February 1st 2019,

10th Gastro Foundation Weekend for Fellows; Spier Resort Centre, Stellenbosch

Treat to target in IBD

Gerhard Rogler, Department of Gastroenterology and Hepatology, University Hospital Zürich

UniversitätsSpital Zürich

Universität Zürich[UZH]

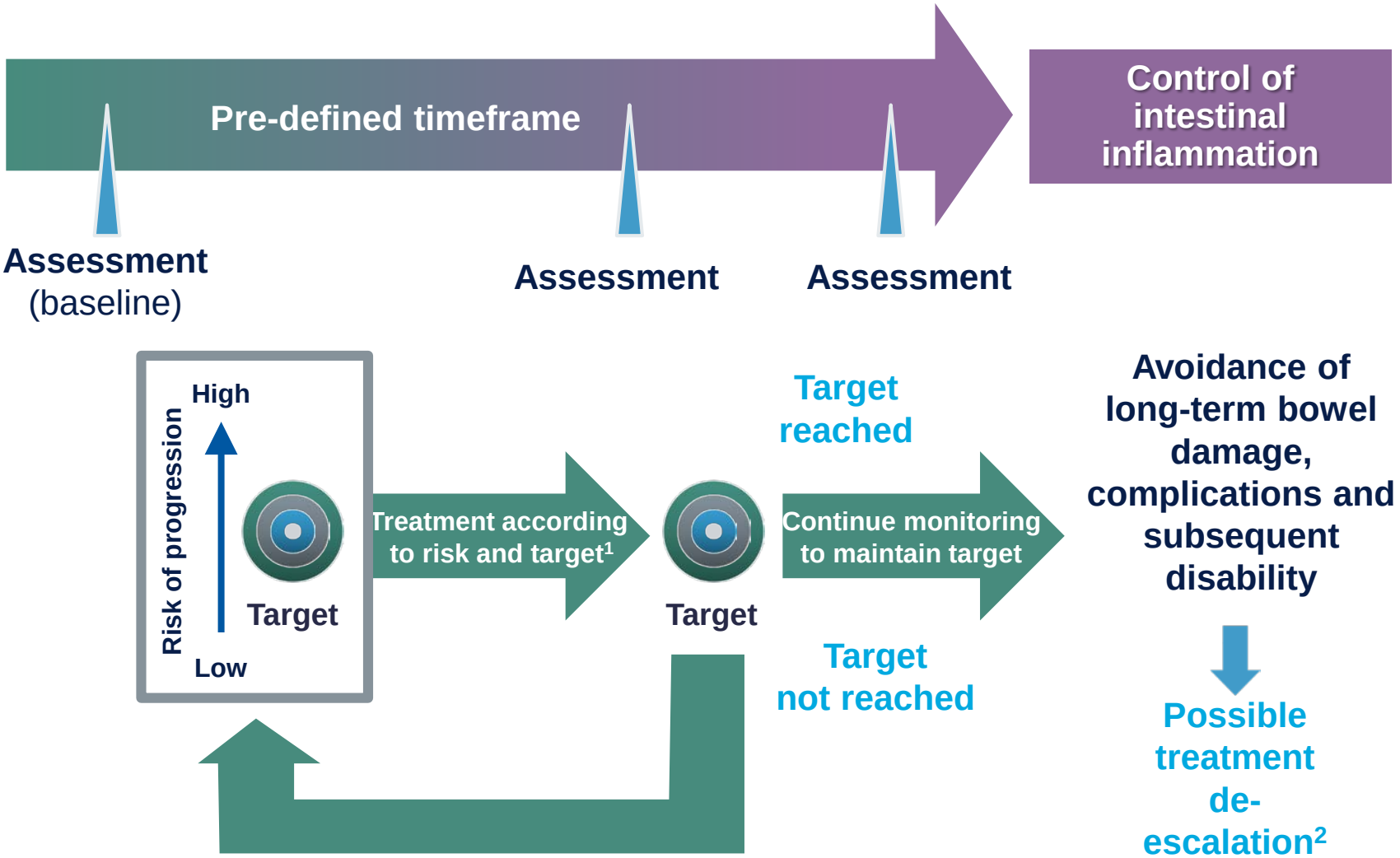
Set the target… Decide the treatment… Assess the target… Reach the target

Patient implication Education Empowerment	Treatment choice Timing Benefit-risk	**Monitoring** Biomarkers Endoscopy/Ultrasound e-health	**Treatment optimisation** Benefit-risk

- What: treatment adaptation and optimisation until the target is reached
- Why: the treatment of a chronic disease for which there is no cure requires a treat-to-target approach

The question is: how to define the target and what is the optimal strategy to reach it

Treat to target concept in IBD



1. Bouguen G, et al. *Clin Gastroenterol Hepatol* 2015;13:1042–50;
2. Colombel JF, et al. *Gastroenterology* 2017;152:351–61

Treat-to-target recommendations in Crohn's disease

the target has 2 dimensions: Quality of Life and intestinal healing

STRIDE

Composite endpoint

Clinical/PRO remission AND **Endoscopic remission**

Defined as resolution of abdominal pain and normalisation of bowel habit

- Assessed at minimum of 3 months during active disease
- Patients' individual goals should also be addressed

Defined as resolution of ulceration

- Should be assessed within 6–9 months after start of therapy
- When endoscopy cannot adequately evaluate inflammation, assess resolution of inflammation by cross-sectional imaging

Adjunctive measures

- **Biomarkers:** CRP and faecal calprotectin are adjunctive measures of inflammation, not targets, for monitoring CD
- **Histology:** histologic remission is not considered a target

CRP, C-reactive protein; PRO, patient-reported outcome

Peyrin-Biroulet L, et al. *Am J Gastroenterol* 2015;110:1324–38

Treat-to-target recommendations in ulcerative colitis

the target has 2 dimensions: Quality of Life and intestinal healing

STRIDE

Composite endpoint

Clinical/PRO remission	AND	Endoscopic remission
Defined as resolution of rectal bleeding and normalisation of bowel habit • Should be assessed at minimum of 3 months during active disease • Patients' individual goals (eg QoL, mood disorders, fatigue, work productivity) should also be addressed: normalisation of QoL as ultimate goal		**Defined as resolution of friability and ulceration at flexible sigmoidoscopy or colonoscopy** (Mayo 0–1) • Should be assessed within 3–6 months after start of therapy

Adjunctive measures of disease activity that may be useful in selected cases

- **Biomarkers:** CRP and faecal calprotectin are adjunctive measures of inflammation, not targets, for monitoring UC
- **Histopathology:** is a sensitive measure of inflammation but is not a target due to lack of evidence of clinical utility

CRP, C-reactive protein; PRO, patient-reported outcome; QoL, quality of life

So, how to apply Treat-to-target in daily practice?

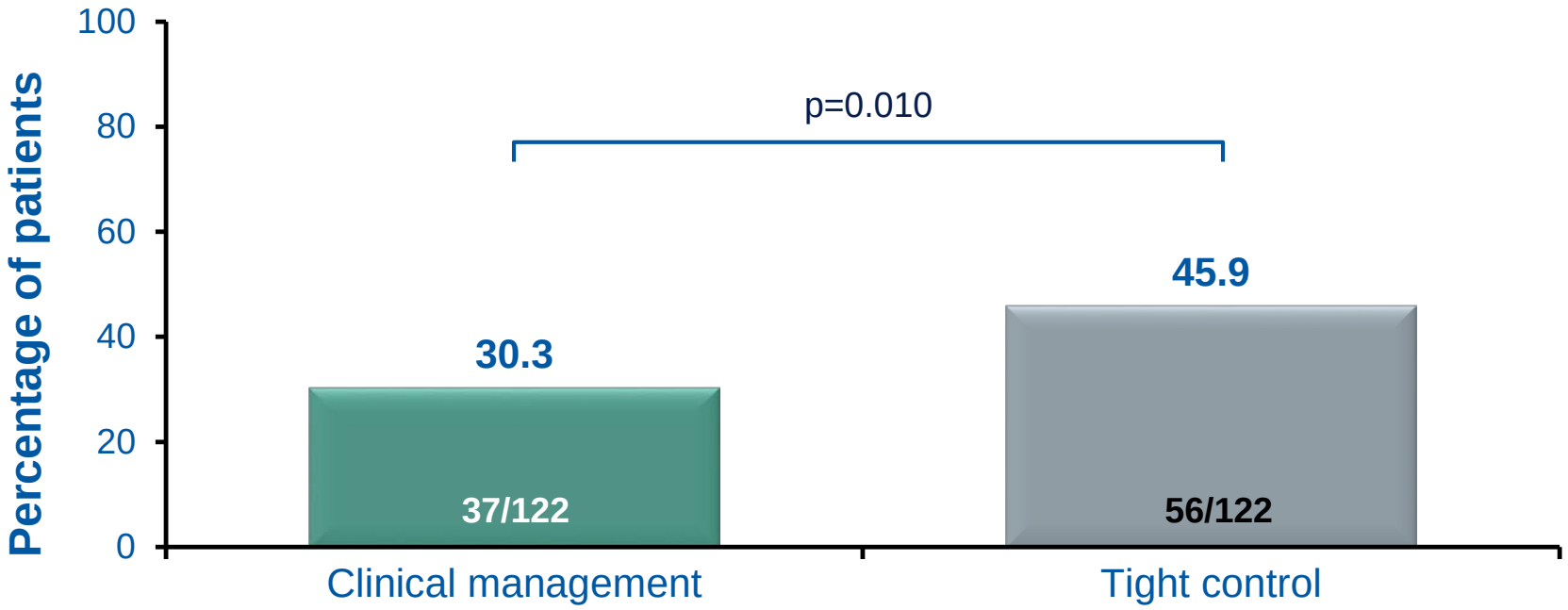
- Tailor and define the target with the patient
- Adapt the treatment strategy and the monitoring to the risk of disease progression and complications
- Optimize benefit/risk and benefit/cost
- Proceed step by step, re-assess and redefine target

Set the target… Decide the treatment… Assess the target… Reach the target

the target has 2 dimensions: Quality of Life and intestinal healing

CALM: primary endpoint at 48 weeks after randomisation

Mucosal healing (CDEIS <4) and no deep ulcerations

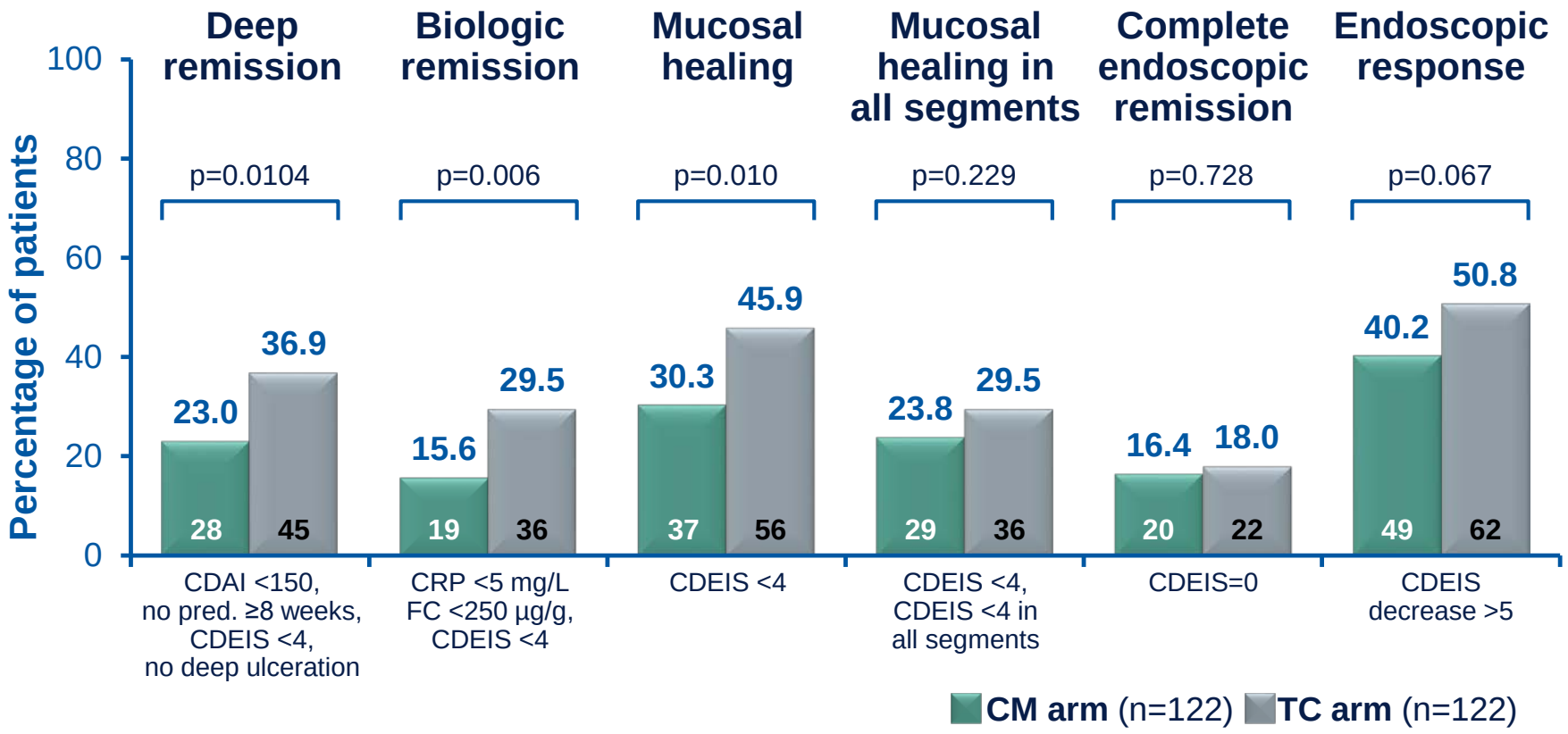


Higher rates of mucosal healing and no deep ulceration observed in early CD when treating to a target of biomarker levels (CRP and faecal calprotectin)**, compared with symptom-driven clinical management**

CDEIS: Crohn's disease endoscopic index of severity

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

CALM: secondary endpoints at 48 weeks after randomisation



Higher rates of mucosal healing and deep remission observed in early CD when treating to a target of biomarker levels (CRP and faecal calprotectin)**, compared with symptom-driven clinical management**

CDAI: Crohn's disease activity index; CDEIS: Crohn's disease endoscopic index of severity; CRP: C-reactive protein; FC: faecal calprotectin; pred.: prednisone

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

Potential benefits and risks of “treat to target”

Benefits

Improved outcomes through better disease monitoring

Disease modification: reduction of damage

Risks

Unrealistic targets: Mucosal healing only achieved in 40% of patients: Rapid rotation of drugs possible, frustrated patients, frustrated physicians

Over-treatment: cost and safety

Increased complexity of treatment algorithms

Risk of immunogenicity

Added risk from endoscopic procedures or invasive tests

Mucosal healing: Lack of a “common definition”

“Working definition” for mucosal healing:

- UC: Mayo score of ≤1
- CD: abscence of ulcers >5 mm

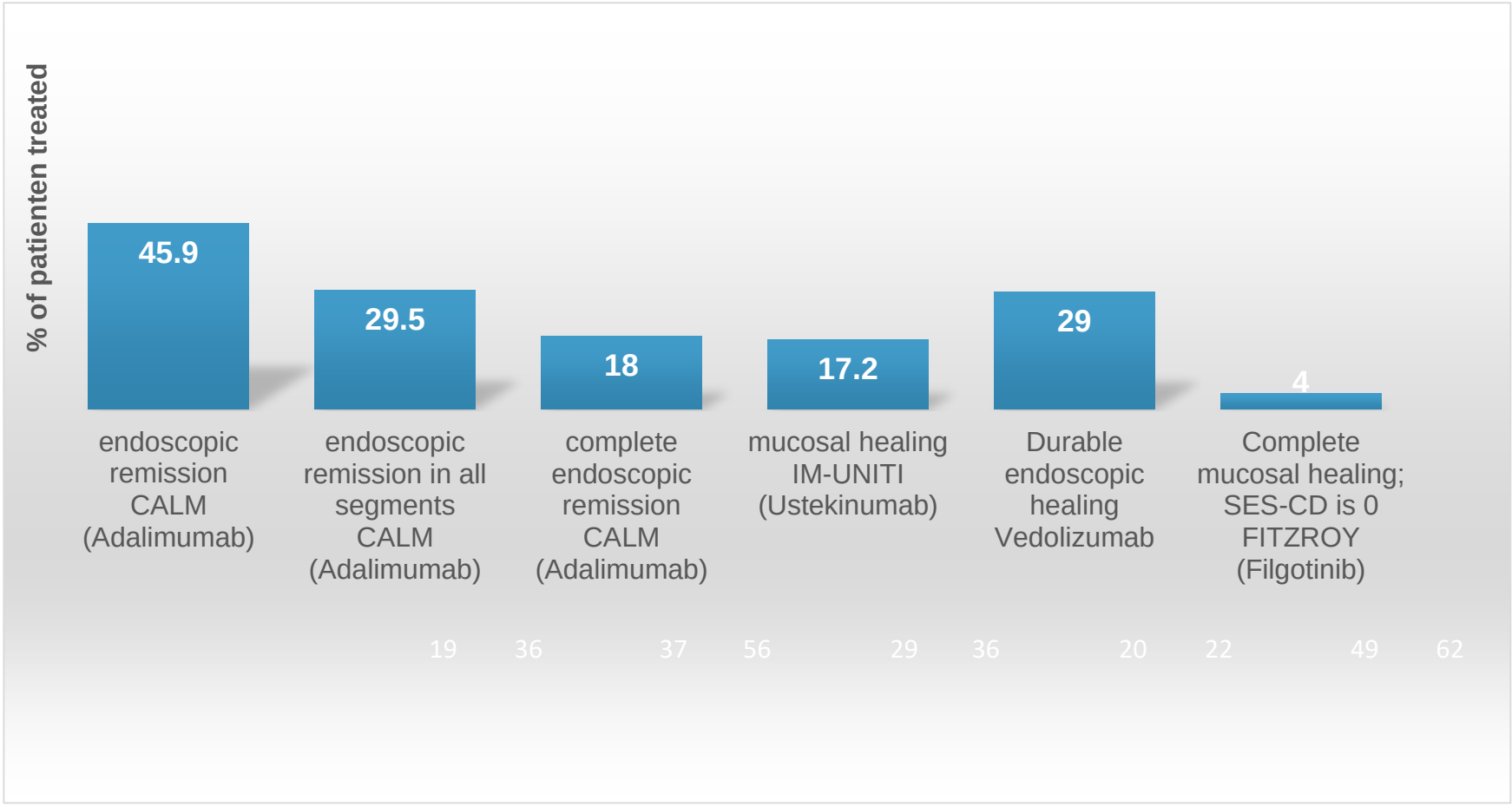
Alternative: quantitative endpoints (CDEIS, SES-CD, UCEIS)

- More responsive to change
- Complex as a treatment goal, not realistic in daily practice

Evidence for the working definition for mucosal healing?

- Association with relevant long-term outcomes
- No evidence for treating to these goals

Mucosal healing rates in recent clinical trials in CD

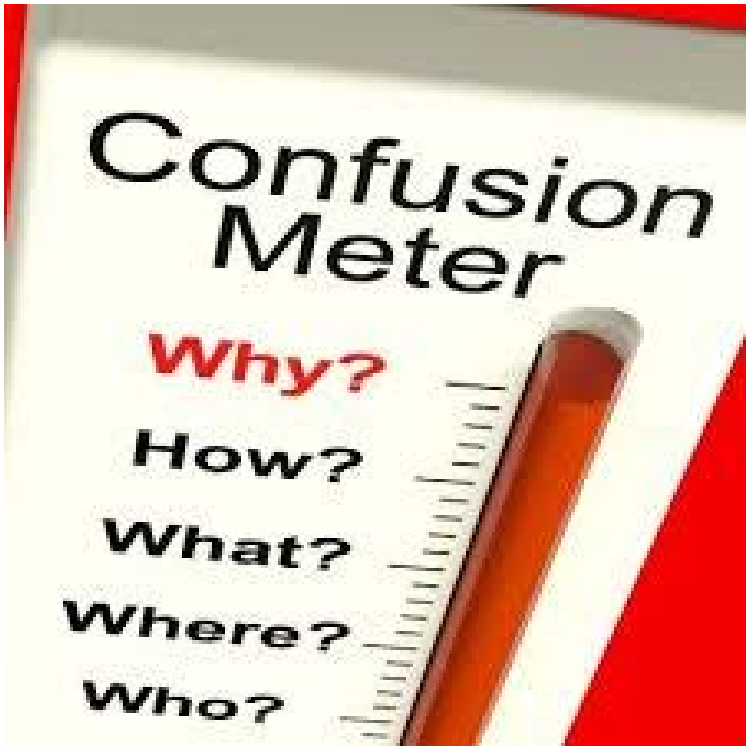


Colombel JF, et al. Gastroenterology 2017;152(Suppl 1):S155.
Colombel JF, et al. Gastroenterology 2017;152(Suppl 1):S155.
Colombel JF, et al. Gastroenterology 2017;152(Suppl 1):S155.
Rutgeerts P et al. UEGW 2016 #OP 104
Noman et al, J Crohns Colitis. 2017 Sep 1;11(9):1085-1089.
Vermeire S, et al. Lancet. 2017 Jan 21;389(10066):266-275.

People with good intentions
make promises.
People with good character
keep them.

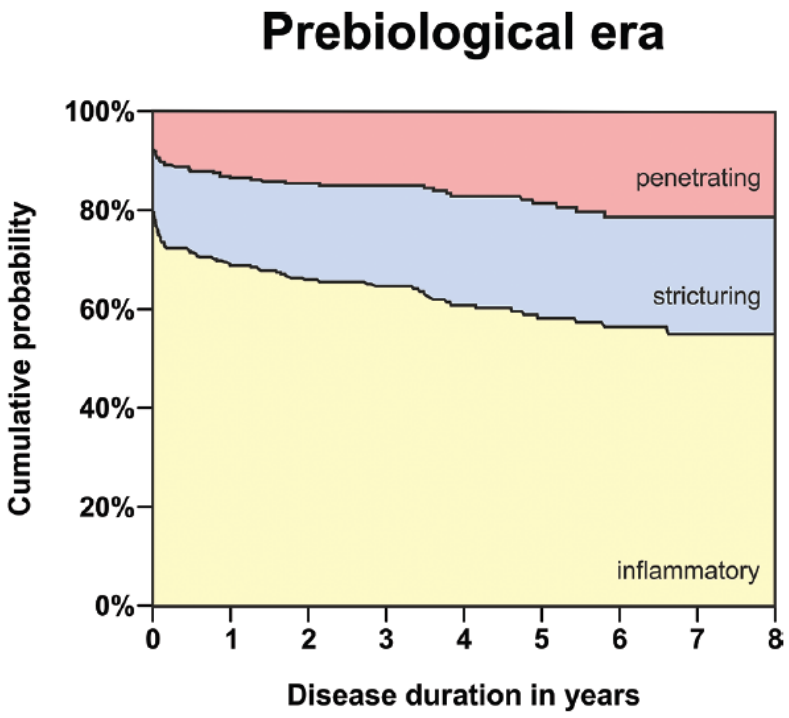
- Unknown

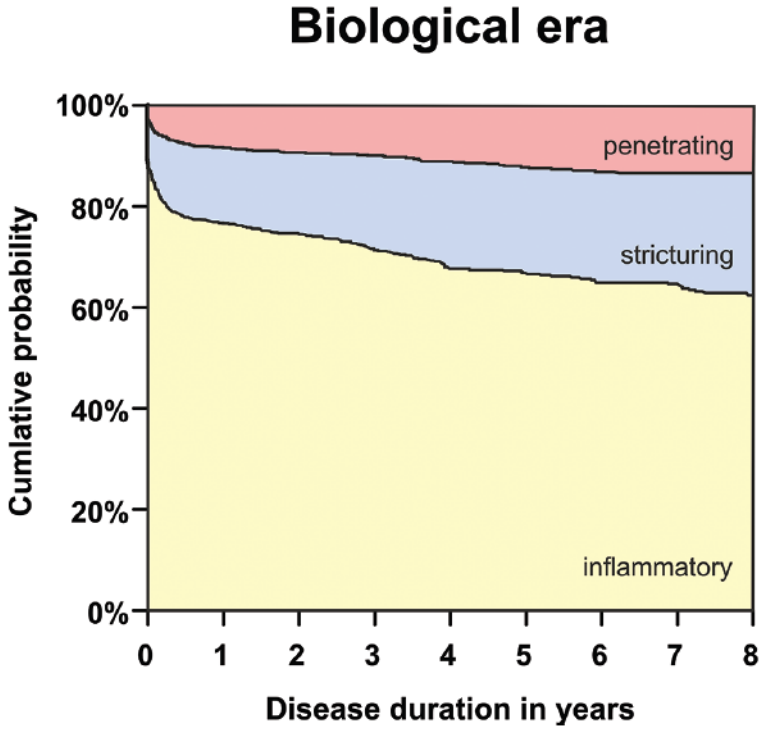
Changing treatments too early due to “unmet targets”



Does current medical therapy prevent intestinal damage?

Incident IBD cases South-Limburg Area; Population-based IBD cohort with >93% coverage
«Pre-biological cohort»: 1991-1998
«Biologic cohort»: 1999 – 2011 (Follow up until 2014)





➔ **Similar risk to develop fibrosis in the pre- and biological era**

Treat to target in other diseases: Always beneficial?

- 2015 ADA/EASD position statement on treatment of T2D: therapy should be escalated every 3 months if patients do not achieve target HbA1c [1]
- A study of more than 40,000 T2D patients in 5 European countries and in the US, reveals that only 8.1% reached target at 3 months [2]
- More recent RCTs and meta-analyses have shown no difference of intensive glycemic control vs. a conventional approach (an HbA1c level of approximately 8.0% [3,4]
- In contrast, a 2- to 3-fold increase in the risk of hypoglycemia with intensive treatment was found [3,4]
- Hypoglycemia is associated with cardiovascular events, cognitive impairment, fractures, death, and decreased quality of life. [5,6]

[1] *Diabetes Care. 2015;38:140-149*
[2] *Diabetes Obes Metab. 2017; DOI:10.1111/dom.12927*
[3] *Montori VM, et al Ann Intern Med. 2009;150(11):803–808.*
[4] *Hemmingsen B, et al. Cochrane Database Syst Rev. 2013;(11):CD008143.*
[5] *McCoy RG, et al. Endocr Pract. 2013;19(5):792–799.*
[6] *McCoy RG, et al. Diabetes Care. 2012;35(9):1897–1901.*

“Treat to target” must be individualized

- Mucosal healing only achieved in 40% of patients: Rapid rotation of drugs possible, frustrated patients, frustrated physicians
- Risk of over-treatment: risk/benefit studies are missing
- Increased complexity of treatment algorithms/too rapid rotation of drugs
- Added risk from endoscopic procedures or invasive tests
- Treat to target is seen now more critical also in other diseases
- **Treatment target need to be individualized!!!**

Thank you for your attention