@alearmuzzi

How should we monitor the IBD patients today?

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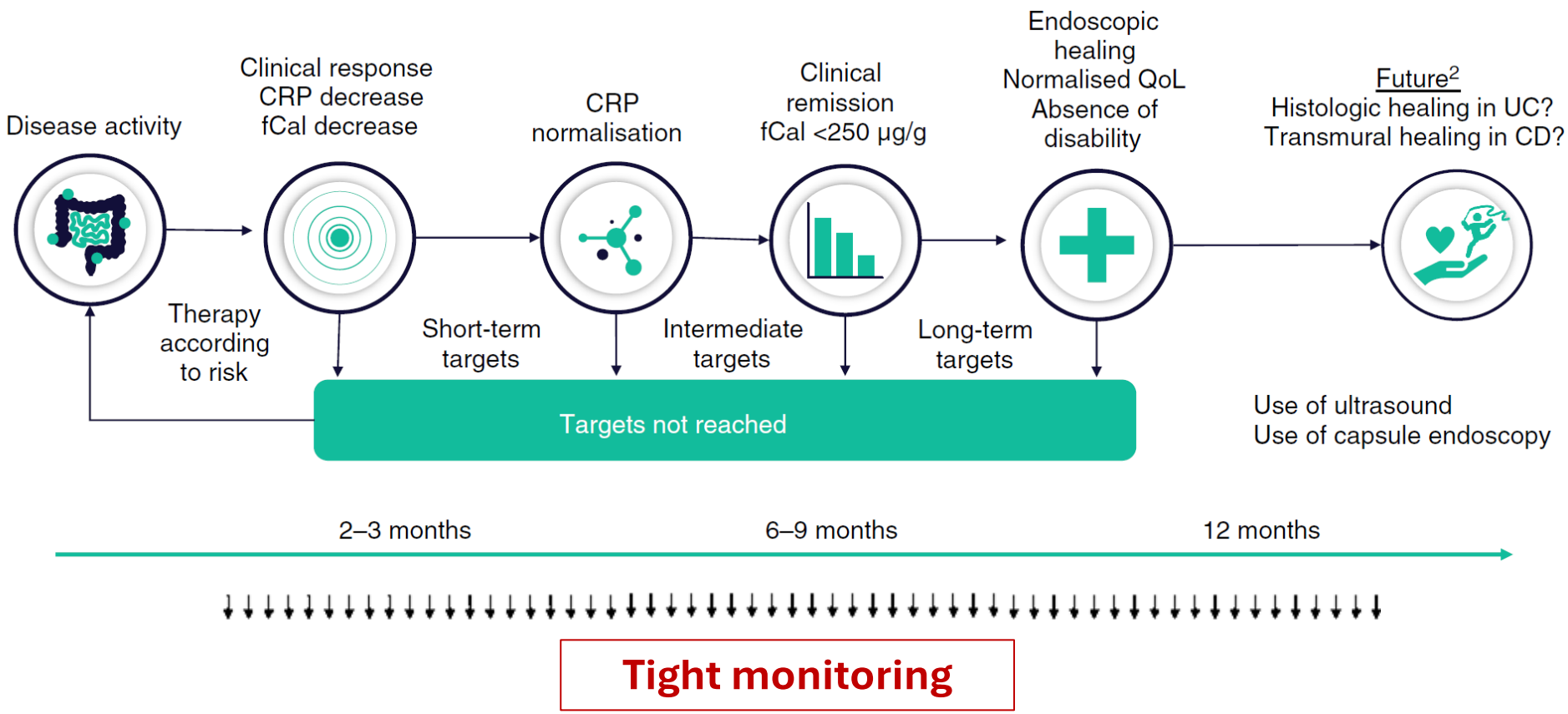
Disclosures

- Consulting/advisory board fees from AbbVie, Abivax, Alfa Sigma, Astra Zeneca, Biogen, Boehringer Ingelheim, Bristol-Myers Squibb, Celltrion, Eli-Lilly, Ferring, Galapagos, Gilead, Giuliani, Janssen, Lionhealth, Merck, Nestlé, Pfizer, Protagonist Therapeutics, Roche, Sanofi, Samsung Bioepis, Sandoz, Takeda, Teva Pharmaceuticals, Tillots Pharma

- Speaker's fees from AbbVie, Abivax, AG Pharma, Alfa Sigma, Biogen, Bristol-Myers Squibb, Celltrion, Eli-Lilly, Ferring, Galapagos, Gilead, Janssen, Lionhealth, Merck, Novartis, Pfizer, Roche, Samsung Bioepis, Sandoz, Takeda, Teva Pharmaceuticals

- Research grants from Biogen, Merck, Pfizer, Takeda

Managing patients with IBD



Adapted from Dignass A, et al. Aliment Pharmacol Ther 2023

Estimated time-to-target in IBD

Treatment, mean number of weeks	Clinical Response	Clinical Remission	Normalization of CRP/ESR	Decrease of FCalp	Endoscopic Healing
Crohn's Disease (n=39)					
Oral CS/EEN	2	4	5	8	13
Budesonide	3	6	8	10	15
Thiopurines	11	15	15	17	24
Methotrexate	9	14	14	15	24
Anti-TNF	2-4	4-6	9	11	17
Vedolizumab	11	17	15	17	24
Ustekinumab	7	13	11	14	19
Ulcerative Colitis (n=36)					
Oral 5-ASA	4	8	8	10	13
Systemic steroids	2	2	5	8	11
Locally active steroids[2]	3	8	8	9	13
Thiopurines	11	15	15	15	20
Adalimumab	6	11	10	12	14
Infliximab	5	10	9	11	13
Vedolizumab	9	14	14	15	18
Tofacitinib	6	11	9	11	14

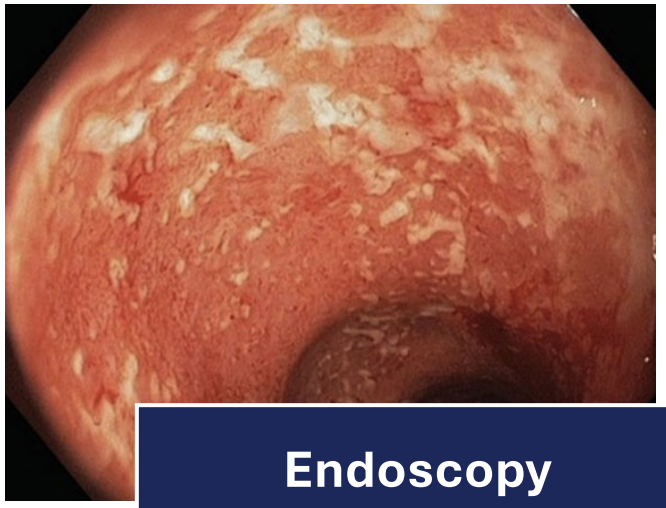
Adapted from: Turner D, et al. Gastroenterology. 2021;160:1570-83

Monitoring tools

A good monitoring tool:

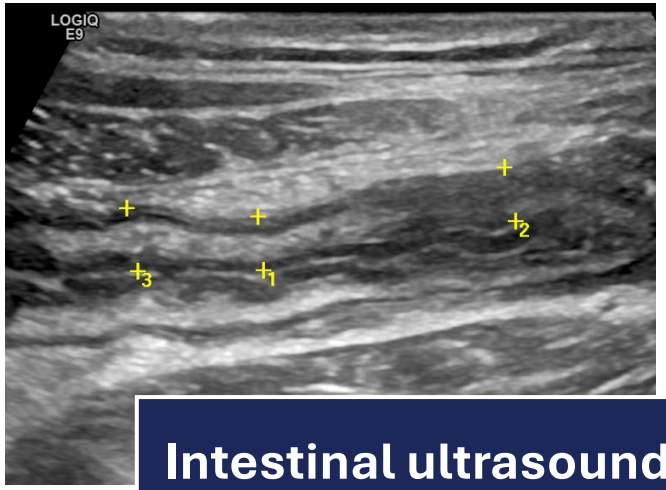
- Well accepted by patients
- Correlates well with target
- Reproducible
- Able to capture subtle changes
- Non-invasive
- Inexpensive

Patient reported outcomes



Endoscopy

Biomarkers

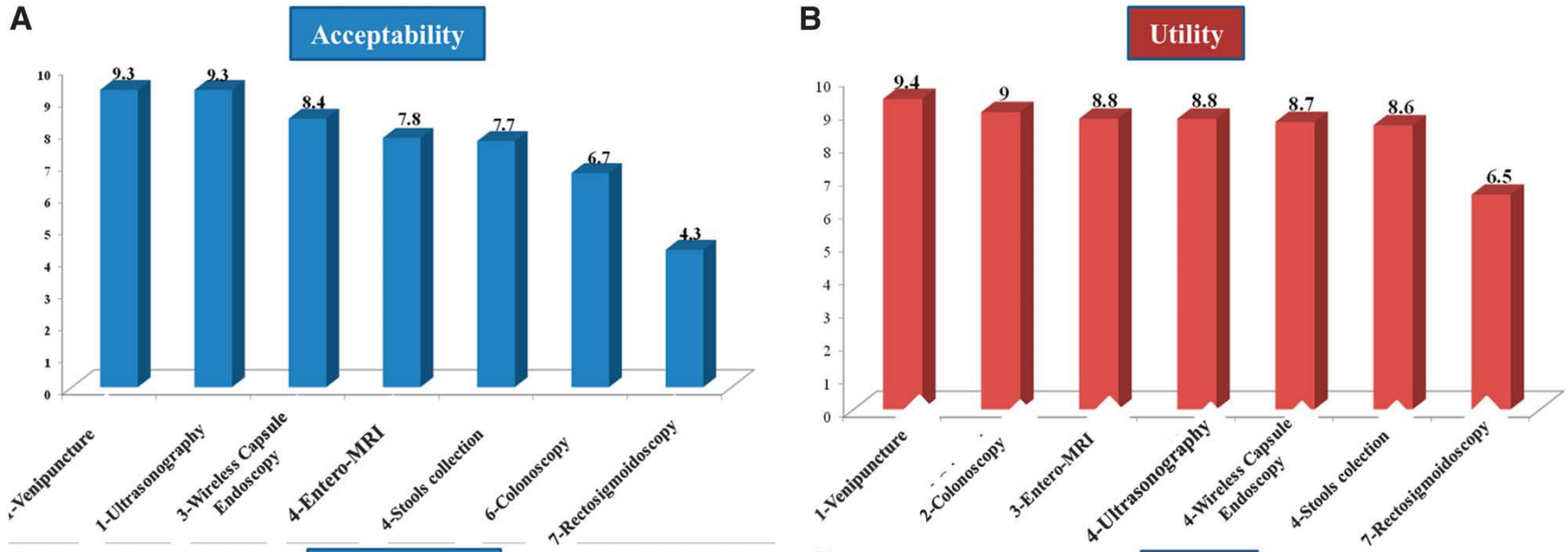


Intestinal ultrasound

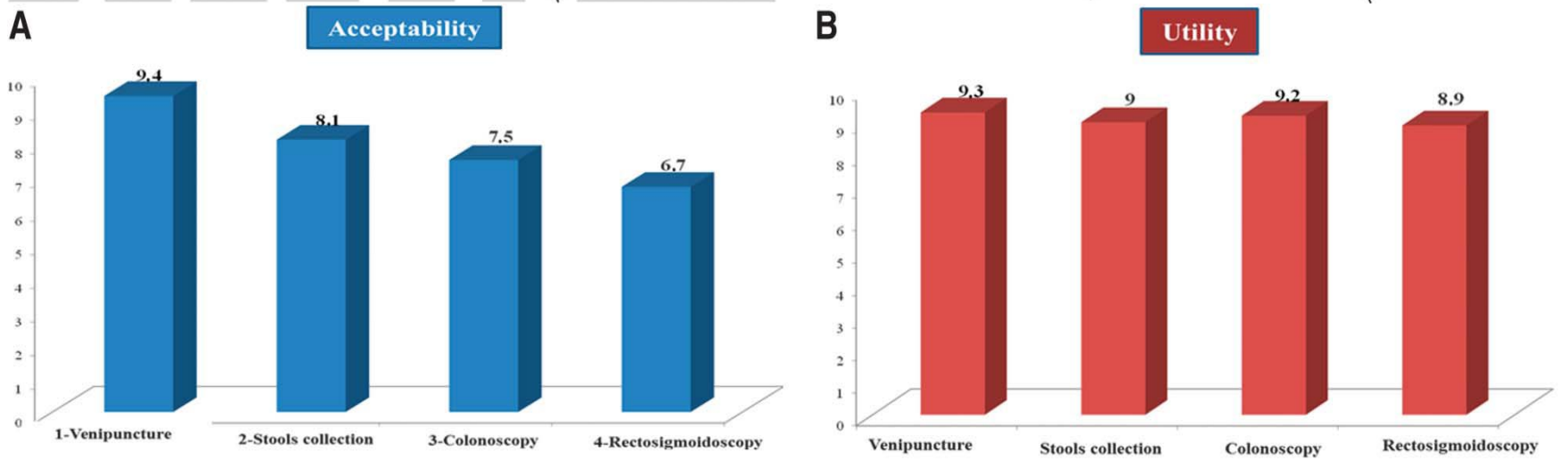
Comparative Acceptability and Perceived Clinical Utility of Monitoring Tools

Survey on 916 patients with IBD

CD



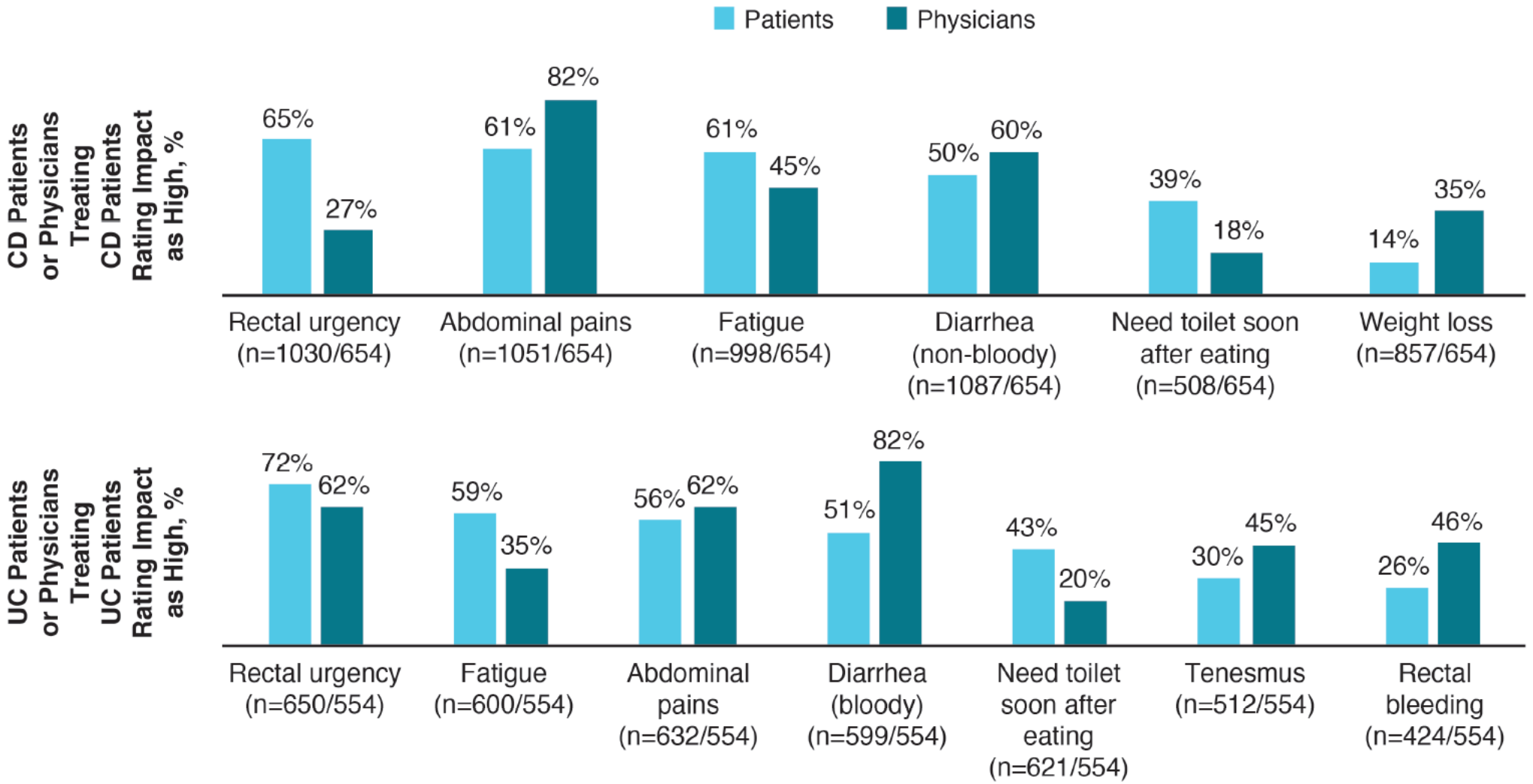
UC



Buisson A, et al. Inflamm Bowel Dis 2017

Patient Reported Outcomes

Symptoms reported by IBD patients and physicians to have the greatest impact on QoL

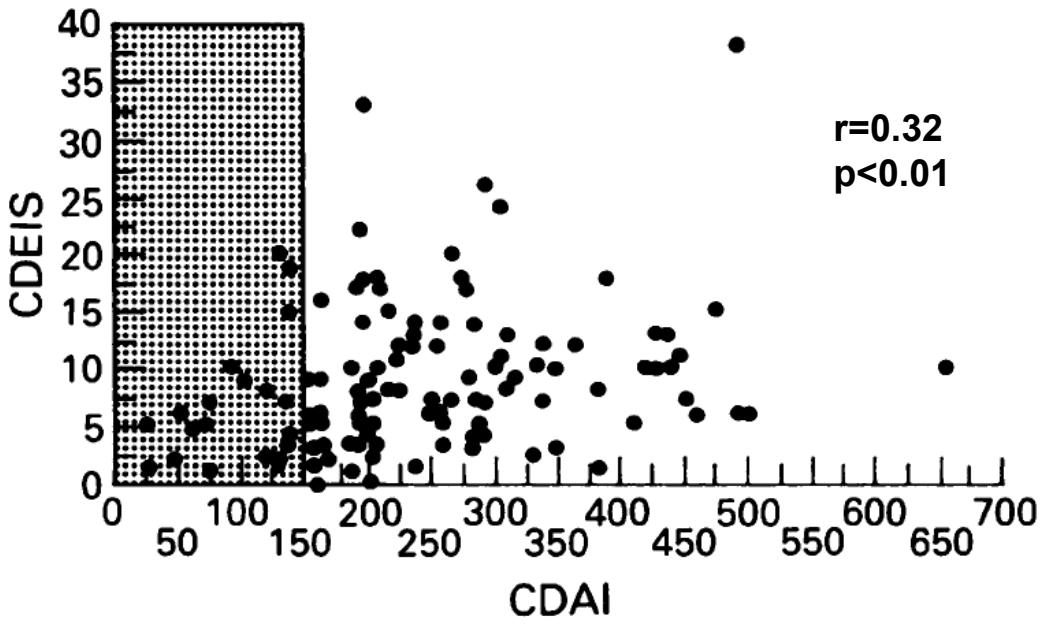


2398 patients with IBD (1368 CD, 1030 UC) and 654 physicians completed the GAPPS surveys

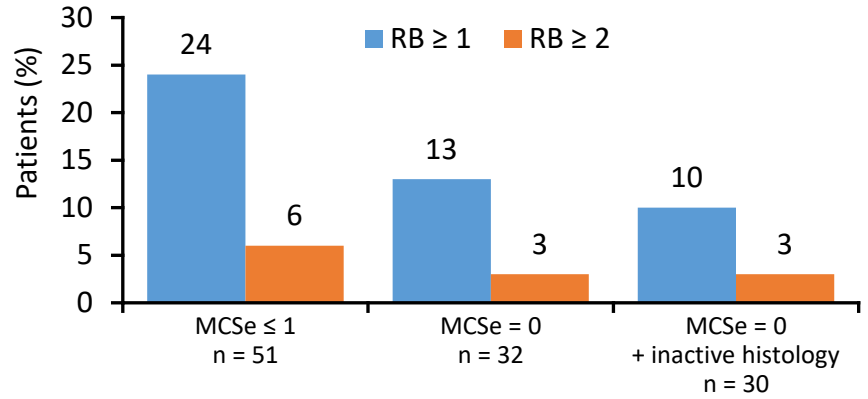
Rubin DT, et al. Inflamm Bowel Dis 2021

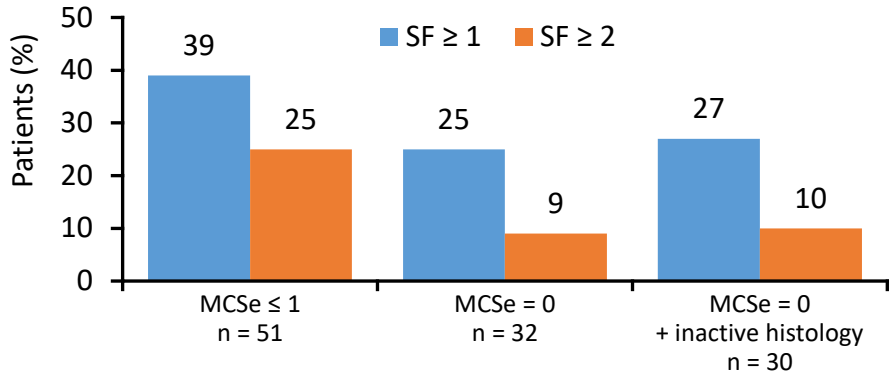
Poor correlation between symptoms and endoscopic lesions in IBD (CD > UC)

Crohn's disease



Ulcerative colitis





Cellier C, et al. Gut 1994;35:231-5

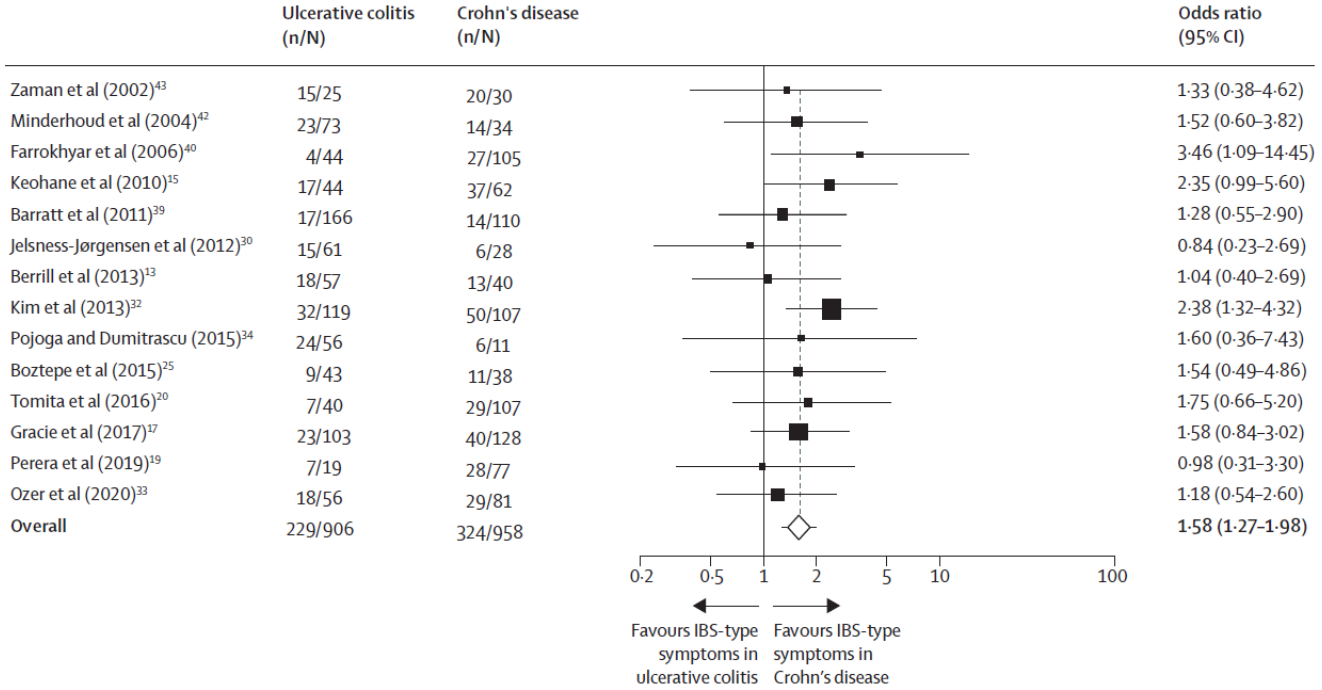
Colombel JF, et al. Gut 2017;66:2063-8

Prevalence of IBS-type symptoms in patients with IBD in remission: systematic review and meta-analysis (N 3169; 27 studies)

Subgroup analyses of prevalence of IBS-type symptoms in IBD

	Number of studies	Total number of patients	Number of patients meeting criteria for IBS-type symptoms	Pooled prevalence of IBS-type symptoms (95% CI)	I^2	p value*
Criteria used to define remission						
All IBD patients according to primary definition of remission used in the study	27	3169	992	32·5% (27·4–37·9)	90·1%	<0·0001
Validated clinical disease activity index	15	1924	621	33·6% (26·3–41·2)	91·8%	<0·0001
Physician's global assessment	8	837	274	34·1% (24·6–44·3)	89·0%	<0·0001
Endoscopic healing	6	704	174	23·5% (17·9–29·6)	59·9%	0·029
Faecal calprotectin <100 µg/g	4	470	139	35·1% (28·1–42·6)	38·7%	0·18
Histological remission	2	246	64	25·8% (20·2–31·7)	NA	NA
Criteria used to define presence of IBS-type symptoms						
Rome III	16	1985	659	33·5% (27·6–39·6)	87·7%	<0·0001
Rome II	8	888	239	31·5% (19·2–45·4)	94·3%	<0·0001
Rome IV	2	198	61	29·6% (19·4–40·9)	NA	NA
Manning	1	98	33	33·7% (24·4–43·9)	NA	NA
Type of IBD						
Ulcerative colitis	22	1825	527	28·7% (22·9–34·8)	87·2%	<0·0001
Crohn's disease	15	1050	366	36·6% (29·5–44·0)	82·9%	<0·0001

ORs for IBS-type symptoms in IBD in remission (CD vs UC)



Fairbrass KM, et al. Lancet Gastroenterol Hepatol 2020;5:1053-62

Monitoring with clinical symptoms/PROs

Monitoring tool	Target	Definition	Limitations
HBI (CD)	Clinical response Clinical remission	Decrease ≥3 points ≤4 points	Poor sensitivity and specificity for intestinal inflammation Risk of undertreatment or overtreatment No assessment of disease extent and complications
SCCAI (UC)	Clinical response Clinical remission	Decrease >30% ≤2 points	
pMS (UC)	Clinical response Clinical remission	Decrease >2 points <3 & no subscore >1	
PRO-2 (CD & UC)	Clinical response Clinical remission	Decrease ≥50% in AP ad SF score (CD) Decrease ≥50% in RB ad SF score (UC) AP score ≤1 and SF score ≤3 (CD) RB score 0 and SF score 0 (UC)	

HBI: Harvey-Bradshaw index; SCCAI: Simple clinical colitis activity index; pMS: partial Mayo Score; PRO-2: Patients Reported Outcome-2

Biomarkers

C-reactive protein in Ulcerative colitis

454 patients with UC, 5 year follow up

	Proctitis	Procto-sig	Left sided	Extended	All UC patients
CRP ≤ 10 mg/L	88%	80%	60%	56%	71%
CRP 11-50 mg/L	8%	18%	32%	27%	20%
CRP 51-99 mg/L	3%	1%	5%	8%	5%
CRP ≥ 100 mg/L	1%	0%	3%	9%	4%

CRP is normal in most UC patients

CRP did not differ between endoscopic remission and endoscopic inflammation

It's more commonly abnormal in extended colitis > proctitis

CRP is high in ASUC

CRP levels did not predict colectomy during 5 year follow up (except for a sub-group with extensive disease)

Henriksen M, et al. Gut 2008

C-reactive protein in Crohn's disease

200 patients with Crohn's disease, 5 year follow up

Table 3 C-reactive protein (CRP) levels at diagnosis in 176 patients with Crohn's disease according to localisation and behaviour of disease and for all patients with Crohn's disease

	Terminal ileum L1, n = 46	Colon L2, n = 77	Ileocolon L3, n = 50	Upper GI L4, n = 3
Mean/median	44/28	54/33	54/32	38/37
SEM	7.7	7.0	7.3	3.2
Range	0–238	0–266	0–230	33–44
Number of patients with CRP ⩽ 10 mg/l	14 (30%)	20 (26%)	10 (20%)	0 (0%)
Number of patients with CRP 11–50 mg/l	18 (39%)	31 (40%)	19 (38%)	3 (100%)
Number of patients with CRP 51–99 mg/l	8 (17%)	15 (20%)	12 (24%)	0 (0%)
Number of patients with CRP ⩾ 100 mg/l	6 (13%)	11 (14%)	9 (18%)	0 (0%)
	Nonstricturing nonpenetrating B1, n = 106	**Stricturing B2, n = 49**	**Penetrating B3, n = 21**	**All patients with Crohn's disease, n = 176**
Mean/median	50/26	56/42	49/35	51/33
SEM	5.8	7.6	9.0	4.1
Range	0–266	0–230	0–152	0–266
Number of patients with CRP ⩽ 10 mg/l	32 (30%)	8 (16%)	4 (19%)	44 (25%)
Number of patients with CRP 11–50 mg/l	41 (39%)	21 (43%)	9 (43%)	71 (40%)
Number of patients with CRP 51–99 mg/l	17 (16%)	12 (25%)	6 (29%)	35 (20%)
Number of patients with CRP ⩾ 100 mg/l	16 (15%)	8 (16%)	2 (10%)	26 (15%)

SEM, standard error of the mean.

Most patients with Crohn's disease (75%) had elevated CRP levels at diagnosis

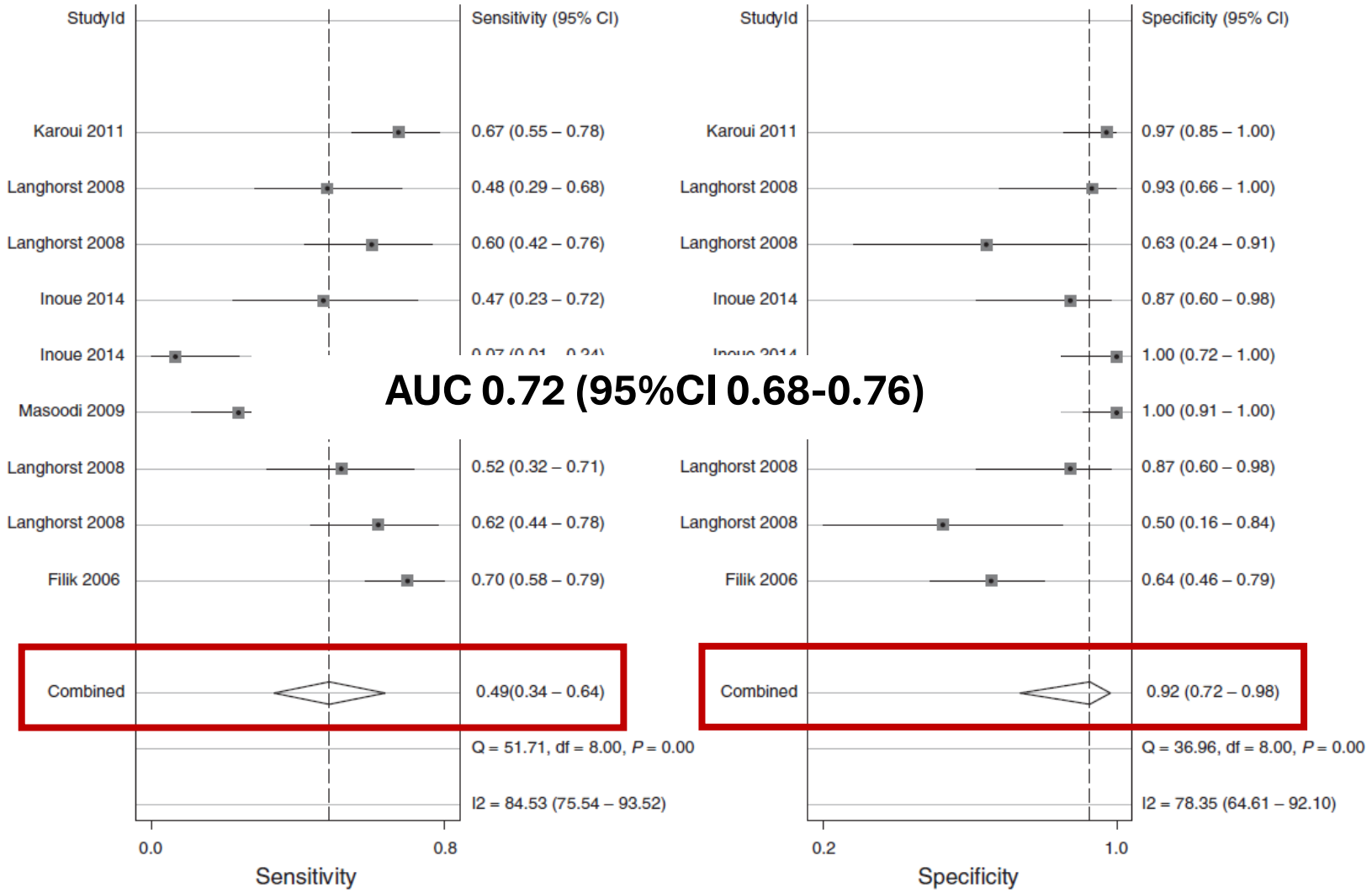
No differences in CRP between different disease location / behavior

No association between CRP levels and risk of surgery, except in the L1 sub-group

- CRP levels did not predict relapse in this cohort of 654 IBD patients
- CRP levels at diagnosis and after 1 yr predicted surgery in subgroups of patients (L1)

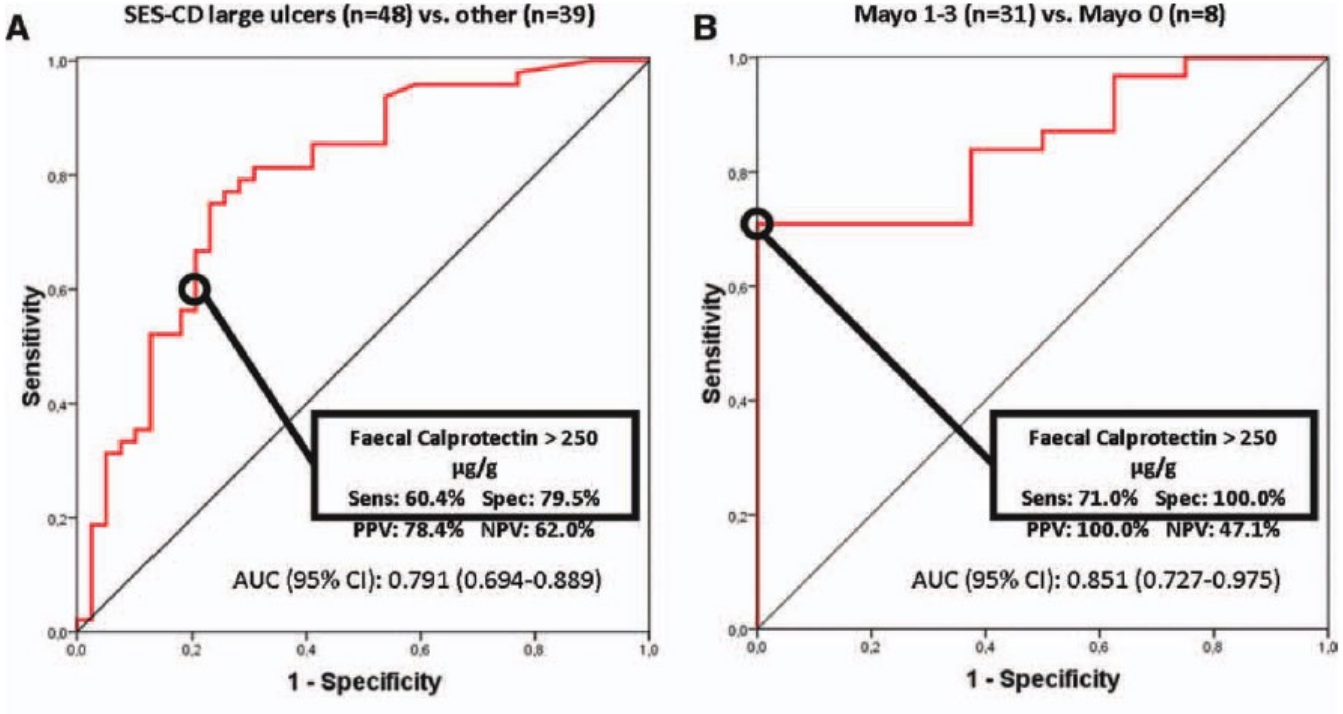
Henriksen M, et al. Gut 2008

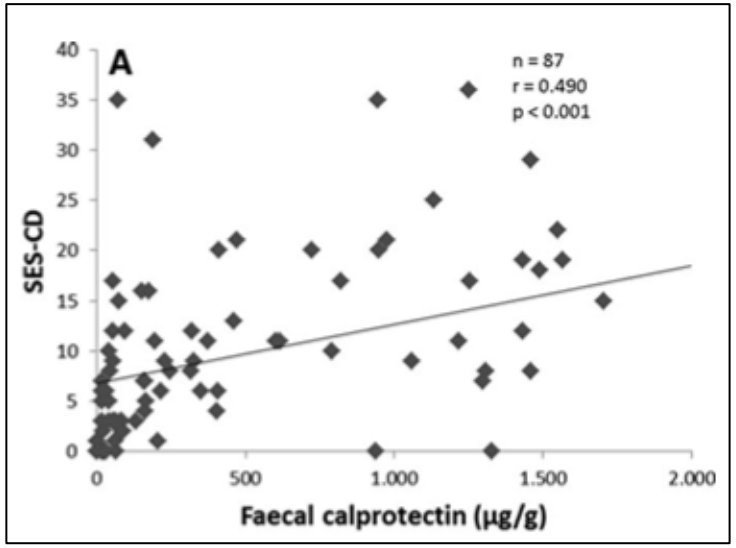
CRP for Detection of Endoscopic Activity in Symptomatic IBD Patients: A Systematic Review and Meta-Analysis

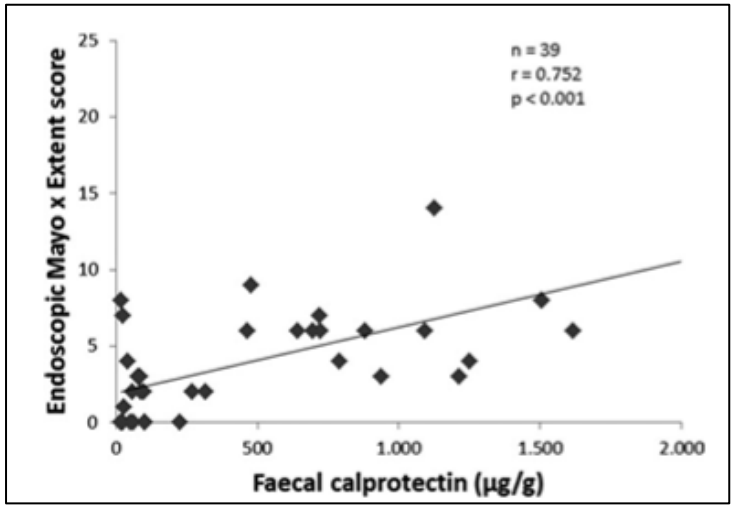


Mosli M, et al. Am J Gastroenterol 2015

FCalp is a Surrogate Marker for Endoscopic Lesions in IBD

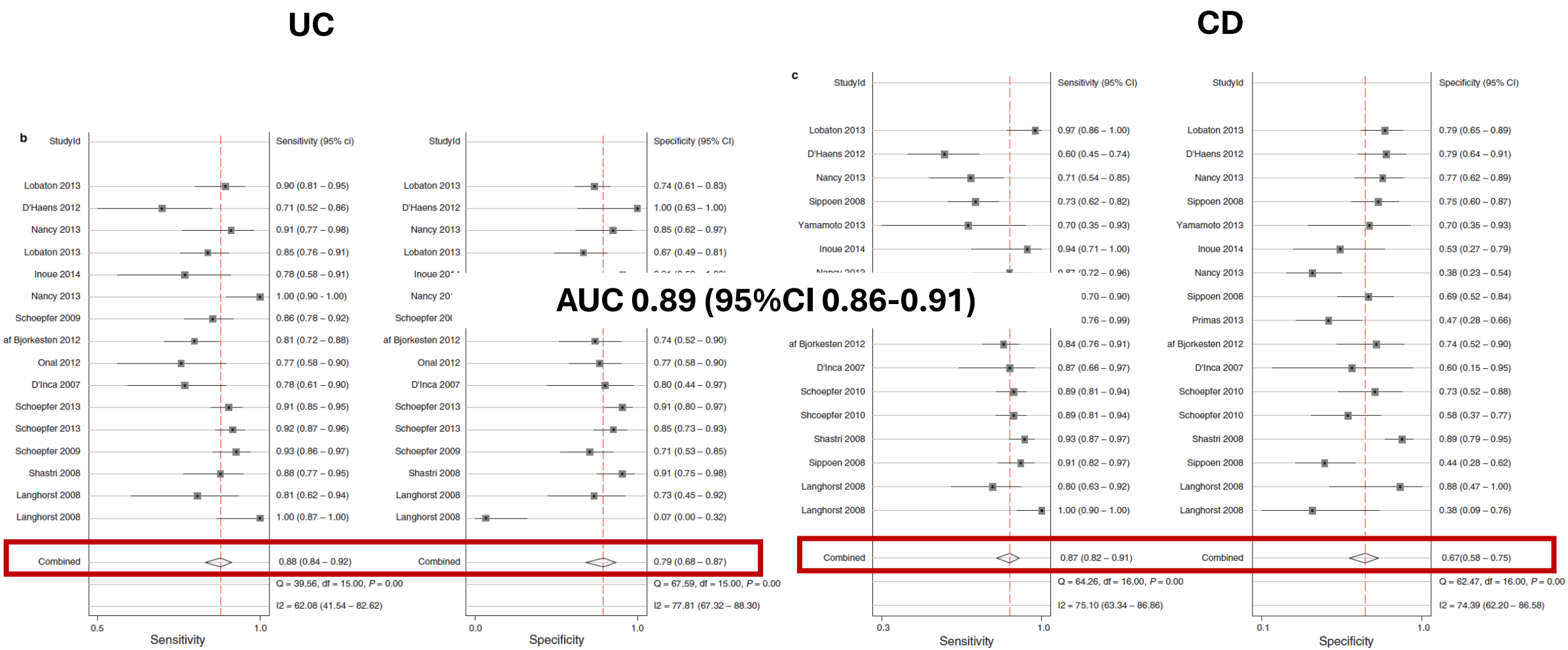






D'Haens G, et al. Inflamm Bowel Dis. 2012

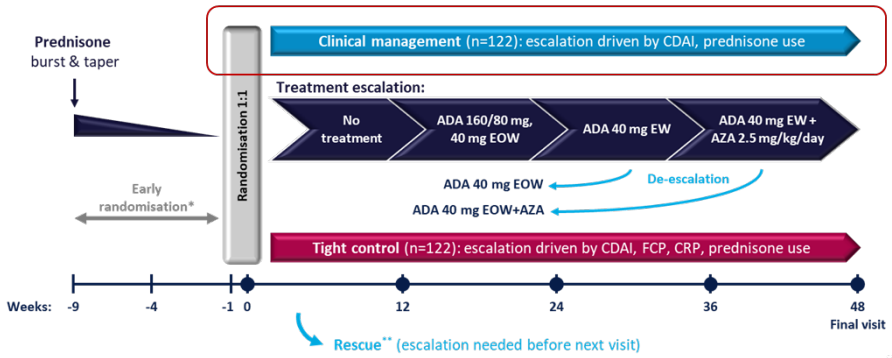
FCalp for Detection of Endoscopic Activity in Symptomatic IBD Patients: A Systematic Review and Meta-Analysis



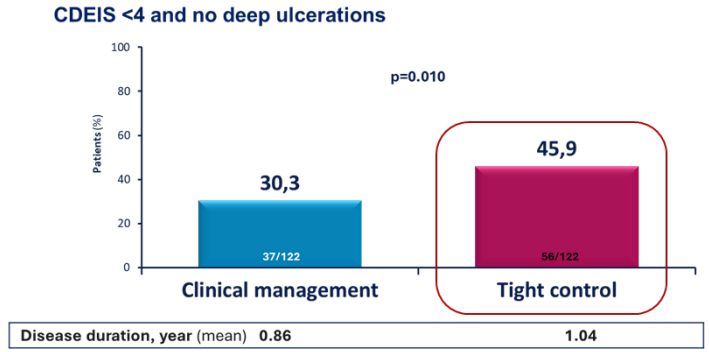
Mosli M, et al. Am J Gastroenterol 2015

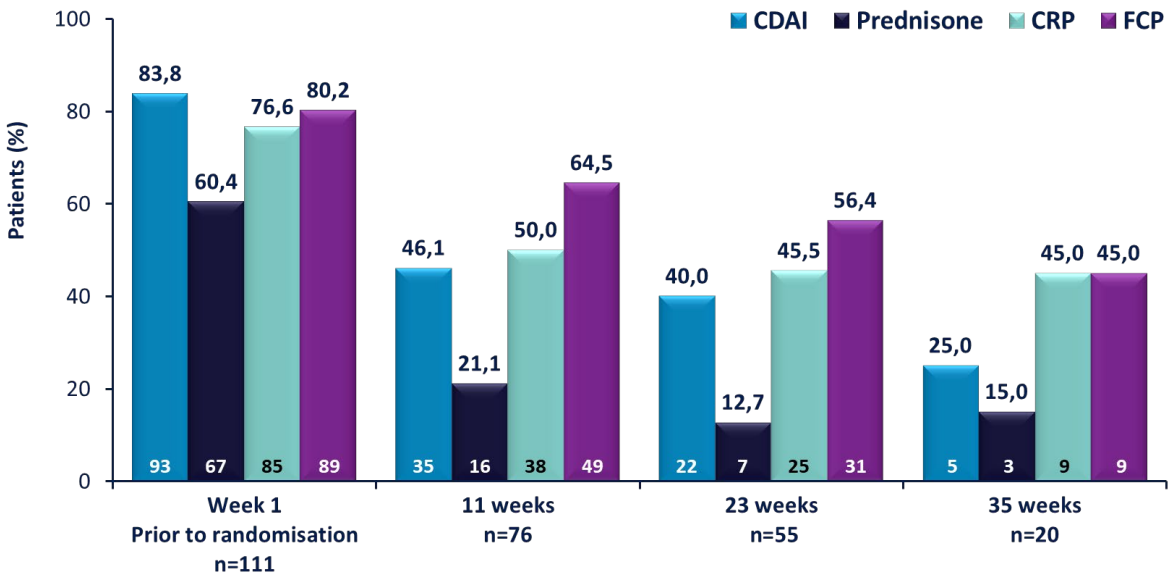
CALM: reasons for escalation (TC arm) and treatment options over time

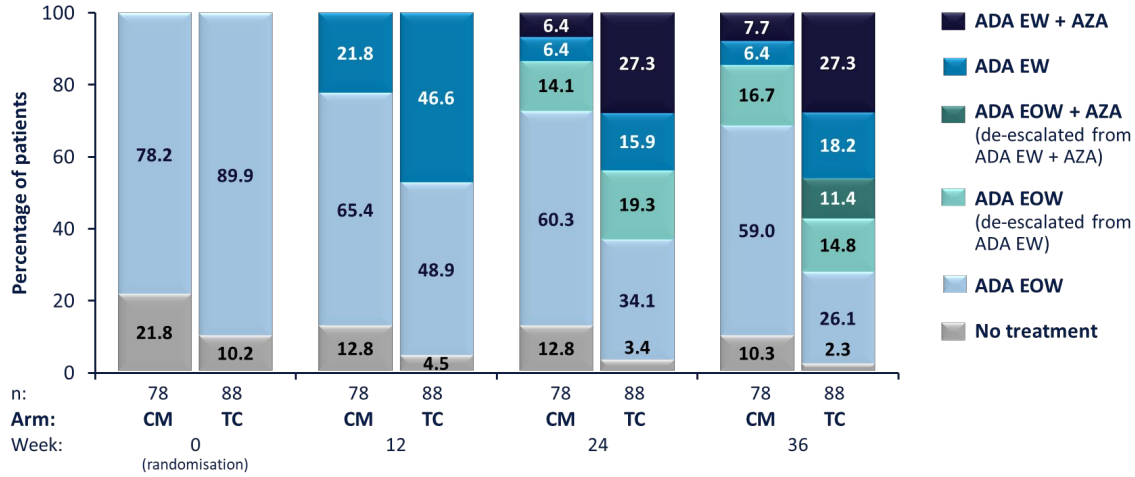
Study design



Primary endpoint at 48 weeks after randomisation

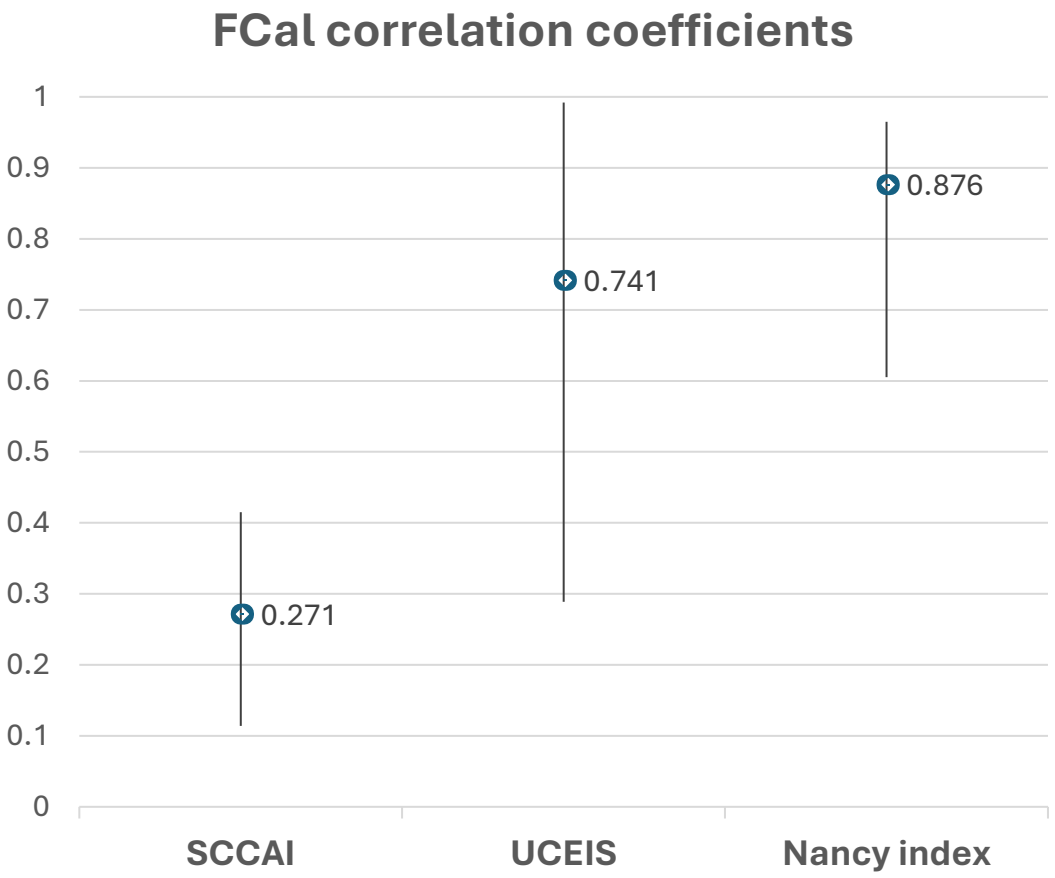






Colombel JF, et al. Lancet 2017;390:2779–89

FCalp Thresholds as a Surrogate for Endoscopic and Histological Disease Activity in UC - a Prospective Analysis



- Median FCal thresholds for remission using endoscopic, histological, or combined criteria were **71 µg/g** [range 8-624], **91 µg/g** [range 8-858], and **67 µg/g** [range 8-479], respectively

- Threshold for active disease:
  - **187 µg/g for UCEIS** (area under the curve [AUC] 0.915)
  - **72 µg/g for Nancy** [AUC 0.824]
  - **187 µg/g for combined** endoscopic and histological criteria [AUC 0.936].

Walsh A et al. J Crohns Colitis. 2019;13(4):424–430.

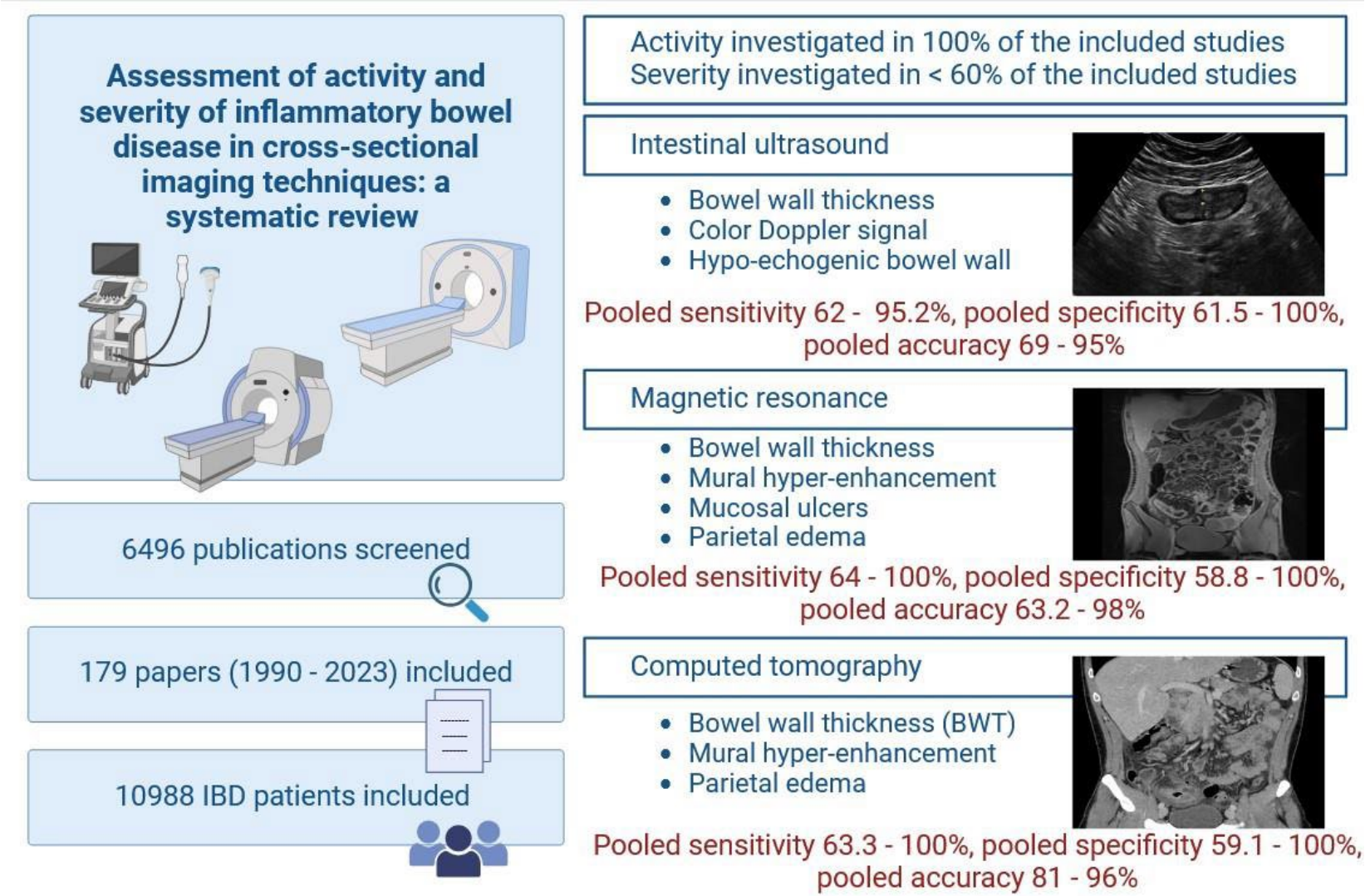
Monitoring with biomarkers

Monitoring tool	Target	Definition	Advantages	Limitations
CRP	Normalization	CRP ≥ 5-10 mg/L is abnormal	Easily obtained Cheap Can diagnose complications	Low specificity and sensitivity Less reliable for low-grade or localized inflammation Gives no information about location or severity
Fecal calprotectin	Normalization	≥ 250 µg/g: Associated with active endoscopic disease and ulceration <100 µg/g: Associated with endoscopic remission (post-op)	Gut-specific Non-invasive Correlates with mucosal inflammation	No information about location or severity of disease Patient avoidance Less sensitive for proximal small bowel and limited-extent disease
	Improvement	Reduction by ≥50%		

Vermeire S, et al. Gut 2006;55:426–31;Jukic A, et al. Gut 2021;70:1978–88

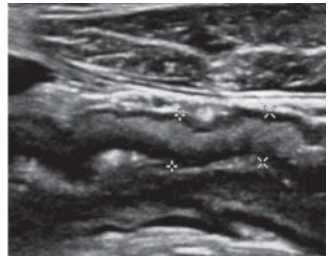
Intestinal Ultrasound

Assessment of activity and severity of IBD in cross-sectional imaging techniques: a systematic review

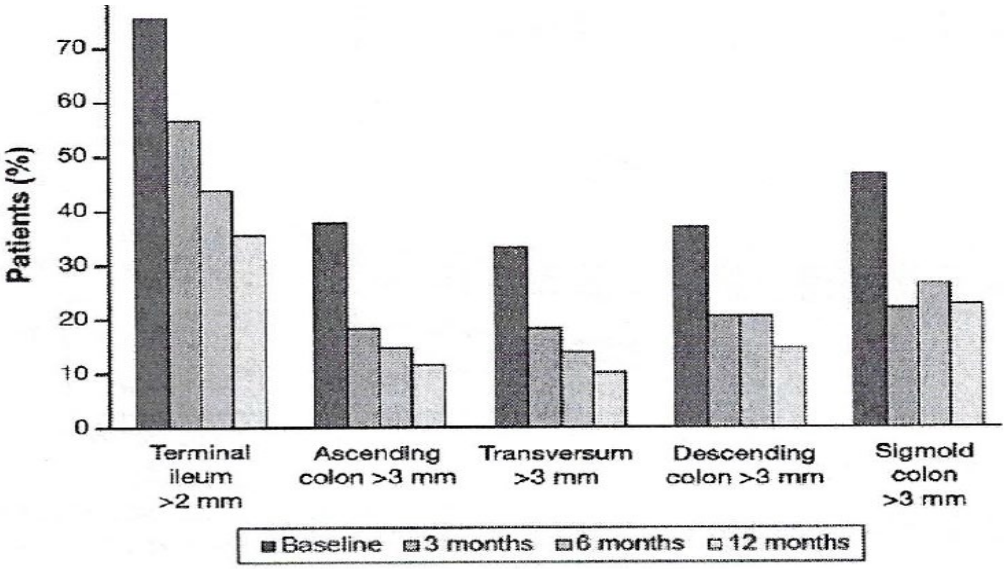


Dal Buono A, et al JCC 2025 Feb 4:jjaf023. doi: 10.1093/ecco-jcc/jjaf023

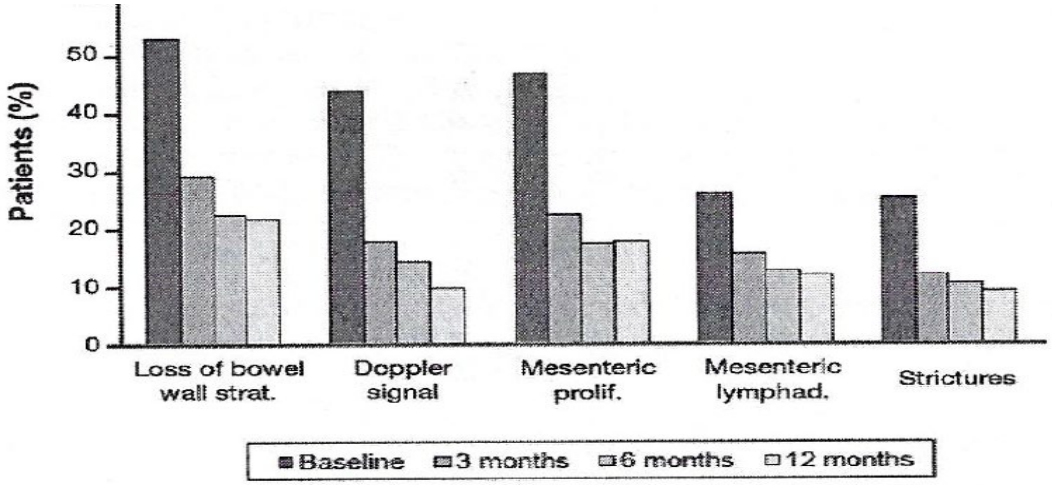
IUS to Monitor CD Activity (TRUST study)



Prospective - 234 pts HB index ≥7 (biological or steroid therapy)



Bowel Wall Thickening

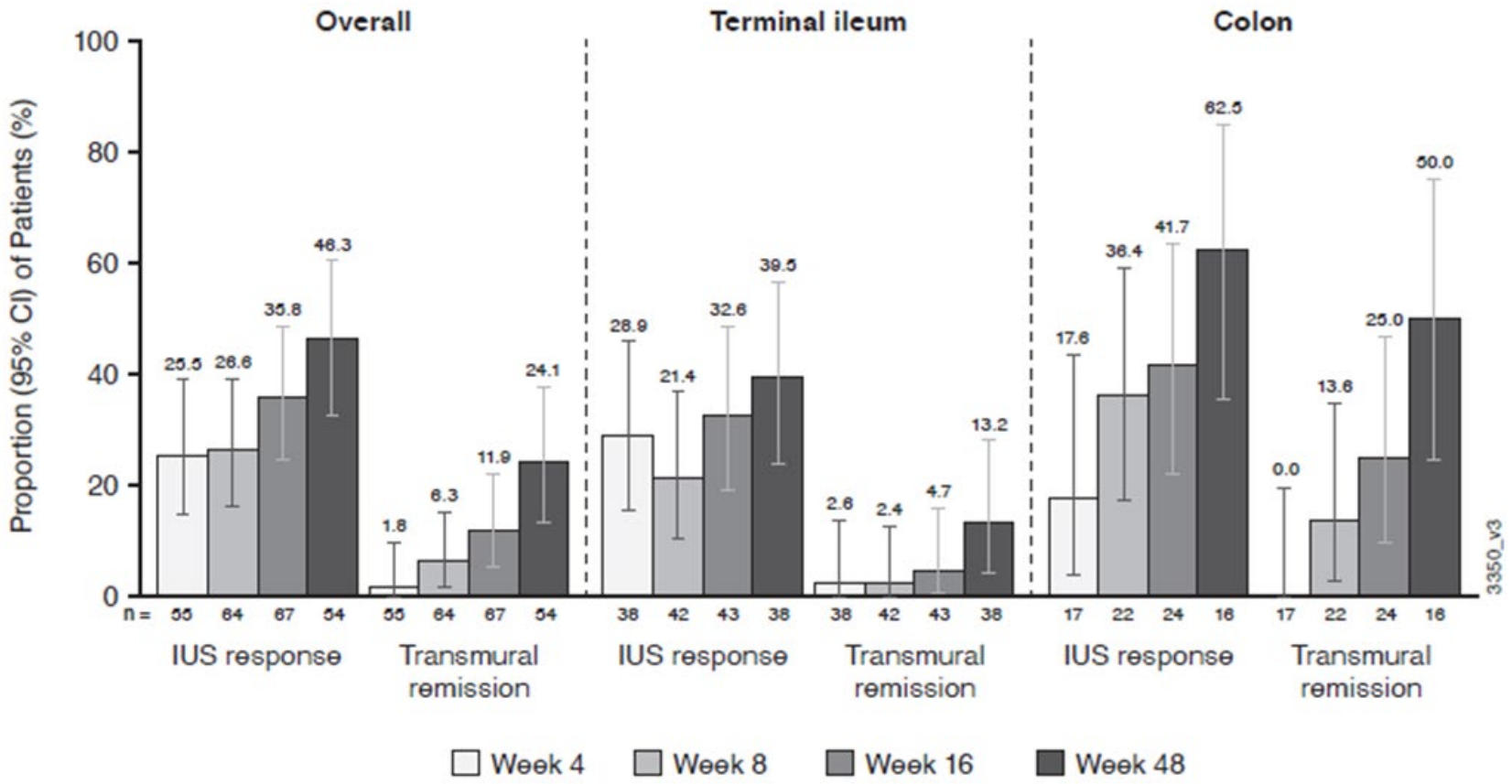


BW and abdominal changes

TRansabdominal Ultrasonography of the bowel in Subjects with Crohn's disease To monitor disease activity

Kucharzik T, et al . CGH 2017

Early IUS response and transmural healing over time



Reliability between IUS response as early as W8 and endoscopic response and biomarker outcomes at W48 suggests IUS may be a useful tool in predicting later endoscopic response

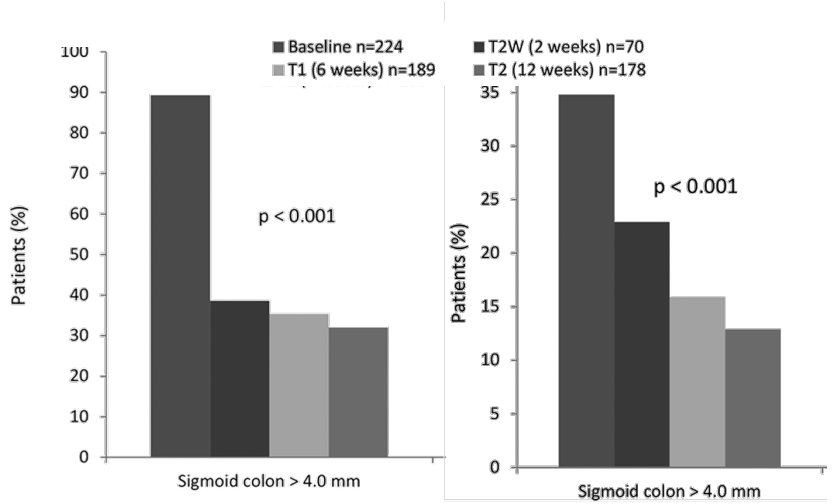
The IUS RAS was used for the analysis. Normalization of BWT was defined as terminal ileum ≤ 2 mm and colon ≤ 3 mm.

The most affected segments at baseline were the ileum in 65% and colon in 35% of patients

Kucharzik T, et al. Clinical Gastroenterol Hepatol 2023

IUS to Monitor UC Activity (TRUST&UC study)

Multicenter, prospective study
224 UC patients (SCCA Index ≥5)



Proportion of patients with increased BWT over the study period

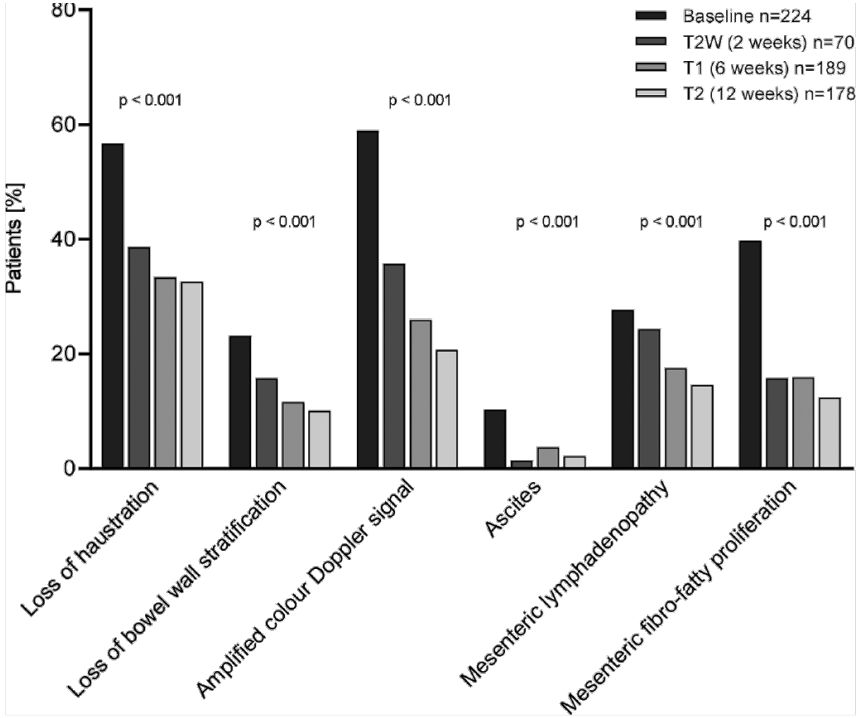


Table 2 Normalisation of BWT (mm) at T2 (week 12) versus clinical response; X^2 test

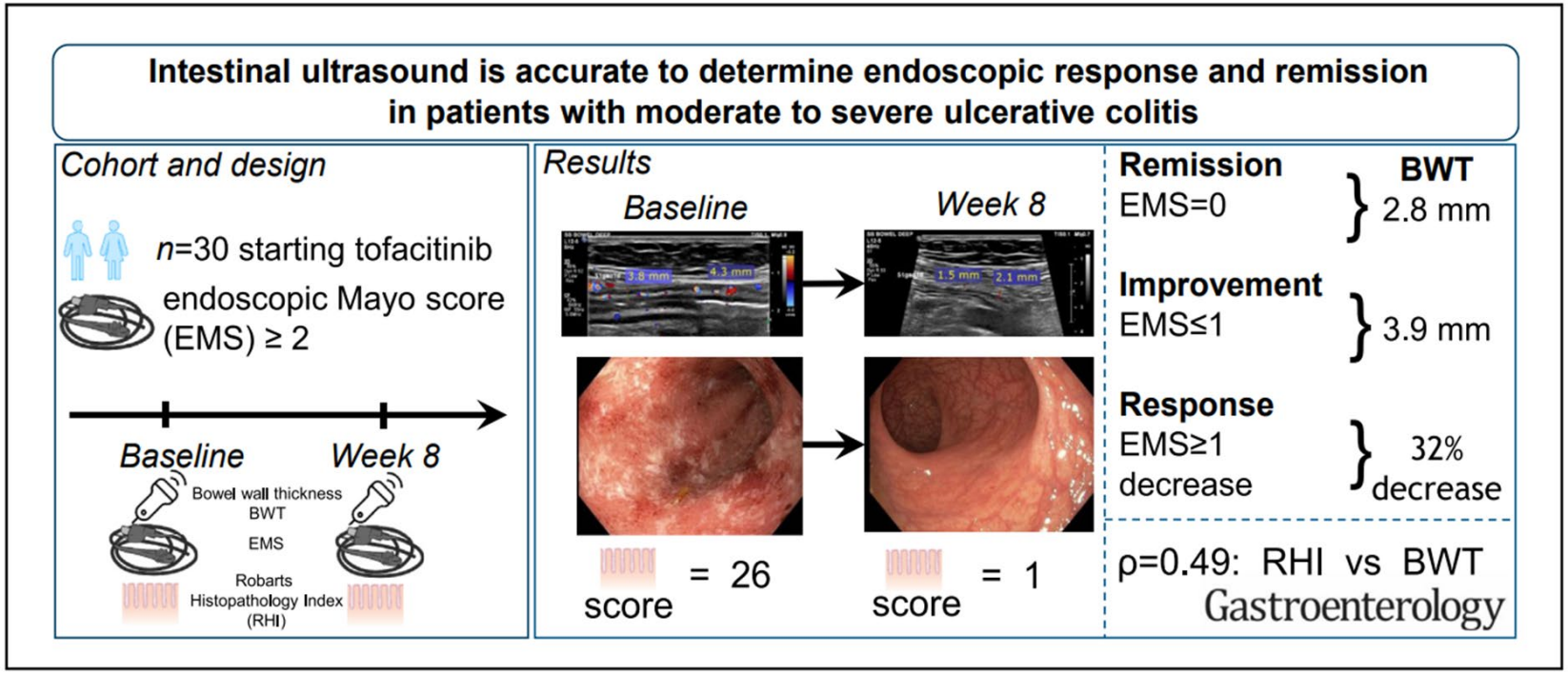
	Sigmoid colon	
	BWT normalisation	No BWT normalisation
Clinical response at T2	% (n)	% (n)
Yes	90.5 (95)	68.5 (50)
No	9.5 (10)	31.1 (23)
	P<0.001	

Table 4 Normalisation of BWT at T2 (week 12) vs normalised FC; X^2 test

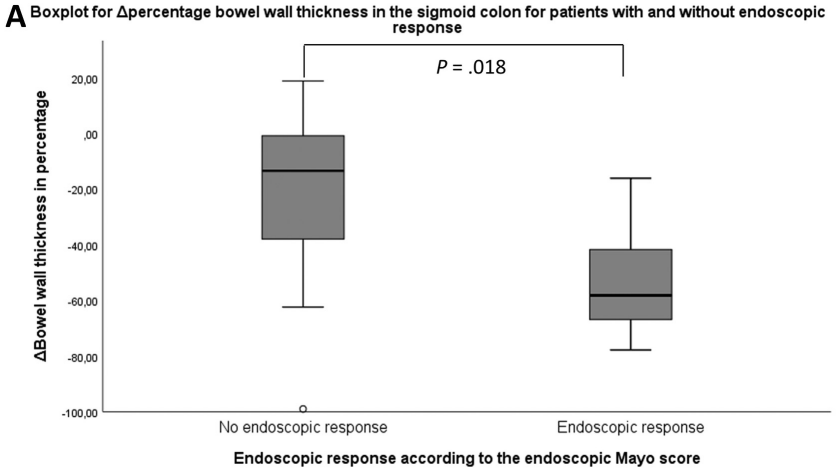
	Sigmoid colon	
	BWT normalisation	No BWT normalisation
Calprotectin <250 µg/g at T2	% (n)	% (n)
Yes	48.9 (23)	22.2 (6)
No	51.1 (24)	77.8 (21)
	P=0.023	

Maaser C, et al. Gut 2020

IUS is accurate to determine endoscopic response and remission in patients with moderate to severe UC: a longitudinal prospective cohort study

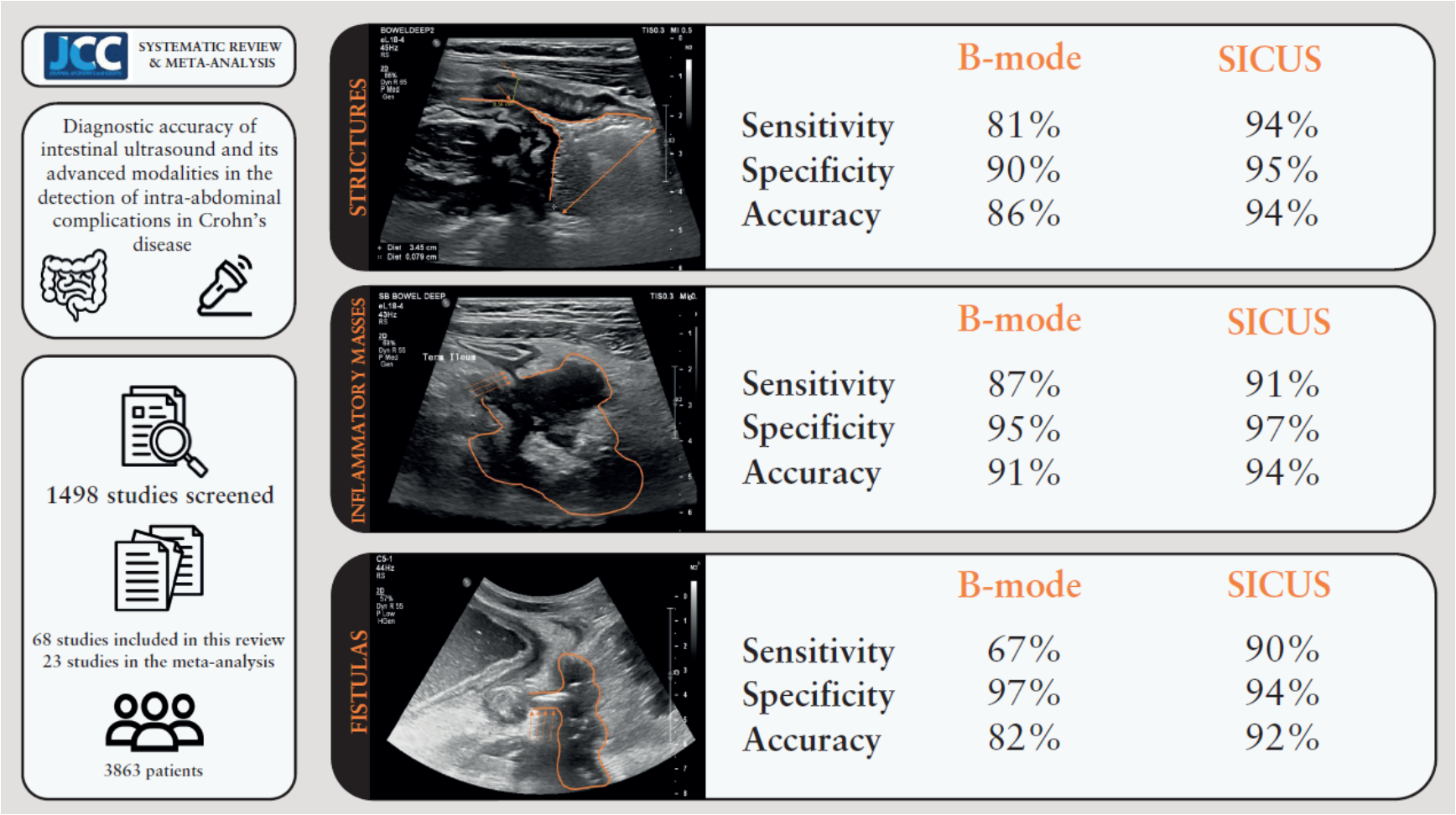


Change in BWT (%)



de Voogd F, et al Gastroenterology 2022;163:1569-81

Diagnostic Accuracy of IUS in the Detection of Intra-Abdominal Complications in CD: A Systematic Review and Meta-Analysis



Stricture definition: increased BWT ≥3 or ≥4 mm; narrowed lumen, not further specified or <10 mm; prestenotic dilation ≥25 or ≥30 mm (in 82%, 93%, 95% of the studies, respectively)
Inflammatory masses definition: round hypoechoic lesions in 93%, with irregular wall in 67%, and containing air and/or hypoechoic debris in 70% of the studies
Fistula definition: hypoechoic tracts with or without hyperechoic content observed between bowel loops, or between bowel loops and other structures suche as the bladder, skin, or mesentery. These items were reported in 97% and 82% of the studies, respectively

Pruijt MJ, et al JCC 2024;18:958-72

Monitoring with intestinal ultrasound

Monitoring tool	Target	Definition	Limitations
Bowel wall thickness (CD, UC)	Bowel wall normalization Bowel wall thickness improvement	<3 mm Decrease of >1 mm or 20%	Severity scores not widely used nor validated Limited by body habitus and pelvic location Limited in assessing extent Less useful to assess disease limited to the mucosa Limited in differentiating active vs chronic
MUC (UC)	Transmural healing	MUC score > 6.2 mm reflects active disease	
UC-IUS (UC)	Transmural healing		
IBUS-SAS (CD, UC-?)	Transmural healing	IBUS-SAS score in CD > 42.9 reflects active disease	
SUS-CD (CD)	Transmural healing	SUS-CD ≥ 1 reflects endoscopic active disease SUS-CD score of ≥3 reflects moderately active endoscopic disease	
BUSS (CD)	Transmural healing	BUSS ≤ 3.52 predicts endoscopic remission	

IBUS-SAS=International bowel ultrasound segmental activity score; MUC. Milan ultrasound criteria; UC-IUS=Ulcerative colitis intestinal ultrasound score; BUSS: Bowel ultrasound score; SUS-CD=Simple ultrasound score for Crohn's disease

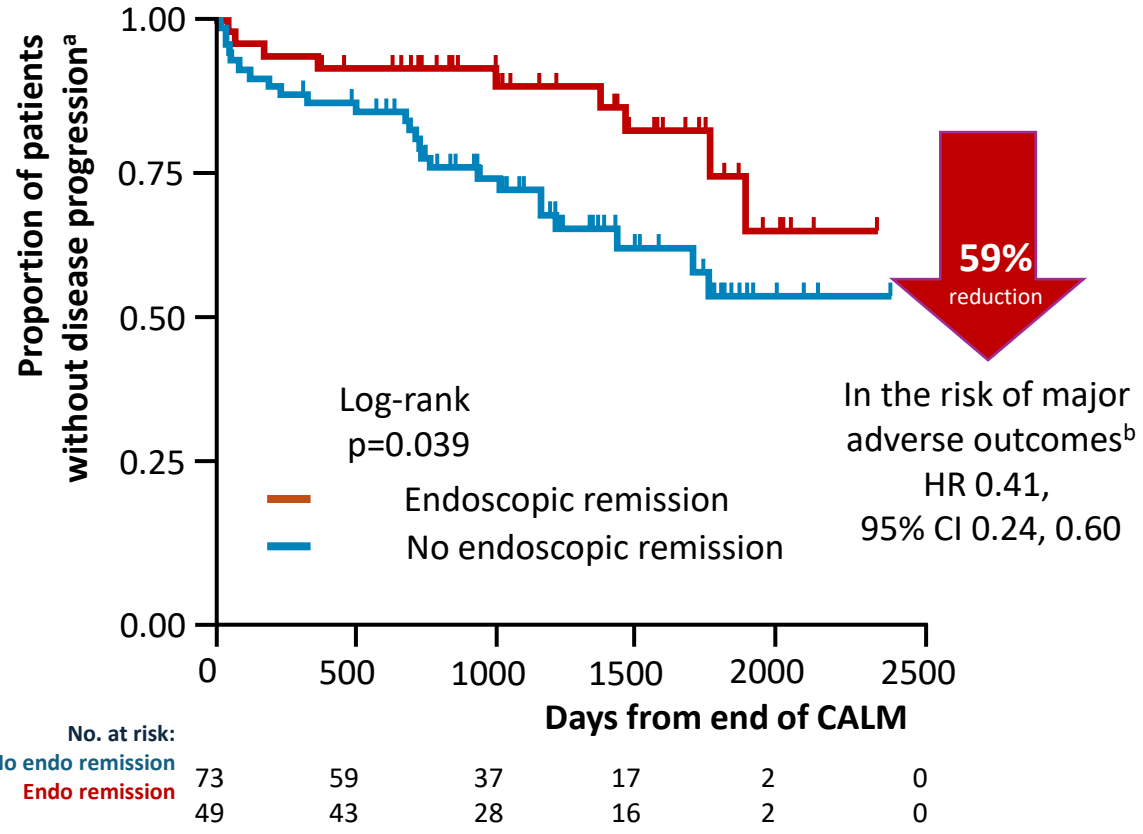
Sævik F, et al. JCC. 2021, Novak KL, et al. JCC. 2021, Allocca M, et al. Clin Gastroenterol Hepatol. 2022, Allocca M, et al. JCC. 2023; G Dragoni, et al. JCC 2021, Bots S, et al. JCC 2021

Endoscopy

Driver of CD course: endoscopic/deep remission

Endoscopic remission

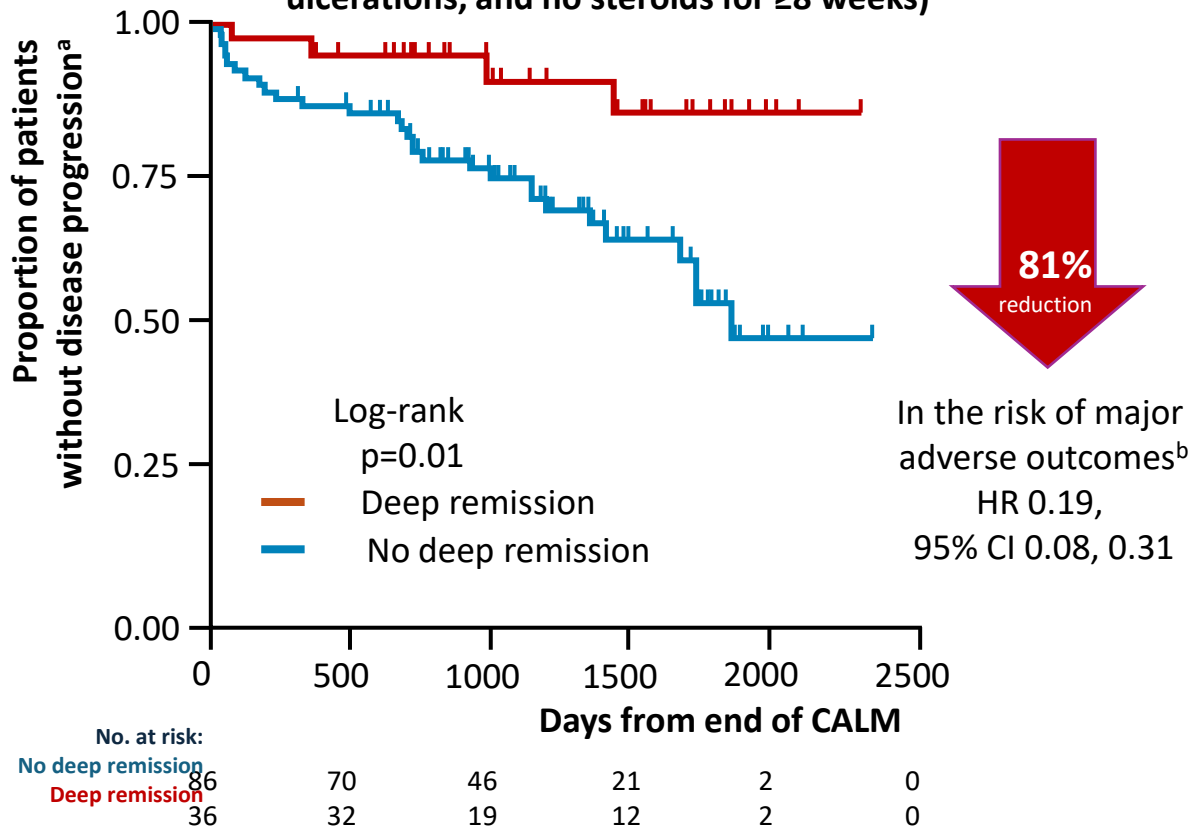
(CDEIS <4 with no deep ulcers)



No. at risk:						
No endo remission	73	59	37	17	2	0
Endo remission	49	43	28	16	2	0

Deep remission

(CDAI <150, CDEIS <4 with no deep ulcerations, and no steroids for ≥8 weeks)



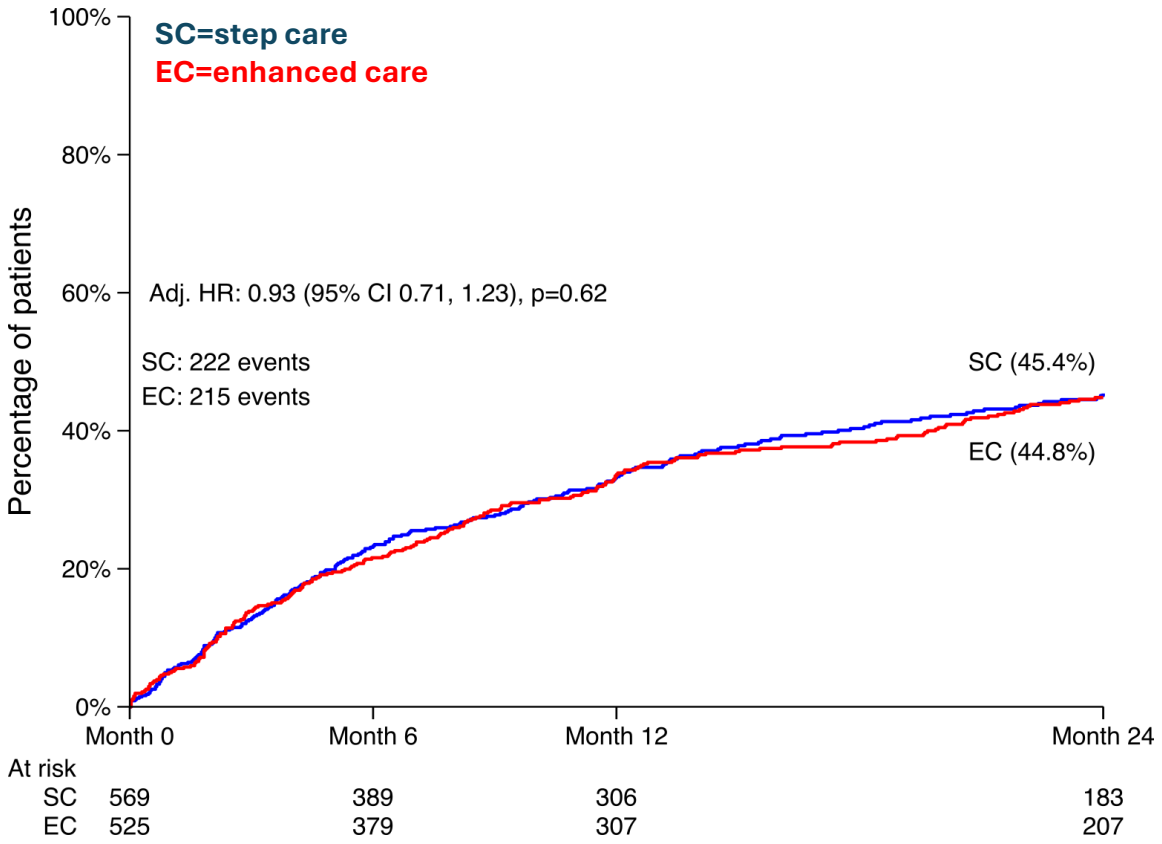
No. at risk:						
No deep remission	86	70	46	21	2	0
Deep remission	36	32	19	12	2	0

[a]Disease progression defined as any major adverse outcome: composite of new internal fistula/abscess, stricture, perianal fistula/abscess, CD hospitalization, or CD surgery since end of CALM; [b]Adjusted for CALM treatment arm, age, sex, disease duration, baseline CRP, baseline calprotectin, disease location, smoking, prior surgery, and history of stricturing disease.; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CDEIS, Crohn's Disease Endoscopic Index of Severity; CI, confidence interval; CRP, C-reactive protein; endo, endoscopic; HR, hazard ratio

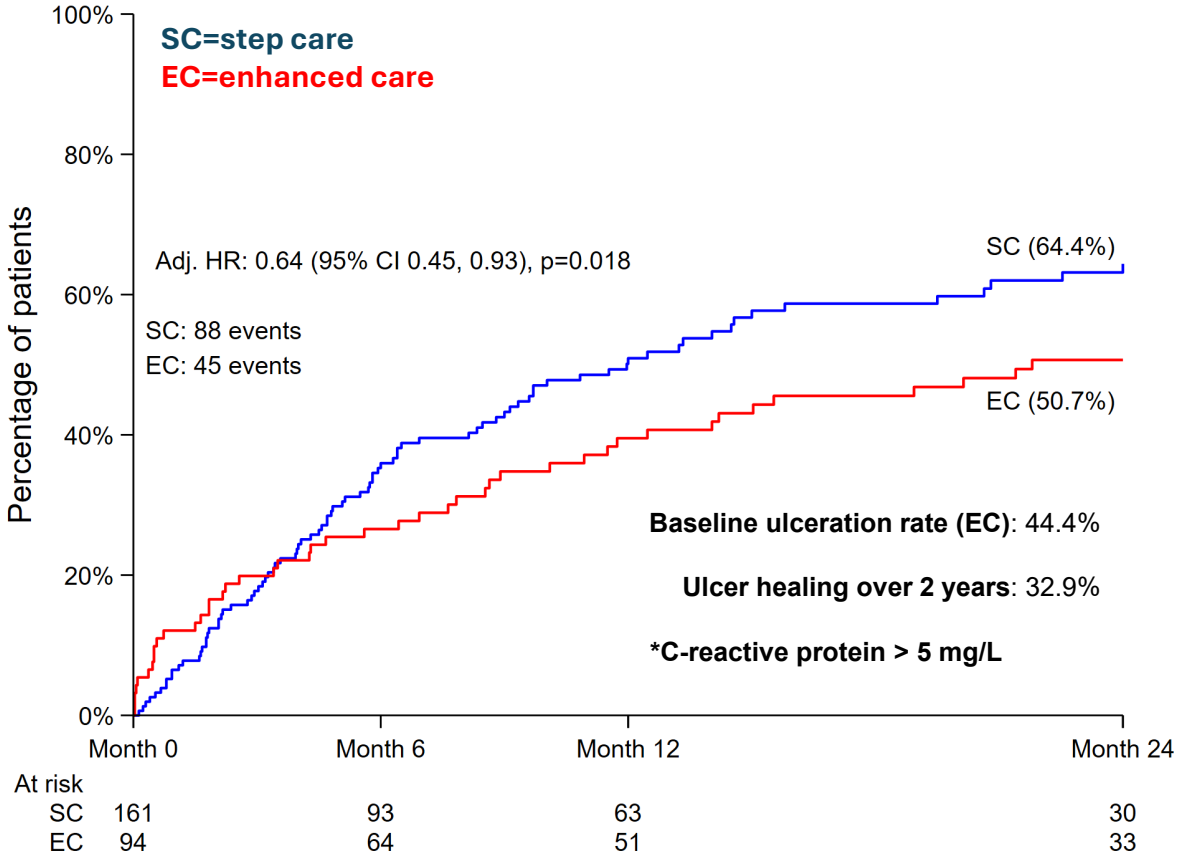
Adapted from Ungaro RC, et al. Gastroenterology 2020;159:139–47

REACT2: treat to MH

Primary outcome: CD-related complications



CD-related complication in patients with active* disease and baseline ulcers



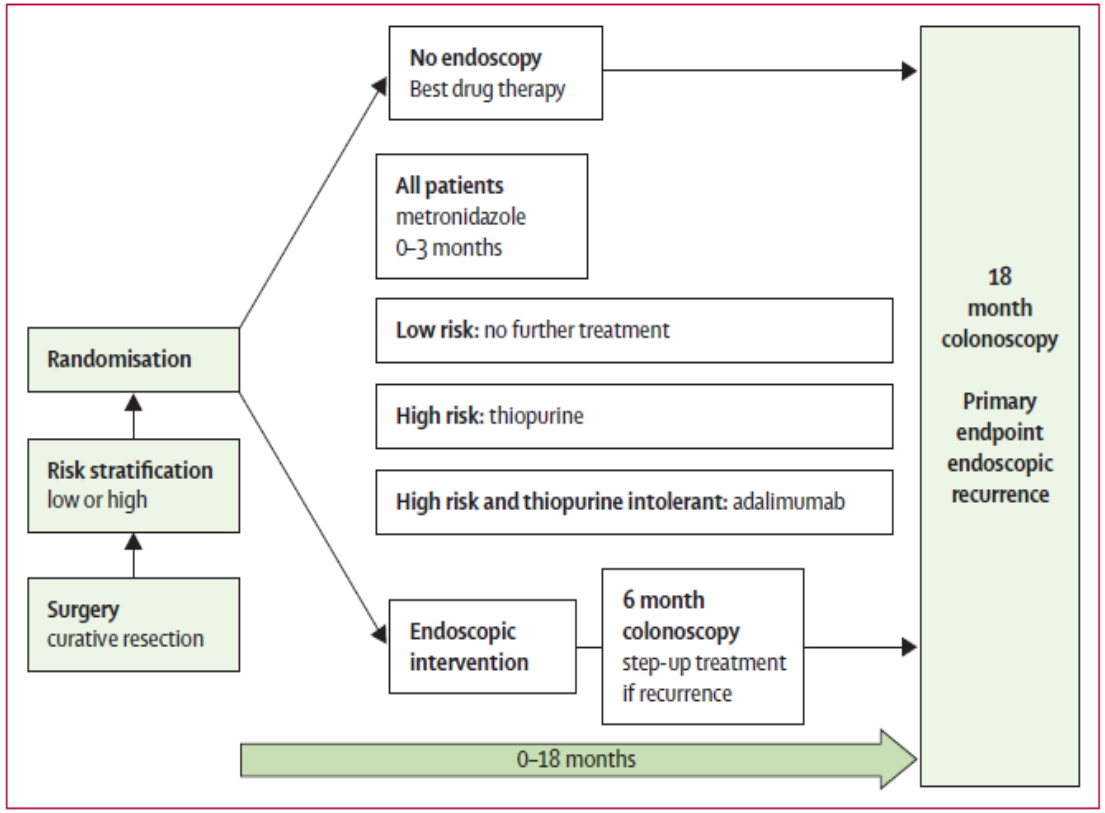
Treating to a target of ulcer healing may be more effective than symptom-based management in patients with evidence of active inflammation

- **Primary outcome - Risk of first CD-related complication at 24 months**, including:
  - **Surgery**
  - **Non-surgical events**
  - **Hospitalizations**
  - **CD medication, procedure-related hospitalizations and surgeries**

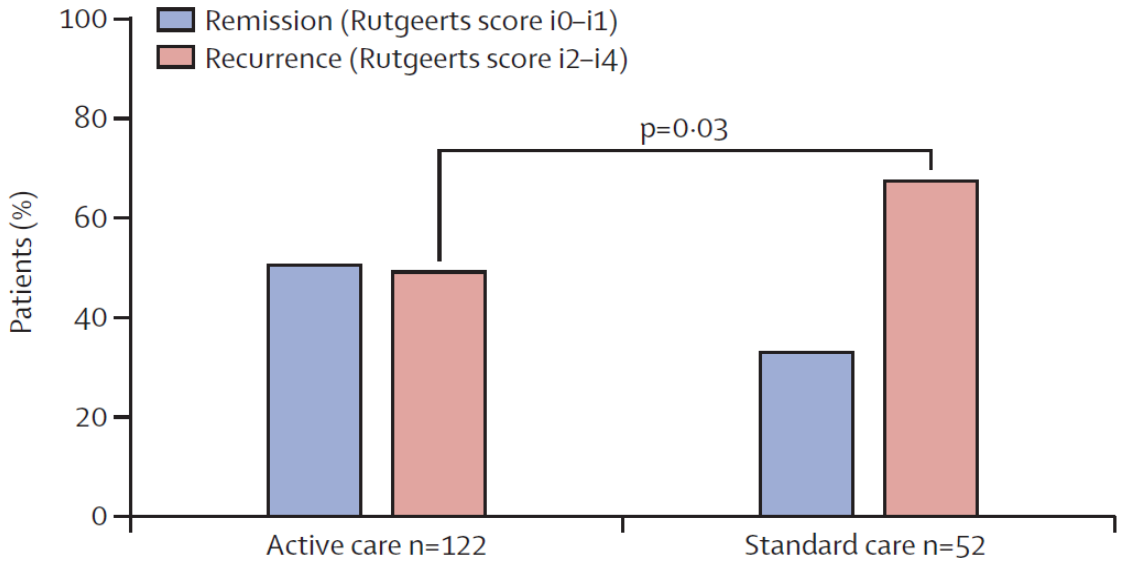
Jairath V, et al UEGW 2022:OP110

Intensification of prophylactic therapy guided by colonoscopy (POCER)

Crohn's disease management after intestinal resection: a randomized trial



Primary Endpoint: Endoscopic recurrence at 18 months

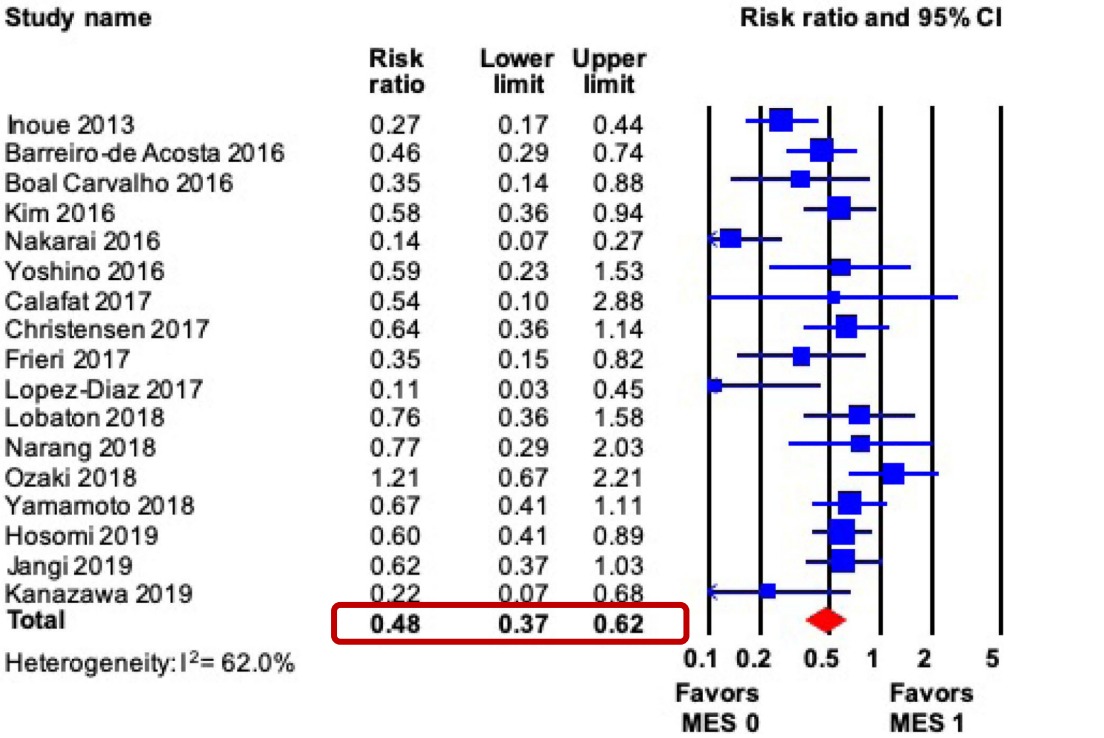


Stepping up treatment at 6 months brought 38% of patients with endoscopic recurrence into remission 1 year after stepping up treatment

De Cruz P, Lancet 2015;385:1406–17

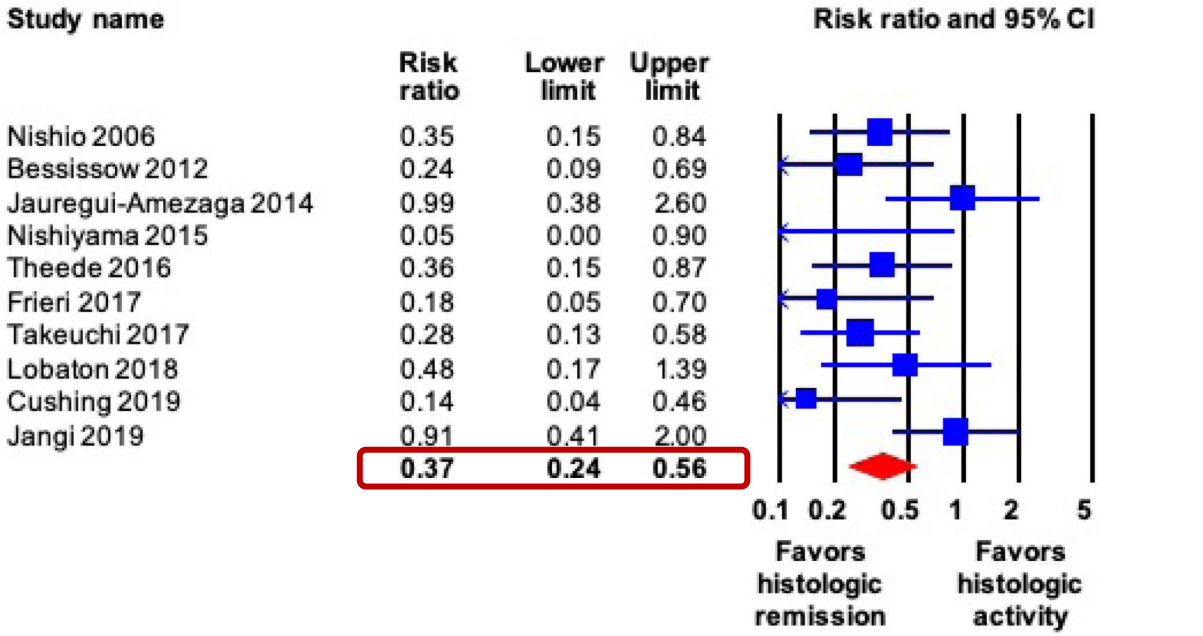
Drivers of UC course:
Endoscopic, histologic, histo-endoscopic healing
(meta-analysis of 17 studies, 2608 patients with UC in clinical remission)

Risk of clinical relapse in patients with clinical remission achieving endoscopic remission (MES 0 or equivalent) vs. mild endoscopic activity (MES 1 or equivalent)



MES 0 (vs MES 1):
52% lower risk of clinical relapse

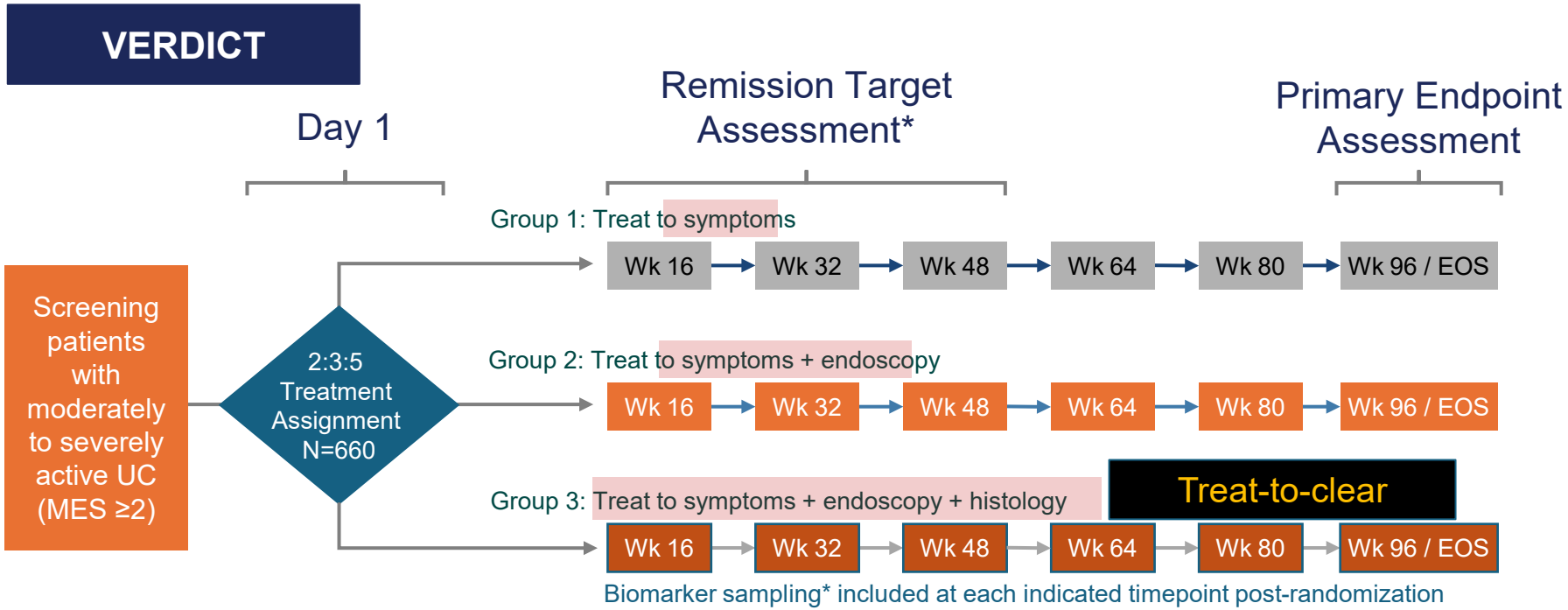
Risk of clinical relapse in patients in endoscopic remission achieving histologic remission vs. persistent histologic activity



MES 0 + Histologic remission:
63% lower risk of clinical relapse

Yoon H, et al. Gastroenterolology. 2020;159:1262–75

In actiVE Ulcerative Colitis, a RanDomIzed Controlled Trial for Determination of the Optimal Treatment Target (VERDICT)



Primary endpoint:

Difference in time to UC-related complication, including hospitalization, colectomy, use of rescue therapy, UC treatment-related or disease-related complication between treatment target groups 1 and 3

Patients with active UC randomized to 3 treatment target groups:

- Group 1: corticosteroid-free symptomatic remission
- Group2:corticosteroid-free endoscopic + symptomatic remission
- Group 3: corticosteroid-free histological + endoscopic + symptomatic remission

Target assessed at weeks 16, 32, 48

- If target is reached → continue therapy
- If target is not reached → treatment and/or dose escalation will be administered

*Also completed at Week 8

EudraCT Number: 2019-002485-12. ClininicalTrials.Gov: NCT04259138

EOS, end of study; MES, Mayo endoscopic subscore; UC, ulcerative colitis; Wk, week.

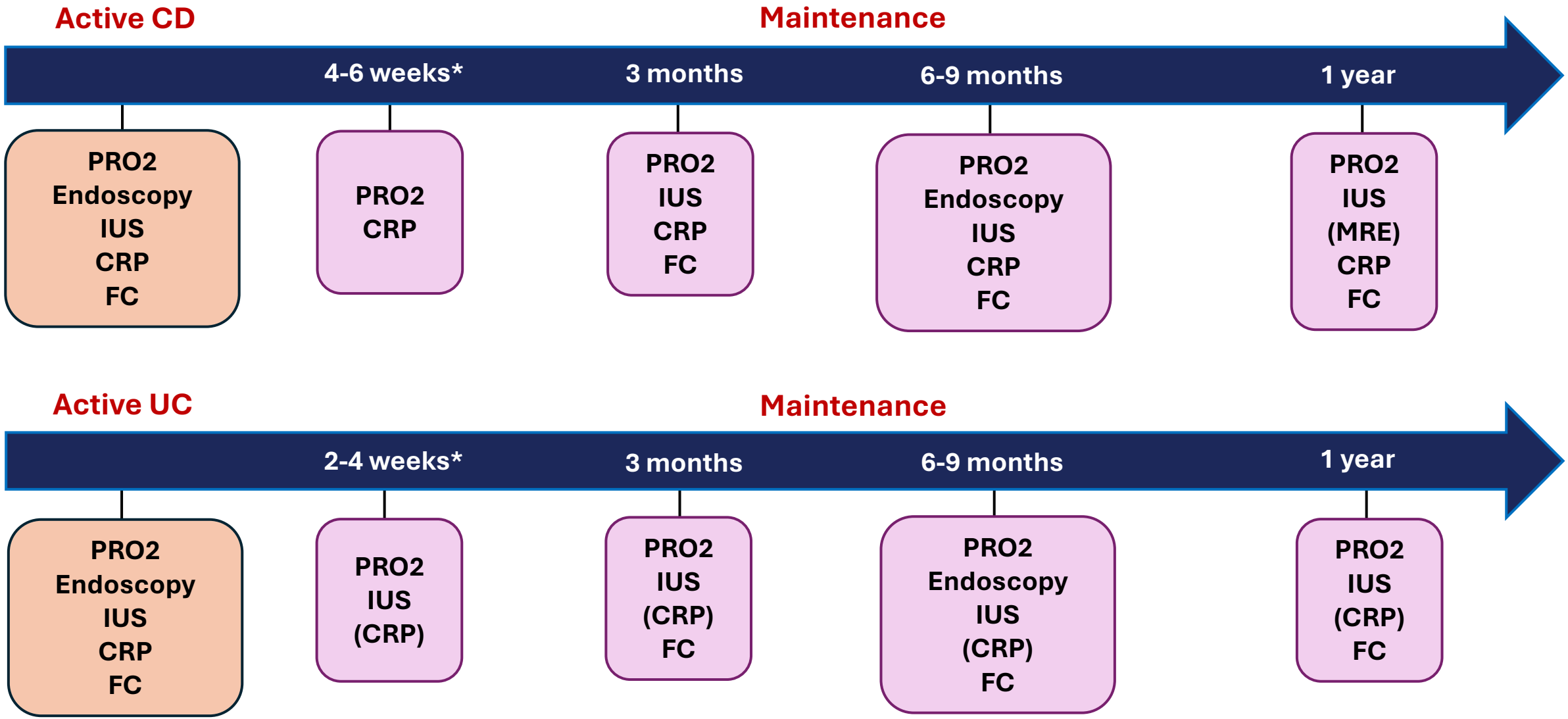
ClinicalTrials.gov. Determination of the Optimal Treatment Target in Ulcerative Colitis (VERDICT). Available from: https://clinicaltrials.gov/show/NCT04259138. Accessed June 2022.

Monitoring with endoscopy

Monitoring tool	Target	Definition	Limitations
SES-CD	Endoscopic response Endoscopic healing	Decrease >50% Ulcer subscores =0	Risk of complications associated with procedure Poor tolerability of bowel preparation Poor acceptability Costs Unable to assess bowel proximal to TI Variability of scoring
CDEIS	Endoscopic response Endoscopic healing	Decrease >50% No ulcers and score <3	
MES	Endoscopic response Endoscopic healing	Decrease ≤1 points 0 points	
UCEIS	Endoscopic response Endoscopic healing	Decrease ≤2 points 0 points	
Video capsule endoscopy-Lewis score	Mucosal healing	<135 points	Risk of capsule retention; poor tolerability of bowel preparation; lack of access; inability to perform biopsies; variability of scoring; limited ability to assess disease complications

SES-CD: Simple endoscopic score for Crohn's disease; CDEIS: Crohn's disease endoscopic index of severity; MES: Mayo endoscopic score; UCEIS: Ulcerative colitis endoscopic index of severity

Monitoring algorithm with integration of monitoring tools



*Depending on disease activity