Heart Failure in Renal Transplant Recipients

KDIGO Controversies Conference on Heart Failure in Chronic Kidney Disease

May 27, 2017

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Co-Chair, KDIGO Guideline for the Evaluation of Candidates for Kidney Transplantation

Outline

- Prevalence of LV Dysfunction at Referral/Transplantation
- Pre-Transplant LV Function and Transplant Outcomes
- Effect of Kidney Transplantation on LV Function
- Treatment of CHF (ACE/ARBs) in the Kidney Transplant Population

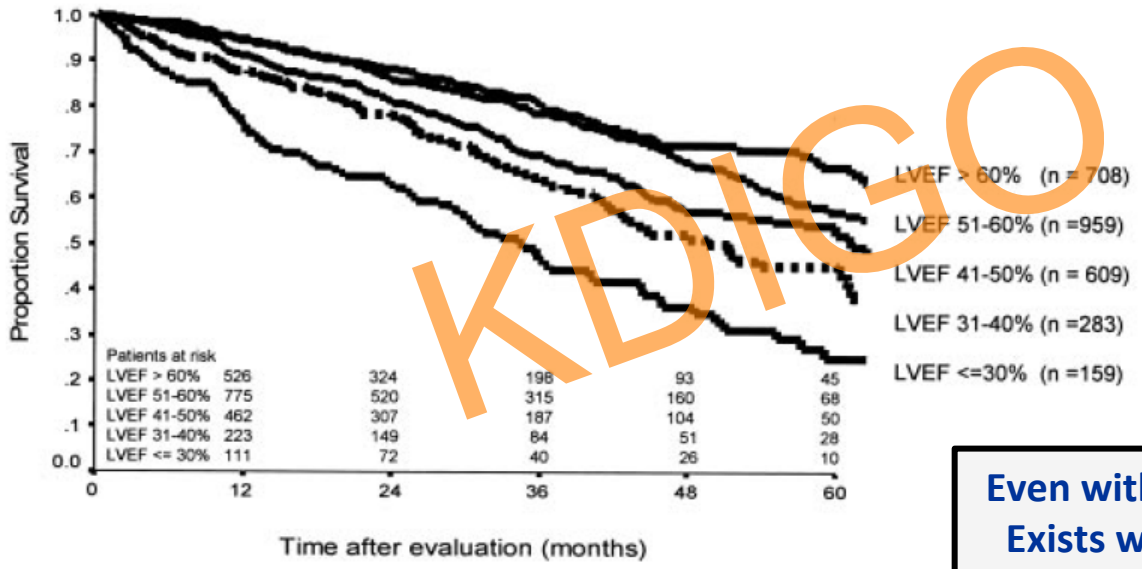
Prevalence of LV Dysfunction at Referral/Transplantation

Systolic Dysfunction Portends Increased Mortality among Those Waiting for Renal Transplant

Angelo M. de Mattos,* Andrew Siedlecki,* Robert S. Gaston,* Gilbert J. Perry,†
Bruce A. Julian,* Clifton E. Kew II,* Mark H. Deierhoi,‡ Carlton Young,‡ John J. Curtis,* and
Ami E. Iskandrian†

N=4214 evaluated and listed for Transplant

N=2,718 had gated-SPECT if: age >50, history of CV disease, DM



Even with the Selection Bias that Exists with Transplant Referral

24.9% had LVEF ≤50%

10.5% had LVEF ≤40%

LVEF ≤ 30%: Median Survival ~36 months

J Am Soc Nephrol 19: 1191–1196, 2008

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Table 2. Multivariable analysis: Mortality after evaluation

Parameter	Adjusted HR	95% CI	*P*
LVEF ≤30%	2.3	1.79 to 3.06	<0.001
LVEF 31 to 40%	1.6	1.21 to 1.99	<0.001
LVEF 41 to 50%	1.3	1.03 to 1.57	0.020
LVEF 51 to 60%	1.0	Reference	
LVEF >60%	0.8	0.65 to 1.05	0.100
Diabetes	1.6	1.33 to 1.91	<0.001
Ischemia	1.2	1.04 to 1.48	0.017
Months on dialysis	1.0	1.01 to 1.02	0.020
Male gender	0.8	0.70 to 0.98	0.025
Hypertension	0.8	0.62 to 0.98	0.030
Obesity status	0.7	0.59 to 0.99	0.050
Age >50 yr	1.1	0.94 to 1.29	0.200
Black race	0.6	0.30 to 1.16	0.100
Anemia	1.1	0.94 to 1.29	0.200
Low socioeconomic status	1.1	0.93 to 1.31	0.300

LVEF ≤30% had strongest association with mortality

J Am Soc Nephrol 19: 1191–1196, 2008

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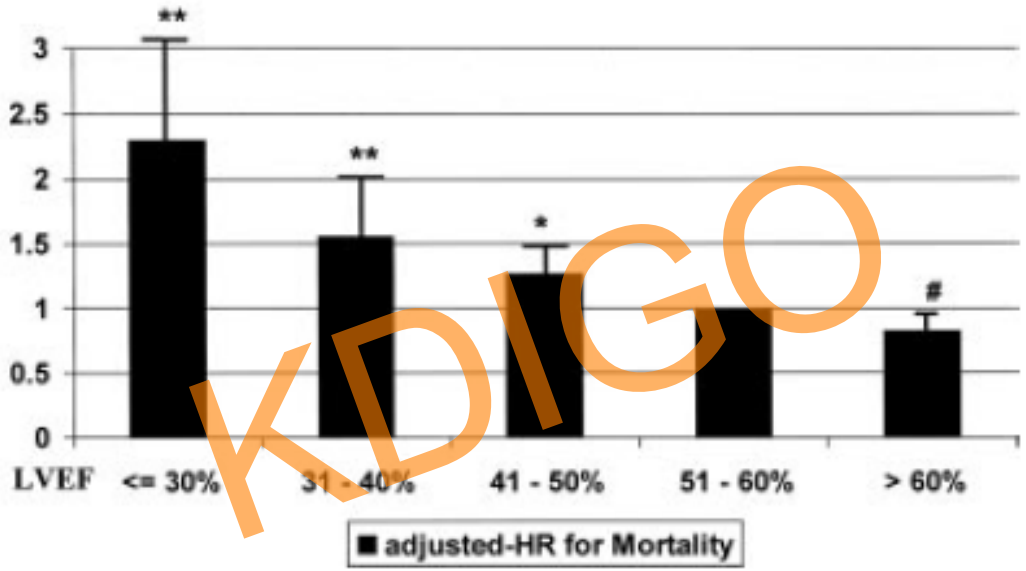


For each percent increment in LVEF - adjusted mortality risk decreased by 2.5%

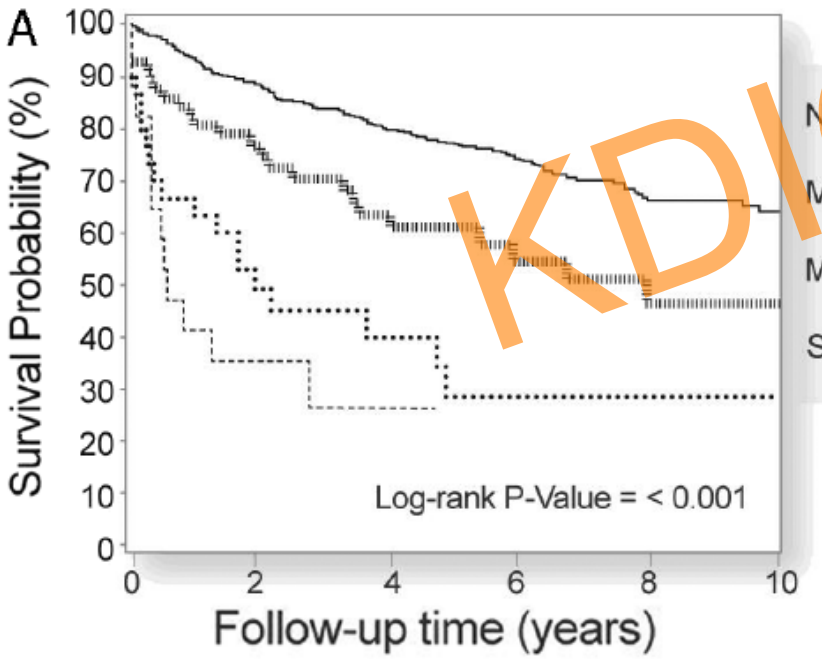
In a Highly Selected Wait-List Population LV Function Strongly Associated with Mortality

J Am Soc Nephrol 19: 1191–1196, 2008

Do Echocardiographic Parameters Predict Mortality in Patients With End-Stage Renal Disease?

Elizabeth J. Stallworthy,[1] Helen L. Pilmore,[2,3,6] Mark W.I. Webster,[4] Karishma K. Sidhu,[4] Elizabeth M. Curry,[1] Pieta Brown,[5] and Anish Scaria[5]

N=739 had an echo and were assessed for transplantation



LV Function

Normal, n=613 (85.5%)

Mildly impaired, n=57 (7.9%)

Moderately impaired, n=30 (4.2%)

Severely impaired, n=17 (2.4%)

14.5% had LVEF ≤50%

LVEF ≤ 30%: Median Survival ~1 year

Transplantation 2013;95: 1225

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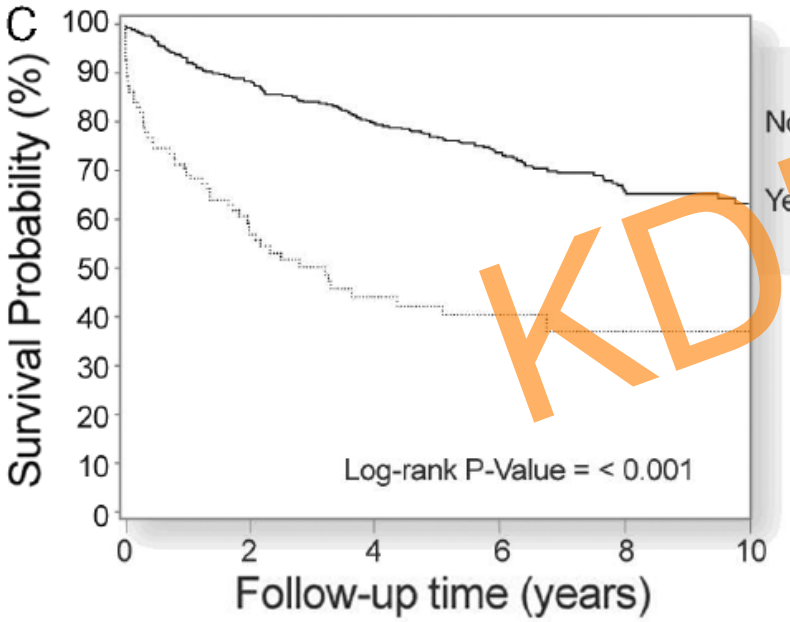

Regional Wall Motion Abnormalities Associated with Survival

Median Survival ~3 years

Transplantation 2013;95: 1225

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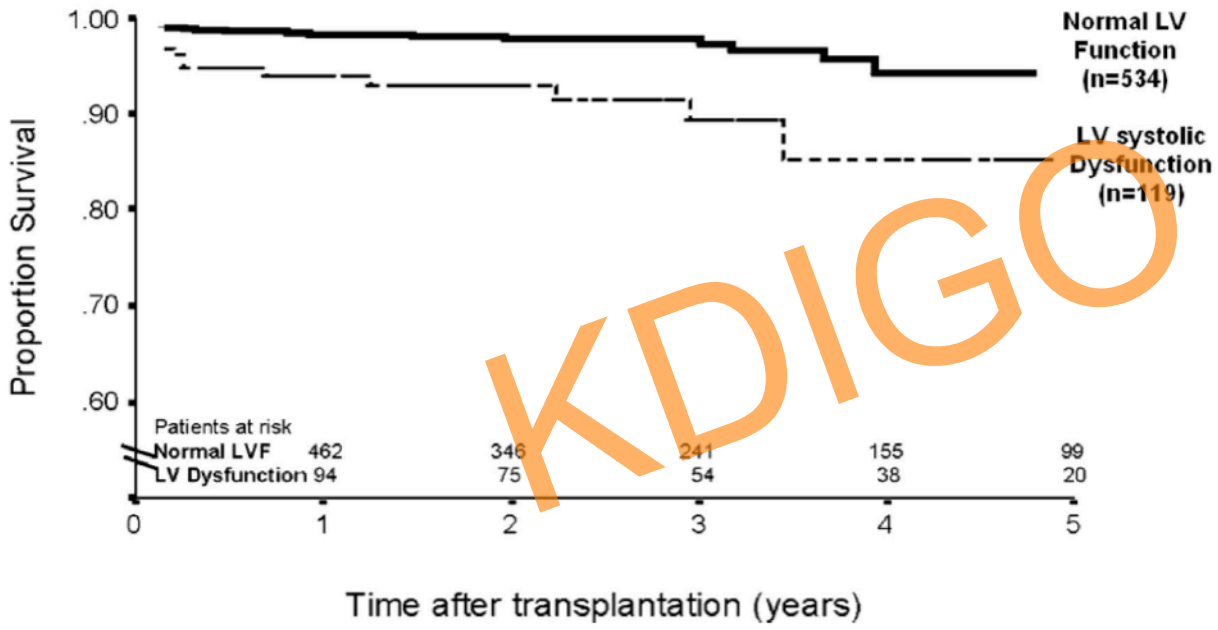
Variable	All-cause mortality		Cardiovascular mortality	
	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*
Subjective LV function (compared with normal)				
Mild impairment	1.14 (0.70–1.85)	0.61	1.47 (0.73–2.95)	0.28
Moderate impairment	1.36 (0.71–2.59)	0.35	1.26 (0.47–3.39)	0.65
Severe impairment	2.71 (1.36–5.39)	0.005	4.60 (1.66–12.72)	0.003
PHT/RVD[a]	1.91 (1.28–2.83)	0.001	1.45 (0.76–2.74)	0.26
RWMA[a]	1.95 (1.32–2.88)	<0.001	2.30 (1.31–4.04)	0.004

Transplantation 2013;95: 1225

The Impact of Left Ventricular Systolic Dysfunction on Survival After Renal Transplantation

Andrew Siedlecki,[1,4] Margaret Foushee,[2] John J. Curtis,[2] Robert S. Gaston,[2] Gilbert Perry,[3] Ami E. Iskandrian,[3] and Angelo M. de Mattos[2]



EF < 45%: 18.2% at time of transplantation

Mean EF in this Group: 36.7 ± 6.7%

Mean Time to Cardiac-Related Death: 1.5 ± 1.7 years

Transplantation • Volume 84, Number 12, December 27, 2007

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	Adjusted HR	95% CI	*P* value
Cardiac death			
LV systolic dysfunction	4.8	2.09–11.21	<0.001
Left heart catheterization pretransplant	3.1	1.20–8.25	0.02
Male	2.8	1.20–6.69	0.02
Waitlist time (per month)	1.03	1.01–1.05	0.04
Serum albumin (per mg/dL)	0.4	0.17–0.98	0.046
Overall mortality			
Waitlist time (per month)	1.03	1.01–1.04	0.001
LV systolic dysfunction	2.0	1.21–3.46	0.008
Serum albumin (per mg/dL)	0.6	0.31–0.98	0.04
Systolic BP >140 mm Hg	2.1	0.96–4.63	0.06

LV Systolic Dysfunction in those who Survived Long Enough to be Transplanted was also Associated with Mortality

Transplantation • Volume 84, Number 12, December 27, 2007

What is the Effect of Kidney Transplantation on LV Function?

Uremic Myocardiopathy

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Key Words. Uremia · Myocardiopathy · Reversible · Kidney transplant · Dialysis

Abstract. The authors report on the myocardiopathy of seven patients with end-stage renal disease, characterized by fever, in four patients; tachycardia, gallop rhythm, pericardial rub, in most of patients; signs and symptoms of cardiac failure and increased cardiac area and alterations of the EKG in all patients. Good remission of the symptoms was achieved in two patients by hemodialysis and by successful renal transplantation in the others. The likely etiologic factors of the syndrome are discussed.

Nephron *15:* 17–28 (1975)

Reversal of Left Ventricular Dysfunction after Renal Transplantation

Richard K. Burt, MD; Shalina Gupta-Burt, MD; Wadi N. Suki, MD; Camilo G. Barcenas, MD; James J. Ferguson, MD; and Charles T. Van Buren, MD

Table 2. *Case History Data Base on the Four Patients Who Had Renal Transplantation**

Variable	Patient 1	2	3	4
Renal failure data				
Cause of ESRD	Chronic glomerulonephritis	Diabetes	Poststreptococcal glomerulonephritis	Focal glomerulosclerosis
Type of dialysis	Hemodialysis	CCPD	CAPD, hemodialysis	CAPD, hemodialysis
Duration of dialysis, *mo*	24	12	60	9
Cardiac parameters before transplantation				
Blood pressure, *mm Hg*	125/80	140/90	120/80	124/90
Weight, *kg*	58.6	61.8	62.7	67.7
Right heart catheterization				
Central venous pressure, *mm Hg*	5	. . .	2	7
Pulmonary artery pressure, *mm Hg*	48/26	61/33	34/20	40/26
PCWP, *mm Hg*	20	35	18	19
Left heart catheterization				
Ejection fraction, %	31	20	35	20
Cardiac output, *L/min*	3.6	8.2	3.9	8.4
LVEDP, *mm Hg*	26	30	23	24
Noninvasive				
Ejection fraction, %	. . .	21†, 20‡	24†	25‡
Medications§	nifedipine, digoxin, isosorbide	captopril, digoxin, isosorbide, insulin	digoxin, furosemide, theophylline	hydralazine
Cardiac parameters after transplantation				
Blood pressure, *mm Hg*	120/80	140/90	120/80	150/90
Weight, *kg*	63.6	60.5	63.2	63.6
Ejection fraction ‖, %	69‡	48†, 56†	43‡	45¶
Medications	Cyclosporin A, prednisone, propranolol, hydralazine	Cyclosporin A, prednisone, clonidine, nifedipine, insulin	Cyclosporin A, prednisone, digoxin	Cyclosporin A, prednisone, captopril, cardiazem

Uremic Cardiomyopathy – Common Features

1. All Patients had Symptomatic CHF (NYHA Class III/IV)
2. Normal Coronary Arteries on Angiogram
3. Diffuse Hypokinesis with low EF
4. LV Dilatation
5. Symptoms Completely Resolved Post-Transplant
6. Post-Tx LV showed normal wall motion or minimal hypokinesis with significant improvement in EF

Annals of Internal Medicine. 1989;**111**:635-640.

IMPACT OF RENAL TRANSPLANTATION ON UREMIC CARDIOMYOPATHY[1]

PATRICK S. PARFREY,[2–4] JOHN D. HARNETT,[2] ROBERT N. FOLEY,[2] GLORIA M. KENT,[2]
DAVID C. MURRAY,[5] PAUL E. BARRE,[6] AND RONALD D. GUTTMANN[6]

N=102 Dialysis Patients who Underwent Kidney Transplantation

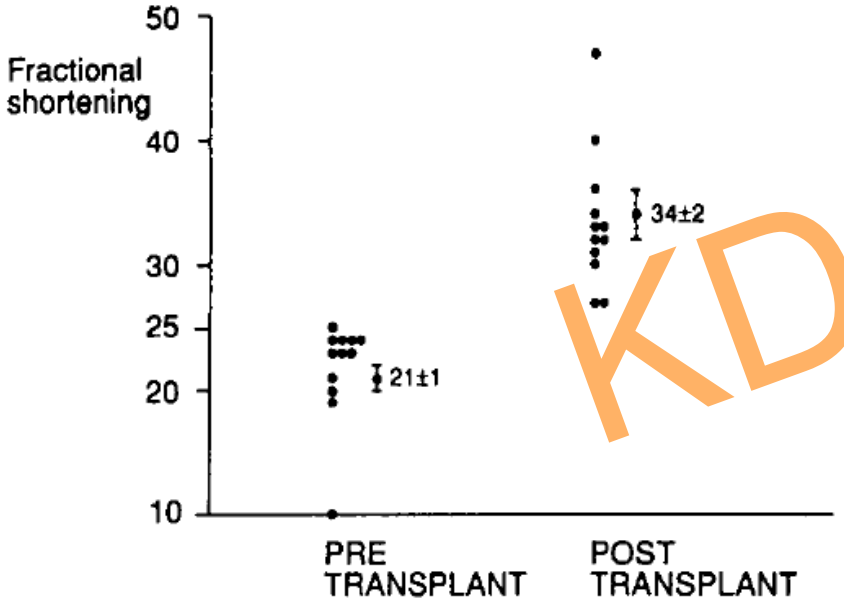
	Before transplant				After transplant				P
	Mean	SD	n	%	Mean	SD	n	%	
Dimensions									
Left atrial diameter (mm)	39	6			37	5			0.002
LV end diastolic diameter (mm)	52	7			50	6			0.004
LV end systolic diameter (mm)	34	7			31.5	6			0.001
Ventricular septal wall thickness in diastole	12.2	3			11.7	2.4			0.07
Posterior LV wall thickness in diastole	12.1	2.5			11.7	2			0.018
Fractional shortening (%)	35	8.5			37	7			0.04
LV mass index (g/m^2)	152	50			130	36			<0.0001
LV volume (ml/m^2)	84	35			71	28			<0.0001
Diagnosis									
Concentric LV hypertrophy			41	41			37	37	NS
LV dilatation			32	32			29	29	NS
Systolic dysfunction			12	12			0	0	0.001
Normal echocardiogram			17	17			36	36	0.004

Systolic Dysfunction: 12% Pre-Transplant - 0% Post-Transplant

Normal Echo: 17% Pre-Transplant - 36% Post-Transplant

Parfrey et al, Transplantation, 60:908, 1995

Patients with Systolic Dysfunction Showed Significant Improvement



	Before transplant[a]	After transplant[a]	P
Systolic dysfunction			
Left atrium (mm)	39±4	37±4	NS
LV end diastole (mm)	55±8	51±6	0.05
LV end systole (mm)	43±7	34±6	0.01
Post LV wall thickness in diastole (mm)	12.3±2.7	11.8±1.9	NS
Fractional shortening	21.5±4.6	33.5±5.6	<0.001
LV mass index (g/m^2)	167±55	133±31	<0.001
LV volume (ml/m^2)	104±41	75±24	<0.001

Are the Improvements Just From:

Improved BP control?

Normalization of the Hgb?

Correction of Volume Overload?

Thrombosis/Closure of AVF?

Effect of Kidney Transplantation on Left Ventricular Systolic Dysfunction and Congestive Heart Failure in Patients With End-Stage Renal Disease

Ravinder K. Wali, MD,* Gregory S. Wang, MD,† Stephen S. Gottlieb, MD,‡ Lavanya Bellumkonda, MD,* Riple Hansalia, MD,† Emilio Ramos, MD,* Cinthia Drachenberg, MD,‖ John Papadimitriou, MD,‖ Meredith A. Brisco, MD,† Steve Blahut, PHD,* Jeffrey C. Fink, MD,* Michael L. Fisher, MD,‡ Stephen T. Bartlett, MD,§ Matthew R. Weir, MD*

N=103 Patients with LVEF < 40%

Mean EF 31.6 ± 6.7%

~Half had LVEF < 30%

Median of 2 hospitalizations for CHF before Tx Evaluation

51% had CAD – Most Revascularized Pre-Tx and None had Inducible Ischemia at Time of Transplantation

N=72 (70%) Improved with LVEF ≥ 50% by One Year

Mean EF 58.8 ± 6.8%

N=16 (15%) Improved with LVEF 40-50%

Mean EF 42.1 ± 2.4%

N=16 (15%) Did Not Improve (LVEF < 40%)

Mean EF 31.6 ± 4.9%

Overall, 86% had Increase in LVEF of at Least 5% (by MUGA)

Pre-Tx LVEF <30%: 68% had Post-Tx LVEF > 50%

JACC Vol. 45, No. 7, 2005

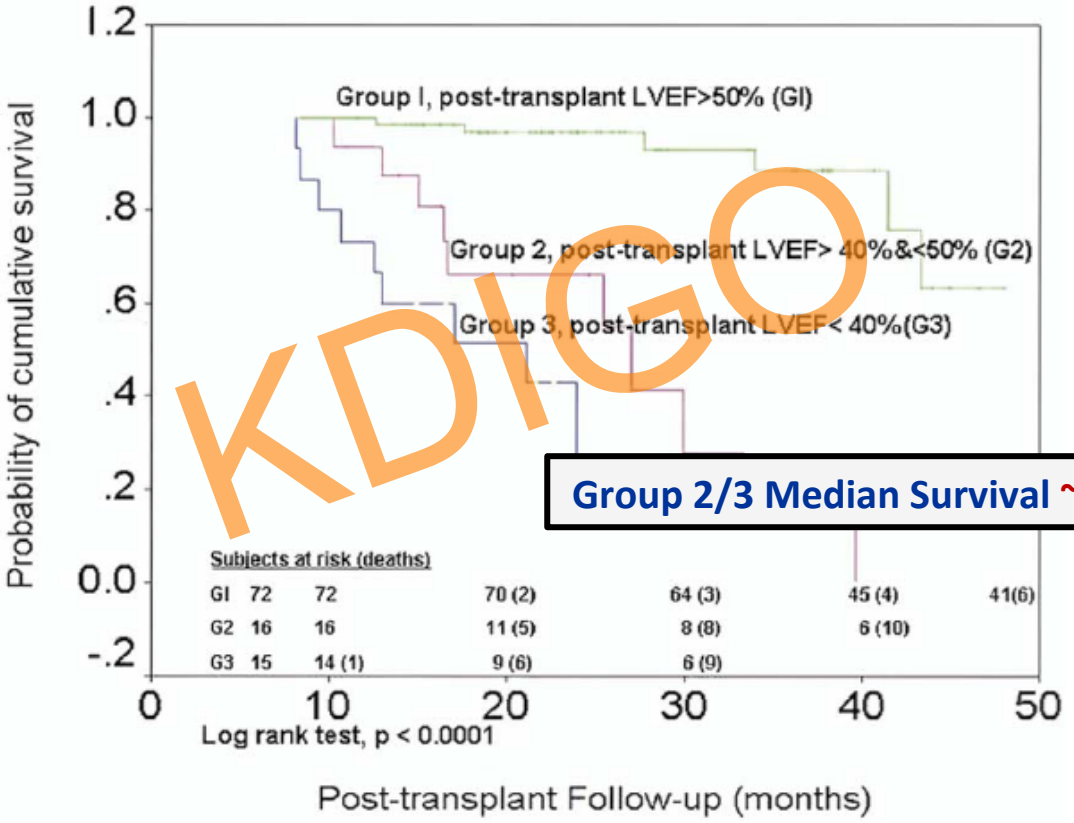
Time on Dialysis Pre-Transplant only Factor Associated with Failure to Improve LV Function

	OR	95% CI	p Value
Pretransplant covariates			
Age (yrs)	0.98	0.88–1.09	0.75
Race (African-American)	0.60	0.05–6.11	0.83
Gender (male)	0.31	0.02–3.6	0.95
Time on dialysis (months)	0.82	0.74–0.91	0.001
Diabetes mellitus (yes/no)	2.11	0.22–19.5	0.50
Coronary artery disease (yes/no)	1.2	0.11–14.3	0.33
URR (%)	0.94	0.74–1.08	0.45
Post-transplant covariates			
MAP (mm Hg)	1.16	0.99–1.36	0.05
Hematocrit (%)	1.99	0.72–1.36	0.95
Albumin (mg/dl)	2.7	0.19–37.7	0.45
Post-PTH-I (pg/dl)	1.00	0.99–1.02	0.18
Beta-blockers (yes/no)	2.8	0.20–40.5	0.43
ACE-I (yes/no)	0.22	0.03–1.58	0.13

Every One Month Increase in Dialysis Time Decreased Likelihood of Normalizing LV Function by 18%

JACC Vol. 45, No. 7, 2005

Failure to Improve LV was Associated with Reduced Survival



Group 2/3 Median Survival ~1.5-2.5 yrs

JACC Vol. 45, No. 7, 2005

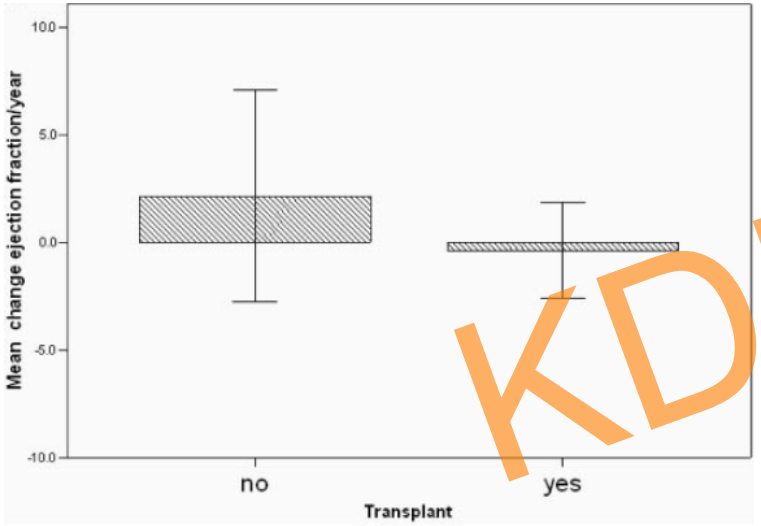
Multiple Studies have Shown Improvement in LV Function with Kidney Transplantation

1. Lai et al. The effect of renal transplantation on left ventricular function in hemodialysis patients. *Clin Nephrol* 18:74, 1982
2. Fleming et al, Improved cardiac function after renal transplantation. *Postgraduate Medical Journal* 61: 525-528, 1985
3. Van den Broek et al. Improved left ventricular function after renal transplantation. *Med J Aust*; 154: 279, 1991
4. Abouma et al. Reveersal of myocardial dysfunction following renal transplantation. *Transplantation Proceedings*; 25: 1034, 1993.
5. Sahagun-Sanchez et al, The Effect of kidney transplant on Cardiac function: An echocardiographic perspective. *Echocardiography* 18(6), 2001
6. Melchor et al. Kidney transplantation in patients with ventricular ejection fraction less than 50%: features and posttransplant outcome. *Transplantation Proceedings*; 34: 2539-2540, 2002
7. Oppert et al. Improvement of left ventricular function and arterial blood pressure 1 year after SPK. *Transplantation Proceedings*; 34: 2251-2252, 2002
8. Dudziaka et al. Cardiovascular Effects of Successful Renal Transplantation: A 30-Month Study on Left Ventricular Morphology, Systolic and Diastolic Functions. *Transplantation Proceedings*; 37(2): 1039–1043, 2005
9. Vaidya et al. Effect of Renal Transplantation for Chronic Renal Disease on Left Ventricular Mass; *The American Journal of Cardiology*; Volume 110, Issue 2, 2012, Pages 254–257
10. ……
11. …..

Renal Transplantation Is Not Associated with Regression of Left Ventricular Hypertrophy: A Magnetic Resonance Study

Rajan K. Patel,*† Patrick B. Mark,*† Nicola Johnston,‡ Ellon McGregor,† Henry J. Dargie,‡ and Alan G. Jardine*†

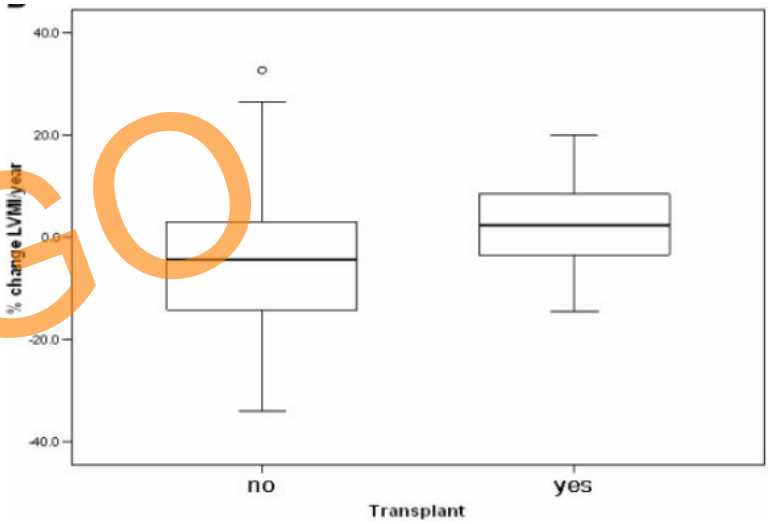
Mean Change in Ejection Fraction Per Year



2.1% per year

-0.4% per year

Mean Change in LVMI Per Year



-3.6% per year

2.8% per year

No Significant Difference in any of the Cardiac Parameters Measured

Proportion with LVH in both Groups was 68% and did not Change in Follow-up

Clin J Am Soc Nephrol 3: 1807–1811, 2008.

Effect of Transplantation on LV Function

- **Most Reports have Demonstrated Improvement in LV Function Post Kidney Transplantation**
  - **Publication Bias? Patient Selection Bias?**

- **Key is to select those who will most likely improve:**
  - **Pure "uremic" cardiomyopathy**
    - **Diffuse hypokinesis with normal coronaries**
  - **Anticipated short dialysis duration**
    - **Living donor; Deceased donor (local allocation rules/donor rate)**
  - **Absence of RWMA and ischemia**
    - **Questionable role of correcting ischemia in asymptomatic patients**
  - **Overall burden of disease 'low'**

Ontario Deceased Donor Kidney/Kidney-Pancreas (KP)/ Pancreas after kidney (PAK) Transplantation Allocation Algorithm

1. Medically urgent pediatric patients (<18 yrs), ABO identical then compatible
2. Medically urgent adult patients, ABO identical then compatible
3. Pediatric patients (<18 yrs), ABO identical then compatible
4. Multi organ patients, ABO identical then compatible
5. Kidney-Pancreas/Pancreas after kidney patients, ABO identical then compatible
6. Kidney list exchange patients with identical ABO within donor hospital
7. Patients </= 55yrs with identical then compatible ABO
8. Patients >55yrs with identical then compatible ABO
9. Out of Province patients
10. UNOS

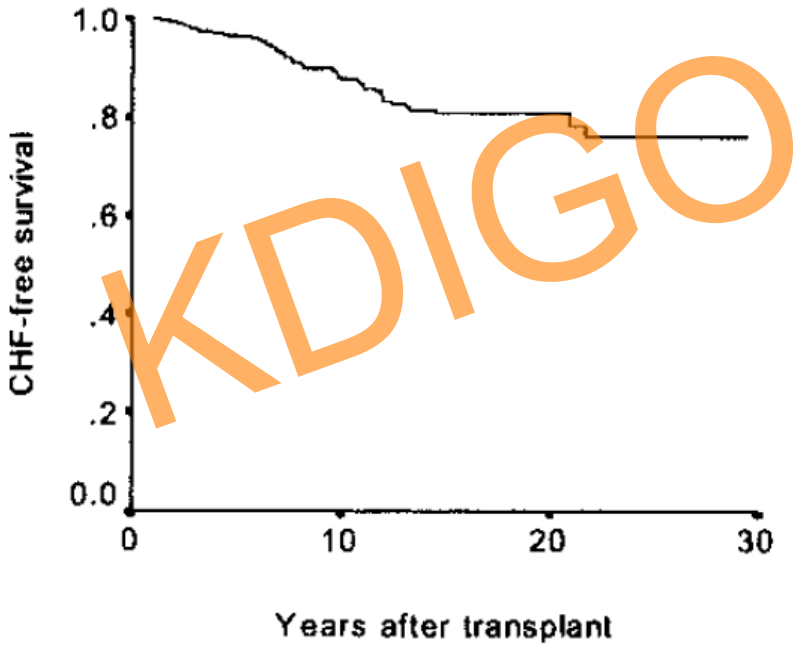
Category	Definition
Overriding Priority	a. Medically urgent patients. Specifically: • Patients with cardiomyopathy associated with uremia, or loss of dialysis access in patient with reasonable survival expectation

What is the Incidence and Outcome of *de novo* CHF Following Kidney Transplantation?

Congestive Heart Failure in Renal Transplant Recipients: Risk Factors, Outcomes, and Relationship with Ischemic Heart Disease

CLAUDIO RIGATTO,* PATRICK PARFREY,† ROBERT FOLEY,† CAROL NEGRIJN,† CARRIE TRIBULA,* and JOHN JEFFERY*

N=638 Transplant Patients free from CV Disease at 1-Year Post-Transplantation

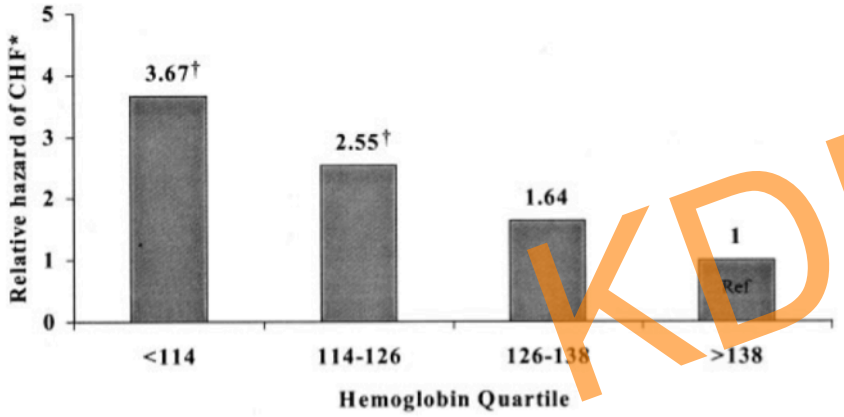


3.6% at 5-Years
12.1% at 10-Years
21.6% at 20-Years

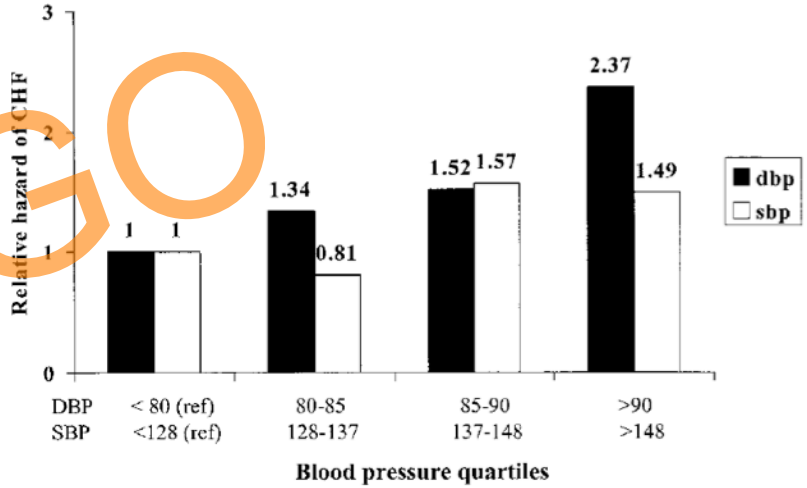
Incident Rate of CHF: 2-5x higher than General Population (Framingham)
Incident Rate of IHD: Similar to the General Population (Framingham)

J Am Soc Nephrol 13: 1084–1090, 2002

Hemoglobin and BP strongly Associated with *de novo* CHF



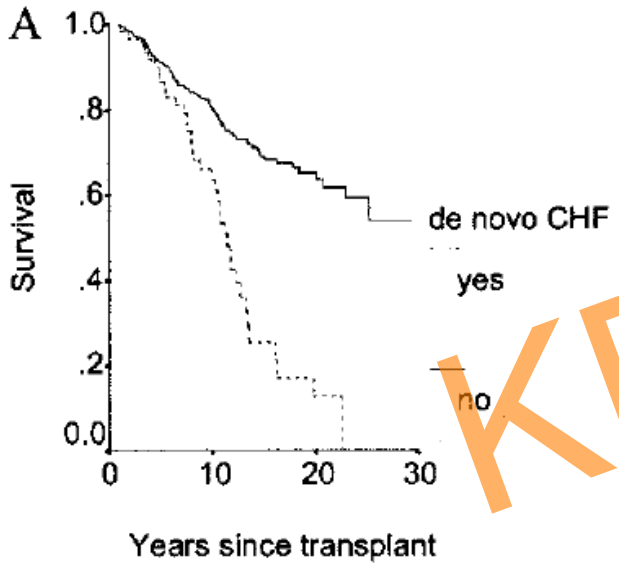
Risk of CHF Increased as Hemoglobin Declined



Risk of CHF Increased as BP Increased

DBP >>> SBP

De novo CHF Associated with Worse Survival



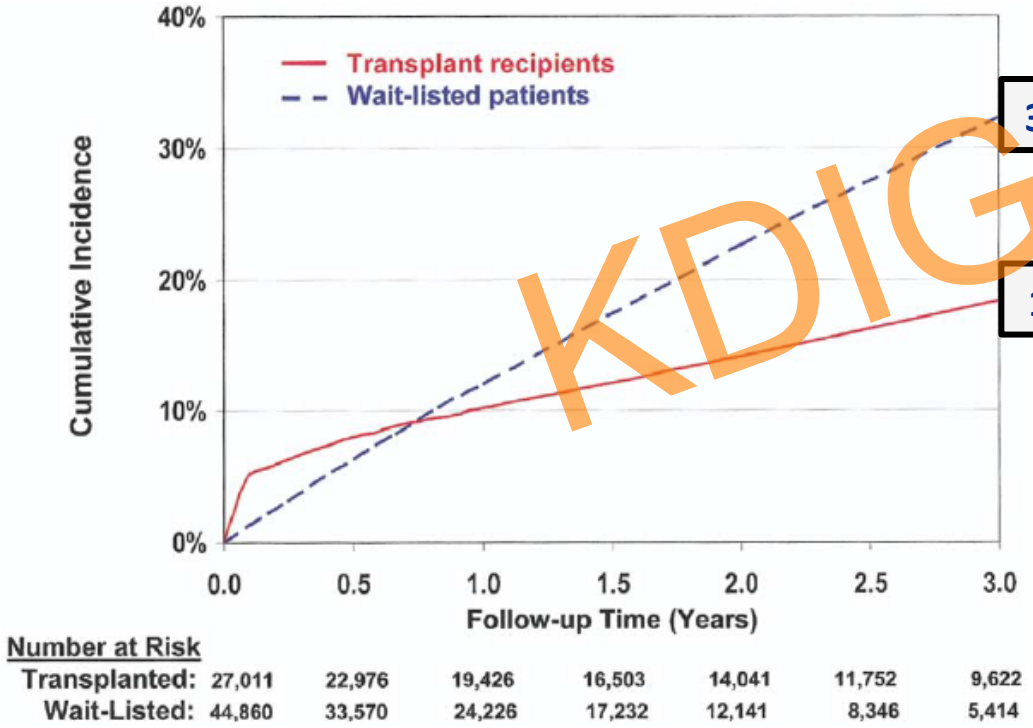
Variable	Relative Hazard	*P*
Age	1.04 (1.03 to 1.06)	<0.001
Diabetes	2.23 (1.65 to 3.00)	<0.001
De novo CHF	1.78 (1.21 to 2.61)	0.003
De novo IHD	1.50 (1.05 to 2.13)	0.02

J Am Soc Nephrol 13: 1084–1090, 2002

De Novo Congestive Heart Failure After Kidney Transplantation: A Common Condition With Poor Prognostic Implications

Krista L. Lentine, MD, Mark A. Schnitzler, PhD, Kevin C. Abbott, MD, Leiming Li, MS, Thomas E. Burroughs, PhD, William Irish, PhD, and Daniel C. Brennan, MD

Excluded Patients with a History of CHF



CHF Incidence at 36-months

- Age > 60 - 28.8%
- BMI > 30 - 25.4%
- Diabetes - 25.1%
- Angina - 30.7%
- MI - 37.7%
- DGF - 25.7%

American Journal of Kidney Diseases, Vol 46, No 4 (October), 2005: pp 720-733

Independent Correlates of *de novo* CHF

Age (y)		
18-30	1.00 = Reference	
31-44	1.23 (1.06-1.41)	0.005
45-60	1.90 (1.66-2.18)	<0.0001
60+	2.49 (2.16-2.87)	<0.0001
Delayed graft function	1.40 (1.33-1.54)	<0.0001
Posttransplantation complications		
Hypertension†	1.51 (1.37-1.66)	<0.0001
Anemia†	1.51 (1.40-1.63)	<0.0001
De novo diabetes†	1.51 (1.34-1.71)	<0.0001
Graft failure†	3.20 (2.86-3.58)	<0.0001
Myocardial infarction†	2.59 (2.23-3.02)	<0.0001

American Journal of Kidney Diseases, Vol 46, No 4 (October), 2005: pp 720-733

De Novo Congestive Heart Failure After Kidney Transplantation: A Common Condition With Poor Prognostic Implications

Krista L. Lentine, MD, Mark A. Schnitzler, PhD, Kevin C. Abbott, MD, Leiming Li, MS, Thomas E. Burroughs, PhD, William Irish, PhD, and Daniel C. Brennan, MD

Mortality after CHF Diagnosis

14.5% at 1-year

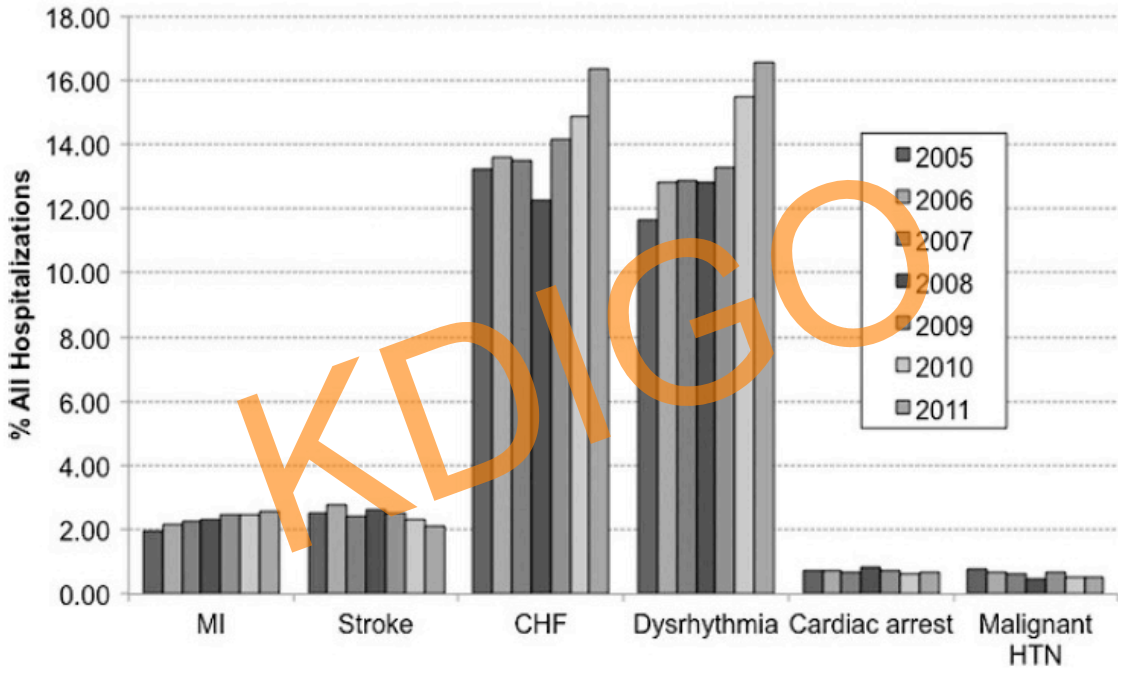
21.2% at 2-Years

	Death-Censored Graft Failure	All-Cause Graft Loss	Death
De novo CHF*	2.72 (2.44-3.02)†	2.78 (2.57-3.01)†	2.63 (2.37-2.92)‡

American Journal of Kidney Diseases, Vol 46, No 4 (October), 2005: pp 720-733

Patterns of Care and Outcomes in Cardiovascular Disease After Kidney Transplantation in the United States

Amit K. Mathur, MD, MS,[1,2,3] Yu-Hui Chang, MPH, PhD,[2] D. Eric Steidley, MD,[1] Raymond Heilman, MD,[1] Narjeet Khurmi, MD,[1] Nabil Wasif, MD,[2,3] David Etzioni, MD,[2,3] and Adyr A. Moss, MD[1,3]



CHF Most Common CV Diagnosis

16% of all Post-Transplant Admissions and Increasing since 2005

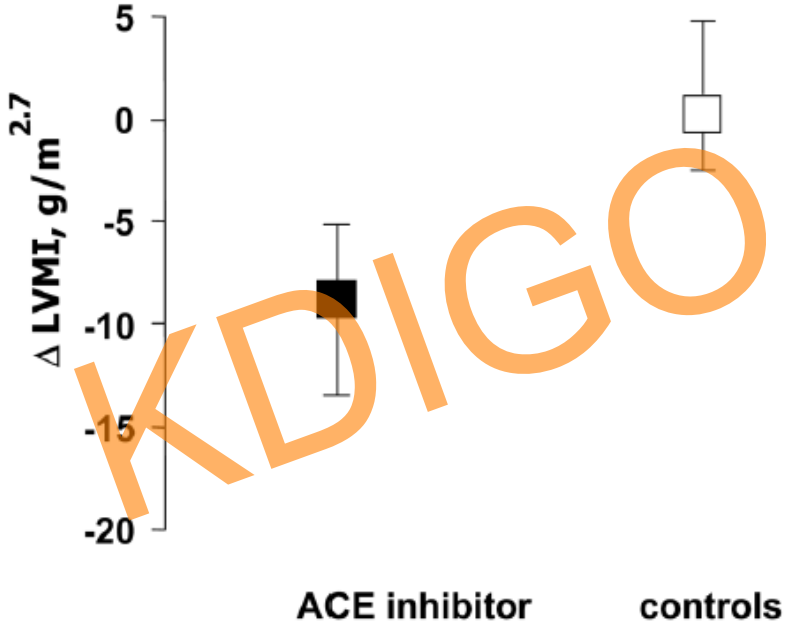
Transplantation Direct 2017;3: e126

Treatment of CHF: ACE-Inhibitors and ARBs in the Kidney Transplant Population

Observational Data is Conflicting

ACE Inhibitors and Persistent Left Ventricular Hypertrophy After Renal Transplantation: A Randomized Clinical Trial

Ernesto Paoletti, MD,[1] Paolo Cassottana, MD,[2] Marco Amidone, MD,[1] Maurizio Gherzi, MD,[1] Davide Rolla, MD,[1] and Giuseppe Cannella, MD, PhD[1]



N=70 Patients with Persistent LVH 6-12 Months Post-Transplant

Randomized to Lisinopril or No Therapy

American Journal of Kidney Diseases, Vol 50, No 1 (July), 2007: pp 133-142

ACE Inhibitors and Persistent Left Ventricular Hypertrophy After Renal Transplantation: A Randomized Clinical Trial

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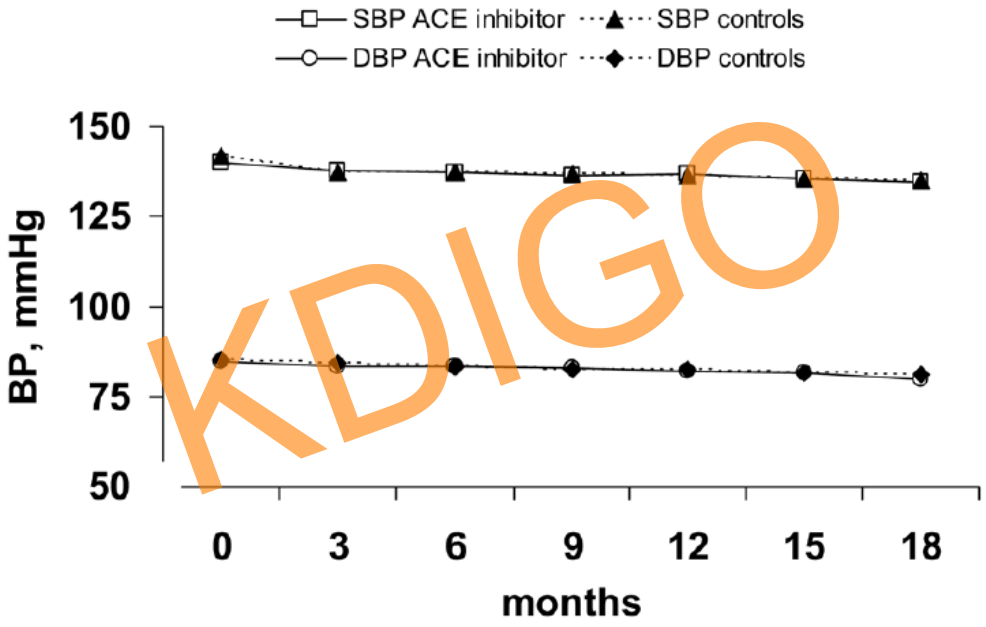

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	ACE Inhibitors			Controls			Effect ACE Inhibitor *v* Controls
	LVMi at Baseline	LVMi at 18 Months	ΔLVMi	LVMi at Baseline	LVMi at 18 Months	ΔLVMi	Δ (95% CI)
Cyclosorine	66.6 ± 17.5	51.2 ± 15.9	−15.4 ± 13.0	59.9 ± 10.3	59.6 ± 9.6	−0.3 ± 9.5	15.1 ± 3.5 (7.9-22.2) $P < 0.001$
Tacrolimus	59.1 ± 7.1	57.0 ± 10.4	−2.1 ± 10.0	60.0 ± 14.3	63.4 ± 16.3	3.4 ± 14.8	5.5 ± 4.6 (−3.9-14.9) $P = 0.2$

Effect Modification Present

Lisinopril Appeared to Only Work in Patients Receiving Cyclosporine

American Journal of Kidney Diseases, Vol 50, No 1 (July), 2007: pp 133-142

Candesartan improves blood pressure control and reduces proteinuria in renal transplant recipients: results from SECRET

Thomas Philipp[1], Franck Martinez[2], Helmut Geiger[3], Bruno Moulin[4], Georges Mourad[5], Roland Schmieder[6], Michel Lièvre[7], Uwe Heemann[8] and Christophe Legendre[2]

	Candesartan n=255	Placebo n=247
Total no. of composite primary events	13 (5.1%)	13 (5.3%)
All-cause mortality	3 (1.18%)	4 (1.62%)
Cardiovascular morbidity events	9 (3.53%)	5 (2.02%)
All-cause graft failure	1 (0.39%)	6 (2.43%)

Largest ACE/ARB RCT in Kidney Transplant Recipients

Stopped Early for 'Futility'

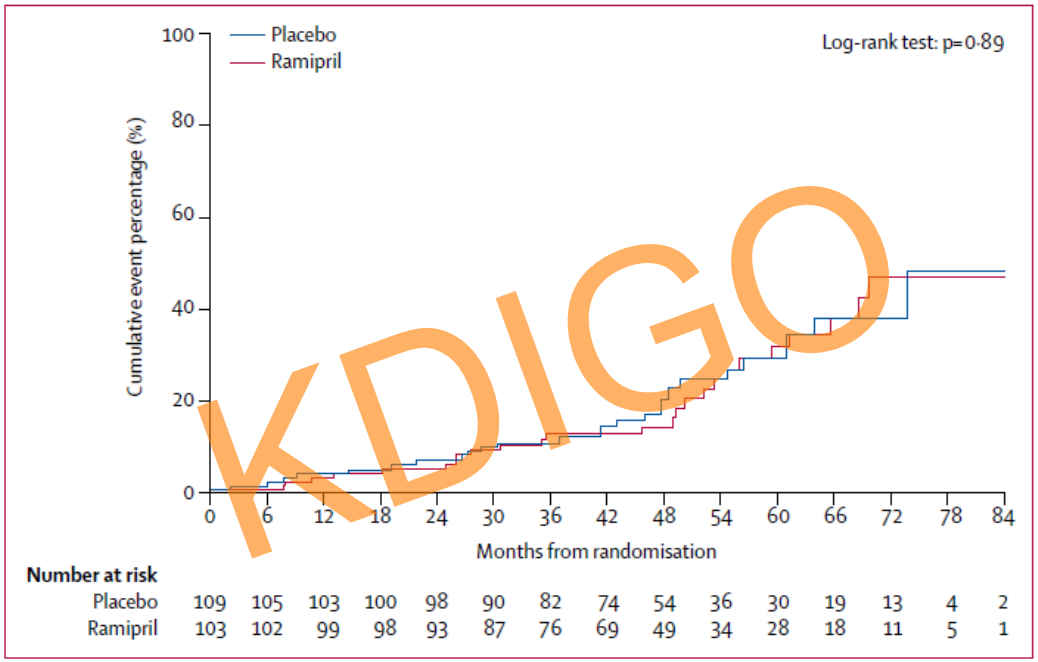
Mean Follow-up 20-months

Relatively Low-Risk: Diabetes 11%, CVD 15%, Mean Proteinuria 130 mg/day

Nephrol Dial Transplant (2010) 25: 967–976

Ramipril versus placebo in kidney transplant patients with proteinuria: a multicentre, double-blind, randomised controlled trial

Greg A Knoll, Dean Fergusson*, Michaël Chassé, Paul Hebert, George Wells, Lee Anne Tibbles, Darin Treleaven, David Holland, Christine White, Norman Muirhead, Marcelo Cantarovich, Michel Paquet, Bryce Kiberd, Sita Gourishankar, Jean Shapiro, Ramesh Prasad, Edward Cole, Helen Pilmore, Valerie Cronin, Debora Hogan, Tim Ramsay, John Gill*



N=212 Kidney Transplant Recipients Randomized to Ramipril or Placebo (Blinded)

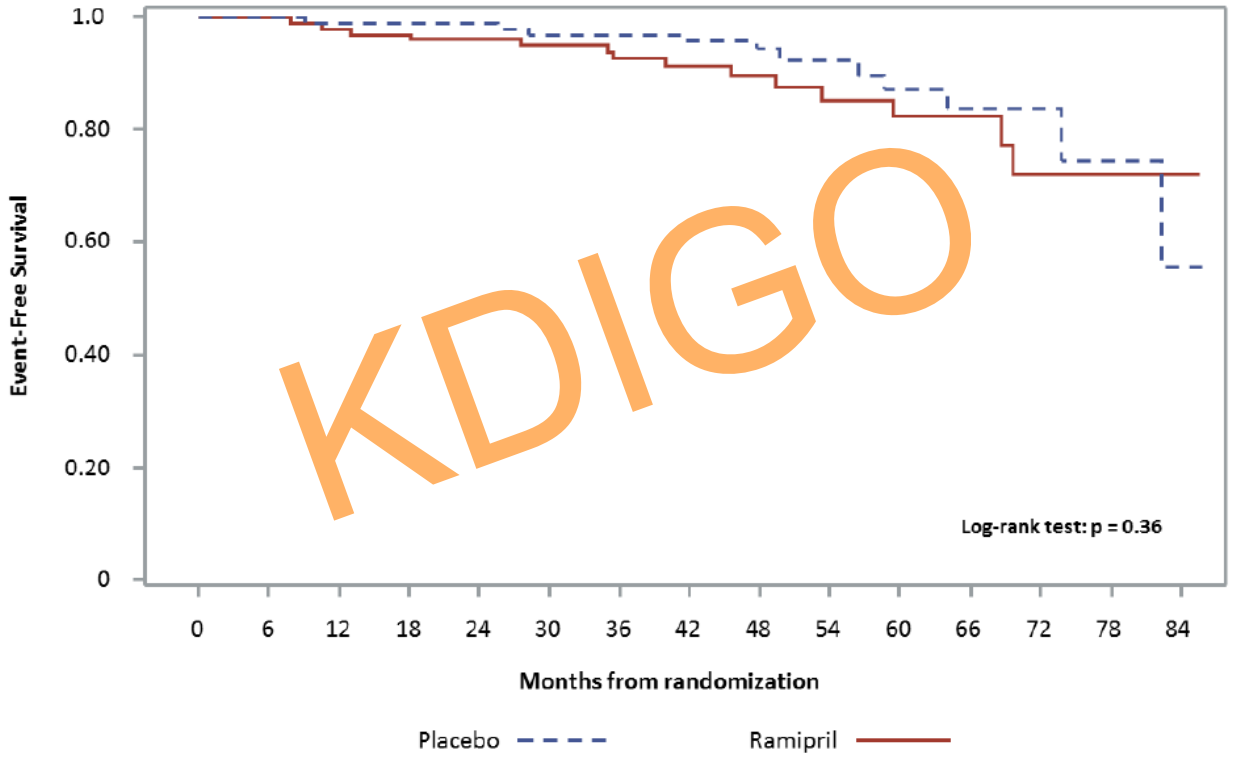
Mean Follow-up 48-months (Longest Follow-Up 7 Years)

Fairly High-Risk: Diabetes 43%, Hypertension 93%, Hyperlipidemia 67%, CVD 25%, Age >60 yrs 34%, Pr >0.5 g/day 43%

Knoll et al, The Lancet Diabetes & Endocrinology; 4(4): 318-326, 2016

Ramipril versus placebo in kidney transplant patients with proteinuria: a multicentre, double-blind, randomised controlled trial

Greg A Knoll, Dean Fergusson*, Michaël Chassé, Paul Hebert, George Wells, Lee Anne Tibbles, Darin Treleaven, David Holland, Christine White, Norman Muirhead, Marcelo Cantarovich, Michel Paquet, Bryce Kiberd, Sita Gourishankar, Jean Shapiro, Ramesh Prasad, Edward Cole, Helen Pilmore, Valerie Cronin, Debora Hogan, Tim Ramsay, John Gill*



No Difference in Overall Survival

Knoll et al, The Lancet Diabetes & Endocrinology; 4(4): 318-326, 2016

Ramipril versus placebo in kidney transplant patients with proteinuria: a multicentre, double-blind, randomised controlled trial

Greg A Knoll, Dean Fergusson*, Michaël Chassé, Paul Hebert, George Wells, Lee Anne Tibbles, Darin Treleaven, David Holland, Christine White, Norman Muirhead, Marcelo Cantarovich, Michel Paquet, Bryce Kiberd, Sita Gourishankar, Jean Shapiro, Ramesh Prasad, Edward Cole, Helen Pilmore, Valerie Cronin, Debora Hogan, Tim Ramsay, John Gill*

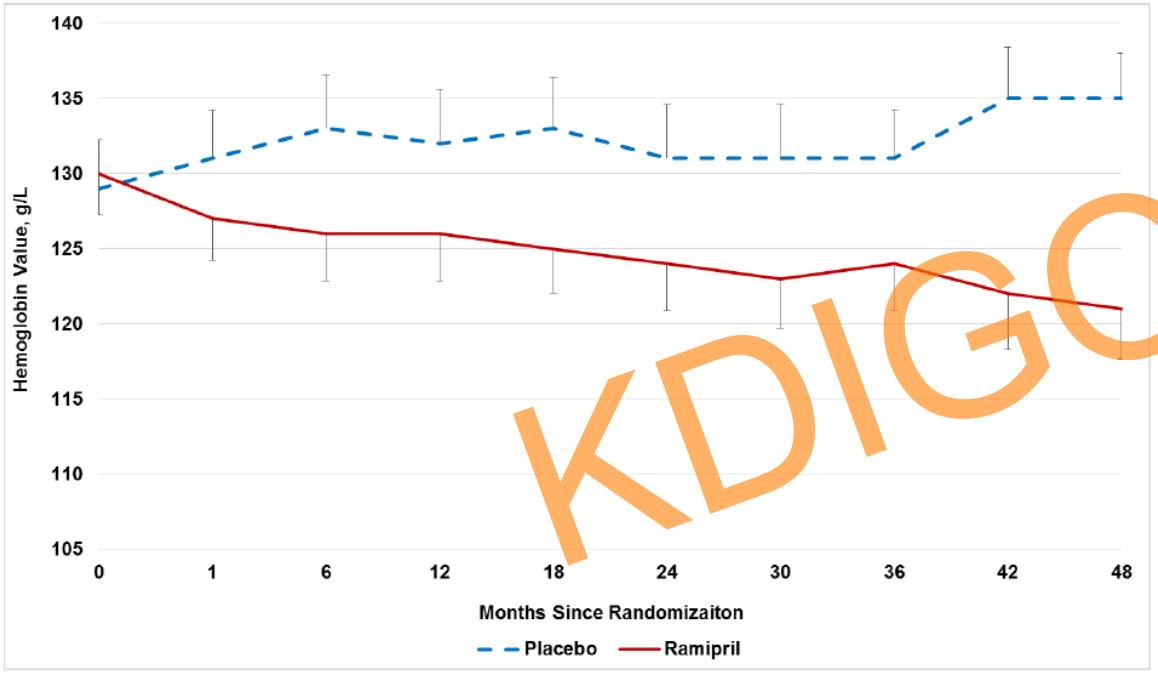
	Placebo (n=109)	Ramipril (n=103)	Risk ratio or mean difference (95% CI)
Cardiovascular events			
Myocardial infarction	6 (6%)	2 (2%)	0·35 (0·07 to 1·69)
TIA or stroke	4 (4%)	1 (1%)	0·27 (0·04 to 1·79)
Amputation	0	4 (4%)	..
Congestive heart failure	2 (2%)	3 (3%)	1·57 (0·27 to 9·22)
Revascularisation events	5 (5%)	7 (7%)	1·47 (0·48 to 4·48)
PCI or CABG	4 (4%)	2 (2%)	0·52 (0·10 to 2·80)
Peripheral	0	5 (5%)	..
Cerebral	1 (1%)	0	..

17/109=15.6% **17/103=16.5%**

No Difference in CV Events

Knoll et al, The Lancet Diabetes & Endocrinology; 4(4): 318-326, 2016

ACE-Inhibitors are not Benign in this Population



Mean Difference at End of Trial:
-14 g/L (-22 to -7 g/L)

Significant Decline in Hgb Over Time in Ramipril Group

Knoll et al, The Lancet Diabetes & Endocrinology; 4(4): 318-326, 2016

Adverse Events More Common on Ramipril

	Placebo (n=109)	Ramipril (n=103)	p value
Total	24 (22%)	39 (38%)	0·02
Angioedema	0	1 (1%)	0·49
Cough	0	4 (4%)	0·05
Hyperkalemia*	1 (1%)	5 (5%)	0·11
Anemia*	22 (20%)	25 (24%)	0·51
Other	1 (1%)	4 (4%)	0·20

*Hyperkalemia defined as serum potassium ≥6·0 mmol/L; anaemia defined as haemoglobin ≤100 g/L.

Blinded Study Drug Stopped Because of Adverse Event

Ramipril - 9%

Placebo - 2%

P=0.03

Knoll et al, The Lancet Diabetes & Endocrinology; 4(4): 318-326, 2016

Renin-Angiotensin System Blockade and Long-term Clinical Outcomes in Kidney Transplant Recipients: A Meta-analysis of Randomized Controlled Trials

Swapnil Hiremath, MD,[1,2,3] Dean A. Fergusson, PhD,[1] Nicholas Fergusson, BSc,[1] Alexandria Bennett, BSc,[1] and Greg A. Knoll, MD[1,2,3]

Trial	Intervention	Control	Sample Size	Mean F/U	Inclusion Criteria	Funding Source
Midtvedt[27] (2001)	Lisinopril	Nifedipine	123	1 y	Diastolic blood pressure ≥ 95 mmHg	Not reported
Amara[26] (2010)	Lisinopril	Standard care	47	1 y	Chronic allograft nephropathy; severe renal impairment; ≥1 g/24 h proteinuria	Mersey Kidney Research, Liverpool, Renal Transplant Fund, and Liverpool Dialysis Unit Fund
Philipp[15] (2010)	Candesartan	Placebo	502	1.7 y	Negative enalapril test; ≥25 mL/min creatinine clearance	Industry (Takeda)
Ibrahim[13] (2013)	Losartan	Placebo	153	5 y	First or second Tx; Scr < 2.5 mg/dL	National Institute of Diabetes and Digestive and Kidney Diseases (Merck donated drug)
Paoletti[28] (2013)	Lisinopril	Standard care	70	10 y	Nondiabetic; left ventricular hypertrophy	No funding
Salzberg[29] (2014)	Telmisartan	Placebo	131	1.25 y	Scr within 0.5 mg/dL of baseline over 3 mo	Industry (Amgen funded, Boehringer-Ingelheim donated drug)
Knoll[14] (2015)	Ramipril	Placebo	212	4 y	eGFR ≥ 20 mL/min/1.73 m^2 and proteinuria ≥ 0.2 g/d	Canadian Institutes for Health Research
Mandelbrot[6] (2015)	Ramipril	Placebo	264	1 y	First kidney Tx; eGFR ≥ 40 mL/min; urine protein-creatinine ratio > 0.3 mg/mg	Industry (Pfizer)

N= 8 Trials Involving n=1,502 Patients

Except for Paoletti Study, None Targeted CHF or LV Function

Study Inclusion Criteria

- RCT

- ACE or ARB

- ≥ 1-Year of Follow-up

- Reported Clinically Important Outcome (e.g. Death, Graft loss etc)

Am J Kidney Dis. 2017;69(1):78-86

Renin-Angiotensin System Blockade and Long-term Clinical Outcomes in Kidney Transplant Recipients: A Meta-analysis of Randomized Controlled Trials

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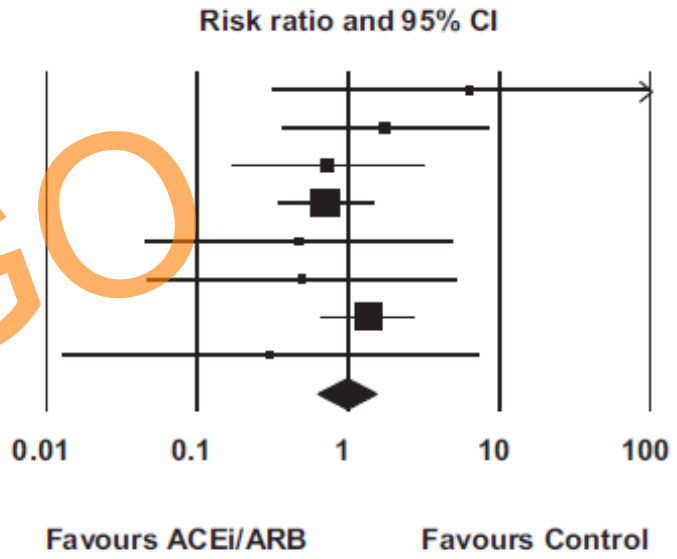
Trial	Year	Risk ratio	95% CI		p	Dead / Total RAS blockade	Dead / Total Control
Midtvedt	2001	6.36	0.31	129.85	0.2	2 / 54	0 / 69
Amara	2010	1.76	0.36	8.70	0.5	4 / 25	2 / 22
Philipp	2010	0.73	0.16	3.21	0.7	3 / 255	4 / 247
Ibrahim	2013	0.71	0.33	1.49	0.4	10 / 77	14 / 76
Paoletti	2013	0.47	0.04	4.97	0.5	1 / 36	2 / 34
Salzberg	2014	0.49	0.05	5.30	0.6	1 / 66	2 / 65
Knoll	2015	1.35	0.64	2.83	0.4	14 / 103	11 / 109
Mandelbrot	2015	0.30	0.01	7.41	0.5	0 / 138	1 / 126
Summary RR		**0.96**	**0.62**	**1.51**	**0.9**		

Q 4.8; p 0.87; $I^2 = 0\%$



Mortality Nearly Identical in ACE/ARB vs Control

ACE/ARB: 35/754 = 4.6%

Control: 36/748 = 4.8%

Am J Kidney Dis. 2017;69(1):78-86

THE LANCET
Diabetes & Endocrinology

When evidence doesn't generalise: the case of ACE inhibition

This trial is a timely reminder that although generalisability of treatment benefit can usually be assumed, the size of benefit cannot. True evidence-based practice evolves from strategically planned research targeted at evidence gaps, and requires that clinicians are prepared to challenge their own cognitive biases to implement that evidence in their practice.

Angela C Webster, Nicholas B Cross*

Summary

1. Approximately 15 to 25% of patients referred for kidney transplant evaluation have evidence of LV dysfunction.

2. Many reports have shown improvements in cardiac function parameters as well as resolution of symptomatic CHF following kidney transplantation

3. LV dysfunction at the time of transplantation and 'failure to normalize' LV function are both important risk factors for poor outcomes. Selecting appropriate candidates who will ultimately improve is not straightforward and will require further study.

4. de novo CHF is common post-transplant and is associated with inferior graft and patient outcomes

5. With respect to treatment, there remains insufficient evidence whether ACE/ARBs improve clinical outcomes in kidney transplant recipients. Further RCTs using ACE/ARB will be challenging if not impossible to conduct given known benefits in the non-CKD population, 'perceived' benefit in transplant patients and their common use as anti-hypertensives in this population.

Heart Failure in Renal Transplant Recipients

KDIGO Controversies Conference on Heart Failure in Chronic Kidney Disease

May 27, 2017

Greg Knoll MD MSc

Professor of Medicine, University of Ottawa

Senior Scientist, Ottawa Hospital Research Institute

Co-Chair, KDIGO Guideline for the Evaluation of Candidates for Kidney Transplantation