Risks to the Living Kidney Donor

Mumbai, India, February 9, 2014

Question 1

The first successful living kidney donation was in:

A. 1944
B. 1954
C. 1964
D. 1974
E. Other/don't know

First Successful Living Kidney Donation in 1954

Ronald Herrick (right) donated a kidney to his twin brother when they were 23 years old.

Ronald died 56 years later (age 79) from complications of heart disease.

What are the short term consequences of kidney donation?

Perioperative Deaths Following Live Kidney Donation

Characteristic	Within 3 Months		*P* Value
	No. of Deaths	Rate per 10 000 Donors (95% CI)	
Live donors (n = 80 347)	25	3.1 (2.0-4.6)	<.001
Matched cohort (n = 80 347)	3	0.4 (0.1-1.1)	

D Segev, et al. *JAMA* 2010; 303: 959

Short-Term Consequences of Kidney Donation

- Mortality 3/10,000 (0.03%)
- Major perioperative complications
- Pain and discomfort
- Time off work and other costs

What are the long term consequences of kidney donation?

Possible Long-Term Consequences of Kidney Donation

- Increased risk for ESRD
  - Reduced GFR "intercept"
  - Reduced GFR "slope"

Question 2

Among healthy individuals the average rate of decline in GFR with age is:

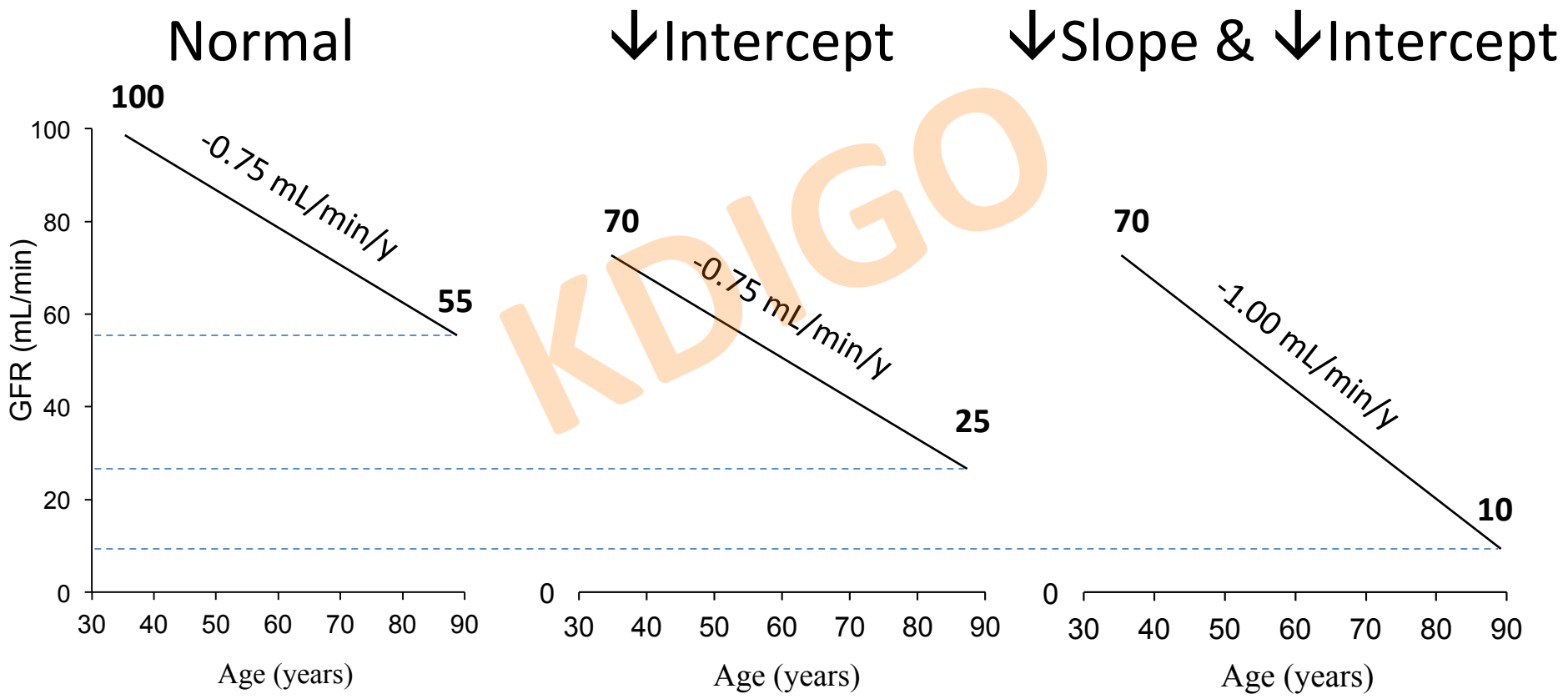
A. 0 mL/min/1.73m^2 per year
B. -0.25 mL/min/1.73m^2 per year
C. -0.75 mL/min/1.73m^2 per year
D. -1.00 mL/min/1.73m^2 per year
E. -1.25 mL/min/1.73m^2 per year
F. None of the above

Decline in GFR with Age in Longitudinal Studies

Population	N	Method	Decline (mL/min/y)
Men[1]	293	24 h C_{Cr}	-0.90
Men[2]	254	24 h C_{Cr}	-0.75
Men[3]	459	eGFR	-0.98
Women[4]	1697	eGFR	-0.90
PREVEND[5]	6894	eGFR	-0.55
Japan[6]	120,727	eGFR	-0.36
Men[7]	2249	eGFR	-1.21
Women[7]	2192	eGFR	-1.19

[1]Rowe JW et al., *J Gerontol* 1976; 31: 155
[2]Lindeman RD, *Kidney Int* 1984; 26: 861
[3]Kim R, et al., Normative Aging Study. *JAMA* 1996:275:1177
[4]Nurses Health Study. *J Am Soc Nephrol* 2002:13:427A
[5]Halbesma N et al., *J Am Soc Nephrol* 2006; 17: 2582
[6]Imai E et al., *Hypertens Res* 2008; 31: 433
[7]Kronborg J et al., *Nephrol Dial Transplant* 2008; 23: 2818

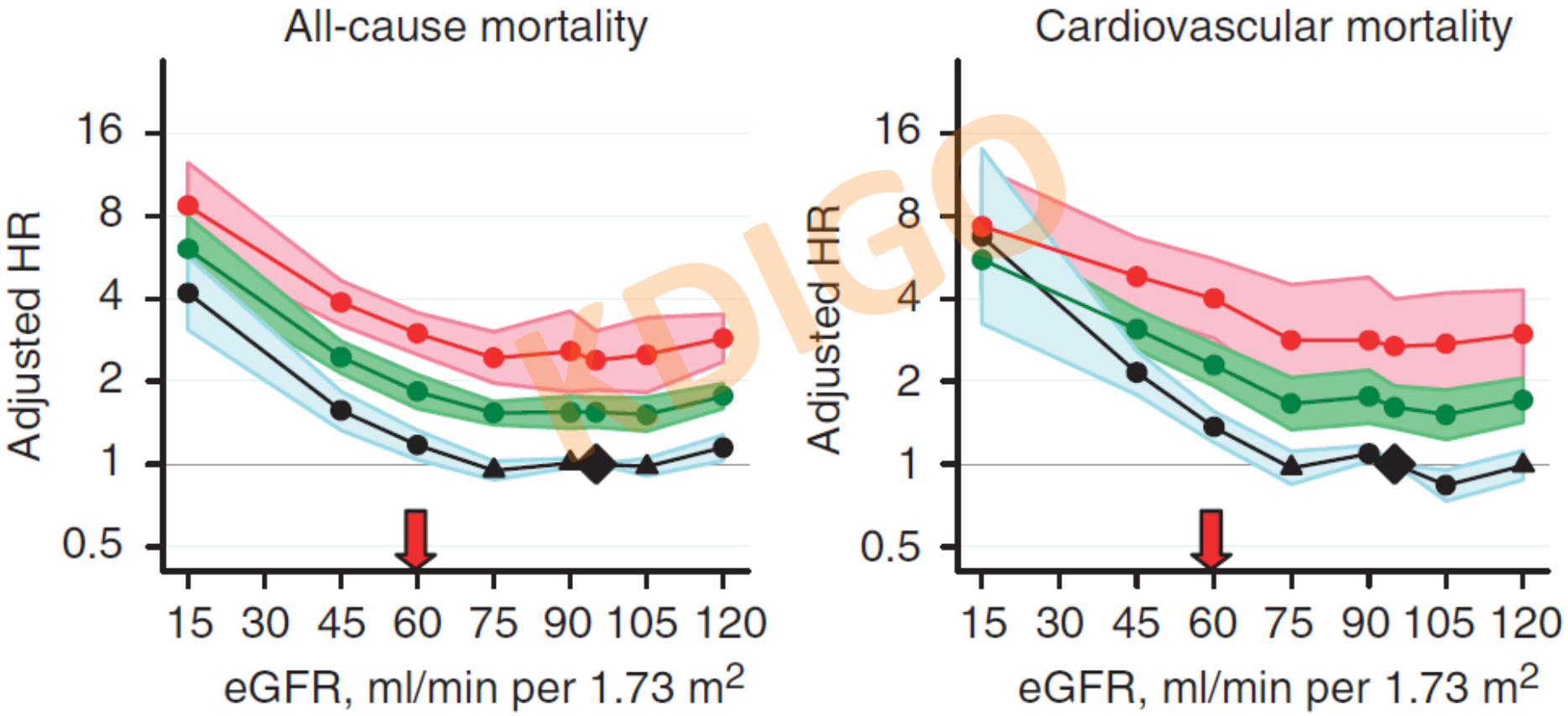
Predicting the Effect of Donation on GFR Decline from Age 35 to 85 years



Possible Long-Term Consequences of Kidney Donation

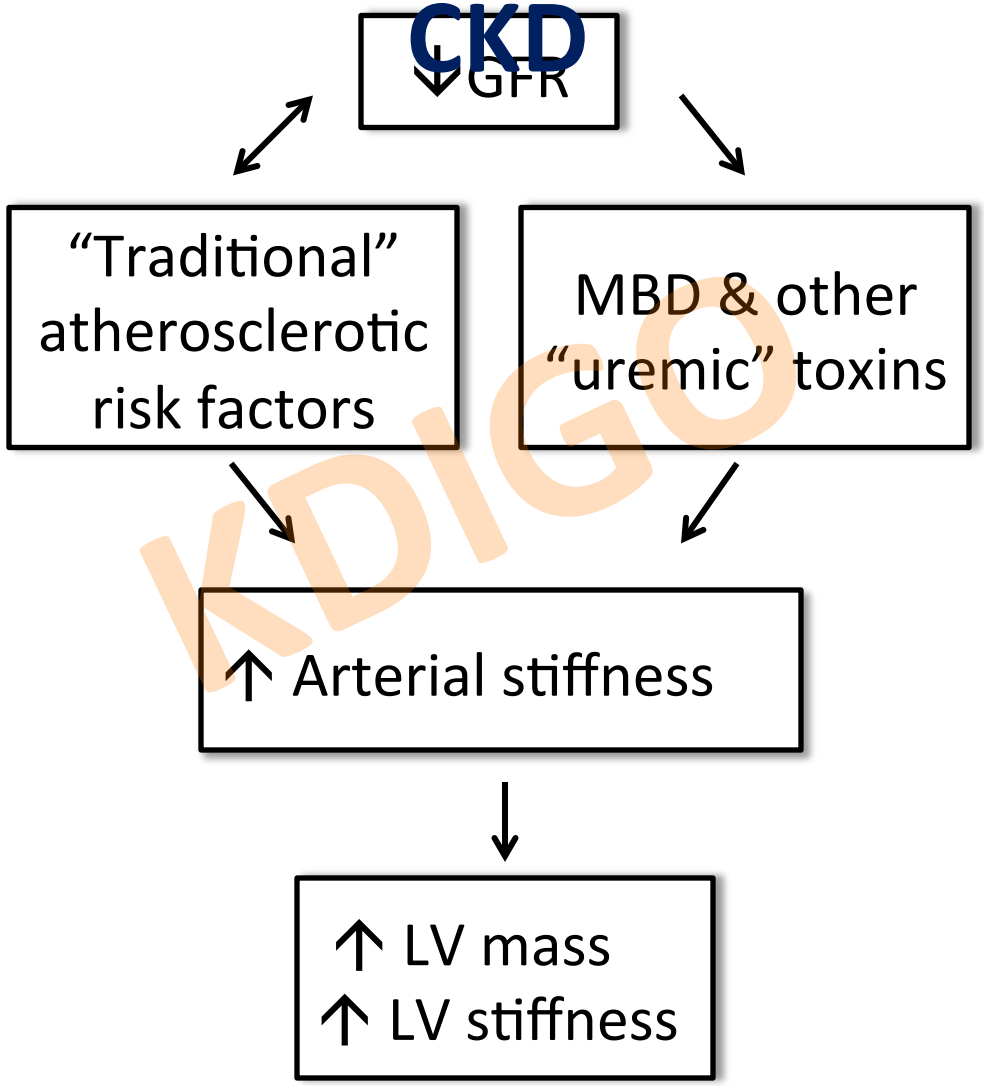
- Increased risk for ESRD
  - Reduced GFR "intercept"
  - Reduced GFR "slope"
- Increased risk for CVD
  - Arteriosclerotic disease
  - Diastolic dysfunction

CKD as a Risk Factor for CVD



AS Levey, et al. *Kidney Int* 2011; 80:17

Pathogenesis of CVD in CKD



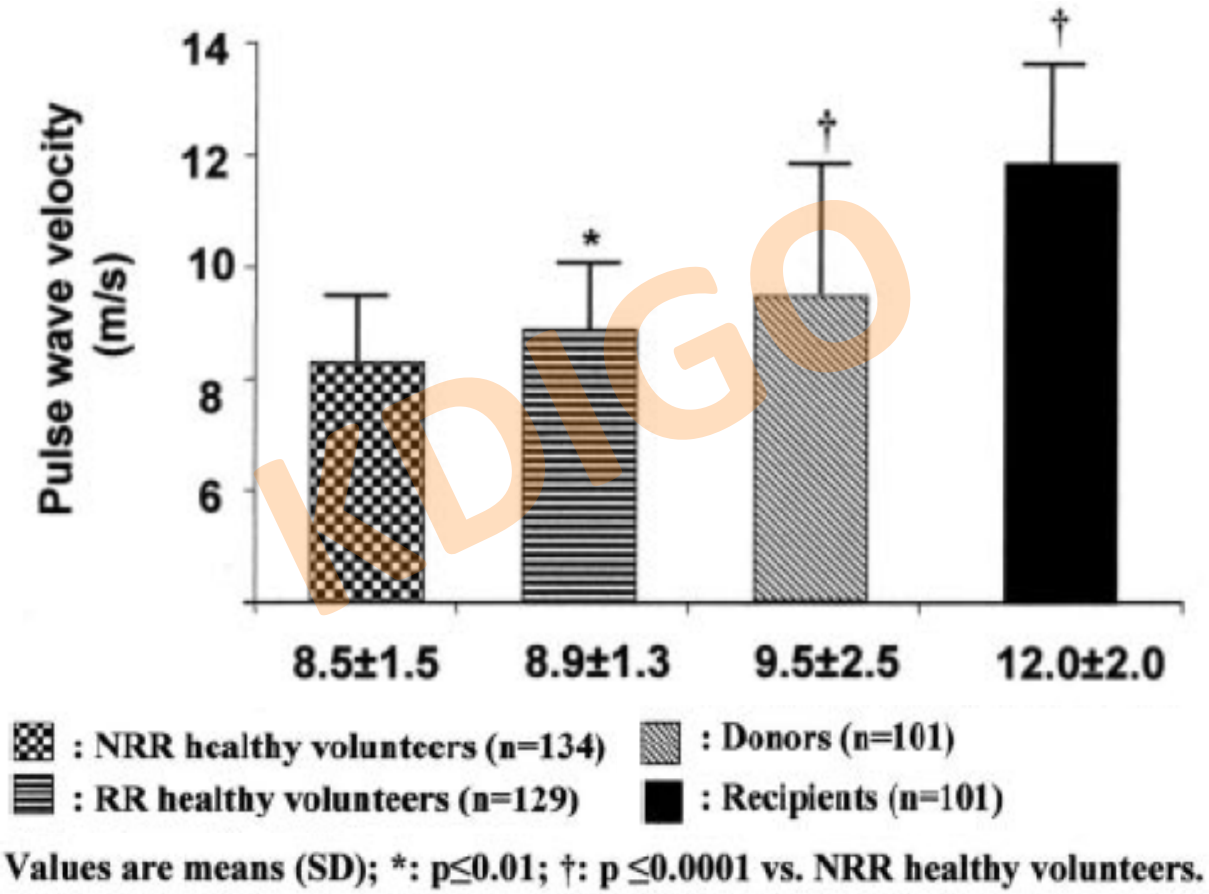
Independent Association between Aortic PWV and eGFR

Variable	Adjusted[1] PWV estimate (s.e.)	*P* value
Age (per 10 year interval)	0.95 (0.05)	<0.0001
eGFR (per 10 ml/min/1.73m^2)	–0.23 (0.04)	<0.0001
Glucose (per 10 mg/dl)	0.04 (0.01)	0.0017
Race black vs. white	0.39 (0.12)	0.0016
Race other vs. white	0.16 (0.23)	0.4749
MAP (per 1 mm Hg)	0.04 (0.00)	<0.0001
Waist circumference (per 1 cm)	–0.01 (0.00)	0.0007
Diabetes (yes vs. no)	1.51 (0.13)	<0.0001
Female (vs. male)	–0.31 (0.11)	0.0054

Adjusted for waist circumference

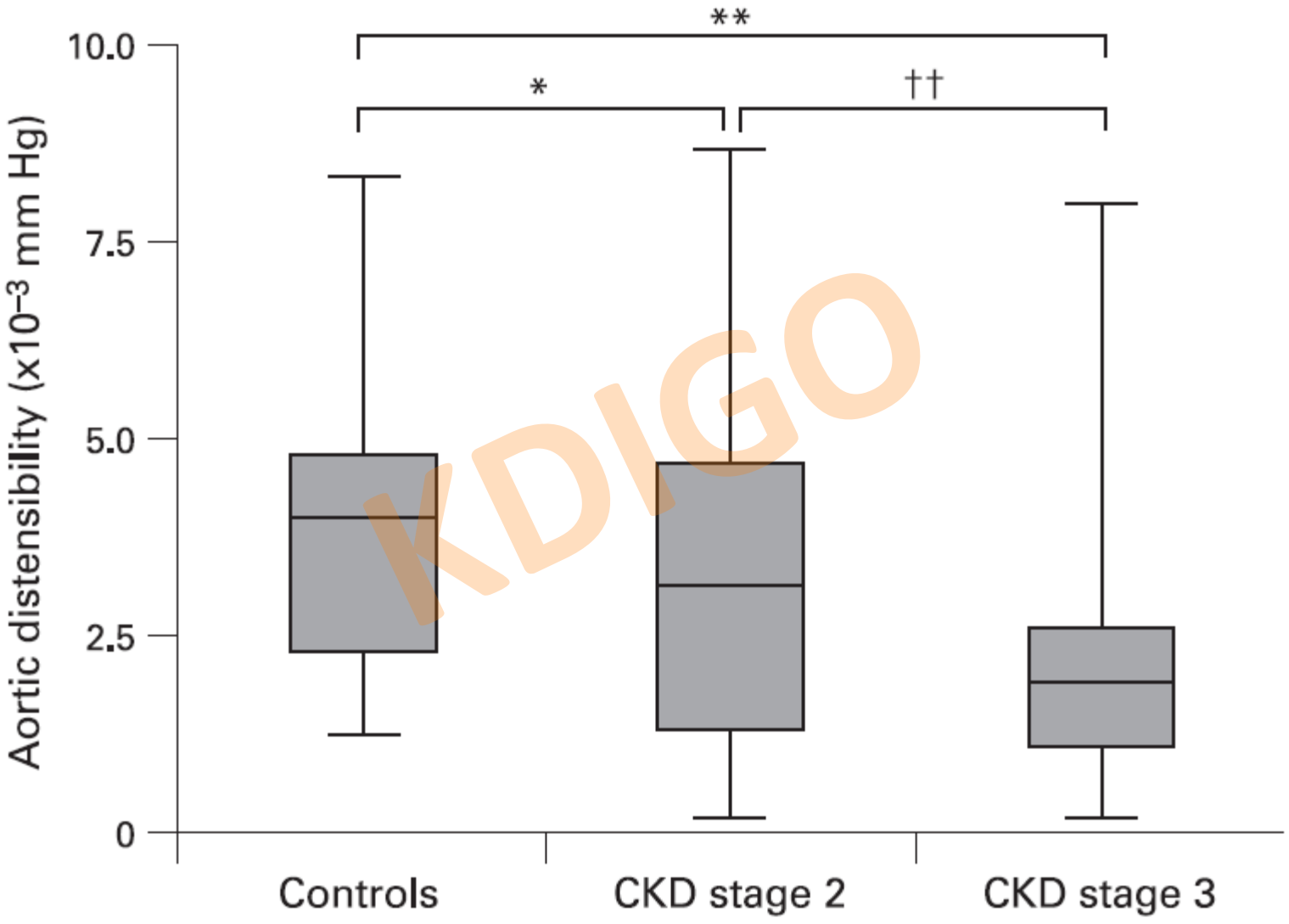
RR Townsend et al *Am J Hypertens* 2010; 23:282

Aortic PWV in Donors and Controls



SA Bahous, et al. *Hypertension* 2006;47;216

Aortic Distensibility Measured with CMR



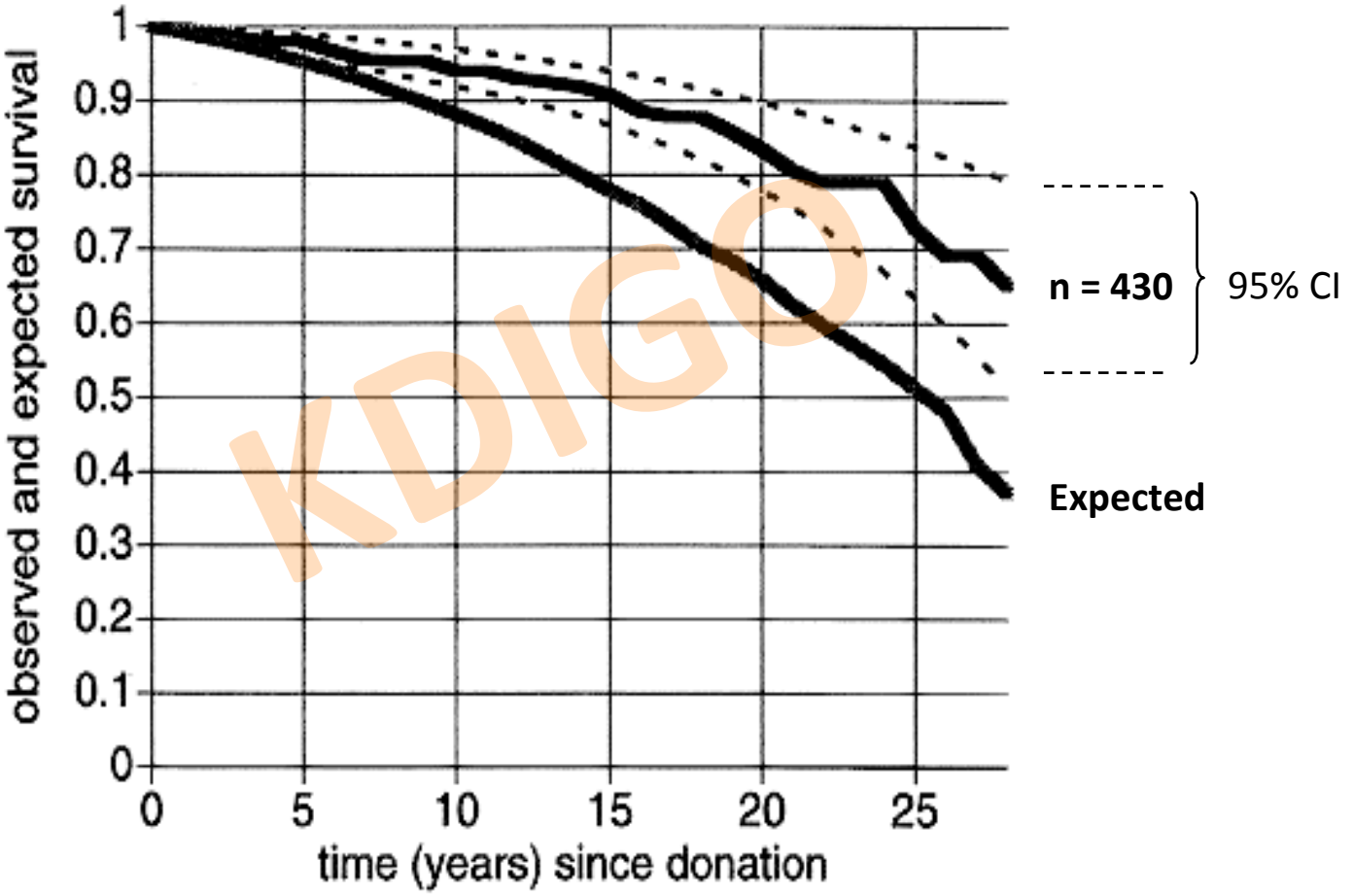
NC Edwards et al *Heart* 2008;94:1038

Question 3

The quality of evidence that kidney donation is safe in the long term is:

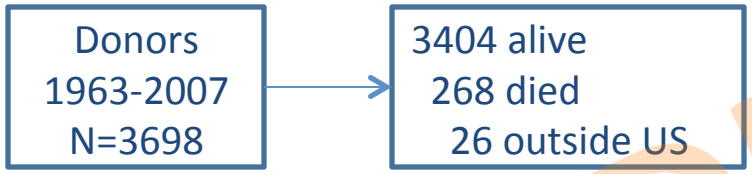
A. Very poor
B. Poor
C. Fair
D. Good
E. Very good

“Kidney Donors Live Longer”



I Fehrman-Ekholm, et al. *Transplantation* 1997; 64:976

Long-Term Consequences of Kidney Donation



HN Ibrahim, et al. *N Engl J Med* 2009;360:459

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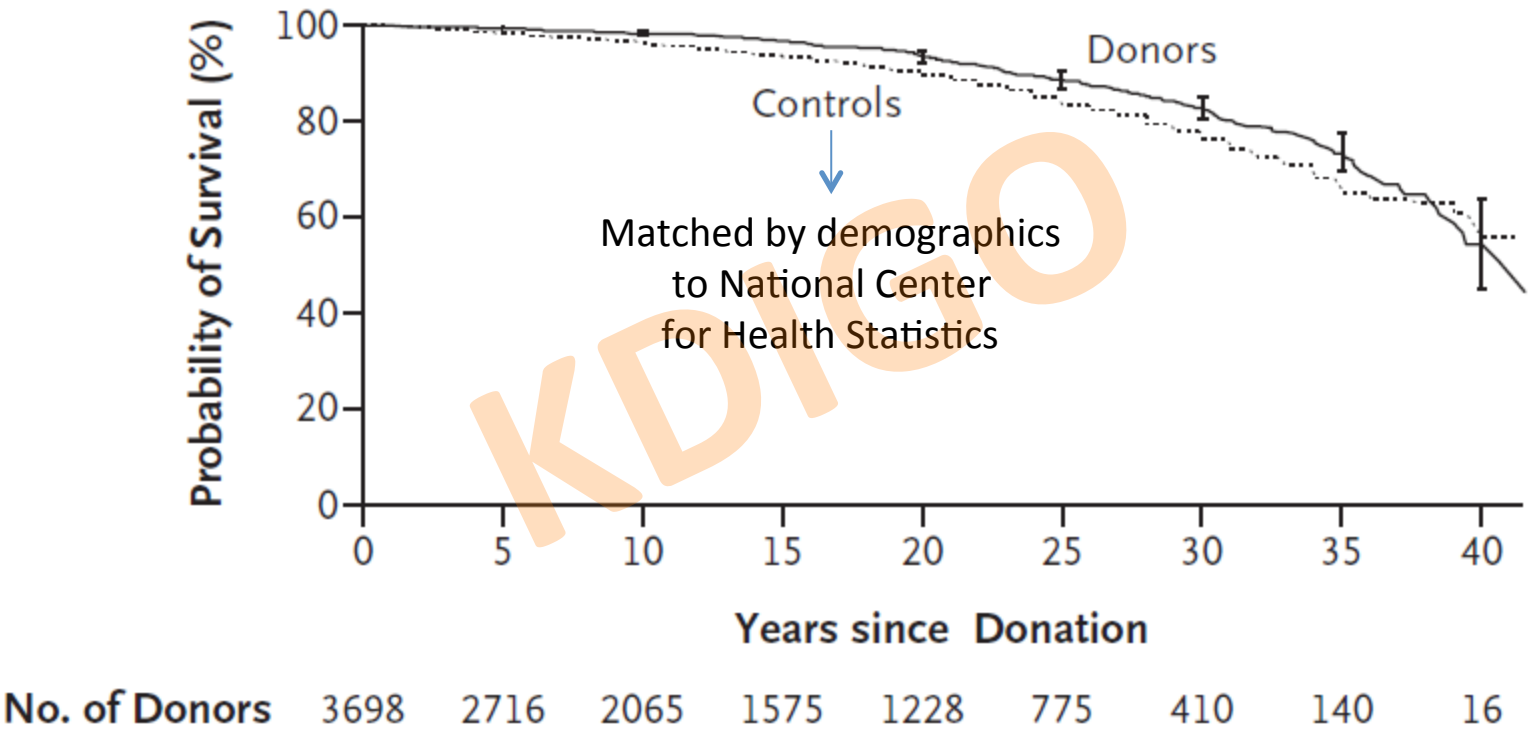

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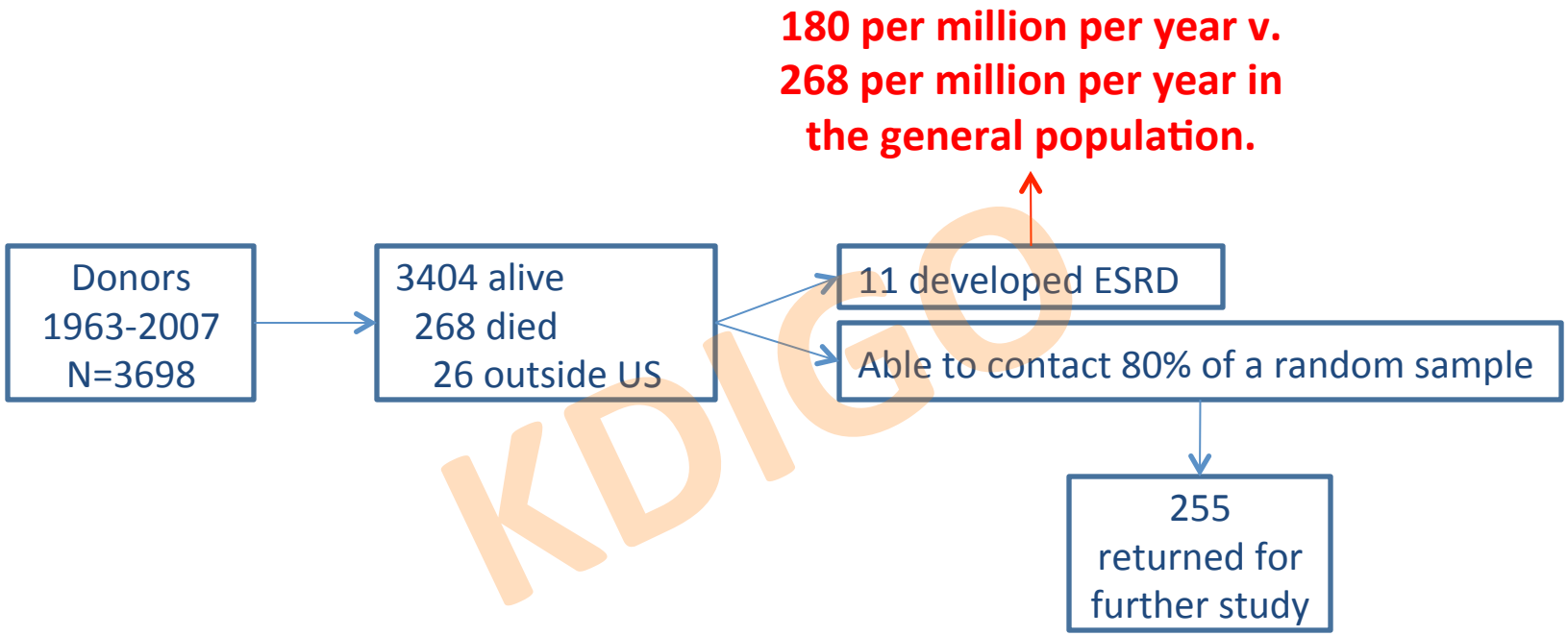
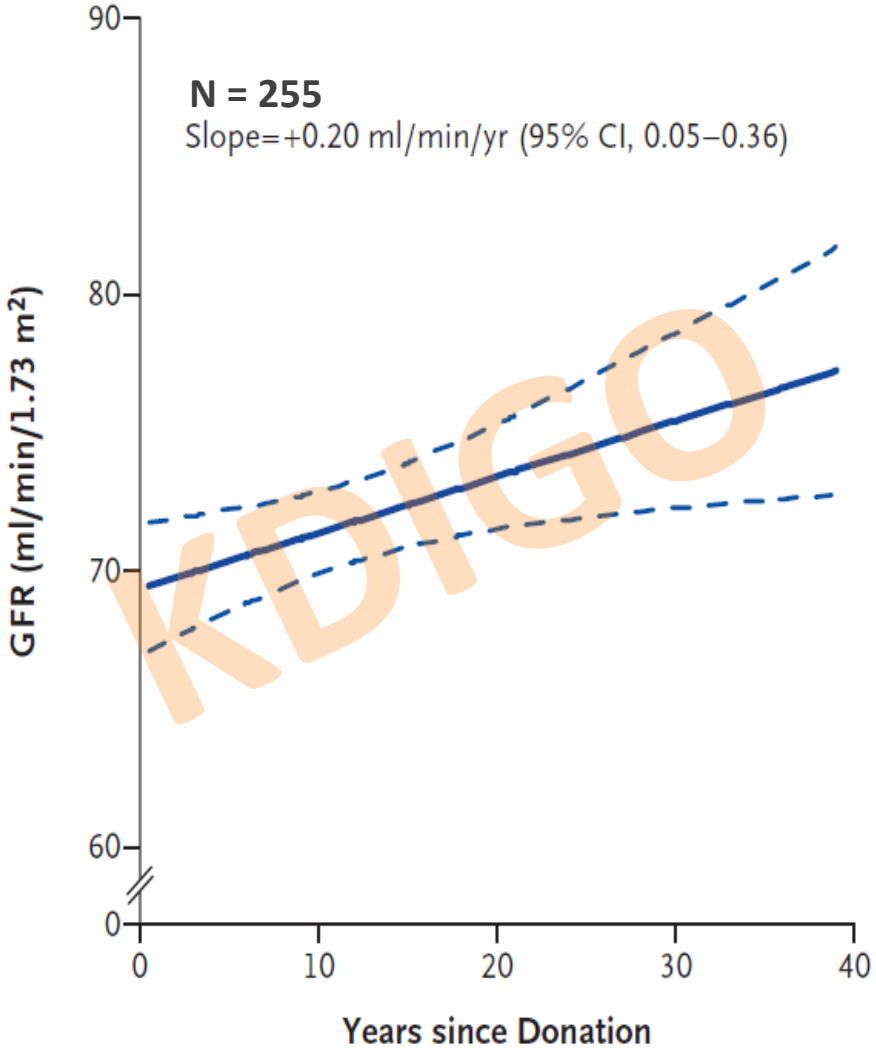


HN Ibrahim, et al. *N Engl J Med* 2009;360:459

GFR by Time after Donation



HN Ibrahim et al *N Engl J Med* 2009;360:459

Donors versus NHANES Controls

Variable	Kidney Donors (N=255)	Controls† (N=255)	P Value
Blood pressure			
Systolic (mm Hg)	121.8±14.6	125.9±19.1	0.003
Diastolic (mm Hg)	73.0±8.9	71.0±16.5	0.07
Systolic ≥140 mm Hg or diastolic ≥90 mm Hg (%)	14.4	18.7	0.19
GFR (ml/min/1.73 m²)§	63.7±11.3	81.6±18.5	<0.001
Urinary albumin-to-creatinine ratio			
Natural-log–transformed value	1.65±1.2	2.10±1.0	<0.001
>0.03 (%)	9.1	8.9	1.00
Hemoglobin (g/dl)	13.7±1.2	14.5±1.2	<0.001
Glucose (mg/dl)	90.9±11.9	102.8±33.1	<0.001
Cholesterol (mg/dl)	186.2±33.1	205.2±41.1	<0.001
Triglycerides (mg/dl)	124.5±95.6	174.3±182.5	<0.001
High-density lipoprotein cholesterol (mg/dl)	50.4±16.5	54.5±16.4	0.001
Clinical conditions (%)¶			
Diabetes	3.1	5.9	0.10
Cancer	8.2	14.5	0.01
Coronary heart disease	4.3	3.9	0.81
Cerebrovascular accident or transient ischemic attack	0.4	1.9	0.10
Use of antihypertensive drugs (%)¶	24.7	28.8	0.83
Current smoker (%)	14.5	21.5	0.03

NH Ibrahim, et al. *N Engl J Med 2009*; 360:459

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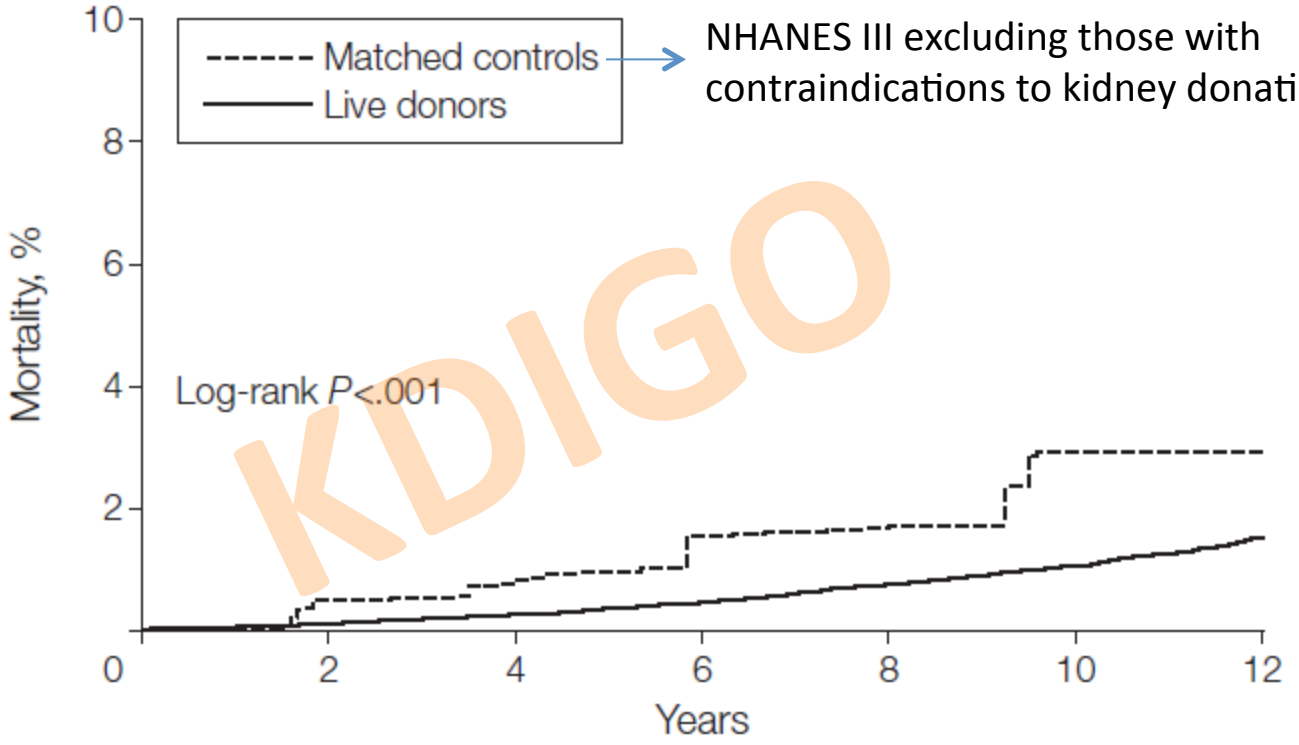
Should we conclude that kidney donation causes:

- Increasing GFR with age
- Lower BP
- Lower urine albumin
- Lower blood glucose
- Lower cholesterol
- Less cancer
- Less cigarette smoking
- Longer life

or that donors were healthier than controls from the start?

NH Ibrahim, et al. *N Engl J Med 2009*; 360:459

Long-Term Survival Following Live Kidney Donation



No. at risk							
Matched controls	80 347	67 966	54 998	41 679	19 259	5896	127
Live donors	80 347	68 230	55 282	42 154	29 657	18 960	10 436

D Segev, et al. *JAMA* 2010; 303: 959

CVD and Hypertension in Living Kidney Donors: Analysis of Administrative Data in Ontario, Canada

	Donors (n =1,278)	Controls (n=6,369)
Death or major cardiovascular events		
No. of events (%)	16 (1.3)	107 (1.7)
Mean (SD) years of follow-up (%)	6.2 (3.2)	6.2 (3.2)
No. events per 1000 person years	2.0	2.7
Model based risk ratios (95% CI)	0.7 (0.4–1.2)	1.0 (reference)

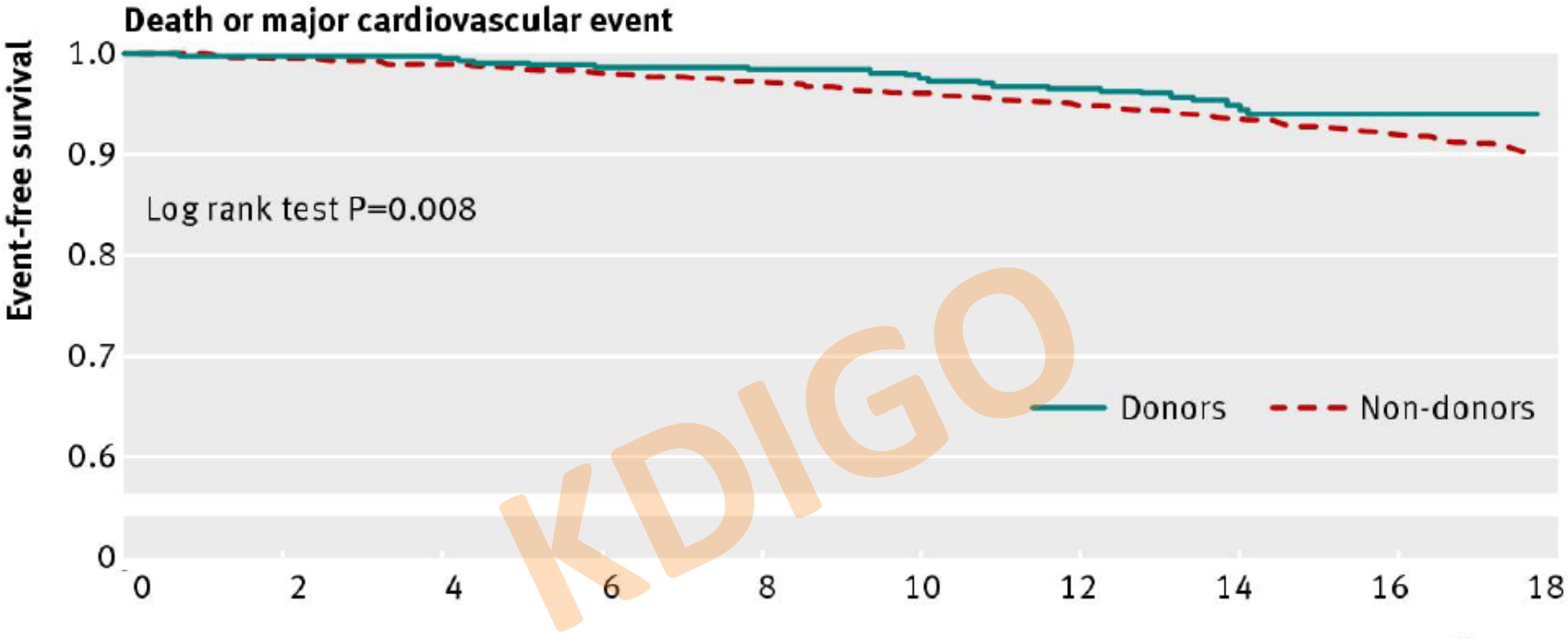
AX Garg, et al. *Transplantation* 2008; 86: 399

CVD and Hypertension in Living Kidney Donors: Analysis of Administrative Data in Ontario, Canada

	Donors (n =1,278)	Controls (n=6,369)
Diagnosis of hypertension		
Number of events (%)	205 (16.3)	746 (11.9)
Number of events per 1000 person years	29.1	20.6
Model based risk ratios (95% CI)	1.4 (1.2–1.7)	1.0 (reference)

AX Garg, et al. *Transplantation* 2008; 86: 399

CVD in Kidney Donors: Matched Cohort Study



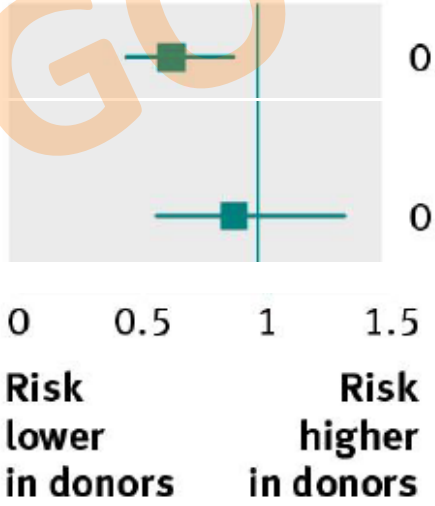
No of people at risk

Non-donors									
20 280	18 149	14 146	10 825	8181	5744	3636	1948	664	0
Donors									
2028	1832	1455	1124	857	609	386	209	72	0

AX Garg, et al. *BMJ* 2012; 344: e1203

CVD in Kidney Donors: Matched Cohort Study

Study	No of events/ No at risk: Donor	No of events/ No at risk: Control	Event rate/ 10 000 person years: Donor	Event rate/ 10 000 person years: Control	Hazard ratio (95% CI)	Hazard ratio (95% CI)	Interaction test P value
Death or major cardiovascular event							
Overall	42/2028	610/20 280	2.8	4.1		0.7 (0.5 to 0.9)	
Major cardiovascular event (death censored)							
Overall	26/2028	287/20 280	1.2	1.4		0.9 (0.6 to 1.4)	



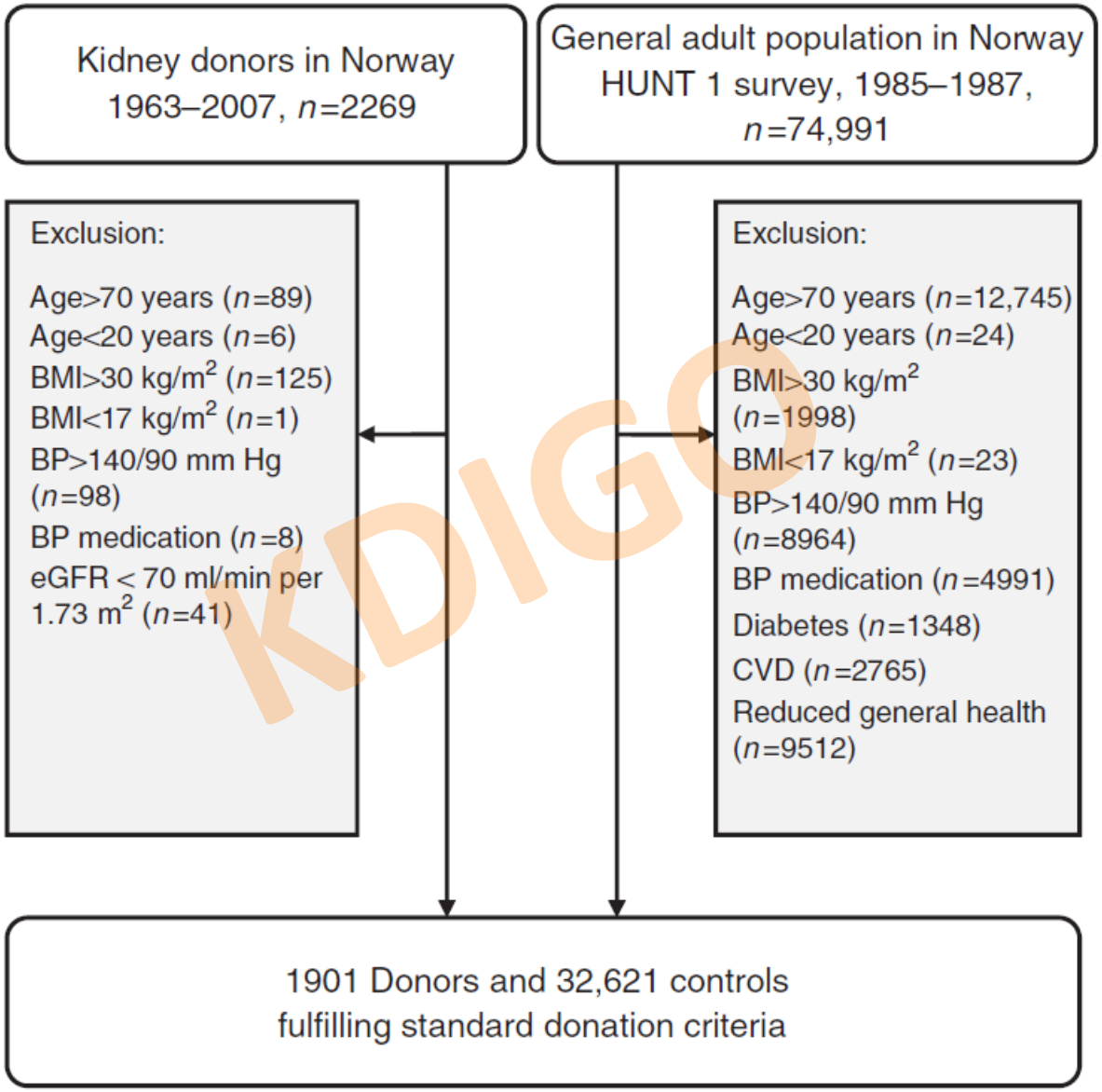
AX Garg, et al. *BMJ* 2012; 344: e1203

Long-Term Risks for Kidney Donors

- 1901 individuals donating a kidney 1963 – 2007
  - All were Caucasian, 80% were 1st degree relatives
  - Median Follow-up 15.1 years
  - 224 deaths (30.4% cardiovascular)
- 32,621 potential kidney donor controls 2007
  - From the Health Study of Nord-Trøndelag (HUNT)
  - Median Follow-up 24.9 years
  - 2425 deaths (28.4% cardiovascular)

G Mjøen et al. *Kidney Int* online publication November 27, 2013

Long-Term Risks for Kidney Donors



G Mjøen et al. *Kidney Int* online publication November 27, 2013

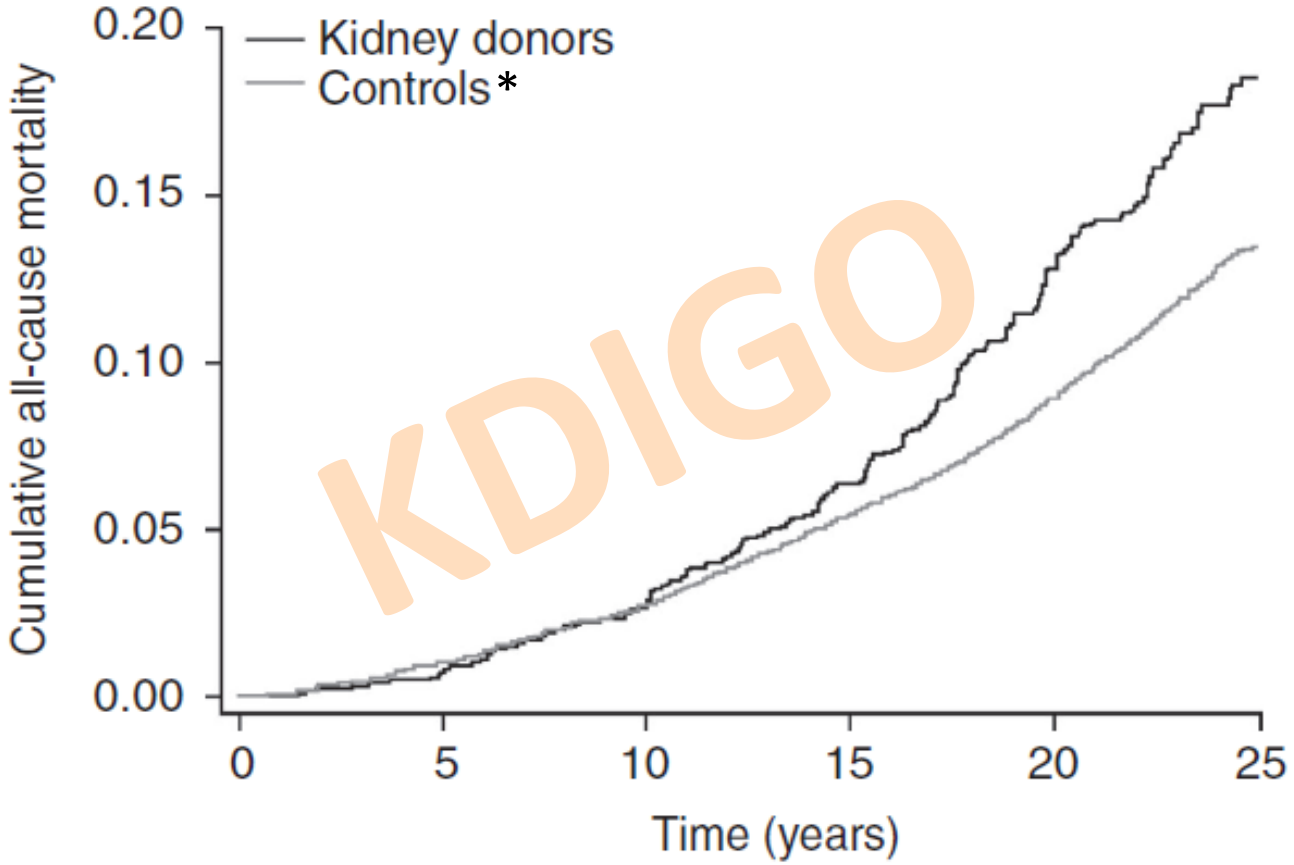
Baseline Characteristics

	Donors	Controls
Age, years	46.0±11.5 (N=1901)	37.6±11.7 (N=32,621)
Male gender, %	41.0 (N=1901)	46.9 (N=32,621)
Current smoking, %	41.5 (N=1375)	39.5 (N=25,993)
Systolic BP, mmHg	123.3±10.0 (N=1768)	121.4±10.4 (N=31,398)
Diastolic BP, mmHg	77.4±7.2 (N=1768)	77.2± 7.9 (N=31,394)
BMI, kg/m^2	24.2± 2.8 (N=1558)	23.5± 2.6 (N=31,421)

Data were missing for smoking (27.4%), systolic BP (6.3%), and BMI (17.3%)

G Mjøen et al. *Kidney Int* online publication November 27, 2013

All-Cause Mortality for Kidney Donors



*Matched to donors for age, sex, systolic BP, BMI, and smoking status.

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All-Cause Mortality: Unadjusted

Variable	HR (95% CI, P-Value)
Kidney donation	2.49 (2.13–2.91, $P<0.001$)
Inclusion year	0.95 (0.93–0.97, $P<0.001$)
Age, years	1.10 (1.10–1.11, $P<0.001$)
Male	1.62 (1.49–1.73, $P<0.001$)
Systolic BP	1.04 (1.03–1.04, $P<0.001$)
Smoking	1.64 (1.50–1.79, $P<0.001$)
BMI	1.12 (1.11–1.14, $P<0.001$)

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All-Cause Mortality: Adjusted*

Variable	HR (95% CI, P-Value)
Kidney donation	1.48 (1.17–1.88, $P = 0.001$)
Inclusion year	0.95 (0.93–0.98, $P < 0.001$)
Age, years	1.10 (1.10–1.11, $P < 0.001$)
Male	1.44 (1.32–1.58, $P < 0.001$)
Systolic BP	1.00 (1.00–1.01, $P = 0.45$)
Smoking	1.97 (1.80–2.15, $P < 0.001$)
BMI	1.02 (1.00–1.04, $P = 0.06$)

*Adjusted for age, gender, year of inclusion, systolic BP, smoking, and BMI.

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Cardiovascular Mortality: Unadjusted

Variable	HR (95% CI, P-Value)
Kidney donation	3.18 (2.39–4.23, $P<0.001$)
Inclusion year	0.90 (0.87–0.94, $P<0.001$)
Age, years	1.13 (1.13–1.14, $P<0.001$)
Male	2.23 (1.92–2.60, $P<0.001$)
Systolic BP	1.05 (1.05–1.06, $P<0.001$)
Smoking	1.82 (1.55–2.14, $P<0.001$)
BMI	1.17 (1.14–1.21, $P<0.001$)

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Cardiovascular Mortality: Adjusted*

Variable	HR (95% CI, P-Value)
Kidney donation	1.52 (0.95–2.43, $P = 0.08$)
Inclusion year	0.92 (0.87–0.98, $P = 0.005$)
Age, years	1.13 (1.12–1.14, $P < 0.001$)
Male	2.04 (1.71–2.44, $P < 0.001$)
Systolic BP	1.01 (1.00–1.02, $P = 0.15$)
Smoking	2.30 (1.94–2.72, $P < 0.001$)
BMI	1.05 (1.01–1.08, $P = 0.006$)

*Adjusted for age, gender, year of inclusion, systolic BP, smoking, and BMI.

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Risk of ESRD: Unadjusted

Variable	HR (95% CI, P-Value)
Kidney donation	18.99 (8.63–41.76, $P<0.001$)
Inclusion year	0.76 (0.70–0.83, $P<0.001$)
Age, years	1.04 (1.01–1.07, $P=0.003$)
Male	0.94 (0.46–1.91, $P=0.86$)
Systolic BP	1.03 (1.00–1.07, $P=0.14$)
Smoking	1.09 (0.48–2.46, $P=0.83$)
BMI	1.19 (1.02–1.38, $P=0.03$)

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Risk of ESRD: Adjusted*

Variable	HR (95% CI, P-Value)
Kidney donation	11.42 (4.43–29.40, $P < 0.001$)
Inclusion year	0.91 (0.83–1.00, $P = 0.04$)
Age, years	1.03 (1.00–1.06, $P = 0.04$)
Male	1.04 (0.51–2.11, $P = 0.10$)
Systolic BP	—
Smoking	—
BMI	—

*Adjusted for age, gender, year of inclusion, systolic BP, smoking, and BMI.

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Long-Term Risk of ESRD Attributable to Live Kidney Donation

- 96,217 live kidney donors (between 1994-2011)
- Controls from NHANES
- Matched by age, gender, race, education, BMI, systolic blood pressure, and smoking history .

A Muzaale et al. *Am J Transplant* 2013; 13(S5): 204

15-year Cumulative Incidence of ESRD (%) Attributable to Live Kidney Donation

	Live donors	Controls
All races	0.31	0.04
Caucasian	0.23	0.00
African-American	0.75	0.24
Hispanic	0.33	0.07

A Muzaale et al. *Am J Transplant* 2013; 13(S5): 204

Question 4

Many studies of kidney donors have been flawed by:

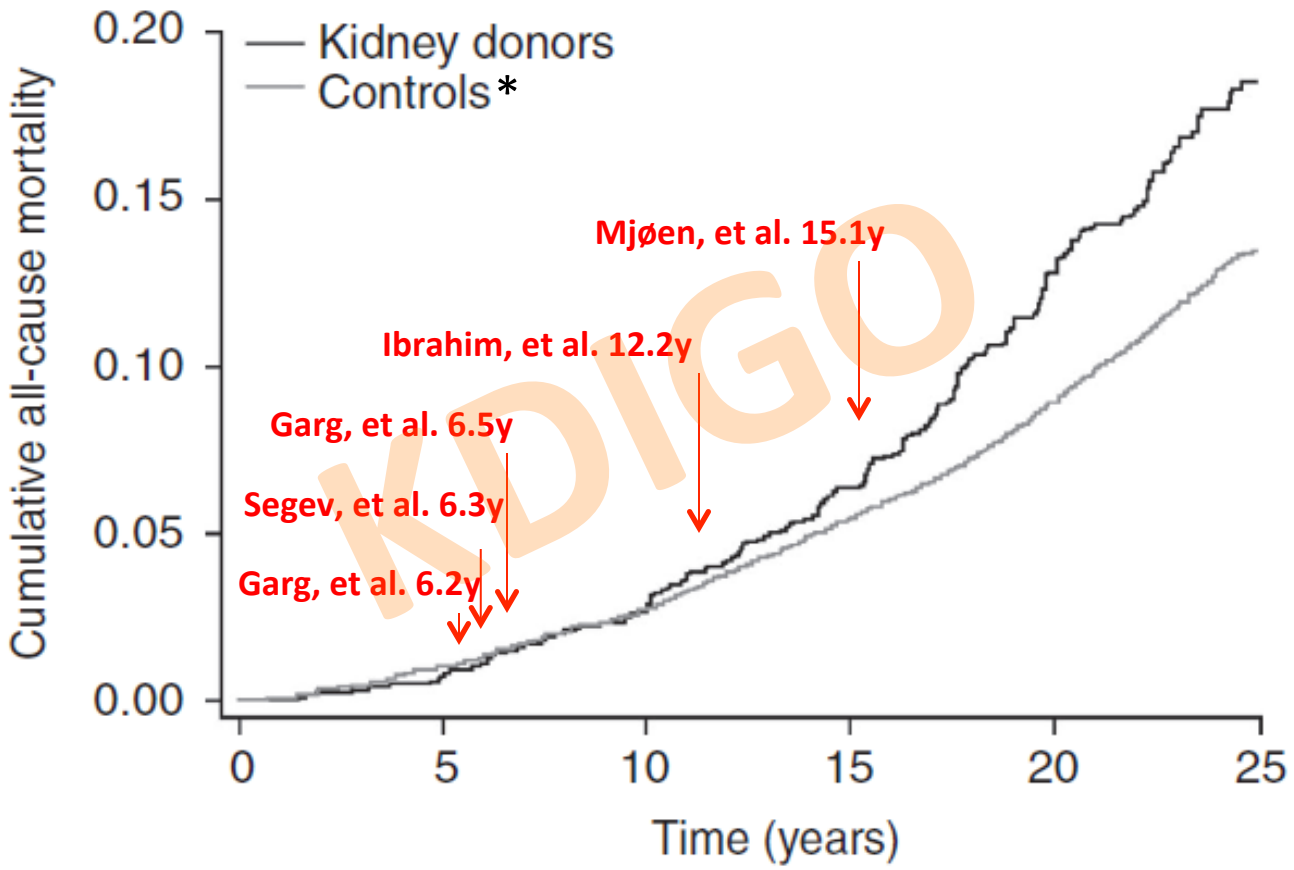
A. A lack of suitable controls
B. Cross-sectional design
C. Short follow-up
D. All of the above
E. None of the above

What is the (quality of) evidence that kidney donation is safe in the long term?

Many studies of kidney donors have been flawed by:

- A lack of suitable controls
- Cross-sectional design
- Short follow-up
- Few measurements of GFR
- Selection bias
- Changes in donor selection

All-Cause Mortality for Kidney Donors



*Matched to donors for age, sex, systolic BP, BMI, and smoking status.

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AJKD

Original Investigation

A Prospective Controlled Study of Kidney Donors: Baseline and 6-Month Follow-up

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BL Kasiske, et al. *Am J Kidney Dis. 2013;* 62(3):577

Prospective Controlled Study of Kidney Donors

	Baseline Visit		6-mo Visit	
Variable	Controls	Donors	Controls	Donors
mGFR (mL/min)	106.5 ± 19.3 (n = 186)	106.7 ± 18.6 (n = 181)	104.9 ± 20.2 (n = 194)	74.3 ± 12.9 * (n = 193)
mGFR (mL/min/1.73 m^2)	96.9 ± 15.3 (n = 186)	96.9 ± 15.3 (n = 181)	94.6 ± 15.1 (n = 194)	67.6 ± 10.1 * (n = 193)
UPCR (g/g)	61 [50-114] (n = 196)	66 [50-128] (n = 175)	62 [50-128] (n = 195)	70 [50-116] (n = 201)
UACR (mg/g)	5.0 [4.0-6.9] (n = 186)	5.0 [3.8-5.8] (n = 167)	5.0 [4.0-6.6] (n = 193)	5.0 [3.3-5.4] (n = 198)
Hemoglobin (g/dL)	13.6 ± 1.2 (n = 194)	13.6 ± 1.2 (n = 198)	13.6 ± 1.4 (n = 193)	13.1 ± 1.2 * (n = 194)

BL Kasiske, et al. *Am J Kidney Dis. 2013;* 62(3):577

Prospective Controlled Study of Kidney Donors

	Baseline Visit		6-mo Visit	
Variable	Controls	Donors	Controls	Donors
Homocysteine (mg/L)	1.20 ± 0.35 (n = 193)	1.22 ± 0.39 (n = 176)	1.20 ± 0.34 (n = 196)	1.49 ± 0.43* (n = 198)
Uric acid (mg/dL)	4.8 ± 1.1 (n = 200)	4.6 ± 1.1 (n = 198)	4.9 ± 1.2 (n = 198)	5.3 ± 1.1* (n = 200)

BL Kasiske, et al. *Am J Kidney Dis. 2013;* 62(3):577

Prospective Controlled Study of Kidney Donors

Variable	Baseline Visit		6-mo Visit	
	Controls	Donors	Controls	Donors
Serum calcium (mg/dL)	9.16 ± 0.38 (n = 200)	9.26 ± 0.38 (n = 199)	9.19 ± 0.38 (n = 198)	9.24 ± 0.42 (n = 200)
Serum phosphorus (mg/dL)	3.49 ± 0.52 (n = 198)	3.52 ± 0.50 (n = 199)	3.49 ± 0.48 (n = 198)	3.30 ± 0.48* (n = 200)
PTH (pg/mL)	42.8 ± 16.3 (n = 199)	42.3 ± 17.8 (n = 180)	42.8 ± 15.6 (n = 198)	52.7 ± 20.9* (n = 200)

BL Kasiske, et al. *Am J Kidney Dis. 2013;* 62(3):577

Prospective Controlled Study of Kidney Donors

	Baseline Visit		6-mo Visit	
Variable	Controls	Donors	Controls	Donors
Cholesterol (mg/dL)	186 ± 37 (n = 200)	185 ± 35 (n = 198)	186 ± 36 (n = 197)	186 ± 35 (n = 199)
LDL cholesterol (mg/dL)	112 ± 33 (n = 198)	110 ± 31 (n = 196)	111 ± 30 (n = 193)	110 ± 31 (n = 193)
HDL cholesterol (mg/dL)	55.2 ± 16.5 (n = 200)	56.2 ± 14.5 (n = 198)	54.9 ± 16.4 (n = 198)	54.1 ± 13.9 (n = 197)
Triglycerides (mg/dL)	77 [55-113] (n = 200)	76 [57-111] (n = 198)	80 [59-119] (n = 197)	84 [64-124] * (n = 199)
Lipoprotein(a) (mg/dL)	12.0 [5-41] (n = 199)	16.0 [5-49] (n = 181)	16.0 [5-43] (n = 198)	20 [5-55] (n = 200)
Hemoglobin A_{1c} (%)	5.3 ± 0.34 (n = 196)	5.2 ± 0.32 (n = 177)	5.3 ± 0.36 (n = 195)	5.3 ± 0.31 (n = 197)

BL Kasiske, et al. *Am J Kidney Dis. 2013;* 62(3):577

Question 5

Among kidney donors the risk for ESRD is:

A. Reduced
B. Unchanged
C. Slightly increased
D. Moderately increased
E. Don't know

Question 6

Among kidney donors the risk of death is:

A. Reduced
B. Unchanged
C. Slightly increased
D. Moderately increased
E. Don't know

Thank you!