2017 CST-Astellas Canadian Transplant Fellows Symposium

Critical Review of Pivotal Trials in Transplantation: Two Studies that Will Change your Practice in 2017

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Canadian Transplant Fellows Symposium
Monday, September 25th, 2017

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Disclosures

- Research and educational grants from Astellas Pharma Canada

Two Randomized Clinical Trials for Discussion Today

- Knoll et al. Levofloxacin for BK virus prophylaxis following kidney transplantation: a randomized clinical trial. *JAMA* 2014;312:2106-14.
- Niemann et al. Therapeutic hypothermia in deceased organ donors and kidney-graft function. *N Engl J Med* 2015;373:405-14.

Original Investigation

Levofloxacin for BK Virus Prophylaxis Following Kidney Transplantation
A Randomized Clinical Trial

Greg A. Knoll, MD; Atul Humar, MD; Dean Fergusson, PhD; Olwyn Johnston, MD; Andrew A. House, MD; S. Joseph Kim, MD, PhD; Tim Ramsay, PhD; Michaël Chassé, MD; Xiaoli Pang, MD; Jeff Zaltzman, MD; Sandra Cockfield, MD; Marcelo Cantarovich, MD; Martin Karpinski, MD; Louise Lebel, BScN; John S. Gill, MD, MS

Knoll et al. *JAMA* 2014;248:564-77.

Background

- BK virus (BKV) infection has emerged as a major complication of kidney transplantation
- BKV infection progresses through discrete stages: viruria, viremia, and then nephropathy; latter leads to graft failure in 10 to 100% of affected patients
- Treatment of established BKV infection mainly involves reduction in immunosuppression and BKV monitoring – risk of rejection and variable efficacy
- Observational studies suggest that quinolone antibiotics may reduce risk of BK viruria, viremia, and nephropathy

Knoll et al. *JAMA* 2014;248:564-77.

Study Objective

- To assess the efficacy and safety of levofloxacin versus placebo for the prevention of BK viruria
  - *Hypothesis:* Levofloxacin, given in sufficient dosage early after kidney transplantation, can significantly reduce BK viruria

Knoll et al. *JAMA* 2014;248:564-77.

Study Design

- Multi-centre, double-blind, placebo-controlled, parallel-group, randomized trial
- Three-month course of quinolone antibiotic levofloxacin vs. placebo
- Eligible patients randomly assigned 1:1
- Allocation via web-based central randomization in variable blocks stratified by centre
- Patients, investigators, staff, and outcome assessors blinded to randomization scheme and intervention
- Staff at central laboratory performing BKV measurements not aware of treatment allocation

Knoll et al. *JAMA* 2014;248:564-77.

Study Population

- Inclusion Criteria
  - Adult kidney transplant recipients (age ≥ 18 years old)
- Exclusion Criteria
  - Patient unable to provide informed consent
  - More than 5 days since transplantation
  - BKV nephropathy with previous transplant
  - History of allergic reaction with quinolone antibiotic, quinolone-associated tendinitis, or tendon rupture
  - QTc interval ≥ 450 ms or on medications that could prolong QT interval
  - Pregnant or breastfeeding
  - Required quinolone antibiotic for more than 14 days
  - Multi-organ transplant (including kidney-pancreas)
  - Enrolled another interventional trial
  - History of rhabdomyolysis
  - Significant allergic reaction to 3 or more classes of antibiotics

Knoll et al. *JAMA* 2014;248:564-77.

Intervention

- Target dosage: levofloxacin 500 mg/d (2 x 250 mg capsules) for 3 months administered orally once daily
- At each study visit, creatinine clearance estimated using Cockcroft-Gault formula and dosage of levofloxacin adjusted based on guidelines
- Medication started as soon as patient able to take oral medications but within 5 days after transplantation (goal is to prevent early viral replication)
- Levofloxacin was encapsulated to ensure that placebo was identical in appearance to study medication

Knoll et al. *JAMA* 2014;248:564-77.

Other Trial Maneuvers

- All participants received prophylaxis against CMV and PJP based on established guidelines
- Data collected on all co-interventions such as immunosuppressive strategies
- Quinolones for bacterial prophylaxis not permitted
- If quinolone necessary, study drug temporarily withheld and cultures obtained
- Once cultures available, patient switched to non-quinolone regimen unless only quinolone sensitive (study medication held during this time)
- All non-study use of quinolones documented

Knoll et al. *JAMA* 2014;248:564-77.

Outcome Measures

- Primary Outcome
  - Time to occurrence of BK viruria within first year after kidney transplantation
  - BK viruria: 500 copies/mL or more of BKV DNA in urine (tested by central laboratory at University of Alberta, Edmonton)
- Secondary Clinical Outcomes
  - Quantitative BKV load in urine
  - BK viremia: 25 copies/mL or more of BKV DNA in plasma
- Secondary Safety Outcomes
  - Adverse events (acute rejection, C. diff. diarrhea, other infections, quinolone resistant positive cultures, transplant failure, mortality)

Knoll et al. *JAMA* 2014;248:564-77.

Statistical Analysis 1

- Intention-to-treat with follow-up censored at time of study withdrawal, death, transplant failure, loss to follow-up, end of study (52 weeks), or early study termination
- Log-rank test, stratified by centre, to compare time to occurrence of BK viruria in treatment vs. placebo groups
- Kaplan-Meier survival curves plotted to visually assess differences in cumulative incidence over time
- Sensitivity analyses
  - Multiple imputation for 46 of 1406 missing viruria values
  - Time to sustained viruria (2 consecutive positive viruria)

Knoll et al. *JAMA* 2014;248:564-77.

Statistical Analysis 2

- Events by treatment group compared using mean difference (continuous variables) and risk ratios (dichotomous variables)
- To account for potential imbalances between groups, Cox proportional hazards model were fitted to adjust for age, sex, re-graft status, donor type (deceased vs. living), and use of immunosuppressant medication
- Exploratory analyses in following clinical subgroups: age, sex, re-graft status, donor type (deceased vs. living), and immunosuppression

Knoll et al. *JAMA* 2014;248:564-77.

Sample Size Estimate

- Based on data from literature, estimated that 35% of patients in placebo group would develop BK viruria by 1 year after transplantation
- Detect clinically important absolute reduction in BK viruria of 20% (from 35% to 15%) with 2-sided α = 0.05, β = 0.20, and 5% loss to follow-up
- 154 patients (77 per group) required
- Minimal clinically important difference of 20% justified based on survey of experts from Canadian Renal Transplant Study group and investigative team

Knoll et al. *JAMA* 2014;248:564-77.

Results

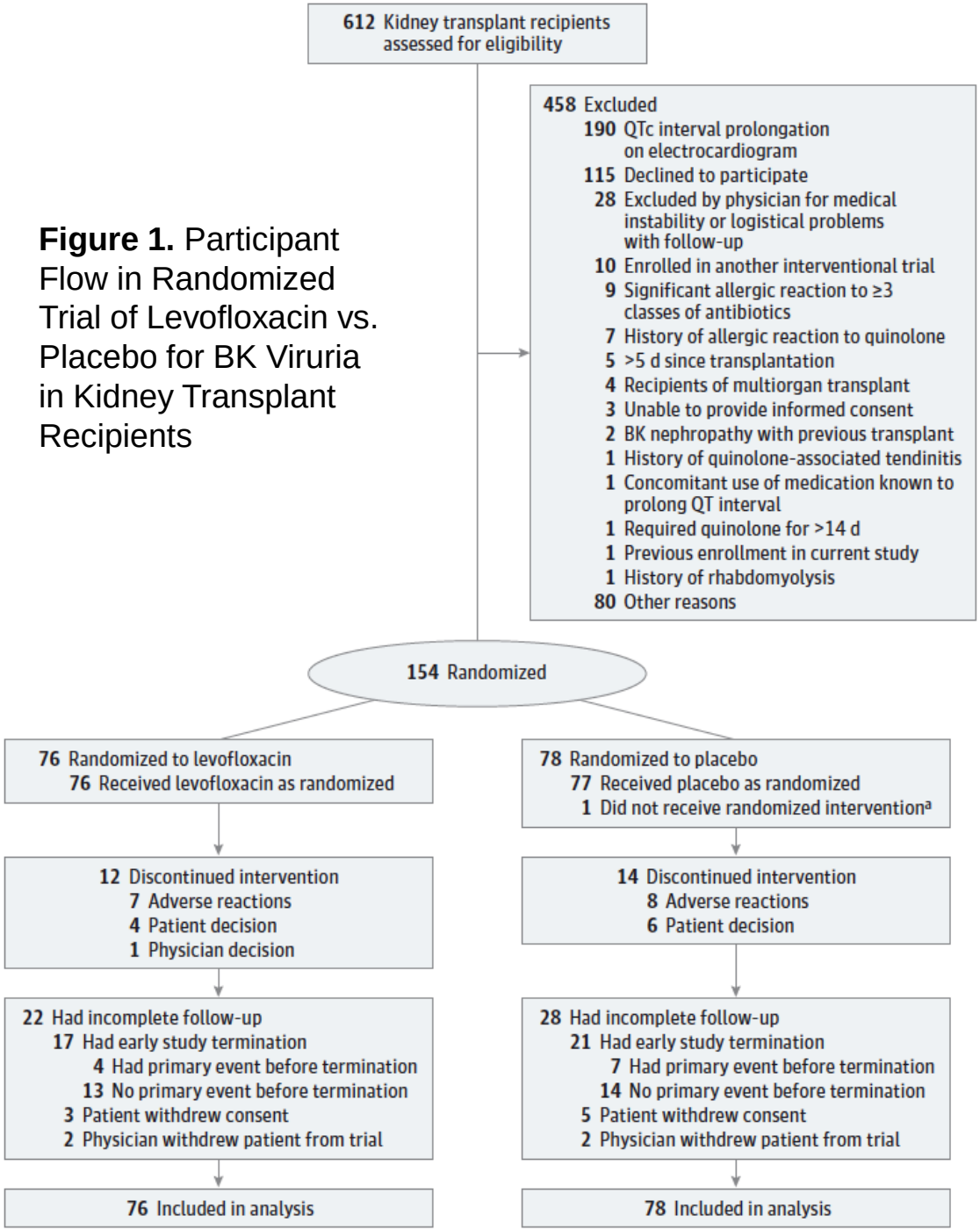


Figure 1. Participant Flow in Randomized Trial of Levofloxacin vs. Placebo for BK Viruria in Kidney Transplant Recipients

Table 1. Baseline Participant Characteristics[a]

Characteristics	Levofloxacin Group (n = 76)	Placebo Group (n = 78)
Age, mean (SD), y	47.8 (14.2)	48.2 (12.7)
Female	27 (35.5)	16 (20.5)
Body mass index, mean (SD)[b]	27.0 (4.7)	27.0 (5.2)
Race		
White	49 (64.5)	50 (64.1)
Black	3 (3.9)	7 (9.0)
Asian	3 (3.9)	7 (9.0)
Aboriginal	4 (5.3)	1 (1.3)
Other	14 (18.4)	11 (14.1)
Unknown	3 (3.9)	2 (2.6)
Primary etiology of renal disease		
Glomerulonephritis	18 (23.7)	12 (15.4)
Polycystic kidney disease	14 (18.4)	16 (20.5)
Diabetes mellitus	9 (11.8)	15 (19.2)
Hypertension	4 (5.3)	5 (6.4)
Other	26 (34.2)	25 (32.1)
Unknown	5 (6.6)	5 (6.4)

Knoll et al. *JAMA* 2014;248:564-77.

Table 1. Baseline Participant Characteristics[a]

Characteristics	Levofloxacin Group (n = 76)	Placebo Group (n = 78)
Comorbidities		
Diabetes	16 (21.1)	19 (24.4)
Previous cancer	7 (9.2)	4 (5.1)
Cardiovascular disease (coronary, cerebral, or peripheral vascular disease)	5 (6.6)	10 (12.8)
Hepatitis C antibody positive	1 (1.3)	1 (1.3)
Hepatitis B surface antigen positive	1 (1.3)	3 (2.0)
Donor type		
Living	46 (60.5)	47 (60.3)
Deceased	30 (39.5)	31 (39.7)
Transplant		
Primary	68 (89.5)	74 (94.9)
Repeat	8 (10.5)	4 (5.1)
Ureteric stent	73 (96.1)	73 (96.6)

Knoll et al. *JAMA* 2014;248:564-77.

Table 1. Baseline Participant Characteristics[a]

Characteristics	Levofloxacin Group (n = 76)	Placebo Group (n = 78)
Induction immunosuppression	73 (96.1)	75 (96.2)
Basiliximab	48 (63.2)	58 (74.4)
Antithymocyte globulin	25 (32.9)	17 (21.8)
No induction	3(4.0)	3 (3.9)
Maintenance immunosuppression at time of randomization		
Tacrolimus	55 (72.4)	61 (78.2)
Cyclosporine	2 (2.6)	5 (6.4)
Mycophenolate mofetil or sodium	75 (98.7)	75 (96.2)
Corticosteroid	50 (65.8)	48 (61.5)

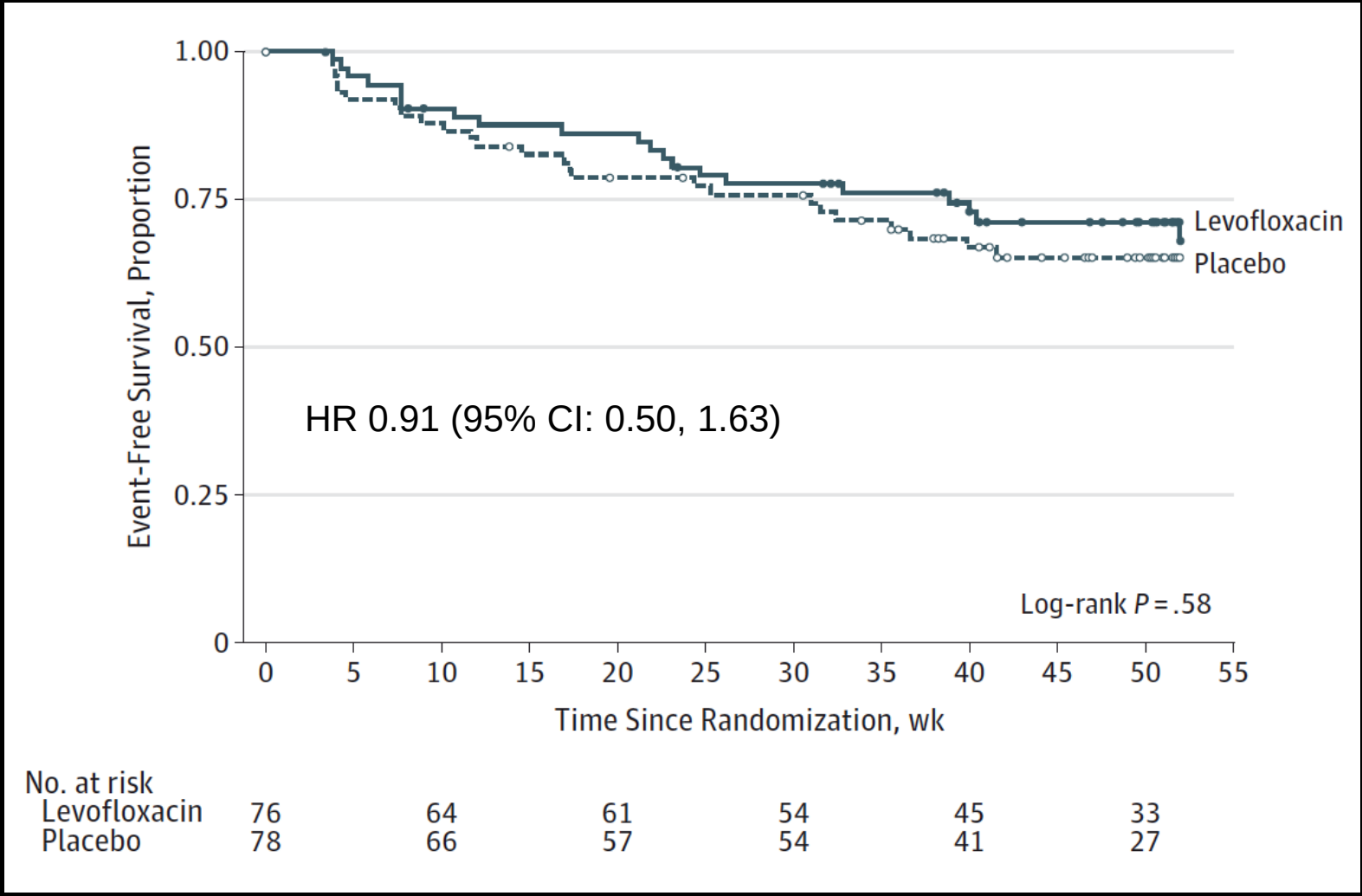
Knoll et al. *JAMA* 2014;248:564-77.

Table 2. Clinical Outcomes

Clinical End Points	Levofloxacin Group (n = 76)	Placebo Group (n = 78)	Risk Ratio or Mean Difference (95% CI)
Viruria			
No. (%)	22 (29.0)	26 (33.3)	0.87 (0.54 to 1.39)
Initial BK viral titer, copies/mL			
Mean (SD)	2.1×10^8 (9.2×10^8)	1.9×10^9 (7.5×10^9)	-1.7×10^9 (-4.9×10^9 to 1.6×10^9)
Median (IQR)	1.7×10^4 (1.0×10^4 to 1.1×10^6)	9.8×10^4 (1.0×10^4 to 1.1×10^8)	
Peak BK viral titer, copies/mL			
Mean (SD)	3.4×10^8 (9.4×10^8)	2.8×10^9 (8.1×10^9)	-2.5×10^9 (-6.0×10^9 to 9.9×10^9)
Median (IQR)	6.8×10^6 (1.0×10^4 to 2.2×10^8)	1.3×10^7 (3.5×10^4 to 1.5×10^9)	
Viremia			
No. (%)	6 (7.9)	9 (11.5)	0.68 (0.26 to 1.76)
Initial BK viral titer, copies/mL			
Mean (SD)	7550 (16 542)	4503 (5419)	3046 (−10 430 to 16 522)
Median (IQR)	560 (500 to 1880)	1965 (500 to 7700)	
Death, No. (%)	0	0	
Allograft loss, No. (%)	0	1 (1.3)	
Acute rejection, No. (%)	6 (7.9)	5 (6.4)	1.2 (0.41 to 3.67)

Knoll et al. *JAMA* 2014;248:564-77.

Figure 2: Time to First Episode of Viruria



Knoll et al. *JAMA* 2014;248:564-77.

Table 3. Safety Outcomes

Outcomes	Levofloxacin Group (n = 76)[a]	Placebo Group (n = 78)[a]	Risk Ratio or Mean Difference (95% CI)
Hospitalization	22 (29.0)	26 (33.3)	0.84 (0.53 to 1.35)
≥1 Infection	45 (59.2)	35 (44.9)	1.32 (0.97 to 1.81)
No. of infections per patient			
Mean (SD)	1.4 (1.6)	1.3 (2.2)	0.1 (−0.5 to 0.7)
Median (interquartile range)	1 (0 to 2)	0 (0 to 2)	
Infections	n = 113	n = 119	
Urinary tract/pyelonephritis	42 (37.2)	45 (37.8)	0.98 (0.70 to 1.37)
Cytomegalovirus	39 (34.5)	39 (32.8)	1.05 (0.73 to 1.51)
Pneumonia	4 (3.5)	2 (1.7)	2.11 (0.46 to 9.71)
Cellulitis	3 (2.7)	1 (0.8)	3.16 (0.46 to 21.9)
Line related	1 (0.9)	0	
Bacteremia	0	1 (0.8)	
Clostridium difficile	0	0	
Other	24 (21.2)	31 (26.1)	0.82 (0.51 to 1.29)
Culture-positive infections	n = 30	n = 46	
Quinolone sensitive	10 (33.3)	26 (56.5)	0.59 (0.33 to 1.00)
Quinolone resistant	14 (46.7)	15 (32.6)	1.43 (0.81 to 2.50)
Quinolone intermediate	0	4 (8.7)	
Quinolone sensitivity not reported by laboratory	6 (20.0)	1 (2.2)	9.2 (1.55 to 56.70)

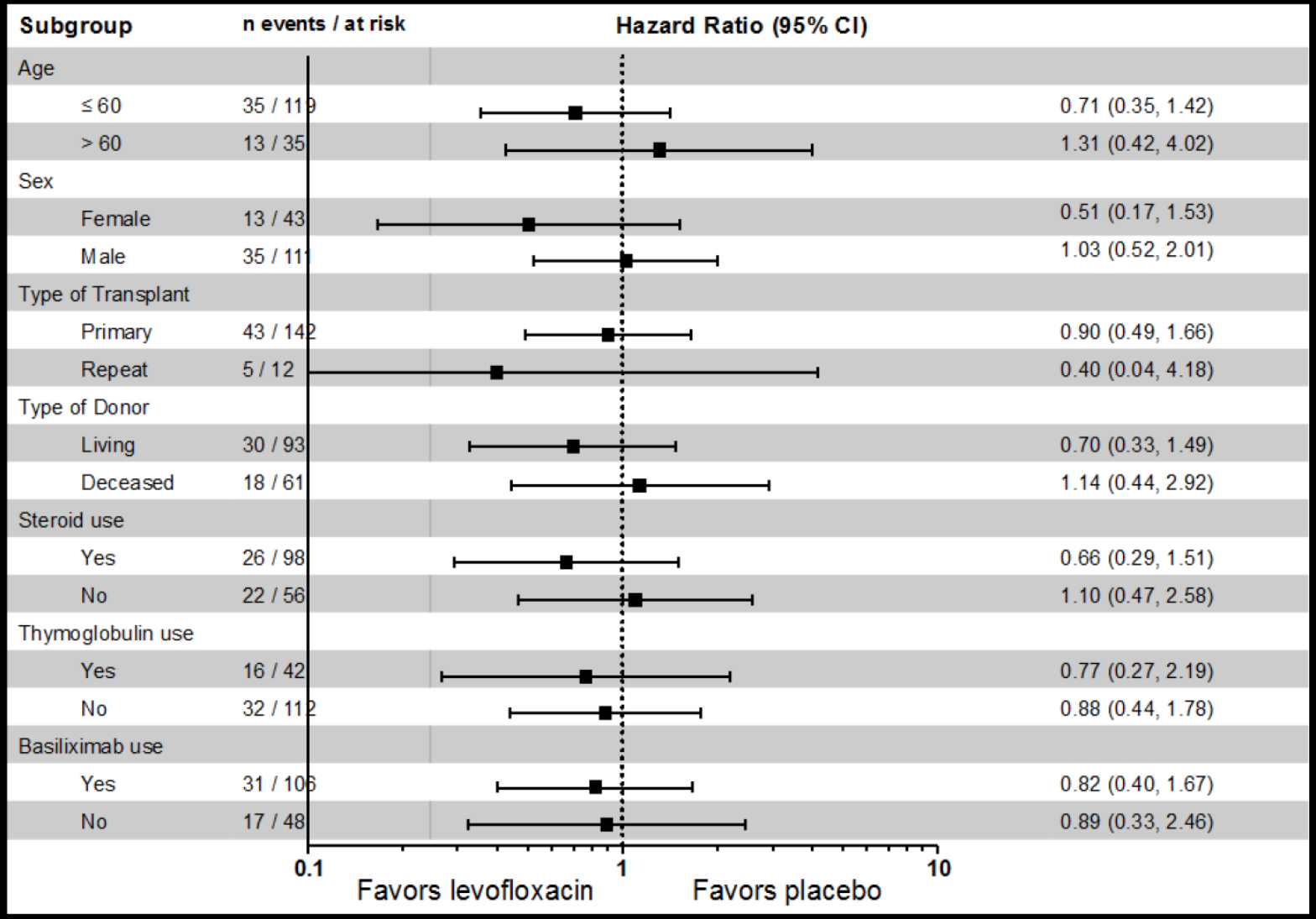
Knoll et al. *JAMA* 2014;248:564-77.

Table 3. Safety Outcomes

Outcomes	Levofloxacin Group (n = 76)[a]	Placebo Group (n = 78)[a]	Risk Ratio or Mean Difference (95% CI)
QTc prolongation on electrocardiogram	3 (4.0)	4 (5.1)	0.77 (0.20 to 2.98)
Suspected tendinitis	6 (7.9)	1 (1.3)	6.16 (0.76 to 49.95)
Significant hypoglycemia	3 (4.0)	5 (6.4)	0.62 (0.17 to 2.25)
Rash	1 (1.3)	1 (1.3)	1.03 (0.11 to 9.70)
Diarrhea	36 (47.4)	30 (38.5)	1.23 (0.86 to 1.79)
Serum creatinine, mean (SD), μmol/L			
At 4 wk	138.3 (70.9)	140.5 (86.2)	−2.1 (−27.3 to 23.1)
At 8 wk	125.2 (115.3)	132.0 (46.6)	−6.8 (−21.4 to 7.7)
At 12 wk	127.0 (49.1)	129.3 (52.9)	−2.3 (−19.0 to 14.3)
At 16 wk	125.0 (49.3)	126.1 (42.6)	−1.2 (−16.4 to 14.1)
At 20 wk	121.5 (42.0)	125.0 (38.1)	−3.4 (−16.8 to 10.0)
At 24 wk	120.8 (44.2)	124.9 (37.3)	−4.2 (−17.7 to 9.4)
At 32 wk	119.1 (40.1)	124.1 (35.6)	−5.0 (−17.8 to 7.8)
At 40 wk	120.4 (41.4)	126.7 (44.5)	−6.3 (−21.2 to 8.6)
At 52 wk	118.2 (40.6)	125.8 (45.6)	−7.5 (−24.0 to 8.9)
Patients with ≥1 other serious adverse event not listed above	22 (28.9)	26 (33.3)	0.85 (0.53 to 1.35)
Total No. of other serious adverse events	27	29	

Knoll et al. *JAMA* 2014;248:564-77.

Table S1: Subgroup Analyses



Knoll et al. *JAMA* 2014;248:564-77.

Internal Validity

- Strengths
  - Well randomized, rigorous blinding maintained, very good adherence to study medication
  - All virologic tests performed centrally at reference laboratory with validated assay used for clinical purposes
  - Comprehensive assessment of potential adverse effects
- Limitations
  - Trial follow-up terminated early due to resource restrictions for 27 patients who had not developed viruria (all completed minimum of 8 months follow-up)
  - Viremia or nephropathy as endpoint may have been more clinically relevant but viruria appears prior to both and sample size would be prohibitively large for viremia or nephropathy

Knoll et al. *JAMA* 2014;248:564-77.

External Validity

- Recruitment at multiple Canadian kidney transplant centres
- Representative sample of most kidney transplant recipients in North America
- Contemporary immunosuppressive protocols and post-transplant care
- Question whether findings apply to other patients such as kidney-pancreas transplant recipients or regrafts with prior BKV infection

Knoll et al. *JAMA* 2014;248:564-77.

Summary and Conclusions

- Among kidney transplant recipients, a 3-month course of levofloxacin initiated early after transplantation did not prevent BK viruria
- The intervention was associated with an increased risk of adverse events such as bacterial resistance
- These findings do not support the use of levofloxacin to prevent BK virus infection after kidney transplantation

Knoll et al. *JAMA* 2014;248:564-77.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 30, 2015 VOL. 373 NO. 5

Therapeutic Hypothermia in Deceased Organ Donors and Kidney-Graft Function

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Niemann et al. *N Engl J Med* 2015;373:405-14.

Background

- Therapeutic hypothermia (i.e., targeted temperature management) is an established intervention to protect neurologic function in patients with cardiac arrest, stroke, and asphyxia
- Role of therapeutic hypothermia in protecting the kidney is less certain
- Current protocols stipulate that normothermia (which frequently requires active warming) be maintained in deceased organ donors
- Effect of targeted hypothermia to protect kidney function during donation process is uncertain

Niemann et al. *N Engl J Med* 2015;373:405-14.

Study Objective

- To conduct a prospective, randomized, controlled trial in two large organ donation service areas to test the potential benefit and safety of targeted hypothermia in deceased organ donors on the risk of delayed graft function in the recipients of their kidneys.

Niemann et al. *N Engl J Med* 2015;373:405-14.

Study Population

- All donors identified by two organ procurement organizations in their respective donation service areas between 20-Mar-2012 and 17-Oct-2013
- Participating OPO's included California Transplant Donor Network (Northern California) and OneLegacy (Southern California and Nevada)
- All donors for whom written authorization for research to be performed was on file and who were ≥ 18 years of age were considered for enrollment

Niemann et al. *N Engl J Med* 2015;373:405-14.

Table S1. United Network for Organ Sharing Region 5 donor management goals.

Donor Management Goals	Parameters
Mean arterial pressure	60–110 mm Hg
Central venous pressure	4–12 mm Hg
Ejection fraction	≥50%
Vasopressors*	≤1 and low dose
Arterial blood gas pH	7.3–7.5
PaO_2/FIO_2	≥300
Serum Sodium	≤155 mmol/L
Urine output	≥ 0.5 mL/kg/hr over 4 hrs
Glucose	≤180 mg/dL

*Low dose of vasopressors was defined as: Dopamine ≤ 10 mcg/kg/min, Phenylephrine ≤ 60 mcg/min, and Norepinephrine ≤ 10 mcg/min

Niemann et al. *N Engl J Med* 2015;373:405-14.

Inclusion Criteria

- Legal determination of death by neurologic criteria
- Any gender or ethnicity
- Age 18 years or greater at the time of death
- Authorization for research from the authorizing surrogate or by First Person Authorization via either state donor registry or advanced directive
- Mean arterial pressure > 60 mmHg for more than one hour without an increase in vasopressors

Niemann et al. *N Engl J Med* 2015;373:405-14.

Exclusion Criteria

- Donors after determination of circulatory death (DCD)
- Age under 18 years
- No research authorization
- ESRD and/or dialysis at time of current hospitalization
- Coagulopathy
- Donor considered candidate for in-situ split liver
- Chronic medical condition precluding general acceptance for transplantation
- Additional outlying factors for exclusion were determined on a case-by-case basis with the PI and the study coordinator

Niemann et al. *N Engl J Med* 2015;373:405-14.

Randomization

- Authorization obtained for research and declaration of death by neurologic criteria
- Donors assigned by computer-generated block randomization to mild hypothermia (34.0 to 35.0°C) or normothermia (36.5 to 37.5°C)
- Randomization stratified
  - Organ procurement organization
  - Donor status (ECD or non-ECD)
  - Receipt of hypothermia treatment before declaration of death by neurologic criteria

Niemann et al. *N Engl J Med* 2015;373:405-14.

Intervention

- Donors assigned to therapeutic hypothermia allowed to spontaneously reach body temperature of 34.0 to 35.0°C or cooled using forced-air systems or passive-cooling devices (whatever available)
- Donors assigned to normothermia kept warm (at 36.5 to 37.5°C) with use of same devices
- Temperature management followed study protocol and uniformly applied across all donor hospitals by coordinators of the OPOs.

Niemann et al. *N Engl J Med* 2015;373:405-14.

Outcome Measures

- Primary
  - Delayed graft function (recipient's requirement for dialysis during the first week after transplantation)
  - Derived from data reported to OPTN/UNOS and processed by SRTR (SN 89%, SP 98% for DGF)
- Secondary
  - Rate of individual organs transplanted in each treatment group
  - Number of organs transplanted from each enrolled deceased donor

Niemann et al. *N Engl J Med* 2015;373:405-14.
Potluri et al. *Clin J Am Soc Nephrol* 2016;11:324-31.

Statistical Analysis 1

- Trial designed to enroll max. of 500 donors to have 90% power to detect 30% relative difference in rate of DGF between study groups at two-sided type 1 error of 5%)
- Interim analyses to determine if trial should be stopped early for efficacy or futility
- Primary efficacy analysis used logistic regression model and GEE method for DGF with term for randomized treatment group and adjustments for covariates
- Pre-specified (ECD status) and post-hoc subgroup analyses also performed

Niemann et al. *N Engl J Med* 2015;373:405-14.

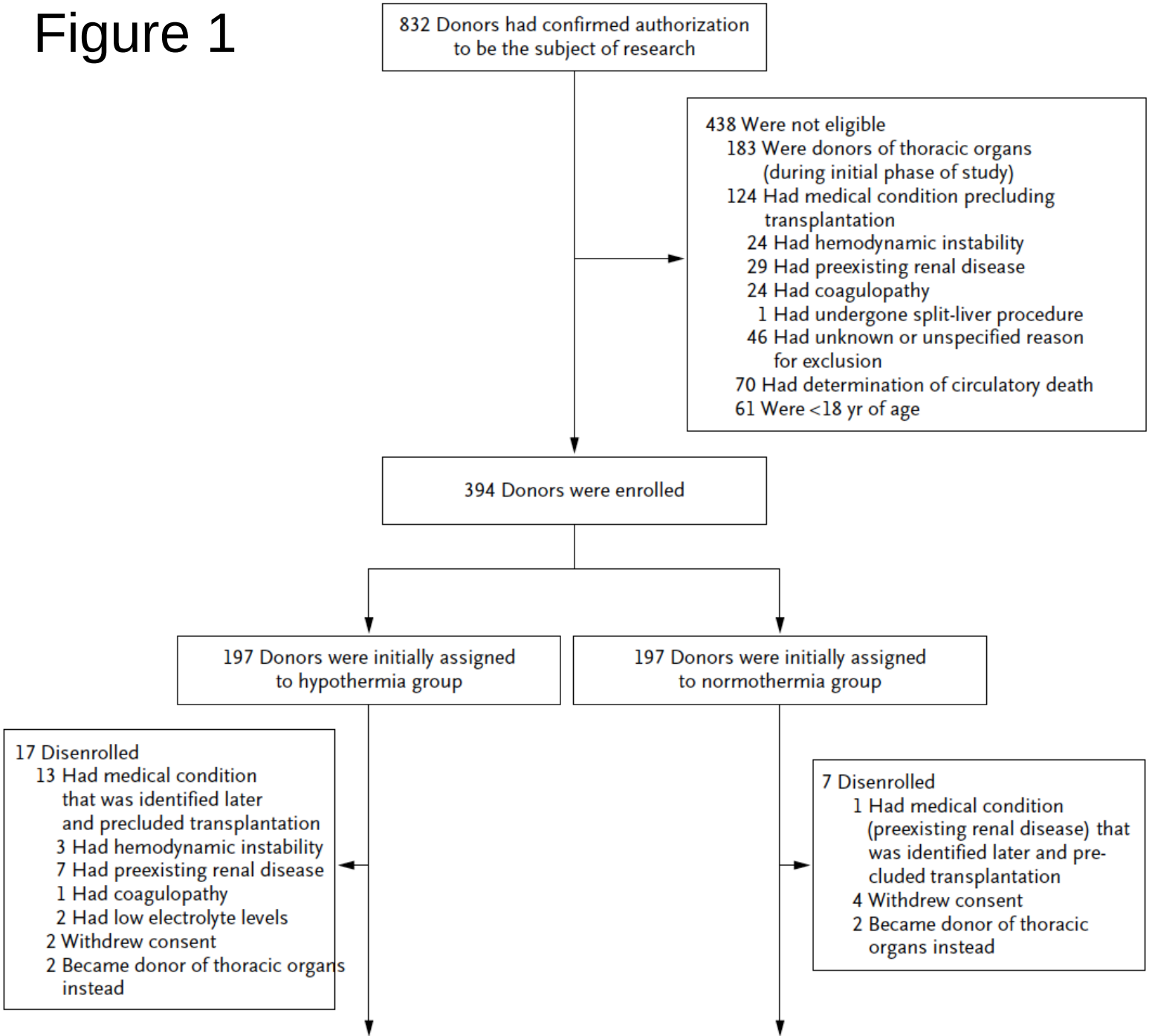
Statistical Analysis 2

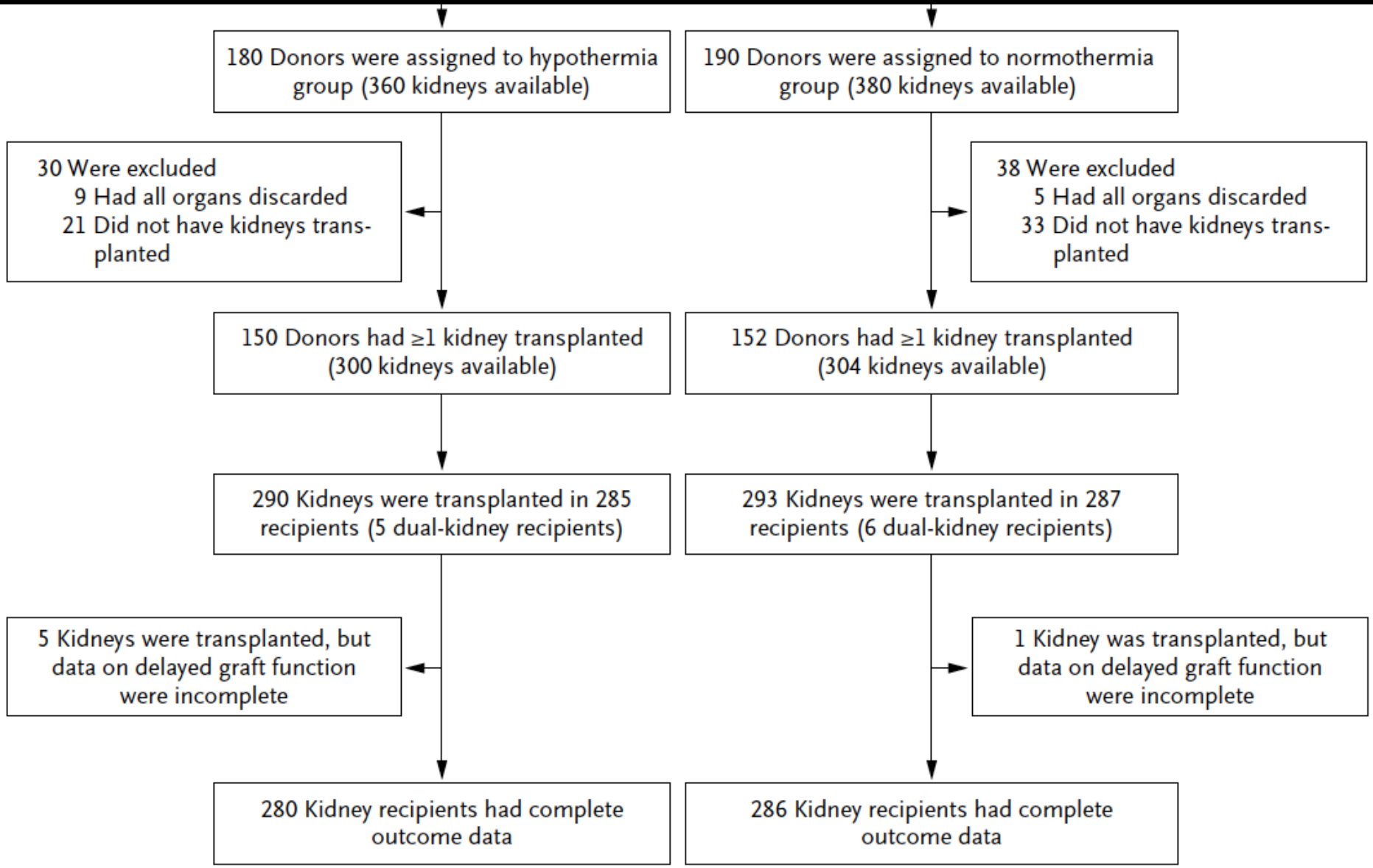
- Comparisons between treatment groups made using Wilcoxon rank-sum test, chi-square test, or Fisher's exact test when appropriate
- Secondary outcomes used chi-square test to compare proportion of donors in each treatment group whose hearts, lungs, livers, or pancreases were transplanted
- All statistical tests were two-sided and significance level for primary end point adjusted to be 0.0474 to account for single interim analysis

Niemann et al. *N Engl J Med* 2015;373:405-14.

Results

Figure 1


832 Donors had confirmed authorization to be the subject of research
438 Were not eligible
183 Were donors of thoracic organs (during initial phase of study)
124 Had medical condition precluding transplantation
24 Had hemodynamic instability
29 Had preexisting renal disease
24 Had coagulopathy
1 Had undergone split-liver procedure
46 Had unknown or unspecified reason for exclusion
70 Had determination of circulatory death
61 Were <18 yr of age
394 Donors were enrolled
197 Donors were initially assigned to hypothermia group
197 Donors were initially assigned to normothermia group
17 Disenrolled
13 Had medical condition that was identified later and precluded transplantation
3 Had hemodynamic instability
7 Had preexisting renal disease
1 Had coagulopathy
2 Had low electrolyte levels
2 Withdrew consent
2 Became donor of thoracic organs instead
7 Disenrolled
1 Had medical condition (preexisting renal disease) that was identified later and precluded transplantation
4 Withdrew consent
2 Became donor of thoracic organs instead



Niemann et al. *N Engl J Med* 2015;373:405-14.

Early Stoppage

- Preplanned interim analysis to assess whether the trial should be stopped early for efficacy or futility was conducted after approximately half the anticipated donors were enrolled
- On the basis of a recommendation by the data and safety monitoring board, the trial was discontinued early owing to overwhelming efficacy

Niemann et al. *N Engl J Med* 2015;373:405-14.

Table 1. Characteristics of the Donors Who Donated at Least One Kidney.*

Variable	Hypothermia Group (N=150)	Normothermia Group (N=152)	P Value
Organ-procurement organization — no. (%)			0.65
A	68 (45.3)	73 (48.0)	
B	82 (54.7)	79 (52.0)	
Age — yr	45±15	45±15	0.82
Sex — no. (%)			1.0
Female	56 (37.3)	56 (36.8)	
Male	94 (62.7)	96 (63.2)	
Height — m	1.71±0.10	1.71±0.10	0.95
Weight — kg	84.7±21.5	85.3±21.6	0.75
Body-mass index†	28.9±6.8	29.3±7.3	0.77
Expanded-criteria donor at enrollment — no. (%)‡	40 (26.7)	41 (27.0)	1.0
KDPI score — %§	51±29	53±28	0.53
Prior hypothermia — no. (%)	18 (12.0)	18 (11.8)	1.0
Creatinine level — mg/dl			
At enrollment	1.1±0.6	1.1±0.6	0.62
Last recorded in ICU	1.1±0.8	1.2±0.8	0.06
Glomerular filtration rate — ml/min/1.73 m^2¶			
At enrollment	89.2±50.8	89.0±43.1	0.80
Last recorded in ICU	103.4±58.1	88.2±43.9	0.03

Table S2. Temperature and cooling data for donors who donated at least one kidney.

	Hypothermia (N = 150)	Normothermia (N = 152)	*P* Value
Temperature (ºC)			
Enrollment	36.5 ± 0.7	36.5 ± 0.6	0.44
Prior to organ recovery	34.6 ± 0.7	36.8 ± 0.4	< 0.001
Method of Temperature Control			< 0.001
Arctic Sun	5 (3.3)	0 (0.0)	
Bair Hugger	0 (0.0)	9 (5.9)	
Blanket	112 (74.7)	81 (53.3)	
Fan	4 (2.7)	4 (2.6)	
Ice Packs	7 (4.7)	2 (1.3)	
None	13 (8.7)	51 (33.6)	
Other	7 (4.7)	3 (2.0)	
Unknown	2 (1.3)	2 (1.3)	
Core Temperature Measurement			0.43
Bladder	57 (38.3)	72 (47.4)	
Esophageal	1 (0.7)	1 (0.7)	
Rectal	85 (57.0)	75 (49.3)	
Other	6 (4.0)	4 (2.6)	
Target Temperature Reached in 4 hours	122 (81.3%)	149 (98.0%)	< 0.001
Time at Target Temperature (hours)	16.9 (10.2-29.4)	n/a*	

Data are mean ± SD or No. (%), or median (interquartile range). Data missing for 1 donor in hypothermia group; * all donors were in the normothermic range at enrollment

Table 2. Characteristics of the Organ Recipients.*

Variable	Recipient of Kidney from Hypothermia Group	Recipient of Kidney from Normothermia Group	P Value
Age			0.14
No. of recipients with data	238	238	
Mean — yr	52.3±13.5	53.4±15.4	
Sex — no./total no. (%)			0.40
Female	91/238 (38.2)	101/238 (42.4)	
Male	147/238 (61.8)	137/238 (57.6)	
Body-mass index			0.57
No. of recipients with data	224	225	
Mean	27.2±5.3	26.9±5.5	
Warm-ischemia time			0.11
No. of recipients with data	148	147	
Mean — min	34±19	38±21	
Cold-ischemia time			0.02
No. of recipients with data	281	286	
Mean — hr	13.9±7.3	15.6±8.3	
Delayed graft function — no. of recipients/total no. (%)	79/280 (28.2)	112/286 (39.2)	0.008

Table 3. Results of the Primary Efficacy Analysis.*

Variable	Odds Ratio for Delayed Graft Function (95% CI)	P Value
Hypothermia vs. normothermia	0.62 (0.43–0.92)	0.02
Organ-procurement organization, A vs. B	0.85 (0.57–1.28)	0.43
Standard-criteria donor vs. expanded-criteria donor	1.21 (0.69–2.13)	0.50
Creatinine level at enrollment, per 1-mg-per-deciliter increase	1.99 (1.42–2.80)	<0.001
Donor age, per 1-yr increase	1.04 (1.02–1.05)	<0.001
Kidney cold-ischemia time, per 1-hr increase	1.03 (1.00–1.05)	0.04

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Figure 2: Subgroup Analyses

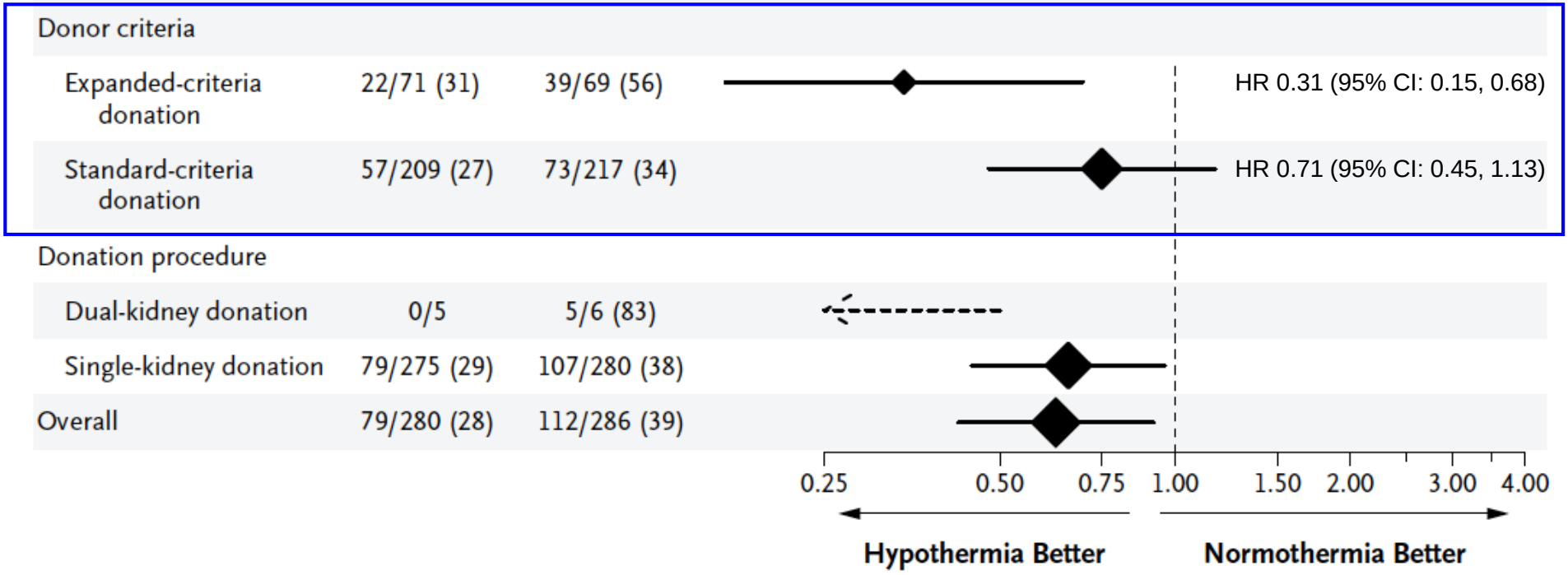

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Table S6. Organs Transplanted by Treatment Group

	Hypothermia Group (N = 180)	Normothermia Group (N = 190)	*P* Value
Number of Organs Transplanted			
Total	570	587	—
Mean ± SD	3.2 ± 1.9	3.1 ± 1.8	0.87
Median (interquartile range)	3.0 (2.0-4.0)	3.0 (2.0-4.0)	0.87
Kidneys			0.70
Both	140 (77.8)	141 (74.2)	—
One	10 (5.6)	11 (5.8)	—
None	30 (16.7)	38 (20.0)	—
Number of Kidneys Transplanted			
Total	290	293	
Mean ± SD	1.6 ± 0.8	1.5 ± 0.8	0.41
Median (interquartile range)	2.0 (2.0-2.0)	2.0 (1.0-2.0)	0.41
Heart Transplanted	46 (25.6)	49 (25.8)	1.0
Liver Transplanted	129 (71.7)	135 (71.1)	0.91
Lungs Transplanted			0.79
Both	40 (22.2)	44 (23.2)	—
One	3 (1.7)	5 (2.6)	—
None	137 (76.1)	141 (74.2)	—
Pancreas or Islets Transplanted	19 (10.6)	15 (7.9)	0.47

Data are mean ± SD, median (interquartile range), No., or No. (%)

Adverse Events

- Four adverse events in total
  - Hypothermia group: one episode of dysrhythmia and one episode of systemic hypertension
  - Normothermia group: two episodes of cardiac arrest before organ recovery

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Another Way to Look at the Results

- 79 of 280 (28.2%) recipients of donor kidneys from hypothermia group experienced DGF
- 112 of 286 (39.2%) recipients of donor kidneys from normothermia group experienced DGF
- Absolute risk difference = 11.0% (95% CI: 3.2, 18.7)
- Number needed to treat = 9.1 (95% CI: 5.4, 31.1)

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Number Needed to Treat

- Hypothermia in donors to reduce DGF — NNT = 10
- Hypothermia for neuroprotection after CPR — NNT = 6
- Lung-protective ventilation and 28-day death — NNT = 10
- CABG and death over 10 years — NNT = 25
- Anticoagulation in AF for stroke prevention — NNT = 25
- ASA and death after heart attack — NNT = 42
- BP reduction for stroke prevention — NNT = 67
- Bisphosphonates for hip fracture prevention — NNT = 100
- Machine perfusion of kidneys to reduce DGF — NNT = 18

Internal Validity

- Differences in characteristics of deceased donors who did vs. did not provide consent for research
- Ascertainment of outcomes and covariates from national registry data (DGF status missing in 5 hypothermia patients and 1 normothermia patient)
- Impact of including in primary outcome 30 donors in hypothermia group and 38 donors in normothermia group whose kidneys were never transplanted
- Awareness by recipient team of donor's allocated treatment group

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External Validity

- Only single donor had both kidneys pumped on perfusion machine after recovery
- Does not apply to donors after determination of circulatory death or DCD (which comprises about a third of deceased donor activity in Ontario)
- Organ function of non-kidney transplants is unknown or yet to be reported (could be readily ascertained from SRTR)
- Optimal duration of cooling to achieve effect unclear

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Summary and Conclusions

- Therapeutic hypothermia in deceased neurologically declared donors reduced the risk of DGF by 38% compared to donors exposed to normothermia
- Number needed to treat is approximately 10 (i.e., 10 donors must be treated with hypothermia in order to prevent 1 DGF episode in kidney transplant recipients)
- Application of these findings across the provinces will require an assessment of benefits of hypothermia beyond perfusion pumping, impact on function of non-kidney organ transplants, and logistics of widespread adoption across all donation hospitals

Questions