

Treatment of Mild-Moderate Crohn's Disease

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Mesalazine in Crohn
Ferring sponsored breakfast meeting
UEGW Prague, September 2004

Treatment of Mild-Moderate Crohn's Disease

Evidence vs. Experience

Treatment of Mild-Moderate Crohn's Disease

Evidence *and* Experience

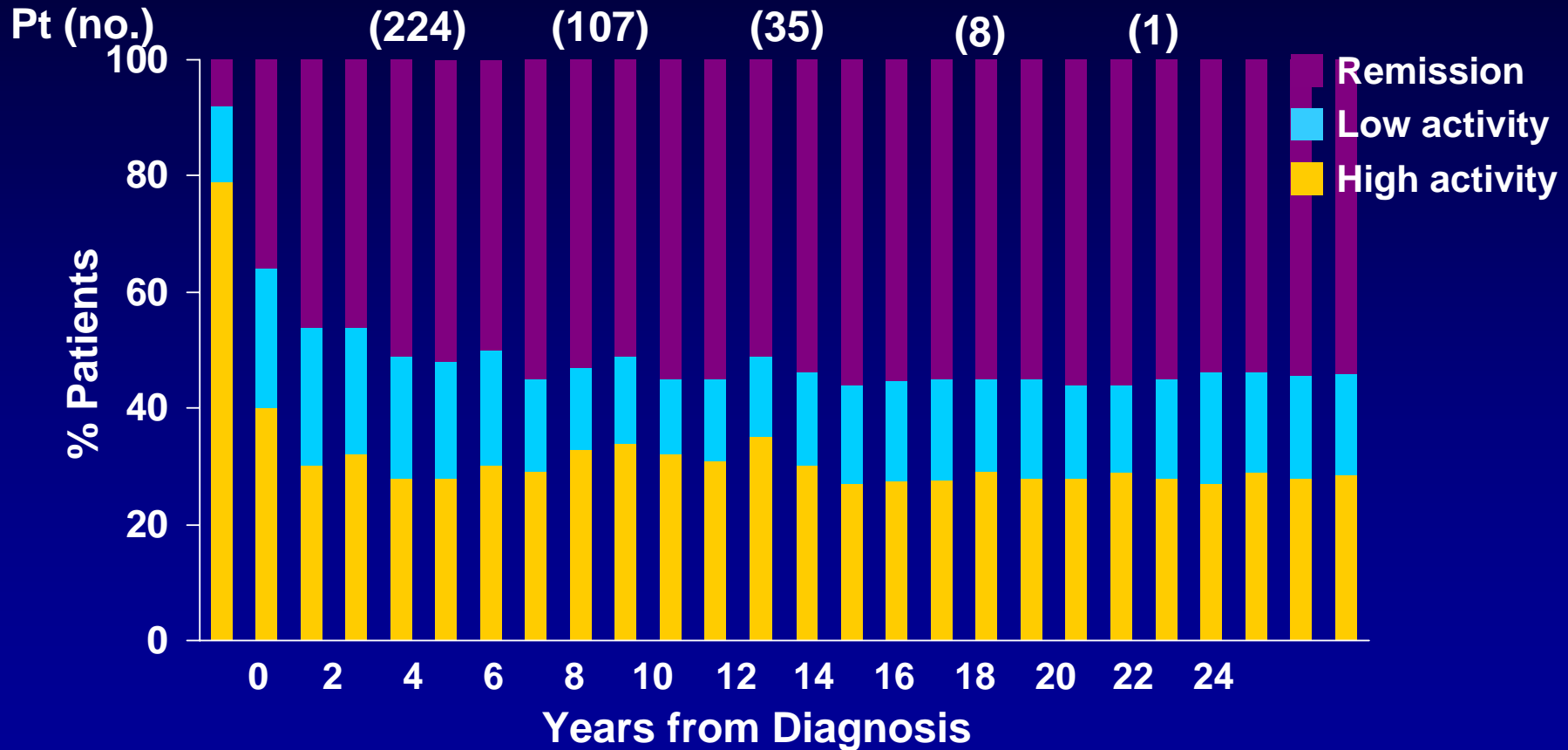
Current Goals of Therapy

- Induce, maintain clinical remission
- Improve patient quality of life
- Minimize disease-, therapy-related complications
- Decrease hospitalization/surgery, overall cost
- Re-establish growth velocity in children

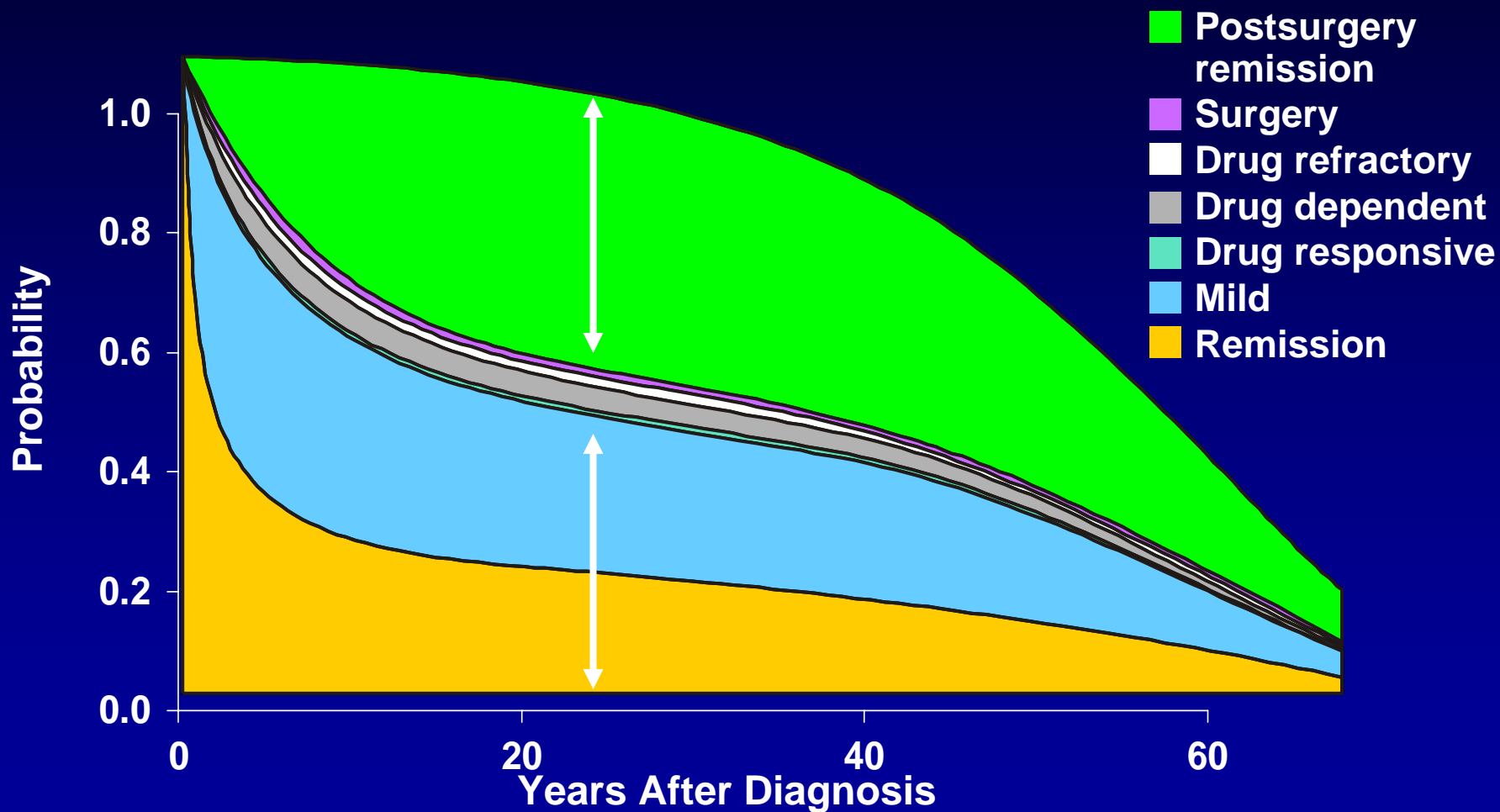
Cautions in Interpreting Trial Reports

- Response
 - CDAI, HB, etc.
 - Level of response
 - CDAI >50, 70, 100
- Remission rates
 - Clinical
 - Endoscopic
 - Surgical

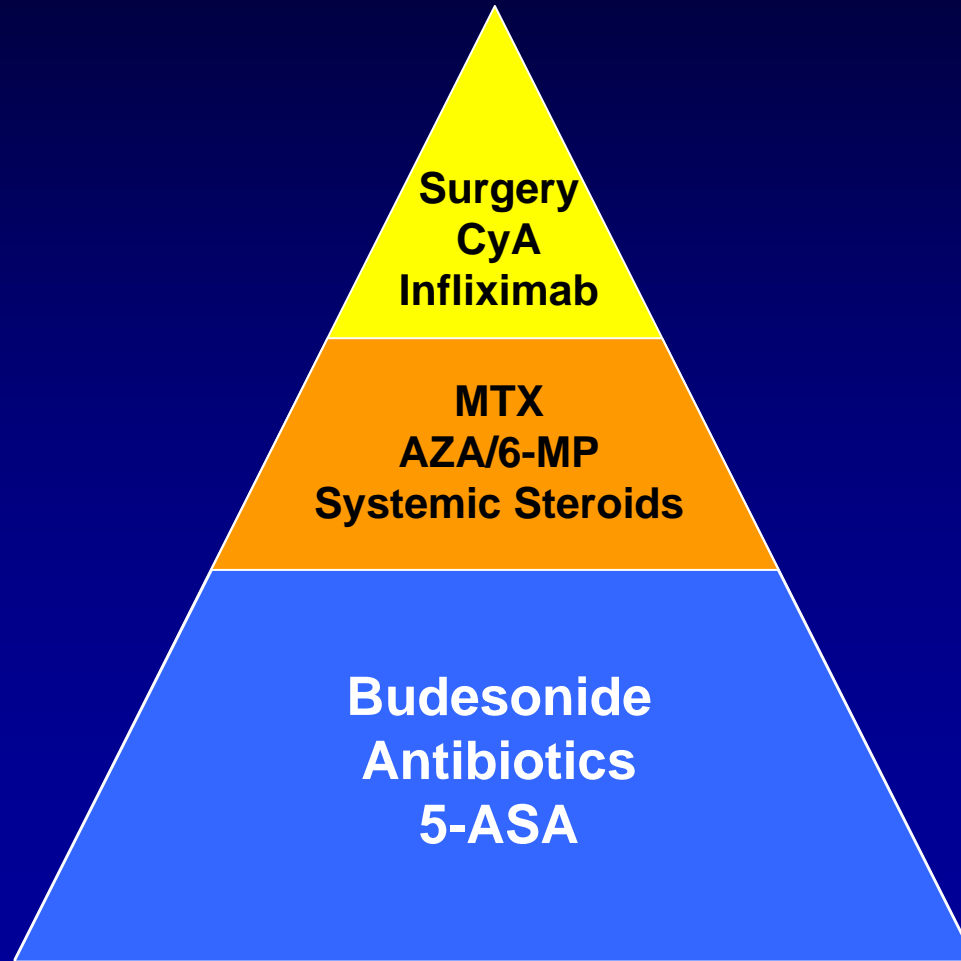
CD Activity Distribution in Population Series



Proportion of CD Patients in Each Treatment State by Year Since CD Diagnosis



ACG Practice Guidelines: Therapeutic Pyramid



Conventional Treatments: Induction of Clinical Response/Remission

<i>Drug</i>	<i>Dose</i>	<i>Response</i>
5-ASA	1.5–4 g/d	43%–64%
Oral prednisone	0.25–0.75 mg/kg/d	60%–78%
Budesonide	9mg	55-60%
Antibiotics		
Metronidazole	10-20 mg/kg	40-50%
Ciprofloxacin	1g	55%
Infliximab	5mg/kg	80%
Placebo		8%–50%

Corticosteroids in Crohn's Disease

Faubion et al. (Olmsted County, 1970-93)

“Only 43% of Inception Cohort Ever Required Steroids”

5-Aminosalicylate Use in Crohn's Disease

- Olmsted County
 - 30% receive 5-ASA during any given year
- Copenhagen County
 - 80% received 5-ASA for at least one year during the 1st 3 years

Silverstein et al, Gastroenterology 1999

Munkholm et al, Scand J Gastroenterol 1995

Outcome of Corticosteroid Therapy for CD

1-month
outcomes

Remission
48%

Improv'd
32%

No change
20%

12-month
outcomes

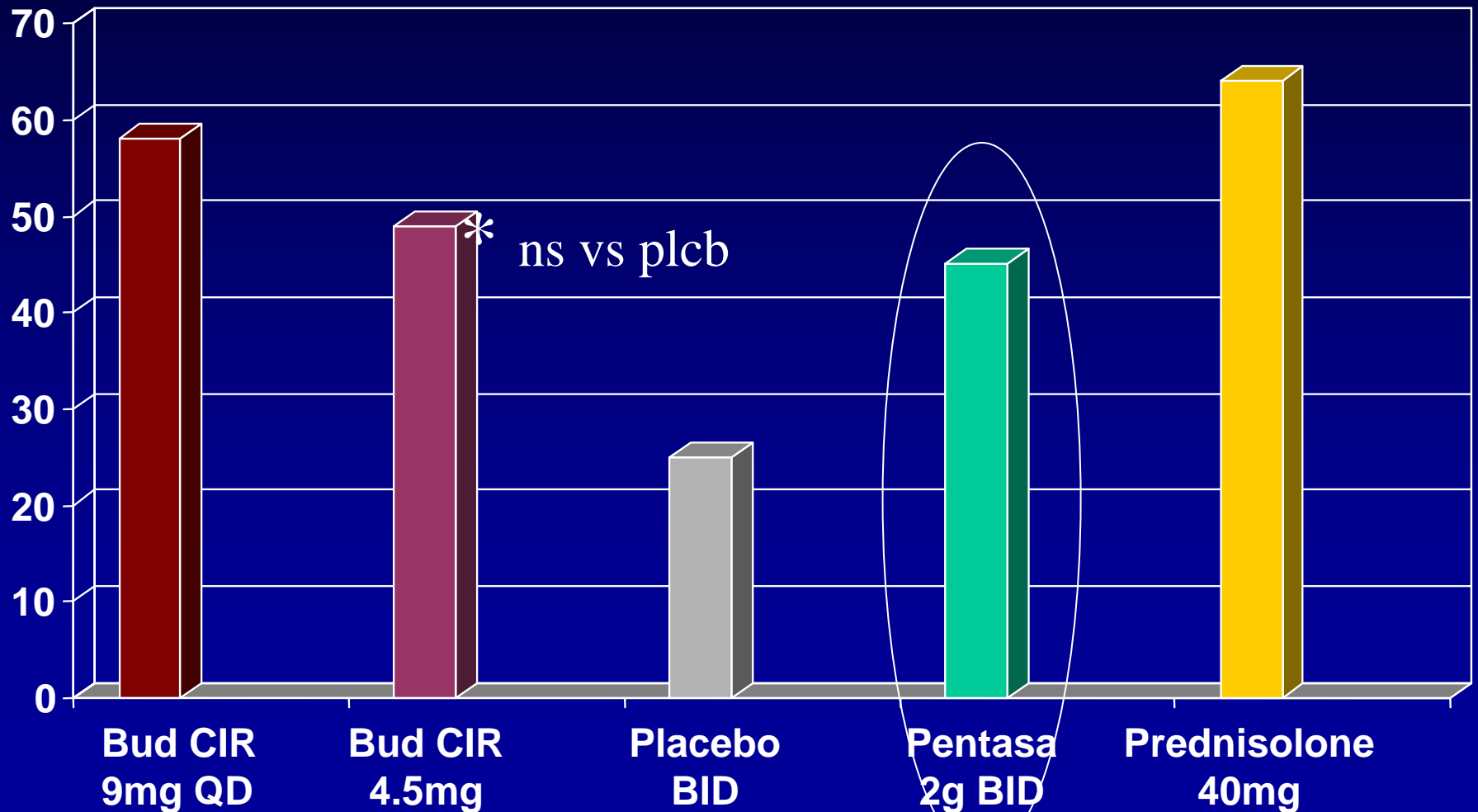
Remission 54%	Relapse 46%
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Improved 57%	Relapse 43%
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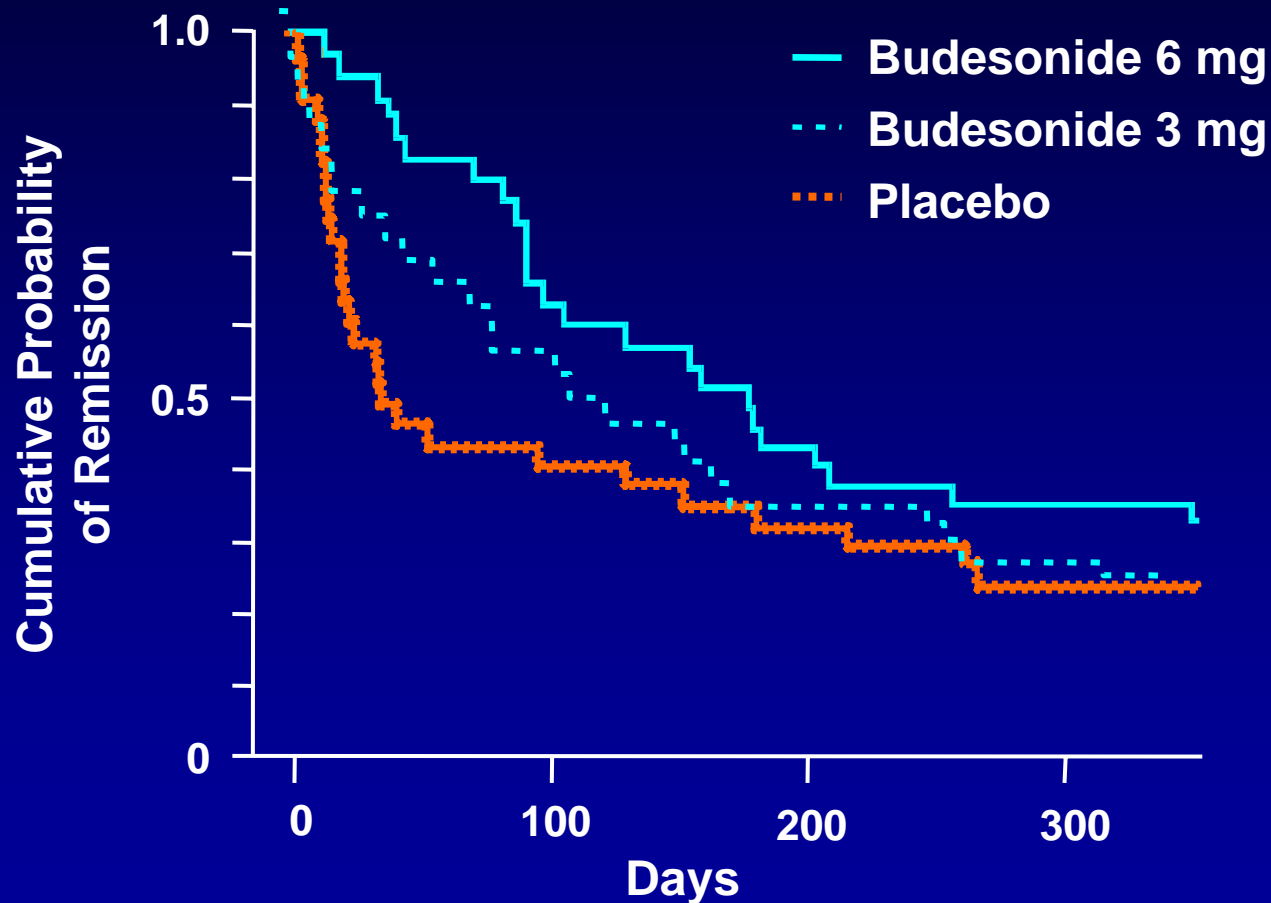
* Remission @ 12 Months=25%

Remission Rates in Acute Crohn's Studies with Budesonide CIR

Remission rates at
8 weeks (%)



Oral Budesonide: (Lack of) Efficacy as Maintenance Therapy



Adapted from Greenberg GR et al. *Gastroenterology*. 1996;110:45.

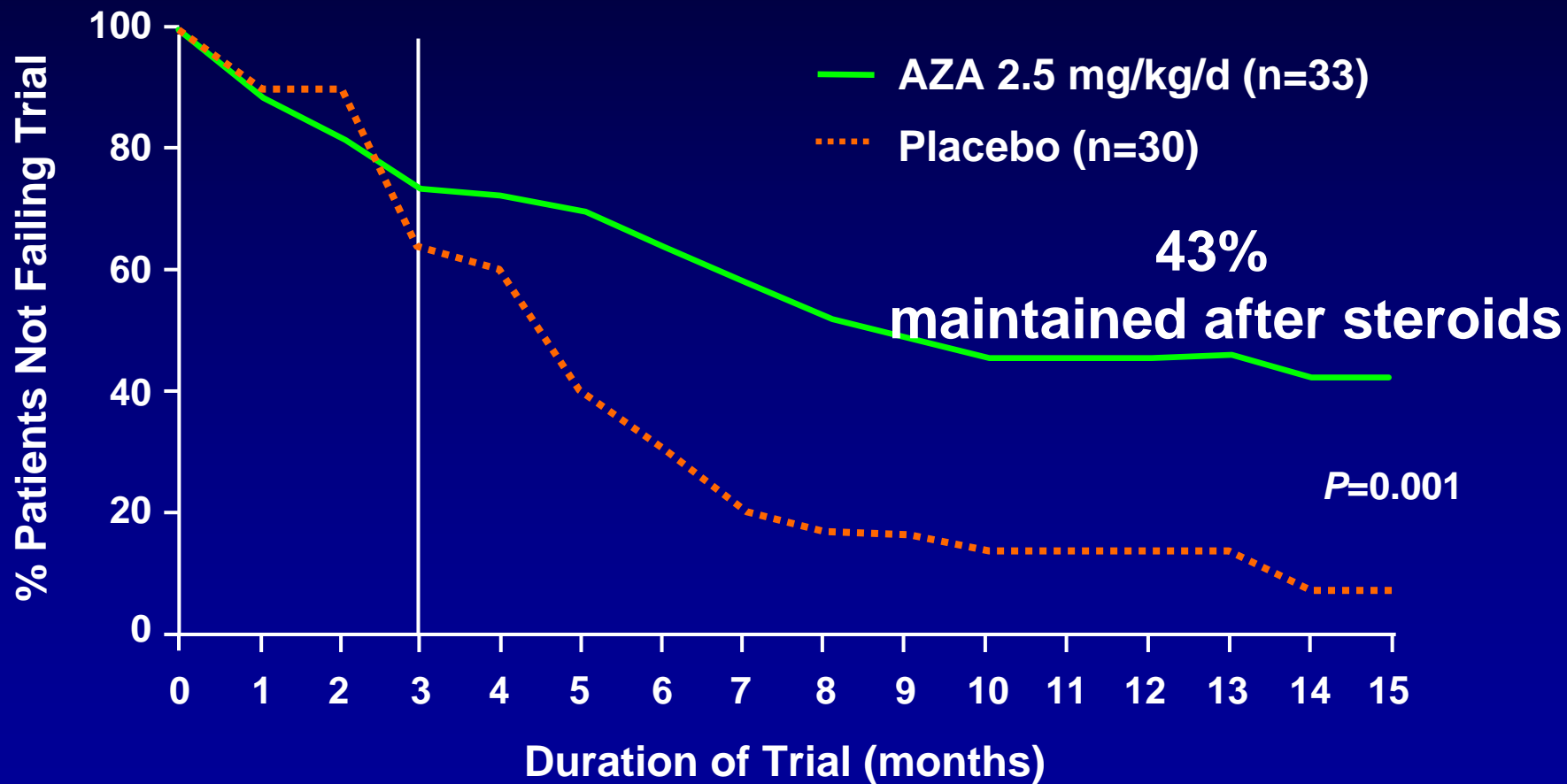
Short-term (10 weeks) Adverse Effects of Budesonide and Prednisolone in Active Crohn's Disease

<u>Adverse effect</u>	<u>CIR Budesonide (%)</u>	<u>Prednisolone (%)</u>
Moon face	17	35
Acne	6	23
Swollen ankles	2	11
Easy bruising	2	7
Hirsutism	2	2
Buffalo hump	1	3
Skin striae	0	0
Other	9	16
Total	40	98

CIR, controlled ileal release.

Rutgeerts P et al. *N Engl J Med.* 1994;331:842-845.

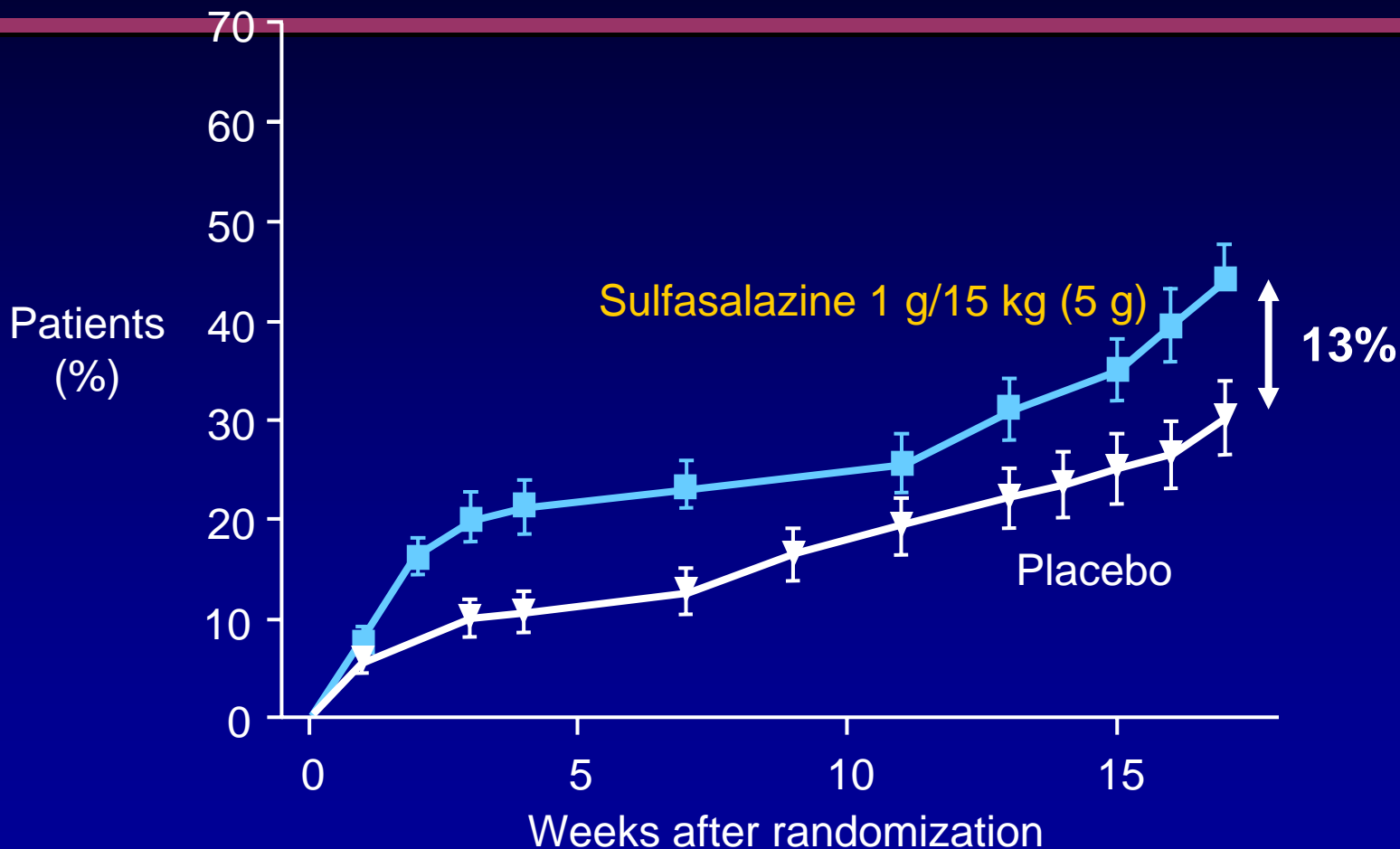
Efficacy of AZA as Maintenance after Steroid Therapy in Adults With CD*



*Remission induced by prednisolone tapered over 12 wk

Reproduced with permission from Candy S et al. *Gut*. 1995;37:674.

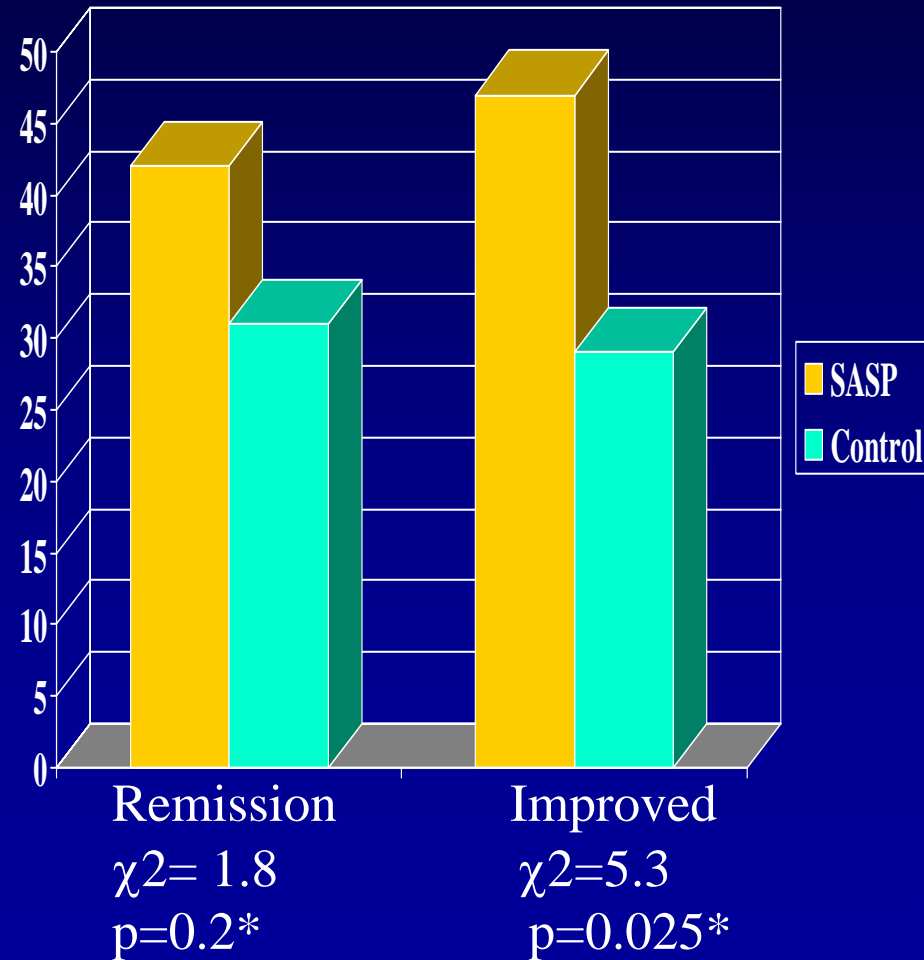
NCCDS: Response to Therapy for Active Crohn's Disease



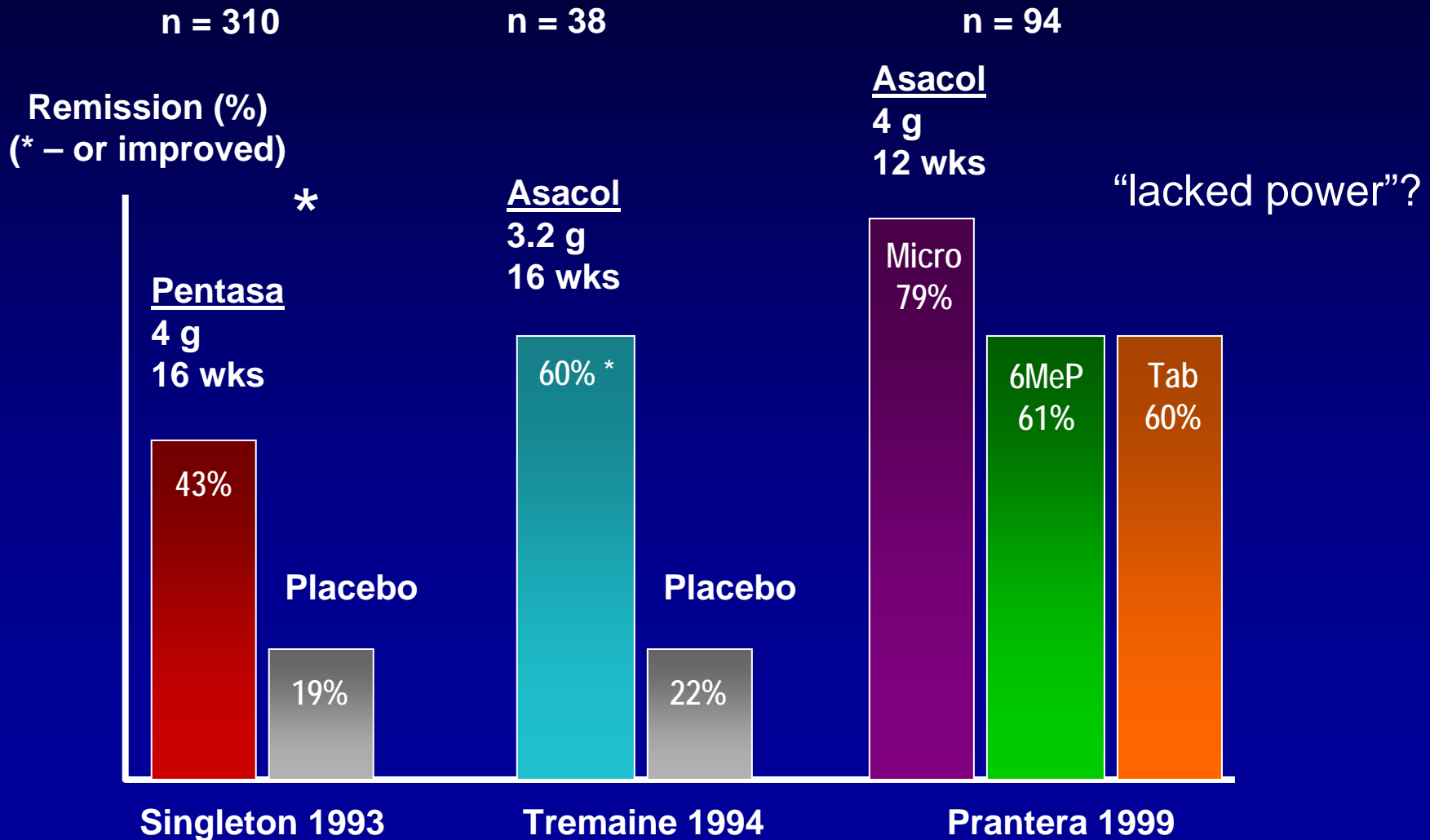
NCCDS, National Cooperative Crohn's Disease Study.
Summers RW et al. *Gastroenterology*. 1979;77:847-869.

Sulfasalazine in Active Crohn's

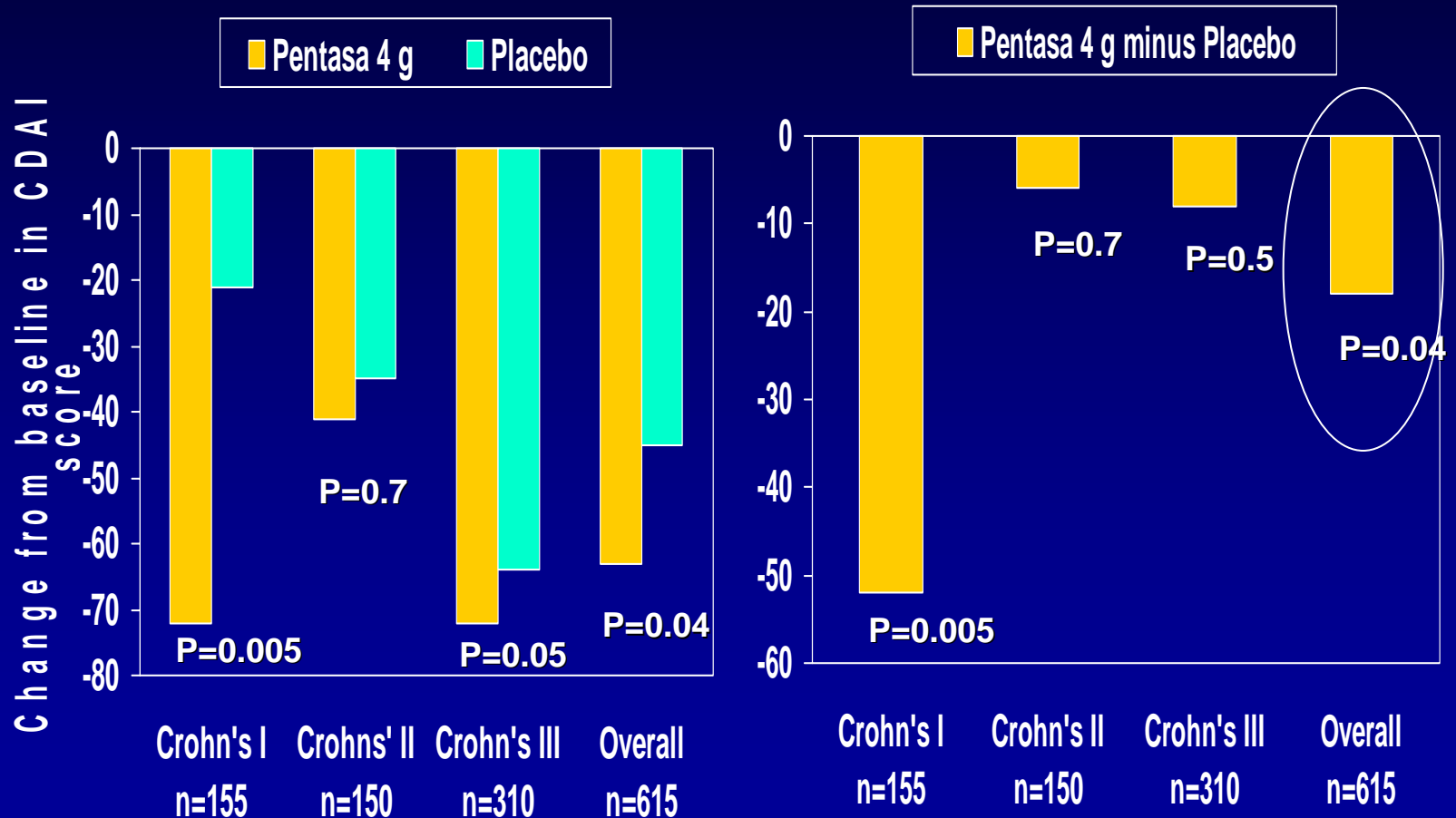
Trial	Dose	N	Wks	End-pt
Anthonisen	3g/ P	17	4X1	Clinical
ECCDS	3 g/P	112	6	CDAI Rem
NCCDS	1.5/kg/P	151	17	CDAI Rem
Ursing	3g/Met	78	16	CDAI Rem** Clinical**
Van Hees	4.5g/P	26	26	Clinical



“High-dose” Mesalazine in Crohn’s Disease: Induction of Remission

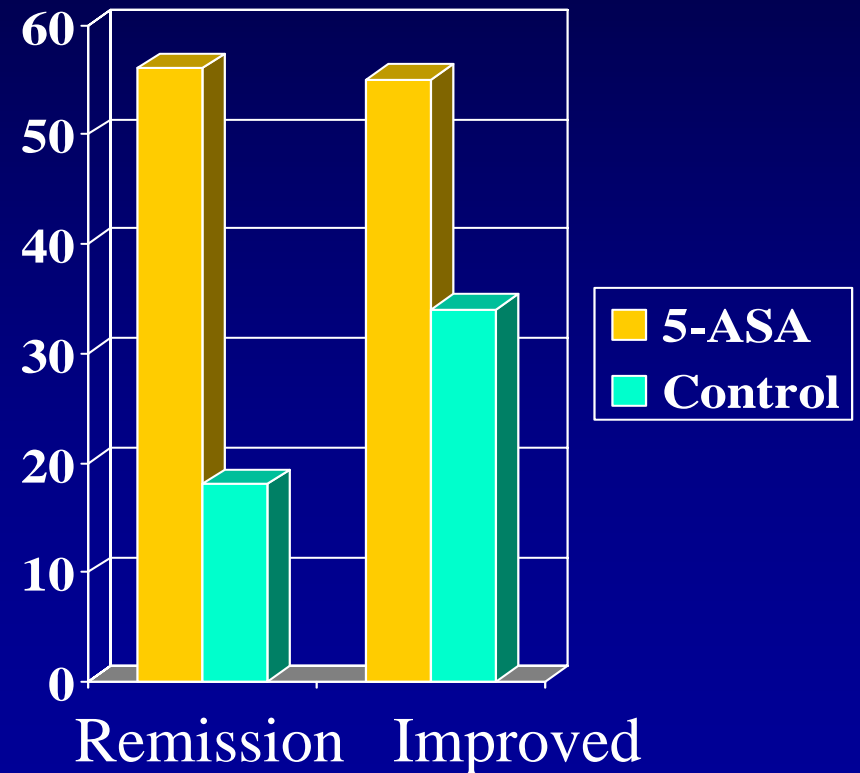


*Meta-analysis of Pentasa 4g/day in Active Crohn's Disease



Mesalazine in Active Crohn's

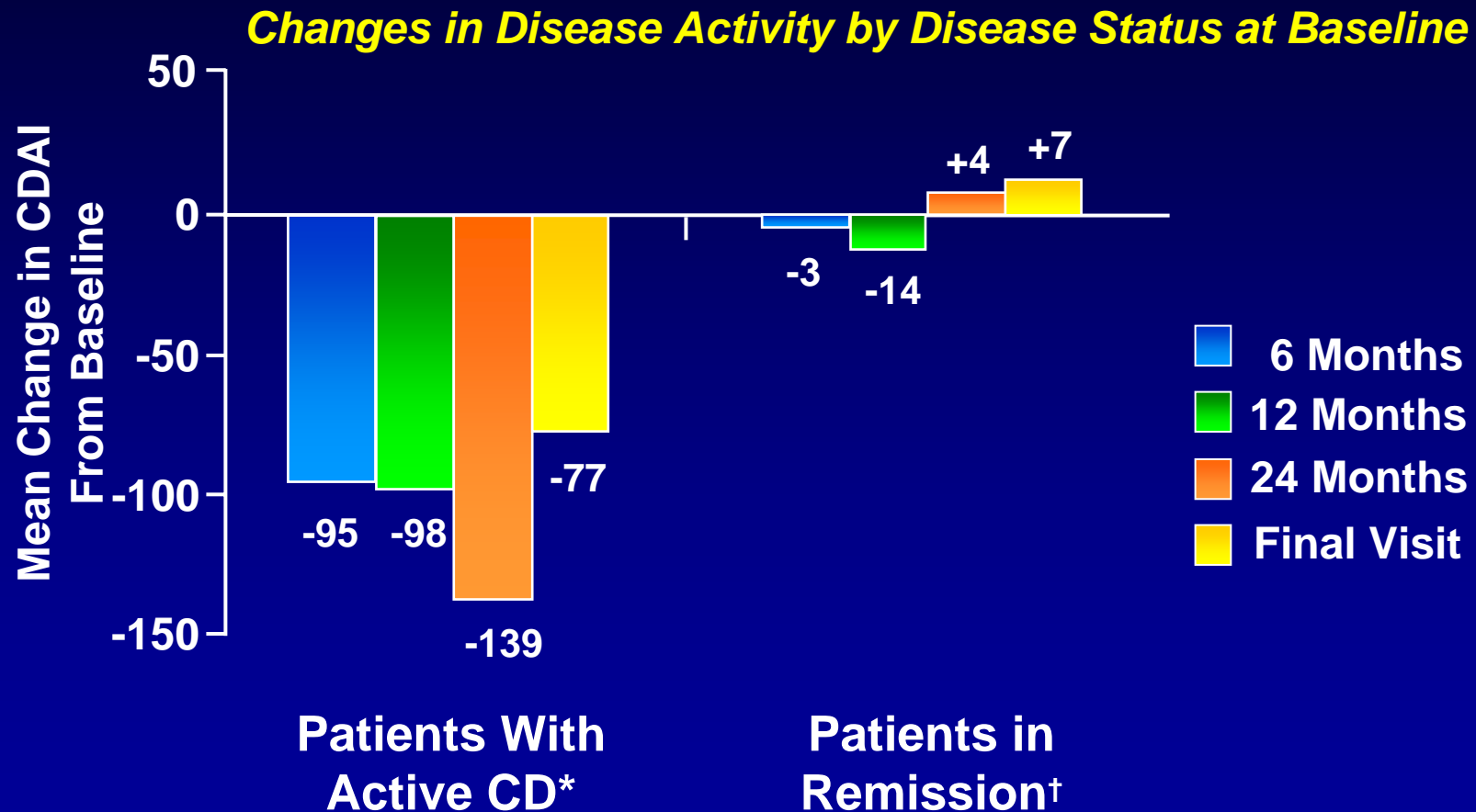
Trial	Drug	Comparator	total N	Weeks	End-point
Mahida	P 1.5	Plc	40	6	HBI -2pts
Rasmusse	P1.5		18	6	Clinical CDAI Rem
Rasmusse	P 1.5	Plc	67	16	Clinical
Colombel	P 4	Cipro	40	6	CDAI Rem
Tremaine	Asa 3.2	Plc	38*	16	Clinical
			18 on steroids		
Thomsen	P 4	Bud	182	8	CDAI Rem
				16	CDAI Rem
Prantera	Asa Tab	Me-Pred	94	12	CDAI Rem
	Asa Gran				
Gross	Salo 4.5	Me-Pred	34	8	CDAI Rem
Singleton	Pen 4	Plc	155	16	CDAI Rem



$\chi^2= 15.6$
 $p<0.001$

$\chi^2=6.7$
 $p<0.01$

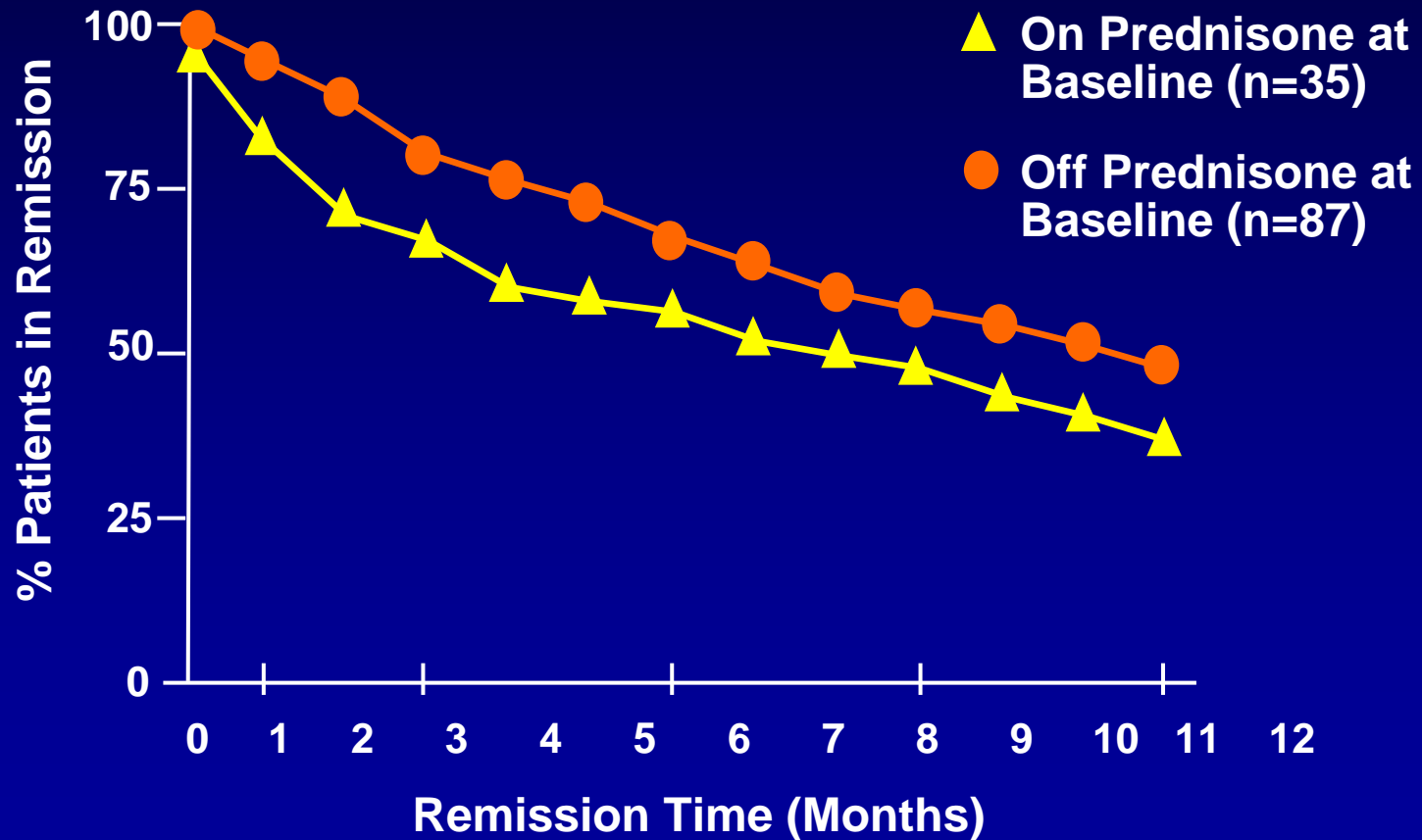
Efficacy of Mesalazine for the Long-Term Management of CD



*CDAI ≥ 150 at baseline; †CDAI < 150 at baseline

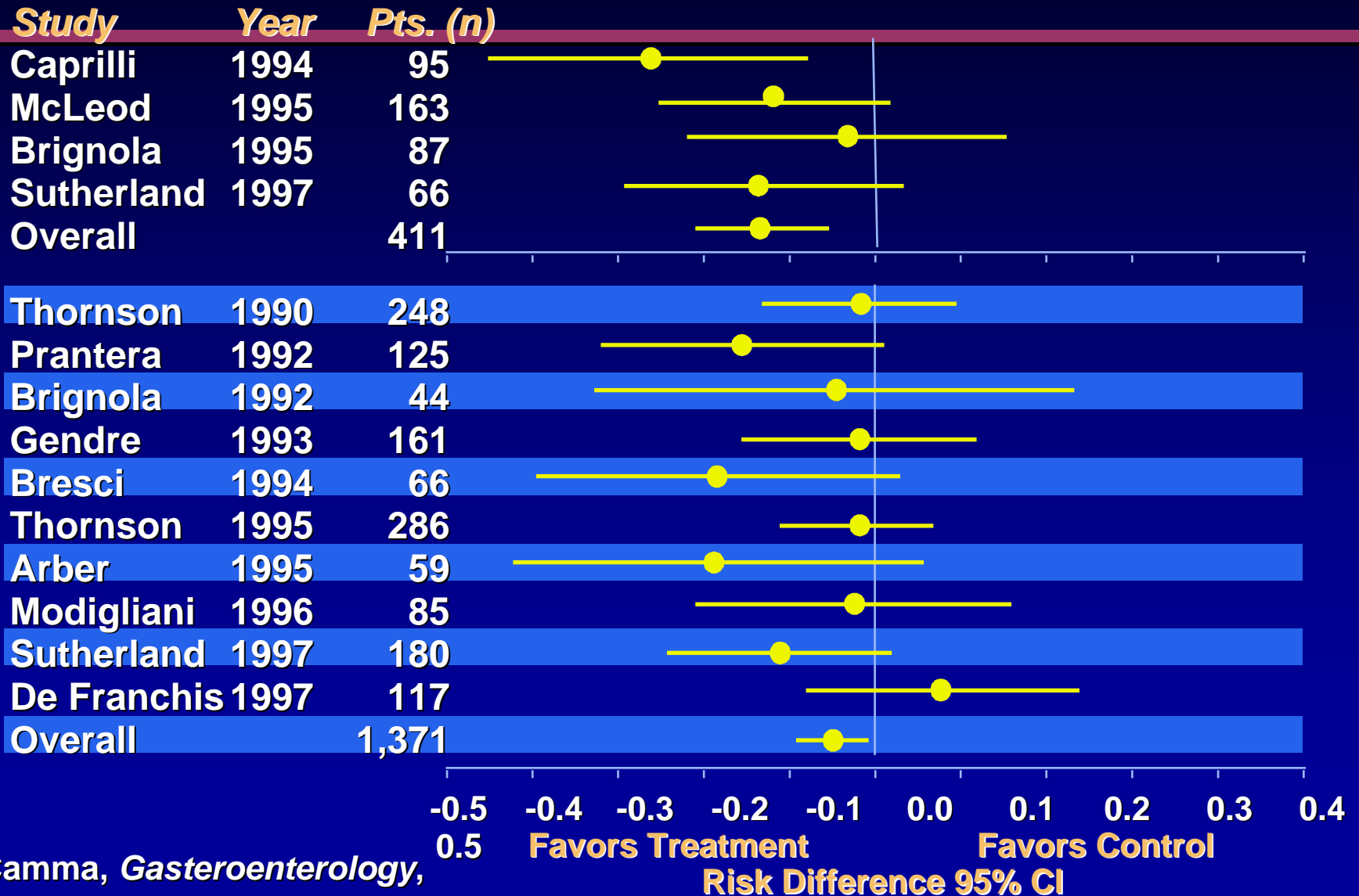
Efficacy of Mesalazine for the Long-Term Management of CD

*Length of Remission for Patients in Remission at Baseline**

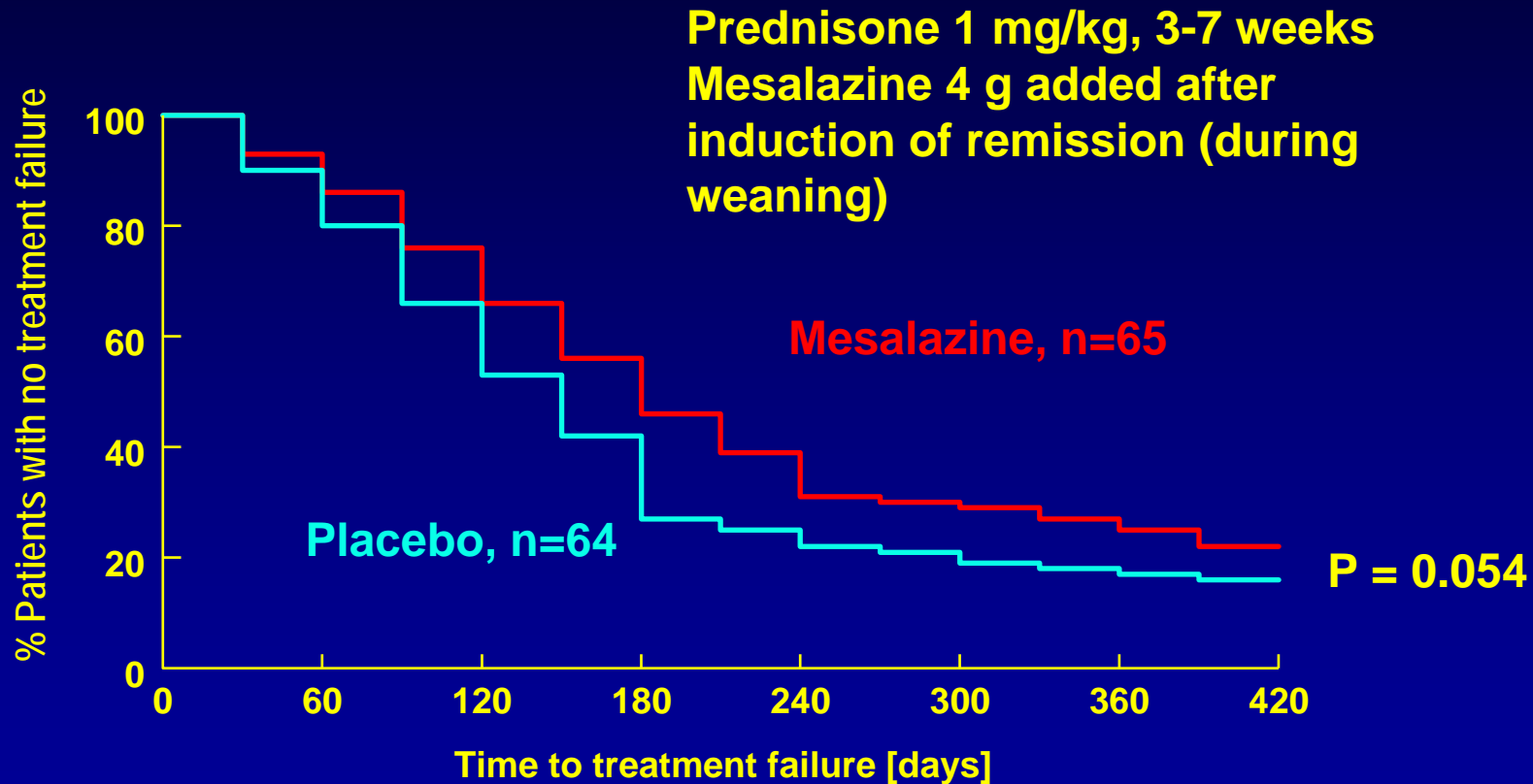


*CDAI <150 at baseline

Mesalazine Maintenance of Remission in Crohn's Disease



Is Mesalazine Steroid-Sparing in Crohn's Disease?



Placebo: 19 % steroid dependent

Mesalazine: 6% steroid dependent

5-ASA Maintenance Trials

Complexities

- Heterogeneous populations
- Definitions of response
- Post-Medical Induction
 - Aminosalicylates
 - Antibiotics
 - Steroids
- Post-surgical
 - Inflammatory, Strictureing, Fistulizing Indications

Sequential Strategies for Crohn's Disease

Induction

Maintenance

Aminosalicylate-----→

Aminosalicylate

Antibiotics-----→

Antibiotic (?)

Corticosteroids-----→

AZA/6-MP/MTX/Infliximab

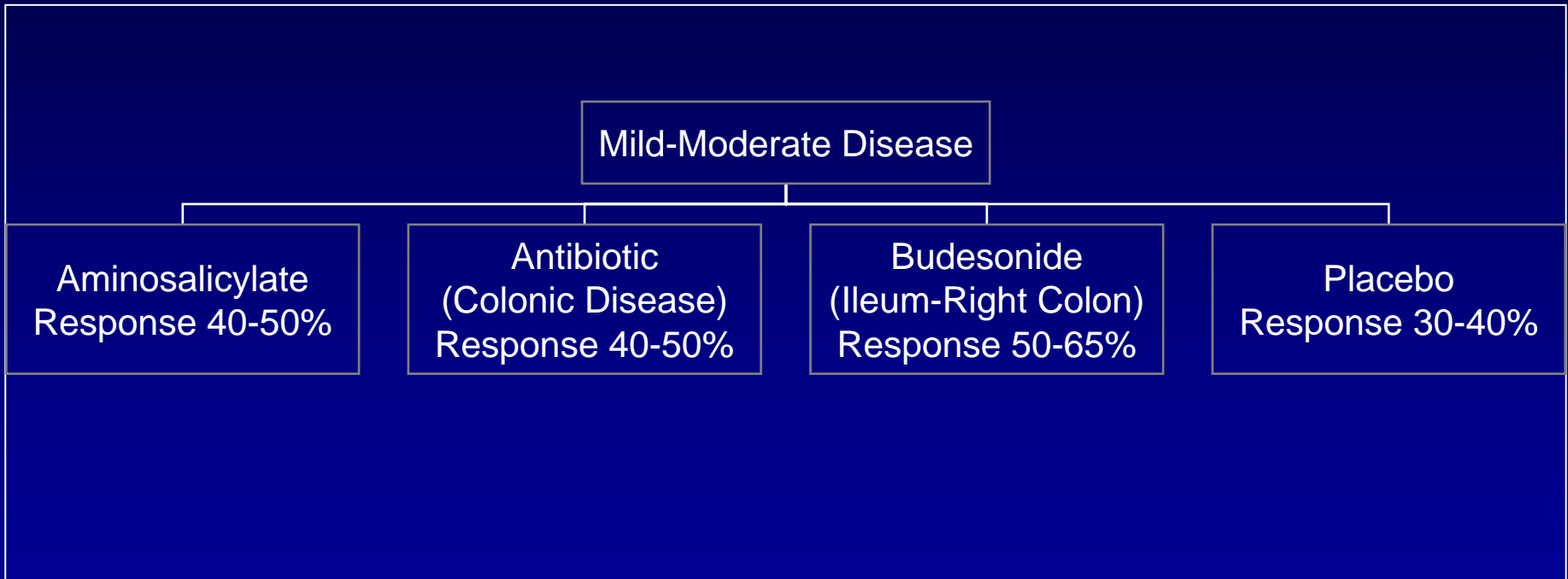
Infliximab-----→

Infliximab (+aza/mtx?)

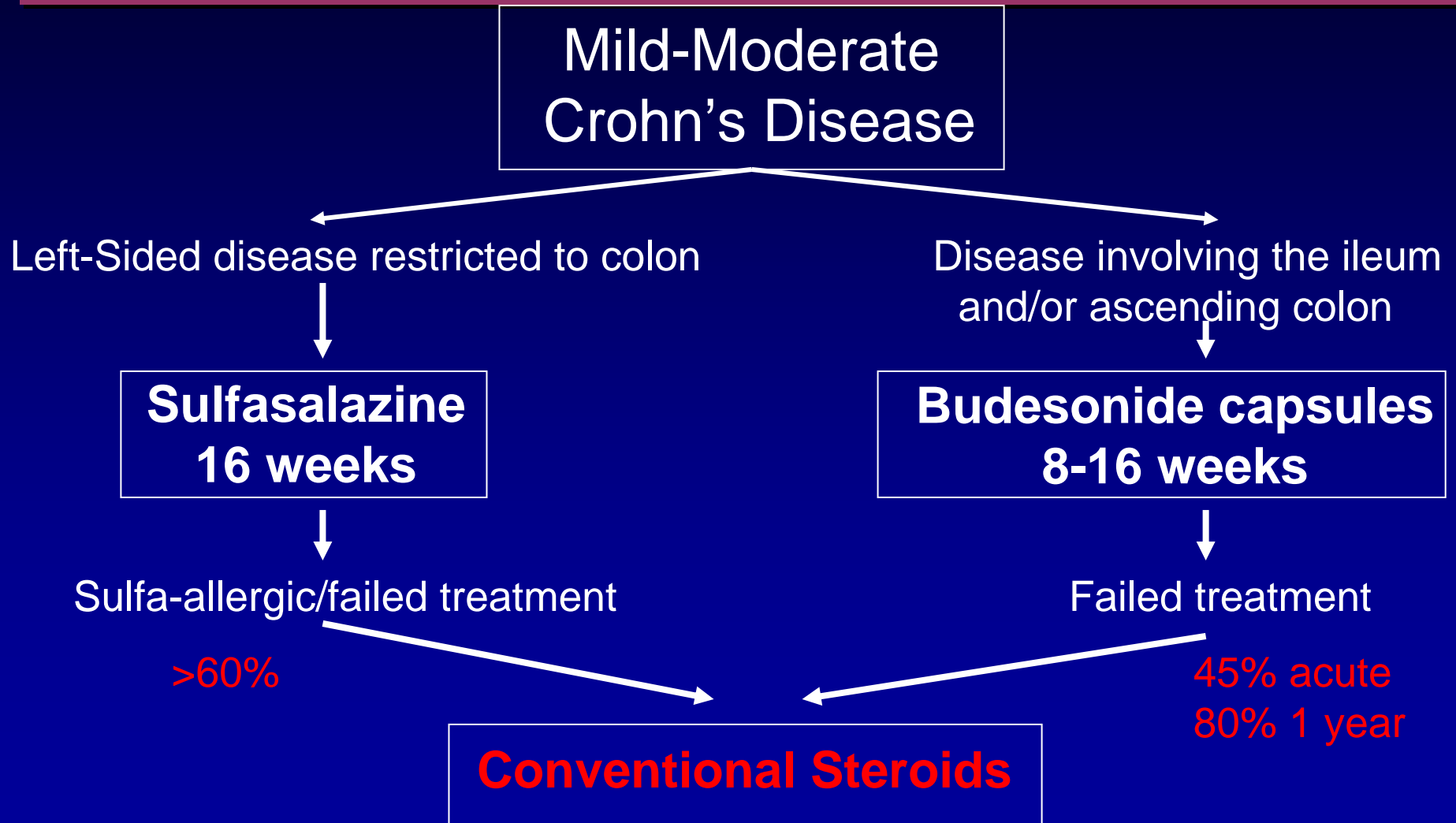
Surgery-----→

6-MP/5-ASA/Infliximab (?)

Outcomes for Mild-Moderate Disease

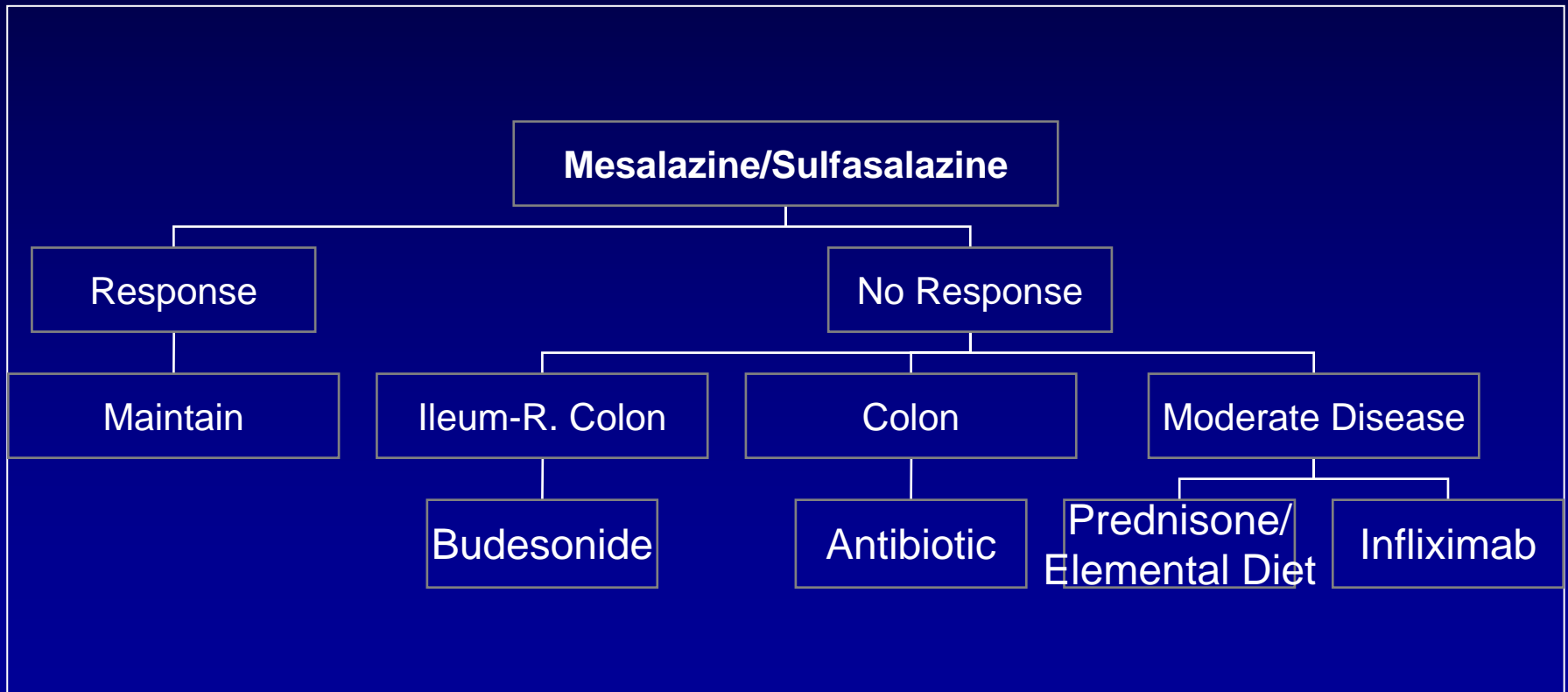


“Evidence-Based” Approach of Sandborn & Feagan



Evidence/Experience

Aminosalicylate Induction



“Publication Bias”

- 1993 Pentasa I Marion Labs
- 1994 Pentasa II Marion Merrel Dow
- 1997 Pentasa III Hoechst Marion Roussel

- 2000 Meta-analysis solicited Ferring
 - Rejected
 - 2004 Accepted Clinical Gastro & Hepatology

5-ASA in Crohn's Disease

- Use is supported by both clinical experience and evidence
- Advocated in U.S. and U.K. Guidelines
- Clinical Utilities
 - Mild-Moderate Disease
 - Maintenance of Remission after 5-ASA induction
 - ? Post-operative sub-groups?
- Long-term safety established

**Prescriptions are Written on
Paper...
Not in Stone**

Advance to more potent, more toxic agents if no initial response or relapse