Annals of Internal Medicine | Review

Meta-Analysis: Risk for Hypertension in Living Kidney Donors

Neil Boudville, MD; G.V. Ramesh Prasad, MD; Greg Knoll, MD, MSc; Norman Muirhead, MD; Heather Thiessen-Philbrook, MMath; Robert C. Yang, MD; M. Patricia Rosas-Arellano, MD, PhD; Abdulrahman Housawi, MD; and Amit X. Garg, MD, PhD, for the Donor Nephrectomy Outcomes Research (DONOR) Network*

Background: The risk for hypertension after kidney donation remains uncertain.

Purpose: To see whether normotensive adults who donate a kidney develop higher blood pressure and risk for hypertension compared with nondonor adults acting as control participants.

Data Sources: MEDLINE, EMBASE, and Science Citation Index were searched from 1966 until November 2005 for articles published in any language. Reference lists of pertinent articles were also reviewed.

Study Selection: The authors selected studies involving 10 or more healthy normotensive adults who donated a kidney and in whom blood pressure was assessed at least 1 year later.

Data Extraction: Two reviewers independently abstracted data on study and donor characteristics, blood pressure measurements, outcomes, and prognostic features. Comparison data were abstracted from donor studies with control participants. Thirty primary authors provided additional data.

Data Synthesis: Forty-eight studies from 28 countries followed a total of 5145 donors. Before surgery, the average age of donors was 41 years, the average systolic blood pressure was 121 mm Hg, and the average diastolic blood pressure was 77 mm Hg for all studies. In controlled studies in which the average follow-up was at least 5 years after donation (range, 6 to 13 years), blood pressure was 5 mm Hg higher in donors than in control participants (the weighted mean for systolic blood pressure using 4 studies involving 157 donors and 128 control participants was 6 mm Hg [95% CI, 2 to 11 mm Hg], and the weighted mean for diastolic blood pressure using 5 studies involving 196 donors and 161 control participants was 4 mm Hg [CI, 1 to 7 mm Hg]). There was statistical heterogeneity among the 6 controlled studies that assessed hypertension; an increase in risk was noted in 1 study (relative risk, 1.9 [CI, 1.1 to 3.5]).

Limitations: Most studies were retrospective and did not include control groups that were assembled and followed along with donors. Approximately one third of the donors had incomplete follow-up information.

Conclusions: On the basis of the limited studies conducted to date, kidney donors may have a 5–mm Hg increase in blood pressure within 5 to 10 years after donation over that anticipated with normal aging. Future controlled, prospective studies with long periods of follow-up will better delineate safety and identify donors at lowest risk for long-term morbidity.

Ann Intern Med. 2006;145:185-196. www.annals.org

For author affiliations, see end of text.

*For a list of DONOR Network Investigators, see the Appendix, available at www.annals.org.

Despite its advantages, living kidney donation remains a complex ethical, moral, and medical issue. Living kidney donation is practiced with the expectation that the risk for minimal short-term and long-term harm for the donor is outweighed by the psychological benefits of altruism and improved recipient health. The short-term complications of living donation are well established (1). However, the long-term risk for hypertension remains uncertain. A better understanding of this risk is central to donor selection and consent. This knowledge guides health policy on reimbursing costs of antihypertensive medication and the need for ongoing surveillance of the more than 80 000 persons who have donated a kidney (2). The primary question of this review was whether normotensive adults who donate a kidney develop higher blood pressure and risk for hypertension compared with healthy nondonors acting as control participants. Reasons for considerably different estimates in the literature were also explored in meta-regression.

Methods

Study Selection

We included studies in any language that examined 10 or more healthy normotensive adults who donated a kidney and had their blood pressure assessed at least 1 year later. We compiled citations from MEDLINE and EMBASE bibliographic databases from 1966 through November 2005. An experienced librarian developed the search strategies using sensitive terms for identifying clinical prognostic studies of living kidney donors (3, 4). We pilot-tested the search strategies and modified them to ensure that they identified known eligible articles. The final strategies included the terms *living donors, cohort studies, course, longitudinal studies, hypertension,* and *blood pressure*. We also compiled citations from information provided by primary study authors, the Science Citation Index, the "Related Articles" feature on PubMed, reference lists of previous

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Context

Does kidney donation increase a person's risk for hypertension?

Contribution

This review found 10 studies that compared blood pressure between kidney donors and healthy adults with similar age, sex, and ethnicity. Studies suggested that within 5 to 10 years of donation, kidney donors may have about a 5–mm Hg increase in blood pressure over that anticipated with normal aging.

Cautions

Actual risks for hypertension were unclear because studies did not define hypertension uniformly and had incomplete follow-up information on many donors.

Implications

We need large, prospective, controlled studies with prolonged follow-up to better inform potential kidney donors of long-term risks associated with donation.

—The Editors

reviews (5, 6), and reference lists of all studies included in our review. All citations were downloaded into Reference Manager, version 10.0 (Thomson ISI Research-Soft, Philadelphia, Pennsylvania).

Pairs of reviewers independently evaluated the eligibility of each citation, and the full-text article was retrieved if either reviewer considered the citation potentially relevant. For all English-language publications, pairs of reviewers independently evaluated the eligibility of the full-text article; disagreements were resolved by a third reviewer. With the help of translators, a single reviewer evaluated the eligibility of all non–English-language full-text articles. When data from the same group of donors were described in multiple publications, we reviewed all of the publications and cited the most representative one.

Data Abstraction

Pairs of reviewers independently abstracted the following data from all English-language studies meeting eligibility criteria: setting, methods, donor characteristics, control group characteristics, prognostic features, and hypertension outcomes. Disagreements were resolved by a third reviewer. For Czechoslovakian, Dutch, French, German, Italian, Japanese, Norwegian, Serbo-Croatian, and Spanish articles, data were abstracted by a single reviewer with the help of a translator. We attempted to contact primary authors of all included studies to confirm data and obtain missing data.

Statistical Analysis

Reviewer agreement on study eligibility was quantified by using the κ statistic. Variance estimates for changes in blood pressure before and after donation were not reported in most studies. If not reported, variance estimates were derived from t-statistics when available. Otherwise, variance estimates were calculated with

$$SE_{\Delta} = \sqrt{SE_{pre}^2 + SE_{post}^2 - (2 \times \rho_{\Delta} \times SE_{pre} \times SE_{post})},$$

where ρ_{Δ} represents the correlation between the blood pressure measurements before and after donation (7). For the 2 studies that reported predonation, postdonation, and change variance estimates, we calculated average correlation coefficients of 0.92 and 0.84 for systolic blood pressure and diastolic pressure, respectively. To be conservative, we used a correlation of 0.5 to impute missing change variance estimates in the final meta-regression. We performed sensitivity analyses to this choice of correlation, and the results were qualitatively similar.

For this study-level meta-analysis, the Q statistic was used to determine whether between-study heterogeneity was present; a P value less than 0.1 was considered statistically significant. The I^2 statistic was used to quantify the magnitude of heterogeneity, with values of 0% to 30%, 31% to 50%, and greater than 50% representing mild, moderate, and notable heterogeneity, respectively (8). When justified, results were mathematically pooled by using techniques that accounted for within-study and between-study heterogeneity (random-effects method) (9–11).

Reasons for diversity in study results were explored by using univariate and multivariate meta-regressions of donor cohorts: mixed models for continuous outcomes (PROC MIXED procedure, SAS statistical software, SAS Institute, Inc., Cary, North Carolina) and logistic normal random-effects models for binary outcomes (PROC NLMIXED procedure, SAS statistical software, SAS Institute, Inc.). At the study level, the association between the following donor characteristics and outcomes of hypertension, postdonation blood pressure, and change in blood pressure were considered: average age, the proportion of donors who were female, and average predonation blood pressure. Although potential donors vary in race, sex, and age at the time of nephrectomy, all are healthy and are confirmed to have normal blood pressure and renal function through rigorous evaluation. Nonetheless, we hypothesized that similar to the general population, donors would be more likely to develop hypertension if they were older, were male, and had a higher predonation blood pressure. Similarly, features of study methods associated with blood pressure outcomes after donation were considered. In meta-regression, we tested whether the study was conducted prospectively, the proportion of donors lost to follow-up, the duration of follow-up after nephrectomy, and the method by which blood pressure was assessed. For each meta-regression, only studies for which the factor of interest was available were included in the analysis. The explanatory ability of each factor was quantified by the propor-

Table 1. **Characteristics of Living Kidney Donor Studies Examining Blood Pressure Changes and the Incidence of Hypertension***

Study, Year (Reference)†	Primary Location	Donors, *n*	Years of Donation	Prospective Study	Mean Patient Age (Range), *y*‡	Women, %
Mimran et al., 1993 (15)	Montpellier, France	18	NR	Yes	47 (20–62)	56
Yasumura et al., 1988 (16)	Kyoto, Japan	124	1970–1986	No	50 (21–71)	66
Sobh et al., 1989 (17)	Mansoura, Egypt	45	NR	No	26 (22–64)	53
Friedlander et al., 1988 (18)	Iowa City, Iowa	12	1980–1985	Yes	36 (19–61)	75
Kostakis et al., 1997 (19)	Athens, Greece	255	1986–1996	No	59 (24–82)	74
Beekman et al., 1994 (20)	Leiden, the Netherlands	47	1981–1988	Yes	35 (20–66)	49
Tondo et al., 1998 (21)	Parma, Italy	10	1986–1996	No	46 (NR)	30
Hida et al., 1982 (22)	Bohseidai, Japan	34	1976–1981	Yes	55 (24–66)	59
Rizvi et al., 2005 (23)	Karachi, Pakistan	736	1986–2003	No	33 (NR)	50
Thiel, 1998 (24)	Basel, Switzerland	181	1993–1997	Yes	48 (25–72)	NR
Abomelha et al., 1993 (25)	Riyadh, Saudi Arabia	70	1979–1989	Yes	31 (18–58)	29
Liu et al., 1992 (26)	St. Leonards, Australia	17	NR	No	48 (27–61)	76
Siebels et al., 2003 (27)	Munich, Germany	122	1994–2001	Yes	51 (21–77)	80
Basseri et al., 1995 (28)	Tehran, Iran	87	NR	No	32 (17–58)	43
Enger, 1973 (29)	Oslo, Norway	13	1963–1971	Yes	48 (29–65)	69
Ghahramani et al., 1999 (30)	Shiraz, Iran	136	1988–1997	Yes	34 (NR)	NR
Mendoza et al., 1987 (31)	Mexico City, Mexico	152	1968–1985	No	26 (NR)	57
Liounis et al., 1988 (32)	Sydney, Australia	39	1975–1986	No	37 (21–52)	72
Gonzalez et al., 1989 (33)	New York, New York	25	1976–1987	No	36 (20–58)	68
Fourcade et al., 2002 (34)	Lyon, France	99	1967–1994	No	37 (18–57)	54
Dunn et al., 1986 (35)	Nashville, Tennessee	250	1970–1984	Yes	34 (18–67)	44
ter Wee et al., 1994 (36)	Groningen, the Netherlands	15	1983	No	37 (NR)	40
O'Donnell et al., 1986 (37)	Johannesburg, South Africa	33	1966–1984	No	37 (NR)	45
Miller et al., 1985 (38)	New York, New York	47	1984	No	40 (18–60)	68
Rodríguez-Iturbe et al., 1985 (39)	Maracaibo, Venezuela	25	NR	No	NR (20-60)	44
Mareković et al., 1992 (40)	Zagreb, Yugoslavia	50	1973–1990	No	49 (23–69)	34
Prandini et al., 1987 (41)	Bologna, Italy	32	1970–1980	No	42 (22–54)	72
Chen et al., 1992 (42)	Taipei, Taiwan	76	1980–1991	No	44 (18–66)	59
Borchhardt et al., 1996 (43)	Vienna, Austria	22	1966–1994	No	49 (NR)	68
D'Almeida et al., 1996 (44)	Porto Alegre, Brazil	110	1977–1993	No	35 (NR)	NR
Gracida et al., 2003 (45)	Mexico City, Mexico	628	1992–2001	Yes	35 (18–64)	49
Schostak et al., 2004 (46)	Berlin, Germany	53	1974–2002	No	47 (NR)	56
Horcickova et al., 2002 (47)	Prague, Czech Republic	93	1966–1999	No	49 (26–69)	68
Lumsdaine et al., 2003 (48)	Edinburgh, United Kingdom	47	1986–2000	No	NR (NR)	NR
Wiesel et al., 1997 (49)	Heidelberg, Germany	67	1967–1995	No	NR (NR)	NR
Najarian et al., 1992 (50)	Minneapolis, Minnesota	472	1963–1980	No	34 (18–68)	69
Toronyi et al., 1998 (51)	Budapest, Hungary	30	1973–1996	No	NR (NR)	83
Haberal et al., 1998 (52)	Ankara, Turkey	102	1975–1996	No	41 (21–65)	56
Undurraga et al., 1998 (53)	Santiago, Chile	74	NR	No	39 (NR)	73
Talseth et al., 1986 (54)	Oslo, Norway	70	1969–1974	No	46 (33–55)	47
Eberhard et al., 1997 (55)	Hannover, Germany	29	1973–1990	No	NR (NR)	76
Fehrman-Ekholm et al., 2001 (56)	Stockholm, Sweden	348	1964–1995	No	49 (22–76)	74
Williams et al., 1986 (57)	Philadelphia, Pennsylvania	38	NR	No	39 (19–59)	68
Watnick et al., 1988 (58)	New Haven, Connecticut	29	1969–1978	No	NR (NR)	45
Mathillas et al., 1988 (59)	Göteborg, Sweden	46	1965–1973	No	46 (23–70)	57
Saran et al., 1997 (60)	Newcastle, United Kingdom	47	1963–1982	No	NR (NR)	51
Iglesias-Márquez et al., 2001 (61)	San Juan, Puerto Rico	20	1977–1980	No	41 (NR)	60
Goldfarb et al., 2001 (62)	Cleveland, Ohio	70	1963–1975	No	40 (19–57)	59

* NR = not reported.
† Studies are arranged by the average number of years after donation.
‡ Age is reported at the time of donation.

Table 2. **Studies of Living Kidney Donors Examining Blood Pressure Changes and the Incidence of Hypertension***

Study, Year (Reference)†	Predonation		Donors Lost to Follow-up, %	Mean Years after Donation (Range)	Postdonation				Change	
	Mean Systolic Blood Pressure (SD), *mm Hg*‡	Mean Diastolic Blood Pressure (SD), *mm Hg*‡			Mean Systolic Blood Pressure (SD), *mm Hg*‡	Mean Diastolic Blood Pressure (SD), *mm Hg*‡	Incidence of Hypertension, %‡	Use of Antihypertensive Medications, %§	Mean Systolic Blood Pressure (SD), *mm Hg*‡	Mean Diastolic Blood Pressure (SD), *mm Hg*‡
Mimran et al., 1993 (15)	123 (11)	74 (8)	NR	1.2 (NR)	130 (16)	81 (11)	22	NR	7 (4)‖	6 (2)‖
Yasumura et al., 1988 (16)	NR	NR	49	1.5 (NR)	NR	NR	0	2	NR	NR
Sobh et al., 1989 (17)	NR	85 (10)	NR	1.9 (1 to 10)	NR	82 (10)	7	NR	NR	−3 (10)¶
Friedlander et al., 1988 (18)	118 (9)	76 (7)	46	2 (1 to 3)	125 (10)	80 (7)	45	NR	7 (9)¶	4 (6)¶
Kostakis et al., 1997 (19)	NR	NR	24	2 (NR)	NR	NR	0	NR	NR	NR
Beekman et al., 1994 (20)	NR	NR	0	2 (NR)	NR	NR	0	NR	NR	NR
Tondo et al., 1998 (21)	NR	NR	0	2.1 (0.2 to 5)	NR	NR	0	NR	NR	NR
Hida et al., 1982 (22)	127 (15)	76 (13)	0	2.8 (0.5 to 5)	126 (14)	77 (11)	NR	NR	−1 (14)¶	0.2 (12)¶
Rizvi et al., 2005 (23)	126 (13)	79 (9)	40	3 (0.5 to 18)	123 (15)	81 (10)	10	NR	−3 (1)‖	2 (1)‖
Thiel, 1998 (24)	125 (16)	80 (10)	0	3 (NR)	129 (16)	81 (9)	2	NR	4 (16)¶	1 (10)¶
Abomelha et al., 1993 (25)	NR	NR	64	3.1 (1 to 10)	NR	NR	3	NR	NR	NR
Liu et al., 1992 (26)	NR	NR	NR	3.1 (0.1 to 10)	124 (16)	78 (33)	NR	NR	NR	NR
Siebels et al., 2003 (27)	NR	NR	24	3.2 (0 to 5)	118 (NR)	70 (NR)	2	7	NR	NR
Basseri et al., 1995 (28)	108 (NR)	66 (NR)	0	3.2 (1 to 8)	110 (NR)	68 (NR)	0	0	2 (NR)	2 (NR)
Enger, 1973 (29)	NR	NR	0	3.5 (0.5 to 8)	NR	NR	8	8	NR	NR
Ghahramani et al., 1999 (30)	NR	NR	21	3.6 (0.3 to 9)	NR	NR	24	NR	NR	NR
Mendoza et al., 1987 (31)	120 (8)	77 (5)	15	3.7 (0.1 to 12)	122 (27)	79 (17)	9	NR	2 (24)¶	2 (15)¶
Liounis et al., 1988 (32)	122 (13)	77 (9)	5	3.9 (1 to 11)	125 (26)	81 (10)	19	8	4 (22)¶	4 (10)¶
Gonzalez et al., 1989 (33)	115 (11)	77 (6)	43	4.2 (0.5 to 12)	120 (13)	82 (10)	16	NR	5 (12)¶	5 (2)‖
Fourcade et al., 2002 (34)	116 (13)	71 (9)	0	4.3 (0.1 to 19)	116 (12)	68 (10)	2	NR	0 (7)	−3 (8)
Dunn et al., 1986 (35)	119 (NR)	76 (NR)	18	4.4 (0.5 to 15)	122 (15)	77 (9)	14	NR	3 (NR)	1 (NR)
ter Wee et al., 1994 (36)	NR	NR	38	4.9 (2 to 13)	NR	NR	0	0	NR	NR
O'Donnell et al., 1986 (37)	NR	75 (5)	62	5.8 (3 to 18)	NR	83 (10)	33	3	NR	8 (2)‖
Miller et al., 1985 (38)	NR	NR	77	6 (2 to 15)	NR	NR	33	7	NR	NR
Rodríguez-Iturbe et al., 1985 (39)	NR	NR	7	6 (1 to 11)	134 (20)	80 (10)	16	NR	NR	NR
Mareković et al., 1992 (40)	107 (8)	79 (8)	NR	6.1 (1 to 15)	135 (13)	89 (8)	10	NR	28 (12)¶	10 (8)¶
Prandini et al., 1987 (41)	NR	NR	22	6.2 (5 to 17)	119 (10)	75 (7)	0	NR	NR	NR
Chen et al., 1992 (42)	119 (16)	74 (10)	0	6.4 (NR)	118 (14)	78 (11)	10	NR	−1 (15)¶	4 (11)¶
Borchhardt et al., 1996 (43)	NR	NR	NR	6.4 (0.7 to 24)	134 (8)	86 (4)	23	5	NR	NR
D'Almeida et al., 1996 (44)	NR	NR	67	6.6 (1 to 14)	NR	NR	14	NR	NR	NR
Gracida et al., 2003 (45)	NR	NR	0	6.7 (0.5 to 10)	NR	NR	1	NR	NR	NR
Schostak et al., 2004 (46)	NR	NR	48	6.9 (NR)	NR	NR	36	30	NR	NR
Horcickova et al., 2002 (47)	NR	NR	NR	7.1 (0.2 to 31)	NR	NR	27	NR	NR	NR
Lumsdaine et al., 2003 (48)	NR	NR	69	7.1 (NR)	NR	NR	17	4	NR	NR
Wiesel et al., 1997 (49)	NR	NR	43	8 (NR)	NR	NR	27	NR	NR	NR
Najarian et al., 1992 (50)	117 (12)	73 (11)	25	8.3 (1 to 19)	122 (16)	76 (4)	7	NR	5 (14)¶	3 (8)¶
Toronyi et al., 1998 (51)	NR	NR	62	8.9 (NR)	NR	NR	17	17	NR	NR
Haberal et al., 1998 (52)	132 (21)	NR	32	10.2 (0.7 to 22)	140 (21)	NR	9	9	8 (21)¶	NR
Undurraga et al., 1998 (53)	119 (14)	76 (9)	NR	10.9 (1 to 21)	130 (20)	88 (13)	49	NR	11 (7)	12 (5)
Talseth et al., 1986 (54)	132 (10)	82 (7)	5	11 (10 to 12)	140 (17)	90 (7)	8	3	8 (3)‖	8 (2)‖
Eberhard et al., 1997 (55)	NR	NR	79	11.1 (5 to 20)	121 (12)	77 (7)	29	17	NR	NR
Fehrman-Ekholm et al., 2001 (56)	NR	NR	13	12.5 (2 to 33)	NR	NR	36	15	NR	NR
Williams et al., 1986 (57)	NR	NR	32	12.6 (10 to 18)	133 (21)	83 (12)	47	NR	NR	NR
Watnick et al., 1988 (58)	NR	NR	19	13 (9 to 18)	136 (36)	84 (18)	62	10	NR	NR
Mathillas et al., 1988 (59)	NR	NR	13	14.9 (10 to 20)	NR	NR	39	23	NR	NR

Table 2—**Continued**

Study, Year (Reference)†	Predonation		Donors Lost to Follow-up, %	Mean Years after Donation (Range)	Postdonation				Change	
	Mean Systolic Blood Pressure (SD), *mm Hg*‡	Mean Diastolic Blood Pressure (SD), *mm Hg*‡			Mean Systolic Blood Pressure (SD), *mm Hg*‡	Mean Diastolic Blood Pressure (SD), *mm Hg*‡	Incidence of Hypertension, %‡	Use of Antihypertensive Medications, %§	Mean Systolic Blood Pressure (SD), *mm Hg*‡	Mean Diastolic Blood Pressure (SD), *mm Hg*‡
Saran et al., 1997 (60)	NR	NR	21	19.6 (13 to 31)	NR	NR	74	28	NR	NR
Iglesias-Márquez et al., 2001 (61)	NR	NR	NR	20 (NR)	NR	NR	25	NR	NR	NR
Goldfarb et al., 2001 (62)	123 (12)	79 (7)	47	25 (20 to 32)	136 (19)	79 (9)	48	6	13 (5)‖	0 (8)¶

* NR = not reported.
† Studies are arranged by the average number of years after donation.
‡ Definitions of hypertension and a summary of various methods to assess blood pressure are presented in the Results section.
§ Percentage use of antihypertensive medications after donation is reported for the number of donors in each study.
‖ Variance estimates were derived from *t*-statistics.
¶ Variance estimates were imputed by using the formula as described in the Statistical Analysis section.

tion of between-study variability on the logit scale for binary outcomes and the proportion of between-study variability for continuous outcomes (11). A 2-tailed *P* value of 0.05 or less was considered statistically significant for binary outcomes, whereas for continuous outcomes, statistical significance was inferred by the proportion of variability explained by the factor and from the size of residual variance (11). Best-fit lines in meta-regression graphs were generated by generalized estimating equations (SAS procedure, PROC GENMOD, SAS statistical software) (12, 13). The generalized estimating equation models used estimates from the meta-regression models as the input values and were weighted by the estimated variances. An exchangeable correlation matrix was assumed for all such models. For models of binary outcomes, a binomial distribution with the logit link was used; for models of continuous outcomes, a normal distribution with the identity link was used. The 95% CI for each best-fit meta-regression line was computed as

$$g^{-1}(x_j' \hat{\beta} \pm z_{1-\alpha/2}\sigma_x),$$

where g is the link function, x_j is the vector of covariates, z is the percentile of the normal distribution, and σ_x is the estimated standard error of the linear predictor. The variance estimate of the linear predictor was calculated as

$$\sigma_x^2 = x_j' \Sigma x_j,$$

where Σ is the empirical covariance matrix. The number of studies comparing donors with control participants was small and precluded meta-regression of these results. All analyses were conducted using SAS, version 8.02 (SAS Institute Inc.), and RevMan, version 4.2 (Cochrane Collaboration, Oxford, United Kingdom). Results were graphed in R 2.0.1 (R Foundation for Statistical Computing, Vienna, Austria).

Role of the Funding Sources

This review was supported by the London Multi-Organ Transplant Program, the Canadian Institutes of Health Research, the Physicians Services Incorporated Foundation, and the Canadian Council for Donation and Transplantation. Dr. Garg was supported by a Canadian Institutes of Health Research Clinician Scientist Award. Dr. Yang was supported by a Biomedical Fellowship from the Kidney Foundation of Canada. The study sponsors had no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

RESULTS

We screened 2886 citations and retrieved and evaluated the eligibility of 262 full-text articles. In addition to excluding studies ineligible for our review, we excluded 1 study that only reported mean arterial pressure in the absence of systolic blood pressure, diastolic blood pressure, or hypertension results (14). Some study cohorts also contained a substantial number of extended-criteria donors with hypertension, proteinuria, or a glomerular filtration rate of less than 80 mL/min per 1.73 m^2 before surgery and did not separate reported outcomes from healthy donors. Because this review focused on risk for hypertension in healthy donors, such studies were also considered ineligible. The chance-corrected agreement was good between 2 independent reviewers who evaluated study eligibility (κ = 0.83).

Description of Studies, Methods, Donors, Control Participants, and Outcome Assessment

Forty-eight studies from 28 countries followed a total of 5145 donors an average of 7 years after donation (median, 6 years; range, 1 to 25 years) and were published from 1973 to 2005 (15–62). These studies, along with the change in blood pressure after donation and the proportion of donors who developed hypertension, are shown in **Tables 1** and **2**. Most studies were conducted in Europe (46%), followed by North America (21%), Asia (17%), Central or South America (8%), Australia (4%), and Africa (4%). The median number of donors per study was 49,

with the largest cohorts following 348, 472, 628, and 736 donors, respectively (23, 45, 50, 56). Forty-two primary authors were successfully contacted, and 30 provided additional data or confirmed the accuracy of abstracted data (17–19, 23–27, 31, 33–39, 41–43, 45, 46, 50, 52, 54, 56–58, 60–62).

Of the 48 studies, 23% initially decided to prospectively follow donors in time, 13% had donor outcomes measured at fixed years postdonation, 83% defined how blood pressure was measured, 77% provided a definition of hypertension, and 92% described the total number of donors from which the participating sample was selected. An average of 31% (range, 0% to 79%) of eligible participants were lost to follow-up in each of the 40 studies that reported this variable. Four studies described the characteristics of donors lost to follow-up (57, 58, 60, 62).

Before surgery, the mean donor age was 41 years (range, 26 to 59 years), the mean glomerular filtration rate was 111 mL/min per 1.73 m^2 (range, 91 to 151 mL/min per 1.73 m^2), the mean systolic blood pressure was 121 mm Hg (range, 107 to 132 mm Hg), the mean diastolic blood pressure was 77 mm Hg (range, 66 to 85 mm Hg), and the mean arterial blood pressure was 96 mm Hg (range, 86 to 97 mm Hg) for all studies. Fifty-eight percent of all donors were women. With the exception of 1 study (58), a minority of all donors were black. With the exception of 3 studies (21, 24, 28), almost all donors were genetically related to the recipient: When reported, 50% were parents, 40% were siblings, and 5% were children. Spouses made up only 7% of donors. No study described the use of laparoscopy for kidney removal.

Twelve of the studies also collected data on nondonor control participants to determine whether an increase in blood pressure after donation was above that attributable to normal aging (17, 26, 35, 37–39, 44, 50, 53, 54, 57, 58). Of these, 2 studies either used control participants who were younger than their donors or required control participants to have a normal blood pressure, serum creatinine level, and urine protein level at follow-up as a prerequisite to participate (26, 39). Control participants from these 2 studies were not considered further because doing so could lead to a possible exaggerated risk attributed to donation. In the remaining 10 studies, control participants were healthy volunteers or persons being evaluated as potential donors who were of similar age, sex, race, or height distributions as donors. In all studies, control groups were assembled at the time of donor follow-up evaluation. With the exception of 1 study (38), no studies seemed to follow control participants prospectively from the time of donor surgery.

When reported, blood pressure was usually measured by a transplant center nurse or physician (93%). Other methods included 24-hour ambulatory blood pressure measurement (27, 55) and averaged readings from an oscillometric device (Dinamap, GE Medical Systems Information Technologies, Inc., Milwaukee, Wisconsin) (15). Study definitions of hypertension varied in their combined use of different thresholds of systolic blood pressure, diastolic blood pressure, and use of antihypertensive medication. Thresholds for systolic blood pressure were 130 mm Hg (45, 55), 140 mm Hg (23, 27, 28, 32, 33, 39, 43, 44, 47, 53, 57–60, 62), 150 mm Hg (35), and 160 mm Hg (38, 48), whereas thresholds for diastolic blood pressure were 80 mm Hg (45, 55), 90 mm Hg (15, 23, 24, 27, 28, 32, 33, 35, 37–39, 42, 44, 47, 48, 50, 53, 57, 58, 60, 62), 95 mm Hg (20, 31, 34, 59), 100 mm Hg (17), and 105 mm Hg (54). Fifty-six percent of studies included the use of antihypertensive medications in their reported definition of hypertension.

Risk for Blood Pressure Elevation

Controlled studies were reviewed to determine whether increases in blood pressure after donation were above those attributable to normal aging. There was no statistical heterogeneity between studies in which the average follow-up was at least 5 years (range, 6 to 13 years) after donation, suggesting that these studies could have been theoretically sampled from a common distribution. For systolic blood pressure, there were 4 studies totaling 157 donors and 128 control participants (chi-square, 0.57; $P = 0.90$; $I^2 = 0\%$), and for diastolic blood pressure, there were 5 studies totaling 196 donors and 161 control participants (chi-square, 6.33; $P = 0.176$; $I^2 = 37\%$). Thus, these results were mathematically pooled to improve statistical power for detecting any true latent effect (**Figure 1**). Most of the studies showed a statistically nonsignificant trend of increased blood pressure after donation. Because of the observed variability in blood pressure, none of the primary studies had an adequate sample size to detect a minimum 4–mm Hg increase in blood pressure with at least 80% statistical power. However, the pooled estimates were statistically significant. Approximately 1 decade after transplant surgery, donors had a 5–mm Hg increase in blood pressure (the weighted mean increase for systolic blood pressure was 6 mm Hg [95% CI, 2 to 11 mm Hg], and the weighted mean increase for diastolic blood pressure was 4 mm Hg [CI, 1 to 7 mm Hg]) compared with control participants.

Risk for Hypertension

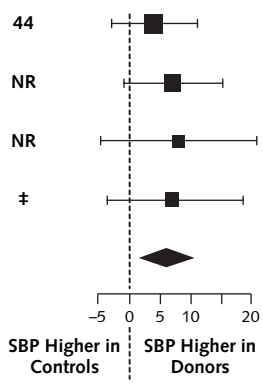
Six studies with average follow-up times ranging from 2 to 13 years assessed the risk for hypertension in 249 donors compared with 161 control participants (**Figure 2**). An increased risk for hypertension after donation was reported in 1 study (relative risk, 1.9 [CI, 1.1 to 3.5]) (58). Because of the observed incidence of hypertension in control participants, none of the primary studies had an adequately sized sample to detect a minimum 1.5-fold increase in risk after donation with at least 80% statistical power. Because of the statistical heterogeneity between the studies, results were not mathematically pooled (chi-square, 10.1; $P = 0.074$; $I^2 = 50\%$).

Predonation Donor Characteristics Associated with Outcomes

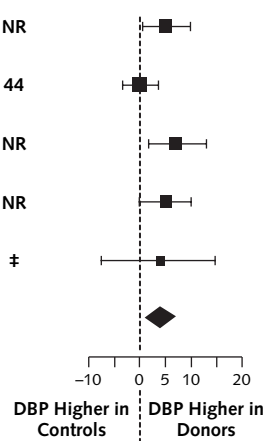
Among healthy donors with normal predonation blood pressure and renal function, the primary studies described many prognostic features associated with increases in blood pressure and hypertension at follow-up. Within donors, many of these features clustered together, with multivariate regression only conducted in a minority of cases. The sample sizes of many these studies were also small, which limited statistical power to detect certain as-

Figure 1. **Meta-analysis of controlled studies of systolic blood pressure (*SBP*) and diastolic blood pressure (*DBP*) at least 5 years after kidney donation.**

Study, Year (Reference)	Donors, after Donation				Control Participants			Mean Difference in SBP (95% CI), *mm Hg*
	Mean Years after Donation, (Range)*	Donors, *n*	Mean Value SBP (SD), *mm Hg*†	Use of Antihypertensive Medications, %	Controls, *n*	Mean Value SBP (SD), *mm Hg*†	Use of Antihypertensive Medications, %	
Najarian et al., 1992 (50)	8 (1–19)	57	134 (15)	32	50	130 (21)	44	4 (–3.1 to 11.1)
Undurraga et al., 1998 (53)	11 (1–21)	30	125 (18)	NR	30	118 (13)	NR	7 (–0.9 to 15.2)
Talselth et al., 1986 (54)	11 (10–12)	32	140 (23)	10	32	132 (29)	NR	8 (–4.8 to 20.8)
Williams et al., 1986 (57)	13 (10–18)	38	136 (25)	‡	16	129 (16)	‡	7 (–3.7 to 18.5)
Pooled estimate		157	133 (6)		128	126 (8)		6 (1.6 to 10.5)

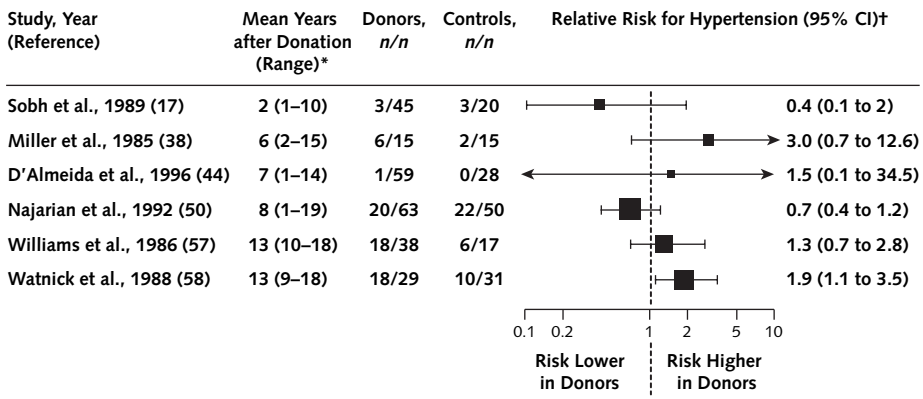


Study, Year (Reference)	Donors, after Donation				Control Participants			Mean Difference in DBP (95% CI), *mm Hg*
	Mean Years after Donation, (Range)*	Donors, *n*	Mean Value DBP (SD), *mm Hg*†	Use of Antihypertensive Medications, %	Controls, *n*	Mean Value DBP (SD), *mm Hg*†	Use of Antihypertensive Medications, %	
O'Donnell et al., 1986 (37)	6 (3–18)	33	83 (10)	3	33	78 (9)	NR	5 (0.4 to 9.7)
Najarian et al., 1992 (50)	8 (1–19)	63	80 (8)	32	50	80 (11)	44	0 (–3.5 to 3.5)
Undurraga et al., 1998 (53)	11 (1–21)	30	86 (13)	NR	30	79 (9)	NR	7 (1.7 to 12.9)
Talselth et al., 1986 (54)	11 (10–12)	32	90 (10)	10	32	85 (10)	NR	5 (0.1 to 9.9)
Williams et al., 1986 (57)	13 (10–18)	38	85 (25)	‡	16	82 (16)	‡	4 (–7.6 to 14.5)
Pooled estimate		196	84 (5)		161	80 (3)		4 (0.9 to 6.7)



The size of each square is inversely proportional to the variability of the study estimate. NR = not reported. *Studies are arranged by the average number of years after donation. †A summary of various methods to assess blood pressure are presented in the Results section. ‡Study reported that a percentage of donors were taking antihypertensive medication but did not quantify the amount.

Figure 2. **Controlled studies of hypertension risk after kidney donation.**



Results were not mathematically pooled because of statistical heterogeneity between studies (chi-square, 10.1; $P = 0.074$; $I^2 = 50\%$). The size of each square is inversely proportional to the variability of the study estimate. *Studies are arranged by the average number of years after donation. †Definitions of hypertension and a summary of various methods to assess blood pressure are presented in the Results section.

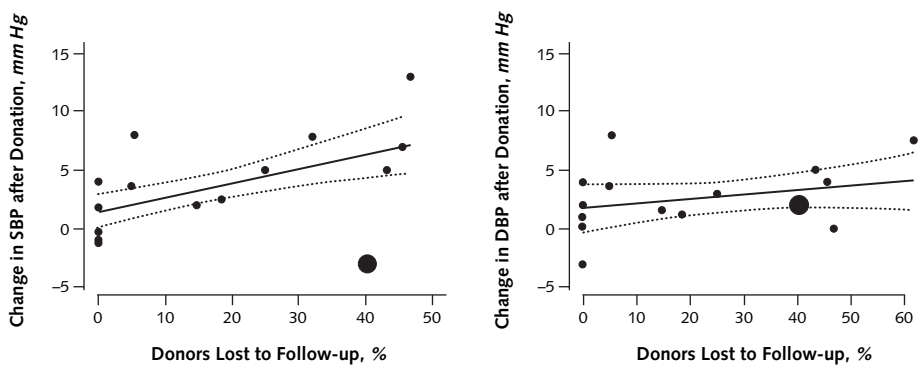
sociations even if they existed. Prognostic features associated with larger increases in blood pressure, higher blood pressure, or hypertension at follow-up included older age at the time of donation, age (usually >60 years) (45, 54, 56, 62, 63), male sex (56, 64), higher predonation blood pressure (15, 54, 63), higher than ideal body weight (45, 63), and a lower predonation glomerular filtration rate (63). Potential associations were described for a family history of hypertension (61) and black compared with white ethnicity (14). No association was shown for increased predonation uric acid level or cholesterol level (45).

In study-level meta-regression, higher average predonation systolic and diastolic blood pressure was associated with higher average postdonation systolic and diastolic blood pressure, respectively (explaining >19% of the between-study variability). Studies with a larger proportion of female donors showed lower average postdonation systolic blood pressures. The proportion of female donors, average donor age at the time of surgery, and average predonation systolic or diastolic blood pressure were not associated with the incidence of hypertension after donation (*P* values ranged from 0.28 to 0.61), nor were they associated with a change in systolic and diastolic blood pressure.

Study Methods Associated with Outcomes

Reported incidence of hypertension varied significantly among all of the donor studies ($P < 0.001$), with

Figure 3. **Studies with a higher proportion of donors lost to follow-up.**



These studies on average showed a higher increase in blood pressure after donation, explaining 72% of the between-study variability for a change in systolic blood pressure (*SBP*) after donation and 59% for a change in diastolic blood pressure (*DBP*) after donation. This association remained statistically significant after adjustment for duration of follow-up. The area of each circle is proportional to the number of donors in each study. Best-fit lines with 95% CIs are from meta-regression. See the Methods section.

differences in follow-up time after nephrectomy only accounting for 42% of the between-study variability. Studies with a higher proportion of donors lost to follow-up showed higher increases in blood pressure after donation, explaining more than 59% of the between-study variability (**Figure 3**). This association remained statistically significant after adjustment for duration of follow-up after donation. Neither the manner in which blood pressure was assessed nor whether the study was conducted prospectively was associated with hypertension outcomes ($P = 0.119$ and $P = 0.67$, respectively).

Discussion

Forty-eight studies of living donors varied greatly in methodologic rigor, methods of blood pressure assessment, and conclusions about whether donation increases blood pressure and the subsequent risk for hypertension. To develop consensus, we mathematically pooled results from a subset of small inconclusive studies that compared blood pressure in donors with that in nondonor control participants. In this meta-analysis, donating a kidney increased blood pressure by 5 mm Hg above that anticipated with normal aging.

Strengths and Weaknesses of This Review

The current study extends a previous quantitative review (5) in several ways. We identified 35 new articles, including 4 controlled studies (37, 44, 53, 58). The comprehensive search makes it unlikely that relevant studies were missed. Article identification, selection, and data abstraction were all performed independently in duplicate to minimize any potential biases arising from subjectivity. We also translated non–English-language articles and obtained unpublished information or clarifications from most primary study authors. Sources of bias were analyzed, and reasons for diversity in the published literature were explored. Finally, we justified our clinical and statistical reasons for mathematically combining certain results.

The results of any review are inherently limited by the quality of the primary studies. Data were often collected retrospectively, and many studies followed donors for less than 1 decade. On average, 31% of surviving donors were lost to follow-up, and in some studies larger numbers of eligible donors were missing (25, 37, 38, 44, 48, 51, 55). Estimates of long-term risk may be biased in either direction if donors who are followed systematically differ from nonparticipants in development of relevant outcomes. For example, **Figure 3** shows that higher blood pressure after surgery was evident in studies in which more patients were lost to follow-up, leading to the hypothesis that donors who became hypertensive were more likely to keep in touch with their transplant physicians than those who did not become hypertensive. For this reason, long-term risks presented in this review may be exaggerated. Conversely, transplant centers may be reluctant to report adverse outcomes after this perceived iatrogenic event. Furthermore, we are interested in knowing what a donor's blood pressure would be if he or she had elected not to donate a kidney. The use of transplant-eligible nondonor control participants would best guide such inferences. However, in most of the existing primary studies, control participants were not assembled and followed prospectively with donors, nor was an absence of hypertension and relevant comorbid conditions confirmed when the comparable donor had surgery. Although persons accepted as kidney donors pass a rigorous set of tests and are expected to have good long-term health, those in the general population may be less fit. Thus, it remains possible that publication biases and the type of control participants used in the primary studies minimized any long-term risks attributable to donation.

Among the controlled studies, blood pressure and hypertension were assessed similarly in donors and control participants, and observed differences suggested a true increase in risk. However, inconsistent definitions of hypertension in the primary studies often relied on higher thresholds for systolic and diastolic blood pressure than those used today, which complicates the use of these results for modern-day donors.

We abstracted predonation donor characteristics associated with postdonation outcomes from the primary studies and considered such factors in additional regression analyses. Obtaining individual-patient data from 48 studies to perform patient-level regression was impractical, and deriving such data using imputation techniques from aggregate summaries remains controversial (5). Thus, our analyses were conducted at the study level, using meta-regression on subsets of studies for which information was available. These results should be considered exploratory, because associations identified across studies may not always reflect the same relationship within studies (65).

Informed Consent, Drug Cost Reimbursement, Donor Selection, and Follow-up

Providing better estimates of long-term hypertension risk will improve the informed consent process for potential donors. According to current data, it is plausible that donation increases the risk for or hastens the onset of hypertension over subsequent decades (66). However, the decision to become a donor comes out of an intense desire to help a recipient, and most donors would disregard any warnings of a future increase in blood pressure or increased risk for hypertension (67). For those select donors who do carefully consider risk and benefit (67) or in those circumstances in which the recipient has strong preferences, disclosure of these results might influence the decision to donate. For persons who consider accepting kidneys from altruistic strangers or paid donors (68, 69), risk–benefit can also be considered.

Some organizations advocate that donors be reimbursed for expenses related to donation, including transportation, accommodation, and child care costs. This concept differs from payment for financial gain. Many

countries have now implemented relevant health policies (such as federal grants, tax incentives, extended leave, and social programs) that reimburse living donors for such expenses (70). For these initiatives, a better understanding of the risk for hypertension after kidney donation might guide the need to reimburse the donor for antihypertensive prescription costs or associated higher insurance premiums.

A more complex issue relates to the selection of extended-criteria donors who have a history of hypertension before surgery. There is a paucity of current data to guide such practice. A decision to proceed in these cases should be made by an experienced transplant team who carefully considers the treatment preferences of the donor and recipient and judiciously uses the evidence summarized here for normotensive persons who become donors. It remains prudent to counsel and follow all donors, regardless of their predonation health state, to manage risk factors in an attempt to prevent hypertension and future cardiovascular disease.

Conclusions and Future Research

On the basis of the limited studies conducted to date, living kidney donors may have a 5–mm Hg increase in blood pressure within 5 to 10 years of donation over that anticipated with normal aging. Although randomly assigning eligible individuals to donation would provide the best estimate of nephrectomy effect (71), conducting such a study is impractical. Rather, results of our meta-analysis of existing literature will be best confirmed or refuted by a large, prospective, multicenter cohort study with representative numbers of donors and appropriate control participants (72). Inclusion of racially diverse, older, and genetically unrelated donors will help define whether there are any differential effects of donation among such individuals. Many previous studies were conducted in an era when higher thresholds were used to diagnose hypertension. The use of modern criteria, which also account for concurrent proteinuria and lower glomerular filtration rate, will increase the number of hypertensive events in follow-up and facilitate a better estimation of risk. In the general population, every 10–mm Hg increase in systolic blood pressure and 5–mm Hg increase in diastolic blood pressure is associated with a 1.5-fold increase in death from ischemic heart disease and stroke (73). Whether an increase in blood pressure from kidney donation is similarly prognostic requires future consideration, because closer surveillance and early intervention in otherwise healthy adults could offset any such risk.

From University of Western Ontario, London, Ontario, Canada; University of Western Australia, Perth, Australia; University of Toronto, Toronto, Ontario, Canada; University of Ottawa, Ottawa, Ontario, Canada; and McMaster University, Hamilton, Ontario, Canada.

Acknowledgments: The authors thank Jan Challis, MLIS, who provided administrative help; Nick Barrowman, PhD, Brian Haynes, MD, PhD, and Joel Ray, MD, MSc, for statistical and methodologic advice; and William Clark, MD, for his support. The authors also thank the 30 authors of included studies who generously confirmed and provided information and performed additional analyses for this review.

Grant Support: By the London Multi-Organ Transplant Program, the Canadian Institutes of Health Research, the Physicians Services Incorporated Foundation, and the Canadian Council for Donation and Transplantation. Dr. Garg was supported by a Canadian Institutes of Health Research Clinician Scientist Award, and Dr. Yang was supported by a Biomedical Fellowship from the Kidney Foundation of Canada.

Potential Financial Conflicts of Interest: None disclosed.

Requests for Single Reprints: Amit X. Garg, MD, PhD, Division of Nephrology, London Kidney Clinical Research Unit, Room ELL-101, Westminster Tower, London Health Sciences Centre, 800 Commissioners Road East, London, Ontario N6A 4G5, Canada; e-mail, amit.garg@lhsc.on.ca.

Current author addresses are available at www.annals.org.

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Current Author Addresses: Dr. Boudville: Division of Nephrology, University of Western Australia, Verdun Street, Nedlands, WA 6050, Australia.
Dr. Prasad: Division of Nephrology, University of Toronto, St. Michael's Hospital Health Centre, 61 Queen Street East, 9th Floor, Toronto, Ontario M5C 2T2, Canada.
Dr. Knoll: Division of Nephrology, University of Ottawa, The Ottawa Hospital, 1967 Riverside Drive, Ottawa, Ontario K1H 7W9, Canada.
Drs. Muirhead, Yang, Rosas-Arellano, Housawi, and Garg and Ms. Thiessen-Philbrook: Division of Nephrology, London Kidney Clinical Research Unit, Room ELL-101, Westminster Tower, London Health Sciences Centre, 800 Commissioners Road East, London, Ontario N6A 4G5, Canada.

Appendix: The Donor Nephrectomy Outcomes Research (DONOR) Network Investigators

Dr. Neil Boudville, Dr. Larry Chan, Dr. Amit X. Garg, Dr. Colin Geddes, Dr. Eric Gibney, Dr. John Gill, Dr. Martin Karpinski, Dr. Scott Klarenbach, Dr. Greg Knoll, Dr. Norman Muirhead, Dr. Chirag Parikh, Dr. Ramesh Prasad, Dr. Leroy Storlsey, Dr. Sudha Tata, Dr. Darin Treleaven, and Dr. Robert Yang.