

# Equivalent outcomes with primary and retransplantation in African-American deceased-donor renal allograft recipients

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**Background.** Graft survival following renal retransplantation has been inferior to that following primary allografting, particularly in African Americans (AAs) receiving deceased-donor (DD) kidneys.

**Methods.** Among 166 AA DD renal allograft recipients transplanted from July 2001 through July 2007, we compared the outcomes of 26 (16%) receiving a second graft with those of 140 primary cases. All patients received either thymoglobulin (ATG) or an IL-2 receptor antagonist for induction, and were maintained on either tacrolimus or sirolimus + mycophenolate mofetil ± prednisone.

**Results.** When compared with primary transplants, regrafts received kidneys from older donors, were younger, more sensitized, more likely to receive ATG and to be maintained on prednisone, received more doses of ATG, and were less likely diabetic. There was no difference between primary and retransplant groups in overall patient or graft survival; incidence of acute rejection, CMV infection, BK nephropathy, or new-onset diabetes mellitus; and serum creatinine at 1 year.

**Conclusion.** AA renal allograft recipients can undergo a second DD transplant with intermediate-term outcomes comparable to that of a primary graft, despite the presence of multiple immunologic and non-immunologic high-risk factors, by extending the course of ATG induction and continuing prednisone therapy in the vast majority of cases. (*Surgery* 2009;146:646-53.)

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DESPITE THE IMPROVEMENT in overall outcomes following renal transplantation observed over the years, the sheer growth in the number of transplants performed has resulted in more patients suffering allograft loss and being considered for retransplantation. Indeed, the absolute number of kidney retransplants has grown by 40% over the past decade,<sup>1</sup> and this number will continue to increase, particularly given the current trend of using more marginal donor organs and transplanting higher-risk recipients. Unfortunately, however, graft survival following renal

retransplantation has traditionally been inferior to that following primary transplantation.<sup>2-5</sup>

The high-risk nature of regraft recipients is generally attributed to their development of elevated panel reactive antibody (PRA) levels due to prior allosensitization and increased chance of acute rejection (AR). Despite development of more sensitive flow cytometry (FC) crossmatching techniques, the ability to better identify donor-specific alloantibody, and the introduction of more potent induction and maintenance immunosuppressants, a recent report from the Scientific Registry of Transplant Recipient database continues to demonstrate significantly lower 1-, 3-, and 5-year graft survivals for repeat living- and deceased-donor (DD) renal transplant patients when compared with primary recipients, with significantly worse 3-year outcomes even after adjusting for donor and recipient factors.<sup>1</sup>

African Americans (AAs) continue to be considered a high-risk subgroup of renal allograft

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recipients, with an increased risk of acute and chronic rejection and graft loss.<sup>6</sup> Along these lines, 2 large database studies examining patients transplanted from 1988–1997<sup>7</sup> and from 1987–2002<sup>8</sup> both identified recipient AA ethnicity as one of the most influential factors negatively affecting renal regraft outcome. Moreover, AA recipients tend to have higher levels of HLA-DR mismatching, also noted to be a highly significant factor predicting poorer regraft survival,<sup>7–11</sup> and are more likely to receive a DD kidney, another independent negative predictor of retransplant outcome.<sup>3–7</sup> To our knowledge, there are no prior reports comparing outcomes of first and second renal allografts in adult AA kidney transplant patients utilizing contemporary induction and maintenance immunosuppressive protocols, with a particular focus on DD recipients. It was our hypothesis that we could achieve results in AA retransplant recipients equivalent to those undergoing primary transplantation via selective intensification of induction and maintenance immunosuppression, despite the presence of multiple other immunologic and nonimmunologic risk factors for poorer outcome.

## PATIENTS AND METHODS

This is a retrospective observational study of adult HIV-negative AAs undergoing their first ( $n = 140$ ) or second ( $n = 26$ ) DD renal transplant at our center from July 2001–July 2007 and followed through July 2008. Approval was obtained from the Wayne State University Human Investigation Committee. Transplant candidates who were positive for hepatitis C virus (HCV) by quantitative PCR (polymerase chain reaction) RNA testing underwent liver biopsy, and if cirrhosis was not present, were cleared for renal transplantation.

Transplants were performed following negative T- and B-cell anti-human globulin (AHG) cross-matches, and, beginning on October 1, 2002, following negative T- and B-cell FC crossmatches for all retransplants and for primary transplants with current and/or peak PRA  $\geq 20\%$ . Cutoffs for positivity of T- and B-cell FC crossmatches were 40-channel shift and 50-channel shift, respectively. Current sera were defined as being up to 6 weeks old. Unacceptable HLA antigens were determined based on monthly screening of serum samples by ELISA prior to 2006, and by a highly-sensitive, solid-phase Luminex assay with both phenotype identification and single-antigen panels thereafter. Patients with past positive (defined as having a positive AHG or FC crossmatch on peak serum  $>6$

months old) but currently crossmatch negative were transplanted. With regard to retransplants, we had no policy in place specifying acceptable degrees of HLA mismatching or avoidance of prior donor antigens from the first allograft (repeat mismatches).

Prior to July 2003, all first transplants received induction therapy with either Thymoglobulin (ATG; 1.5 mg/kg/d for 4–11 days) or basiliximab (20 mg on postoperative days 0 and 4), based on recipient risk factors.<sup>12</sup> These included age, PRA, and presence or absence of comorbid conditions, such as cardiovascular disease or HCV serostatus. All primary recipients transplanted after July 2003, as well as all retransplants during the entire study period, received ATG. Patients were started on mycophenolate mofetil 2 g/d postoperatively, with subsequent dose adjustment for gastrointestinal side effects or leukopenia. Methylprednisolone 250 mg IV was given intraoperatively, followed by doses of 125, 100, and 100 mg on subsequent days. Prior to July 2003, all patients were maintained on oral prednisone, with tapering to 30 mg by 1 week, 10 mg at 3 months, and 5 mg at 6–12 months. After July 2003, steroids were maintained after day 3 in those patients with current PRA  $\geq 50\%$  or who were on prednisone at the time of transplant, with a tapering schedule as follows: 20 mg/d at 1 week, 10 mg/d at 1 month, and 5 mg/d at 6 weeks. All other patients underwent early steroid withdrawal (ESW) after the initial 4 doses.<sup>13</sup>

The third agent, tacrolimus or sirolimus, was started within 24–48 hours after surgery based on early graft function as described in detail previously.<sup>14</sup> The target trough levels for both agents were 10–12 ng/ml during the first 6 months; 8–12 ng/ml from 6–12 months; 8–10 ng/ml for 1–2 years; and 6–8 ng/ml thereafter. Patients with cytomegalovirus (CMV)+ serostatus received valganciclovir 450 mg/d for 3 months, while CMV– patients who received a kidney from a CMV+ donor received 900 mg/d for 3 months, with dose adjustment according to renal function in all cases.

Delayed graft function (DGF) was defined as the need for hemodialysis during the first week post-transplant. All episodes of AR were confirmed by biopsy and graded according to Banff 97 criteria. Borderline or grade I rejection episodes were treated with methylprednisolone 500 mg IV for 3 days, followed by a steroid taper. Steroid-resistant grade I and grade II rejections were treated with 5–7 daily doses of ATG with target absolute CD3 counts  $\leq 10$  cells/ $\mu$ l, and antibody-mediated

rejection with the addition of intravenous immunoglobulin  $\pm$  plasmapheresis.

The primary endpoints of the study were patient and graft survival, with secondary endpoints being the incidence of DGF, AR, CMV infection, new-onset diabetes mellitus (NODM), and BK nephropathy. Graft loss was defined as return to dialysis or death with a functioning graft. The presence of pp65 antigenemia or quantitative PCR  $>400$  copies/ml was considered diagnostic of CMV infection in the presence of suggestive clinical symptoms, signs, and/or laboratory studies. NODM was diagnosed in nondiabetic recipients with fasting blood glucose  $>125$  mg/dl on at least 2 occasions over a 1-month period, or by the need for hypoglycemic agents for more than 1 month. The primary cause of end-stage renal disease (ESRD) was categorized as hypertension, diabetes, glomerulonephritis, cystic disease, or other.

Demographic data are reported as counts, percentages, or mean values  $\pm$  standard deviation. Comparison of demographic and outcome variables between groups was performed using Chi-square or the Student *t* test, as appropriate. Primary endpoints were compared between groups using Kaplan-Meier analysis.  $P \leq .05$  was regarded as statistically significant.

## RESULTS

**Patient demographics.** Table I summarizes the donor and recipient characteristics of the primary and retransplant groups, both notable for a high fraction of recipient HCV positivity and AA donors, high degree of overall HLA and HLA-DR mismatching, and long waiting times. The groups were also comparable with regard to donor and recipient sex, recipient body mass index, cold ischemic time, maintenance agent initiated, and mean follow-up. Regrafted patients, however, were younger, more highly sensitized, more likely to receive ATG with longer courses of therapy, less likely to undergo ESW, and received kidneys from older donors. In addition, when compared with first transplants, retransplant recipients were less likely to have diabetes and more likely to have glomerulonephritis as the cause of ESRD (Table II). For retransplants, median primary graft survival was 3.7 years (range, 1 day–14.9 years), with 4 grafts lost within the first 6 months, and the mean time interval between primary and secondary allografting was  $10.1 \pm 4.0$  years. FC crossmatching was performed in 106 first (76%) and 14 (54%) second transplants ( $P = .02$ ).

**Patient survival.** Sixteen patients died in the primary group and 2 in the retransplant group, with the causes summarized in Table III. There was

no significant difference in overall patient survival between the primary and retransplant groups (89% vs 92%;  $P = .57$ ; Fig 1), with 1-year actual rates of 96% and 100%, respectively.

**Graft survival.** Forty-one grafts were lost in the primary group and 10 in the retransplant group, with the causes given in Table IV. There were no differences in the causes of graft loss between the 2 groups. There was also no significant difference in overall graft survival between primary and retransplant patients over the entire follow-up period (71% vs 62%;  $P = .62$ ; Fig 2), with a 1-year actual rate of 92% in both groups. Moreover, censoring graft survival for death with function did not produce any difference between the groups ( $P = .35$ ). Finally, there were no deaths or graft losses due to progression of liver disease or infection in HCV+ recipients in either group.

**Secondary endpoints.** There were no significant differences between the primary and retransplant groups with regard to the incidence of DGF, AR, NODM, CMV infection, BK nephropathy, or renal function at 1 year (Table V). There was also no difference in the severity of AR episodes between the groups, in that 10 of 42 first transplant recipients and 1 of 9 second transplants required ATG treatment (24% vs 11%;  $P = .40$ ).

## DISCUSSION

The results of our study suggest that intermediate-term outcomes can be achieved in DD AA renal allograft recipients following a second transplant that are equivalent to those following primary transplantation with the judicious use of contemporary pretransplant immunologic screening along with induction and maintenance immunosuppressants. Despite a higher degree of sensitization and utilization of FC crossmatching in a smaller fraction of cases, retransplant patients demonstrated incidence and severity of AR episodes no greater than those observed in primary recipients, presumably due to using ATG induction in all cases and to extending the course of ATG beyond 4 doses and administering maintenance steroids in the vast majority of patients. This increased immunosuppressive burden, however, was not associated with decreased patient survival or higher rates of CMV infection, BK nephropathy, NODM, or development of infection or liver disease in HCV+ recipients. Moreover, we made no attempt to pre-select donors for retransplant candidates based on degrees of HLA mismatching or avoidance of repeat mismatches from the first allograft. Overall, regraft recipients displayed the typical set of AA-associated high-risk factors for

**Table I.** Patient demographics

Variable	Primary (n = 140)	Retransplant (n = 26)	P value
<b>Donor</b>			
Age	31 ± 14	37 ± 12	.03
Race (AA%)	40	39	.80
Male (%)	55	58	.80
DCD + ECD (%)	4.3	0	.24
<b>Recipient</b>			
Age	50 ± 12	42 ± 13	<.005
Male (%)	66	73	.71
BMI	27 ± 5	25 ± 4	.13
Years ESRD	5.6 ± 3.1	6.3 ± 4.4	.38
HCV+ (%)	29	19	.50
Diabetic	31%	0%	<.001
Current PRA >10%	7%	69%	<.001
Peak PRA >10%	36%	96%	<.001
HLA-A, B, DR mismatches (0–6)	4.0 ± 1.6	4.1 ± 1.4	.75
HLA-DR mismatches (0–2)	0.7 ± 0.7	0.6 ± 0.6	.36
≥1 HLA-DR mismatch (%)	59%	54%	.65
CMV donor+/recipient- (%)	14%	4%	.16
Cold ischemic time (hr)	12 ± 8	10 ± 7	.21
ATG/basiliximab	70%/30%	100%/0%	.001
Doses ATG	5.0 ± 1.1	6.4 ± 1.9	<.001
>4 doses ATG (%)	38	85	<.0001
Tacrolimus/sirolimus	81%/19%	89%/11%	.30
ESW (%)	51	15	<.001
Follow-up (years)	3.3 ± 2.0	3.7 ± 2.0	.37

DCD, Donation after cardiac death; ECD, extended criteria donor.

**Table II.** Causes of ESRD in the primary and retransplant groups

Cause	Primary (n = 140)	Retransplant (n = 26)	P value
Hypertension (%)	49	35	.17
Glomerulonephritis (%)	19	46	.002
Diabetes (%)	21	0	.009
Cystic disease (%)	2	8	.13
Other (%)	9	11	.63

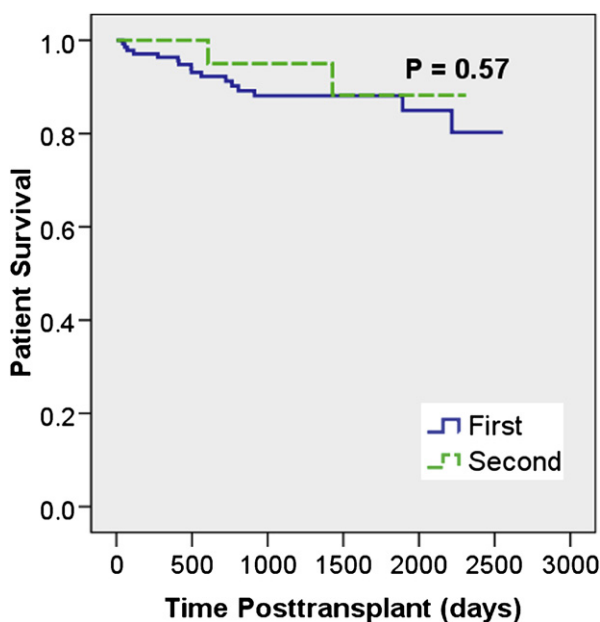
poorer outcome (prolonged times on dialysis, high fraction of HCV positivity, poor HLA matching, high incidence of DGF, and high fraction of AA donors) to a degree equivalent to that of the primary cases, and even with use of significantly older donor organs, achieved a similar graft survival with similar causes of graft loss using the protocol described herein. One recent, large, single-center study, which included patients transplanted over a 15-year period, reported equivalent short- and long-term primary graft and regraft survival rates, but included only 6% AAs and purposely minimized HLA-DR mismatching in the retransplant group.<sup>15</sup> Although our study was

clearly limited by the relatively small number of retransplant recipients and lack of long-term follow-up, it is the first to our knowledge to examine retransplant outcomes in DD AA recipients receiving current immunosuppression.

Several donor, recipient, and transplant-related factors may be important in producing the equivalent outcomes observed in our retransplant recipients based on prior reports in the literature. First, although no intentional protocol restriction was made, no diabetics underwent retransplantation at our institution, and regraft recipients were more likely to have developed ESRD on the basis of glomerulonephritis as opposed to hypertension, when compared with first transplants. It is well established that the mortality rate for diabetics following graft loss is significantly higher than that of nondiabetics, reported to be 70% versus 30% at 4 years in 1 series,<sup>3</sup> with the relative death risk ranging from 1.76- to 3.69-fold in 3 other reports.<sup>16-18</sup> As a result of this increased mortality from cardiovascular and infectious causes, when taken together with the fact that regrafts wait on the list at least as long as primary recipients due to increased allosensitization,<sup>1</sup> significantly fewer diabetics (and those with increased comorbidities

**Table III.** Causes of patient death in the primary and retransplant groups

Primary (n = 140)	Retransplant (n = 26)
Cardiovascular (6)	Ruptured iliac aneurysm at site of prior transplant nephrectomy (1)
Sepsis (6)	Sepsis (1)
Malignancy (2)	
Gun shot wound (2)	

**Fig 1.** Patient survival of AAs receiving first ( $n = 140$ ) or second ( $n = 26$ ) DD renal transplant.

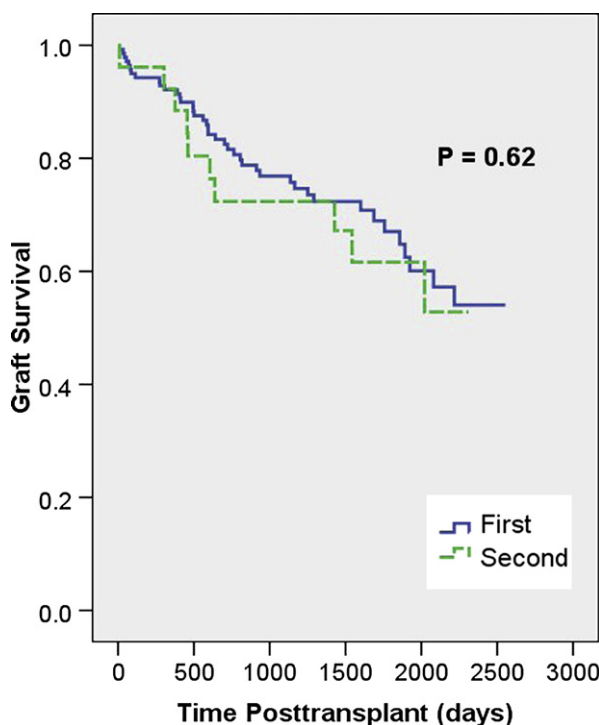
in general) make it to repeat transplantation.<sup>11,15,19</sup> As a result, there is a clearly a natural selection bias occurring with regard to retransplantation, with suitable candidates representing a comparatively lower-risk group of “healthier” patients.<sup>20</sup>

Second, the use of both T- and B-cell FC crossmatching in half of the regraft cases may have eliminated higher immunologic risk donors from consideration, thereby decreasing the chances of accelerated AR and/or graft loss due to AR. Indeed, the only graft loss due to AR in the retransplant group occurred on day 10 in a patient with current and peak PRA of 16% and 99%, respectively, who was transplanted prior to the initiation of our FC crossmatch protocol. Along these lines, others have noted a significant improvement in regraft survival following the introduction of T-cell FC crossmatching,<sup>3,10,21</sup> and Laszda<sup>22</sup> found that a strongly positive B-cell flow

**Table IV.** Causes of graft loss in the primary and retransplant groups

Primary (n = 140)	Retransplant (n = 26)
Death with function (16, 11.4%)	Death with function (2, 7.7%)
Chronic allograft nephropathy (9, 6.4%)	Chronic allograft nephropathy (2, 7.7%)
Noncompliance (6, 4.3%)	Noncompliance (2, 7.7%)
AR (3, 2.1%)	AR (1, 3.8%)
FSGS (3, 2.1%)	FSGS, BK nephropathy (1, 3.8%)
Thrombosis (2, 1.4%)	Thrombotic microangiopathy (1, 3.8%)
MPGN (1, 0.7%)	MPGN (1, 3.8%)
Primary nonfunction (1, 0.7%)	

FSGS, Focal segmental glomerulosclerosis; MPGN, membranoproliferative glomerulonephritis.

**Fig 2.** Graft survival of AAs receiving first ( $n = 140$ ) or second ( $n = 26$ ) DD renal transplant.

crossmatch identified HLA-DR mismatched patients who were at risk for graft loss. Along these lines, Mahoney et al<sup>23</sup> demonstrated that a positive B-cell FC crossmatch was strongly associated with early graft loss in a subset of retransplant recipients with previous graft survival time  $\leq 3$  months.

**Table V.** Secondary endpoints in the primary and retransplant groups

Cause	Primary (n = 140)	Retransplant (n = 26)	P value
DGF (%)	48	42	.79
AR (1 year, %)	21	12	.28
AR (overall, %)	30	35	.66
NODM (%)	27*	31	.71
CMV infection (%)	8	4	.96
BK nephropathy (%)	1	4	.18
Serum creatinine (1 year) (mg/dl)	1.7 ± 0.8	1.7 ± 0.9	.92

\*Of 97 patients at risk.

Finally, Thompson et al<sup>8</sup> suggest that short of avoiding HLA-DR incompatible donors, one might routinely perform a final B-cell FC crossmatch in regraft candidates in order to pick up otherwise undetectable sensitization to class II and even additional class I antigens on B cells, as we have done in our study.

Third, although not specified by protocol, none of our regraft recipients received kidneys from extended criteria donors (ECDs). In a single-center study, Sellers et al<sup>24</sup> found that patient, graft, and death-censored graft survival were significantly worse in retransplant recipients of ECD versus non-ECD kidneys, and Miles et al<sup>25</sup> more recently demonstrated that retransplantation with ECD kidneys does not offer a survival advantage when compared with remaining on dialysis. It would appear that ECD kidneys should be used with caution in the retransplant setting, and that these candidates may be better off remaining on the waiting list until a non-ECD kidney becomes available.

Given the relatively small number of retransplant recipients in our study, we were not able to perform a meaningful multivariate regression analysis examining the risk factors predicting adverse outcomes specifically in this cohort of AA DD patients. This kind of analysis has been previously reported by other investigators using national registry or large single-center databases, but with the drawback of including all regrafts regardless of ethnicity and donor source transplanted over long time periods and/or with noncurrent immunosuppressive regimens.<sup>7-11,15</sup> In addition to HLA-DR mismatching and AA recipient, other risk factors for graft loss noted in these studies that may have positively (by their absence) or negatively (in their presence) influenced our retransplant outcomes include shorter duration of previous graft,<sup>7,9,10,15</sup> prior graft loss from AR,<sup>15</sup> waiting time >1 year,<sup>15</sup> female donor,<sup>8,10</sup> donor age >50,<sup>7,15</sup> DGF,<sup>15</sup> male recipient,<sup>7</sup> recipient BMI >30,<sup>7</sup> increasing PRA,<sup>7,9</sup> and cold ischemic time >24 hours.<sup>11,12</sup>

In conclusion, we have demonstrated that AA renal allograft recipients can undergo a second, DD transplant with intermediate-term outcomes comparable to that of a primary graft, despite the presence of multiple immunologic and nonimmunologic high-risk factors. We believe that the use of standard criteria donors, FC crossmatching, and selective intensification of contemporary immunosuppression, with extension of the ATG induction course and continuance of prednisone therapy in the vast majority of cases, may have contributed to these positive results. Certainly our findings will need to be verified in larger numbers of regraft recipients with longer follow-up.

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## DISCUSSION

**Dr Robert Stratta** (Winston-Salem, NC): This is an interesting single center retrospective experience comparing

primary versus retransplantation of the kidney in exclusively African-American recipients.

Their findings are both provocative and in some respects counterintuitive. The reason why African-Americans are a high risk group are myriad and include biologic as well as nonbiologic factors. The reasons why retransplants are high risk compared to primary transplants also include multiple immunologic as well as nonimmunologic factors. It is important to emphasize the high risk nature of this recipient population—namely younger age, African-American ethnicity, high incidence of delayed graft function, hepatitis C positive, highly sensitized, lack of HLA matching, high proportion of African-American donors, and prolonged duration of pre-transplant dialysis, all of which individually are risk factors for adverse outcomes after transplant.

The authors correctly point out some keys to success with kidney transplantation in the African-American recipient, including avoidance of expanded criteria and donation after cardiac death donors, prolonged duration of their depleting antibody induction, use of maintenance steroids, absence of diabetes, and flow cytometry cross matching. With these thoughts in mind I have the following questions:

First, what determines the duration of ATG induction therapy in your retransplantations? Second, it appears that a death censored analysis might show a higher incidence of late, greater than one year, graft loss in your retransplant patients. I would like to you comment on that.

Third, do you perform surveillance biopsies in retransplant patients? If so, does your protocol differ compared to primary transplants?

And finally do you monitor donor-specific antibodies following retransplantation and administer IVIG/pheresis if antibody levels increase?

**Dr Kristian L. Brown** (Detroit, MI): The duration of Thymoglobulin therapy is partially based upon the risk factors that the patients present with.

**Dr Scott A. Gruber** (Detroit, MI): We do protocol biopsies on all of our steroid-free patients but not on those receiving steroids. And we do donor-specific antibody testing at 1, 3, 6, and 12 months, and then yearly thereafter.

**Dr Mark I. Aeder** (Cleveland, OH): Dr Brown, I congratulate you on a nice presentation because you bring up an issue that's really difficult. There are 70,000 people awaiting kidney transplantation today, and 20% of them clearly are here for retransplant. And we know that African-Americans are a challenged population in retransplant. So it brings me to a couple of questions. One is, when you take a look at the expanded criteria donors, you only have 4.3% of your primary transplants receiving ECD or cardiac death donors and none of your retransplant patients doing this. This is well below the national average. Twenty percent of all deceased donor transplants are a combination of both ECD and DCD donors. I can tell you, in our program, we are over 50% based on our patient population. So I would like to

know, how much of a factor is this in the outcomes you are seeing in your African-American population to be able to get that kind of number of standard criteria donors? That's not always an option for us.

Next, I think Dr Stratta brought it up and this is that your primary transplants were older, they had more diabetics, and we didn't see any death-censored data between the 2 groups. Dr Stratta brought it up and I am going to ask you, do you have any idea that if you took out the leading cause of graft failure today, which is death with a functioning graft, and most often due to cardiovascular causes, if you take out those patients, do you see a difference in overall graft survival? Then just one other question that I have for you. I just looked at your cold ischemic time, and seeing 10 or 12 hours is just incredible. I'm just wondering how your institution is able to achieve such low cold ischemic times on your deceased donor grafts.

**Dr Scott A. Gruber** (Detroit, MI): Let's start with the last one first. Our cold ischemic times are short. We

generally take very few kidneys from the outside, so we are able to maintain these fairly short cold ischemic times. The decreased fraction of diabetics in the retransplants was not by choice, was not by protocol. Very few diabetics, who have such a high incidence of death after first graft loss due to cardiovascular and infectious causes, get to be retransplanted. It's almost a self-selection in that regard. I agree that we have been slow to use ECD donors. Our feeling is that if we transplant the highest risk recipients in the country, it's hard also to add to that the highest risk donors and also keep our outcomes fairly good. Now, this group was from 2001–2007, before ECDs became identified as such. So the term "ECD" really only evolved in 2004 or 2005. But you're absolutely right, even after that we have been slower than other programs to use ECDs because of our high risk recipients. Death censoring? We didn't show it here, but there is still no overall statistically significance difference in graft survival between the 2 groups.