



Cardiovascular Risk Reduction in Kidney Transplant Recipients

Istvan Mucsi

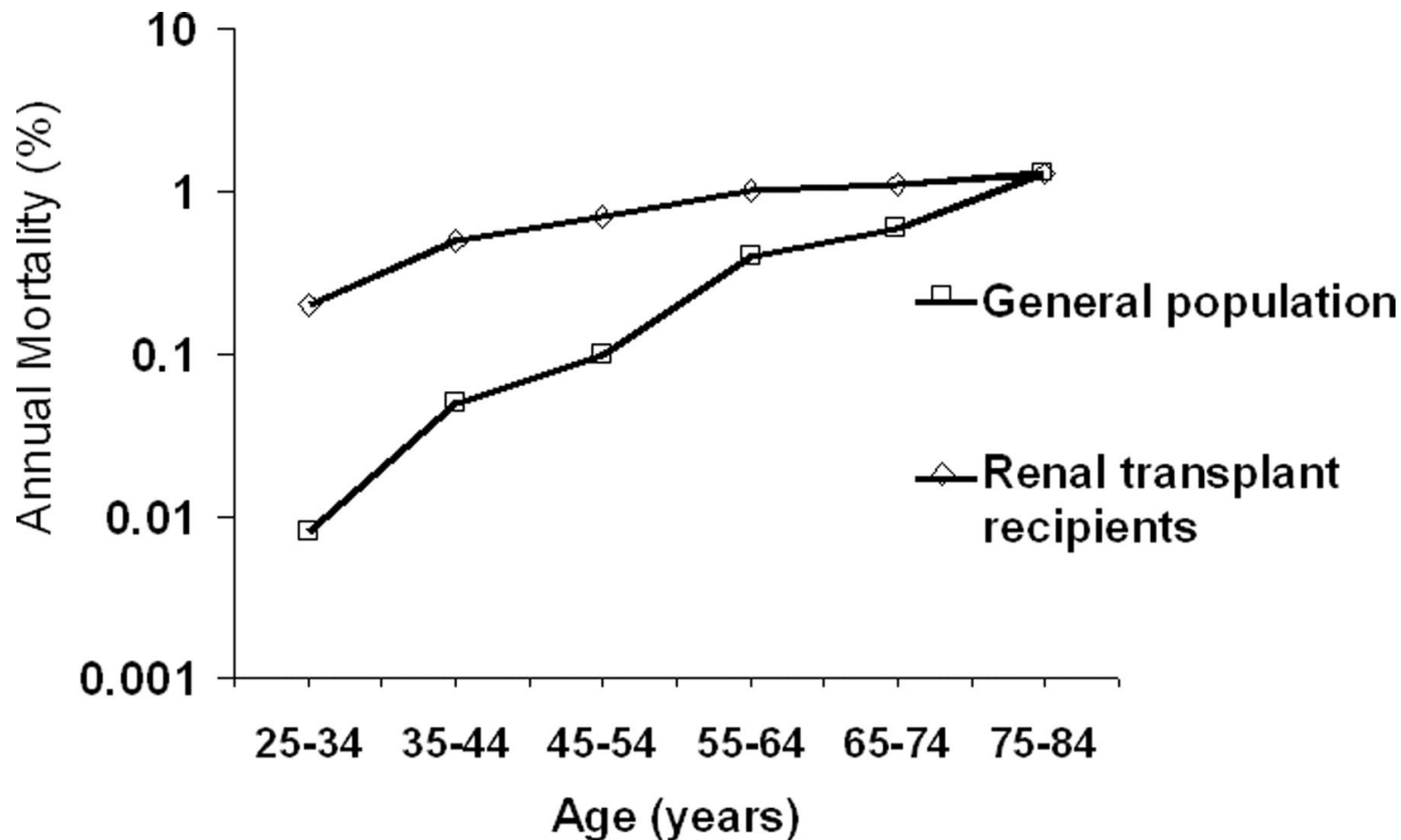
University Health Network, Toronto, Ontario, Canada
and
Semmelweis University Budapest, Hungary

Conflict of interest: none

Lots to talk about....

- Risk assessment, risk prediction
- Early/peri-op risk – pre-tx screening
- CVD and CV risk factors in Tx
- Hypertension
- DM
- Lipids
- Obesity
- Bone – FGF23
- Psycho-social factors - depression
- Prediction, assessment, follow-up
- How to manage...

Cardiovascular mortality in kidney transplant recipients



The ESRD cycle

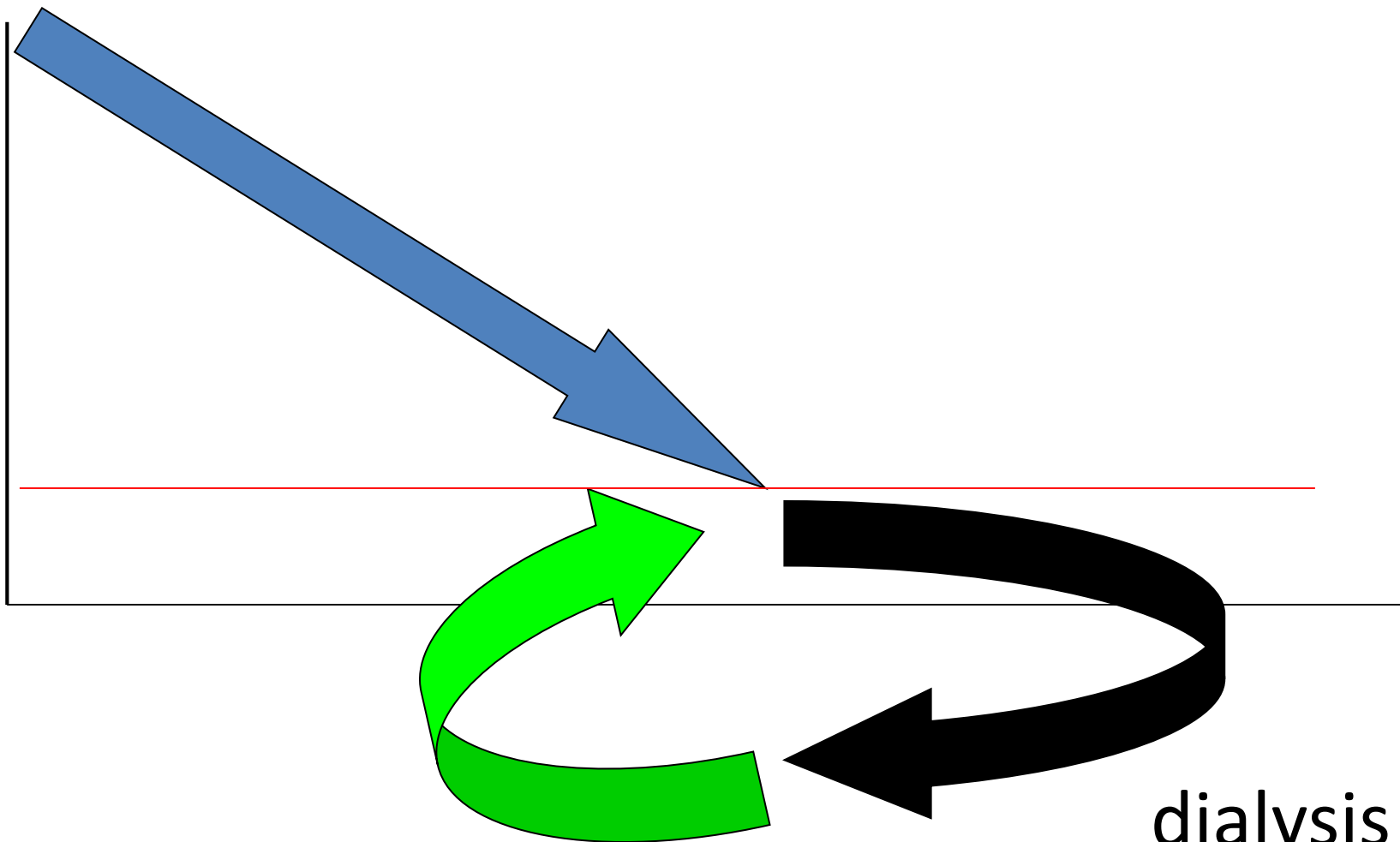
GFR ml/min/1,73 m²

120

15

transplantation

dialysis



Association of pre-transplant dialysis duration with outcome in kidney transplant recipients: a prevalent cohort study

Adam Remport • Andras Keszei • Eszter Panna Vamos •
Marta Novak • Jeno Jaray • Laszlo Rosivall •
Istvan Mucsi • Miklos Zsolt Molnar

Int Urol Nephrol. 2011 Mar;43(1):215-24

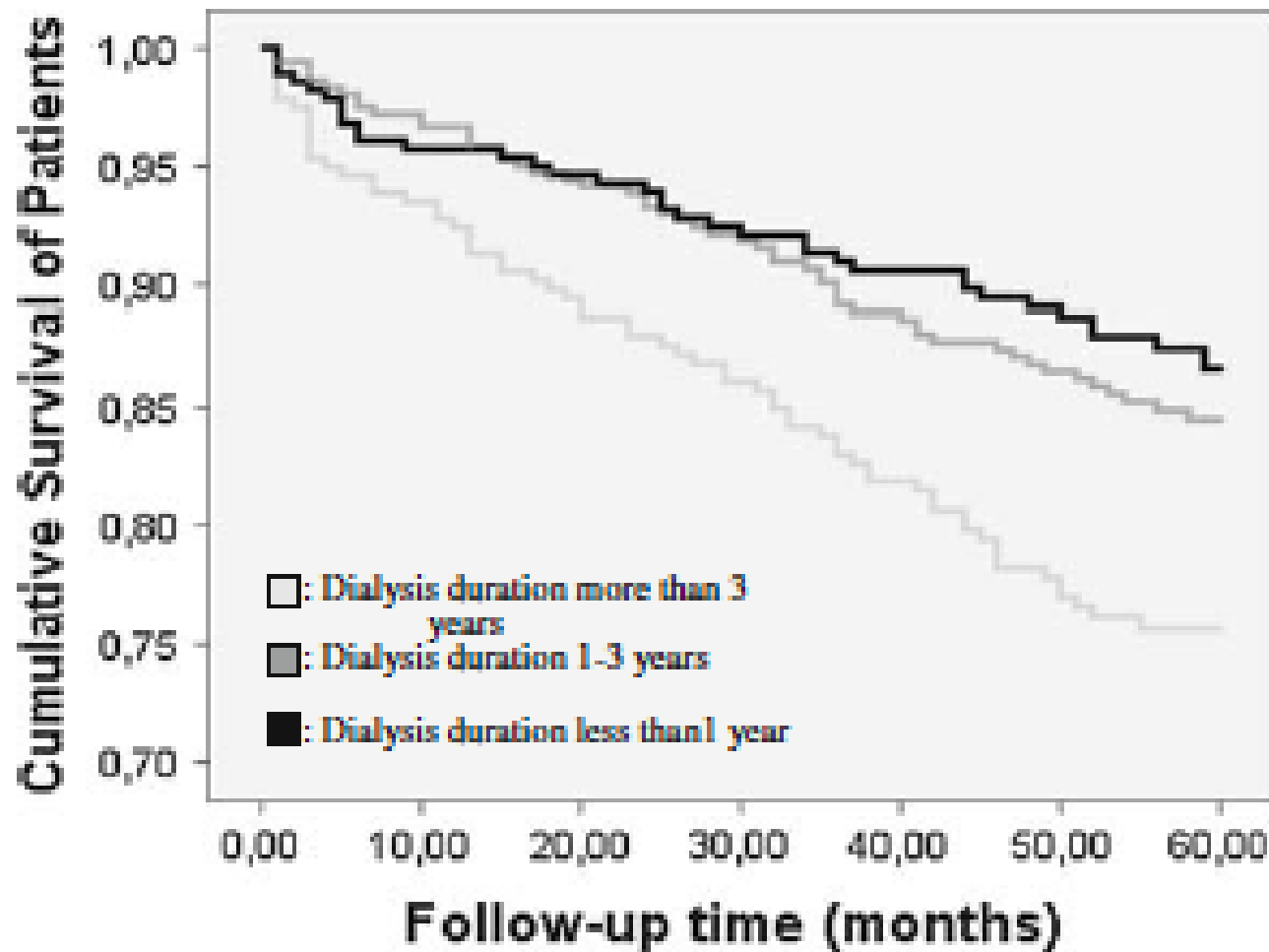
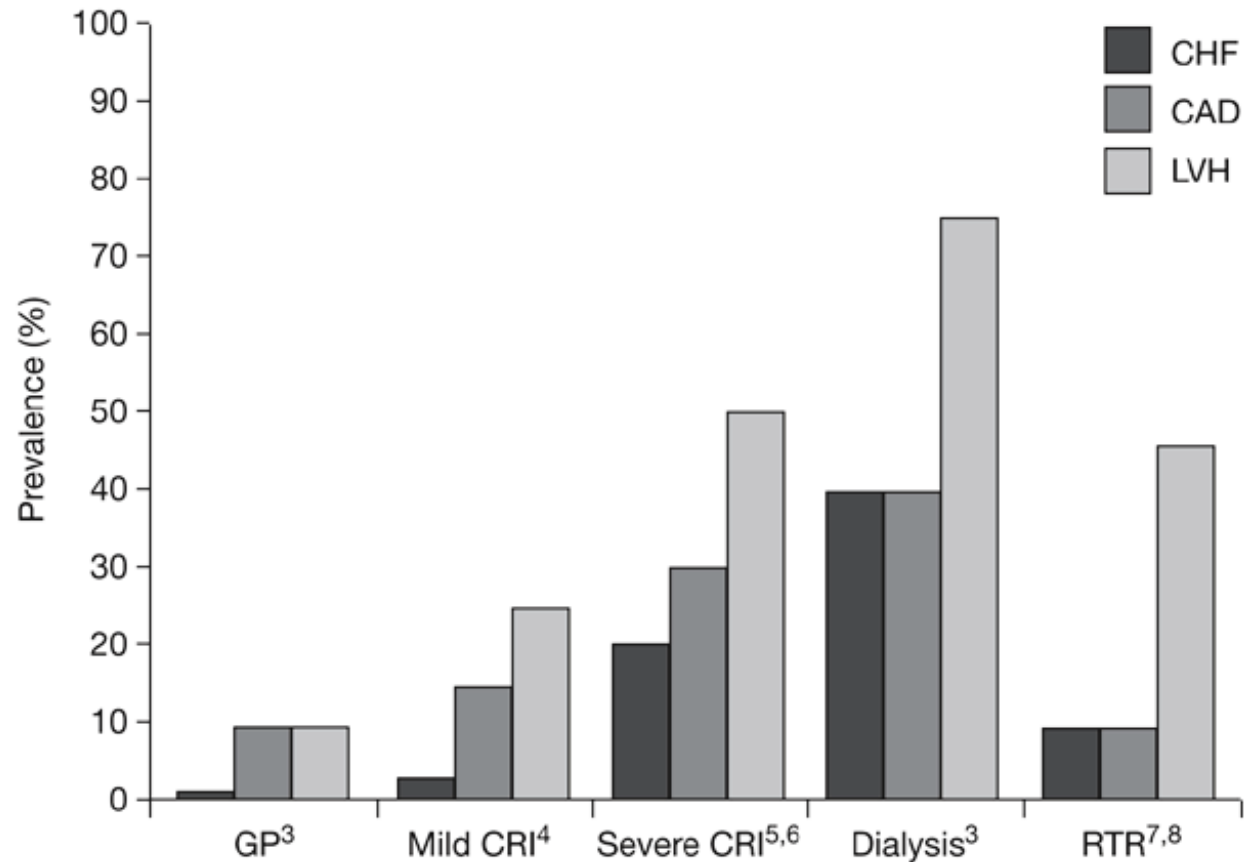
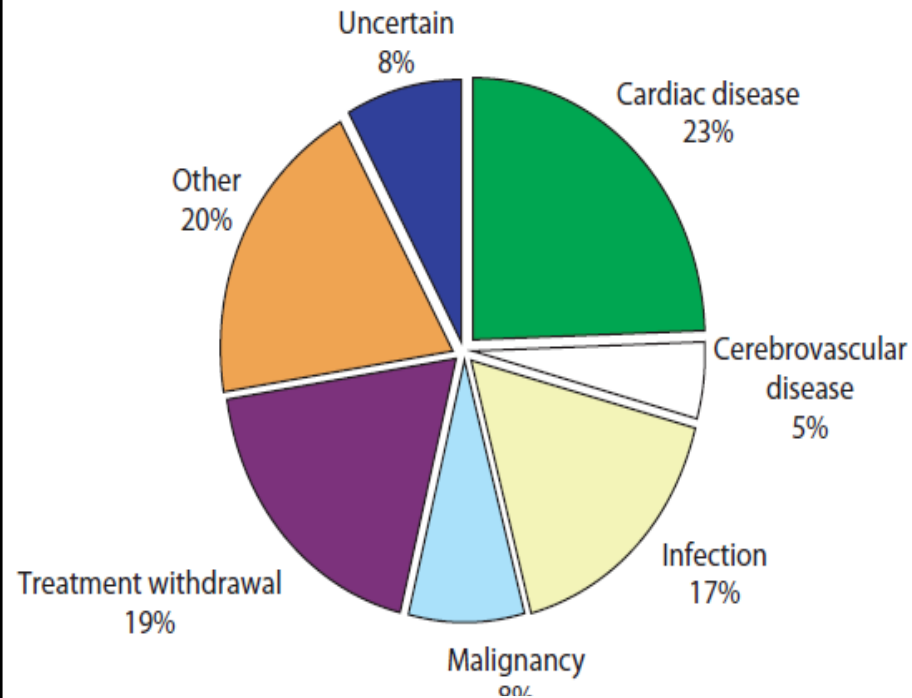


Figure 1 Prevalence of cardiovascular disease in patients with renal disease

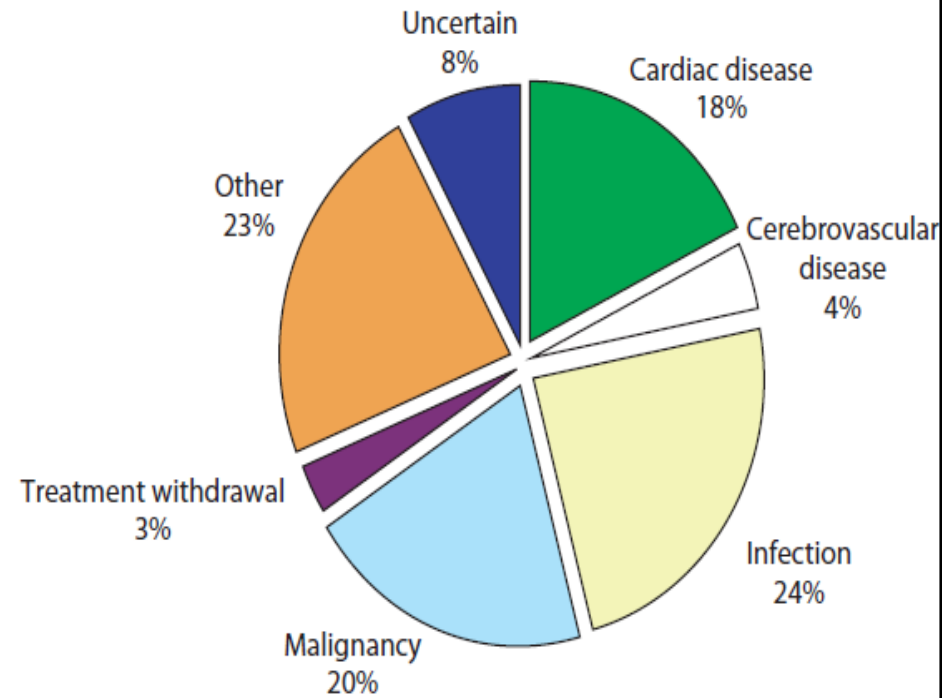


Rigatto C and Parfrey P (2006) Therapy Insight: management of cardiovascular disease in the renal transplant recipient *Nat Clin Pract Nephrol* **2**: 514–526 doi:10.1038/ncpneph0253

Dialysis

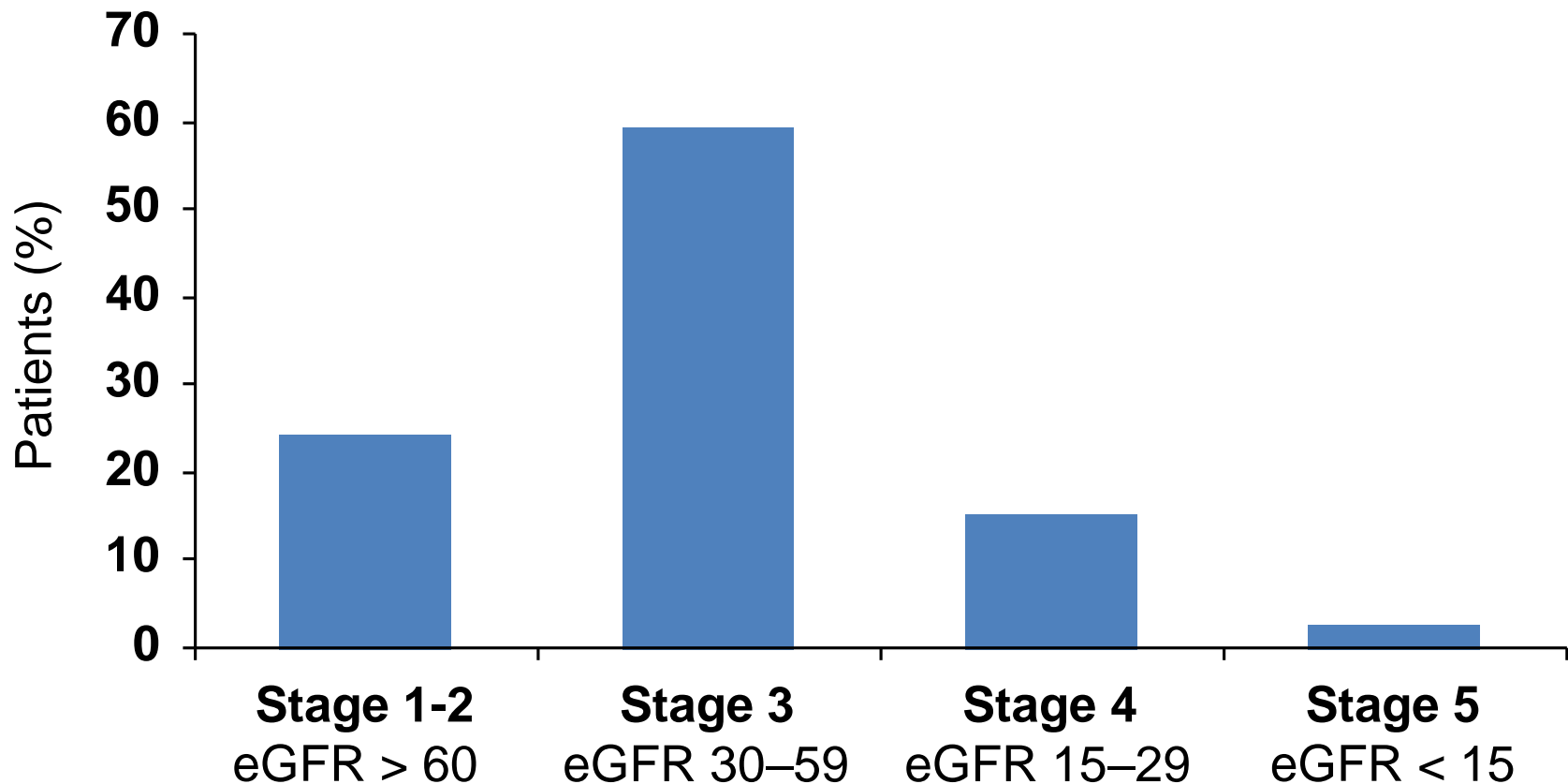


RTx



Cause of mortality; UK Renal Registry – courtesy Dr. D Goldsmith

Majority of transplant recipients have kidney function equivalent to stage 3 CKD or worse (UK data)

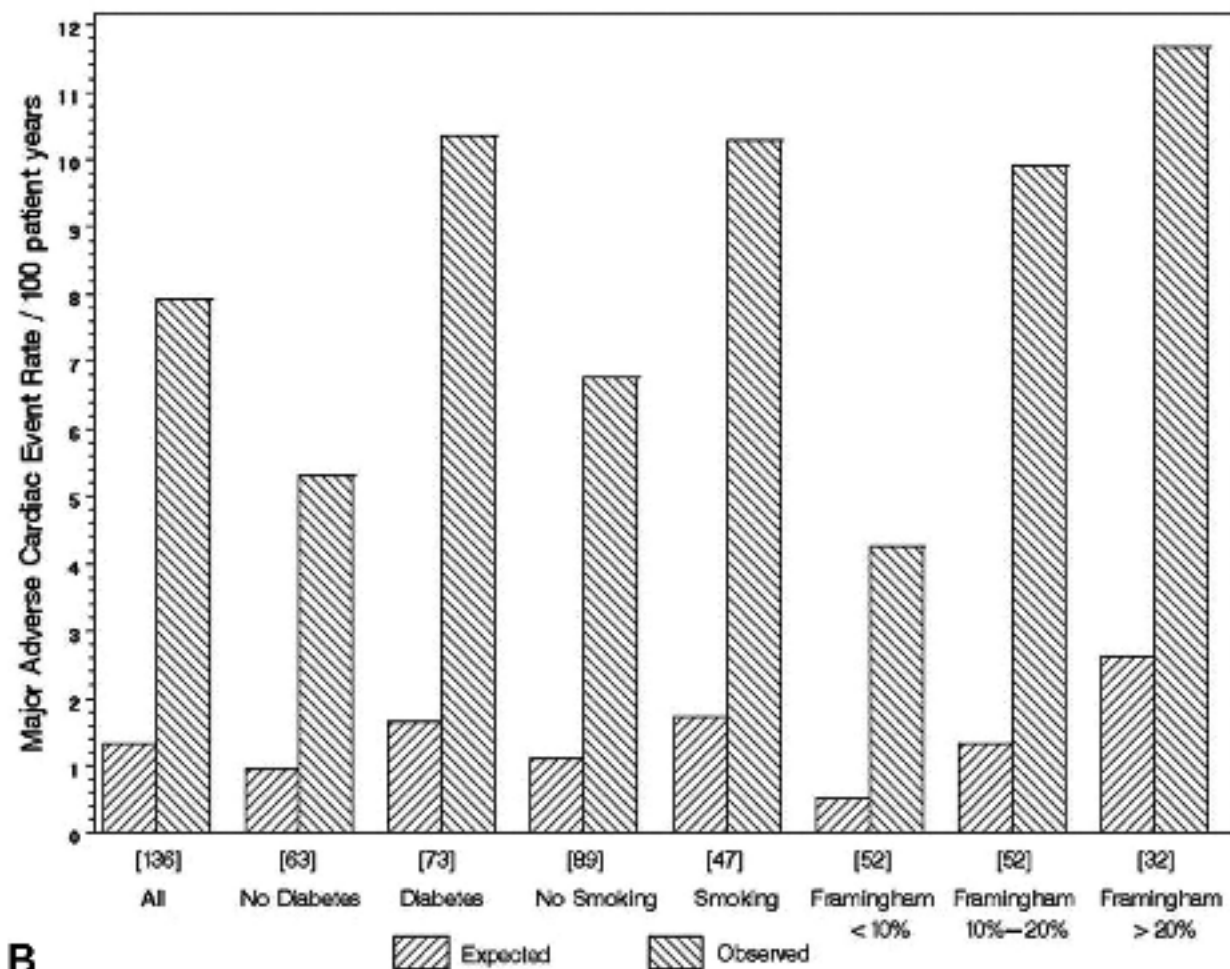


19,074 adult patients with a functioning kidney transplant at the end of 2005
UK Renal Registry Report 2006. Chapter 1.

Assessing CV risk

Framingham Risk Score and Novel Cardiovascular Risk Factors Underpredict Major Adverse Cardiac Events in Kidney Transplant Recipients

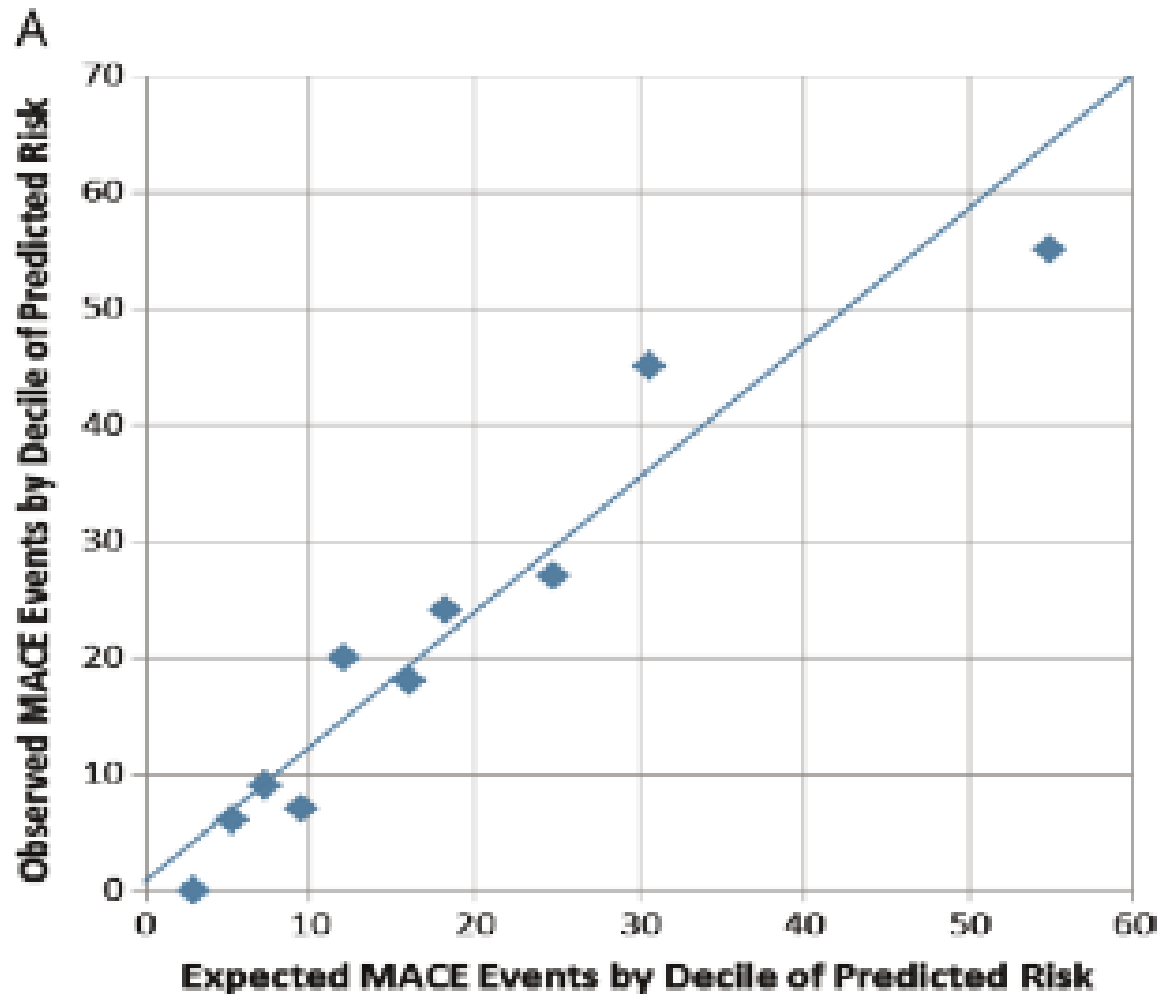
Samuel A. Silver,¹ Michael Huang,² Michelle M. Nash,² and G. V. Ramesh Prasad^{1,2,3}



Transplantation
2011;92: 183–189

The External Validation of the Cardiovascular Risk Equation for Renal Transplant Recipients: Applications to BENEFT and BENEFT-EXT Trials

Inga Soveri,^{1,7} Jon Snyder,² Hallvard Holdaas,³ Ingar Holme,⁴ Alan G. Jardine,⁵
Gilbert J. L'Italien,⁶ and Bengt Fellström¹



- age,
- Previous coronary heart disease
- Smoking
- serum creatinine,
- diabetes mellitus,
- LDL-cholesterol (for MACE only),
- total time on renal replacement therapy (for MACE only),
- number of transplants

Risk prediction

- Framingham Risk Score
- Age
- LDL/total cholesterol
- HDL-cholesterol
- Blood pressure
- Presence of diabetes
- Smoker status
- Lisbon conference (2007)
- age 60 years
- dyslipidemia
- hypertension,
- diabetes mellitus,
- smoking,
- prior cardiovascular disease,
- years on dialysis,
- left ventricular hypertrophy

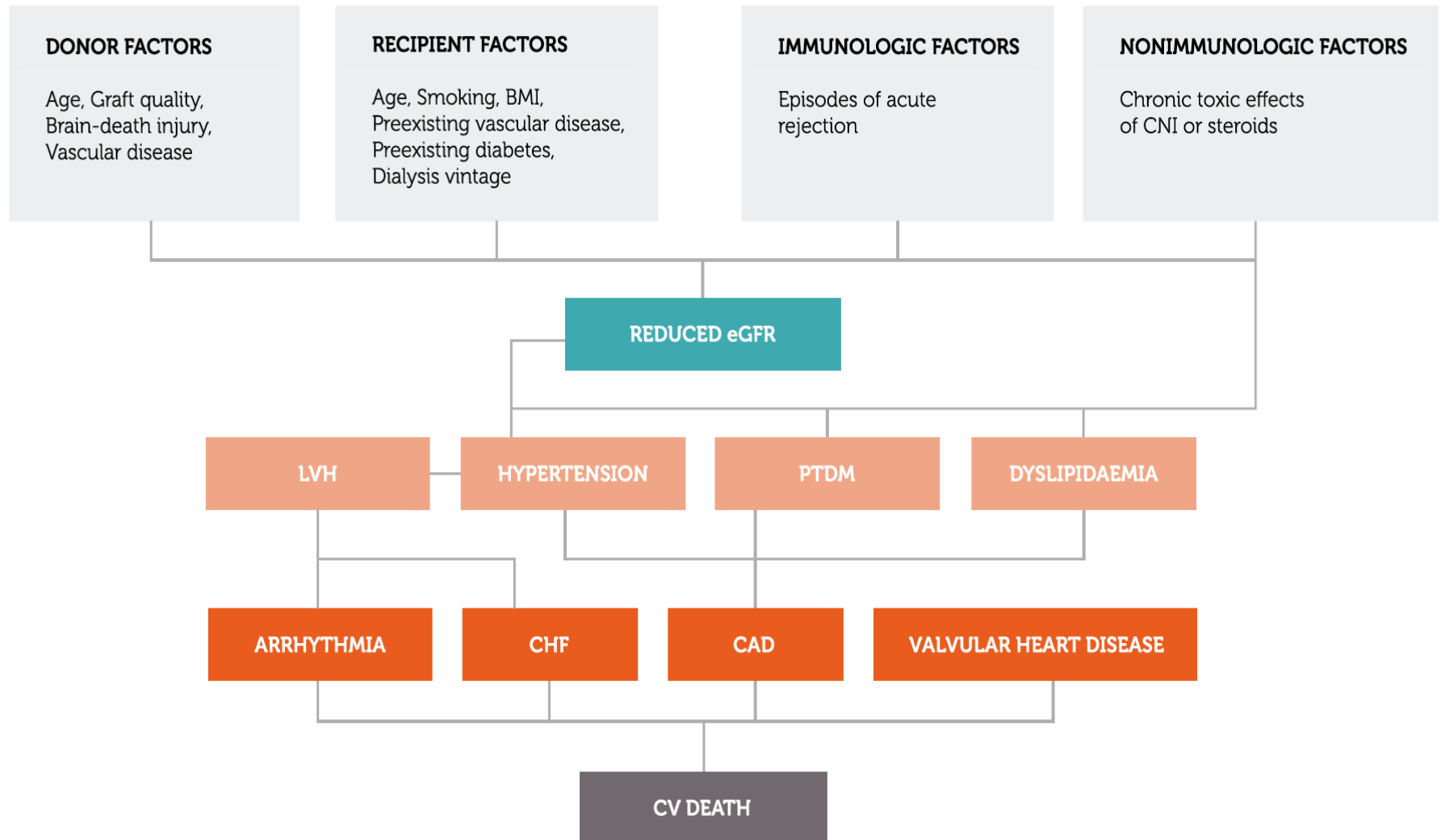
Cardiovascular morbidity and mortality after kidney transplantation

Sokratis Stoumpos,¹ Alan G. Jardine^{1,2} and Patrick B. Mark^{1,2}

Transpl Int. 2014 Jul 31. doi:
10.1111/tri.12413. [Epub ahead of print]

Pre transplant factors

Post transplant factors



Management of cardiovascular disease in patients with kidney disease

Mark R. Kahn, Michael J. Robbins, Michael C. Kim and Valentin Fuster

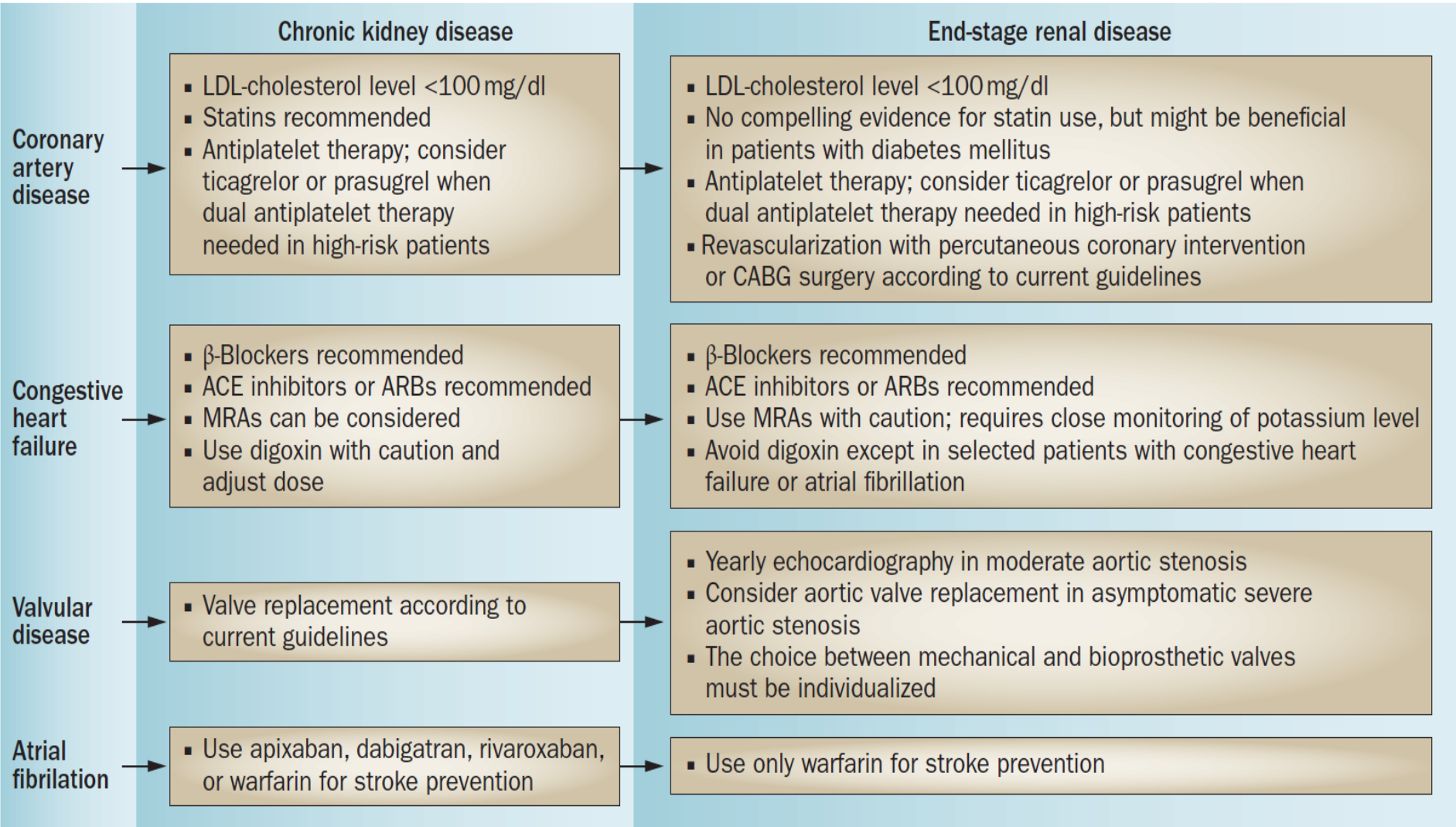


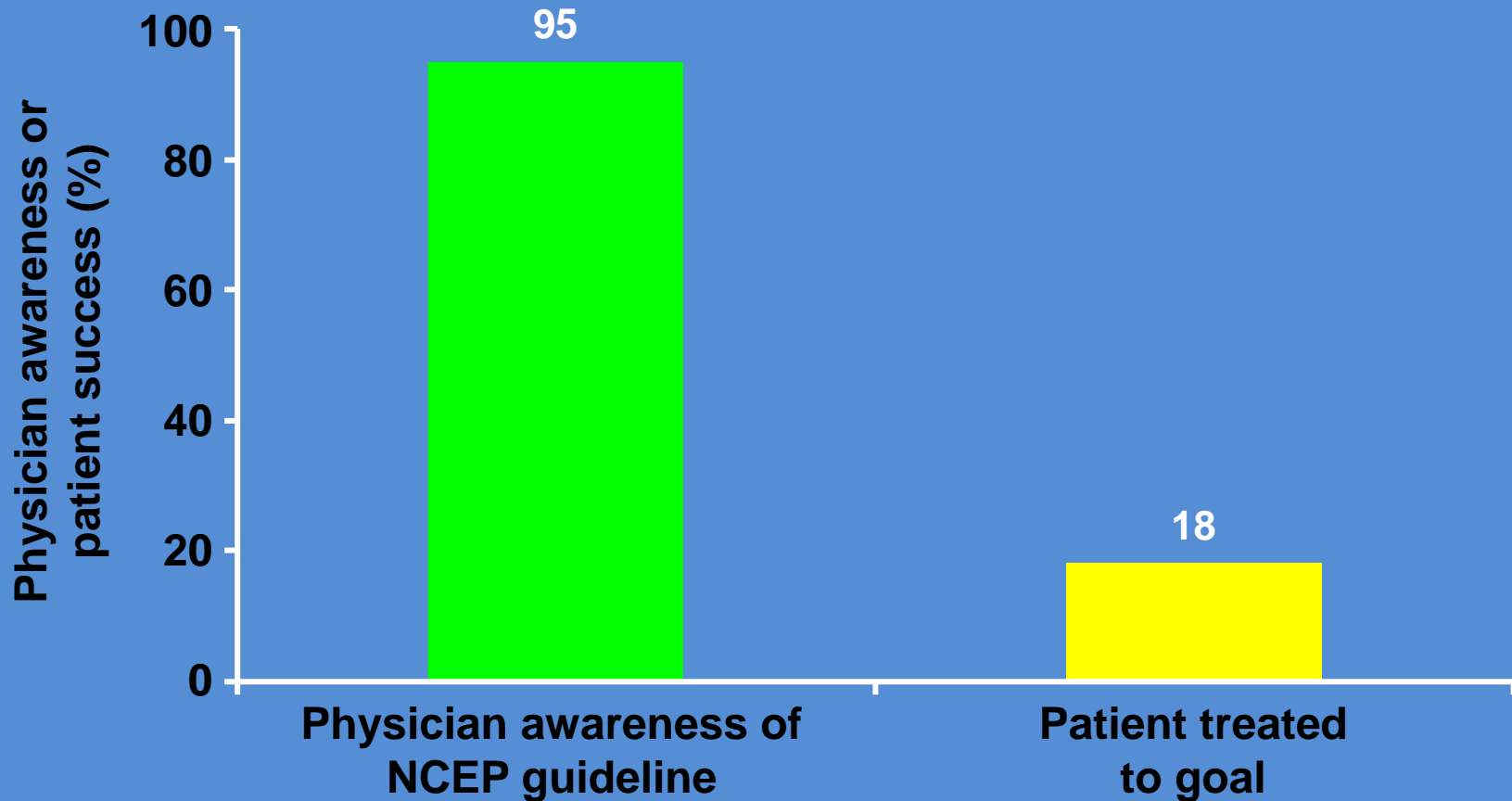
Table 4. Traditional and nontraditional risk factors for CVD in renal transplant recipients

Traditional Risk Factors	Nontraditional Risk Factors
Older age	Decreased kidney function
Male gender	CNI
Family history of CVD	Proteinuria
Diabetes	Anemia
Hypertension	C-reactive protein
Dyslipidemia	Oxidative stress
low HDL	Advanced glycation end products
high LDL	Inflammation
Physical inactivity	Homocysteine
Left ventricular hypertrophy	Uric acid
Menopause	Hyperparathyroidism
Tobacco use	Obesity
	Thrombogenic factors

Djamali, A. et al. Clin J Am Soc Nephrol 2006;1:623-640

CAD treatment gap in the community

Provider awareness does not equal successful implementation



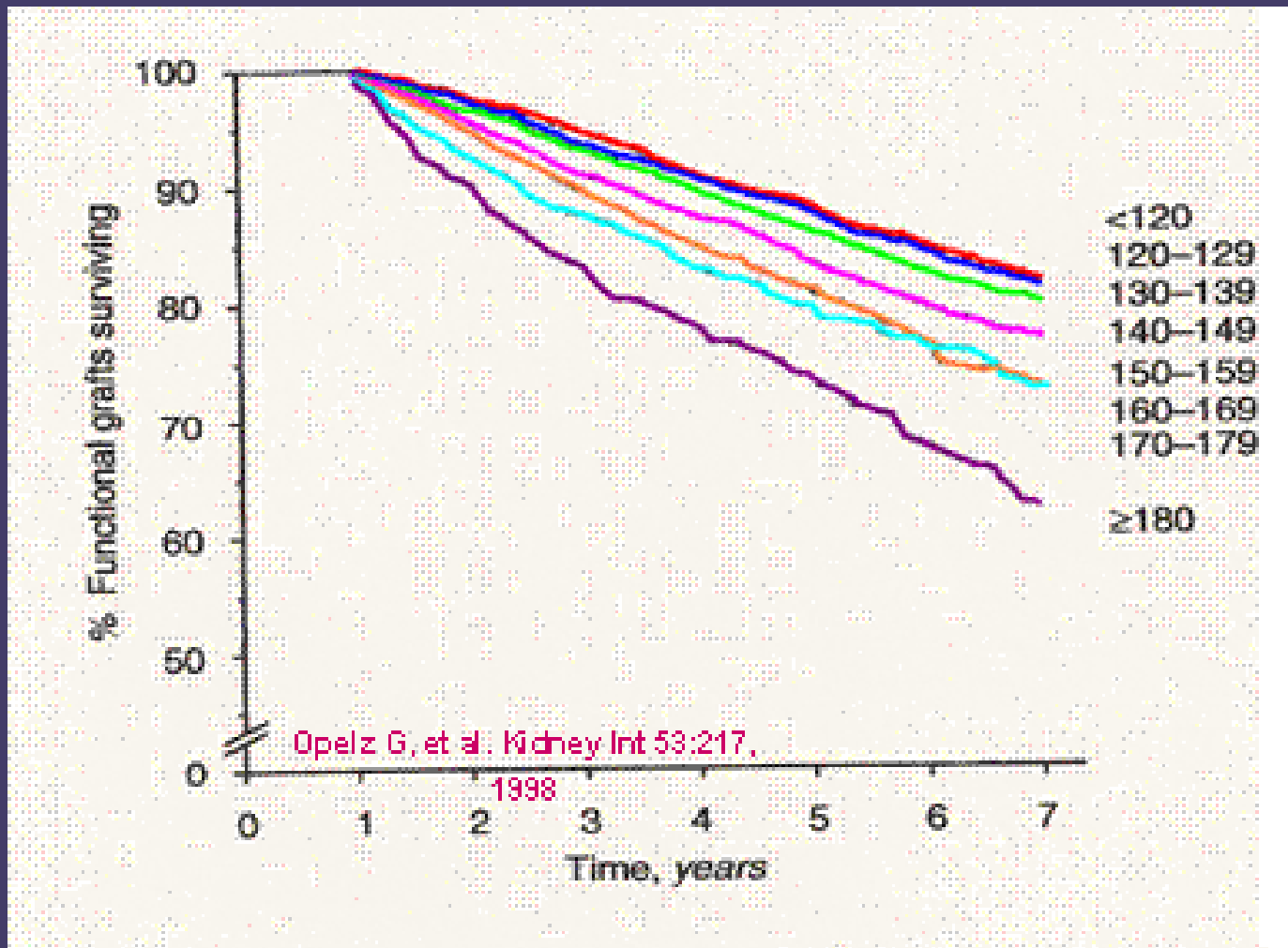
NCEP = National Cholesterol
Education Program

Pearson TA, et al. Arch Intern Med 2000;160:459–67

The world would be a better place if
we kept six of the ten
commandments. Any six.

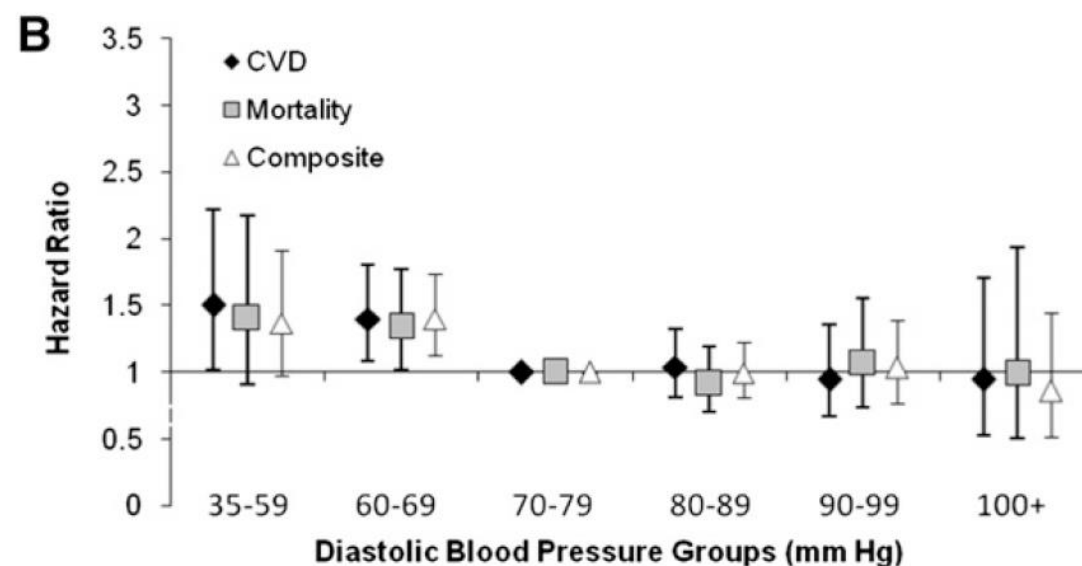
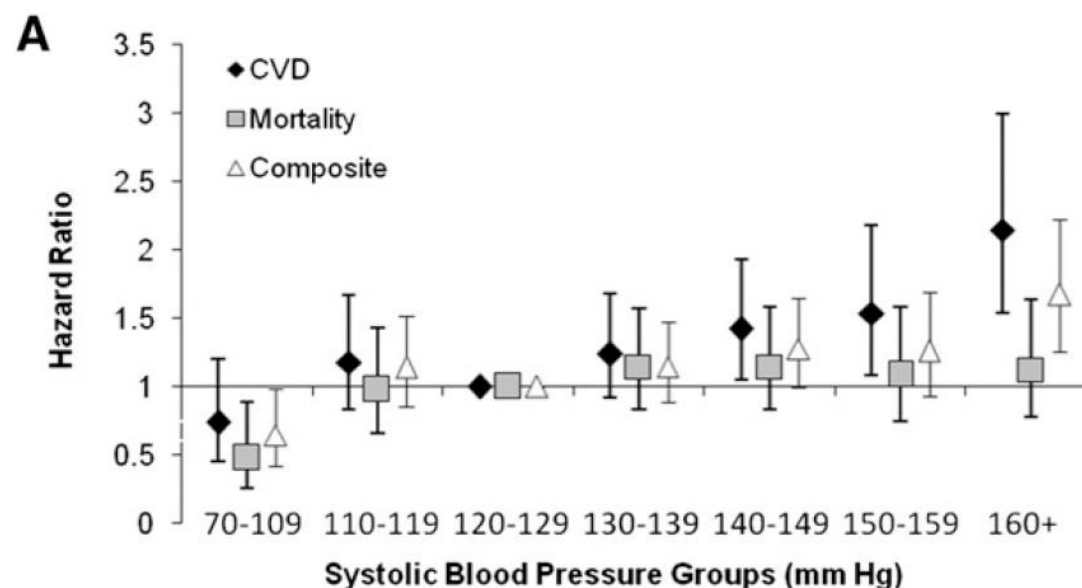
Hypertension

Blood Pressure One Year after Kidney Transplantation and Graft Outcome



Opelz G et al. [*Kidney Int.* 1998 Jan;53\(1\):217-22.](#)

Myra A. Carpenter,* Alin John,[†] Matthew R. Weir,[‡] Stephen R. Smith,[§]
Lawrence Hunsicker,^{||} Bertram L. Kasiske,[¶] John W. Kusek,^{**} Andrew Bostom,^{††}
Anastasia Ivanova,* Andrew S. Levey,[‡] Scott Solomon,^{‡‡} Todd Pesavento,^{§§} and
Daniel E. Weiner[†]



2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults

Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8)

Paul A. James, MD; Suzanne Oparil, MD; Barry L. Carter, PharmD; William C.ushman, MD; Cheryl Dennison-Himmelfarb, RN, ANP, PhD; Joel Handler, MD; Daniel T. Lackland, DrPH; Michael L. LeFevre, MD, MSPH; Thomas D. MacKenzie, MD, MSPH; Olugbenga Ogedegbe, MD, MPH, MS; Sidney C. Smith Jr, MD; Laura P. Svetkey, MD, MHS; Sandra J. Taler, MD; Raymond R. Townsend, MD; Jackson T. Wright Jr, MD, PhD; Andrew S. Narva, MD; Eduardo Ortiz, MD, MPH

- hypertensive persons aged 60 years or older to a BP goal of less than **150/90mmHg** and hypertensive persons 30 through 59 years of age to a diastolic goal of less than 90mmHg;
- there is insufficient evidence in hypertensive persons younger than 60 years for a systolic goal, or in those younger than 30 years for a diastolic goal, so the panel recommends a BP of less than **140/90mmHg** for those groups (expert opinion).
- The same thresholds and goals are recommended for hypertensive adults with diabetes or nondiabetic chronic kidney disease (CKD) as for the general hypertensive population < 60 years.
- MODERATE: initiating drug treatment with an ACEI, ARB, calcium channel blocker, or thiazide-type diuretic in the nonblack hypertensive population, including those with diabetes.
- In the black hypertensive population, including those with diabetes, a calcium channel blocker or thiazide-type diuretic is recommended as initial therapy.
- There is moderate evidence to support initial or add-on ACEI/ARB in persons with CKD to improve kidney outcomes.

Observational Modeling of Strict vs Conventional Blood Pressure Control in Patients With Chronic Kidney Disease

Csaba P. Kovesdy, MD; Jun L. Lu, MD; Miklos Z. Molnar, MD, PhD; Jennie Z. Ma, PhD; Robert B. Canada, MD; Elani Streja, PhD; Kamyar Kalantar-Zadeh, MD, MPH, PhD; Anthony J. Bleyer, MD, MS

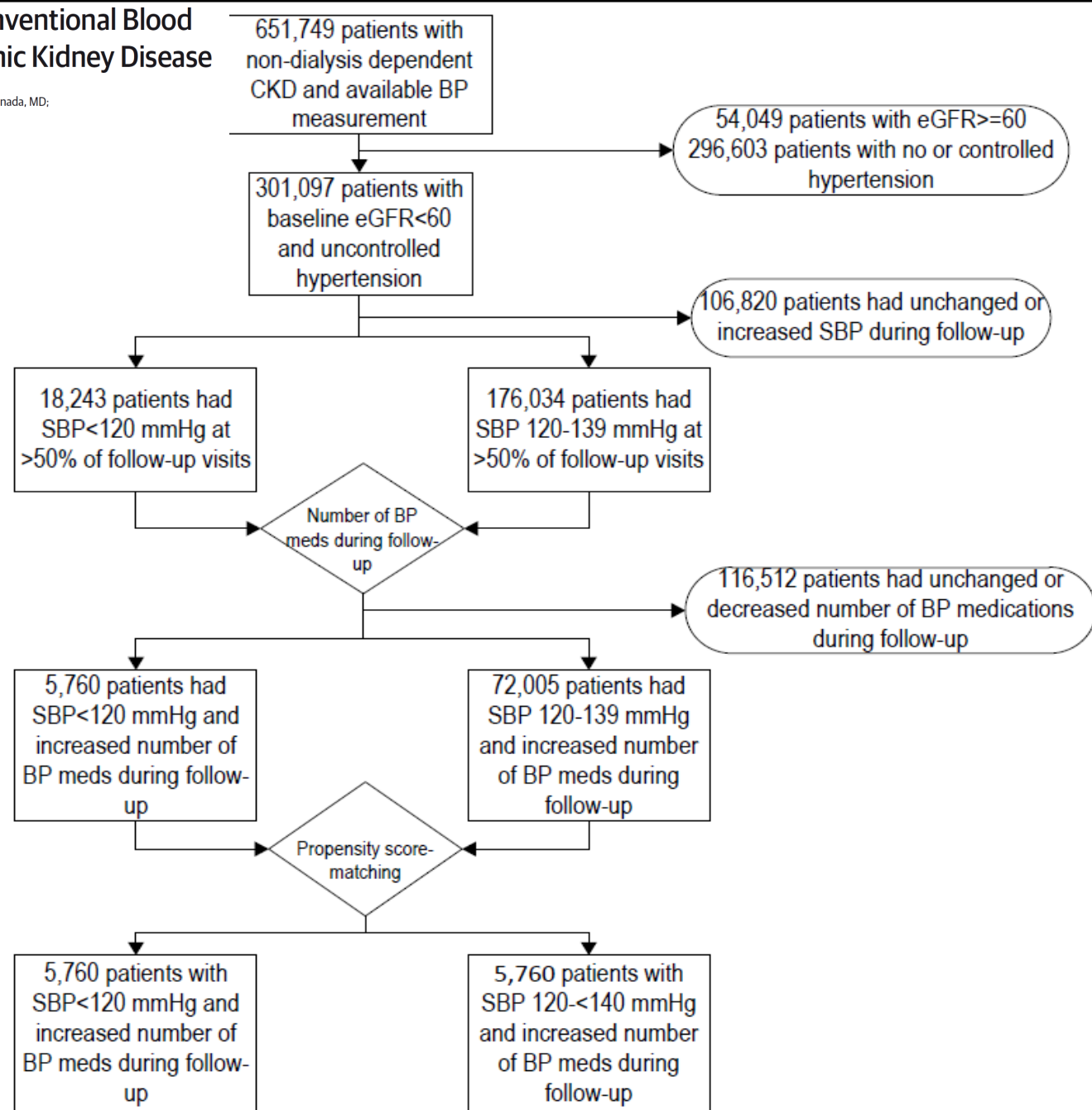
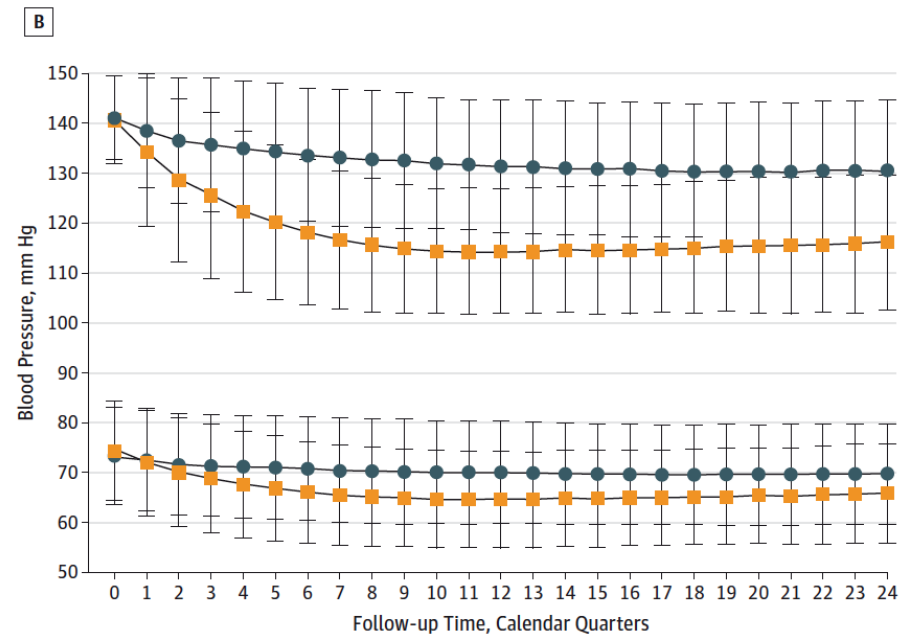
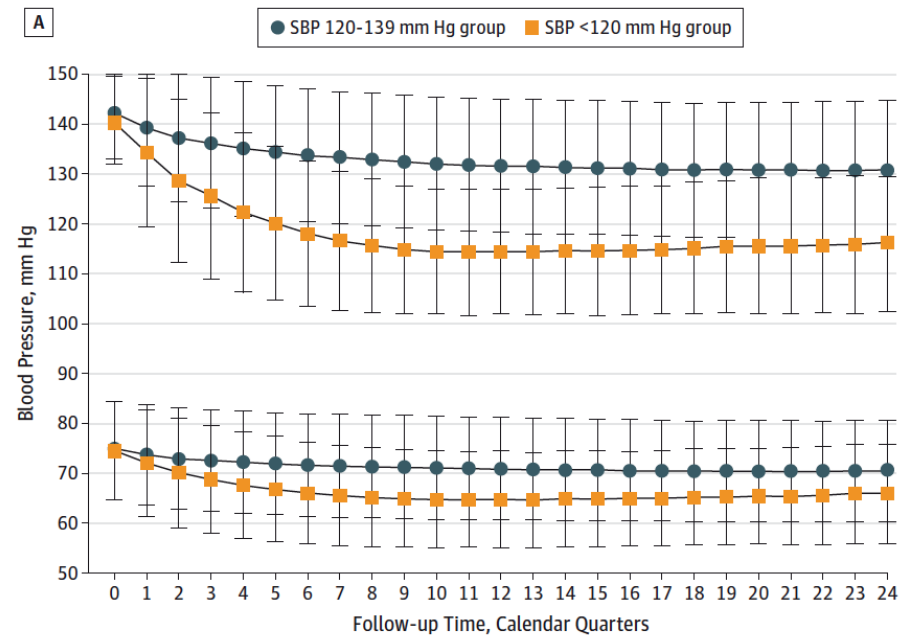


Figure 2. Follow-up Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) in Patients With SBP Less Than 120 vs 120 to 139 mm Hg



Observational Modeling of Strict vs Conventional Pressure Control in Patients With Chronic Kidney

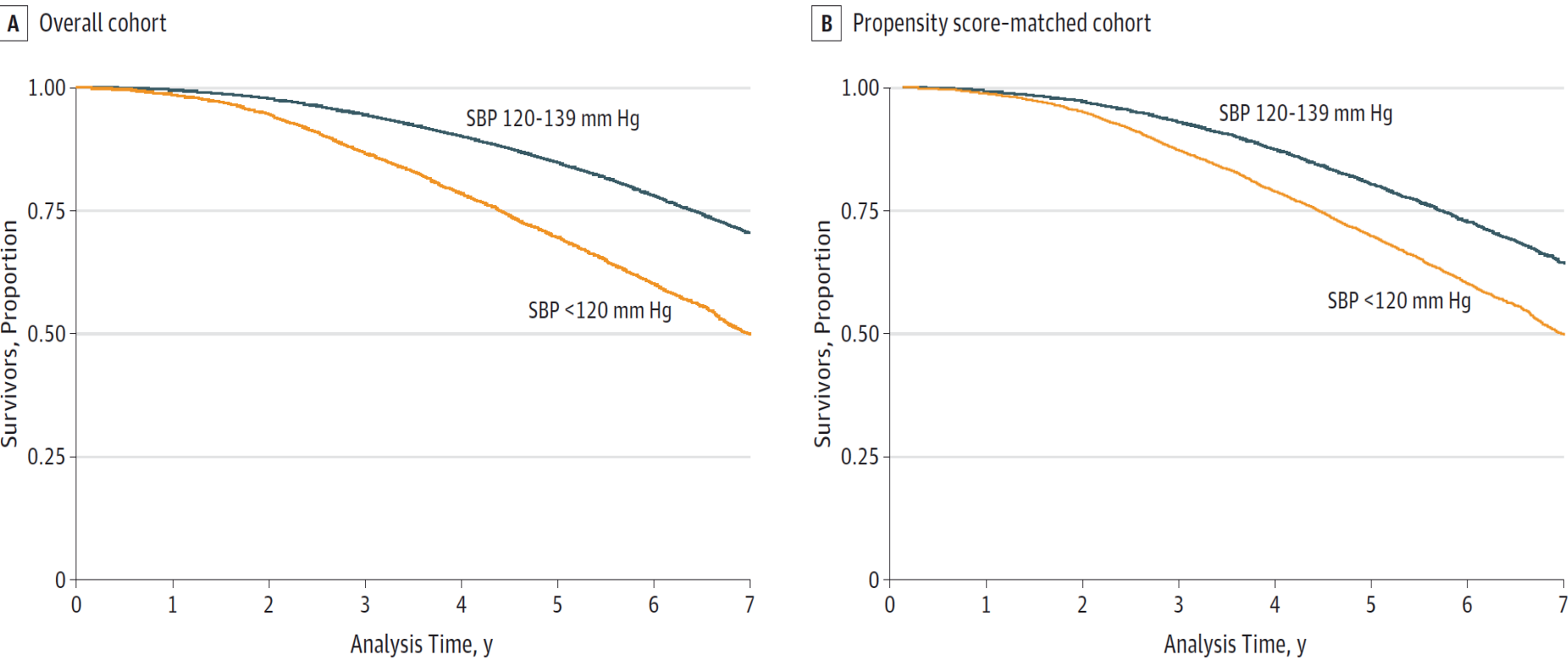
Csaba P. Kovesdy, MD; Jun L. Lu, MD; Miklos Z. Molnar, MD, PhD; Jennie Z. Ma, PhD; Robert B. Canada, MD; Elani Streja, PhD; Kamyar Kalantar-Zadeh, MD, MPH, PhD; Anthony J. Bleyer, MD, MS

JAMA Intern Med. 2014 Aug 4.
doi:
10.1001/jamainternmed.2014.
3279.

Observational Modeling of Strict vs Conventional Blood Pressure Control in Patients With Chronic Kidney Disease

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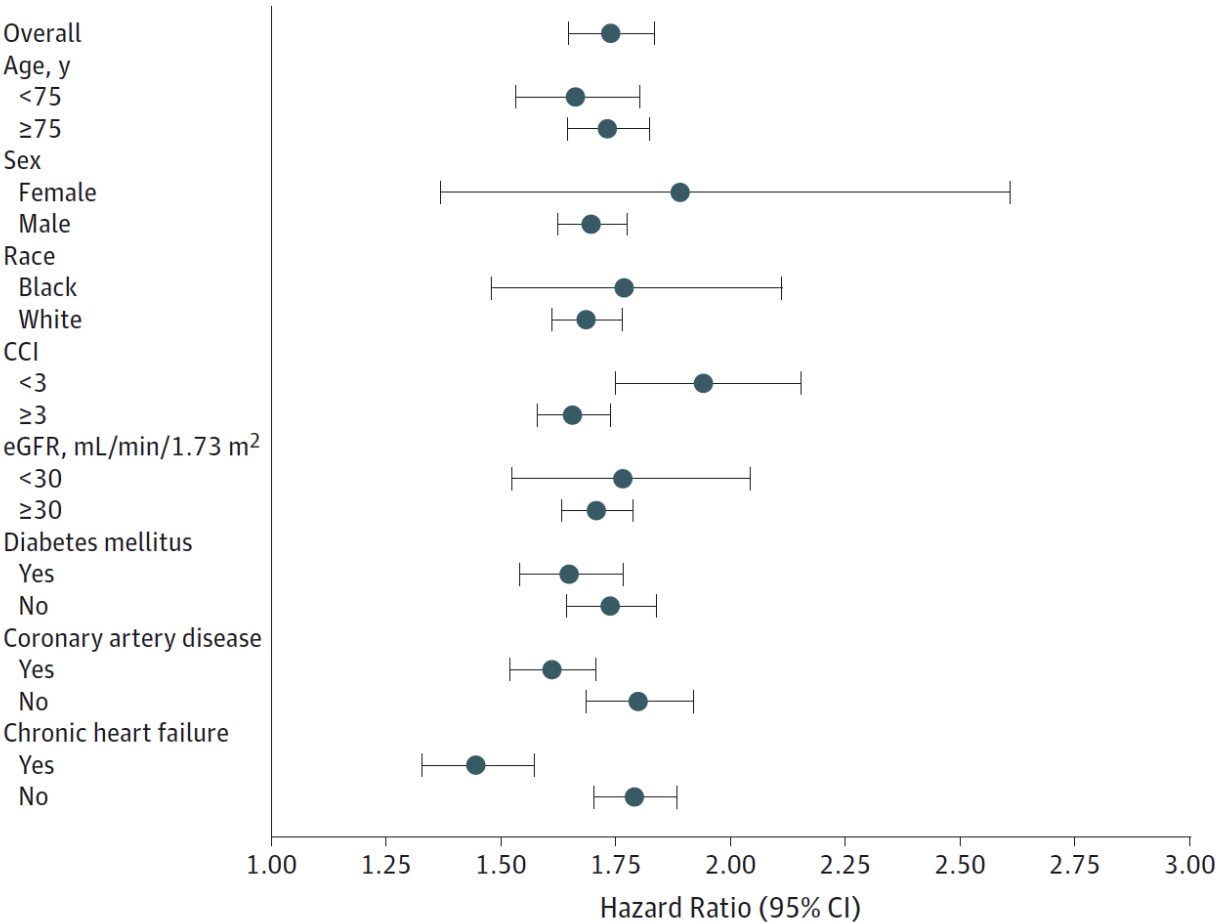
Figure 3. Kaplan-Meier Survival Curves of Patients With Follow-up Systolic Blood Pressure (SBP) Less Than 120 vs 120 to 139 mm Hg



Observational Modeling of Strict vs Conventional Blood Pressure Control in Patients With Chronic Kidney Disease

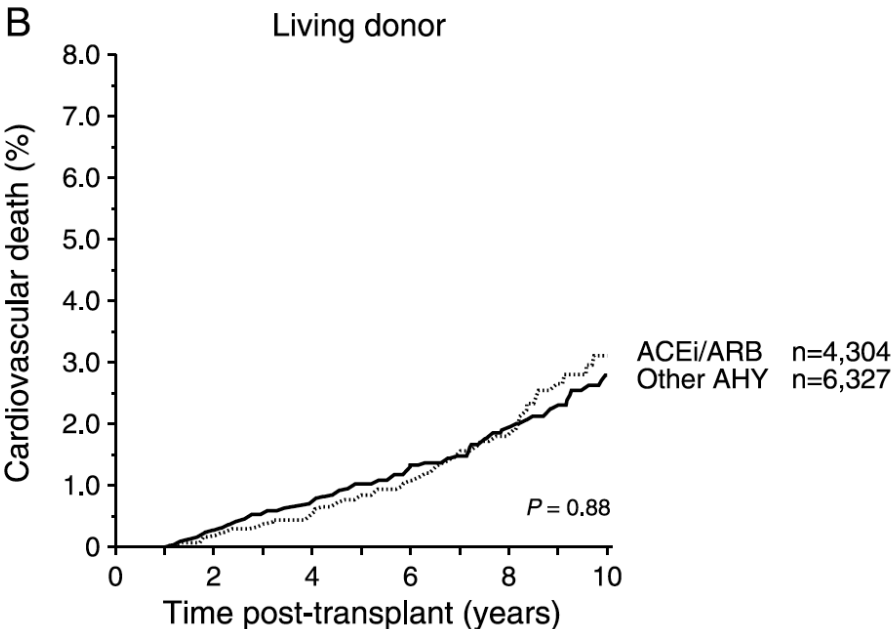
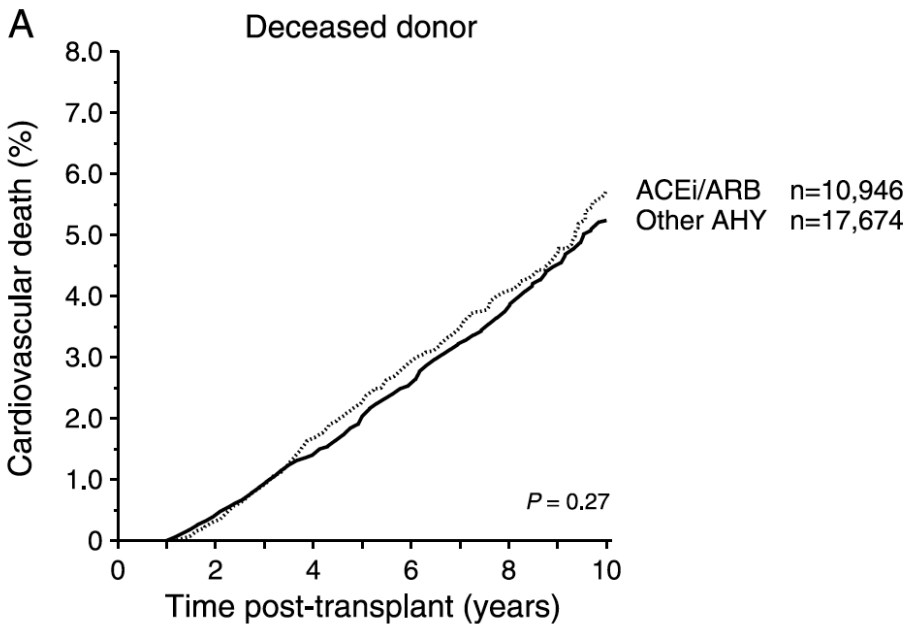
Csaba P. Kovesdy, MD; Jun L. Lu, MD; Miklos Z. Molnar, MD, PhD; Jennie Z. Ma, PhD; Robert B. Canada, MD; Elani Streja, PhD; Kamyar Kalantar-Zadeh, MD, MPH, PhD; Anthony J. Bleyer, MD, MS

Figure 4. Propensity Score–Adjusted Hazard Ratios of All-Cause Mortality Associated With Systolic Blood Pressure Less Than 120 vs 120 to 139 mm Hg in Various Subgroups of Patients in the Overall Cohort



Cardiovascular Death in Kidney Recipients Treated With Renin–Angiotensin System Blockers

Gerhard Opelz and Bernd Döhler



Angiotensin-Converting Enzyme Inhibitor, Angiotensin Receptor Blocker Use, and Mortality in Patients With Chronic Kidney Disease

Miklos Z. Molnar, MD, PhD,^{*,†,‡} Kamyar Kalantar-Zadeh, MD, MPH, PhD,^{*,†} Evan H. Lott,[§] Jun Ling Lu, MD,^{||} Sandra M. Malakauskas, MD, PhD,^{¶,#} Jennie Z. Ma, PhD,[#] Darryl L. Quarles, MD,^{||} Csaba P. Kovesdy, MD^{||,**}

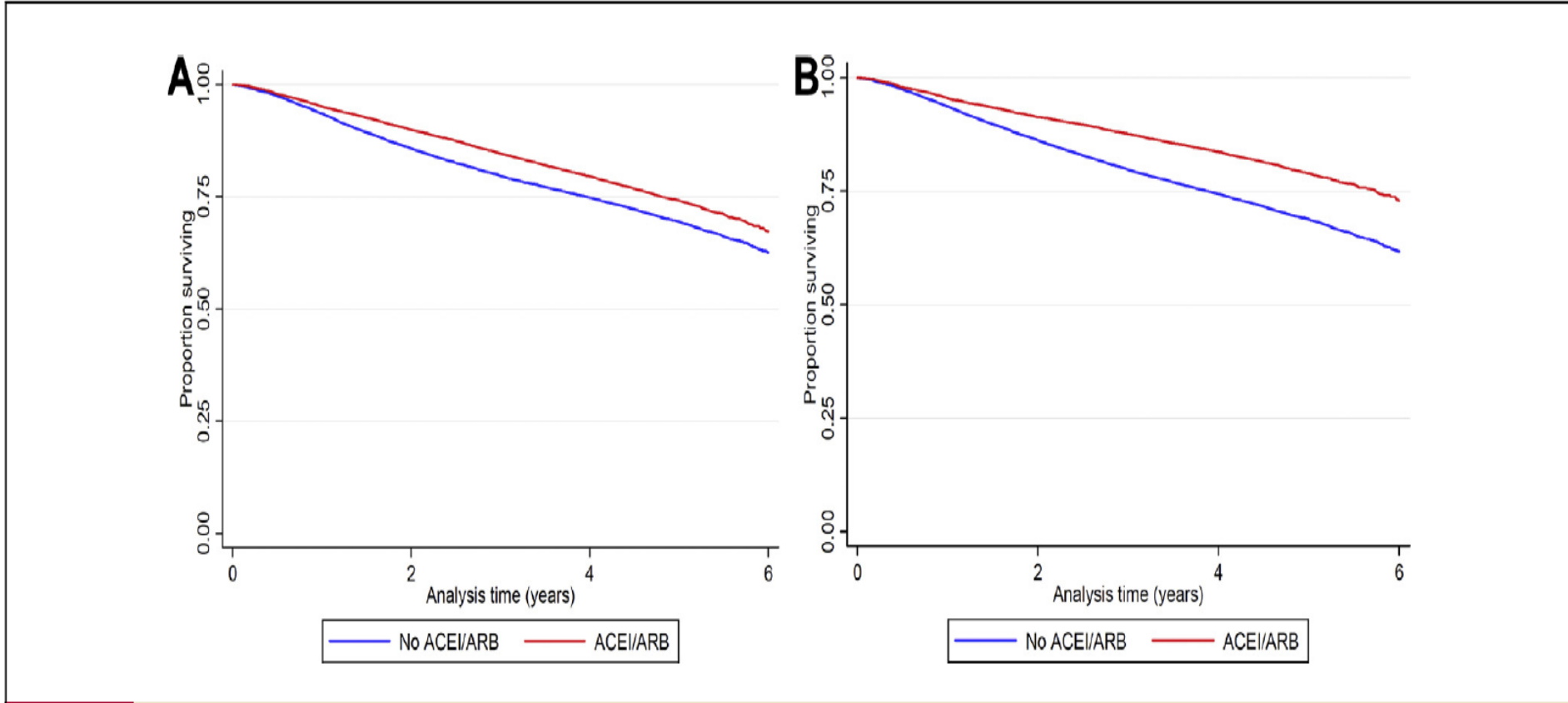


Figure 1

Kaplan-Meier Survival Curves of 20,247 Patients Treated With ACEIs/ARBs and 20,247 Untreated Patients Matched by Propensity Scores

Angiotensin-Converting Enzyme Inhibitor,
Angiotensin Receptor Blocker Use, and Mortality
in Patients With Chronic Kidney Disease

Miklos Z. Molnar, MD, PhD,*†‡ Kamyar Kalantar-Zadeh, MD, MPH, PhD,*‡ Evan H. Lott,§
Jun Ling Lu, MD,|| Sandra M. Malakauskas, MD, PhD,¶# Jennie Z. Ma, PhD,#
Darryl L. Quarles, MD,|| Csaba P. Kovesdy, MD||**

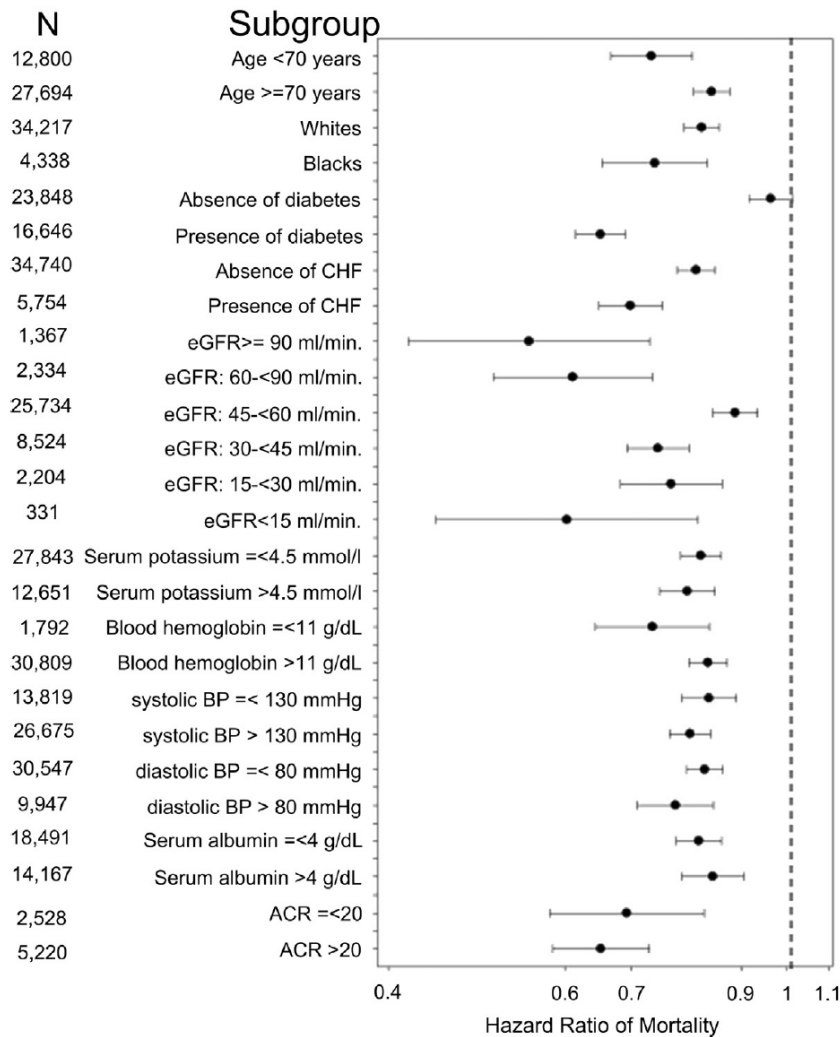


Figure 2 Hazard Ratios (95% CIs) of All-Cause Mortality Associated With ACEI/ARB Administration in Various Subgroups of 40,494 Propensity Score-Matched Patients With Nondialysis-Dependent CKD

Antiplatelet agents

Effects of Antiplatelet Therapy on Mortality and Cardiovascular and Bleeding Outcomes in Persons With Chronic Kidney Disease

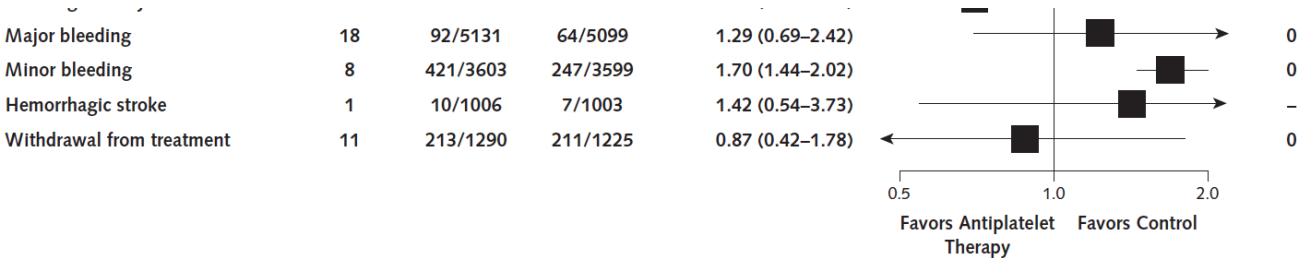
A Systematic Review and Meta-analysis

Suetonia C. Palmer, MB ChB, PhD; Lucia Di Micco, MD; Mona Razavian, MB BS; Jonathan C. Craig, MB ChB, DCh, MM, PhD; Vlado Perkovic, MB BS, PhD; Fabio Pellegrini, MSc; Massimiliano Copetti, MSc, PhD; Giusi Graziano, MSc; Gianni Tognoni, MD; Meg Jardine, MB BS, PhD; Angela Webster, MB BS, PhD; Antonio Nicolucci, MD; Sophia Zoungas, MD, PhD; and Giovanni F.M. Strippoli, MD, PhD, MPH, MM

Ann Intern Med. 2012;156:445-459.

Figure 2. Summary of treatment effects for antiplatelet agents in persons with chronic kidney disease.

Benefits for antiplatelet therapy among persons with CKD are uncertain and are potentially outweighed by bleeding hazards



Dyslipidemia

Dyslipidemia Following Kidney Transplantation: Diagnosis and Treatment

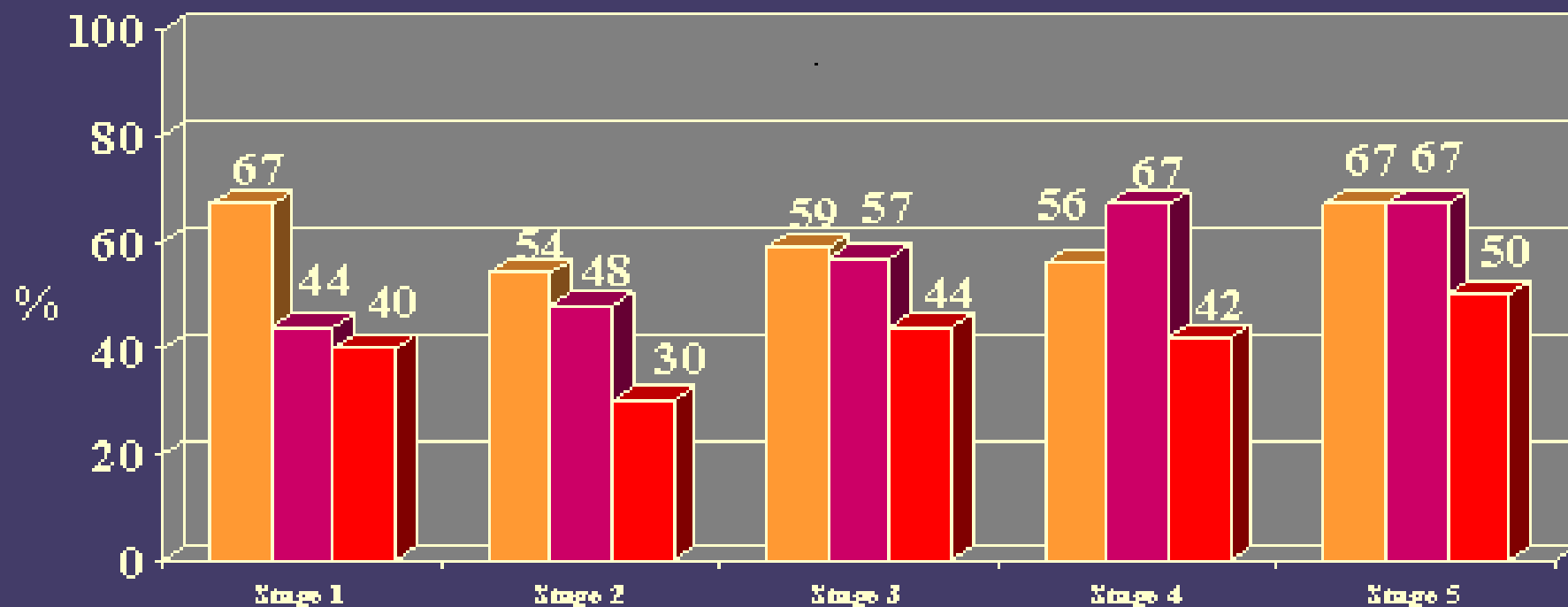
Table 2. Effect of immunosuppressive drugs on lipid parameters

Drug	TC	LDL-C	HDL-C	TG
Cyclosporine	↑↑	↑↑	↓	↑↑
Tacrolimus	↑	↑	↓	↑
Sirolimus	↑↑	↑↑	↓	↑↑↑
Everolimus	↑↑	↑↑	↓	↑↑↑
Mycophenolate mofetil	—	—	—	—
Azathioprine	—	—	—	—
Prednisone	↑	↑	↑	↑
Deflazacort	↑	↑	↑↑	↑
HDL-C—high-density lipoprotein cholesterol; LDL-C—low-density lipoprotein cholesterol; TC—total cholesterol; TG—triglyceride.				

Prevalence of Hyperlipidemia in Renal Transplant Patients Based on CKD Stage

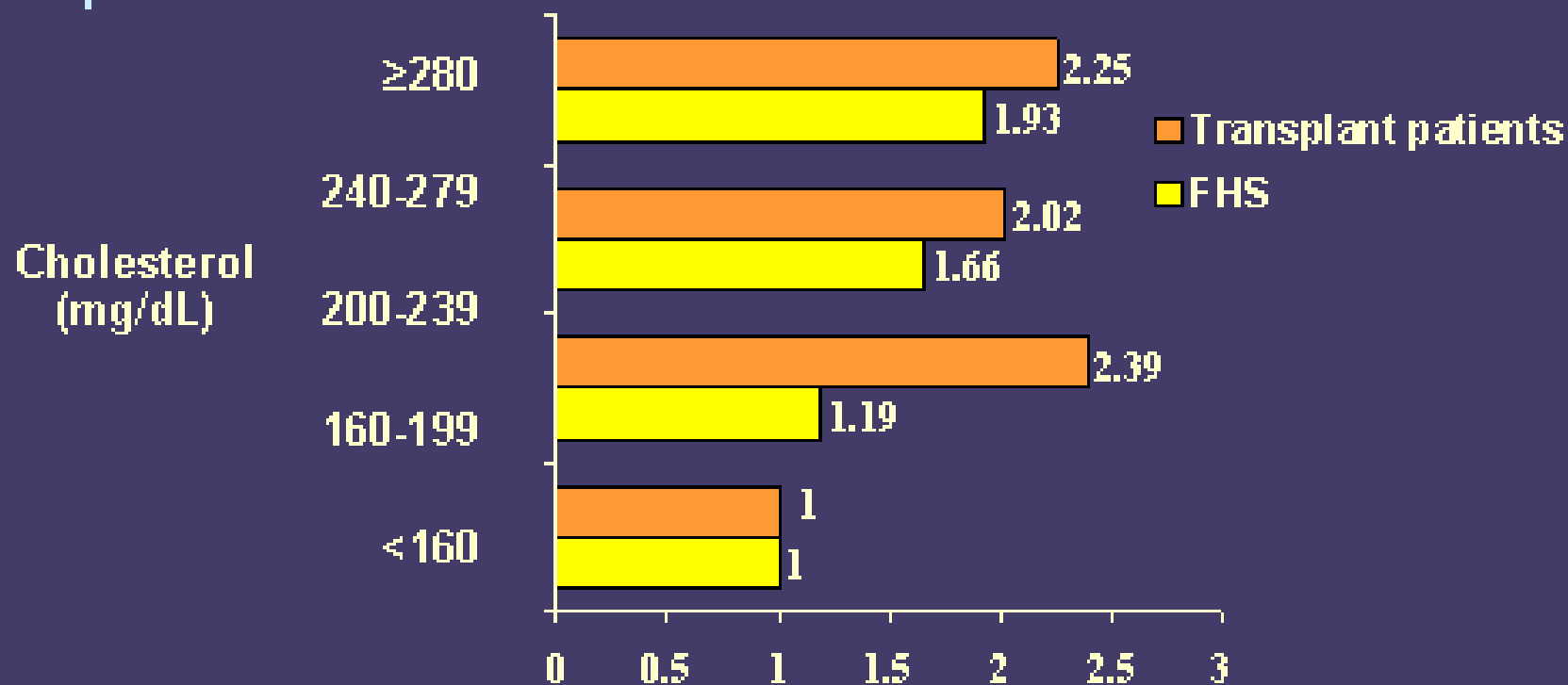
Karthikeyan V, Am J Transplant 4:262-269,2004

Cholesterol ≥ 200 mg/dl Triglycerides ≥ 150 mg/dl
Lipid Lowering Therapy



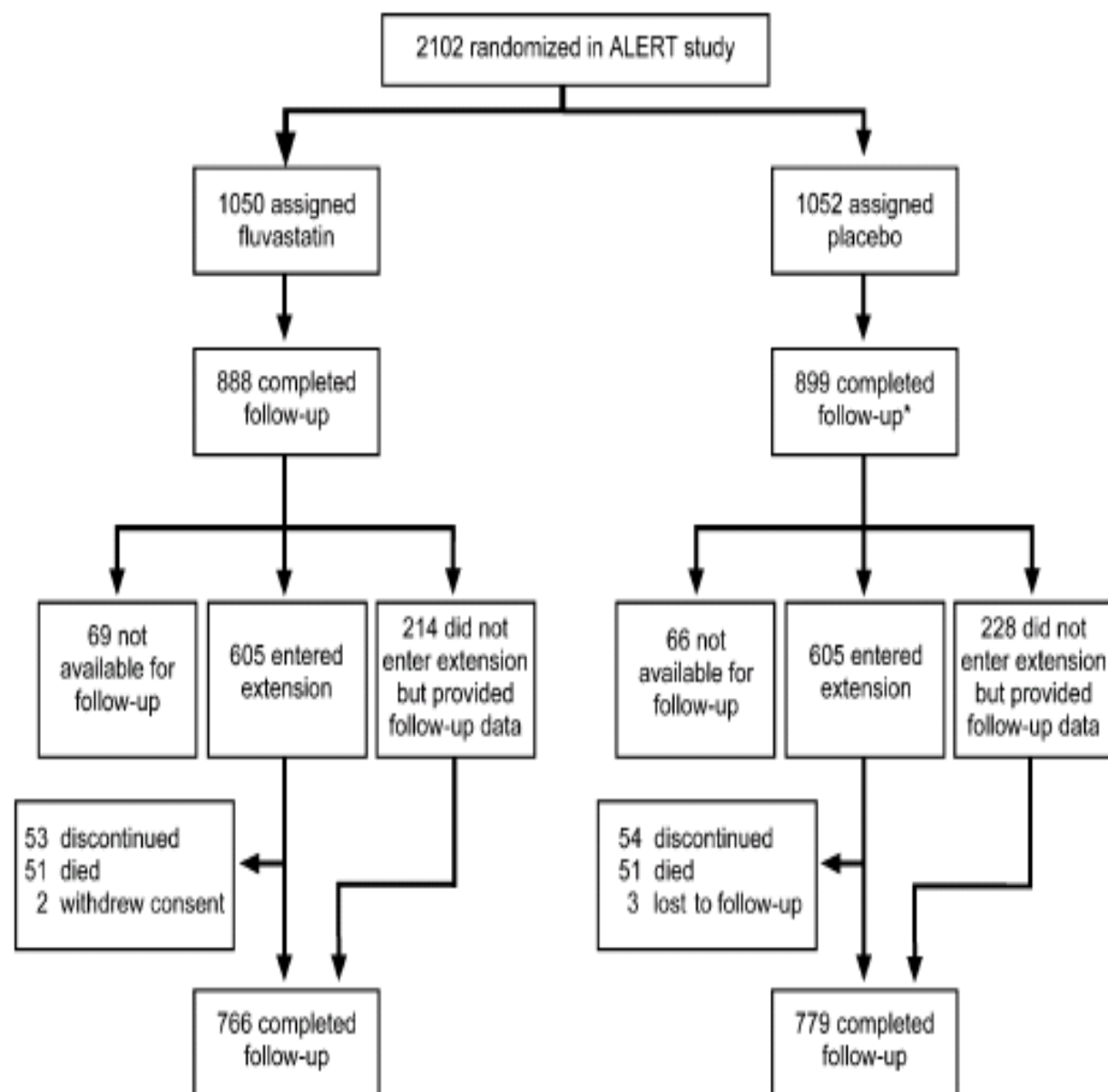
Hypercholesterolemia: Relative Risk for Ischemic Heart Disease in Patients More Than One Year After Renal Transplantation

Relative Risk of IHD in Males From the Framingham Heart Study (FHS) or Transplant Patients



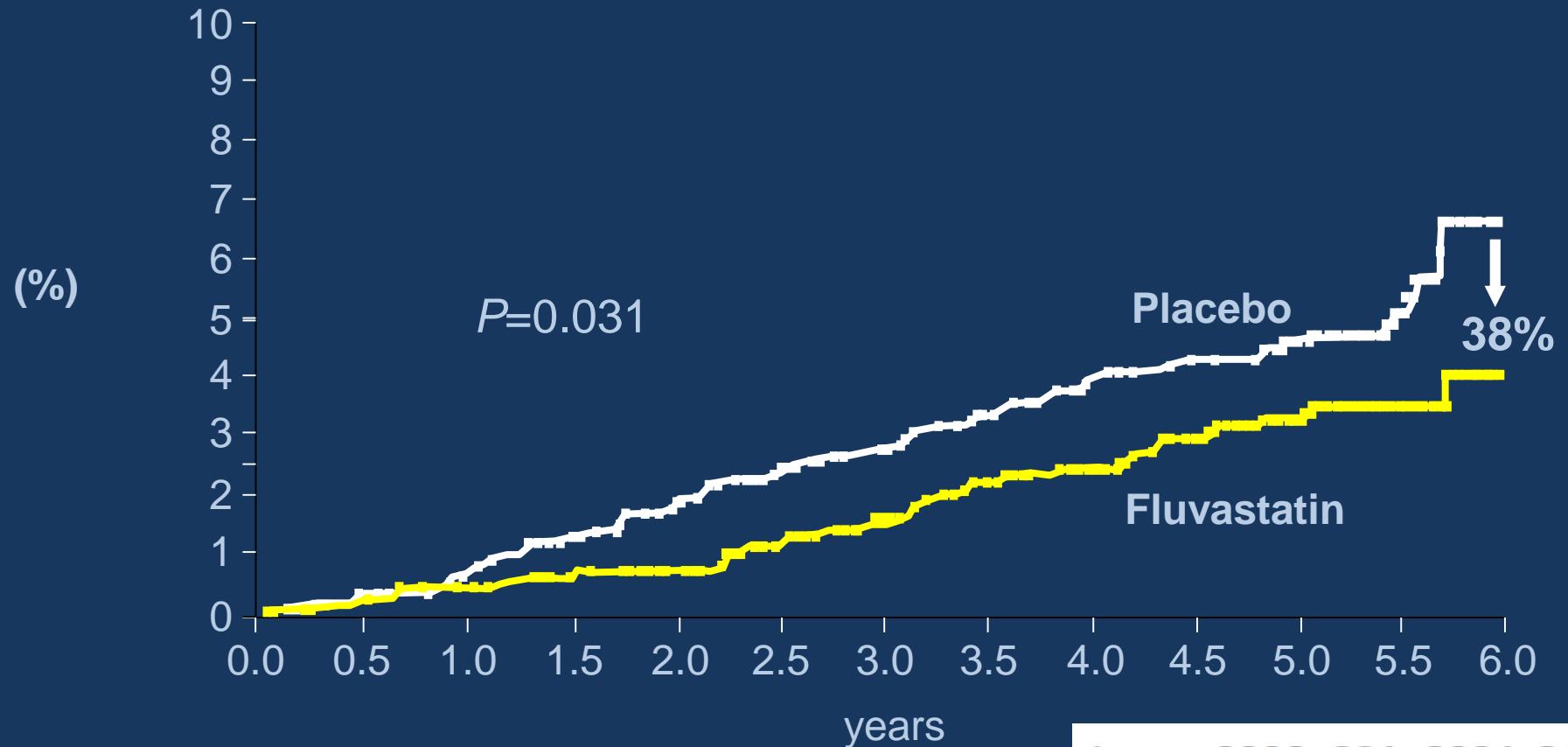
Kasiske BL et al. *J Am Soc Nephrol*. 2000;65:1735-1743.

Wilson PWF et al. *Circulation*. 1998;97:1837-1847.



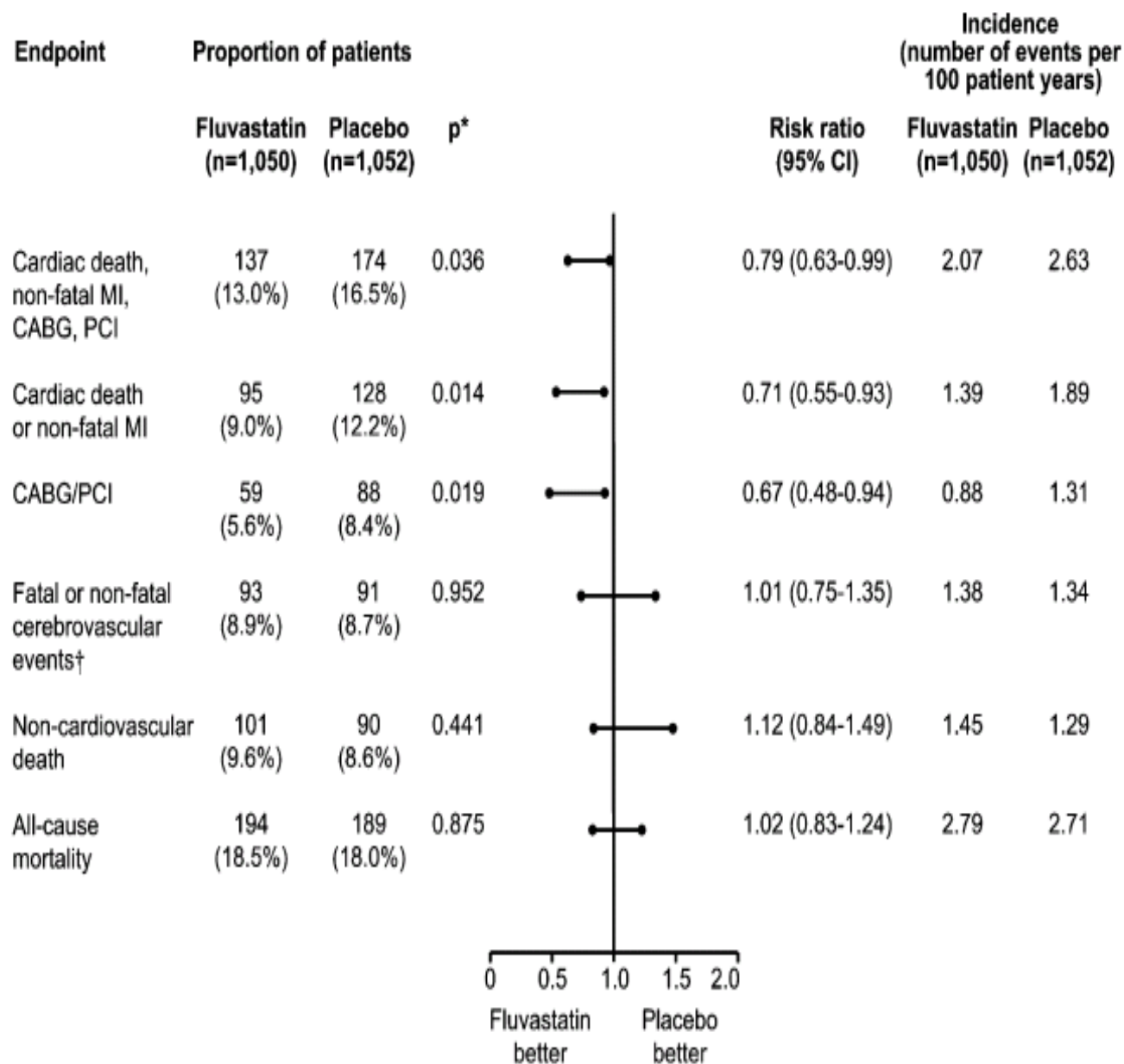
Effect of fluvastatin on cardiac outcomes in renal transplant recipients: a multicentre, randomised, placebo-controlled trial

Hallvard Holdaas, Bengt Fellström, Alan G Jardine, Ingar Holme, Gudrun Nyberg, Per Fauchald, Carola Grönhagen-Riska, Søren Madsen, Hans-Hellmut Neumayer, Edward Cole, Bart Maes, Patrice Ambühl, Anders G Olsson, Anders Hartmann, Dag O Solbu, Terje R Pedersen, on behalf of the Assessment of LEscol in Renal Transplantation (ALERT) Study Investigators*

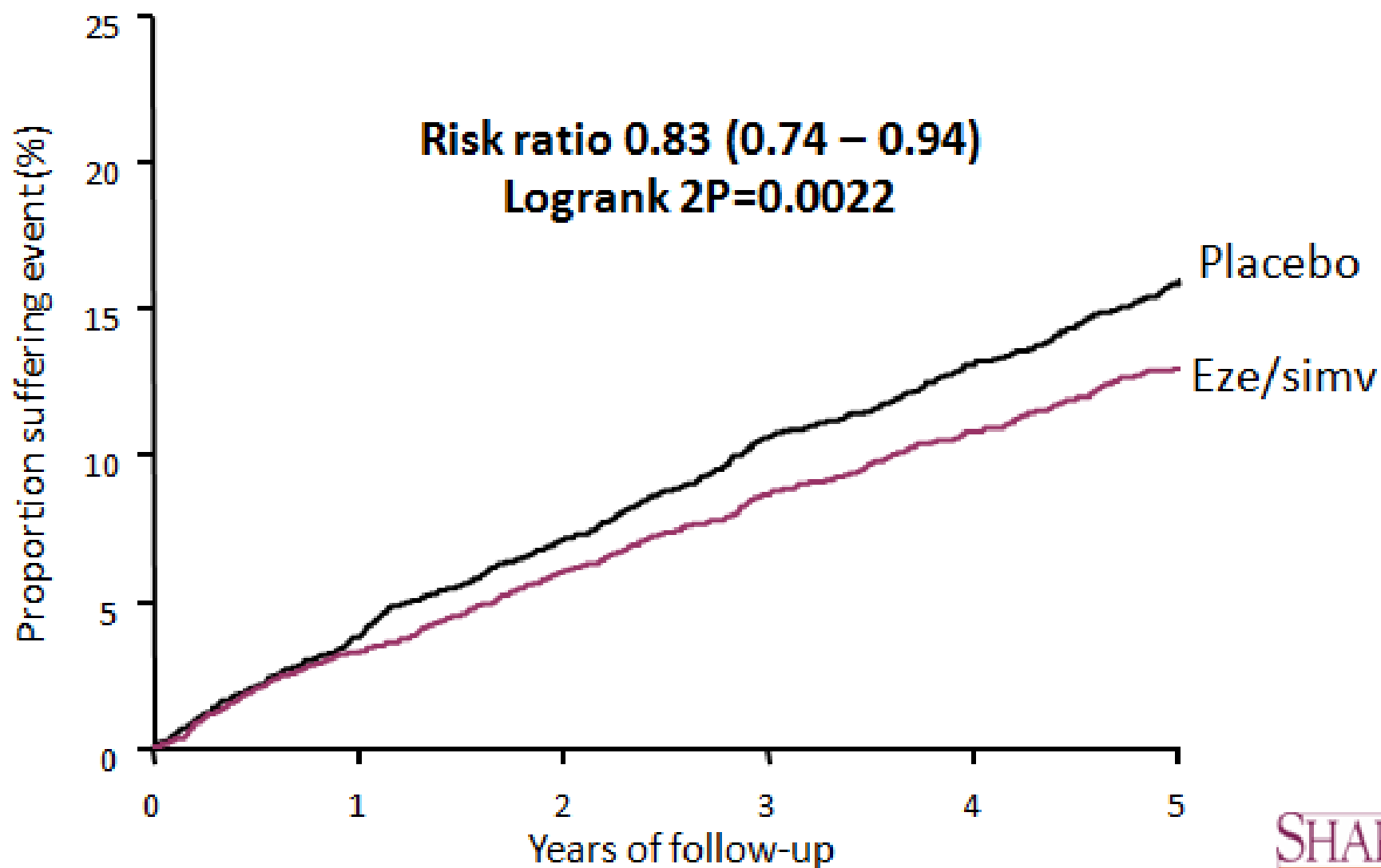


ITT, intent-to-treat population.

Lancet 2003; **361**: 2024–31.



SHARP: Major Atherosclerotic Events



Effect of statins on cardiovascular events in patients with mild to moderate chronic kidney disease: a systematic review and meta-analysis of randomized clinical trials

BMC Cardiovascular Disorders 2014, 14:19

Xiao Zhang^{1†}, Chun Xiang^{1†}, Yu-Hao Zhou^{2†}, An Jiang^{3†}, Ying-Yi Qin¹ and Jia He^{1*}

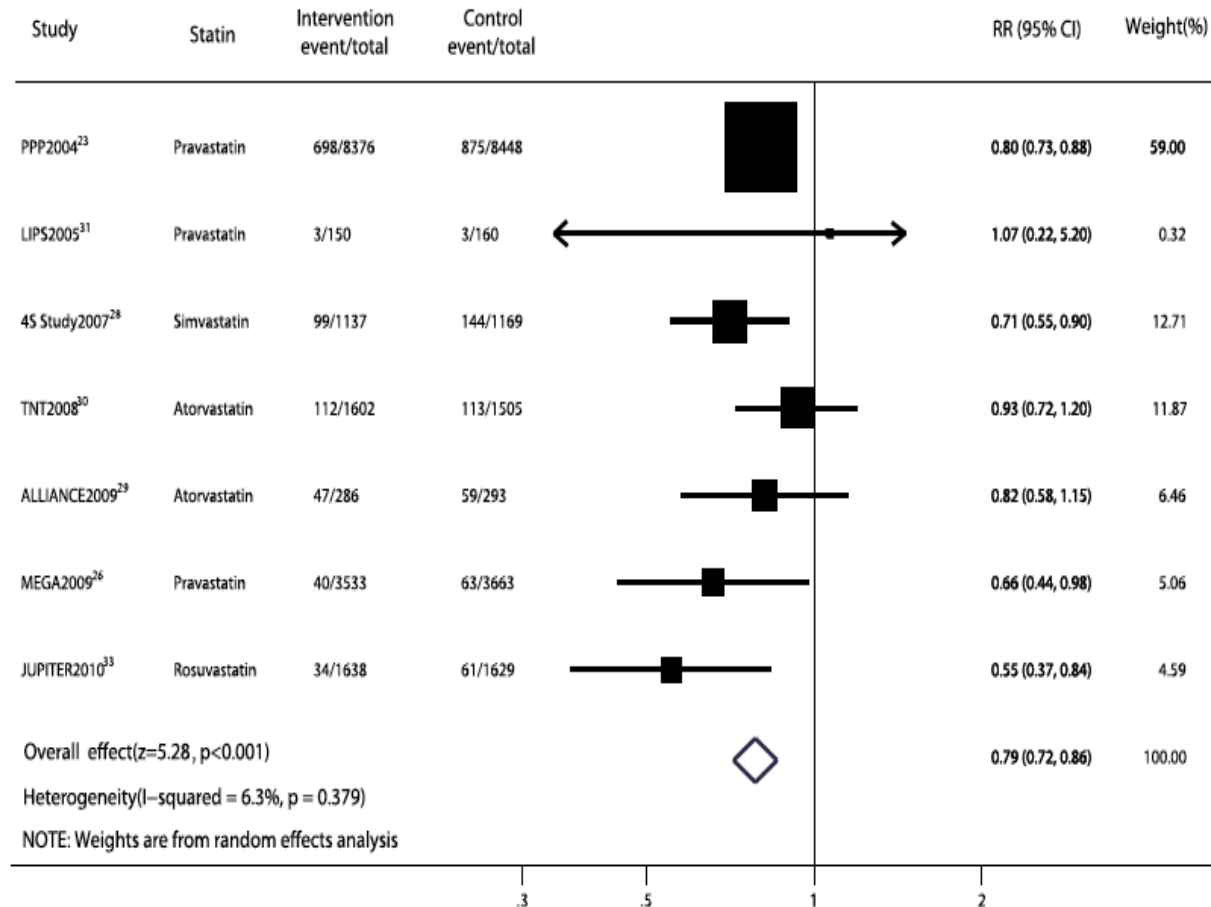
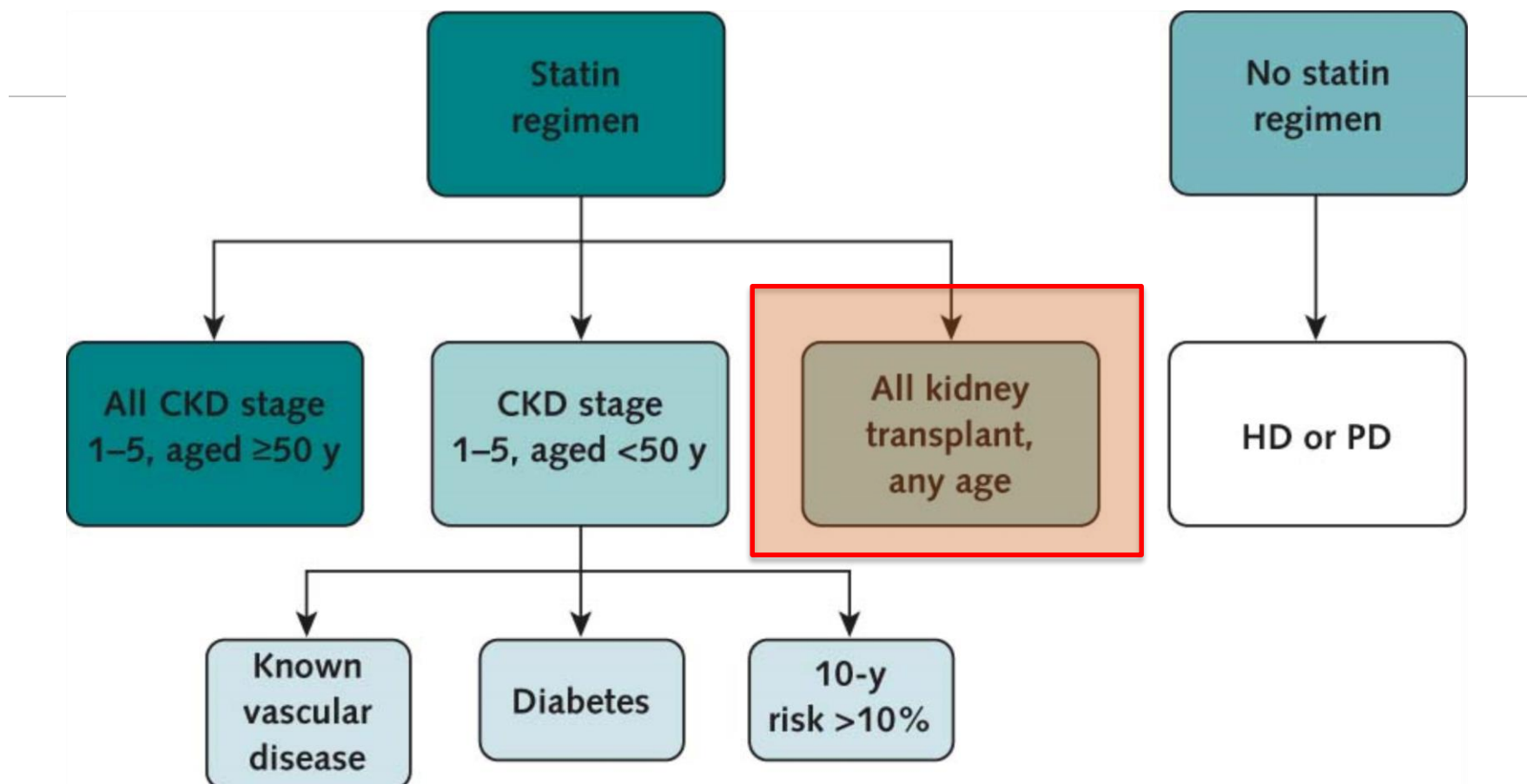


Figure 3 Forest plot of the effect of statin on total mortality in patients with mild to moderate chronic kidney disease.

From: Lipid Management in Chronic Kidney Disease: Synopsis of the Kidney Disease: Improving Global Outcomes 2013 Clinical Practice Guideline



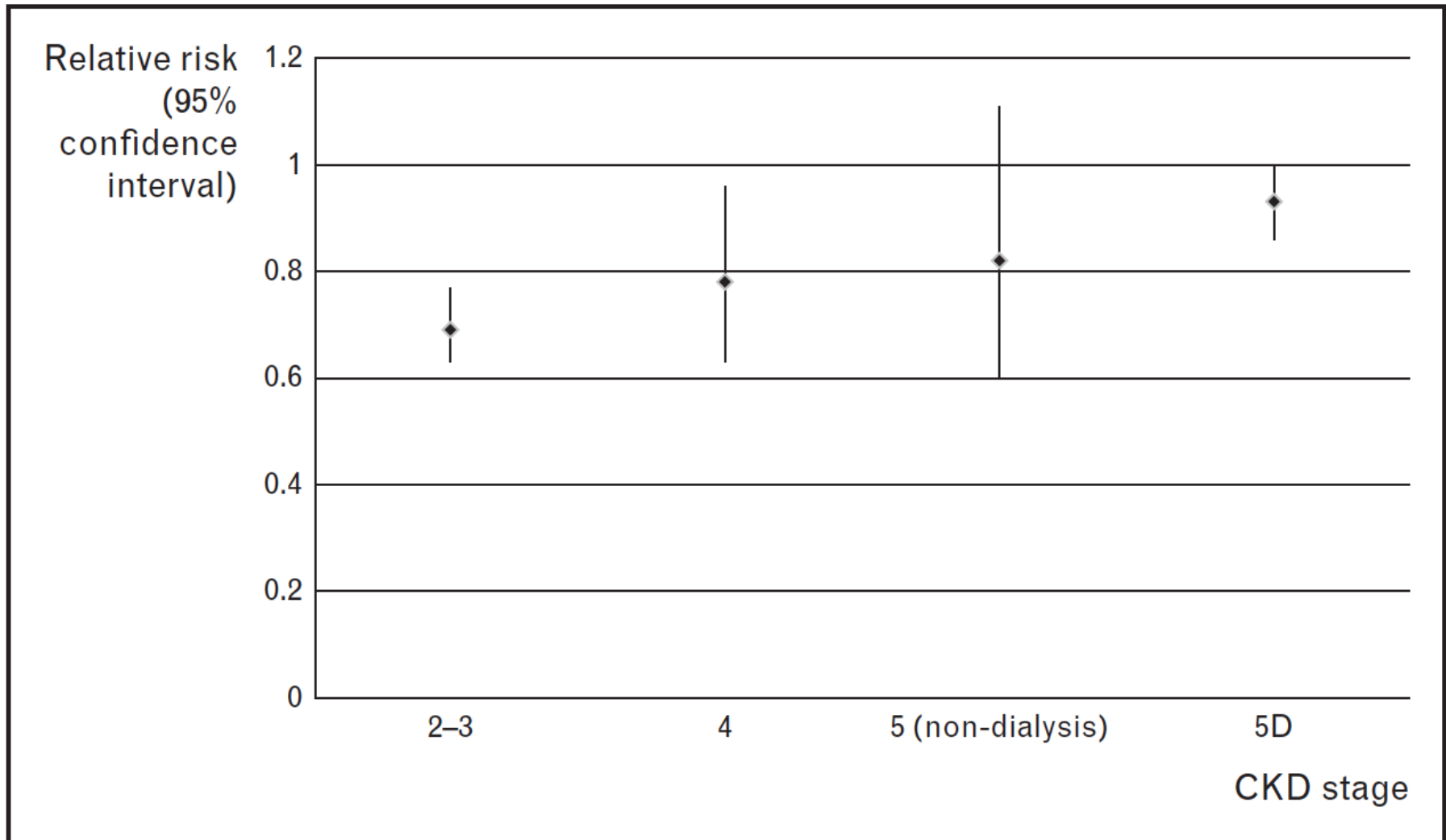
Algorithm for cholesterol-lowering treatment in persons with CKD.

Boxes represent recommendations about whether to prescribe a statin regimen. Boxes with dark and medium green fill represent strong recommendations; lighter green and white boxes represent weak recommendations. Recommended statin regimens are shown in Table 1 and include statin monotherapy or statin/ezetimibe for those with CKD stage 3a to 5 and statin monotherapy for all other CKD populations. CKD = chronic kidney disease; HD = hemodialysis; PD = peritoneal dialysis.

Do patients with chronic kidney disease get optimal cardiovascular risk reduction?

Curr Opin Nephrol Hypertens 2014,
23:267–274

Mark K. Elliott, Jennifer A. McCaughan, and Damian G. Fogarty



HMG CoA reductase inhibitors (statins) for kidney transplant recipients (Review)

Cochrane Database Syst Rev. 2014 Jan 28;1:CD005019. doi: 10.1002/14651858.CD005019.pub4

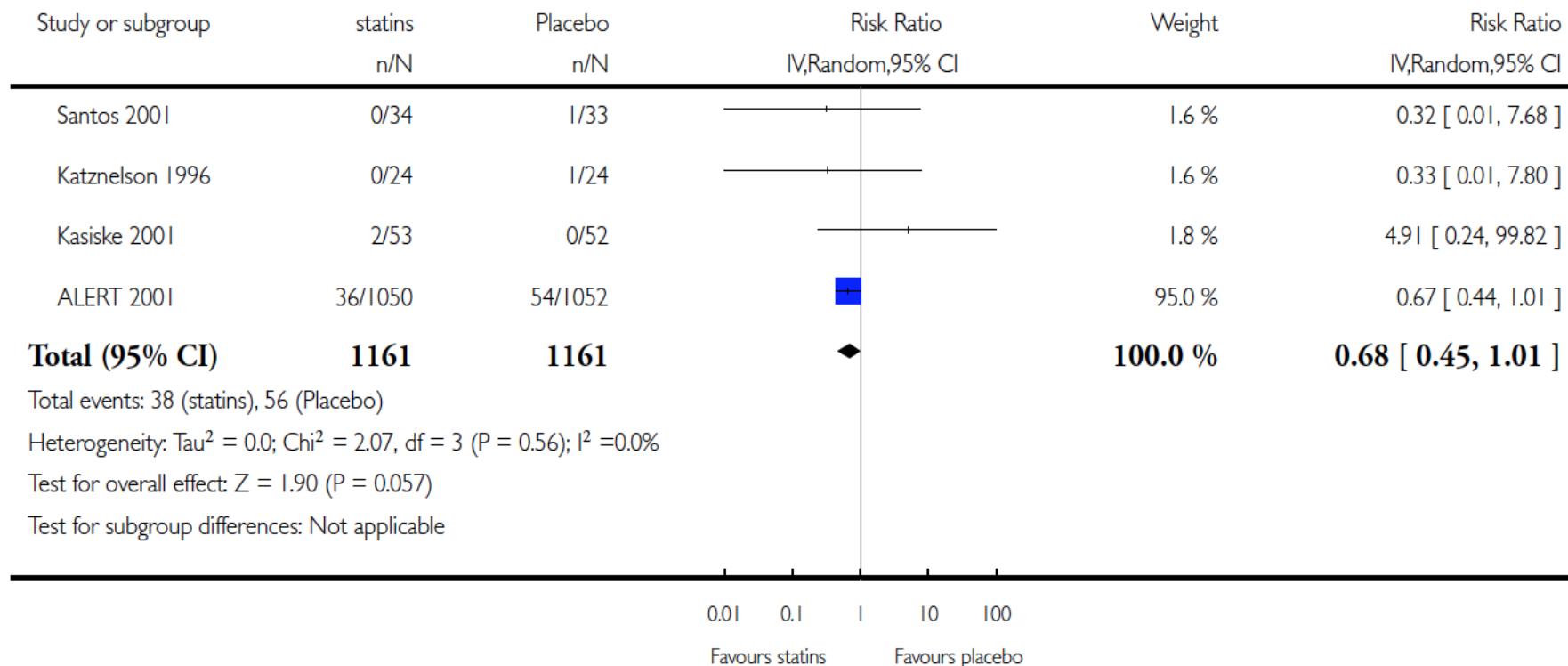
Palmer SC, Navaneethan SD, Craig JC, Perkovic V, Johnson DW, Nigwekar SU, Hegbrant J, Strippoli GFM

Analysis 1.1. Comparison 1 Statins versus placebo, Outcome 1 Cardiovascular mortality.

Review: HMG CoA reductase inhibitors (statins) for kidney transplant recipients

Comparison: 1 Statins versus placebo

Outcome: 1 Cardiovascular mortality



HMG CoA reductase inhibitors (statins) for kidney transplant recipients (Review)

Cochrane Database Syst Rev. 2014 Jan 28;1:CD005019. doi: 10.1002/14651858.CD005019.pub4

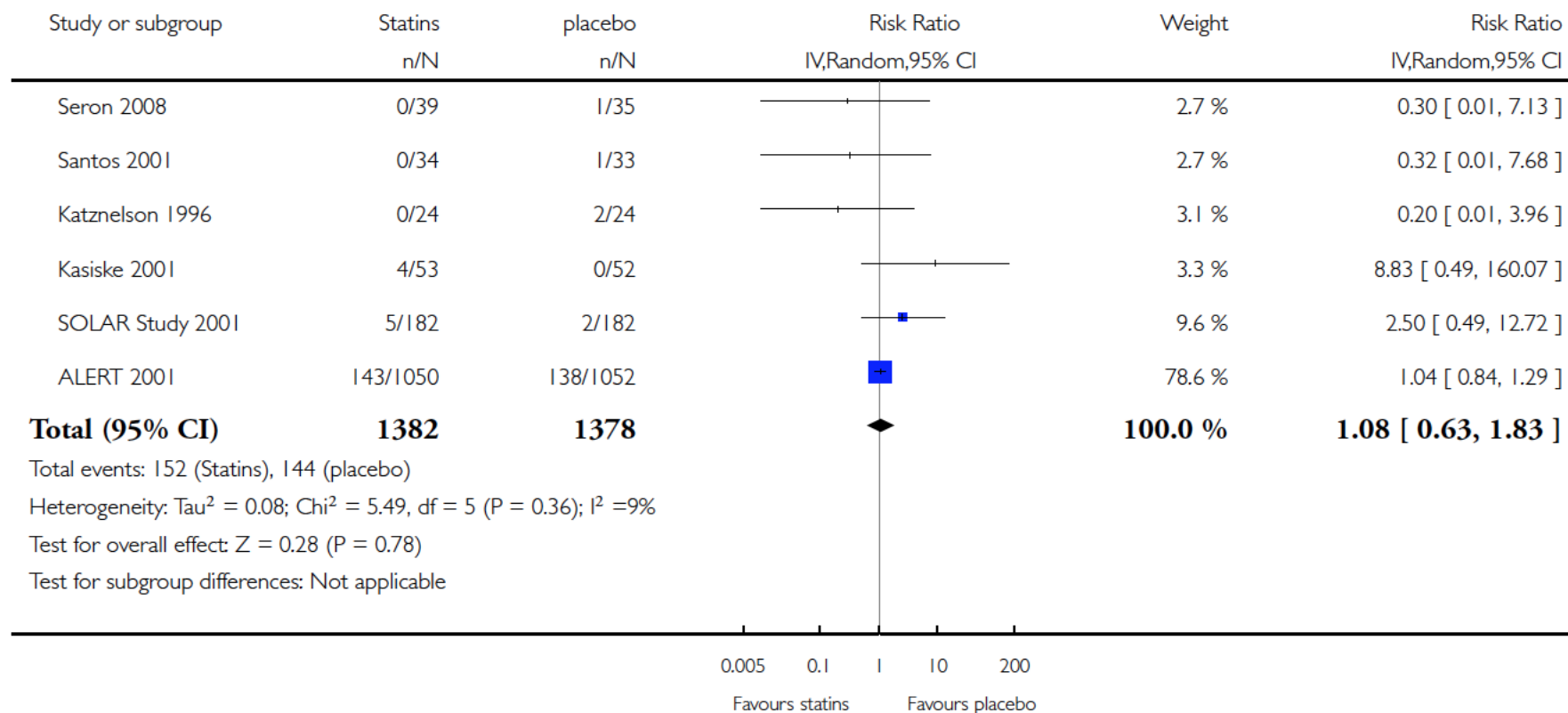
Palmer SC, Navaneethan SD, Craig JC, Perkovic V, Johnson DW, Nigwekar SU, Hegbrant J, Strippoli GFM

Analysis 1.2. Comparison 1 Statins versus placebo, Outcome 2 All-cause mortality.

Review: HMG CoA reductase inhibitors (statins) for kidney transplant recipients

Comparison: 1 Statins versus placebo

Outcome: 2 All-cause mortality



Palmer SC, Navaneethan SD, Craig JC, Perkovic V, Johnson DW, Nigwekar SU, Hegbrant J, Strippoli GFM

Statin versus placebo or no treatment for adults kidney transplant recipients

Patient or population: adults with chronic kidney disease
Settings:
Interventi
Comparis

Outcomes

Major car

All-cause

Cardiovas

*The basi
assumed

CI: Confidence interval; RR: Risk Ratio

Statins may reduce cardiovascular events in kidney transplant recipients, although treatment effects are imprecise. Statin treatment has uncertain effects on overall mortality, stroke, kidney function, and toxicity outcomes in kidney transplant recipients

d on the

Multidisciplinary care

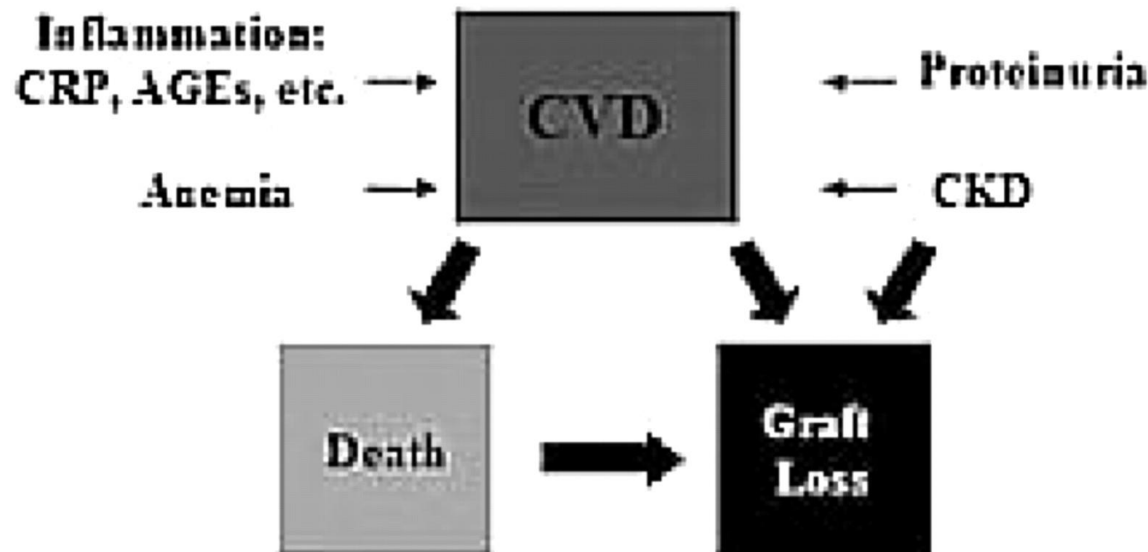
How to improve outcome in kidney transplanted patients?

An important issue for long term patient outcomes is to reduce ISU toxicity and to manage CV disease.

- Before Tx :
 - Dialysis vintage
 - CV management
 - CV interventions
- After Tx: medical management
 - HTN
 - DM
 - Dyslipidaemia
 - Obesity
 - Smoking
 - Inflammation
 - Anemia
 - Bone
 - ...



**cardiovascular disease
management after renal
transplantation**



Steno 2: Intensive Therapy

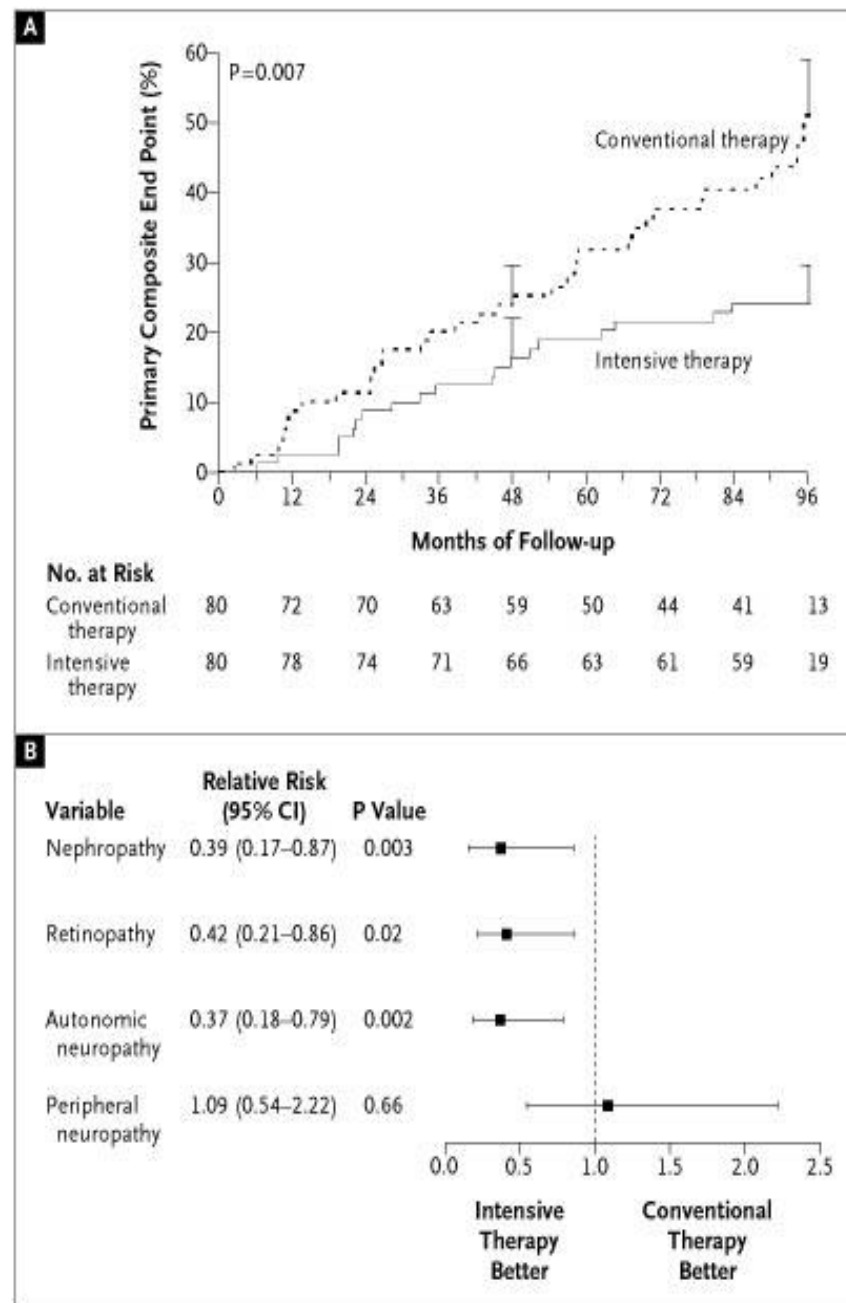
NB: combined cardio/renal protection

- Multidisciplinary team (MD, nurse, dietician)
- Diet
- Exercise 30 minutes 3 – 5x/wk
- Smoking cessation courses
- ACEI/ARB independent of BP
- Vitamin – mineral supplement
- ASA
- Glycemic control
- BP control
- Lipid control

Steno 2: Outcomes

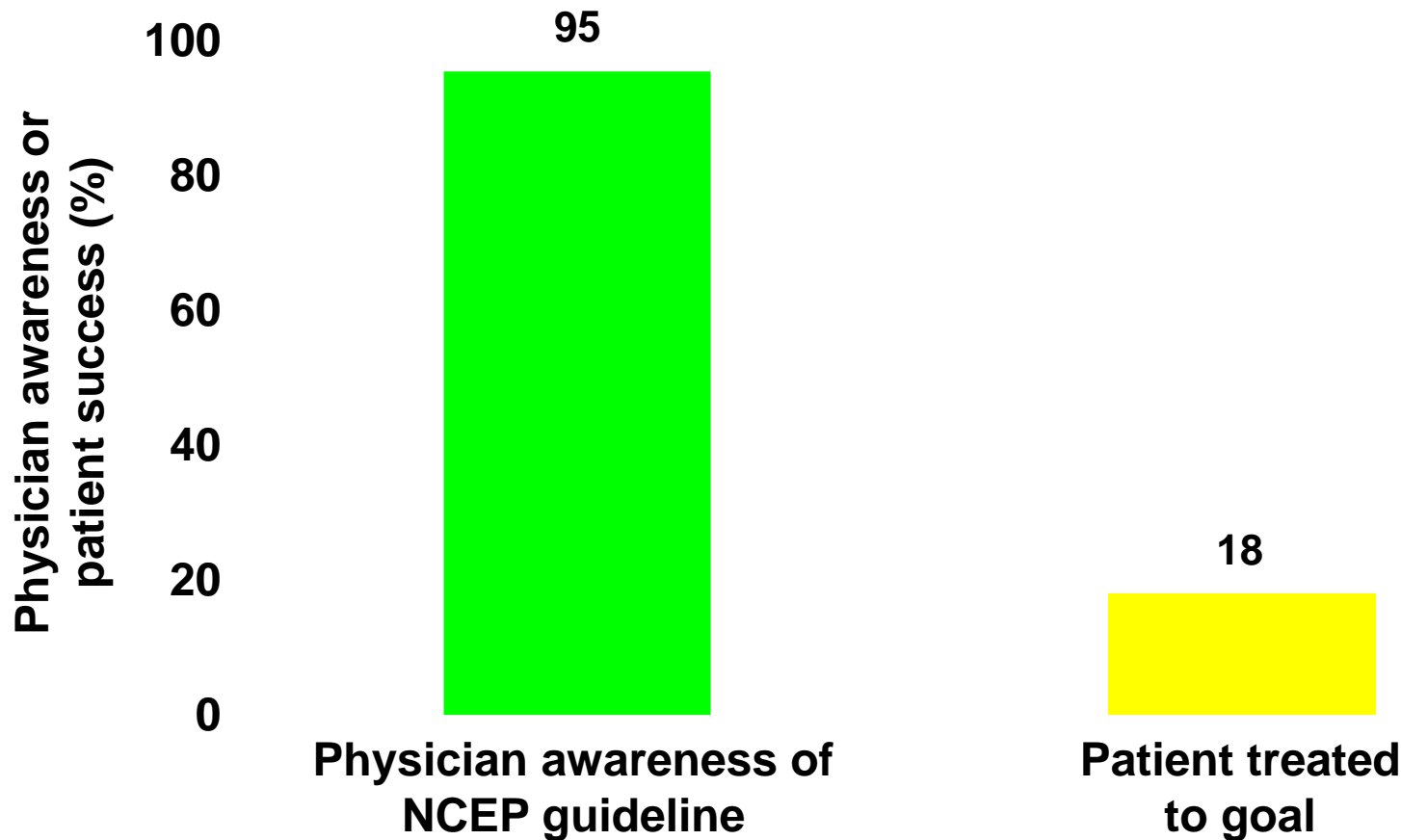
- Hazard ratio = 0.47 in favor of intensive group (.24 - .73, $p=0.008$)
- Absolute RR = 20%
- NNT 5 patients to prevent one CV event in 7.8 years

Gaede P et al. NEJM 2003; 348: 383-393



CAD treatment gap in the community

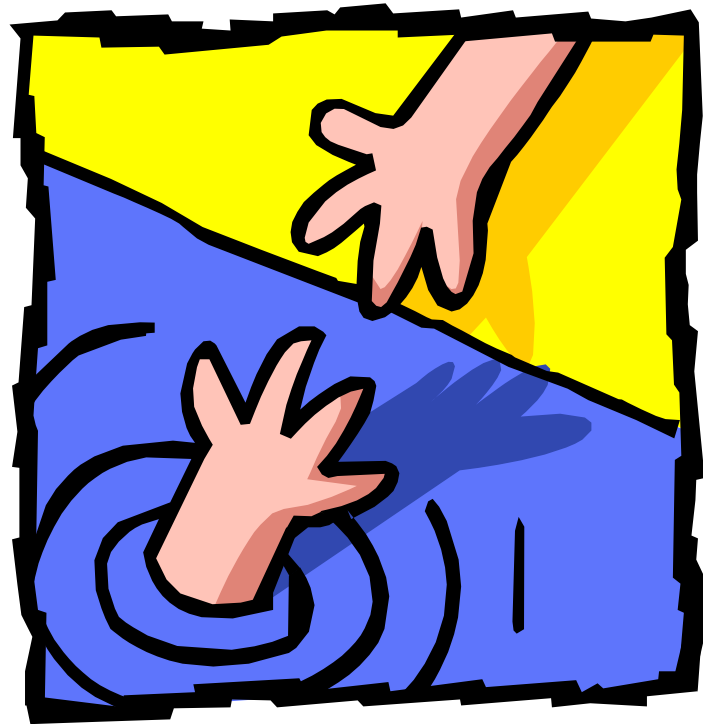
Provider awareness does not equal successful implementation



NCEP = National Cholesterol
Education Program

Pearson TA, et al. Arch Intern Med 2000;160:459–67

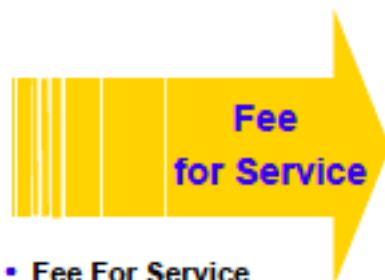
We Cannot Do This Alone!



Multidisciplinary care

- Education program
- Protocollized clinic f/u
- Protocollized lab
- Regular audits/CQI
- Nephrologist
- Nurse practitioner
- Social worker/psychologist
- Dietician
- Pharmacist
- Physiotherapist

Un-managed



- Fee For Service
 - Inpatient focus
 - O/P clinic care
 - Low Reimbursement
 - Poor Access and Quality
 - Little oversight
- No organized networks
- Focus on paying claims
- Little Medical Management

Coordinated Care



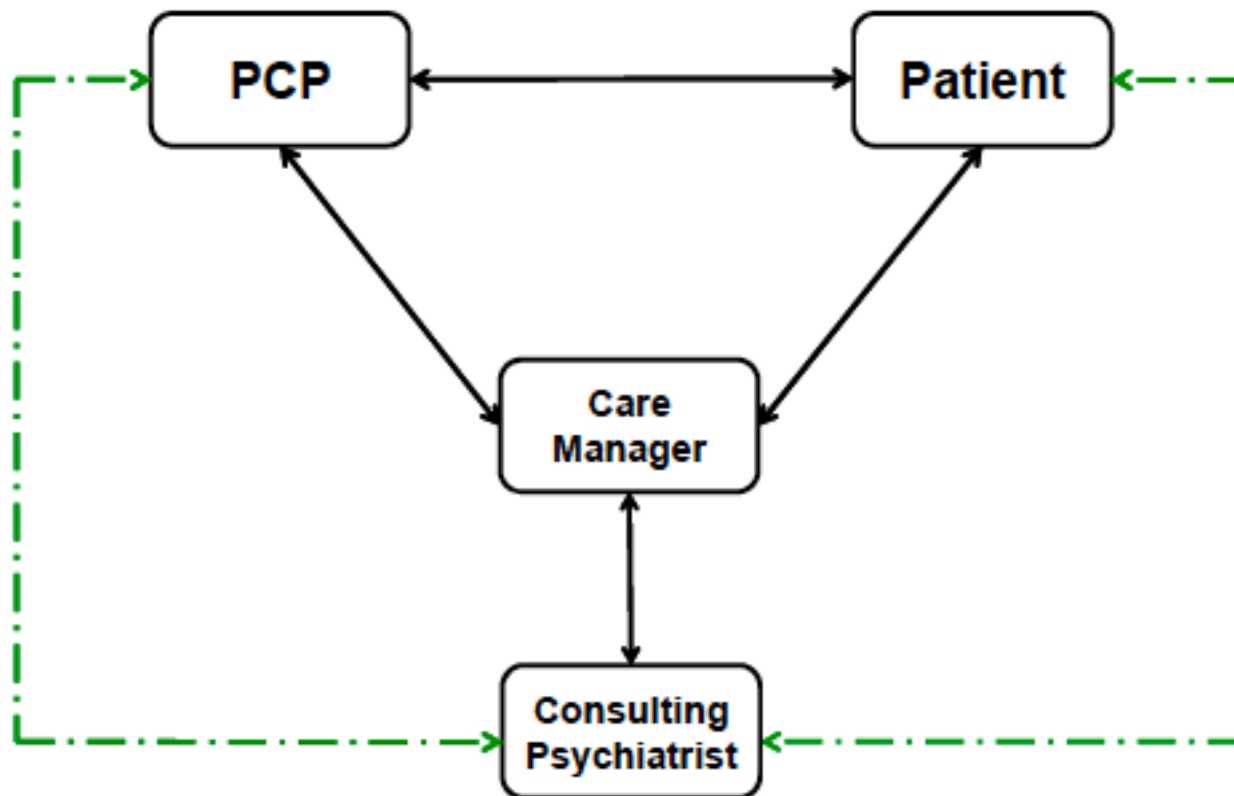
- Organized care delivery
 - Aligned incentives
 - Linked by HIT
- Integrated Provider Networks
- Focus on cost avoidance and quality performance
 - PC Medical Home
 - Care management
 - Transparent Performance Management

Patient Centered



- Patient Care Centered
 - Personalized Health Care
 - Productive and informed interactions between Patient and Provider
 - Cost and Quality Transparency
 - Accessible Health Care Choices
 - Aligned Incentives for wellness
- Multiple integrated network and community resources
- Aligned reimbursement/care management outcomes
- Rapid deployment of best practices
- Patient and provider interaction
 - Information focus
 - Aligned self care management
 - E-health capable

Team Approach



Collaborative Care - I

Systematic collaboration of primary care providers and mental health providers to improve care for depression and other common mental disorders

Over 40 RCTs for depression

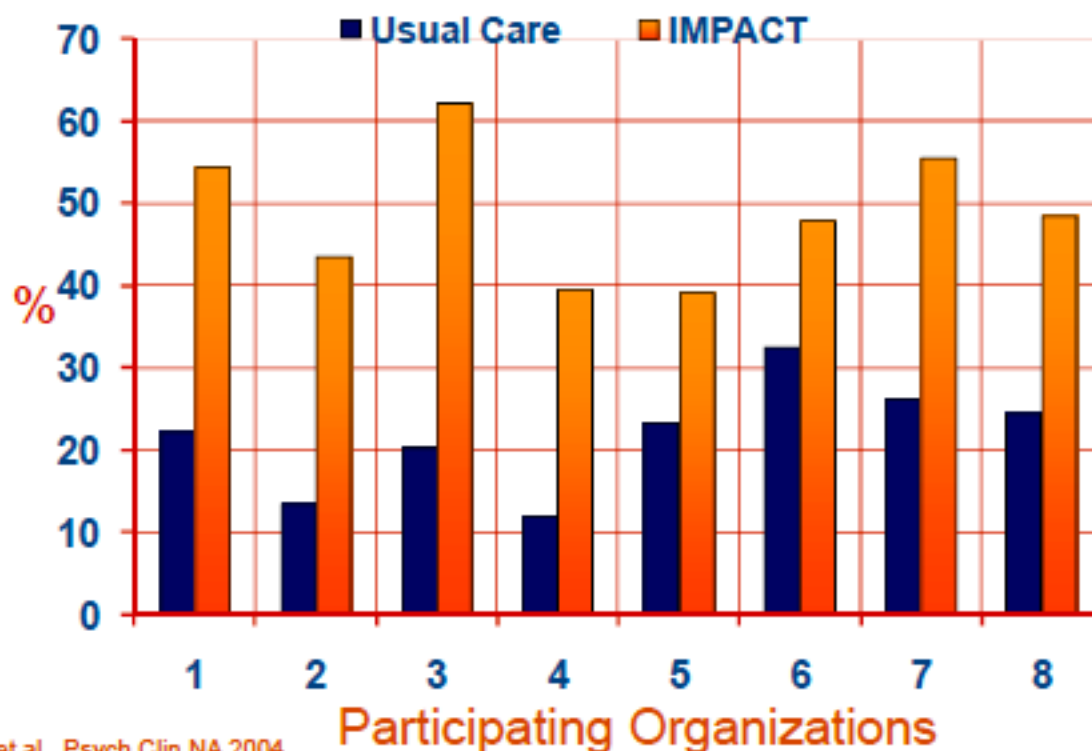
- Gilbody S. et al., *Arch Int Medicine*; Dec 2006

Several recent RCTs for anxiety disorders

- CALM Study (Roy Byrne et al); PTSD (Zatzick et al)

IMPACT Doubles Effectiveness of Care for Depression

50 % or greater improvement in depression at 12 months



Unützer et al., Psych Clin NA 2004

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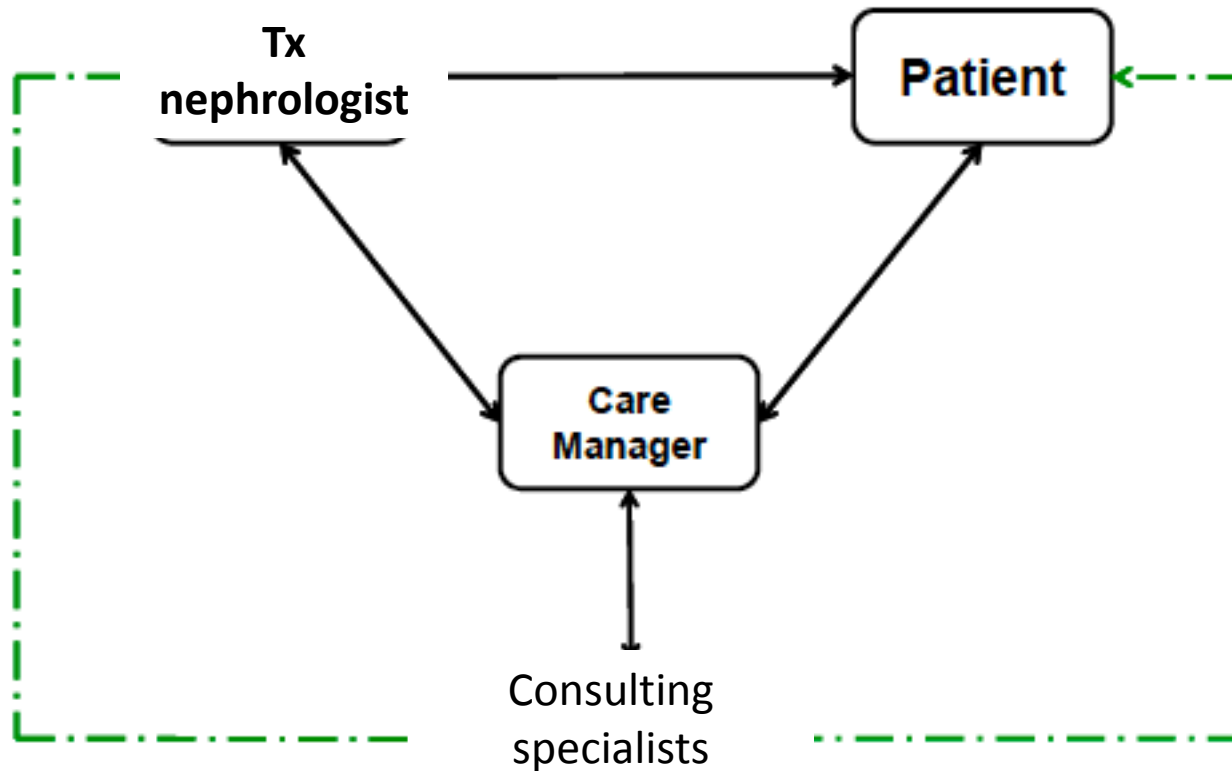
AIMS CENTER | Advancing Integrated Mental Health Solutions

Collaborative Care for Patients with Depression and Chronic Illnesses

Wayne J. Katon, M.D., Elizabeth H.B. Lin, M.D., M.P.H., Michael Von Korff, Sc.D.,
Paul Ciechanowski, M.D., M.P.H., Evette J. Ludman, Ph.D.,
Bessie Young, M.D., M.P.H., Do Peterson, M.S., Carolyn M. Rutter, Ph.D.,
Mary McGregor, M.S.N., and David McCulloch, M.D.

As compared with controls, patients in the intervention group had greater overall 12-month improvement across glycated hemoglobin levels (difference, 0.58%), LDL cholesterol levels (difference, 6.9 mg per deciliter [0.2 mmol per liter]), systolic blood pressure (difference, 5.1 mm Hg), and SCL-20 depression scores (difference, 0.40 points) ($P<0.001$). Patients in the intervention group also were more likely to have one or more adjustments of insulin ($P=0.006$), antihypertensive medications ($P<0.001$), and antidepressant medications ($P<0.001$), and they had better quality of life ($P<0.001$) and greater satisfaction with care for diabetes, coronary heart disease, or both ($P<0.001$) and with care for depression ($P<0.001$).

Team Approach



The world would be a better place if
we kept six of the ten
commandments. Any six.

Summary and conclusion

- Multiple traditional and novel/Tx specific risk factors are prevalent in KTx patients and are associated with increased mortality/CV events
- Assessing and treating BP, glucose and lipid metabolism and BP is likely beneficial
- Uncertainty about the targets and treatment choices still exists
- Lifestyle modifications and medications are likely to improve outcomes

Summary and conclusion

- Psycho-social factors contribute to increased CV risk and poor outcome
- Multidisciplinary “risk management clinics”,

providing complex bio-psycho-social care

- are necessary to target all the risk factors among kidney transplant recipients to improve patient outcomes

**I PUT REDBULL IN MY COFFEE THIS MORNING
INSTEAD OF WATER**



AND NOW I CAN SEE NOISES