Preventing Cardiovascular Complications In Kidney Transplantation

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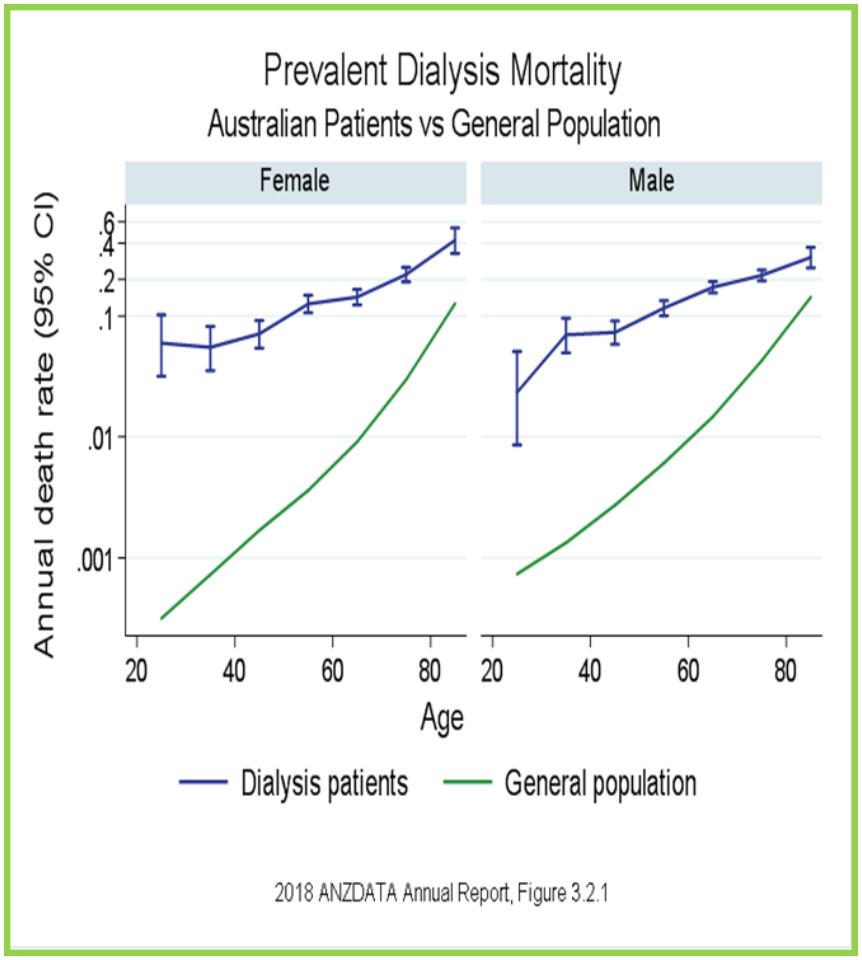
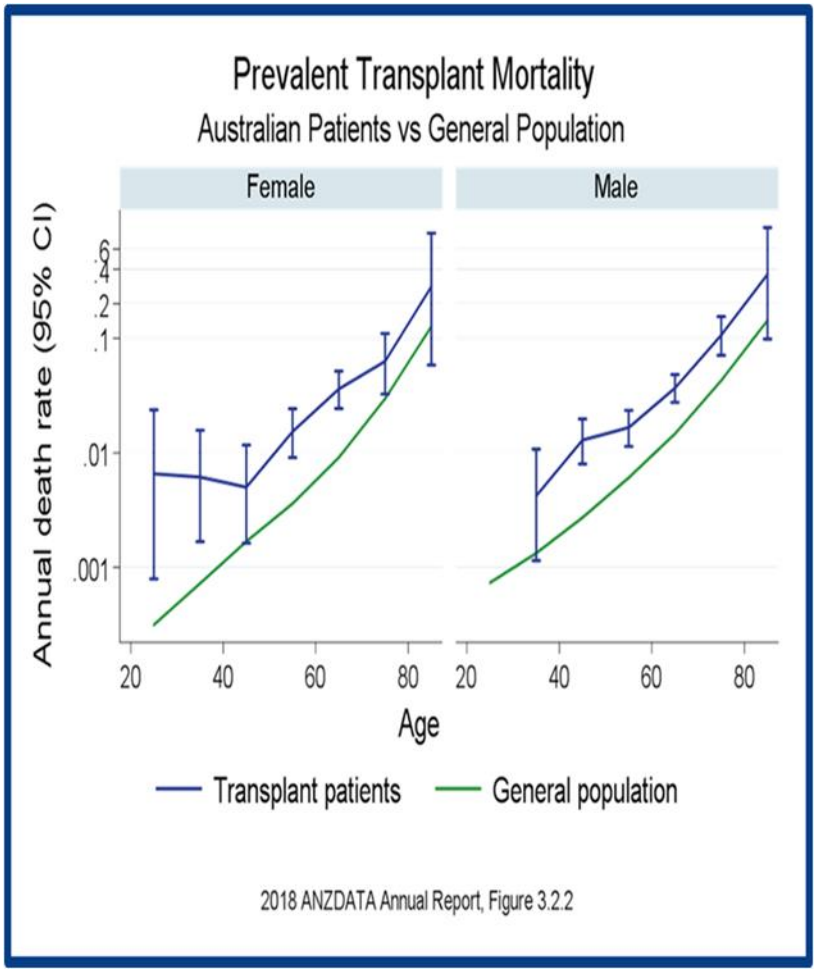
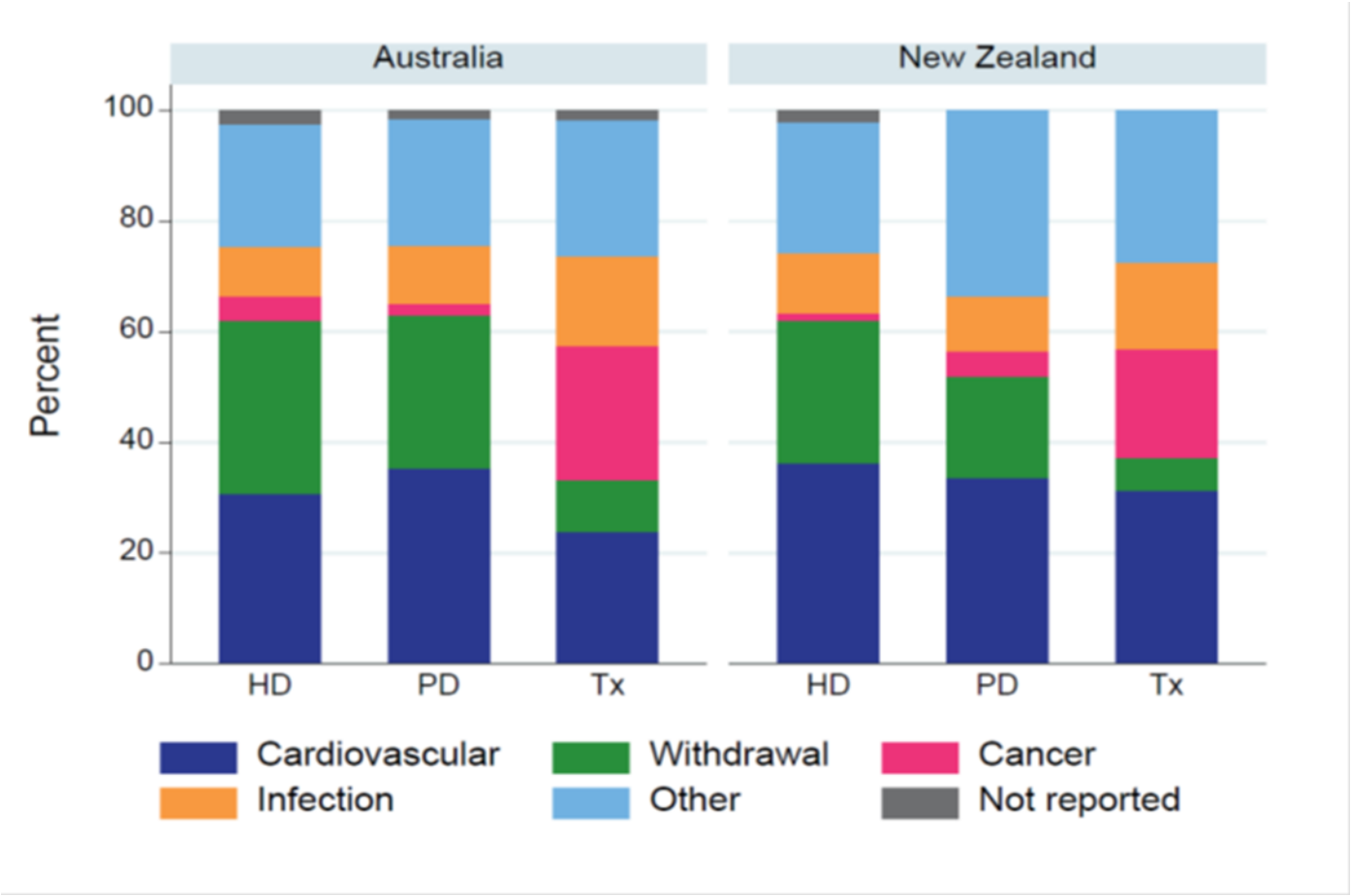
Death After Kidney Transplantation

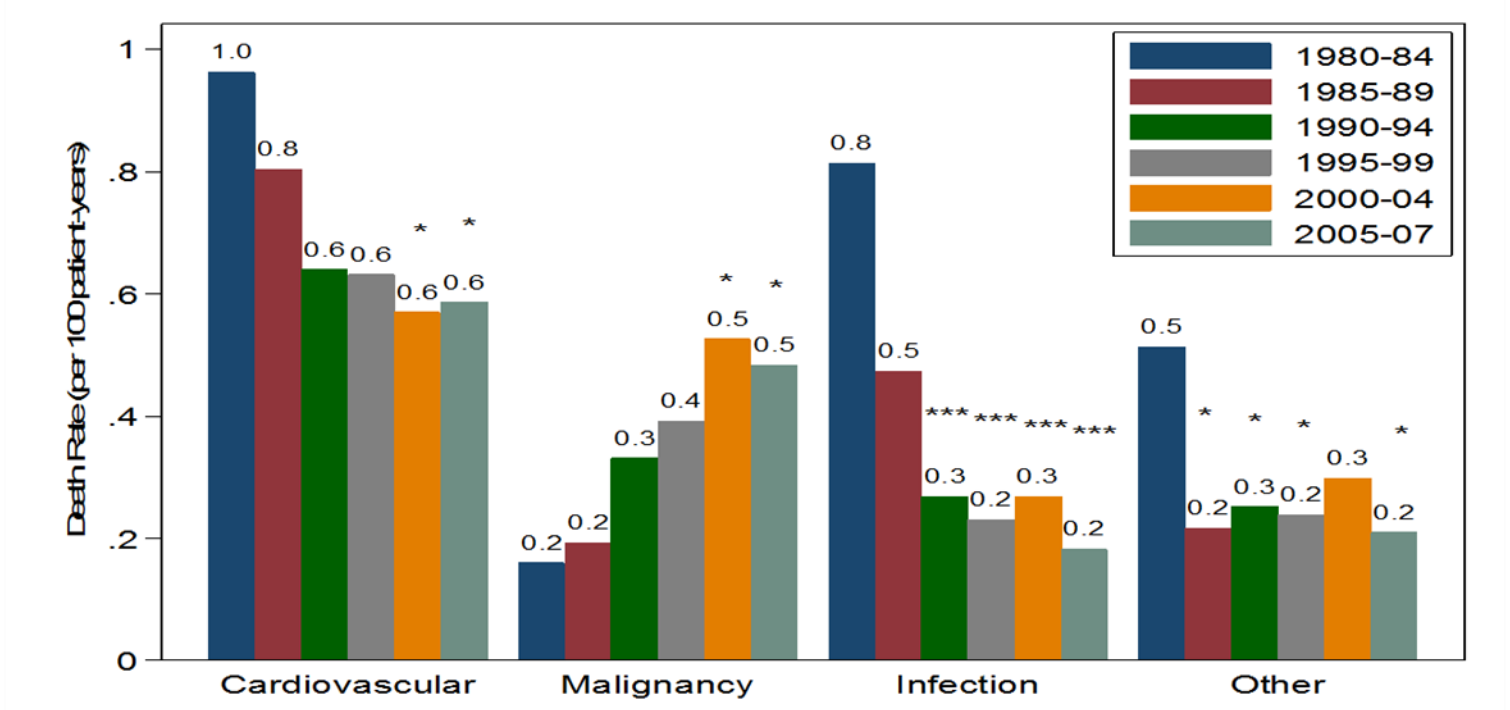




Cause of Death

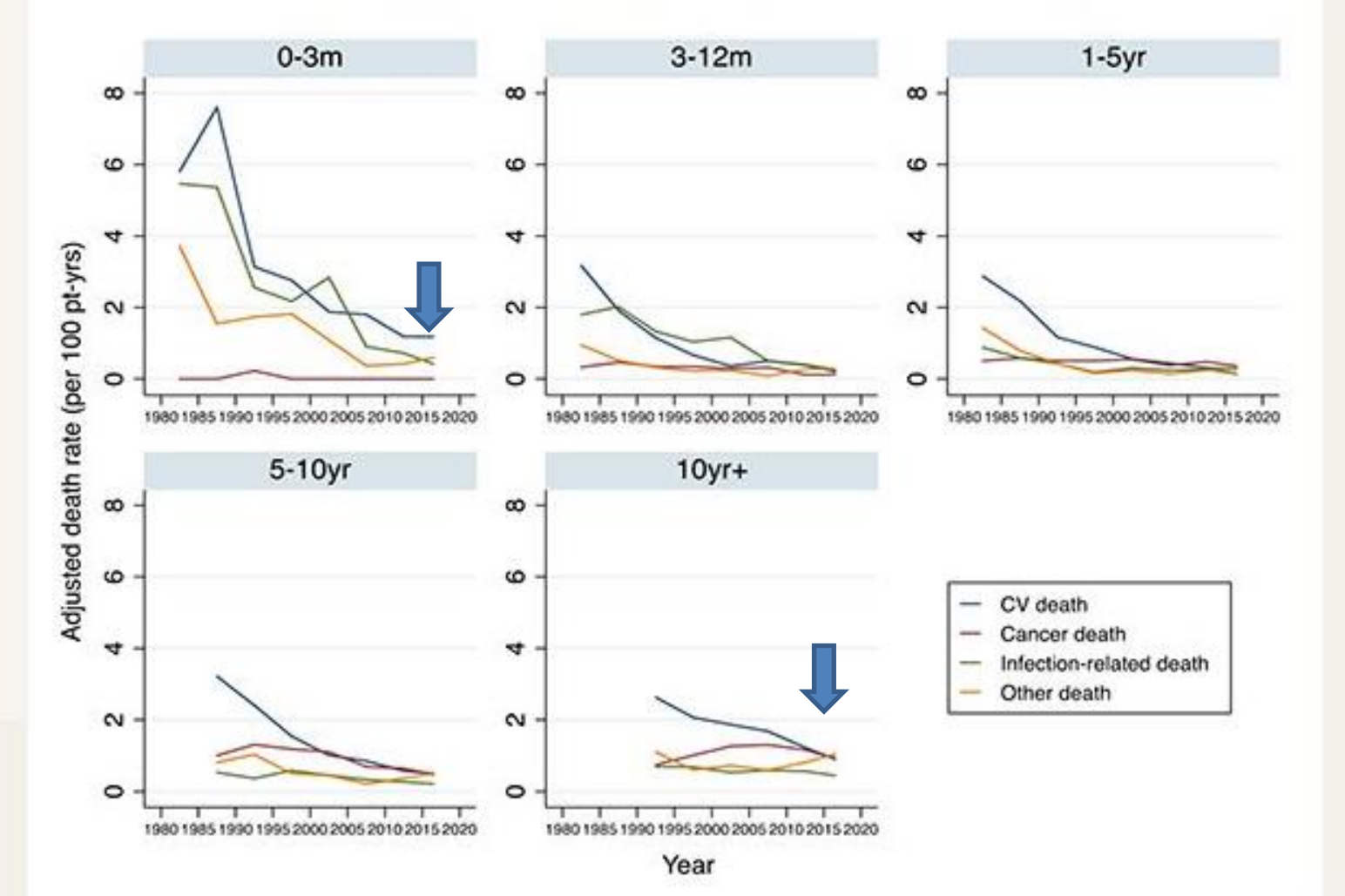


CVS Death After Kidney Transplantation

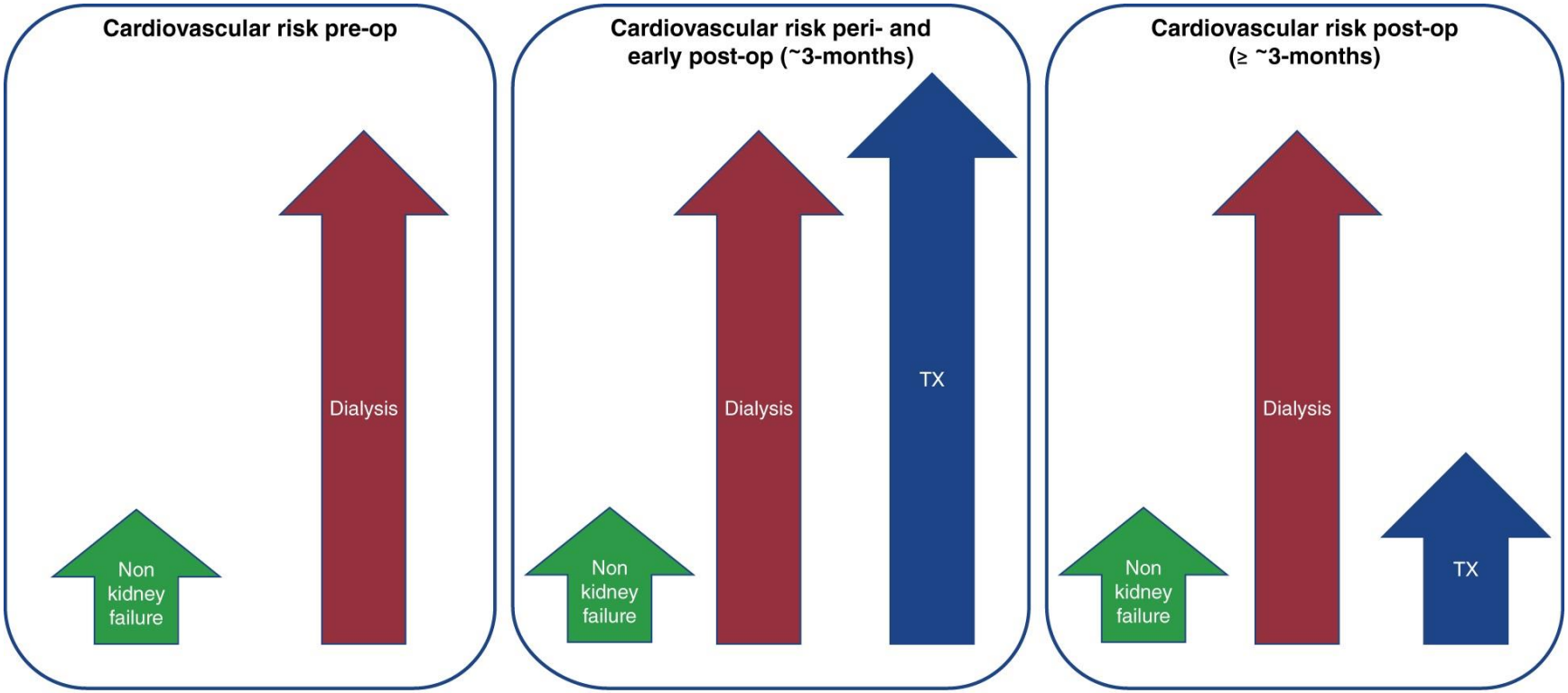


Pilmore: Transplantation 2010

Death and Time After Transplant

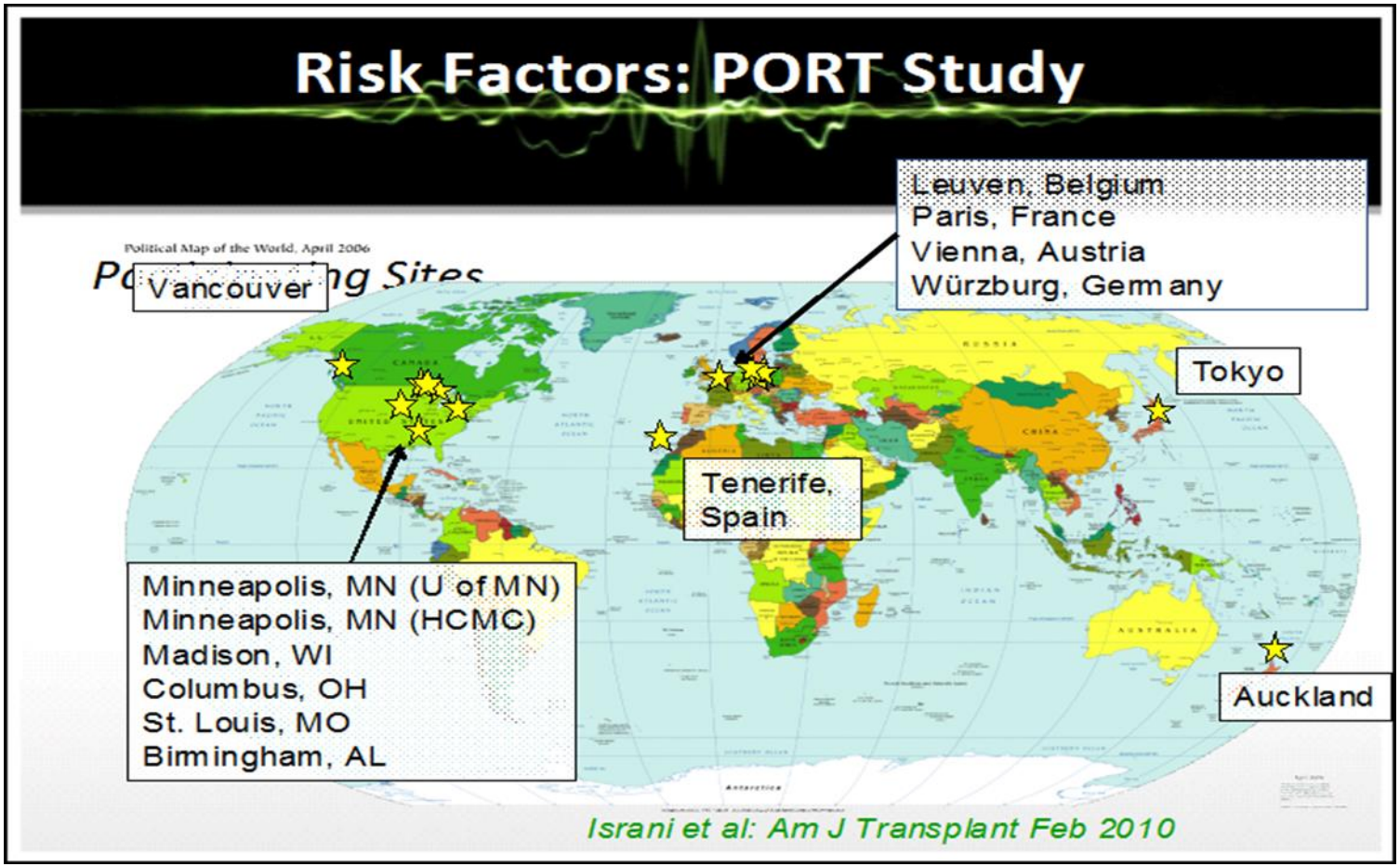


Ying JASN 2020



*TX = Kidney transplant

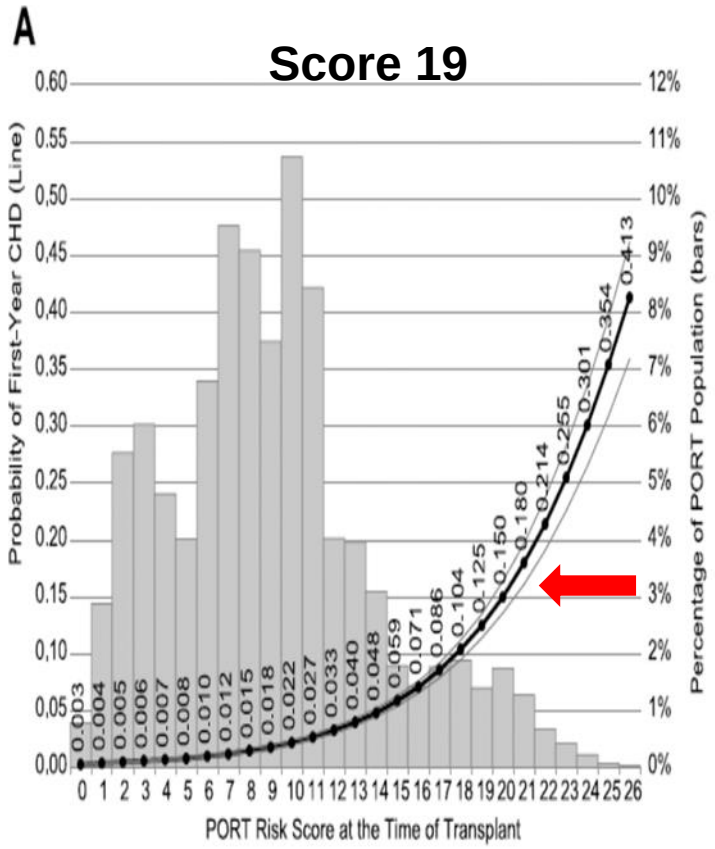
Predictors of Cardiac Events



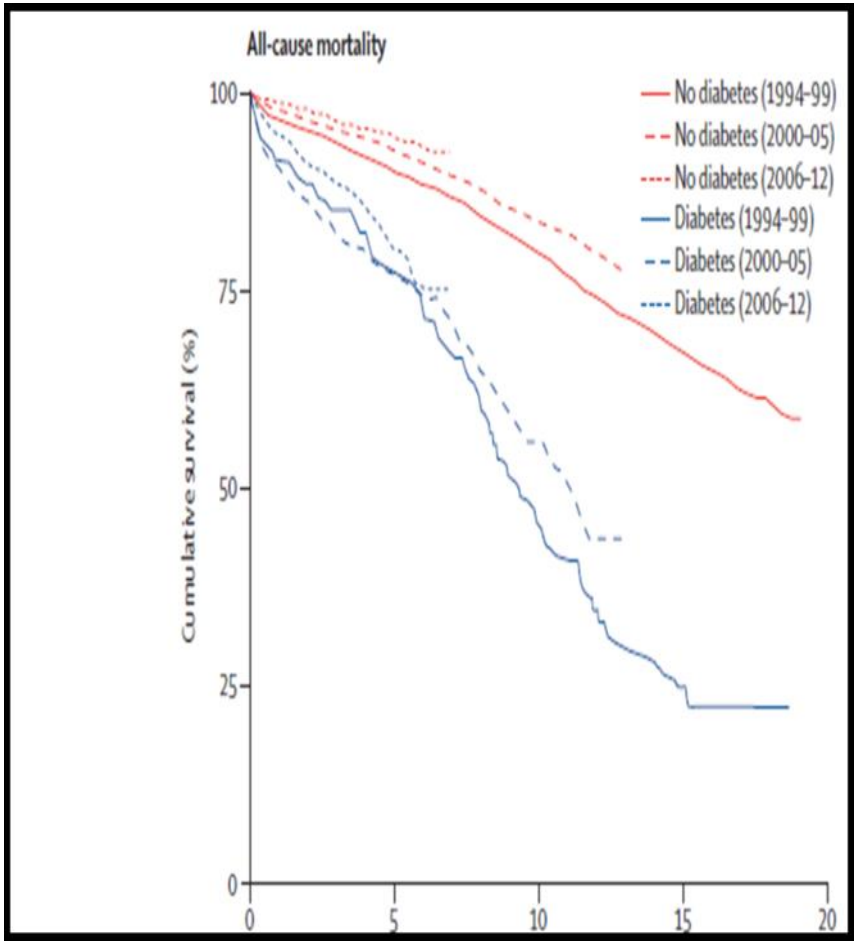
Predictors of MACE Year 1

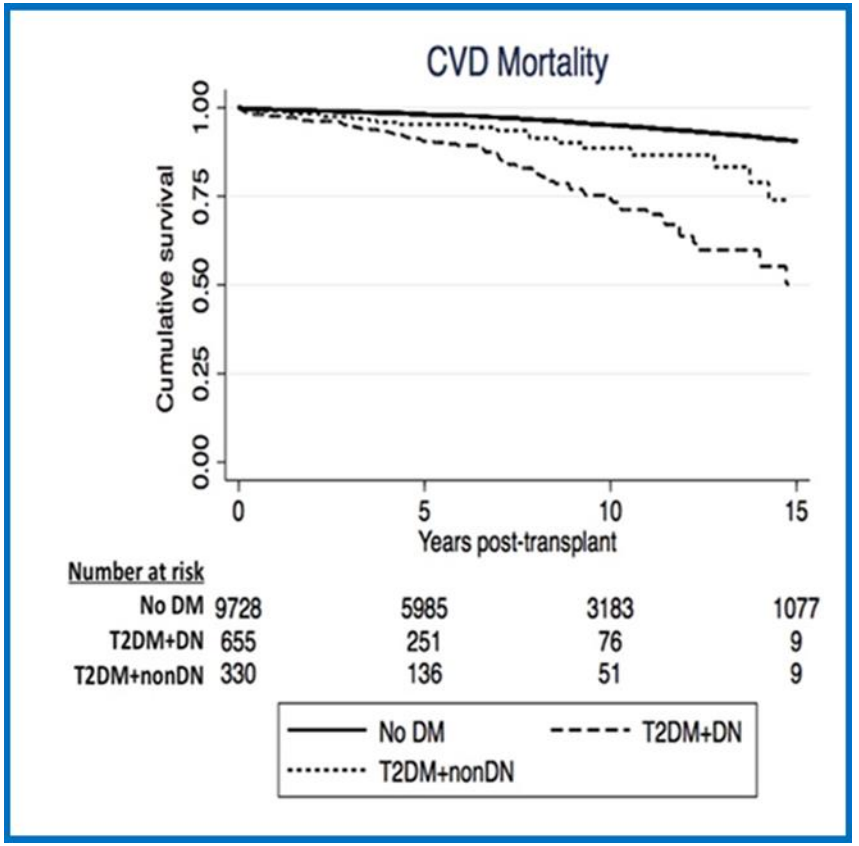
- Increasing Age
- Male Gender
- Diabetes
- Cancer
- Previous CVS Events
- BMI > 35
- Duration dialysis > 2 years

Male:1
Age >65: 8
Diabetic: 3
Previous Stent: 7
Deceased Donor Transplant: 1



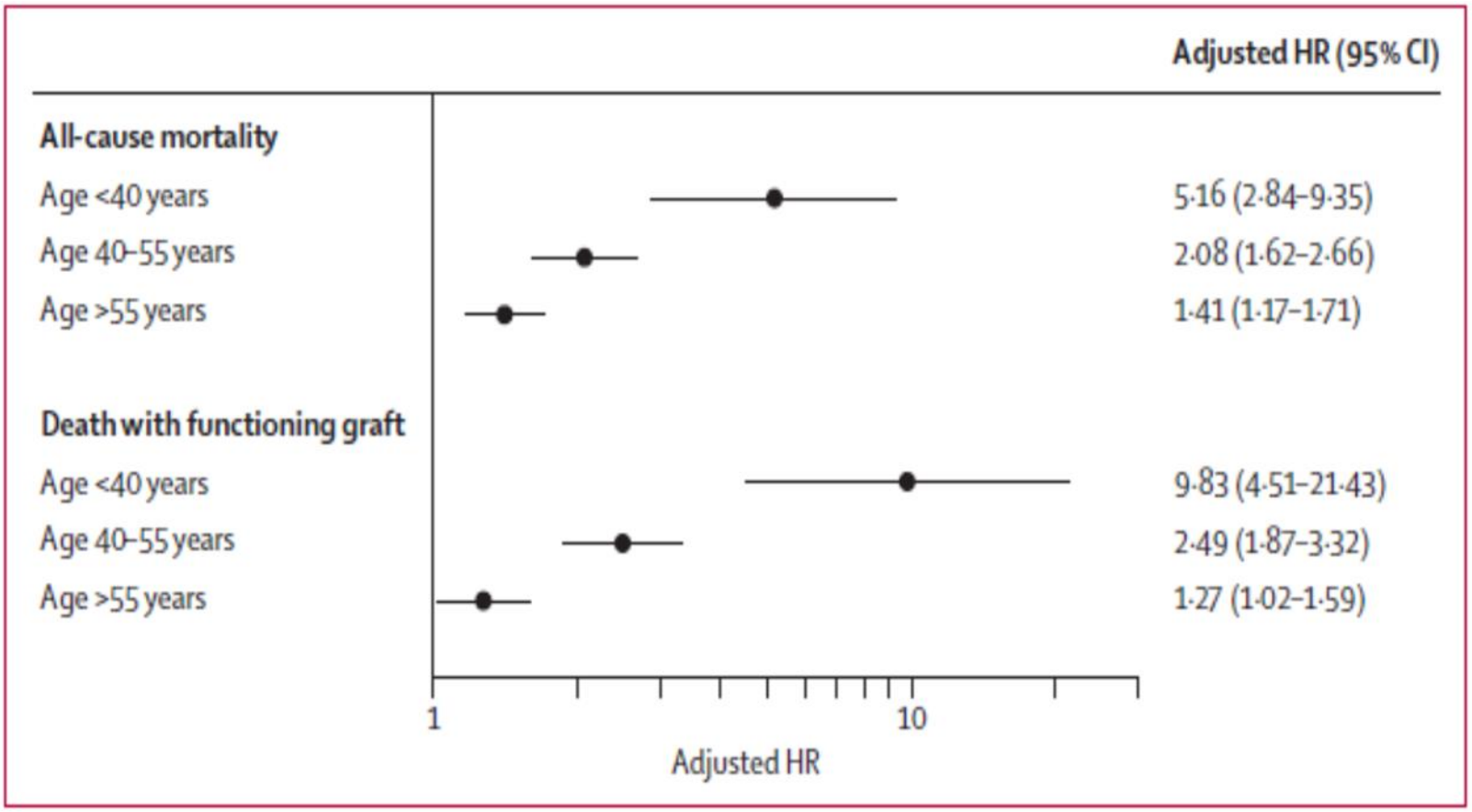
Diabetes as predictor of CVS death



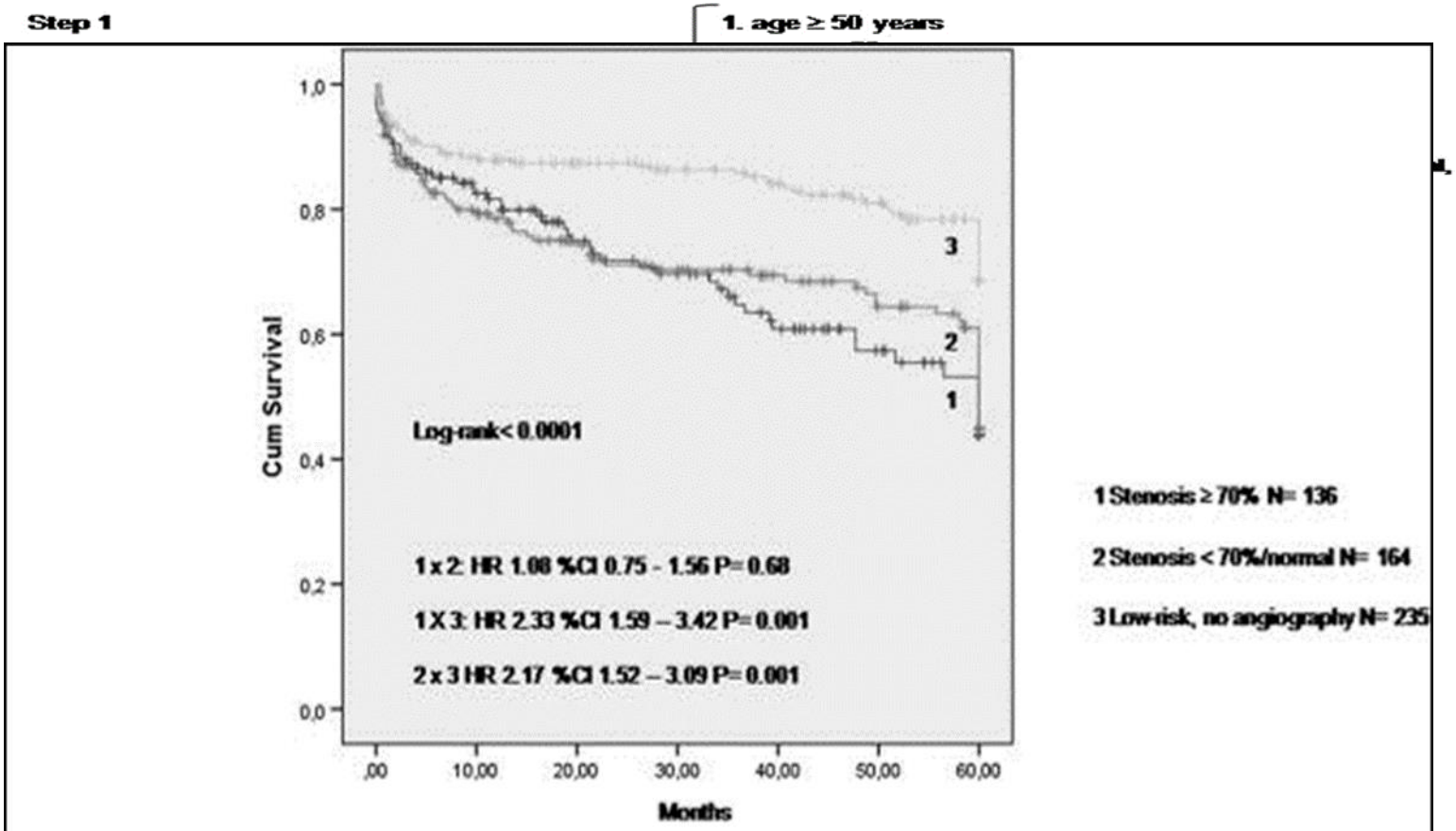


Lim Lancet Diabetes Endocrinol 2017:5: 26 - 33

Diabetes risk factor at all ages



Ischemic Heart Disease and Risk



Known IHD

TABLE 2.

Multivariate analysis (Cox proportional hazards model) for variables associated with coronary events in renal transplant patients

Variable	HR	95% CI	*P*
Age, y	1.02	0.99-1.06	0.24
Body mass index, kg/m^2	1.07	0.99-1.15	0.06
Sex	1.06	0.77-1.46	0.70
Smoking	1.33	0.91-1.95	0.14
Diabetes	1.22	0.63-2.38	0.55
Angina	2.17	1.10-4.43	0.02
Hypertension	0.91	0.60-1.37	0.64
Cardiovascular disease	1.14	0.58-2.23	0.71
Coronary artery disease	3.81	1.58-9.92	0.003

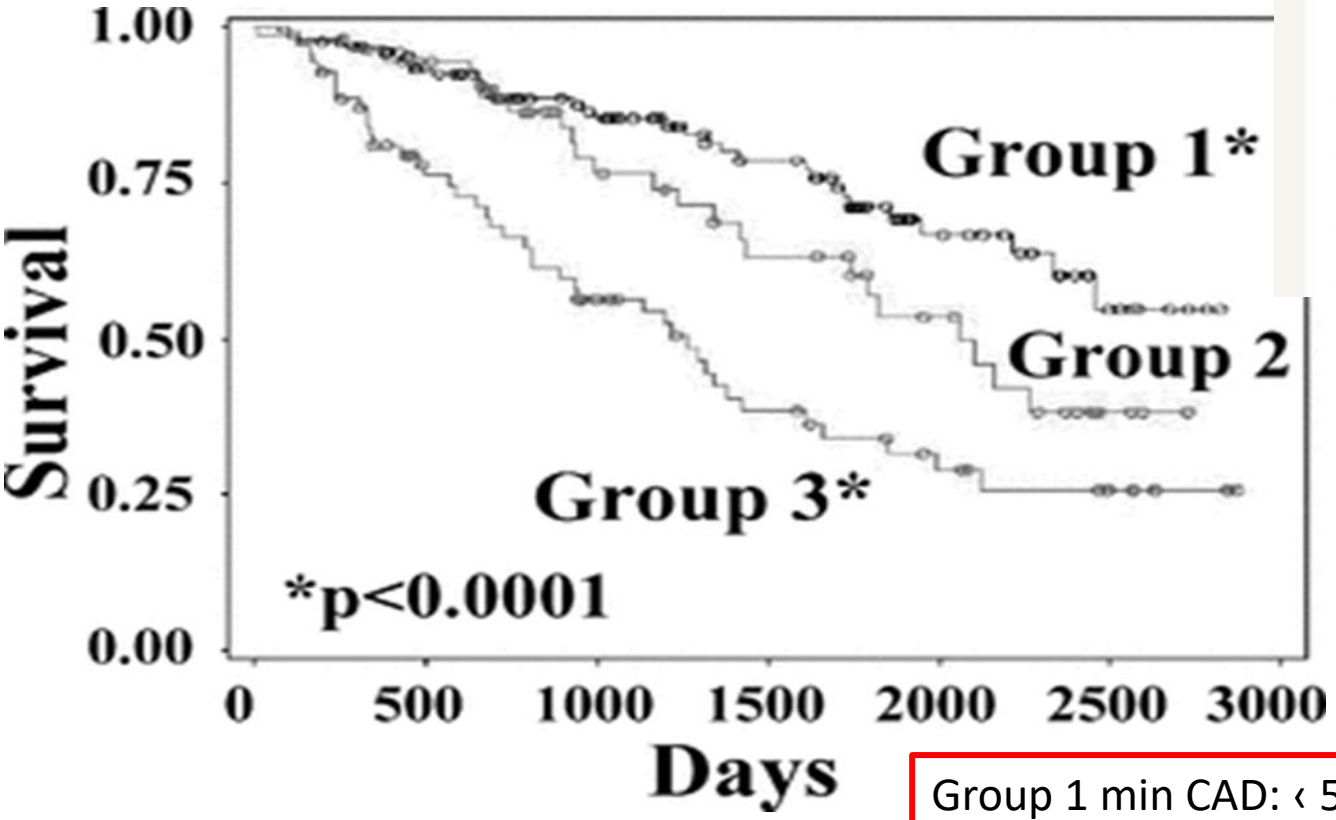
De Lima Transplantation 2016; 100: 1580

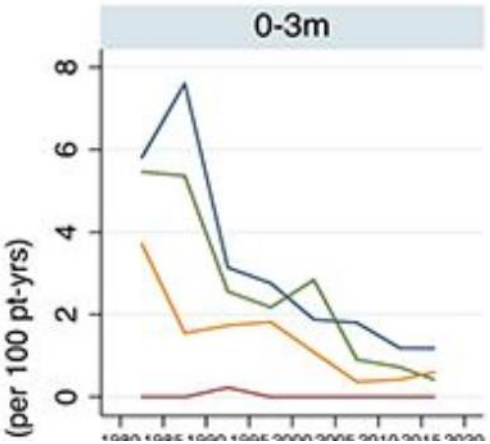
Cardiac Disease Pre-Transplant

- Predicts events after transplantation
- Often asymptomatic
- In transplant assessment setting testing commonly done
  - To assess coronary anatomy
    - Often done as functional test
    - Stress Scintigraphy or Stress Echocardiography
  - To determine LV function
  - To assess for pulmonary hypertension
  - To assess for valvular heart disease
- Results of testing may determine eligibility for listing
- Results of CAD testing have traditionally led to revascularisation to allow transplantation.

How to prevent patients dying of CVS disease early post transplant

- Patient Selection

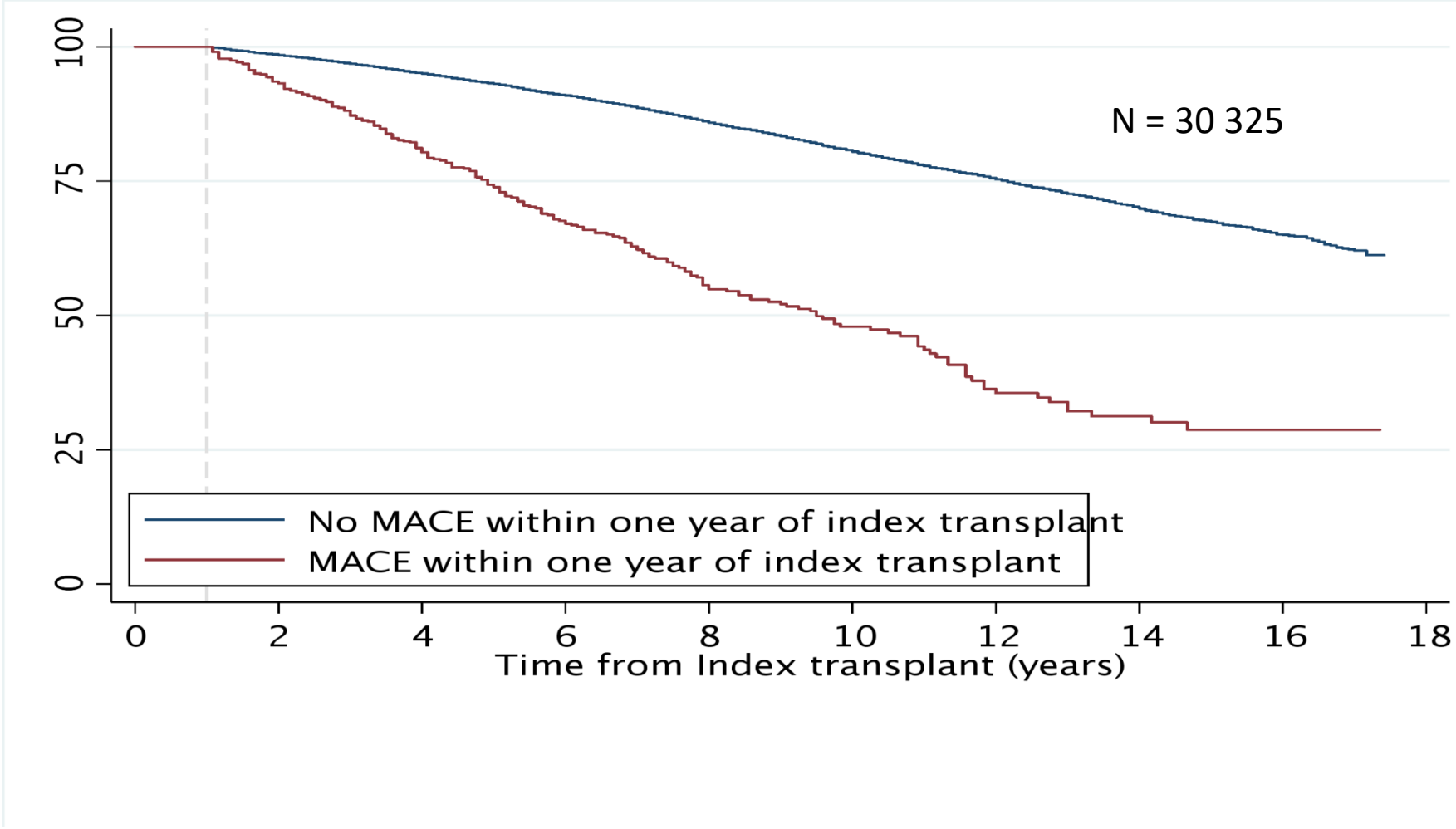




Group 1 min CAD: ‹ 50% stenosis
Group 2: single vessel disease > 50%
Group 3: multi-vessel disease >50%

Jones AJT 2009 Aug;9(8):1846-52

Early MACE after transplant predictor of mortality



Shariff KI

How do we select patients?

2012 AHA/ACCF Recommendations for Noninvasive Stress Testing in KTx Candidates

Class IIb, LOE C Recommendation

- **Noninvasive stress testing** may be considered in KTx candidates **without active cardiac conditions** based on the presence of **>=3 CAD risk factors**, regardless of functional status

Risk Factors in KTx Candidates

- DM, prior CVD, >1 yr on dialysis, LVH, age > 60, smoking, HTN, dyslipidemia

(Lisbon Conference Report)

Number of risk factors that should prompt testing remains to be determined, but >=3 deemed reasonable

[Lentine et al. *Circulation* 2012;126:617]

KDIGO: Transplant Candidate Guideline 2020

13.1: Evaluate all candidates for the presence and severity of cardiac disease with history, physical examination, and electrocardiogram (ECG) *(Not Graded)*.

13.2: Patients with signs or symptoms of active cardiac disease (e.g., angina, arrhythmia, heart failure, symptomatic valvular heart disease) should undergo assessment by a cardiologist and be managed according to current local cardiac guidelines prior to further consideration for a kidney transplant *(Not Graded)*.

13.3: We suggest that asymptomatic candidates at high risk for coronary artery disease (CAD) (e.g., diabetes, previous CAD, etc.) or with poor functional capacity undergo non-invasive CAD screening. *(2C)*

ECG on admission for renal transplant

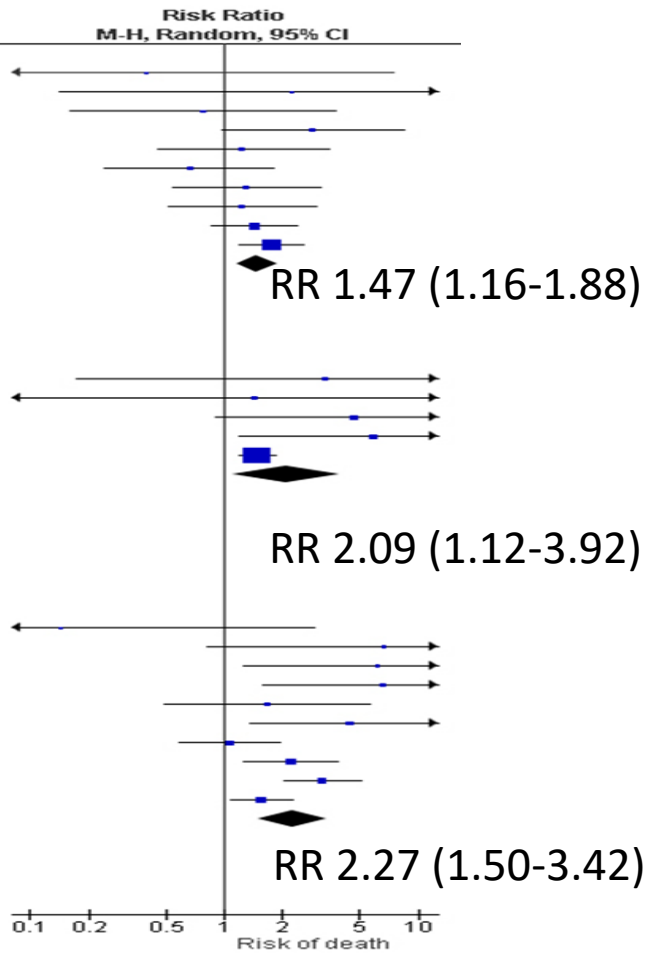
	Hazard ratio	95% confidence interval	*p* value
Myocardial infarction			
None	ref		
Silent	2.03	1.25–3.30	.004
Clinical	2.15	1.24–3.74	.007
Age >65 years	1.72	1.07–2.75	.02
Male gender	1.12	0.80–1.57	.5
Diabetes mellitus	1.92	1.35–2.74	<.001
Hypertension	0.94	0.44–2.01	.9
Hyperlipidemia	0.99	0.70–1.41	>.9
Years of dialysis	1.01	0.97–1.06	.6
Living donor	0.59	0.39–0.89	.01

No
SM
CM

Santana AJT 2022

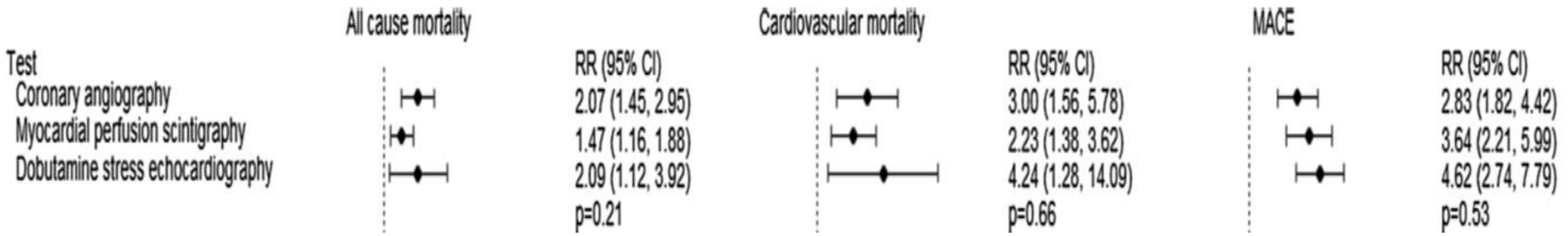
Does Screening Predict Events?

Study or Subgroup	Abnormal test Events	Total	Normal test Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
6.1.1 Myocardial perfusion scintigraphy						
Feola 2002	0	21	3	61	0.7%	0.40 [0.02, 7.49]
Philipson 1986	7	53	0	7	0.8%	2.22 [0.14, 35.28]
Vandenberg 1996	2	16	4	25	2.4%	0.78 [0.16, 3.78]
Venkataram 2008	50	128	3	22	5.1%	2.86 [0.98, 8.38]
Derfler 1991	4	9	5	14	5.7%	1.24 [0.45, 3.43]
Leonardi 2009	4	52	29	250	5.8%	0.66 [0.24, 1.81]
Patel 2003	7	54	12	120	7.7%	1.30 [0.54, 3.11]
Morrow 1983	5	18	15	67	7.8%	1.24 [0.52, 2.96]
Le 1994	18	39	18	56	22.6%	1.44 [0.86, 2.39]
Atkinson 2011	9	10	19	37	41.6%	1.75 [1.20, 2.55]
Subtotal (95% CI)		**400**		**659**	**100.0%**	**1.47 [1.16, 1.88]**
Total events	106		108			
Heterogeneity: Tau² = 0.00; Chi² = 6.90, df = 9 (P = 0.65); I² = 0%						
Test for overall effect: Z = 3.14 (P = 0.002)						
6.1.2 Dobutamine stress echocardiography						
West 2000	2	20	0	13	4.2%	3.33 [0.17, 64.33]
Brennan 1997	0	5	2	42	4.4%	1.43 [0.08, 26.41]
Reis 1995	4	29	2	68	12.2%	4.69 [0.91, 24.19]
Sharma 2005	5	37	2	88	12.8%	5.95 [1.21, 29.28]
Bergeron 2007	94	193	94	284	66.4%	1.47 [1.18, 1.83]
Subtotal (95% CI)		**284**		**495**	**100.0%**	**2.09 [1.12, 3.92]**
Total events	105		100			
Heterogeneity: Tau² = 0.14; Chi² = 5.05, df = 4 (P = 0.28); I² = 21%						
Test for overall effect: Z = 2.31 (P = 0.02)						
6.1.3 Coronary angiography						
Bennett 1978(70%stenosis)	2	4	4	7	0.0%	0.88 [0.27, 2.82]
Manske 1992	6	26	0	0		Not estimable
Eschertzhuber 2005	0	52	2	37	1.7%	0.14 [0.01, 2.90]
Worthley 2003	4	15	1	25	3.3%	6.67 [0.82, 54.21]
Sharma 2005	5	36	2	89	5.2%	6.18 [1.26, 30.41]
Philipson 1986	10	23	2	30	6.1%	6.52 [1.58, 26.92]
Bennett 1978(50%stenosis)	4	6	2	5	7.6%	1.67 [0.50, 5.61]
Enkiri 2011	9	23	3	34	7.8%	4.43 [1.34, 14.65]
Kahn 2011	25	212	16	145	15.4%	1.07 [0.59, 1.93]
Atkinson 2011	19	23	9	24	16.1%	2.20 [1.27, 3.82]
Kumar 2011	36	184	29	473	17.6%	3.19 [2.02, 5.05]
Braun 1984	17	25	33	75	19.1%	1.55 [1.07, 2.24]
Subtotal (95% CI)		**625**		**937**	**100.0%**	**2.27 [1.50, 3.42]**
Total events	135		99			
Heterogeneity: Tau² = 0.20; Chi² = 21.20, df = 9 (P = 0.01); I² = 58%						
Test for overall effect: Z = 3.89 (P < 0.0001)						



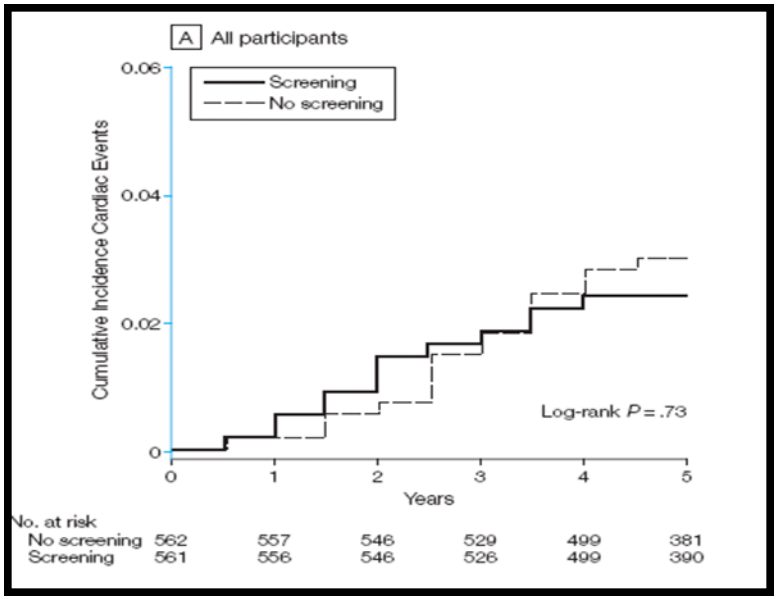
Cochrane Review

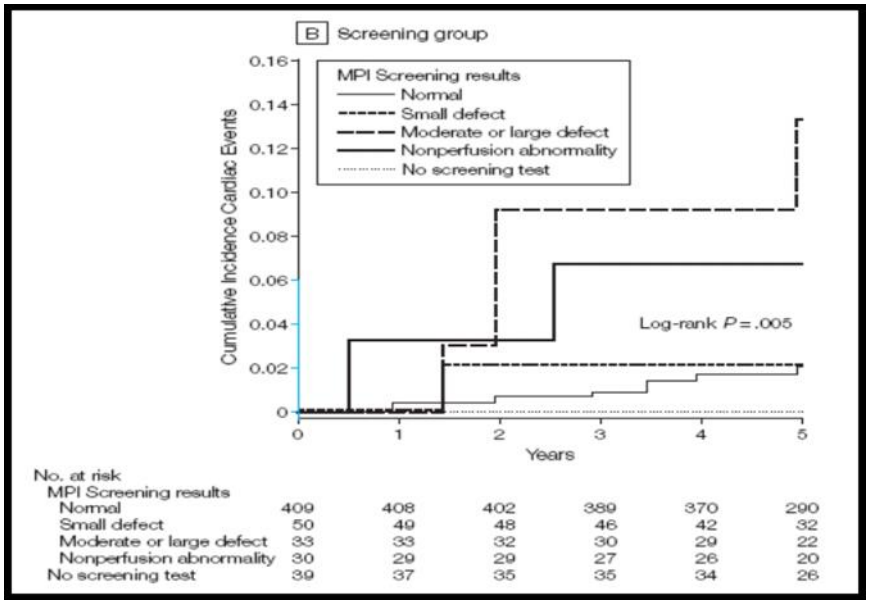
Which Test is Best?



Wang Transplantation 2015 Apr;99(4):731-45

Does Screening itself reduce CVS events?

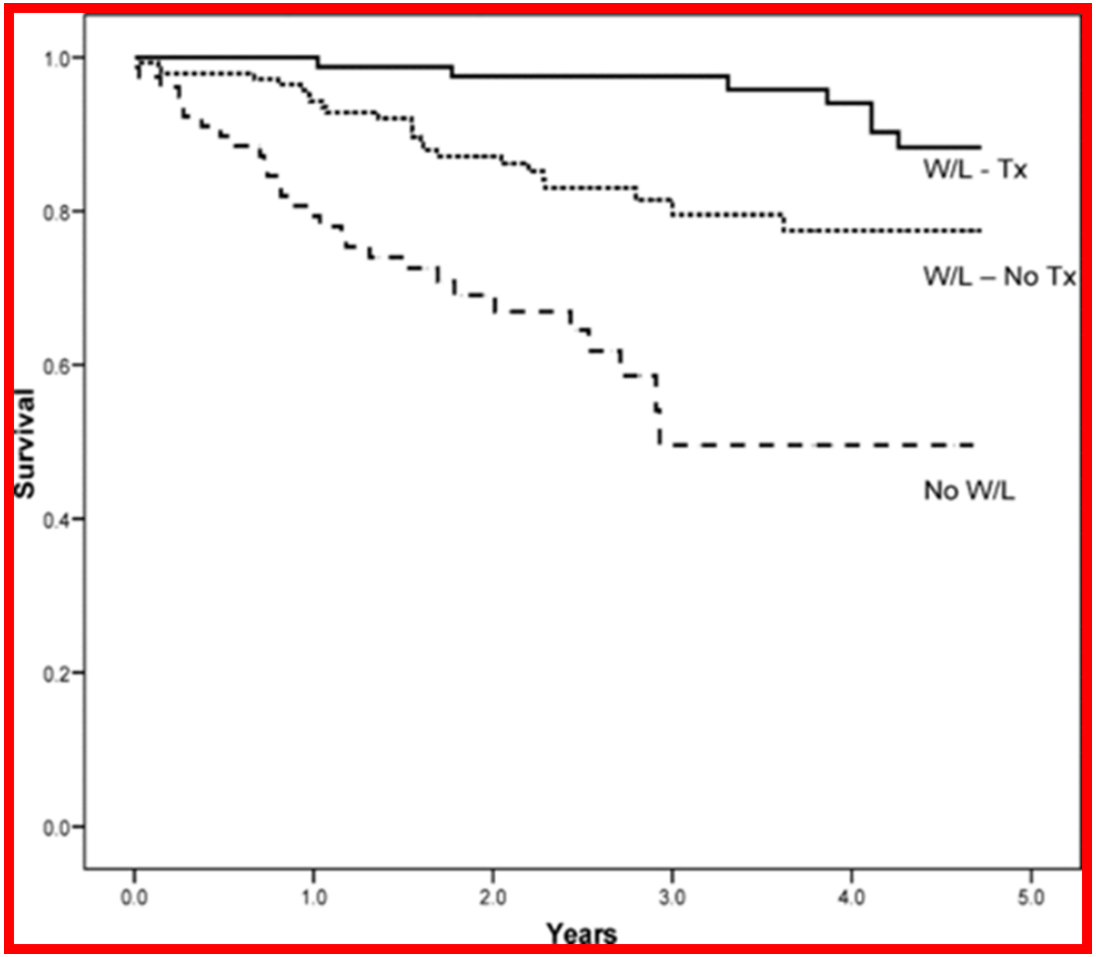




DIAD Study RCT of cardiac screening in diabetics
Therapeutic options after Stress Test decided clinically – not mandated
N = 1123

Young JAMA 2009; 301: 1547

Screening may exclude patients from Wait-listing



Patel AJT 2008; 8: 1673

Registry Data update

- Instrumental Variable (IV) Analysis in US cohort
- IV analysis attempts to draw causal inference from observational data.
- Selected the facility/programme-level pre transplant testing as the IV for pre-transplant CAD testing
- Idea is that pre-transplant testing rate would only be associated with patient's clinical outcome as mediated by the patient's receipt of CAD testing
- Hypothesised that pretransplant CAD testing was associated with a lower rate of cardiac events after kidney transplantation

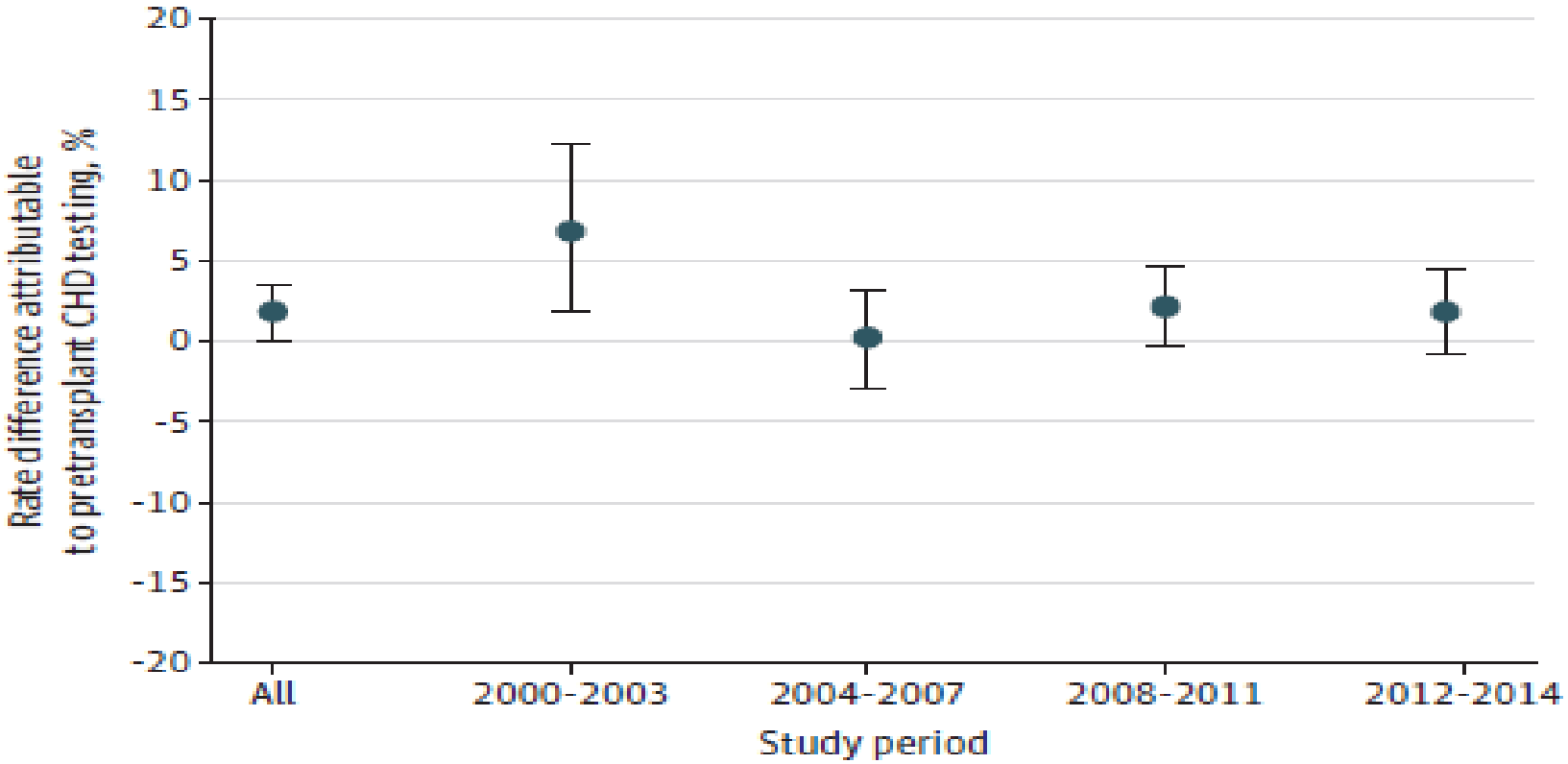
Xingxing et al JAMA 2023; 183 (2): 1341 - 141

Instrumental Variable

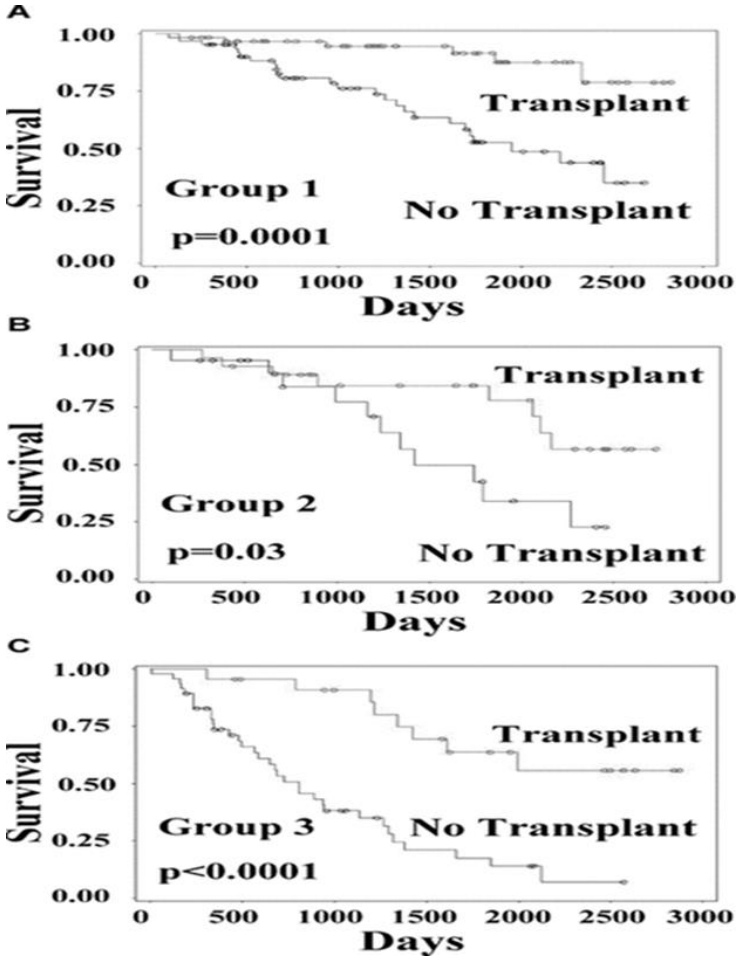
- Proportion of low risk waitlisted patients who underwent elective CAD testing in year prior to transplant
- Divided into quintiles of units
- Lowest Quintile tested 24%
- Highest Quintile tested 56%
- Low risk defined as
  - Younger than 60 years
  - No DM
  - No known CAD

Primary Outcome

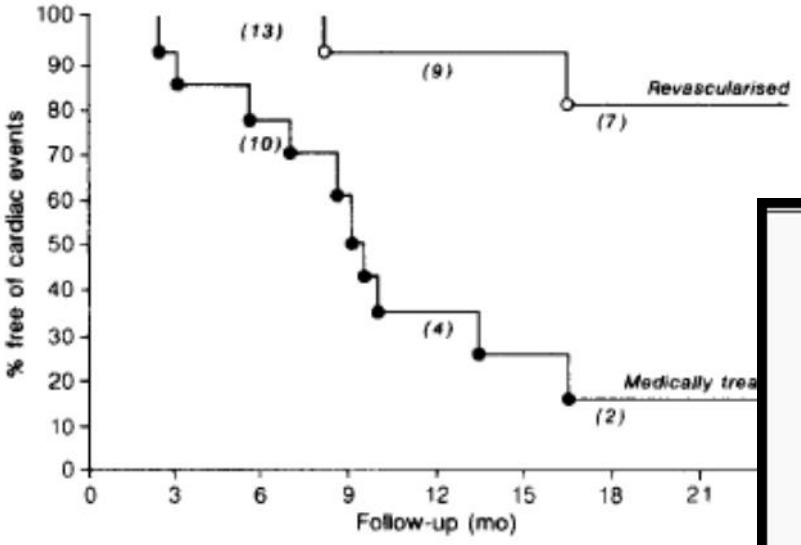
Figure 2. Association of Pretransplant Coronary Heart Disease (CHD) Testing With Death or Acute Myocardial Infarction Rate Within 30 Days Posttransplant



Potential harms of screening

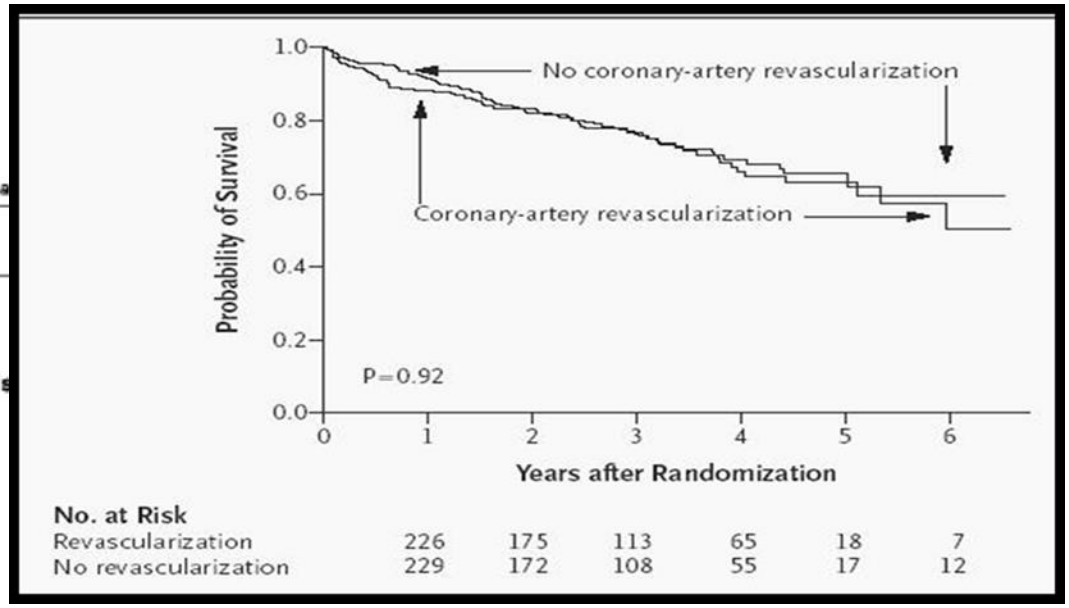


What to do when you find CAD in patient under assessment for Transplantation



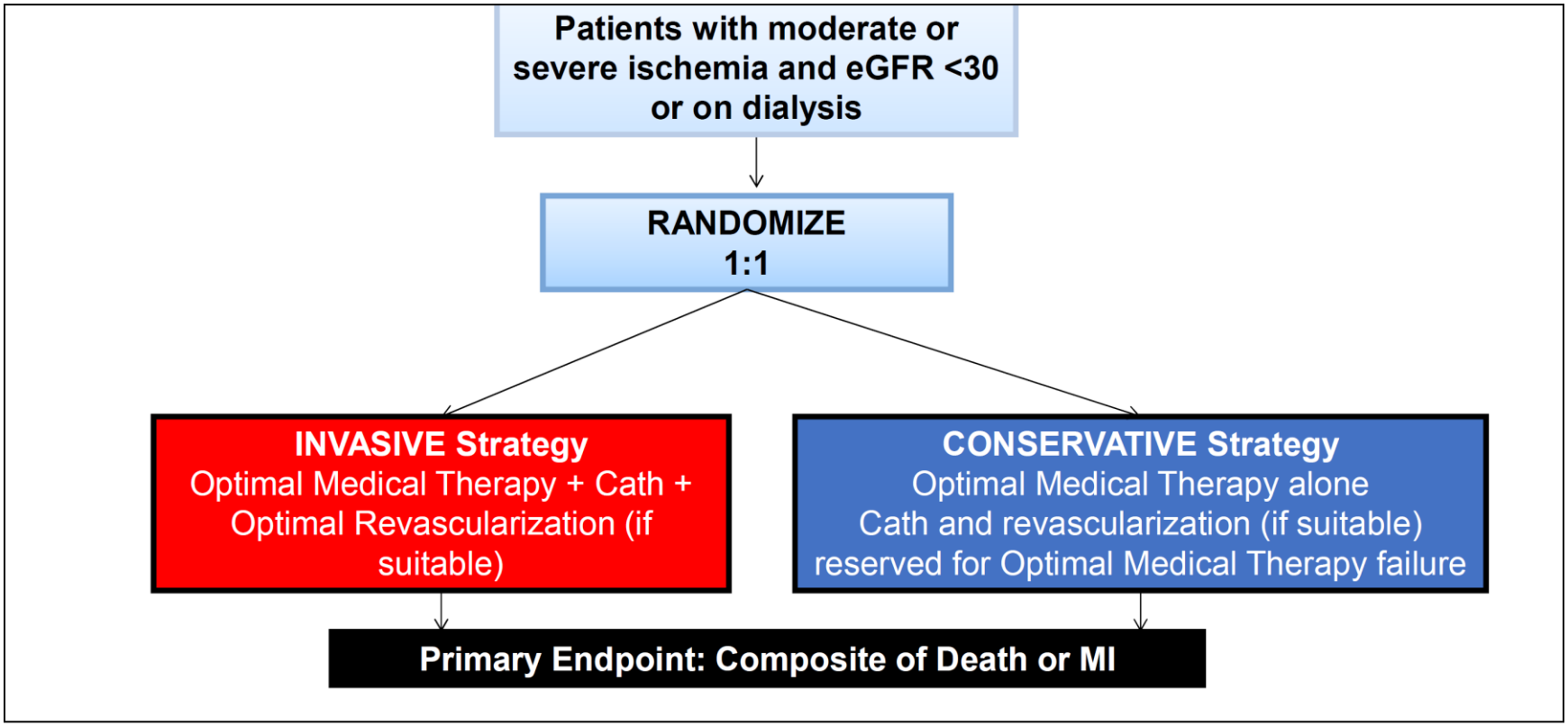
Cardiovascular events in medically treated and revascularis patients.

Manske Lancet 1992



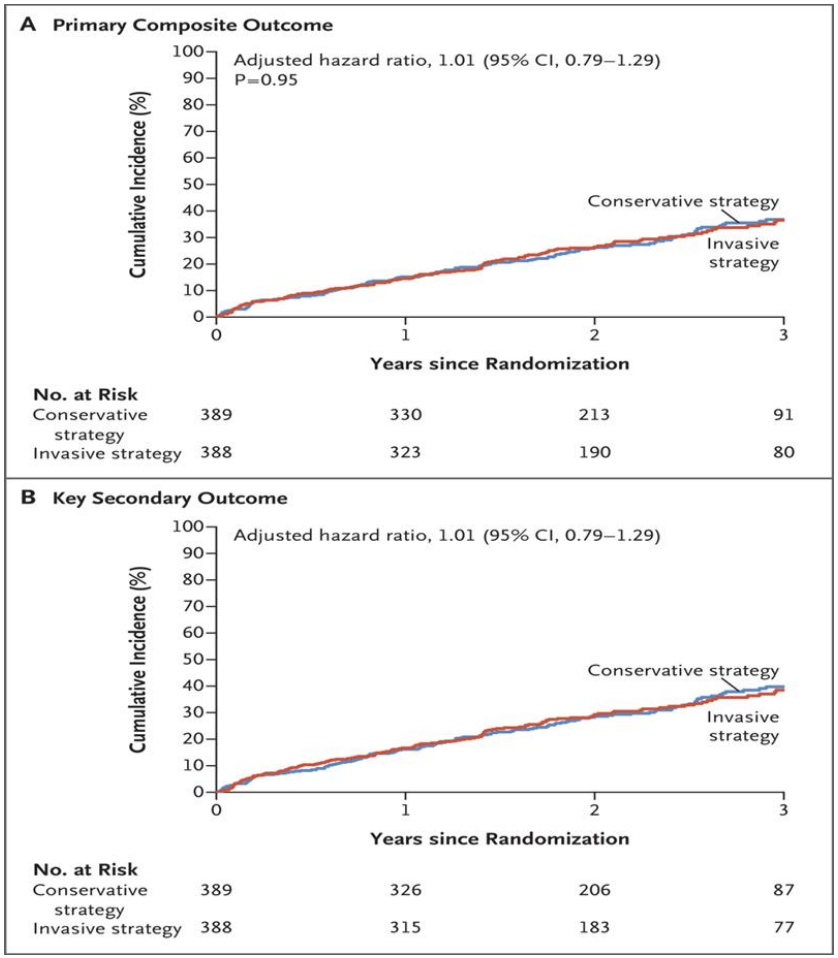
McFalls *et al* NEJM 2004; 351(27): 2795

Ischemia CKD



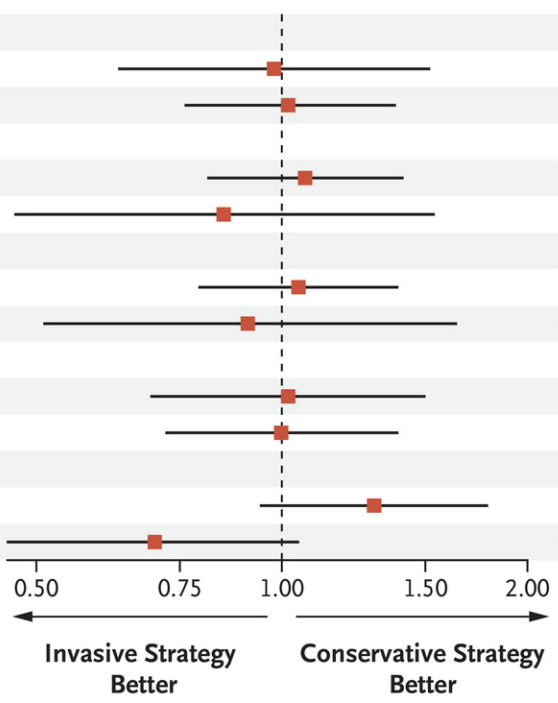
Coronary Angiography in 85%;
Revascularisation 50%
Of Invasive Group

Bangalore A Heart J 2018


A Primary Composite Outcome
Adjusted hazard ratio, 1.01 (95% CI, 0.79–1.29)
P=0.95
Cumulative Incidence (%)
100
90
80
70
60
50
40
30
20
10
0
Conservative strategy
Invasive strategy
0
1
2
3
Years since Randomization
No. at Risk
Conservative strategy 389 330 213 91
Invasive strategy 388 323 190 80
B Key Secondary Outcome
Adjusted hazard ratio, 1.01 (95% CI, 0.79–1.29)
Cumulative Incidence (%)
Conservative strategy
Invasive strategy
Years since Randomization
No. at Risk
Conservative strategy 389 326 206 87
Invasive strategy 388 315 183 77

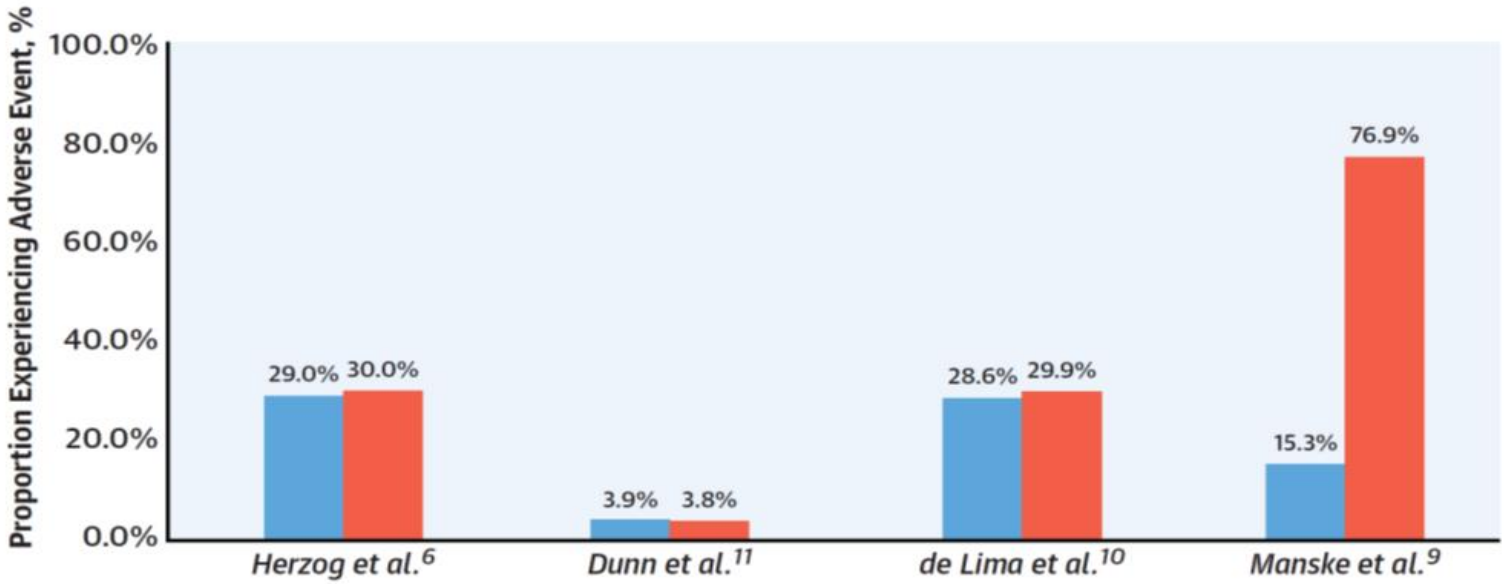
Ischemia-CKD

Subgroup	No. of Patients	Percent of Patients	Estimated 3-Yr Event Rate (%)		Adjusted Hazard Ratio (95% CI)
			Invasive strategy	Conservative strategy	
Diabetes	777				
No		42.9	25.3	25.1	0.98 (0.63–1.52)
Yes		57.1	44.5	47.5	1.02 (0.76–1.38)
New or more frequent angina	775				
No		81.3	36.8	37.0	1.07 (0.81–1.41)
Yes		18.7	30.7	31.4	0.85 (0.47–1.54)
GBMT at baseline	727				
No		85.0	37.6	34.2	1.05 (0.79–1.39)
Yes		15.0	38.4	46.1	0.91 (0.51–1.64)
Dialysis	777				
No		46.6	34.4	32.9	1.02 (0.69–1.50)
Yes		53.4	38.1	39.9	1.00 (0.72–1.39)
Degree of baseline ischemia	775				
Moderate		61.4	39.4	32.8	1.30 (0.94–1.79)
Severe		37.8	30.3	42.3	0.70 (0.46–1.05)



Summary of Trials

FIGURE 1 Treatment of Myocardial Ischemia Among Renal Transplant Candidates in Selected Studies



Sample size	194	17,304	136	26
Year Published	2021	2019	2016	1992
Design	RCT	Registry	Registry	RCT
Comparators	Invasive/conservative	Stress testing/No stress testing	Revascularization/Medical	Revascularization/Medical
Endpoint	All-cause death or MI	MI	Mortality	Unstable angina, MI, cardiac death
Time point	3 years	30 days post KT	3 years	8.4 months

Guideline updates

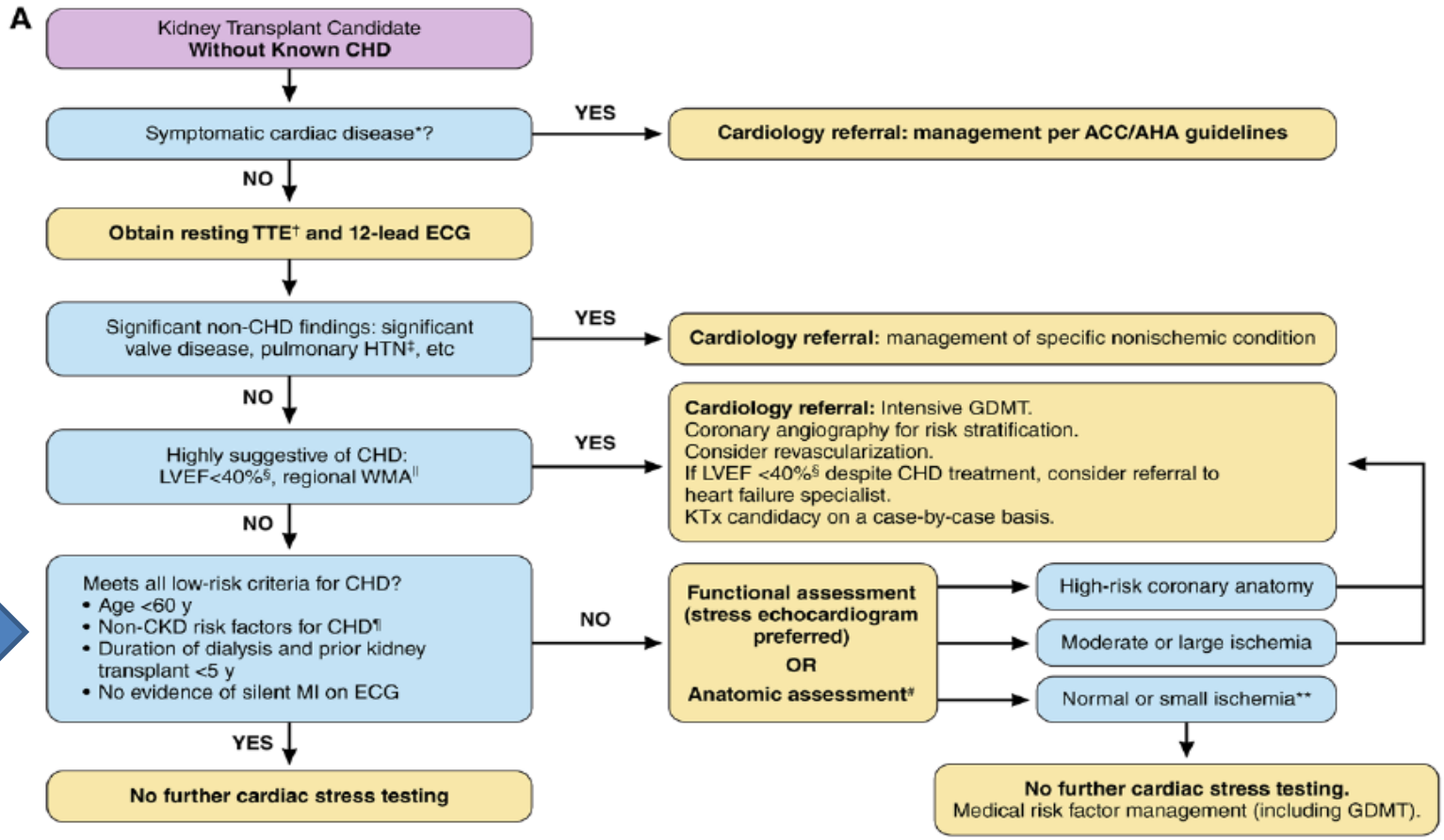
KDIGO 2020

- Recommend that asymptomatic candidates with known CAD **not** be revascularised exclusively to reduce perioperative cardiac events
- Suggest that patients with asymptomatic, advanced triple vessel coronary disease be excluded from kidney transplantation unless they have an estimated survival which is acceptable according to national standards (2D)

ACC/AHA/SCIA guidelines 2021 – Coronary Revascularisation

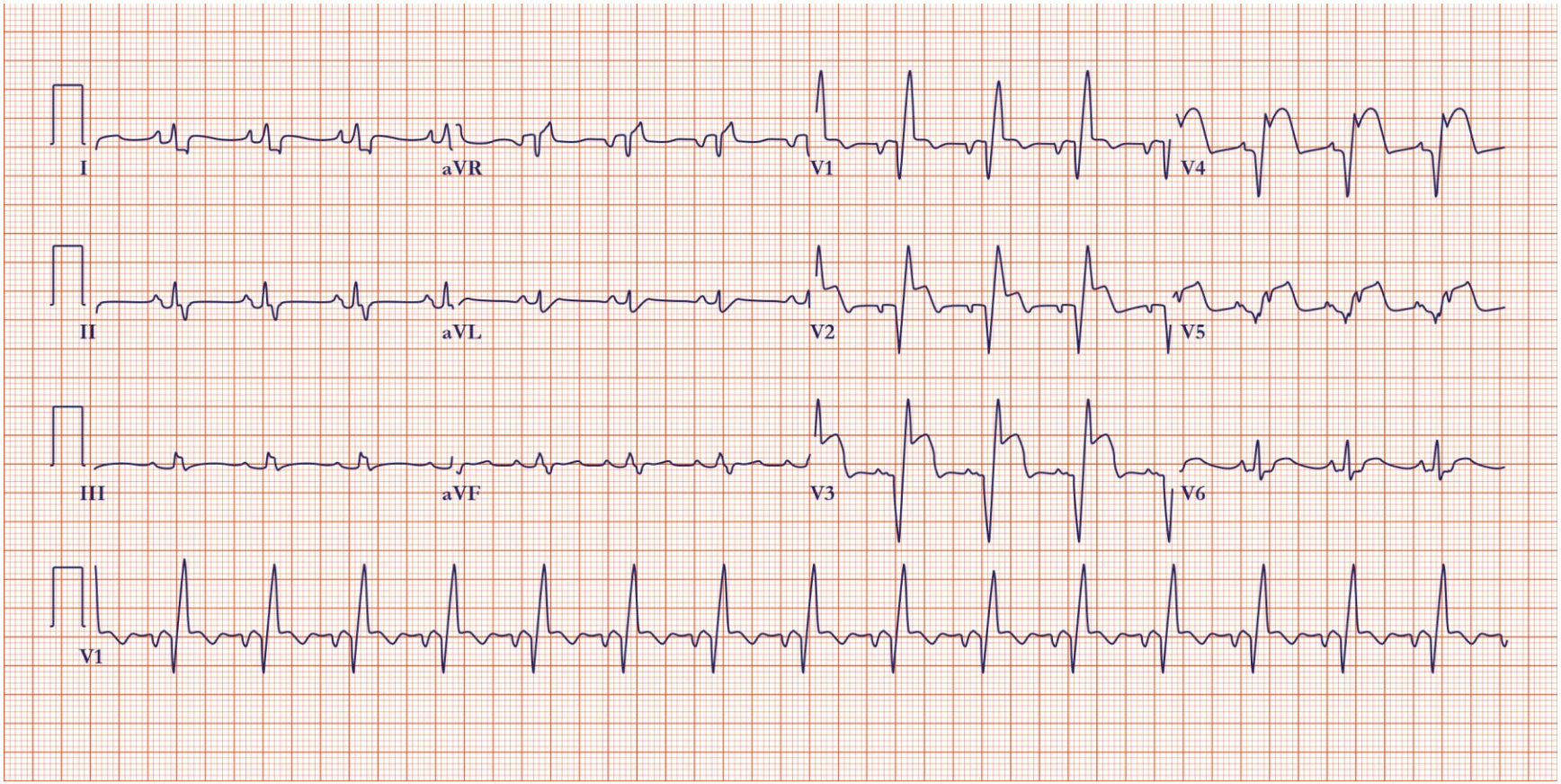
- In asymptomatic patients with stable CAD and CKD routine angiography and revascularisation are not recommended if there is no compelling benefit

Updated AHA statement 2022



CKD risk factors: DM, Cerebrovascular disease, PVD

Patients with recent CVS events



Myocardial Infarction and Stents

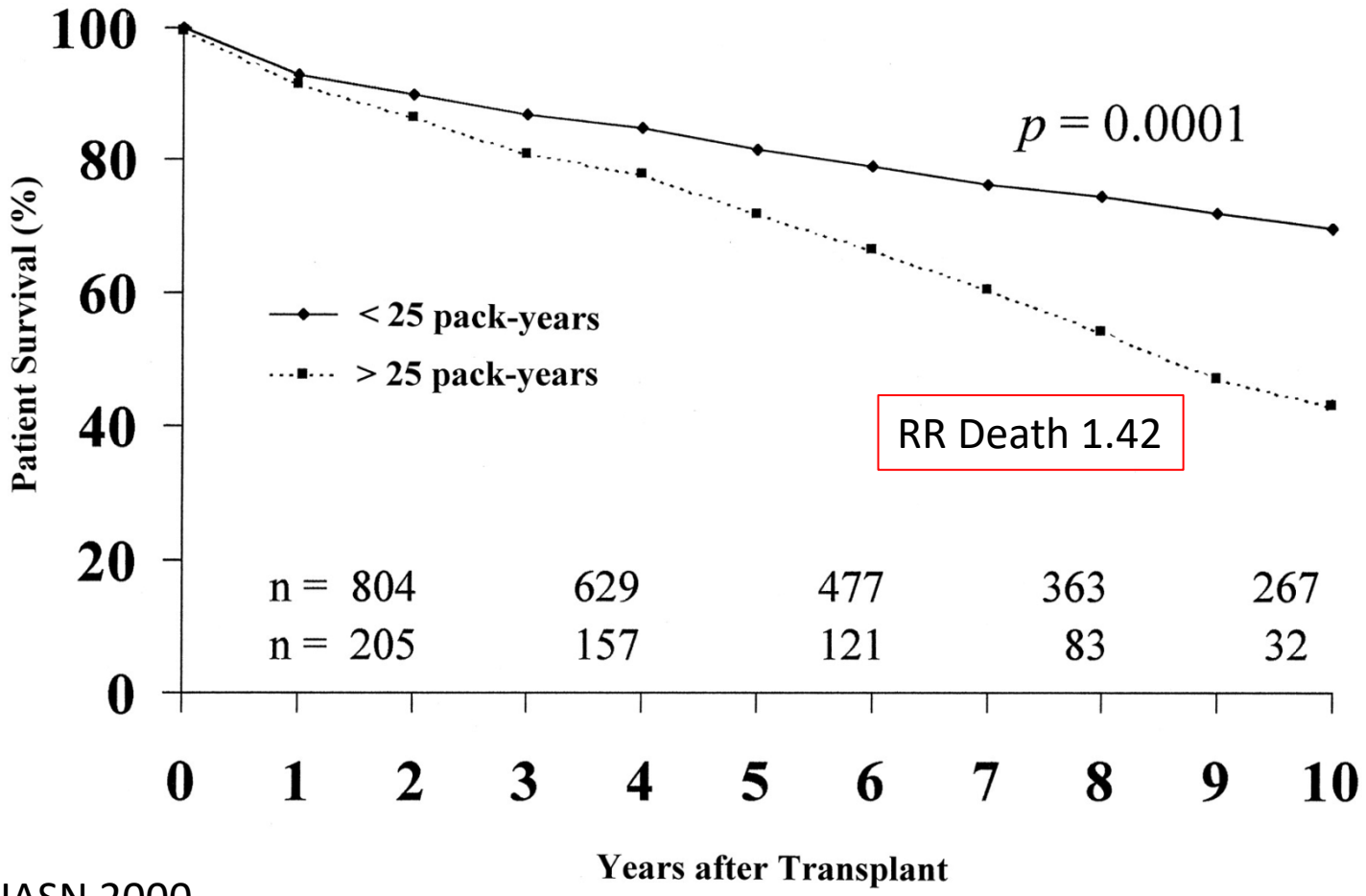
- Evidence that mortality is high in patients having surgery after a recent MI
  - Post operative mortality
  - Less than one month post MI 32.8%
  - 90 – 180 days post MI 5.9%
- Stents generally treated with Dual Anti-Platelet Therapy (DAPT)
  - Increased risk of bleeding
  - Duration of DAPT changing
  - Currently 1 month BMS
  - 6 – 12 Months DES
  - Cardiology guidelines most helpful

13.9: We suggest that candidates who have a myocardial infarction be assessed by a cardiologist to determine whether further testing is warranted and when they can safely proceed with kidney transplantation *(2B)*.

13.10: We suggest that transplantation be delayed an appropriate amount of time after placement of a coronary stent as recommended by the patient's cardiologist (*2B*).

What else can you do to prevent CVS events and death?

- Smoking

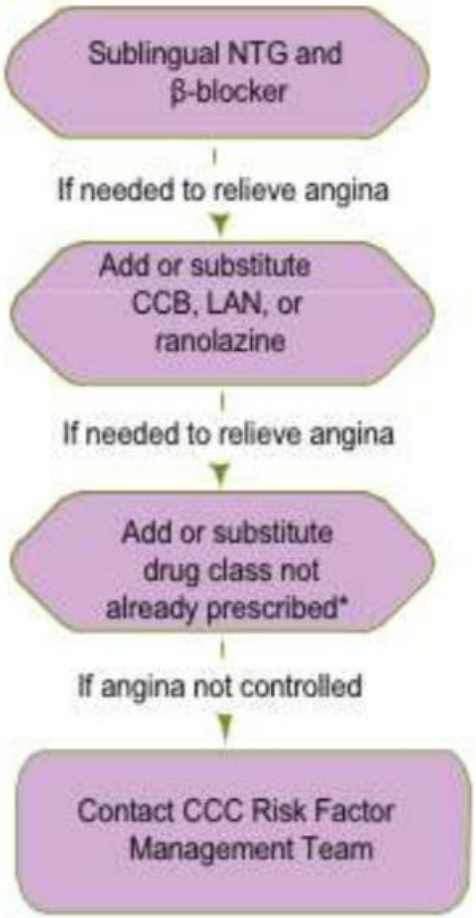


Kasiske JASN 2000

Optimal Medical Treatment: Ischemia CKD

- Smoking cessation
- Physical activity ≥30 minutes of moderate intensity for ≥5days per week
- <7% of calories from saturated fats
- BP <130/80mmHg
- LDL-C <70mg/dl
- BMI<25 if initial BMI 25-27.5 and 10% relative weight loss if initial BMI >27.5
- HbA1c <8%
- Antiplatelet therapy with Aspirin (P2Y12 receptor antagonist in patients with contraindication to aspirin)

ANGINA THERAPY



*Consider (not in order of preference): ivabradine, nicorandil, perhexiline, trimetazidine, where approved. LAN=long-acting nitrate

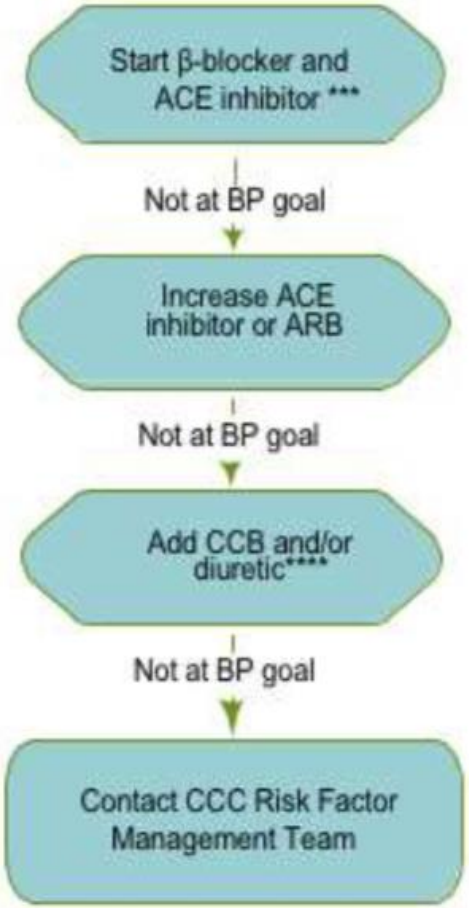
LIPID LOWERING THERAPY

Goal: LDLC <70mg/dL (1.8 mmol/L)

**Where available

HYPERTENSION THERAPY

Goal: Systolic BP <130 mmHg

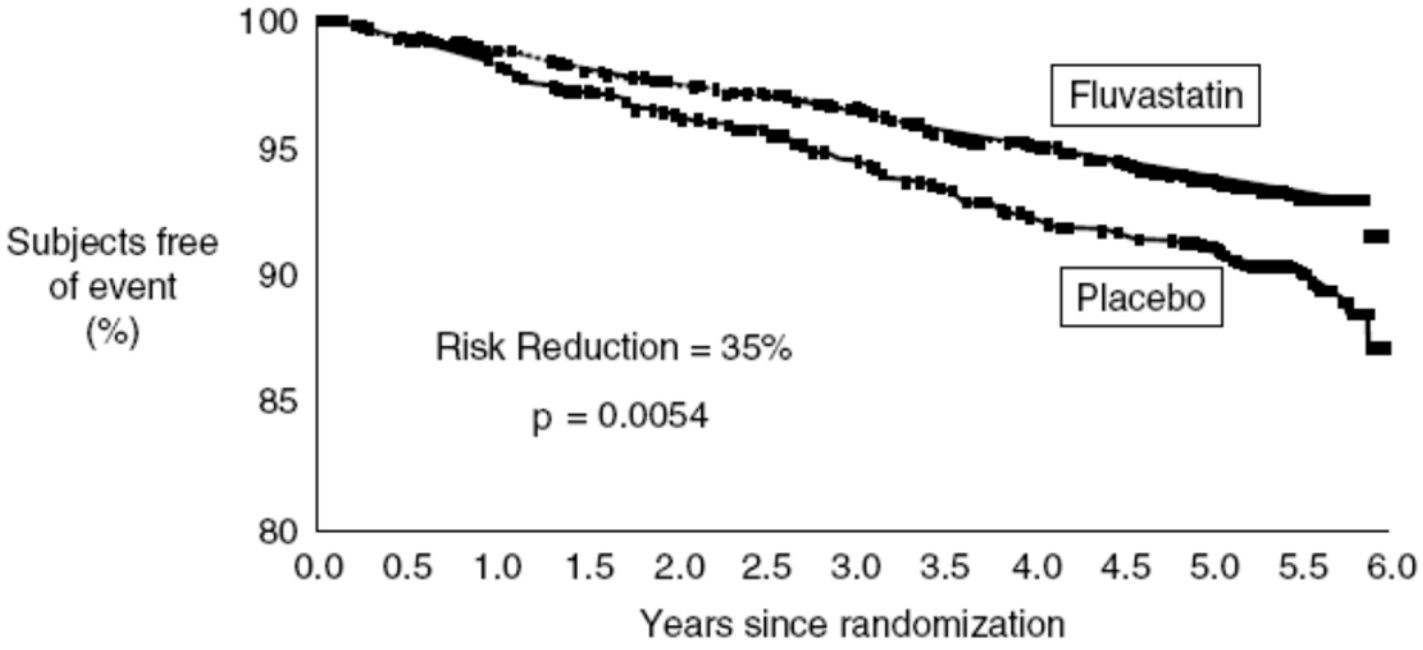


***Or ARB if appropriate. Monitor serum potassium closely in participants not on dialysis

Lipid Management

- KDIGO Lipid Guideline 2013
  - In adult kidney transplant patients suggest treatment with statin
  - Based on ALERT trial of fluvastatin
  - 35% reduction in risk of cardiac death or non-fatal MI

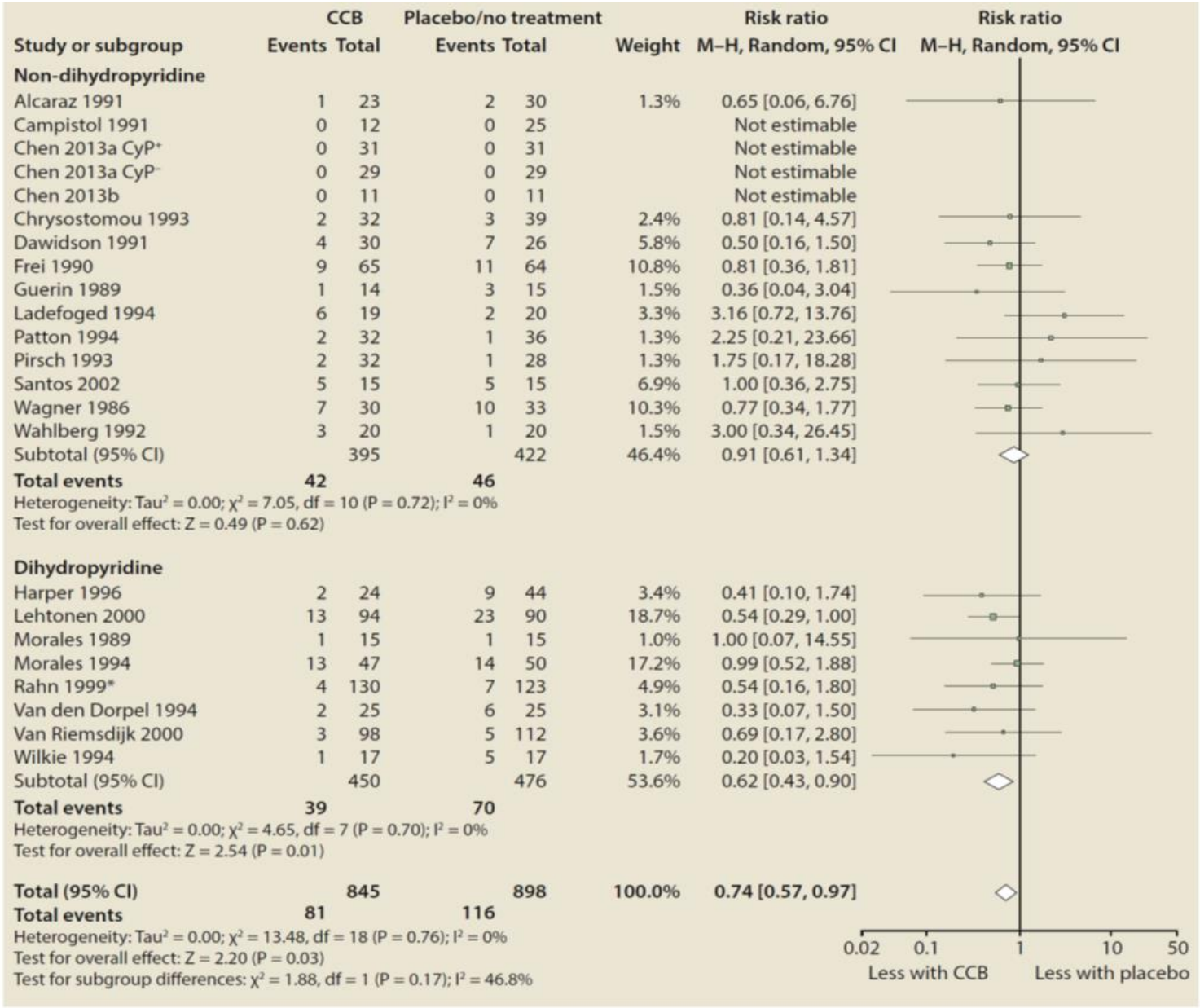
p



Treatment of Hypertension

KDIGO Management of Blood Pressure in CKD 2021 (Chapter 4)

- Recommendations all made on basis of meta-analyses: individual RCT not significant
- Treat adult kidney transplant patients to a target BP <130/80 (compared to 120/80 in non transplant CKD – SPRINT)
- Dihydropyridine CCB or ARB be used first line – dihypdropyridine CCB OR 0.62 graft loss, ARB RR 0.35 graft loss
- **No benefit of any BP med in transplant in meta-analyses for CVS events or mortality**
- *Recommend adequately powered RCT to evaluate CV and kidney effects of systolic BP <120 versus <130*
- *Recommend adequately powered RCT of ARB versus dihypdropyridine CCB (caveat being that would potentially require >10,000 in trial*

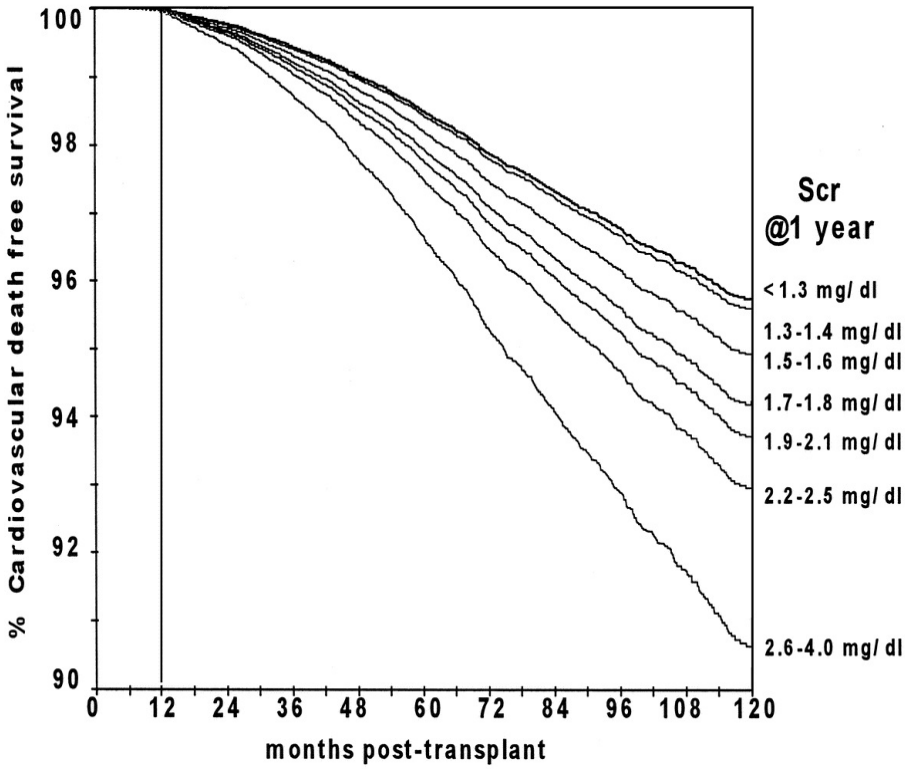

CCB
Placebo/no treatment
Risk ratio
Risk ratio
Study or subgroup
Events Total
Events Total
Weight
M–H, Random, 95% CI
M–H, Random, 95% CI
Non-dihydropyridine
Alcaraz 1991 1 23 2 30 1.3% 0.65 [0.06, 6.76]
Campistol 1991 0 12 0 25 Not estimable
Chen 2013a CyP+ 0 31 0 31 Not estimable
Chen 2013a CyP- 0 29 0 29 Not estimable
Chen 2013b 0 11 0 11 Not estimable
Chrysostomou 1993 2 32 3 39 2.4% 0.81 [0.14, 4.57]
Dawidson 1991 4 30 7 26 5.8% 0.50 [0.16, 1.50]
Frei 1990 9 65 11 64 10.8% 0.81 [0.36, 1.81]
Guerin 1989 1 14 3 15 1.5% 0.36 [0.04, 3.04]
Ladefoged 1994 6 19 2 20 3.3% 3.16 [0.72, 13.76]
Patton 1994 2 32 1 36 1.3% 2.25 [0.21, 23.66]
Pirsch 1993 2 32 1 28 1.3% 1.75 [0.17, 18.28]
Santos 2002 5 15 5 15 6.9% 1.00 [0.36, 2.75]
Wagner 1986 7 30 10 33 10.3% 0.77 [0.34, 1.77]
Wahlberg 1992 3 20 1 20 1.5% 3.00 [0.34, 26.45]
Subtotal (95% CI) 395 422 46.4% 0.91 [0.61, 1.34]
Total events 42 46
Heterogeneity: Tau² = 0.00; χ² = 7.05, df = 10 (P = 0.72); I² = 0%
Test for overall effect: Z = 0.49 (P = 0.62)
Dihydropyridine
Harper 1996 2 24 9 44 3.4% 0.41 [0.10, 1.74]
Lehtonen 2000 13 94 23 90 18.7% 0.54 [0.29, 1.00]
Morales 1989 1 15 1 15 1.0% 1.00 [0.07, 14.55]
Morales 1994 13 47 14 50 17.2% 0.99 [0.52, 1.88]
Rahn 1999* 4 130 7 123 4.9% 0.54 [0.16, 1.80]
Van den Dorpel 1994 2 25 6 25 3.1% 0.33 [0.07, 1.50]
Van Riemsdijk 2000 3 98 5 112 3.6% 0.69 [0.17, 2.80]
Wilkie 1994 1 17 5 17 1.7% 0.20 [0.03, 1.54]
Subtotal (95% CI) 450 476 53.6% 0.62 [0.43, 0.90]
Total events 39 70
Heterogeneity: Tau² = 0.00; χ² = 4.65, df = 7 (P = 0.70); I² = 0%
Test for overall effect: Z = 2.54 (P = 0.01)
Total (95% CI) 845 898 100.0% 0.74 [0.57, 0.97]
Total events 81 116
Heterogeneity: Tau² = 0.00; χ² = 13.48, df = 18 (P = 0.76); I² = 0%
Test for overall effect: Z = 2.20 (P = 0.03)
Test for subgroup differences: χ² = 1.88, df = 1 (P = 0.17); I² = 46.8%
0.02
0.1
1
10
50
Less with CCB
Less with placebo

Long Term – Graft Function

TABLE 2. Cox regression for cardiovascular death

Variable	RR	CI	*P*
Recipient age (yr)	1.053	1.049–1.058	<0.001
African American recipient	0.88	0.77–0.99	0.048
Cause of ESRD (GN)	(1)		
Hypertension	1.61	1.36–1.92	<0.001
Diabetes	3.78	3.26–4.38	<0.001
ESRD time (preemptive)	(1)		
<6 months	1.28	1.04–1.57	0.018
6–12 months	1.30	1.07–1.57	0.009
12–24 months	1.37	1.14–1.64	0.001
>24 months	1.51	1.26–1.81	<0.001
Living donation	0.86	0.74–0.98	0.028
Transplantation (yr)	0.95	0.92–0.98	<0.001
Serum creatinine at 1 year (≤1.2)	(1)		
1.3–1.4	1.03	0.89–1.20	0.686
1.5–1.6	1.19	1.02–1.39	0.025
1.7–1.8	1.37	1.16–1.62	<0.001
1.9–2.1	1.49	1.25–1.76	<0.001
2.2–2.5	1.67	1.38–3.03	<0.001
2.6–4.0	2.26	1.85–2.75	<0.001

RR, relative risk; CI, confidence interval.



Renal Function at 1 Year post transplant

Transplantation75(8):1291-1295, April 27, 2003

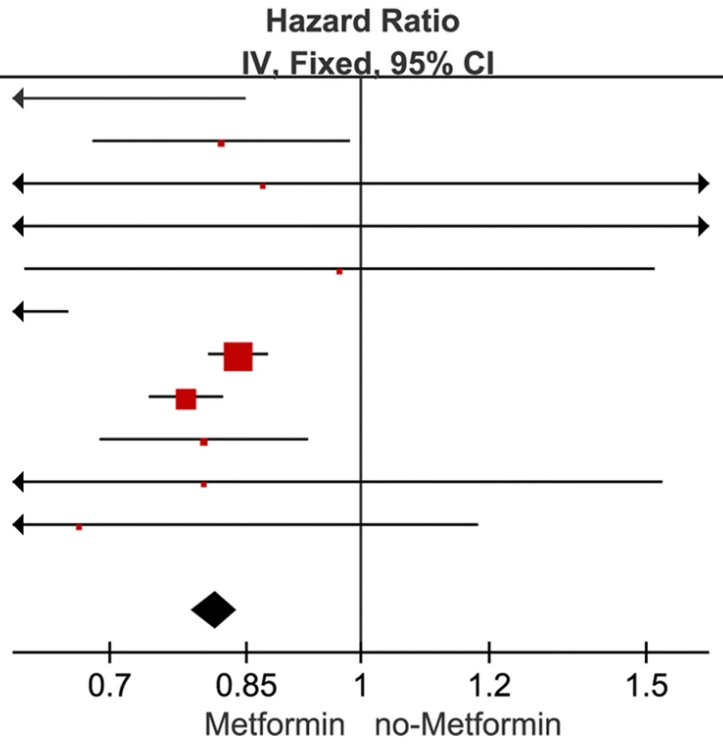
Diabetes Management

- Metformin
- All cause and CVS Mortality

N =1,066,408
40 Studies

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
Evans 2006	-0.5276	0.1857	0.7%	0.59 [0.41, 0.85]
Johnson 2005	-0.1985	0.0933	3.0%	0.82 [0.68, 0.98]
Liu 2016	-0.1393	0.3364	0.2%	0.87 [0.45, 1.68]
Preiss	1.1217	1.6415	0.0%	3.07 [0.12, 76.63]
Rachmani 2002	-0.0305	0.2284	0.5%	0.97 [0.62, 1.52]
Raee 2017	-2.1203	0.8698	0.0%	0.12 [0.02, 0.66]
Retwinski 2018	-0.1744	0.0217	54.8%	0.84 [0.80, 0.88]
Romero 2013	-0.2485	0.0269	35.7%	0.78 [0.74, 0.82]
Schramm 2011	-0.2231	0.0755	4.5%	0.80 [0.69, 0.93]
Shah 2010	-0.2231	0.3324	0.2%	0.80 [0.42, 1.53]
Sillars 2010	-0.4005	0.2893	0.3%	0.67 [0.38, 1.18]
Total (95% CI)			**100.0%**	**0.81 [0.79, 0.84]**

Heterogeneity: Chi² = 14.25, df = 10 (P = 0.16); I² = 30%
Test for overall effect: Z = 12.88 (P < 0.00001)



Cardiovascular Diabetology 2019 **; 18**, 96

CVS Disease and Transplantation – current knowledge

- CVD still the commonest cause of death post transplantation
- Early events probably partly preventable by careful assessment pre transplantation
- In all likelihood stress testing in low risk patients does not result in better CVS outcomes
- CARSK will help
- No benefit in revascularisation of asymptomatic patients
- In the long term careful attention to lifestyle factors, lipids and renal function likely beneficial