Northwestern

How to Treat a Patient with Crohn's After They Have Undergone Intestinal Resection

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Disclosures

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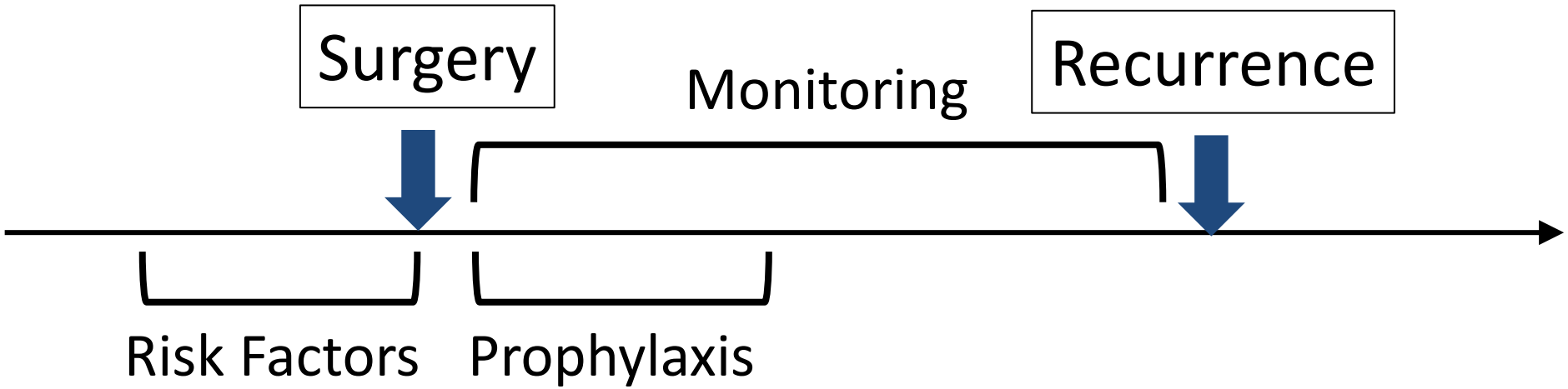
- Acknowledgement - Miguel Regueiro


OAG
GAMIFICATION
Parambir - Game Code:
WHITEOUT

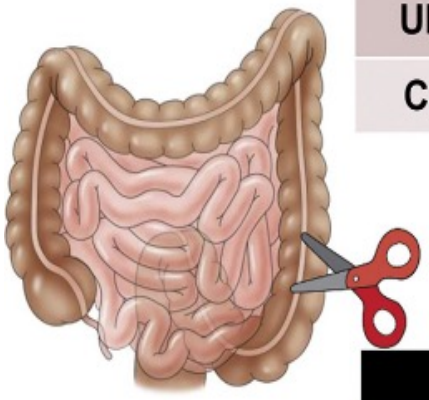
Learning Objectives

- Understand natural history of post-operative Crohn's disease
- Identify risk factors for recurrence
- Review medical options for prevention of recurrence and/or treatment

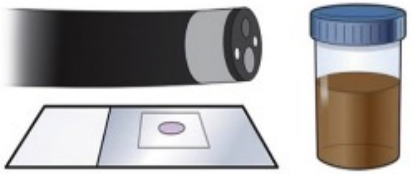
Natural History and Opportunities



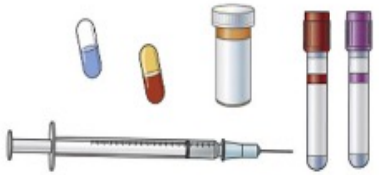
Surgery Remains Common



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

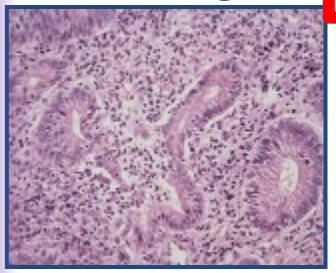


After 2000			
	1-y risk of surgery	5-y risk of surgery	10-y risk of surgery
Ulcerative colitis	2.8% (2.0-3.9)	7.0% (5.7-8.6)	9.6% (6.3-14.2)
Crohn's disease	12.3% (10.8-14.0)	18.0% (15.4-21.0)	26.2% (23.4-29.4)

Tsai L, et al. Clin Gastroenterol Hepatol. 2021 Oct;19(10):2031-2045

Natural History of Disease Recurrence After Surgery

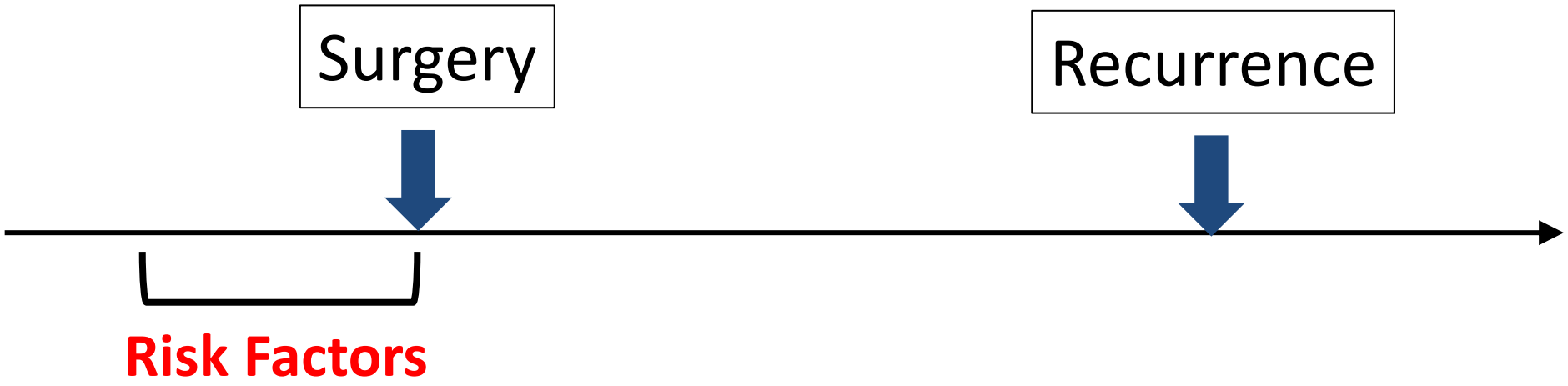
Recurrence is clinically silent initially

Histologic	Endoscopic	Radiologic	Clinical	Surgical
				
Within 1 week	**70-90% by 1 yr**	**Tissue damage**	**30% 3 yr 60% 5 yr**	**50% by 5 yrs**

Surgery

D'Haens GR, et al. *Gastroenterology*. 1998;114(2):262-267. Olaison G, et al. *Gut*. 1992;33(3):331-335. Rutgeerts P, et al. *Gastroenterology*. 1990;99(4):956-963. Sachar DB. *Med Clin North Am*. 1990;74(1):183-188.

Risk Factors



Post-Op Risk Factors

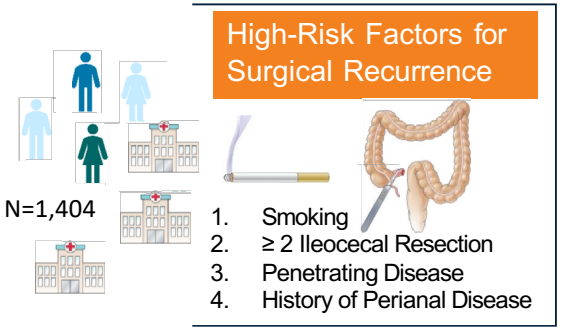
Factor Category	Risk Factor Associated	
Patient	Age	Family history of IBD
	Sex	Active smoking
	Race	
Disease	Age of disease onset	Anatomic extent involved/length of resection
	Time to surgery from diagnosis	Clinical activity at surgery
	Prior surgical resection	Prior medical therapies
	Disease location	Disease behavior = Penetrating disease
Genetics	NOD2/CARD15	CARD8
Serology	Anti-Saccharomyces cerevisiae (ASCA)	Anti-flagellin (cBIR)
	Outer membrane protein C (Omp-C)	Anti-glycan
	Pseudomonas I2	
Microbiome	Proteus	Fusobacteria
	Lachnospiraceae	Faecalibacterium
Operative Intervention	Surgical approach (laparoscopic/laparotomy)	Anastomotic orientation, technique
	Blood transfusion requirement	Mesenteric excision extent
	Excision margin length	Strictureplasty
	Perioperative complication	
Histology	Margin involvement	Myenteric and submucosal plexitis
	Granulomas	Transmural inflammation
Other "-omics"	Tissue and transcriptomics	Urinary metabolomics

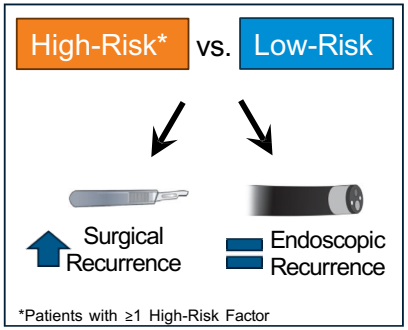
AGA Risk Factor Stratification

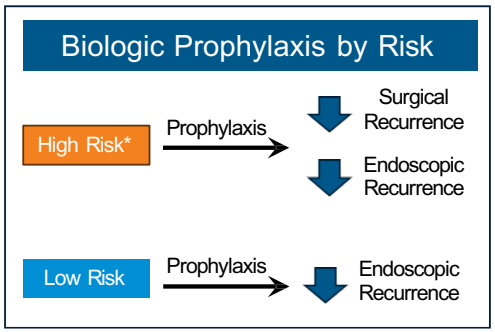
Risk Group	Patient and Disease Characteristics	Clinical Recurrence (>18 months post-op)	Endoscopic Recurrence (>18 months post-op)
Low Risk	> 50 years old Non-smoker 1st surgery (short segment <10cm) Ds. Duration > 10 years	20%	30%
High Risk	< 30 years old Smoker 2 or more prior surgeries	50%	80%

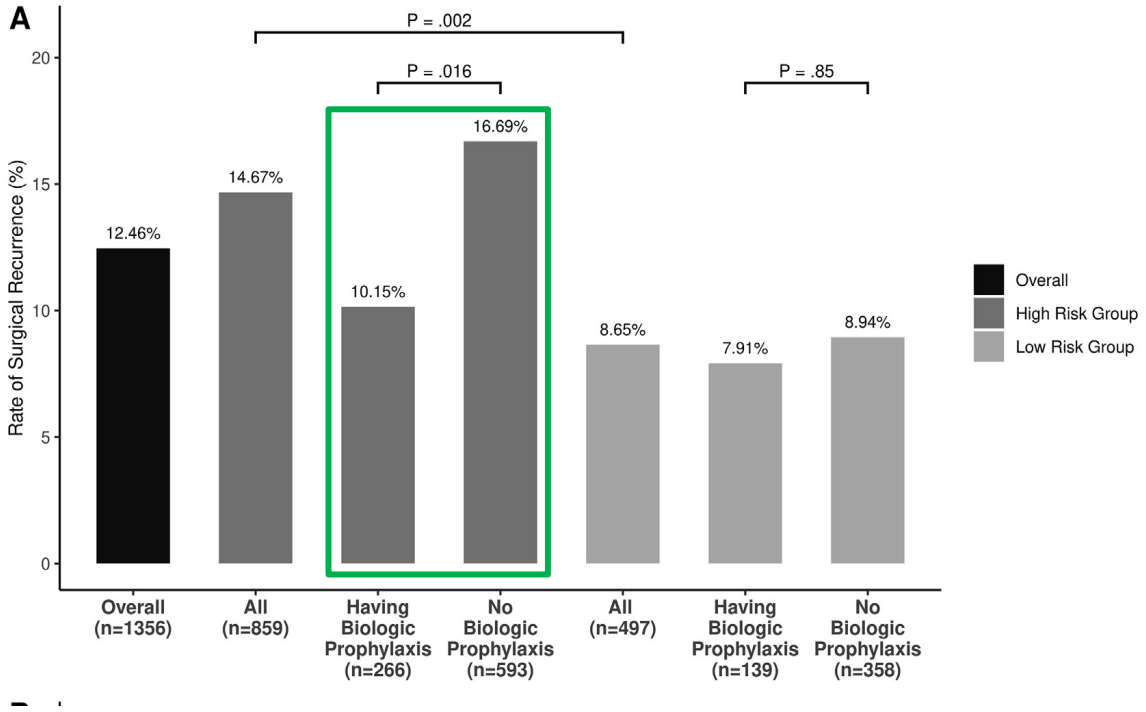
Regueiro M, et al. Gastroenterology. 2017;152(1):277-295.
Nguyen GC, et al. *Gastroenterology*. 2017;152(1):271-5.

Routine Practice Confirmation of Risk Factor Stratified Prevention



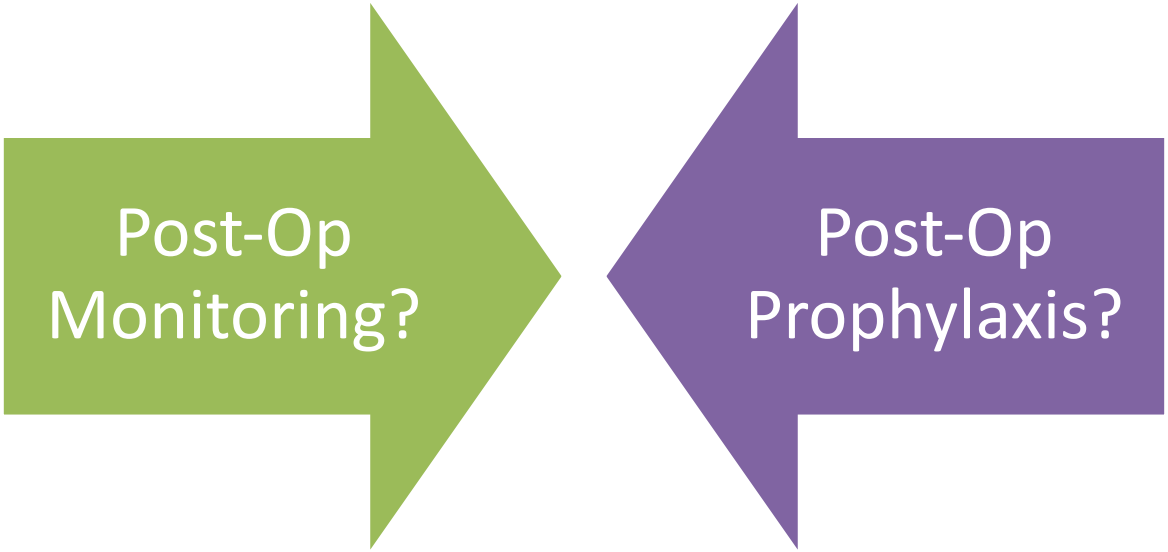






Shah et al. *CGH* 2023

Wait and Watch or Treat?



Balance between over treatment and risk of progression?
Identify patients in the right 'window' of recurrence?
Do the therapies work as well post-operatively?

Crohn's disease management after intestinal resection: a randomized post-operative Crohn's endoscopic recurrence (POCER) trial

Primary Outcome: 18 mos Endoscopic Recurrence

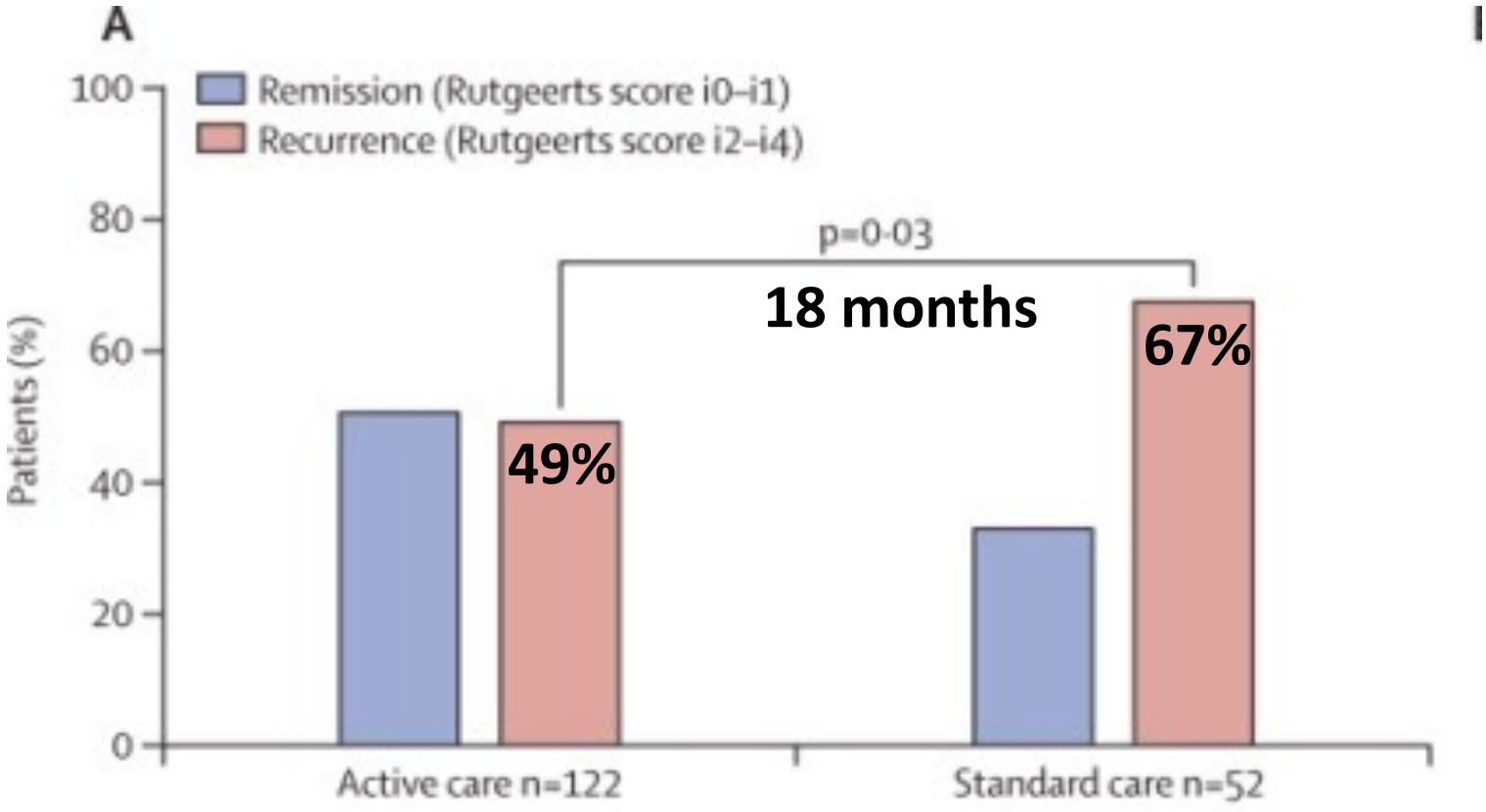
Randomization: Group 1 had a 6 month colonoscopy (if active disease then escalate treatment) vs Group 2 no 6 month colonoscopy

All patients received postop metronidazole x 3 mos

Low Risk for recurrence: No additional Medication
High Risk for recurrence: Thiopurine or Adalimumab if intolerant or previously failed thiopurine

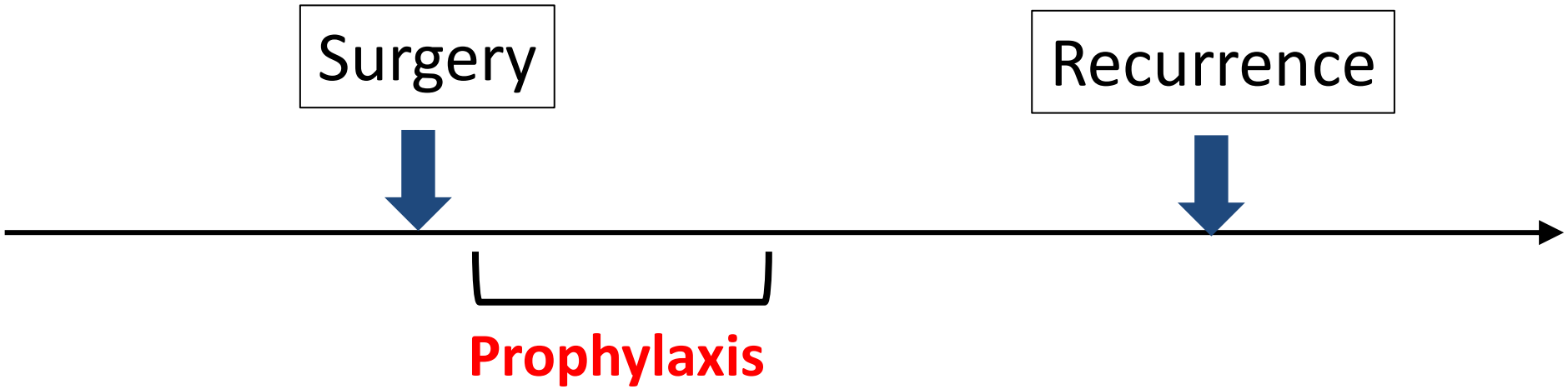
De Cruz P, et al. *Lancet* 2015

Active Monitoring Resulted in Lower Endoscopic Recurrence



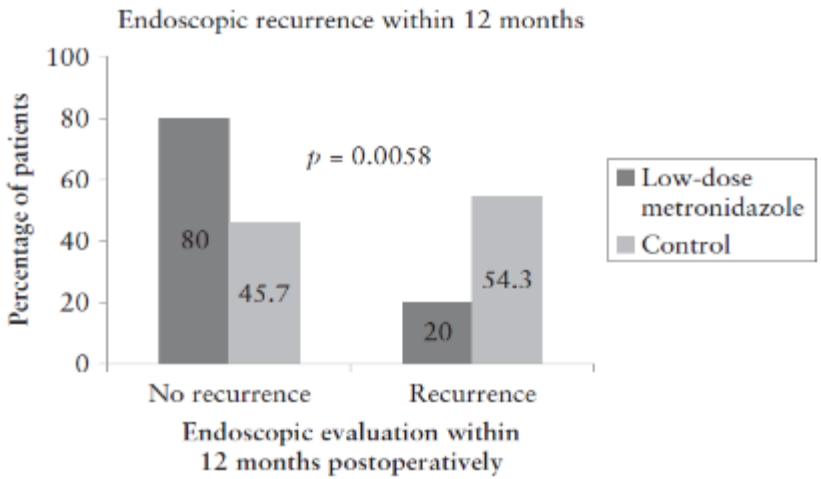
De Cruz P, et al. *Lancet* 2015

Prophylaxis



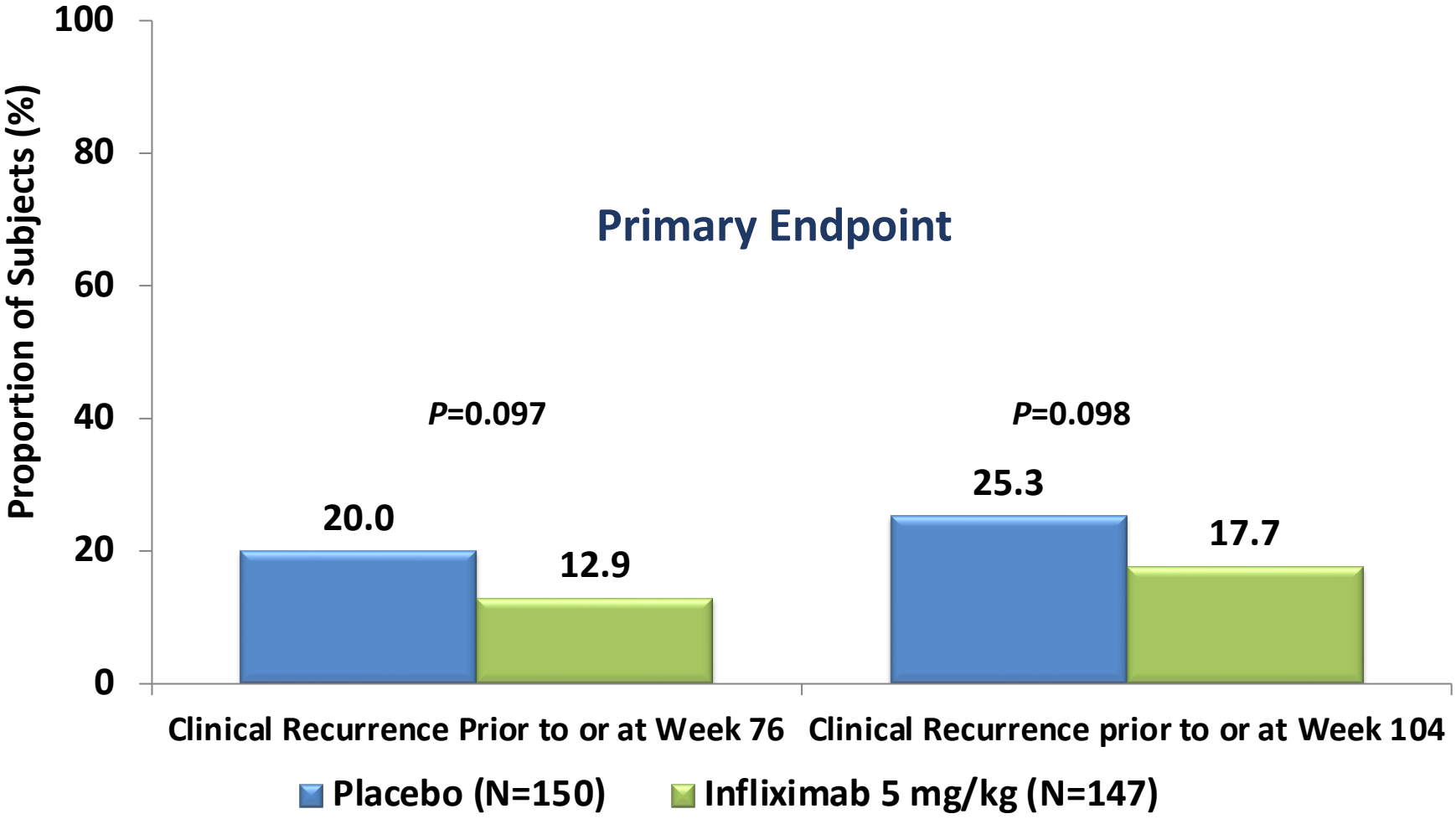
Medical Prophylaxis

Therapy/Intervention	POR Prevention
Curcumin	-
Vitamin D	-
Enteral Nutrition	+
Probiotics	-
Nitroimidazole/Antibiotics	+
Anti-AIEC	?
Mesalamine	-
Budesonide	-
Thiopurines	+/-
Anti-TNF	+++
Vedolizumab	++



Shah R, Click B. Therap Adv Gastroenterol. 2021;
Glick et al *Journal of Crohn's and Colitis* 2019

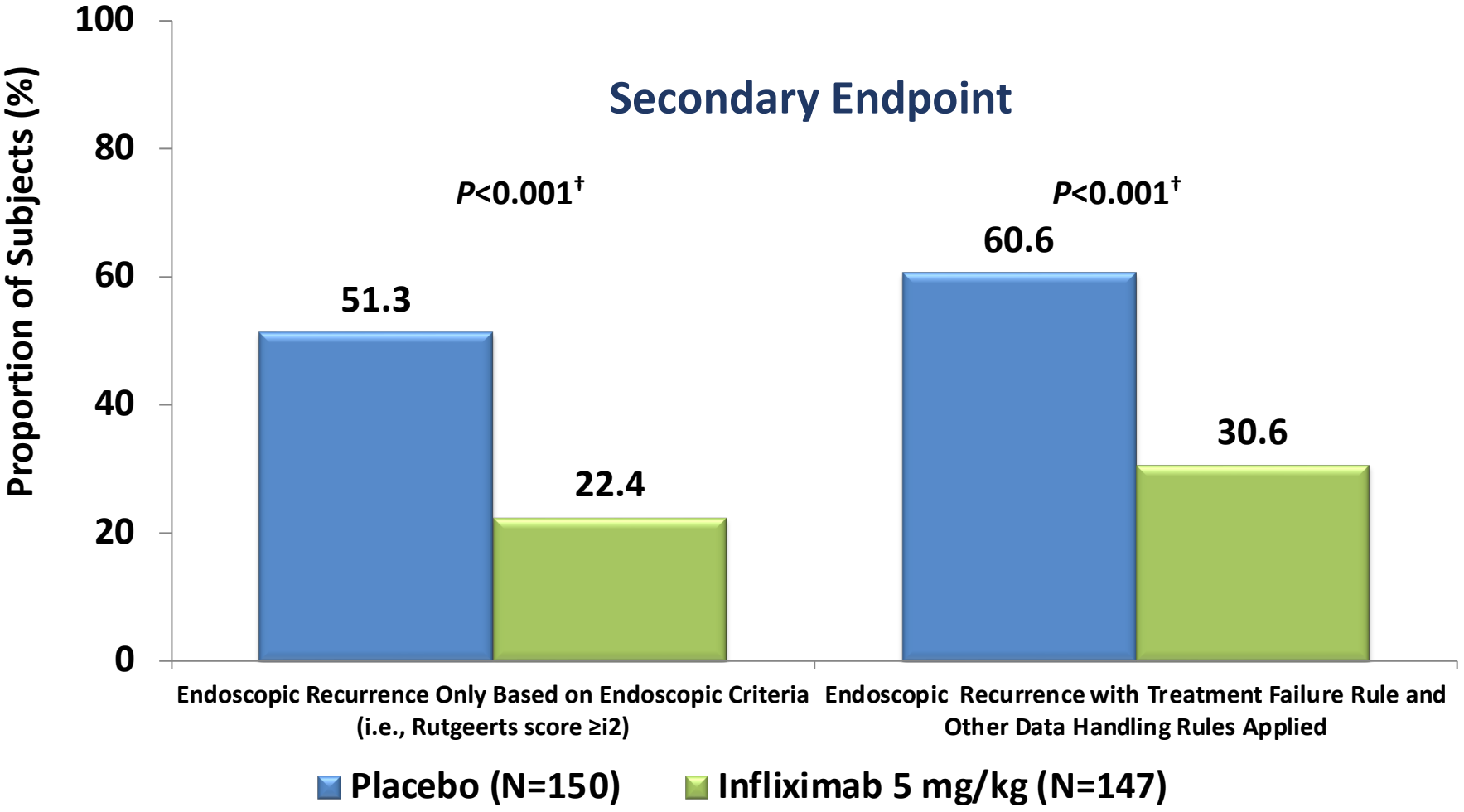
PREVENT - Infliximab



P-values based on the Cochran-Mantel-Haenszel chi-square test stratified by the number of risk factors for recurrence of active CD (1 or >1) and baseline use (yes/no) of an immunosuppressive (ie, AZA, 6-MP, or MTX).

Regueiro M, et al. *Gastroenterology.* 2016;150(7):1568-1578.

PREVENT - Infliximab



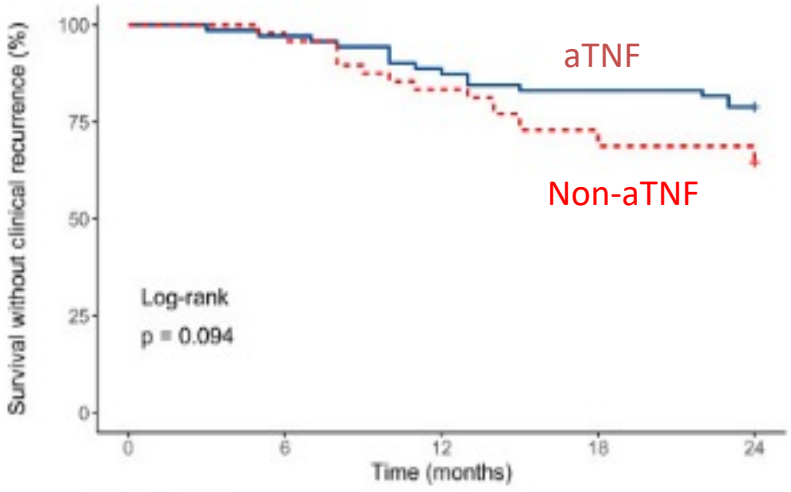
†Nominal p-values based on the Cochran-Mantel-Haenszel chi-square test stratified by the number of risk factors for recurrence of active CD (1 or >1) and baseline use (yes/no) of an immunosuppressive (ie, AZA, 6-MP, or MTX).

Regueiro M, et al. *Gastroenterology.* 2016;150(7):1568-1578.

What if they ‘failed’ anti-TNF prior to surgery?

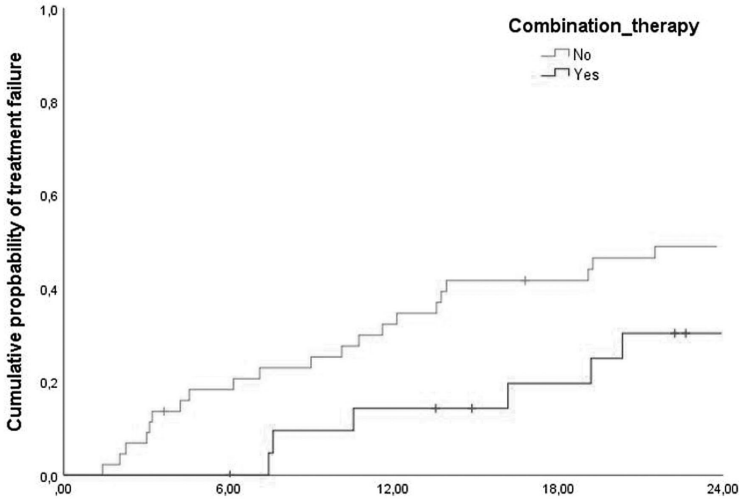
Feasible to use anti-TNF mechanism post-operatively:

1. If using them, consider use of concomitant IM
2. If they had true ‘primary non-response’ pre-surgery, then consider alternative mechanism



No difference in prior aTNF reason for failure

PNR to preop aTNF: higher risk of POR (HR 3.7 [1.32-10.35])



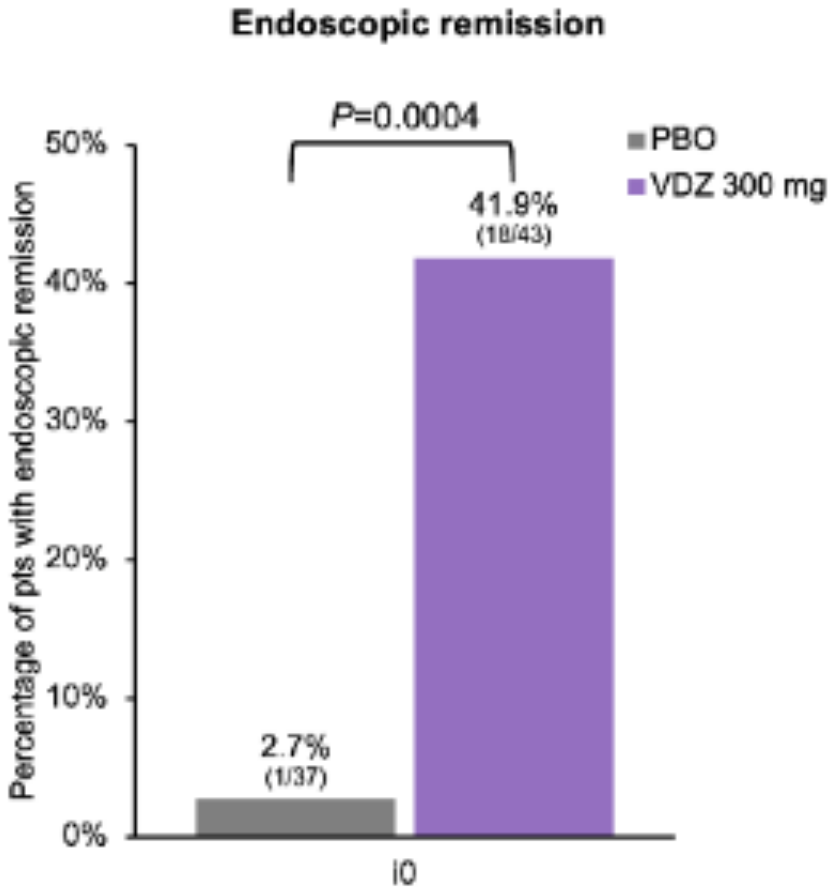
ten Bokkel Huinink S et al. E J Gastro & Hep 2023

Vedolizumab Post-op prevention

Prospective RCT preventive effect of VDZ 300 mg q8w on recurrence of CD following ICR with anastomosis

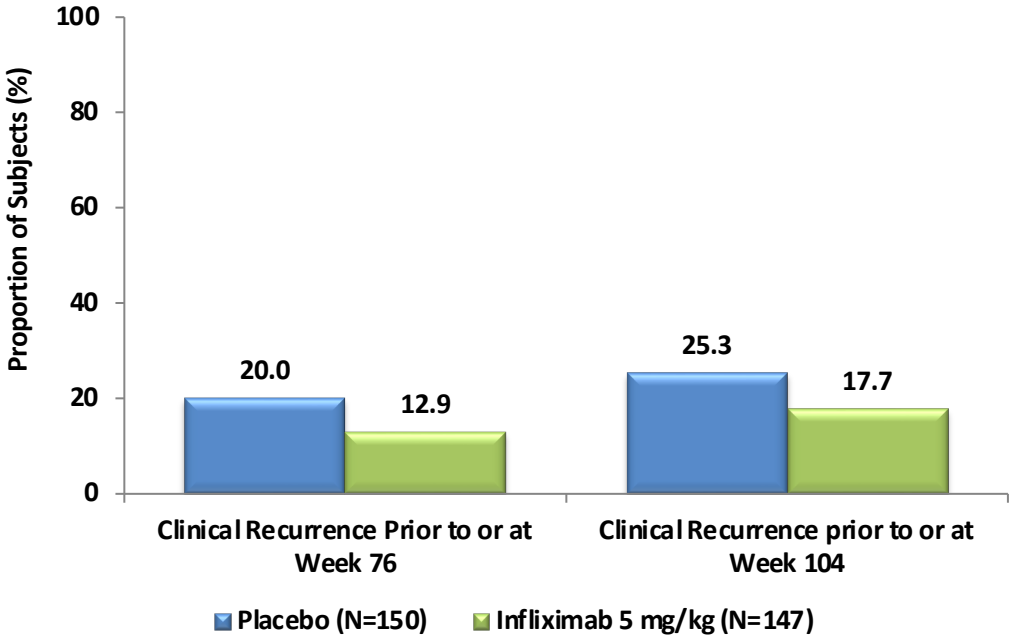
- ≥1 risk factor for recurrence: active smoking, ≥1 prior resection, surgery for perforating complication (abscess, fistula); prior anti-TNF

- VDZ or PBO within 4 wk after surgery; ileocolonoscopy performed 6 mo post-surgery; central scoring using modified Rutgeerts' score



D'Haens et al. ECCO 2023

Clinical Recurrence is low with IFX and VEDO, and no different than Placebo



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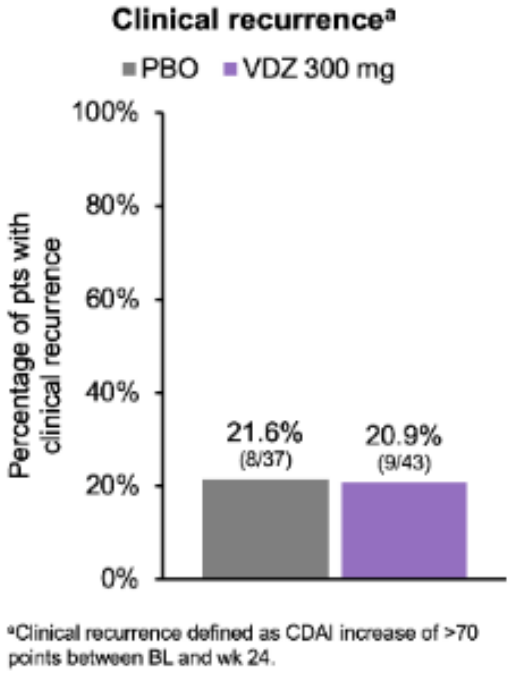
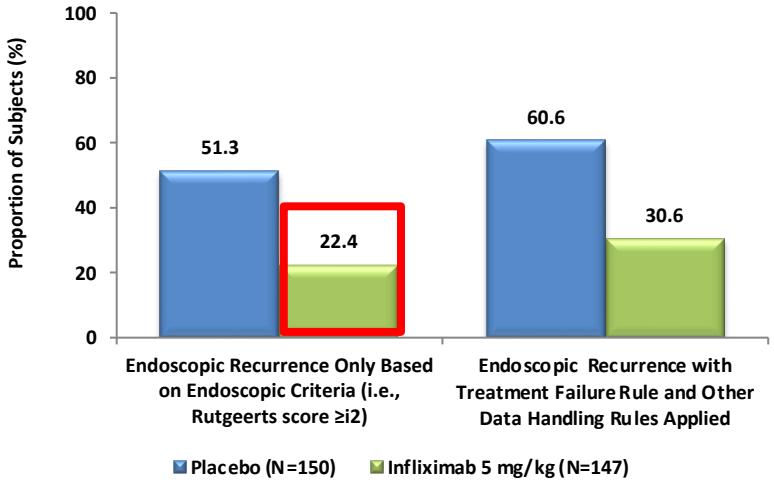


D'Haens et al. ECCO 2023

Endoscopic recurrence
IFX = 22.4% and VEDO = 23.3%



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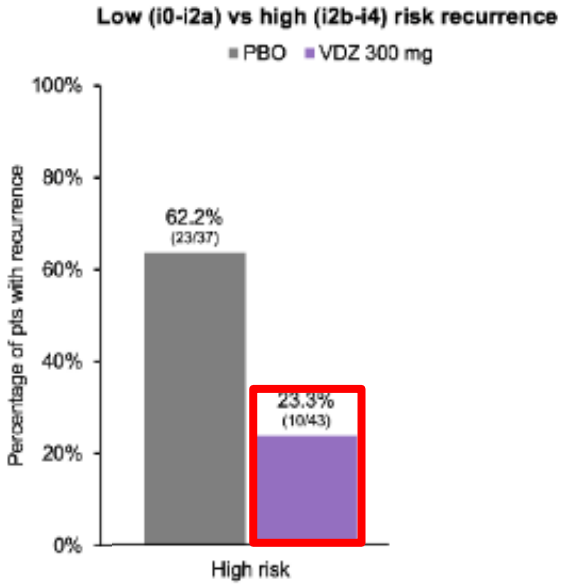
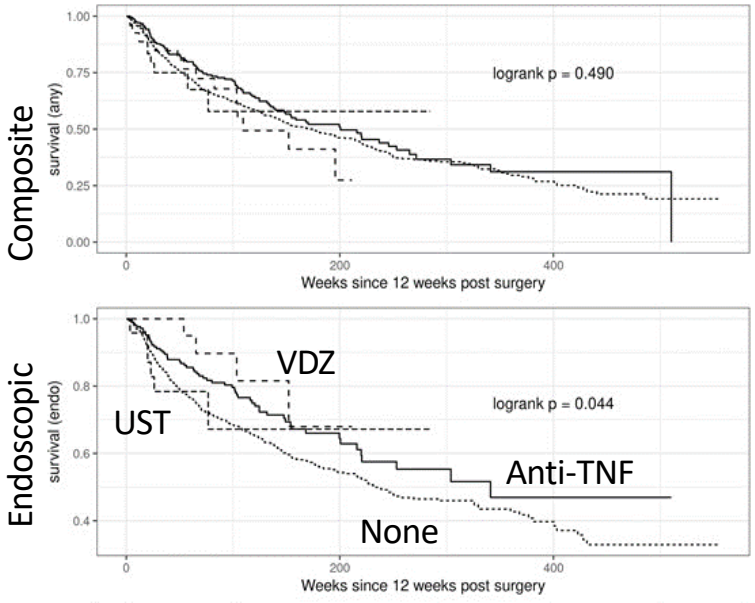


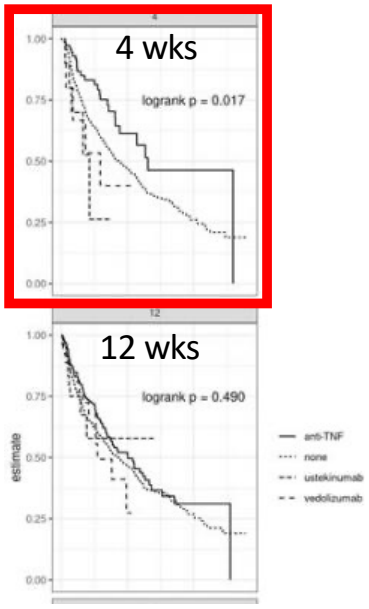
D'Haens et al. ECCO 2023

Note: different study design and endpoints

It may be more about time-to-initiation (within 4 weeks) rather than which biologic



Biologic initiation

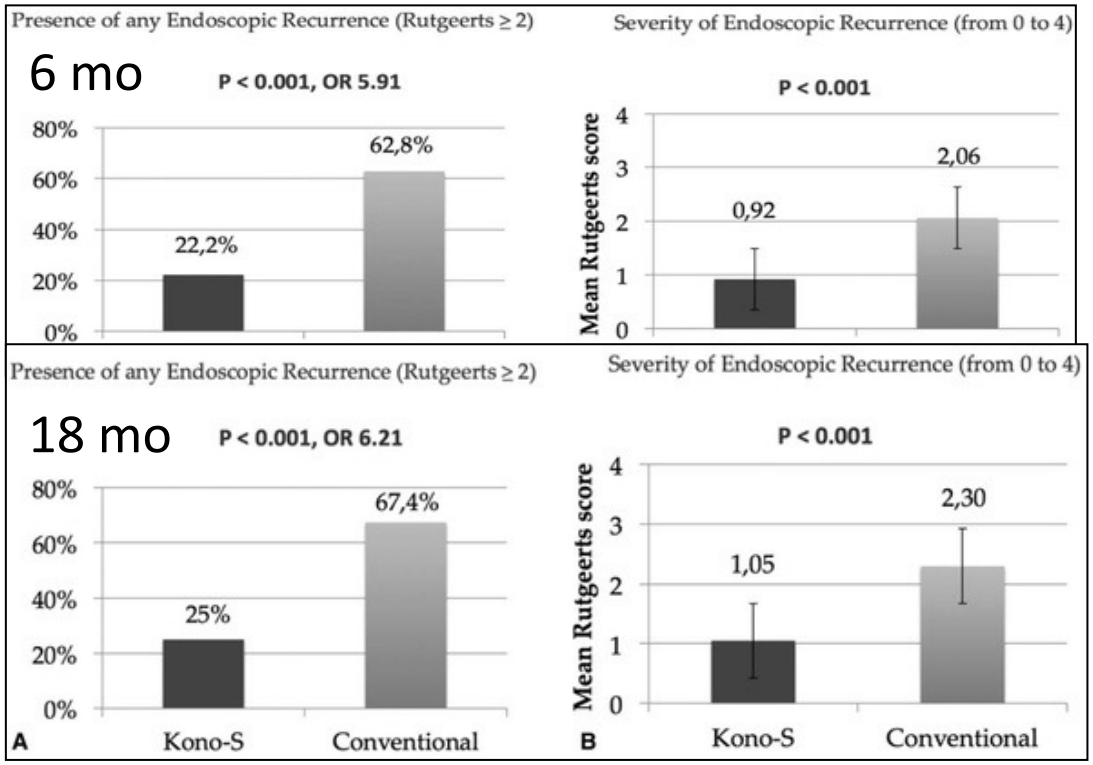


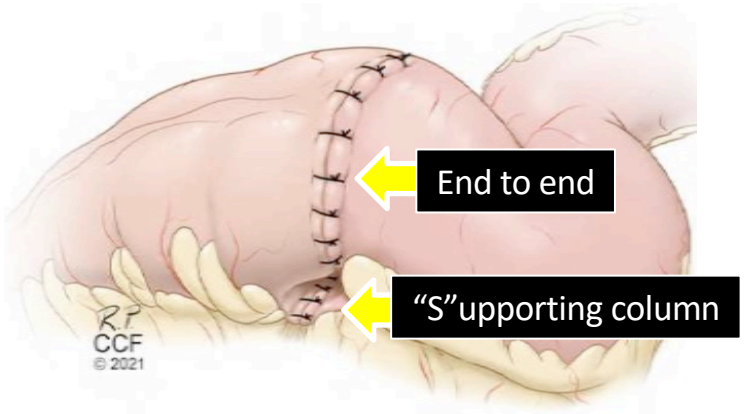
	Any POR aHR (95% CI)	Endoscopic POR aHR (95% CI)
Starting within 4 weeks		
Anti-TNF	0.61 (0.40, 0.93)	0.49 (0.28, 0.84)
Vedolizumab	1.44 (0.59, 3.56)	0.40 (0.05, 2.86)
Ustekinumab	2.06 (0.84, 5.06)	1.77 (0.56, 5.62)
Starting within 4-12 weeks		
Anti-TNF	0.85 (0.67, 1.09)	0.71 (0.53, 0.96)
Vedolizumab	1.14 (0.64, 2.03)	0.44 (0.16, 1.20)
Ustekinumab	1.25 (0.60, 2.60)	1.26 (0.54, 2.93)
Starting within 12-24 weeks		
Anti-TNF	0.88 (0.69, 1.11)	0.78 (0.59, 1.03)
Vedolizumab	0.87 (0.45, 1.68)	0.45 (0.16, 1.22)
Ustekinumab	1.10 (0.57, 2.11)	1.12 (0.54, 2.34)

Axelrad JE, et al. Inflamm Bowel Dis. 2022 Jul 29: PMID: 35905032.

Does the Surgery Matter?

SuPREMe-CD: Kono-S to Prevent POR

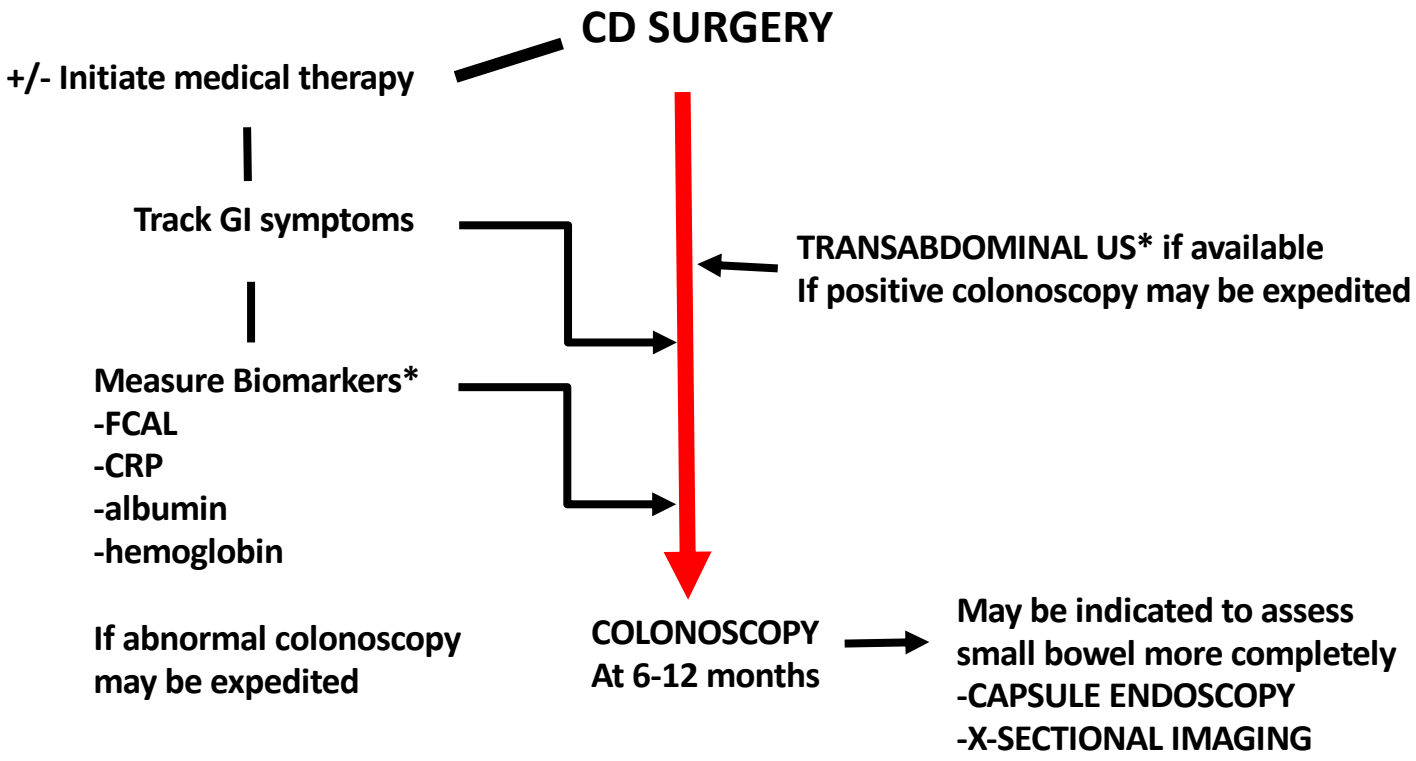




Luglio G, et al. Annals of Surgery. 2020;272(2):210–217.


Surgery
Monitoring
Recurrence

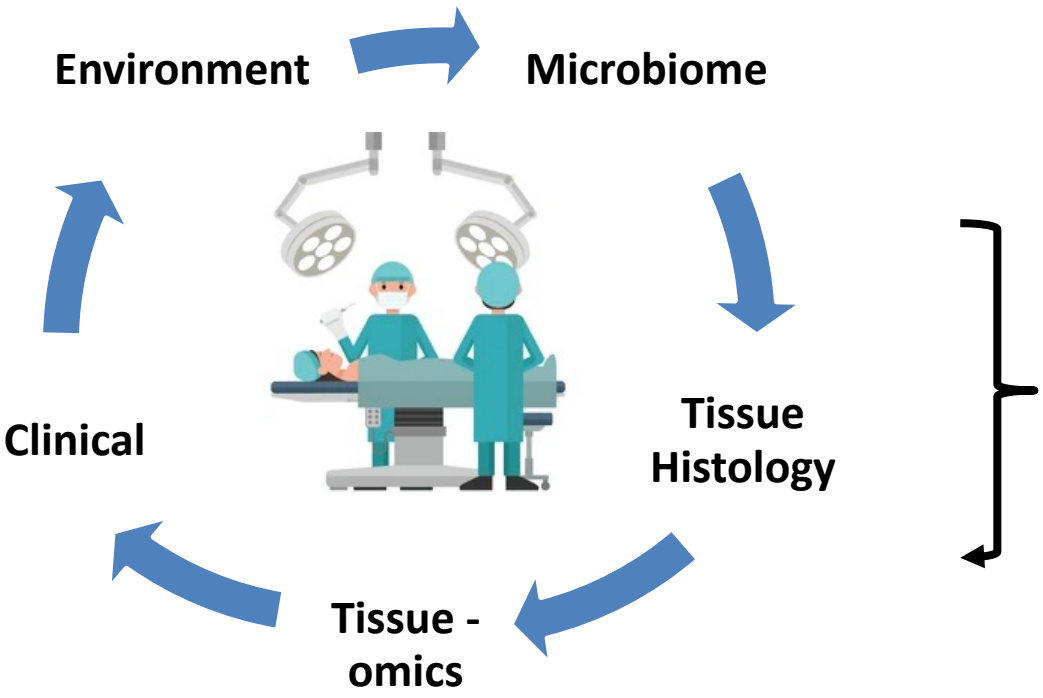
Algorithm for Post Op CD: Emphasis on Monitoring



*consider at 3 months

Bernstein C, Regueiro M *JCG* 2023

Future State of Postop Crohn's



Individualized Risk Score

"Combination Therapy"
Selective microbial altering
Immune modifying
Dietary strategies

Non-invasive monitoring
Confirmatory endoscopy

Take-Home Points – Postop Crohn's

- Postoperative recurrence common in some, not others
- Penetrating disease, young age, and recurrent surgery may be predictors of recurrence – these are the high-risk patients
- Lifestyle may modify recurrence: smoking cessation, diet
- TNFi and Vedo may prevent recurrence in high-risk patients (if previous TNFi failure, then I suggest Vedo)
- Small bowel US (CTE/MRE) and fecal calprotectin are noninvasive ways to monitor postoperative recurrence
- A postop colonoscopy within 12 months has become standard of care, but remaining questions:
  - Who to start postop meds immediately (and which one)?
  - Who to wait on postop meds (not too long or "damage too far gone")?