Treat to target in IBD: why the uptake is still a challenge?

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Treatment goals in other disease areas

Targeted treatment programs in diabetology and cardiology:

- Success in terms of adoption
- Demonstrated benefits over long-term patient outcomes

Condition	Treatment goal/target
Diabetes	**$HbA1_c$:** <7%
Hypertension	**BP:** 140/90 mmHg (135/80 for patients with diabetes) **LDL-cholesterol:** 70 mg/dL to decrease incidence of cardiac events

$HbA1_c$ = glycoslated haemoglobin
LDL = low-density lipoprotein

Targets and tight control in RA

- Rheumatology and management of RA had reached a new era:
  - Significant advances in treatments
  - Significant advances in biometry (validated composite measures)
  - Enhanced understanding of optimal treatment strategies

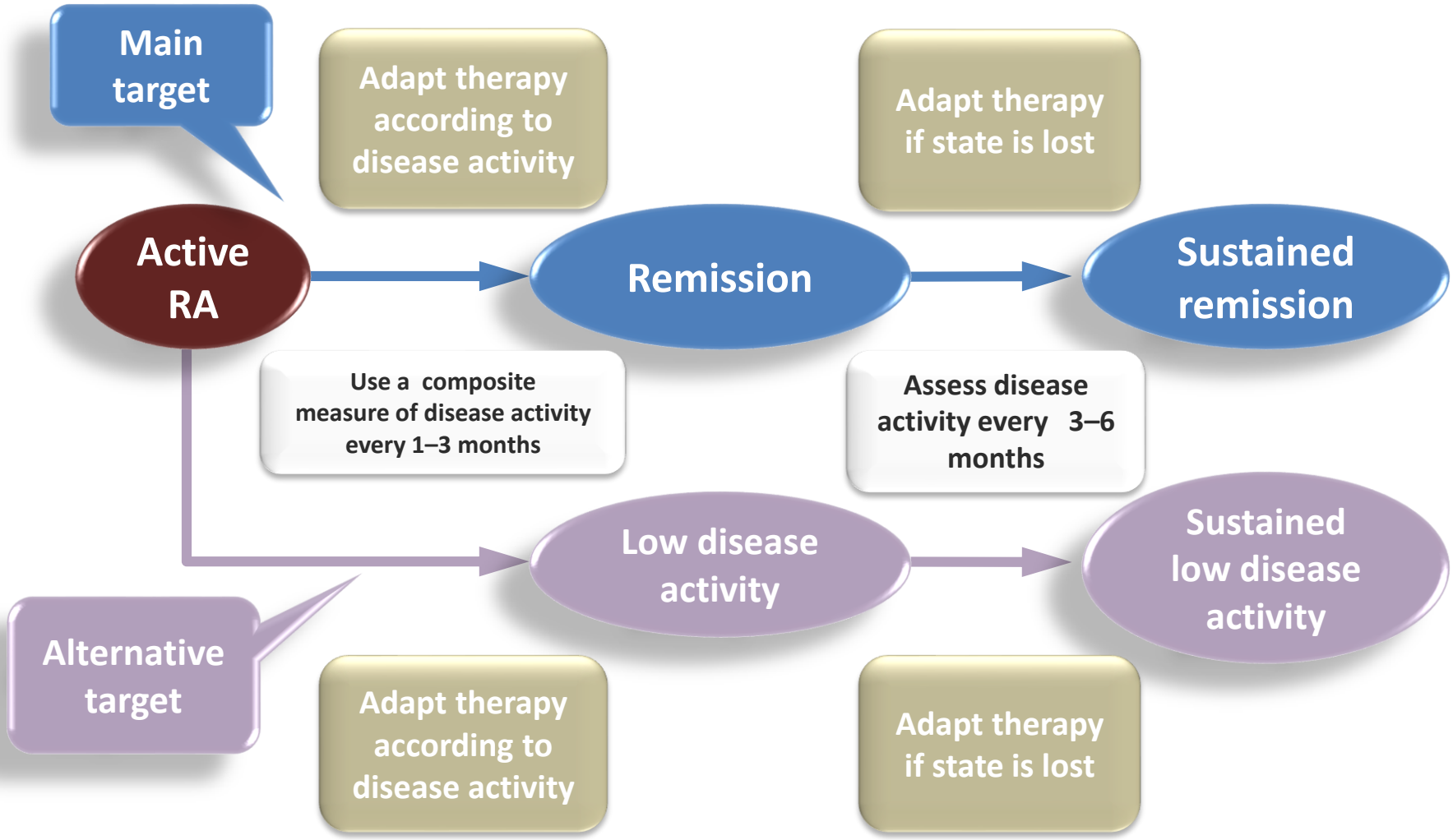
- Challenge: Wide heterogeneity of outcome expectations and treatment strategies in daily clinical practice

- Solution: Clear outcome targets and tight disease control had to be integrated into standard practice

Goals of RA therapy

- Reduce signs and symptoms
- Retard/halt joint destruction
- Normalise physical function/QoL (productivity)
- Induce remission
- Reduce co-morbidities
- Improve survival

Algorithm to treat RA to target



Smolen JS, *et al. Ann Rheum Dis* 2010;69:631–7

IBD are complex diseases

- Make the diagnosis quickly and accurately
- Assess disease severity and determine prognosis
- Risk factors of a more severe disease course
- Select and initiate therapy to induce and maintain remission
- Adjust therapies to achieve a target
- Modify long-term outcomes of the disease
- Monitor for relapse
- Monitor for drug-related and disease-related complications

Treatment goals

Induce clinical remission (absence of symptoms)

Avoid short- and long-term toxicity of treatment

Enhance quality of life

Maintain steroid-free remission

- Avoid repeated courses of steroids

Induce "deep" remission

- Biologic remission (normalization of biomarkers)
- Mucosal healing

Prevent complications (hospitalizations, surgery, etc)

Reduce cancer risk

Reenaers C, et al. *World J Gastroenterol* 2012;18(29):3823–27; Panaccione R, et al. *J Crohns Colitis* 2012;6(Suppl 2):S235–42.

STRIDE
Selecting targets of remission in inflammatory bowel disease

Selecting targets of remission in IBD: summary of the overall process

Steering Committee meeting	Steering Committee met to agree the objectives, process, format and timelines of the project, and to identify the key questions to be answered
Literature review	Systematic literature review conducted by Fellows, guided by Mentors on the Steering Committee, to answer the key questions posed
Draft recommendations	Steering Committee divided into “task forces” to develop draft recommendations based on the literature review
Voting meeting	**Working Group (Steering Committee & Fellows) meet to vote on finalised statements, clearly define and prioritise targets for use in daily practice and outline a composite target with clinical utility in CD and UC**
Outputs	Steering Committee, with members of the Working Group, generate outputs and dissemination activities

STRIDE
Selecting targets of remission in inflammatory bowel disease

Work stream groups (UC and CD)

1. **Clinical targets**
   - Leads: G. Van Assche and P. Lakatos
   - Fellows: G. Bouguen (San Diego)
2. **Endoscopic scoring systems**
   - Leads: G. D'Haens and P. Marteau
   - Fellows: M. Samaan (London) and B. Pariente (Paris)
3. **Histopathology**
   - Leads: R. Riddell and S. Travis
   - Fellows: R. Bryant (Oxford) and S. Winer (Toronto)
4. **Imaging**
   - Leads: J. Panes and W. Bemelman
   - Fellows: G. Fiorino (Milan) and I. Ordas (Barcelona)
5. **Biomarkers**
   - Leads: R. Panaccione and M. Silverberg
   - Fellows: T. Murdoch (Calgary) and S. O'Donnell (Dublin)
6. **Patient-reported outcomes**
   - Leads: B. Sands and P. Munkholm
   - Fellows: J. Ruel (Quebec) and S. Krishnareddy (New York)

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Selecting targets of remission in inflammatory bowel disease

Example summary table

Work stream:_____	CD	UC
What is the target?		
How to measure the target?		
How frequently should the target be measured?		
Is the target already used in clinical studies/trials? What are the data supporting that this should be the target?		
Can the target be used routinely in clinical practice?		
Assign priority of target for routine clinical practice (H/M/L)		

STRIDE

Selecting targets of remission in inflammatory bowel disease

Literature review: questions addressed within each workstream

1. What is the target?
2. How to measure it?
3. Is it already used in clinical studies/trials? What are the data supporting that this should be the target?

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Selecting targets of remission in inflammatory bowel disease

Final voting statements

Statement 1

- The primary patient-related outcome for ulcerative colitis should be resolution of rectal bleeding and normalisation of bowel habit.
- The primary patient-related outcome for Crohn's disease should be resolution of abdominal pain and normalisation of bowel habit.

Statement 2

- In Crohn's disease, in addition to resolution of abdominal pain and altered bowel habit, the patient's individual goals should also be addressed.
- In ulcerative colitis, in addition to resolution of rectal bleeding and altered bowel habit, the patient's individual goals should also be addressed.

UC management: a practical example

- A.D. 50 years old, male
- Bus driver
- UC (left-sided) since 2007
- Steroid-dependent, azathioprine refractory
- UC flare (6-7 stools/day, obvious blood, ulcers at endoscopy)
- GMS=10
- Starts anti-TNF

- G.M. 47 years old, female
- Secretary
- UC (left-sided) since 2009
- Steroid-dependent, azathioprine refractory
- UC flare (7 stools/day, obvious blood, ulcers at endoscopy)
- GMS=10
- Starts anti-TNF

UC management: a practical example

- 12 weeks later
- 2-3 stools, no blood
- Mucosal healing
- Steroids completely stopped
- Still urgency, low QoL, work impairment, fatigue

- 12 weeks later
- 2-3 stools, no blood
- Mucosal healing
- Steroids completely stopped
- No urgency, good QoL, no work impairment

Global Mayo Score ≤ 2

Same UC remission?

STRIDE
Selecting targets of remission in inflammatory bowel disease

Final voting statements: UC and CD

Statement 3

- The frequency of outcome assessment should be tailored to the patient's symptoms, with a minimum of every 3 months until resolution.
- The frequency of outcome assessment after symptom resolution should be at least every 6 to 12 months.

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Selecting targets of remission in inflammatory bowel disease

Endoscopic goals

Statement 1

- A Mayo endoscopic sub-score of 0 is the optimal target. A Mayo endoscopic sub-score of 1 should be a minimum target.

Statement 2

- In Crohn's disease, absence of ulceration is the target.

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Selecting targets of remission in inflammatory bowel disease

Are biomarkers goals in IBD?

Statement 1

- Available biomarkers including CRP and fecal calprotectin are not targets.

Statement 2

- CRP and fecal calprotectin are adjunctive measures of inflammation for monitoring in UC. Failure of CRP or fecal calprotectin normalization (below lab-specific cutoff) should prompt further endoscopic evaluation, irrespective of symptoms.

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Selecting targets of remission in inflammatory bowel disease

Imaging as a target in IBD

Statement 1

- When endoscopy cannot adequately evaluate inflammation, resolution of inflammation as assessed by cross-sectional imaging is a target in CD.

Statement 2

Cross-sectional imaging is not a target in UC.

STRIDE

Selecting targets of remission in inflammatory bowel disease

When to assess targets in IBD?

Statement 1

- Endoscopic assessment should be performed within 3 to 6 months after the start of therapy.

Statement 2

- Endoscopic or cross-sectional imaging assessment should be performed within 6-9 months after the start of therapy.

STRIDE
Selecting targets of remission in inflammatory bowel disease

Crohn's disease
What is the consensus target?

- The target for Crohn's disease is a combination of:
  - **Clinical/PRO remission** defined as resolution of abdominal pain and diarrhea/altered bowel habit which should be assessed at a **minimum of 3 months** during the active disease

  and

  - **Endoscopic remission** defined as resolution of ulceration at ileocolonoscopy (or resolution of findings of inflammation **on cross sectional imaging** in patients who cannot be adequately assessed with ileocolonoscopy) which should be assessed **at 6-9 month intervals** during the active phase

  – **Adjunctive measures of disease activity that may be useful in the management of selected patients but are not a target include:**
    - CRP
    - Fecal calprotectin
  – **Measures of disease activity that are not a target:**
    - Histology

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Selecting targets of remission in inflammatory bowel disease

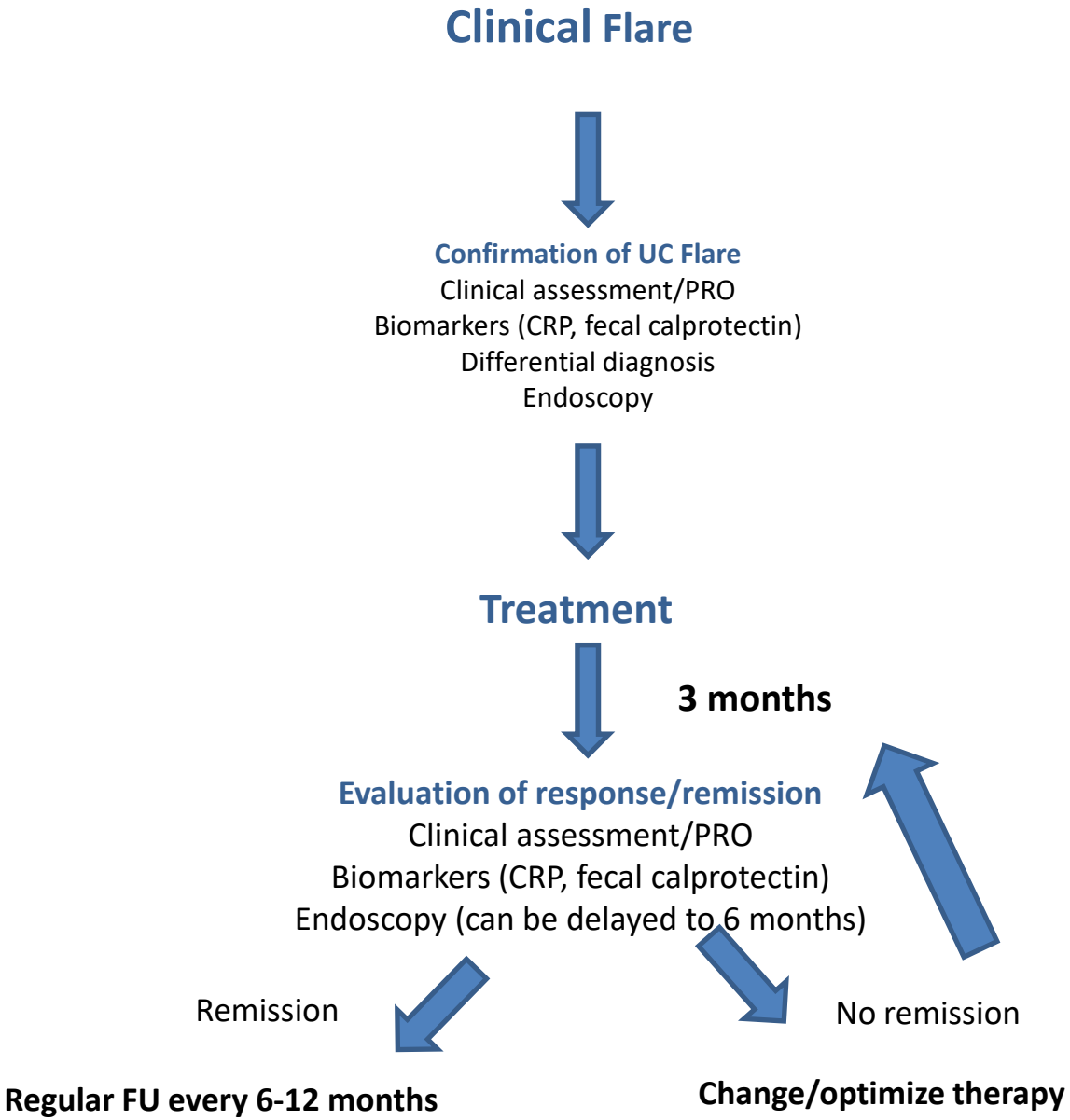
Ulcerative colitis
What is the consensus target?

- The target for ulcerative colitis is a combination of:
  - **Clinical/PRO remission** defined as resolution of rectal bleeding and diarrhea/altered bowel habit which should be assessed at a **minimum of 3 months** during the active disease

  and

  - **Endoscopic remission** defined as resolution of friability and ulceration at flexible sigmoidoscopy or colonoscopy which should be assessed at **3-6 month intervals** during the active phase
  - **Adjunctive measures of disease activity that may be useful in the management of selected patients but are not a target include:**
    - CRP
    - Fecal calprotectin
    - Histology
  - **Measures of disease activity that are not a target:**
    - Cross sectional imaging

Treat to target in UC: a practical example



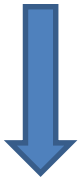
STRIDE Consensus in Clinical Practice: UC

35 year-old female, pancolitis

In remission with 5-ASA since 6 months

Since 10 days, 7-8 bowel movements (2-3 at night, obvious blood, urgency, tenesmus

Cannot sleep at night, significant work impairment



Email/Telephone contact
Outpatient evaluation

STRIDE Consensus in Clinical Practice

- Blood count, CRP, fecal calprotectin, protein, albumin
- Stool culture, Clostridium, parassites

Colonoscopy/RSS

WBC 12000, Hb 10.8, albumin 34 g/L, CRP 3 mg/dL, calprotectin 345, proteins 7.7, negative for infections, Mayo 3 at endoscopy, poor quality of life

Targets

Control of symptoms
Restore quality of life
Mucosal healing

STRIDE Consensus in Clinical Practice

Therapy
Steroids+5-ASA
Steroids+AZA
Anti TNF ± AZA

Planning for target resolution

10-12 weeks

WBC 6800, Hb 13,5, albumin 34 g/L, protein 7.7
PMS 0, good quality of life, CRP 0.5 mg/dL, calprotectin 77
Within 6 months: RSS Mayo 1

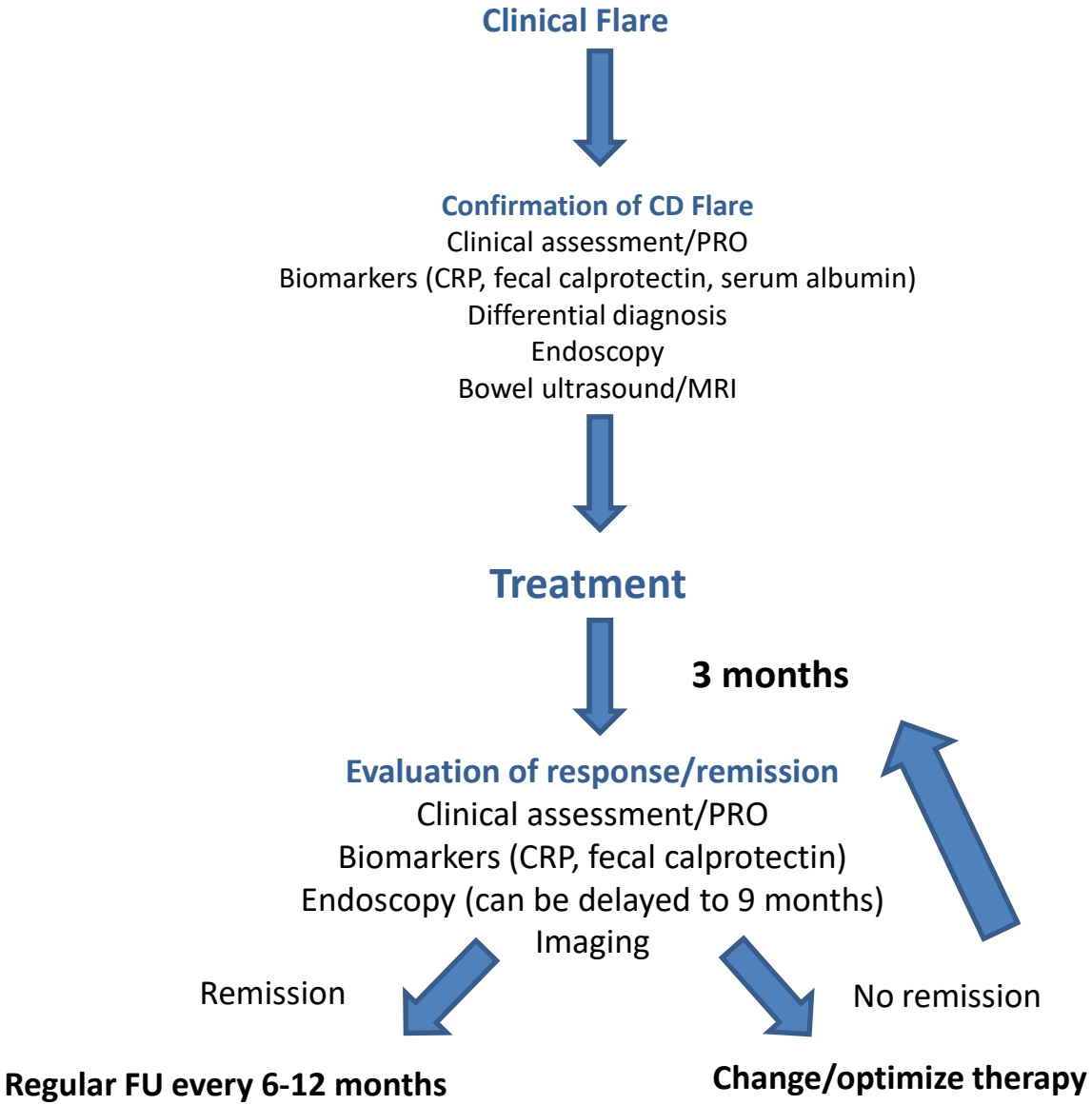
Targets

Control of symptoms ☺
Restore quality of life ☺
Mucosal healing ☺

Next Targets

Maintenance of remission
Maintenance of quality of life
Maintenance of mucosal healing
Prevention of relapse
Prevention of CRC

STRIDE Consensus in Clinical Practice: CD



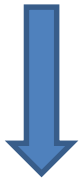
STRIDE Consensus in Clinical Practice

20 year-old male, ileo-colonic Crohn's disease

In remission with azathioprine since 24 months

Since 7 days, 5 bowel movements, nocturnal symptoms, abdominal pain, arthralgia

Cannot sleep at night, disability for joint pain, worsening of quality of life



Email/Telephone contact
Outpatient evaluation

STRIDE Consensus in Clinical Practice

- Blood count, CRP, fecal calprotectin, protein, albumin
- Stool culture, Clostridium, parassites

Colonoscopy/RSS
Bowel ultrasound

WBC 11300, Hb 11.6, albumin 38 g/L, CRP 5 mg/dL, calprotectin 1370, proteins 6.9, negative for infections, SES-CD 18 at endoscopy, poor quality of life, no complications at bowel ultrasound

Targets

Control of symptoms (including EIM)
Restore quality of life and remove disability
Mucosal healing
Maintenance of remission

STRIDE Consensus in Clinical Practice

Therapy
Steroids+AZA
Anti TNF ± AZA

Planning for target resolution

12 weeks

WBC 5400, Hb 13,5, albumin 44 g/L, protein 7.2
HBI=0, resolution of arthralgia, good quality of life, CRP 0.44 mg/dL, calprotectin 27
Within 6-9 months: Endoscopy → SES-CD=3
Bowel ultrasound: resolution of inflammation, absence of complications

Targets

Control of symptoms ☺
Restore quality of life ☺
Mucosal healing ☺

Next Targets

Maintenance of symptom-free remission
Maintenance of quality of life
Maintenance of mucosal healing
Prevention of relapse/bowel damage
Prevention of CRC

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Guideline on the development of new medicinal products for the treatment of Ulcerative Colitis

- New drugs intended for the treatment of UC are expected to **provide symptomatic relief** to the patient based on a documented effect on the inflammatory process

- …**lack of control of inflammation** even in the presence of control of symptoms **is correlated with poor long term outcome**

- **Symptomatic relief should be evaluated by patient related outcomes (PRO)…**Whereas these may be used provided that they are adequately validated, this guideline recommends the **further development and validation of PRO instruments** for the use **as primary outcome parameter in clinical trials in UC**

- A significant effect on both aspects of the disease is required (**co-primary endpoints**). Composite indices should include both symptoms and MH…

Ulcerative Colitis: Clinical Trial Endpoints

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

August 2016
Clinical/Medical

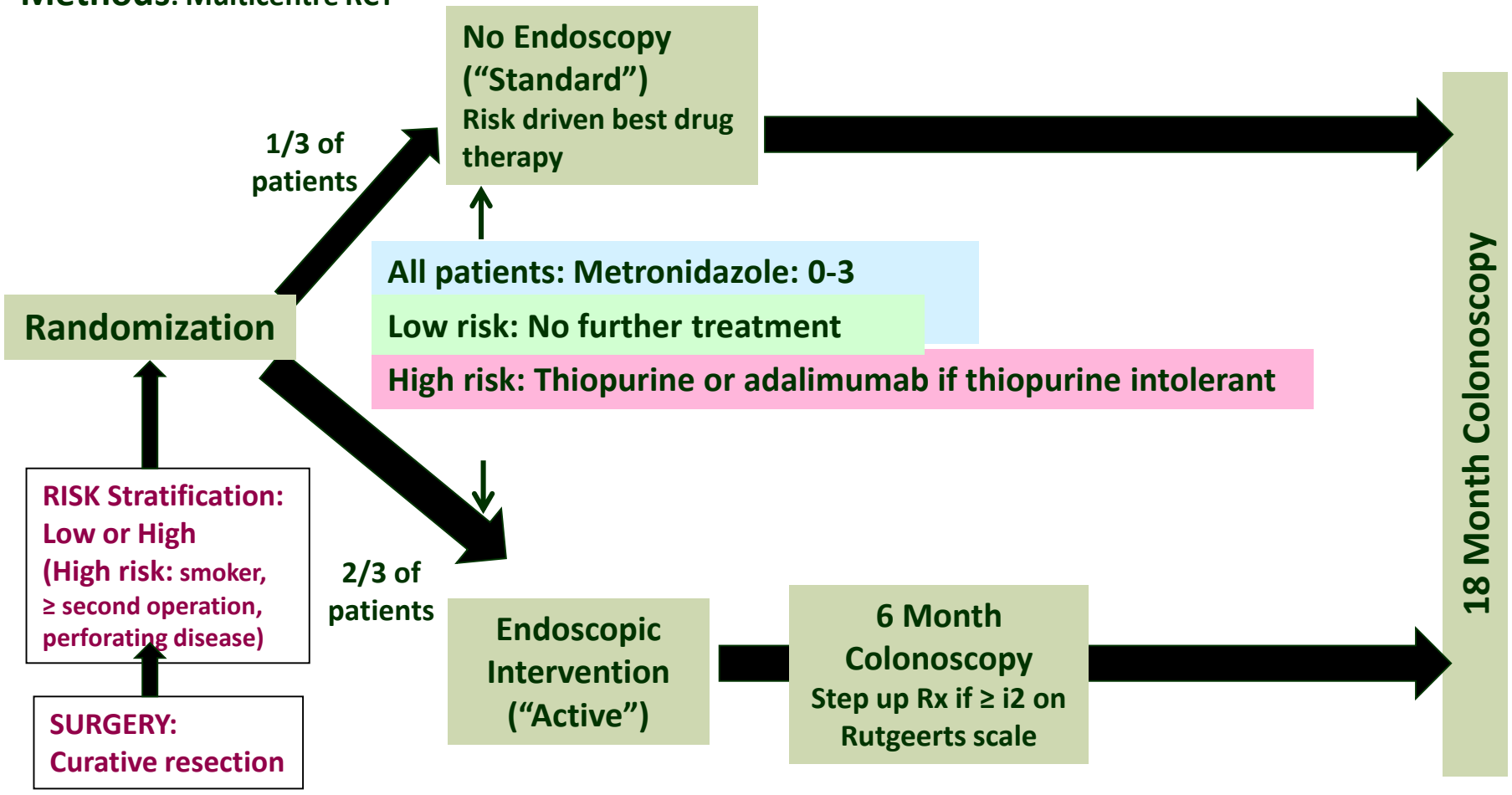
- There are **three clinical outcome assessment types** relevant to the measurement of UC signs and symptoms:
  - **Patient-reported outcome**
  - **Observer-reported outcome**
  - **Clinician-reported outcome**

- FDA believes that the **ideal primary efficacy assessment tool** used in clinical trials to support marketing approval for the treatment of UC would consist of the following scales:
  - A **signs and symptoms assessment scale**, best measured by a **patient-reported outcome**
  - An **endoscopic and histological assessment scale**, best measured by a **clinician-reported outcome instrument**.

Treat to target: what evidence?

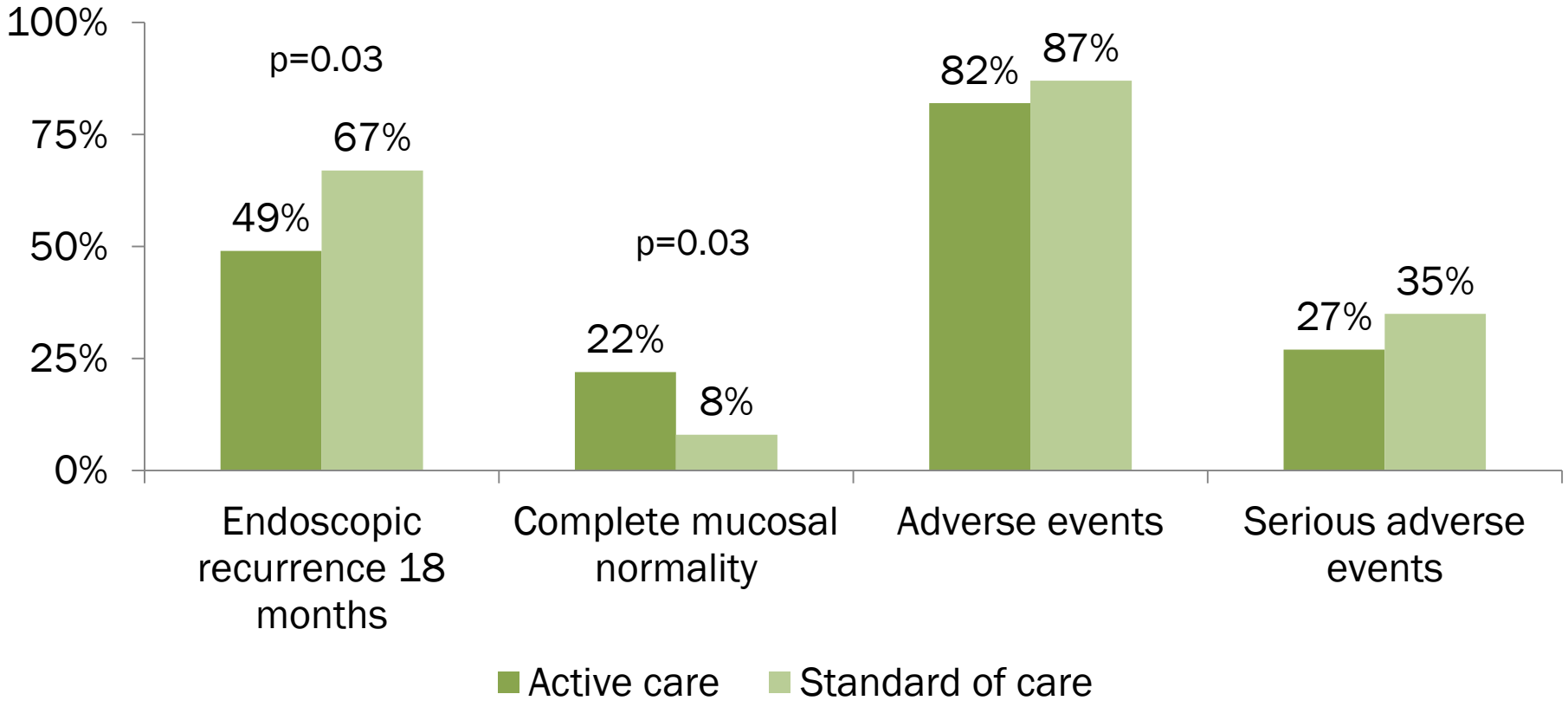
POCER Study: Postoperative Crohn's Disease Endoscopic Recurrence

Methods: Multicentre RCT

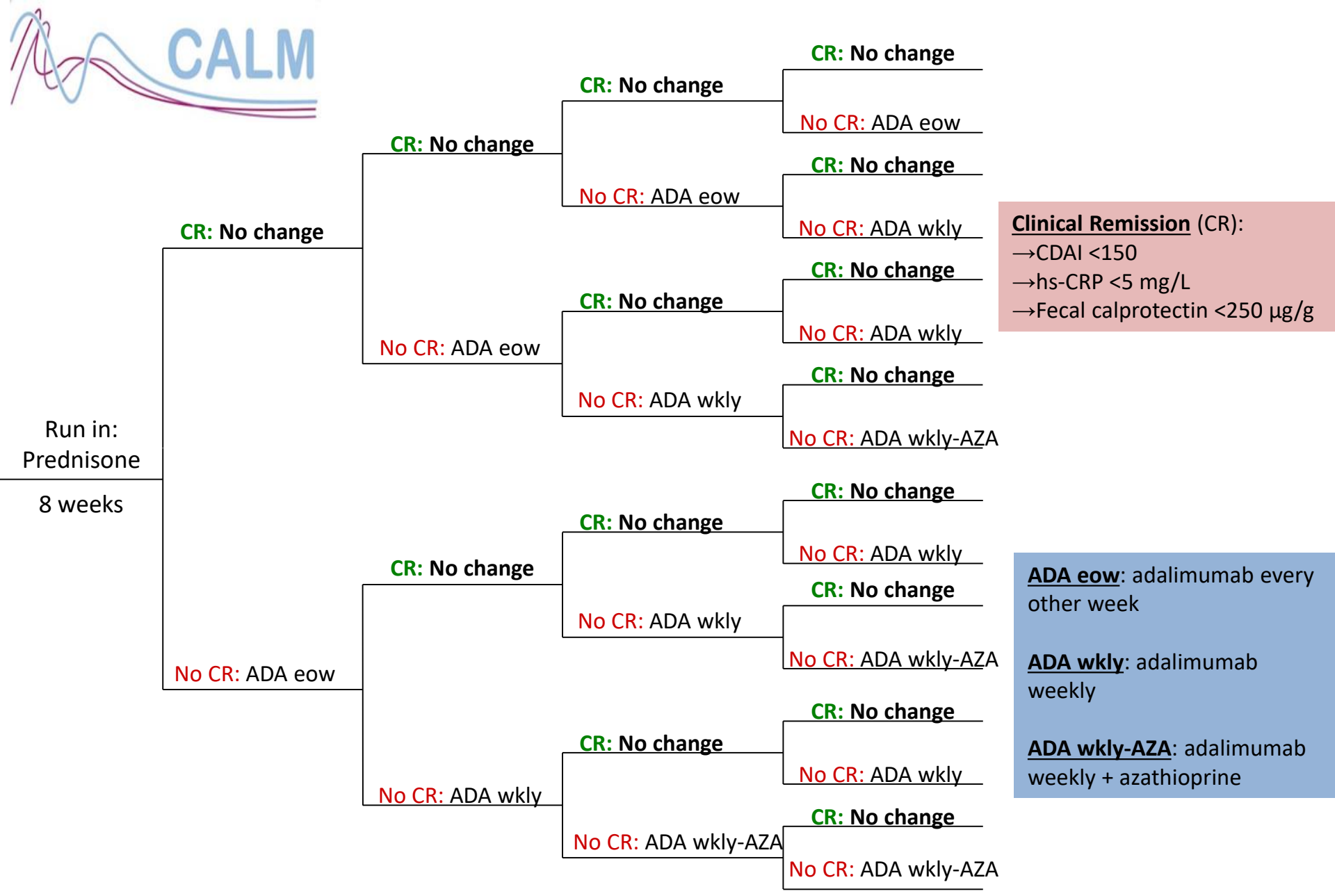


De Cruz et al. Lancet 2015 Volume 385, No. 9976, p1406–1417, 11 April 2015

Results



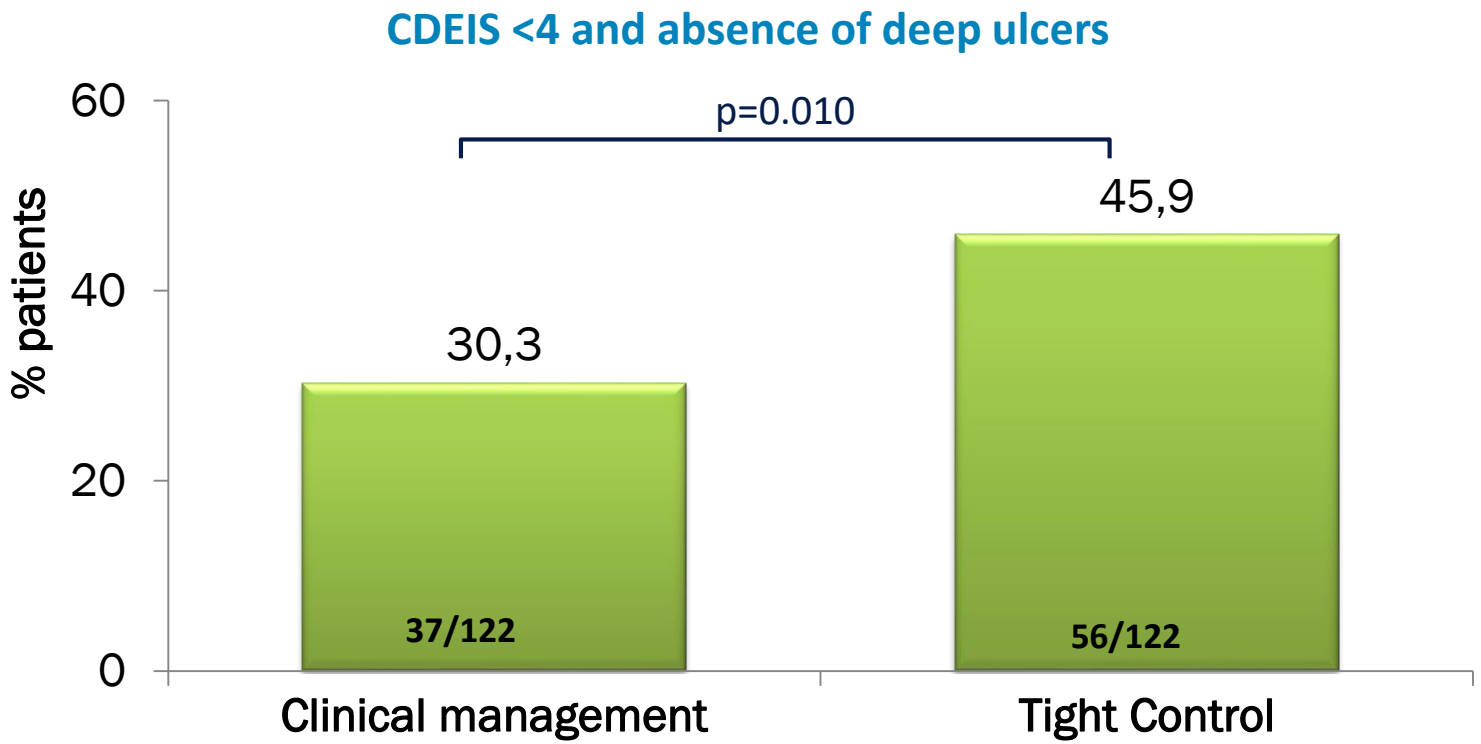
Smoking (odds ratio [OR] 2.4, 95% CI 1.2-4.8, p=0.02) and the **presence of two or more clinical risk factors** including smoking (OR 2.8, 95% CI 1.01-7.7, p=0.05) increased the risk of endoscopic recurrence.



Evaluation of CDAI, hsCRP and fecal calprotectin at week 8, 20, 32 and 44 (**Success criteria visits**)

Change of regimen at week 9, 21, 33, 45 if clinical remission not acheved (**Key visits**)

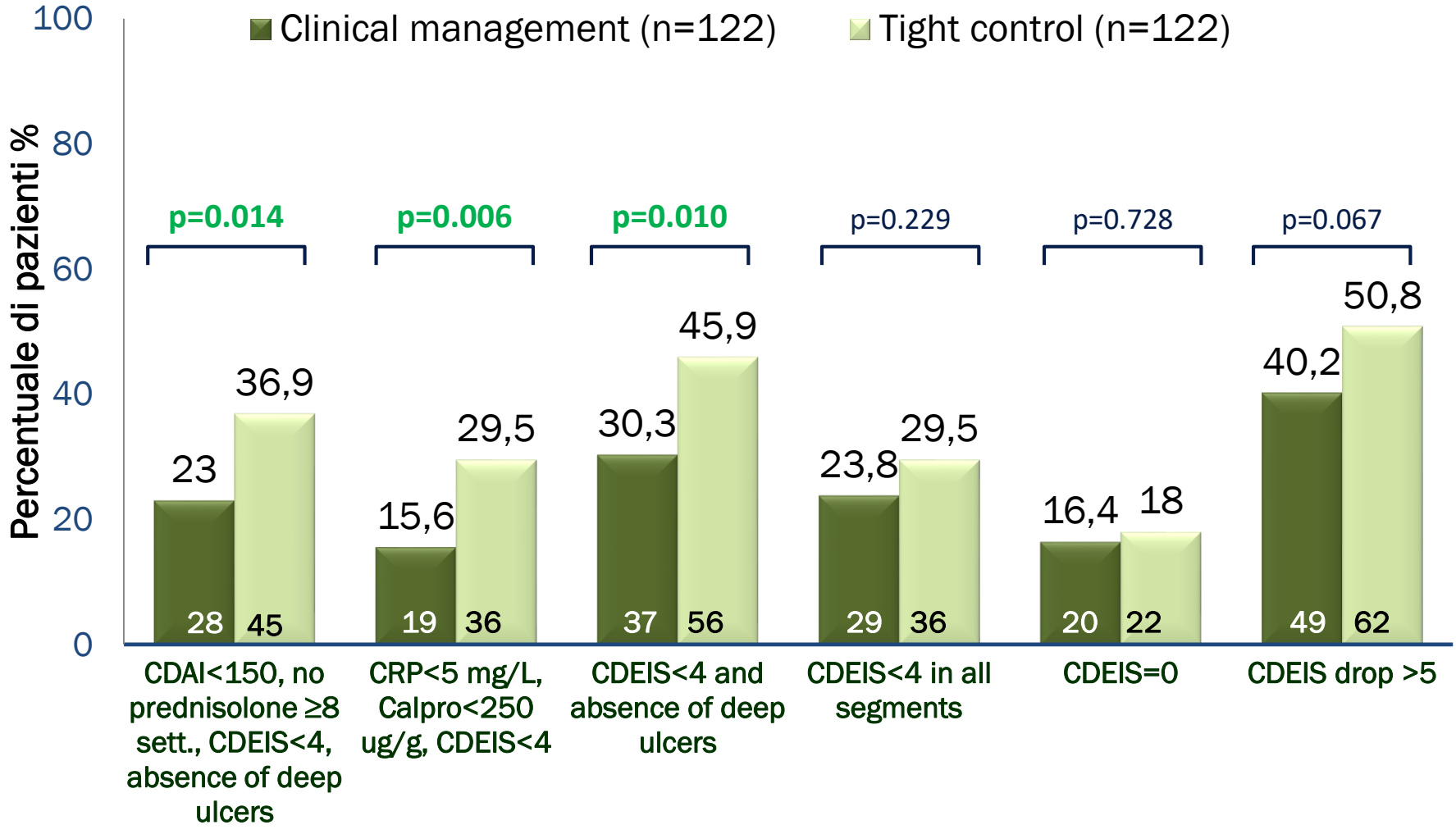
Primary endpoint
Mucosal Healing at week 48



Endoscopic scoring is based on site read.
Cochran-Mantel-Haenszel test stratified by smoking status (yes/no) and weight (<70/≥70 kg) at screening.
Net reclassification improvement (NRI) analysis.

Colombel JF, et al. Gastroenterology 2017;152(Suppl 1):S155
Colombel JF et al. Lancet 2017;
DOI: http://dx.doi.org/10.1016/S0140-6736(17)32641-7

Secondary endpoints at week 48



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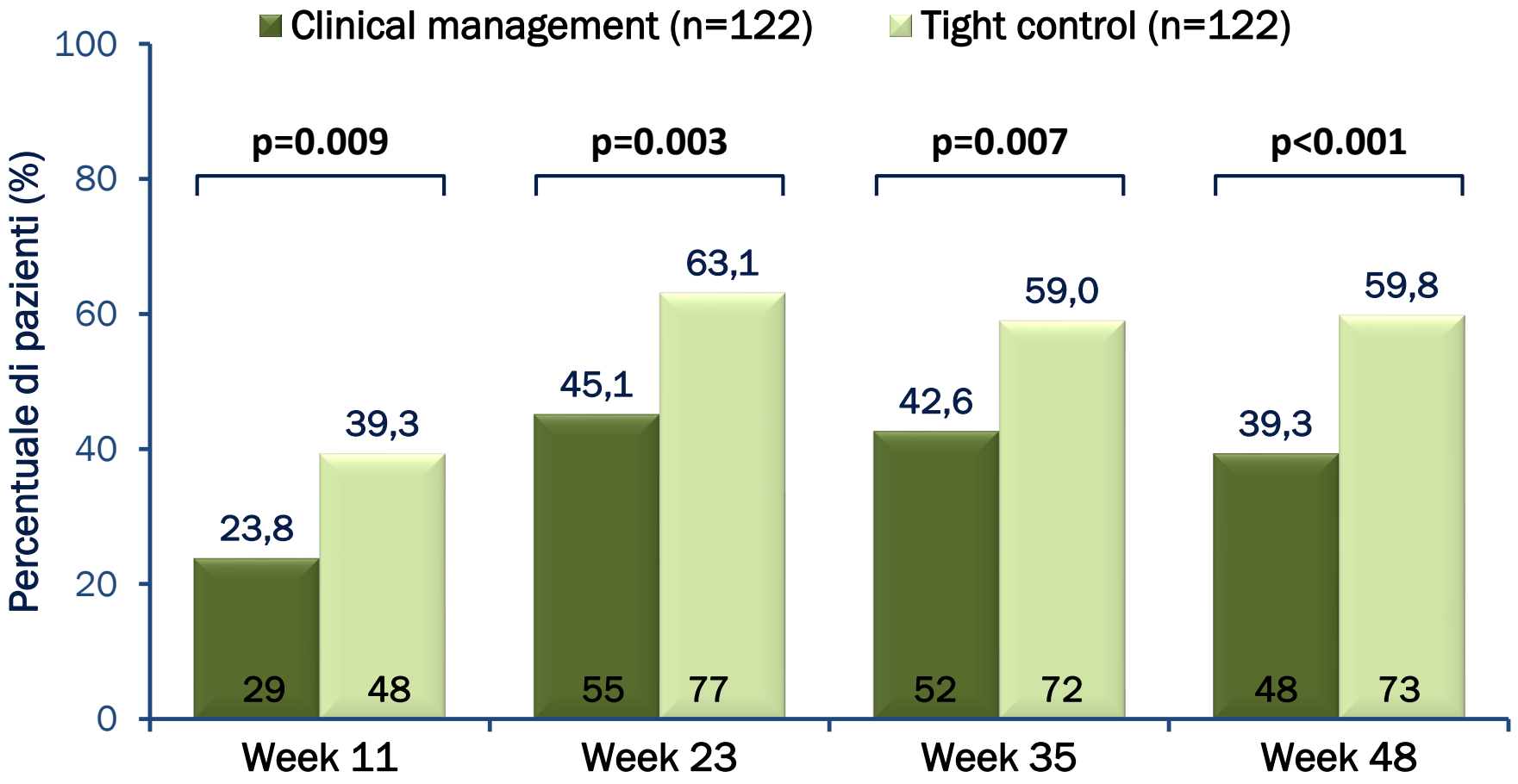
Colombel JF et al. Lancet 2017;
DOI: http://dx.doi.org/10.1016/S0140-6736(17)32641-7

Steroid-free remission



Cochran-Mantel-Haenszel test stratified by smoking status (yes / no) and weight (<70 / ≥70 kg) at screening. NRI analysis.

Colombel JF, et al. Gastroenterology 2017;152(Suppl 1):S155

Colombel JF et al. Lancet 2017; DOI: http://dx.doi.org/10.1016/S0140-6736(17)32641-7

CONCLUSIONS
Pros And Cons of Treat to Target

Pros

Objective measure of inflammation

Timing for changing uneffective therapy

Strategic flow and check

Focus on different aspects of the disease

Cons

Direct robust evidence is still lacking

Time consuming

Next challenge

Validation of PROs
Replacement of colonoscopy with non invasive markers
More evidence on predictors
More evidence on how to tailor T2T approach on individual basis
Clearer indications on the follow-up


IX
CONGRESSO
NAZIONALE
IG-IBD
Where tradition
meets
innovation
IGIBD
the Italian Group for the study of
Inflammatory Bowel Disease
FIRENZE
Convitto della Calza
29 novembre - 1 dicembre 2018

GRAZIE