

How should we monitor the IBD patients today?

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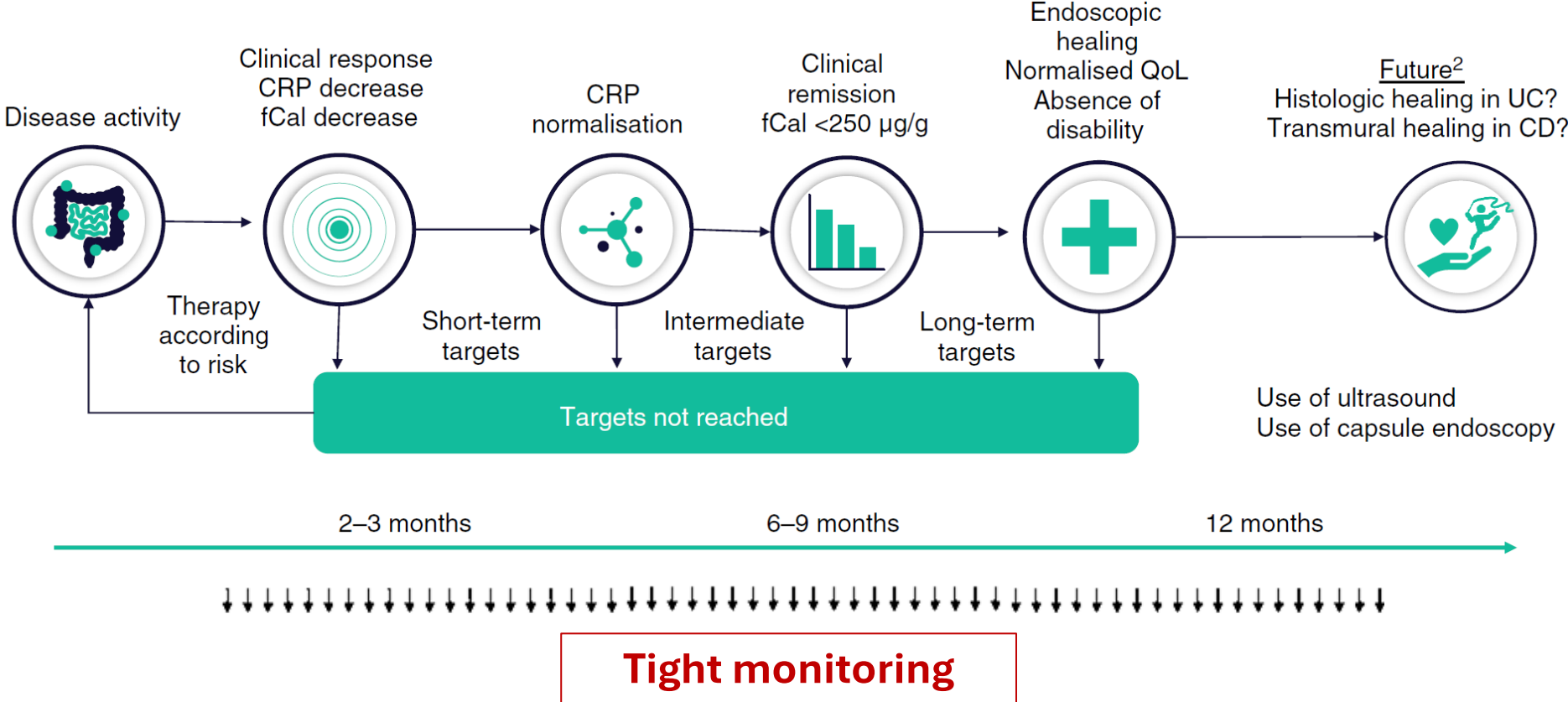
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Disclosures

- 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
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Managing patients with IBD



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

Estimated time-to-target in IBD

| Treatment, <u>mean number of weeks</u> | 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 |

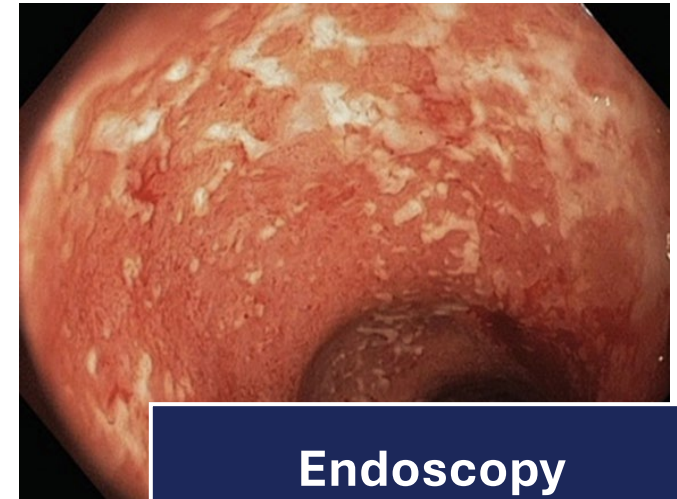
Monitoring tools

A good monitoring tool:

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



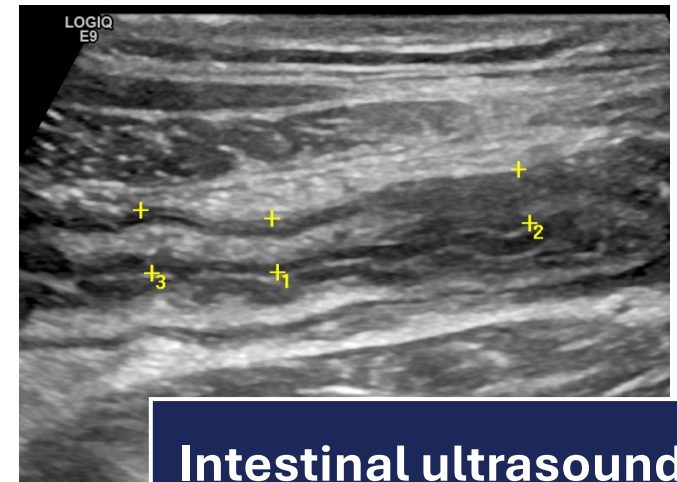
Patient reported outcomes



Endoscopy



Biomarkers

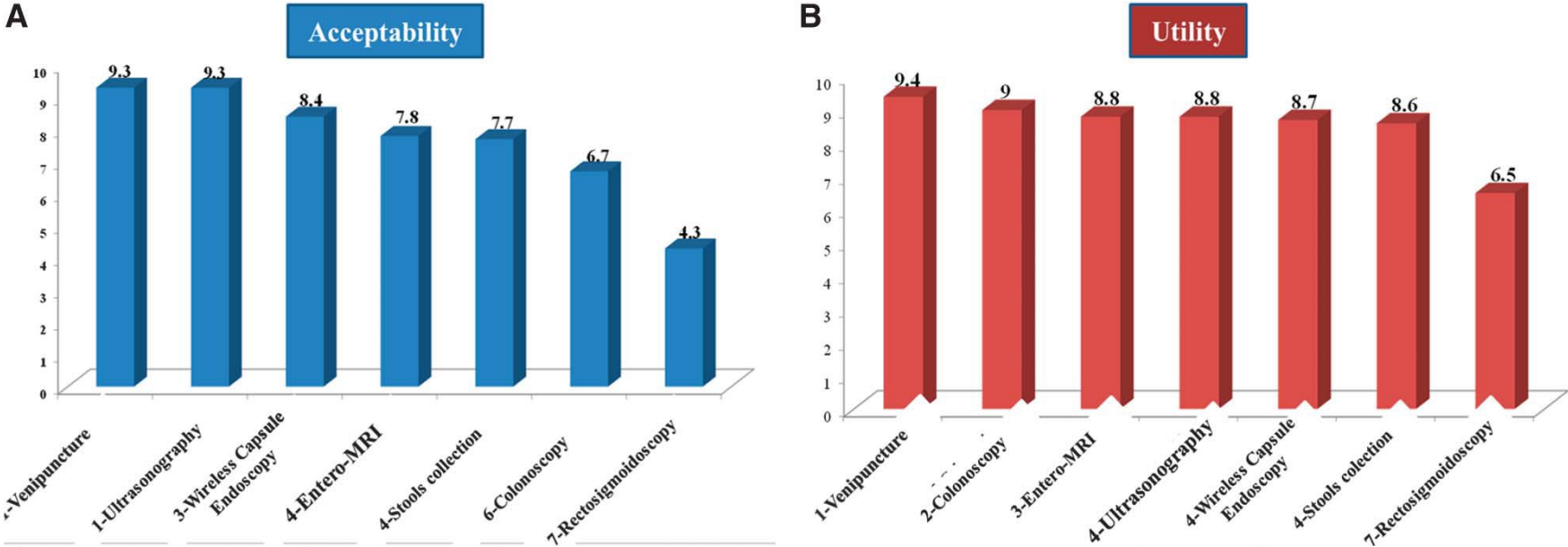


Intestinal ultrasound

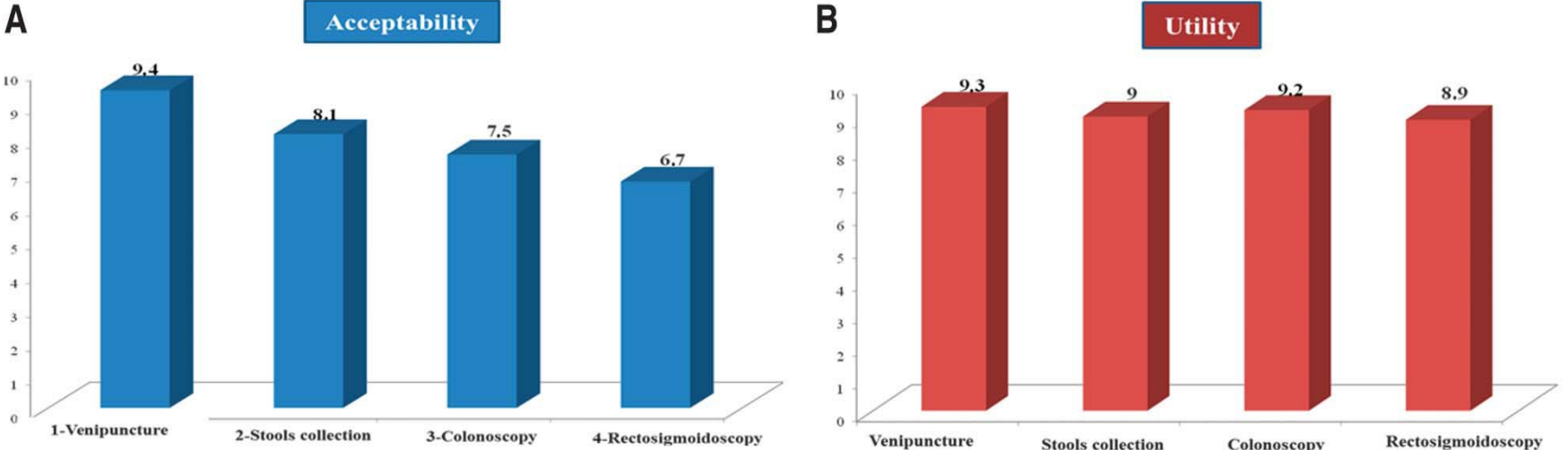
Comparative Acceptability and Perceived Clinical Utility of Monitoring Tools

Survey on 916 patients with IBD

CD

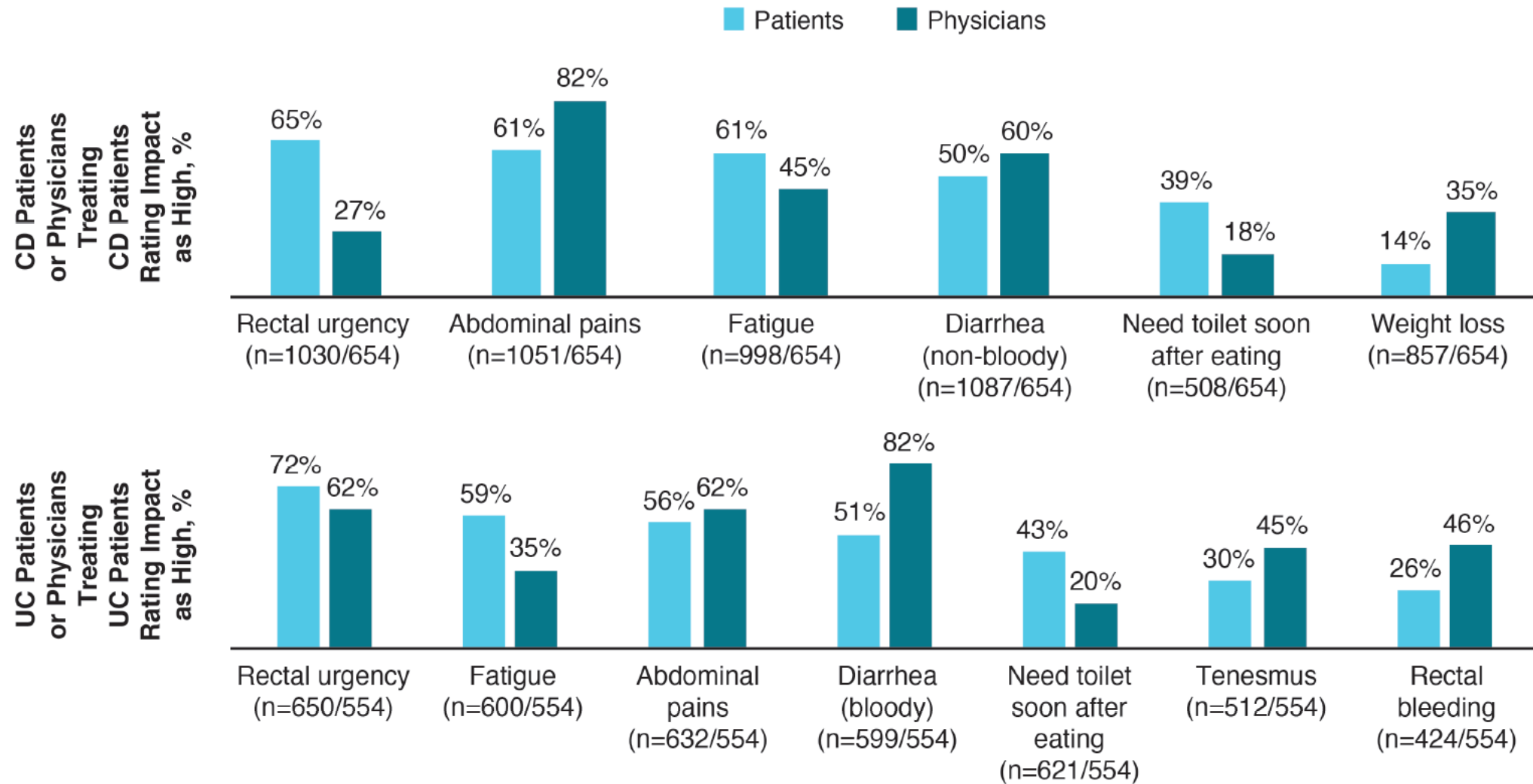


UC



Patient Reported Outcomes

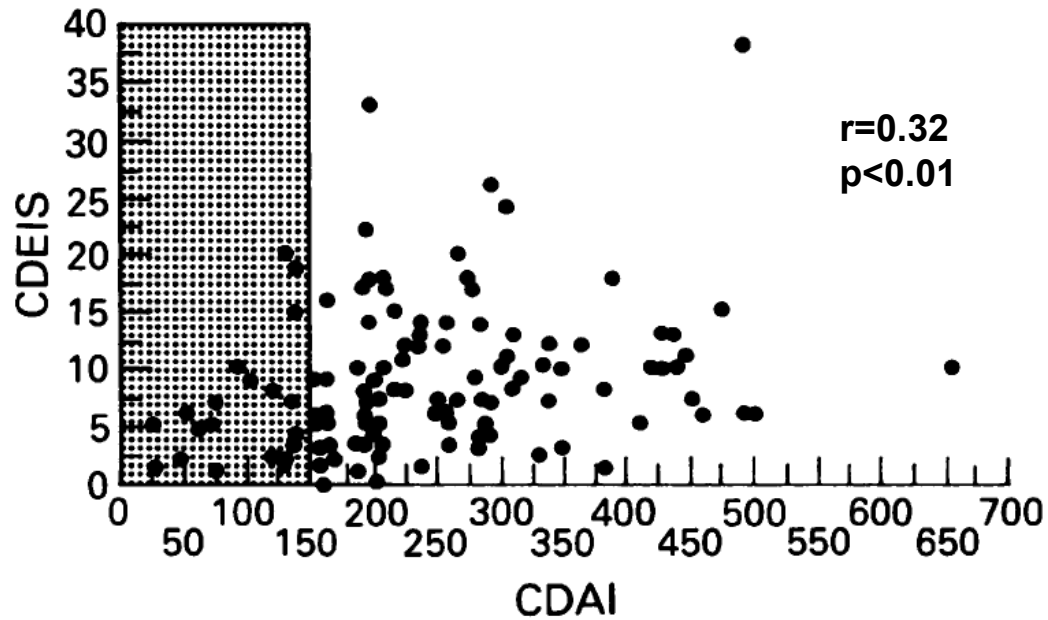
Symptoms reported by IBD patients and physicians to have the greatest impact on QoL



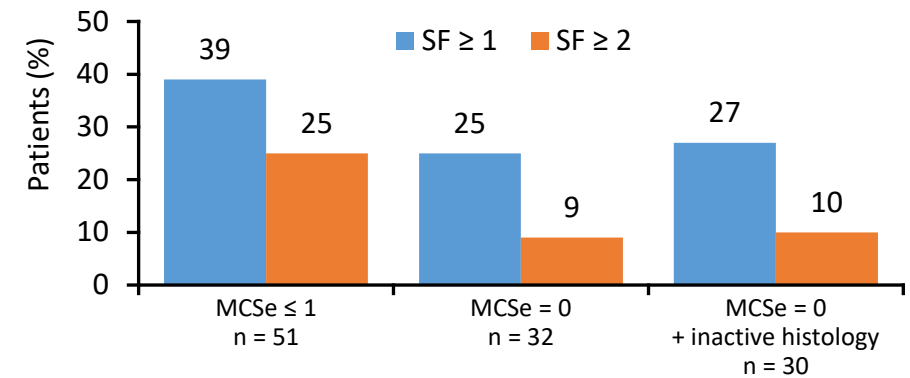
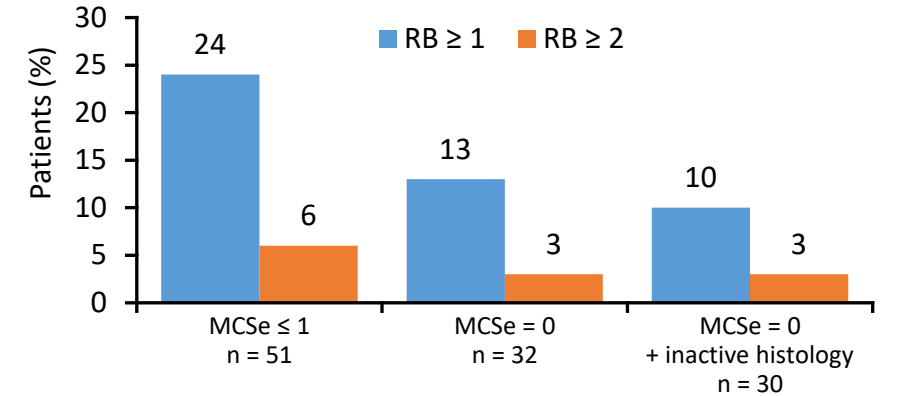
2398 patients with IBD (1368 CD, 1030 UC) and 654 physicians completed the GAPPS surveys

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

Crohn's disease



Ulcerative colitis

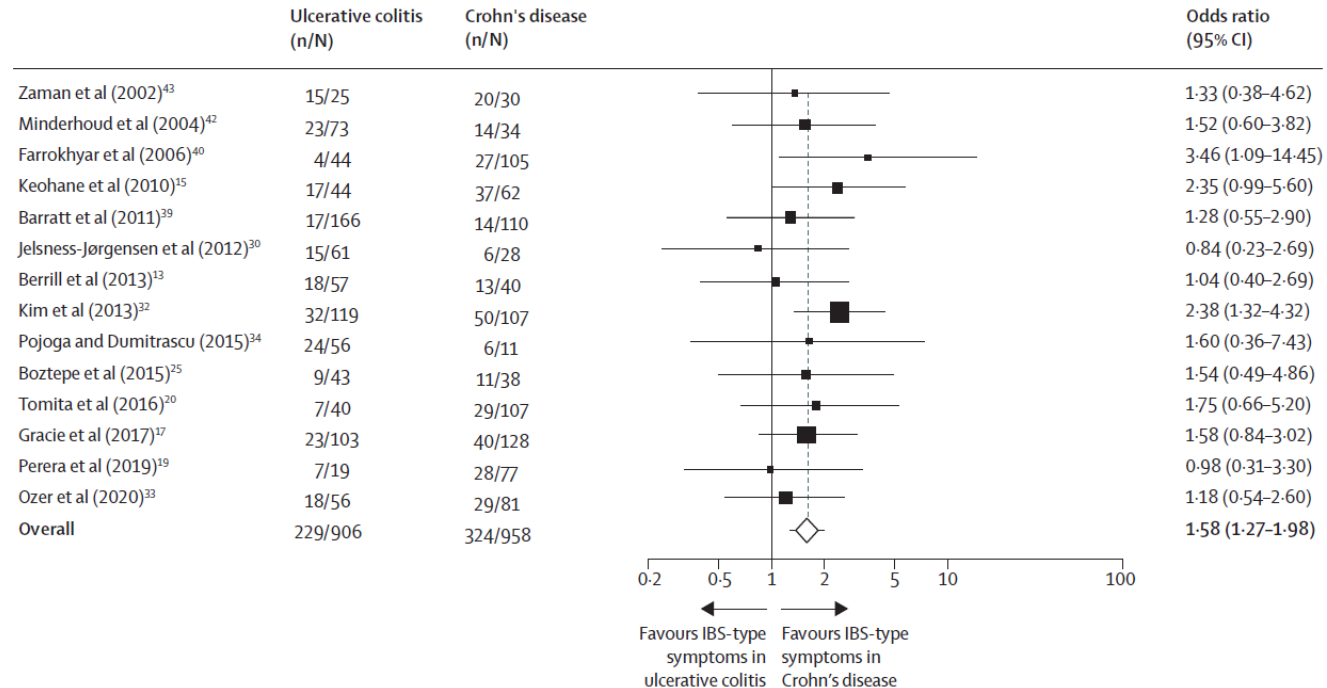


Prevalence of IBS-type symptoms in patients with IBD in remission: systematic review and meta-analysis (N 3169; 27 studies)

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)



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 |
| SCCAI (UC) | Clinical response Clinical remission | Decrease $> 30\%$ ≤ 2 points | |
| pMS (UC) | Clinical response Clinical remission | Decrease > 2 points < 3 & no subscore > 1 | Risk of undertreatment or overtreatment |
| PRO-2 (CD & UC) | Clinical response Clinical remission | Decrease $\geq 50\%$ in AP ad SF score (CD) Decrease $\geq 50\%$ in RB ad SF score (UC) AP score ≤ 1 and SF score ≤ 3 (CD) RB score 0 and SF score 0 (UC) | No assessment of disease extent and complications |

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)

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.

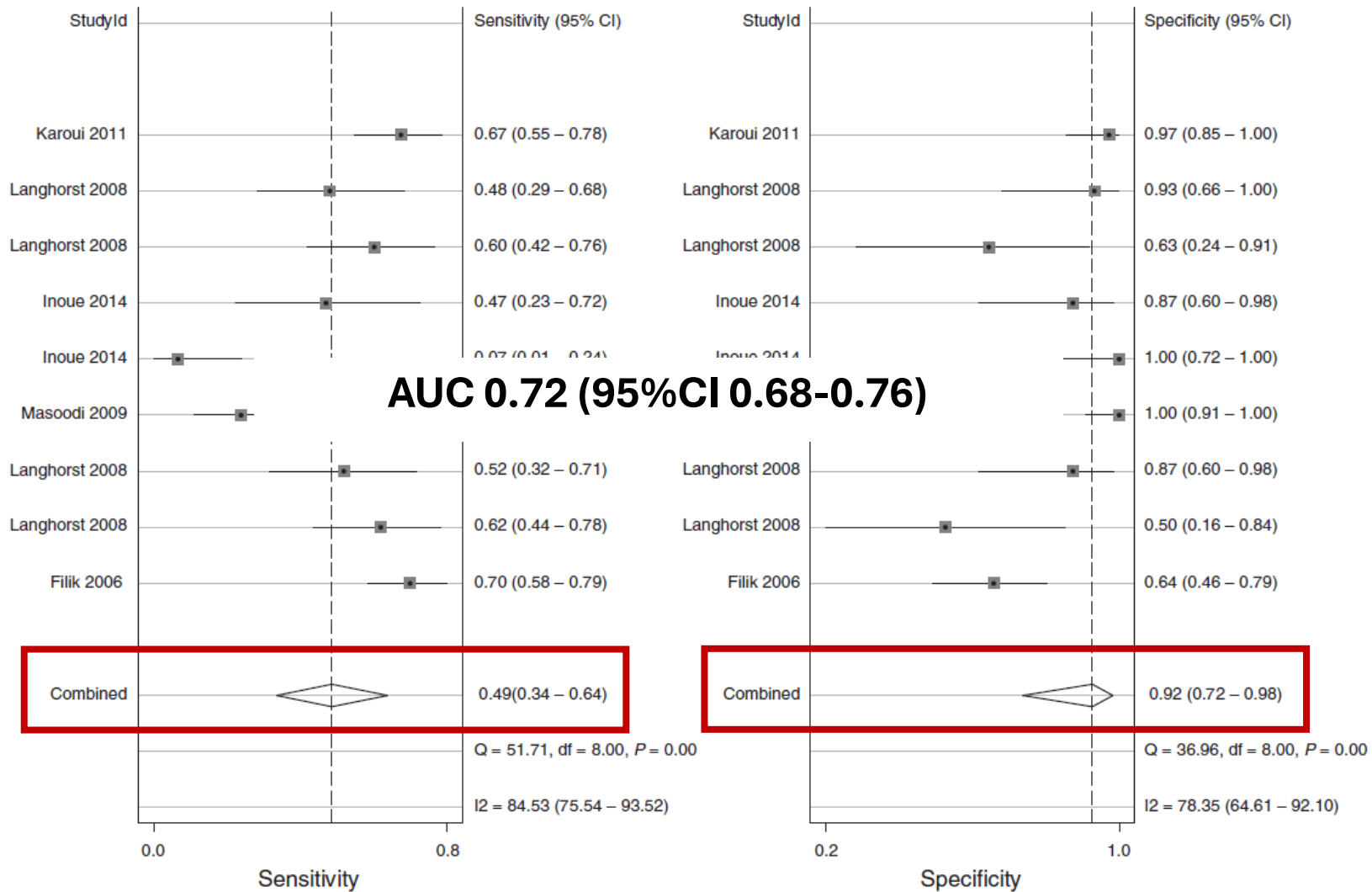
Most patients with Crohn's disease (75%) had elevated CRP levels at diagnosis

No differences in CRP between different disease location / behavior

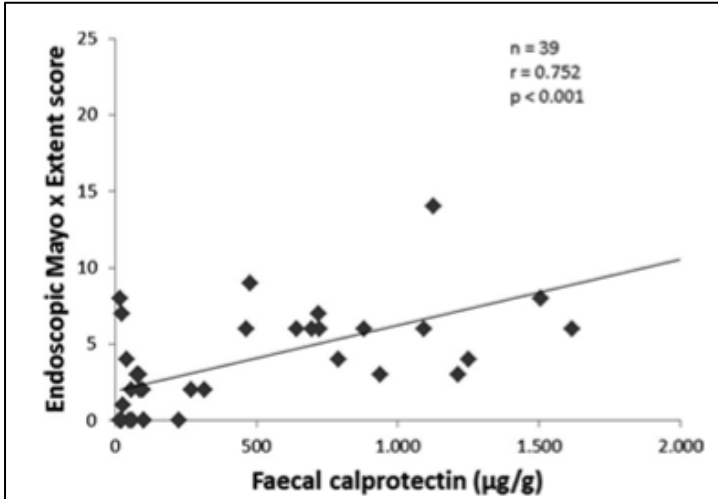
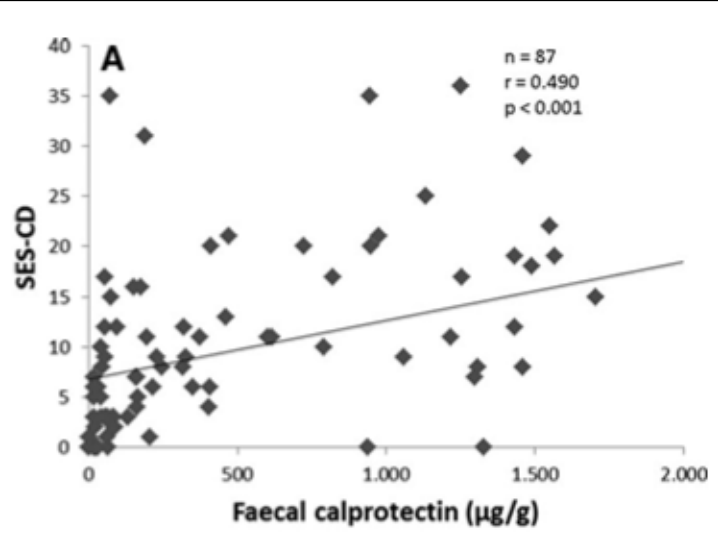
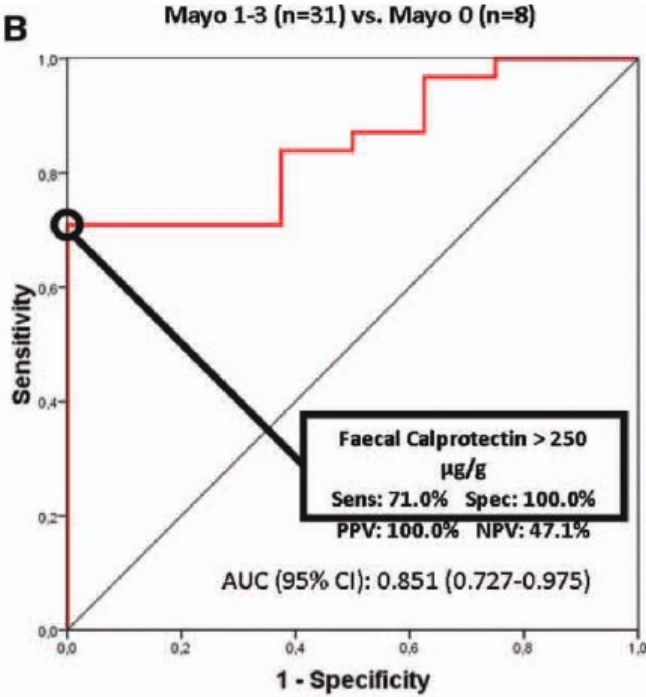
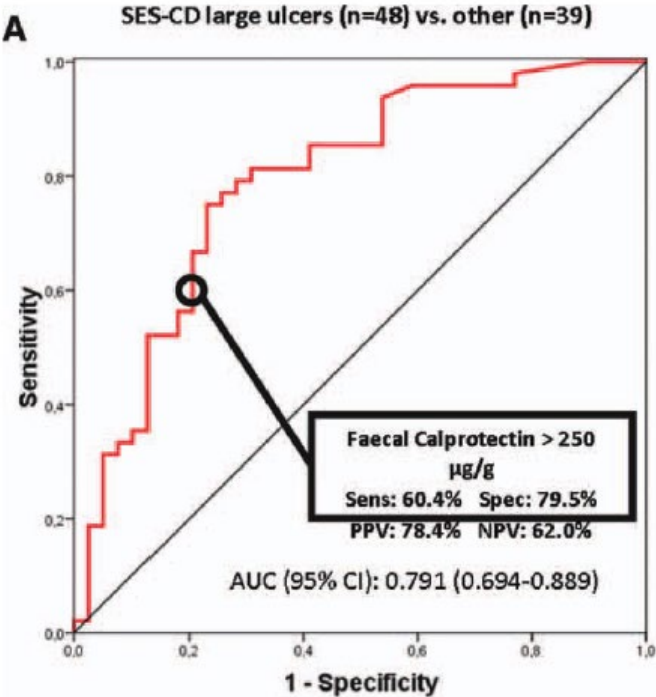
No association between CRP levels and risk of surgery, except in the L1 sub-group

- 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)

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



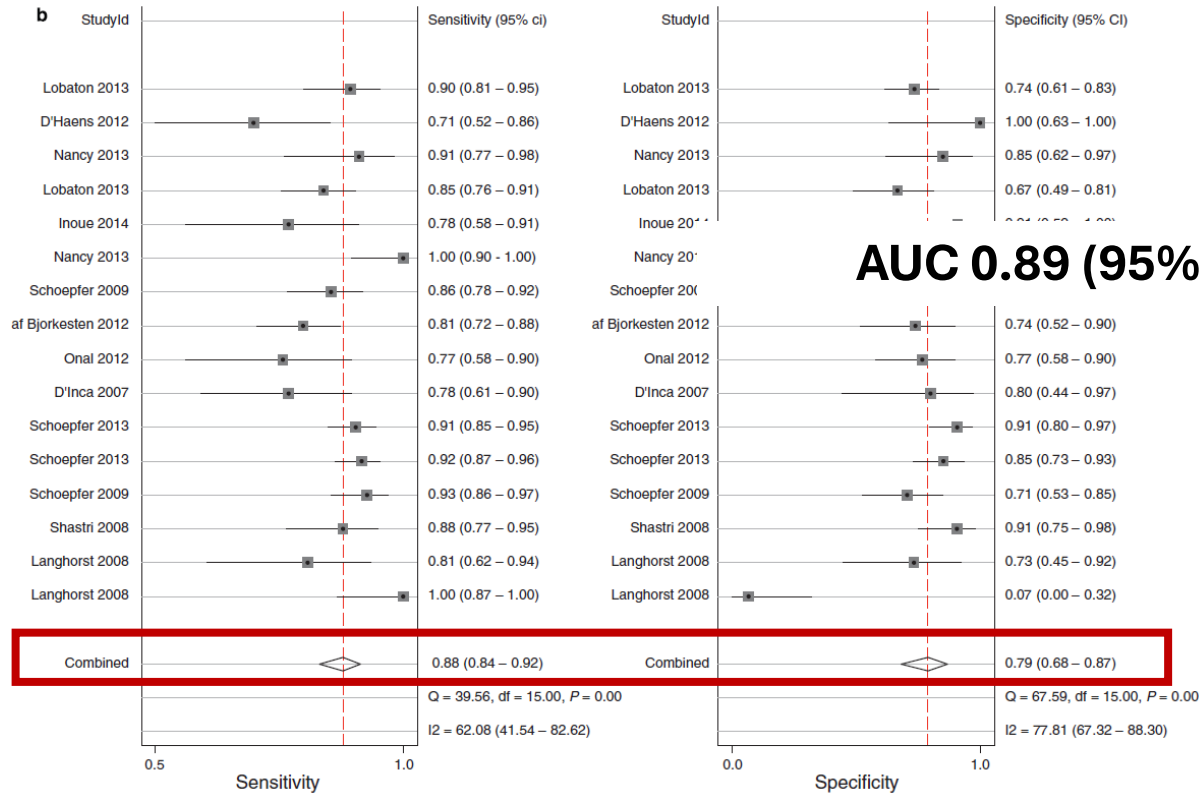
FCalp is a Surrogate Marker for Endoscopic Lesions in IBD



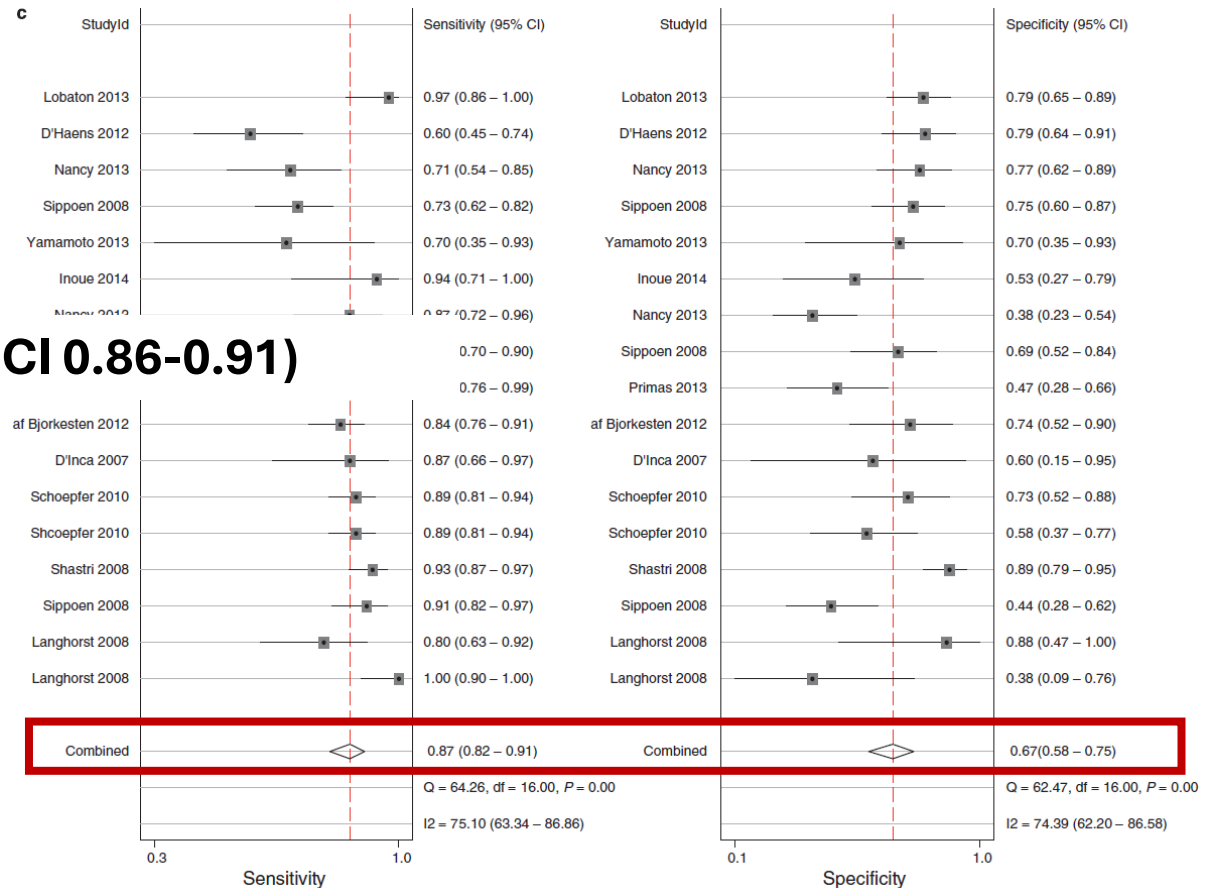
FCalp for Detection of Endoscopic Activity in Symptomatic IBD Patients: A Systematic Review and Meta-Analysis

UC

CD

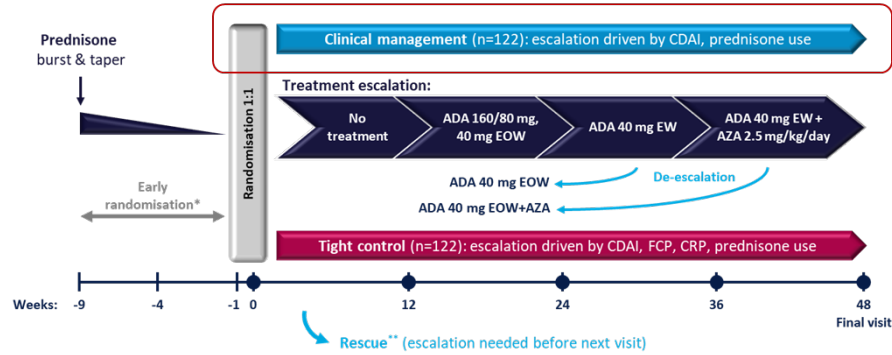


AUC 0.89 (95%CI 0.86-0.91)

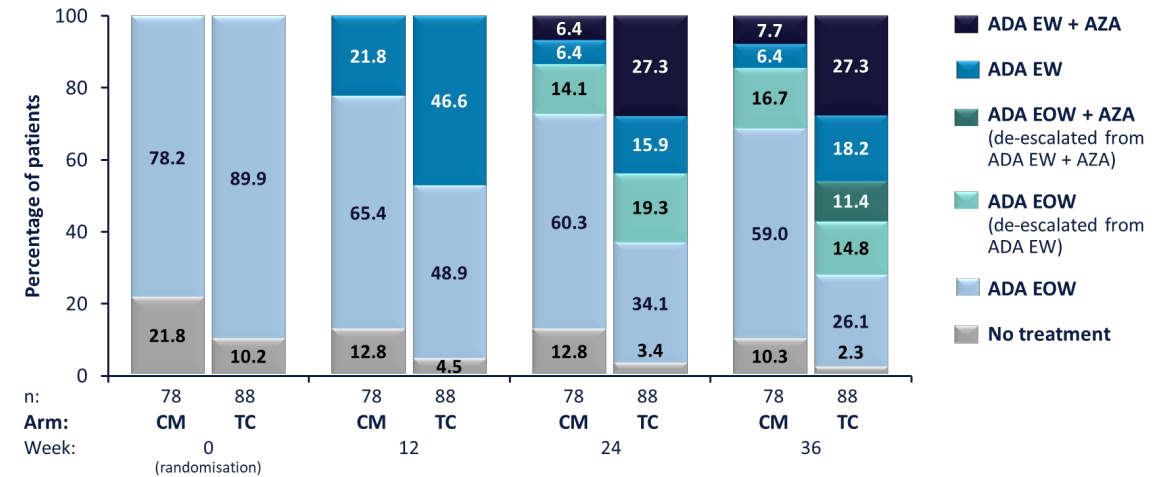
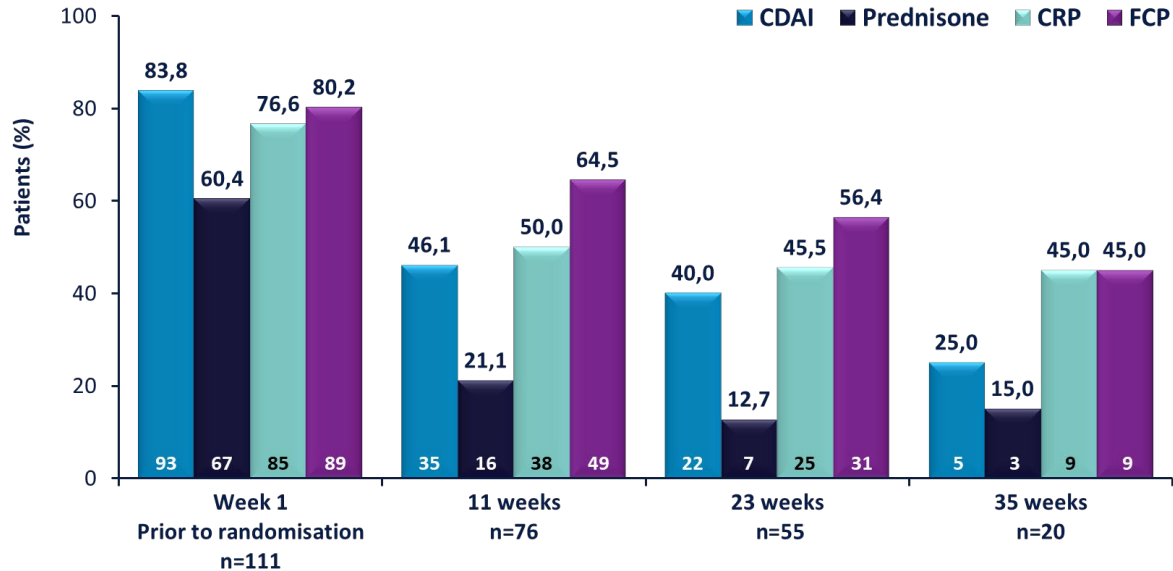
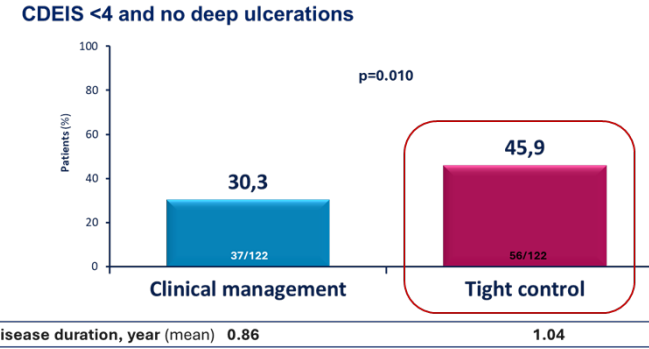


CALM: reasons for escalation (TC arm) and treatment options over time

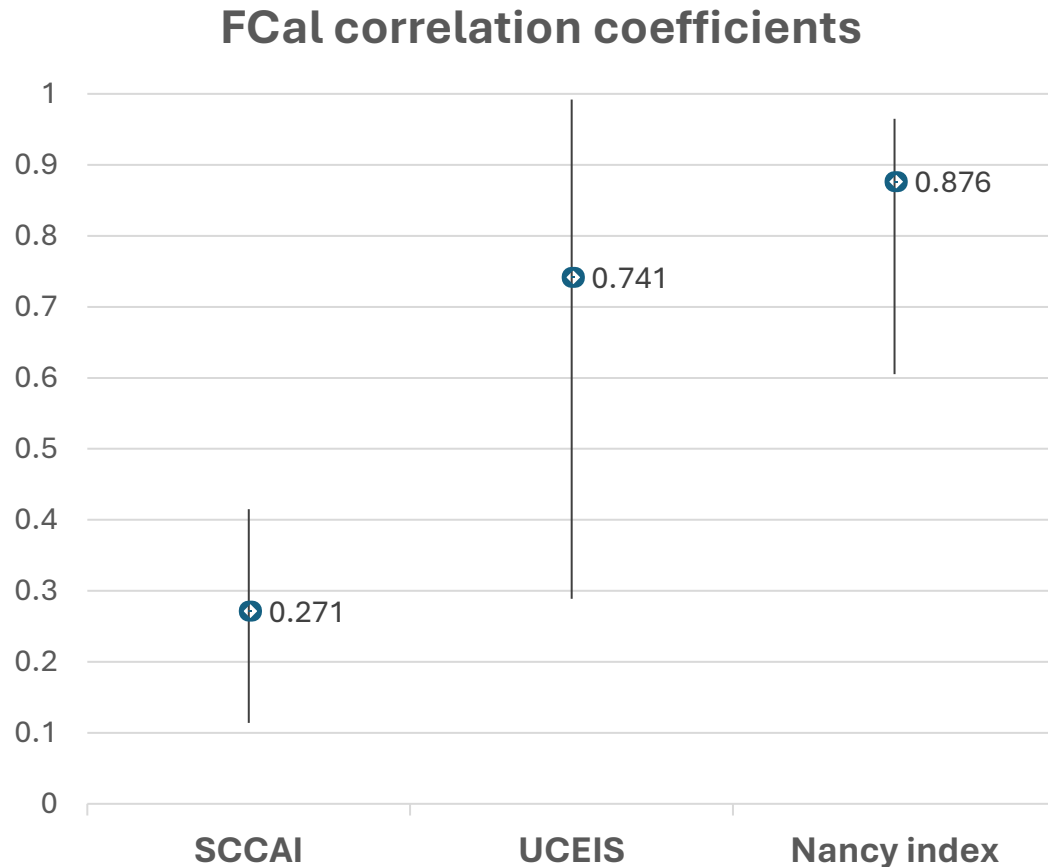
Study design



Primary endpoint at 48 weeks after randomisation



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 $\mu\text{g/g}$** [range 8-624], **91 $\mu\text{g/g}$** [range 8-858], and **67 $\mu\text{g/g}$** [range 8-479], respectively
- Threshold for active disease:
 - **187 $\mu\text{g/g}$ for UCEIS** (area under the curve [AUC] 0.915)
 - **72 $\mu\text{g/g}$ for Nancy** [AUC 0.824]
 - **187 $\mu\text{g/g}$ for combined** endoscopic and histological criteria [AUC 0.936].

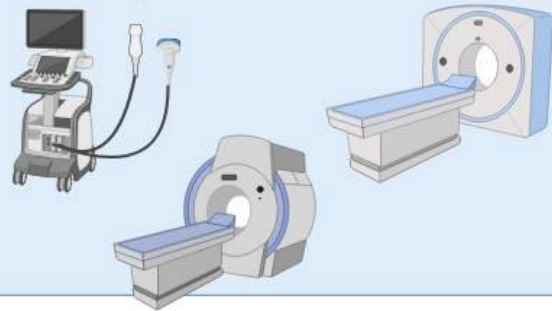
Monitoring with biomarkers

| Monitoring tool | Target | Definition | Advantages | Limitations |
|---------------------------|---------------|--|--|---|
| CRP | Normalization | CRP \geq 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 | \geq 250 μ g/g: Associated with active endoscopic disease and ulceration <100 μ g/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 \geq 50% | | |

Intestinal Ultrasound

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

Assessment of activity and severity of inflammatory bowel disease in cross-sectional imaging techniques: a systematic review



6496 publications screened



179 papers (1990 - 2023) included



10988 IBD patients included



Activity investigated in 100% of the included studies
Severity investigated in < 60% of the included studies

Intestinal ultrasound

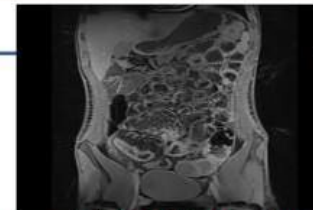
- Bowel wall thickness
- Color Doppler signal
- Hypo-echogenic bowel wall



Pooled sensitivity 62 - 95.2%, pooled specificity 61.5 - 100%,
pooled accuracy 69 - 95%

Magnetic resonance

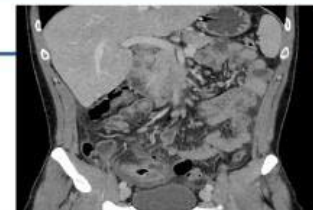
- Bowel wall thickness
- Mural hyper-enhancement
- Mucosal ulcers
- Parietal edema



Pooled sensitivity 64 - 100%, pooled specificity 58.8 - 100%,
pooled accuracy 63.2 - 98%

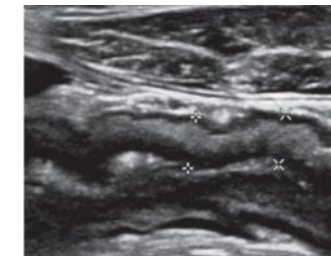
Computed tomography

- Bowel wall thickness (BWT)
- Mural hyper-enhancement
- Parietal edema

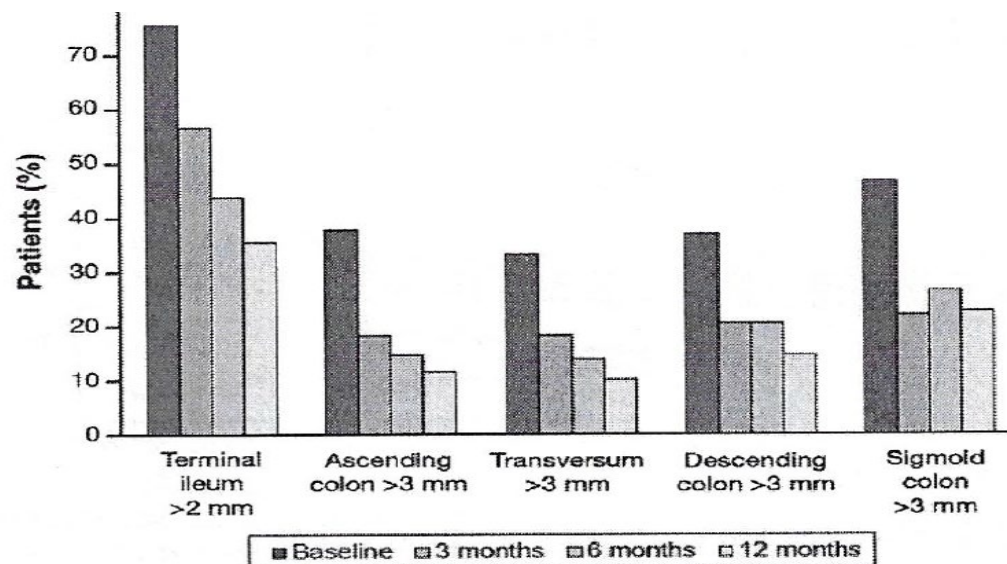


Pooled sensitivity 63.3 - 100%, pooled specificity 59.1 - 100%,
pooled accuracy 81 - 96%

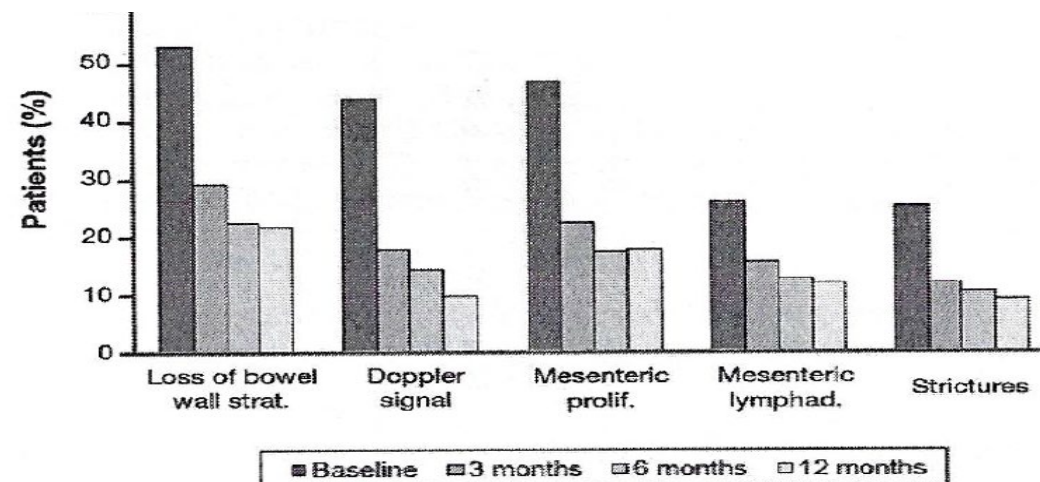
IUS to Monitor CD Activity (TRUST study)



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

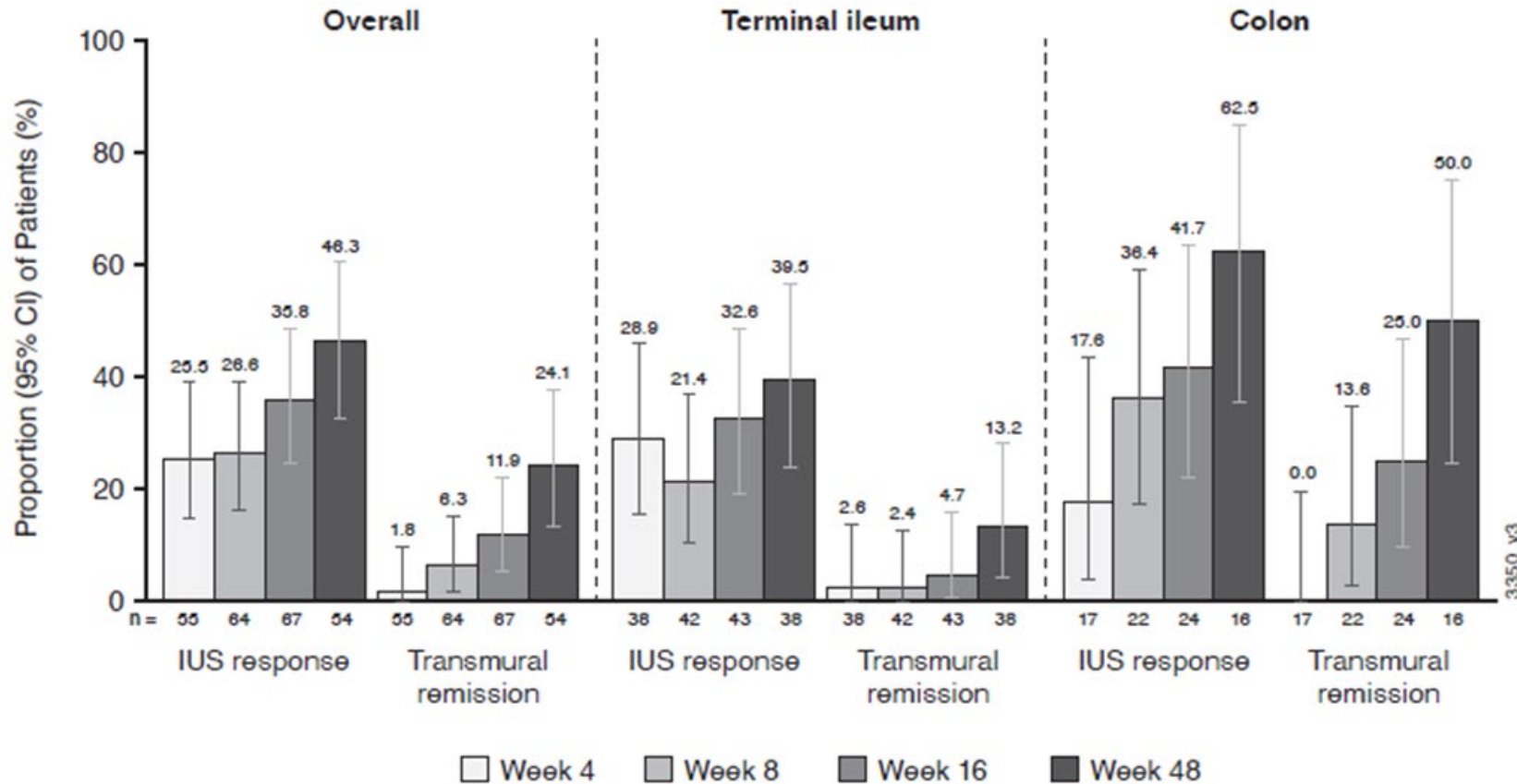


Bowel Wall Thickening



BW and abdominal changes

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

IUS to Monitor UC Activity (TRUST&UC study)

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

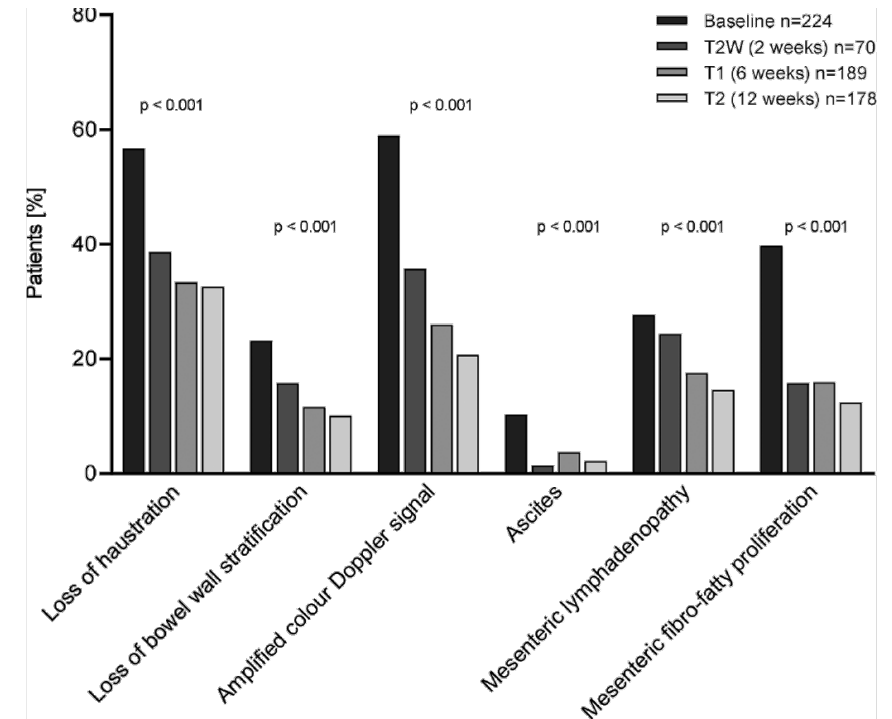
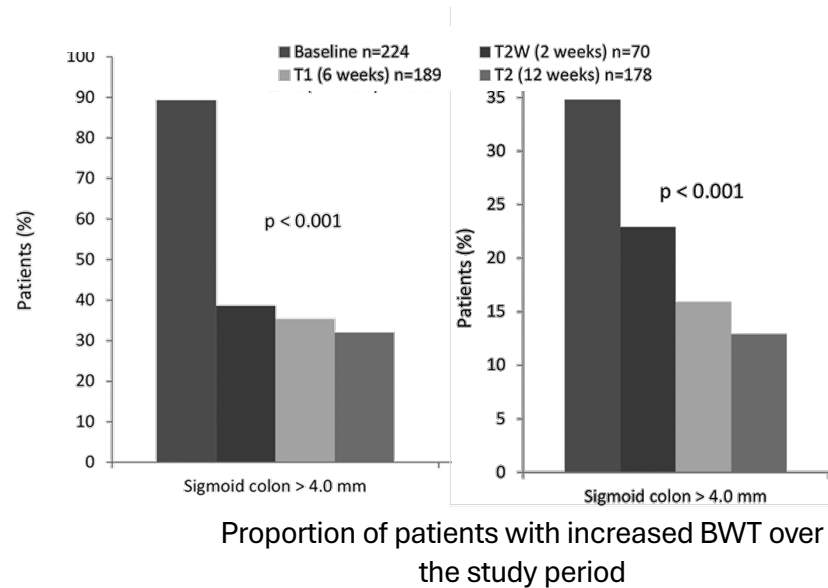


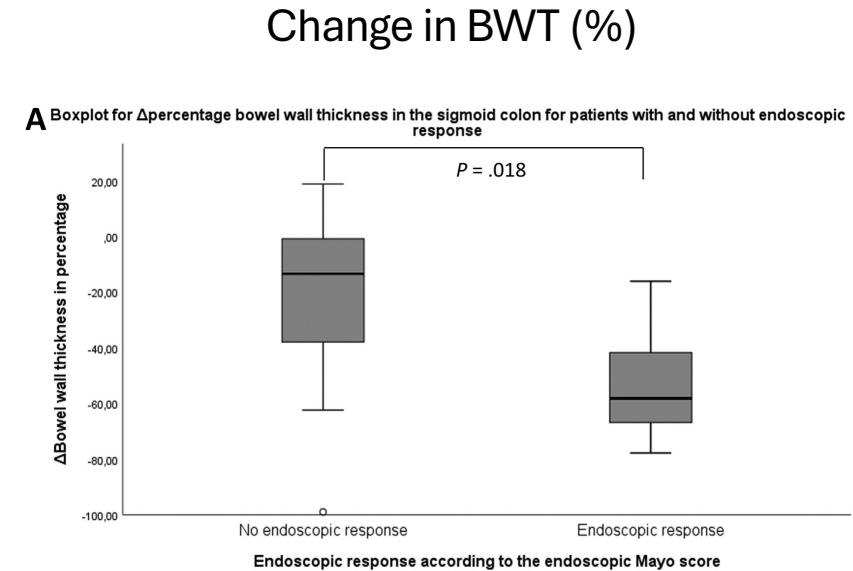
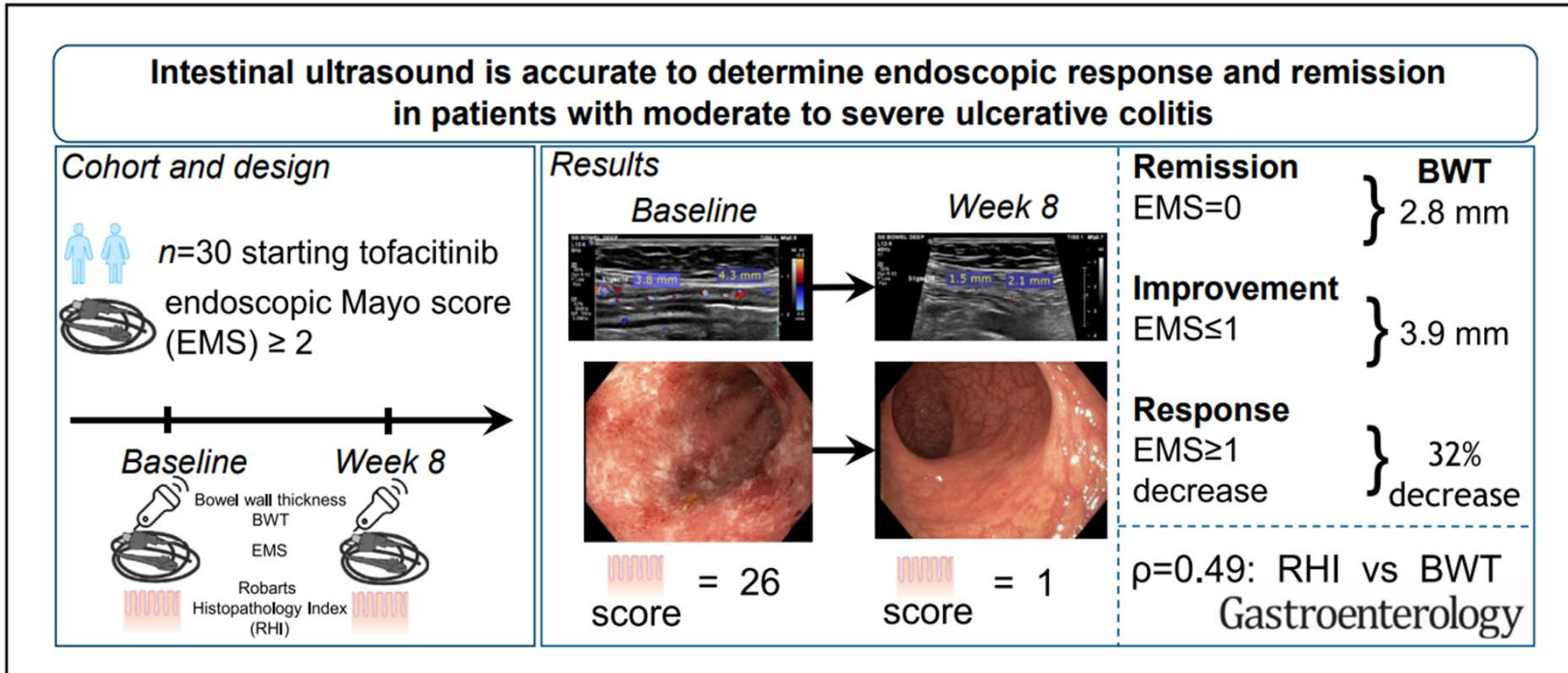
Table 2 Normalisation of BWT (mm) at T2 (week 12) versus clinical response; χ^2 test

| | 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; χ^2 test

| | Sigmoid colon | |
|---|-------------------|----------------------|
| | BWT normalisation | No BWT normalisation |
| Calprotectin <250 $\mu\text{g/g}$ at T2 | % (n) | % (n) |
| Yes | 48.9 (23) | 22.2 (6) |
| No | 51.1 (24) | 77.8 (21) |
| | P=0.023 | |

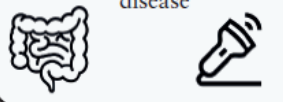
IUS is accurate to determine endoscopic response and remission in patients with moderate to severe UC: a longitudinal prospective cohort study



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

JCC SYSTEMATIC REVIEW & META-ANALYSIS

Diagnostic accuracy of intestinal ultrasound and its advanced modalities in the detection of intra-abdominal complications in Crohn's disease



1498 studies screened

68 studies included in this review
23 studies in the meta-analysis

3863 patients

| | B-mode | SICUS |
|----------------------------|--------|-------|
| STRICTURES | | |
| Sensitivity | 81% | 94% |
| Specificity | 90% | 95% |
| Accuracy | 86% | 94% |
| INFLAMMATORY MASSES | | |
| Sensitivity | 87% | 91% |
| Specificity | 95% | 97% |
| Accuracy | 91% | 94% |
| FISTULAS | | |
| Sensitivity | 67% | 90% |
| Specificity | 97% | 94% |
| Accuracy | 82% | 92% |

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 such as the bladder, skin, or mesentery. These items were reported in 97% and 82% of the studies, respectively

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 |
| MUC (UC) | Transmural healing | MUC score > 6.2 mm reflects active disease | Limited by body habitus and pelvic location |
| UC-IUS (UC) | Transmural healing | | Limited in assessing extent |
| IBUS-SAS (CD, UC-?) | Transmural healing | IBUS-SAS score in CD > 42.9 reflects active disease | |
| SUS-CD (CD) | Transmural healing | SUS-CD \geq 1 reflects endoscopic active disease SUS-CD score of \geq 3 reflects moderately active endoscopic disease | Less useful to assess disease limited to the mucosa Limited in differentiating active vs chronic |
| BUSS (CD) | Transmural healing | BUSS \leq 3.52 predicts endoscopic remission | |

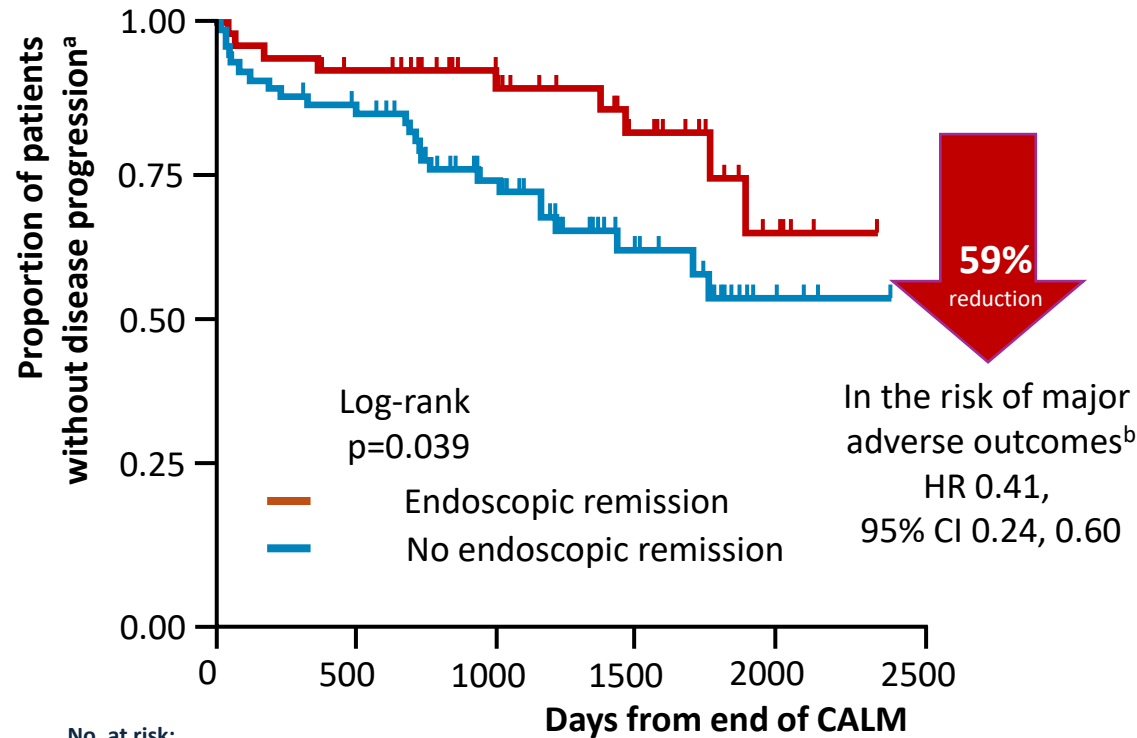
IBUS-SAS=International bowel ultrasound segmental activity score; MUC. Milan ultrasound criteria; UC-IUS=Ulcerative colitis intestinal ultrasound score; BUSS: Bowel ultrasound score; SUS-CD=Simple ultrasound score for Crohn's disease

Endoscopy

Driver of CD course: endoscopic/deep remission

Endoscopic remission

(CDEIS <4 with no deep ulcers)

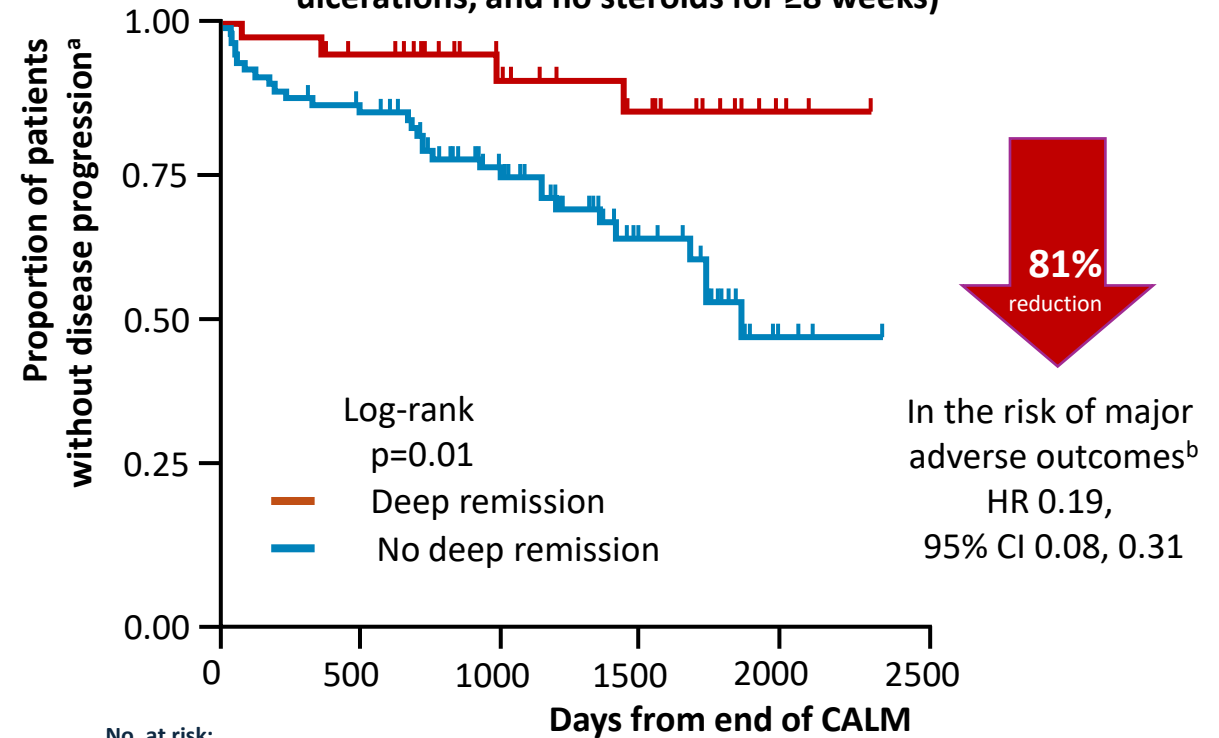


No. at risk:

| | 0 | 500 | 1000 | 1500 | 2000 | 2500 |
|-------------------|----|-----|------|------|------|------|
| 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)



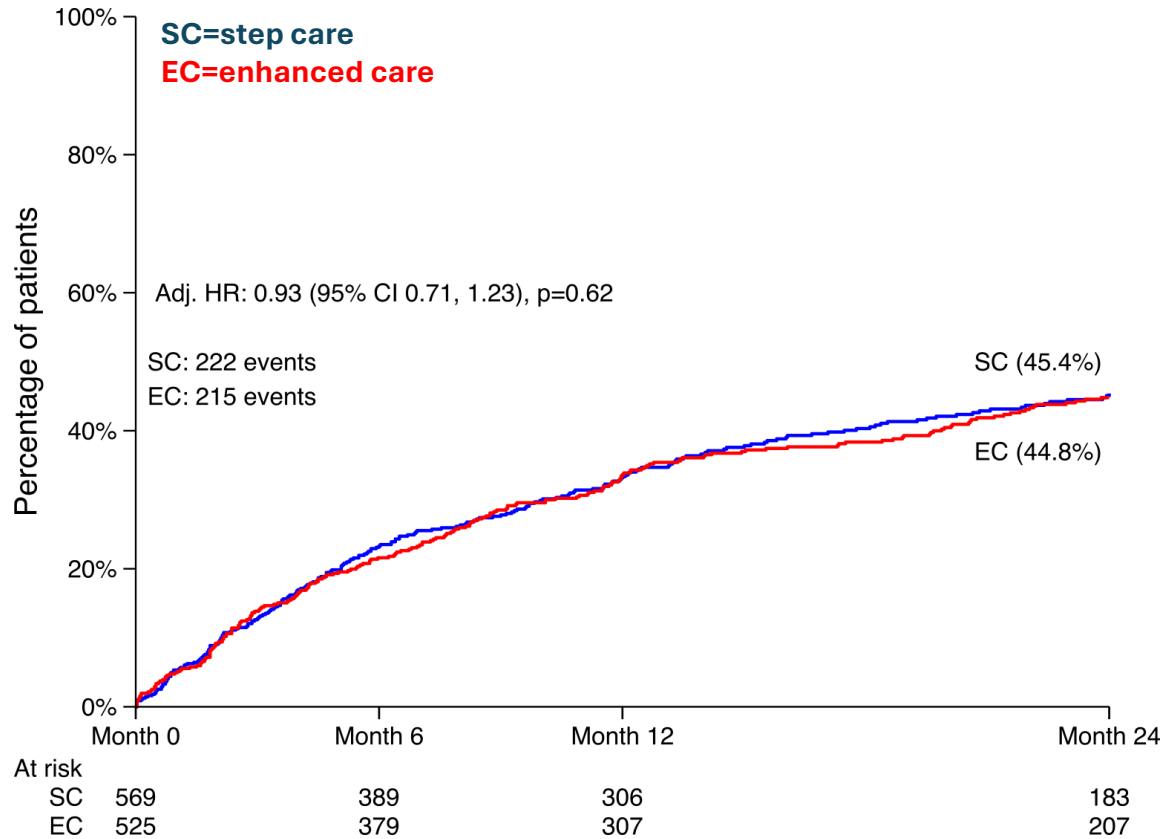
No. at risk:

| | 0 | 500 | 1000 | 1500 | 2000 | 2500 |
|-------------------|----|-----|------|------|------|------|
| No deep remission | 86 | 70 | 46 | 21 | 2 | 0 |
| Deep remission | 36 | 32 | 19 | 12 | 2 | 0 |

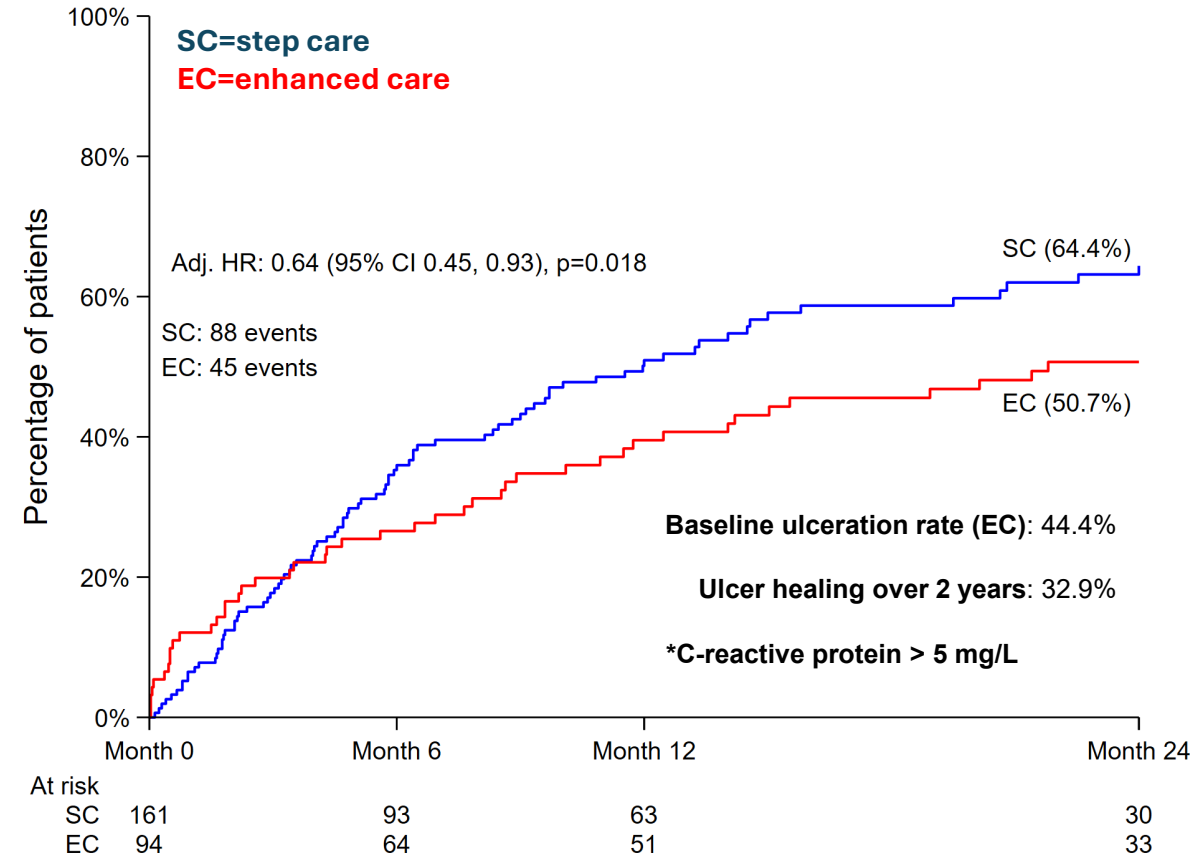
^aDisease progression defined as any major adverse outcome: composite of new internal fistula/abscess, stricture, perianal fistula/abscess, CD hospitalization, or CD surgery since end of CALM; ^bAdjusted for CALM treatment arm, age, sex, disease duration, baseline CRP, baseline calprotectin, disease 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

REACT2: treat to MH

Primary outcome: CD-related complications



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

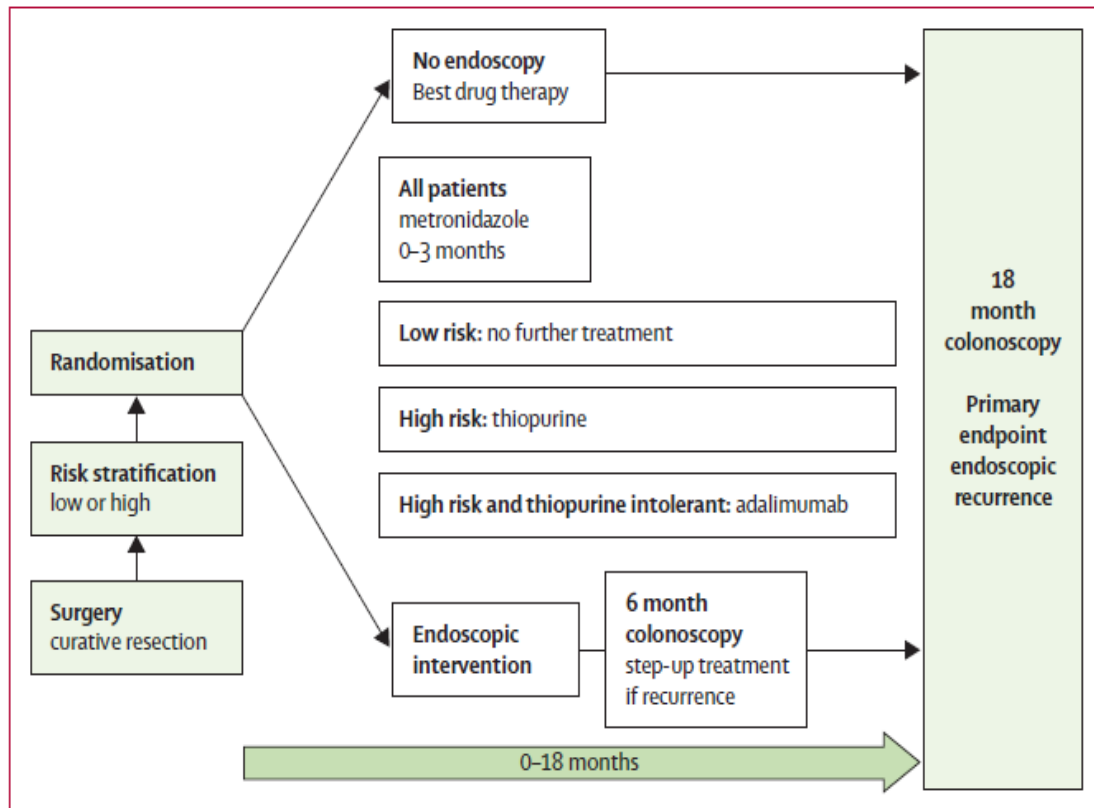


Treating to a target of ulcer healing may be more effective than symptom-based management in patients with evidence of active inflammation

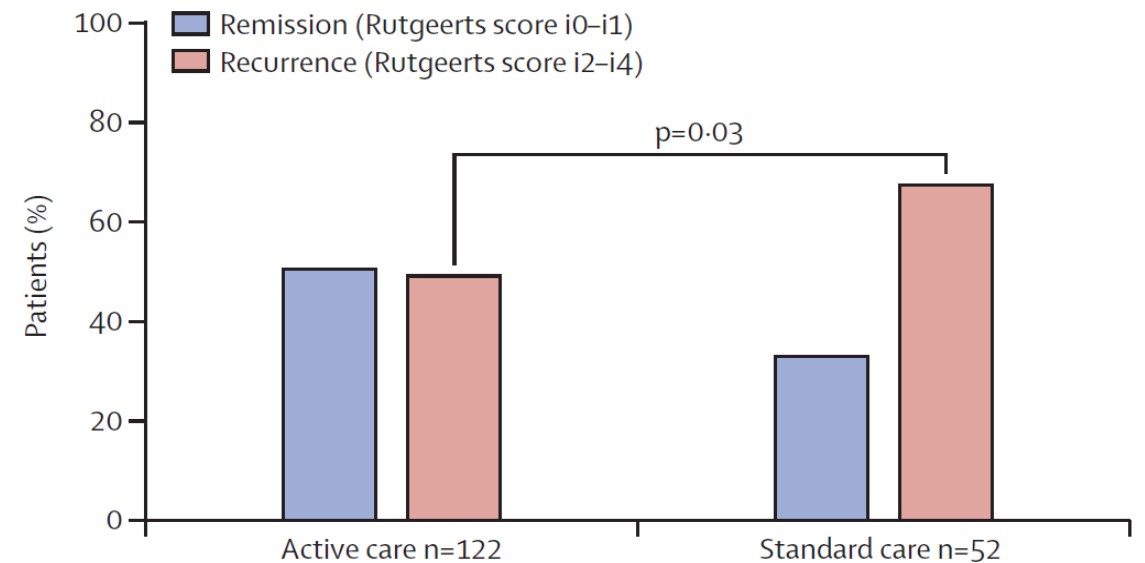
- **Primary outcome** - Risk of first CD-related complication at 24 months, including:
 - Surgery
 - Non-surgical events
 - Hospitalizations
 - CD medication, procedure-related hospitalizations and surgeries

Intensification of prophylactic therapy guided by colonoscopy (POCER)

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



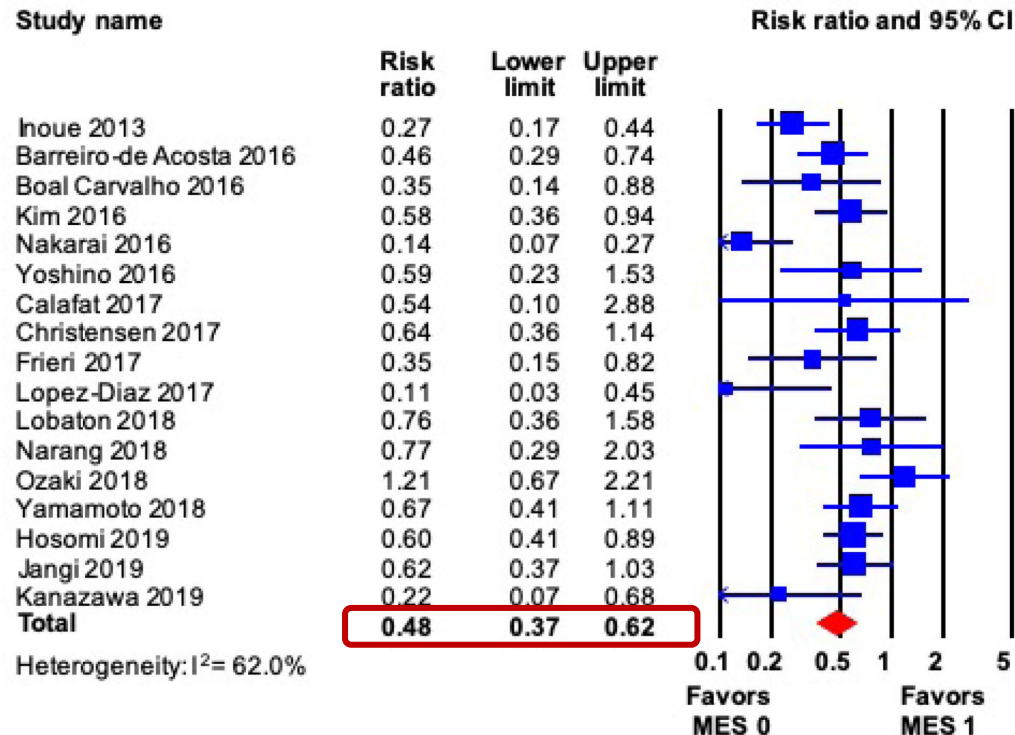
Primary Endpoint: Endoscopic recurrence at 18 months



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

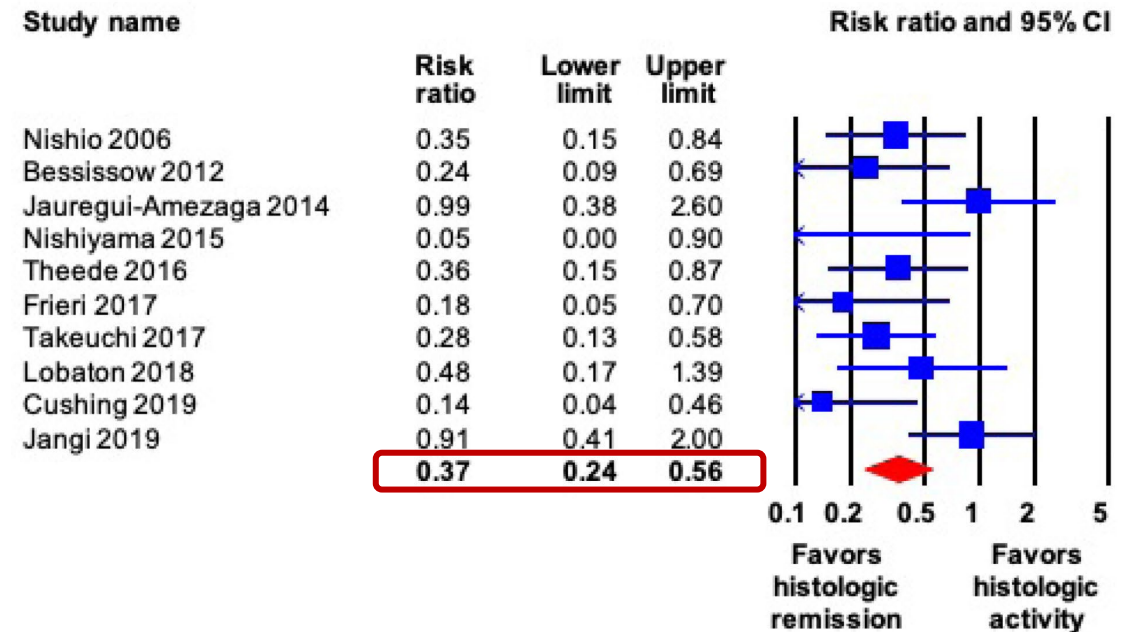
Drivers of UC course: Endoscopic, histologic, histo-endoscopic healing (meta-analysis of 17 studies, 2608 patients with UC in clinical remission)

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



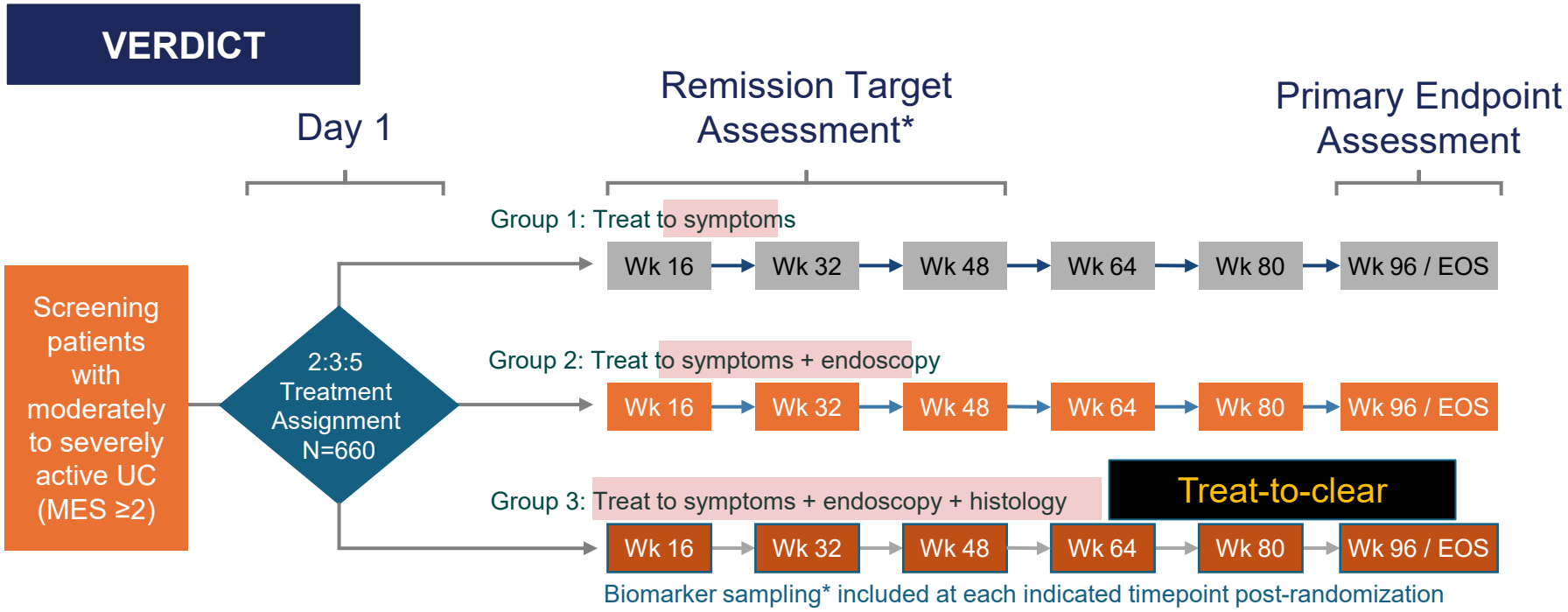
**MES 0 (vs MES 1):
52% lower risk of clinical relapse**

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**

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



Patients with active UC randomized to 3 treatment target groups:

- Group 1: corticosteroid-free symptomatic remission
- Group 2: 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

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

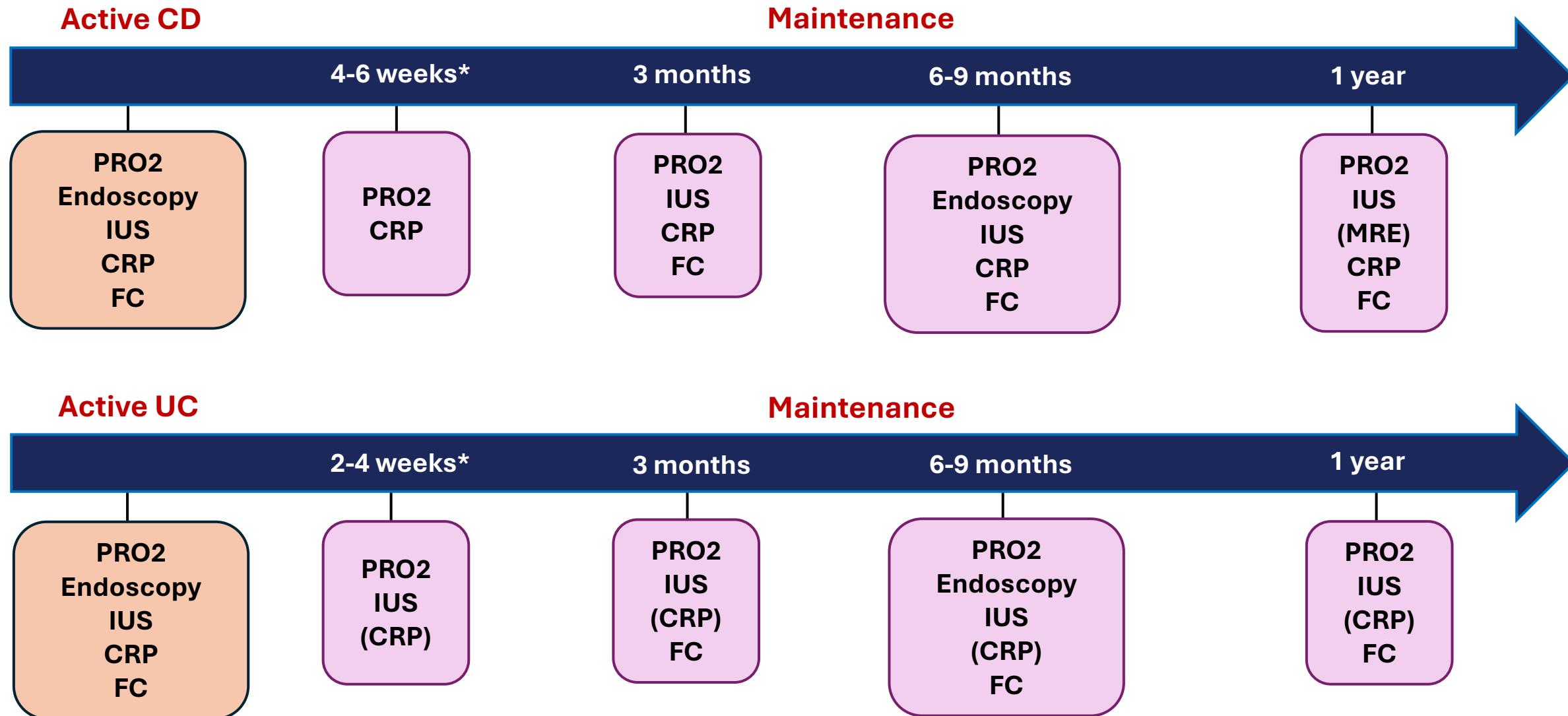
*Also completed at Week 8
 EudraCT Number: 2019-002485-12. ClinicalTrials.gov: NCT04259138
 EOS, end of study; MES, Mayo endoscopic subscore; UC, ulcerative colitis; Wk, week.
 ClinicalTrials.gov. Determination of the Optimal Treatment Target in Ulcerative Colitis (VERDICT). Available from: <https://clinicaltrials.gov/show/NCT04259138>. 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 | |

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