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Protocolized fluid therapy in brain-dead donors: The multi-center randomized MOnIToR trial

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Abstract

BACKGROUND—Critical shortages of organs for transplantation jeopardize many lives. Observational data suggest that better fluid management for deceased organ donors could increase

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organ recovery. We conducted the first large multi-center randomized trial in brain-dead donors to determine whether protocolized fluid therapy increases organs transplanted.

METHODS—We randomly assigned donors to either protocolized or usual care in eight organ procurement organizations. A “protocol-guided fluid therapy” algorithm targeting cardiac index, mean arterial pressure and pulse pressure variation was used. Our primary outcome was the number of organs transplanted per donor and our primary analysis was intention-to-treat. Secondary analyses included: 1) modified intention-to-treat where only subjects able to receive the intervention were included, and 2) twelve-month survival in transplant recipients. The study was stopped early.

RESULTS—We enrolled 556 donors; 279 protocolized care, 277 usual care. Groups had similar characteristics at baseline. The study protocol could be implemented in 76% of subjects randomized to the intervention. There was no significant difference in mean number of organs transplanted per donor: 3.39 organs per donor, (95%CI: 3.14-3.63) with protocolized care, compared to usual care 3.29 (95%CI: 3.04-3.54) (mean difference, 0.1, 95%CI: -0.25 to 0.45; p=0.56). In modified intention-to-treat analysis the mean number of organs increased (3.52 organs per donor, 95%CI: 3.23-3.8) but was not statistically significant (mean difference, 0.23, 95%CI: -0.15-0.61; p=0.23). Among the 1430 recipients of organs from study subjects, with data available, 56 deaths (7.8%) occurred in the protocolized care arm and 56 (7.9%) in the usual care arm in the first year (Hazard Ratio: 0.97, p=0.86).

CONCLUSIONS—In brain-dead organ donors, protocol-guided fluid therapy compared to usual care may not increase the number of organs transplanted per donor.

Keywords

Organ donation; clinical trial; transplantation; functional hemodynamic monitoring; fluid management; brain death

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Despite efforts to increase organ donation [1-4], there remains a critical shortage in both organ donors and organs transplanted per donor [5, 6]. Strategies to increase recovery of organs from donors are therefore urgently needed. Compared to historical controls, donor management with increased attention to fluid resuscitation has been shown to reduce cardiovascular collapse and increase the number of organs transplanted per donor [7]. However, excessive fluid may also cause organ edema. Optimal management of donor hemodynamics, as in the live patient, aims to achieve euvolemia, maintain blood pressure, and attain a cardiac output to achieve gradients of perfusion pressure and blood flow that promote organ function with minimal use of vasoactive-drug support. While there are several reasons why not all potential organs are donated and subsequently transplanted, hemodynamic instability of the donor is an important and modifiable factor.

One method to assess fluid optimization is to examine the Pulse Pressure Variation (PPV) while receiving positive pressure mechanical ventilation [8-11]. We previously reported an association between increased PPV, indicating fluid responsiveness, and increased levels of inflammatory mediators in the donor [12]. Furthermore, increased concentrations of the circulating inflammatory mediator interleukin (IL)-6 in donors was shown to predict six-month hospital-free survival in recipients [13]. We therefore conducted the first large

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multicenter randomized trial (MOnIToR) in brain-dead donors to determine if protocolized fluid therapy would increase organs transplanted, and improve survival in the recipients compared to usual care.

METHODS

Detailed study methods and statistical analysis plan have been published previously [14]. Abbreviated methods follow.

Study Oversight

From October 8, 2009 to March 23, 2013, we enrolled organ donors cared for by organ procurement coordinators from eight organ procurement organizations (OPOs) in the US. The trial was approved by each participating OPO scientific committee with oversight by the University of Pittsburgh Committee for Oversight of Research and Clinical Training Involving Decedents (CORID). Where required, additional approval by local institutional review boards was sought.

LiDCO Ltd provided equipment education, training and support. An external advisory committee was assembled and included content experts and an independent statistician. The committee was chaired by an investigator outside of the coordinating center and not affiliated with any participating OPO (RP). The committee reviewed study conduct and the results of the interim analysis and made recommendations to the MOnIToR executive committee. This study used data from the Scientific Registry of Transplant Recipients (SRTR). The SRTR data system included data on all donors, wait-listed candidates and transplant recipients in the US, submitted by the members of the Organ Procurement and Transplantation Network (OPTN), and has been described elsewhere [15]. The Health Resources and Services Administration (HRSA), U.S. Department of Health and Human Services provides oversight to the activities of the OPTN and SRTR contractors. All the authors vouch for the integrity and the accuracy of the analysis and for the fidelity of the study to the protocol.

Selection of Subjects

Subjects were older than 16 years of age, were declared brain dead and were considered eligible for organ donation. An arterial catheter in place or a plan to place one was also required for enrollment. Donors were excluded from the study when research consent was not granted or there was inability to perform minimally invasive hemodynamic monitoring. Patients receiving lithium therapy; known severe aortic regurgitation, intra-cardiac shunts, or on intra-aortic balloon pump; receiving extracorporeal membrane oxygenation or ventricular assist device support were also excluded.

Intervention

After obtaining research consent, entry criteria and other baseline data was entered into a web-based enrollment application. Donors were assigned a study identification number and treatment allocation. Randomization was 1:1 into each arm, achieved using a web-based randomization system. Randomization was stratified according to the donor's age ≥65 vs.

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<65. In the usual care arm, the donor was managed according to local standards, which did not include functional hemodynamic monitoring. In the protocolized arm, a non-invasive hemodynamic monitor (LiDCO *Plus*, LiDCO Ltd, London, UK) was connected to the donor's indwelling arterial catheter and calibrated. A protocol guiding fluid therapy (Figure 1) was followed until transfer to the operating room for organ procurement.

Outcome Measures and Definitions

The primary outcome measure was the number of organs transplanted per donor. Secondary outcomes included: i) Number of organs recovered regardless of whether transplanted; ii) The observed (O) versus expected (E) organs transplanted (O/E) ratio; iii) Recipient survival to six months and iv) Six month hospital-free survival (6mHFS) in recipients—defined as recipient survival in days after transplantation in the first 6 months (6mHFS = days alive up to 180 days after transplantation minus index hospital length of stay in days).

Statistical Analysis

Our primary analysis was an intention-to-treat (ITT) analysis of the mean number of organs transplanted per donor in each group with one interim and a final analysis. As described previously [14], we planned in advance for a modified intention-to-treat (mITT) analysis where only subjects able to receive the intervention were included in the protocolized care arm (excluding donors when devices were unavailable, incompatible with local hospital equipment, or where technical problems unrelated to the subjects precluded use of the device). In addition we planned for a ‘responder’ analysis where donors in the protocol arm were judged to have responded to care by protocol. This determination was made by consensus of three investigators (AA, RM, JAK) based on changed in hemodynamics including PPV and blinded to study outcomes as previously described [14]. Finally, we calculated the observed (O) versus expected (E) organs transplanted (O/E) ratio as previously described [16]. A detailed description of this metric has been reported previously [14, 16].

The study was designed to enroll 960 subjects in order to detect a difference of 0.5 organs per donor assuming a mean of 3.1 organs transplanted per donor. A single interim analysis was conducted after accrual of 50% of the initially planned subjects (480). Results of Interim Analysis were forwarded to the Executive Steering committee, who determined that the trial did not meet the stopping criteria set by O'Brien-Fleming criterion, and the study was continued until March 23, 2013 when study resources would be exhausted.

Donor characteristics between Protocolized and Usual Care groups were compared using Wilcoxon's test for continuous data (e.g., Age) and chi-square tests with correction for continuity for categorical variables or its exact version, or the Fisher's test as appropriate. The primary endpoint of number of organs transplanted was presented using the mean and 95% Wald confidence intervals separately for the two arms, and the mean difference between the two arms were tested using two-sample two-sided t-test. The secondary endpoints of number of organs recovered and the observed/expected ratio was analyzed using same statistical methods.

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The secondary endpoint six-month hospital free survival (6mHFS) was analyzed using survival analysis methodology as some recipients were lost to follow up before 180 days. Kaplan-Meier survival curves were used to visually investigate the differences in the distribution of 6mHFS between the two arms while log-rank test was used to compare differences between two arms. A Cox proportional hazard model was used to quantify the hazard ratio and the results were presented as point estimate and 95% confidence interval. Overall recipient survival was calculated as the time from transplant to death. Since many of the recipients were censored, the analysis was limited to 12-month follow-up after transplantation. Usual methods of survival analysis, namely, Kaplan-Meier curves, log-rank test, and Cox model was used respectively to investigate the survival pattern across arms, to test the difference in distribution, and to quantify the hazard ratio. We conducted two pre-planned subgroup analyses examining expanded criteria donors (ECD) vs. standard criteria and age ≥65 vs <65 separately.

Sensitivity Analyses

Aborted cases (e.g. discovery of metastatic cancer or various infections or serology) are typically excluded from the assessment of number of organs transplanted from each donor. For all primary and secondary analyses aborted cases were excluded. However, as a sensitivity analysis we also reran our primary and secondary analyses considering aborted cases as having contributed zero organs.

Provider survey

In order to elucidate the opinions of the bedside coordinators as to relative ease of delivering the intervention, we conducted a brief post-study survey. The survey questions are provided in the supplement (Table S3).

RESULTS

Study subjects

We enrolled 556 brain dead organ donors; 279 were randomly assigned to protocolized care and 277 to usual care. Study flow is shown in Figure 2; 48 donors were aborted after randomization by the OPOs per standard protocols (e.g. a donor found to have metastatic cancer). No follow-up data are available on aborted cases. Characteristics of the remaining 508 donors are shown in Table 1 and are well balanced between groups. Protocolized care was associated with increased use of fluids. However, there were no differences in vasoactive medication use between the two groups (Table 2)

Number of organs transplanted

The distribution of organs transplanted from each group is shown in Table 3. We found no significant difference in the mean number of organs transplanted per donor with 3.39 (95% CI: 3.14-3.63) organs per donor in the protocolized care arm compared to 3.29 (3.04-3.54) organs per donor in the usual care arm (mean difference, 0.10, 95%CI: -0.25 to 0.45; p=0.56). In the mITT analysis the mean number of organs transplanted per donor increased (3.52 organs per donor, 95%CI: 3.23-3.8) but was not statistically significant (mean difference, 0.23, 95%CI: -0.15-0.61; p=0.23). Finally, in the ‘responder’ analysis the mean

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number of organs transplanted per donor increased further to 3.87±2.16 bringing the mean difference to 0.58±2.07 (95% CI -0.02 to 1.19; p=0.059). These results are illustrated in Figure 3.

Preplanned subgroup and sensitivity analyses

The mean number of organs transplanted from standard criteria donors was nearly identical by study arm: 3.92 for protocolized and 3.94 for usual care; p=0.96. For the ECD group, 1.83 organs were transplanted from protocolized care versus 1.66 for usual care (difference 0.16 (-0.30 to 0.63); p=0.49. Only 52 donors were ≥65 years of age and the mean number of organs transplanted was 1.0 for both study groups. We performed sensitivity analyses repeating ITT and mitt analysis where aborted cases were considered to have contributed zero organs (rather than being excluded). The results were very similar to the analysis presented above (data not shown).

Recipient outcomes

Among the 1476 recipients (740 in Protocolized Care and 736 in Usual Care) of organs from study subjects for whom data were available from SRTR, 1430 (718 in Protocolized Care and 712 in Usual Care) had survival data available. Of these, within the first 12 months of transplantation, 56 deaths (7.8%) occurred in the protocolized care arm and 56 (7.9%) in the usual care arm [Hazard Ratio: 0.97 (0.66-1.42), p=0.86. Survival curves for recipients of organs from donors in the ITT and mITT cohorts are shown in Figure S2. No statistically significant differences were observed between treatment arms in either group.

Finally, the distribution of six-month hospital-free survival was almost identical between recipients of organs from protocolized and usual care donors with median (25^{th} percentile, 75^{th} percentile) 171 (164-175) vs. 171 (163-174) days (p=0.35).

Post-study provider survey

Results of our survey are provided in the supplement (Table S3). Notably, while more than 50% of procurement coordinators found the protocol easy to follow, none (0%) classified the hemodynamic monitor device as ‘easy’ to use. While the protocol was implemented in 76% of subjects randomized to the intervention, only about a third of coordinators reported strictly adhering to the protocol.

DISCUSSION

MOnIToR is the only large multicenter randomized controlled trial of organ donor management published to date. Our results demonstrate that protocolized fluid therapy is not superior to usual care whether considering a strict ITT or a modified ITT analysis. Although these results are disappointing several important findings should be noted. First, large scale, multicenter, pragmatic trials have not been the norm in donor management. Prior studies have generally been small and single-center investigations [7, 17, 18] and outcomes have often been limited to short term organ functional assessments. This has led to adoption of clinical practices based on low-level evidence. For example, thyroid hormone has been commonly used in organ donors based on small case series. A recent meta-analysis of four

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existing RCTs (n=209) showed no benefit [19]. Similar results have been reported with corticosteroids [20]. Other trials have focused on specific organs. Mascia and colleagues randomized 118 potential lung donors across 12 centers to a lung protective ventilation strategy and reported a doubling (from 27% to 54%) of the number of organs transplanted without impacting six-month recipient survival [21]. Low-tidal volume ventilation was not standard for donors our trial. Similarly, Schnuelle and colleagues conducted a randomized, open-label, multicenter, parallel-group trial of 264 brain-dead kidney donors and found that low-dose dopamine infusion resulted in less dialysis in the recipients [22]. Our study demonstrates that large pragmatic trials are feasible in donors—using sample sizes necessary for detecting realistic effect sizes.

Second, though our study demonstrates feasibility, complex interventions that rely on skilled operators or, as in our study, availability and functionality of equipment, are less well suited to this area of medicine [23-26]. Organ procurement coordinators have difficult jobs caring for donors at different institutions with different types of cardiac monitors and different cultures.

Third, as to the effect of the intervention itself, the effect size, if there is any, is likely to be smaller than hypothesized. The mITT analysis likely reflects the “best case scenario” and showed a point estimate for difference between groups of 0.23 organs (95%CI: -0.15-0.61; p=0.23). Thus the true effect, while possibly reaching 0.5 organs is more likely about half this difference. In order to find a difference of only 0.23 organs we would have required a sample size of 4182 donors. A trial of this magnitude was beyond our resources and would have required involvement of many more OPOs. Finally, although an increase of 0.23 organs per donor extrapolates to a nearly 7% increase in available organs, which could result in thousands of lives saved, it nevertheless falls short of the desired impact. New interventions that increase organ yield such as therapeutic hypothermia [27-29] are being studied. However, given the magnitude of the problem and the potential for benefit, new interventions are needed.

Our protocolized fluid therapy was provided on a background of routine hemodynamic management. Prior to our study and to date, there is no consensus regarding the use of inotropes in the management of donors and therefore it was not possible to protocolize this aspect of care. Our study protocol focused on fluids and vasopressors and left inotropes and other agents at the discretion of the clinicians managing the donor. However, our analysis of protocol “responders” suggests that efforts to improve donor hemodynamics are likely worthwhile. Indeed responders nearly achieved a significant improvement in the number of organs used and the point estimate was greater than the originally hypothesized difference of 0.5 organs. Unfortunately less than a third of donors (29%) randomized to the intervention met our criteria for response, suggesting that either more effective interventions are needed or that some donors do not have modifiable hemodynamics.

We have faced several challenges conducting the study, some were expected and have been reported previously [30-32]. Our study highlights the fact that complex interventions are challenging and perhaps simpler interventions could prove to be more effective in achieving goals of donor care. Despite the extensive training we provided, some coordinators had

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difficulties with LiDCO calibration and many felt that it was time consuming. In our post-study survey it was clear that none of the providers felt that the intervention was easy and more than 40% classified it as hard. Indeed, only 76% of donors randomized to the intervention were able to receive it because of logistical problems including cable incompatibility, calibration problems or simply the lack of equipment on site. Although most found the protocol itself easy to follow, a simpler monitor system might have facilitated delivery of the intervention.

Unfortunately, it will take several years before new treatments can be developed and new trials can be conducted. While we await these developments we continue to be faced with an ever-increasing demand for organs and an ever-growing number of potential recipients dying for lack of these organs. For those practitioners using protocol-guided fluid therapy it is reassuring that our intervention did not appear to reduce organs in any subgroup or secondary analysis. Neither were any differences seen in major recipient outcomes such as length of hospitalization or 1-year survival. This suggests that recipients of organs taken from protocolized care donors fared as well as those receiving organs from usual care and that the extra 0.1 organs “rescued” by the intervention (or 0.3 in the mITT analysis) did not result in lower quality of organs transplanted. Indeed it is notable that in subgroup analysis, extended-criteria donors accounted for all the effect seen in the ITT analysis where again a smaller absolute, but similar relative (about 10%), increase was observed but failed to reach significance.

In conclusion, compared to usual care, protocolized fluid therapy on a background of routine hemodynamic management did not increase the number of organs transplanted from brain dead organ donors. More effective (and perhaps easier to implement) strategies are needed. Our trial demonstrates the feasibility of studying such interventions using a network of OPOs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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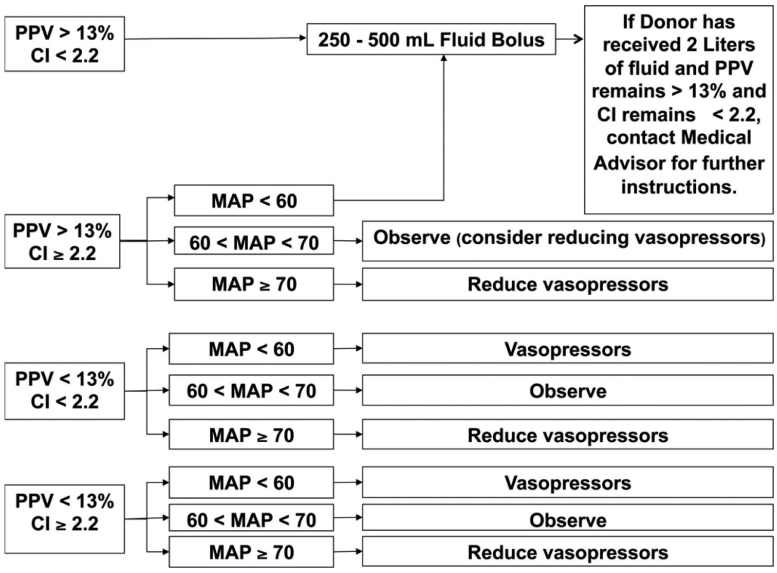

Figure 1.

MOnIToR protocol-guided hemodynamic management

PPV: pulse-pressure variation; CI: cardiac index; MAP: mean arterial pressure.

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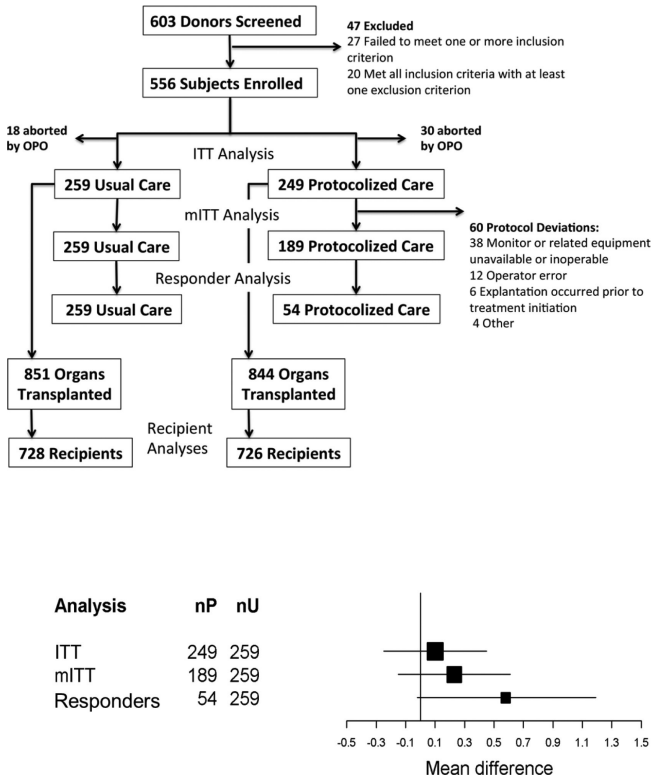

Figure 2.

Study flow chart

ITT: intention-to-treat; mITT: modified intention-to-treat; OPO: organ procurement organization.

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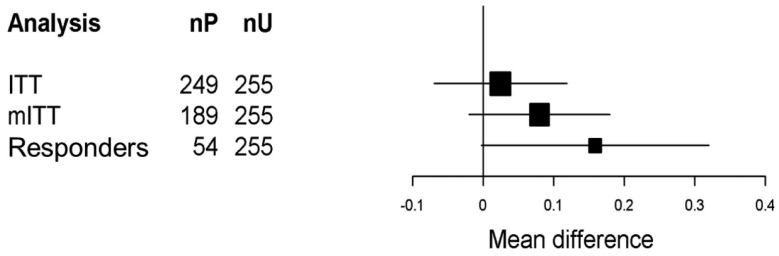

Figure 3.

Results of Primary and Secondary Analyses. Shown are differences in mean number of organs transplanted (top) and differences in the ratio of observed versus predicted organs per donor (bottom). Positive difference favors the protocolized arm; nP and nU are the sample sizes in the protocolized and usual care arms respectively. ITT: intention-to-treat; mITT: modified intention-to-treat.

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Table 1

Donor characteristics by Intervention Arm

Donor Characteristics	All (n = 508)^	Protocolized Arm (n=249)	Usual Care Arm (n=259)	p-value#
Age in years	44(29, 56)	43(29, 55)	46(28, 56)	0.35
Donor Race				0.49
Black or African American	65(12.8)	31(12.4)	34(13.1)	
White	419(82.5)	209(83.9)	210(81.1)	
Other	24(4.7)	9(3.6)	15(5.8)	
Donor ABO				0.78*
A1: A1	91(17.9)	49(19.7)	42(16.2)	
A1B: A1B	5(1)	4(1.6)	1(0.4)	
A2: A2	10(2)	3(1.2)	7(2.7)	
A2B: A2B	1(0.2)	0(0.0)	1(0.4)	
A: A	88(17.3)	38(15.3)	50(19.3)	
AB: AB	9(1.8)	4(1.6)	5(1.9)	
B: B	52(10.2)	29(11.6)	23(8.9)	
O: O	252(49.6)	122(49)	130(50.2)	
Donor Gender				0.84
Female	241(47.4)	117(47)	124(47.9)	
Male	267(52.6)	132(53)	135(52.1)	
Donor History of Diabetes				0.22**
1: NO	451(88.8)	224(90)	227(87.6)	
2: YES, 0-5 YEARS	20(3.9)	11(4.4)	9(3.5)	
3: YES, 6-10 YEARS	10(2)	2(0.8)	8(3.1)	
4: YES, >10 YEARS	25(4.9)	12(4.8)	13(5)	
5: YES, DURATION UNKNOWN	2(0.4)	0(0.0)	2(0.8)	
Donor hypertension				0.94
No	295(58.3)	145(58.5)	150(58.1)	
Yes	211(41.7)	103(41.5)	108(41.9)	
Donor history of hypertension				0.98
1: NO	297(58.5)	145(58.2)	152(58.7)	
2: YES, 0-5 YEARS	94(18.5)	46(18.5)	48(18.5)	
3: YES, 6-10 YEARS	41(8.1)	19(7.6)	22(8.5)	
4: YES, >10 YEARS	56(11)	30(12)	26(10)	
5: YES, UNKNOWN DURATION	18(3.5)	8(3.2)	10(3.9)	
998: UNKNOWN	2(0.4)	1(0.4)	1(0.4)	
Donor Meets Expanded Criteria				0.42
No	370(73)	185(74.6)	185(71.4)	
Yes	137(27)	63(25.4)	74(28.6)	

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Donor Characteristics	**All (n = 508)^**	**Protocolized Arm (n=249)**	**Usual Care Arm (n=259)**	**p-value#**
Age ≥65 Years				0.89
	456(89.8)	224(90)	232(89.6)	
	52(10.2)	25(10)	27(10.4)	

^ Patient characteristics of 48 aborted donors were not available;

From two-sided t-test for Age, from Chi-square test for others;

* Based on A, B, AB, and O, p-value = exact Chi-square test

** p-value = exact Chi-square test

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Table 2

Use of fluid and medications by intervention arm

Variable	Protocolized Care	Usual Care	P Value
Fluids infused (ml)	1,229.10	986.18	0.037
Mean (SD)	(2,502.12)	(2,195.98)	
Medications used (%)			
Antihypertensives	56 (24.9)	56 (22.2)	0.49
Vasodilators	14 (6.6)	9(3.5)	0.13
DDAVP	67 (29.6)	79 (30.86)	0.77
Vasopressin	121 (53.5)	130 (50.5)	0.52
Inotropes/vasopressor	195 (49.8)	196 (50.1)	0.72

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Table 3

Number of organs transplanted by intervention arm

Number of Organs Transplanted	Intervention		Total (508)
	Protocolized Care N=249	Usual Care N=259	
0	20(8.03)	21(8.11)	41
1	28(11.24)	38(14.67)	66
2	28(11.24)	39(15.06)	67
3	65(26.1)	47(18.15)	112
4	38(15.26)	43(16.60)	81
5	28(11.24)	29(11.20)	57
6	24(9.64)	21(8.11)	45
7	15(6.02)	17(6.56)	32
8	3(1.20)	4(1.54)	7
Summary			Difference
Mean (sd) 95% CI	3.39(1.97) (3.14, 3.63)	3.29(2.05) (3.04, 3.54)	0.10(2.01) (−0.25, 0.45)
p-value from t-test (pooled)			**t_{506} = 0.58, p** =0.56