Choosing and Positioning Biologic Therapy for Crohn's Disease:
(Still) Looking for the Crystal Ball

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Objectives

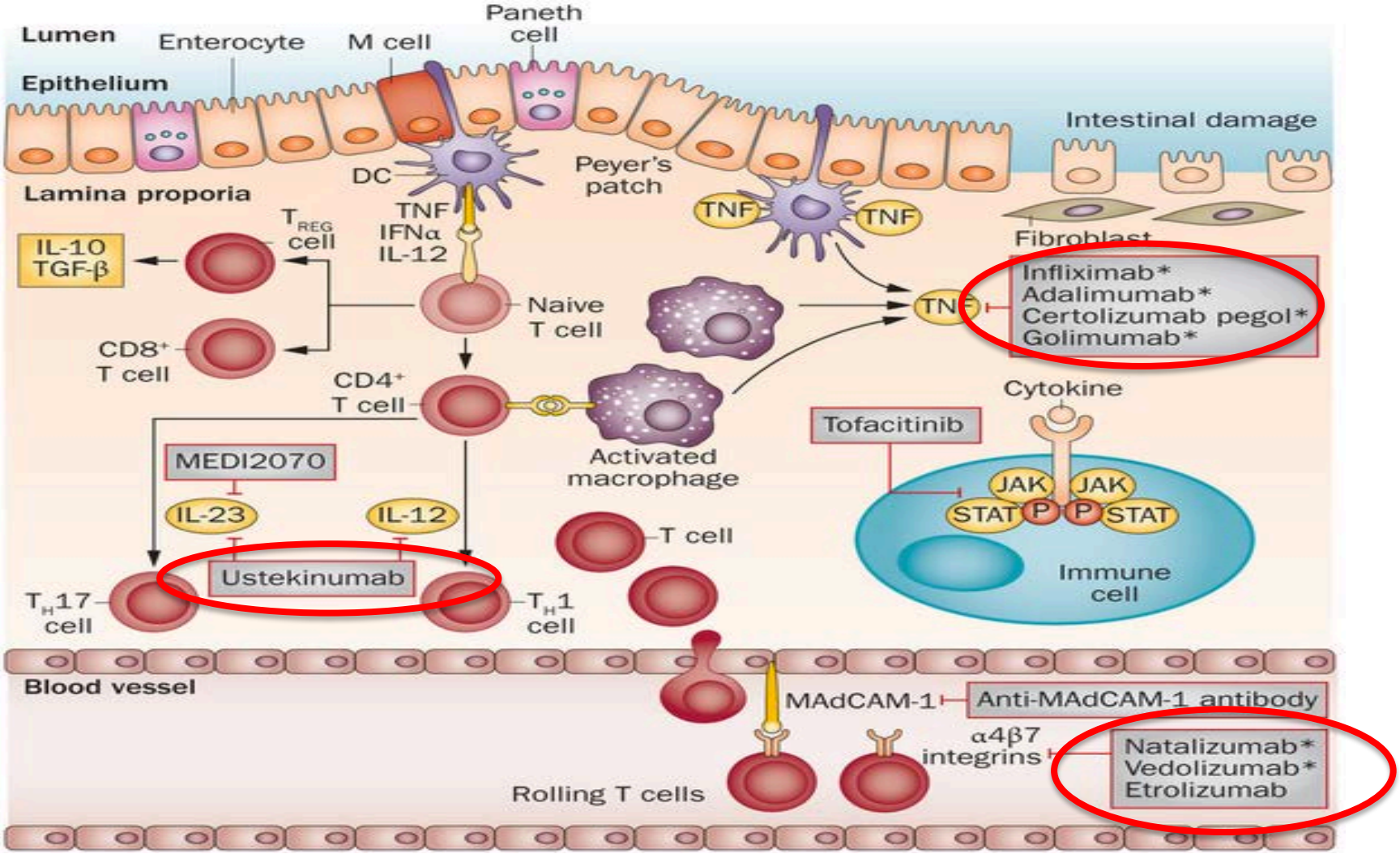
1. Comparative efficacy of biologics for CD
2. Comparative safety of biologics
3. Speed of onset of action
4. Predictors of response

A pledge before we begin

1. I will OBJECTIVELY CONFIRM presence of inflammation in my patients with CD before any treatment change
2. I will OBJECTIVELY CONFIRM resolution of inflammation after any treatment initiation before declaring success
3. I will OPTIMIZE my index biologic before conceding failure
4. I will NOT RESORT to chronic corticosteroids or narcotics to help myself or the patient, or to avoid difficult conversations
5. I will clearly and objectively discuss RISKS with biologic therapies with my patients (rather than let the Internet discuss)

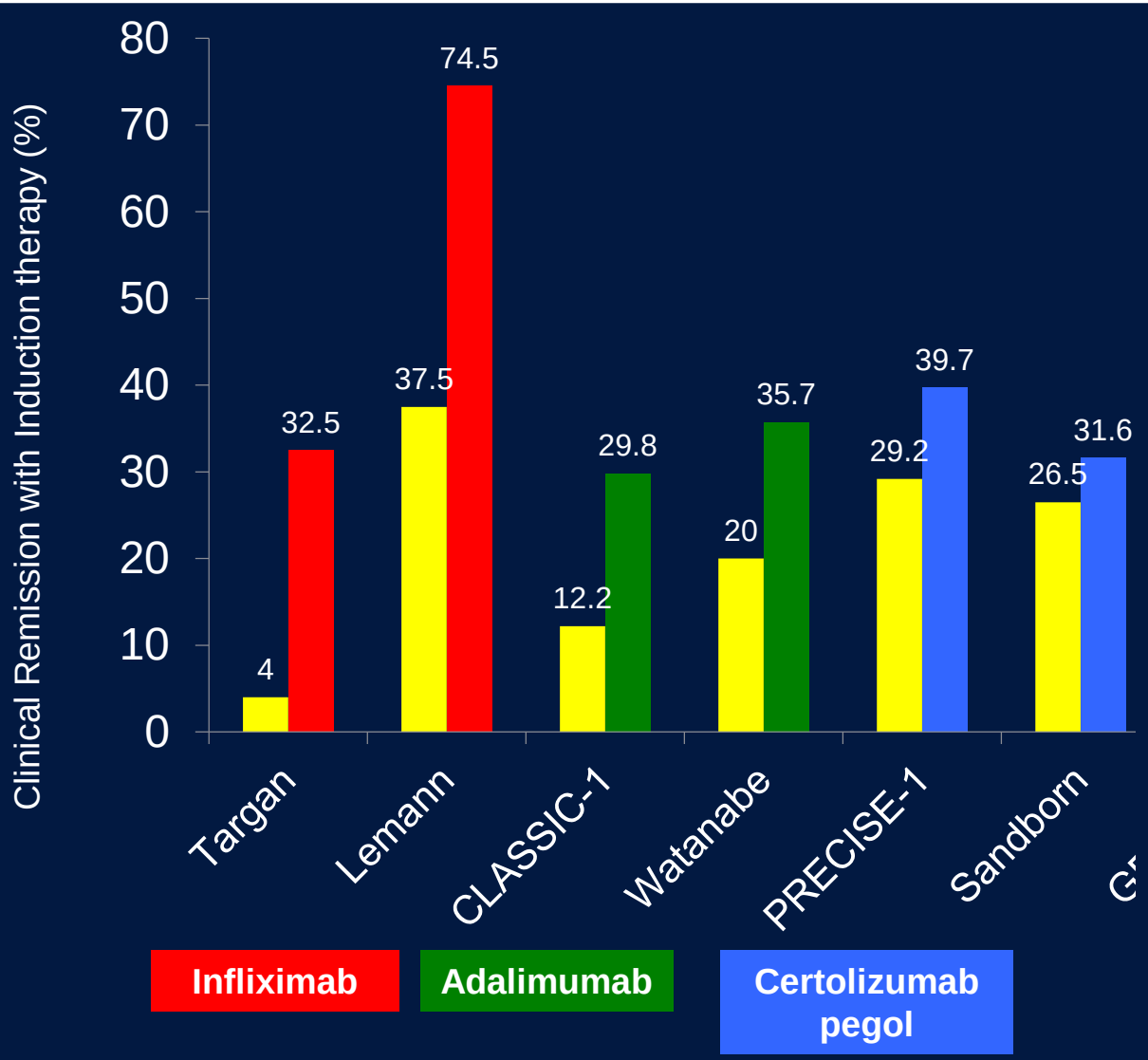
Comparative Efficacy of Different Biologics in Crohn's Disease

Biologics for Moderate-Severe **CROHN'S DISEASE**

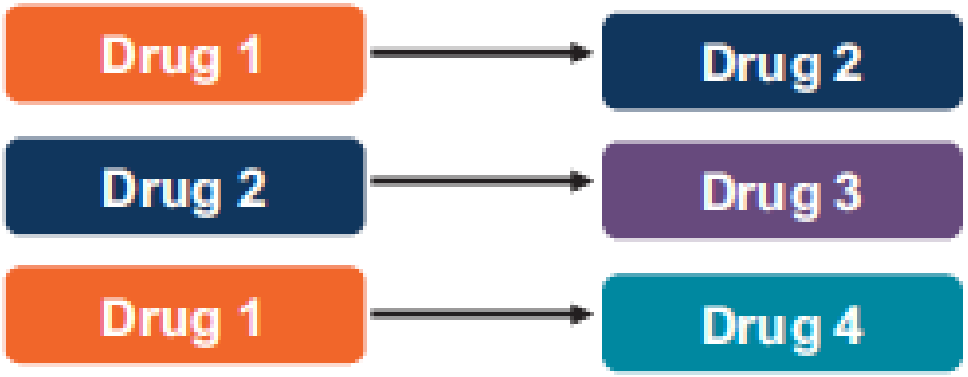


Danese, et al. Nat Rev Gastroenterol Hepatol 2015:12:537

Efficacy of biologics in **CROHN'S DISEASE**
Biologic-naïve patients



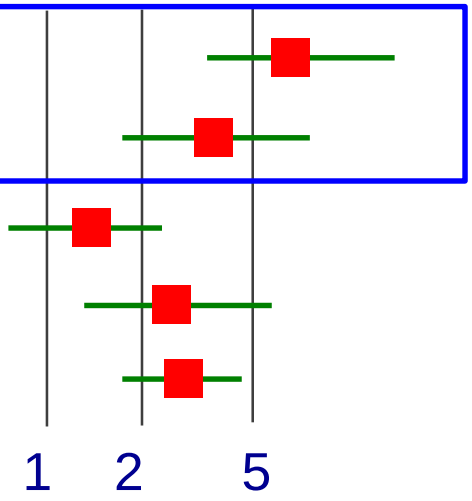
Traditional Pairwise Meta-analysis



Mills, et al. JAMA 2012;308:1246; Capriani et al. Ann Intern Med 2013;159:130; Singh S. Clin Transl Gastroenterol 2017;8:e93

Comparative Efficacy:
First-line Therapy for Induction of Remission

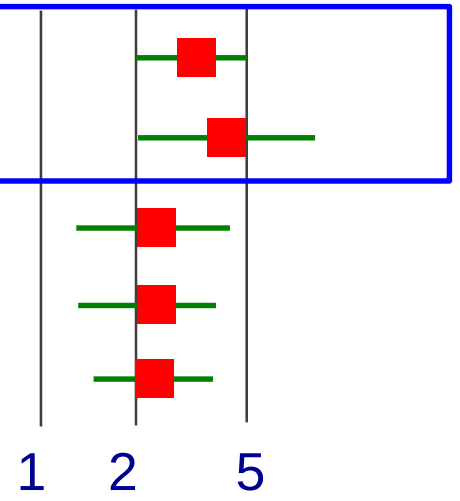
Drug	Odds ratio	Lower limit	Upper limit	SUCRA ranking
Infliximab	**5.90**	2.78	12.51	**0.93**
Adalimumab	**3.80**	1.76	8.18	**0.75**
Certolizumab Pegol	1.36	0.89	2.08	0.20
Vedolizumab	2.69	1.36	5.32	0.55
Ustekinumab	2.75	1.76	4.32	0.56



Singh, et al. Aliment Pharmacol Ther 2018

Comparative Efficacy:
Maintenance of Remission
(among Responders to Induction therapy)

Drug	Odds ratio	Lower limit	Upper limit	SUCRA ranking
Infliximab	**3.06**	1.91	4.91	**0.73**
Adalimumab	**4.89**	3.09	7.74	**0.98**
Certolizumab Pegol	2.25	1.51	3.35	0.47
Vedolizumab	2.20	1.40	3.34	0.46
Ustekinumab	2.02	1.35	3.03	0.36



Singh, et al. Aliment Pharmacol Ther 2018

Estimated Rates of **INDUCTION and MAINTENANCE of Remission**

FIRST-LINE Crohn's Disease

Agent	Induction of Clinical Remission	Maintenance of Clinical Remission	GRADE Quality of Evidence
Placebo	**16%**	**22%**	
Infliximab			
Adalimumab			
Certolizumab pegol			
Vedolizumab			
Ustekinumab			

Singh, et al. Aliment Pharmacol Ther 2018

Estimated Rates of **INDUCTION and MAINTENANCE of Remission**

FIRST-LINE Crohn's Disease

Agent	Induction of Clinical Remission	Maintenance of Clinical Remission	GRADE Quality of Evidence
Placebo	**16%**	**22%**	-
Infliximab	**53**	**46**	⊕⊕◯◯ [Low]
Adalimumab	**42**	**57**	⊕⊕⊕◯ [Moderate]
Certolizumab pegol	21	38	⊕⊕◯◯ [Low]
Vedolizumab	34	38	⊕⊕⊕◯ [Moderate]
Ustekinumab	34	36	⊕⊕⊕◯ [Moderate]

Singh, et al. Aliment Pharmacol Ther 2018

Estimated Rates of **INDUCTION of Clinical Remission**
SECOND-LINE Crohn's Disease

Agent	Induction of Clinical Remission	SUCRA Ranking Probability	GRADE Quality of Evidence
Placebo	**9%**	**0%**	-
Adalimumab*	25	91%	⊕⊕◯◯ [Low]
Vedolizumab	12	35%	⊕⊕⊕◯ [Moderate]
Ustekinumab	19	71%	⊕⊕◯◯ [Low]

*Adalimumab was selectively studied in patients with PRIOR RESPONSE to infliximab who then develop secondary loss of response or intolerance; patients with primary non-response to infliximab were excluded

Singh, et al. Aliment Pharmacol Ther 2018

Anticipated Head-to-Head Trials

1. **Ustekinumab vs. Adalimumab** (SEAVUE – NCT03464136)
   - 52-week trial, 350 patients; Double-blind, double-dummy
   - Anticipated completion – December 2020
2. **Brazikumab** (anti-IL23) **vs. Adalimumab vs. placebo**
   - 52-week trial, 11400 patients; double-blind, double-dummy, placebo and active comparator controlled
   - Anticipated completion – December 2022
3. **Standard vs. high-dose Adalimumab** (SERENE CD)
   - Compares standard ADA dose (160/80) vs. higher induction dose, and standard vs. higher vs. TDM-guided maintenance
   - 52-week trial, 940 patients

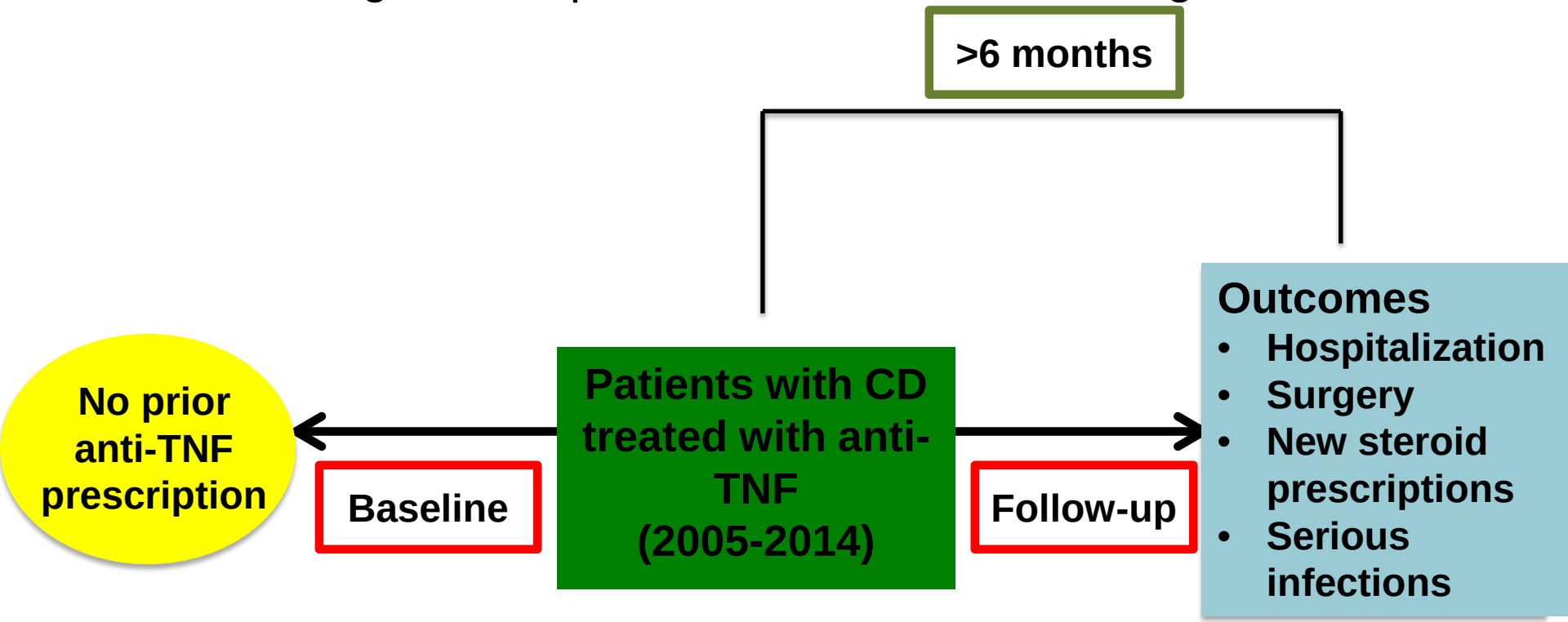
Real-world/Observational Comparative Effectiveness Studies

WILEY APT Alimentary Pharmacology & Therapeutics

Comparison of infliximab with adalimumab in 827 biologic-naïve patients with Crohn's disease: a population-based Danish cohort study

S. Singh[1] | N. N. Andersen[2] | M. Andersson[2] | E. V. Loftus Jr.[3] | T. Jess[2,4]

- Population-based, propensity score-matched cohort study
- Denmark, 2005-14
- Biologic-naïve patients with CD
- 2908 biologic-naïve patients with CD, between ages 15-75



Singh, et al. Aliment Pharmacol Ther 2018

Infliximab vs. Adalimumab for Crohn's disease

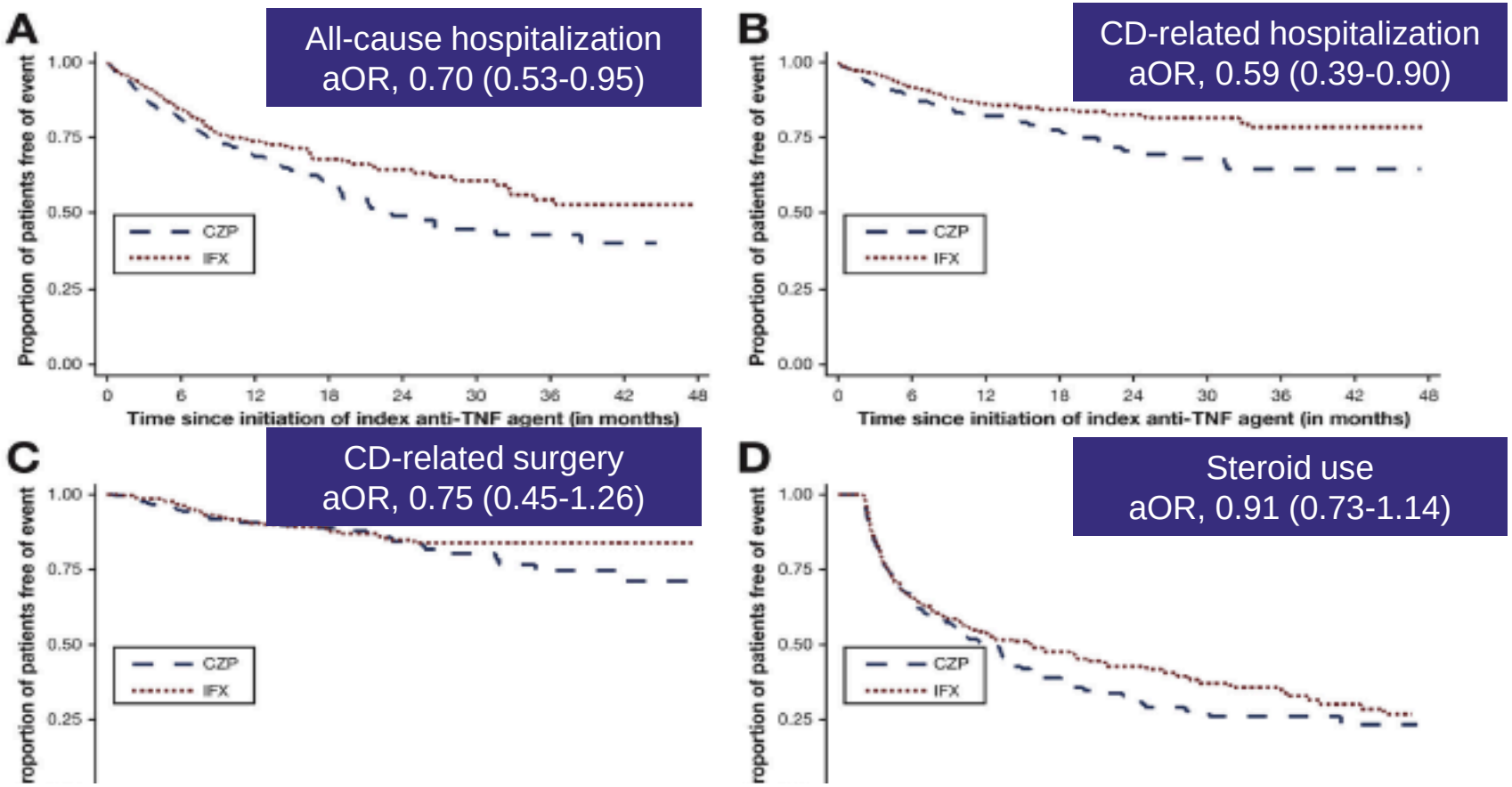
Patient-relevant outcomes after starting index anti-TNF agent	Events per 100 Patient-Yrs (Propensity-score matched)		Hazard ratio (95% CI) (IFX vs. ADA as reference)
	IFX (n=315)	ADA (n=512)	
Effectiveness Outcomes			
All-cause hospitalization	**43.7**	**45.8**	**1.35 (1.03-1.79)**
CD-related hospitalization	18.7	21.0	1.23 (0.83-1.81)
Major abdominal surgery	5.5	7.9	0.81 (0.43-1.52)
Steroid prescription	7.6	11.9	0.88 (0.48-1.64)
Safety Outcomes			
Serious infection	1.9	10.3	0.95 (0.24-3.81)

Singh, et al. Aliment Pharmacol Ther 2018

Comparative Effectiveness and Safety of Anti–Tumor Necrosis Factor Agents in Biologic-Naive Patients With Crohn's Disease

Siddharth Singh,[*,‡,§] Herbert C. Heien,[‖] Lindsey R. Sangaralingham,[‖] Stephanie R. Schilz,[‖] Michael D. Kappelman,[¶] Nilay D. Shah,[‖,#,**] and Edward V. Loftus Jr[*]

Clinical Gastroenterology and Hepatology 2016;14:1120–1129



Infliximab vs. Certolizumab pegol for Crohn's disease

Singh, et al. Clin Gastroenterol Hepatol 2018

Vedolizumab vs. Anti-TNF Agents in CD: VICTORY Consortium

- Propensity score-matched, retrospective cohort study
- VICTORY Consortium, 16 sites across US
- 1200 patients, 1:1 for vedolizumab vs. anti-TNF; consecutive patients initiated on biologic at individual sites since 2014

	Overall (Vedo vs. anti-TNF)	Anti-TNF-naïve	Anti-TNF-exposed
Clinical remission	0.92 (0.47-1.70)	0.92 (0.46-1.86)	0.97 (0.52-1.82)
Steroid-free clinical remission	1.26 (0.42-3.83)	2.53 (0.97-6.60)	1.57 (0.37 – 6.58)
Endoscopic remission	1.31 (0.61-2.78)	0.86 (0.32-2.33)	1.04 (0.43-2.52)

Dulai, et al. ECCO 2018, personal communication

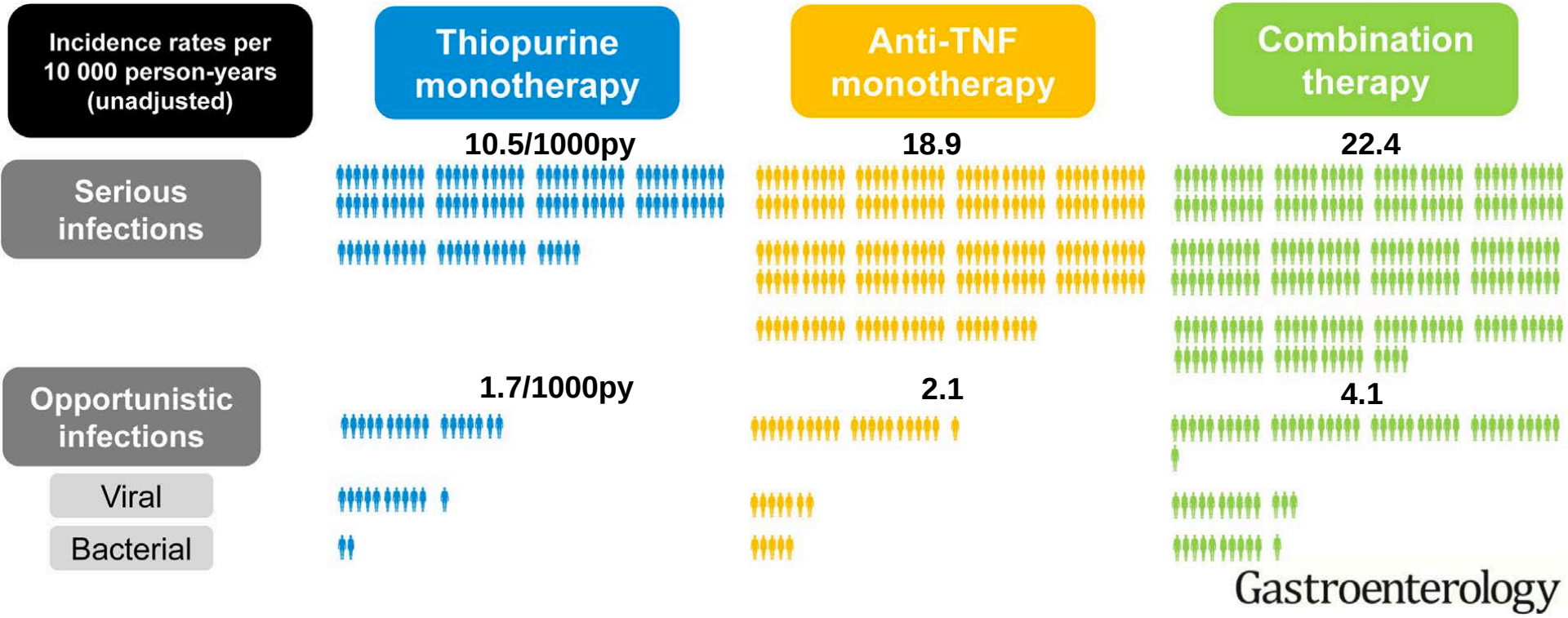
Overall and Comparative Safety of Biologic Therapy in IBD

Serious infections
Malignancy risk, especially lymphoma

Risk of Serious and Opportunistic Infections Associated With Treatment of Inflammatory Bowel Diseases

Julien Kirchgesner,[1,2,3] Magali Lemaitre,[1] Fabrice Carrat,[2] Mahmoud Zureik,[1,5] Franck Carbonnel,[4] and Rosemary Dray-Spira[1]

Gastroenterology 2018;155:337–346



Risk Factors for **Serious and/or Opportunistic Infections** in Anti-TNF-treated Patients

- 2,226 **ADA-treated patients from clinical trials**; 35y, 60% females
- 47% on concomitant immunomodulators, 39% on steroids; 27% with fistulae

Risk of serious infection

Risk factors*	HR	95% CI
100-point increase in CDAI	**1.39**	**1.19-1.63**
ADA+Immunomodulator vs. ADA	0.68	0.38-1.24
ADA + Corticosteroids vs. ADA	**2.40**	**1.33-4.35**

*Similar results if limited to non-CD-related serious infections, or opportunistic infections

- **TREAT Registry**, Infliximab
- Risk factors for DEATH – prednisone (HR, 2.1), narcotic use (HR, 1.8) and age (HR, 1.1)

Risk of serious infection

Risk factors*	HR (95% CI)
Moderate-severe disease activity	**2.24** (1.57-3.19)
Narcotic analgesics	**1.98** (1.44-2.73)
Prednisone therapy	**1.57** (1.17-2.10)
Infliximab	**1.43** (1.11-.84)

Underlying DISEASE ACTIVITY and Corticosteroid use is associated with increased risk of infections

Osterman, et al. Am J Gastroenterol 2016;111:1806; Lichtenstein, et al. Am J Gastroenterol 2012;107:1409

Disease-related risk factors for serious infections in IBD

Type of infection	Rate per 10,000 pt-yrs – all patients
Pneumonia	17
Abdominal abscess	9
Catheter sepsis	
Sepsis	
Cellulitis	
Central line infection	6
Perirectal abscess	5
Pelvic abscess	5
Intestinal abscess	4
Wound infection	3
Postoperative abscess	2

MODERATE TO SEVERE ACTIVITY = strongest predictor of serious infection (HR 2.2)

Inadequate disease control is a KEY risk factor for infections

Lichtenstein et al. Am J Gastroenterol, 2012.

Potentially preventable infections

Type of infection	Rate per 10,000 pt-yrs – all patients
Pneumonia	17
Abdominal abscess	9
Catheter sepsis	
Sepsis	
Cellulitis	
Central line infection	
Perirectal abscess	
Pelvic abscess	
Intestinal abscess	
Wound infection	
Postoperative abscess	2

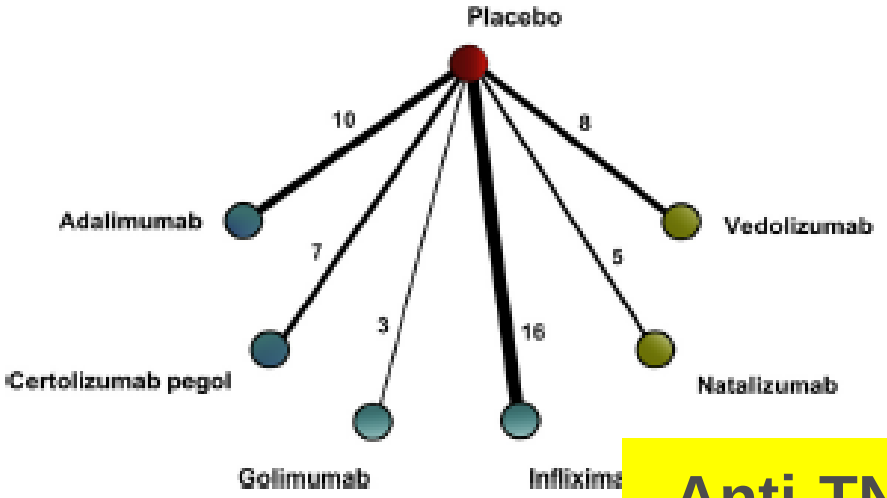
Measures where we can improve care for the hospitalized patient?

1. Improving nutritional status pre-op
2. Removing indwelling catheters as early as possible
3. Close monitoring of wound sites post-op
4. Incentive spirometry
5. Appropriate steroid tapering pre- & post-op

Biologic Therapies and Risk of Infection and Malignancy in Patients With Inflammatory Bowel Disease: A Systematic Review and Network Meta-analysis

Stefanos Bonovas,* Gionata Fiorino,* Mariangela Allocca,* Theodore Lytras,[‡,§,‖] Georgios K. Nikolopoulos,[‖] Laurent Peyrin-Biroulet,[¶] and Silvio Danese[#]

Clinical Gastroenterology and Hepatology 2016;14:1385–1397



- 44 trials of biologic agents; 14,032 patients
- Serious infection: 2.1%

Anti-TNF vs. anti-integrin

Safety Outcome	Odds Ratio	95% CI
Serious infection	1.04	0.60-1.78
Opportunistic infection	0.95	0.28-3.28
ANY infection	1.06	0.26-1.90
Malignancy	0.87	0.26-2.88

Comparative safety
Anti-TNF agents vs. Vedolizumab

Biologic Monotherapy

	Vedolizumab	Anti-TNF	Odds Ratio	95% CI
Serious Infections	4.1%	10.1%	0.37	0.13-1.02
Serious Adverse Events	4.7%	14.5%	**0.29**	**0.12-0.73**

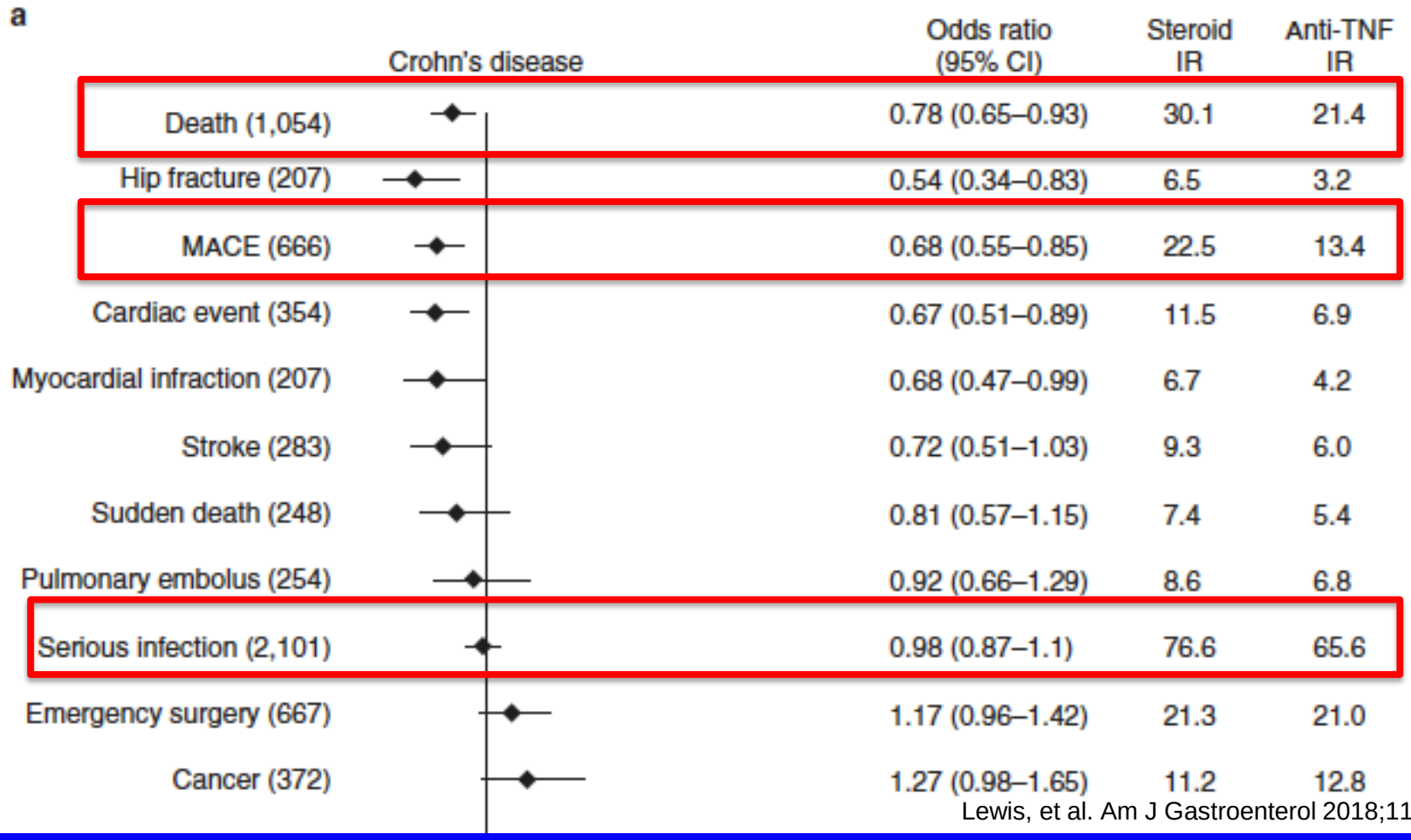
Biologic + Steroids + Immunomodulator

	Vedolizumab	Anti-TNF	Odds Ratio	95% CI
Serious Infections	11.5%	13.9%	0.81	0.31-2.07
Serious Adverse Events	14%	14%	0.66	0.27-1.65

Vedolizumab monotherapy is associated with lower risk of serious infections vs. anti-TNF monotherapy …
But safety advantage lost when used in combination

Dulai, et al. ECCO 2018

Comparative safety
Anti-TNF agents vs. Prolonged Corticosteroids



Lewis, et al. Am J Gastroenterol 2018;113:405

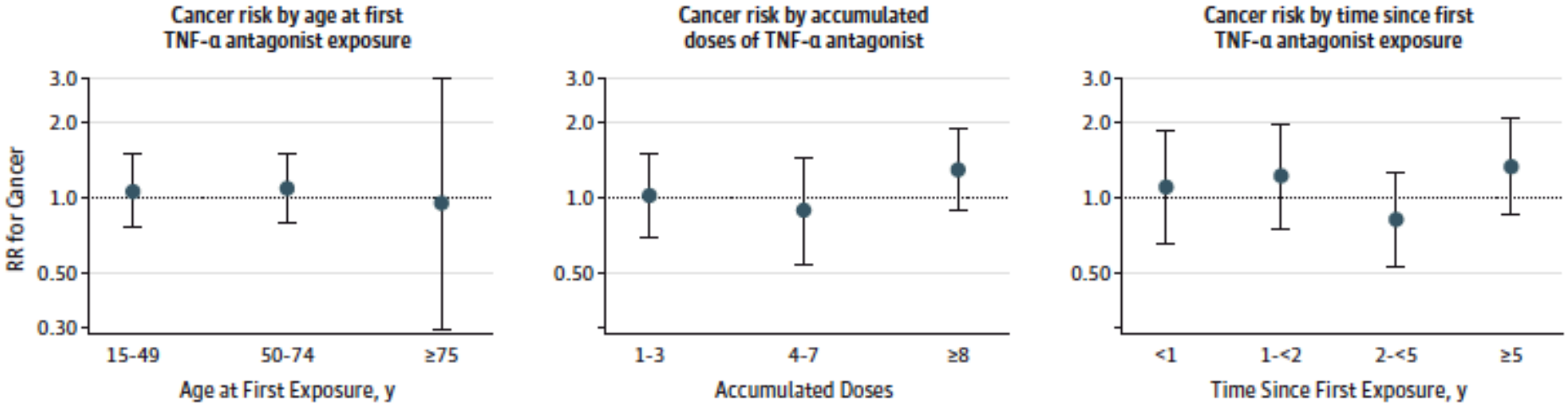
Lower risk of death, major adverse cardiovascular events, fractures in anti-TNF-treated patients vs. long-term corticosteroids, without an increase in risk of serious infections

Original Investigation

Association Between Tumor Necrosis Factor-α Antagonists and Risk of Cancer in Patients With Inflammatory Bowel Disease

Nynne Nyboe Andersen, MD; Björn Pasternak, MD, PhD; Saima Basit, MSc; Mikael Andersson, MSc; Henrik Svanström, MSc; Sarah Caspersen, MD; Pia Munkholm, MD, DMSc; Anders Hviid, MSc, DMSc; Tine Jess, MD, DMSc

Figure 2. Risk of Cancer According to Age at First Exposure to a TNF-α Antagonist, Accumulated Doses of TNF-α Antagonists, and Time Since First Dose of a TNF-α Antagonist, Comparing Exposed and Unexposed Patients With Inflammatory Bowel Disease



Exposed								
Person-years	15007	3261	149	6694	4664	7083	3115	3591	7190	4545
Cases, No.	38	40	3	31	18	32	16	19	23	23

Anti-TNF therapy is NOT associated with increased risk of cancer in patients with IBD

Nyboe Andersen, et al. JAMA 2014;311:2406

JAMA | Original Investigation

Association Between Use of Thiopurines or Tumor Necrosis Factor Antagonists Alone or in Combination and Risk of Lymphoma in Patients With Inflammatory Bowel Disease

Magali Lemaitre, PhD; Julien Kirchgesner, MD, MSc; Annie Rudnichi, MD; Fabrice Carrat, MD, PhD; Mahmoud Zureik, MD, PhD; Franck Carbonnel, MD, PhD; Rosemary Dray-Spira, MD, PhD

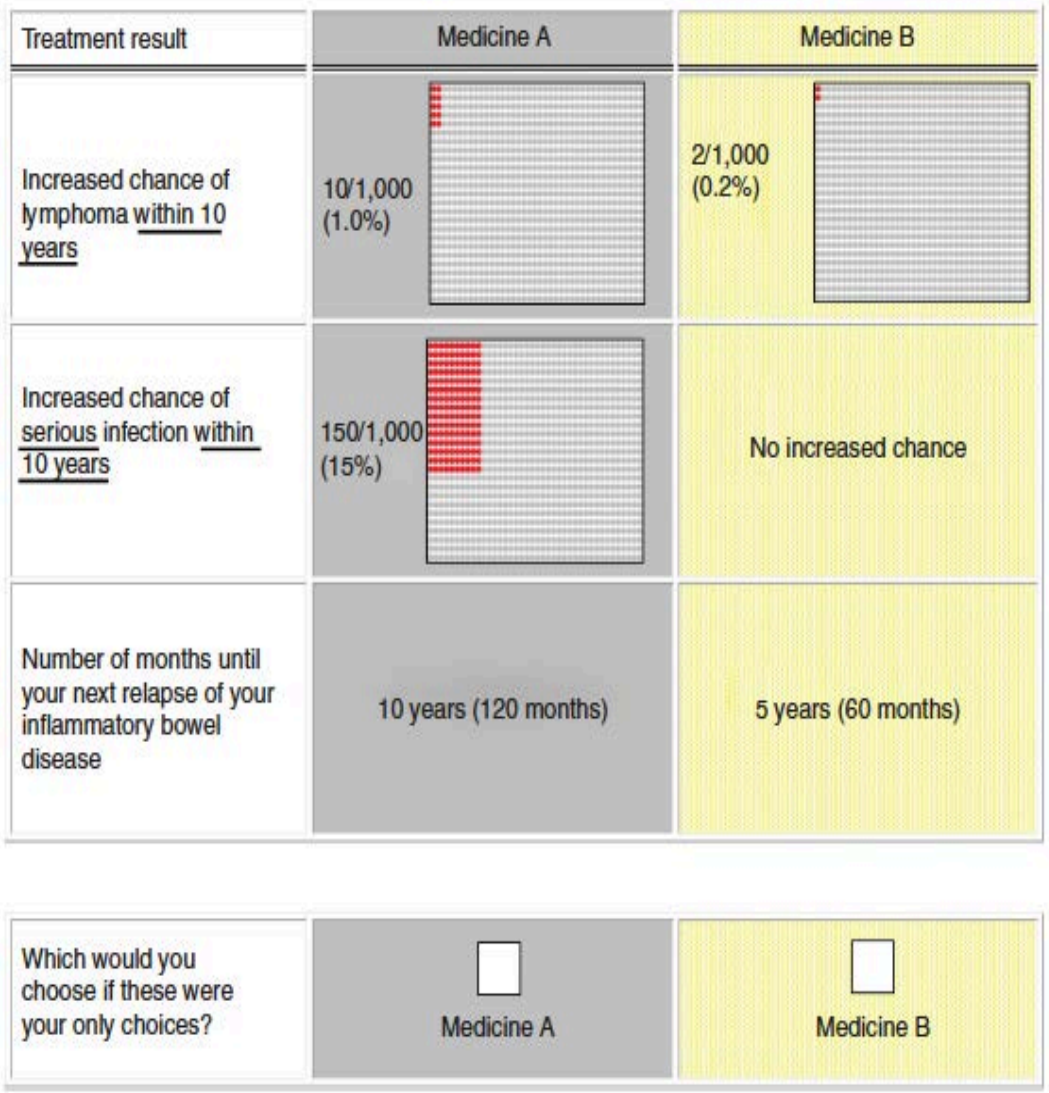
Lymphoma Type	Overall (1 060 336 PY)		Unexposed to Thiopurines or Anti-TNF Agents (838 611 PY)		Exposed to Thiopurine Monotherapy (129 743 PY)		Exposed to Anti-TNF Monotherapy (77 229 PY)		Exposed to Combination Therapy (14 753 PY)	
	No. of Events	IR per 1000 PY (95% CI)	No. of Events	IR per 1000 PY (95% CI)	No. of Events	IR per 1000 PY (95% CI)	No. of Events	IR per 1000 PY (95% CI)	No. of Events	IR per 1000 PY (95% CI)
All Patients										
All lymphoma	336	0.32 (0.28-0.35)	220	0.26 (0.23-0.29)	70	0.54 (0.41-0.67)	32	0.41 (0.27-0.55)	14	0.95 (0.45-1.45)

Lymphoma Type	Exposed to Thiopurine Monotherapy vs Unexposed to Thiopurines or Anti-TNF Agents		Exposed to Anti-TNF Monotherapy vs Unexposed to Thiopurines or Anti-TNF Agents	
	Crude HR (95% CI)	Adjusted HR (95% CI)[a]	Crude HR (95% CI)	Adjusted HR (95% CI)[a]
All Patients				
All lymphoma	2.06 (1.58-2.70)	2.60 (1.96-3.44)	1.57 (1.08-2.28)	2.41 (1.60-3.64)

Thiopurine monotherapy and anti-TNF monotherapy may be associated with increased risk of lymphoma in patients with IBD … and risk is highest with combination therapy

Kirchgesner et al. Gastroenterology 2018;155:337

What risks are our PATIENTS willing to take?



- Discrete choice experiment, in 202 patients with IBD (70% in remission)
- To avoid disease relapse over next 5 years, patients are willing to accept a 28% chance of serious infection, and 1.8% chance of lymphoma

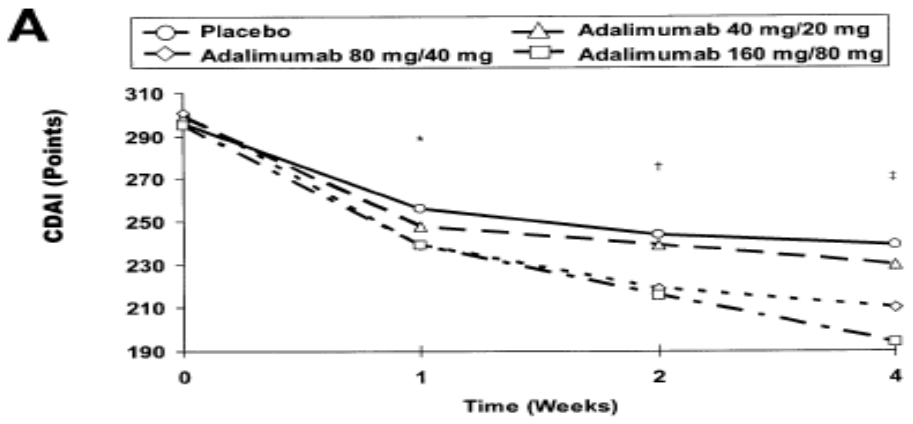
Bewtra, et al. Am J Gastroenterol 2015;110:1675

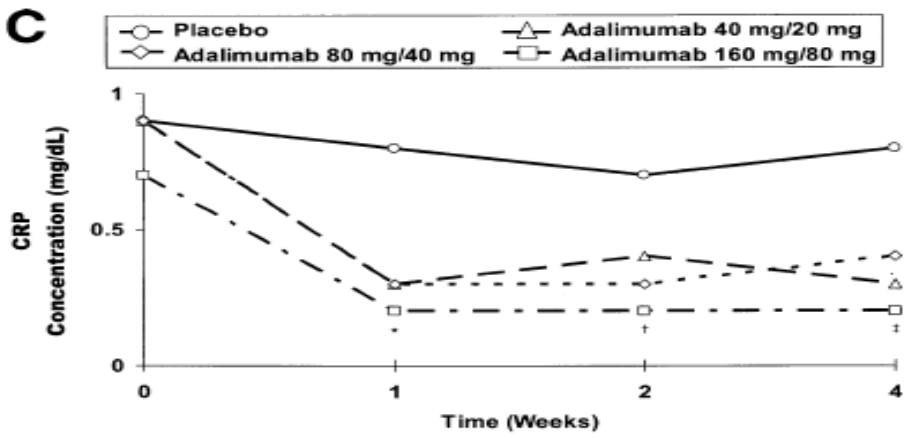
Overall and Comparative Efficacy and Safety of Different Biologics Agents

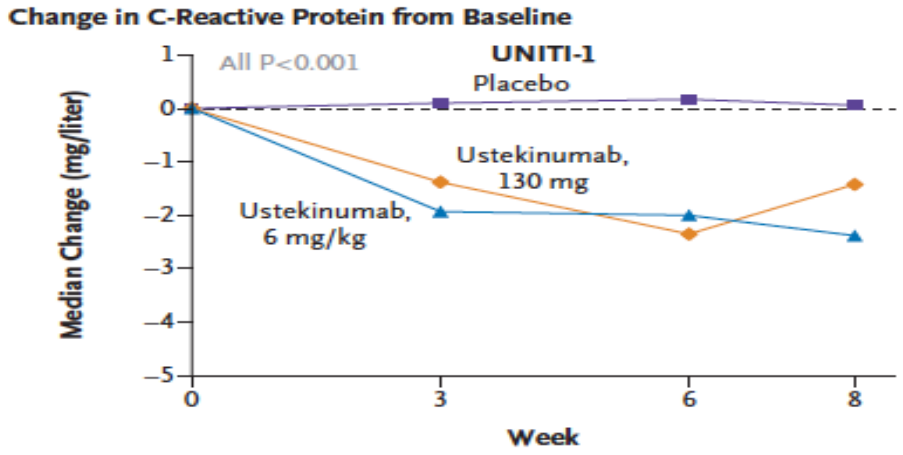
1. Anti-TNF agents (infliximab, adalimumab) are the most-effective first-line agents for Crohn's disease
2. Ustekinumab (anti-IL12/23) is probably the most effective second-line agent for Crohn's disease, especially in patients with primary non-response to anti-TNF agents
3. Combination therapy (biologic + immunomodulators ± corticosteroids) carries highest risk of infection, followed by anti-TNF monotherapy
4. Uncontrolled disease, needing repeated corticosteroids, probably carries highest risk of infections; achieving and maintaining corticosteroid-free remission is safest
5. Combination therapy, as well as monotherapy with thiopurines and anti-TNF agents, is associated with increased risk of lymphoma
6. Limited data on comparative safety of newer non-TNF biologics

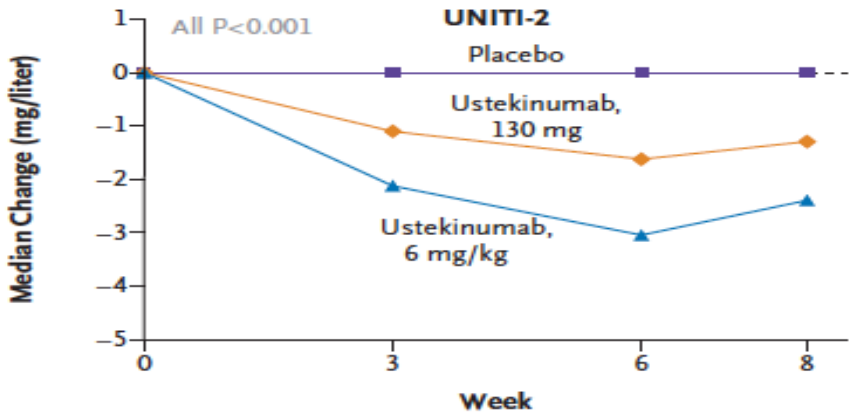
Speed of Onset of Action

Anti-TNF agents and ustekinumab





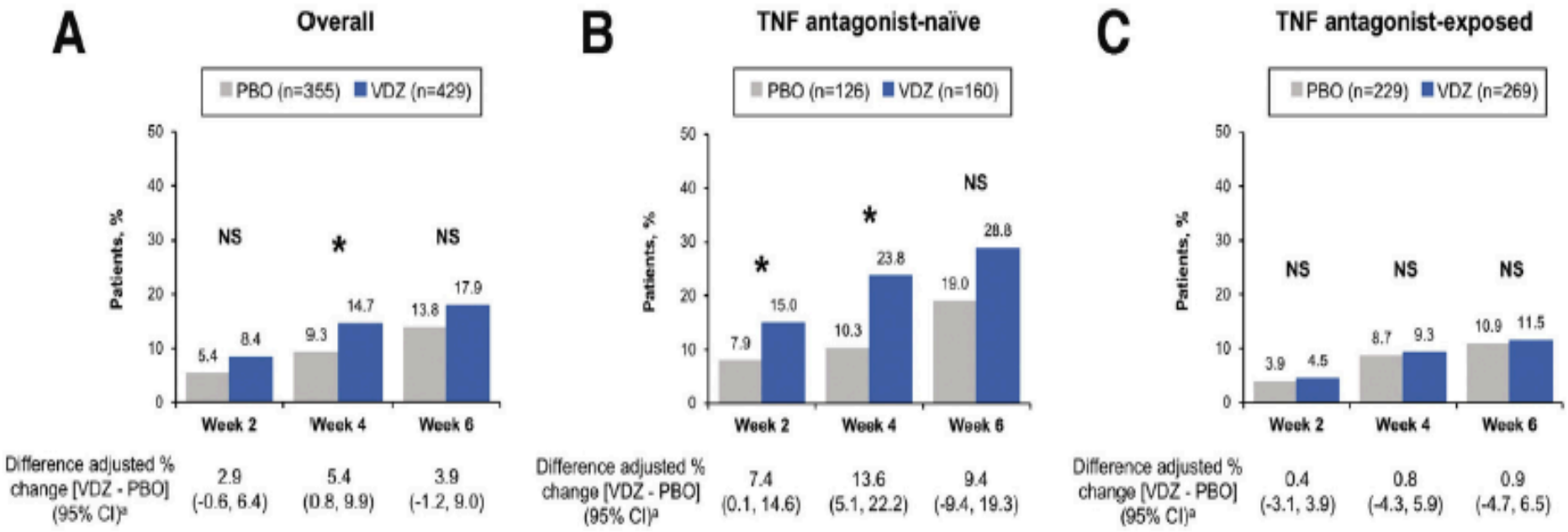




Anti-TNF agents and ustekinumab have a rapid onset of action in patients with CD

Hanauer, et al. Gastroenterology 2017; Feagan, Sandborn, et al. N Engl J Med 2016;375:1946

Vedolizumab for Crohn's Disease



Vedolizumab has relatively rapid onset of clinical in biologic-naïve patients vs. anti-TNF exposed patients

Predictors of symptomatic improvement by week 2 – low CDAI, disease duration <2y and concomitant corticosteroids

Feagan, et al. Clin Gastroenterol Hepatol 2019

Predictors of Response to Biologic Therapy

Predictors of Failure of Anti-TNF agents (and probably all biologic agents)

Clinical Factors	Pharmacokinetic Factors
Disease duration >2y	Low albumin
Penetrating and perianal disease	High inflammatory burden
Prior surgery	Male sex
Smoking	High body mass index

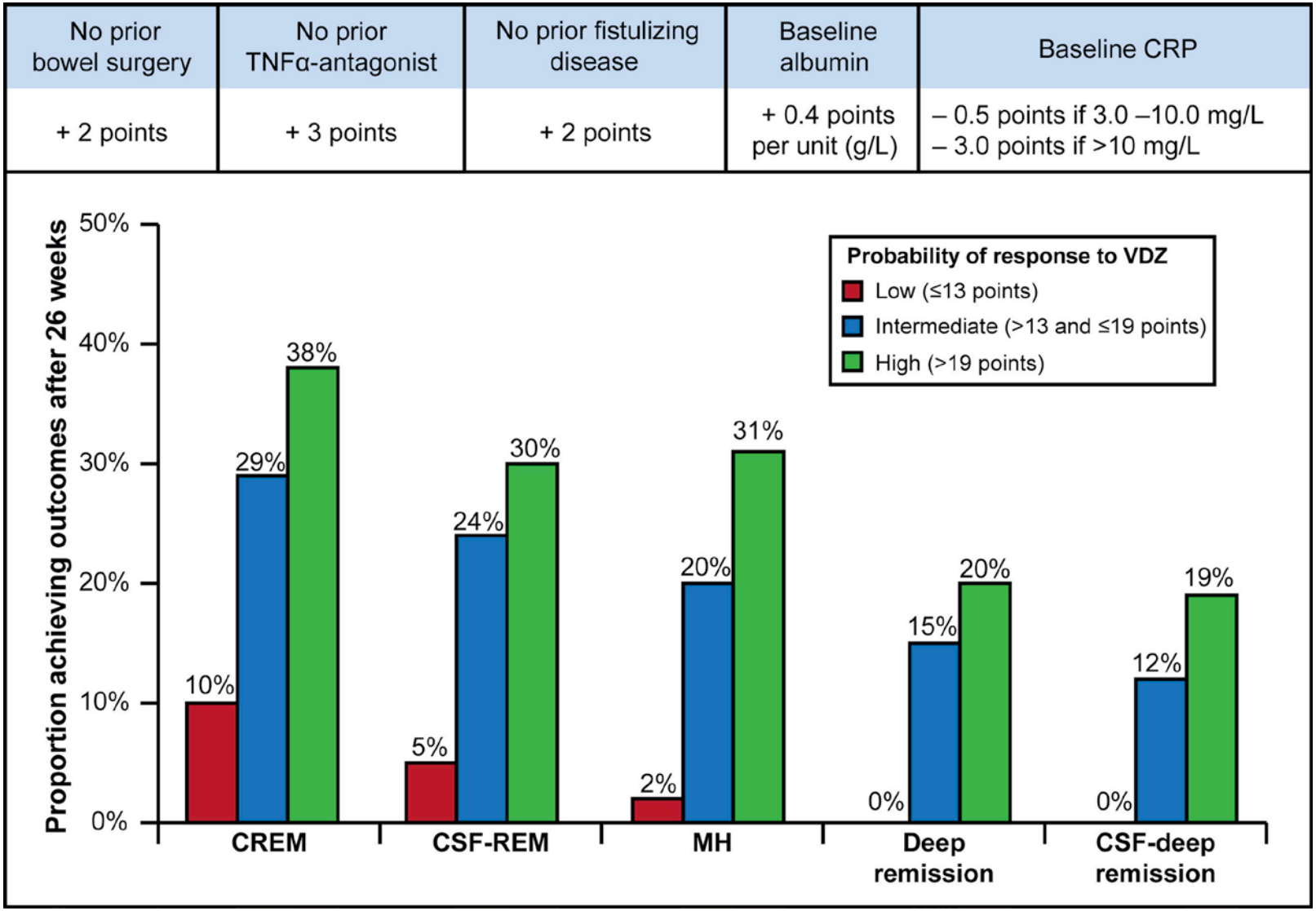
BMI (kg/m²)							
≥ 25	18.5-24.9	< 18.5	≥ 25	18.5-24.9	< 18.5		
2.5%	8.9%	21.5%	9.4%	28.6%	53.0%	≥ 65	Age (years)
2.0%	7.4%	18.3%	7.8%	24.7%	48.0%	41-64	
0.7%	2.8%	7.4%	2.9%	10.5%	24.8%	26-40	
0.2%	0.9%	2.5%	0.9%	3.6%	9.4%	≤ 25	
No			Yes				
Prior Surgery							

Predicted probability of being a primary non-responder to infliximab

Ding, et al. Aliment Pharmacol Ther 2015; Billiet, et al. J Crohns Colitis 2015

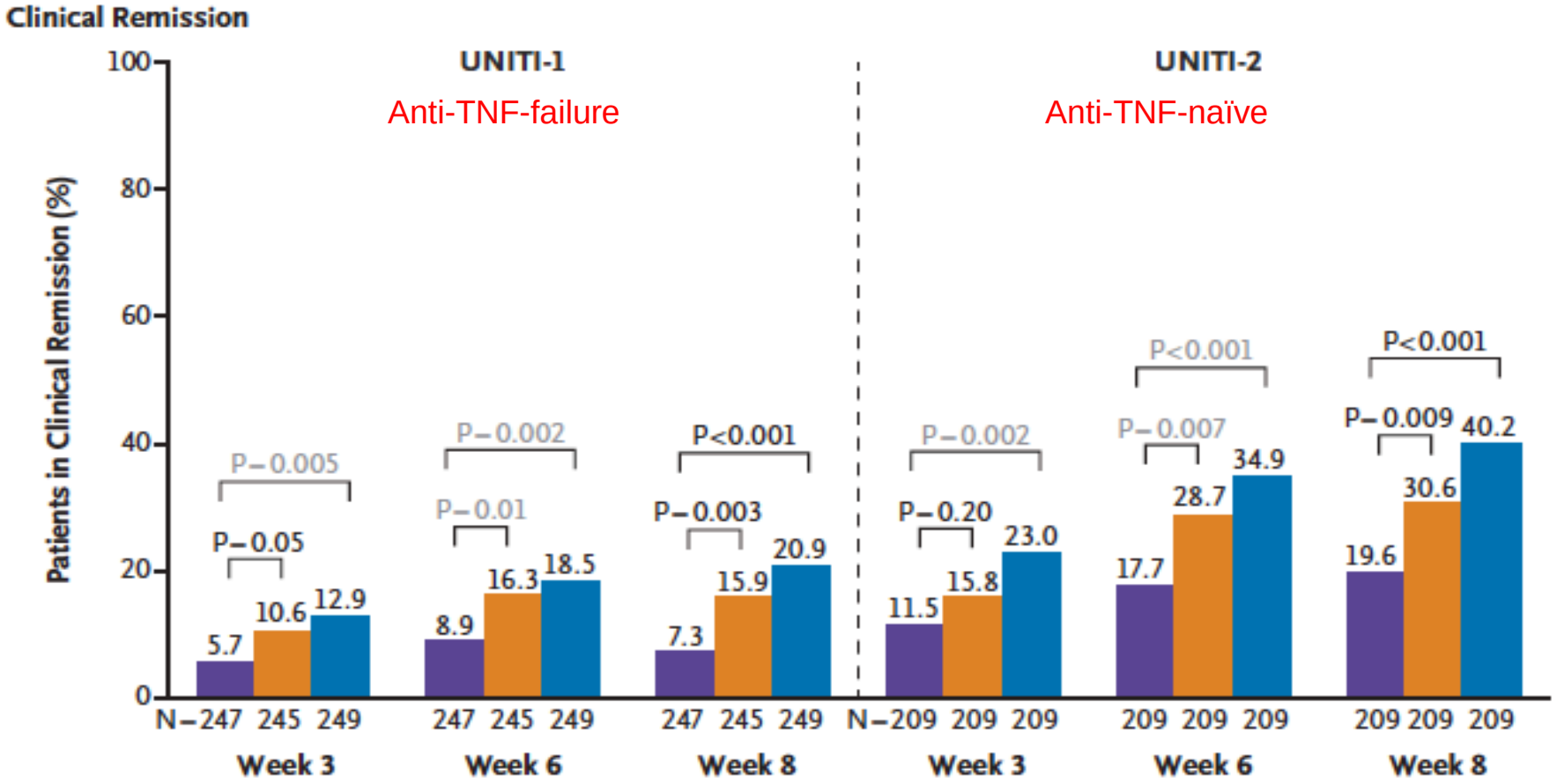
Clinical Prediction Tool for Vedolizumab in Crohn's Disease

No prior bowel surgery	No prior TNFα-antagonist	No prior fistulizing disease	Baseline albumin	Baseline CRP
+ 2 points	+ 3 points	+ 2 points	+ 0.4 points per unit (g/L)	– 0.5 points if 3.0 –10.0 mg/L – 3.0 points if >10 mg/L



Dulai, et al. Gastroenterology 2018:155:687

Ustekinumab for Crohn's Disease
Induction of Remission



Feagan, Sandborn, et al. N Engl J Med 2016;375:1946

My Approach to Choosing Biologics in CD

Favor infliximab or adalimumab	Favor ustekinumab	Favor vedolizumab
Extensive small bowel disease	Severe disease in setting of active or recent malignancy (particular hematological malignancies)	Moderate disease, with low-risk phenotype in risk-averse patients
Internal penetrating disease (after source control in patients with intra-abdominal abscess)	Associated psoriasis or cutaneous complications	Moderate disease in setting of active or recent malignancy
Perianal disease	Preferred second-line agent for most patients with CD	Moderate disease in setting of multiple comorbidities
High inflammatory burden		Post-operative prophylaxis
Prominent extra-intestinal manifestations		