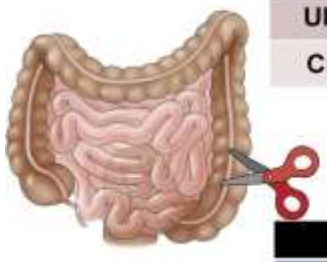
Prevenzione della recidiva post-chirurgica della Malattia di Crohn: Impiego dei farmaci biotecnologici: per quali pazienti?

Daniela Pugliese
Fondazione Policlinico Universitario A. Gemelli IRCCS

Contemporary risk of surgery in CD



Before 2000			
	1-y risk of surgery	5-y risk of surgery	10-y risk of surgery
Ulcerative colitis	4.8% (3.7-6.1)	9.5% (7.8-11.4)	15.2% (12.6-18.2)
Crohn's disease	23.6% (18.3-29.9)	35.7% (29.2-42.9)	46.5% (36.7-56.6)

Improved management

After 2000			
	1-y risk of surgery	5-y risk of surgery	10-y risk of surgery
Ulcerative colitis	2.8% (2.0-3.9)	7.0% (5.7-8.6)	9.6% (6.3-14.2)
Crohn's disease	12.3% (10.8-14.0)	18.0% (15.4-21.0)	26.2% (23.4-29.4)

Clinical Gastroenterology and Hepatology

A Risk of Re-Resection by 5-years in Patients with Crohn's Disease with Prior Surgery

Study name	Event rate	Lower limit	Upper limit	Events/Total Total
O'Keefe 1970-1979	0.226	0.112	0.404	7 / 31
Shinagawa 1982-2002	0.293	0.261	0.328	203 / 692
Burr 1990-1995	0.200	0.093	0.379	6 / 30
Boualit 1988-2004	0.169	0.114	0.244	22 / 130
Nguyen 1988-2008	0.230	0.206	0.256	244 / 1061
Burr 1996-2001	0.082	0.043	0.150	9 / 110
Benchimol 1994-2007	0.250	0.215	0.287	138 / 553
Nguyen 1996-2007	0.243	0.228	0.259	715 / 2943
Beelen 1991-2015	0.108	0.102	0.115	883 / 8172
Vester-Andersen 2003-2004	0.175	0.099	0.288	11 / 63
Burr 2002-2007	0.122	0.083	0.175	24 / 197
Shinagawa 2002-2016	0.185	0.164	0.208	218 / 1179
Burr 2008-2013	0.109	0.068	0.170	16 / 147
Risk of Re-Resection by 5-YEARS	**0.177**	**0.135**	**0.229**	**2496 / 15308**

Event rate and 95% CI

0.00 0.25 0.50

Risk of Re-resection

B Risk of Re-Resection by 10-years in Patients with Crohn's Disease with Prior Surgery

Study name	Event rate	Lower limit	Upper limit	Events/Total Total
O'Keefe 1970-1979	0.419	0.261	0.596	13 / 31
Shinagawa 1982-2002	0.549	0.512	0.586	380 / 692
Burr 1990-1995	0.467	0.299	0.642	14 / 30
Boualit 1988-2004	0.292	0.221	0.376	38 / 130
Nguyen 1988-2008	0.340	0.312	0.369	361 / 1061
Burr 1996-2001	0.182	0.120	0.265	20 / 110
Benchimol 1994-2007	0.360	0.321	0.401	199 / 553
Nguyen 1996-2007	0.320	0.303	0.337	942 / 2943
Beelen 1991-2015	0.184	0.176	0.193	1504 / 8172
Vester-Andersen 2003-2004	0.222	0.136	0.341	14 / 63
Burr 2002-2007	0.162	0.117	0.221	32 / 197
Shinagawa 2002-2016	0.409	0.381	0.437	482 / 1179
Risk of Re-Resection by 10-YEARS	**0.313**	**0.241**	**0.396**	**3999 / 15161**

Event rate and 95% CI

0.00 0.50 1.00

Risk of Re-resection

Tsai L, CGH 2021

Strategies in postoperative prophylaxis

- **Intensive prophylaxis**
  - All patients treated post-operatively according to risk stratification
  - Can be adjusted according to risk
  - Cost, overtreatment, side-effects
  - Acceptance: patients and doctors

- **Early intervention / 'Tight control'**
  - Risk stratification at surgery
  - Early endoscopic monitoring
  - Intervention based on objective markers rather than clinical symptoms
  - Reduced costs, better acceptance

Risk factors for postoperative recurrence in Crohn's disease

Table 3. Risk factors for POR of CD.

Risk factors
• Age
• Gender
• IBD family history
• Smoking
• Disease-related risks (duration prior to first surgery, location, behavior, perianal disease)
• Disease-treatment modifiers (perioperative steroid use, anti-inflammatory use)
• Surgical risk factors (anastomosis, margins of resection, laparoscopic *versus* open, strictureplasty)
• Postoperative complications
• Histology (myenteric plexitis, granulomas, lymphatic vessel density, and transmural activity)
• Genetics
• Microbiome

CD, Crohn's disease; IBD, inflammatory bowel disease; POR, postoperative recurrence.

Patients' related

Diseases related

Surgery related

Patients' related

Shah R, Therapeutic Advances in Gastroenterology 2021

Risk stratification for Recurrence of CD After Surgical Resection

TABLE 2. Definitions of High Risk According to Current Guidelines

Guidelines	High-Risk Definition	
	≥1 of Following Factors	≥2 of Following Factors
AGA[11]	Age ≤30 y	—
	Active smoking	
	≥2 prior surgeries for penetrating disease, with or without perianal disease	
ECCO[7]	Current smoking	—
	Prior intestinal surgery	
	Penetrating disease at index surgery	
	Perianal location	
	Granulomas in resection specimen	
	Myenteric plexitis	
BSG[10]	—	Active smoking
		Penetrating disease
		Multiple resections
		Perianal fistulae
		Extensive small bowel disease (≥50 cm ileum)
		Residual active disease
		Granulomas or myenteric plexitis

Joustra V, IBD 2021

A not-validated model

- Outcome and population heterogeneity among studies
- Postoperative medical treatment as an important confounder
- Long-term evidence of benefit of an early prophylactic treatment in high-risk patients is limited

Natural History and Risk Stratification of Recurrent Crohn's Disease After Ileocolonic Resection: A Multicenter Retrospective Cohort Study

TABLE 4. Univariate Associations of High-Risk Patients Who Have Surgery With Endoscopic Recurrence (Rutgeerts score ≥i2b)

Without histology (N = 142)		OR (95% CI)	*P*
AGA definition	≥1 factors present (n = 98, 69%)	1.06 (0.52-2.17)	0.87
	≥2 factors present (n = 29, 20.4%)	1.85 (0.81-4.23)	0.15
	All 3 factors present (n = 7, 4.9%)	1.57 (0.34-7.29)	0.57
ECCO definition	≥1 factors present (n = 99, 69.7%)	1.50 (0.72-3.10)	0.28
	≥2 factors present (n = 43, 30.3%)	1.50 (0.73-3.07)	0.27
	≥3 factors present (n = 14, 9.9%)	4.87 (1.30-18.29)	0.02*
BSG definition	≥2 factors present (n = 52, 36.6%)	1.25 (0.63-2.48)	0.52
	≥3 factors present (n = 17, 12%)	3.16 (1.05-9.49)	0.04*
With histology (n = 95)			
ECCO definition	≥1 factors present (n = 78, 82.2%)	1.50 (0.52-4.35)	0.45
	≥2 factors present (n = 35, 36.9%)	1.96 (0.84-4.58)	0.12
	≥3 factors present (n = 18, 19%)	3.29 (1.07-10.13)	0.04*
BSG definition	≥2 factors present (n = 42, 44.2%)	1.74 (0.77-3.94)	0.19
	≥3 factors present (n = 19, 20%)	3.65 (1.19-11.15)	0.02*

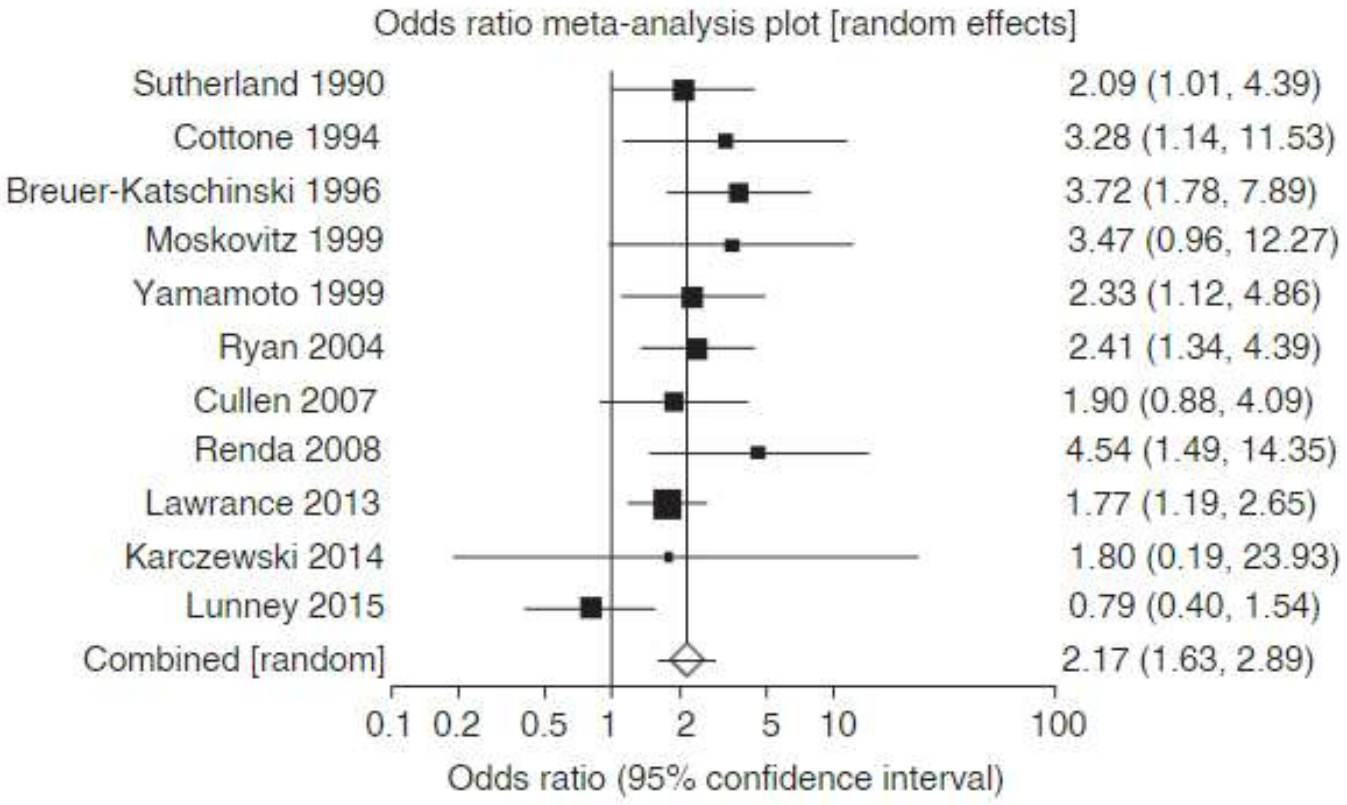
142 patients after ileocolonic resection
No prophylatic therapy
Outcome: endoscopic POR

Active smoking postsurgery, previous bowel resections
Montreal classification of A3 associated with increased risk of POR

Joustra V, IBD 2021

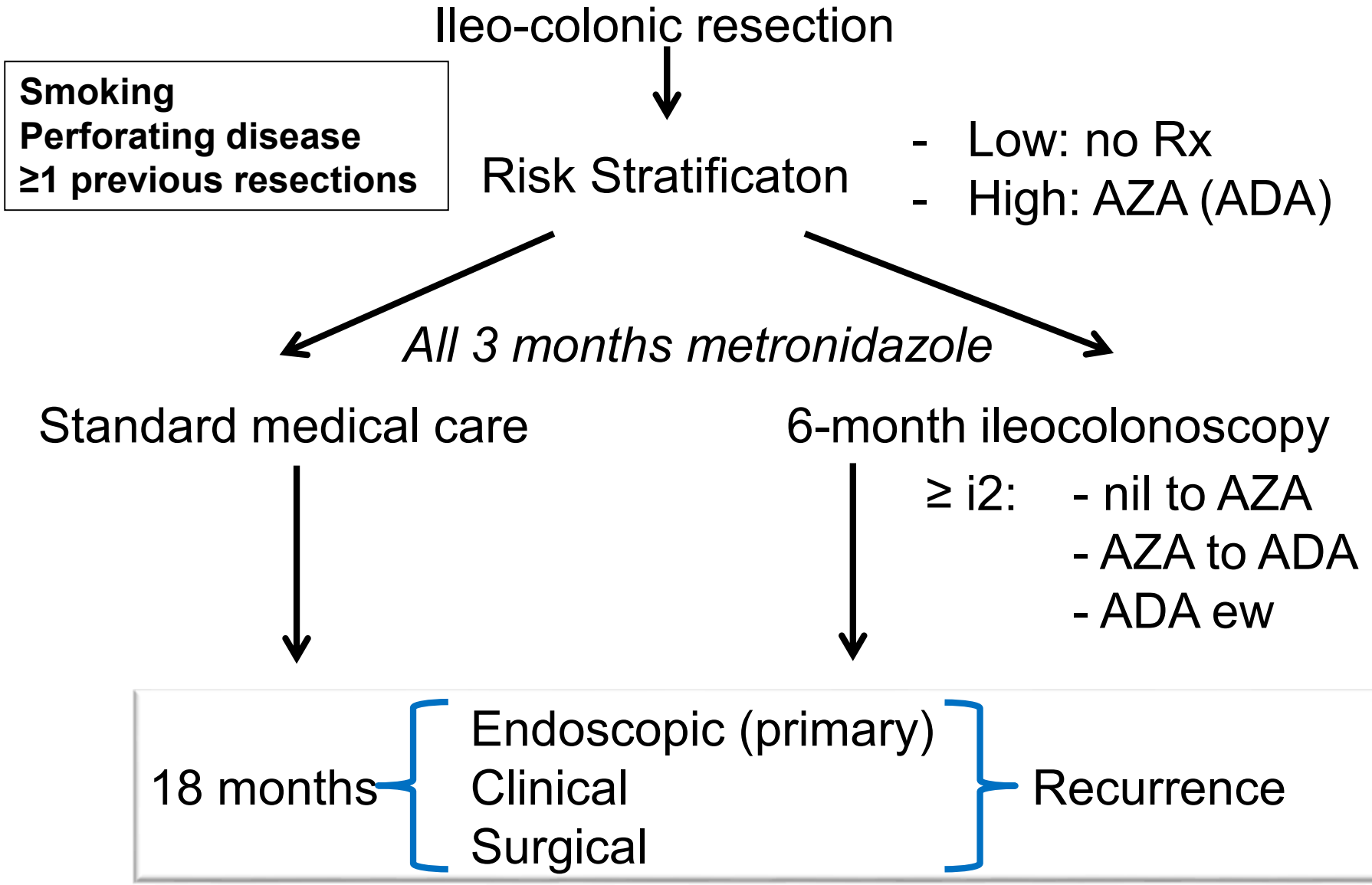
Smoking for sure

Forest plot of effect of smoking on need for second surgery



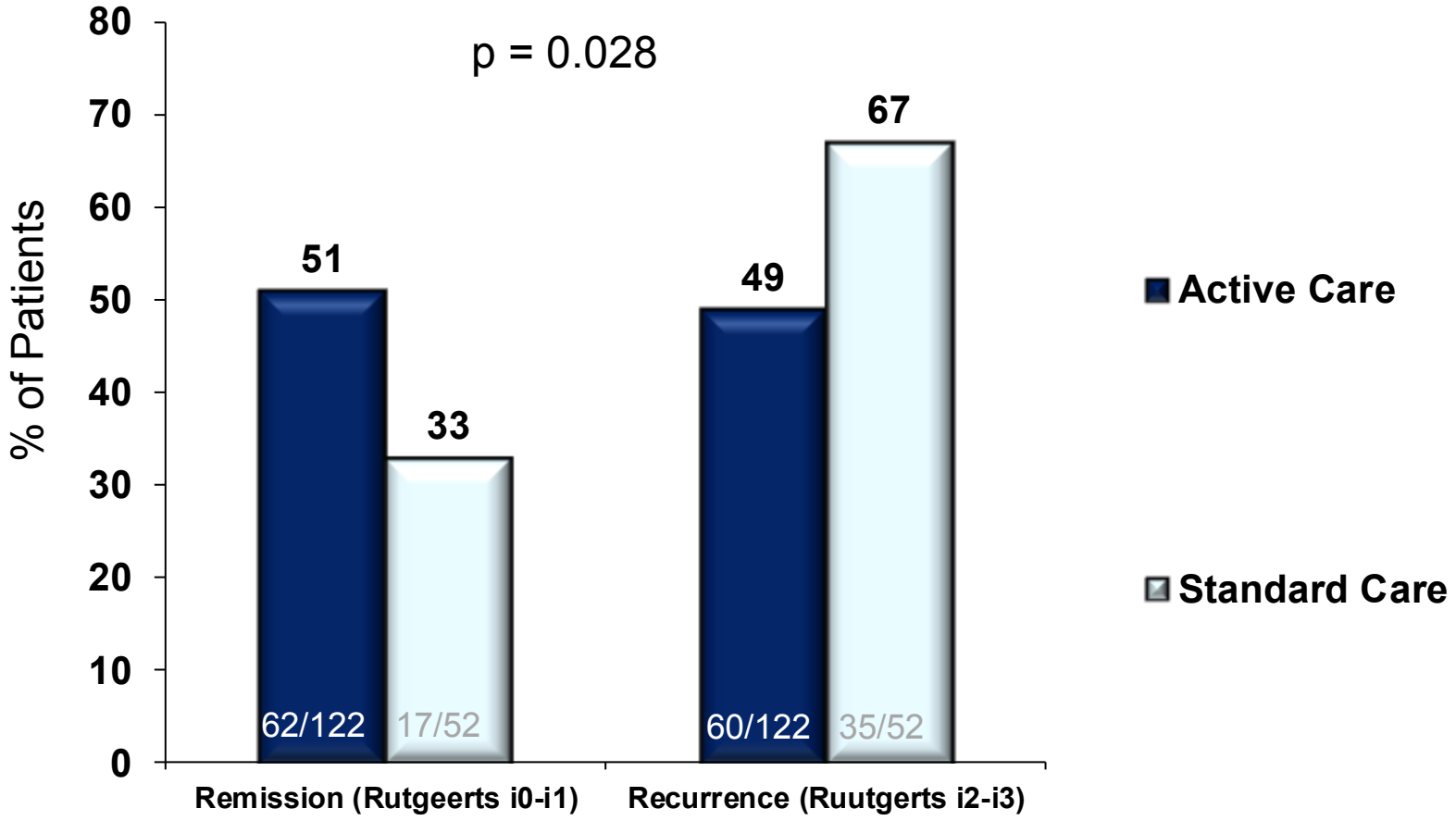
To N, APT 2016

POCER trial Study design (NCT00989560)



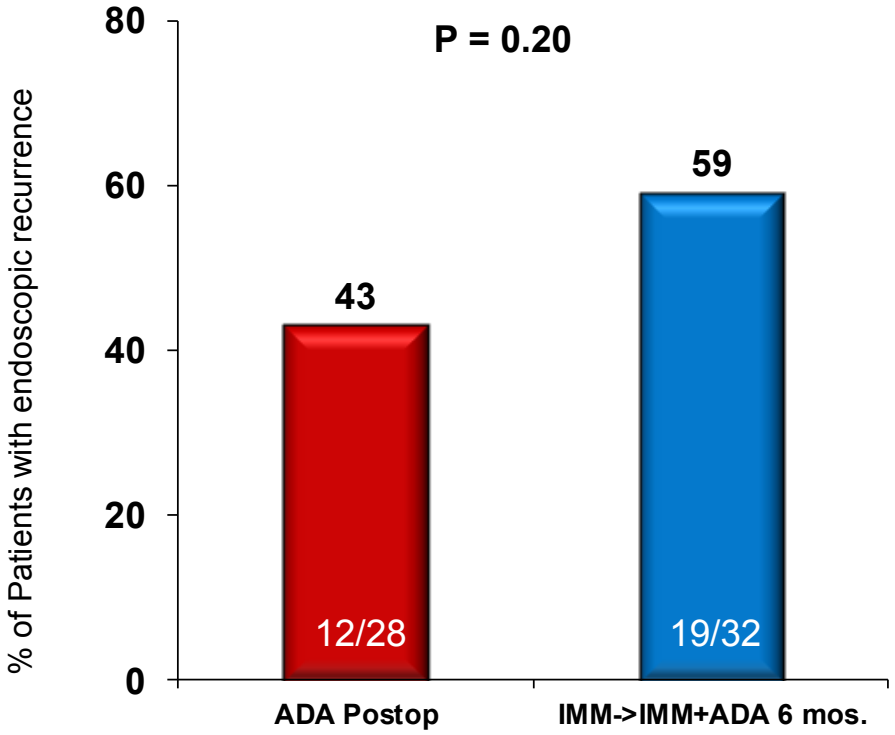
POCER: Primary Outcome
Endoscopic Recurrence at 18 months

Active Care (tight monitoring) vs Standard Care



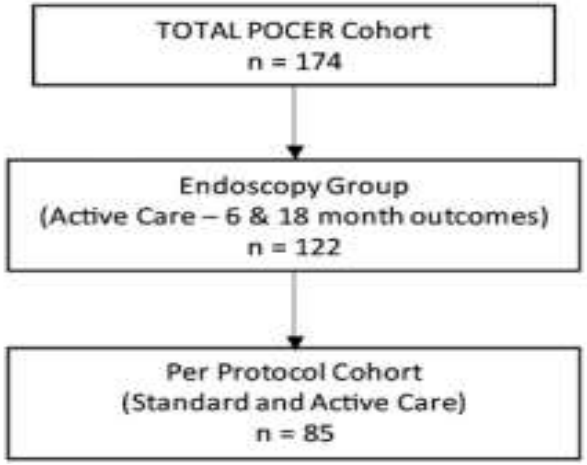
De Cruz P, et al Lancet 2015.

POCER: Immediate post-operative adalimumab vs selective use after endoscopic recurrence



De Cruz P, et al Lancet 2015.

POCER risk



5 endoscopic parameters:

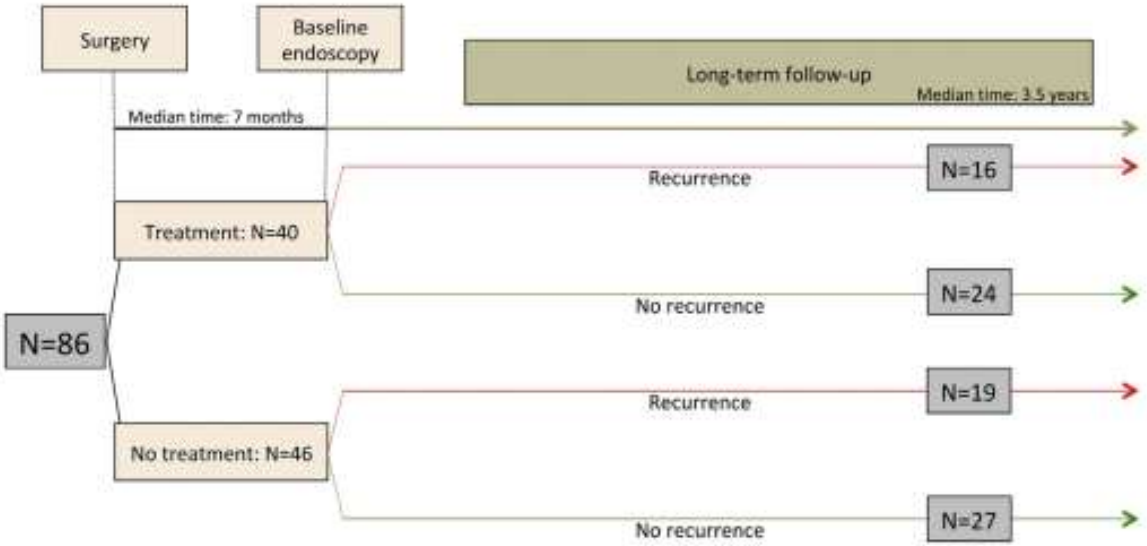
- **anastomotic ulcer depth (superficial vs deep)**
- number of ulcers (0, ≤2, >2)
- ulcer size (1-5 mm, ≥6 mm)
- **circumferential extent of ulceration (<25%, > 25%)**
- stenosis

POCER Index	Ulcer Depth	Circumference	Total at 6 Mo, n (%)	Total at 18 Mo, n (%)	Rutgeerts Score of ≥i2 (recurrence) at 18 Mo, n (%)	Rutgeerts Score of <i2 (remission) at 18 Mo, n (%)	Odds Ratio for Recurrence at 18 Mo	95% CI
0	None	None	31 (36.5)	40 (47.1)	8 (27.6)	23 (41.1)	1	—
1	Superficial <2 mm	<25%	31 (36.5)	31 (36.5)	9 (31.0)	22 (39.3)	1.2	0.3-4.5
2	Superficial <2 mm	≥25%	15 (17.7)	11 (12.9)	7 (24.1)	8 (14.3)	2.5	0.6-11.6
3	Deep ulceration, at least 1 ulcer ≥2 mm	<25%	5 (5.9)	1 (1.2)	3 (10.3)	2 (3.6)	4.3	0.6-30.9
4	Deep ulceration, at least 1 ulcer ≥2 mm	≥25%	3 (3.5)	2 (2.4)	2 (6.9)	1 (1.8)	5.7	1.1-30.9
≥2	—	—	23 (27)	14 (16.5)	13 (15.3)	1	2.9	1.1-7.8

The POCER index at 6 months was associated with endoscopic recurrence at 18 months (OR, 1.5; 95% CI, 1.2-2.0; P = 0.002; AROC 0.70; 95% CI, 0.57-0.82), but the Rutgeerts score was not (OR, 1.2; 95% CI, 0.8-1.8; P = 0.402).

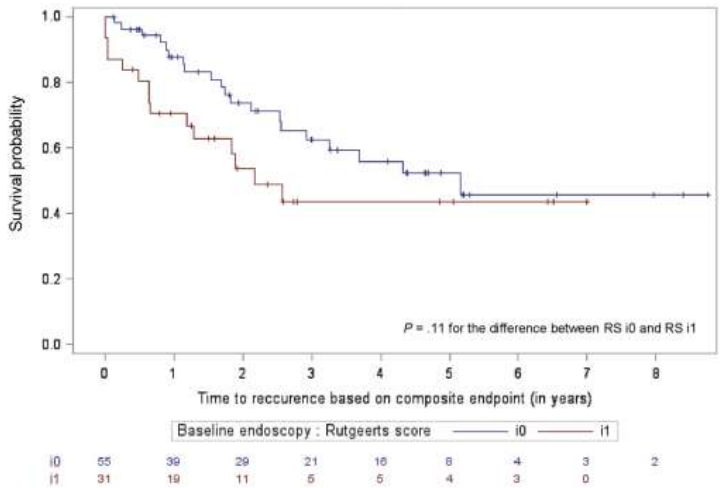
De Cruz P, IBD 2021

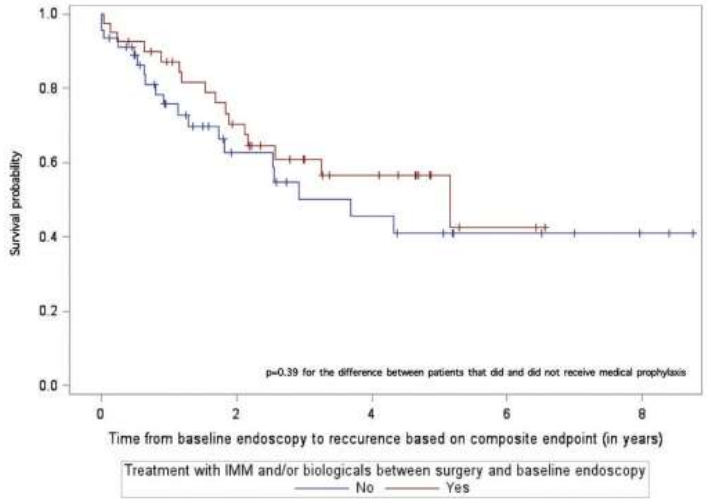
Risk of Late Postoperative Recurrence of Crohn's Disease in Patients in Endoscopic Remission After Ileocecal Resection, Over 10 Years at Multiple Centers



POR: clinical recurrence, IBD-related hospitalization, occurrence of bowel damage, need for endoscopic balloon dilatation of the anastomosis, and need to repeat the surgery

40% late recurrence after a median fup of 3.5 years

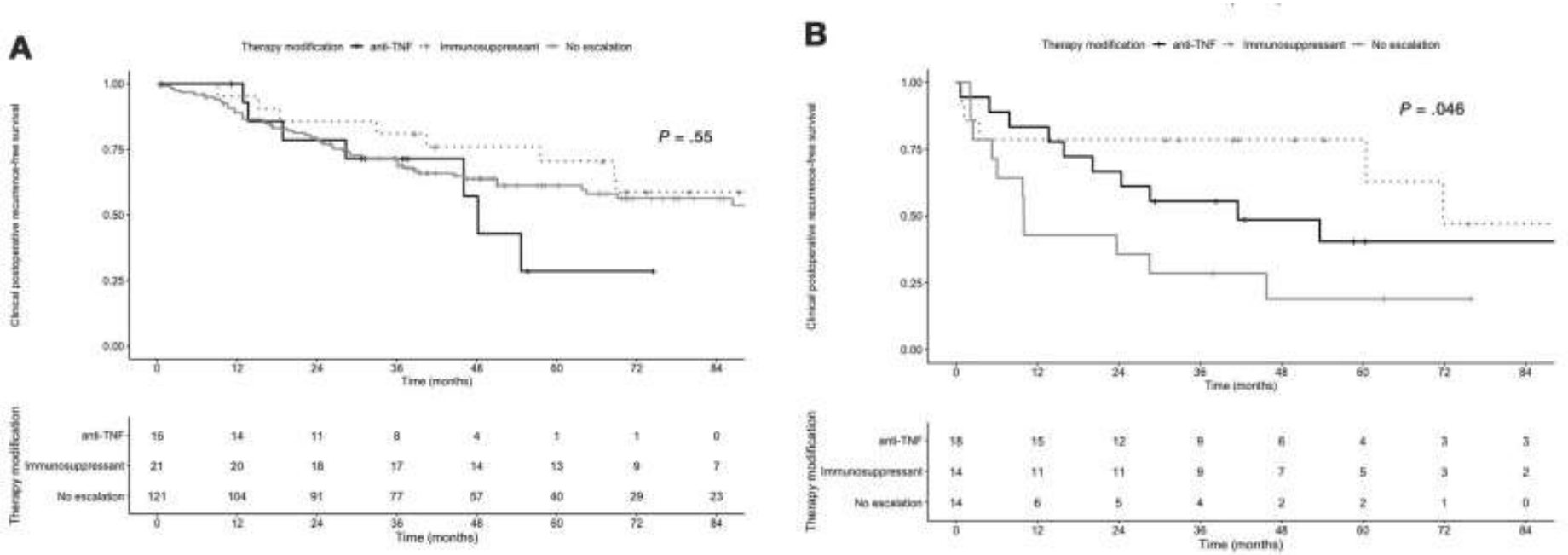




Pouillon L CGH 2021

Rates of Postoperative Recurrence of Crohn's Disease and Effects of Immunosuppressive and Biologic Therapies

365 CD patients (2000 to 2013)
POR: occurrence of CD symptoms along with biologic, radiologic, and/or endoscopic features of disease activity



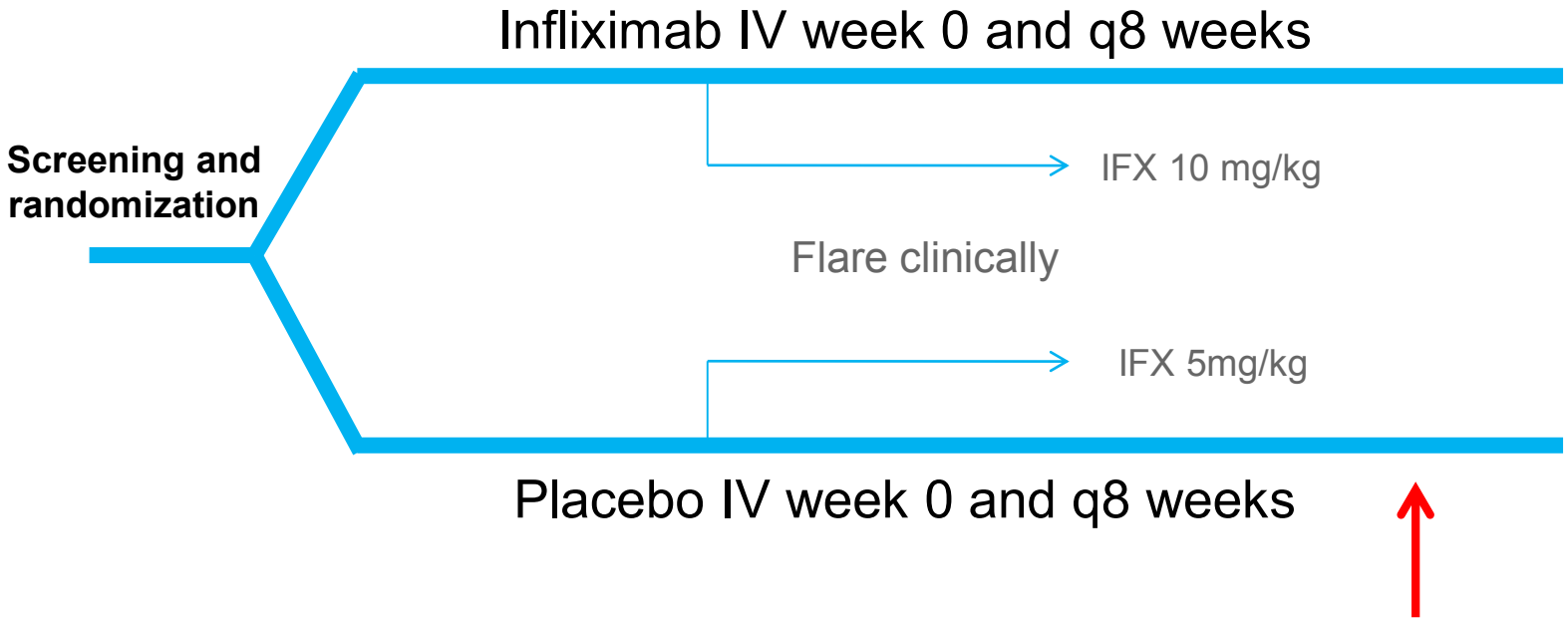
Rivière P, GCH 2021

Prospective controlled anti-TNF trials in the post-op setting

Study	Patient N	Drug	Endoscopic recurrence n (%)	Clinical recurrence n (%)	Remission definition	Outcome (months)
INTENSIVE PROPHYLAXIS						
Sorrentino 2007	7 16	IFX + MTX 5-ASA	0 (0) 12 (75)	0 (0) 4 (25)	Hanauer < 2 Rutgeerts < 2	24
Regueiro 2009	11 13	IFX PLB	1 (9) 11 (85)	0 (0) 5 (39)	CDAI < 150 Rutgeerts < 2	12
Yoshida 2012	15 16	IFX No treatm	30 (20) 13 (81)	2 (13) 4 (25)	CDAI < 150 Rutgeerts < 2	12
Savarino 2013	16 18 17	ADA 5-ASA AZA	1 (6) 15 (83) 11 (65)	2 (12) 9 (50) 6 (35)	Hanauer < 2 Rutgeerts < 2	24
Armuzzi 2013	11 11	IFX AZA	1 (9) 4(36)	1 (9) 1 (9)	HBI < 8 Rutgeerts < 2	12
Regueiro 2016	147 150	IFX PLB	/	18 (12)* 30(20)	45 (30.6) 90 (60)	76 weeks
Lopez-Sanroman 2017	45 40	ADA AZA	8/24 (33.3) 11/37 (29.7)	25 (92.6) 37 (100)	CDAI < 200	12

* Primary endpoint: clinical recurrence before or at week 76 and endoscopic recurrence

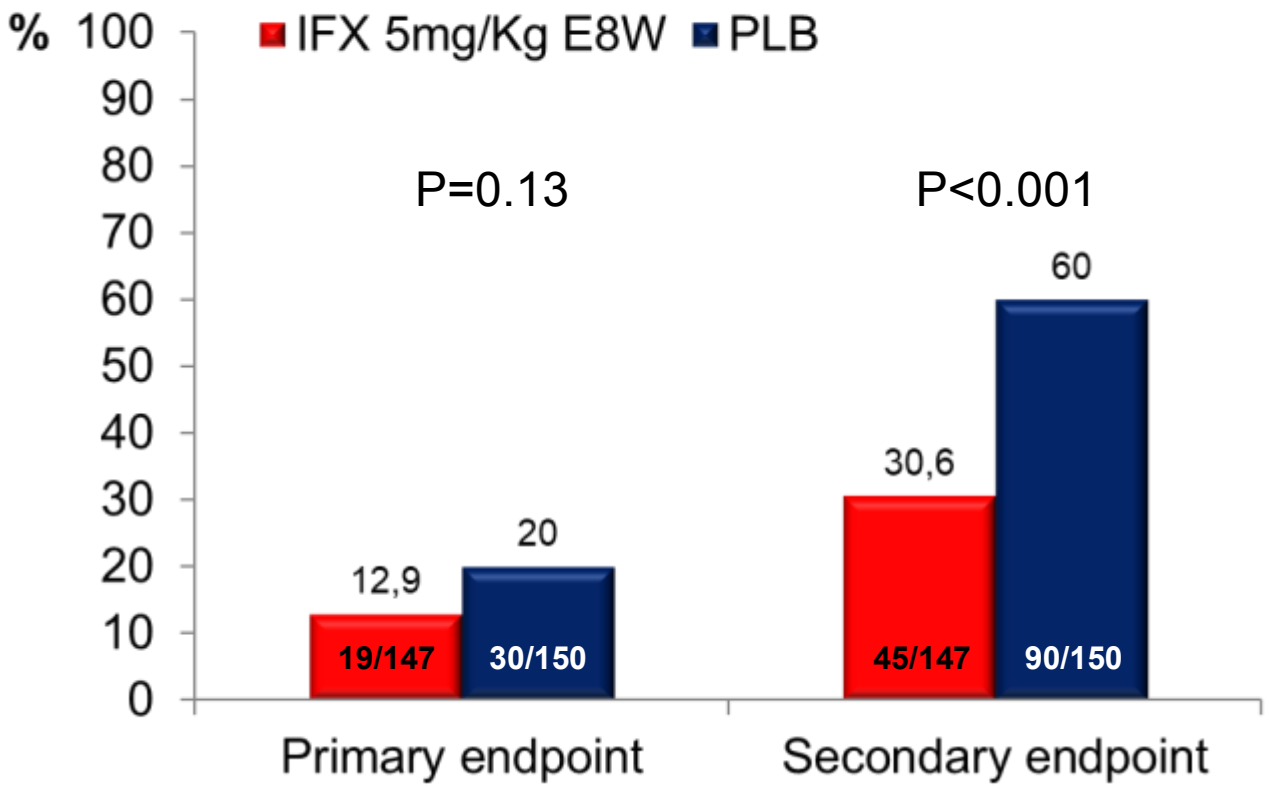
PREVENT Study design (NCT01190839)



Primary endpoint
Week 76
clinical recurrence (ΔCDAI 70 and >200) and evidence of endoscopic recurrence

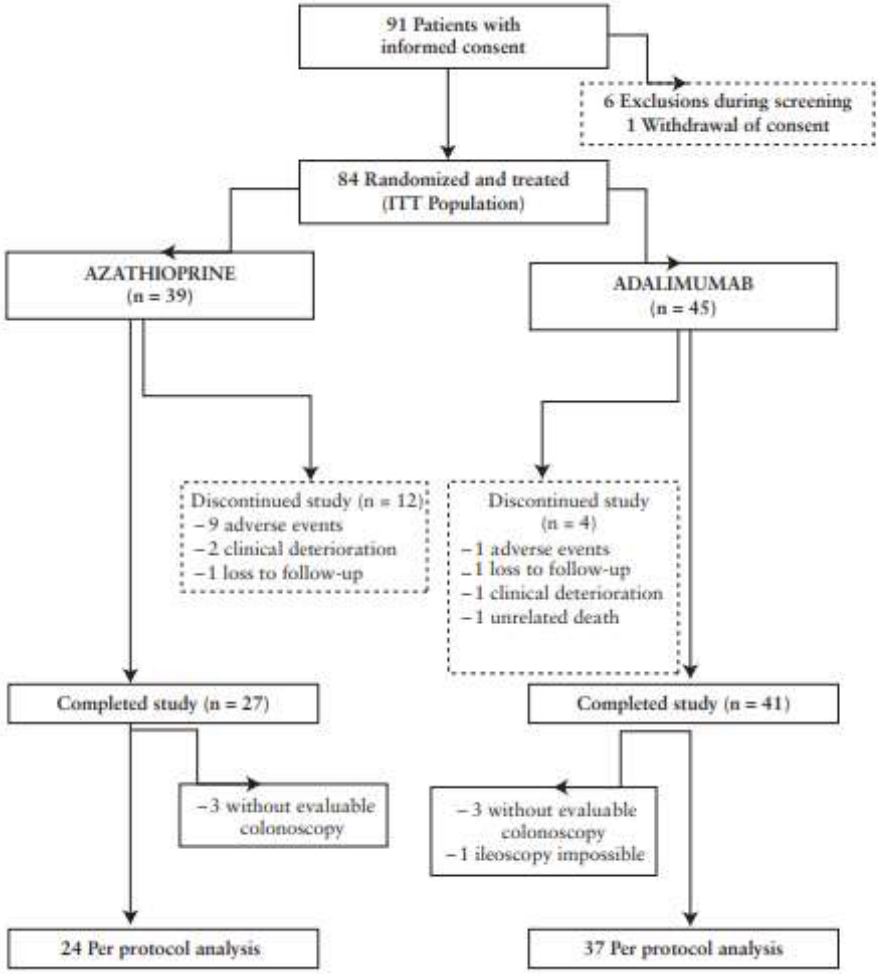
Regueiro M, Gastroenterology 2016

PREVENT Study
Primary and secondary endpoints



Regueiro M, Gastroenterology 2016

Adalimumab vs Azathioprine in the Prevention of Postoperative Crohn's Disease Recurrence. A GETECCU Randomised Trial

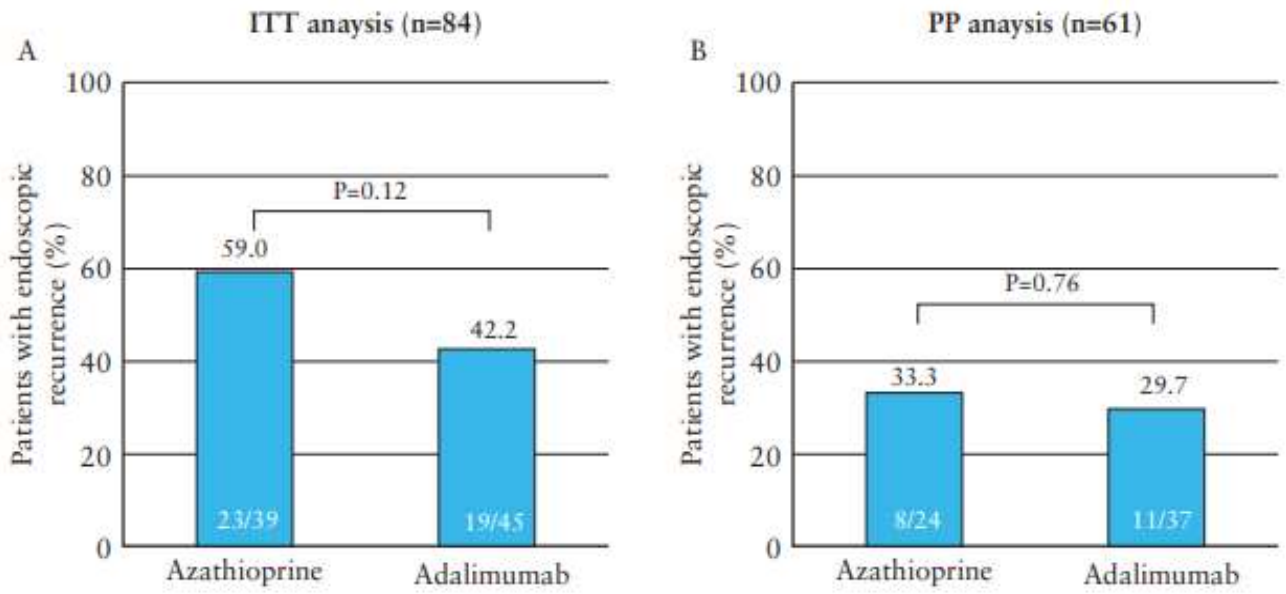


Primary endpoint: endoscopic recurrence at week 52
Secondary endpoints: clinical remission at week 24 and 52

Clinical remission: CDAI < 200

López-Sanromán A, JCC 2017

Adalimumab vs Azathioprine in the Prevention of Postoperative Crohn's Disease Recurrence. A GETECCU Randomised Trial

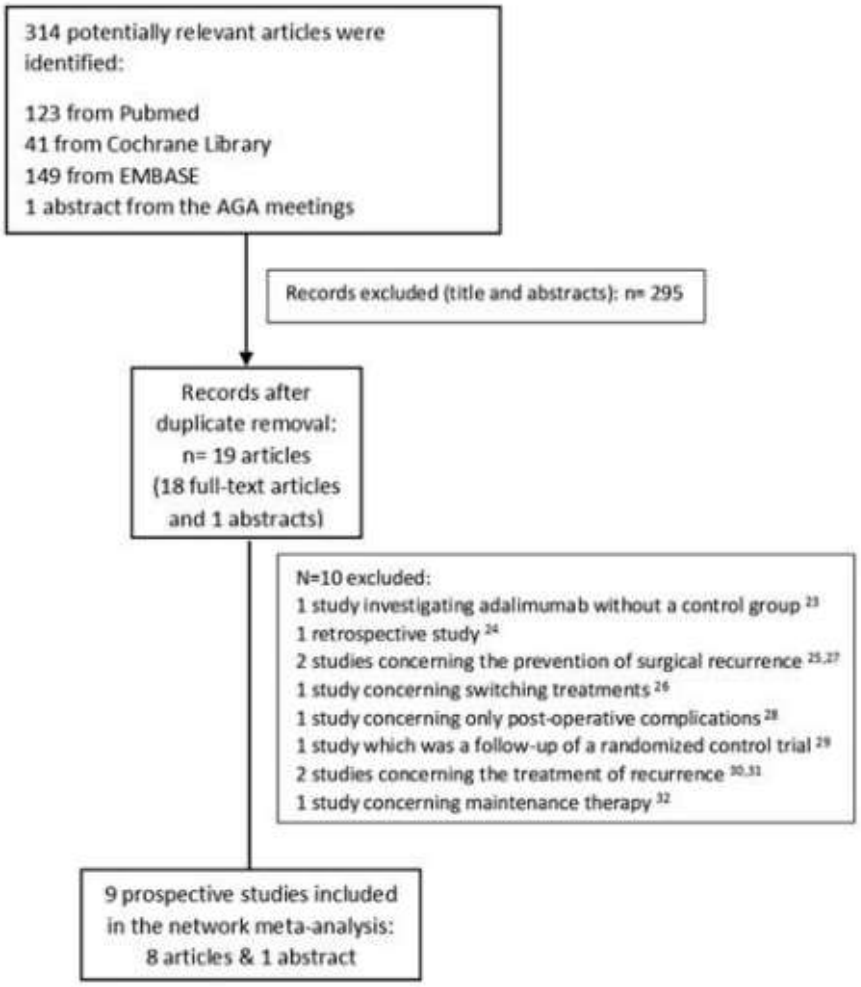


Clinical remission
Week 24 27 [93.1%] 42 [97.7%] 69 [95.8%] p=0.56
Week 52 25 [92.6%] 38 [100.0%] 63 [96.9%] p=0.16

Discontinuation was significantly less frequent in the ADA [4.4%] than in the AZA group [23.2%] (dif.: 18.6% [95% CI 4.1–33.2], p = 0.011)

López-Sanromán A, JCC 2017

Comparative Efficacy of Anti-TNF Therapies For The Prevention of Postoperative Recurrence of Crohn's Disease



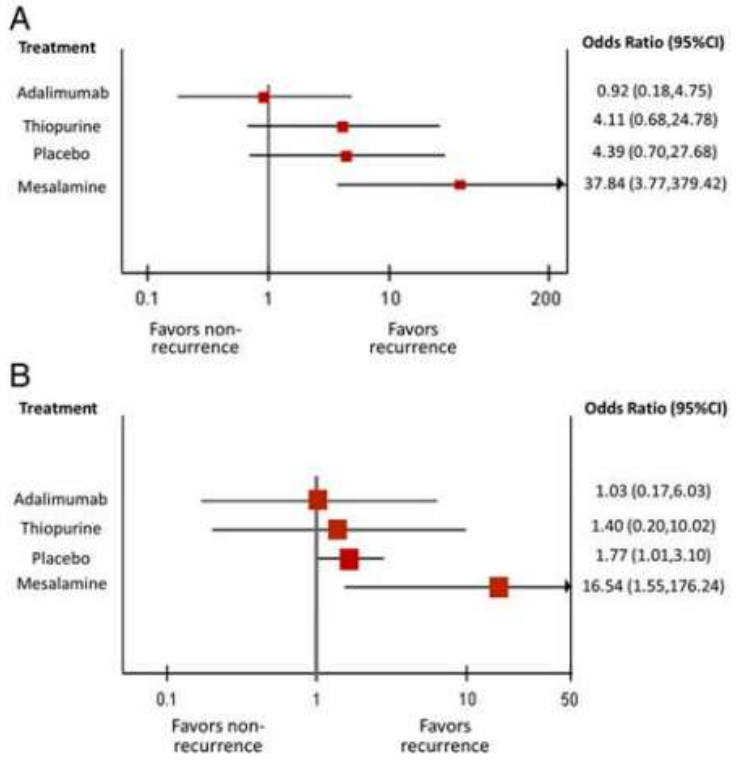
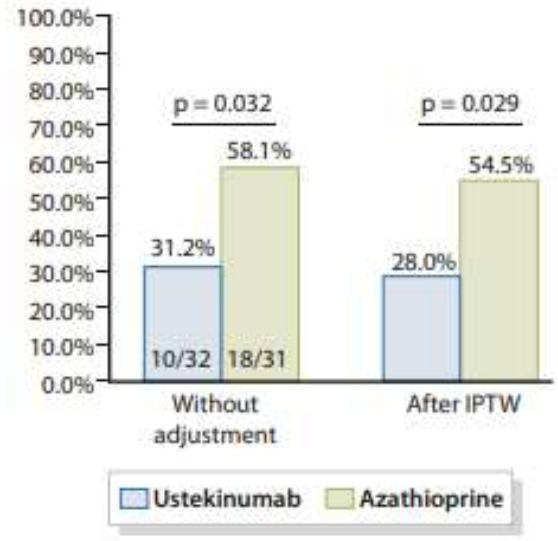


FIGURE 3. Forrest plots for the network meta-analysis of the endoscopic recurrence outcome (A) and clinical recurrence outcome (B). full color online

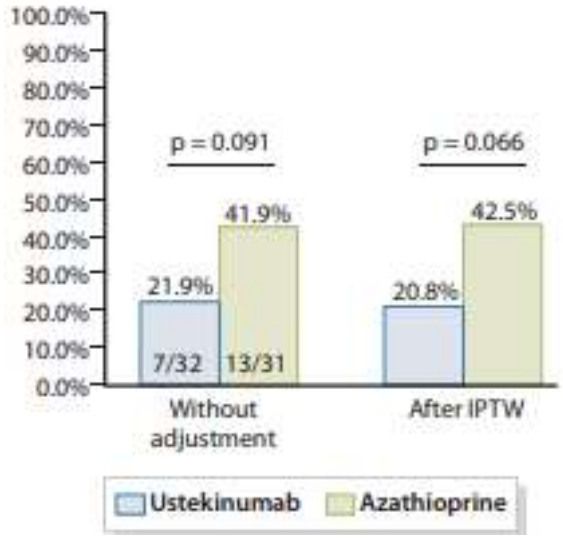
Bakouny Z, J Clin Gastroenterol 2018

Ustekinumab is more effective than azathioprine to prevent endoscopic postoperative recurrence in Crohn's disease

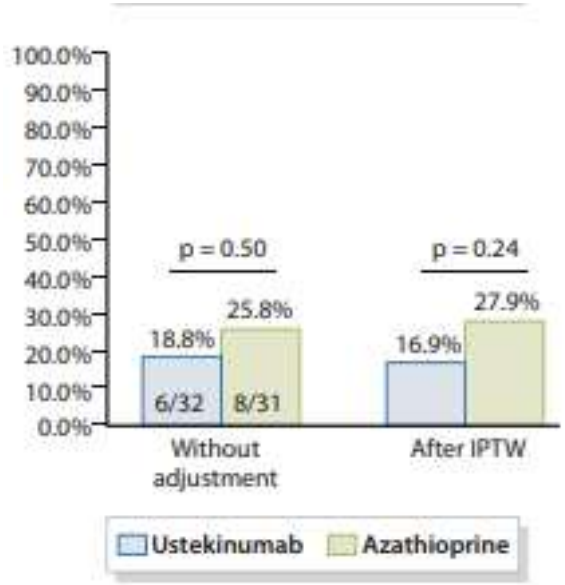
Endoscopic postoperative recurrence (≥i2)



Endoscopic postoperative recurrence (≥i2b)



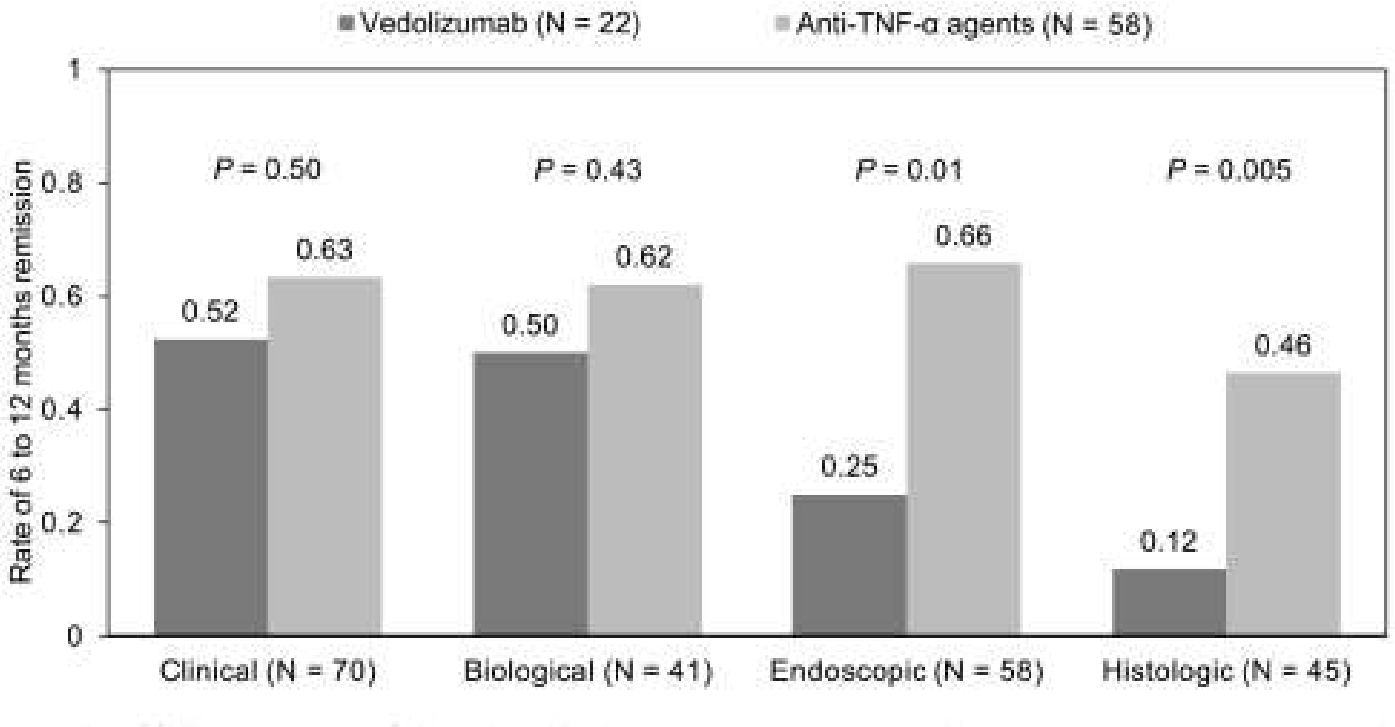
Endoscopic postoperative recurrence (≥i3)



The propensity score adjusted on the main risk factors : smoking, fistulizing phenotype, prior bowel resection, resection length >30 cm and ≥2 biologics before surgery.

Boisson A, UEG 2020

The Use of Vedolizumab in Preventing Postoperative Recurrence of Crohn's Disease



Vedolizumab use was the only factor that was associated with an increased risk of endoscopic recurrence (OR 5.77, 95%CI 1.71–19.4, P = 0.005)

Yamada A, IBD 2018

Conclusions

- There is at present no validated model on risk factors of recurrent Crohn's disease after surgery

- Clinical studies have suggested that anti-TNF therapy could be effective treatment to prevent endoscopic recurrence after surgical resection in Crohn's disease patients bearing high risk of disease recurrence

- While intensive prophylaxis or early intervention / tight control is the most effective strategy in the long-term, it has still to be proven.