

Long-Term Risks to Live Kidney Donors

Simin Goral MD

University of Pennsylvania Medical Center
Philadelphia, Pennsylvania

Outline

- Background
- Survival
- Kidney disease; ESRD, CKD, proteinuria
- Cardiovascular disease: hypertension, ischemia and heart failure
- Risks to pregnancy
- Subgroups of concern: “complex donors”

Kidney Transplantation

- The **best** treatment option for majority of patients with ESRD regardless of sex, race, age or cause of ESRD
 - Increase in life expectancy
 - Better quality of life
 - Decrease in healthcare costs
- The demand for kidney transplantation exceeds the supply of transplantable organs
- Waiting times are quite long

Living Donors

- The survival of a kidney transplanted from a live donor is much better
- Success of live donor transplantation no longer necessitates the consideration of an HLA match unless there is possibility of a transplant from HLA identical sibling
- The survival rate of a kidney transplant from a genetically unrelated donor is excellent

Living Donors

- In 1954: Requiring an identical twin for success
- During the 1980's: Selection of an HLA-matched family member
- Current: any person (irrespective of the HLA match) can be a donor if they are medically and psychosocially suitable
- **It is illegal to buy or sell kidneys or coerce a donor**

Potential Living Donor

- Appropriate for donation from nephrologic standpoint – what is his//her renal risk?
- Healthy enough for surgery?
- Competent, willing to donate; free of coercion
- Medically and psychosocially suitable
- Fully informed of the risks and benefits of donation
- Fully informed of risks, benefits, and alternative treatment available to the recipient

Potential Advantages of Live Donation

- Better short-term and long-term results
- More consistent early function and ease of management
- Avoidance of long wait for cadaveric transplant
- Less delayed graft function
- Less aggressive immunosuppressive regimens
- Surgery can be planned ahead (medical and personal convenience)
- Emotional gain to donor
- Helps relieve stress on national cadaver donor supply

Potential Disadvantages of Live Donation

- Psychological stress to donor and family
- Inconvenience and risk of evaluation process (i.e. IV contrast)
- Operative mortality (0.03% or 1 in 3,500 patients)
- Major perioperative complications (4.4%, range: 0.0 to 13.0%)
- Minor postoperative complications (up to 50%)
- Long-term morbidity
- Risk of traumatic injury to remaining kidney
- Risk for unrecognized chronic kidney disease

Medical Follow-up of Living Kidney Donors by 1 Year After Nephrectomy

- In 2003, our program developed a policy recommending that donors receive medical follow-up by 1- year postnephrectomy
- A retrospective cohort study of 137 live kidney donors at UPenn
- Medically complex donors: hypertension, body mass index ≥ 30 , nephrolithiasis, age 65 years or older, creatinine clearance < 80 mL/min/1.73 m², or had a first-degree relative with diabetes mellitus
- Adequate follow-up: one visit with a nephrologist at our center, or blood pressure, serum creatinine, and urinalysis checked elsewhere

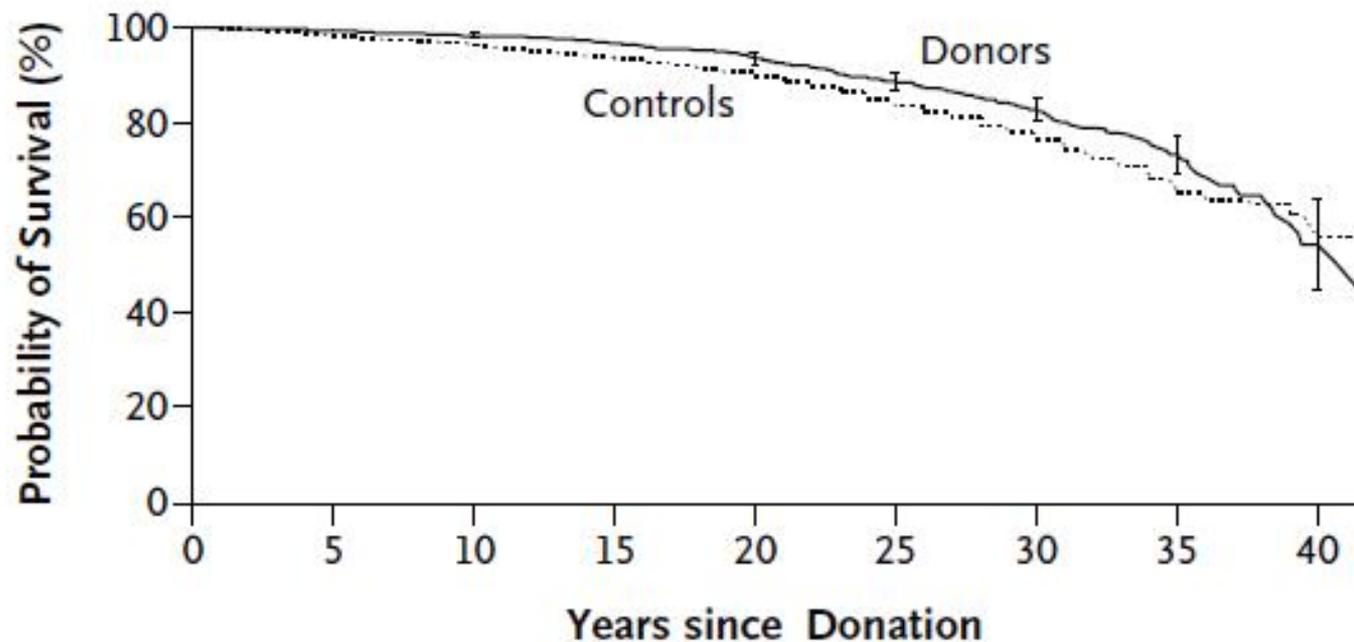
Reese P, et al. Transplant Proc 2009

Medical Follow-up of Living Kidney Donors by 1 Year After Nephrectomy

- Eighty-three donors (61%) had adequate follow-up, 42 did not, and 12 could not be contacted
- At multivariate logistic regression, donors with adequate follow-up were more likely to be medically complex and older than donors with inadequate follow-up
- A substantial minority of donors do not receive recommended care by 1 year after nephrectomy

Mortality

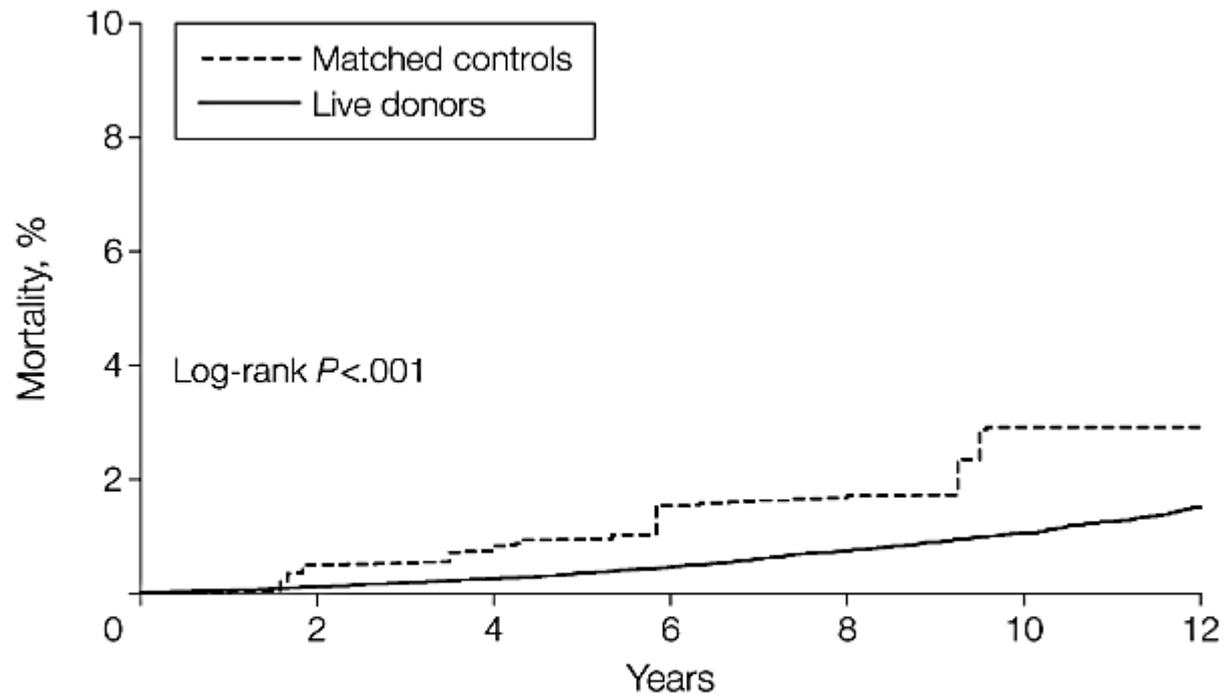
- Peri-operative death rate: 1 in 3,500; did not change during the last 15 years
- Long-term mortality
 - Caucasian donors
 - No higher than demographically-matched individuals in the general population; even better survival in donors
 - *Ibrahim H, et al. NEJM 2009*
 - *Fehrman-Ekholm I, et al. Transplantation 1997*
 - All US donors (median follow-up 6 years)
 - No higher than demographically- and comorbidity-matched individuals in NHANES
 - *Segev et al. JAMA 2010*



No. of Donors	3698	2716	2065	1575	1228	775	410	140	16
---------------	------	------	------	------	------	-----	-----	-----	----

Figure 1. Survival of Kidney Donors and Controls from the General Population.

I bars at 5-year intervals indicate 95% confidence intervals for the probability of survival among kidney donors.



No. at risk							
Matched controls	80 347	67 966	54 998	41 679	19 259	5 896	127
Live donors	80 347	68 230	55 282	42 154	29 657	18 960	10 436

- Kaplan-Meier curves comparing cumulative mortality of live kidney donors and matched controls for the entire cohort of live donors
- Long-term mortality was similar or lower for live kidney donors than for the matched NHANES III cohort throughout the 12-year period of follow-up

Mortality: Issues

- Short follow-up in most of the studies
- Mostly Caucasians studied
- Medically complex donors/subgroups; donors with hypertension, black donors, obese donors-more information needed

End-Stage Renal Disease

- Low relative and absolute risk of ESRD among Caucasian donors
 - Minnesota: 1 in 180 million persons per year versus 1 in 268 persons per year among US Caucasians (<1%)
 - *Ibrahim H, et al. NEJM 2009*
 - Sweden: 6 of 1,112 donors (0.5%) at median 20 years follow-up
 - *Fehrman-Ekholm I, et al. Transplantation 2006*

End-Stage Renal Disease

- OPTN and Center for Medicare and Medicaid Services (CMS) databases: the number of living kidney donors who donated between October 1, 1987 and March 31, 2003 and subsequently developed ESRD
- 126 cases of ESRD among 56,458 living kidney donors (0.22%)

Cherikh WS, et al. Am J Transplant 2011

Table 6. Postdonation ESRD rate per 1000 years at risk all living kidney donors who donated during April 1, 1994–March 31, 2003

		No. of Living Kidney Donors	Total Years at Risk	Number With Postdonation ESRD	ESRD Rate Per 1,000 Years at Risk	Relative Risk of ESRD [95% CL]
Donor Ethnicity	White	29 530	290 629.4	25	0.086	1.00
	Black	5531	54 394.8	23	0.423	4.92 [2.79–8.66]
	All	41 753	410 481.0	55	0.134	
Donor Gender	Female	24 177	237 803.3	21	0.088	1.00
	Male	17 576	172 677.7	34	0.197	2.24 [1.30,3.86]
	All	41 753	410 481.0	55	0.134	

- The living kidney donor ESRD rate was **nearly five times higher for Blacks than for Whites and two times higher for males than females**

- However, these ethnic and gender-related differences were **similar** to those previously reported for ESRD in the general population

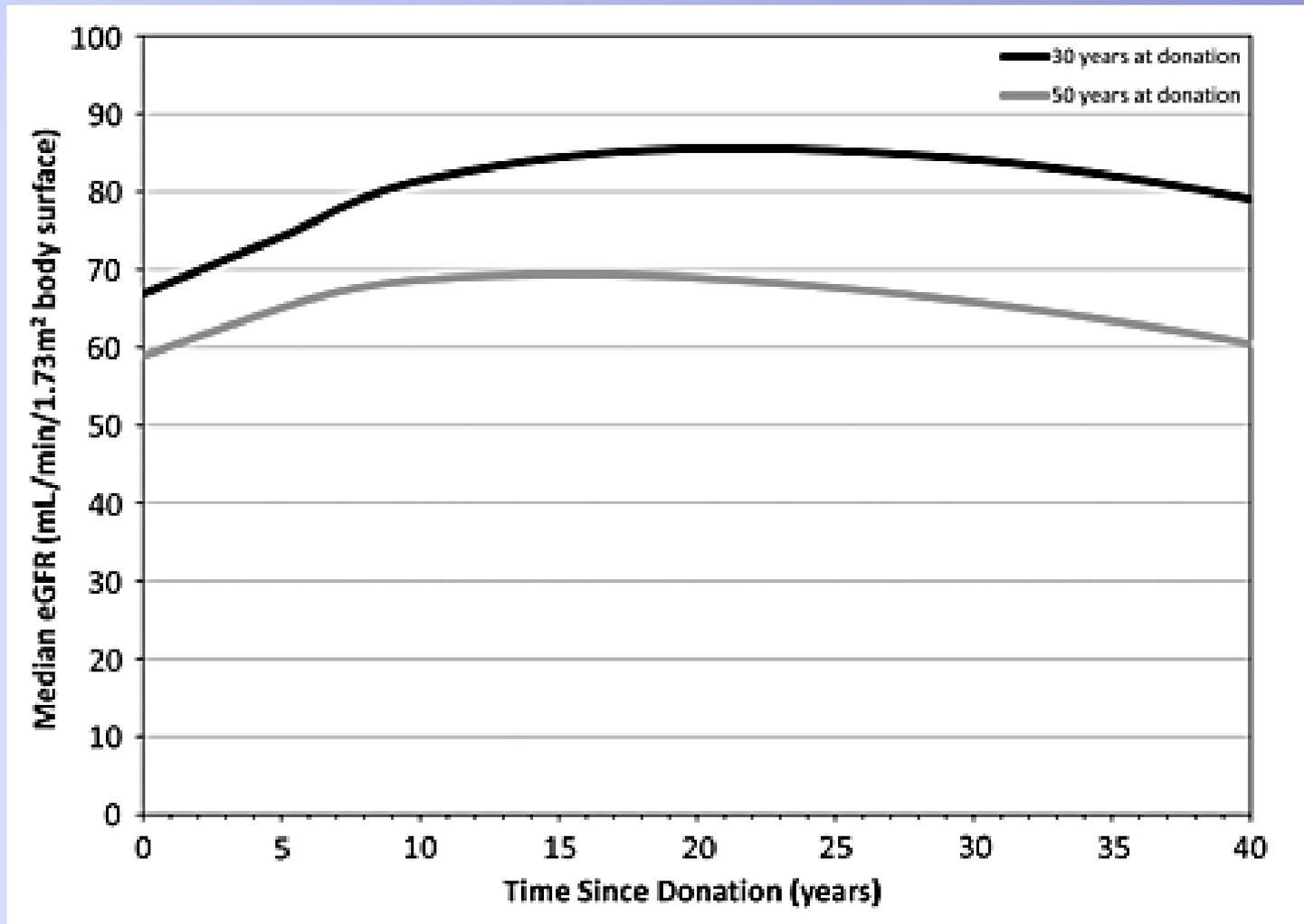
Chronic Kidney Disease

- Conventional definition should not be applied
 - eGFR < 60 ml/min/m² is common among prior kidney donors, but no systemic diseases
 - Direct measurements among white donors suggest GFR in 60 – 70 ml/min range is common at 10 years

Ibrahim H, et al. NEJM 2009 and Rook M, et al. Am J Transplant 2008

- Ten years after nephrectomy, donors had a GFR that was 10 ml/min lower compared to controls; 12% of donors developed a GFR less than 60 ml/min during follow-up

Garg AX, et al. Kidney Int 2006



- For 30-year old donors, the median eGFR typically increases during the first 17 years, then remains constant for ~8 years and slowly declines thereafter. For 50-year-old donors, the median eGFR is expected to increase during the first 15 years or so and then to enter a phase of slight progressive decline

Proteinuria

- Between 1973 and 2001, 152 living donor nephrectomies from Germany; all Caucasian
- Seven of 152 donors had died from nonrenal diseases
- Of the remaining 145, data collection on 135 (93%) donors
- The mean time from nephrectomy to the current evaluation: 11 ± 7 (range 1–28) years

Proteinuria

- A decrease in creatinine-clearance or GFR by 20–25%, but no correlation between residual renal function and blood pressure or the amount of proteinuria in this cohort
- An **increase in urinary protein excretion, but pathological albuminuria was rare**

Long-Term Consequences of Kidney Donation-A Meta-Analysis

- 48 studies from 27 countries: a total of 5048 donors
 - Follow-up: average of 7 years after donation (range 1–25 years); **the average 24 h urine protein: 154 mg/day**; the average GFR: 86 ml/min.
 - In controlled studies **urinary protein was higher in donors- became more pronounced with time** (3 studies in 59 controls/129 donors; controls **83 mg/day** vs donors **147 mg/day**)
 - An initial decrease in GFR after donation was not accompanied by accelerated losses over that anticipated with normal aging (6 studies in 189 controls/239 donors; controls 96 ml/min vs donors 84 ml/min)

24 h urine protein

Source*	Donors, post-donation		Controls		24 h urine protein Mean difference (mg/day) 95% CI
	Years after donation,	24 h urine Protein (mg/day)	24 h urine Protein (mg/day)	24 h urine Protein (mg/day)	
	Mean (range)	N mean (s.d.)	N mean (s.d.)		
D'Almeida <i>et al.</i> ⁴⁵	7 (1–14)	59 151 (125)	28 96 (116)		54 (1, 108)
Williams <i>et al.</i> ⁵⁸	13 (10–18)	37 115 (135)	17 31 (125)		84 (10, 157)
Mathillas <i>et al.</i> ⁶⁰	15 (10–20)	33 306 (320)	14 212 (255)		94 (–79, 267)
Pooled estimate		129 147 (22)	59 83 (30)		66 (24, 108)

- The average 24 h urine protein: 154 mg/day; the average GFR: 86 ml/min

- Kidney donation resulted in small increases in urinary albumin, which increased with time after donation

Proteinuria and Reduced Kidney Function in Living Kidney Donors- A Meta-Analysis

- Ten years after nephrectomy, donors had a GFR that was 10 ml/min lower compared to controls
- 12% of donors developed a GFR less than 60 ml/min during follow-up
- The pooled incidence of proteinuria: 12%

Hypertension

- Higher risk of HTN
 - Mean time since donation was 15 years, ranging from 2 to 43 years
 - 23% (126/546) of donors were on antihypertensive medication
 - An additional 22% (117/543) of the donors were found to have undiagnosed hypertension (BP >140/90 mm Hg) and were not on antihypertensive medication at the time of the medical follow-up
 - Systolic BP increased with both time since donation ($P = 0.002$) and age ($P < 0.001$)

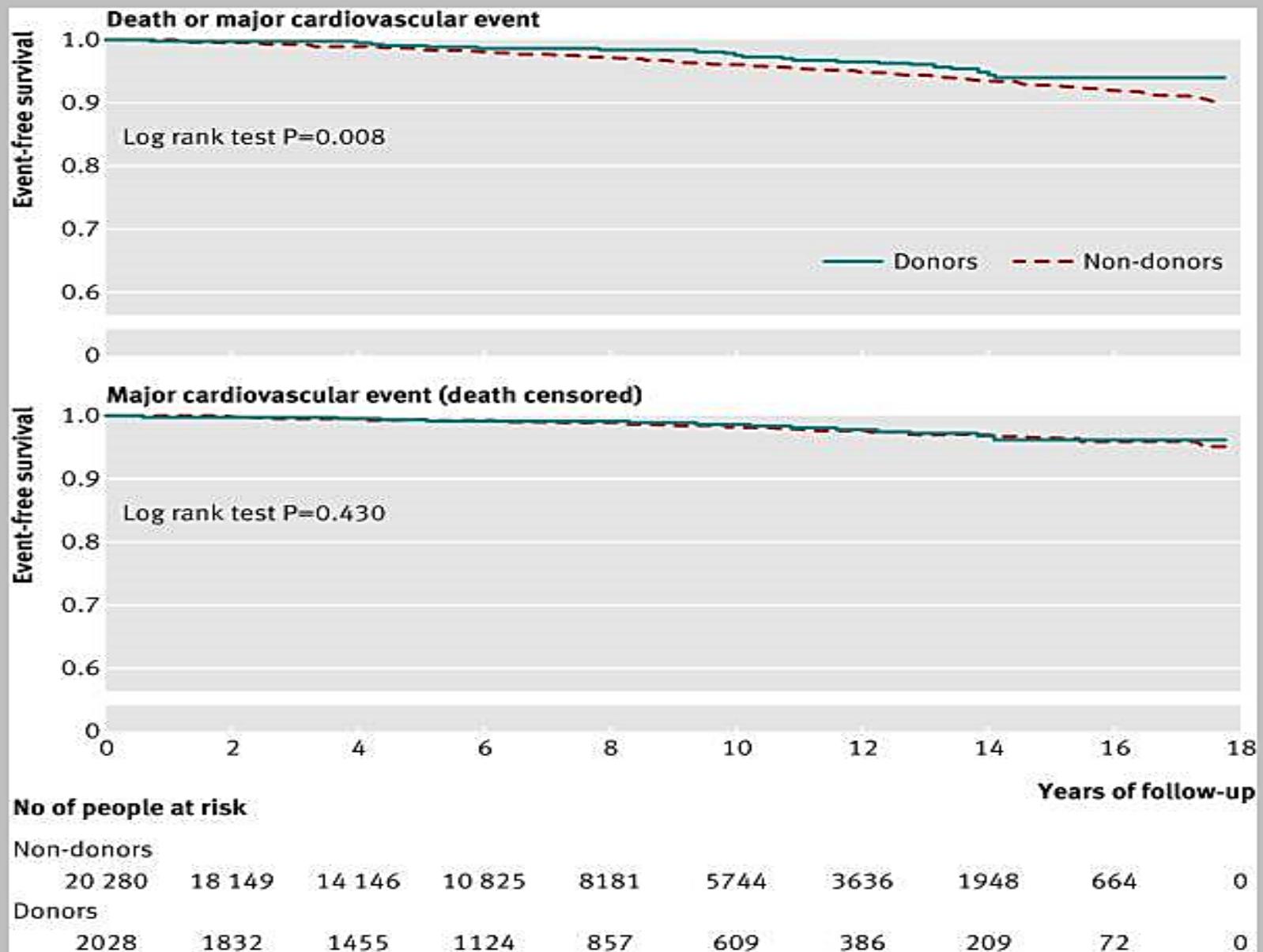
Cardiovascular Disease and Hypertension Risk

- A retrospective cohort from Ontario, Canada between the years 1993 and 2005
- 1278 living donors and 6359 healthy adults as controls
- Follow-up: a mean of 6.2 years (range 1-13 years) after donation
- There was no significant difference in death or cardiovascular events between donors and controls (1.3% vs 1.7%)
- Donors (mean age 41 years) were more frequently diagnosed with hypertension than controls (16.3% vs 12%) but were also seen more often by their primary care physicians

Garg AX, et al for the DONOR Network. Transplantation 2008

Cardiovascular Disease

- A population based matched cohort study in Ontario, Canada
- 2028 living kidney donors and 20,280 matched non-donors; The median follow-up: 6.5 years
- A total of 609 donors and 5744 non-donors were followed for a period of 10 years or more
- The risk of major cardiovascular events in donors is no higher in the first decade after kidney donation compared with a similarly healthy segment of the general population



Garg AX, et al for the DONOR Network BMJ 2012

Long-Term Consequences of Kidney Donation-Hypertension

- 3698 kidney donors who donated kidneys during the period from 1963 through 2007
- From 2003 through 2007: glomerular filtration rate (GFR) and urinary albumin excretion were measured; the prevalence of hypertension, general health status, and quality of life were assessed in 255 donors

Ibrahim H, et al. NEJM 2009

Long-Term Consequences of Kidney Donation-Hypertension

- The survival of kidney donors: similar to that of controls-matched for age, sex, and race or ethnic group
- At a mean of 12 ± 9 years after donation, 85.5% of the subgroup of 255 donors had a GFR of ≥ 60 ml/min, **32.1% had hypertension**, and 12.7% had albuminuria
- **Older age and higher BMI**, but not a longer time since donation, were associated with both lower GFR (< 60 ml/min) and **hypertension**

Ibrahim H, et al. NEJM 2009

Diabetes

- Retrospective study of 4650 living kidney donors from October 1987 through July 2007
- Black donors had a higher risk of diabetes, perhaps lower in magnitude than the association of race with diabetes in the general population

Lentine KL, et al. NEJM 2010

Long-Term Morbidity

- 73 patients who had unilateral nephrectomy
- Normal kidney function, no proteinuria at the time of surgery
- Reasons for nephrectomy: stones in 29, renal mass in 14, hydronephrosis in 11, and renal tuberculosis in 5 patients
- Mean follow-up: 13.6 ± 8.6 years (18 months-35 years)
- 20 in 73 patients (27%) developed proteinuria/renal insufficiency

Table 1. Clinical characteristics of patients at the time of unilateral nephrectomy

	Total (N=73)	Patients who maintained normal renal function (Group I) (N=53)	P value	Patients who later developed proteinuria/ renal insufficiency (Group II) (N=20)
Age years	39.7 ± 14.7 (11–66)	39 ± 14 (11–65)	NS	41 ± 14 (11–66)
Gender	35 M; 38 F	24 M; 29 F	NS	11 M; 9 F
Mean arterial pressure mm Hg	94 ± 12 (70–140)	93 ± 12 (70–140)	NS	98 ± 12 (80–130)
Serum creatinine mg/dL	1 ± 0.1 (0.7–1.4)	0.9 ± 0.1 (0.7–1.3)	NS	1 ± 0.1 (0.9–1.4)
Proteinuria g/24 hours	0	0	NS	0
Body weight kg	68 ± 12 (40–99)	63.5 ± 8.9 (40–85)	<0.001	80.1 ± 12.1 (53–99)
Body mass index kg/m ²	26.2 ± 5.3 (18–41.4)	24.3 ± 3.7 (18–34)	<0.001	31.6 ± 5.6 (22–41.4)

In 14 obese patients (BMI>30 at the time of nephrectomy), 13 (92%) developed proteinuria/renal insufficiency.

Rate of Hypertensive-Diseases of Pregnancy and Birth Complications

- Hypertensive disorders of pregnancy (preexisting HTN, gestational HTN, preeclampsia, eclampsia and preeclampsia superimposed on preexisting HTN): about 10% in general population cohorts
- Average incidence of gestational hypertension: 7.9%; **preeclampsia: 3.3%**; and eclampsia: 0.06%
- Premature birth and low birth weight: overall incidence of 2% to 13%
- In the United States, fetal death (still birth and neonatal death) is less than 1% and maternal death is less than 0.1%

Pregnancy After Kidney Donation

- Retrospective cohort study from Norway: 106 occurred after donation in 69 of the donors
- Mean time from donation to delivery was 5.0 years
- Comparison of female kidney donors to:
 - Pre-donation pregnancies
 - Randomly selected controls from the general population
- Gestational hypertension: in 3/106 (2.8%) pregnancies after donation and in 11/620 (1.8%) pregnancies before donation

Reisaeter AV, et al. Am J Transplant 2009

Table 3. Preeclampsia in births randomly selected from the Medial Birth Registry of Norway and births in kidney donors, Norway 1967–2002

	Birth Registry \approx 1% of births N = 21 511	Donors		p ¹	p ²
		Pregnancy before N = 620	Pregnancy after N = 106		
Preeclampsia N (%)	666 (3.1)	16 (2.6)	6 (5.7)	0.22	0.026

¹The p-value = Fisher's Exact Test, calculated between all three groups.

²Generalized linear mixed models (GLMM) calculated between before and after donation groups. The method adjusts for some mother's contributing with more than one birth causing dependence within the data. Adjusted for mother's age, birth order and year of birth: p = 0.037, 0.017 and 0.047, respectively.

- Small, but statistically significant increase in the risk of preeclampsia (5.7%) after kidney donation (vs **3.3% in** general population)
- The rate of preeclampsia in the control group was 3.1%

Donors-Pregnancy Minnesota Experience

- Donors from 1963 – 2007
- 2102 women “not taking anti-hypertensive medications” and “normal urinary protein excretion” and non-obese
- 490 pregnancies in 239 donors
- Attempts to contact donors by phone, mailing and through recipient
 - Data through questionnaires and telephoning
 - Not validated through medical records

Donors-Pregnancy Minnesota Experience

- Gestational HTN: 5.7%, **preeclampsia 5.5%: similar to Norwegian experience**, gestational diabetes: 2.7%, full-term birth: 73.7%, prematurity: 7.1% and fetal loss 19.2%
- 239 donors with pregnancies after donation had their renal function assessed about 20 years after donation (13 years after last pregnancy)
- Mean serum creatinine: 1.0 mg/dL (88 μ mol/L), 26% were hypertensive and 9% had proteinuria

Pregnancy and Donors

- Women should be asked about prior gestational complications
- Prior preeclampsia or gestational diabetes should probably be a contraindication to donation, especially if there is a family history of kidney disease
- If feasible, donors should complete child-bearing before donation.
- Young female donors should be counseled about increased risk to future pregnancies
 - Post-donation: about 6% will develop pre-eclampsia during pregnancy

Subgroups of Concern

- Obese donors
- Hypertensive donors
- Strong family history of diabetes or hypertension
- Donors over 60 years

Amsterdam Forum Guidelines

- A **GFR** < 80 ml/min or 2 SD below normal (based on age, gender, and BSA corrected to 1.73 per m²) generally preclude donation
- Patients with a **BP** > 140/90 mmHg by ABPM are generally not acceptable as donors
- Patients with a **BMI** > 35 kg/m² should be discouraged from donating
- **Dyslipidemia** alone does not exclude kidney donation (keep an eye on “Metabolic Syndrome”)

Amsterdam Forum Guidelines

- A 24 h urine **protein** of >300 mg is a contraindication to donation
- Individuals with a history of **diabetes** or fasting blood glucose ≥ 126 mg/dl (7.0 mmol/l) on at least two occasions (or 2 h glucose with OGTT ≥ 200 mg/dl (11.1 mmol/l)) should not donate

Amsterdam Forum Guidelines

- Asymptomatic potential donor+history of a **single stone** may be suitable if:
 - No hypercalcuria, hyperuricemia, or metabolic acidosis
 - No cystinuria or hyperoxaluria
 - No urinary tract infection
 - No evidence of multiple stones or nephrocalcinosis on CT scan

Amsterdam Forum Guidelines

- **Stone** formers who should not donate are:
 - Nephrocalcinosis on X ray or bilateral stone disease
 - Stone types with high recurrence rates, and are difficult to prevent

Living Donation

- Among Caucasian donors without risks for future kidney disease
 - Long life and low risk of ESRD
 - No increased risk of cardiovascular disease
- Much less information about medically complex donors – e.g. obese and hypertensive donors