Long-term Kidney Donor Outcomes

Disclosures

None related to this talk

Outline – Donor outcome concerns

a) Need for follow-up (Even before new data on risks)

b) Historical data

c) New data: what is the difference

c) Where we need to be (my opinion) and what are the barriers

Kidney Transplantation Between Seven Pairs of Identical Twins *

JOSEPH E. MURRAY, M.D., JOHN P. MERRILL, M.D., J. HARTWELL HARRISON, M.D.

From the Surgical and Medical Services of the Peter Bent Brigham Hospital and Harvard Medical School

ANN SURG, 148:343. 1958

Health of Donor. The health of the donor dominates all other considerations. A major operation on a normal person, not for his own benefit, requires a brusque re-evaluation of traditional surgical thought. Is any risk, no matter how slight, ever justified? It would appear that the moral justification is found in the safety and security of the donor as well as in the expected degree of success when there is no other available alternative.

A person with one kidney can have a normal life expectancy with normal renal function; in fact, one in every thousand persons is born with only one kidney, often unknown to himself or his physician. Unilaterality does not produce susceptibility to renal disease; however, when trauma, infection, stone or tumor formation supervene in a solitary kidney, the implications are naturally more grave than if two kidneys are present. Traumatic injury to a solitary kidney, although serious, is not necessarily fatal. The relatively low incidence of renal cancer is not increased by the absence of one kidney.

Public Law 108-216:
Organ Donation and Recovery Improvement Act (ODRIA).
http://www.livingdonorassistance.org/documents/Public%20Law%20108-216_Organ%20Donation%20Act.pdf,

2004

An evaluation of living donation practices and procedures.

Such evaluation shall include an assessment of issues relating to informed consent and the health risks associated with living donation (including possible reduction of long-term effects).

Follow-up for Living Donors

" However, there are some scientific questions regarding the effects of stress on the remaining organ. *There could be subtle medical problems that develop decades after the living donation* that are not known at this time because living donation is a relatively new medical procedure. *To ensure the safety of all living donors, it is critical that the long term result of the effects of living donation are studies further."*

Organdonor.gov

ACOT - 2002

Recommendation 3: That *a database of health outcomes for all live donors be established and funded* through and under the auspices of the U.S. Department of Health and Human Services.

ACOT believes that the *primary purpose of such a registry should be to enable the medical community to define accurately the donor risks and benefits of live organ transplantation* so as to give potential donors an accurate risk assessment.

ACOT

2005 ---- Recommendation 42 – ACOT recommends to the Secretary of Health that the OPTN be asked to expeditiously consider all issues associated with the development of a registry for matching living donors…….*paying particular attention to informed consent and the monitoring of long-term outcomes of the donors*

2007 ---- Recommendation 49 – ACOT recommends that the secretary *take action to ensure that data on the general health status of living donors are collected on a nationwide basis by a centralized entity*. The ACOT recommends that such data be collected, *at a minimum, on an annual basis for a period of 10 years post-donation*.

Living Donor Follow-up: State of the Art and Future Directions, Conference Summary and Recommendations, AJT 11:2561-2568, 2011 (Sept, 20,10 Crystal City, Va)

Sponsored by HRSA, NIH (NIAID), ASTS, AST, CST, NKF, NATCO, TTS, OPTN, Cigna Lifesource transplant Network, Optum Health, Astellas Pharma, Genzyme corporation

- broad representation (~ 120): prior kidney donors, physicians, surgeons, medical ethicists, social scientists, donor coordinators, social workers, independent donor advocates and representatives of payer organizations and the federal government

Reasons to continue systematic collection and reporting of donor outcomes:

1) Donor candidates an their potential recipients need accurate outcomes info on which to base informed consent

(especially related to donor ethnicity and selection criteria)

2) To improve the evaluation process and provide reliable counselling for nontraditional donor candidates

3) Surveillance may identify problems at a time intervention is possible

Living Donor Follow-up: State of the Art and Future Directions, Conference Summary and Recommendations, AJT, 2011

Goals:

(1) review limitations of existing data;

(2) assess and define the need for long-term follow-up;

(3) identify the potential system requirements, infrastructure and costs of long-term follow-up and

(4) explore practical options for development and funding of data collection, metrics and endpoints

Recommendations

Complete Data

a) Peri-operative complications @ 3 mos

b) Long-term CVD, ESRD, mortality (?registry)

c) Long-term to accurately determine rates of a small number of pre-defined end-points related to disease-related and psychosocial disabilities

Intermediate-term outcomes in Subgroups

Donor characteristics: ethnicity, obese, older *and* younger, hypertensive and/or those with history that might impact kidney function (borderline GFR, stones, weight loss to meet criteria, previous history of htn or hyperglycemia)

Donation characteristics – Nondirected donors, paired exchanges, chains

Subgroup Studies

Medical outcomes - renal function, proteinuria, blood pressure, development of diabetes and cardiovascular disease

Psychosocial and socioeconomic outcomes

- impact of element of informed consent on outcome
- long-term health-related quality of life
- long-term financial consequences
- identification of psychosocial concerns related to participation in exchange programs or as nondirected donors

Why are there Concerns about the long-term risk of living with 1 kidney?

Removal of 1 kidney is associated with the immediate loss of about 20-30% of renal function.

In the general population,

a) mild decrease in GFR is associated with increased risk of cardiovascular disease and death.

b) ↓ GFR has been associated with increased risk for development of ESRD

But - in the general population, ↓ GFR is associated with kidney disease or aging

Problems with studying long-term donor outcomes:

1) The relatively short time since large numbers of living donor transplants were first done;

2) The relatively small numbers of living donor transplants done in early years;

3) The wide age range (from 18 to >70 years old) of donors.

4) Difficulty finding a matched control population.

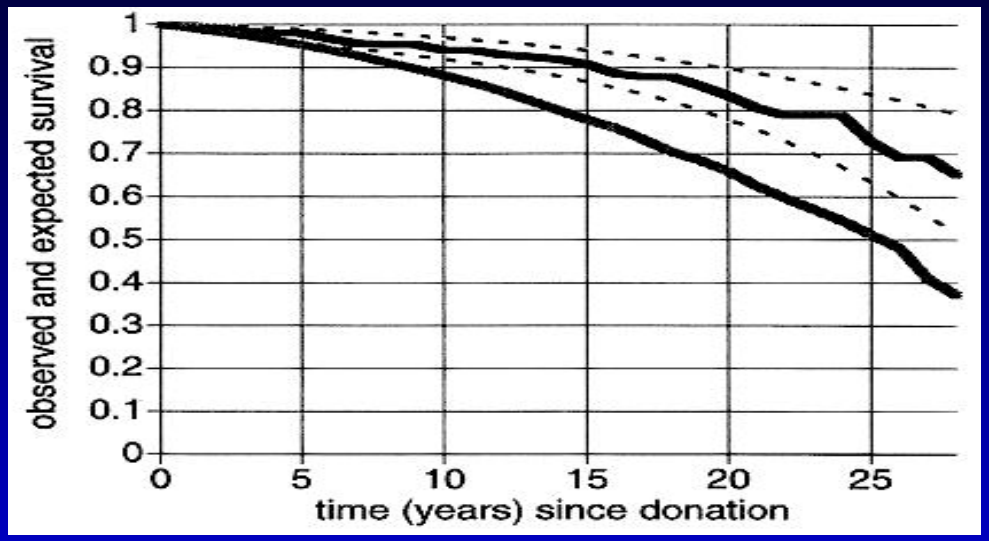
Medical Outcomes Historical Data (Pre-2013)

1) Survival

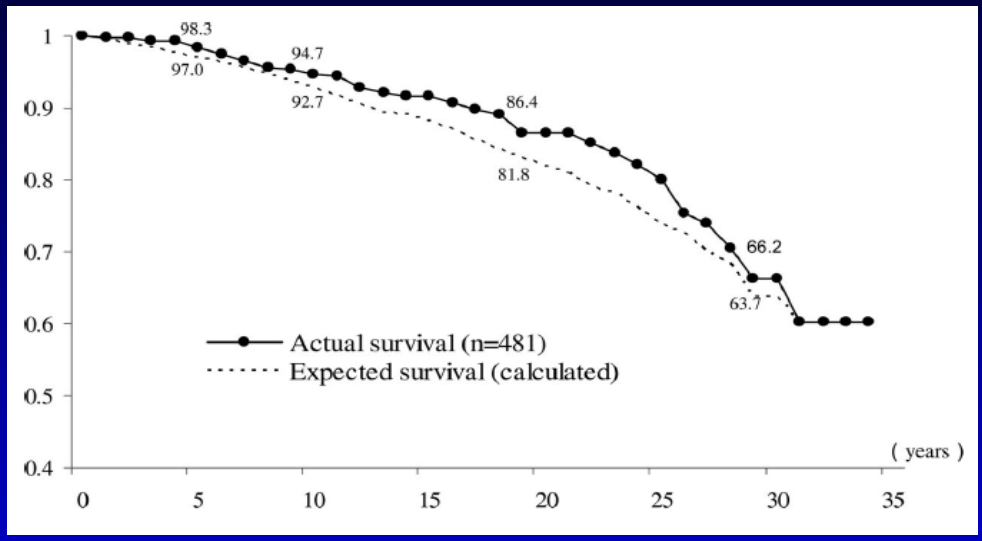
Donors compared to the *general population*

Country	Setting	n	f/u
Sweden[1]	Single center	430	1-35
USA[2]	Single center	3,698	1-45
Japan[3]	Single center	481	1-35
Norway[4]	Single (national) center	2,269	1-48
Fournier[5]	Single center	310	1-53

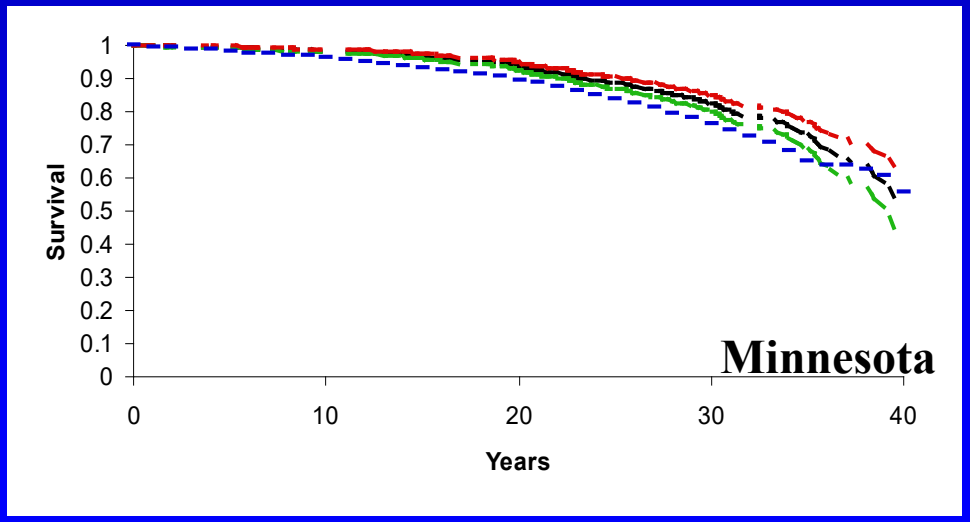
Comparable Survival of Donors vs Gen Pop Worldwide



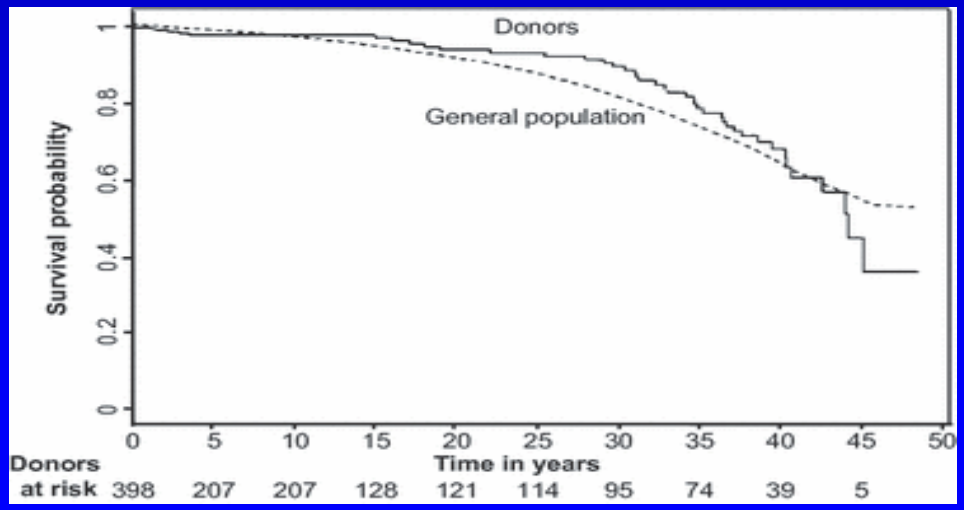
Sweden



Japan



Minnesota

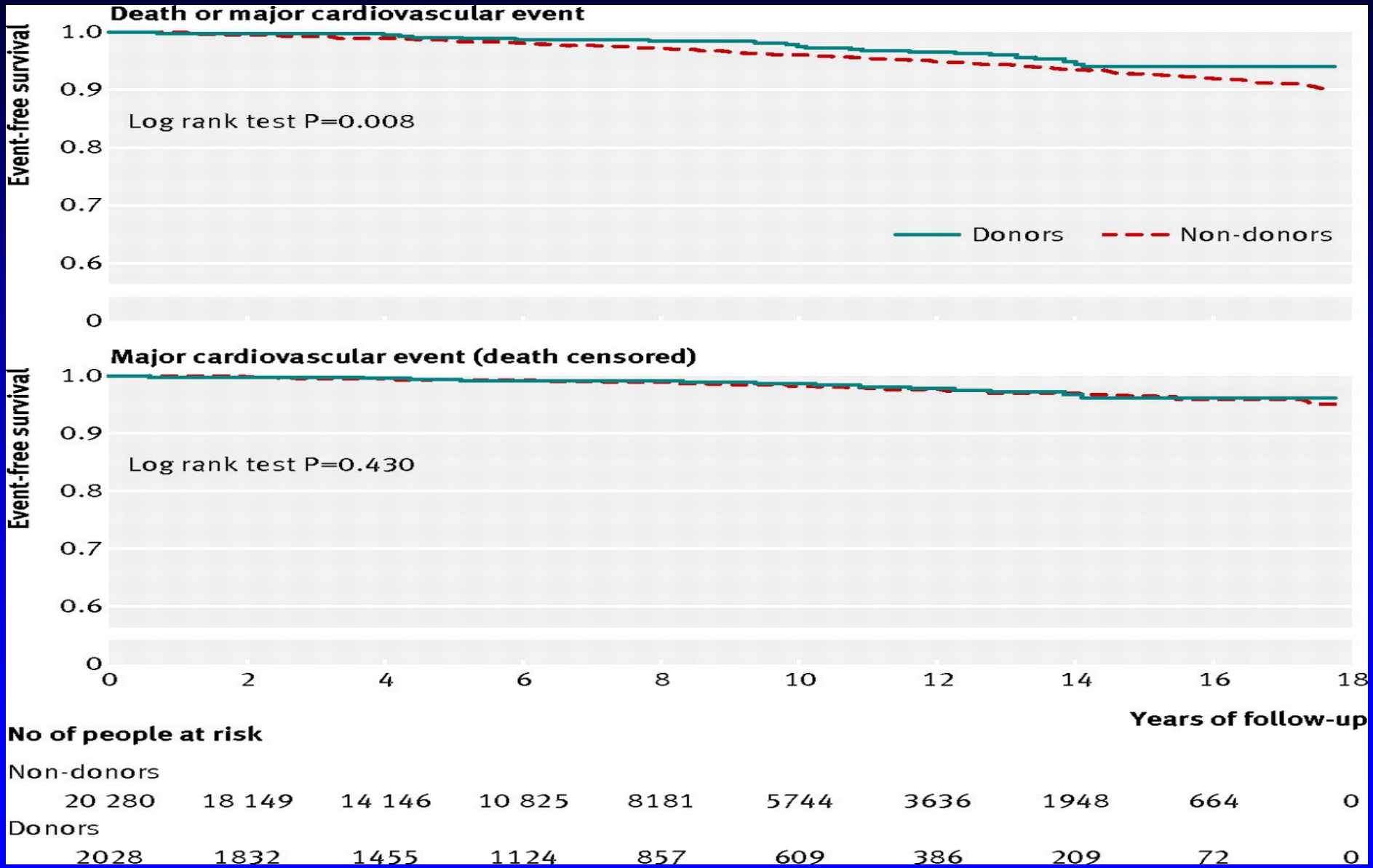


France

Donors Compared to *Healthy Population Controls*

Country	Setting	n	f/u
USA[6]	National registry	80, 347	*1-15*
Canada[7]	Province (Ontario)	2,028	*1-18*

Garg et al, matched cohort



Garg A X et al. BMJ 2012;344:bmj.e1203

Historical Data

2) Kidney Failure

ESRD has been Reported in Donors

But, *No* increase vs *General Population*

1) Sweden – Fehman-Ekholm et al, Transplantation 82: 1646-48, 1996
2) Kasiske et al, Meta-analysis (non-donors and donors) Kid Int 1995
3) Meta-analysis, Garg et al, Kidney International, 70:1801—10, 2006
4) USA – Ibrahim et al, NEJM 360:459-60, 2009
5) USA - Lentine et al, NEJM 36:724-32, 2010
6) France – Fournier et al, Transplant International 25:385-90, 2012

Precursors of ESRD

Proteinuria

Hypertension

Are not increased in long-term donor follow-up studies

b) Postdonation development of type 2 diabetes:

154 former donors; mean time 18±9 yrs post donation

20% had a family hx of Type 2

mean f/u afer diabetes diagnosis = 7.7±7.0 years

- estimated GFR (n=126) = 58.8±16.7 mL/min/1.73m2;

Serial eGFR (n=64); no diff in slope (vs nondiabetic donors)

c) Pregnancy: Increased gestational hypertension and pre-eclampsia: no other impact on mother or baby

Medical Outcomes (2013 -2015)

Matched *Healthy* Controls

Reese et al, Mortality and cardiovascular disease among older live kidney donors, AJT 14:1853, 2014

Studied mortality after donation in *"older" >55 living donors*

- matched 3368 donors with matched healthy nondonors
- median follow-up 8 years
- *no diff in mortality between groups*
- *no diff in mortality or CVD between groups*

2 Recent Studies Suggest ↑ Donor Risk

Mjoen et al, Kidney International, 2013

Muzzale et al, JAMA, 311:579-86, 2014

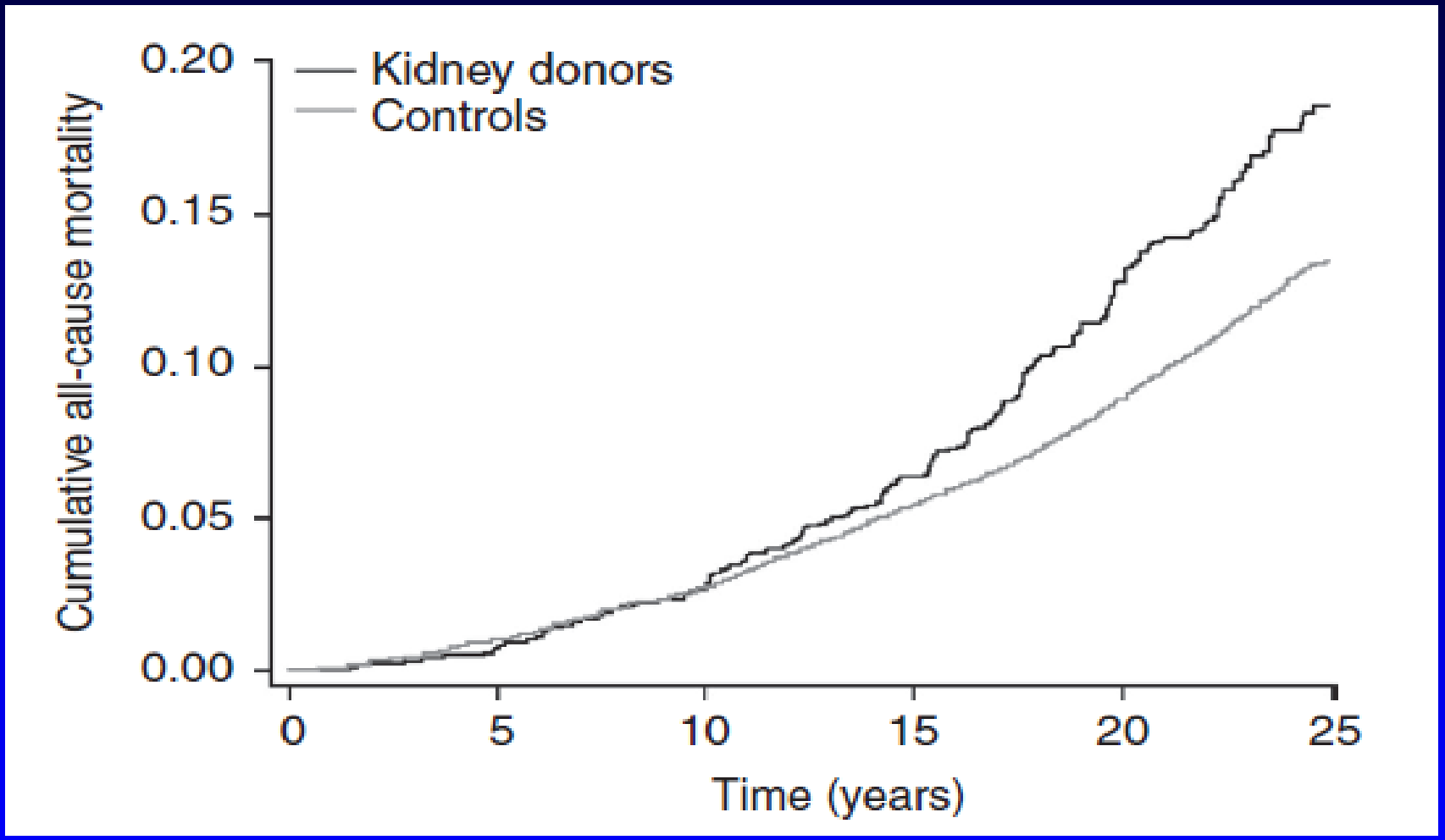
Mjoen et al, Long-term Risks for Kidney Donors, KI: Nov, 2013 (epub)

1901 donors studied (single center/national registry)

Compared to 32,621healthy controls selected from the Health Study of Trondelag population study:

Findings

Donors (vs healthy controls) had increased *all-cause mortality, cardiovascular mortality, and ESRD*



Controls are matched to donors for age, sex, systolic blood pressure, body mass index, and smoking status.

ESRD

1901 donors followed

9 developed ESRD (***0.47%***);

- all 9 were 1st degree relatives;

6 had immunologic disease

median time to ESRD – 18.7 yrs

Relative risk of ESRD was 11.4 (vs non donors)

Muzaale et al, Risk of End Stage Renal Disease Following Live Kidney Donation, JAMA, 311:579-588, 2014

96,217 donors studied (USRDS): 99 (0.1%) with ESRD
(mean - 8.6 yrs)

compared to 9634 controls from NHANES cohort:

17 (0.18%) with ESRD

Matching donors to controls, estimated risk of kidney disease was 30.8 in per 10,000 in donors vs 3.9 in 10,000 nondonors

Muzaale et al

Lifetime risk of ESRD

Donors:	9/1000
Healthy controls:	1.4/1000
General population:	33/1000

Older (vs younger), Afr Am (vs Caucasians) at highest risk

(note: not related to population controls)

Authors of *both* manuscripts concluded that the absolute risk was low and the main importance of the data was for counselling/informing future donor candidates

There have been numerous criticisms of the data (selection of controls, analyses) --- but both found roughly the same result (re: ESRD)

Criticisms have included:

1) selection of controls (where from; limitation of selection)
2) non contemporary cohorts and differences in length of f/u
3) disease rate in controls may have been underestimated
4) in US study, overall ESRD was lower in donors than controls; and cause of disease not known
5) with such a small "n" (8/1901 and 99/96,000) estimating risk is hard

Perhaps the Most Important Concern re: Relevance of the Data

In Norway, all 9 donors with ESRD were 1st degree relatives
(disease was immunologic in 6)

In USA – ESRD higher in relatives vs non-relatives (NS)

Skrunes et al, Familial clustering of ESRD in the Norwegian population, cJASN, 2014

Norwegian Population Registry Norwegian Renal Registry (1980)

Individuals with a first-degree relative with ESRD had a **relative risk of ESRD of 7.2** (95% confidence interval, 6.5 to 8.1)

Relative Risk of ESRD

Herditary causes	-- 36 (95% C.I., 30-42)
nonhereditary causes	-- 3.7 (95% C.I., 3.1 to 4.4)
glomerular disease	-- 5.2 (95% C.I., 4.1 to 6.6)
interstitial disease	-- 4.7 (95% CI., 3.1 to 7.3),
diabetic nephropathy	-- 2.6 (95% C.I., 1.6 to 4.1), ;
hypertensive nephrosclerosis	-- 2.6 (95% C.I., 1.6 to 4.1).
nonhereditary parenchymal renal disease	-- 3.8 (95%., 3.1 to 4.7).
Other	-- 1.6 (0.8 to 3.1)

It may be that all the increased risk reported is related to:

- being a donor, or being a relative who is a donor

Steiner et al, AJT, 14:538-44

Donor loses 30% renal function as a result of nephrectomy

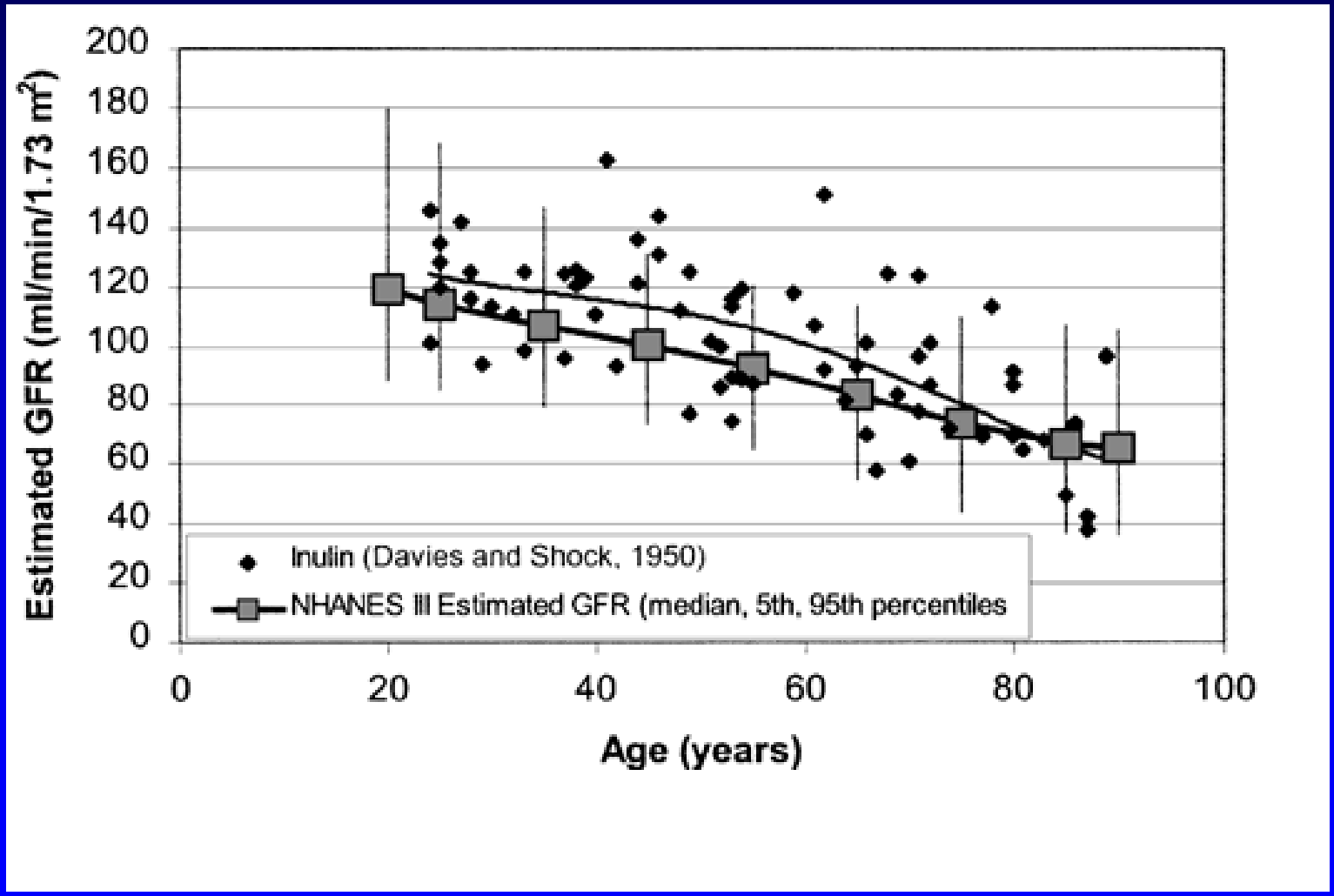
Therefore has less reserve.

All else being equal, a donor will have a low GFR years before a matched non donor. Therefore with normal loss of GFR or with development of disease, a donor has increased risk.

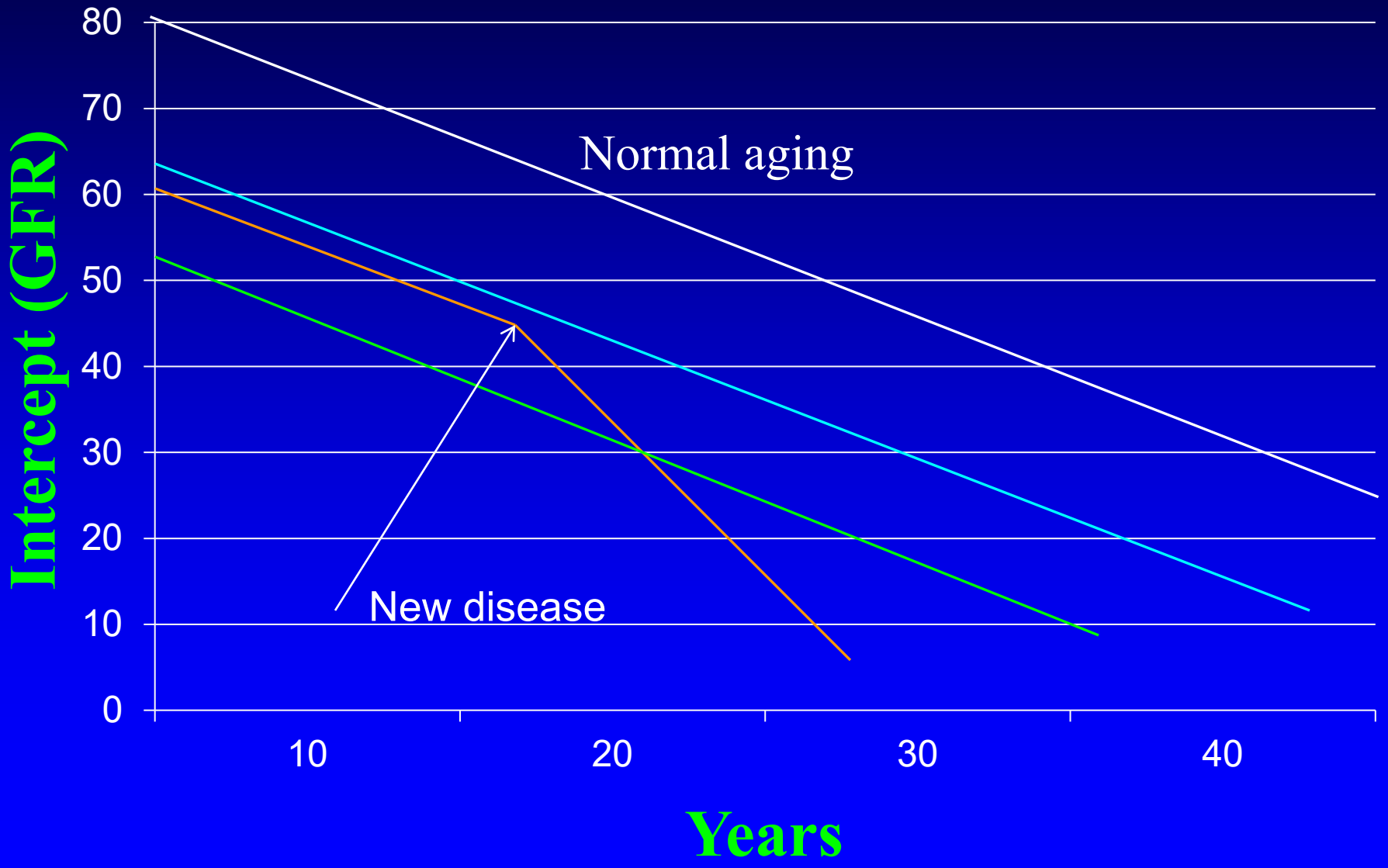
The majority of kidney disease begins in middle age:

- normal young donors are at increased long-term risk than normal older donors
- low normal GFR is a risk for ESRD when kidney disease starts

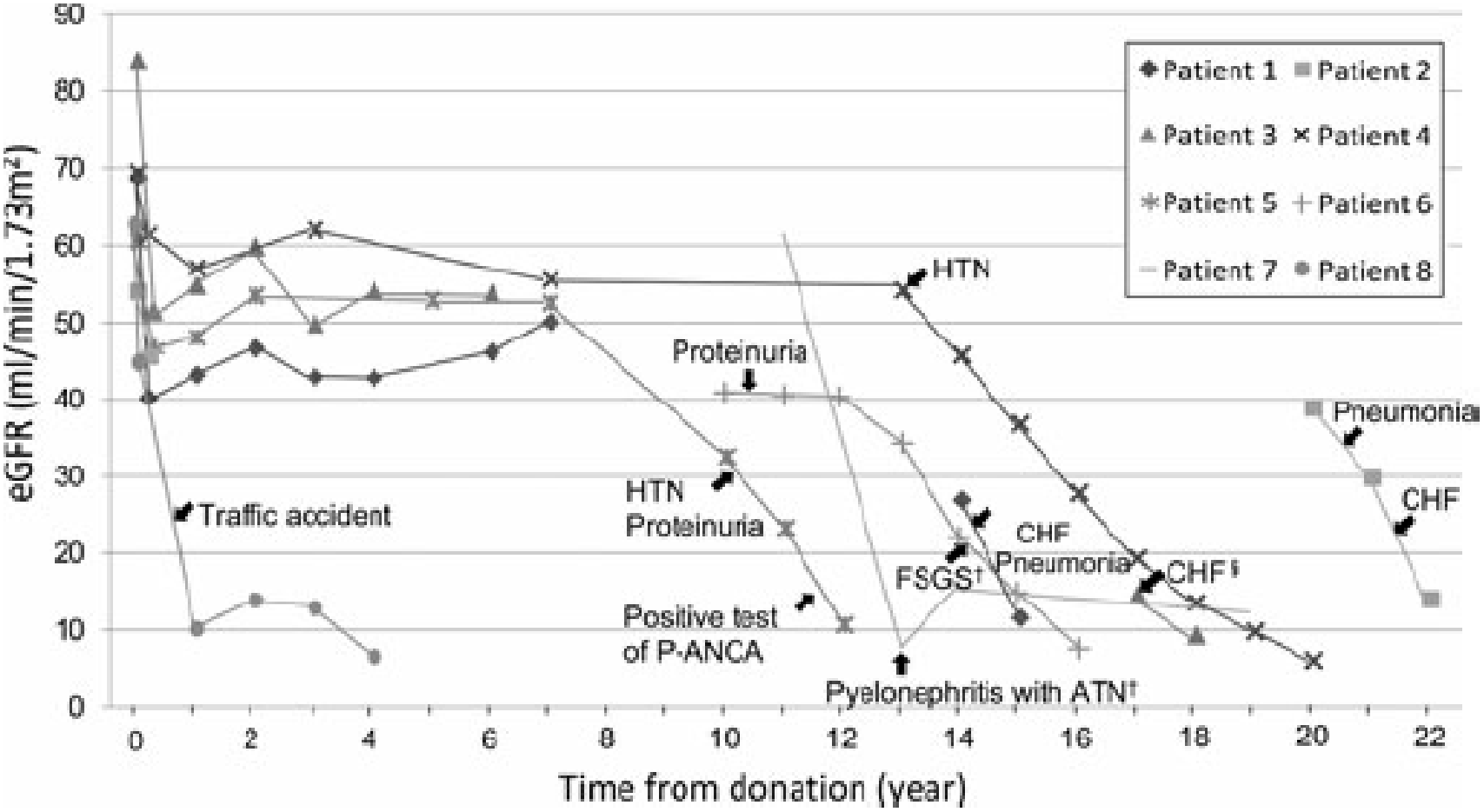
Normal GFR vs Age (NHANES DATA)



Intercept vs Slope



Kido et al, How do living kidney donors develop ESRD? AJT 11:2154-9, 2009



Psychosocial Outcomes

All Outcomes vs Population Controls
(not healthy selected controls)

Health-Related Quality of Life

Numerous studies using Sf-36 or other measures

- each shows that, on average, former donors have the same or better QoL than age and gender matched gen population controls
- *however, in each study there is a proportion of donors (4%-20%) that report decreased QoL*. Often related to poor recipient of graft survival or to donation-related complications

Depression

- lower rate of depression in donors than gen population
- *however, some donors are depressed and relate their depression to the donation experience*

Financial Burden (1137 donors, 2003 and 2014)

Burden ranked from 0 to 10 (none - extreme)

27% ranked their financial burden as ≥5; 8% ≥8.

Burden was ranked ≥5 by 28% of those employed;

10% homemakers;

12% retired;

0% students;

27% unemployed;

25% occupation unknown;

25% with insurance;

37% without.

To cover expenses 36% used money from savings, 24% received a local and/or national grant, 15% borrowed money from family, 7% held a fundraiser, and 5% obtained a bank loan

Limitation to all of this data

Almost all the long-term data, to date, has been provided by a very small number of groups

(single center or registry studies in Europe (Sweden, Netherlands, France), Japan and the USA; registry [big data] in Canada and the USA)

1) There is little long-term data on the non-Caucasian donor;

2) Donor acceptance criteria have expanded:

- now include selected older donors; donors with hypertension; and obese donors
- age and obesity are operative risk factors
- Htn, obesity and age are risk factors for ESRD

Long-term studies are necessary in these subgroups

Summary

a) Both government and transplant community wants long-term donor outcome data (and ACOT has advised the Secretary that this should be done);

b) Studies, to date have suggested that *most* donors do well but some have medical and/or psychosocial problems related to donation;

c) Today's donors differ from the population that has been studied for long-term outcomes.

Going Forward – What is Needed (personal opinion)

A) Ongoing extended follow-up (tracking) (medical and psychosocial) of current populations (with appropriate controls) to clearly define risks associated with donation;**

B) Long-term studies (medical and psychosocial) of additional populations (subgroups) to clearly define risks;**

C) Development of a system to evaluate and care for donors having developed medical, psychosocial, problems related to donation.

D) Development of a system so that donation is not a financial burden

** See consensus conf recommendations - AJT 11:2561-2568, 2011