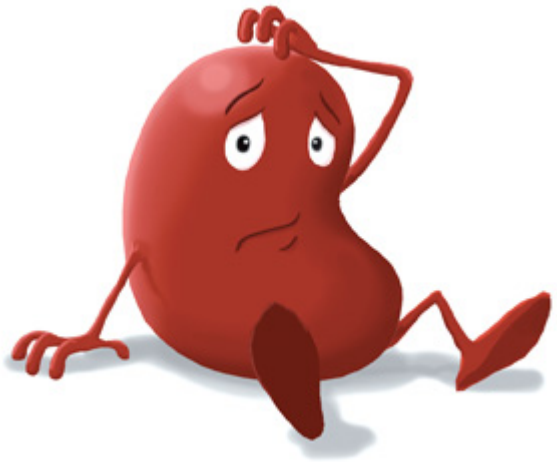
BC KIDNEY DAYS

Hosted by BC Transplant and the BC Renal Agency

2014

Living Kidney Donation
Assessing Risk

Living Kidney Donation



Understanding the Risks

BC KIDNEY DAYS 2014
Hosted by BC Transplant and the BC Renal Agency

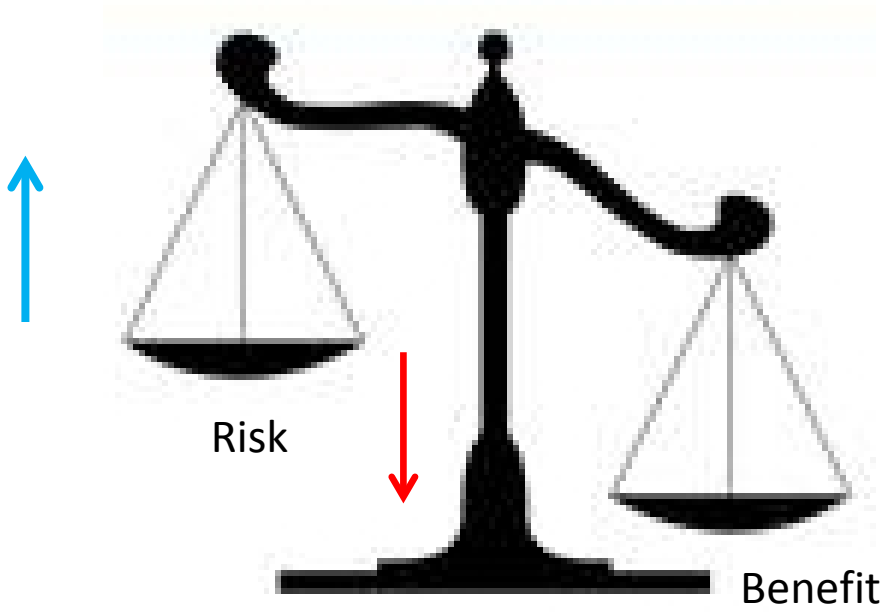
Disclosures

- I am a transplant nephrologist
- I derive income from living donor transplants
- I perform donor workups and advise potential living donors
- I am the Chair of the CBS National Living Donor Advisory Committee

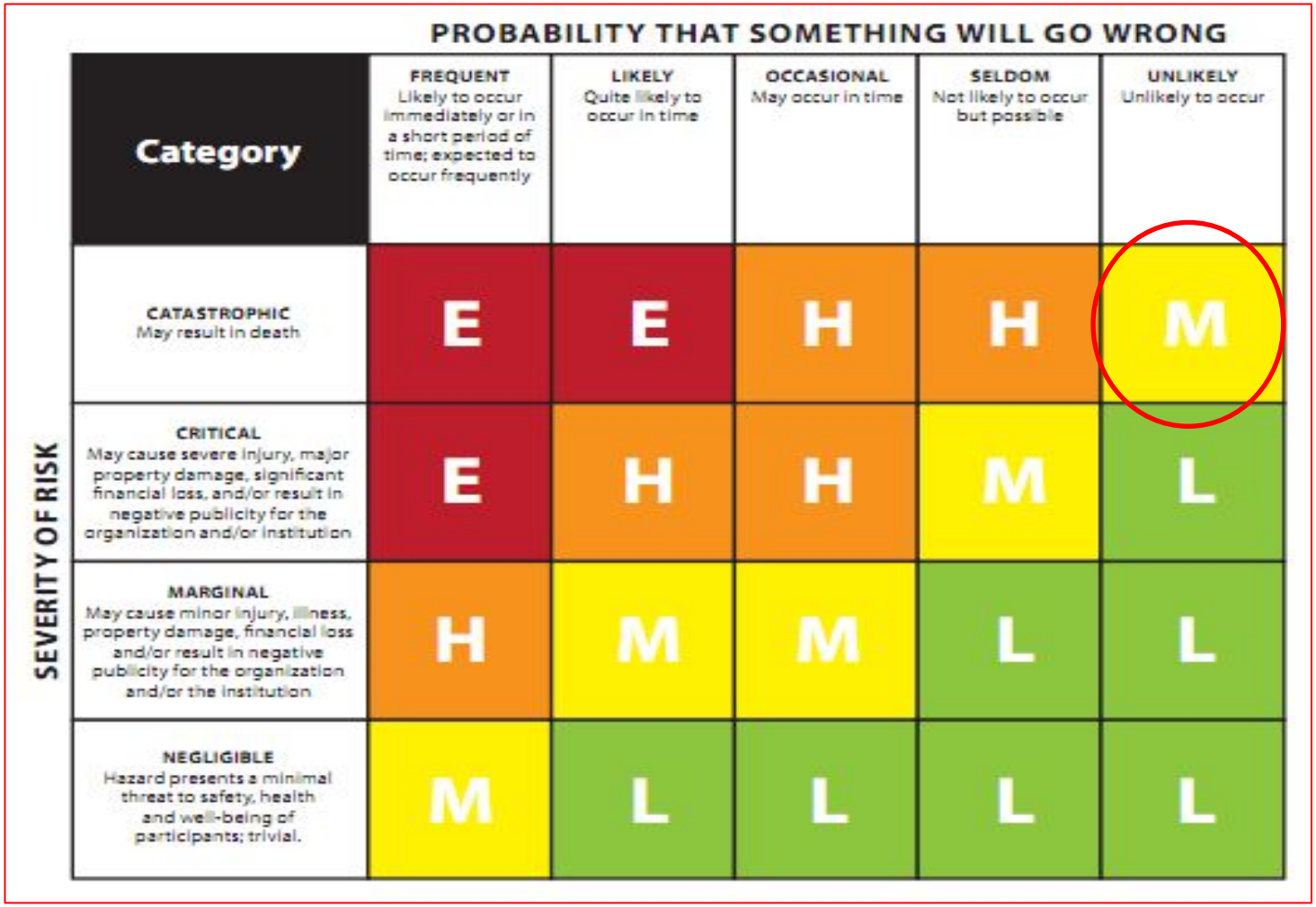
Objectives

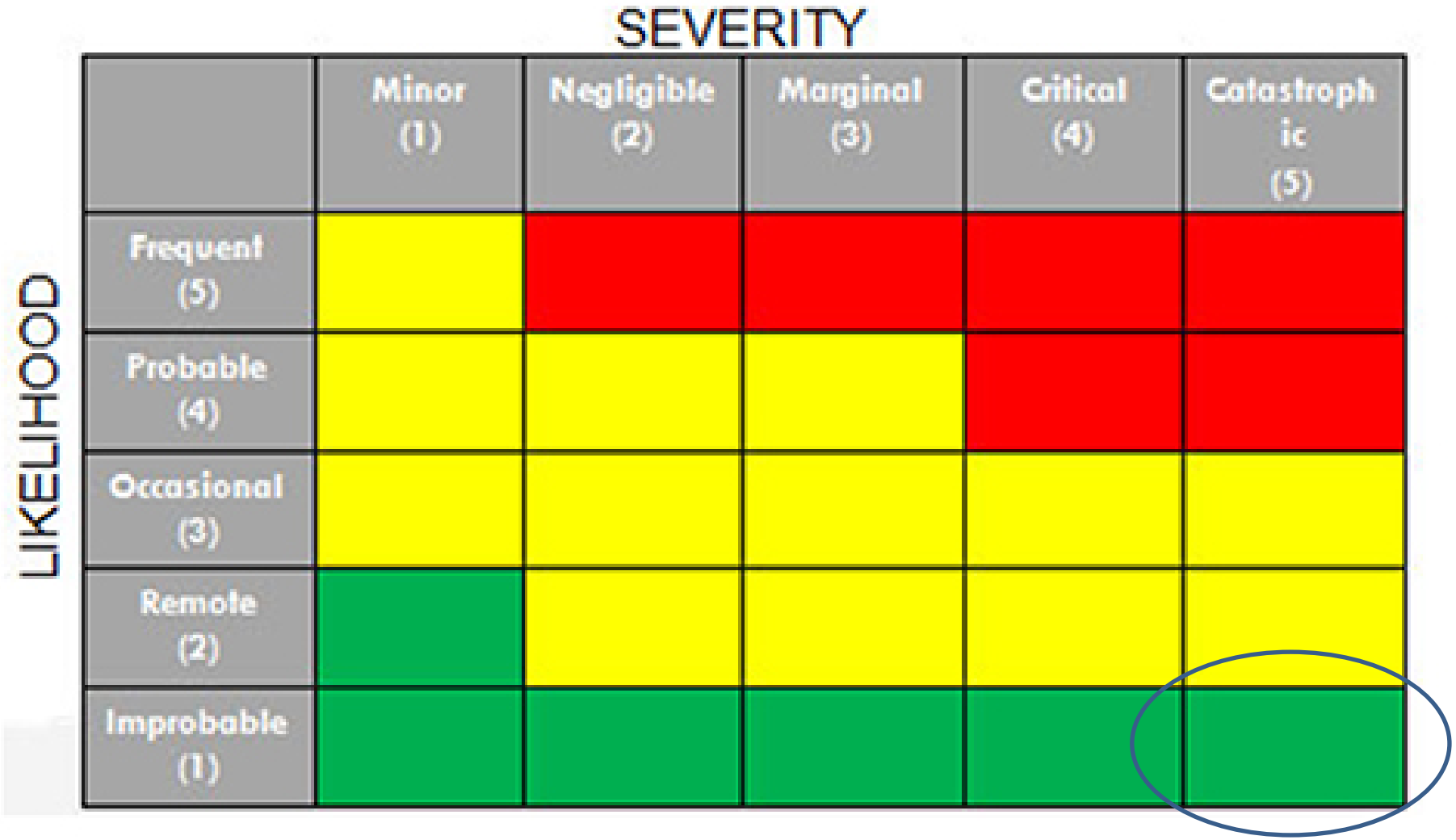
- Provide a framework for donors to understand the risk to them
- Gain the ability to describe to a potential living donor their risk of premature death and kidney disease after donation.
- Understand the strengths and limitations of the available literature on the long-term outcomes for kidney donors.

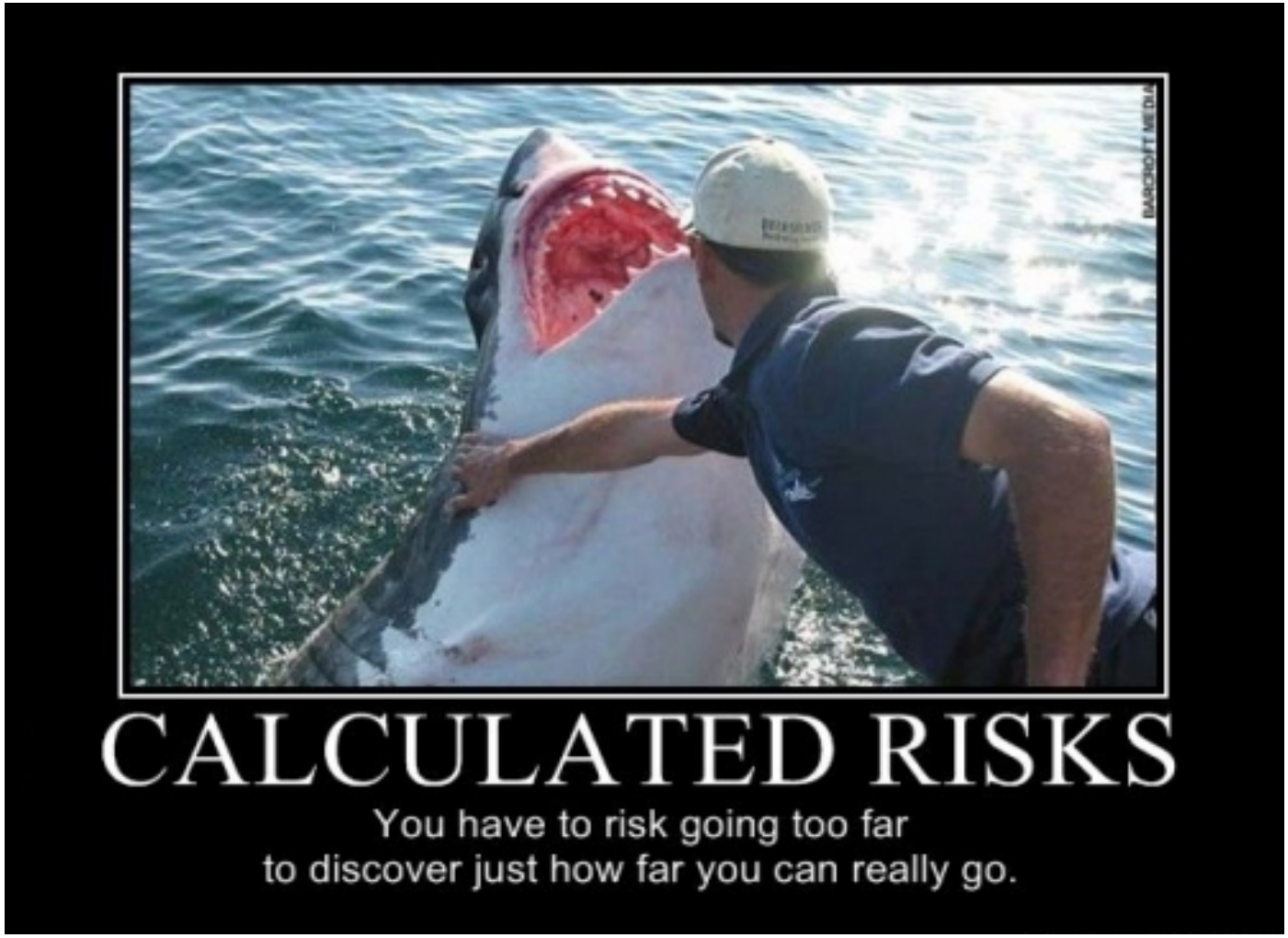
How do individuals make a decision?



How do individuals look at risk?


PROBABILITY THAT SOMETHING WILL GO WRONG
SEVERITY OF RISK
Category
FREQUENT
Likely to occur immediately or in a short period of time; expected to occur frequently
LIKELY
Quite likely to occur in time
OCCASIONAL
May occur in time
SELDOM
Not likely to occur but possible
UNLIKELY
Unlikely to occur
CATASTROPHIC
May result in death
E E H H M
CRITICAL
May cause severe injury, major property damage, significant financial loss, and/or result in negative publicity for the organization and/or institution
E H H M L
MARGINAL
May cause minor injury, illness, property damage, financial loss and/or result in negative publicity for the organization and/or the institution
H M M L L
NEGLIGIBLE
Hazard presents a minimal threat to safety, health and well-being of participants; trivial.
M L L L L




CALCULATED RISKS
You have to risk going too far
to discover just how far you can really go.

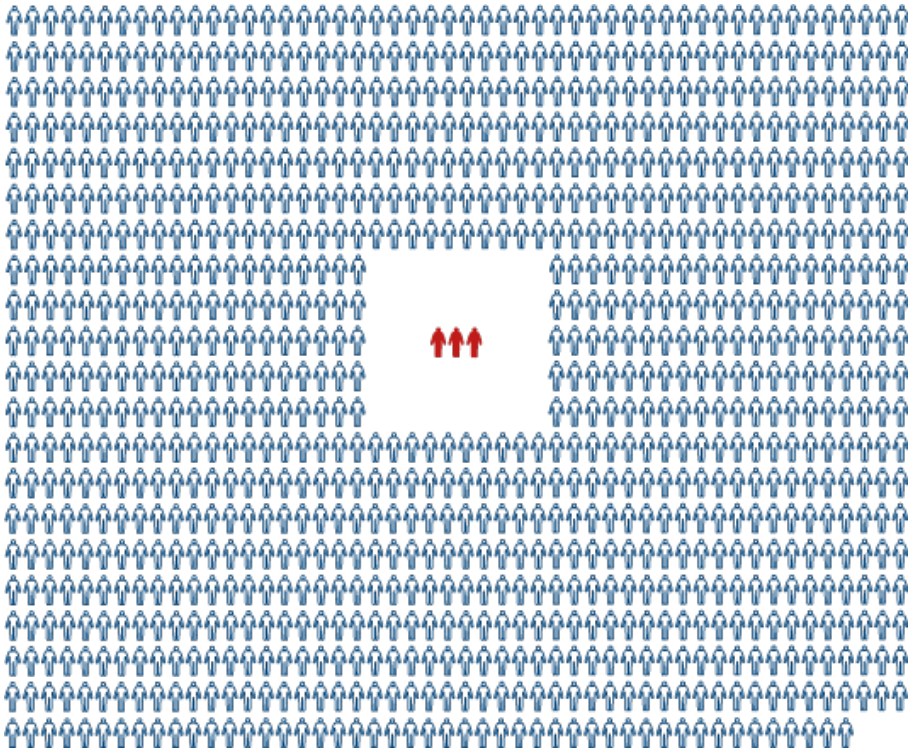
BC KIDNEY DAYS 2014
Hosted by BC Transplant and the BC Renal Agency

Presenting Risk

Not Helpful

- Safe
- Low risk
- Increased risk
- 3 times risk
- 10 times risk

Helpful



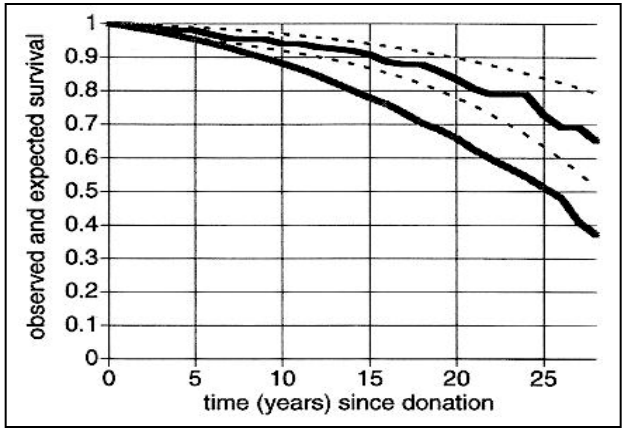
What Risks?

- Early Mortality
- Renal Failure

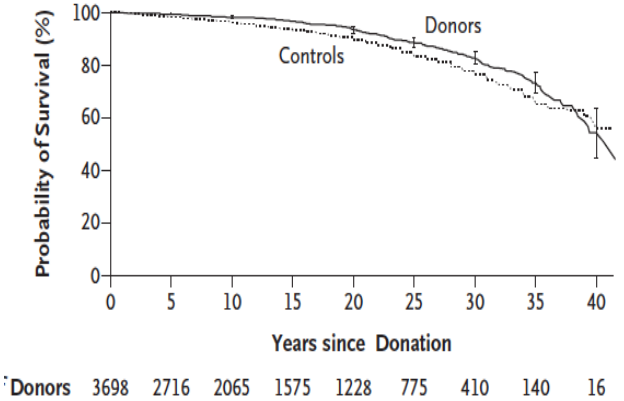
Why is Mortality an Issue?

Author	Country	Setting	N	Follow Up
Fehrman-Ekholm et al, 1997	Sweden	Single center	430	1-35 years
Okamato et al, 2009	Japan	Single center	481	1-35 years
Ibrahim et al, 2009	USA	Single center	3,698	1-45 years
Mjoen et al, 2012	Norway	Single (national) center	2,269	1-48 years
Fournier et al, 2012	Paris	Single center	310	1-53 years

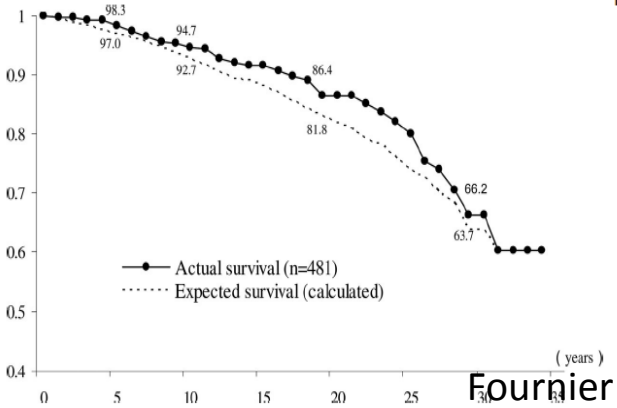
Fehrman-Ekholm n=430



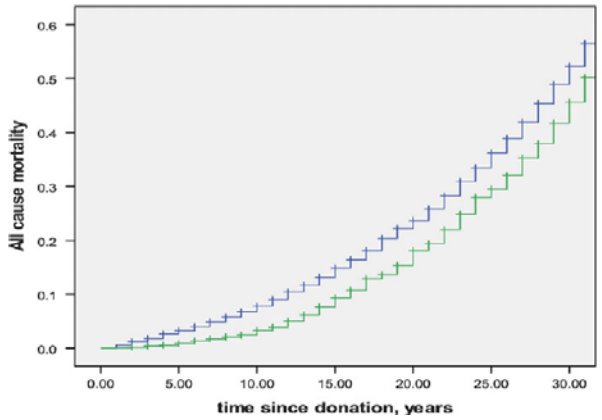
Ibrahim n= 3698



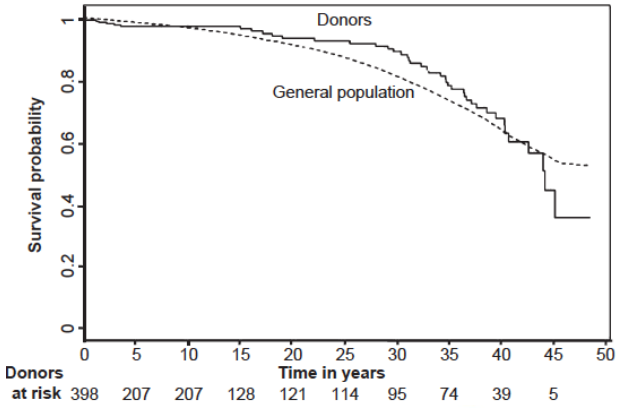
Okamoto n=481



Mjøen N =2269



Fournier N = 310

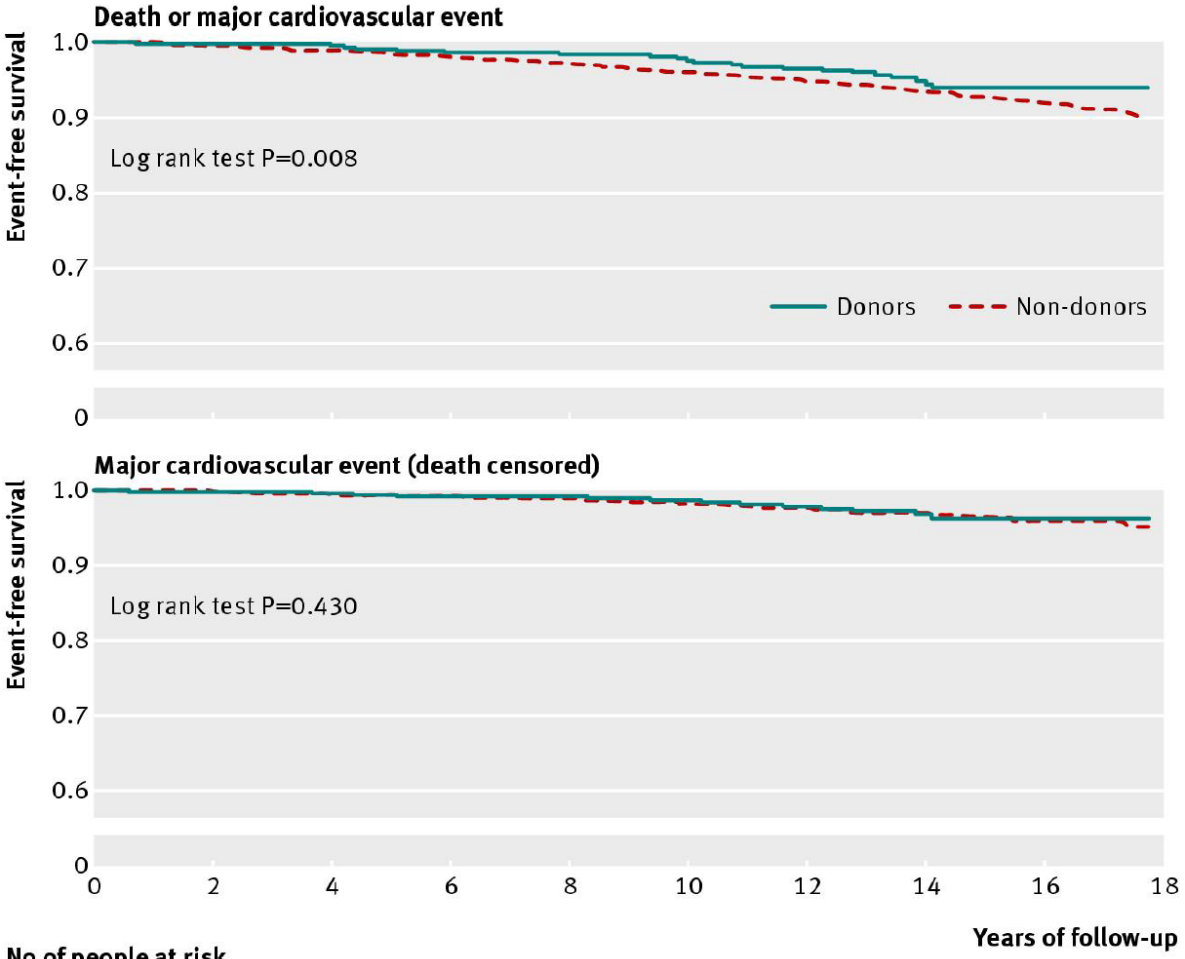


Survival in Donors versus Selected "Healthy" Controls

Author	Data source	Number Follow Up	Outcomes Source	Comparator
Garg 2012	Ontario Canada LKD registry	2,028 1-18 yrs	Linked to provincial death records and medical claims	"Healthy" persons in same databases (screened for baseline comorbidity)
Segev 2010	USA National LKD registry	80,347 1-15 yrs	Linked to death master file	"Healthy" persons from NHANES III (screened for baseline comorbidity)

Ontario donors *vs* Healthy Controls

[Garg et al, *BMJ* 2012; 344:e1203]

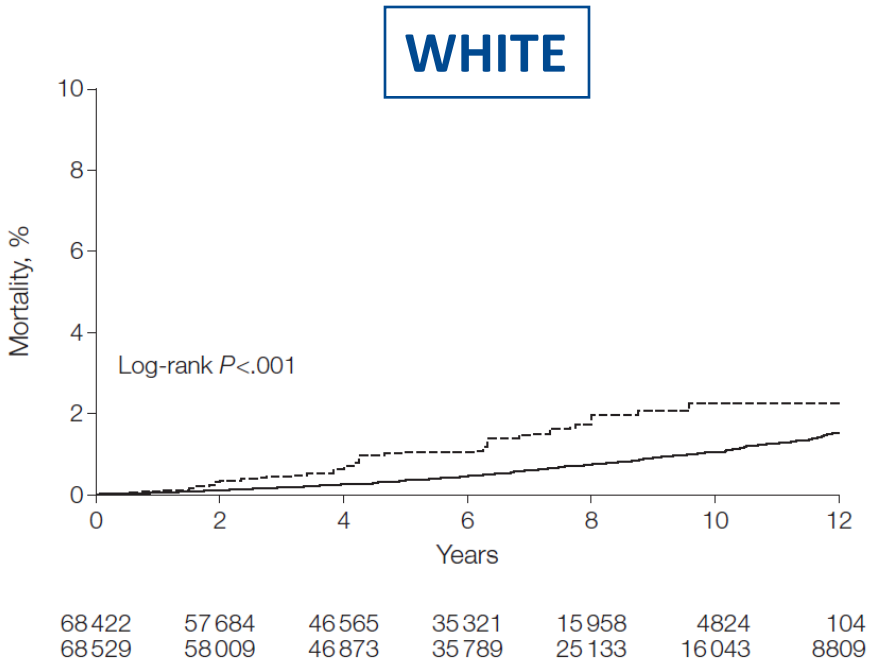


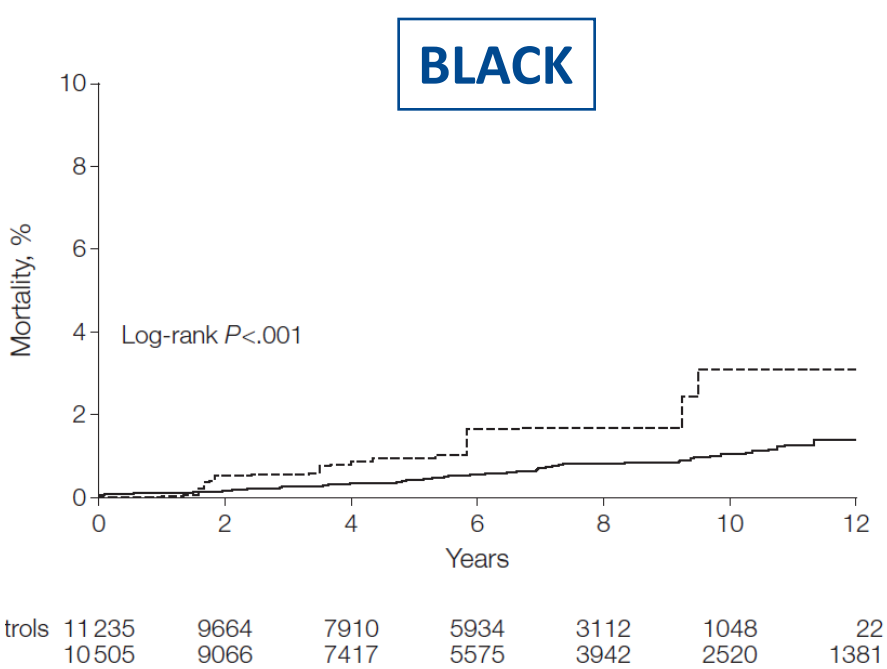
18 years follow-up

BC KIDNEY DAYS 2014
Hosted by BC Transplant and the BC Renal Agency

U.S. Registry Sample *vs* Healthy Controls

- **12-yr** LKD mortality was **similar/lower** than that of "healthy" matched controls
- Including among **sub-groups** stratified by **race**





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

BC KIDNEY DAYS 2014
Hosted by BC Transplant and the BC Renal Agency

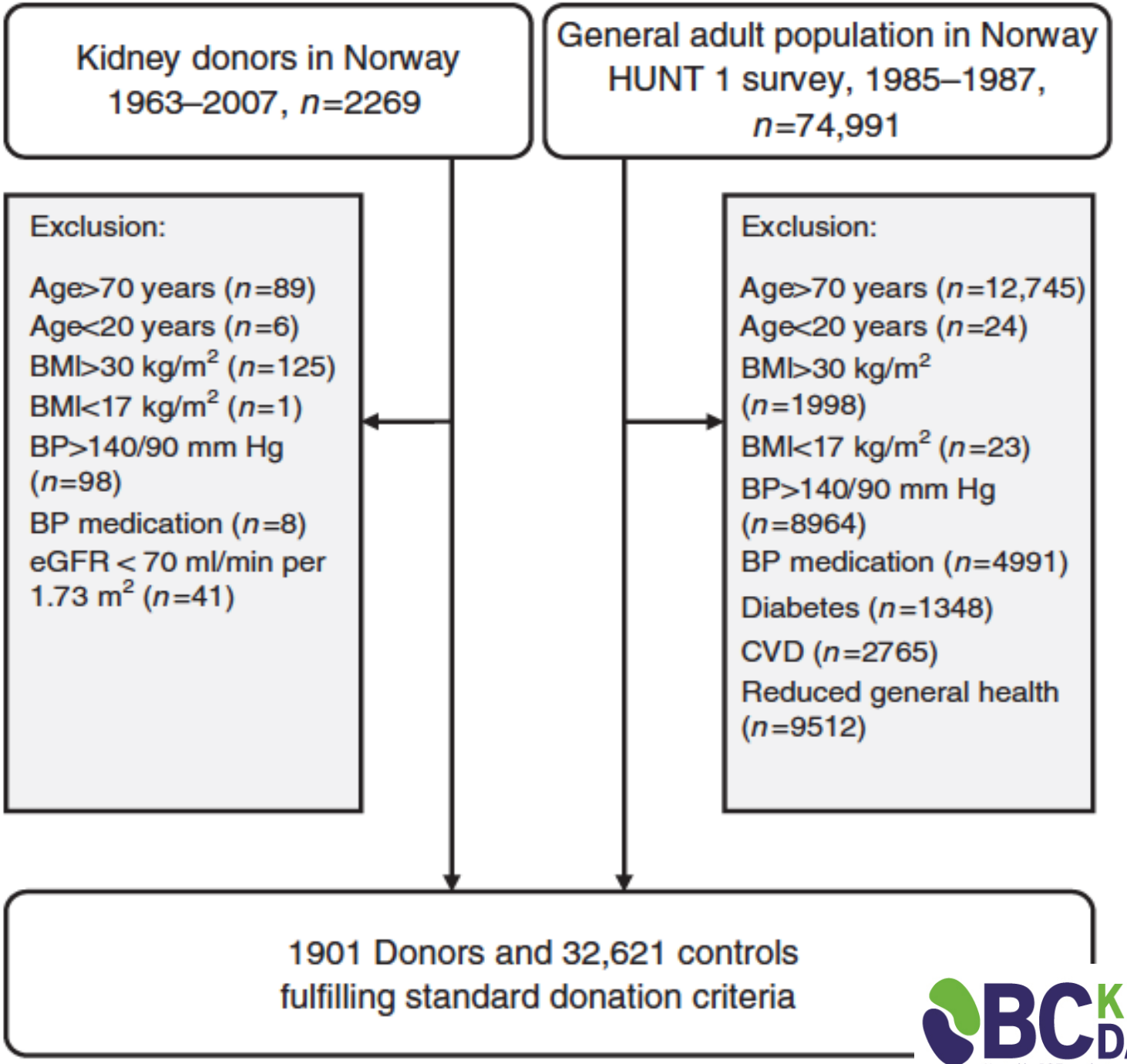
Is it Really That Safe?

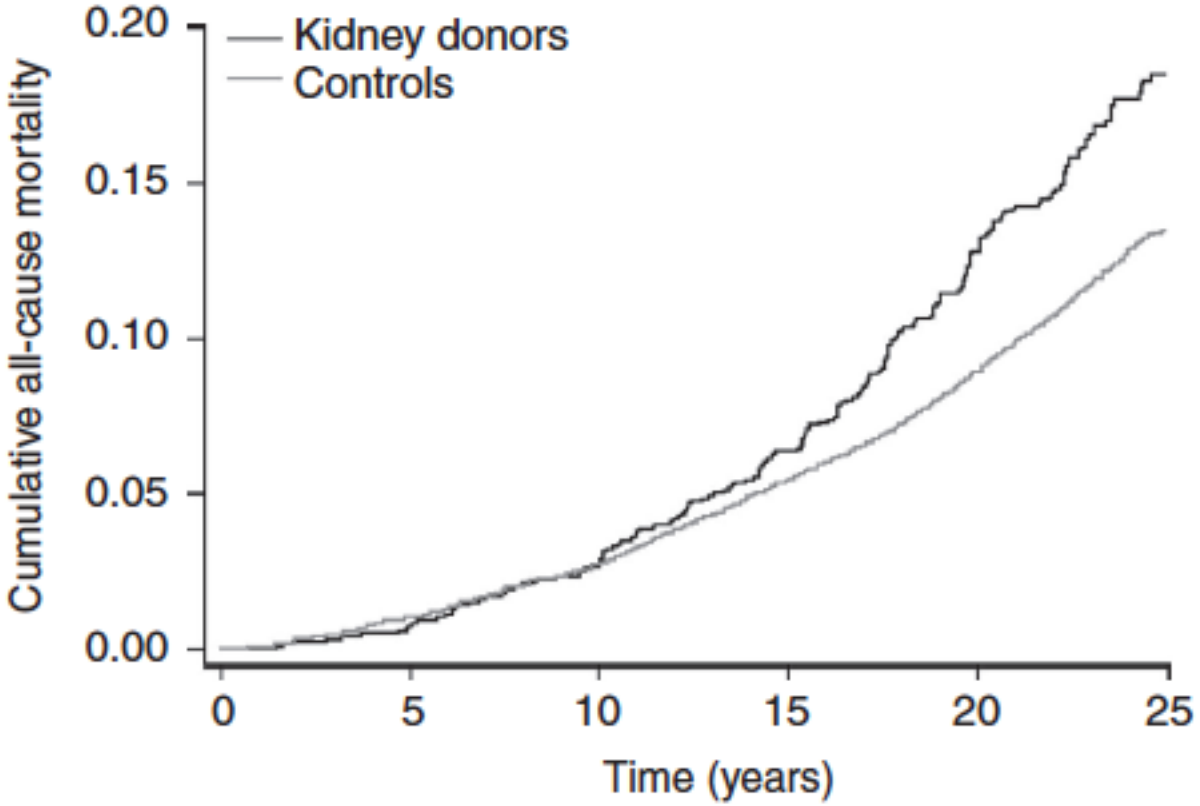
Long-term risks for kidney donors

Geir Mjøen[1], Stein Hallan[2,3], Anders Hartmann[1], Aksel Foss[1], Karsten Midtvedt[1], Ole Øyen[1], Anna Reisæter[1], Per Pfeffer[1], Trond Jenssen[1], Torbjørn Leivestad[4], Pål- Dag Line[1], Magnus Øvrehus[2], Dag Olav Dale[1], Hege Pihlstrøm[1], Ingar Holme[5], Friedo W. Dekker[6] and Hallvard Holdaas[1]

Kidney International 2014 86: 162-7

BC KIDNEY DAYS 2014
Hosted by BC Transplant and the BC Renal Agency





Hazard Ratio All Cause Mortality
1.31 (1.11 – 1.52)

BC KIDNEY DAYS 2014
Hosted by BC Transplant and the BC Renal Agency

Baseline Characteristics of Donors and Controls

	Kidney Donors	Controls
Age, years	46.0 ± 11.5	37.6±11.7
Male gender, %	41.0	46.9
Current smoking, %	41.5	39.5
Systolic BP, mm Hg	123.3±10.0	121.4±10.4
Diastolic BP, mm Hg	77.4±7.2	77.2±7.9
BMI, kg/m^2	24.2±2.8	23.5±2.6

Limitations - Control group

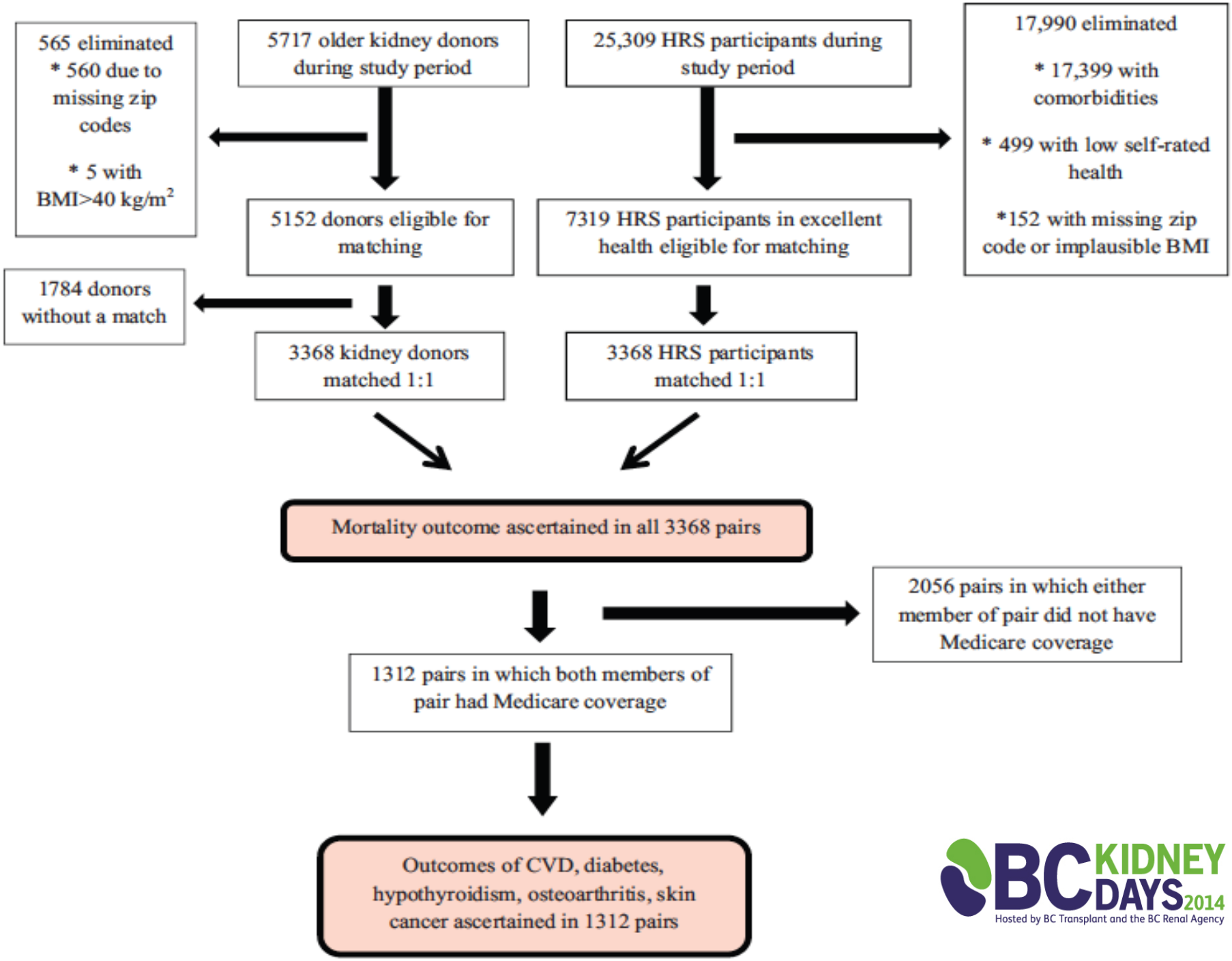
- Significant differences between donors and controls
  - Age: Donors 46.0 ± 11.5 versus 37.6 ± 11.7
  - Era: Donors 1963-2007 versus 1985-87 controls
  - Smoking: More donors smoked
  - Controls come from one community where donors come from all over the country

Mortality and Cardiovascular Disease Among Older Live Kidney Donors

Reese PP et al AJT 2014; 14: 1853 -1861

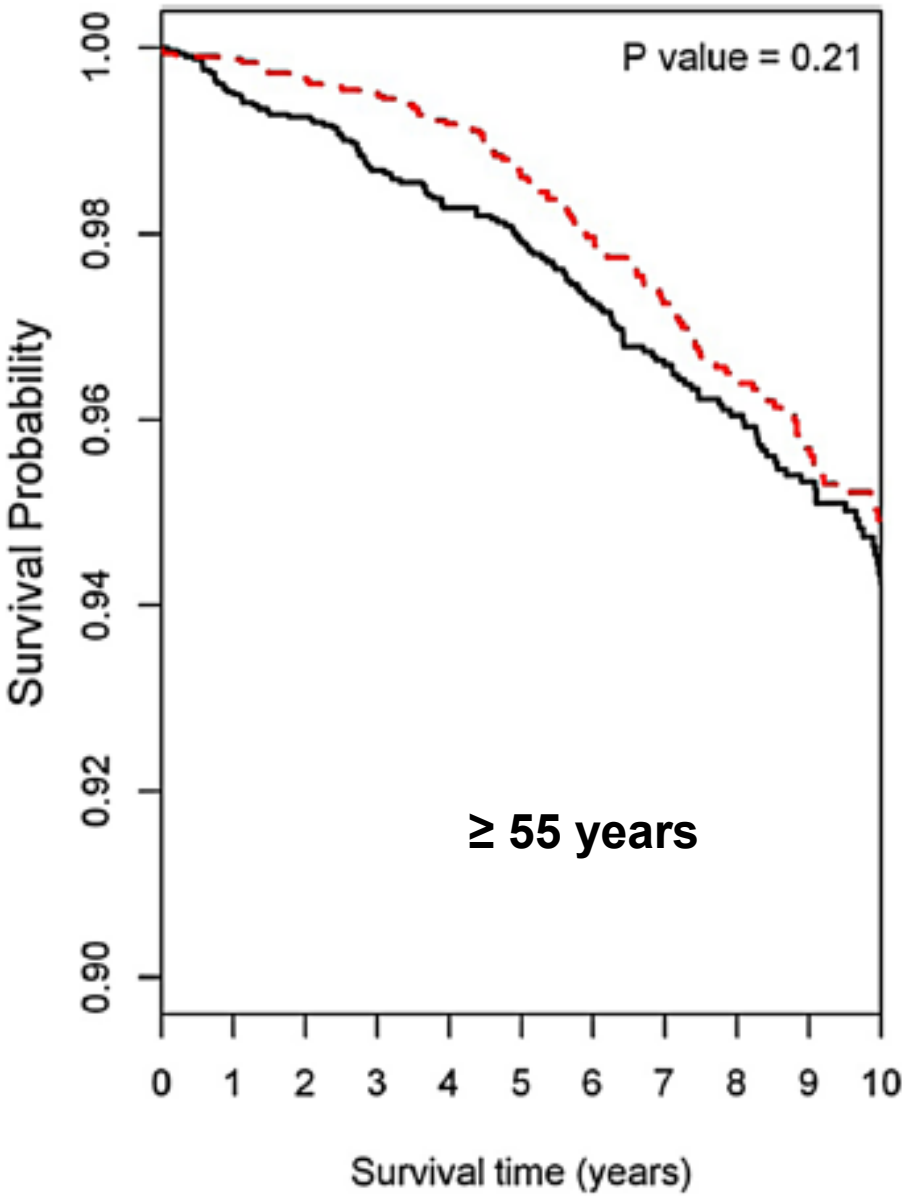
Design features:

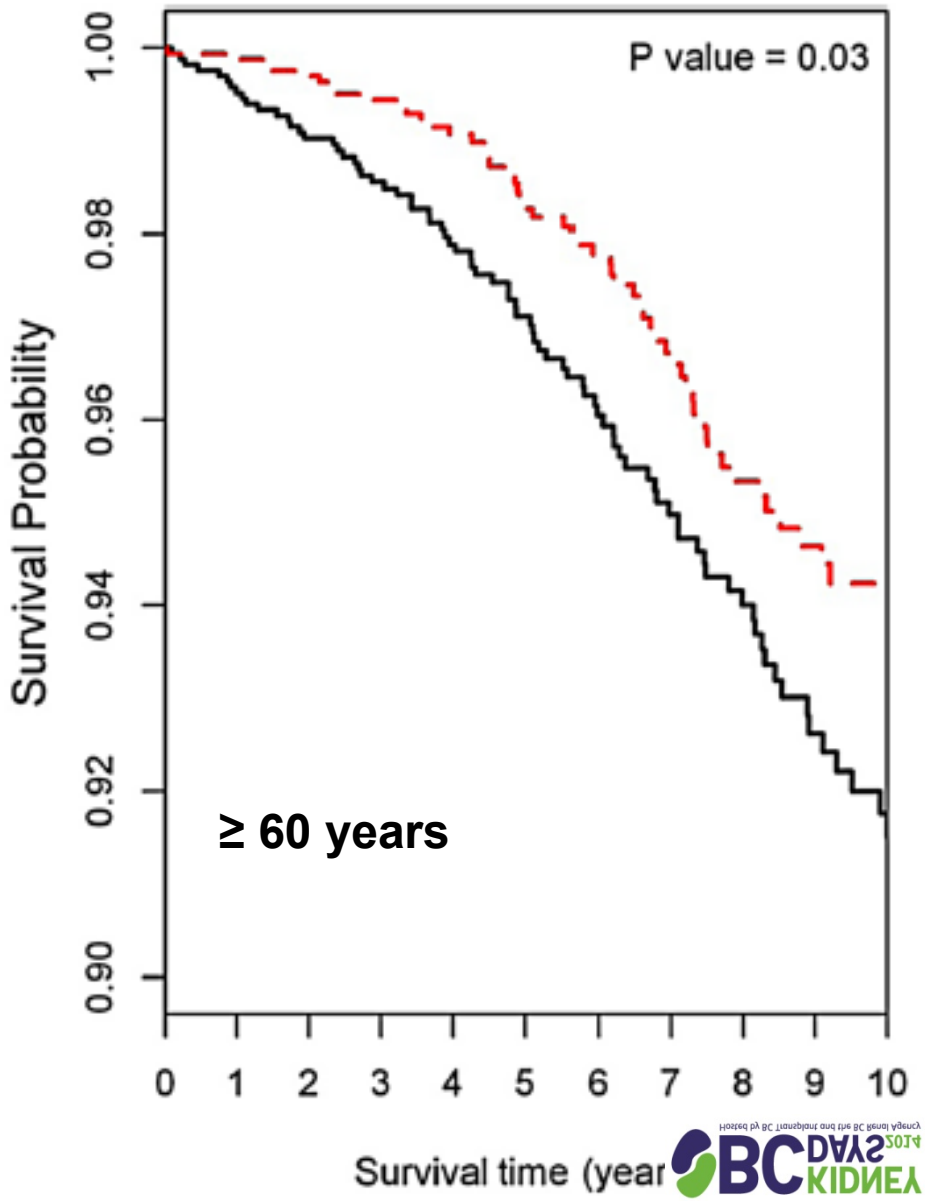
- Donors and controls were from the same era
  - Controls were participants in Health and Retirement Study
- Effort to minimize ascertainment bias
  - Death Master File used for outcome of death
  - For non-fatal outcomes identified from Medicare Claims
    - Matched pairs of donors and controls censored when either member of pair lost Medicare coverage
  - ESRD outcomes not reported because of concerns with use of Medicare claims for this outcome



BC KIDNEY DAYS 2014
Hosted by BC Transplant and the BC Renal Agency

No difference in Survival





What about risk of kidney disease?

ESRD in Living Donor Cohorts

Author	Country	Setting	FU (yrs)	ESRD	
Fehrman-Ekholm et al, 2006	Sweden	Single center		0.5%	(6/1112)
Rosenblatt , 2008	USA	Single center	1-46	0.3%	(4/3591)
Ibrahim et al, 2009	USA	Single center	1-45	0.3%	(11/3698)
Lentine et al, 2010	USA	National, insurance claims	mean 7.7	0.7% AA 0.5% Hisp 0% White	
Wafa et al, 2011	Egypt	Single center	1-23	0.4%	(8/2000)
Cherikh et al, 2011	USA	National	mean 9.8	0.2%	(126/56K)
Fournier et al, 2012	Paris	Single center	1-53	0.9%	(3/310)

When person-time available, no increase identified vs rates in gen pop

Research

Original Investigation

Risk of End-Stage Renal Disease Following Live Kidney Donation

Abimereki D. Muzaale, MD, MPH; Allan B. Massie, PhD; Mei-Cheng Wang, PhD; Robert A. Montgomery, MD, DPhil; Maureen A. McBride, PhD; Jennifer L. Wainright, PhD; Dorry L. Segev, MD, PhD

JAMA. 2014;311(6):579-586. doi:10.1001/jama.2013.285141

Strengths of This Study

- Includes every donor in U.S.
- Rigorous outcome assessment of ESRD in donors

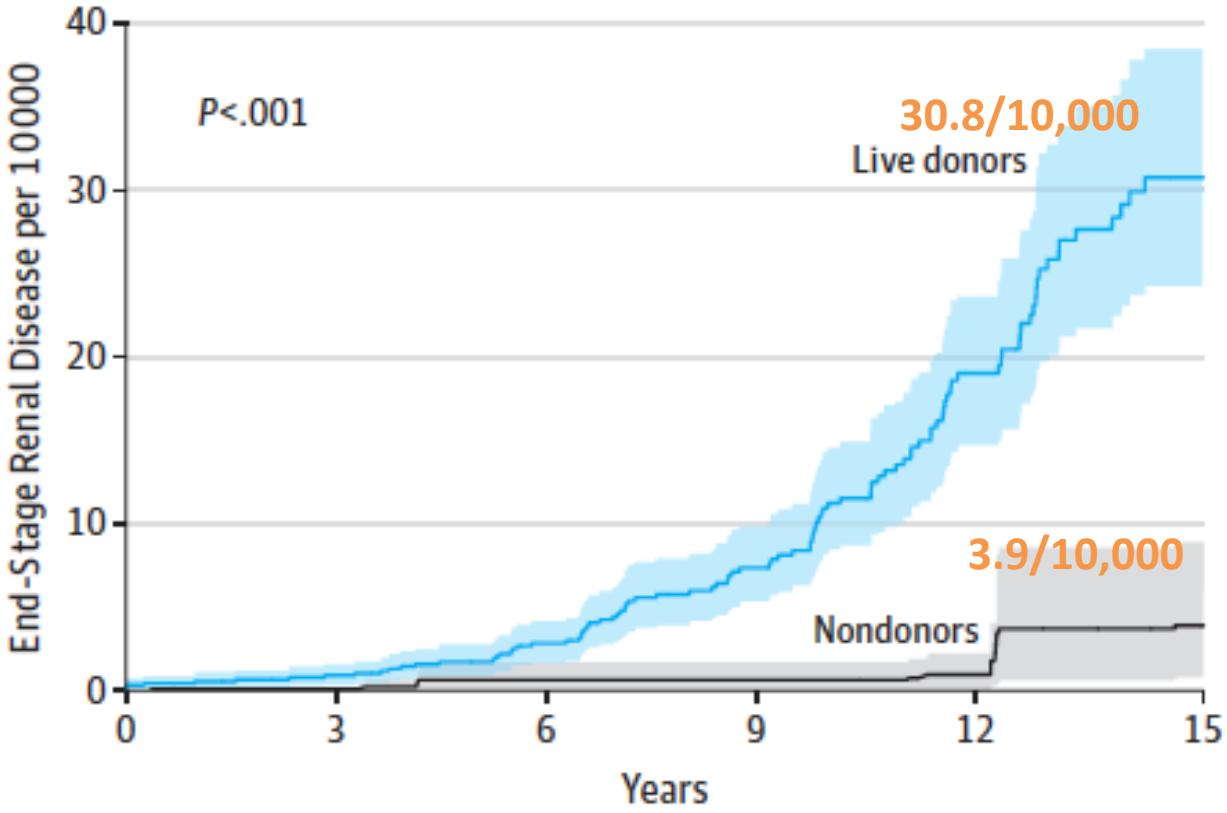
	No. of Donors	Cases of ESRD	Cumulative Incidence of ESRD at 15 Years per 10 000 (95% CI)
All donors[a]	96 217	99	30.8 (24.3-38.5)
Age at donation, y			
18-39	46 344	50	29.4 (21.4-40.2)
40-49	28 994	17	17.4 (10.1-30.0)
50-59	16 840	25	54.6 (34.8-85.4)
≥60	4039	7	70.2 (30.4-161.8)
Sex			
Women	56 775	42	21.1 (14.9-29.9)
Men	39 442	57	44.1 (32.9-59.1)
Race			
White/other	71 769	50	22.7 (15.6-30.1)
Black	12 387	36	74.7 (47.8-105.8)
Hispanic	12 061	13	32.6 (17.9-59.1)
Relationship to recipient[b]			
Biological	64 897	83	34.1 (26.9-43.3)
Nonbiological	31 081	16	15.1 (08.7-26.3)

	Number	Years	ESRD Outcome Source	Median Maximum Follow Up	Crude ESRD Incidence
Donors reported to OPTN	96,217	April 1, 1994 – Nov 30, 2011	CMS 2728 Activation to transplant Waiting List	7.6 years 15 years	99 cases 10.3 per 10,000
Controls NHANES III Healthy sub-set	20,024 9,364	1988 – 1994	CMS 2728	15 years 15 years	17 cases 18.2 per 10,000

BC KIDNEY DAYS 2014
Hosted by BC Transplant and the BC Renal Agency

Incidence of ESRD in Donors Versus Controls

A Cumulative incidence of end-stage renal disease

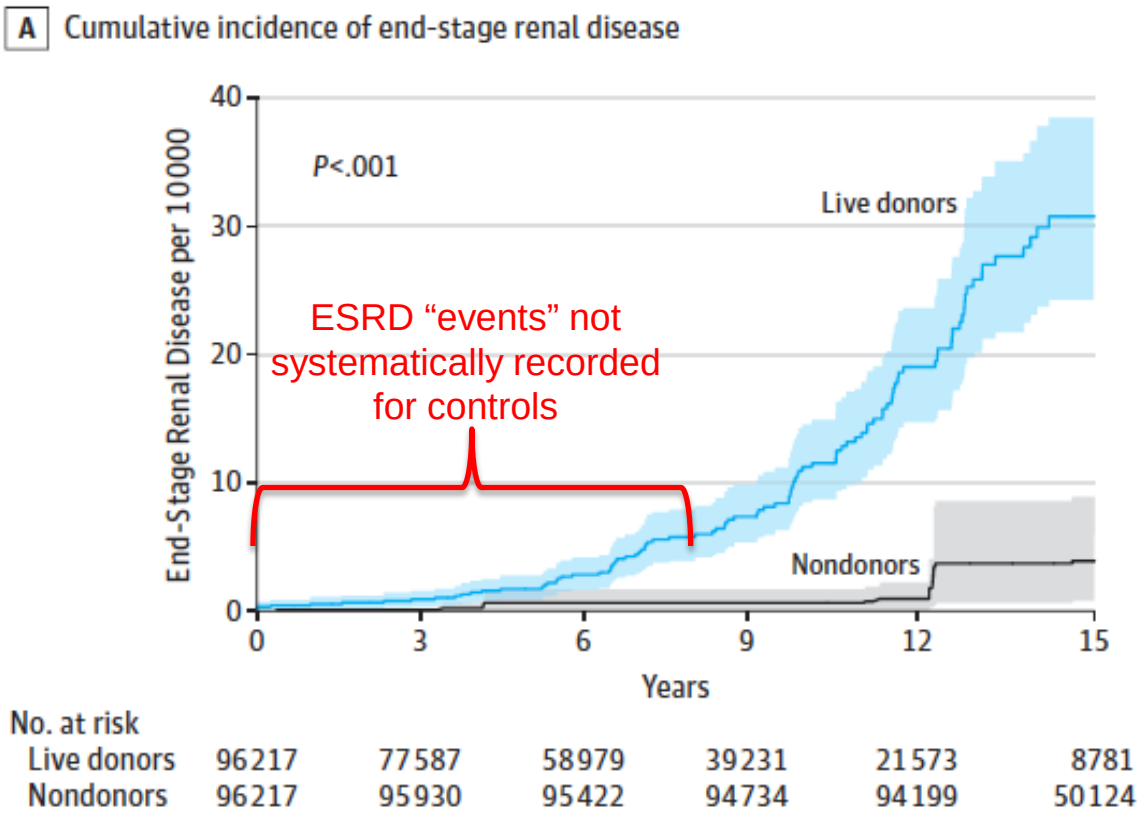


No. at risk						
Live donors	96217	77587	58979	39231	21573	8781
Nondonors	96217	95930	95422	94734	94199	50124

	Number	Years	ESRD Outcome Source	Median Maximum Follow Up	Crude ESRD Incidence
Donors reported to OPTN	96,217	April 1, 1994 – Nov 30, 2011	CMS 2728 Activation to transplant Waiting List	7.6 years 15 years	99 cases 10.3 per 10,000
Controls NHANES III Healthy sub-set	20,024 9,364	1988 – 1994	CMS 2728	15 years 15 years	17 cases 18.2 per 10,000

Different Outcome Assessment

Limitation
Differential ascertainment of ESRD in donors/non-donors



- **NHANES cohort 1988-94 versus donors 1994 -2011**
- **CMS 2728 form instituted in 1995**
  - **ESRD cases in non-donor controls not captured 1988-94**
  - **Explains why ESRD event rate in controls is initially flat**

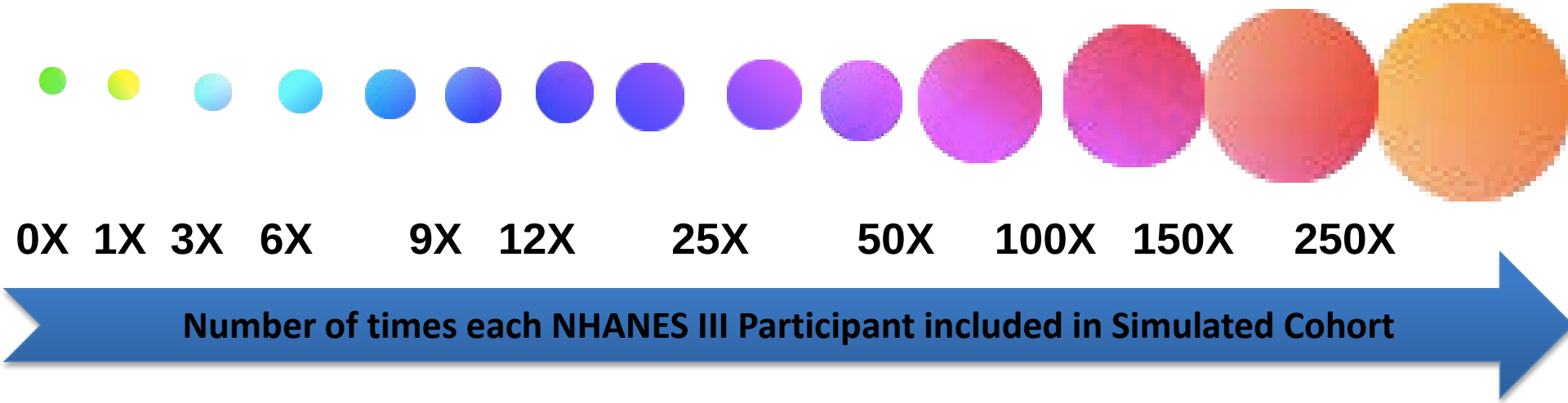
	Number	Years	ESRD Outcome Source	Median Maximum Follow Up	Crude ESRD Incidence
Donors reported to OPTN	96,217	April 1, 1994 – Nov 30, 2011	CMS 2728 Activation to transplant Waiting List	7.6 years 15 years	99 cases 10.3 per 10,000
Controls NHANES III Healthy sub-set	20,024 9,364	1988 – 1994	CMS 2728	15 years 15 years	17 cases 18.2 per 10,000

10 X Fewer actual controls

Relationship between "Healthy" NHANES III Participants and Simulated Control Group

- 9634 "Healthy" NHANES III → 17 ESRD
- 96,217 Simulated Controls → 36 ESRD

- Subgroups of NHANES III participants of varying N
- Frequency of inclusion in Simulated Cohort depends on “Fit” to donors
- The 17 NHANES III who developed ESRD are embedded in the Sub-groups



Why is this problematic if Simulated Controls were chosen without knowledge of the outcome?

- ESRD was rare (n = 17)
- We do not know the frequency with which the NHANES III participants (with and without ESRD) were included in the Simulated Cohort

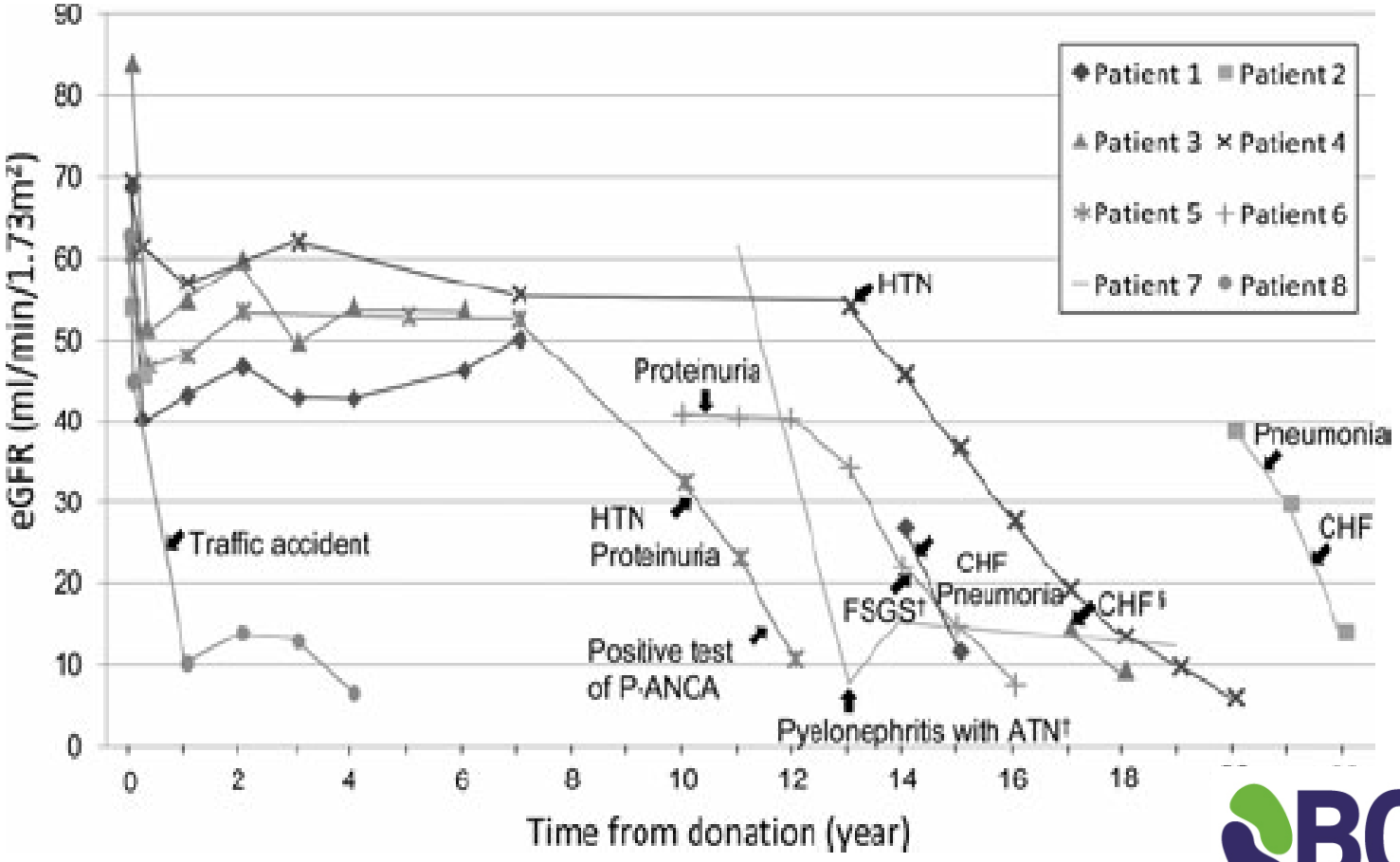
What do I conclude from this study?

- Risk of ESRD in US Donors at 15 years is 3 in 1000
- Some individuals will develop kidney failure in their lifetime because they donated

How do LKD develop ESRD?

[Kido et al. *Am J Transpl* 2009;11:2154]

- ESRD preceded by comorbidity (HTN, proteinuria, CVD, infection)



T. C. Turin, M. Tonelli, B. J. Manns, S. B. Ahmed, P. Ravani, M. James, B. R. Hemmelgarn. **Lifetime Risk of ESRD**. Journal of the American Society of Nephrology, 2012

- Approximately 1 in 40 men and 1 in 60 women of middle age will develop kidney failure if they live into their 90s.
- This equates to a 2.66% risk of kidney failure for men and a 1.76% risk for women if they live into their 90s.

BC KIDNEY DAYS 2014
Hosted by BC Transplant and the BC Renal Agency

My Conclusions

- The donor workup can identify those individuals at greater risk of future kidney disease but it is more reliable in older versus younger donors.
- Risk factors are more important in younger versus older donors.
- GFR matters.

When to rule out donors Canadian Guidelines

- GFR cutoffs
- Diabetes risk
- Hypertension
- Proteinuria/Hematuria

GFR Cut Offs

- If 18 to 30 years old … GFR < 90 mL/min per 1.73 m^2 precludes donation
- If age 31 to 40 … GFR < 85 mL/min per 1.73 m^2 precludes donation
- If age 41 to 65 … GFR < 80 mL/min per 1.73 m^2 precludes donation
- If age > 65 … GFR < 75 mL/min per 1.73 m^2 precludes donation

Acceptance Criteria – Blood Sugar

- FBG x 2 <6.1 mmol/L, HbA1C <6.0%
- FBG 6.1-6.9 mmol/L (IFG) with 2h OGTT <7.8 mmol/L in donors over 50 and HbA1C < 6.0%
- Donors over 50 with history of gestational diabetes and normal FBG and 2h OGTT.
- Donors at higher risk of DM over 50 with normal FBG and 2h OGTT.

Acceptance Criteria - Hypertension

- Normotensive (BP times 2 < 140/90)
- Age > 50 with history of hypertension well controlled on one BP medication and no evidence of target organ damage

Acceptance Criteria Microscopic Hematuria

- Negative workup including renal biopsy
- An individual with thin basement membrane disease (with other testing all being normal) is suitable to become a living kidney donor.

What about the Grey Areas?

- Who gets to decide when the risk is too high?
- For transplant program donor safety over riding priority.
- For individual donor priority may be the recipient.