CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE: ANTIVIRAL DRUGS ADVISORY COMMITTEE

DATE OF MEETING: 1/14/98

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AGENDA

Subcommittee of the Antiviral Drugs Advisory Committee
Center for Drug Evaluation and Research
Agenda for Wednesday, January 14, 1998
OPEN SESSION

Topic: CellCept® (mycophenolate mofetil), Syntex, USA, Incorporated, for immunosuppression following cardiac transplantation.

8:00 a.m.	Call to Order	Henry Masur, M.D., Subcommittee Chair
	Conflict of Interest Statement	Rhonda W. Stover, R.Ph. Executive Secretary
8:05	FDA Introduction	Mark Goldberger, M.D., M.P.H., Director Division of Special Pathogen and Immunologic Drug Products (DSPIDP), Office of Drug Evaluation IV, FDA
8:15	Sponsor Presentation	Mary Jean Stempien, M.S., M.D. Director of Medical Research Roche Global Development
		Richard D. Mamelok, M.D. Clinical Scientist Roche Global Development
		Leslie W. Miller, M.D., FACC Professor of Medicine Director of Cardiovascular Division University of Minnesota
9:30	FDA Presentation	Joyce Korvick, M.D. Medical Officer, DSPIDP
		Michael Elashoff, Ph.D. Biometrics Reviewer, DSPIDP
10:00	Break	
10:15	Open Committee Discussion	
11:00	Open Public Hearing	
12:00 p.m.	Lunch	
1:00	Open Committee Discussion and Recommendations	
5:00	Adjourn	

Subcommittee of the Antiviral Drugs Advisory Committee
Participants for January 14, 1998, CellCept Meeting

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CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE: ANTIVIRAL DRUGS ADVISORY COMMITTEE

DATE OF MEETING: 1/14/98

QUESTIONS

SUBCOMMITTEE OF THE ANTIVIRAL DRUGS ADVISORY COMMITTEE
CENTER FOR DRUG EVALUATION AND RESEARCH
QUESTIONS FOR THE COMMITTEE
WEDNESDAY, JANUARY 14, 1998

1. **Is CellCept safe and effective for the prevention of organ rejection in cardiac allograft recipients?**

2. **Please comment on the design of future cardiac transplant studies, including the choice of control and 6-month endpoints.**

CENTER FOR DRUG EVALUATION AND RESEARCH

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DATE OF MEETING: 1/14/98

SLIDES

FDA Review

NDA 50-722

CellCept (Mycophenolate mofetil)

Joyce A. Korvick, M.D.

Division of Special Pathogens and
Immunologic Drug Products

FDA Review Team: CellCept

Joyce Korvick, M.D.:	Medical
Michael Elashoff, Ph.D.:	Statistical
Lisa Hubbard, R.Ph.:	Project Manager
Mark Seggel, Ph.D.:	Chemistry
Kofi Kumi, Ph.D.:	Biopharmaceutics
Kenneth Hastings, Dr.PH:	Pharm-Toxicology

CellCept

- Introduction
- Study Design
- Cardiac Transplantation Efficacy
- Safety
- Questions

CellCept: Organ Rejection Prophylaxis

- Renal transplant (approved May 3, 1995)
- Cardiac transplant (proposed)

(in combination with cyclosporine and steroids)

Renal Transplant Studies

- Demonstration of efficacy in 3 well controlled studies
- Approval of 2 gm/day dose only
- 3 year follow-up

Cardiac Transplantation Study

MYCS 1864

Study Design MYCS 1864

- 650 patients
- Randomized
- Double-blind
- Azathioprine control arm
- Extensive follow-up
- Angiography and IV ultrasound studies
- Routine endomyocardial biopsies

Study Design: Endpoints

- 6-month death or biopsy-proven rejection with hemodynamic compromise
  - * Superiority
- 12-month patient and graft survival
  - * Equivalence

Study Design and Regulatory Implications

- Azathioprine:
  not approved for cardiac transplant

- Endpoints:
  rejection vs graft/patient survival

FDA Comments:

Efficacy Analysis

Dr. Michael Elashoff
Division of Biometrics IV

Outline

- ITT/Treated
- Rejection
- Survival
- Conclusions

ITT/Treated

- Protocol: primary analysis based on all patients
- Applicant presented both analyses, emphasized treated results

ITT/Treated

- Treated subgroup maintains randomization
- Treated analysis is a relevant analysis
- However, multiple analyses give multiple chances to win
- P-values in treated group should be adjusted
  - rejection
  - survival

Rejection

Co-primary endpoint:	Biopsy-Proven Rejection with HDC at 6 months
Goal:	Superiority

Rejection Endpoint

- Biopsy proven rejection (BPR) or death in first six months
- Rejection must be accompanied by hemodynamic compromise
  - HDC defined as having one or more of eight criteria at the time of rejection

Results: Rejection+HDC

	ITT	Treated
MMF	36.7%	31.8%
AZA	37.5%	34.6%
p-value	.822	.391

Results: Rejection +SHDC (protocol)

	ITT	Treated
MMF	15.6%	8.7%
AZA	14.6%	11.4%
p-value	.834	.306

diff ~ 8%

6 Month Rejection Endpoints

		All Subjects	Treated Subjects
Primary	BPR+HDC	.821	.391
SHDC	BPR+new SHDC	.554	.059
	BPR+prot SHDC	.835	.306
	BPR+inotropic	.826	.117
Secondary	BP/P+okt3/atg	.488	.077
	BPR Grade>=2	.564	.364
	BPR+immunosup	.182	.072
	BPR	.513	.305
Other	BPR Grade >=3	.137	.067
	BP/P+immunosup	.144	.033

- p-values slightly higher than applicant due to continuity correction

Rejection Endpoints

- No planned rejection endpoint was significant
- No unplanned rejection endpoint was significant after multiple comparison adjustment
- MMF had small numerical advantage for most definitions of rejection.
- These endpoints are overlapping.

Summary: Rejection

- On the basis of this trial, applicant did not appear to demonstrate superiority with respect to rejection.

Survival

Co-primary endpoint:	Survival at 12 months
Goal:	Equivalence
Equivalence based on:	Lower bound of 95% confidence interval for difference

Equivalence Example

Difference in survival =

% survival E - % survival S

90% - 87%

3.0%

Equivalence Example

Diff = 3.0%

95% CI = -2.0% to 8.0%

LCB = -2.0%

Equivalent if LCB > -10%

Not equivalent if LCB < -10%

Survival Results

	ITT	Treated
MMF Survival	87.2%	93.8%
AZA Survival	84.8%	88.6%
Difference	2.6%	5.3%
95% CI	-2.5% to 7.6%	.9% to 9.7%
p-value	.402	.037

- p-values slightly higher than applicant due to continuity correction

Treated Results

Applicant focused on LCB for treated analysis (.9%) and associated p-value (.037). However:

- Study was designed to demonstrate equivalence
- Claim of superiority not robust
- Need to adjust for multiple analyses

Summary: Survival

- ITT analysis showed equivalence
- Treated analysis showed equivalence

AZA Efficacy

- Efficacy for survival based on historical data
  - Opeltz 4% survival advantage at 1 yr
  - Shumway 4% survival advantage at 1 yr
- Confounded by time
- Data suggest little additional survival effect past 1 year
- No data presented on 6 month rejection

Conclusion

- Study showed equivalence for survival
- Study did not show superiority for rejection, but MMF appeared to have similar effect to AZA for rejection

CellCept Safety

CellCept Safety

Safety Parameter	CARDIAC		RENAL		
	MMF 3g (N=289)	AZA (N=289)	MMF 2g (N=330)	MMF 3g (N=336)	AZA (N=326)
Deaths	8.0%	14.5%	5.1%	6.4%	5.2%
Malignancies	6.9%	6.9%	6.8%	6.4%	4.9%
OI's	53.3%	43.6%	46.7%	47.6%	46.0%
Serious AE	10.4%	6.9%	3.3%	7.6%	7.4%
Premature Withdrawal due to AEs	14.5%	15.6%	11.9%	15.8%	13.2%

Summary: Cardiac Study

- CellCept similar to azathioprine for prevention of biopsy-proven rejection or death at 6 months
- CellCept is at least as good as azathioprine for the prevention death or retransplantation at one year.
- Safety profile similar to renal studies

Questions

yes

not substantial evidence of this

- Is CellCept safe and effective for the prevention of organ rejection in cardiac allograft recipients?
- Please comment on the design of future cardiac transplant studies, including the choice of control and 6-month endpoints.

MYCOPHENOLATE MOFETIL
IN
CARDIAC TRANSPLANTATION

PRESENTERS

Program Introduction

Mary Jean Stempien, MS, MD
Director, Medical Research
Roche Global Development

Primary Study and Results

Richard D. Mamelok, MD
Clinical Scientist
Roche Global Development

Clinical Perspective

Leslie W. Miller, MD, FACC
Professor of Medicine
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Dale Renlund, MD
Medical Director
Cardiac Transplant Program
Univ of Utah Health
Science Center

GOAL

Roche seeks recommendation regarding approval for use of mycophenolate mofetil (MMF), an immunosuppressant, in cardiac transplantation

CURRENTLY APPROVED INDICATION

CellCept® (mycophenolate mofetil, MMF) is indicated for:

- The prophylaxis of organ rejection in patients receiving allogeneic renal transplants
- Concomitant use with cyclosporine and corticosteroids

MMF RENAL PROGRAM

All three primary efficacy studies demonstrated that MMF reduced the incidence of biopsy-proven rejection, or treatment failure during the first 6 months post-transplant, compared to control

PROPOSED EXTENSION TO INDICATION

CellCept® (mycophenolate mofetil) is indicated for:

- The prophylaxis of organ rejection in patients receiving allogeneic renal or cardiac transplants
- Concomitant use with cyclosporine and corticosteroids

STUDY 1864

- First double-blind, randomized controlled trial of an immunosuppressant in cardiac transplantation
- No precedent in a rapidly evolving field of medicine
- Challenges in study design led to challenges in interpretation

STEERING COMMITTEE MEMBERS

- Jon Kobashigawa, MD - (Chairperson) - UCLA
- Robert Bourge, MD - Univ. of Alabama at Birmingham
- Maria Rosa Costanzo, MD - Rush Presbyterian St. Luke's
- Georges Dureau, MD - Lyon Cedex, France
- Howard Eisen, MD - Temple Univ.
- Anne Keogh, MD - St. Vincent's Hospital, Australia
- Robert Mentzer, MD - Univ. of Kentucky
- Leslie Miller, MD - Univ. of Minnesota
- Dale Renlund, MD - Univ. of Utah
- Frank Smart, MD - Tulane Univ.
- Hannah Valantine, MD - Stanford Univ.

CARDIAC PRESENTATION

- Renal Foundation
- Primary Study 1864
  - Challenges in Design
  - Results
    - Efficacy (Enrolled)
    - Efficacy (Treated)
    - Safety
- Study Conclusions
- Clinical Perspective

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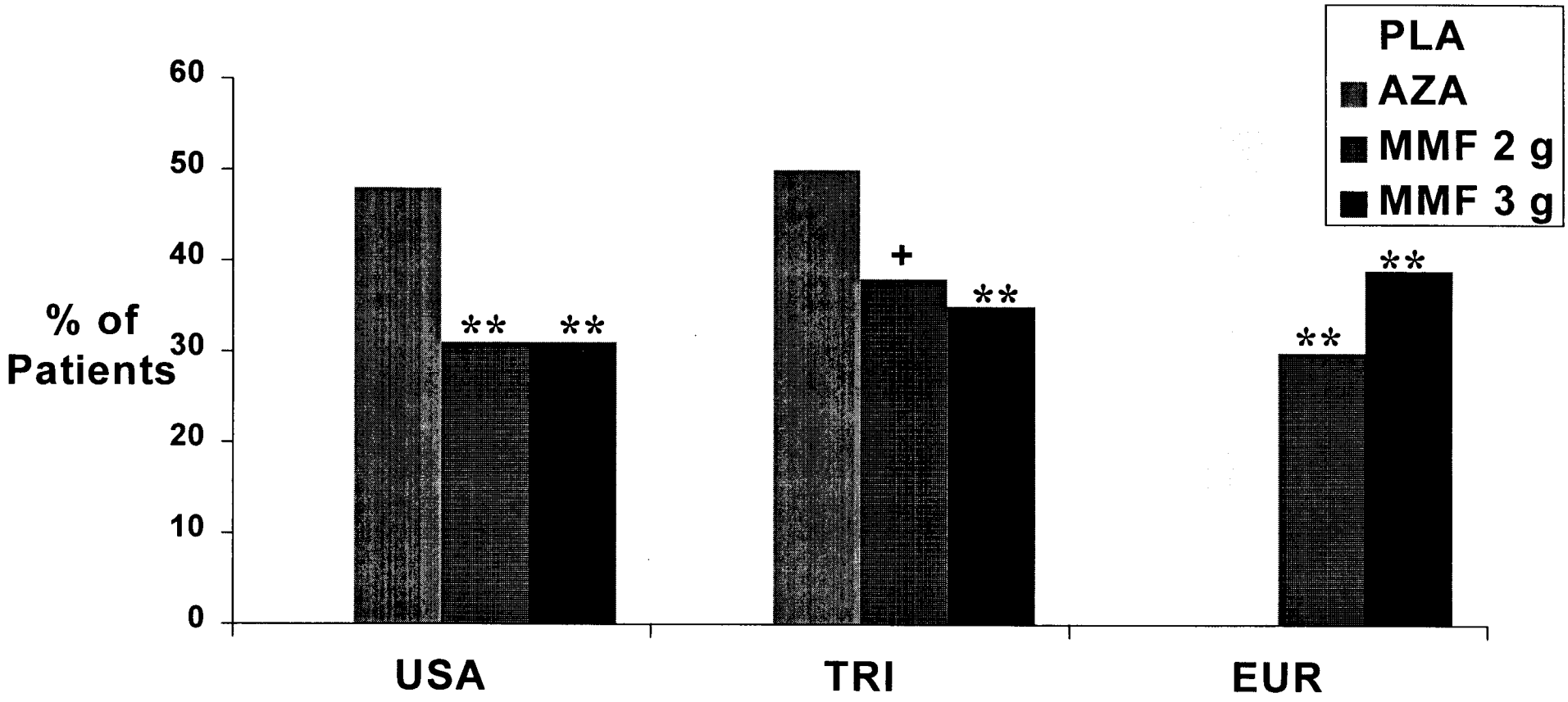
MMF RENAL PROGRAM

3 Randomized Double-Blind Studies (N = 1493):

	USA	TRI	EUR
Control Treatment	AZA 1-2 mg/kg/day	AZA 100-150 mg/day	PLACEBO
MMF Doses	1.0 g BID (MMF 2 g) 1.5 g BID (MMF 3 g)		
Concomitant Immunosuppression	cyclosporine corticosteroids		

BIOPSY- PROVEN REJECTION OR TREATMENT FAILURE - Renal Program



**P < .01, + P=0.0287 *(vs. 0.025 for significance)*

CARDIAC PRESENTATION

- Renal Foundation
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  - Challenges in Design
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    - Efficacy (Enrolled)
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PRIMARY STUDY 1864

STUDY 1864

Objective:

Compare safety and efficacy of MMF with AZA, each in combination with cyclosporine and corticosteroids

CHALLENGES IN DESIGN

- Choice of Control
- Choice of Primary Endpoint

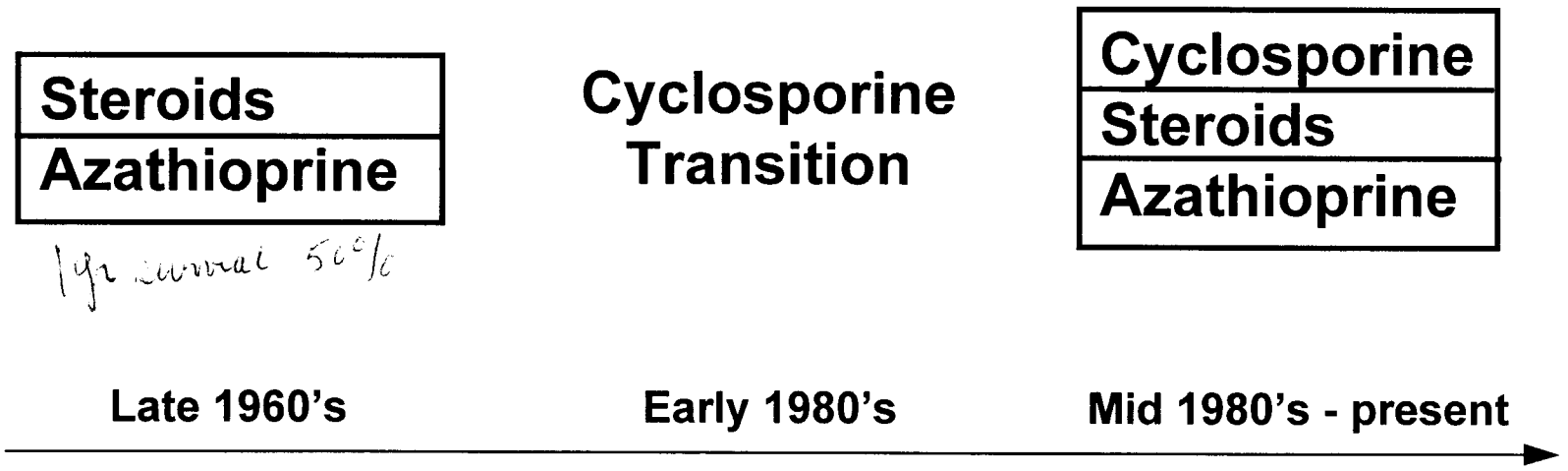
CHALLENGES IN DESIGN: CHOICE OF CONTROL

- 83% of cardiac transplant patients receive triple therapy consisting of AZA, CsA, and corticosteroids [Opelz, 1997]

- Triple therapy is the standard of care in cardiac transplantation

IMMUNOSUPPRESSION IN CARDIAC TRANSPLANTATION

INCREMENTAL DEVELOPMENT HISTORY



ACTIVITY OF AZA IN CARDIAC TRANSPLANTATION

- Based on historically controlled studies and large data bases

- Literature search: 1980-1997

Double Therapy		Triple Therapy
Cyclosporine Steroids	*vs*	Azathioprine Cyclosporine Steroids

EFFICACY OF AZA IN CARDIAC TX
RESULT OF LITERATURE SEARCH (1980-1997)

Primary Author, Year	Triple n	Double n	Δ Survival: Triple - Double 1 Year
Opelz, 1997	13509	1180	4%
Copeland,1990	163	32	22%
Large, 1989	199	90	13%
Shumway, 1988	3220	5637	4%
Bolman, 1985	17	14	11%

yr 29% Surv

?

CHALLENGES IN DESIGN: CHOICE OF PRIMARY ENDPOINT

- Detection and quantification of rejection in cardiac transplantation:
  - Imperfect
  - Evolving

CO-PRIMARY ENDPOINTS

Death or Retransplantation

- **Hypothesis - MMF equivalent to AZA at 1 year post-transplant**

Biopsy-Proven Rejection with hemodynamic compromise

- **Hypothesis - MMF superior to AZA at 6 months post-transplant**

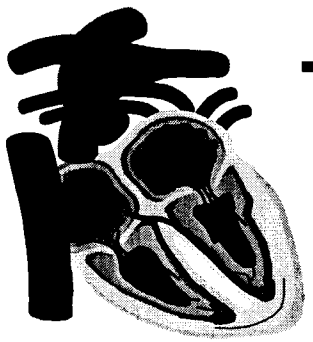
PROTOCOL-SPECIFIED SECONDARY REJECTION ENDPOINTS

- Biopsy-proven
  - ≥ Grade 1A
  - ≥ Grade 2
  - ≥ Grade 3 (planned prior to unblinding)
  - Pulse treated
- Biopsy-proven or suspected
  - Pulse treated
  - Pulse treated with OKT3/ATG

1864 STUDY DESIGN

Design	Double-blind, randomized, multi-center
AZA Control	1.5 - 3 mg/kg/day
MMF	1.5 g BID
Concomitant Immunosuppression	cyclosporine corticosteroids

1864 STUDY PLAN



Rejection Endpoint

Mortality Endpoint

Safety CVD

AZA

MMF

Randomize & Transplant

6 Mos

1 Yr

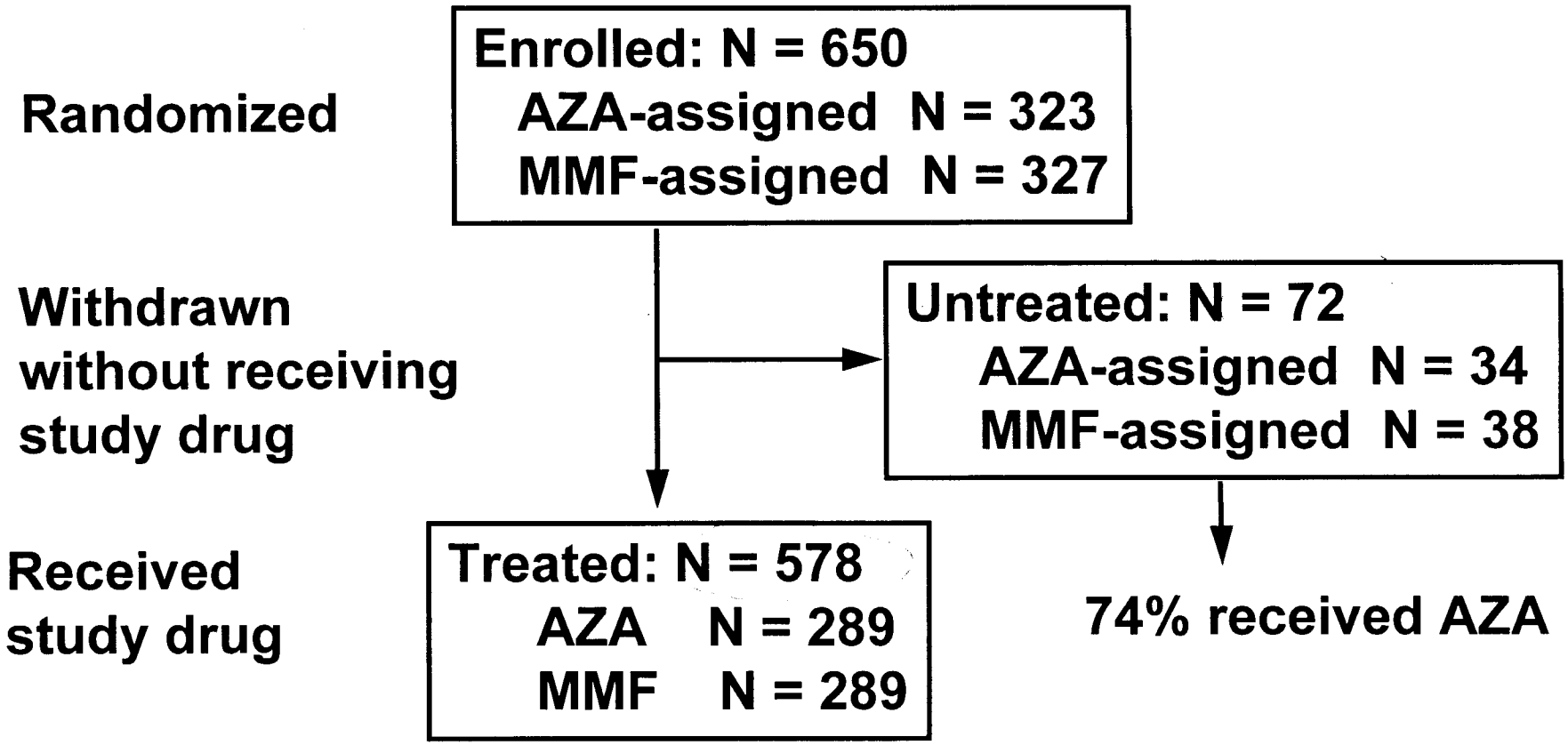
3 Yrs

Total 5 days

DATA COLLECTED FOR CO-PRIMARY ENDPOINTS

- Data collected on all randomized patients both on-study and post-termination
  - Rejection data through 6 months
  - Death/retransplantation data through 1 year

1864 STUDY POPULATION



CARDIAC PRESENTATION

- Renal Foundation
- Primary Study 1864
  - Challenges in Design
  - Results
    - Efficacy (Enrolled)
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- Study Conclusions
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EFFICACY (ENROLLED)

- **Death or Retransplantation**
- **Rejection**

CO-PRIMARY DEATH / RETRANSPLANTATION ENDPOINT - STATISTICAL METHODS

Death or Retransplantation

- Includes on study and post termination data for all patients
- Cochran-Mantel-Haenszel type weighted differences adjusted by investigator

DEATH / RETRANSPLANTATION IN ENROLLED POPULATION

- In the enrolled population
  - The death/retransplantation rate at 1 year was 2.6% lower in the MMF-assigned patients, which was in the range for statistical equivalence

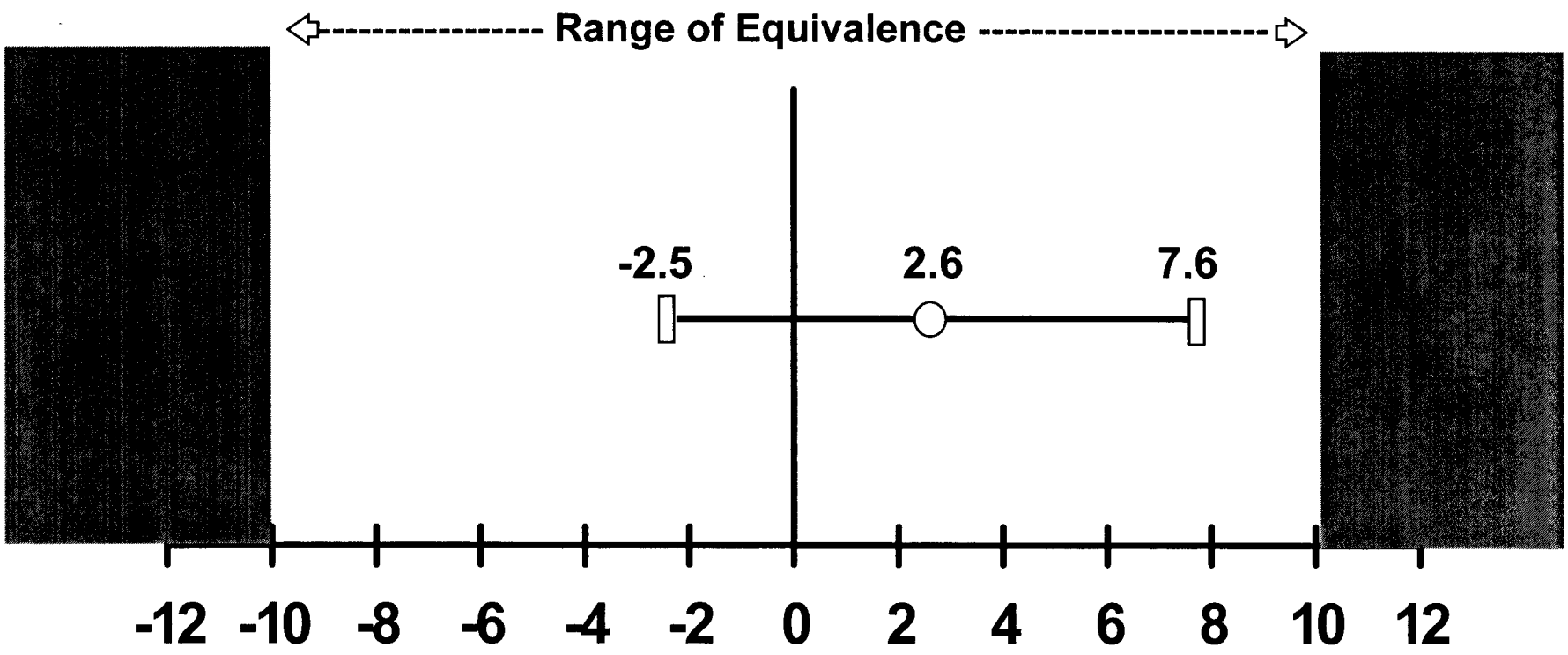
DEATH OR RETRANSPLANTATION

[Enrolled]

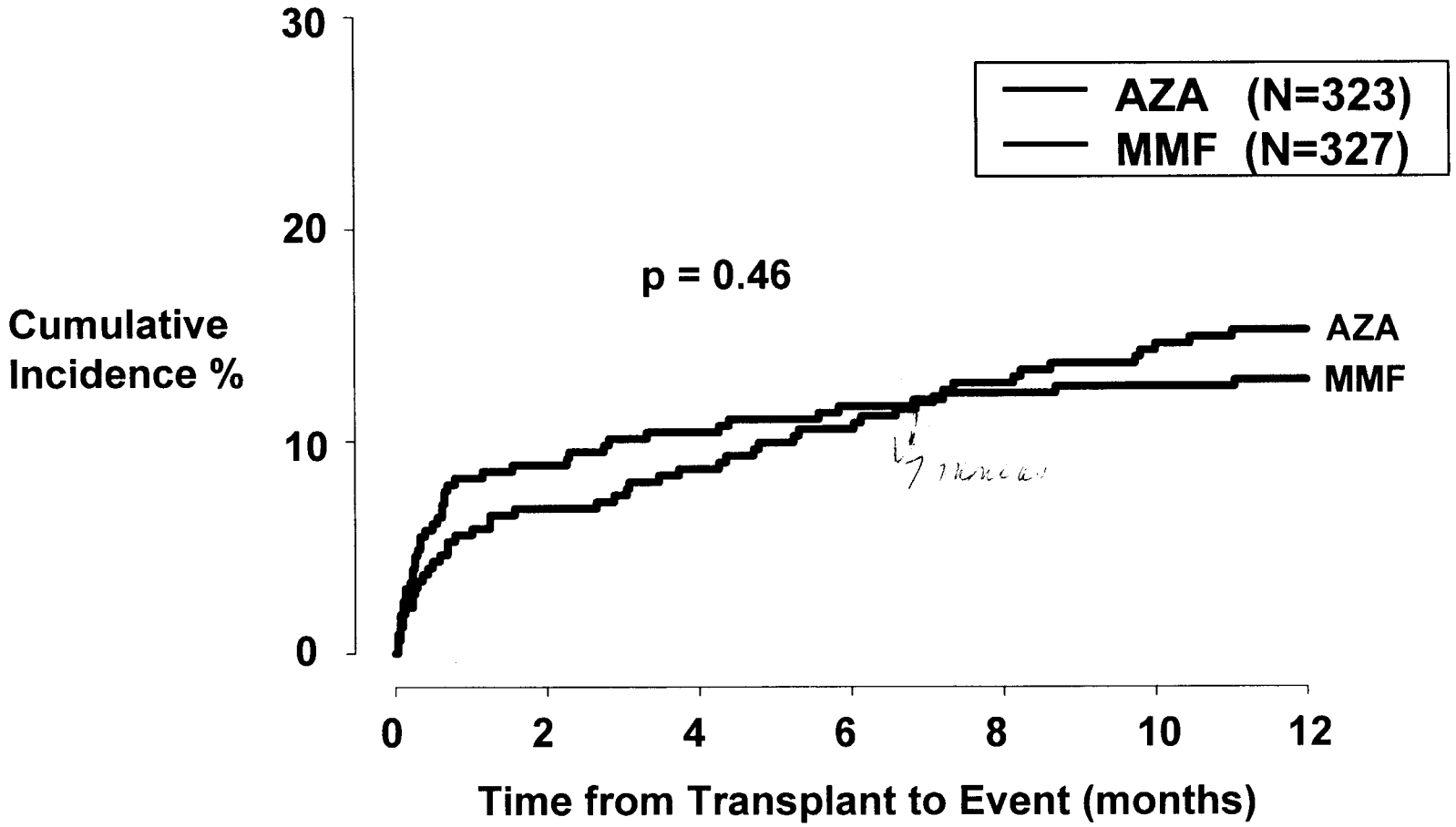
	AZA	MMF
N	323	327
Death or Re-tx	49 (15.2%)	42 (12.8%)
Weighted Treatment Difference	2.6%	
Lower Limit of 97.5% one-sided CI	-2.5%	

1 YEAR DEATH / RETRANSPLANTATION

[Enrolled]



DEATH / RETRANSPLANTATION DURING 1 YEAR [ENROLLED]



Kaplan-Meier Estimates
Log-Rank Test Stratified by Investigator

REJECTION RESULTS IN ENROLLED POPULATION

CO-PRIMARY REJECTION ENDPOINT - STATISTICAL METHODS

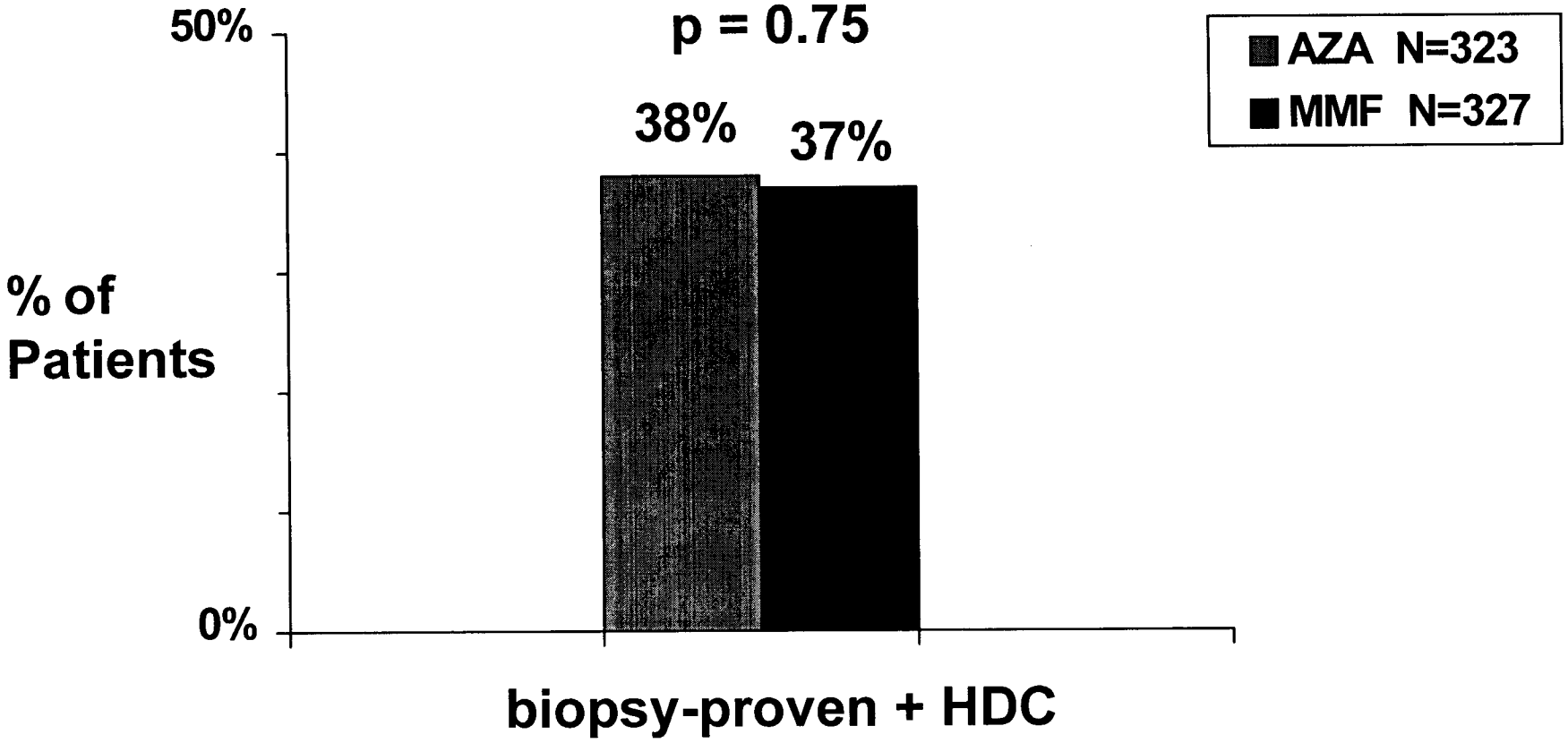
- Includes on study and post- termination data for 6 months for all patients

- Cochran-Mantel-Haenszel test, stratified by investigator

DEFINITION OF HEMODYNAMIC COMPROMISE (PROSPECTIVE)

- Wedge pressure $\geq$ 20 mm or increased by 25%
- Cardiac index < 2.0 l/min/m^2 or decreased by 25%
- Ejection fraction $\leq$ 30%
- Fractional shortening $\leq$ 20% or decreased by 25%
- Pulmonary artery oxygen saturation $\leq$ 60% or decreased by 25%
- New S_3
- Inotropic support

BIOPSY-PROVEN REJECTION WITH HEMODYNAMIC COMPROMISE (HDC) [Enrolled]



PROTOCOL-SPECIFIED SECONDARY REJECTION ENDPOINTS

- Biopsy-proven
  - ≥ Grade 1A
  - ≥ Grade 2
  - ≥ Grade 3 (planned prior to unblinding)
  - Pulse treated (original primary endpoint)
- Biopsy-proven or suspected
  - Pulse treated
  - Pulse treated with OKT3/ATG

SECONDARY REJECTION ENDPOINTS

- In the enrolled population
  - Rates were 2% to 6% lower in MMF-assigned patients but were not significantly different

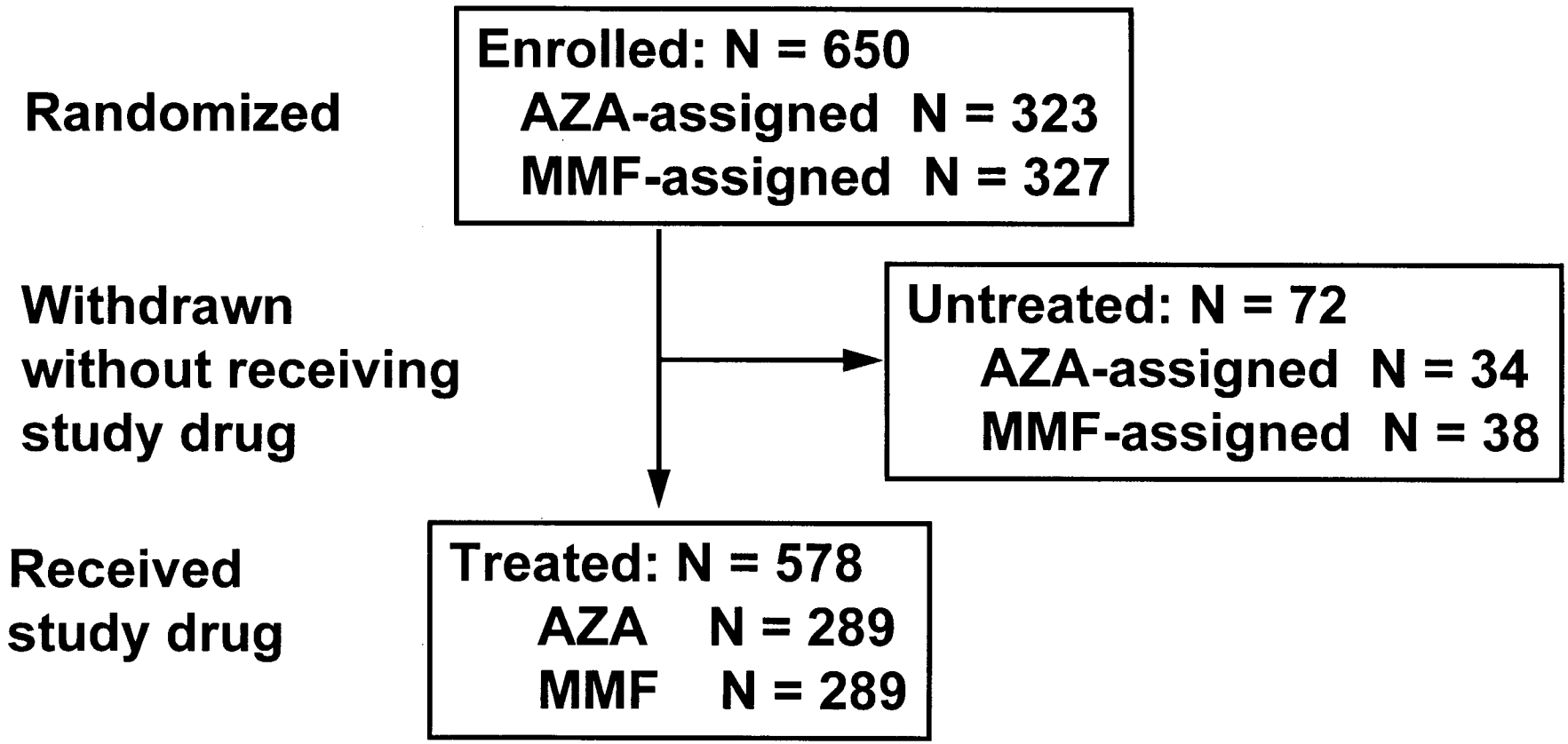
CARDIAC PRESENTATION

- Renal Foundation
- Primary Study 1864
  - Challenges in Design
  - Results
    - Efficacy (Enrolled)
    - Efficacy (Treated)
    - Safety
- Study Conclusions
- Clinical Prespective

LIMITATIONS OF THE ENROLLED POPULATION

- 11% of enrolled patients withdrew without receiving study drug
- Most untreated patients then received open-label AZA
- Differences in treatment effects will be diluted
- Treated population more pharmacologically relevant

1864 STUDY POPULATION



TREATMENT ASSIGNMENTS RANDOM IN TREATED POPULATION

- Treatment assignments blinded when decision made to withdraw patients
- Events leading to withdrawal unrelated to treatment assignment
- Therefore treatment comparisons in this population are valid

BASELINE VARIABLES

[Treated]

- Demography of donors (age, CMV status) and recipients (age, sex, race, CMV status)
- HLA matching
- ABO type
- PRA
- Cold ischemic time

EFFICACY (TREATED)

- Death or Retransplantation
- Rejection

CO-PRIMARY ENDPOINT

Death or Retransplantation:

- **Hypothesis - MMF equivalent to AZA at 1 year post-transplant**

DEATH / RETRANSPLANTATION

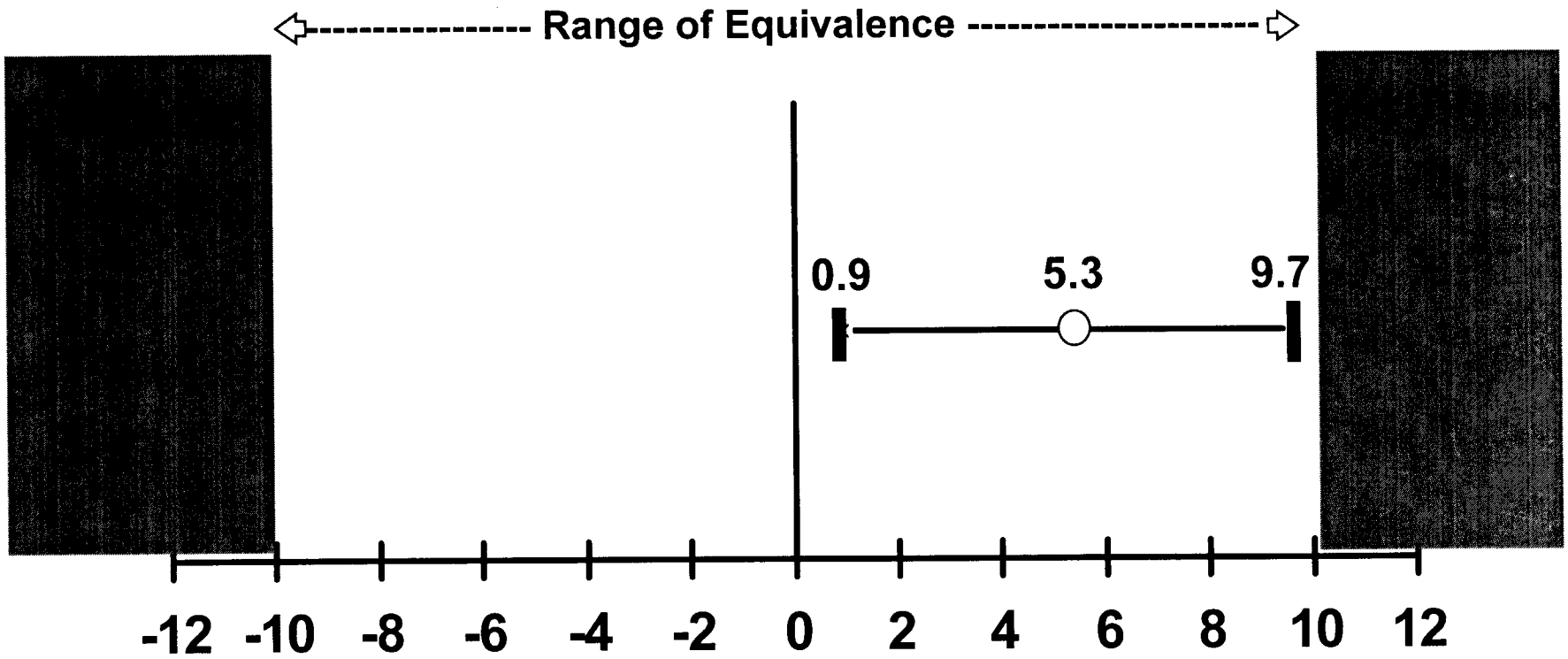
[Treated]

	AZA	MMF
N	289	289
Death or Retx	33 (11.4%)	18 (6.2%)

Weighted Treatment Difference	5.3%
Lower Limit of 97.5% one-sided CI	+ 0.9%

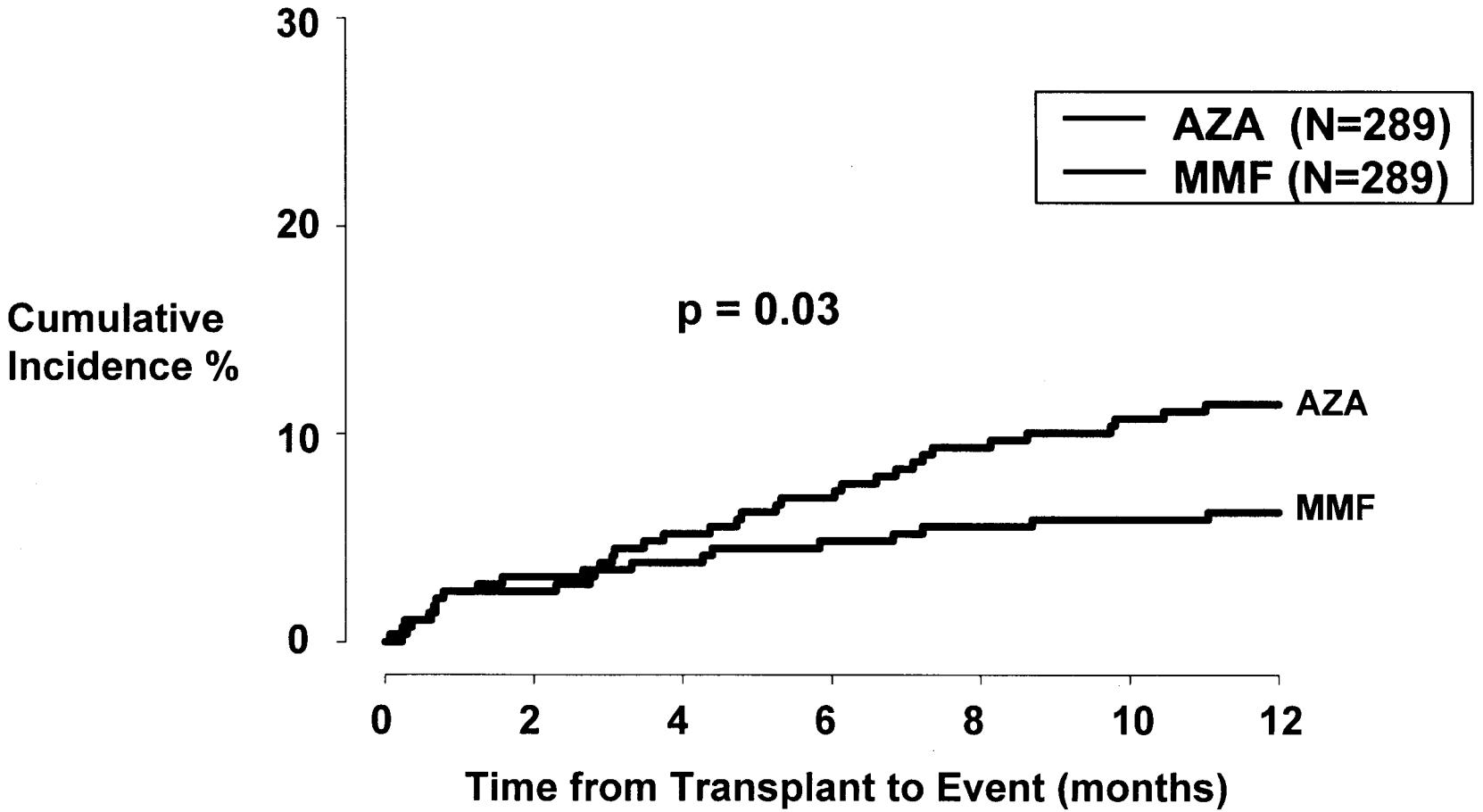
1 YEAR DEATH / RETRANSPLANTATION

[Treated]



DEATH / RETRANSPLANTATION DURING 1 YEAR

[TREATED]



Kaplan-Meier Estimates
Log Rank Test Stratified by Investigator

CONCLUSIONS
DEATH / RETRANSPLANTATION

- Met protocol definition for statistical equivalence
- In the treated population, MMF patients have better survival than AZA patients
- There is support for concluding that MMF may be better than AZA in preventing death/retransplantation

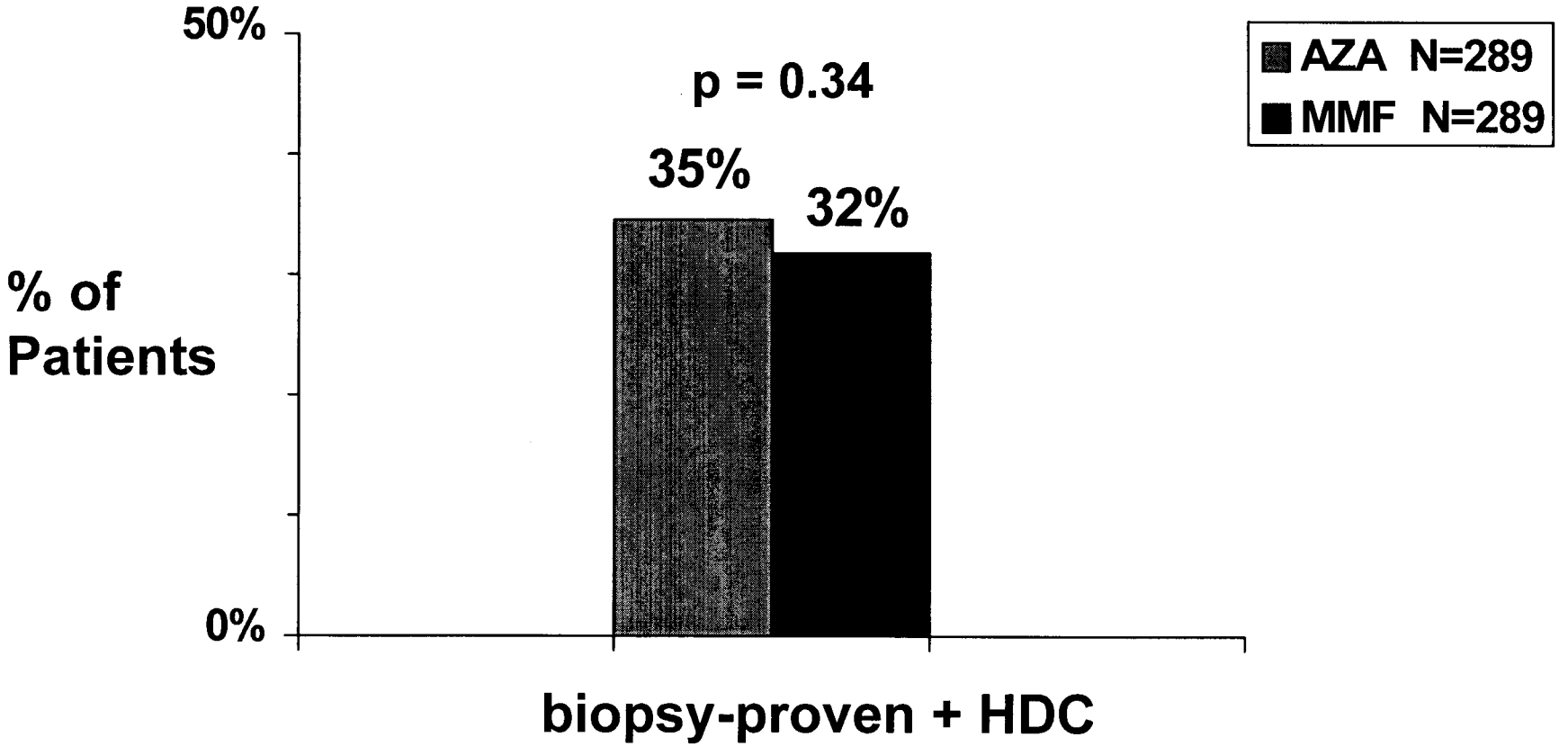
REJECTION RESULTS IN TREATED POPULATION

CO-PRIMARY ENDPOINT

Biopsy-Proven Rejection with HDC

- **Hypothesis - MMF superior to AZA at 6 months post-transplant**

BIOPSY-PROVEN REJECTION WITH HEMODYNAMIC COMPROMISE (HDC) [Treated]



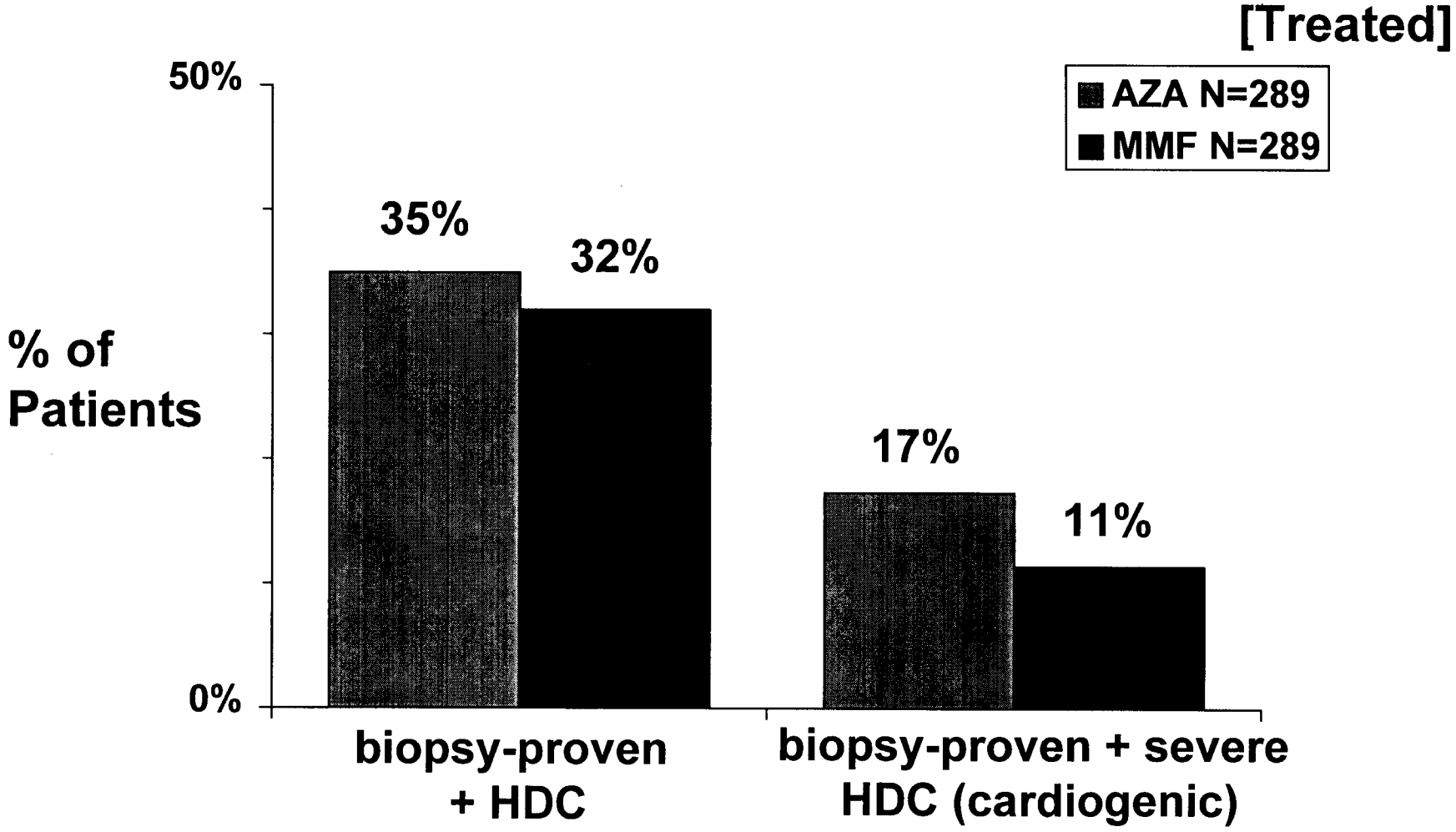
SUPPLEMENTAL POST-HOC REJECTION ENDPOINT

- Steering Committee of transplant experts presented with summary results
- Rates of rejection with HDC about twice as high in the control group as committee had expected when endpoint originally defined
- Steering Committee suggested more restrictive definition

CRITERIA FOR SEVERE HEMODYNAMIC COMPROMISE (CARDIOGENIC)

- Pulmonary capillary wedge pressure $\geq$ 20 mm or 25% increase
- Cardiac index < 2.0 l/min/m^2 or 25 % decrease
- **Ejection fraction $\leq$ 30%**
- Pulmonary artery saturation $\leq$ 60% or 25% decrease
- Presence of new S_3 gallop
- **Fractional shortening $\leq$ 20% or 25% decrease**
- **Inotropic support**

BIOPSY-PROVEN REJECTION WITH SEVERE HEMODYNAMIC COMPROMISE (Cardiogenic)



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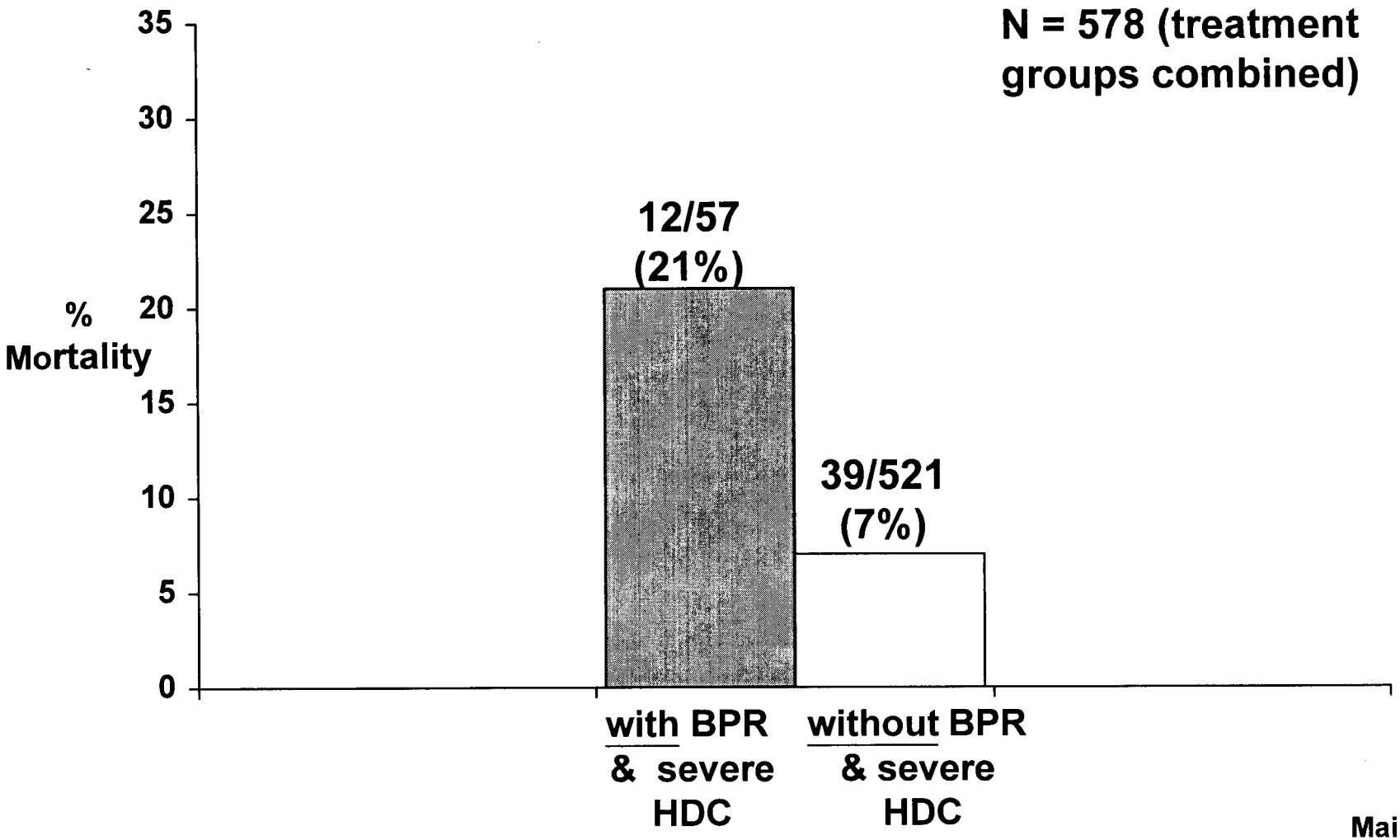
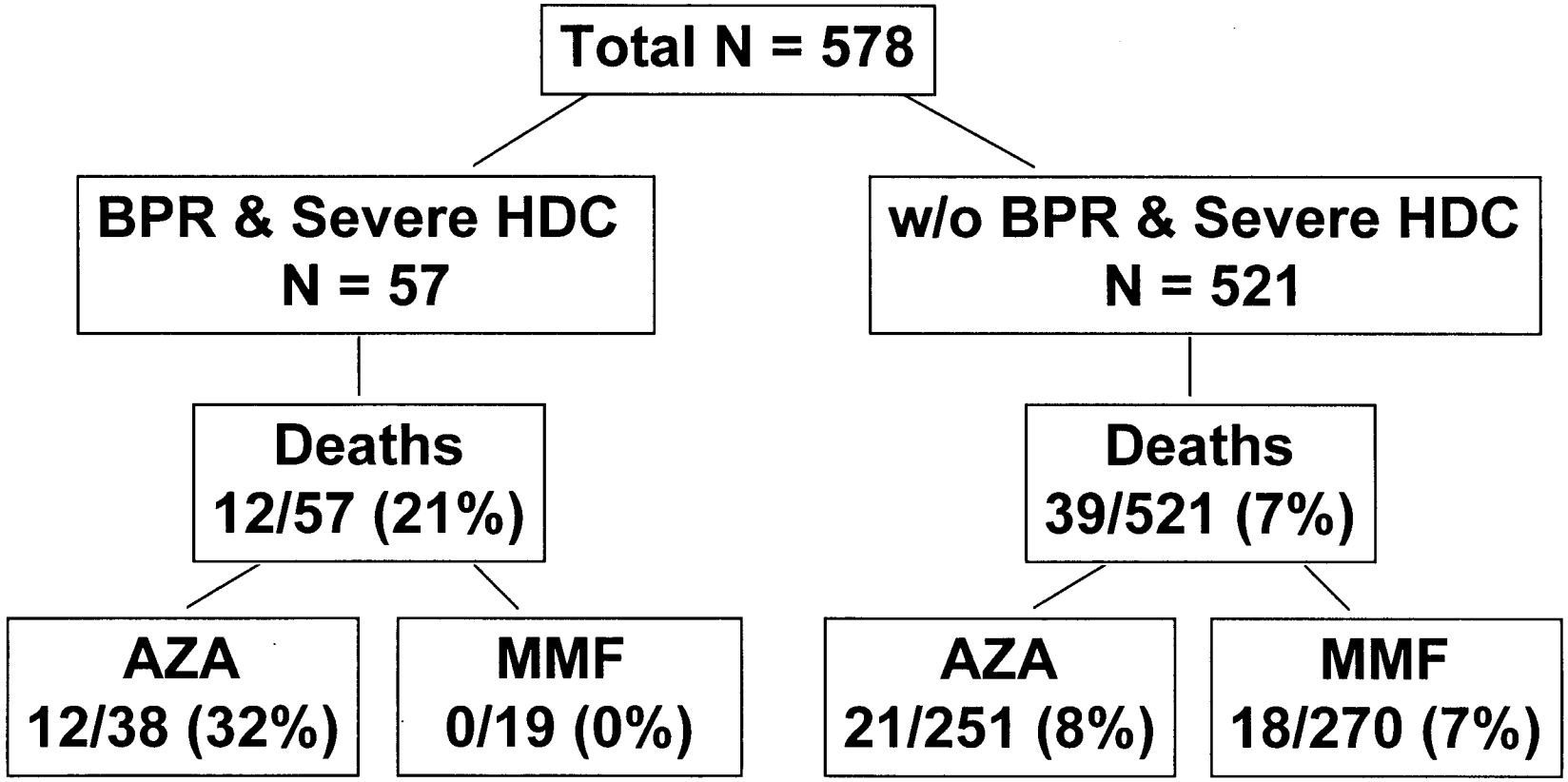
1 YEAR MORTALITY WITH AND WITHOUT BIOPSY-PROVEN REJECTION WITH SEVERE HEMODYNAMIC COMPROMISE (CARDIOGENIC)

[Treated]



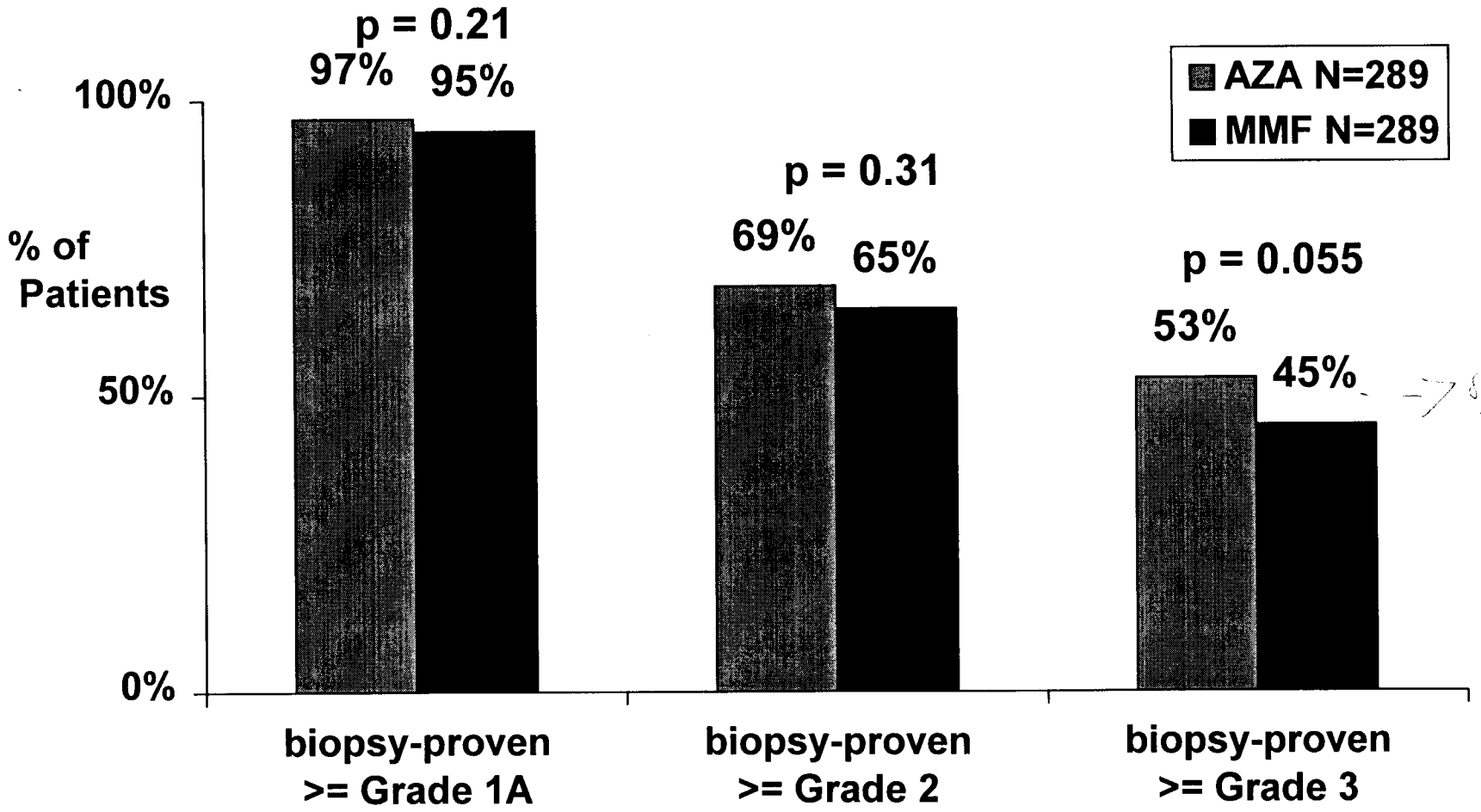
MORTALITY WITH AND WITHOUT BIOPSY-PROVEN REJECTION WITH SEVERE HDC (CARDIOGENIC) [Treated]



SECONDARY REJECTION ENDPOINTS IN TREATED POPULATION

REJECTION RATES AT 6 MONTHS BY ISHLT GRADE

[Treated]



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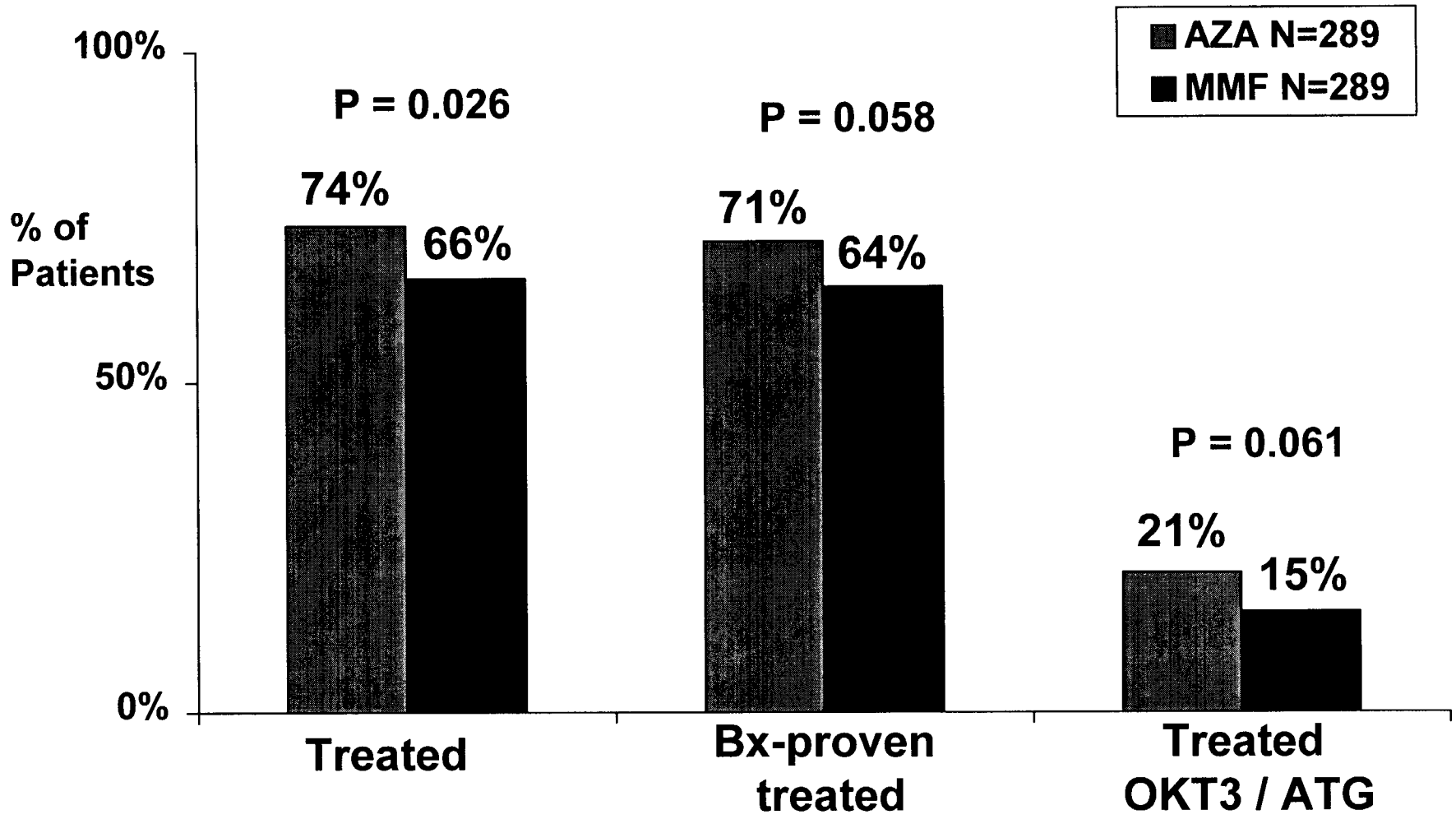
PULSE IMMUNOSUPPRESSION AT 6 MONTHS

[Treated]



MainP-Slide 63

CONCLUSIONS
REJECTION ENDPOINTS

- No difference between MMF and AZA for co-primary rejection endpoint

- MMF appears more effective than AZA in preventing manifestations of severe rejection as measured by
  - ISHLT Grade
  - Need for pulse immunosuppression
  - Severe HDC ("cardiogenic")

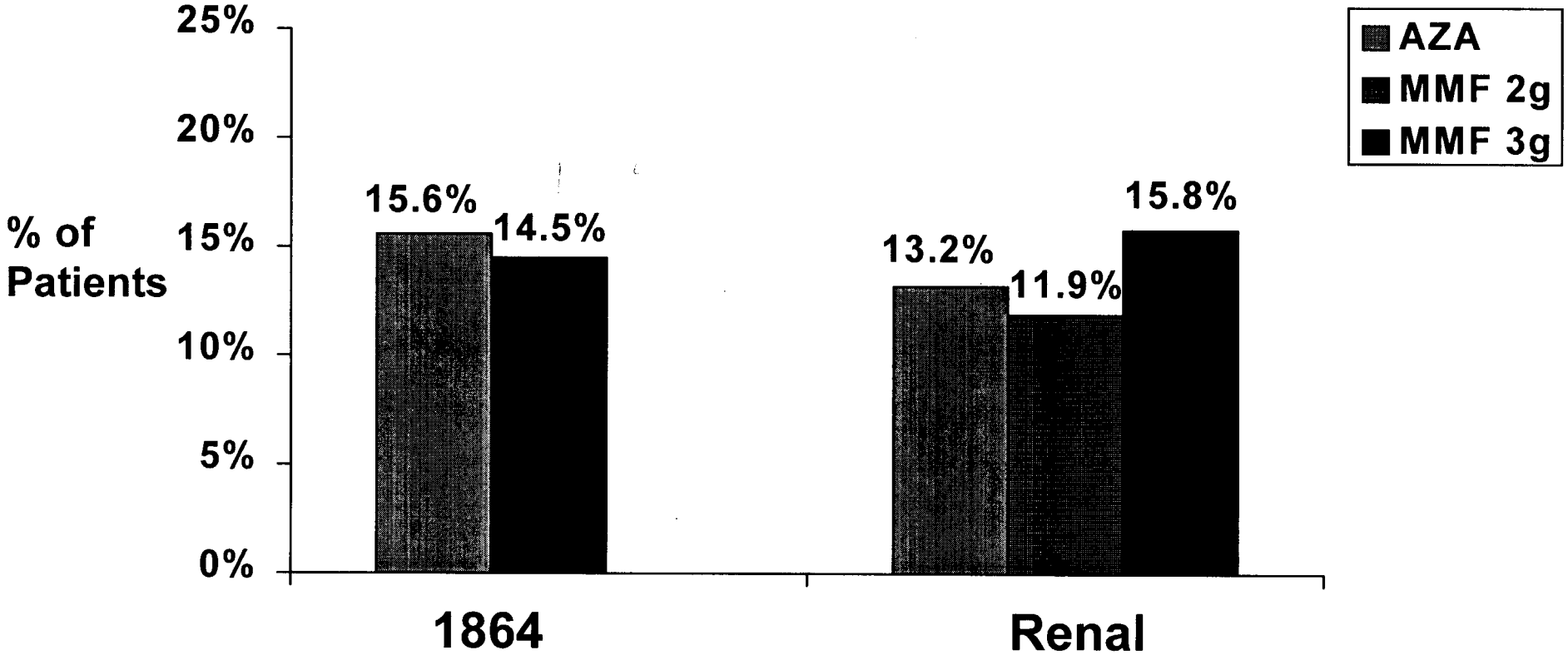
CARDIAC PRESENTATION

- Renal Foundation
- Primary Study 1864
  - Challenges in Design
  - Results
    - Efficacy (Enrolled)
    - Efficacy (Treated)
    - Safety
- Study Conclusions
- Clinical Perspective

OVERALL SAFETY

Relative to AZA, the safety profile of MMF 3g in cardiac transplant is similar to the safety profile of MMF 2g and 3g in renal transplant

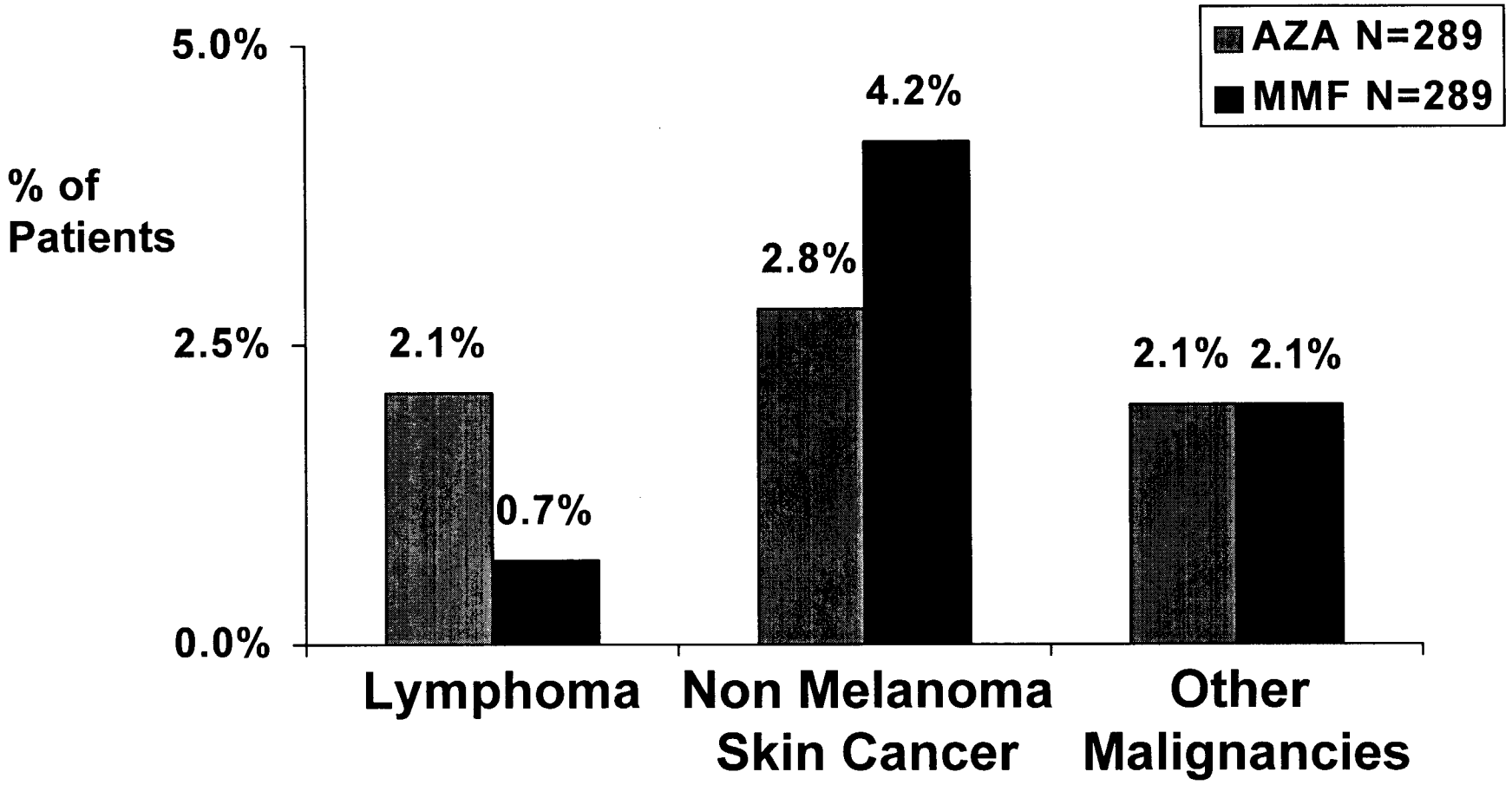
PREMATURE TERMINATION DUE TO ADVERSE EVENT- CARDIAC STUDY (1864) VS RENAL PROGRAM [Treated]



AE'S RESULTING IN REDUCTION, INTERRUPTION OR DISCONTINUATION (>1%)

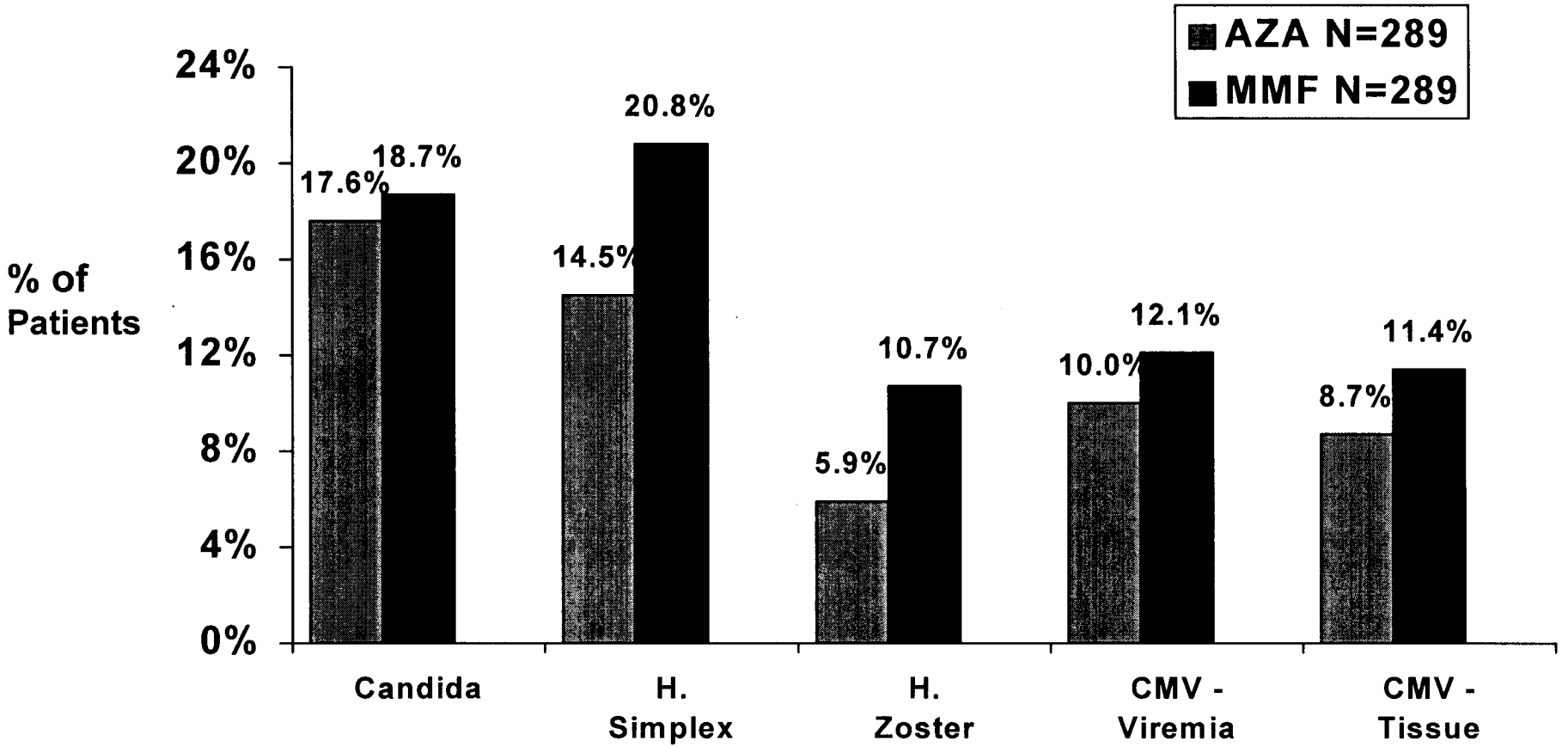
	AZA N=289	MMF N=289
Leukopenia	32.2%	26.0%
Nausea	3.8%	3.8%
Vomiting	2.8%	2.8%
Diarrhea	1.7%	2.4%
Sepsis	2.4%	1.0%
Pneumonia	2.4%	0.7%
Respiratory Infection	1.4%	0.3%

MALIGNANCIES



On study and post termination

OPPORTUNISTIC INFECTIONS



The infections mainly from lack

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MINIMUM ABSOLUTE NEUTROPHIL COUNT

Treatment Group	Minimum ANC (x $10^3/\mu L$)	0-30 Days	31-180 Days	181-365 Days
MMF	> = 2	100.0%	88.7%	93.1%
	0.75 - < 2	0%	8.5%	5.5%
	0.5 - < 0.75	0%	0.4%	0.5%
	< 0.5	0%	2.4%	0.9%
AZA	> = 2	97.1%	90.7%	93.4%
	0.75 - < 2	2.9%	7.7%	6.6%
	0.5 - < 0.75	0%	1.6%	0%
	< 0.5	0%	0%	0%

CONCLUSIONS
SAFETY

- Safety profile for MMF in cardiac transplant is similar to MMF in renal transplant
  - except H. simplex and H. zoster infections are more common in cardiac transplant

CARDIAC PRESENTATION

- Renal Foundation
- Primary Study 1864
  - Challenges in Design
  - Results
    - Efficacy (Enrolled)
    - Efficacy (Treated)
    - Safety
- Study Conclusions
- Clinical Prespective

CONCLUSIONS
STUDY 1864

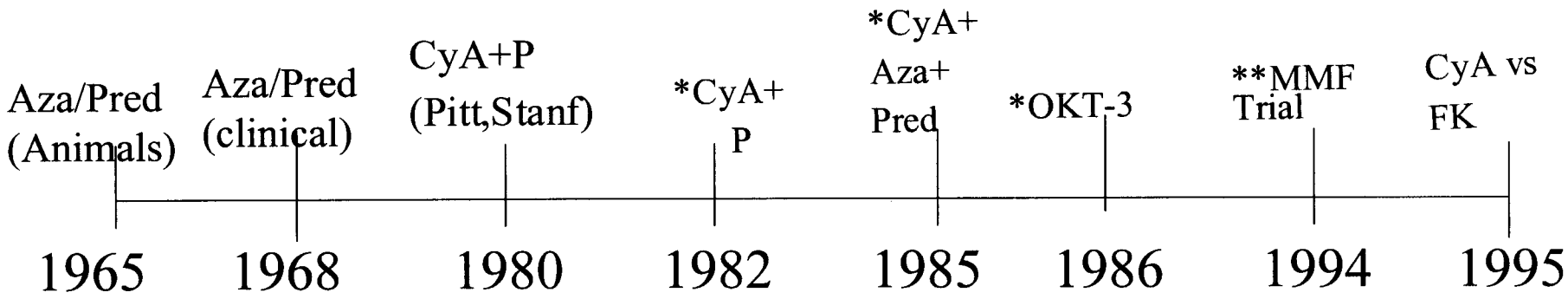
- MMF is efficacious in preventing rejection
- MMF is efficacious in preventing death
- The risk - benefit balance is favorable
- There is evidence to suggest MMF may be superior to AZA

CLINICAL PERSPECTIVE

Unmet Medical Need

- No significant change in one year survival in over 15 years in heart transplantation
- Essentially no Re-Tx option (2%) and no dialysis equivalent
- 50% of patients still have at least one rejection during first year
- Rejection remains #1 cause of death in first year post Tx.

Immunosuppression in Heart Tx



*Changes in practice with no trial data

**1st ever prospective blinded, randomized controlled trial of maintenance Rx

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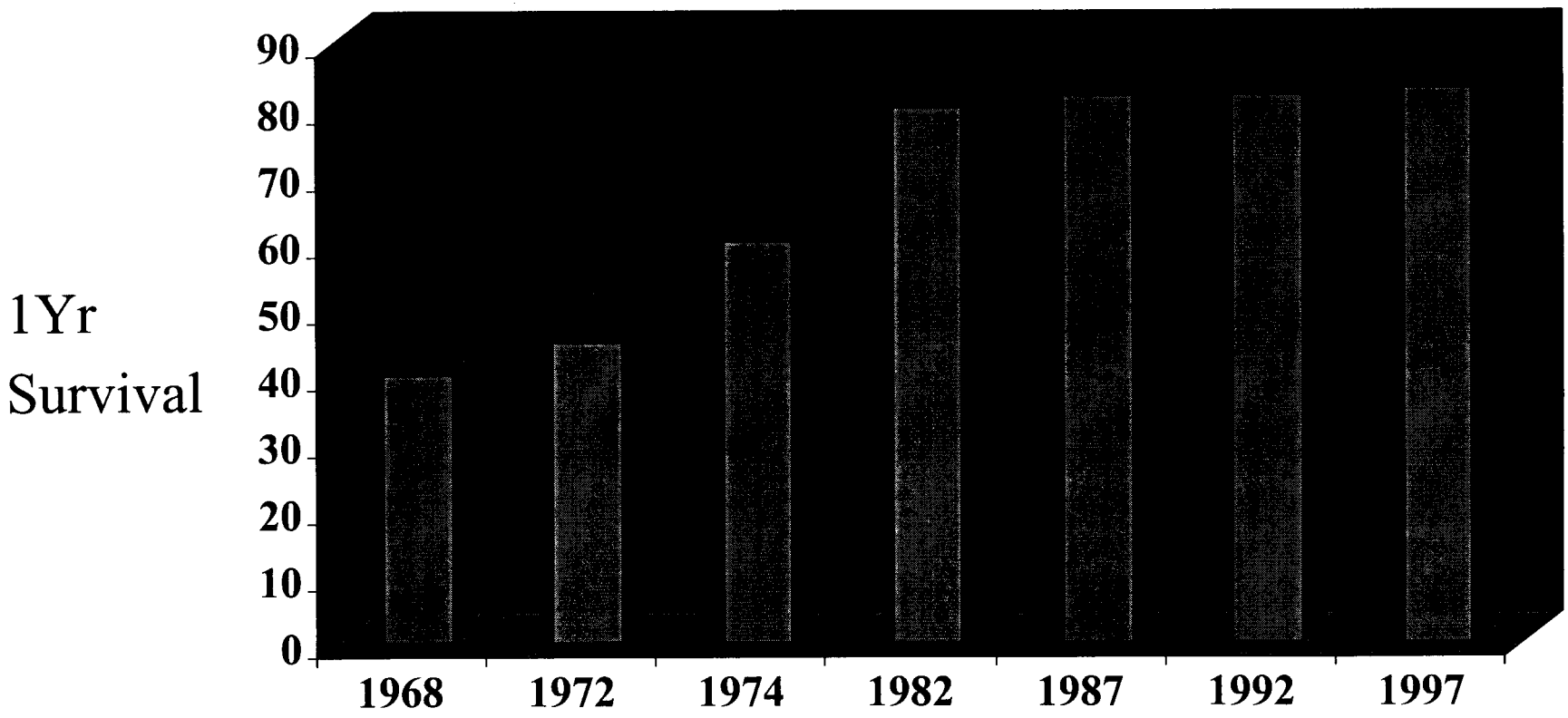
IMMUNOSUPPRESION IN HEART TRANSPLANTATION



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Effect of Azathioprine in CTx

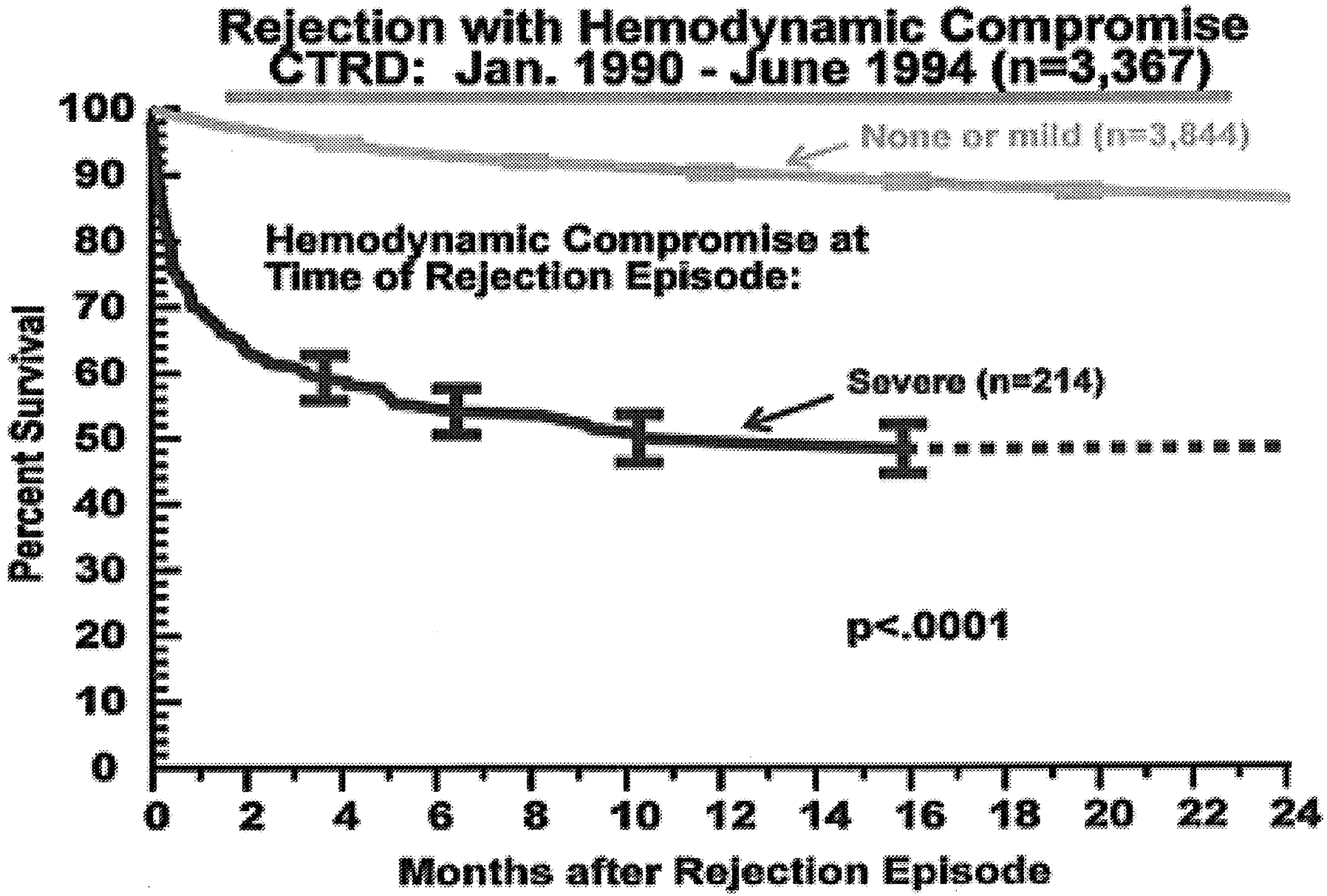
- 60% 1 yr. survival as primary agent before CyA (1980)
- Replaced by CyA at nearly equivalent steroid doses
- Addition to CyA & P allowed nearly 50% reduction in dose of both CyA & P without decrease survival
- Steroid withdrawal data comparable to triple therapy
  CyA+Aza = CyA+Aza+P in 75-80% of patients
- Triple Therapy remains the international standard

Diagnosis of Rejection in CTx

- No biochemical marker or non-invasive test
- HDC Rejection as severe adverse outcome (40% mortality 12 months)
- Fear of HDC mandates surveillance, protocol biopsies (n=13 in Yr 1) not function driven
- No stepwise increase in risk with worsening rejection grade

Diagnosis of Rejection in CTx

- 15% of patients with HDC have no evidence of rejection on biopsy (Mills et al, JHLT October 1997)
- Clinical suspicion is the basis for treatment in 10-15% rej.
- Surveillance biopsies may lead to over interpretation of biopsy findings (Renal Studies)
- Pulse therapy has associated morbidity
- State of the Art: biopsy proved and clinical suspicion


Rejection with Hemodynamic Compromise
CTRD: Jan. 1990 - June 1994 (n=3,367)
None or mild (n=3,844)
Hemodynamic Compromise at
Time of Rejection Episode:
Severe (n=214)
p<.0001
Percent Survival
100
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
12
14
16
18
20
22
24
Months after Rejection Episode

MMF 1864 Study
Important Findings for the Clinician
Rejection with Hemodynamic Compromise

- often associated with irreversible damage and high mortality (30-40% at 1 yr.)
- greatest cause of death in 1st Yr. Post Tx
- dictates the need for surveillance Bx's
- requires very aggressive treatment, related morbidity

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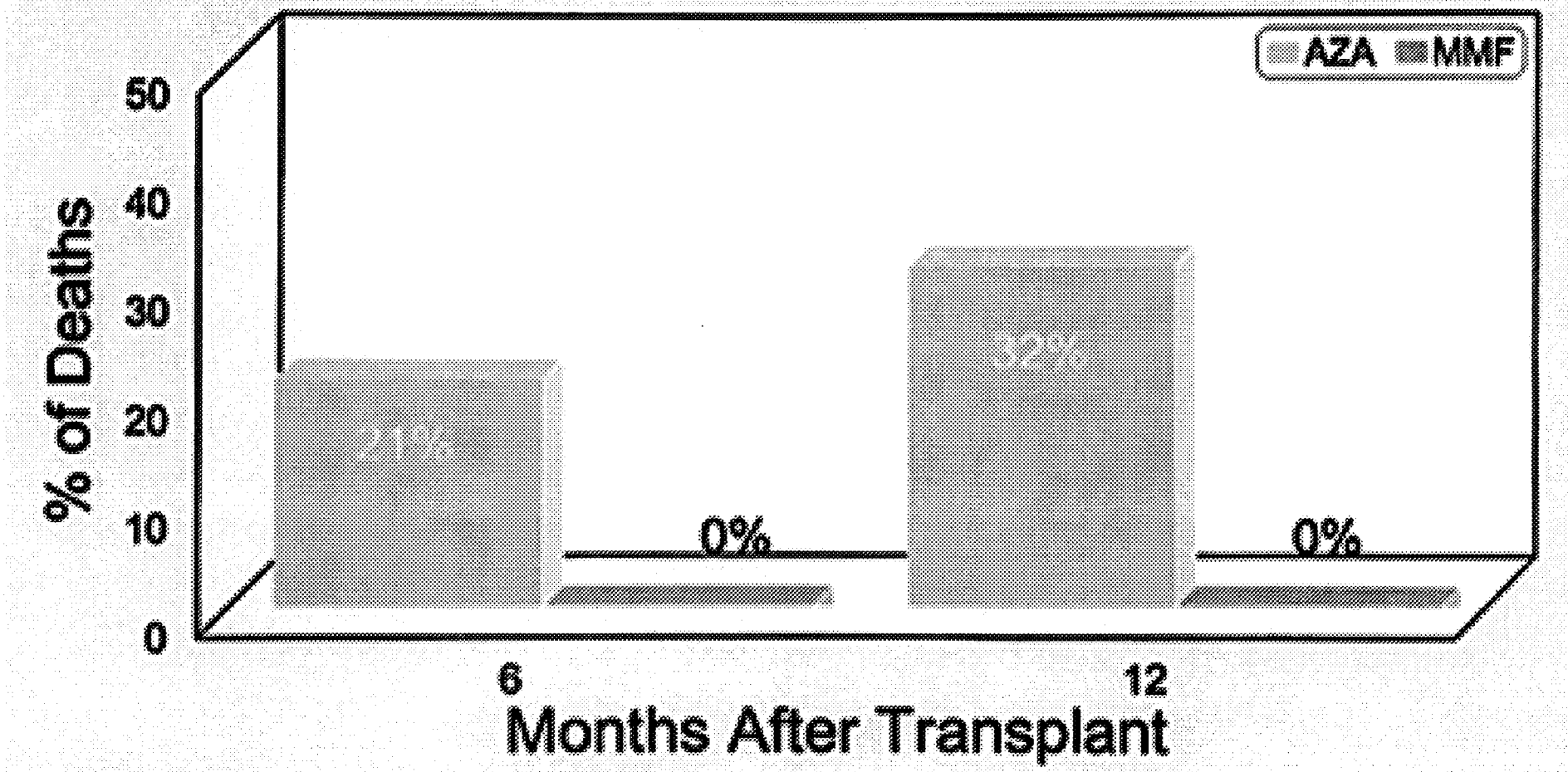
MORTALITY IN PATIENTS WITH HDC REJECTION IN THE TREATED PATIENTS



HDC = Hemodynamic compromise

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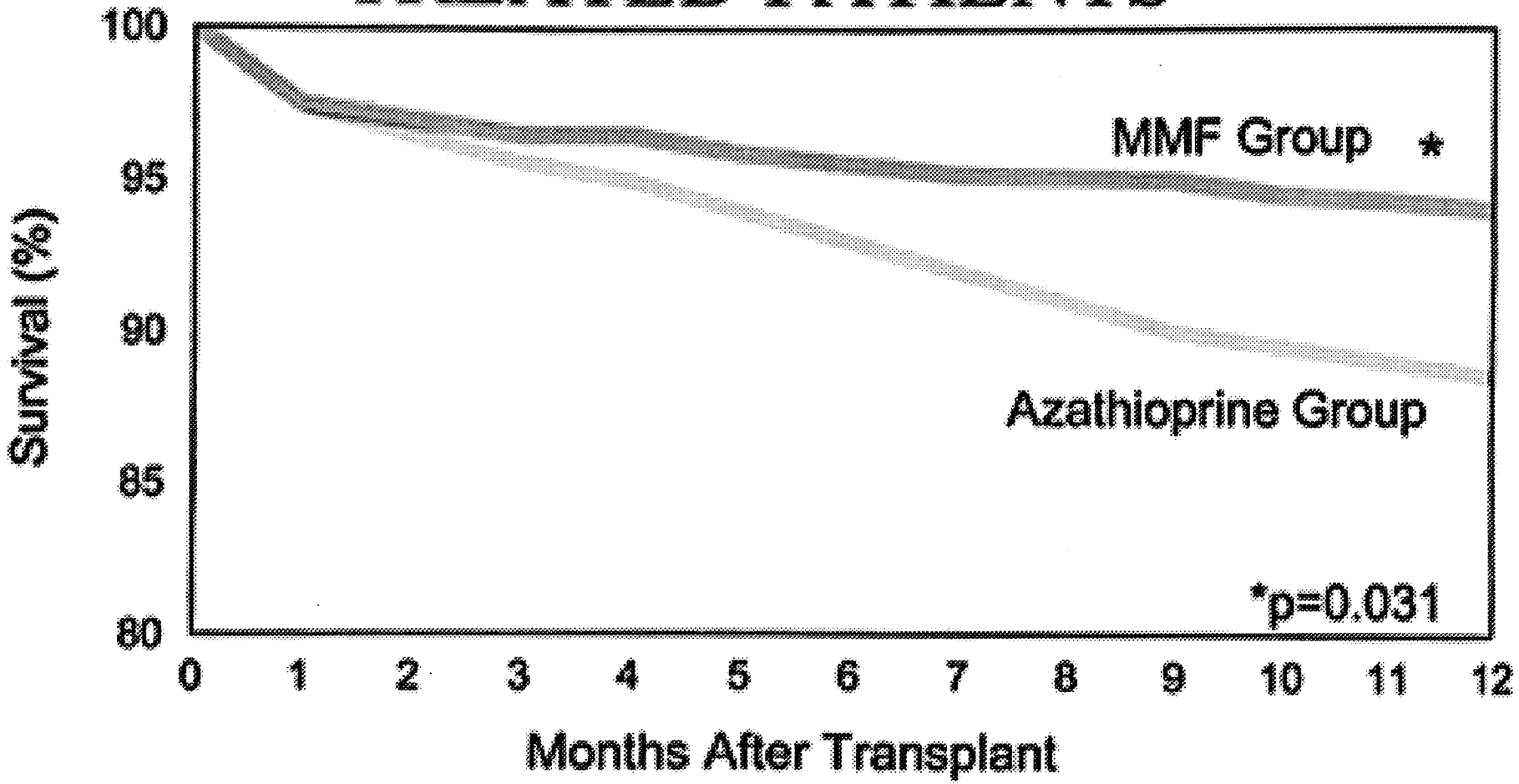
ONE YEAR SURVIVAL IN THE TREATED PATIENTS



MMF 1864 Study
Important Findings for the Clinician:
Rejection Findings

- unlike renal Tx, treat both histologically proven and/or clinically suspected rejection. (composite endpoint)
- 15% of patients with HDC treated had minimal or no evidence of rejection [Mills et al JHLT Oct. 1997]
- MMF had progressive impact with worsening grade
- Consistency of rejection results

Important Findings for the Clinician: Survival

- Treated analysis is first prospective data to ever show a survival benefit in CTx
- benefit is seemingly immunologically related
- greatest impact may be in very high risk patients (those with HDC or worst rejection)

Collective Data on MMF

- Renal Studies-(US, European, Tricont.)

  All 3 showed 50% reduction in acute rejection.

- Cardiac Study (1864)

  All efficacy analyses numerically favor MMF

  Safety and tolerability of 3 gm. dose

- Consistent evidence of efficacy and safety in both organs.

MMF (1864) - A Landmark Study

- Critical contribution to heart transplantation
- Only prospective, randomized, double blind, controlled trial ever done in CTx
- First use of uniform protocols for care/treatment
- First data (treated analysis) to show a survival benefit
- Decreased death from rejection; no increase infect. death
- Significant impact on death following HDC rejection
- Fills the unmet need in CTx

CLOSING REMARKS

- Study 1864 provided special challenges
- Treated population analysis is appropriate and scientifically valid

CLOSING REMARKS

- MMF is effective in renal transplantation
- MMF is efficacious in preventing cardiac rejection and death
- There is evidence to suggest superiority of MMF over AZA
- MMF represents an advance in cardiac transplant immunosuppression