

# Clinical Trials



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# Follow-Up Studies of Panic Disorder

- ◆ Acute treatment with IMI and behavioral group treatment
- ◆ 2.9-year follow
- ◆ Half remained on medication (average dose: 74 mg/d)
- ◆ 40% remained symptomatic

# Long-Term Course Follow-Up Study of Cross-National Collaborative Panic Study

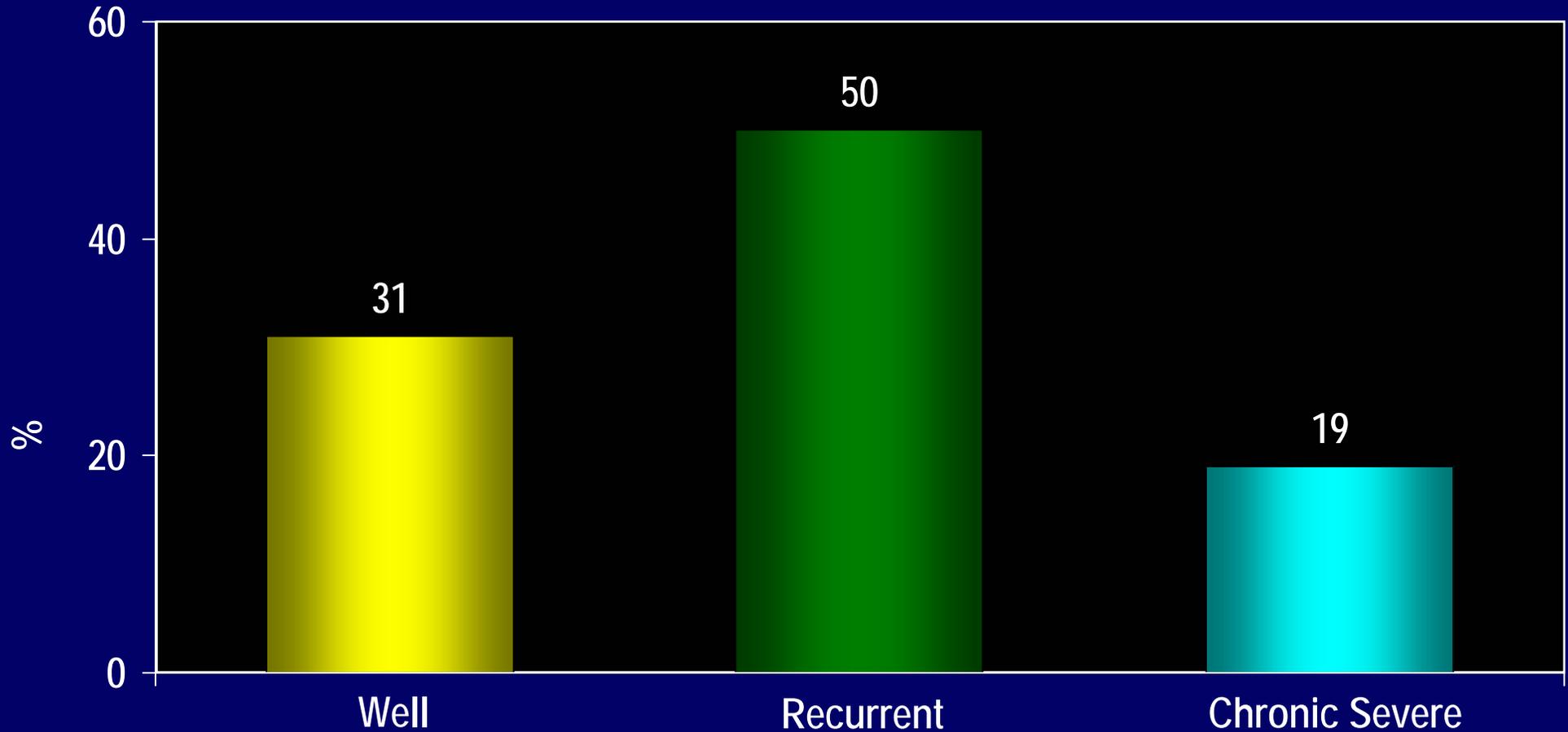
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- ◆ Recruited 423 of the original N=1647
- ◆ Follow-up period: 2-6 years
- ◆ Assessed symptoms and disability
- ◆ Compared post-study year to year before the interview
- ◆ Final sample: N=220

ajacobsen:

Y-axis:  
percentage of  
what?

# Long-Term Course



Katschnig et al. Treatment of Panic Disorder A Consensus Development Conference. 1994;73.

# Determinants of Pharmacologic Treatment Failure in Panic Disorder

## Rates of Discontinuation Due to Side Effects for Antidepressants

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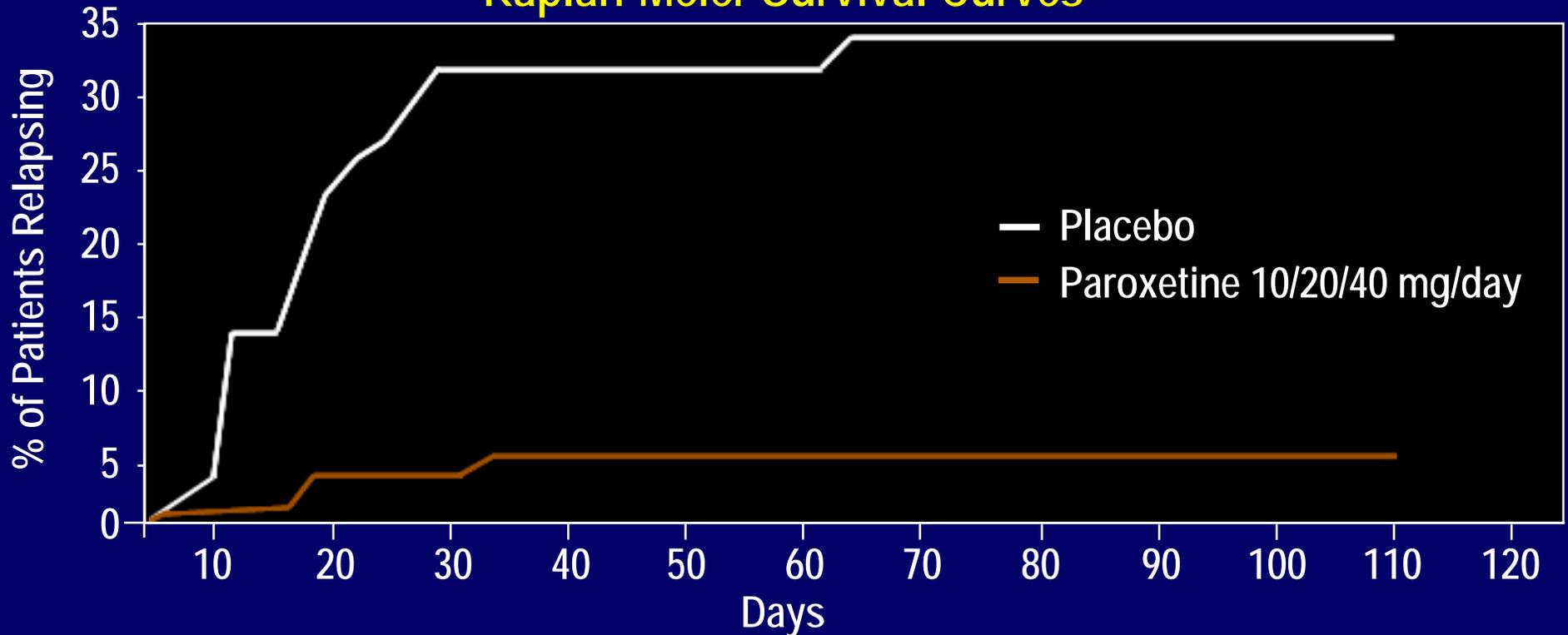
TCA	58%
MAOI	33%
SSRI	29%

# Effective SSRI Treatments

- ◆ Fluvoxamine
- ◆ Paroxetine
- ◆ Sertraline
- ◆ Fluoxetine
- ◆ Citalopram

# Relapse During 3-Month Course of Paroxetine or Placebo (n=105)<sup>1</sup>

Kaplan-Meier Survival Curves



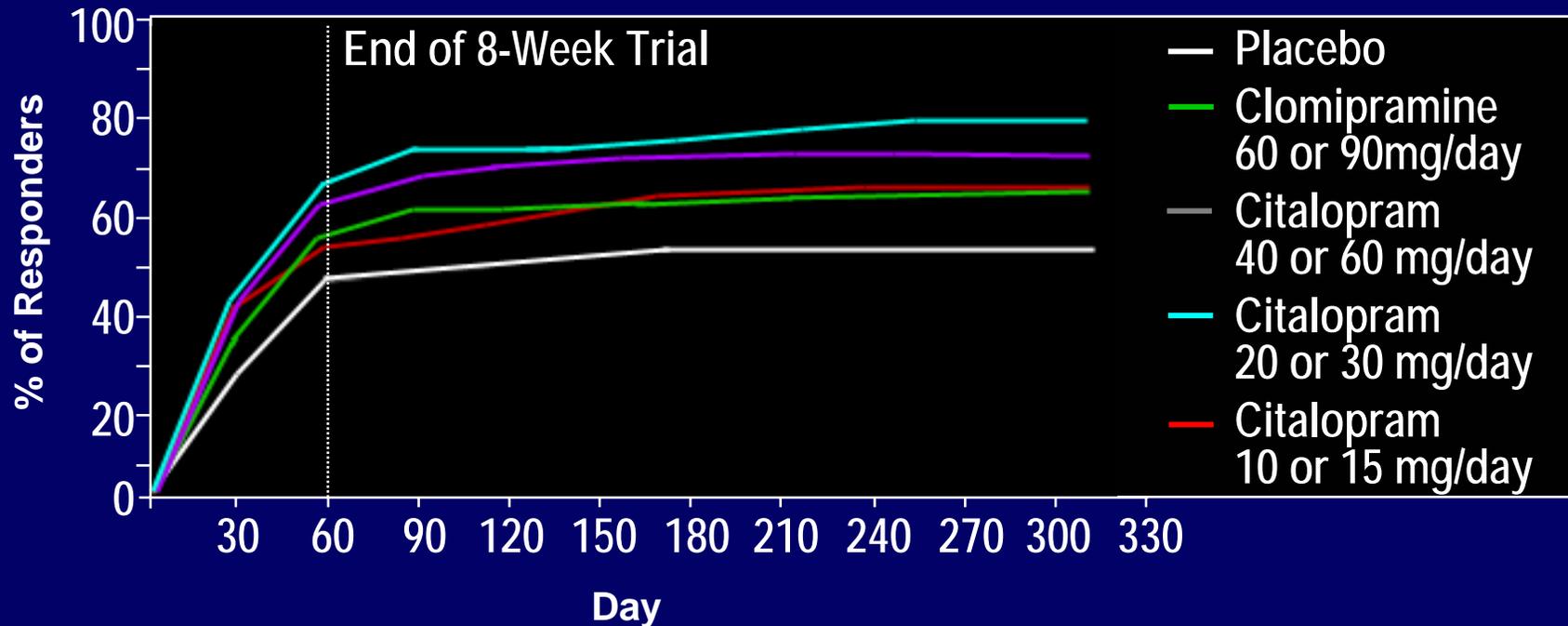
1. Patients with no relapse during 5 months of paroxetine were randomized to 3 months of same-dose paroxetine or placebo.

Burnham et al. 1995.

Lydiard et al. 1998.

# Panic Disorder: Long-Term Treatment

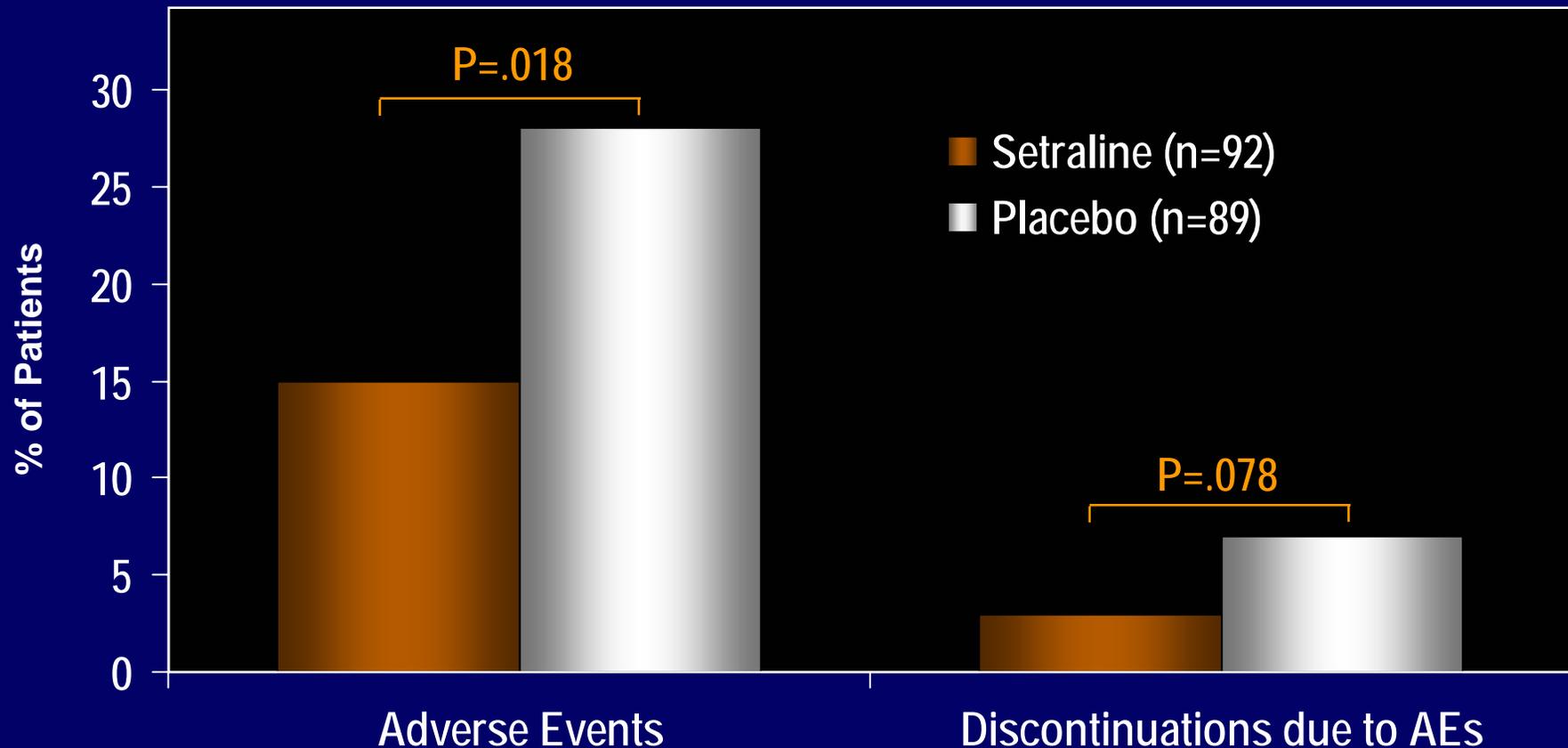
Cumulative Response Rates<sup>1</sup> to Clomipramine and Citalopram (ITT population)



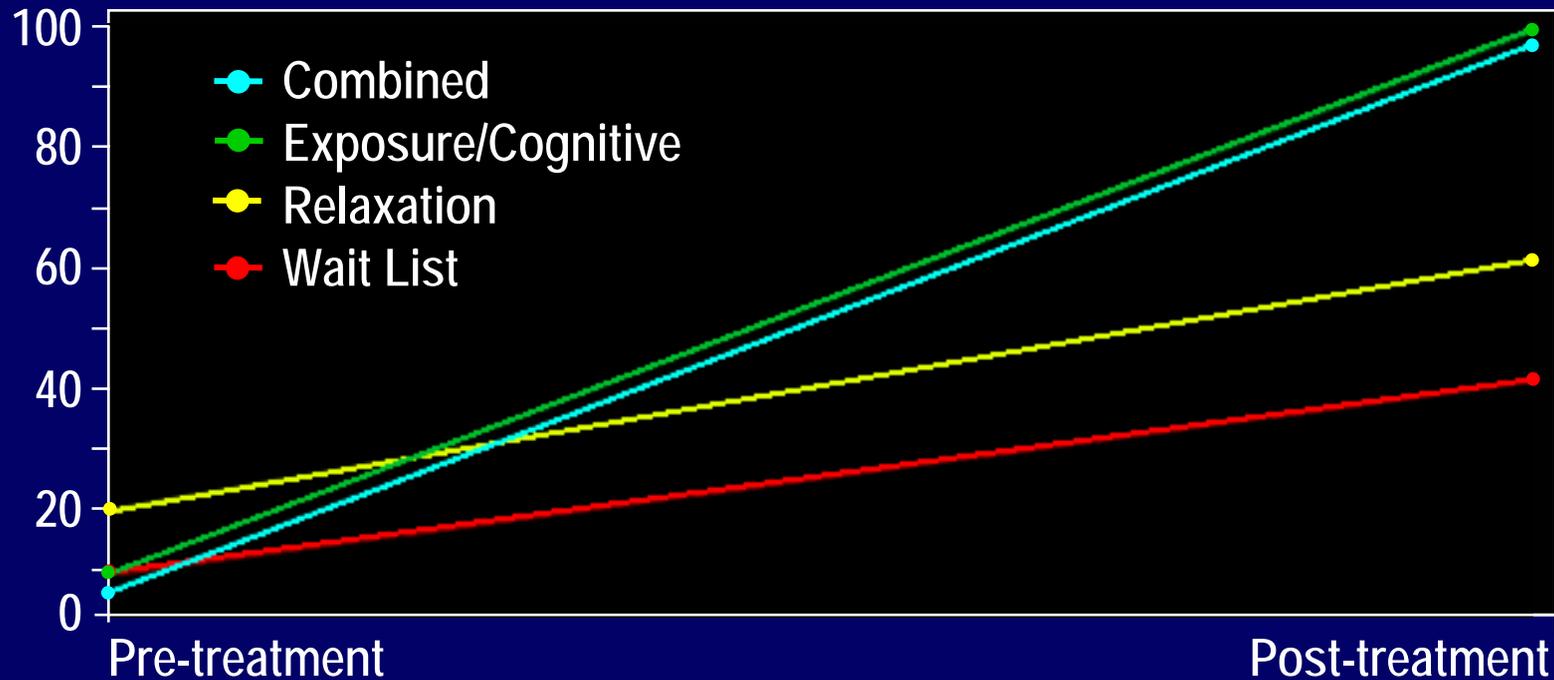
1. Defined using the Clinical Anxiety Scale panic attack item.  
Lepola et al. 1998

# Setraline for Long-Term Treatment of Panic Disorder

Treatment-emergent adverse events during 28-week double-blind phase



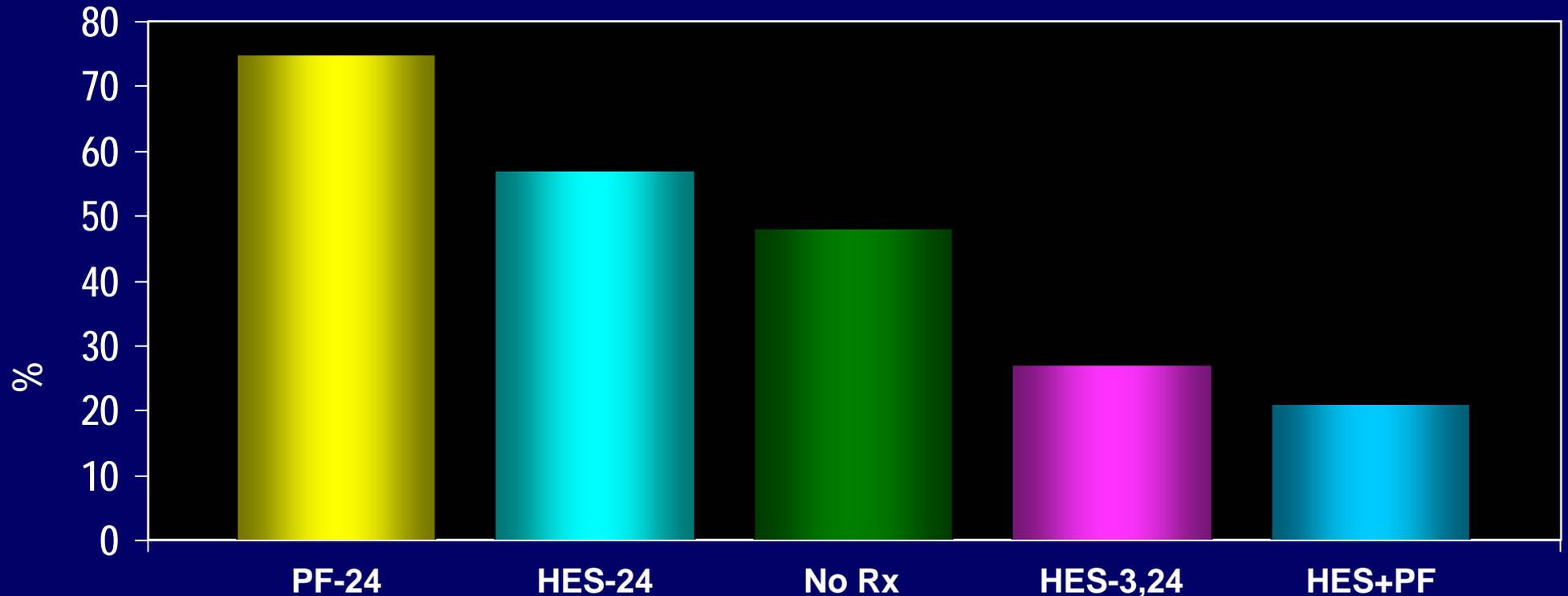
# Percentage of Completers Reporting Zero Panic Attacks



ajacobsen:

Y-axis:  
percentage of  
what?

# CBT Longitudinal Outcome



# Multicenter Panic Study

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**Chairman, Department of Psychiatry**  
**Mount Sinai School of Medicine**

# This Presentation

- ◆ Background: Treatment of Panic Disorder in the late 1980's
- ◆ Multicenter Comparative Treatment Study of Panic Disorder
- ◆ Additional single-site comparison: "Emotion-focused Therapy" (EFT)
- ◆ What's next: Long Term Strategies for Treatment of Panic Disorder

# Treatment Efficacy in 1990

- ◆ **Efficacy documented for several classes of medication**
  - **TCA's ( esp.Imipramine)**
  - **MAO Inhibitors**
  - **High potency benzodiazepines**
  - **Promising initial outcomes for SSRI's**
- ◆ **Well documented efficacy for CBT focused on fear of bodily sensations**
- ◆ **Other psychotherapies (e.g. supportive and “psychodynamic” type) widely used and untested**

## The Problems

- ◆ **Contentiousness regarding comparative efficacy of medication and CBT**
- ◆ **Uncertainty about the value of combining treatment**
- ◆ **Little consistency in assessment methods for Panic Disorder**
- ◆ **Limited awareness of efficacious treatments among clinicians**

**Multicenter Collaborative Study**

**NIMH R10 Grant**

# **Cognitive-Behavioral Therapy, Imipramine, or Their Combination for Panic Disorder**

## **A Randomized Controlled Trial**

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Pittsburgh**

**SW Woods, M.D. Yale  
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# Study Questions

- ◆ Do both cognitive-behavioral treatment and imipramine perform better than placebo medication?
- ◆ Does either active treatment alone perform better than the other?
- ◆ Does combination treatment perform better than monotherapy?

# STUDY DESIGN

n=312

	<b>IMI</b>	<b>PLA</b>	<b>NO PILL</b>
<b>CBT</b>	<b>CI</b> <b>N=65</b>	<b>CP</b> <b>N=63</b>	<b>C</b> <b>N=77</b>
<b>TX CONTROL</b>	-	-	-
<b>NO PSYCHO-TX</b>	<b>I</b> <b>N=83</b>	<b>P</b> <b>N=24</b>	-

# Subjects: DSM III-R Panic Disorder with $\leq$ moderate Agoraphobia\*

## Demographics

63% women

Mean age 36 years

91% white

50% married

\*on no psychotropic  
medications

## Clinical

## Characteristics

Mean duration of PD  $>$   
6 years

27% with current MDD

Mean Panic Disorder  
Severity Scale 1.8

# STUDY TIME LINE

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## PHASES AND DURATIONS



**Major Assessments done at baseline, post-acute, post-maintenance and post follow-up**

**\*IMI/PLA subjects entered maintenance only if they were responders at post-acute assessment**

# Responder Definition

**CGI Improvement** = 1 or 2  
(much or very much improved)

and

**CGI Severity**  $\leq$  3 (mild)

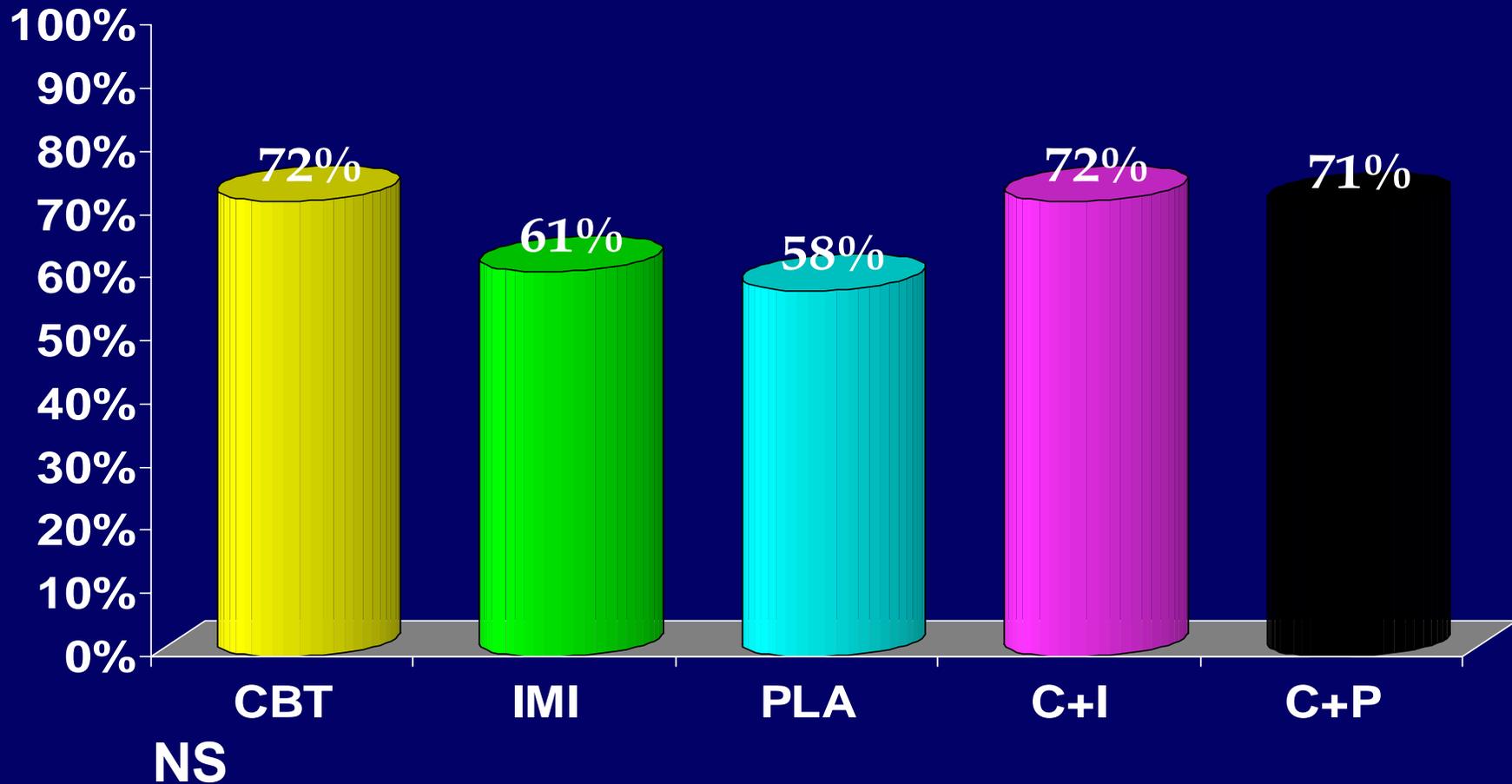
# Main Outcome Measures

- ◆ Clinical Global Impressions Scale (CGI)
  - Overall illness severity and improvement
  - Included PD anchor points
- ◆ Panic Disorder Severity Scale (PDSS)
  - Developed for this study
  - Responder defined as  $\leq 60\%$  baseline score

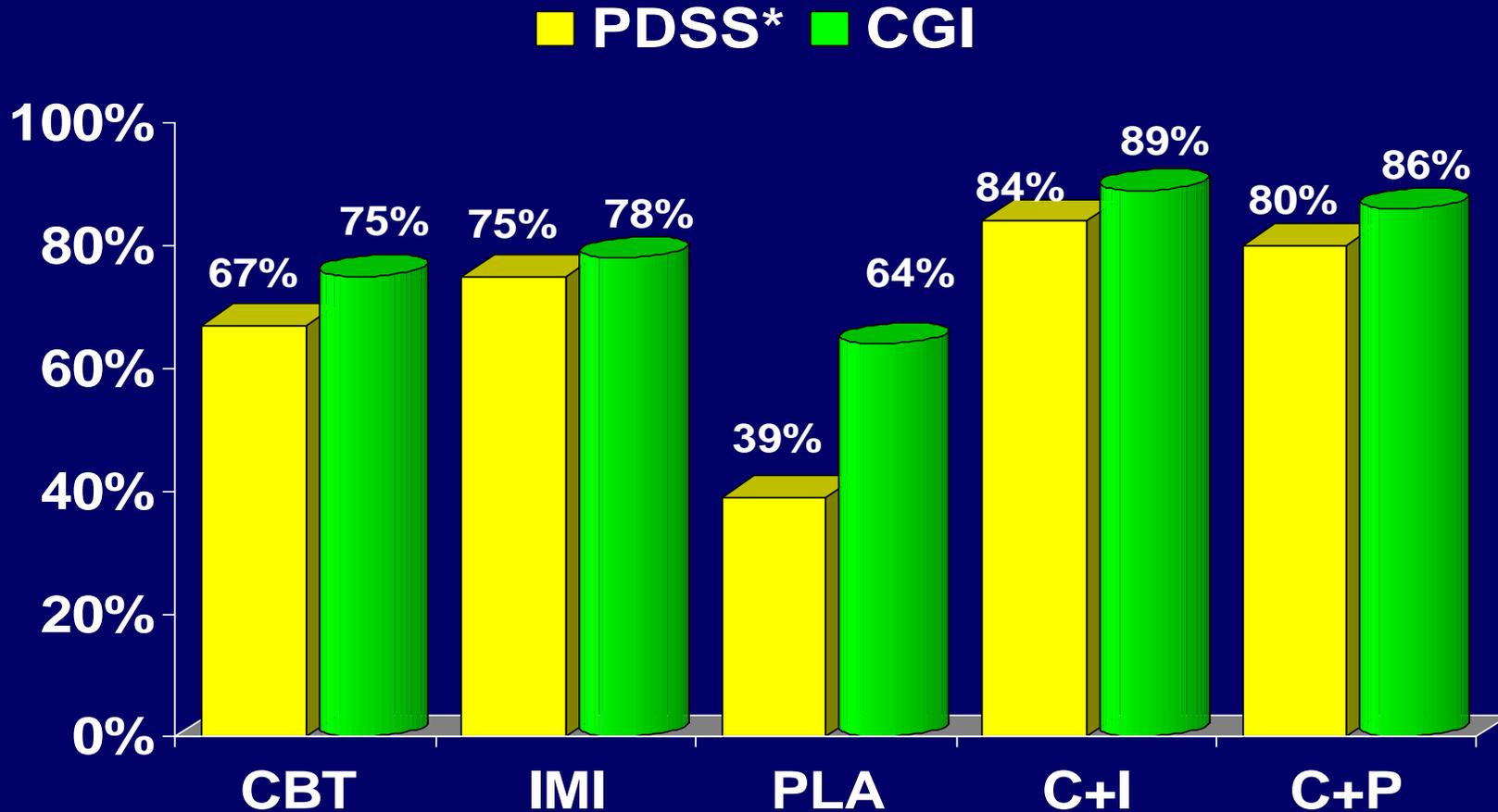
# Panic Disorder Severity Scale

- ◆ Panic Frequency
  - ◆ Distress during Panic Attacks
  - ◆ Anticipatory Anxiety
  - ◆ Agoraphobia
  - ◆ Bodily sensation Phobia
  - ◆ Work Impairment
  - ◆ Social Impairment
- Items rated 0-4
- 0 = none
- 1 = mild
- 2 = moderate
- 3 = severe
- 4 = very severe

# Acute Treatment Completion Rate

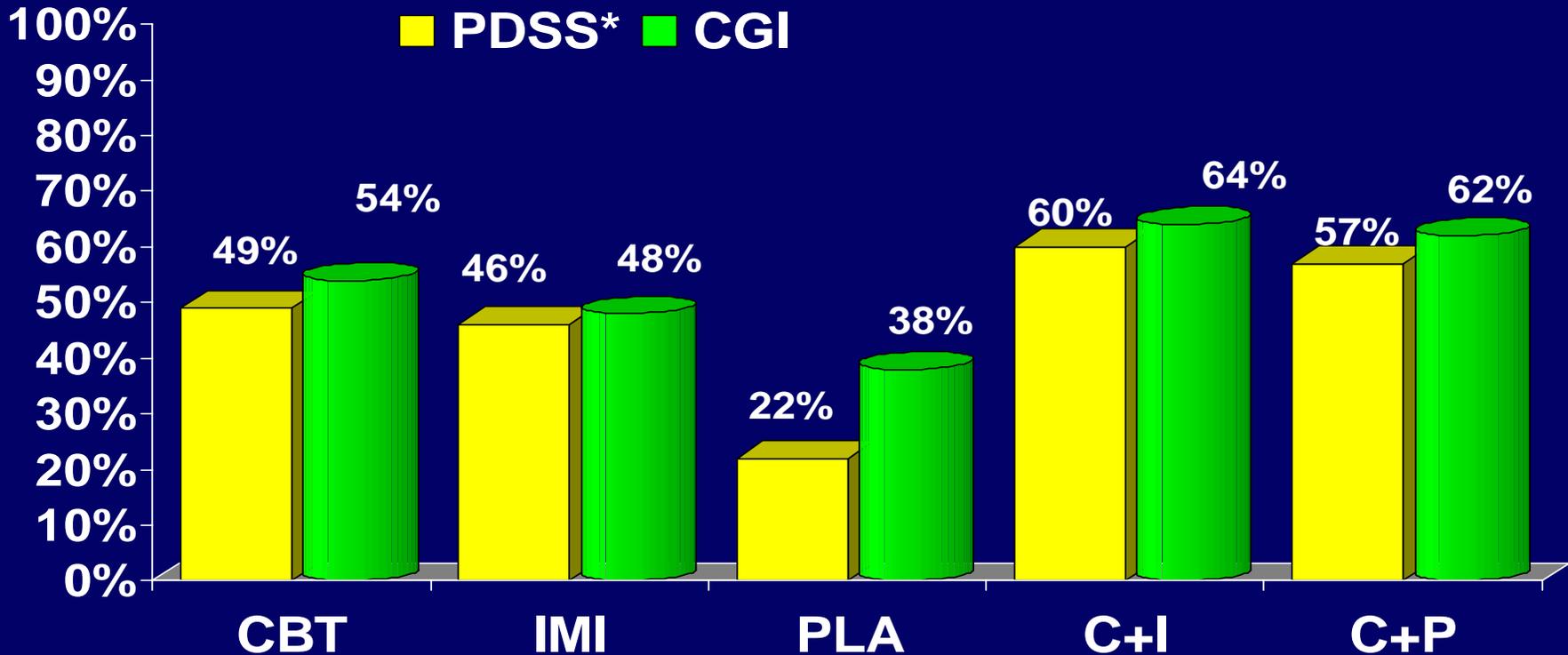


# Response Rate Among Acute Treatment Completers



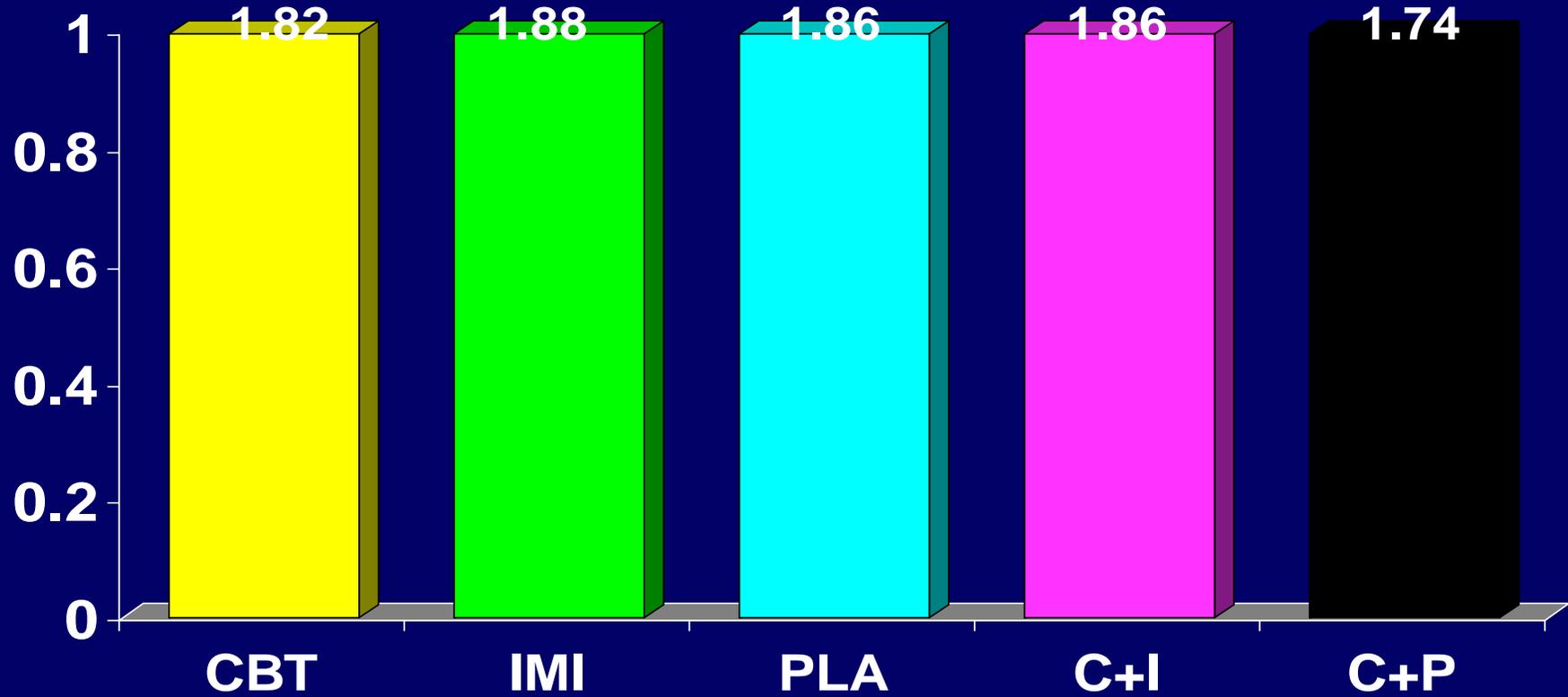
\*  $p = 0.01$ , I v P and CI v C

# Acute Treatment Intent-to-treat Response Rates

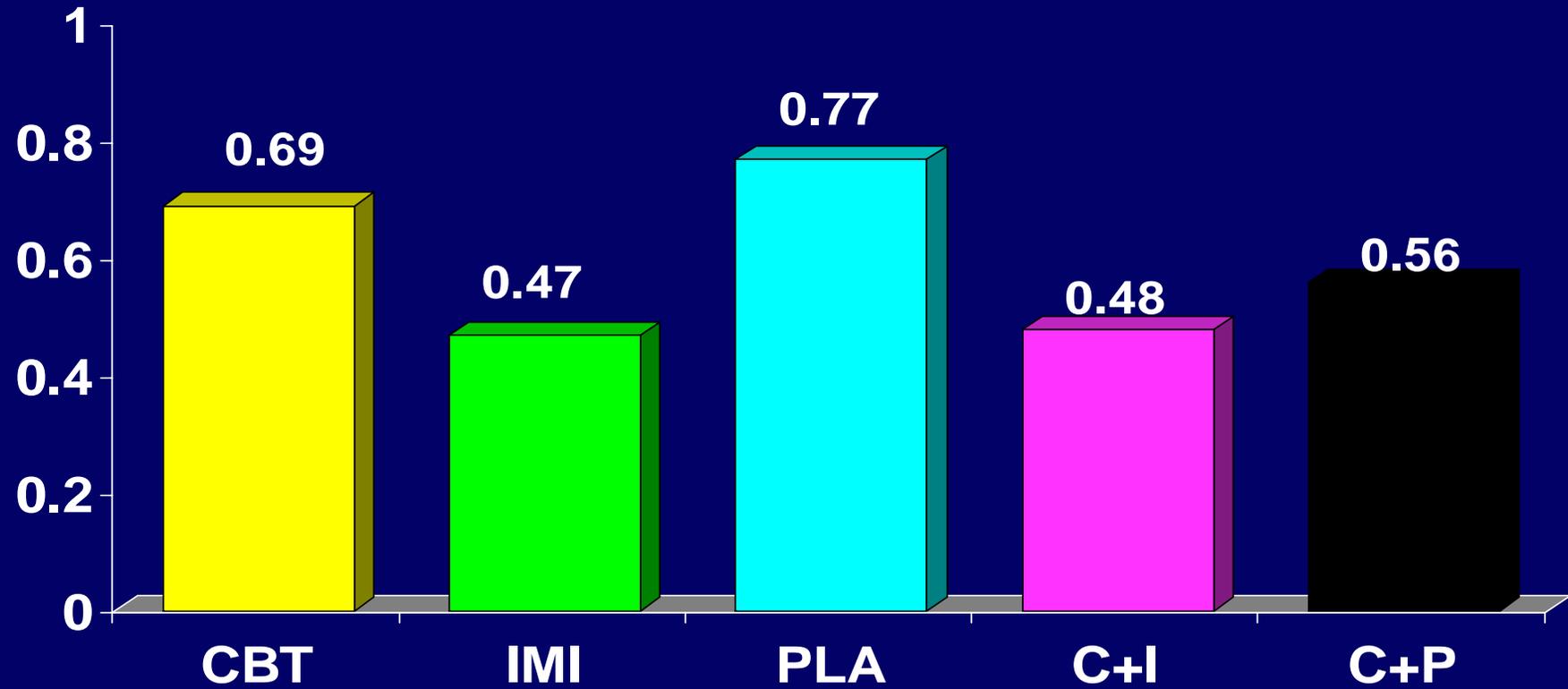


$P = 0.02, I \text{ v } P, C \text{ v } P$

# Mean Baseline PDSS Scores

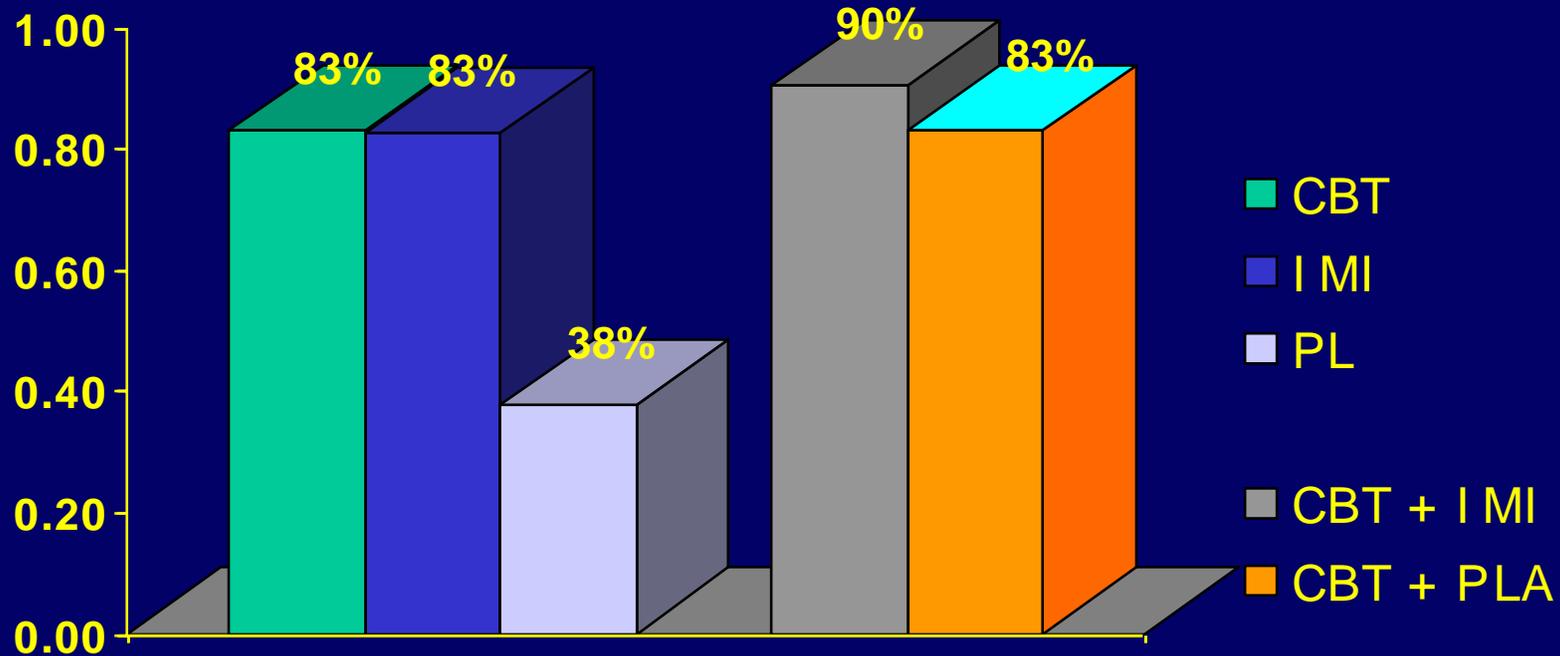


# PDSS Scores in Post-Acute Responders



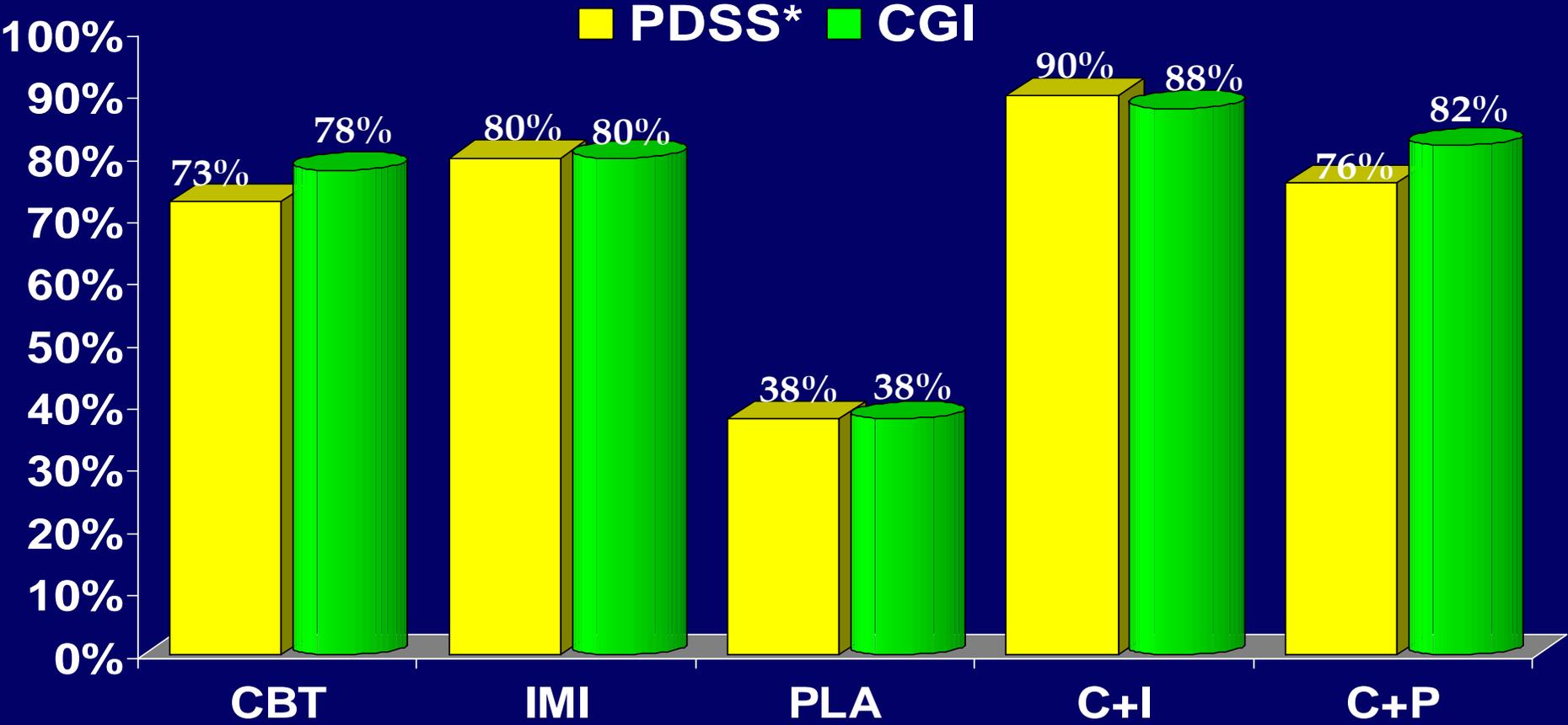
$P = 0.03, I \text{ v } C; CI \text{ v } C$

# Maintenance Completion Among Acute Completing Responders



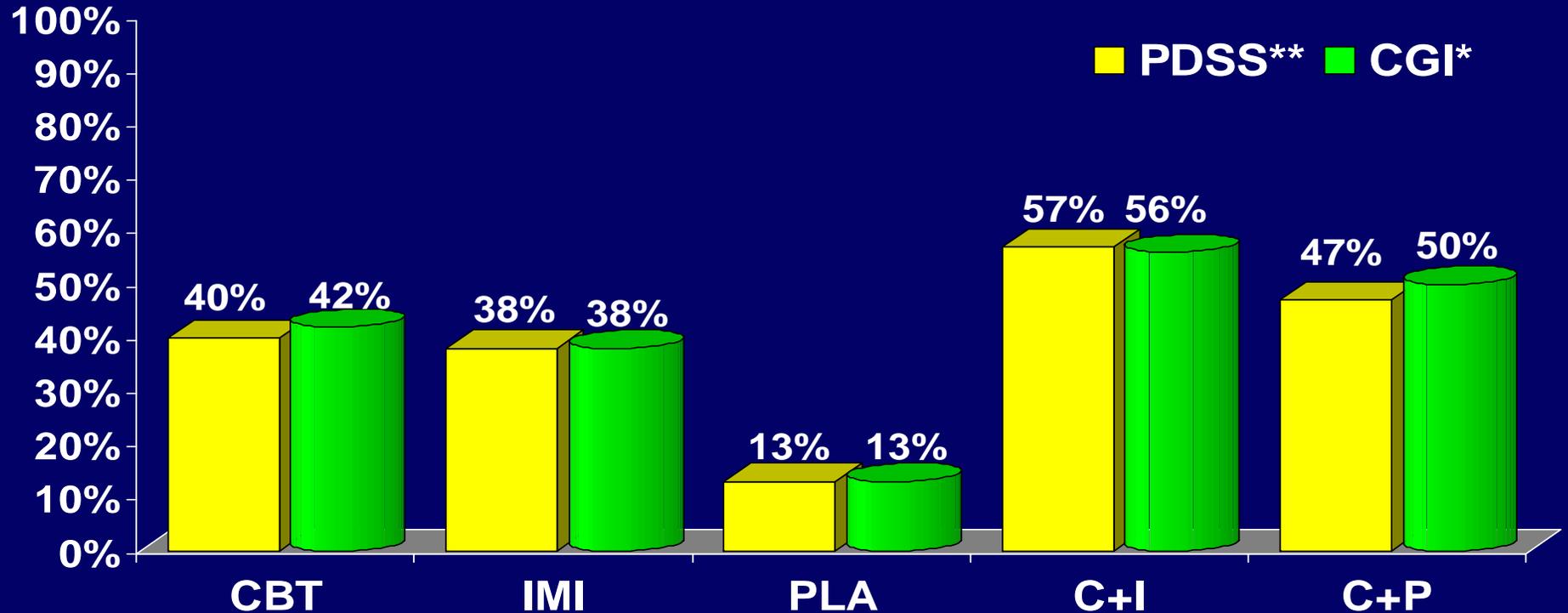
$P = 0.01$  C, I > P, C v I, n.s., CI v CP, C, I, n.s.

# Intend-to-Maintain Post-Maintenance Response Rate



\* P = .03, I v P

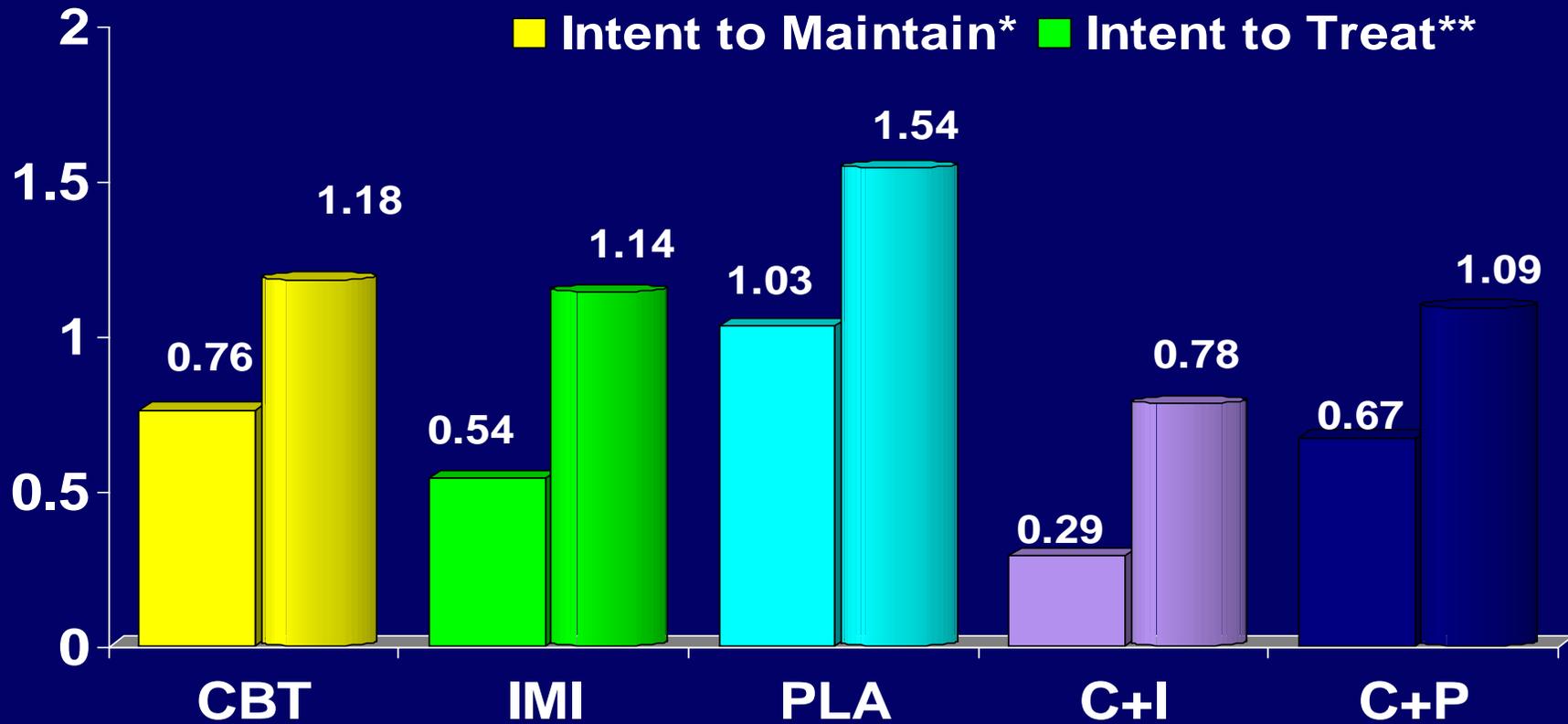
# Intent-to-Treat Post-Maintenance Response Rate



\*\*  $p = .003$ , I v P, C v P, CI v I, CI v C

\*  $p = .003$ , I v P, C v P, CI v I

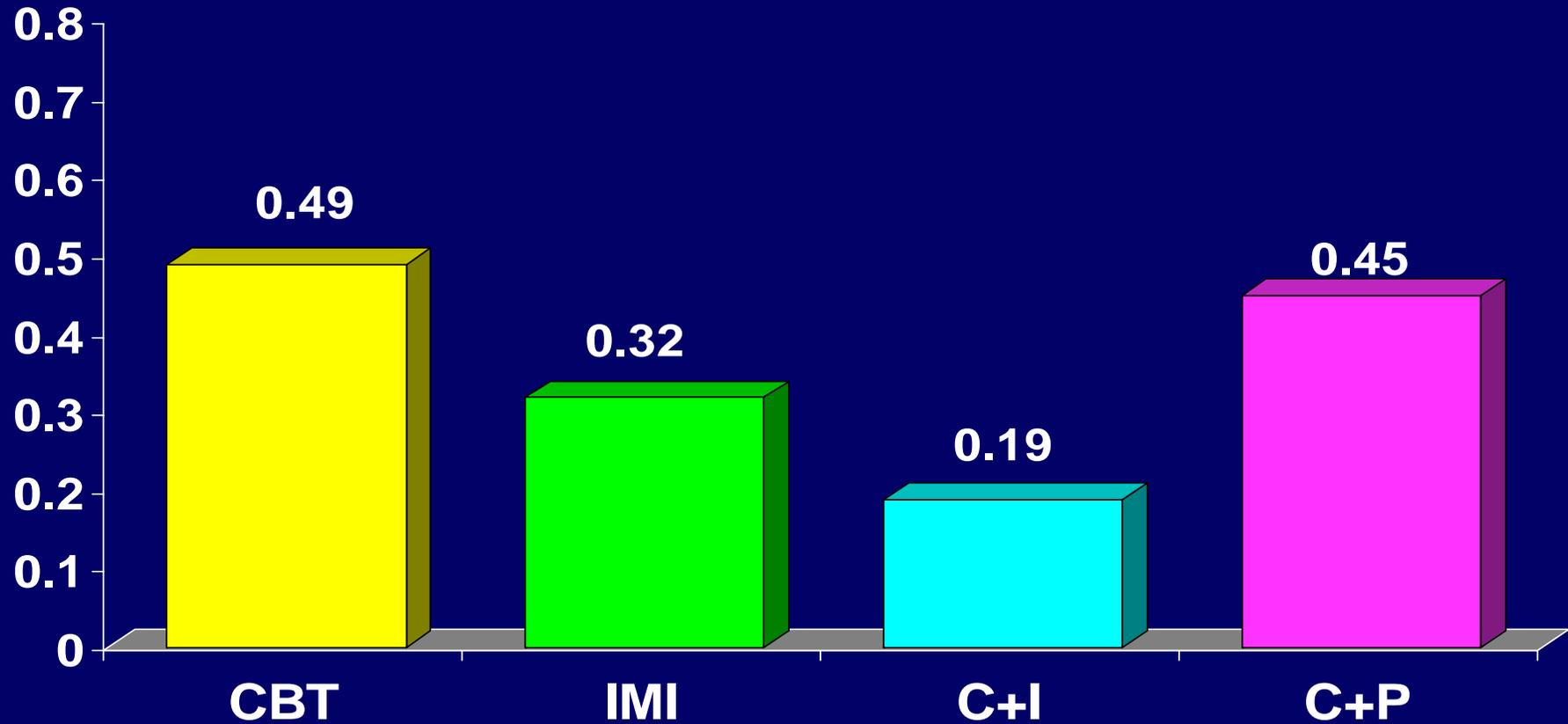
# Post Maintenance PDSS Scores



\*p = 0.005, CI v CP; CI v C

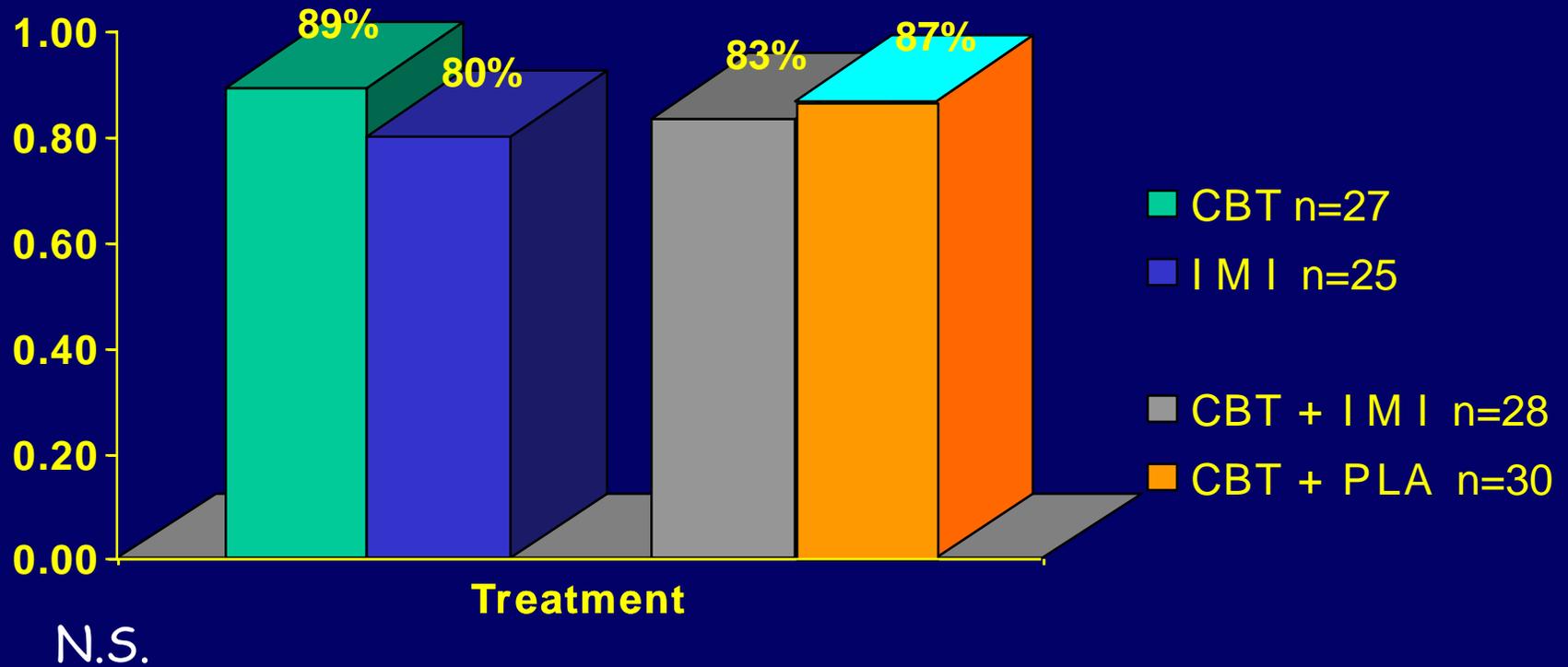
\*\* p = 0.001, CI v CP; CI v C, CI v I

# PDSS Scores in Post-Maintenance Responders

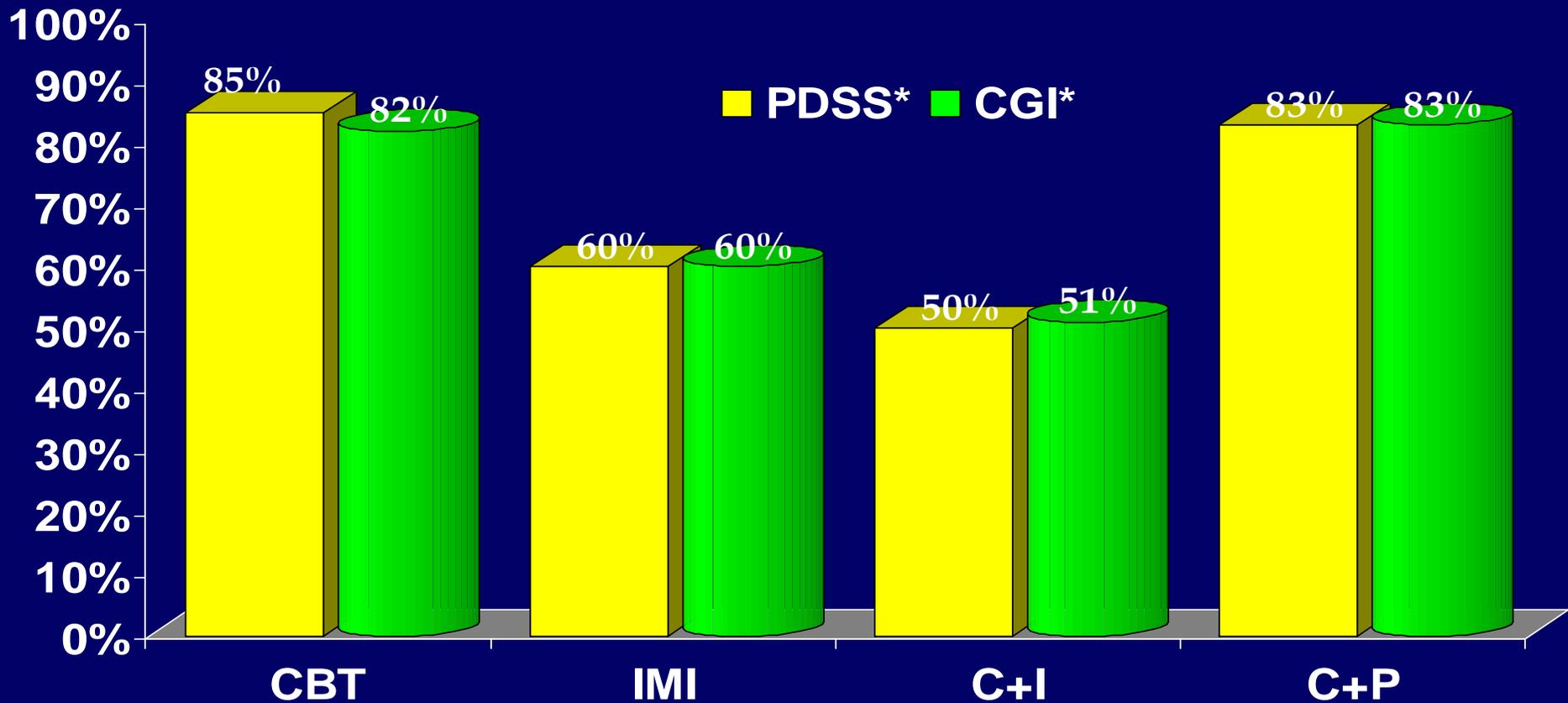


$P = 0.02, CI \ v \ CP, CI \ v \ C$

# Follow-up Completion Among Maintenance Completing Responders

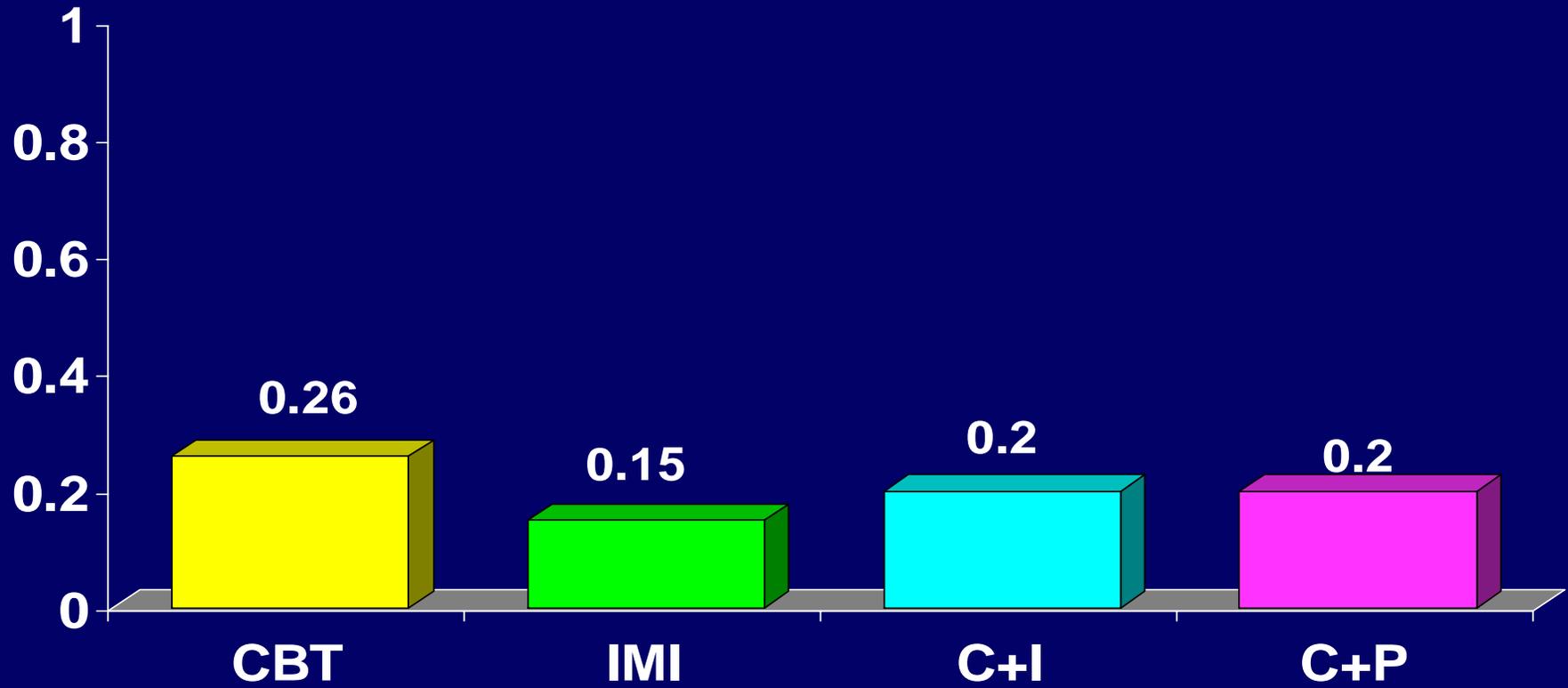


# Intend-to-Follow Response Rate at Follow-up

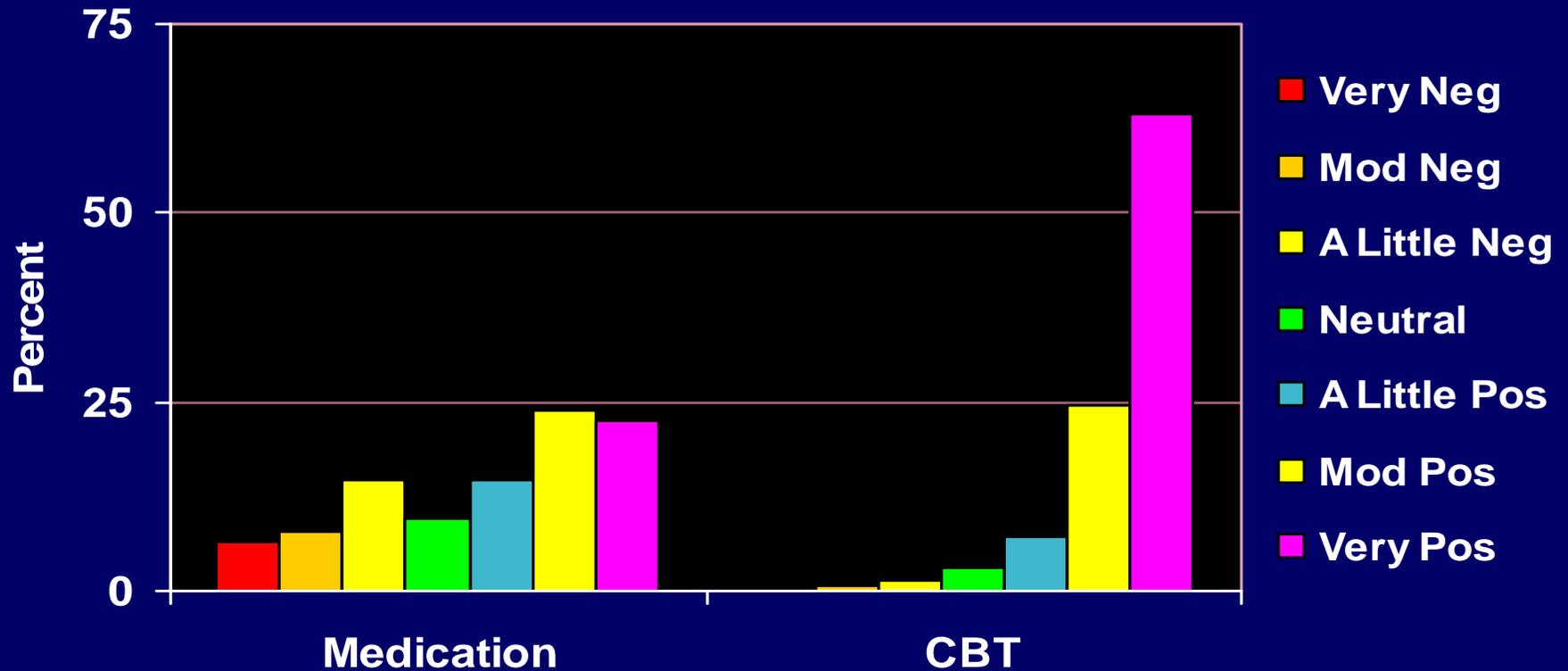


\*  $p = .03$ , CI v CP, CI v C (REVERSE DIRECTION)

# Follow-up Responders PDSS Scores

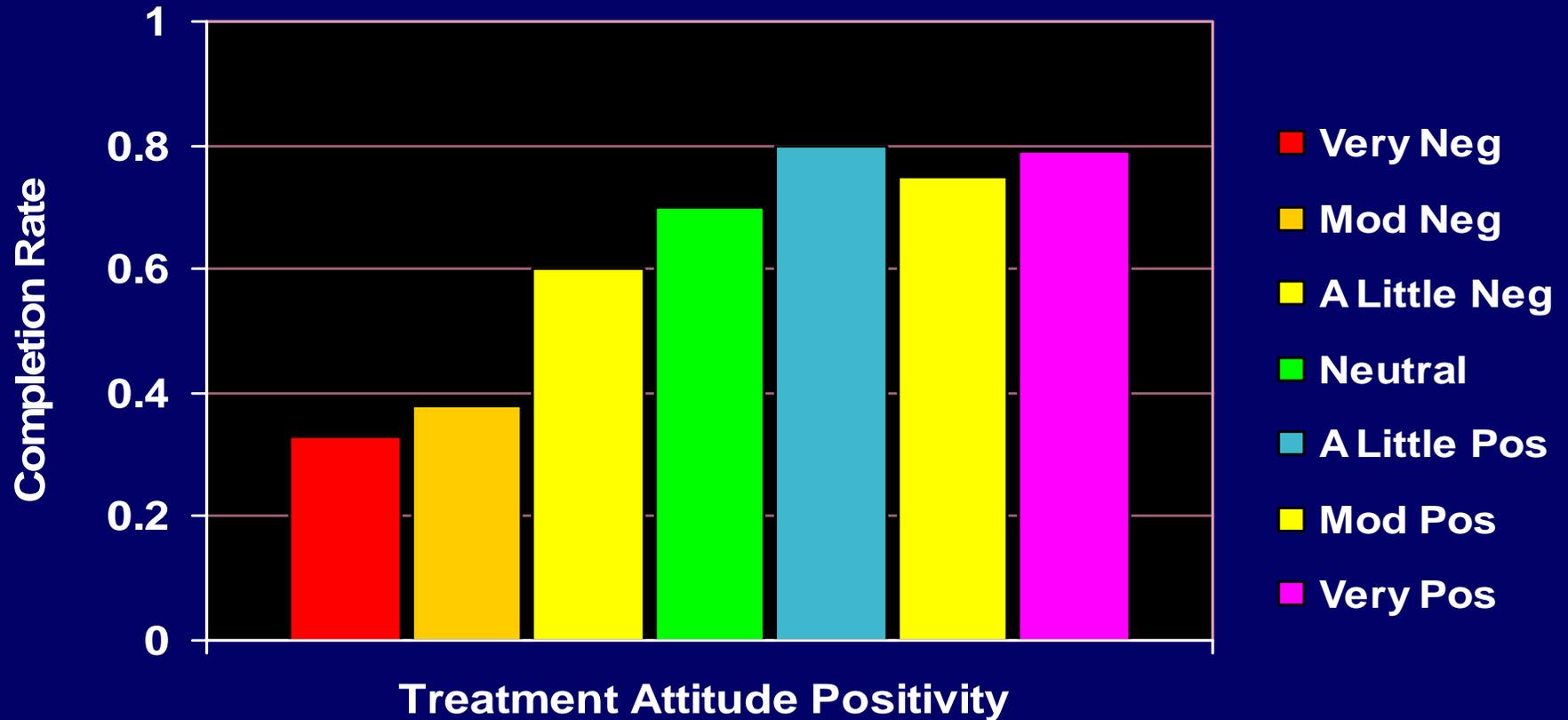


# Attitudes Toward Treatment



# Completion Rates by Attitude

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# Answers to Study Questions

- ◆ Do both cognitive-behavioral treatment and imipramine perform better than placebo medication?

**YES**

- ◆ Does either active treatment alone perform better than the other?

**IMI MORE ROBUST; CBT MORE DURABLE AND MORE POPULAR**

- ◆ Does combination treatment perform better than monotherapy?

**BETTER RESPONSE; HIGHER RELAPSE**