the ultimate CME network

Does One Size Fit All: Should Everyone Get "Top Down" Therapy?

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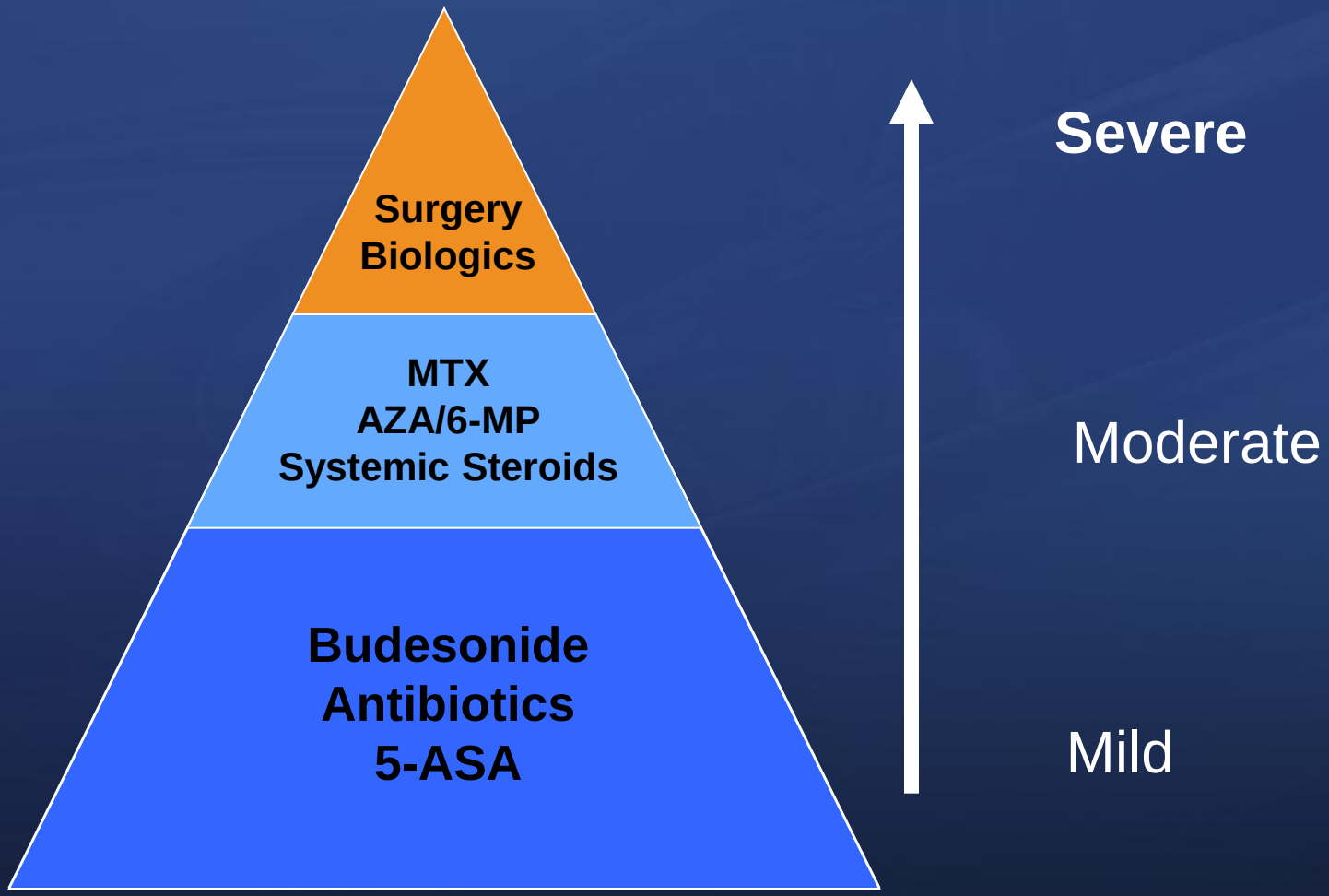
Learning Objectives

- Define “top-down” therapy
- Identify course of Crohn’s disease under conventional (“step up”) approach
- Review risk factors for complicated (progressive) Crohn’s disease
- Balance risks and benefits of “early aggressive therapy”

Treatment Goals Circa 2010

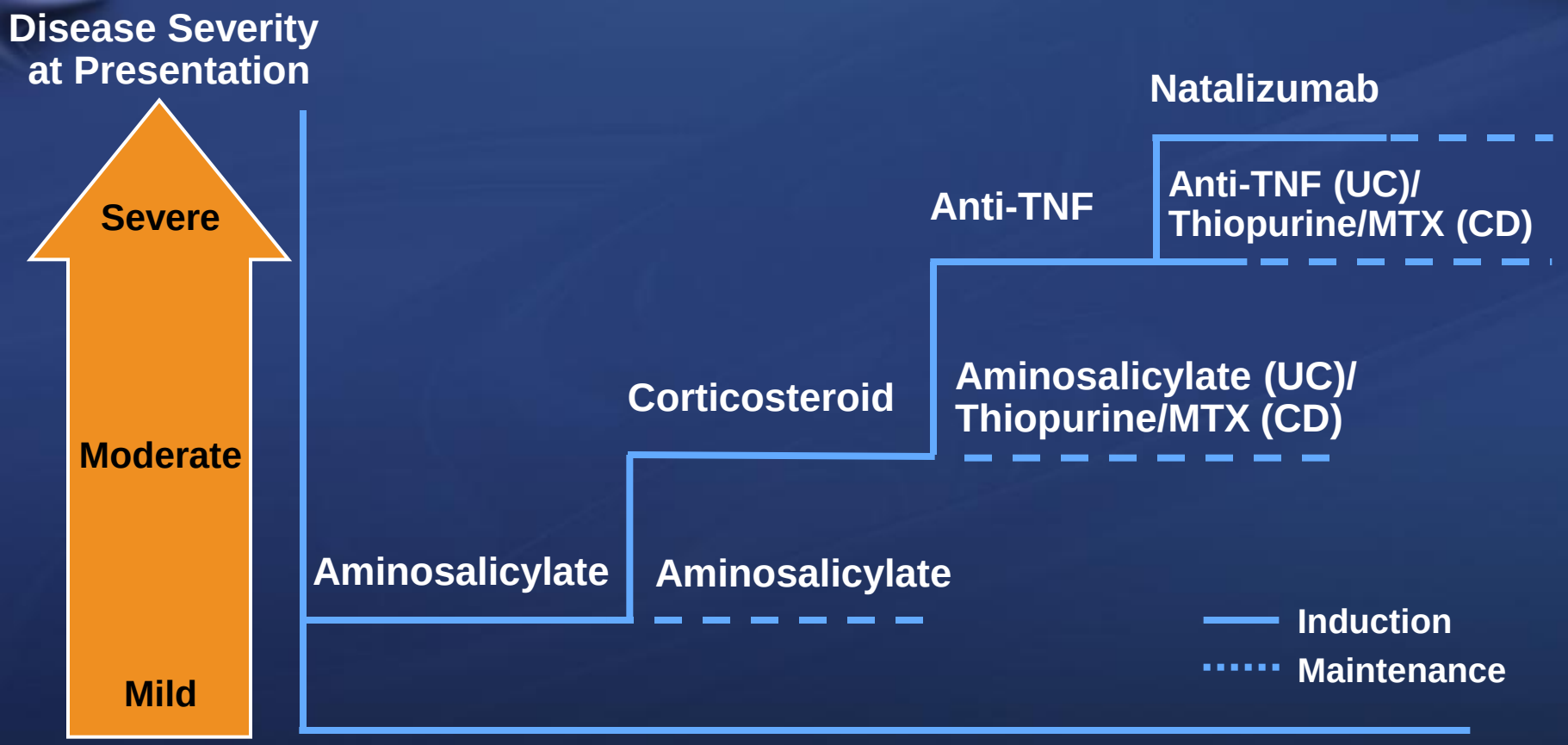
- Induce and maintain response/remission
- Prevent complications
- Improve quality of life
- Restore and maintain nutrition
- Limit surgery

Conventional "Therapeutic Pyramid" for Crohn's Disease



Lichtenstein GR et al. *Inflamm Bowel Dis*. 2004;10:S2–S10.

Sequential Therapies for IBD



Step-Up according to severity at presentation or failure at prior step

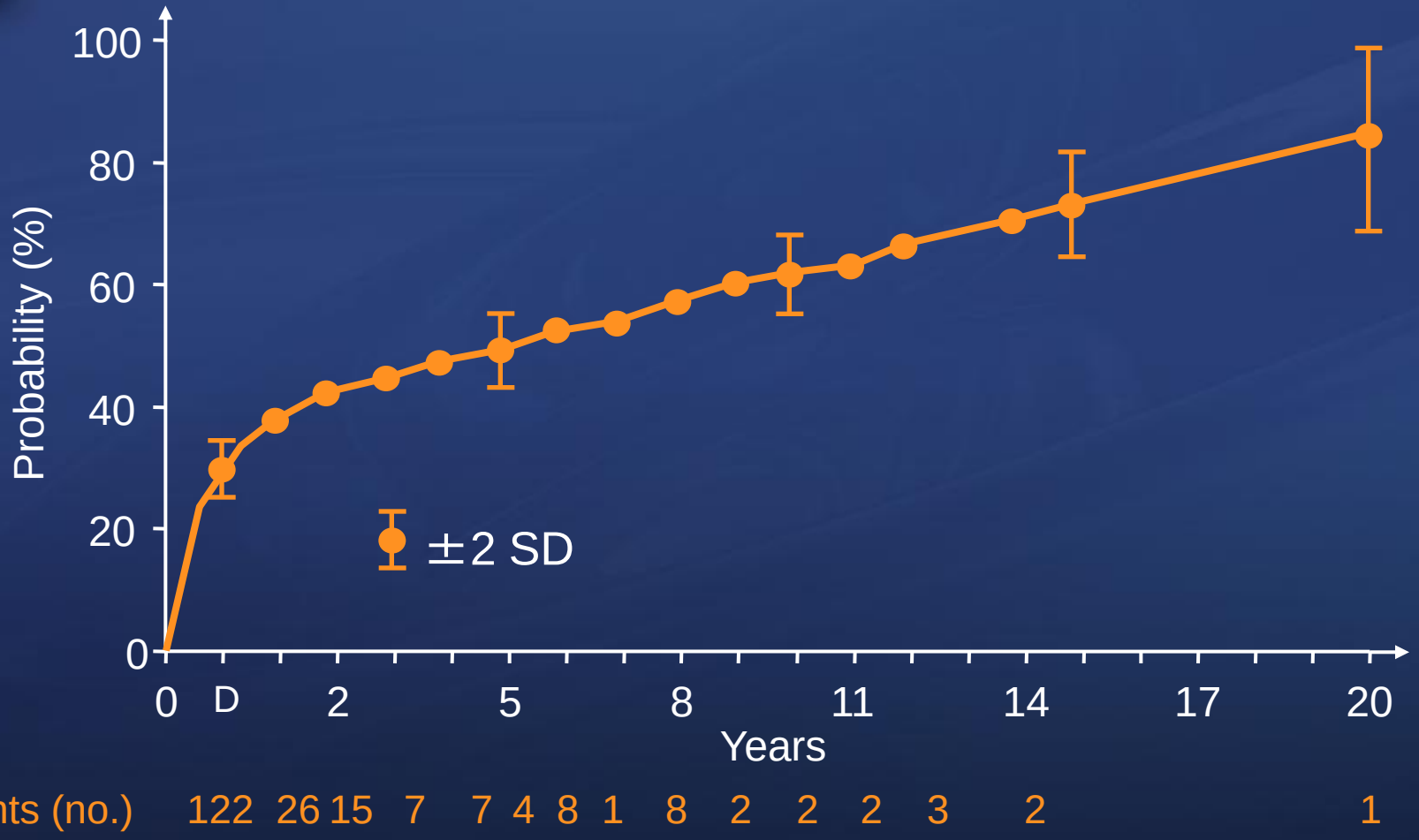
Lichtenstein GR et al. *Inflamm Bowel Dis*. 2004;10:S2–S10.

Step-up Management Approach

- Potential advantages:
  - Patients attain remission with less toxic therapies
  - Potentially more toxic therapies reserved for more severe or refractory disease
  - Minimizes risk of adverse events
  - Cost sparing (short-term?)

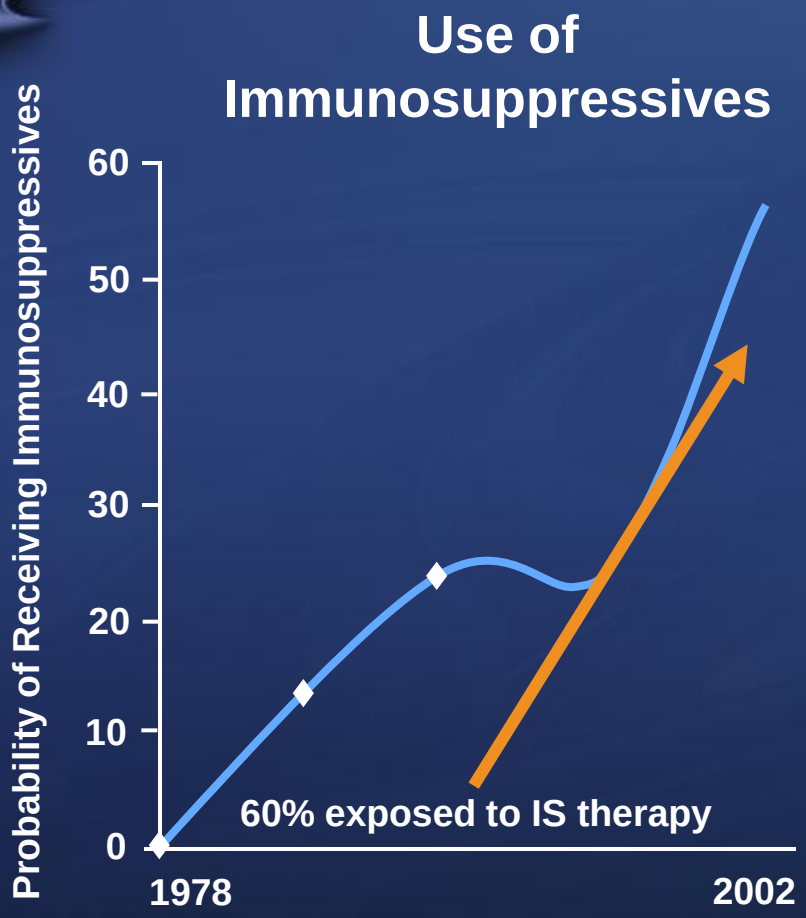
- Potential disadvantages:
  - Patients have to “earn” most effective treatments
  - Decrease in quality-of-life before patients obtain optimal therapy
  - Likelihood of surgery is high
  - Disease is not modified

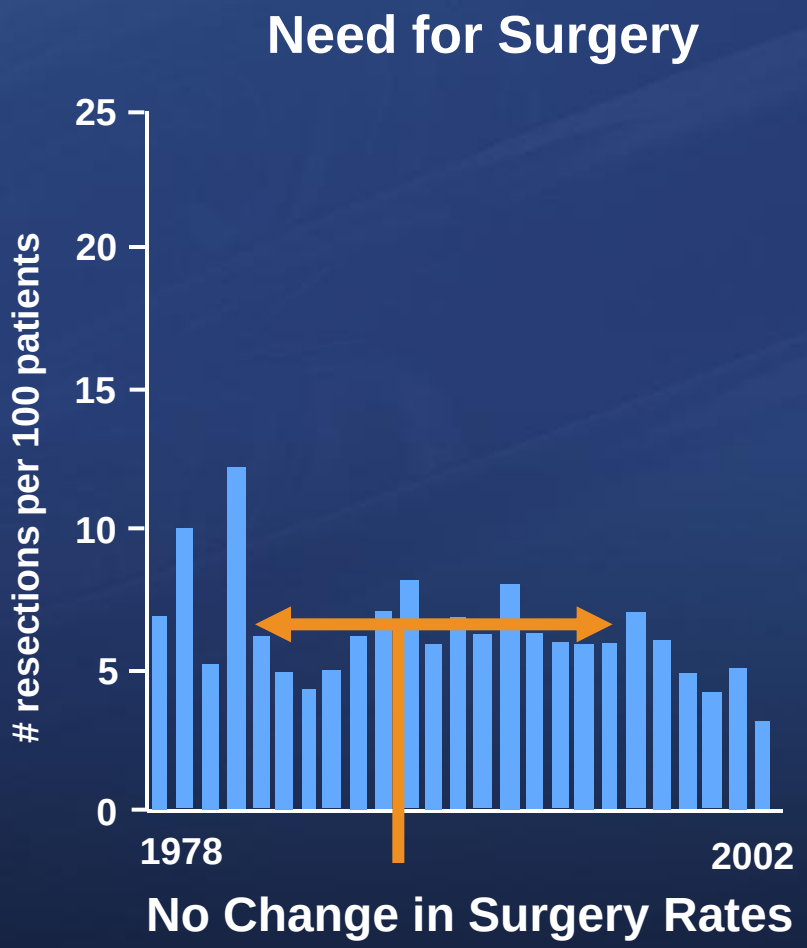
Probability of Surgical Intervention in CD



Munkholm P et al. *Gastroenterology*. 1993;105:1716-1723.

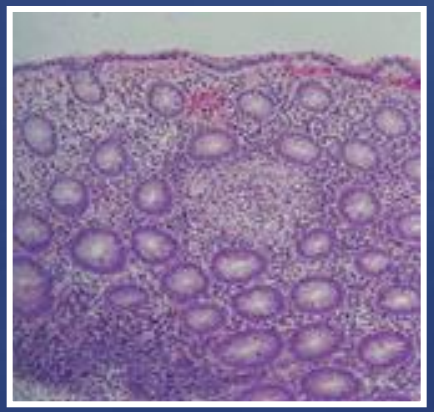
Rate of Surgery for CD and the Use of Immunosuppressives in Paris over 3 Decades

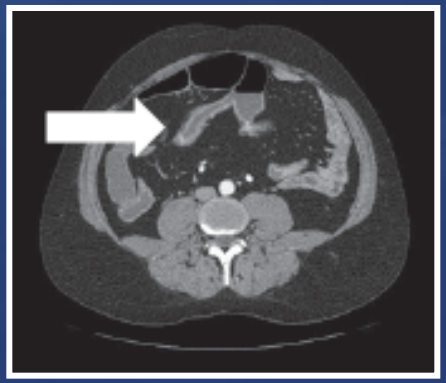




Cosnes J et al. *Gut*. 2005;54:237-241

Longitudinal Course of CD





<u>Preclinical</u> phase:

Subclinical inflammation (immune response and histologic lesions)

<u>Early</u> Crohn's disease:

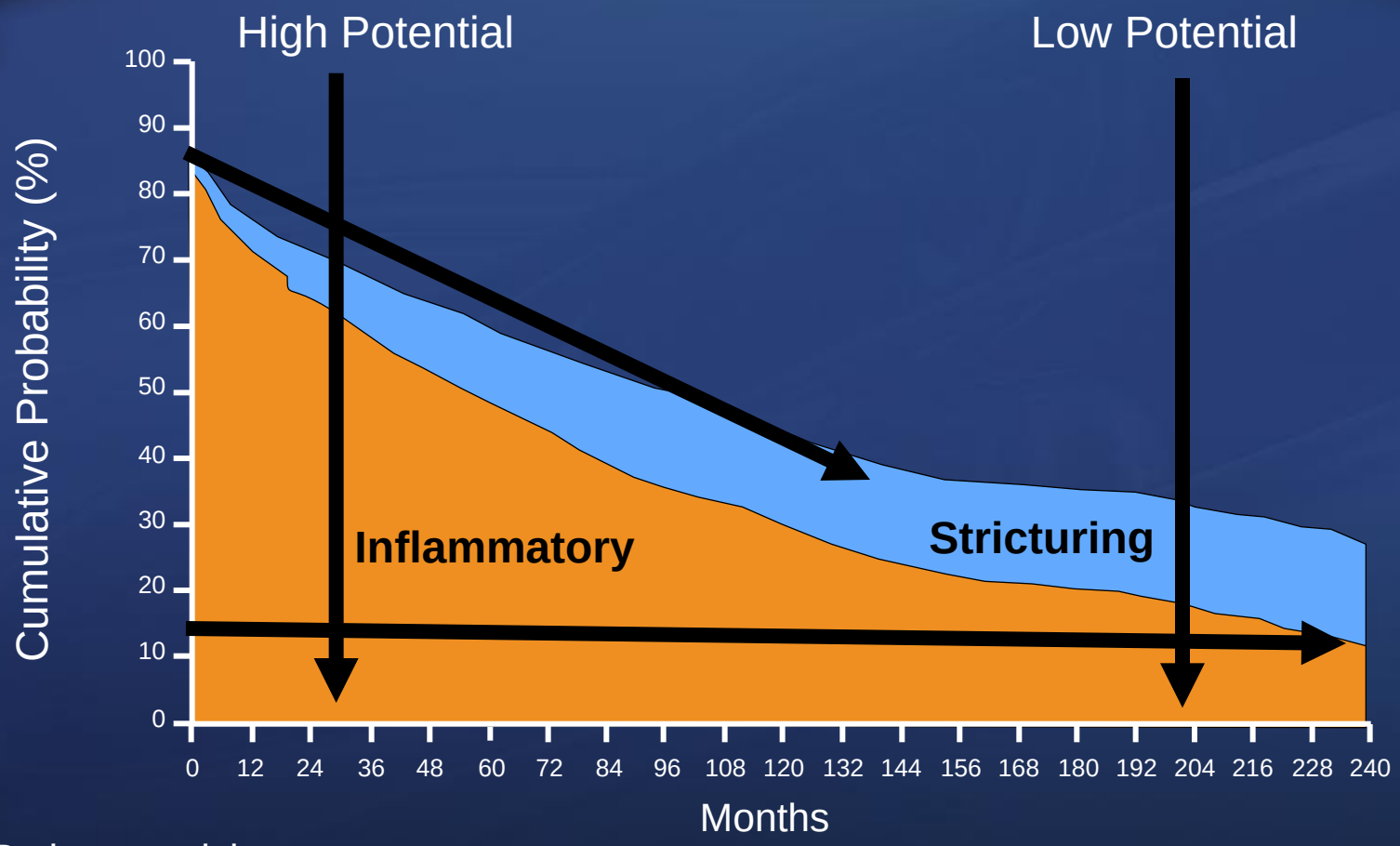
Inflammation (clinical, biological, endoscopic, radiologic evidence of disease activity)

No fistula, abscess, or stricture

Time

Peyrin-Biroulet L et al. *Gut.* 2010;59:141-149.

Impact of Therapy Depends on Degree of Structural Damage and Velocity of Progression

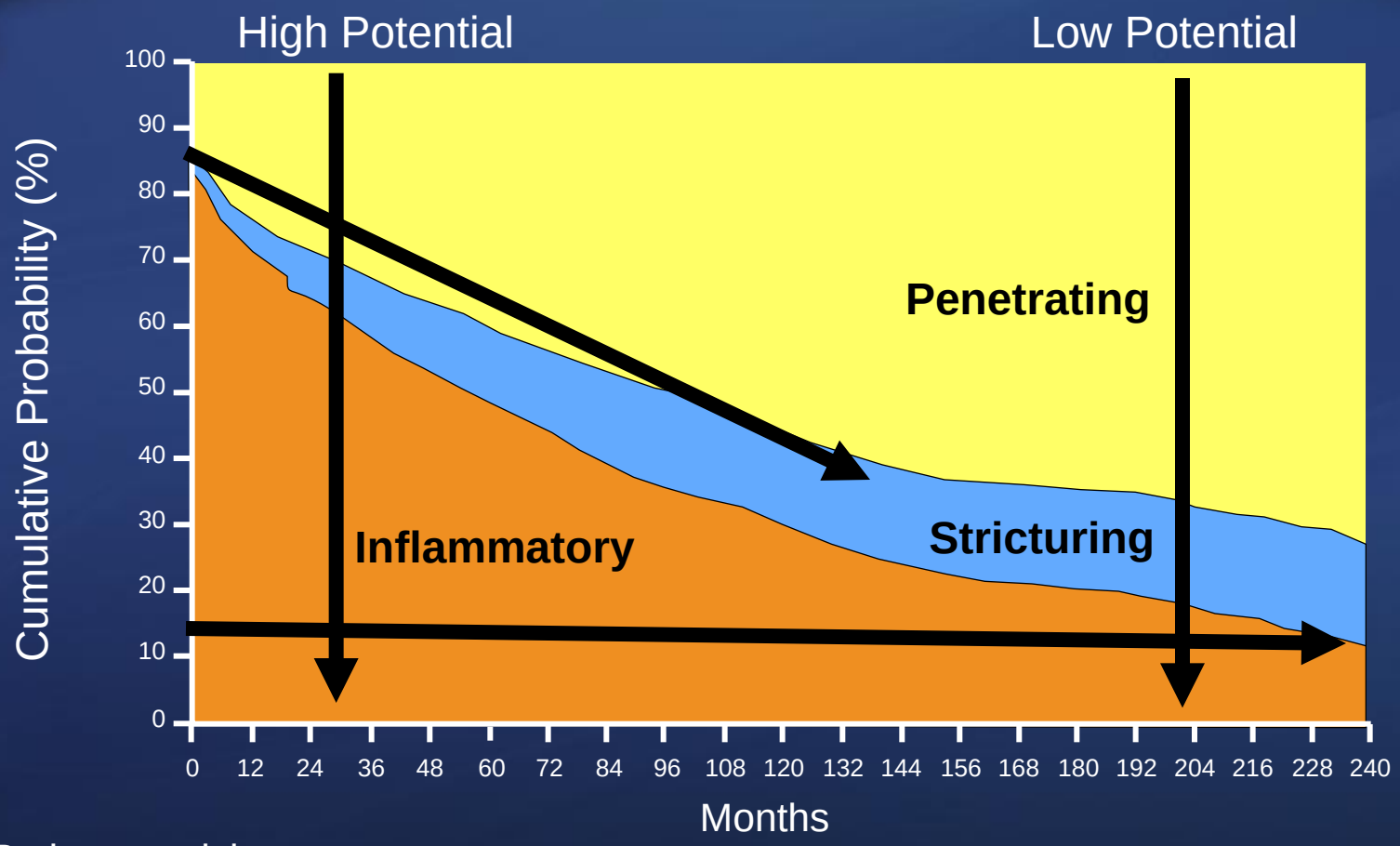


Patients at risk:

N =	2002	552	229	95	37

Cosnes J et al. *Inflamm Bowel Dis*. 2002;8:244-250.

Impact of Therapy Depends on Degree of Structural Damage and Velocity of Progression



Patients at risk:

N =	2002	552	229	95	37

Cosnes J et al. *Inflamm Bowel Dis*. 2002;8:244-250.

Rationale for Early Intervention in CD

- Immunopathology supports concept of early intervention in CD
- Subgroup analyses of large clinical trials suggests TNFα antagonists may be more effective in patients with disease duration ≤1- 2 years
- Adverse events occur less often in *early* rheumatoid arthritis patients treated with TNFα antagonists
- Potential for disease modification to prevent transmural complications (surgery/hospitalization)

Peyrin-Biroulet L et al. *Gut.* 2010;59:141-149.

Can we predict patients who will have a “progressive” course?

Clinical Predictors of Risk of Progressive/ Aggressive Crohn's Disease at Diagnosis

- Young age
- Fistulae
- Need for steroids
- Deep ulcerations
- High serologic titers
- Smoking

Predictors of Disabling Disease 5 Years after Diagnosis

- Age at onset
  - <40 years vs ≥40 years; *P*=.0004
- Location of disease
  - Small bowel + colon vs small bowel only; *P*=.002
- Smoking status
  - Smoker vs ex- or non-smoker; *P*=.09
- Perianal lesion at diagnosis
  - Yes vs no; *P*=.01
- Required steroids for first flare
  - Yes vs no; *P*=.0001

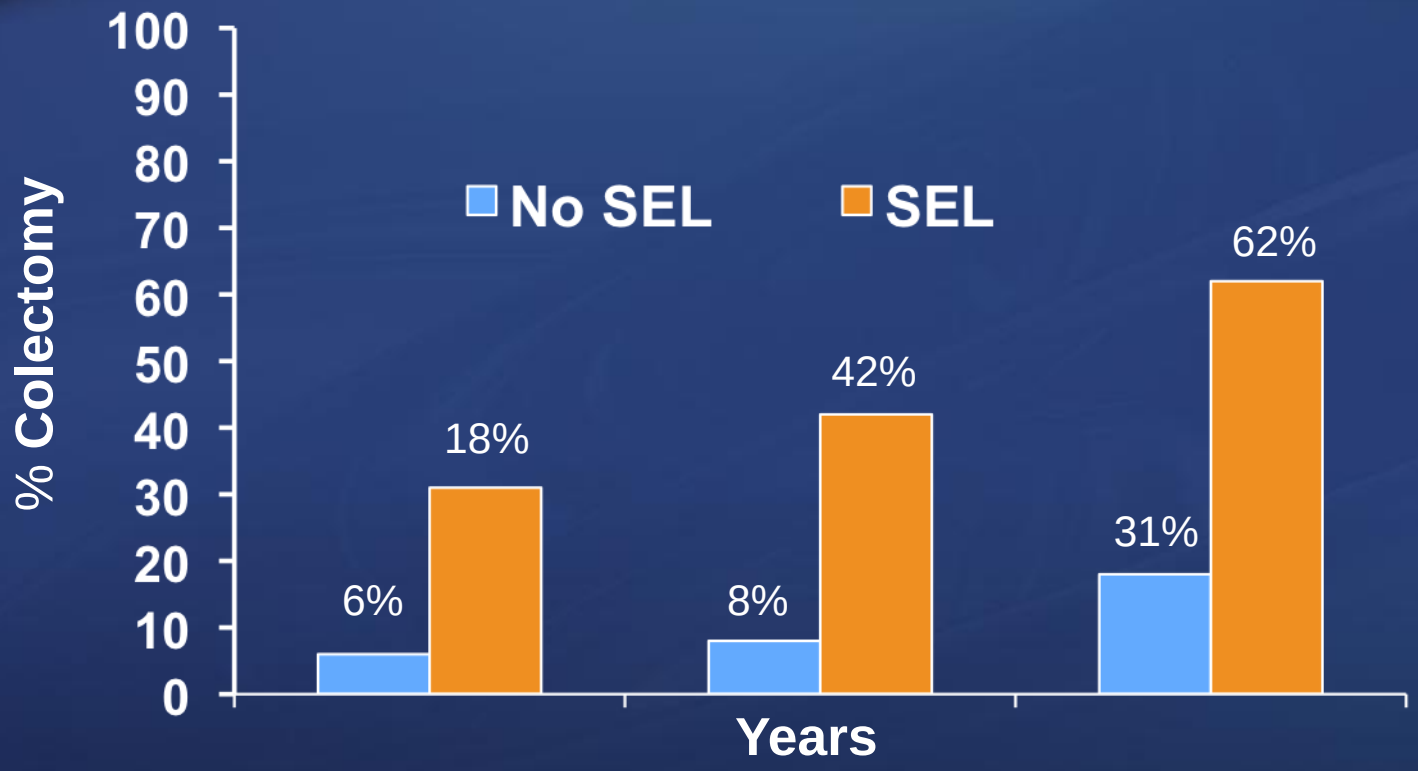
Beaugerie L et al. *Gastroenterology.* 2006;130:650-656.

Predictors of Rapid Progression to Surgery

Factor	Odds Ratio (95% CI)
Current smoker	3.09 (1.47–6.51)
Abdominal pain	1.82 (1.05–3.18)
Nausea/vomiting	2.07 (1.04–4.10)
Ileal localization only	2.22 (1.30–3.81)
Oral corticosteroid use in first 6 months	3.79 (1.90–7.55)

Sands B et al. *Am J Gastroenterol.* 2003;98:2712-2718.

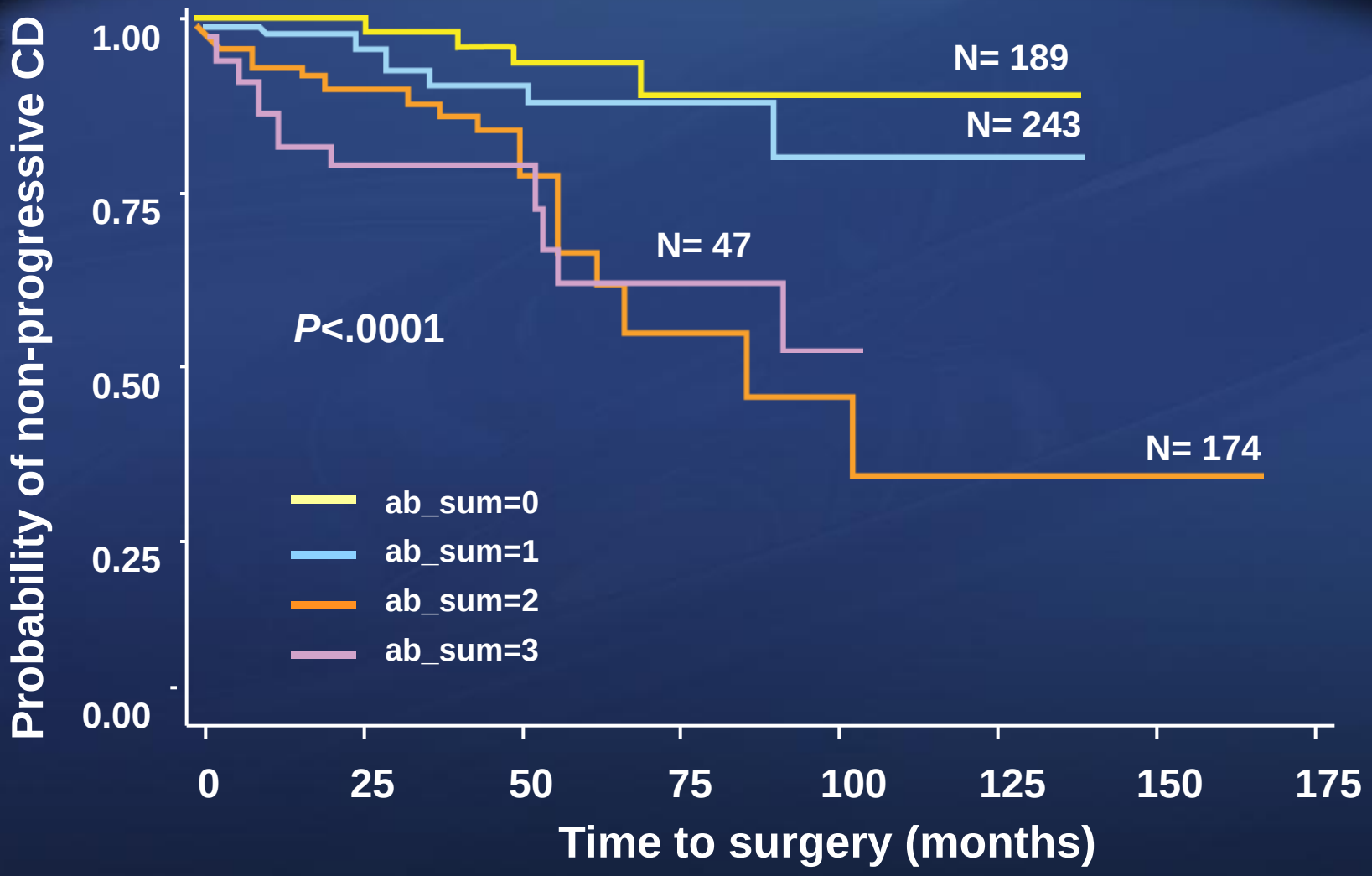
Prognosis of CD Patients with Severe Ulcerations



SELs defined as deep ulcerations >10% of mucosal area with at least one colonic segment
Risk of colectomy associated with severe endoscopic lesions, high CDAI, absence of immunosuppression

SEL=severe endoscopic lesions
Allez M et al. *Am J Gastroenterol*.2002;97:947-953.

Antibody Sum and Surgery

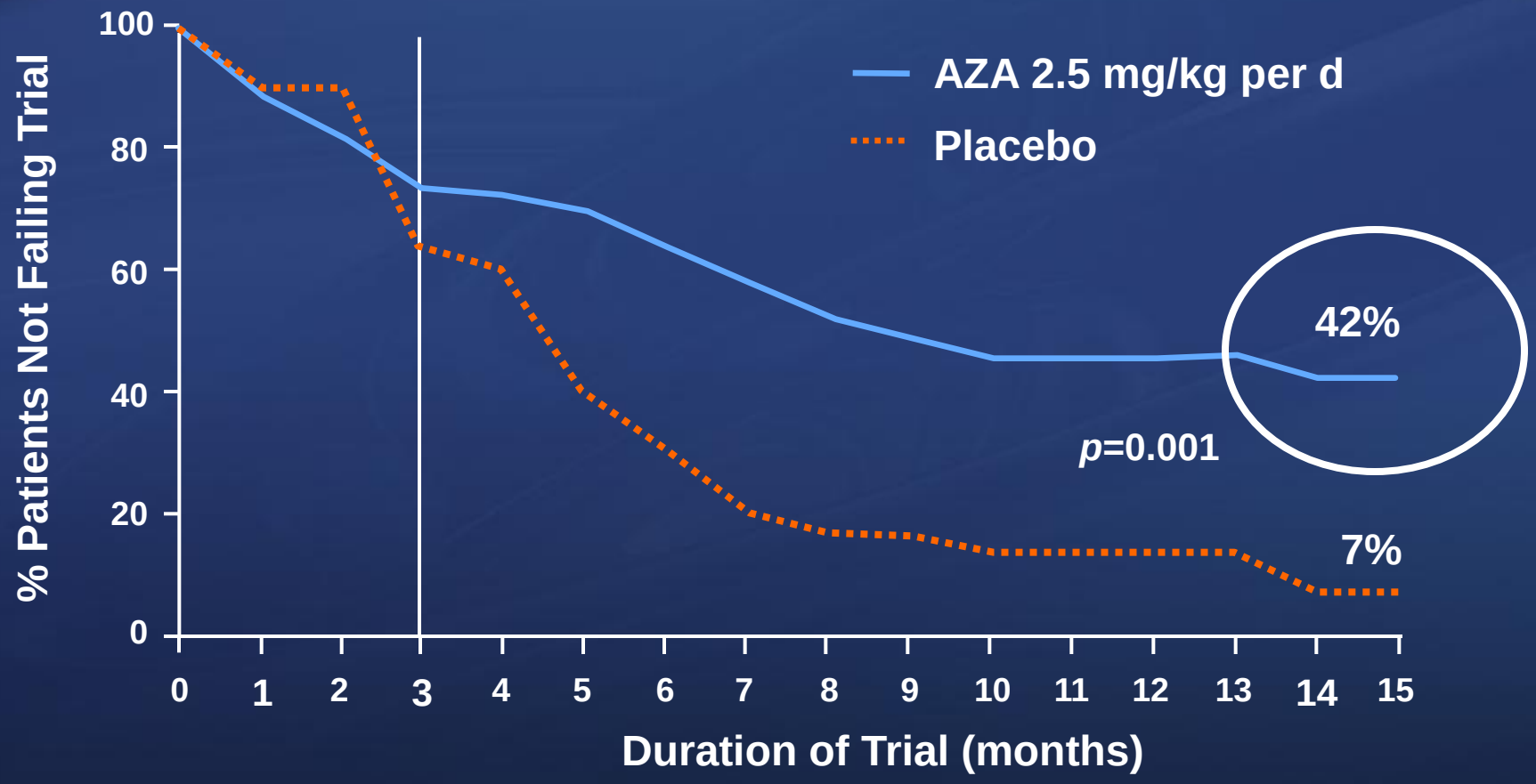


Dubinsky MC et al. *Clin Gastroentrol Hepatol*. 2008;6:1105-1111.

What do we Mean by "Top Down" Therapy?

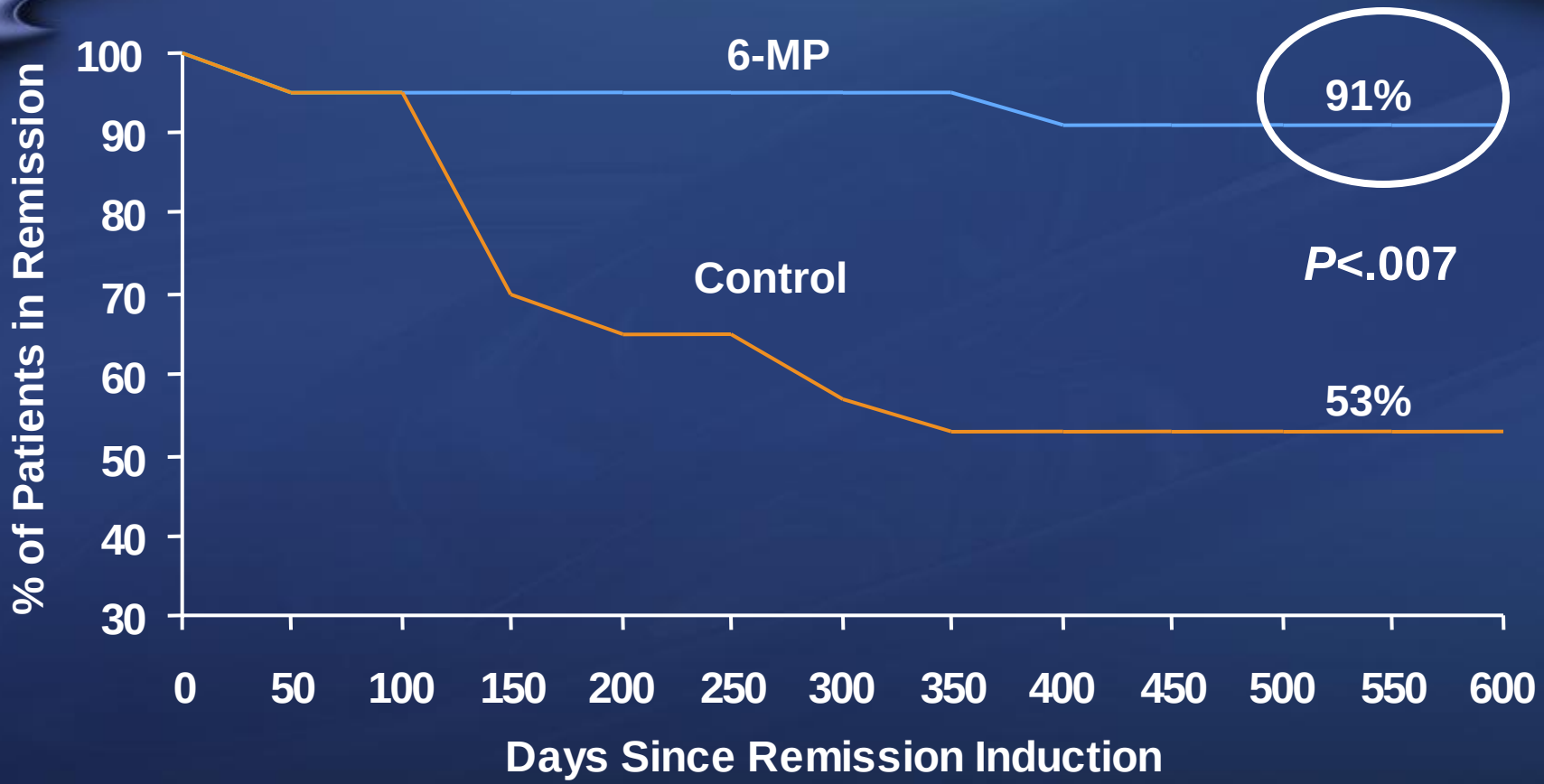
- Early intervention with immunosuppressive
- Early intervention with biologic
- Giving our ***most effective*** therapy at diagnosis (combination biologic + IS)

Efficacy of AZA as Crohn's Disease Maintenance Therapy After Steroids in Adults*



*Remission induced by prednisolone tapered over 12 weeks
Inclusion: Patients were not steroid dependent
Candy S et al. *Gut.* 1995;37:674-678.

Efficacy of 6-MP as Crohn's Disease Maintenance Therapy After Steroids in Steroid-naïve Children

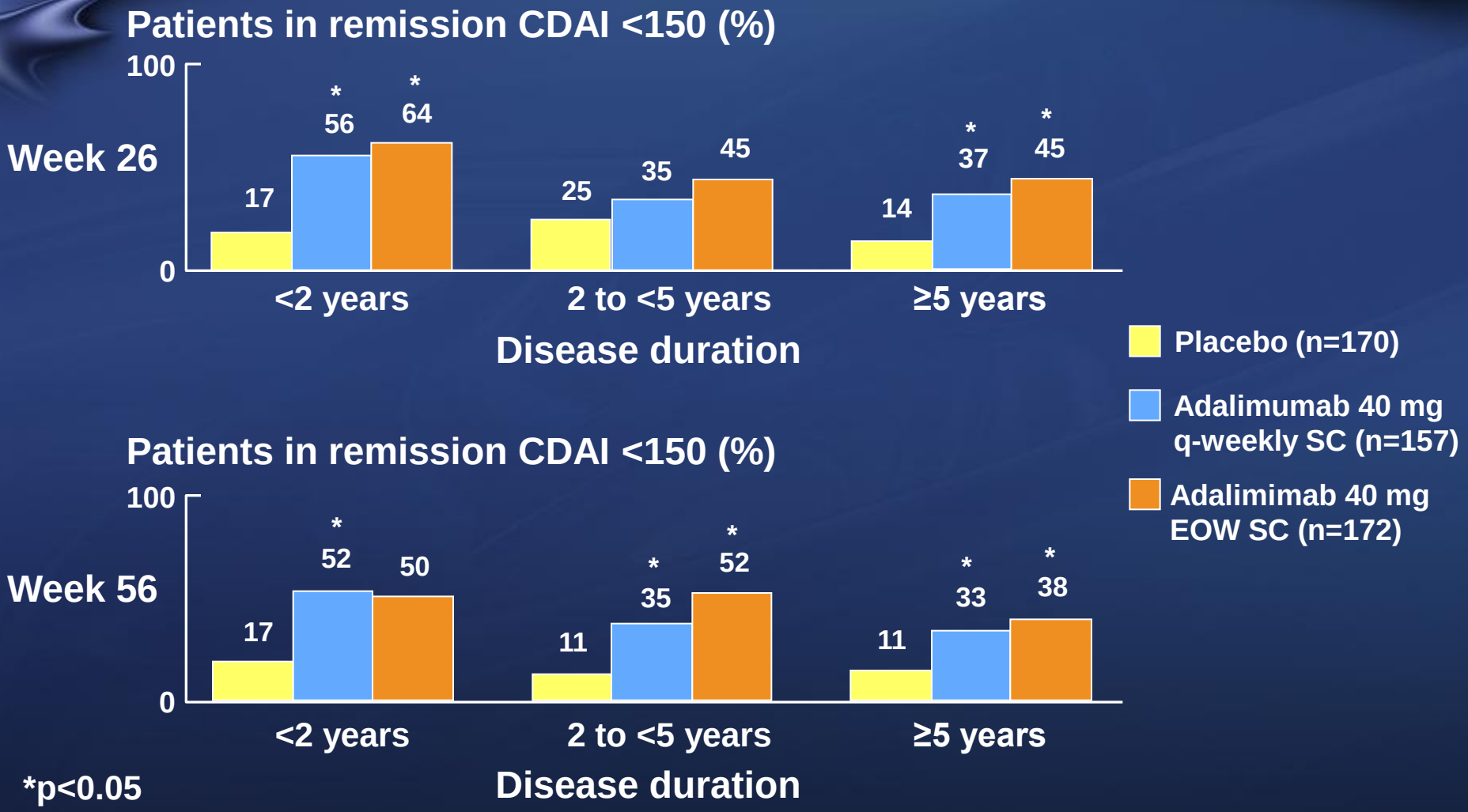


N=55

At baseline, patients received prednisone plus either 6-MP or placebo.
Steroids were tapered after induction of remission.

Markowitz J et al. *Gastroenterology*. 2000;119:895-902.

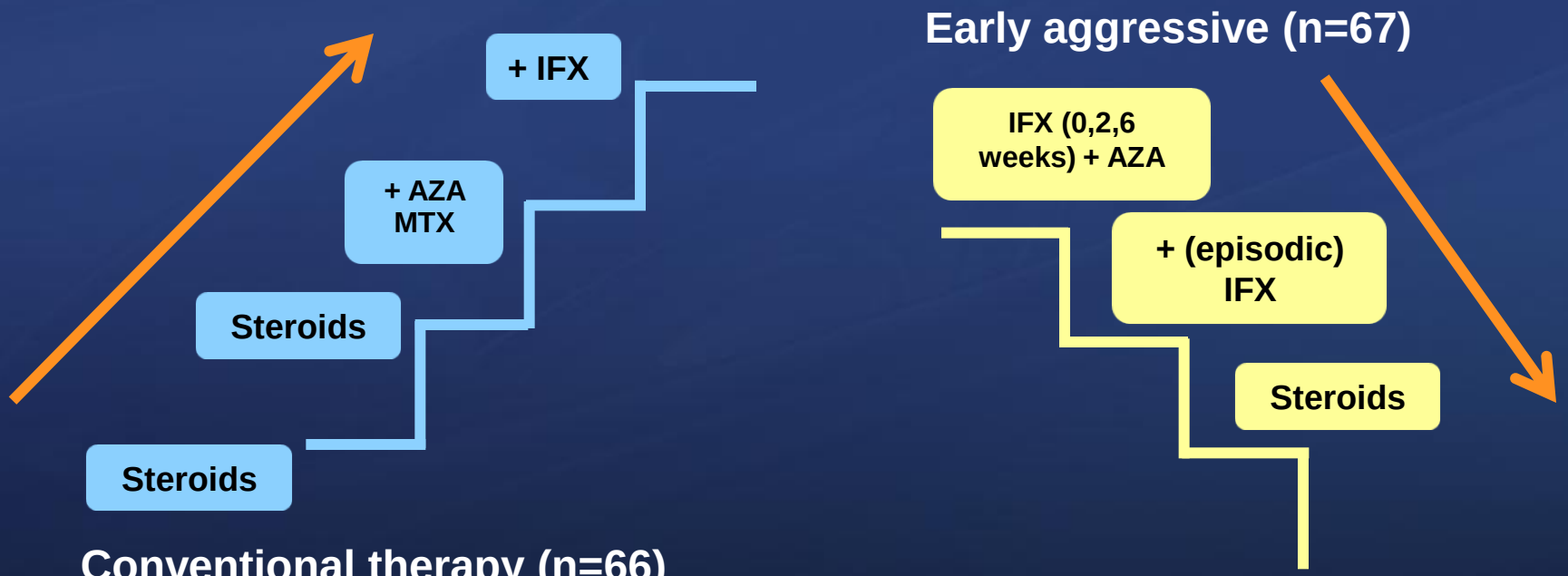
CHARM: Adalimumab in Early Crohn's Disease



Schreiber et al, Gastroenterology 2007; 132: A147 (Abstract 985)

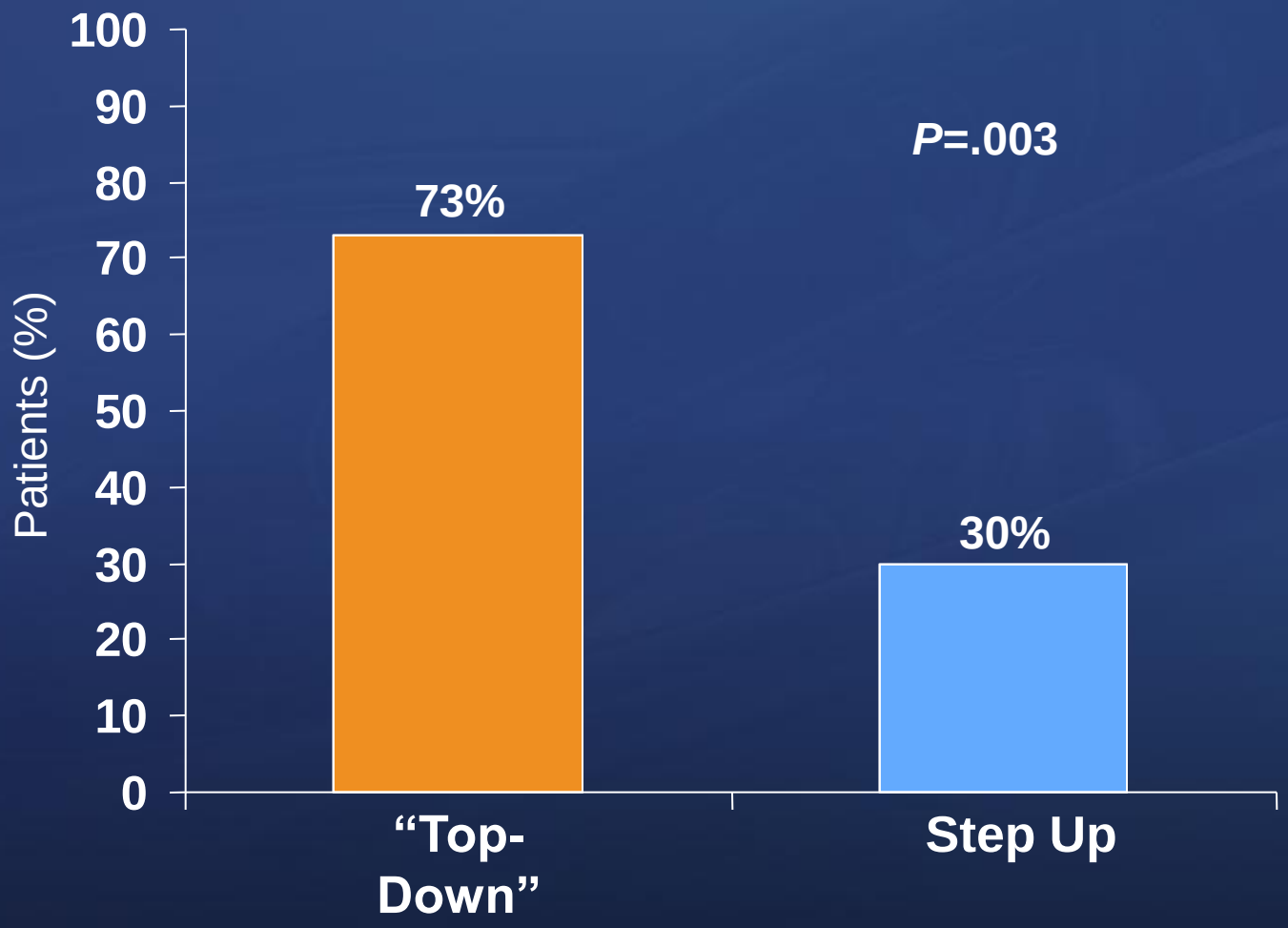
Early Aggressive Biologic Therapy vs Conventional Management of Crohn's Disease

Newly diagnosed, antimetabolite, anti-TNF, or steroid-naïve CD patients (n=133)



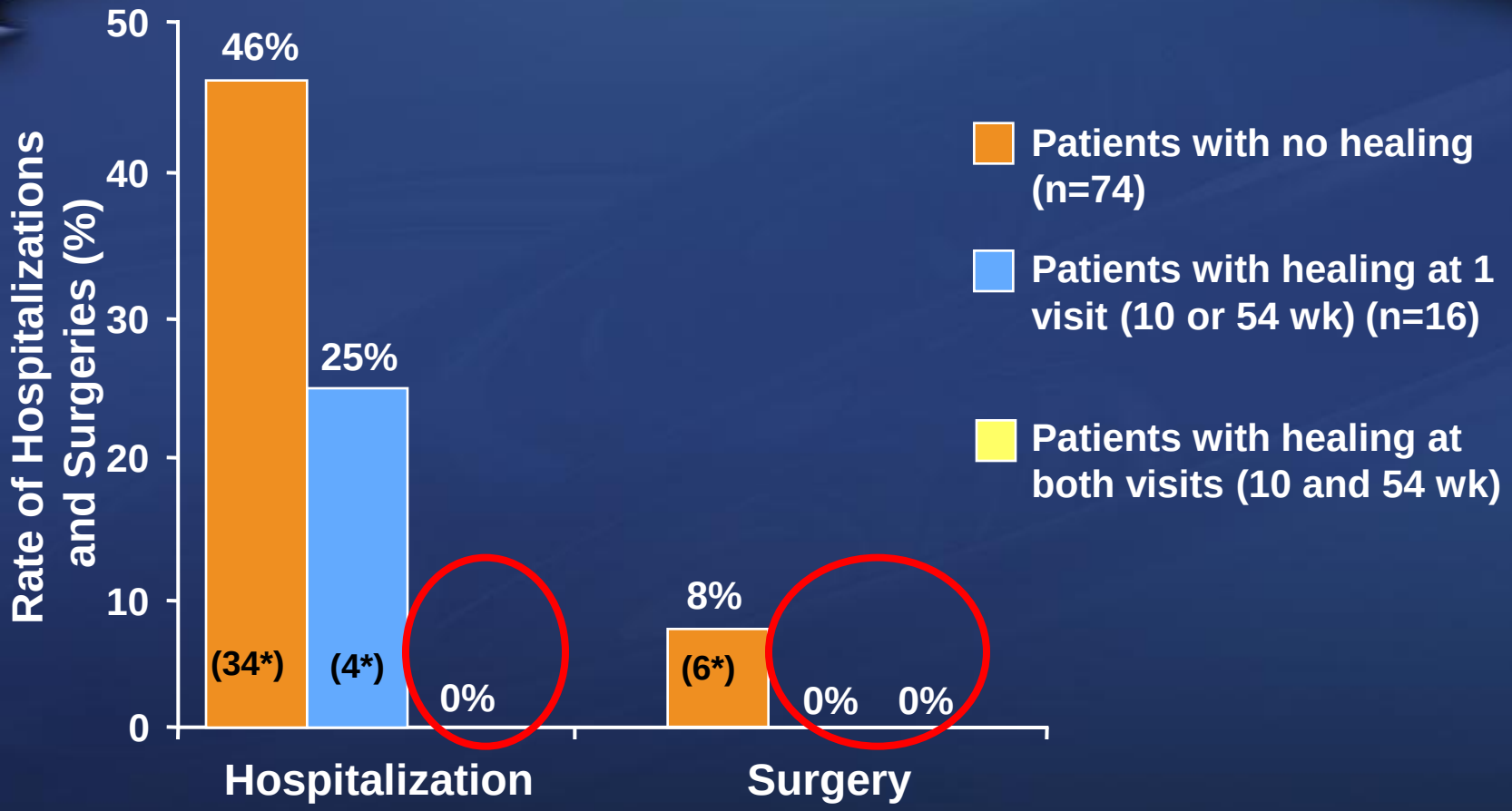
D'Haens G et al. *Lancet.* 2008;371:660-667.

Complete Ulcer Disappearance (Mucosal Healing)



D'Haens G et al. *Lancet.* 2008;371:660-667.

Infliximab: Endoscopic Healing and Reduced Hospitalizations and Surgeries

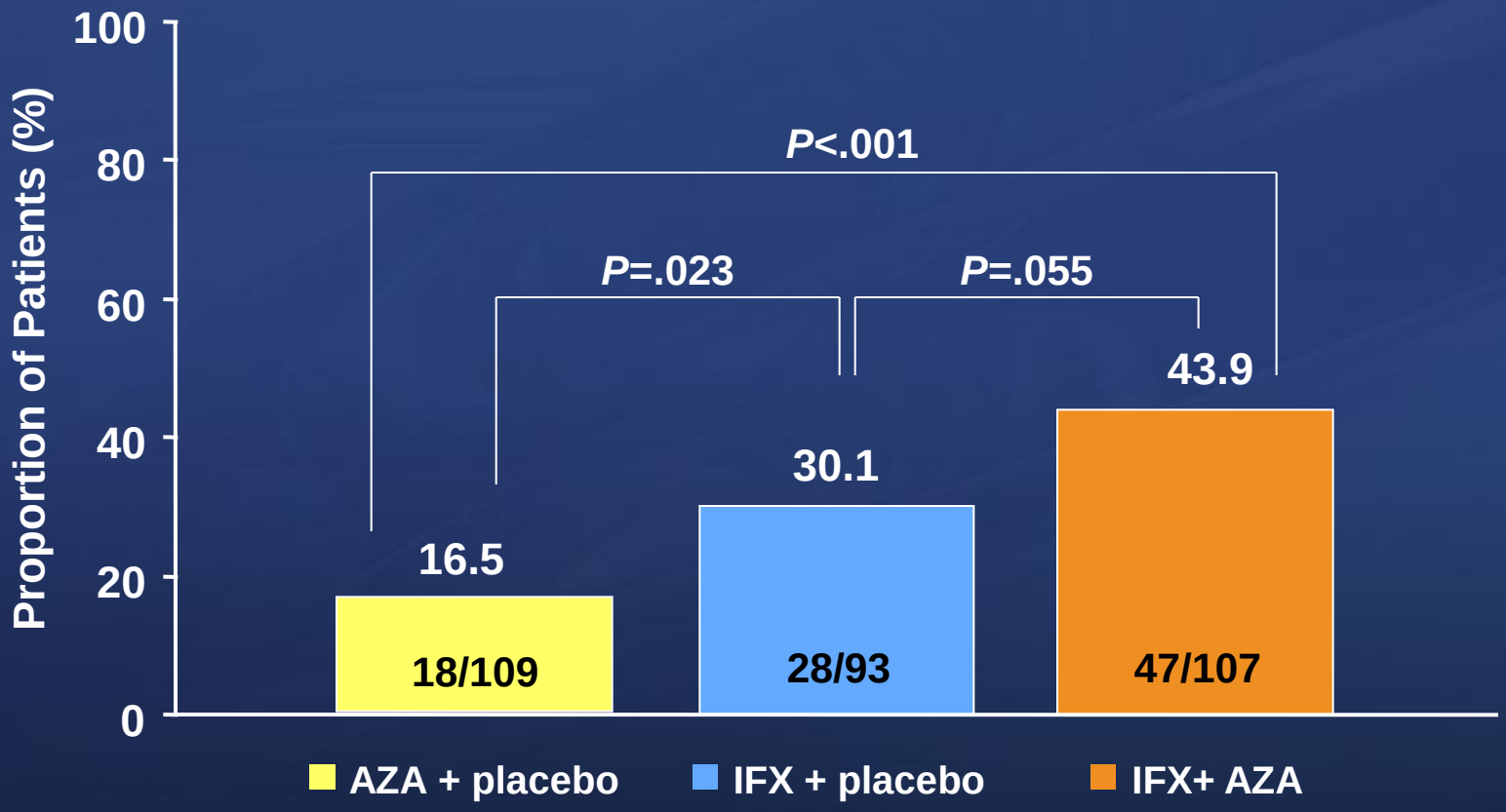


*Number per 100 patients

Rutgeerts P et al. *Gastroenterology.* 2002;123(suppl):43.M2138.

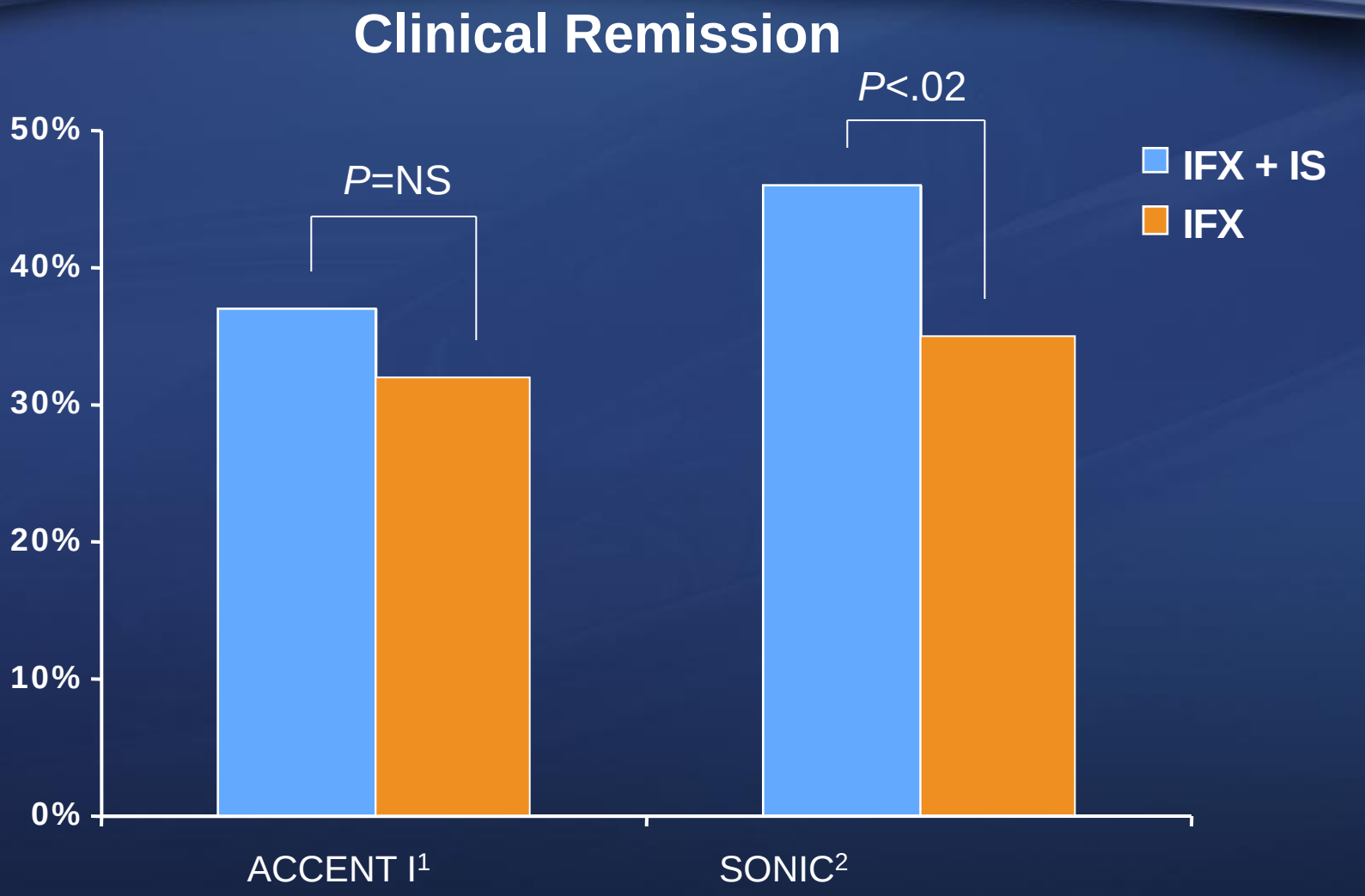
SONIC: Mucosal Healing at Week 26

Primary Endpoint



Columbel JF et al. *N Engl J Med.* 2010;362:1383-1395.

Comparison of Infliximab Trials: Immunosuppressive Experienced vs Naïve Patients



1. Hanauer SB et al. *Lancet*. 2002;359:1541-1549;
2. Colombel JF et al. *N Engl J Med*. 2010;362:1383-1395.

SONIC: Summary of Adverse Events Through Week 50: All Randomized Patients

	AZA + placebo (n=161)	IFX + placebo (n=163)	IFX + AZA (n=179)
Patients with ≥1 AE, n (%)	144 (89.4%)	145 (89.0%)	161 (89.9%)
Patients with ≥1 SAE, n (%)	43 (26.7%)	39 (23.9%)	27 (15.1%)
Serious infections	9 (5.6%)	8 (4.9%)	7 (3.9%)

TB - 1 patient treated with infliximab and azathioprine
Colon cancer - 2 patients treated with azathioprine monotherapy
Death - Post colectomy, in a patient treated with azathioprine monotherapy

Colombel JF et al. *N Engl J Med*. 2010;362:1383-1395.

Which Patients are at Greatest Risk for Serious Infections?

- Older
  - average age = 63 (systematic review); 67 (Mayo)
  - OR 3.0 (95%CI 1.2–7.2) for >50 years *vs* ≤24 years
- Multiple co-morbidities
- Concomitant steroids and/or narcotics
- Long-standing disease

Young "healthy" patients are not in the clear, but probably less at risk

1. Siegel C et al. *Clin Gastroenterol Hepatol.* 2006;4:1017-1024;
2. Colombel JA et al. *Gastroenterology.* 2004;126:19-31;
3. Lichtenstein GR et al. *Clin Gastroenterol Hepatol.* 2006;4:621-630;
4. Toruner M et al. *Gastroenterology.* 2008;134:929-936.

Safety of Biologic Therapies

- Consider risks of underlying condition
  - Lymphoma in RA or IBD
- Consider risks of concomitant medications
  - Corticosteroids
  - Immune suppressants

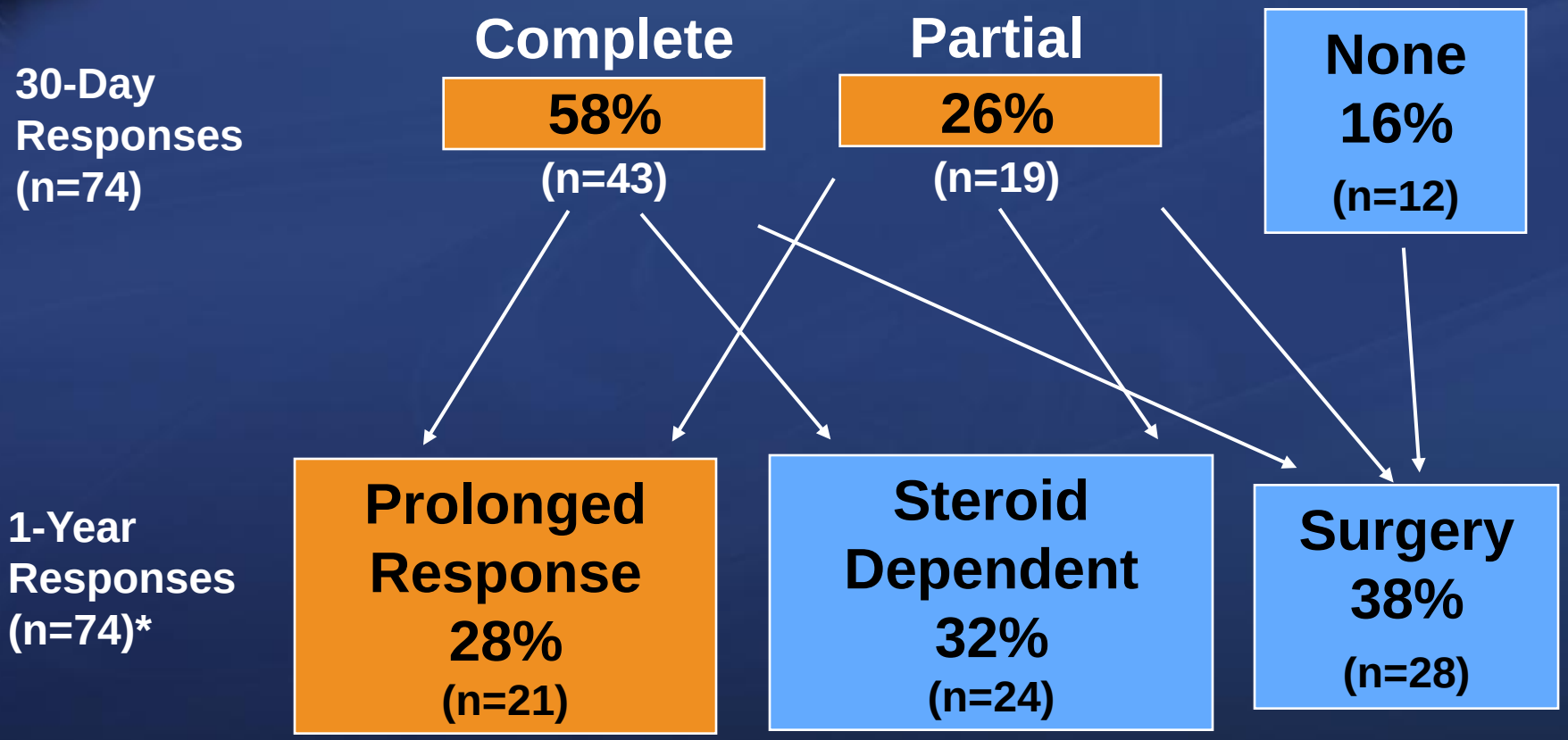
The Problem With Confounding Factors

- Severity of the disease
- Age
- Malnutrition
- Surgery
- Leucopenia
- Concomitant use of other medications

When to Introduce Early-Aggressive Therapies?

The “Tipping Point” may be *need* for Corticosteroids?

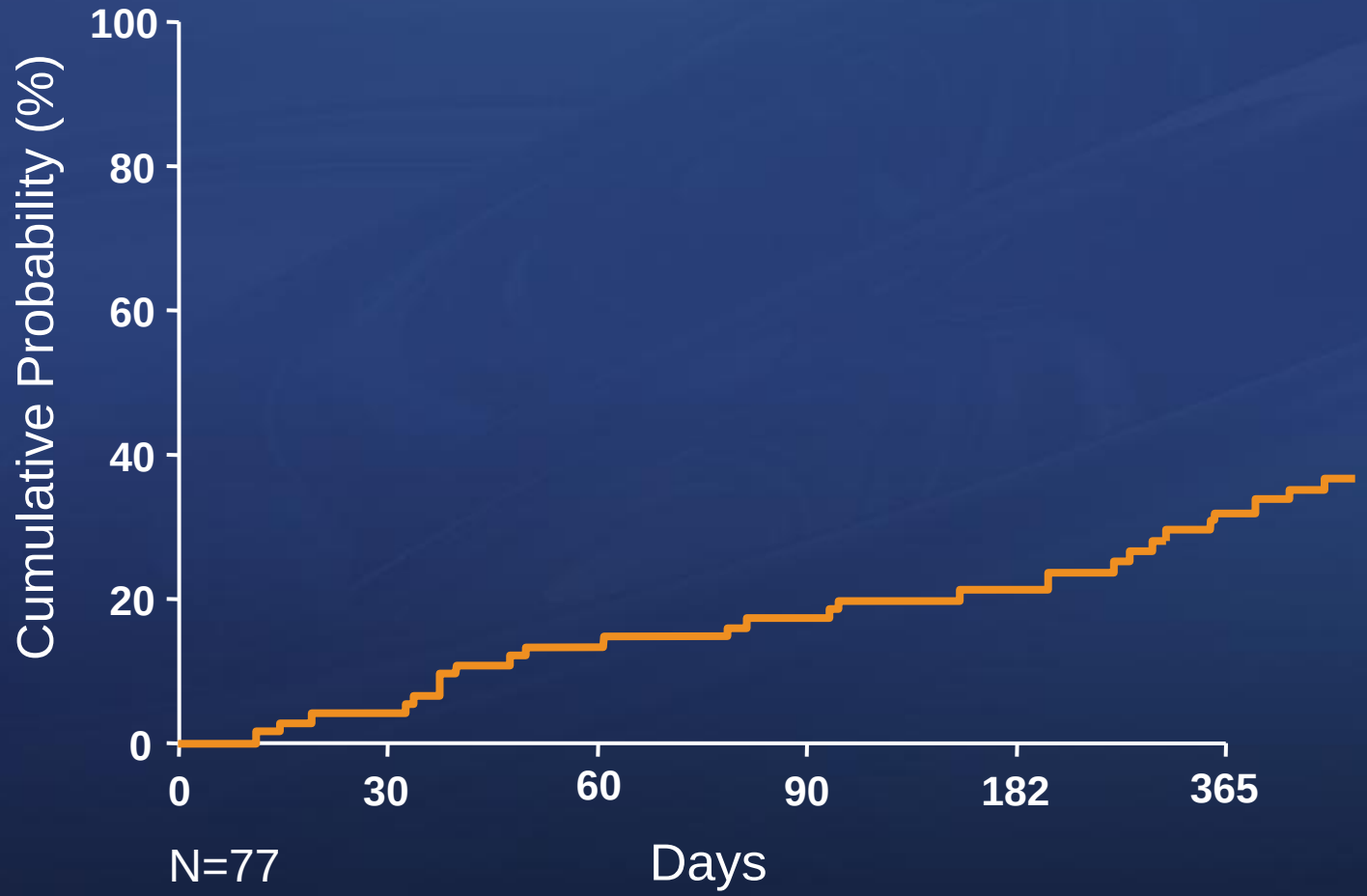
Corticosteroids: Short & Long Term Efficacy in Crohn's Disease



*One patient lost to follow-up

Faubion WA et al. *Gastroenterology*. 2001;121:255-260.

Cumulative Incidence of Surgical Resection Over 1 Year in CD Patients Starting Corticosteroids



Faubion WA et al. *Gastroenterology.* 2001;121:255-260.

So What are the Real Issues Regarding "Early Aggressive" Therapies?

- If biologics cost $1.00 we would not be having these discussions
  - Cost of therapy is the overriding issue for all parties
- Fear of infections/neoplasia
  - Primarily risk of lymphoma in young patients
- Fear of "running out" of options
  - Reserving therapy for refractory patients

Conflict Resolution: Does One Size Fit All?

NO!

So What Should We Do?

- Assess prognosis at diagnosis
  - Initiate therapy according to disease severity and risk of progression
  - Steroids are a “tipping point” for complications and poor prognosis
- Prepare patients for immune suppression
  - PPD, Chest x-ray, vaccinations
- Monitor patients for risks
  - Early assessment of disease progression &/or complications

Current and Future Therapeutic Paradigms

Current

- Bottom-up approach
- Conservative use of immunomodulators
- Goals
  - Induce remission
  - Maintain remission
  - Prevent complications
  - Optimize surgical outcomes

Future

- Initiate therapy ~ to prognosis
- Early-aggressive therapy if bad prognosis
- *Additional* goals
  - Disease *modification*
  - Mucosal healing
  - Pharmacoeconomics
- Disease prevention!