Methodological constraints in the design of clinical trials

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Disclosure

Grants from:

Astellas, Novartis, TEVA, Chiesi

Honorarium for conferences and advisory boards from :

Astellas, Novartis, TEVA, Chiesi

Unmet needs:

Condition	Approved Drugs	Available Therapies	Unmet medical need
Delayed Graft Function	None	Pulsatile perfusion; Donor hypothermia	Incomplete effectiveness
Rejection Prevention-Induction	Basiliximab		Incomplete effectiveness, side effects, infection risk
	ATGAM		
Rejection Prevention-Maintenance	CNIs (cyclosporine, tacrolimus)		Incomplete effectiveness, nephrotoxicity risk, diabetes, chronic allograft injury
	Antiproliferative Agents (azathioprine, mycophenolate, sirolimus, everolimus)		Incomplete effectiveness, side effects, infection risk
Rejection Therapy	Thymoglobulin, ATGAM	corticosteroids	Incomplete efficacy, toxicity
AMR Therapy (clinical and subclinical, acute and chronic, TG)	None	IVIG, rituximab, bortezomib	Incomplete effectiveness
AMR prevention	None	Eculizumab	Incomplete effectiveness
Tolerance (Induction and maintenance)	None		

O'Connell et al. Transplantation 2017 epub ahead of print

Actual challenges

Difficulties to define surrogate outcome variables

Minimum sample size and follow up

Compliance as a source of bias

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History of primary efficacy variables in kidney Tx

~~Graft survival at 1 year~~

Csa vs Aza

When graft loss < 20%

Anonymous. N Engl J Med 1983;309:809–15

History of primary efficacy variables

~~Acute rejection~~

CsA +MMF vs CsA +Aza

When acute rejection < 20%

Halloran P et al. Transplantation 1997;63:39–47

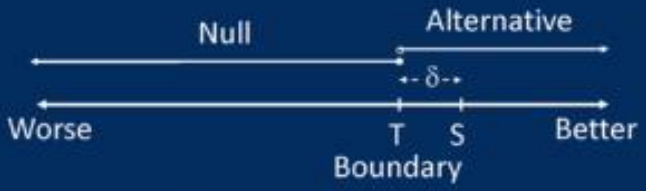
Chapman & Hall/CRC Biostatistics Series

Noninferiority Testing in Clinical Trials

Issues and Challenges

Null hypothesis: $T \leq S - \delta$

Alternative hypothesis: $T > S - \delta$



Tie-Hua Ng

CRC Press
Taylor & Francis Group
A CHAPMAN & HALL BOOK

We need trustful surrogates:

"variables that can be used instead of graft survival"

Early measurement

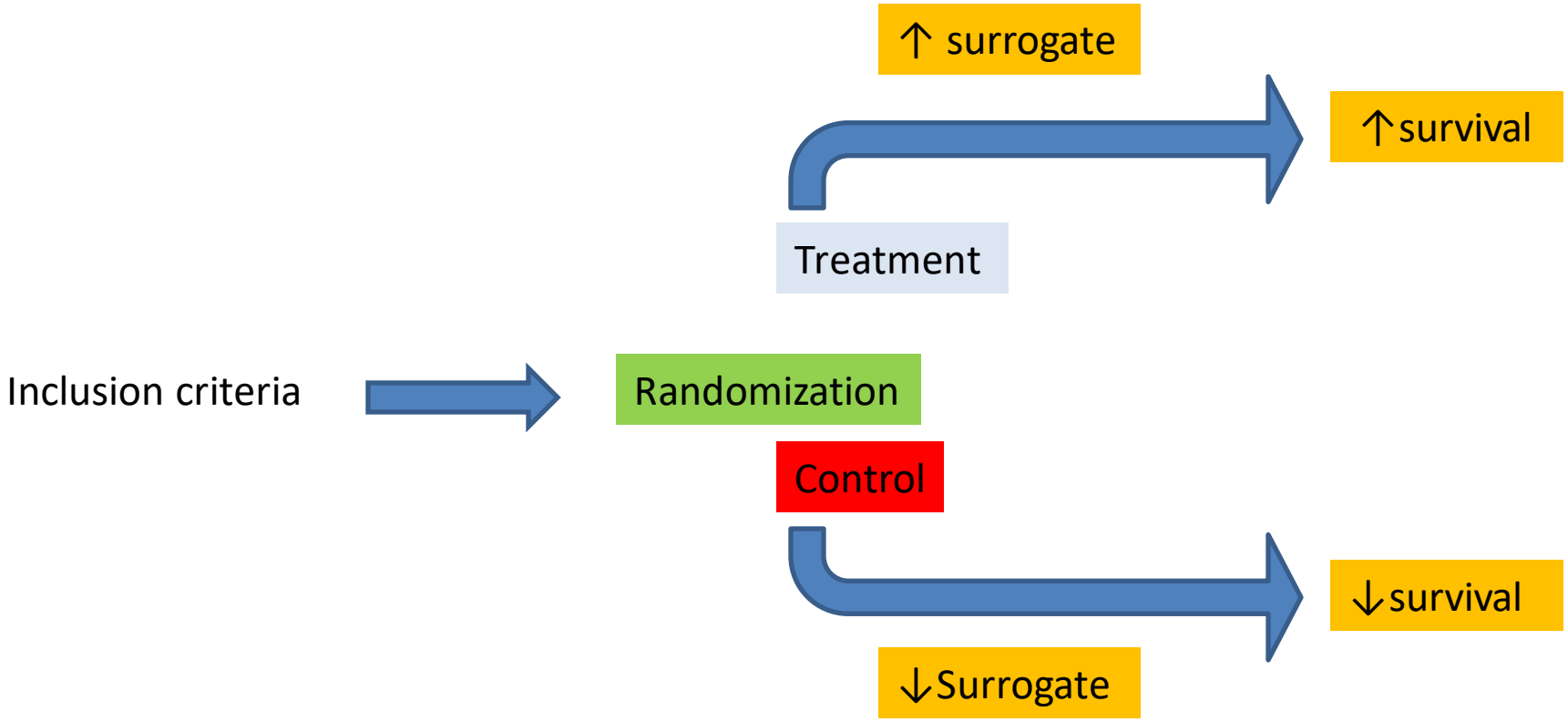
Predicts survival (epidemiological studies)

Changes in the surrogate variable by treatment

imply changes in survival (clinical trials)

Lachenbruch P et al. Am J Transplant 2004;4:451–7

Surrogate biomarker should be developed in clinical trials



Mei-Yin C et al . J Natl Cancer Inst 2013; 105:1677

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We are left behind in a personalized medicine approach

Defining new Surrogate variables:

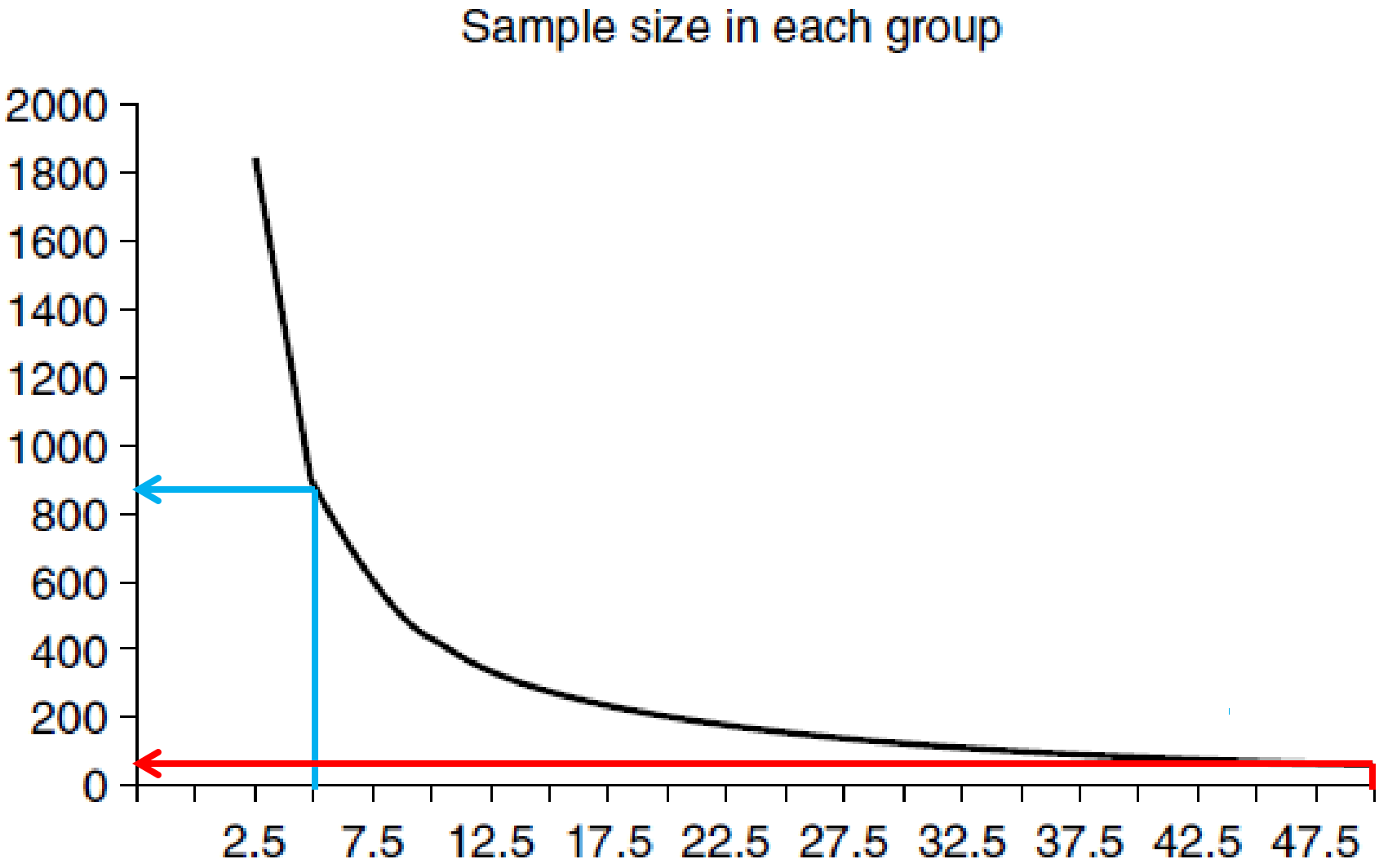
"variables that can be used instead of graft survival"

Ideally, the prevalence of

the surrogate should be 50%

Seron D, & Moreso F. Kidney Int 2007;72:690–697

Minimum sample size to detect a 50% decrease in the main outcome variable (α=0.05 and β=0.20)



Seron D, & Moreso F. Kidney Int 2007;72:690–697

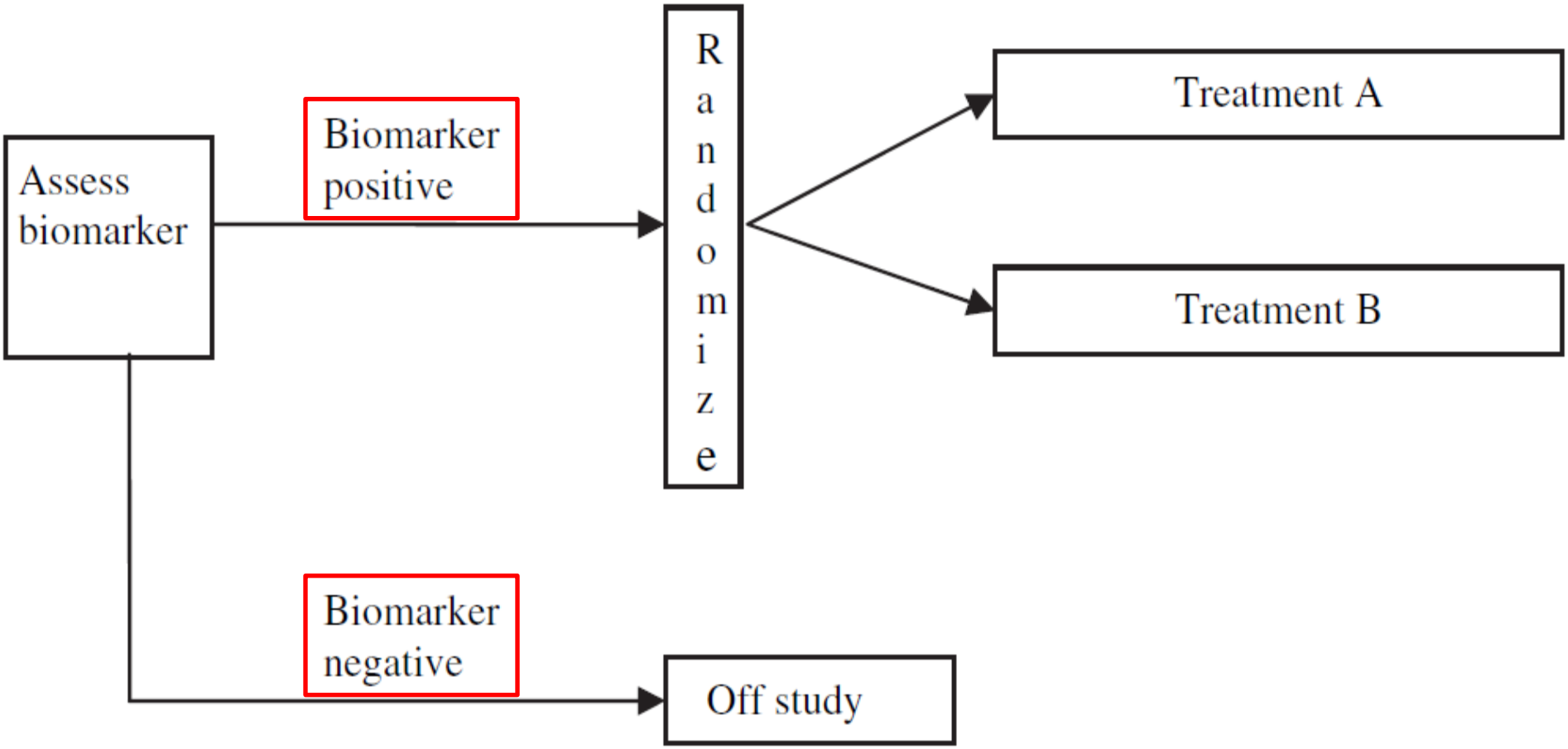
How to design trials in order to approach the ideal prevalence of 50% of the surrogate variable?

a.) select populations at risk (enrichment strategies)

b.) define a composite surrogates

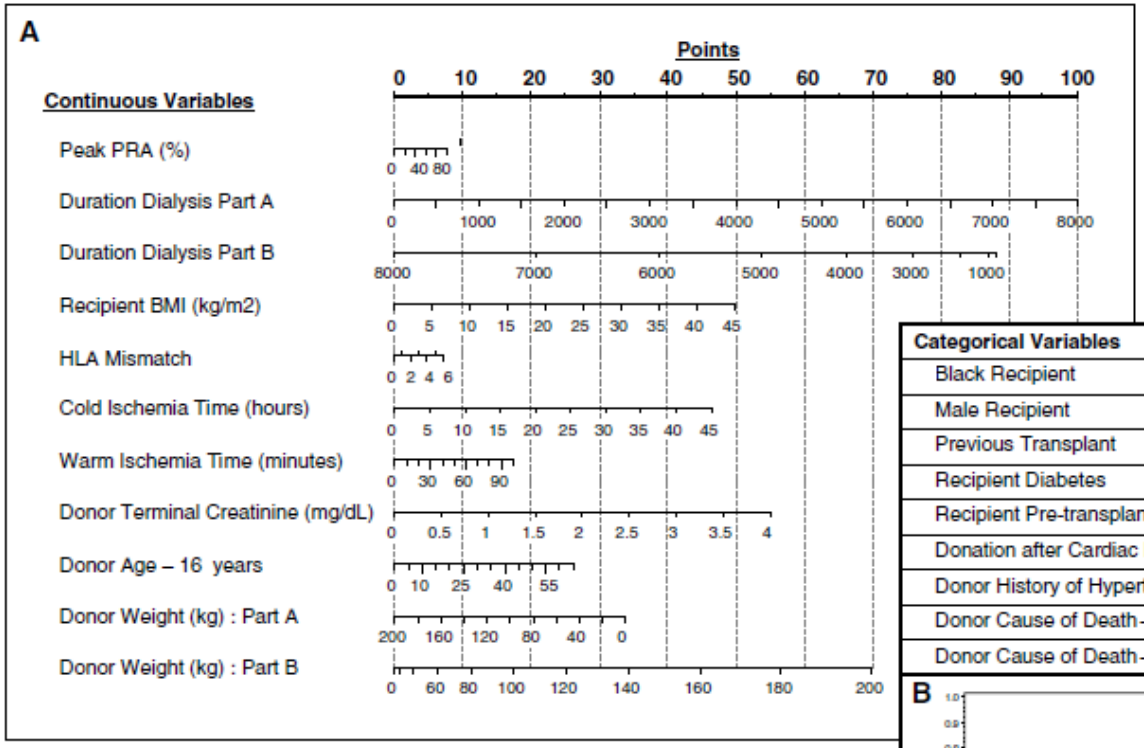
Enrichment design

Biomarker evaluated in all patients but random assignment restricted to patients within set values for biomarker

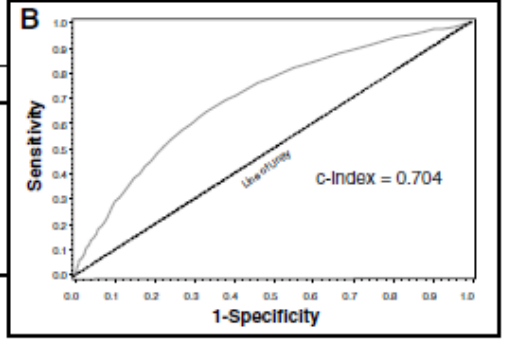


Freidlin B et al. J Natl Cancer Inst 2010; 102: 153

Predicting the prevalence of DGF according to donor and recipient charactristics



Categorical Variables	Points
Black Recipient	6
Male Recipient	9
Previous Transplant	5
Recipient Diabetes	8
Recipient Pre-transplant Transfusion	6
Donation after Cardiac Death	27
Donor History of Hypertension	6
Donor Cause of Death-Anoxia	6
Donor Cause of Death-Cerebrovascular	6



Score 230 DGF 25%

Score 265 DGF 50%

Irish WD et al. Am J Transplant 2010; 10, 2279

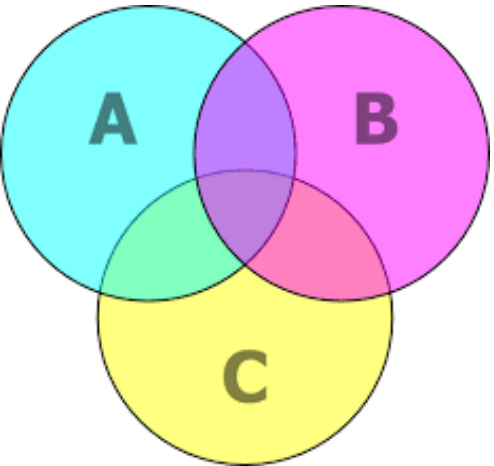
Define composite

Surrogates have to be built with variables showing a positive correlation

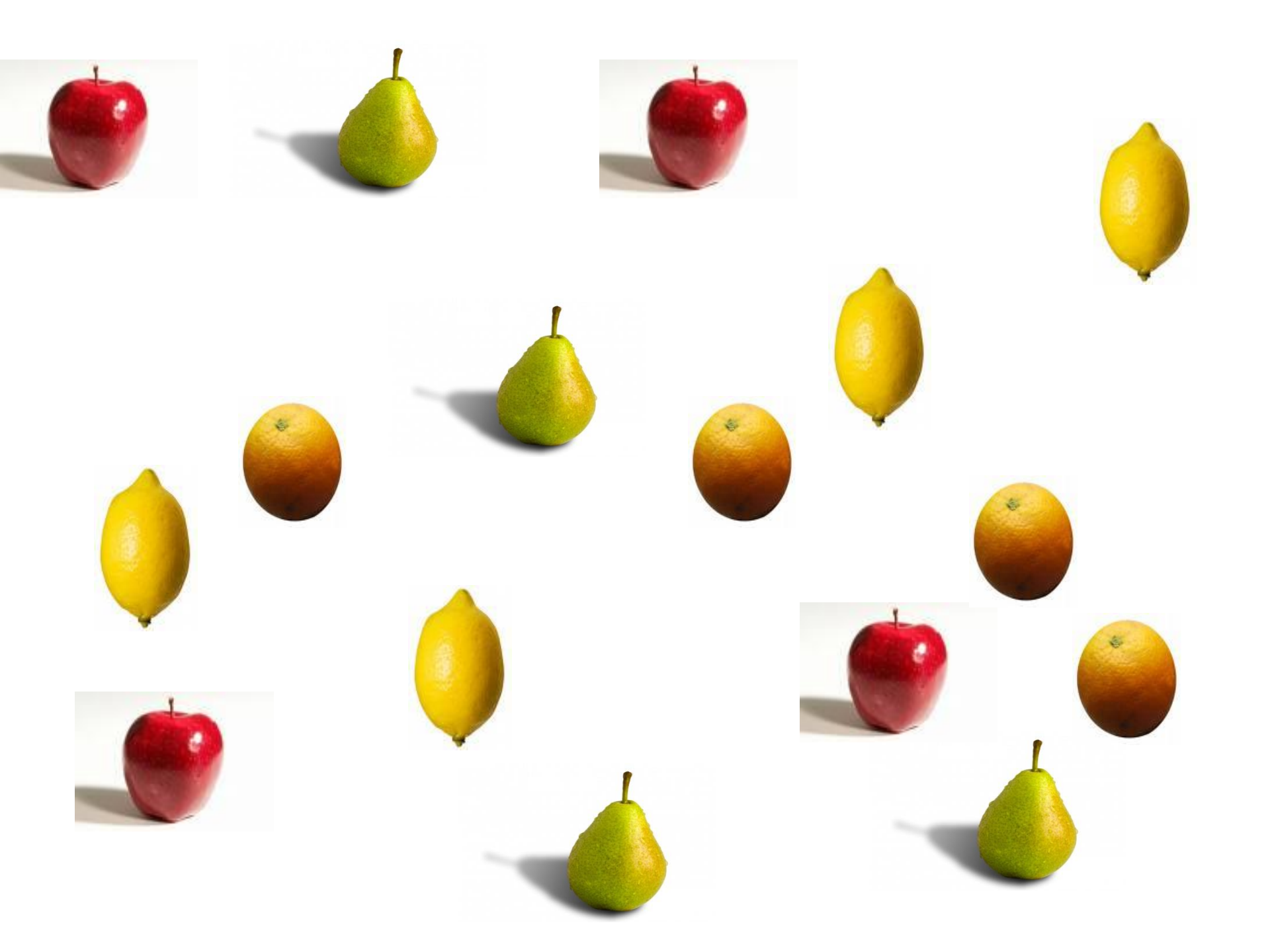
"moving in the same direction"

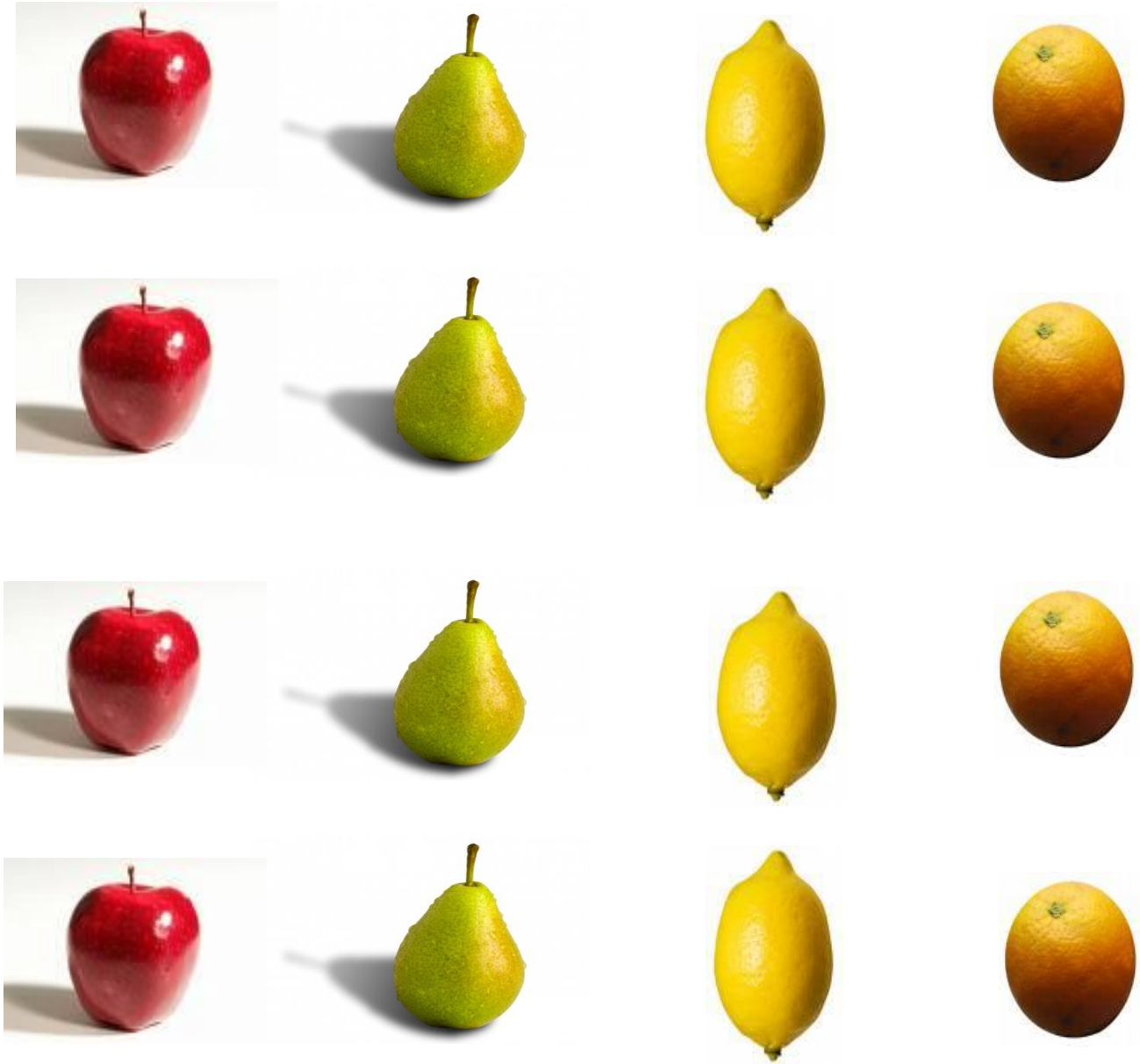
"Measures of alloimmune response"

Primary efficacy variable	Prevalence 1y
Subclinical inflammation	15%
Acute rejection	15%
dnDSA	15%



Prevalence of the composite surrogate ≒ 30%





Cox regression model to assign a risk weight to each variable

$$H(t)=H_0(t) \times \exp(\beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \ldots + \beta_k x_k)$$

Variable	β coefficient
Apple	+5
Pear	+3
Lemon	+1
Orange	+6

Convert a qualitative into a quantitative surrogate variable

Percentage of subclinical rejection

Number of CD45 + cells/ High power field

Converting a qualitative into a quantitative variable

Prevalence of subclinical inflammation 9/106= 8.4%

From 8 to 4 %

769 pts per group

Torres IB et al. Unpublished observation

Converting a qualitative into a quantitative variable

Number of CD45+ cells/hpf 18±17

From 18±17 to 9±17

81 pts per group

"Check for proportionality"

Torres IB et al. Manuscript in preparation

Defining new Surrogate variables:

"variables that can be used instead of graft survival"

How long should be the follow up

Seron D, & Moreso F. Kidney Int 2007;72:690–697

Benefit trial

3 coprimary variables

1.Patient + Graft Survival at 1y

2. Renal function: mGFR < 60 mi/min and/or >10 ml decrease in mGFR 3-12 m

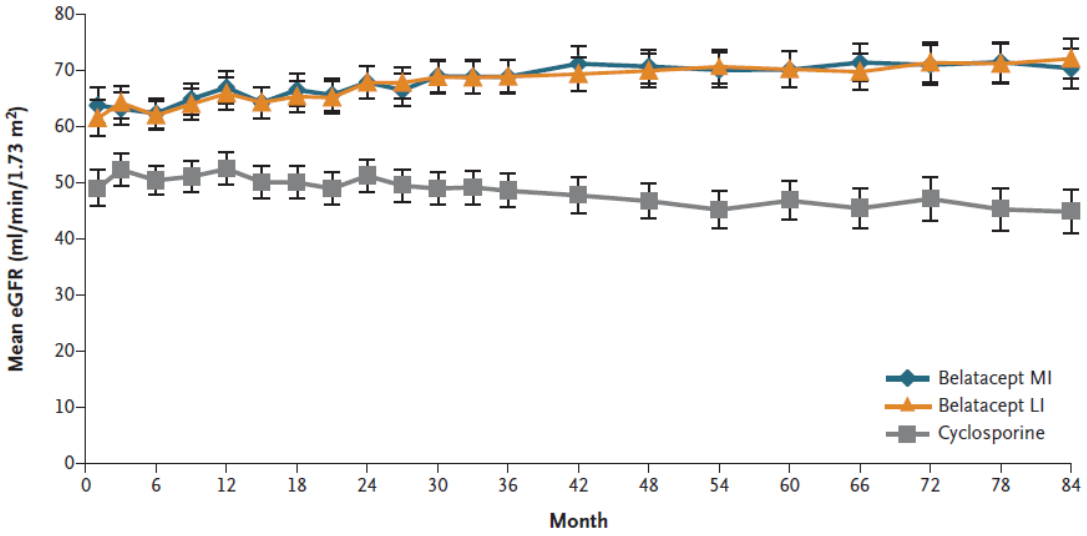
3. Acute rejection

	MI	LI	CsA
Pt and G survival (%)	95	97	93
Renal function (%)	55	54	78 [a,b]
AR (%)	22	17	7 [a]

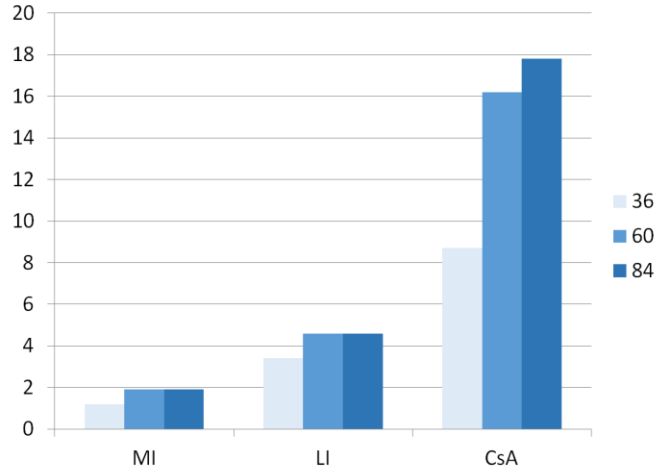
How can we interpret this results?

Vincenti F et al. Am J Transplant 2010; 10: 535

Belatacept and long term outcome

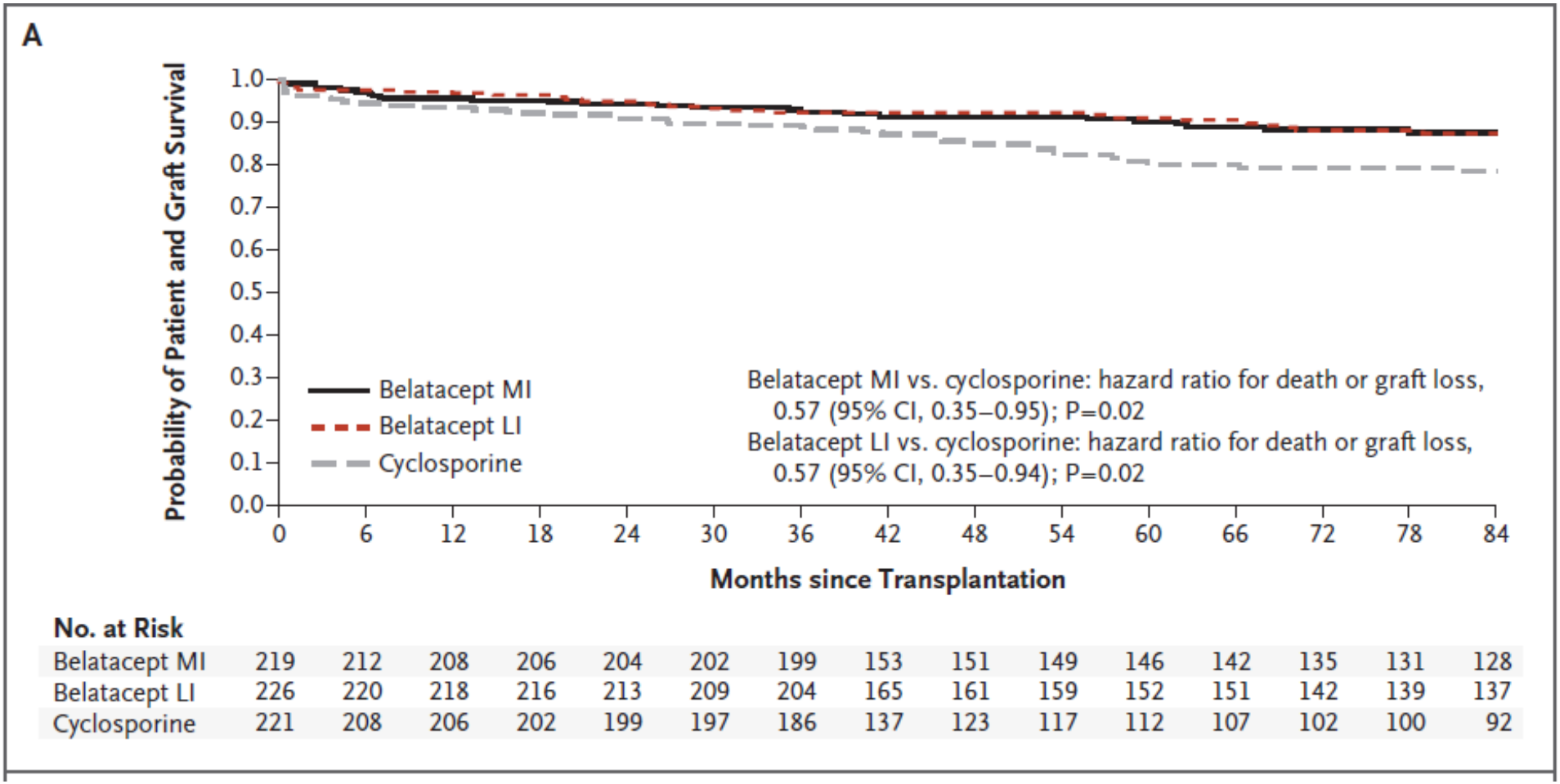


dnDSA



Vincenti F et al. N Engl J Med 2016; 374: 333

Belatacept associated with better eGFR and improved patient and graft survival



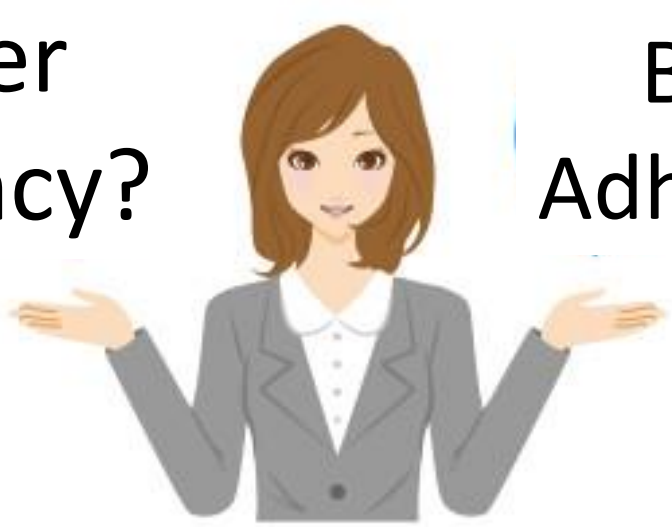
No. at Risk

Belatacept MI	219	212	208	206	204	202	199	153	151	149	146	142	135	131	128
Belatacept LI	226	220	218	216	213	209	204	165	161	159	152	151	142	139	137
Cyclosporine	221	208	206	202	199	197	186	137	123	117	112	107	102	100	92

Vincenti F et al. N Engl J Med 2016; 374: 333

What is the explanation for the superior results of belatacept?

Higher Efficiency?



Better Adherence?

Actual challenges

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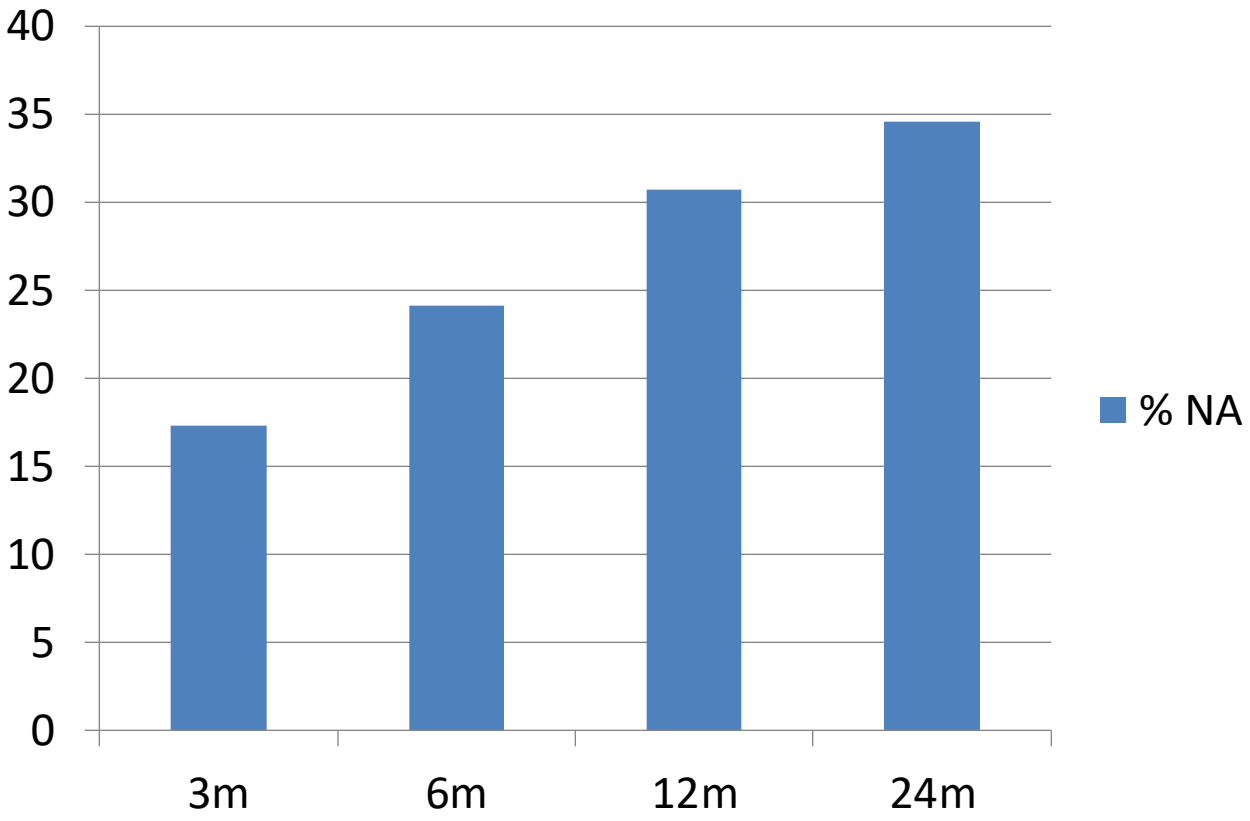
Compliance as a source of bias

Prevalence of non-adherence

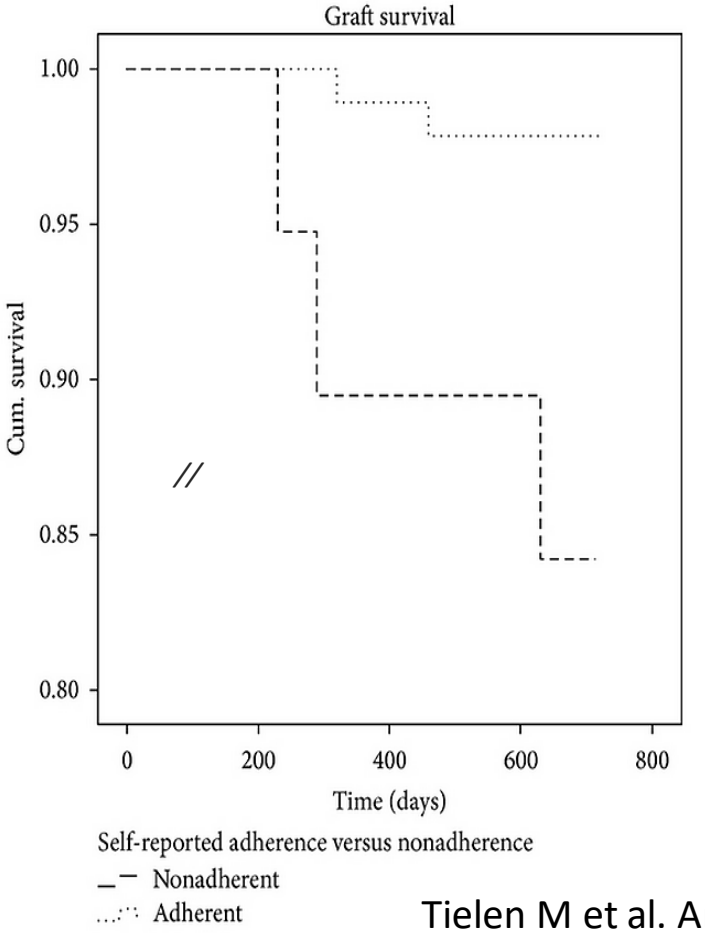
N=312 pts: Morisky scale > 0



Couzi et al et al. Transplantation 2013; 95: 326

Non-adherence is associated with poor graft survival in kidney transplantation

Kaplan-Meier graft survival. The non-adherent group consisted of 19 patients (3 graft failures) and the adherent group consisted of 94 patients (2 graft failures)



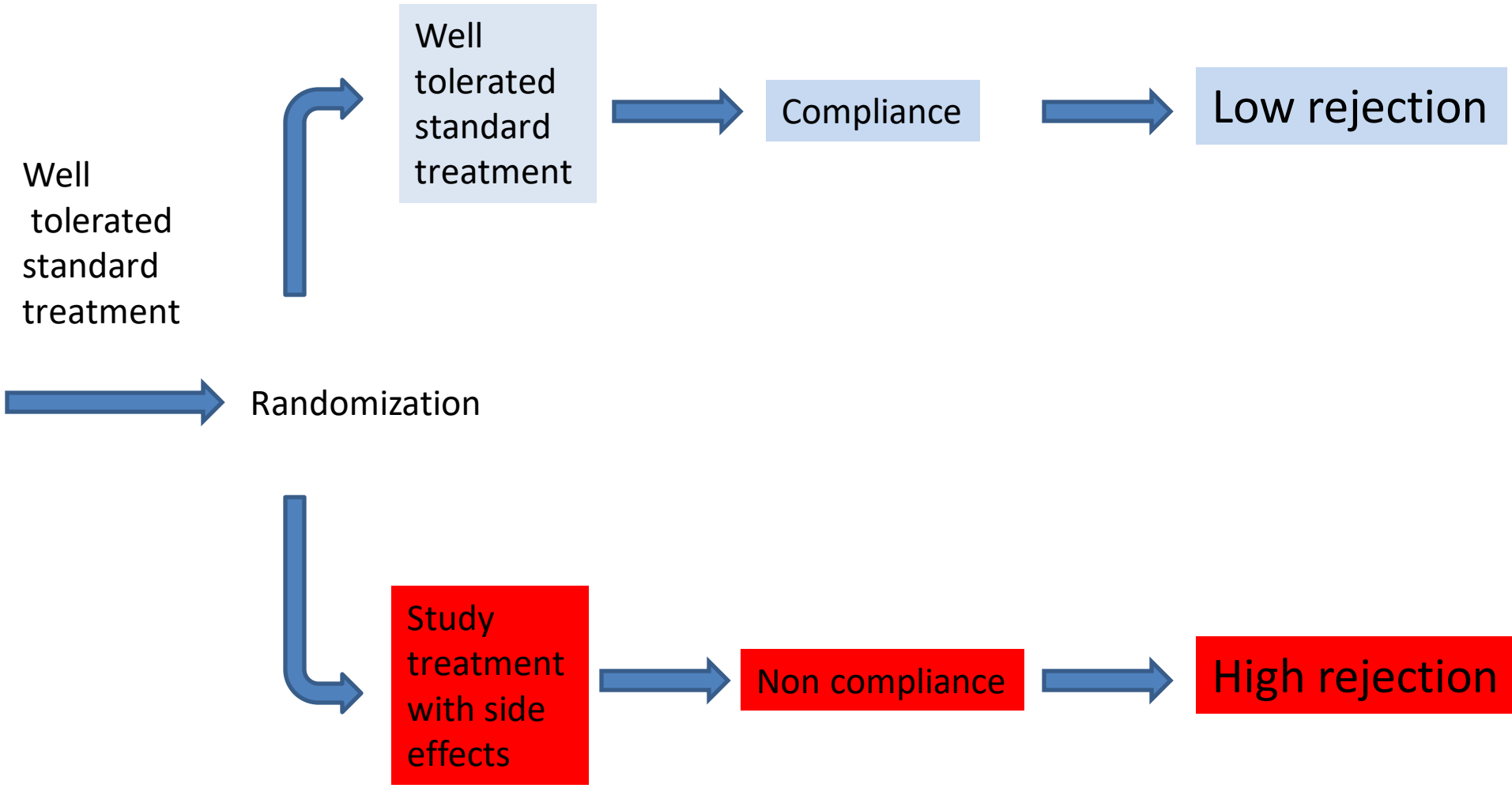
Tielen M et al. Am J Transplant 2014;Article 675301.

Morisky scale yes (0) and no (1)

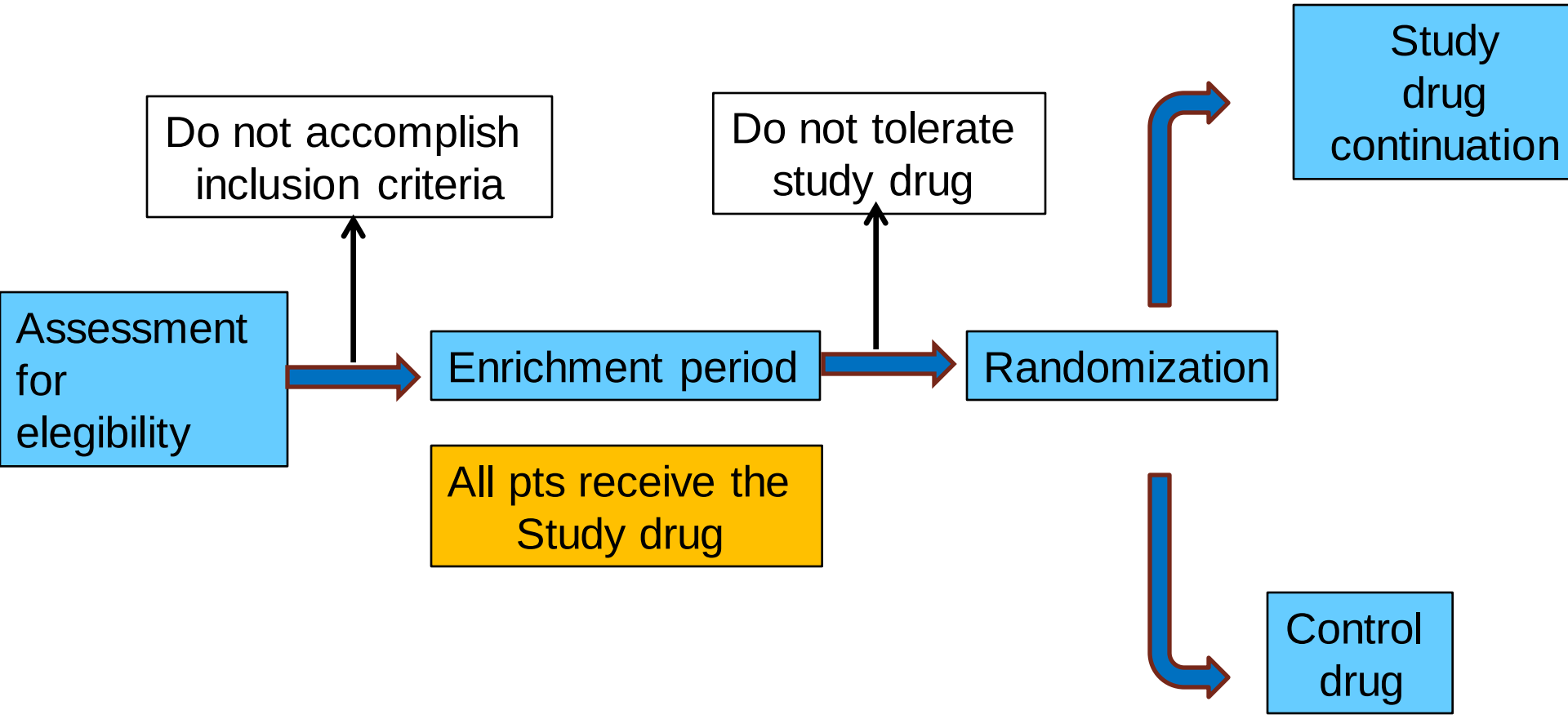
MMAS-4
1. Do you ever forget to take your medicine?
2. Are you careless at times about taking your medicine?
3. When you feel worse taking your medicine, do you stop taking it?
4.) When you feel better do you sometimes stop taking your medicine?

Adherence	MMAS-4 Score
High Adherence	0
Medium Adherence	1-2
Low Adherence	3-4

Byass due to different compliance in study arms



Enrichment strategy to include patients that tolerate the treatment



Summary

Surrogates with high prevalence
- risk stratification
- composite variables

Surrogates can only be characterized in clinical trials

Long term follow up is necessary to validate surrogates

Non compliance a major source of byass in trials