



5-ASA Therapy for Ulcerative Colitis: Positioning and Efficacy

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Malattie Infiammatorie
Croniche Intestinali

DISCLOSURES

	<i>Paolo Gionchetti</i>
Receipt of honoraria or consultation fees	Janssen, Abbvie, Pfizer, Celgene, Takeda, Ferring, MSD, Alfa-Sigma, Amgen, Gilead, Arena, Galapagos, Celltrion, Biogen, Eli-Lilly
Participation in a company sponsored speaker's bureau	Abbvie, Janssen, Takeda, Ferring, Msd, Sofar, Chiesi, Biogen, Eli-Lilly, Alfa-Sigma, Galapagos
Stock shareholder	None
Other support (please specify)	None

Mesalazine in Ulcerative colitis

Standard of care for the treatment and maintenance
of mild to moderate ulcerative colitis

Mesalazine formulations

Oral Branded Formulations

- **pH-dependent**

Eudragit S

Eudragit L

Eudragit FS30D

- **pH & T-dependent**

- **Azoderivatives**

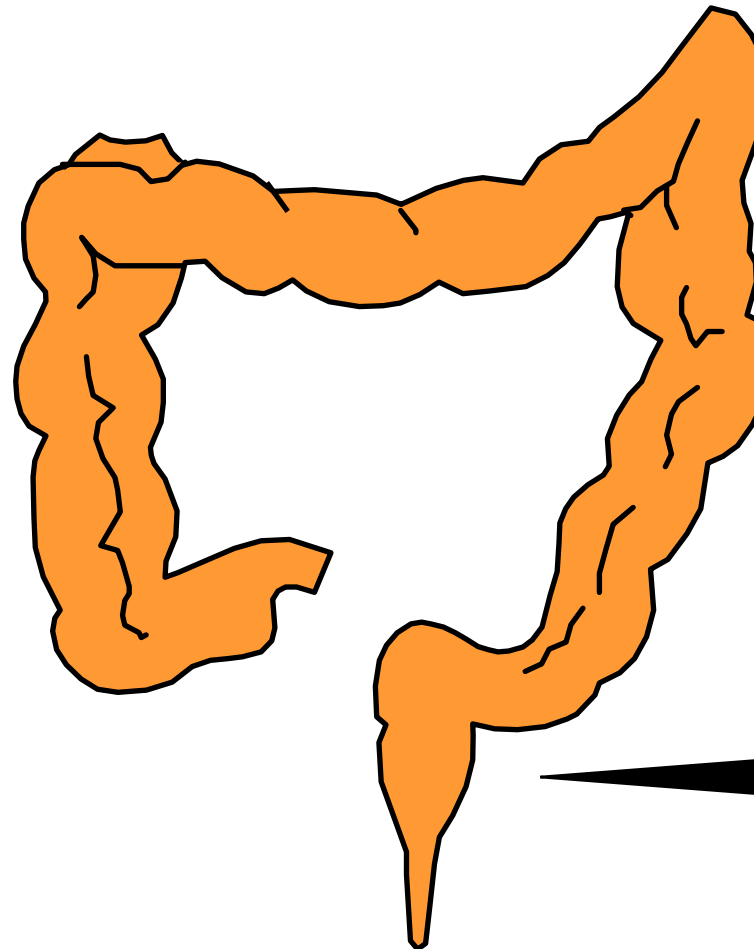
- **MMX Technology**

Topical Formulations

Enemas

Foams

Gels



Suppositories

Management of mild-moderate attacks

Distal Colitis

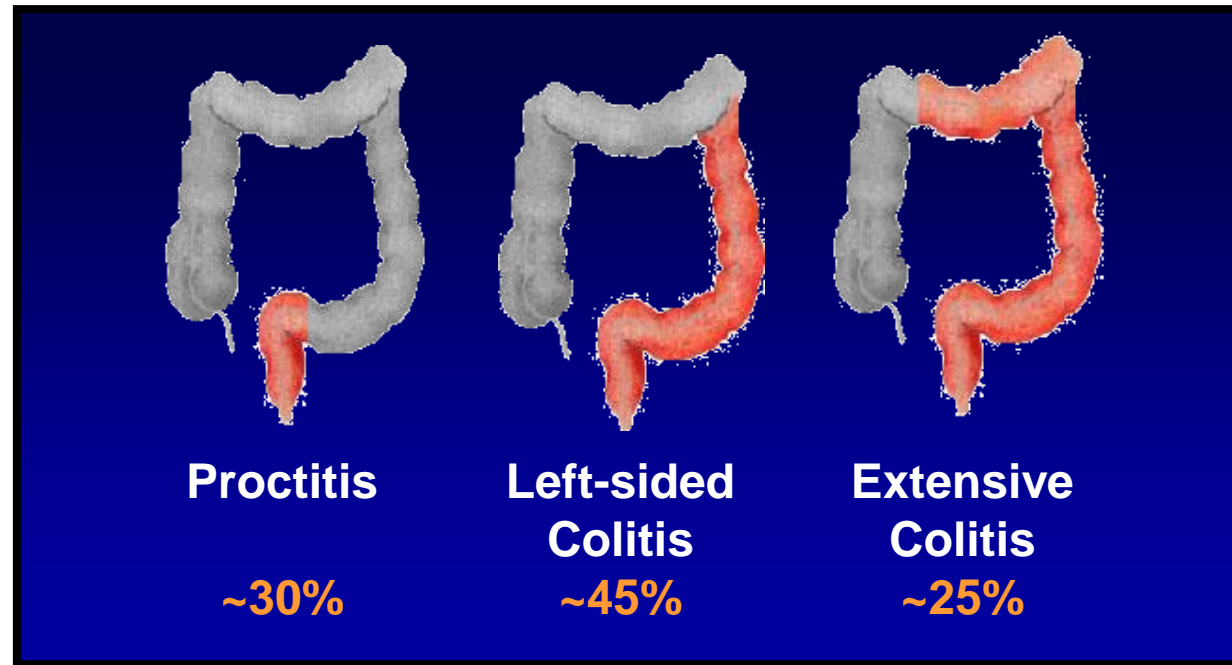
Extensive Colitis

Management of mild-moderate attacks

Distal Colitis

Extensive Colitis

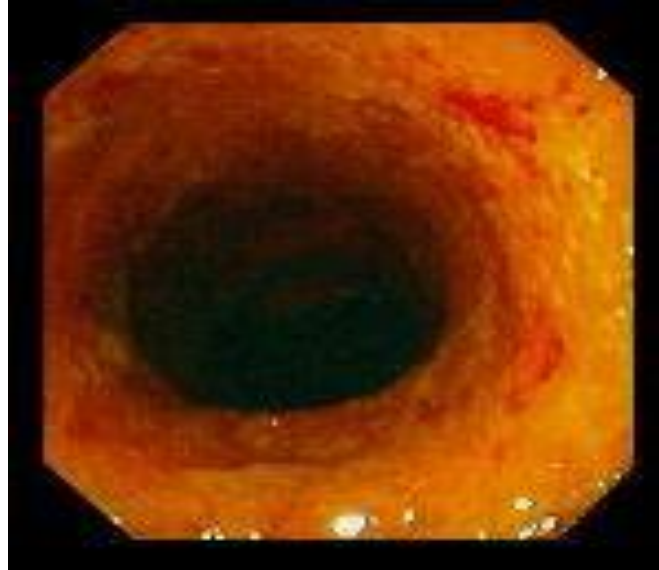
Montreal Classification of Ulcerative Colitis by Endoscopic Extent of Disease



Appears to be useful in distinguishing patients by medical therapy, surveillance management and prognosis



Topical treatment in UC



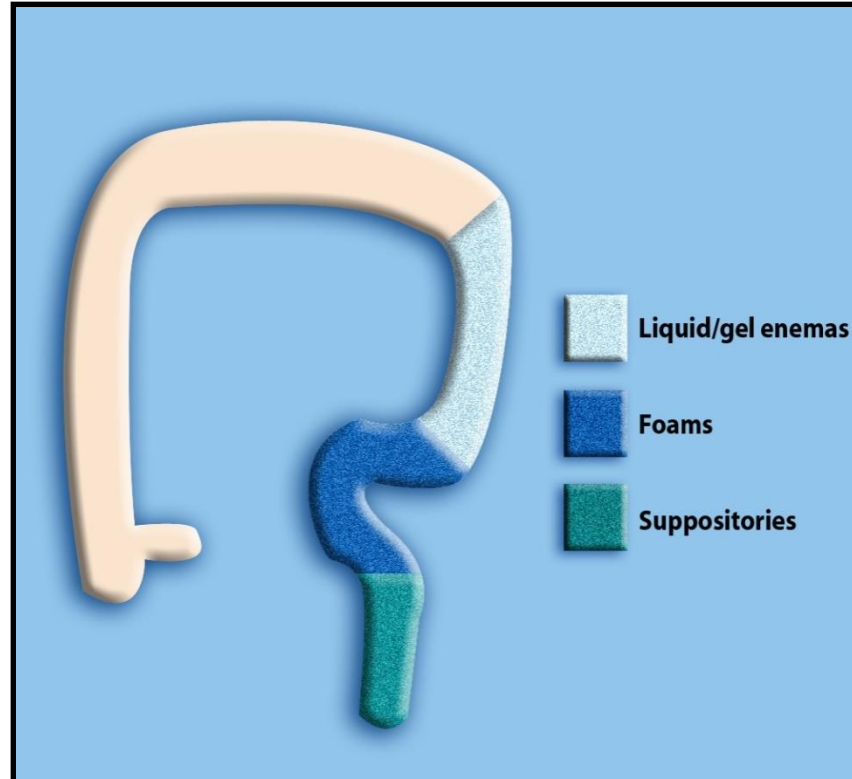
Possibility to administer high doses of active ingredient directly to the superficially inflamed mucosa

Volume is the Key Factor

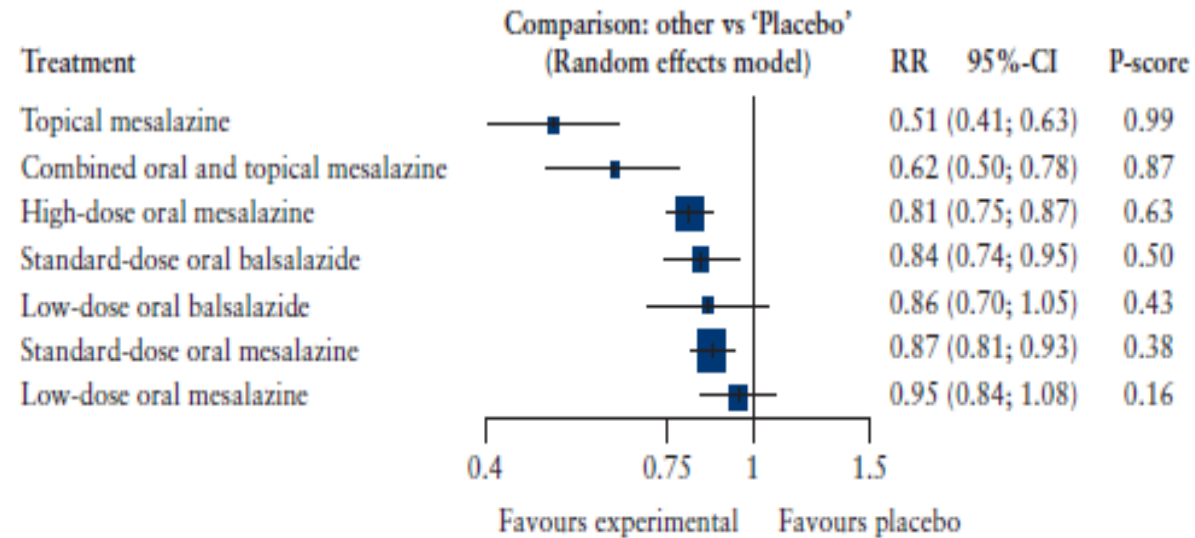


Treatment of Active Distal UC

- Topical therapy preferred treatment
- Corticosteroids and 5-ASAs available in many forms
 - suppositories reach the upper rectum
 - enemas reach splenic flexure and the distal transverse colon



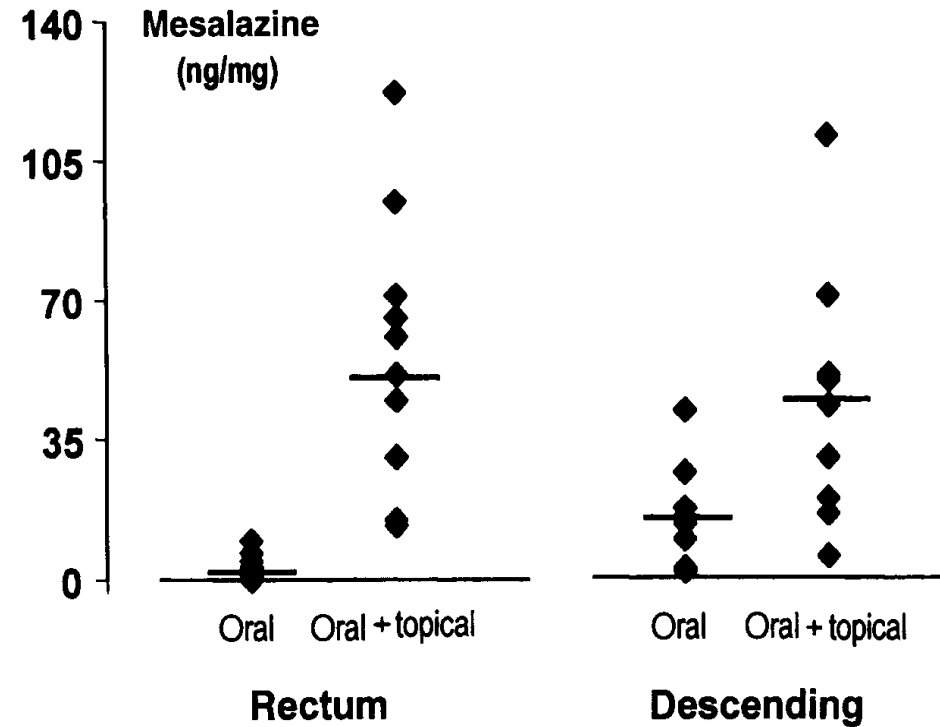
Efficacy of Oral, Topical, or Combined Oral and Topical 5-Aminosalicylates, in Ulcerative Colitis: Systematic Review and Network Meta-analysis



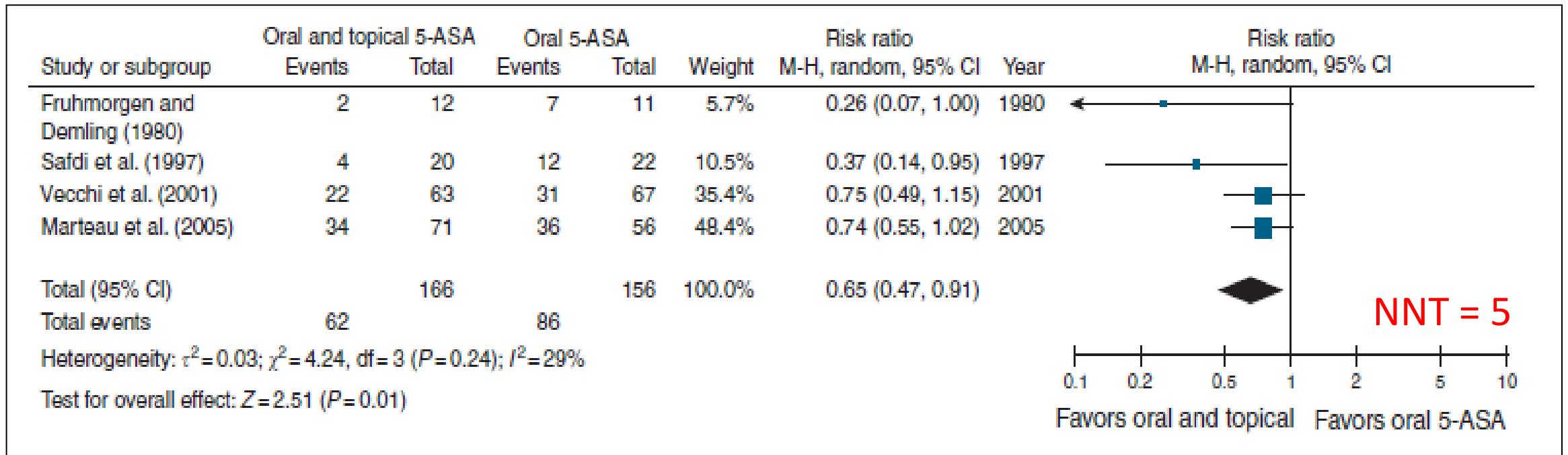
Limited exposure of distal colon to orally-dosed formulation in active distal UC

Stasis in the right colon together with the faster transit in active distal ulcerative colitis determine a reduced exposure of the distal colon to orally-dosed topical agents.

Rectal and colonic mesalazine concentration in UC: oral vs oral plus topical treatment



Oral vs combined (oral+rectal) mesalazine in the induction of remission in left-sided and extensive ulcerative colitis.



Management of mild-moderate attacks

Distal Colitis

Extensive Colitis

Non usiamo i generici
della mesalazina orale!!!
(non ne conosciamo il rilascio)

Oral mesalazine vs placebo in the induction of remission and improvement - Clinical -

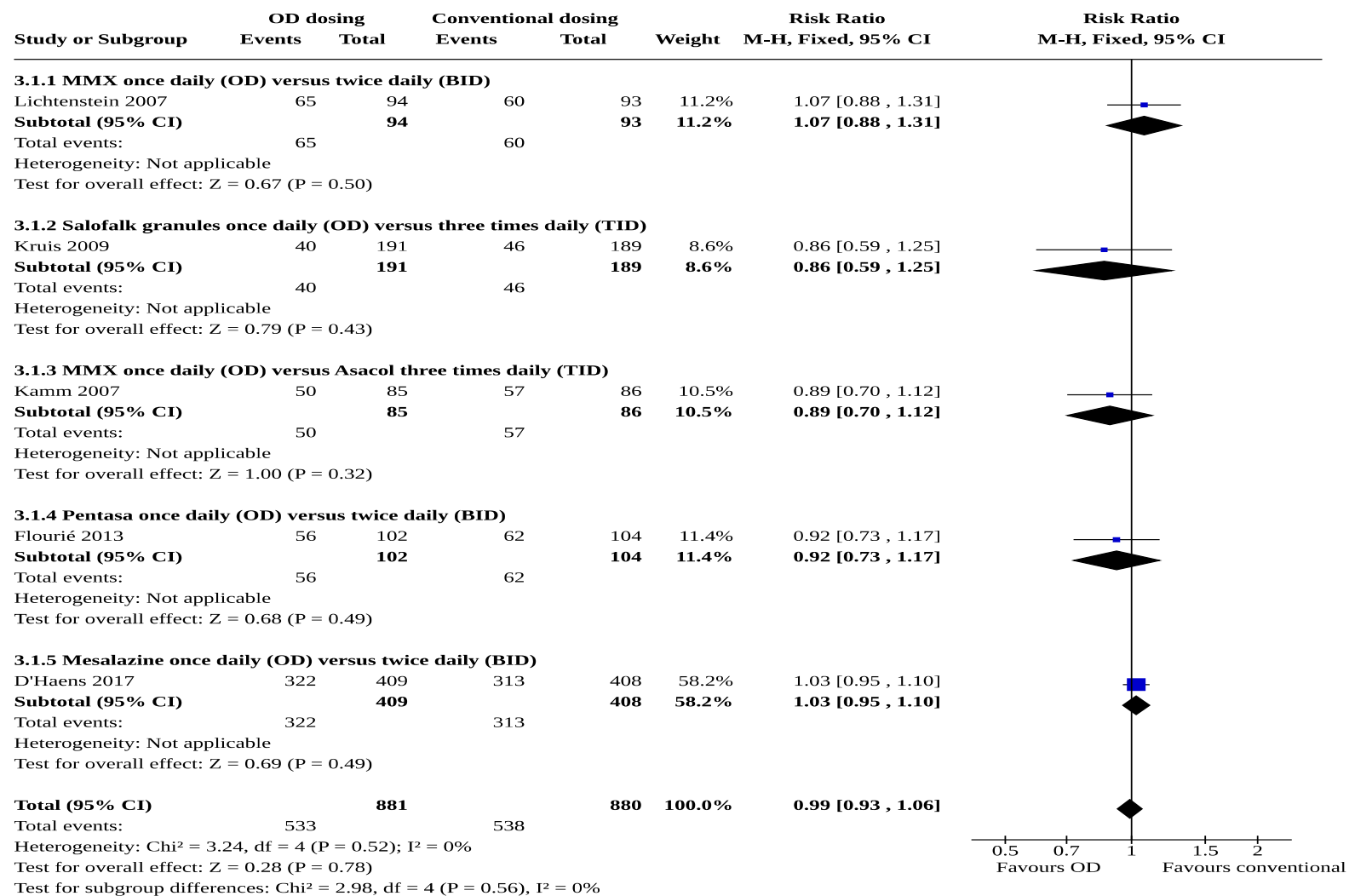
Daily dosage	M/P	Failure to induce remission	M/P	Failure to Induce remission/improvement
<2.0 g	156/75	0.92 (0.84-1.02)	156/75	0.79 (0.64-0.97)
2.0-2.9 g	619/337	0.88 (0.82-0.94)	565/312	0.77 (0.67-0.88)
≥ 3.0 g	775/425	0.83 (0.77-0.88)	738/410	0.57 (0.51-0.65)
Total	1550/837	0.86 (0.82-0.89)	1454/797	0.68 (0.61-0.75)

Oral Mesalazine vs placebo in the induction of remission and improvement - Endoscopy -

Daily dosage	M/P	Failure to induce remission	M/P	Failure to induce remission/improvement
<2.0 g	92/30	0.85 (0.64-1.14)	NA	NA
2.0-2.9 g	275/118	0.86 (0.70-1.05)	157/108	0.73 (0.58-0.92)
≥ 3.0 g	438/201	0.70 (0.56-0.87)	98/53	0.69 (0.49-0.96)
Total	805/349	0.77 (0.67-0.89)	255/161	0.71 (0.59-0.86)

Mesalazine once-daily vs conventional dosage in ulcerative colitis

Induction of remission



ECCO Guidelines: medical treatment of mild-moderate active ulcerative colitis



R1: We recommend 5-aminosalicylates at a dose of ≥ 2 g/ day [d] to induce remission in patients with mildly-to-moderately active UC [strong recommendation; quality of evidence low].

R2: We recommend topical [rectal] 5-ASA at a dose of ≥ 1 g/d for the induction of remission in active distal colitis [strong recommendation, low-quality evidence].

R3: We suggest the use of oral 5-ASA [≥ 2 g/d] combined with topical [rectal] 5-ASA over oral 5-ASA monotherapy for induction of remission in adult patients with active UC of at least rectosigmoid extent [weak recommendation; very low-quality evidence]

Mesalazine in mild-moderate active ulcerative colitis

- Take-home messages: optimize!! -

- **First choice!!**
- Oral: dose-dependent effect (≥ 3 g/d); once daily favours adherence while not affecting efficacy
- Rectal: early effect, likely not dose-dependent, volume more important, maybe the only treatment in distal forms
- Combined Therapy: more effective and more rapid, particularly needed in extensive forms
- Duration: 6 to 8 weeks but evaluation at 10-14 days
- Effectiveness in 70-80 %

Do not forget mesalazine, particularly the topical formulations, as adjuvants also in more complex/active patients!

Mesalazine in ulcerative colitis

Maintenance of remission

Extent of disease is a prediction of disease severity

- At diagnosis:
 - 30–50% rectum or sigmoid
 - 20–30% left-sided
 - **20% pancolitis**

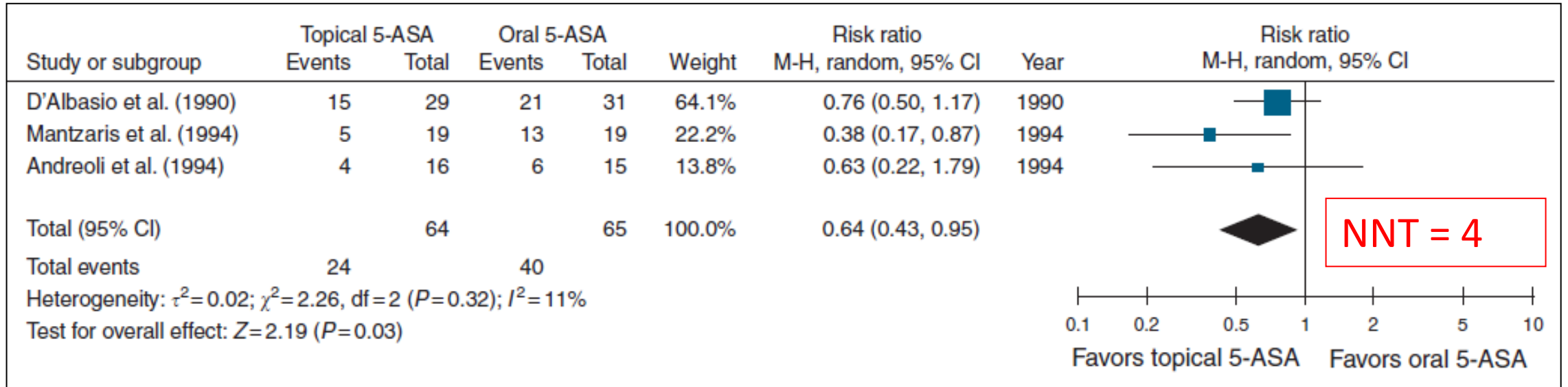
Approximately 30-50%
progress to more
extensive disease

- More extensive disease is associated with:
 - More severe symptoms
 - Higher risk of colectomy (about 4x)

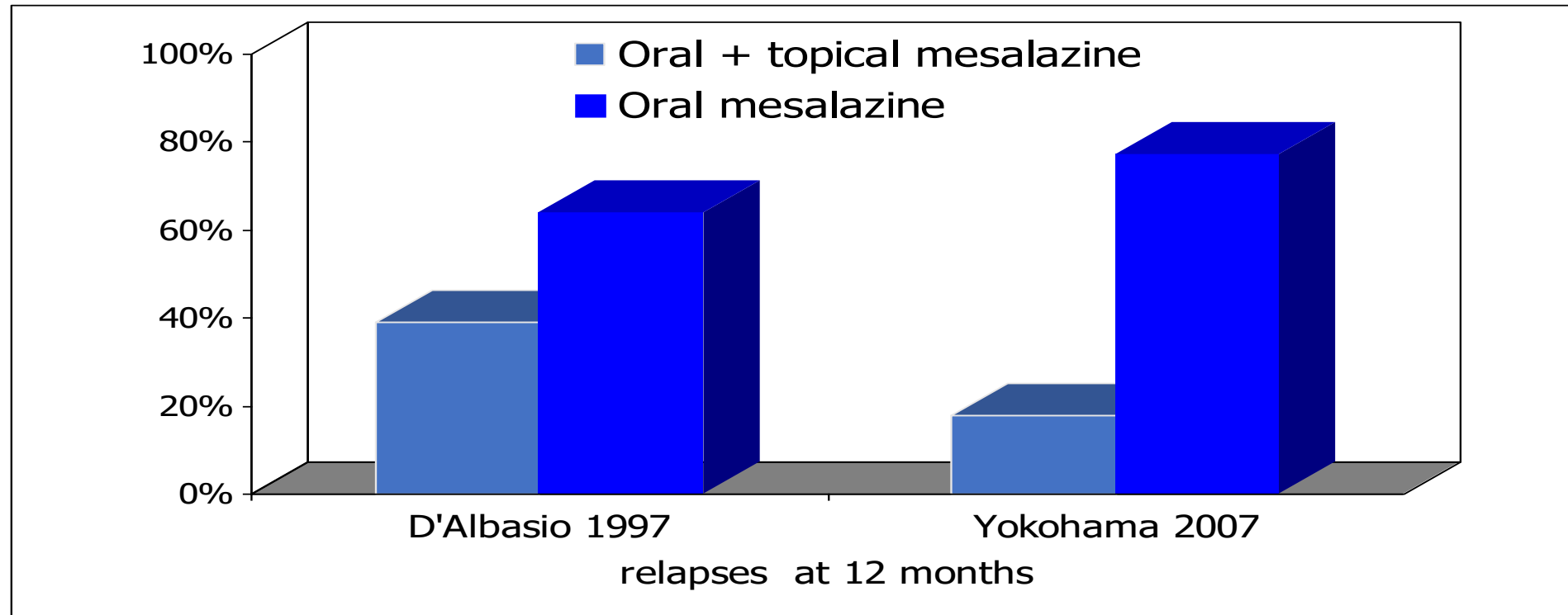
Mesalazine vs placebo in the maintenance treatment of ulcerative colitis

Daily dosage	M/P	Maintenance of clinical or endoscopic remission at 6-12 months
<1.0 g	90/43	0.77 (0.59-1.00)
1.0-1.9 g	665/451	0.65 (0.56-0.76)
≥ 2.0 g	152/154	0.73 (0.60-0.89)
Total	907/648	0.68 (0.61-0.77)

Oral vs Rectal Mesalazine in the prevention of ulcerative proctitis recurrence



Oral vs combined oral+rectal mesalazine in relapse prevention of left colitis



Pooled RR of relapse 0.48 (95% CI = 0.17– 1.38)

ECCO Guidelines: Maintenance of remission in mildly-to-moderately active ulcerative colitis



R8: We recommend the use of oral 5-ASA at a dose ≥ 2 g/day for maintenance of remission in UC patients [strong recommendation; very low quality of evidence].

R9: We suggest the use of topical [rectal] 5-ASA for the maintenance of remission in patients with distal UC [weak recommendation, very low quality evidence]

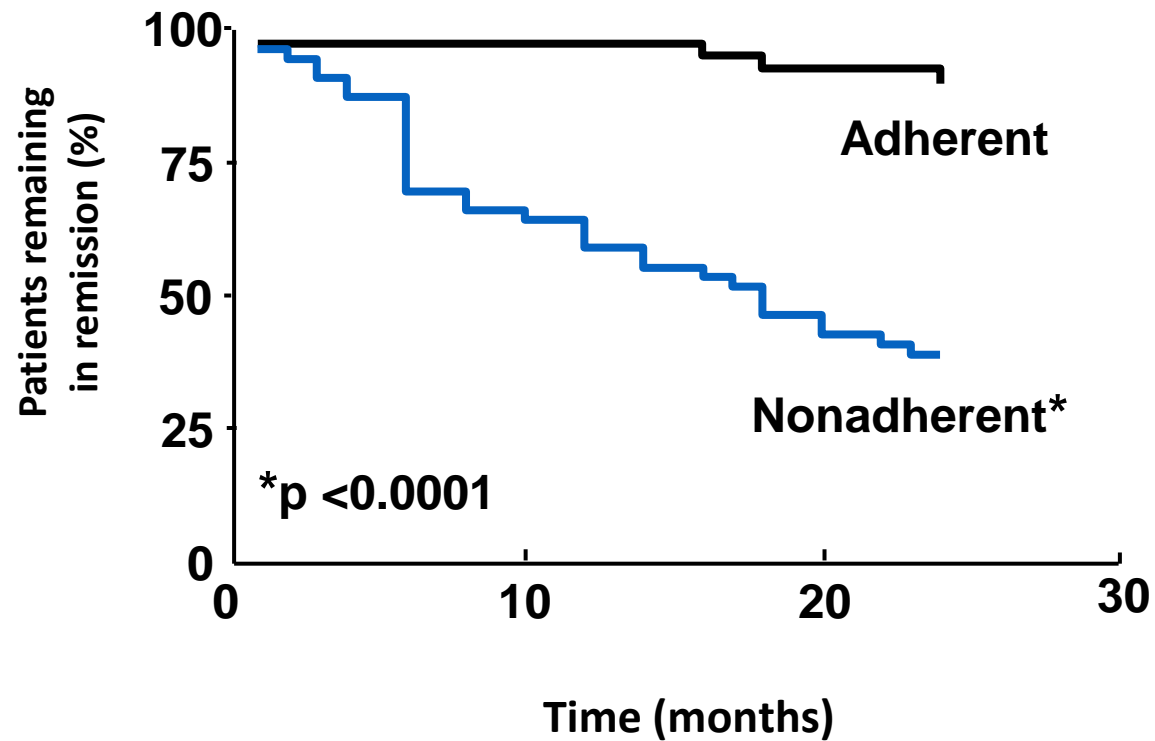
**No Disease Should Be Labeled as
“Refractory” If It Has Not Received Optimal
Therapy**

Suboptimal care in inflammatory bowel disease

Parameters	N	Proportion
Suboptimal dose of 5-ASA	21/33	64%
No topical 5-ASA therapy in distal UC	9/12	75%
Steroids > 3 months	27/35	77%
Failure to use steroid sparing agent	16/27	59%
Inadequate prevention of osteoporosis	21/27	78%
Suboptimal dose of immunomodulatory agents	9/11	82%

67 consecutive patients, American tertiary center (Brigham & Women's)

Non-Compliance with 5-ASA Therapy is Associated with Clinical Recurrence



Mesalazine in ulcerative colitis in remission

- Take-home messages -

- Oral route
- Dose: ≥ 2 g/day
- Single daily assumption
- Topical therapy alone in distal disease? (risk of extension of proctitis 45 %)
- Evaluate combined maintenance treatment in frequently recurrent disease before stepping up
- Check compliance

An open issue: mesalazine for maintenance treatment: how long?

- Go ahead for a long time. But how long?
 - Always for the entire life? **Yes**
 - Even in association with biologics or immunosuppressors? **Yes**

“Science is important. But education is the vector that transmits to every new generation curiosity, passion, and commitment to reimagine the future, extend the limits of human possibility, and achieve a more just social world.”

See [Comment](#) page 1666

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Grazie per la Vostra Attenzione