdominal Symptoms (And Baha Knows This Too)



Black CJ, et al. *Clin Gastroenterol Hepatol*. 2020;18:1238-1239.e1; Chang L, et al. *Am J Gastroe*
P1597. ACG 2023.

I WAS IN



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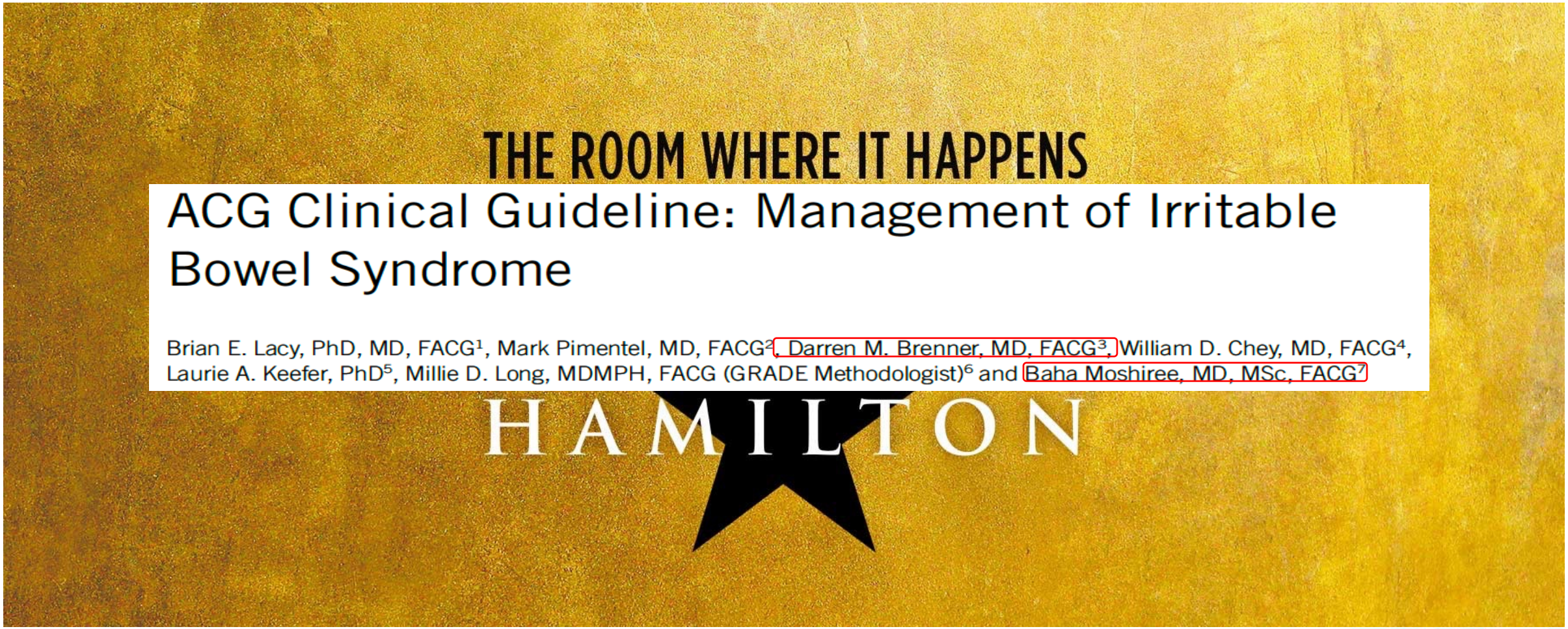
I WAS IN



So Was Baha

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And What Did Those In The Room Decide? It's Ok Baha You Can Tell Us

We used a modified Delphi approach to achieve consensus. Each statement was presented during a monthly phone conference and voted on by all expert authors. Statements were revised and then either presented again on a phone conference or circulated by email. One face-to-face meeting was held. The vote on the final recommendation and quality of evidence for each statement was unanimous. A summary of the recommendations is given in Table 2.

Therapeutic	American College of Gastroenterology (ACG)
Linaclotide	**Strong recommendation for use IBS-C** High quality evidence
Plecanatide	**Strong** recommendation for use IBS-C High quality evidence
Lubiprostone	**Strong** recommendation for use IBS-C Moderate quality evidence
Low FODMAP	**Conditional** recommendation for limited trial Very low quality evidence
PEG laxatives	Conditional suggestion **against** use IBS-C Low quality evidence
Fiber	Strong **suggestion** that soluble fiber be used to treat global IBS symptoms (was for IBS-C & D) Moderate quality evidence

ACG: Global symptom response

AGA: Better than nothing

Lacy BE, et al. *Am J Gastroenterol*. 2021;116:17-44.

PEG Laxatives

In summary, despite the long-term safety and efficacy of PEG for the treatment of chronic constipation in even the most vulnerable subjects (elderly and children), there is no evidence that PEG alleviates abdominal pain and thus global symptoms in patients with IBS-C. We therefore recommend against use of PEG alone for the treatment of global IBS-C symptoms, although we recognize that clinicians may use PEG as first-line treatment of constipation in IBS, given its low cost and availability.

Low FODMAP

In summary, this guideline committee believes that the complexity of the low FODMAP diet, combined with the potential for nutritional deficiencies, and the time and resources required to provide proper counseling on the 3 phases of the plan, requires the services of a properly trained GI dietician. This, however, is not evidence-based but certainly warrants future study. If a trained GI dietician is not available or if a patient cannot afford to see a dietician, it is important for providers to distribute high-quality teaching materials which can allow an IBS patient to implement the diet in a medically responsible manner.

Soluble Fiber

In summary, soluble, viscous, poorly fermentable fiber may provide benefits in IBS. The apparent lack of significant side effects makes fiber a reasonable first line therapy for IBS patients with symptoms. The ability to improve stool viscosity and frequency logically argues for the use of fiber in patients with IBS-C, although the evidence base to support this contention is weak.

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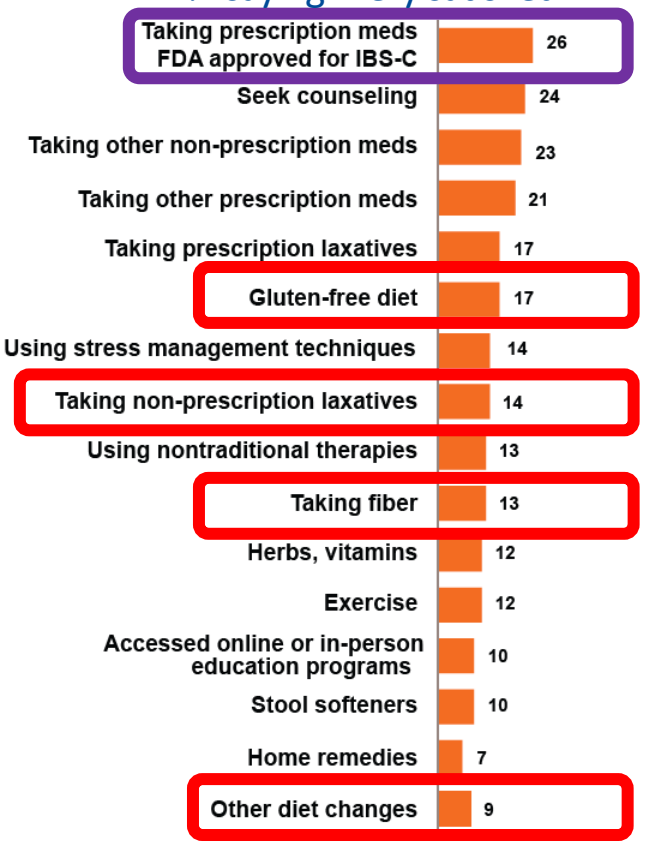
But Don't Take My Word For It...What Sayeth The IBS-C Patient?

- Primary Reasons Patients Seek TREATMENT
  - Abdominal pain (76%)
  - Abdominal Discomfort (64%)
  - Bloating (43%)

- Ave Number of OTCs Tried Before Consulting a Practitioner: 3.3

- Patient Satisfaction With Baha's Wonder Therapeutics



* Data from a survey including 1586 respondents commissioned by the American Gastroenterological Association on IBS in America in 2015.

Shin A and Lembo A. IBS In America. Survey Summary Findings. American Gastroenterological Association. 2015.

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Follow The Evidence/Science/Patients

- IBS is a common disorder characterized by PAIN and assoc abdominal symptoms
- Without these it is NOT IBS
- Abdominal symptoms drive treatment seeking
- Only soluble fiber has been shown to improve global IBS (suggested)
- Fiber loses the battle of the bowel to PEG 3350
- PEG 3350 does not improve and may worsen abd symptoms
- Food may be good but
- Need more data esp in IBS-C
- Low FODMAPs may be harmful
- Limited access to dieticians
- FDA approved therapeutics improve all IBS symptoms as validated in numerous rigorous clinical trials
- We as guideline writers give stronger recommendations to them
- Patients find them more effective
- Cost matters but only if effective (we don't treat ulcers with Tums)

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Step-Up Approach to IBS-C Treatment

Baha Moshiree MD, MSc
Director of Motility
Clinical Professor of Medicine
Atrium Health, Wake Forest University

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IBS Management Principles for Patient-centered Care

Make a positive diagnosis; exclude organic disease

Establish a rapport with the patient; educate and reassure

Categorize IBS subtype based on prevalent stool form (BSFS types 1 and 2)

First-line: lifestyle, dietary modifications, OTC treatments targeting abnormal stool form and most bothersome symptoms

Escalate to FDA-approved prescription therapies as appropriate

Consider off-label and/or psychological therapies as appropriate

Lacy BE, et al. *Am J Gastroenterol*. 2021;117:17-44.

IBS Management Principles for Patient-centered Care

Make a positive diagnosis; exclude organic disease

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Categorize IBS su

pes 1 and 2)

First-line: lifestyle

ing abnormal

stool form and mo

High prescription drug cost and burden of prior authorizations for clinics and HCPs

Escalate to FDA-approved prescription therapies as appropriate

Consider off-label and/or psychological therapies as appropriate

Lacy BE, et al. *Am J Gastroenterol*. 2021;117:17-44.

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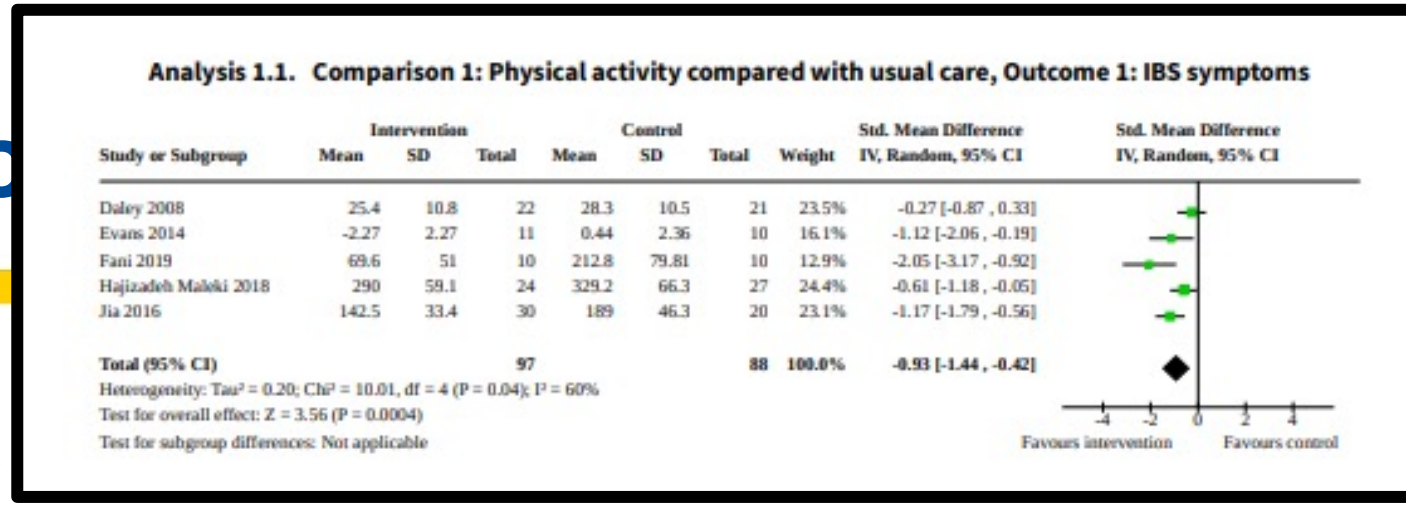
Minimizing Diagnostics for IBS-C:

- No specific testing recommended
- **For All Patients With Suspected IBS: Get a CBC and *age-appropriate CRC screening (age 45 and up)***
- **Routine colonoscopy is *not recommended* in patients with constipation**
- **If severe or medically refractory, consider anorectal physiologic motility testing**

1. Lacy BE, et al. *Am J Gastroenterol*. 2021;117:17-44; 2. Smalley W, et al. *Gastroenterology*. 2019;157:851-854.

Step-up Therapy Wo



Analysis 1.1. Comparison 1: Physical activity compared with usual care, Outcome 1: IBS symptoms

Study or Subgroup	Intervention Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Daley 2008	25.4	10.8	22	28.3	10.5	21	23.5%	-0.27 [-0.87 , 0.33]
Evans 2014	-2.27	2.27	11	0.44	2.36	10	16.1%	-1.12 [-2.06 , -0.19]
Fani 2019	69.6	51	10	212.8	79.81	10	12.9%	-2.05 [-3.17 , -0.92]
Hajizadeh Maleki 2018	290	59.1	24	329.2	66.3	27	24.4%	-0.61 [-1.18 , -0.05]
Jia 2016	142.5	33.4	30	189	46.3	20	23.1%	-1.17 [-1.79 , -0.56]
Total (95% CI)			**97**			**88**	**100.0%**	**-0.93 [-1.44 , -0.42]**

Heterogeneity: $Tau^2 = 0.20$; $Chi^2 = 10.01$, df = 4 (P = 0.04); $I^2 = 60\%$
Test for overall effect: Z = 3.56 (P = 0.0004)
Test for subgroup differences: Not applicable

Std. Mean Difference IV, Random, 95% CI

-4 -2 0 2 4

Favours intervention Favours control

Physical activity[1]

Simple recommendation is for patients to take

Medication review and manipulation[2]

Whenever possible, medications that impair GI transit should be stopped (GLP1- Agonists?, opiates, NSAIDS, others.

Diet and fiber intake[3, 4]

Improve fiber intake; if using a fiber supplement, psyllium (soluble fiber) or Kiwi fruit is recommended because bran fiber may worsen symptoms

OTC laxatives/prescription medications[4]

May include osmotic or stimulant laxatives, prosecretory agents, and centrally acting interventions (e.g., antidepressants) as appropriate for each individual patient Then prescription laxatives may be started

1. Chey WD, et al. *JAMA*. 2015;313:949-958; Nunan D, Cai T, Gardener AD, Ordóñez-Mena JM, Roberts NW, Thomas ET, Mahtani KR. Physical activity for treatment of irritable bowel syndrome. Cochrane Database of Systematic Reviews 2022, Issue 6. Art. No.: CD011497. 2. Lacy BE, et al. *Gastroenterology*. 2016;150:1393-1407; 3. Patel A, et al. *Aliment Pharmacol Ther*. 2016;44:246-258; 4. Ford AC, et al. *Am J Gastroenterol*. 2018;113:1-18.

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Efficacy and Safety of Over-the-Counter Therapies for Chronic Constipation: An Updated Systematic Review

Satish S.C. Rao, MD, PhD[1] and Darren M. Brenner, MD[2]

PEG- Level one evidence: Grade A recommendation

Stimulant laxatives:Stimulant laxatives can be subdivided into 2 categories: diphenylmethane derivatives (e.g., bisacodyl and sodium picosulfate) and plant-based anthraquinones (e.g., senna, aloe, and cascara): Senna: Level I Evidence, Grade A Recommendation Bisacodyl: Level I Evidence, Grade B Recommendation Sodium Picosulfate: Level I Evidence, Grade B Recommendation

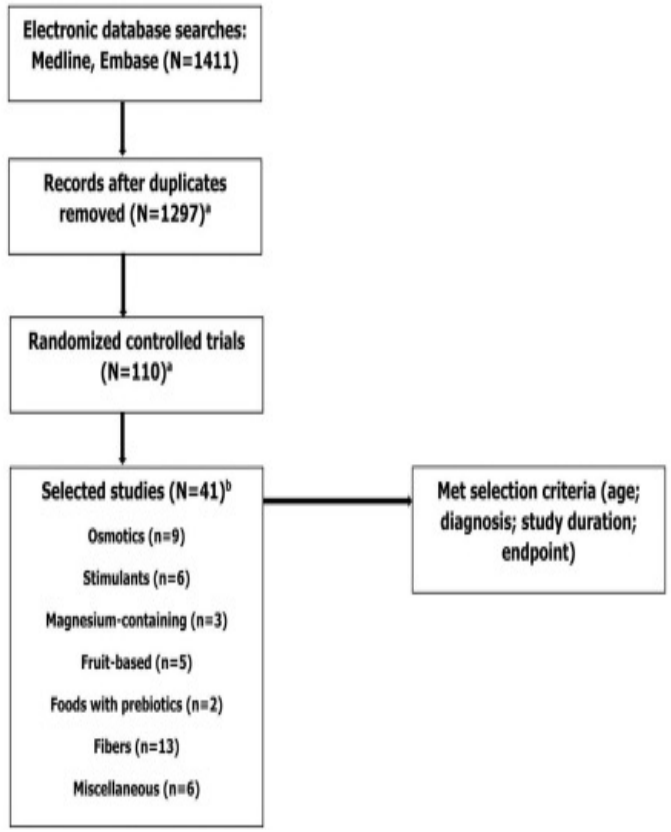
Magnesium-containing Agents: Level I Evidence, Grade B Recommendation

Fruit-based recommendations: Kiwi-based Laxatives: Level I Evidence, Grade B Recommendation Mango-based Laxatives: Level II Evidence, Grade B Recommendation Ficus-based Laxatives: Level II Evidence, Grade B Recommendation Prune-based Laxatives: Level II Evidence, Grade B Recommendation

Foods with prebiotics:Yogurt with Galacto-Oligosaccharides 1 Prune 1 Linseed Oil: Level II Evidence, Grade B Recommendation Rye Bread with Yogurt: Level III Evidence, Grade C Recommendation

Fiber-containing agents: Psyllium: Level II Evidence, Grade B Recommendation Polydextrose: Level I Evidence, Grade I (Insufficient) Recommendation Inulin: Level I Evidence, Grade I (Insufficient) Recommendation Mixed Fiber: Level II Evidence, Grade B Recommendation

Others: polydextrose: Level II Evidence, Grade B Recommendation (patients with CKD) Flaxseed Oil: Level II Evidence, Grade C Recommendation (patients with CKD) Fructo-Oligosaccharide: Level III Evidence, Grade I (Insufficient) Recommendation (patients with CKD)



Rao SS & Brenner DM. *Am J Gastroenterol* 2021;116:1156–1181.

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Outcomes Assessed in AGA IBS Guidelines

IBS-C

Critical

- FDA responder endpoint (≥ 6 of 12 weeks)
- Undesirable outcomes included AEs leading to treatment discontinuation

Important

- Abdominal pain response
- CSBM response
- IBS-QOL improvement
- MCID[a]

Recommendation

- Strong recommendation is most patients should get the treatment.
- Conditional means different choices are appropriate for individual patients based on their preference but majority of patients would want suggested treatment.

Note: Critical and important outcomes varied by therapy.
[a]Improvement over placebo in an outcome of ≥10%.
MCID, minimal clinically important improvement.

Chang L et al. *Gastroenterology.* 2014;147:1149-1172.

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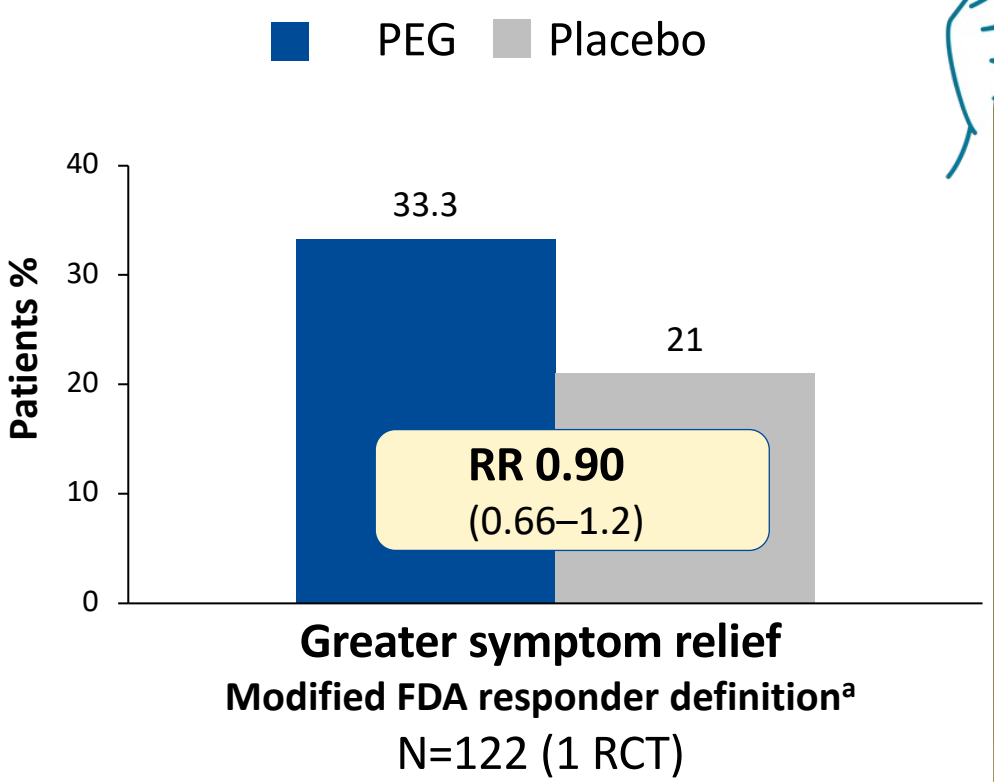
PEG for IBS-C and Safe in Pregnancy!

NNT=8.1



In patients with IBS-C,

the AGA suggests using PEG.

Recommendation
Conditional

Certainty of evidence
Low

- Only one RCT with serious methodological limitations
- Not associated with significant benefit on SBMs or generic quality of life
- Larger, high quality studies needed
- More data on improvement in the number of CSBMs, abdominal pain, treatment withdrawal, IBS-QOL still needed

[a]4-week study.: abdominal pain reduction of >30%, >3 SBMs per week, and an increase of 1 SBM per week.
AE, adverse event; CI, confidence interval; RR, relative risk.
Chang L et al. *Gastroenterology.* 2022;163:118-136.

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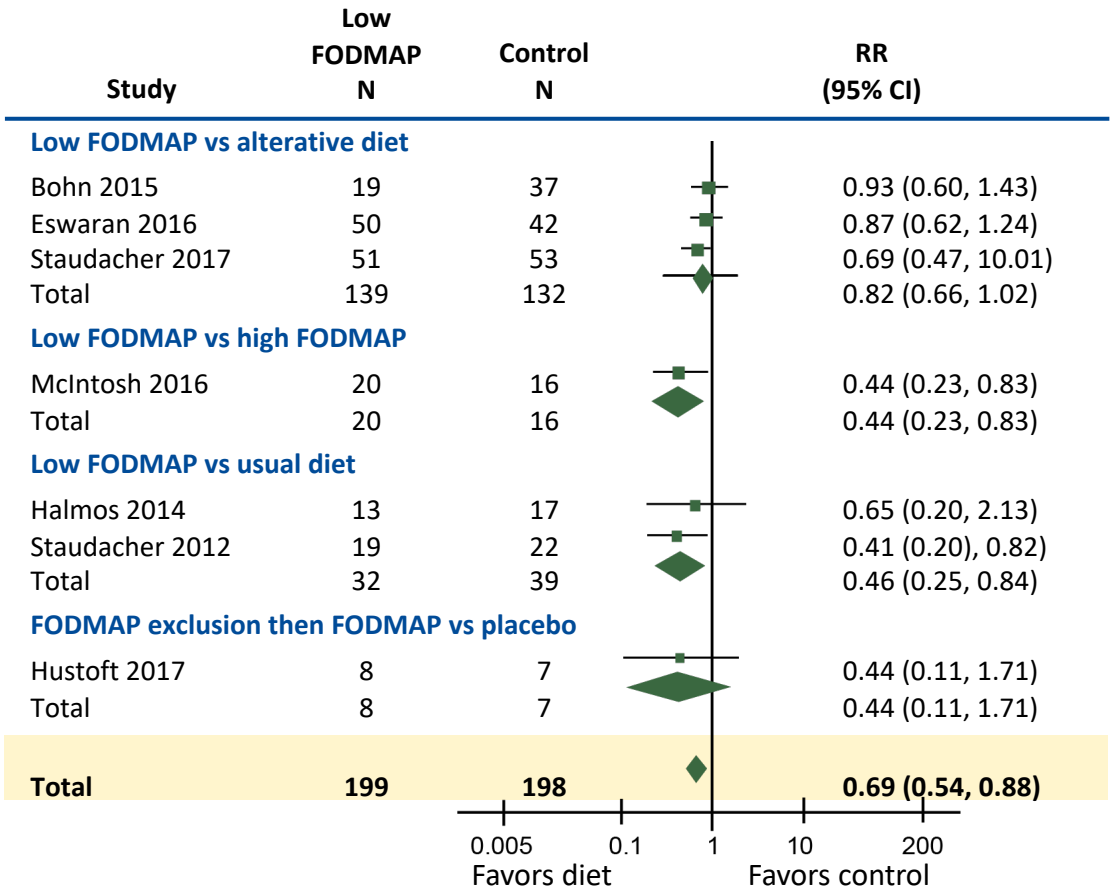
Low FODMAP Diet for IBS

Low FODMAP diet and IBS symptoms[1]



We recommend a limited trial of a low FODMAP diet
in patients with IBS to improve global symptoms[2]

Recommendation
Conditional

Quality of evidence
Very low

- Low FODMAP is the best studied diet for IBS
- Short-term use is recommended
- 3 stages–substitute, reintroduce, personalize
- Risk for vitamin and micronutrient deficiencies with long-term use

1. Dionne J et al. *Am J Gastroenterol.* 2018;113:1290-1300. 2. Lacy BE et al. *Am J Gastroenterol.* 2021;116:17-44.

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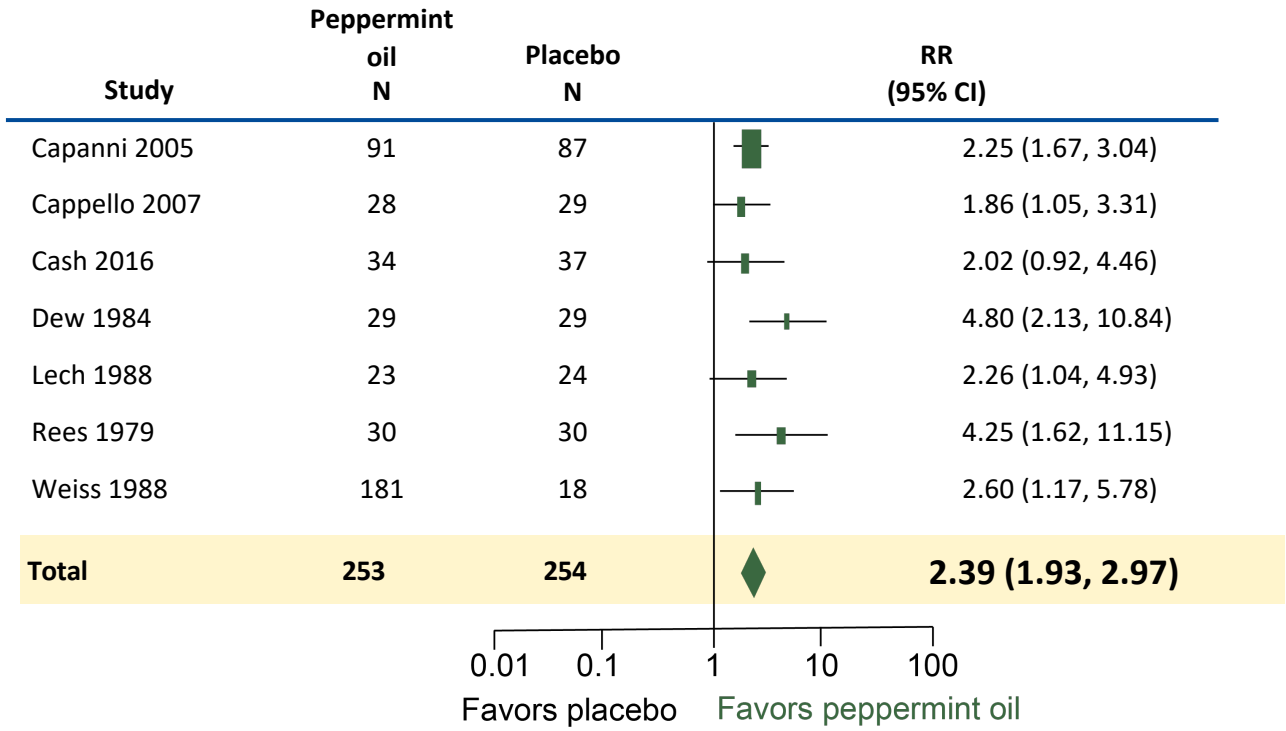
Peppermint for IBS

NNT= 6

RCTs of enteric-coated peppermint oil vs placebo for global improvement of IBS symptoms[1]



We suggest the use of peppermint

to provide relief of global IBS symptoms[2]

Recommendation
Conditional

Quality of evidence
LOW

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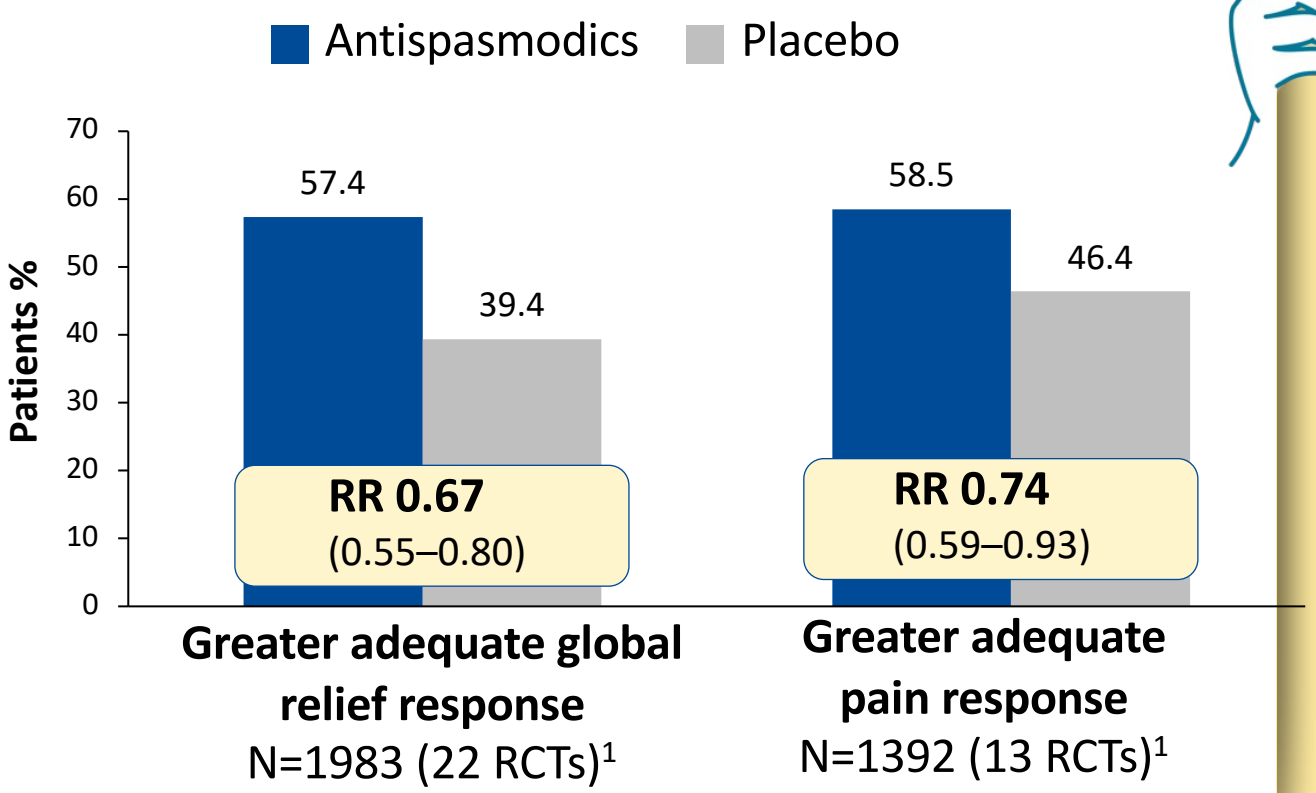
Antispasmodics for IBS

NNT=5.5



In patients with IBS

the AGA suggests using antispasmodics.[2]

Recommendation
Conditional

Certainty of evidence
Low

- The overall quality of evidence was low; there were serious methodological limitations and possible risk of publication bias which led to rating down the evidence to low
- Greater relief of global symptoms
- Pain improvement not clinically meaningful
- **PRN and postprandial use not studied**

AE, adverse event; CI, confidence interval; RR, relative risk.

1. Chang L, et al. *Gastroenterology.* 2014;147:1149-1172; 2.Lembo A, et al. *Gastroenterology.* 2022;163:137-151.

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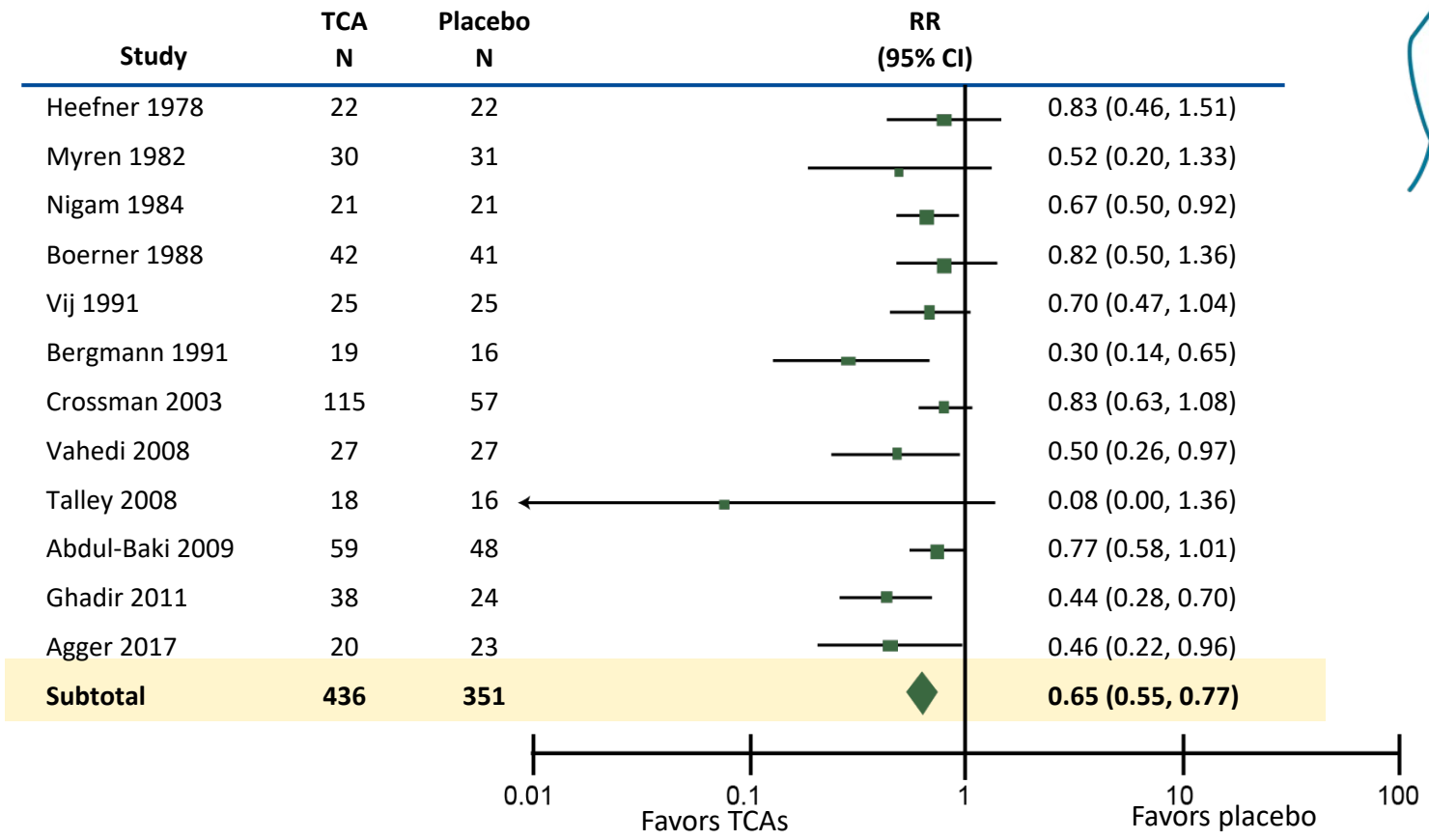
TCAs for IBS - Targeting Pain

NNT=4.5

RCTs of antidepressants vs placebo in IBS[1]



We recommend the use of TCAs
to treat
global IBS symptoms[2]

Recommendation
Conditional

Quality of evidence
Moderate

1. Ford AC et al. *Am J Gastroenterol.* 2018;19:11421-39; 2. Lacy BE et al. *Am J Gastroenterol.* 2021;116:17-44.

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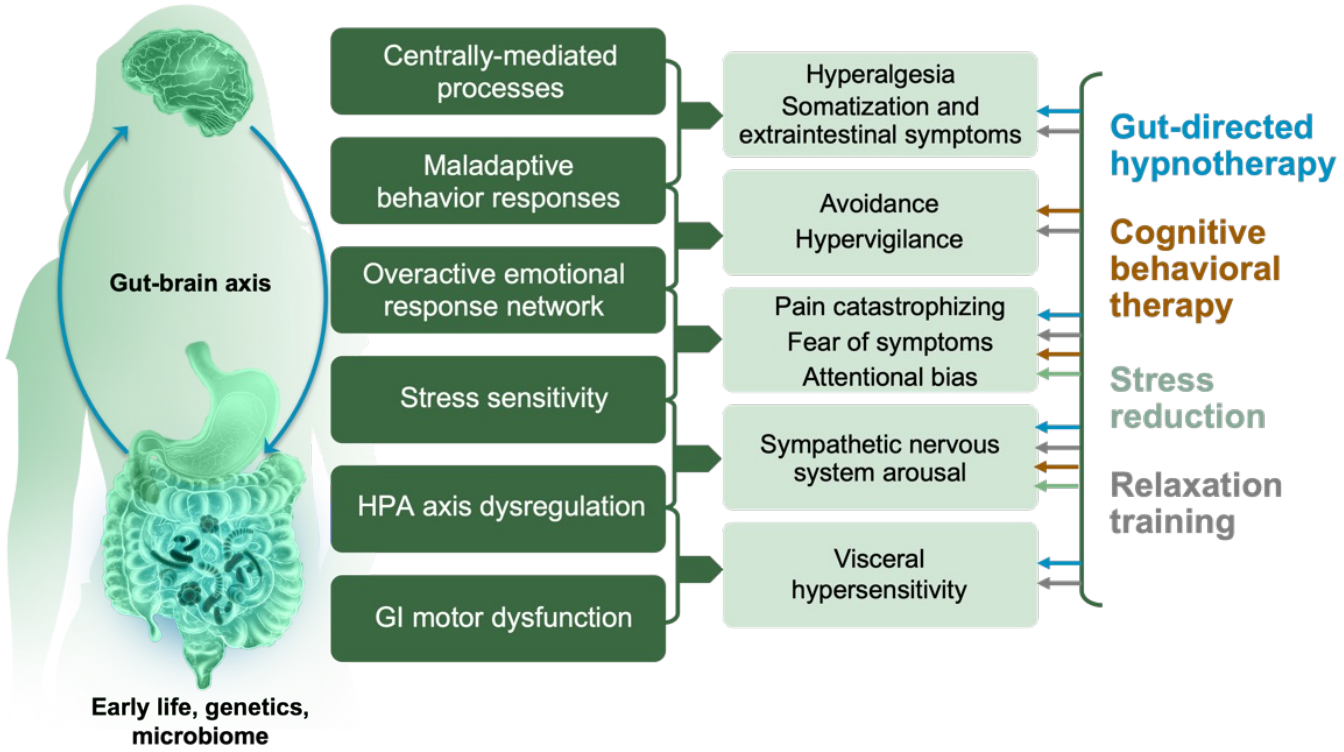
Gut-Directed Psychotherapies for IBS: Why Not First Line Recommendation?

Large RCTs for CBT show benefit (NNT=4)

Gut-directed psychotherapies target cognitive and affective factors that drive symptom experience[1]



We suggest that gut-directed psychotherapies be used to treat global IBS symptoms

Recommendation **Conditional**

Quality of evidence **Very low**

- Multiple gut-directed psychotherapies include CBT and hypnotherapy

CBT, cognitive behavioral therapy.

1. Chey WD, Keefer L, et al. *Gastroenterology*. 2021;160:47-62; 2. Lacy BE, et al. *Am J Gastroenterol.* 2021;116:17-44.

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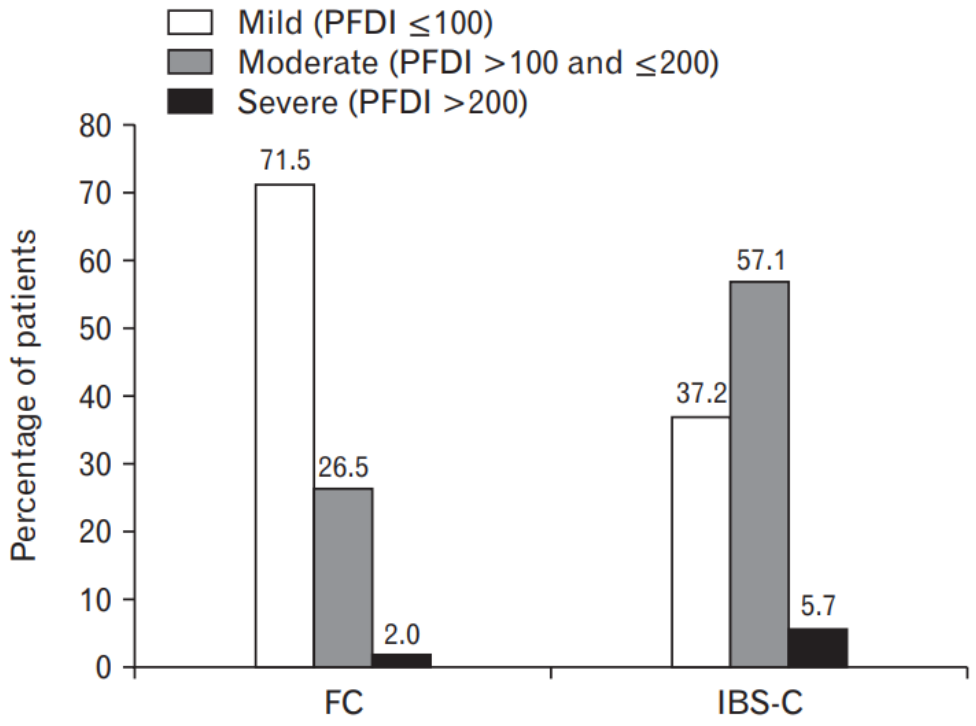
IBS-C Patients Can Also Have Pelvic Floor Disorders

Pelvic floor distress inventory



	IBS-C (n = 43), Mean (95% CI)	*P* Value
Pelvic organ prolapse	38.2 (31.0, 45.4)	.004
Colorectal anal	46.5 (39.6, 53.3)	.04
Urinary	33.7 (24.9, 42.5)	.01
Pelvic floor overall	118 (99.6, 136.3)	.001

Wald A, et al. *Am J Gastroenterol*. 2021;116:1987-2008.

FC, functional constipation; PFDI, Pelvic Floor Distress Inventory.

Singh P, et al. *J Neurogastroenterol Motil*. 2019;25:129-136.

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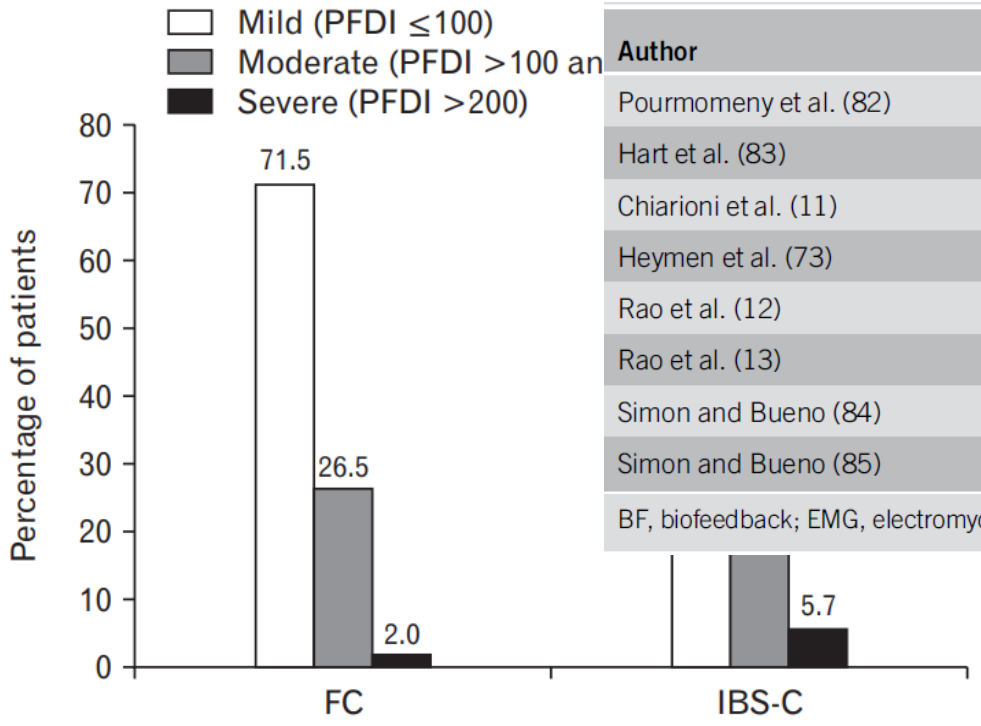
IBS-C Patients Can Also Have Pelvic Floor Disorders

Pelvic floor distress inventory



Author	Sample size	Study type	Comparison made	Outcome
Pourmomeny et al. (82)	65	RCT	Balloon defecation training vs BF	BF superior
Hart et al. (83)	21	RCT	EMG-based BF vs sham BF	BF superior
Chiarioni et al. (11)	99	RCT	PEG vs BF	BF superior
Heymen et al. (73)	84	RCT	BF vs diazepam vs placebo	BF superior to diazepam and placebo
Rao et al. (12)	77	RCT	BF vs sham vs medical care	BF superior to sham and medical care
Rao et al. (13)	26	RCT	BF vs usual medical care	BF superior
Simon and Bueno (84)	30	RCT	EMG-based BF vs control	BF superior
Simon and Bueno (85)	20	RCT	EMG-based BF vs control	BF superior

BF, biofeedback; EMG, electromyography; PEG, polyethylene glycol; RCT, randomized controlled trial.

Pelvic floor overall	118 (99.6, 136.3)	.001

Wald A, et al. *Am J Gastroenterol*. 2021;116:1987-2008.

FC, functional constipation; PFDI, Pelvic Floor Distress Inventory.
Singh P, et al. *J Neurogastroenterol Motil*. 2019;25:129-136.

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Complementary and Alternative Medicine in Irritable Bowel Syndrome: A Systematic Review and Meta-analysis

	Articles	RCTs	Intervention	CAM	Placebo	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality	Effect estimate (95% CI)	
Abdominal pain	55	67		n = 3175	n = 2438						Very low	SMD	
	7	8	Body-based	168	140	V. Ser.	No Ser.	No Ser.	Ser.	No Ser.	Low	−0.04 (−0.36 to 0.28)	
	15	15	Dietary supplements	497	442	Ser.	Ser.	Ser.	Ser.	No Ser.	Low	0.13 (−0.26 to 0.51)	
	6	6	Energy healing	232	232	V. Ser.	No Ser.	No Ser.	Ser.	No Ser.	Low	0.21 (−0.20 to 0.61)	
	17	17	Herbal	1206	1078	Ser	Ser.	Ser.	No Ser.	Ser.	Low	0.47 (0.20–0.75)	
	14	14	Mind-body based	1072	546	V. Ser.	Ser.	Ser.	Ser.	Ser.	Very low	0.29 (−0.01 to 0.59)	
Overall response	44	56		3033	2340						Low	RR	NNT
	5	6	Body-based	145	125	V. Ser.	No Ser.	No Ser.	Ser.	No Ser.	Low	1.32 (0.89–1.95	8 (3–23)
	7	7	Dietary supplements	225	207	Ser.	No Ser.	No Ser.	No Ser.	No Ser.	Moderate	1.95 (1.02–3.73)	4 (2–189)
	3	4	Energy healing	151	148	V. Ser.	No Ser.	No Ser.	Ser.	No Ser.	Low	1.32 (0.99–1.76)	10 (4–303)
	20	20	Herbal	1506	1327	Ser.	No Ser.	No Ser.	No Ser.	Ser.	Moderate	1.57 (1.31–1.88)	5 (4–9)
	12	12	Mind-body based	1006	533	V. Ser.	No Ser.	No Ser.	No Ser.	Ser.	Low	1.67 (1.13-2.49)	5 (3-25)

NOTE. Totals of articles and RCTs do not amount to the sum of the included studies because several articles include multiple RCTs from different CAM categories. Body-based = relaxation, etc. Dietary supplements = aloe vera, etc. Energy healing = acupuncture, etc. Herbal = Curcuma, Tong-Xie, etc. Mind-body based = cognitive behavioral therapy, hypnotherapy, etc.
Ser., Serious; V., Very.

Billings W et al. Potential Benefit With Complementary and Alternative Medicine in Irritable Bowel Syndrome: A Systematic Review and Meta-analysis. *Clin Gastroenterol Hepatol*. 2021;19:1538-1553.e14.

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Complementary and Alternative Medicine in Irritable Bowel Syndrome: A Systematic Review and Meta-analysis

NNT=4 for dietary supplements and NNT=5 for Herbs and Mind-body based therapy

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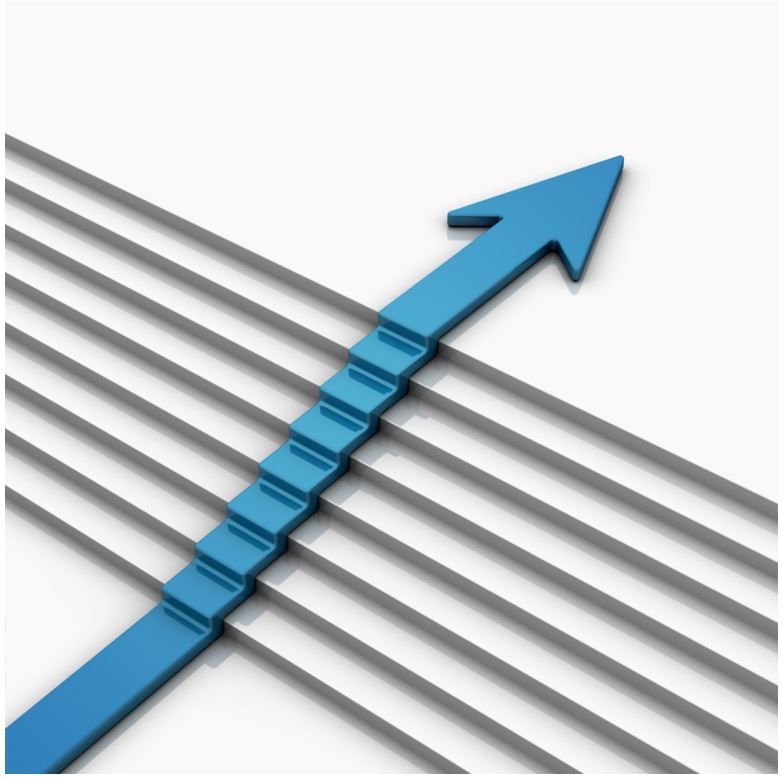
Billings W et al. Potential Benefit With Complementary and Alternative Medicine in Irritable Bowel Syndrome: A Systematic Review and Meta-analysis. *Clin Gastroenterol Hepatol*. 2021;19:1538-1553.e14.

IBS-C Step Up Therapies



In patients with IBS-C, the AGA		NNT=	Strength of Recommendation	Certainty of Evidence
Recommends using	**Linaclotide**	**6.6**	Strong	High
Suggests using	**Tenapanor**	**7.8**	Conditional	Moderate
	Plecanatide	**9.5**	Conditional	Moderate
	Tegaserod[a]	**8.3**	Conditional	Moderate
	Lubiprostone	**9**	Conditional	Moderate
	PEG laxatives	**8.1**	Conditional	Low

[a]Implementation remark: Reapproved for women < 65 years of age without a history of CV ischemic events.

Chang L, et al. *Gastroenterology*. 2022;163:118-136.

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I Can’t Poop: Chronic Idiopathic Constipation vs. Pelvic Floor Dysfunction

Katie Dunleavy, MB BCh BAO

Mayo Clinic, Rochester, MN

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Case Presentation

- 36-year-old female without significant medical history presents with 15-year history of constipation.
- 1 BM per week, Bristol stool type 1-2. Associated with significant straining. She spends several hours in the bathroom to defecate and digitally stimulates transrectally to induce BM. Sensation of incomplete evacuation >50% time. No bleeding.
- Constant abdominal cramping in the LLQ improved with defecation or abdominal massage. Inability to pass gas through the anal canal. Bloating and early satiety. Stable weight.
- Frequent UTIs. Pain with intercourse.
- Associated with irregular menstrual cycles, brain fog, hair loss.

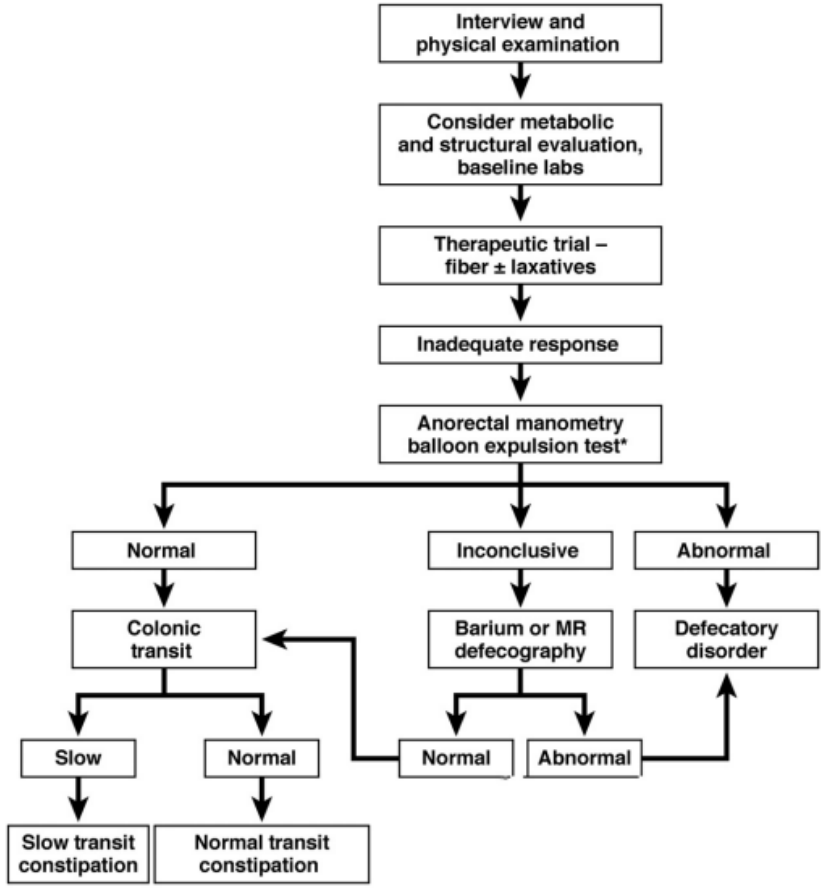
Case Presentation

- Previously trialed medications: fiber, MiraLAX, senna, Colace
- Current medications: Tums, Linaclotide 145 mcg daily
- Social History: Stay at home mom, 3 children (vaginal deliveries with tears), no alcohol, no smoking, no marijuana
- Family History: No history of colorectal cancer, IBD, celiac

Initial Diagnostic Tests

- CBC
- Calcium
- TSH
- Glucose

- Colonoscopy: normal terminal ileum, normal colon



*Because anorectal manometry, rectal balloon expulsion test may not be available in all practice settings, it is acceptable, in such circumstances, to proceed to assessing colonic transit with the understanding that delayed colonic transit does not exclude a defecatory disorder.

Figure 1. Treatment algorithm for chronic constipation. MR, magnetic resonance.

American Gastroenterological Association; Bharucha AE, et al. *Gastroenterology*. 2013;144:211-217.

Question 1:

- What findings on a digital rectal examination would cause you to consider further testing for pelvic floor dysfunction?

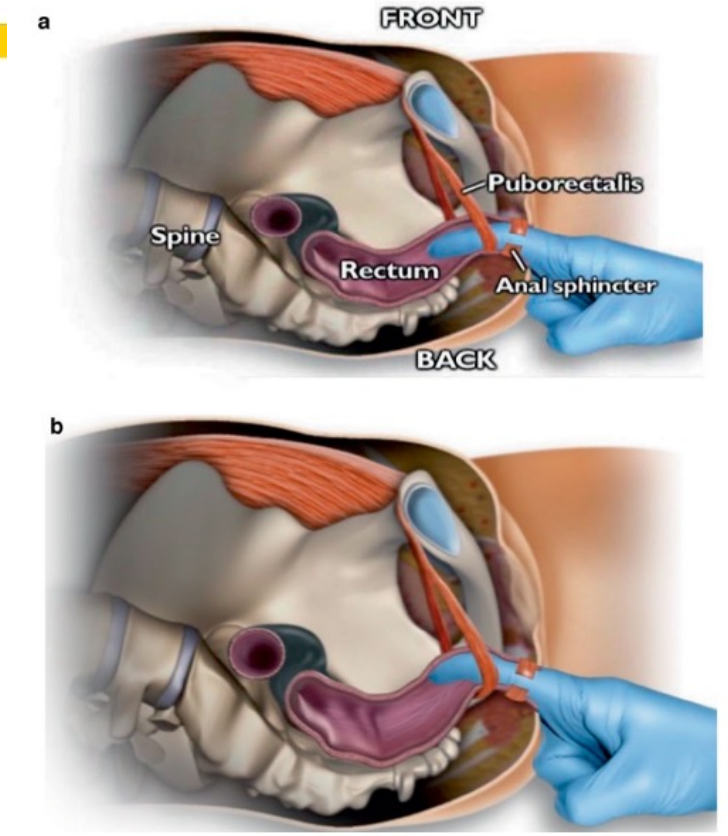


Fig. 2 **a** A schematic illustrating the anatomical components of the DRE examination in the resting state. **b** This schematic illustrates the abnormal paradoxical contraction of the external anal sphincter and puborectalis muscles with fingertip being displaced anteriorly during attempted defecation, suggesting dyssynergic defecation

Rao SSC. *Am J Gastroenterol*. 2018;113:635-638.

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Question 2:

- How do you diagnose dyssynergic defecation?

BOX 1
Rome IV diagnostic criteria for dyssynergic defecation

1. The patient must satisfy diagnostic criteria for functional constipation and/or irritable bowel syndrome with constipation. [a]

2. During repeated attempts to defecate, there must be features of impaired evacuation, as demonstrated by 2 of the following 3 tests: [b]

   a. Abnormal balloon expulsion test

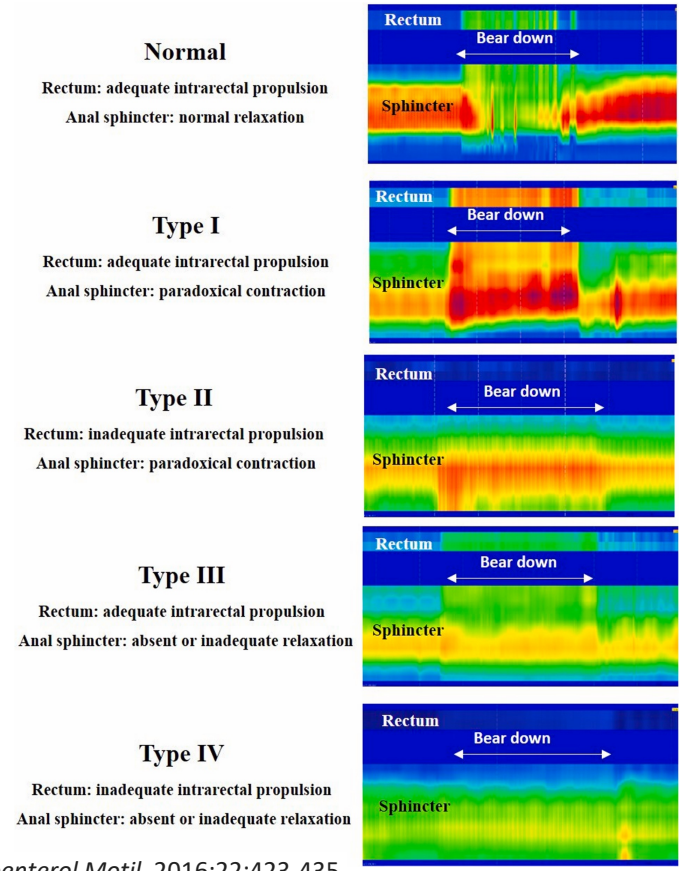
   b. Abnormal anorectal evacuation pattern with manometry or anal surface EMG

   c. Impaired rectal evacuation by imaging

3. Inappropriate contraction of the pelvic floor as measured with anal surface EMG or manometry with adequate propulsive forces during attempted defecation. [b]

[a] Criteria must be fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

[b] These criteria are defined by age- and sex-appropriate normal values for each diagnostic technique.



Picture: Sharma A, et al. *Gastroenterol Clin North Am*. 2022;51:55-69; Rao SS, Patcharatrakul T. *J Neurogastroenterol Motil*. 2016;22:423-435.

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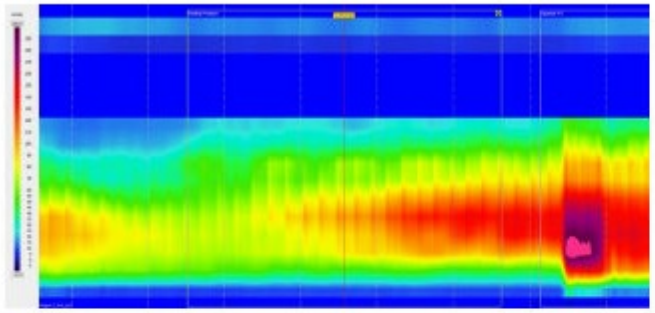
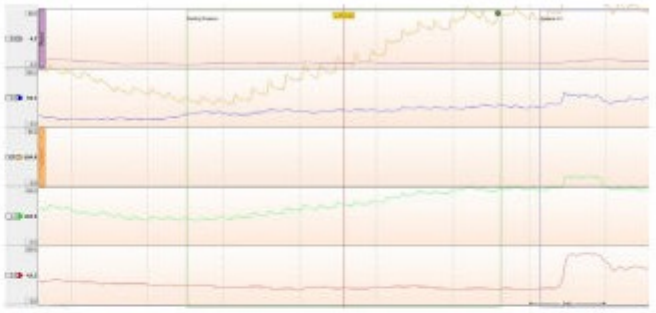
Anorectal Manometry

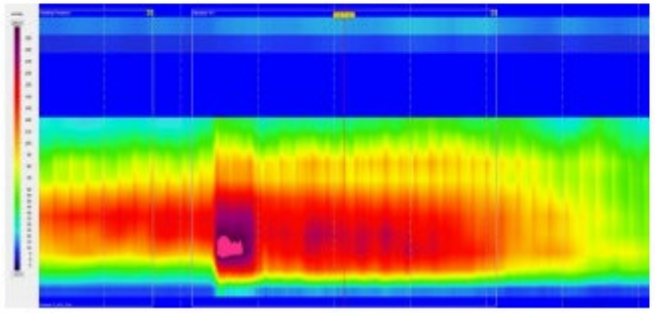
Resting Pressure



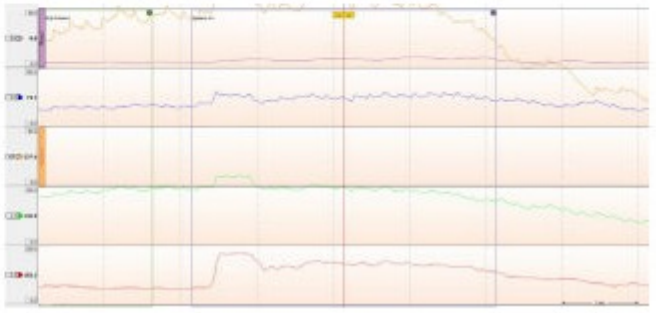
Resting Pressure



Squeeze #1



Squeeze #1



Resting		Normal	**Squeeze**		Normal
Mean Sphincter Pressure(rectal ref.)(mmHg)	101.9		Max. Sphincter Pressure(rectal ref.)(mmHg)	204.2	
Max. Sphincter Pressure(rectal ref.)(mmHg)	147.6		Max. Sphincter Pressure(abs. ref.)(mmHg)	210.0	
Mean Sphincter Pressure(abs. ref.)(mmHg)	106.5		Duration of sustained squeeze(sec)	18.6	
Max. Sphincter Pressure(abs. ref.)(mmHg)	152.3				
Length of HPZ(cm)	4.1				
Length verge to center(cm)	1.9				
Push(attempted defecation)		Normal	**Balloon Inflation**		Normal
Residual Anal Pressure(abs. ref.)(mmHg)	115.1		RAIR	Present	
Percent anal relaxation(%)	33		First sensation(cc)	>300	
Intrarectal pressure(mmHg)	86.0		Urge to defecate(cc)	>300	
Rectoanal pressure differential(mmHg)	-29.1		Discomfort(cc)	>300	

Procedure
Anal and rectal pressures at rest, during squeeze, and simulated evacuation were assessed by high resolution manometry. Rectoanal inhibitory reflex and rectal sensation were evaluated by distending a balloon in the rectum. Rectal balloon expulsion was assessed by timed external passage of the water filled balloon from the rectum in the upright position on commode.

Indications
Constipation

Interpretation / Findings
The anal pressure at rest was high. The anal pressure during squeeze was high. The rectoanal inhibitory reflex was present. Rectal sensation was markedly reduced. During simulated evacuation (maneuver #1), the increase in the intra-rectal pressure was normal, percent anal relaxation was reduced, residual anal pressure was high, and the rectoanal pressure gradient was abnormal. The rectal balloon expulsion test was abnormal (>60 seconds).
In the appropriate clinical context, this profile is suggestive of a rectal evacuation disorder.

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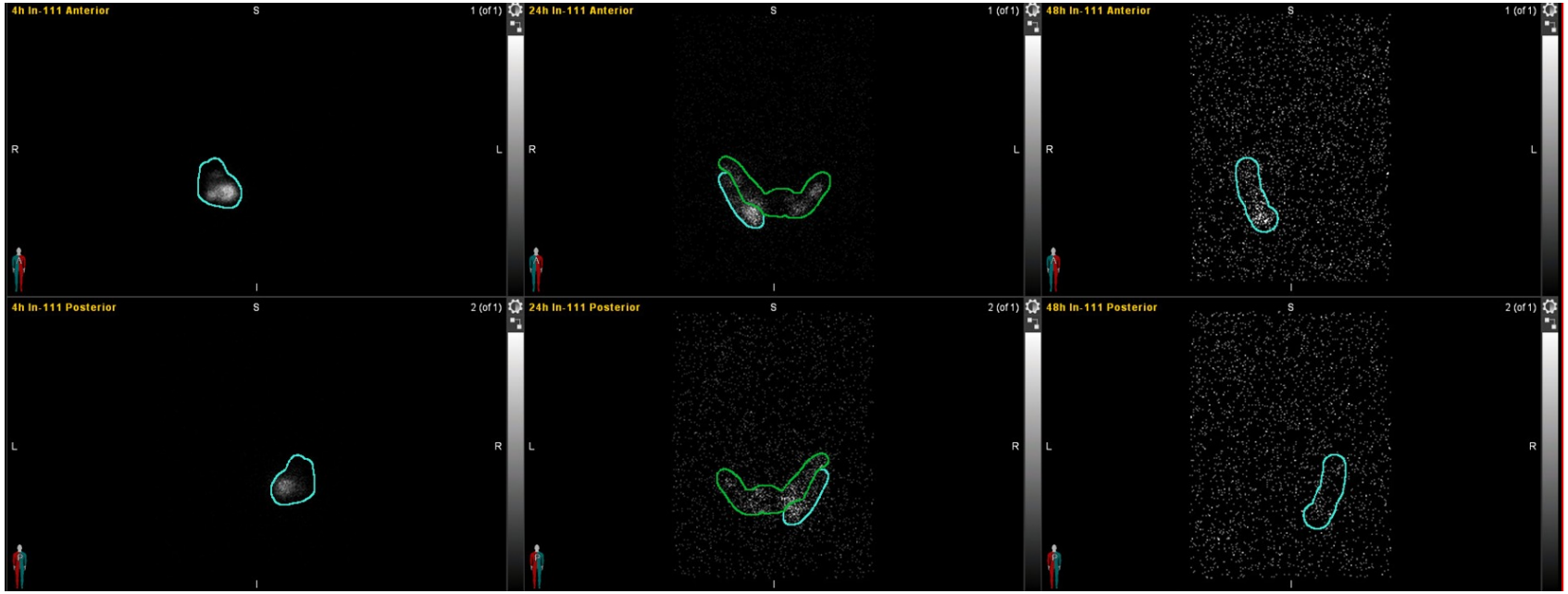
Question 3:

- What findings would you expect on a colonic transit test in a patient with pelvic floor dysfunction?



Picture: Shared with patient permission.

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CASE STUDY

“My Belly Hurts”- Optimizing Abdominal Pain in IBS

Case Presenter: Carl Kay, MD

Moderator: Linda Nguyen, MD

Panel: Kaavita Kongara, MD and Satish Rao, MD, PhD

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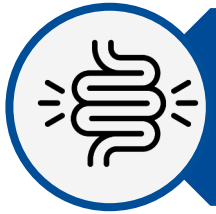
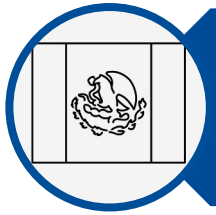
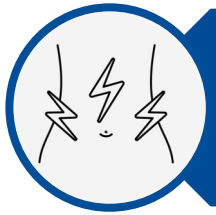
Case Presentation



28-year-old female with altering constipation and diarrhea



Developed after trip to Mexico 1 year ago and persisted



Daily LLQ pain & bloating – ↑ after eating & defecation

Denies weight loss, nocturnal symptoms, bleeding

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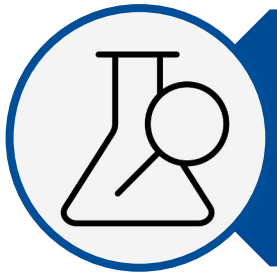
Case Presentation

Normal vitals, physical exam – including detailed rectal exam



Normal CBC, TSH, celiac serologies, CRP, & fecal calprotectin

↓QOL, no social life,
↑absence from work

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First Attempts to Help

Soluble fiber (psyllium) – worse

Lactose-free diet – partial improvement

Generic probiotic – partial improvement

Dicyclomine – no improvement

Predominant symptoms – still LLQ pain, bloating, and constipation

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First Attempts to Help

Soluble fiber (psyllium) – worse

Lactose-free diet – partial improvement

Generic probiotic – partial improvement

Dicyclomine – no improvement

Would you do specific diagnostic tests?

Predominant symptoms – still LLQ pain, bloating, and constipation

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Management Dilemmas

How do you counsel & implement low FODMAP diet?

How would you integrate peppermint oil?

Which neuromodulator (TCA) is your favorite for IBS pain?

When do you integrate secretagogues (e.g., linaclotide)?

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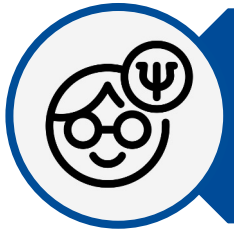
Management Dilemmas

What is the ideal patient for tenapanor therapy?



When/how do you integrate therapist for CBT?

Other pro tips for IBS pain management?

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