Ottawa Hospital
Research Institute
Institut de recherche
de l'Hôpital d'Ottawa

Potential Primary Endpoints in Clinical Trials of Antibody-Mediated Rejection

FDA WORKSHOP on ANTIBODY MEDIATED REJECTION IN KIDNEY TRANSPLANTATION

April 12-13, 2017

Greg Knoll MD MSc
Professor of Medicine, University of Ottawa
Senior Scientist, Ottawa Hospital Research Institute

Disclosure Slide

- **Research Grant Support**
  - **Astellas Canada**
  - **Canadian Institutes of Health Research**

- **No other relevant disclosures**

Allograft Survival

The New England
Journal of Medicine

Volume 309 OCTOBER 6, 1983 Number 14

A RANDOMIZED CLINICAL TRIAL OF CYCLOSPORINE IN CADAVERIC RENAL TRANSPLANTATION

THE CANADIAN MULTICENTRE TRANSPLANT STUDY GROUP

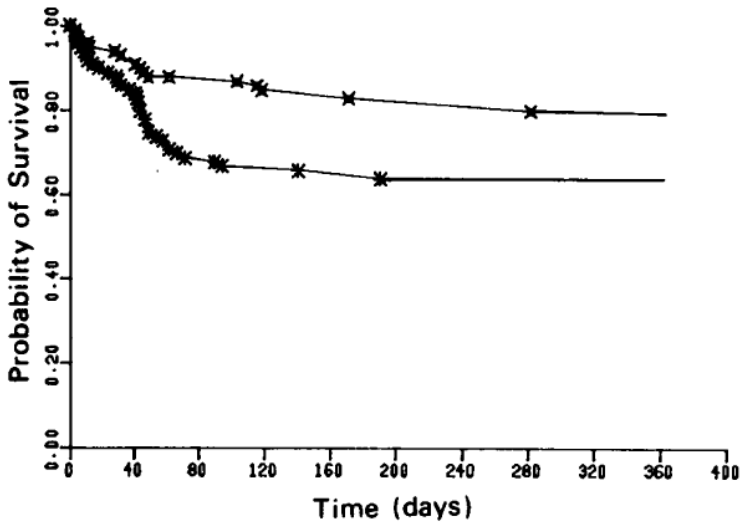


Figure 1. Product-Limit Estimates for Graft Survival in Cyclosporine-Treated Patients (Upper Curve) and Patients Given Standard Therapy (Lower Curve).

1-year Graft Survival
80.4% vs 64.0%
(P=0.005)

Types of Outcome Measures

- **Clinical Endpoint (Patient-important outcome)**
  - Characteristic that reflects how a patient feels, functions or how long they survive
    - Graft survival, patient survival, quality of life
- **Biomarker**
  - Characteristic that is objectively measured as an indicator of normal biologic processes, pathogenic processes or response to therapy
    - Serum creatinine, GFR, proteinuria, BP etc
- **Surrogate End-Point**
  - Biomarker that is used as a substitute for a clinical endpoint.
    - A true surrogate is expected to predict benefit/harm.

Surrogate End-Points

Advantages:

- ✓ **Usually measured earlier in a trial compared to clinical endpoints**
  - **Allows for shorter, cheaper trials to be conducted**
  - **Results in faster decision-making about treatments - (Phase I/II)**

- ✓ **Typically surrogates are continuous variables so all patients in the trial will have an "event"**
  - **Greatly reduces sample size, increases power and reduces cost**

Surrogate End-Points

Disadvantages:

- ✓ **Most biomarkers are NOT valid surrogate endpoints**
- ✓ **Surrogates are difficult to actually validate**
  - **Must be prognostic for a hard, clinical endpoint**
  - **Changes in the surrogate endpoint with treatment must predict changes in the occurrence of clinical endpoints**
  - **Full effect of the treatment on a clinical endpoint should be captured by the surrogate**

Invalid Surrogates may Misrepresent the True Consequences of an Intervention

Bad Surrogate Endpoints

Table 1. Examples of putative surrogate endpoint failures

Disease	Treatment	Effects on		Trials or analyses
		Surrogate endpoint	Clinical endpoint	
Postmyocardial infarction	Anti-arrhythmic agents	Reduced ventricular arrhythmia	Increased sudden death	CAST[41]
Atrial fibrillation	Quinidine	Maintained sinus rhythm at 1 year	Increased mortality	Meta-analysis[2]
Congestive heart failure	Milrinone/Flosequinan/ Epoprostenol	Improved cardiac output/ increased exercise tolerance	Increased mortality	PROMISE[87] PROFILE[88] FIRST[89]
Heart disease in postmenopausal women	Hormone replacement therapy	Favorable effect on serum lipoprotein level	Increased coronary heart disease/myocardial infarction	HERS[90] WHIT[91] PEPI[92]
Heart disease	Cholesterol-lowering agents	Lowering cholesterol level	Increased mortality	WHO[93] Gordon meta-analysis[94]
Osteoporosis	Sodium fluoride	Increased bone mineral density	Increased fracture incidences	[95]
HIV	Zidovudine	Lowering CD4+ cell counts	Failed to reduce opportunistic infection	British-French Concord Trial[96]
Normotensive patients	Management of glaucoma	Lowering intraocular pressure	No effect of treatment on long-term visual field loss	[8]

What Clinical Endpoints are Important to Transplant Patients?

- **Patient Survival**
- **Allograft Survival**
  - Accounts for both Patient Death and Graft Failure
  - Marker of Quality of Life
    - "Time off dialysis" while allograft functioning
  - Marker of Cost
    - Functioning transplant less costly than dialysis
  - 1-year allograft survival has been most commonly used
    - Difficult to use as an endpoint given improvements in early graft survival over time
    - To demonstrate further improvements will require sample sizes that are not feasible

Kidney Transplantation Outcomes

- **Overall** (deceased + living donor combined)
  - 1-year graft survival 94% (SRTR Website)

- **ABMR**
  - Most graft failures occur later
  - 1-year graft survival ~90%

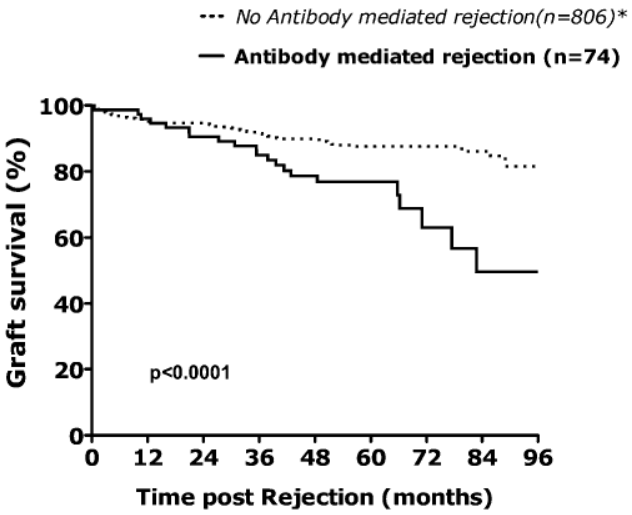
Sample Size Estimates for an ABMR Trial

Superiority Trial

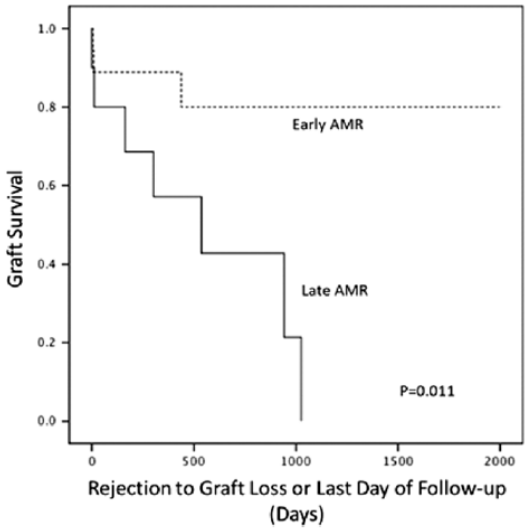
Current 1-yr Graft Survival	Sample Size Required to Show an Improvement in 1-yr Graft Survival to:			
90%	92%	94%	96%	98%
	6,426	1,442	566	276

RITUX ERAH Study
n = 38 patients
(21 Transplant Centers)
(target sample size = 64)

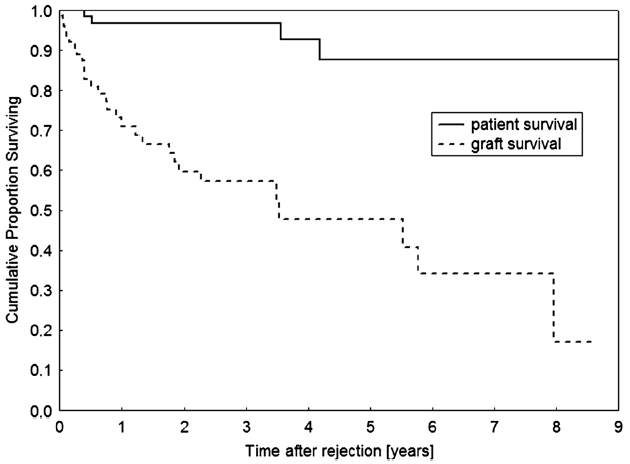
What about Late Allograft Survival as an Endpoint? Outcomes not Clear



J Am Soc Nephrol 25: 2267–2277, 2014.



Transplantation ■ October 2015 ■ Volume 99 ■ Number 10



Ther Apher Dial, Vol. 20, No. 3, 2016

ABMR Outcomes

- Depends on timing of when it occurs: Early vs. Late
- Depends on treatments given
- Due to non-adherence or not

Sample Size Estimates for an ABMR Trial

Superiority Trial

Current 5-yr Graft Survival	Sample Size Required to Show an Improvement in 5-yr Graft Survival to:				
	↑2%	↑10%	↑20%	↑25%	↑50%
50%	51%	55%	60%	63%	75%
	78,480	3,130	776	456	116

RITUX ERAH Study
n = 38 patients
(21 Transplant Centers)
(target sample size = 64)

Graft Survival will Not be a Useful Endpoint for ABMR Trials

- **It will be difficult for new interventions to show a reasonable treatment effect at 1-year or even 5-years using a realistic sample size**
  - **It is unlikely that a new drug to prevent/treat ABMR will be so good that graft survival jumps from 90 to 98% at 1-year or 50 to 60% at 5-years**

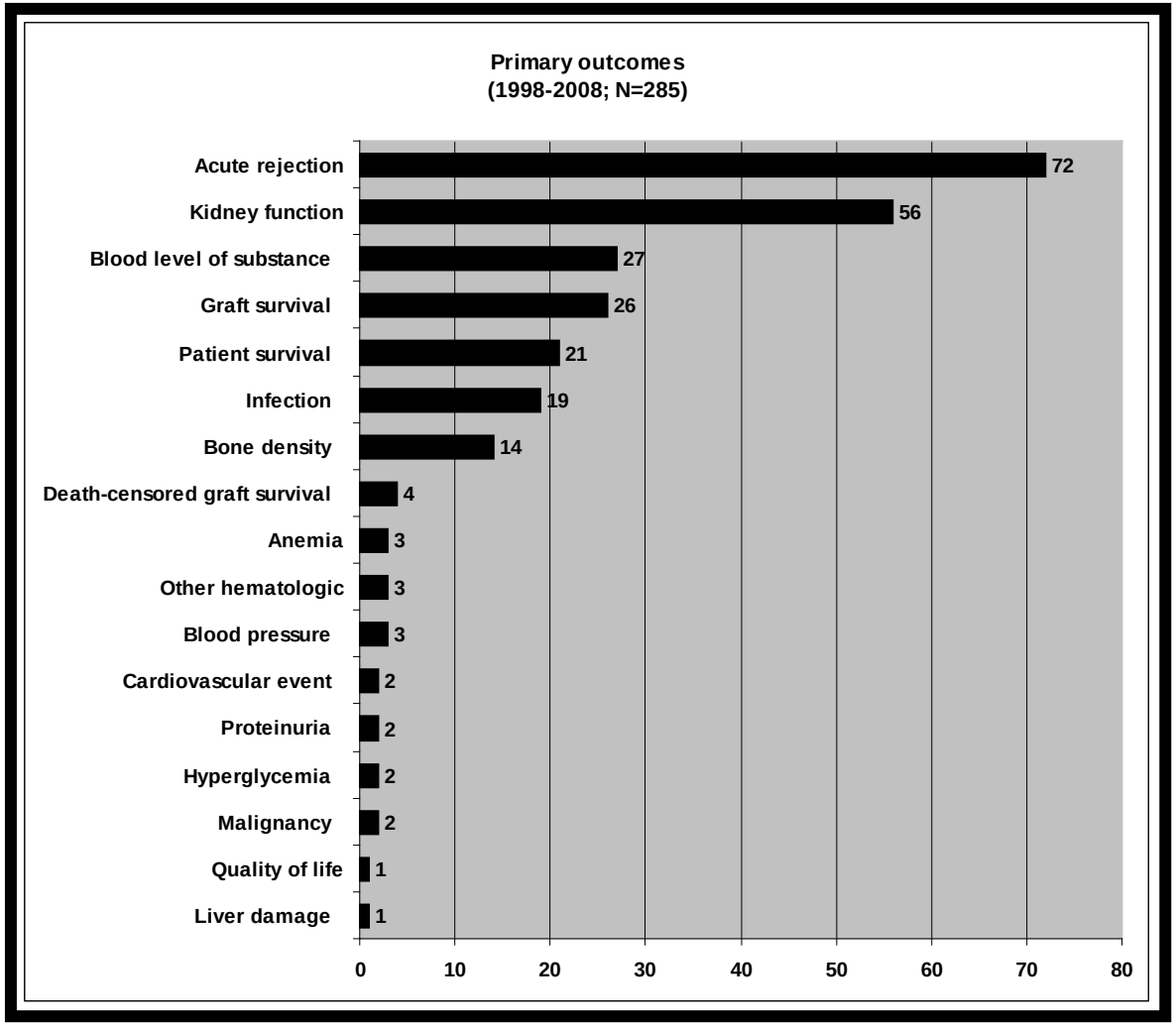
- **Most interventions will likley produce more modest, incremental improvements**
  - **Sample sizes for these studies are just not feasible**

What is the Ideal Endpoint for ABMR Trials?

- **Histology**: freedom from or resolution of ABMR or components (e.g. C4d); freedom from transplant glomerulopathy
- **Conventional Biomarker**: GFR, proteinuria
- **'New' Biomarker**: Prevention/Reduction of Donor Specific Antibody (DSA), complement fixing DSA (C1q binding), gene transcript (mRNA) expression

These Endpoints are all Surrogates Outcome Measures

Most Kidney Transplant Trials do NOT Measure Clinical Endpoints



Systematic Review

All RCTs 1998-2008

N=285

Primary Outcome

Clinical Endpoint: 22%

Surrogate: 78%

Candidate Endpoints for ABMR Trials

Clinical "Hard" Endpoints

- ✓ Patient survival
- ✓ Graft survival
- ✓ Quality of Life

Feasibility Issues

Important but more relevant once we have proven treatments to choose from

Surrogate Endpoints

- ✓ Kidney Function (GFR)
- ✓ Histology
- ✓ Donor Specific Antibody
- ✓ Gene Expression
- ✓ Proteinuria

Is Kidney Function a Valid Surrogate Outcome Measure?

Use of Kidney Function End Points in Kidney Transplant Trials: A Systematic Review

Christine A. White, MD, MSc,[1] Deborah Siegal, MD, MSc,[1] Ayub Akbari, MD, MSc,[2,3] and Greg A. Knoll, MD, MSc[2,3,4]

Kidney Function Endpoints are Common in Transplant Trials

	Primary End Point	Secondary End Point	Other End Point
SCr-based Estimation Equation	21 (57)	48 (59)	15 (37)
4-variable MDRD Study	2	6	0
Cockcroft-Gault	13	28	9
Nankivell	6	11	3
Unknown/other	3	8	1
SCr	18 (49)	57 (70)	30 (73)
mGFR	7 (19)	7 (9)	0 (0)
^{51}Cr-EDTA	2	2	0
Iohexol	2	2	0
^{125}I-iothalamate	1	0	0
Iothalamate	0	1	0
Combination of tracers	1	2	0
Isotopic	1	0	0
SCysC	1 (3)	1 (1)	0 (0)
Measured CCr/unspecified MDRD Study	2 (5)	4 (5)	2 (5)

Marker of kidney function used in 79% of RCTs

eGFR used in 61% of RCTs as primary or secondary outcome

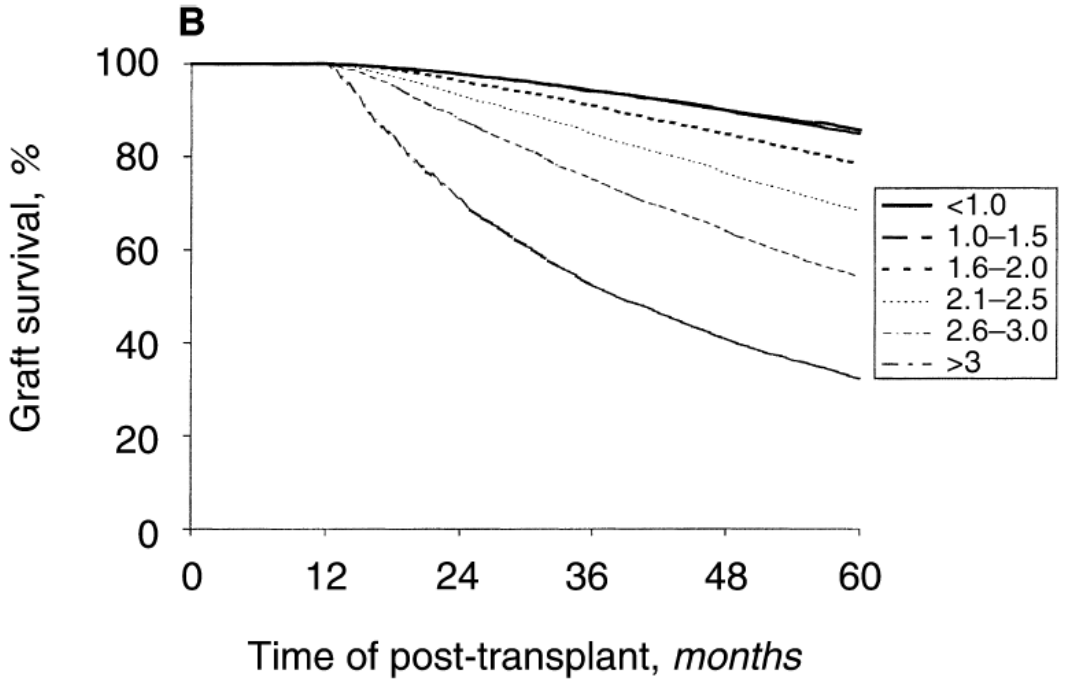
American Journal of Kidney Diseases, Vol 56, No 6 (December), 2010: pp 1140-1157

Is Kidney Function a Valid Surrogate Outcome?

Is Reduced Kidney Function Associated with Worsening Graft Survival?

Post-transplant renal function in the first year predicts long-term kidney transplant survival

SUNDARAM HARIHARAN, MAUREEN A. MCBRIDE, WIDA S. CHERIKH, CHRISTINE B. TOLLERIS, BARBARA A. BRESNAHAN, and CHRISTOPHER P. JOHNSON



Strong association between 1-year serum creatinine and long-term renal graft survival

Authors Conclusion: "….the quality of renal function (creatinine ≤ 1.5 mg/dL at 1 year) should be implemented as a newer endpoint for primary comparative trials"

Kidney International, Vol. 62 (2002), pp. 311–318

Is Kidney Function a Valid Surrogate Outcome?

Rationale for Kidney Function as a Surrogate Endpoint:

Improve Early Renal Function and you will Improve Long-term Graft Survival

Is this Rationale True in RCTs?

Symphony Trial: Tacrolimus-Based Regimen Improved GFR

Table 2. Primary End Point and Selected Secondary End Points.*

End Point	Standard-Dose Cyclosporine (N=390)	Low-Dose Cyclosporine (N=399)	Low-Dose Tacrolimus (N=401)	Low-Dose Sirolimus (N=399)	P Value†
Primary end point					
Mean calculated GFR — ml/min‡	57.1±25.1	59.4±25.1	65.4±27.0	56.7±26.9	<0.001
P value for comparison with tacrolimus	<0.001	0.001	Reference	<0.001	

N Engl J Med 2007;357:2562-75.

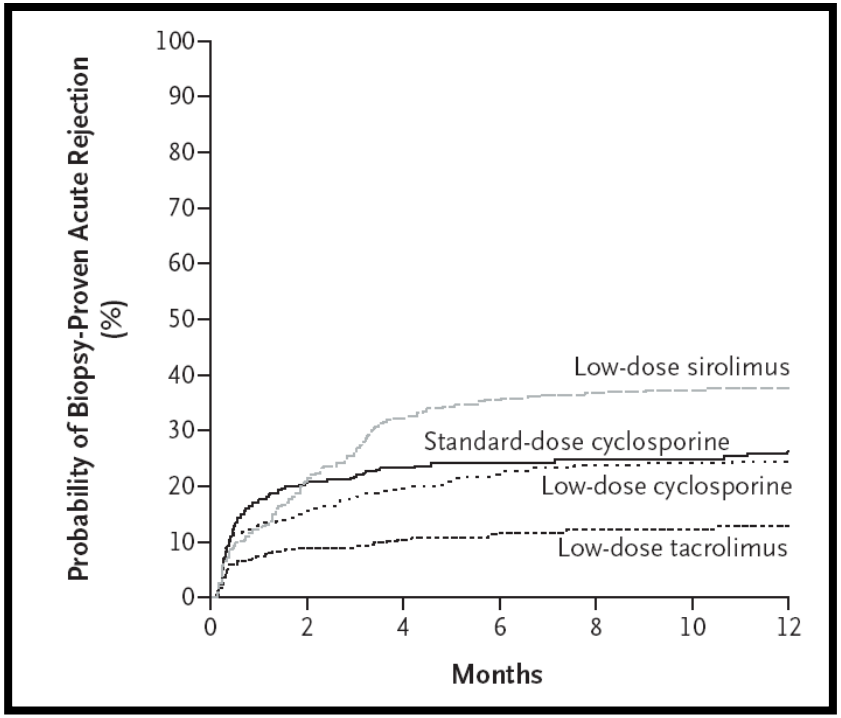
Tacrolimus-Based Regimen Also Associated with Better Allograft Survival

	Standard-Dose Cyclosporine (N = 390)	Low-Dose Cyclosporine (N = 399)	Low-Dose Tacrolimus (N = 401)	Low-Dose Sirolimus (N = 399)	P Value†
Allograft survival‖					
Censored for death of patients with functioning allograft — %	91.9	94.3	96.4	91.7	0.02
P value for comparison with tacrolimus	0.007	0.18	Reference	0.007	
Uncensored for death of patients with functioning allograft — %	89.3	93.1	94.2	89.3	0.02
P value for comparison with tacrolimus	0.01	0.56	Reference	0.01	

N Engl J Med 2007;357:2562-75.

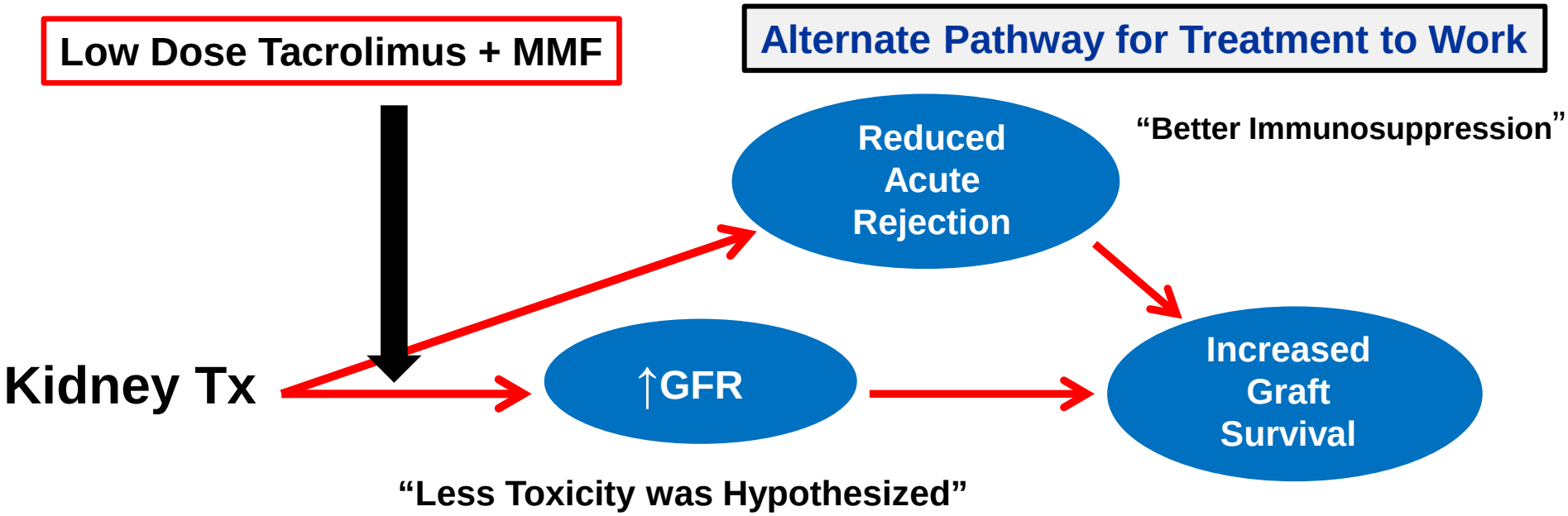
Is Kidney Function a Valid Surrogate Outcome?

- Is the full effect of treatment on clinical endpoint *(graft survival)* captured by the surrogate *(GFR)*?
- Not entirely clear
- Tacrolimus also significantly reduced acute rejection – maybe this was the pathway to improved graft outcome??



N Engl J Med 2007;357:2562-75.

Is GFR a Valid Surrogate Outcome?



Comparison of the Predictive Performance of eGFR Formulae for Mortality and Graft Failure in Renal Transplant Recipients

eGFR is Strongly Associated with Mortality and Graft Loss

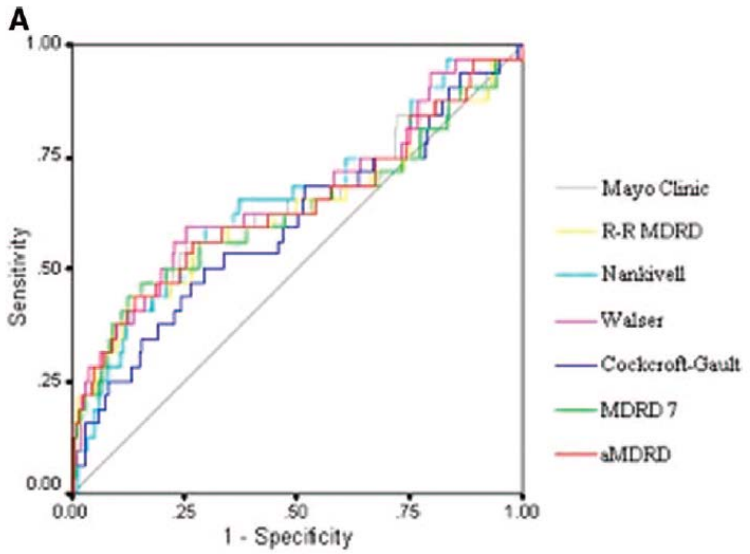
TABLE 2. Mortality: Cox model

Formula studied	Variable	HR	95% CI	*P*
Cockcroft-Gault	eGFR	0.96	0.95–0.98	<0.0001
Walser	eGFR	0.96	0.95–0.98	<0.0001
Nankivell	eGFR	0.97	0.95–0.98	<0.0001
MDRD 7	eGFR	0.97	0.96–0.98	<0.0001
aMDRD	eGFR	0.97	0.96–0.99	0.0004
RR-MDRD	eGFR	0.97	0.96–0.98	0.0001
Mayo Clinic	eGFR	0.97	0.96–0.98	<0.0001

Transplantation 2009;87: 384–392

Comparison of the Predictive Performance of eGFR Formulae for Mortality and Graft Failure in Renal Transplant Recipients

3-year Death-Censored Graft Survival



	c-statistic	95% CI
Cockcroft-Gault	0.597	0.486, 0.709
MDRD 7	0.626	0.504, 0.748
Rule's Refitted MDRD	0.628	0.508, 0.748
Abbreviated MDRD	0.639	0.521, 0.756
Mayo Clinic	0.642	0.525, 0.758
Nankivell	0.650	0.542, 0.758
Walser	0.657	0.544, 0.770

n=1,344 patients

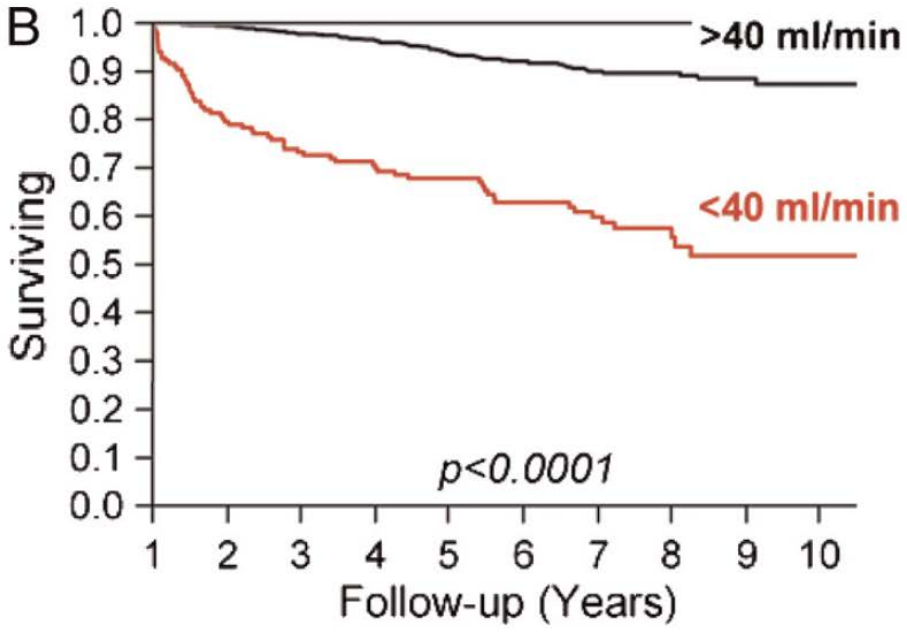
Predictor: 6-month eGFR

Prediction of 5-year graft survival even worse

Transplantation 2009;87: 384–392

Identification and Characterization of Kidney Transplants With Good Glomerular Filtration Rate at 1 Year But Subsequent Progressive Loss of Renal Function

B



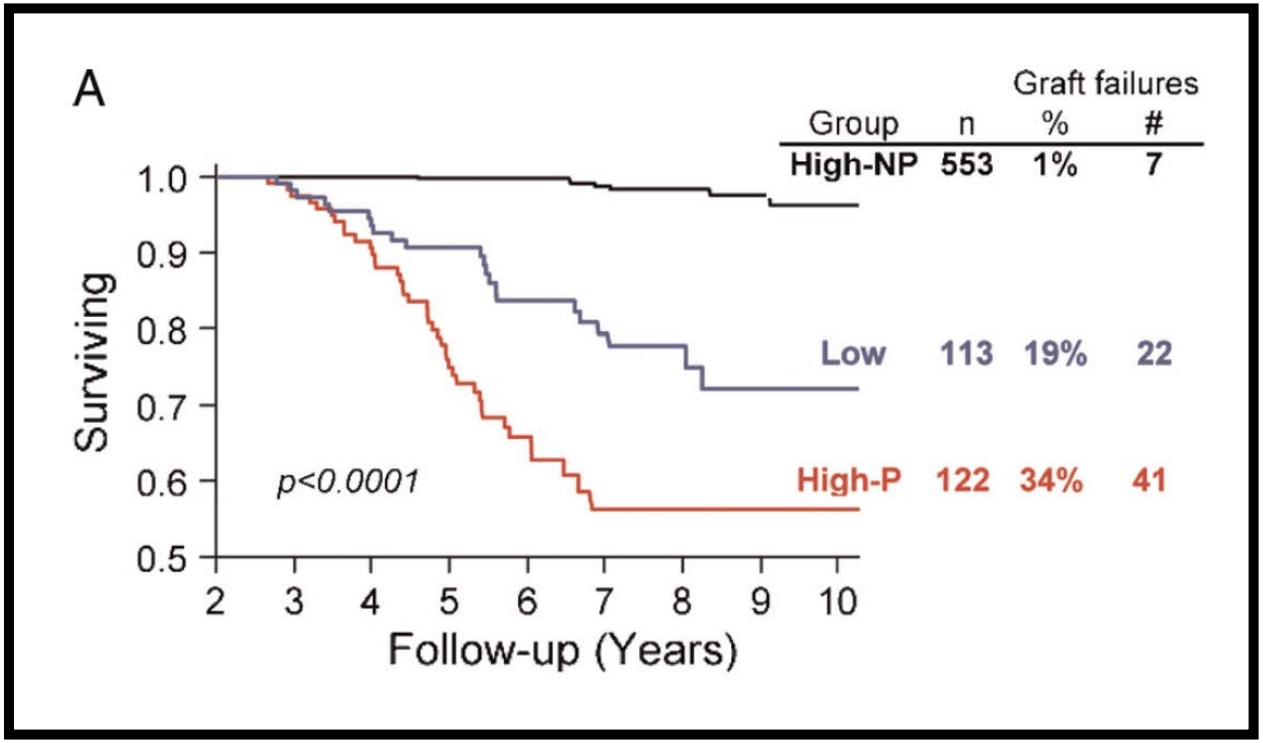
C

	1 year eGFR	
	>40	<40
Interval	(n=729)	(n=167)
Fail 1-2.5 yr	10	38
Fail 2.5-5 yr	32	14
Fail >5 yr	21	14
Total	63	66
	49%	51%

49% of graft failure in this series occurred in patients thought to have an excellent prognosis – i.e. Those with GFR > 40 at 1-year

Transplantation 2012;94: 931–939

Identification and Characterization of Kidney Transplants With Good Glomerular Filtration Rate at 1 Year But Subsequent Progressive Loss of Renal Function



Patients with Good GFR at 1-year who Progressed (High-P) had More Graft Loss than the Low GFR Group

Although not Intuitive, Early Renal Function tells us Little about the Risk of Late Graft Failure in Many Patients

Why is the GFR at a fixed time often poorly predictive of long-term outcomes?

- **eGFR/creatinine may be a poor marker of true GFR**
- **“True GFR” may not reflect severity of underlying disease/pathology in the allograft**
- **One eGFR/creatinine value may not reflect true baseline or ‘steady state’**
- **Lots can occur after 6 or 12 months**
  - **Stop taking medication**
  - **Recurrent disease**
  - **Late rejection**
  - **Other medical complication: e.g. infection, cancer, NODAT, MI, CHF etc**

What about decline in kidney function over time

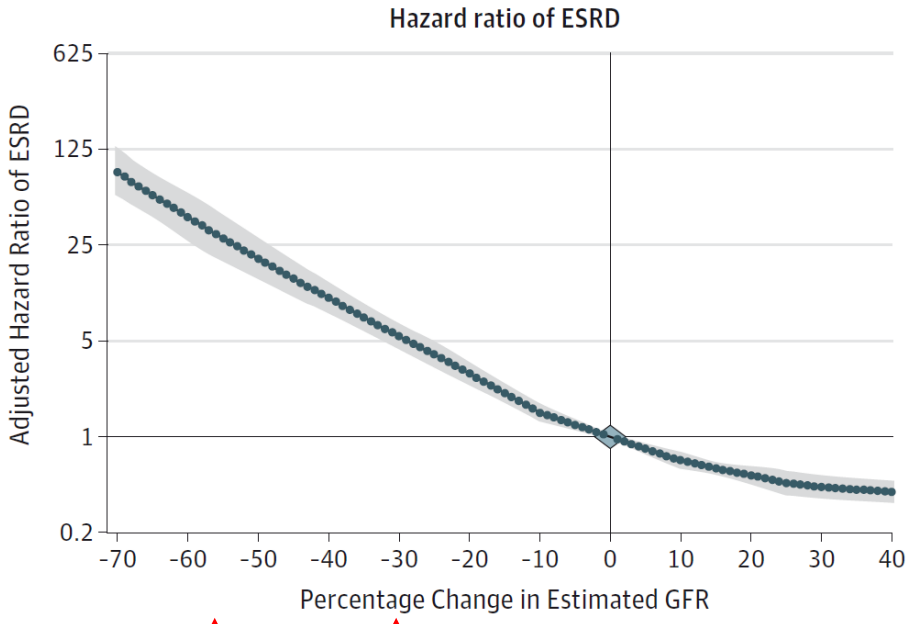
Is this more predictive?

Original Investigation

Decline in Estimated Glomerular Filtration Rate and Subsequent Risk of End-Stage Renal Disease and Mortality

Josef Coresh, MD, PhD; Tanvir Chowdhury Turin, MD, PhD; Kunihiro Matsushita, MD, PhD; Yingying Sang, MSc; Shoshana H. Ballew, PhD; Lawrence J. Appel, MD; Hisatomi Arima, MD; Steven J. Chadban, PhD; Massimo Cirillo, MD; Ognjenka Djurdjev, MSc; Jamie A. Green, MD; Gunnar H. Heine, MD; Lesley A. Inker, MD; Fujiko Irie, MD, PhD; Areef Ishani, MD, MS; Joachim H. Ix, MD, MAS; Csaba P. Kovesdy, MD; Angharad Marks, MBBCh; Takayoshi Ohkubo, MD, PhD; Varda Shalev, MD; Anoop Shankar, MD; Chi Pang Wen, MD, DrPH; Paul E. de Jong, MD, PhD; Kunitoshi Iseki, MD, PhD; Benedicte Stengel, MD, PhD; Ron T. Gansevoort, MD, PhD; Andrew S. Levey, MD; for the CKD Prognosis Consortium

Doubling of Cr (-57% decline in GFR) - Standard Kidney Function Endpoint



HR 32.1 (22.3 - 46.3)

HR 5.4 (4.5 - 6.4)

Examined lesser declines in GFR and association with ESRD

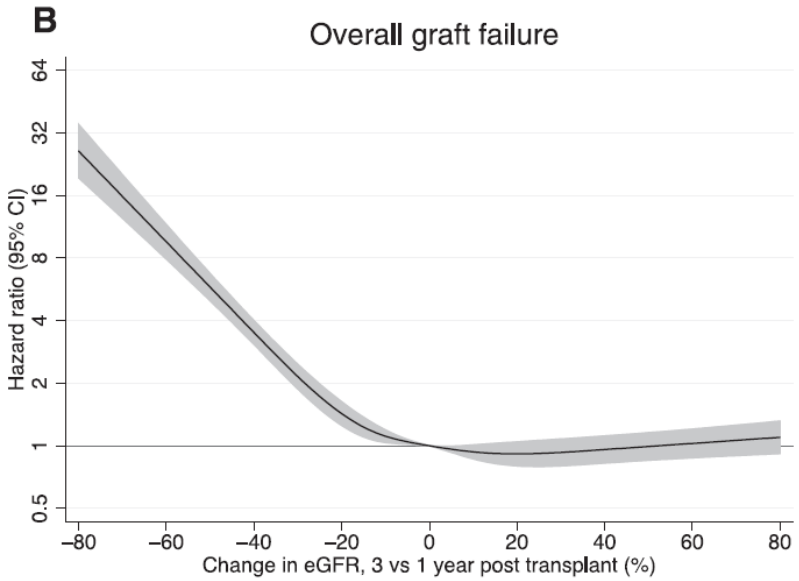
-57% decline or greater:
- **10-yr risk of ESRD 99%**
- **Occurred in 0.79%**

-30% decline or greater:
- **10-yr risk of ESRD 64%**
- **Occurred in 6.9%**

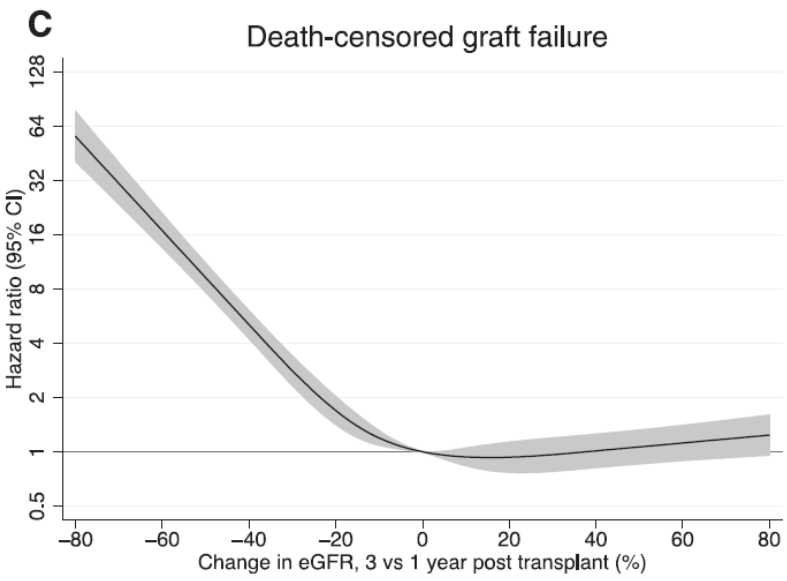
JAMA. 2014;311(24):2518-2531.

Relationship between eGFR Decline and Hard Outcomes after Kidney Transplants

Philip A. Clayton,*†‡ Wai H. Lim,*§ Germaine Wong,*‡‖ and Steven J. Chadban*



HR 3.58 (3.16 - 4.05)



HR 5.14 (4.44 - 5.95)

J Am Soc Nephrol 27: 3440–3446, 2016.

Relationship between eGFR Decline and Hard Outcomes after Kidney Transplants

Philip A. Clayton,*†‡ Wai H. Lim,*§ Germaine Wong,*‡‖ and Steven J. Chadban*†‡

eGFR Decline	Prevalence, %	Graft Failure		Patient Death	
		HR (95% CI)	*c* Statistic	HR (95% CI)	*c* Statistic
≥10%	33	2.09 (1.91 to 2.29)	0.68	1.52 (1.35 to 1.71)	0.75
≥20%	19	2.50 (2.26 to 2.77)	0.69	1.84 (1.62 to 2.10)	0.75
≥30%	10	3.58 (3.16 to 4.05)	0.70	2.20 (1.87 to 2.60)	0.75
≥40%	5	5.24 (4.43 to 6.20)	0.69	2.57 (2.04 to 3.22)	0.75
≥50%	3	7.90 (6.21 to 10.06)	0.67	2.96 (2.17 to 4.04)	0.75

Smaller Declines in GFR Occurred more Commonly

Similar Relationship: GFR Decline and Graft Failure; GFR Decline and Death

c-Statistics Similar – No Specific Cut Point was Better

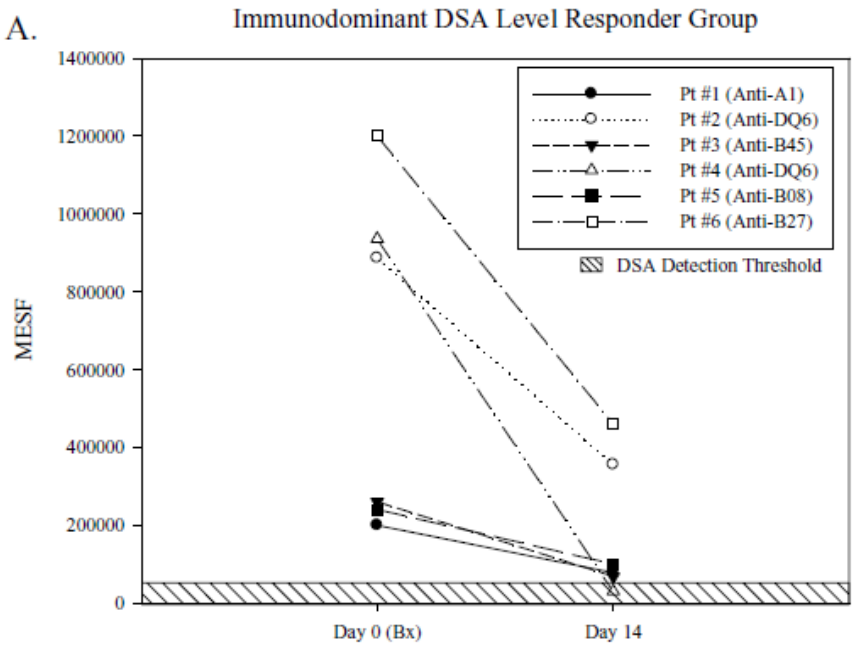
C-Statistics Good but not Great

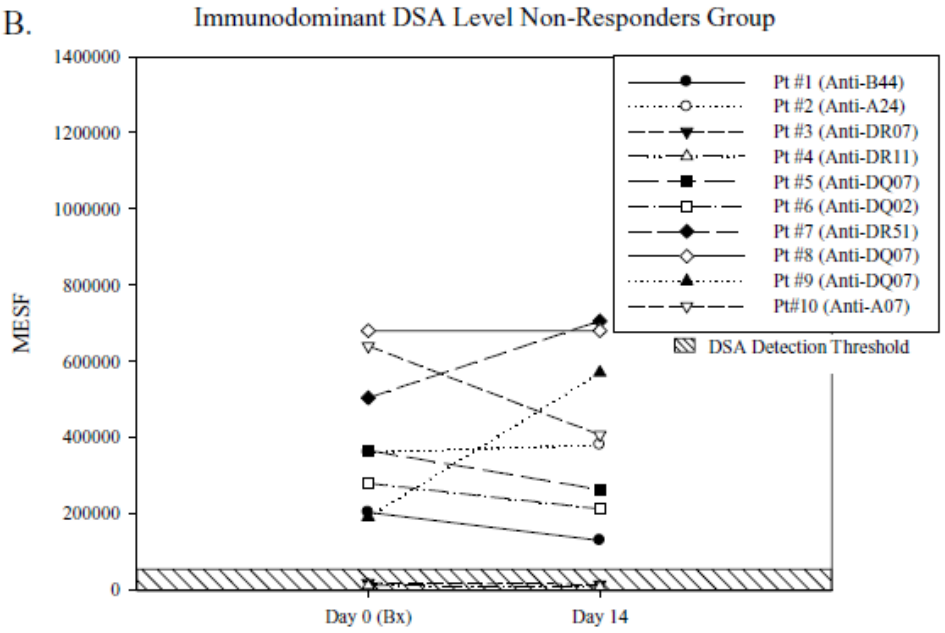
J Am Soc Nephrol 27: 3440–3446, 2016.

Is Donor Specific Antibody (DSA) a Valid Surrogate Outcome Measure?

Reducing De Novo Donor-Specific Antibody Levels during Acute Rejection Diminishes Renal Allograft Loss

M. J. Everly[a,*], J. J. Everly[a], L. J. Arend[c], P. Brailey[b], B. Susskind[b], A. Govil[d], A. Rike[a], P. Roy-Chaudhury[d], G. Mogilishetty[d], R. R. Alloway[d], A. Tevar[a] and E. S. Woodle[a,*]

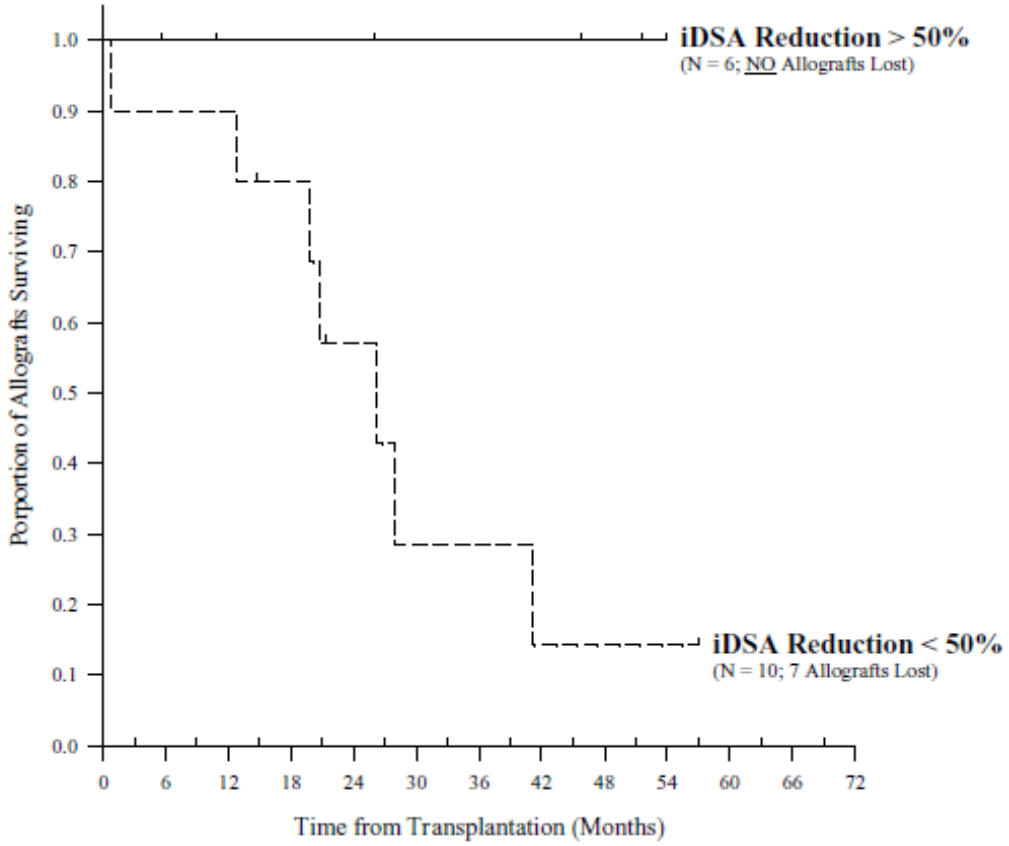




American Journal of Transplantation 2009; 9: 1063–1071

Reducing De Novo Donor-Specific Antibody Levels during Acute Rejection Diminishes Renal Allograft Loss

M. J. Everly[a,*], J. J. Everly[a], L. J. Arend[c], P. Brailey[b], B. Susskind[b], A. Govil[d], A. Rike[a], P. Roy-Chaudhury[d], G. Mogilishetty[d], R. R. Alloway[d], A. Tevar[a] and E. S. Woodle[a,*]



American Journal of Transplantation 2009; 9: 1063–1071

A Banff Component Scoring-based Histologic Assessment of Bortezomib-based Antibody-mediated Rejection Therapy

Basma Sadaka,[1] Nicole S. Ejaz,[2] Adele R. Shields,[2] Michael A. Cardi,[3] George Wadih,[4] David Witte,[5,6] Bassam G. Abu Jawdeh,[1] Rita R. Alloway,[1] and E. Steve Woodle[2]

1-year Graft Survival

>50% Reduction in DSA: 100%

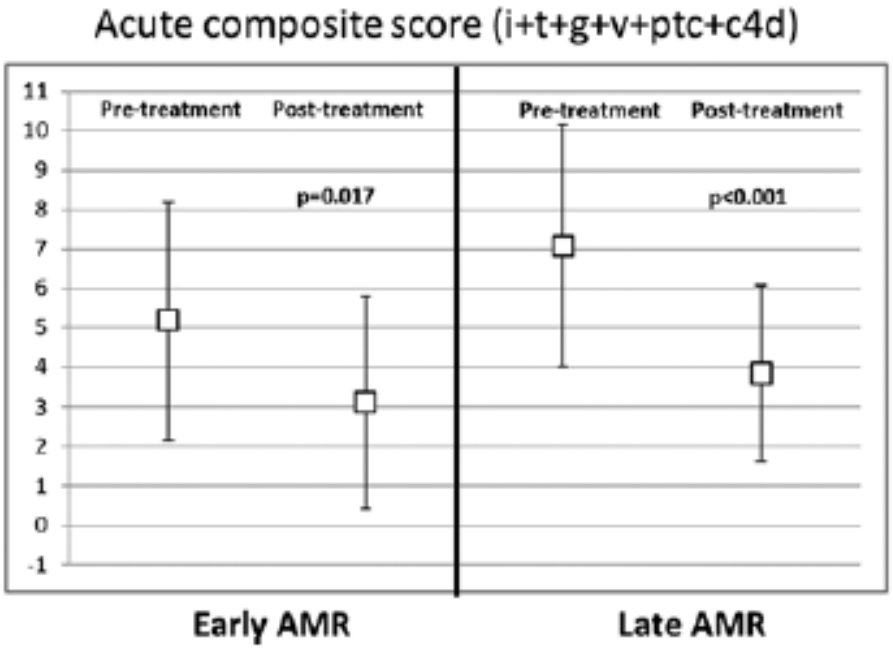
≤50% Reduction in DSA: 57.1%

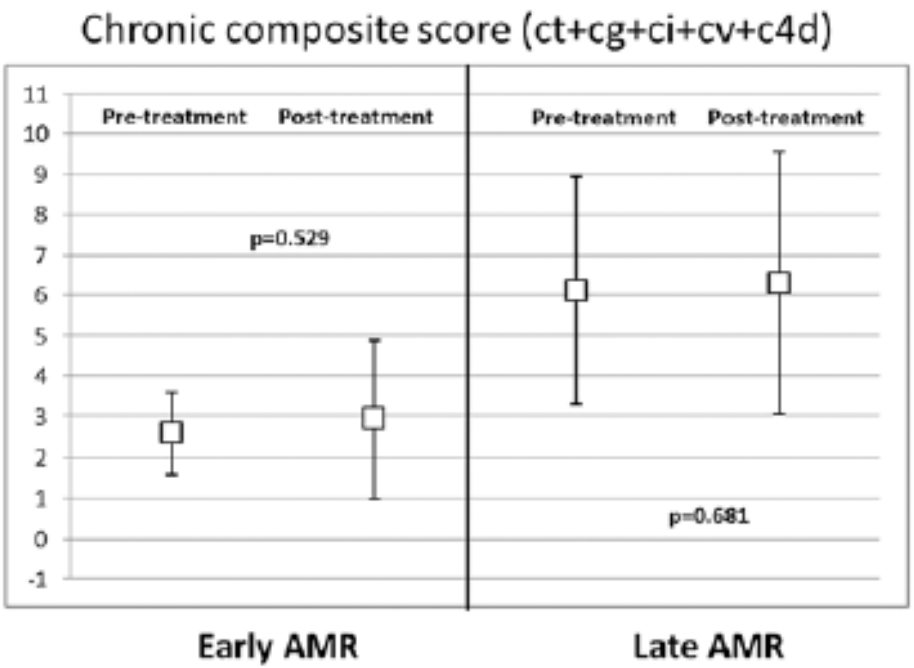
Transplantation ■ August 2015 ■ Volume 99 ■ Number 8

Are Histologic Markers Valid Surrogate Outcome Measures?

A Banff Component Scoring-based Histologic Assessment of Bortezomib-based Antibody-mediated Rejection Therapy

Basma Sadaka,[1] Nicole S. Ejaz,[2] Adele R. Shields,[2] Michael A. Cardi,[3] George Wadih,[4] David Witte,[5,6] Bassam G. Abu Jawdeh,[1] Rita R. Alloway,[1] and E. Steve Woodle[2]



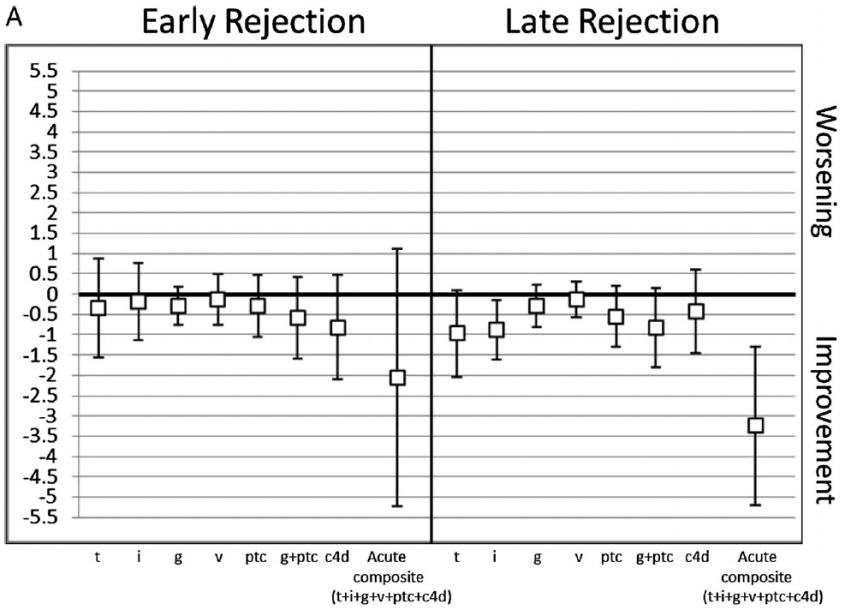


N=55 Treated with Bortezomib

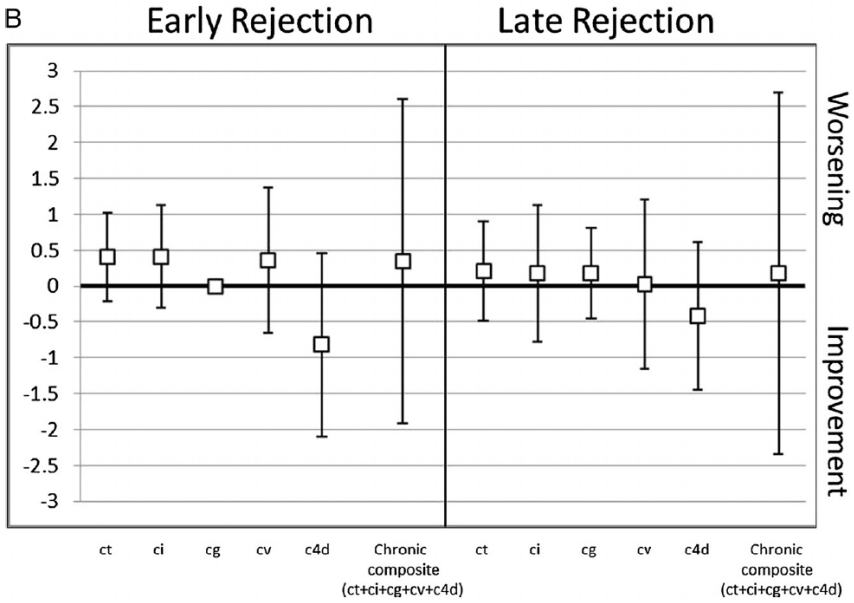
Pre-Post Treatment Biopsies

A Banff Component Scoring-based Histologic Assessment of Bortezomib-based Antibody-mediated Rejection Therapy

Basma Sadaka,[1] Nicole S. Ejaz,[2] Adele R. Shields,[2] Michael A. Cardi,[3] George Wadih,[4] David Witte,[5,6] Bassam G. Abu Jawdeh,[1] Rita R. Alloway,[1] and E. Steve Woodle[2]



Acute Scores



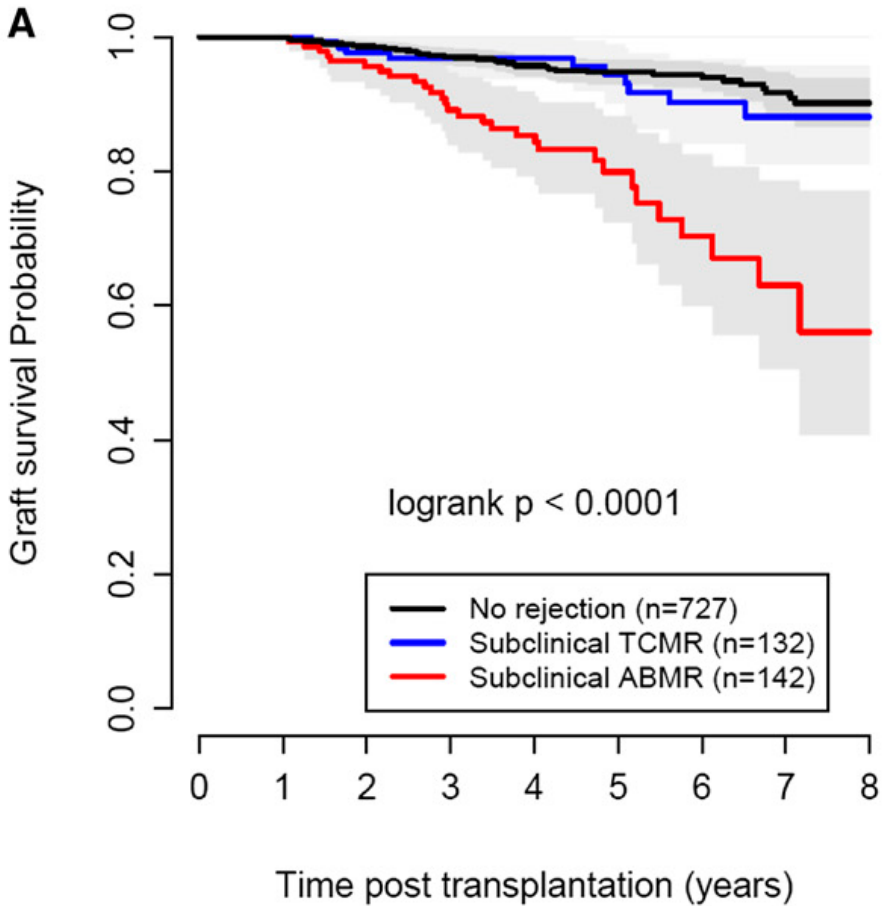
Chronic Scores

Acute Composite Score: Possible Surrogate?

Need Correlation with Late Graft Failure

Subclinical Rejection Phenotypes at 1 Year Post-Transplant and Outcome of Kidney Allografts

Alexandre Loupy,*† Dewi Vernerey,*‡ Claire Tinel,† Olivier Aubert,* Jean-Paul Duong van Huyen,*§ Marion Rabant,§ Jérôme Verine,‖ Dominique Nochy,¶ Jean-Philippe Empana,* Frank Martinez,† Denis Glotz,** Xavier Jouven,* Christophe Legendre,*† and Carmen Lefaucheur**



J Am Soc Nephrol 26: 1721–1731, 2015.

Subclinical Rejection Phenotypes at 1 Year Post-Transplant and Outcome of Kidney Allografts

Parameters	Number of Patients	Number of Events	HR	95% CI	*P* Value
eGFR at 1 yr, ml/min					
eGFR≥60	305	6	1	—	—
30≤eGFR<60	577	38	2.86	1.21 to 6.78	—
eGFR<30	79	28	11.42	4.55 to 28.65	<0.001
Subclinical ABMR					
No	825	45	1	—	
Yes	136	27	2.99	1.81 to 4.96	<0.001
Proteinuria at 1 yr (log_{10} value)	961	72	1.50	1.26 to 1.79	<0.001

Independent of GFR and proteinuria

Absence of ABMR on Biopsy – Possible Surrogate Outcome Measure?

J Am Soc Nephrol 26: 1721–1731, 2015.

Plasma-Derived C1 Esterase Inhibitor for Acute Antibody-Mediated Rejection Following Kidney Transplantation: Results of a Randomized Double-Blind Placebo-Controlled Pilot Study

Table 1: Antibody-mediated rejection scorecard based on biopsy characteristics

Characteristic	Definition
C4d score	Percent of PTC that stained positive for C4d (by immunofluorescence) (0–100%).
Margination score	Percent area (on the allograft biopsy section) involved in PTC margination, by neutrophils and/or monocytes (0–100%).
	Banff Classification (2,9) PTC (margination) score (0, 1, 2, or 3).
Glomerulitis score	Percent of glomeruli (on the allograft biopsy section) that had the appearance of active inflammation (0–100%).
Vasculitis score	Percent of intimal luminal reduction in diameter (0–100%) from the 1 artery (on the allograft biopsy section) considered by the pathologist to be the most damaged by arteritis (arterial inflammation).
	Any inflammation and/or fibrinoid necrosis of the smooth muscle wall on any artery on the section? (yes/no)
	Percent of arterioles affected by inflammation on the section (0–100%).
Glomerulosclerosis score	Percent of glomeruli (on the allograft biopsy section) that had glomerulosclerosis (0–100%).
Chronic glomerulopathy score	Percent of the most involved glomerulus (on the allograft biopsy section) with "double contouring" of the tuft (as determined by the pathologist; 0–100%).
Interstitial fibrosis score	Percent of the cortex (on the allograft biopsy section) that was fibrotic (0–100%).
Chronic vasculitis score	Percent of arterial lumen narrowing by fibrointimal thickening was recorded (0–100%) for the most severely involved artery (on the allograft biopsy section) as determined by the pathologist.

Montgomery et al *American Journal of Transplantation 2016; 16: 3468–3478*

Plasma-Derived C1 Esterase Inhibitor for Acute Antibody-Mediated Rejection Following Kidney Transplantation: Results of a Randomized Double-Blind Placebo-Controlled Pilot Study

Histopathology end point	Placebo (n = 9)			C1 INH (n = 9)			p-value for treatment difference[1]
	Qualifying biopsy	Day-20 biopsy	Change	Qualifying biopsy	Day-20 biopsy	Change	
C4d score							
Mean ± SD	60.8 ± 41.2	15.8 ± 32.9	−45.0 ± 46.9	68.7 ± 41.8	32.6 ± 39.1	−36.1 ± 33.4	0.6498
Margination score							
Mean ± SD	23.0 ± 24.8	17.0 ± 25.8	−6.0 ± 14.0	9.2 ± 15.2	21.8 ± 29.3	12.6 ± 25.9	0.0768
Glomerulitis score							
Mean ± SD	17.0 ± 24.9	23.7 ± 30.9	6.7 ± 26.6	16.3 ± 23.4	19.0 ± 28.8	2.7 ± 13.6	0.6928
Vasculitis score							
Mean ± SD	3.9 ± 7.8	0 ± 0.0	−3.9 ± 7.8	0 ± 0.0	3.2 ± 6.4	3.2 ± 6.4	0.0508
Glomerulosclerosis score							
Mean ± SD	4.2 ± 6.8	2.8 ± 3.6	−1.4 ± 7.8	8.9 ± 9.6	2.6 ± 4.3	−6.3 ± 7.9	0.2042
Chronic glomerulopathy score							
Mean ± SD	0.3 ± 1.0	0.6 ± 1.7	0.2 ± 0.7	0 ± 0.0	0 ± 0.0	0 ± 0.0	0.3322
Interstitial fibrosis score							
Mean ± SD	3.2 ± 6.6	9.1 ± 14.1	5.9 ± 9.8	0.7 ± 1.3	12.2 ± 20.4	11.6 ± 20.9	0.4723
Chronic vasculitis score							
Mean ± SD	8.3 ± 12.8	6.7 ± 11.7	−1.7 ± 18.2	2.6 ± 4.5	5.4 ± 7.7	2.9 ± 9.0	0.5103

None of the biopsy components improved by Day-20

6-month biopsy on subset of n=14 patients

C1 INH: 0/7 (0%) had TG

Placebo: 3/7 (43%) had TG

Montgomery et al *American Journal of Transplantation 2016; 16: 3468–3478*

C1 Inhibitor in Acute Antibody-Mediated Rejection Nonresponsive to Conventional Therapy in Kidney Transplant Recipients: A Pilot Study

D. Viglietti[1,2,†], C. Gosset[1,†], A. Loupy[2,3], L. Deville[4], J. Verine[5], A. Zeevi[6], D. Glotz[1], C. Lefaucheur[1,2,*]

	M0 n = 6	M+6 n = 6	p-value
Histological characteristics (Banff scores)			
g + ptc score, mean ± SD	3.7 ± 1.0	3.0 ± 1.1	0.1585
i + t score, mean ± SD	0.3 ± 0.8	0	0.3173
v score, mean ± SD	0.2 ± 0.4	0	0.3173
cg score, mean ± SD	0.3 ± 0.5	0.5 ± 0.5	0.3173
IF/TA score, ean ± SD	1.2 ± 0.4	1.7 ± 1.0	0.4235
cv score, mean ± SD	1.2 ± 0.4	1.5 ± 0.5	0.1573
C4d deposition, n (%)	5 (83.3)	1 (16.7)	0.0455

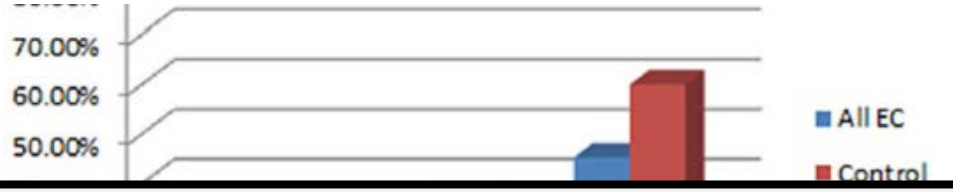
No change in histology except C4d (p=0.045)

GFR improved from 38.7±17.9 to 45.2±21.3 (p=0.027)

American Journal of Transplantation 2016; 16: 1596–1603

Terminal Complement Inhibition Decreases Antibody-Mediated Rejection in Sensitized Renal Transplant Recipients

M. D. Stegall[a,*], T. Diwan[a], S. Raghavaiah[a], L. D. Cornell[b], J. Burns[a,c], P. G. Dean[a], F. G. Cosio[d], M. J. Gandhi[b], W. Kremers[e] and J. M. Gloor[d]



Primary Endpoint: ABMR in first 3-months

Eculizumab: 7.7%

Control: 41%

Transplant Glomerulopathy in Controls vs. Eculizumab			
	3-4 months	1 year	2 year
All EC	0% (0/28)	26.7% (8/30)	45.4% (10/22)
Control	9.3% (4/43)	39.5% (15/38)	63.6% (21/33)
p-value (EC vs. control)	P=0.15	P=0.31	P=0.27

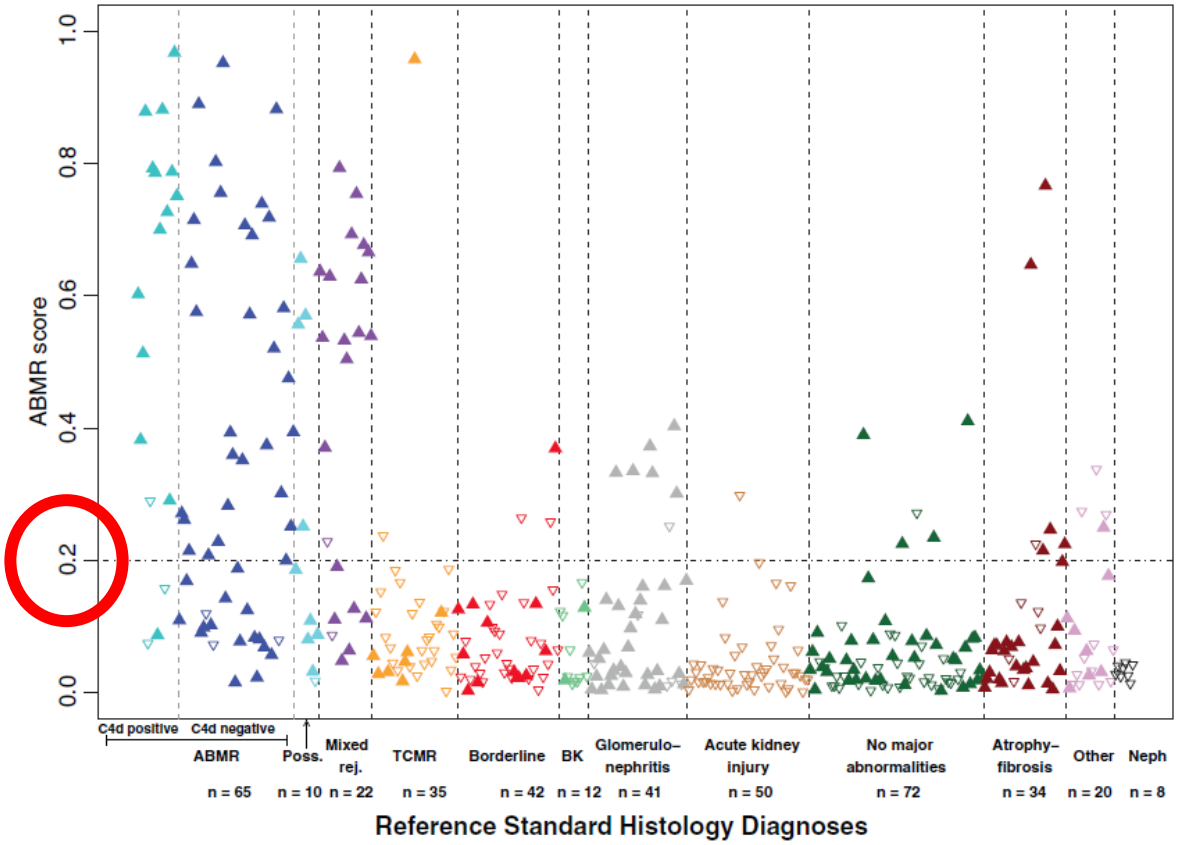
American Journal of Transplantation 2011; 11: 2405–2413

American Journal of Transplantation 2015; 15: 1293–1302

Are Gene Expression Measurements *('Molecular Microscope')* Valid Surrogate Outcome Measures?

Molecular Diagnosis of Antibody-Mediated Rejection in Human Kidney Transplants

J. Sellarés[a,b,†], J. Reeve[a,c,†], A. Loupy[d], M. Mengel[a,c], B. Sis[c], A. Skene[a,e], D. G. de Freitas[f], C. Kreepala[a,g], L. G. Hidalgo[a,c], K. S. Famulski[a,c] and P. F. Halloran[a,g,*]



The classifier output is a score between 0.0 - 1.0

Reflects the probability that ABMR is operating in the biopsy

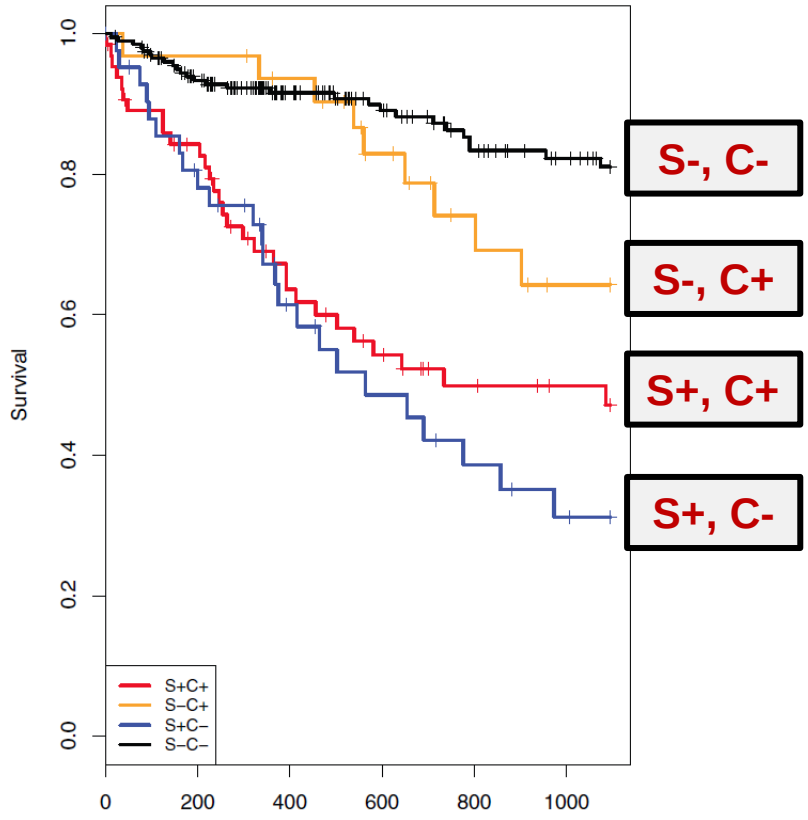
Score of 0.2 used as a threshold to define a case as positive for ABMR

AUC=0.89

American Journal of Transplantation 2013; 13: 971–983

Microarray Diagnosis of Antibody-Mediated Rejection in Kidney Transplant Biopsies: An International Prospective Study (INTERCOM)

P. F. Halloran[1,2,*], A. B. Pereira[1,3], J. Chang[1], A. Matas[4], M. Picton[5], D. De Freitas[5], J. Bromberg[6], D. Serón[7], J. Sellarés[7], G. Einecke[8] and J. Reeve[1,9]



S-, C-

S-, C+

S+, C+

S+, C-

S+ = ABMR score >0.2

S- = ABMR score <0.2

C+ = conventional histology + for ABMR

Any S+ *(ABMR score >0.2)* associated with a bad outcome

C+ on its own associated with late but not early failure

Perhaps ABMR Score could be a possible surrogate?

American Journal of Transplantation 2013; 13: 2865–2874

Composite End-Points for ABMR Trials

Advantages:

- Combine infrequent events together to allow sufficient sample sizes

Potential Disadvantages:

- Components of the endpoint not of similar importance
  - Is persistence of DSA the same as graft loss?
- Components may not occur with similar frequency
  - Often ‘less serious’ endpoint occurs most often
- Different relative risk reductions for each component of the composite
  - Ideal situation occurs when the biology of the components is similar enough so that each has a similar RRR

Predicting Individual Renal Allograft Outcomes Using Risk Models with 1-Year Surveillance Biopsy and Alloantibody Data

Manuel Moreno Gonzales,* Andrew Bentall,†‡ Walter K. Kremers,* Mark D. Stegall,* and Richard Borrows†‡

Clinical Factors: ACR, Serum Albumin, eGFR, Acute Rejection, Race, Sex, Age

Histology at 1-year: Glomerulitis, Chronic Interstitial Fibrosis (g and ci scores)

DSA: (Class II DSA Level)

JASN 27: 3165–3174, 2016

Predicting Individual Renal Allograft Outcomes Using Risk Models with 1-Year Surveillance Biopsy and Alloantibody Data

Risk Calculator

Accurate prediction of kidney transplant failure remains imperfect. A recent study by Borrows et al showed that data available 12 months post transplantation could usefully predict 5-year transplant failure.

The calculator below can be used to accurately predict 5-year death censored renal transplant survival with variables at 1 year post transplantation. For full details on the development the calculator and the statistical models involved we would direct the reader to the published article.

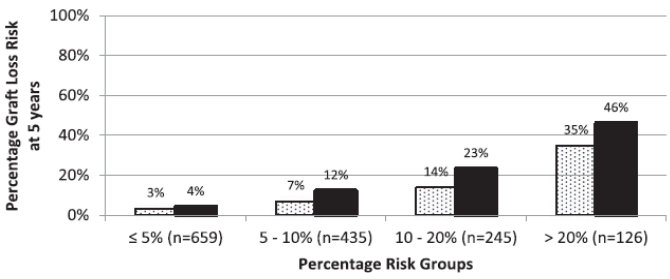
UACR (mg/mmol):	35.2
Albumin (g/L):	37
eGFR (ml/min):	40
Acute rejection (any severity):	No
Recipient Ethnicity:	Asian
Recipient sex:	Female
Recipient age (years):	45

5-year risk % death censored graft loss: 13.6

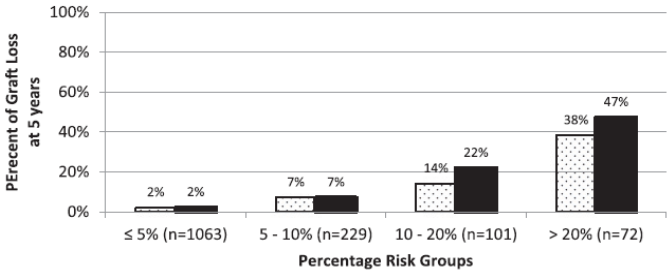
5-year risk % graft loss (including death with graft function): 14.8

Accepted input ranges are as follows
ACR: 0.1-1200 mg/mmol (please note units used)
Albumin: 10-60 g/L
eGFR: 5-120 ml/min (4-variable MDRD Study equation with IDMS-traceable creatinine)

Ethnicities other than White, South Asian, or Black) cannot be accounted for in the score, and therefore ethnicity should be entered as deemed appropriate based on clinical outcomes in that group



B



C

Overall Graft Failure c=0.78

Death-Censored Graft failure c=0.84

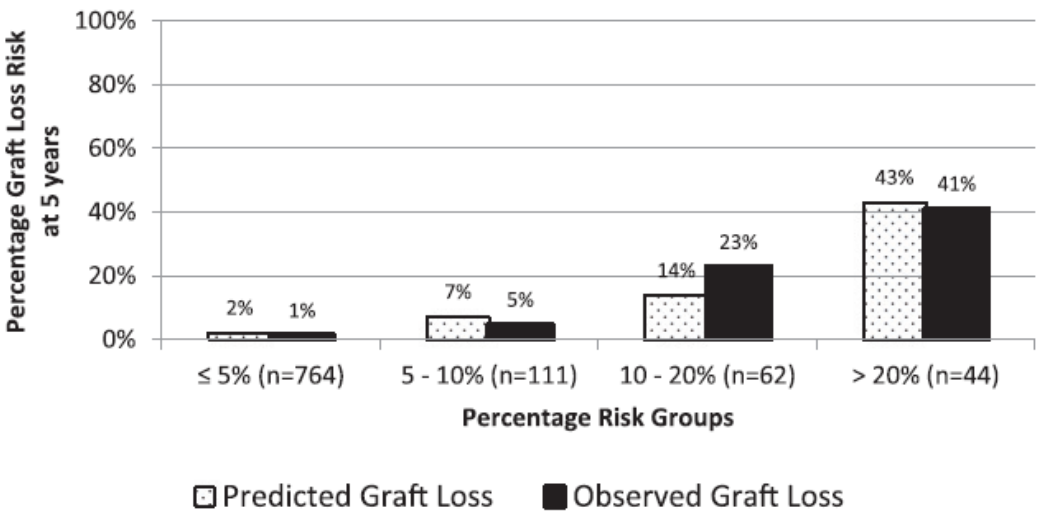
Model Performed Well Except Some Underestimation at Higher Risk Groups

JASN 27: 3165–3174, 2016

Predicting Individual Renal Allograft Outcomes Using Risk Models with 1-Year Surveillance Biopsy and Alloantibody Data

Manuel Moreno Gonzales,* Andrew Bentall,†‡ Walter K. Kremers,* Mark D. Stegall,* and Richard Borrows†‡

Death-Censored Graft Failure



Histology Added to the Model

Glomerulitis and Chronic Interstitial Fibrosis (g and ci scores)

c-Statistic Improved: 0.84 to 0.90

Adding DSA to the Model Did Not Improve Prediction (c=0.82)

JASN 27: 3165–3174, 2016

Molecular Microscope Strategy to Improve Risk Stratification in Early Antibody-Mediated Kidney Allograft Rejection

Alexandre Loupy,[*†] Carmen Lefaucheur,[†‡] Dewi Vernerey,[†§] Jessica Chang,[‖] Luis G. Hidalgo,[‖¶] Thibaut Beuscart,[†] Jerome Verine,[**] Olivier Aubert,[†] Sébastien Dubleumortier,[††] Jean-Paul Duong van Huyen,[*†‡‡] Xavier Jouven,[†] Denis Glotz,[†‡] Christophe Legendre,[*†] and Philip F. Halloran[‖§§]

Table 4. Determinants of kidney transplant graft outcome after acute ABMR (multivariate models) using the ABMR Molecular Score and endothelial DSA-selective transcripts

Parameters	Number of Patients	Number of Events	HR	95% CI	*P* Value
Model 1 with ABMR Molecular Score					
Donor age, yr					
<60	54	11	1	—	—
≥60	20	10	3.84	1.48 to 9.96	0.01
eGFR[a] (ml/min) at the time of rejection					
≥30	52	10	1		
<30	22	11	1.74	0.76 to 4.35	0.23
Humoral histologic score (g+ptc+v+cg+C4d)	74	21	1.43	1.09 to 1.90	0.01
ABMR Molecular Score	74	21	2.22	1.37 to 3.58	0.001

ABMR Molecular Score (*Independent of Histology*) Associated with Graft Failure

ABMR Score Improved Model Discrimination

AUC Significantly Improved from 0.77 to 0.81

Difference = 0.049 (0.047 to 0.052)

J Am Soc Nephrol 25: 2267–2277, 2014.

Is Proteinuria a Valid Surrogate Outcome Measure?

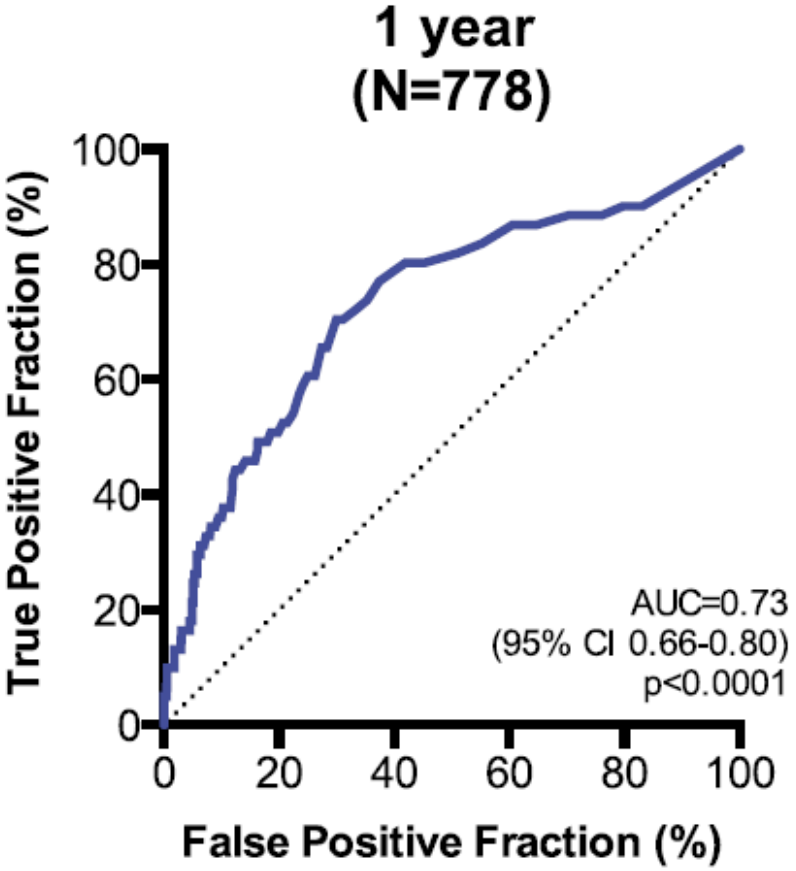
Proteinuria as a Noninvasive Marker for Renal Allograft Histology and Failure: An Observational Cohort Study

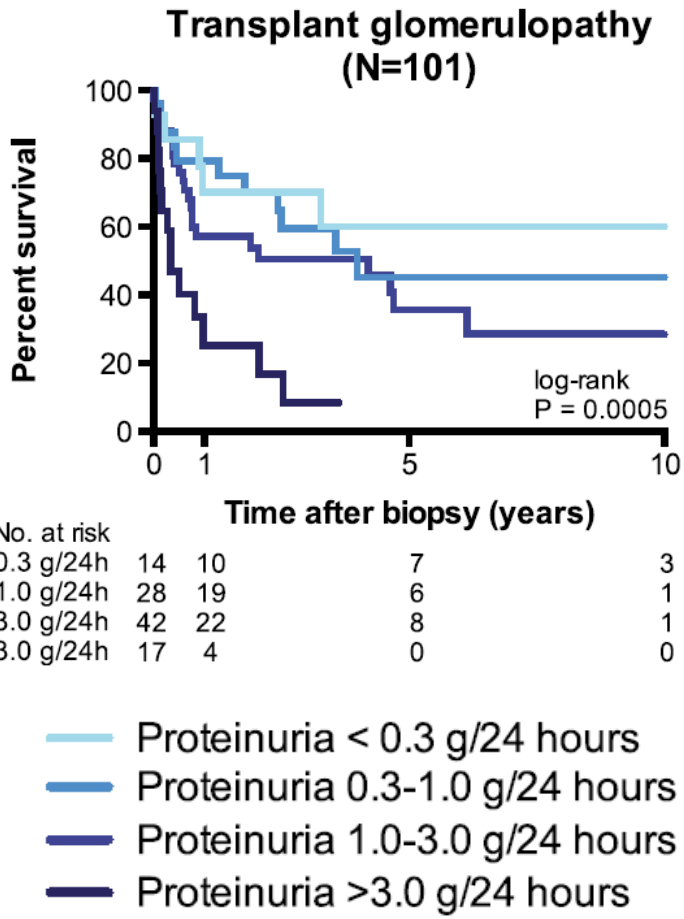
	Parameter	Adjusted Hazard Ratio (95% CI)	*P* Value
Model 2: With proteinuria			
Proteinuria at time of biopsy	0.3–1.0 versus <0.3 g/24 h	1.14 (0.81–1.60)	0.50
	1.0–3.0 versus <0.3 g/24 h	2.17 (1.49–3.18)	<0.001
	>3.0 versus <0.3 g/24 h	3.01 (1.75–5.18)	<0.001
eGFR at time of biopsy	30–45 versus >45 mL/min per m^2	1.76 (0.59–5.30)	0.31
	15–30 versus >45 mL/min per m^2	5.53 (1.99–15.4)	0.001
	<15 versus >45 mL/min per m^2	11.7 (4.17–33.0)	<0.001
Microcirculation inflammation	g+ptc ≥2 versus <2	1.36 (0.97–1.91)	0.07
IF/TA grade	Banff grade 1 versus 0	1.82 (1.25–2.64)	0.002
	Banff grade 2–3 versus 0	3.45 (2.34–5.07)	<0.001
Transplant glomerulopathy	Banff grade 1 versus 0	1.00 (0.55–1.82)	0.99
	Banff grade 2–3 versus 0	1.83 (1.11–3.04)	0.02
De novo/recurrent glomerular disease	Present versus absent	1.35 (0.84–2.19)	0.22
Polyomavirus associated nephropathy	Present versus absent	5.51 (3.06–9.92)	<0.001

Degree of Proteinuria (Independent of Histology) Associated with Graft Failure

J Am Soc Nephrol **27:** 281–292, 2016

1-yr Proteinuria Predictive of Graft Failure at 5-Yrs, Even in those Patients with TG





J Am Soc Nephrol **27:** 281–292, 2016

Which Outcome Measure to Use?

- **Depends on the Trial Purpose**
  - Prevention vs Treatment
- **Focus on Efficacy**
  - Safety endpoints equally important
  - Death, overall infections, BK, CMV, PTLD/Cancer
- **Suggestions for Discussion**
  - NONE are Properly Validated in Trials

ABMR "Treatment" Trial - Potential Composite Endpoint

- **>30% eGFR Decline (from study entry to 1-year later); or**
  (*Function Outcome*)

- **"Bad" features on 12-month Protocol Biopsy; or**
  - **Microvascular Inflammation (g and ptc scores)**
  - **C4d**
  - **TG (cg score)**

  (Histology Outcome)

- **ABMR Molecular Score >0.2 (1-y**
  (Molecular Outcome)

- **<50% Reduction in DSA; or**
  (DSA Outcome)

Completely Arbitrary Selection of Outcomes and Cut-Offs

We Need to Start Measuring Similar Outcomes Pre and Post-Treatment to Determine what is Responsive and Predictive

- **24-hr Protein > 500 mg at 1-yr if TG present on Bx**
  (Proteinuria/'Damage' Outcome)

ABMR "Prevention" Trials – Potential Endpoint

- **Clinical ABMR in the first year using current Banff criteria; or (*Histology + DSA Outcome*)**

- **"Bad" features on 12-month Protocol Biopsy; or**
  - **Microvascular Inflammation (g and ptc scores)**
  - **C4d**
  - **TG (cg score)**

  (Histology Outcome)

- **ABMR Score >0.2 on Protocol Bx; or**
  (Molecular Outcome)

- **Development of dnDSA; or**
  (DSA Outcome)

- **24-hr Protein > 500 mg at 1-yr if TG present on Bx (*Proteinuria/'Damage' Outcome*)**

Summary

- **It is difficult to use patient-important outcomes such as graft survival in ABMR trials given sample sizes required to show realistic treatment effects**
- **Surrogate endpoints are commonly used in renal transplant trials – especially measures of kidney function such as GFR**
- **While convenient from a sample size and power perspective, most surrogates are not well validated**

Summary

- **Surrogate outcomes and composite measures involving several surrogates will be necessary for ABMR trials**
- **Likely candidate outcomes for ABMR studies include GFR, histology, molecular transcripts, DSA and proteinuria as well as combinations of these endpoints**
- **Validation of these endpoints needs to occur – we need to begin measuring candidate outcomes before and after ABMR treatments to see how they respond**
- **Long-term follow-up will be needed for all ABMR trials using surrogates to evaluate their eventual effect on hard clinical endpoints such as graft survival**

Ottawa Hospital
Research Institute
Institut de recherche
de l'Hôpital d'Ottawa

Potential Primary Endpoints in Clinical Trials of Antibody-Mediated Rejection

FDA WORKSHOP on ANTIBODY MEDIATED REJECTION IN KIDNEY TRANSPLANTATION

April 12-13, 2017

Greg Knoll MD MSc
Professor of Medicine, University of Ottawa
Senior Scientist, Ottawa Hospital Research Institute