Changing Epidemiology of Organ Donation After Neurological Determination of Death in Canada and Implications for Transplantation: A Cohort Study In Southern Alberta and Corresponding National Data

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Abstract

Background: The cause of brain injury may influence the number of organs that can be procured and transplanted with donation following neurological determination of death (NDD).

Methods: We performed a cohort study in Southern Alberta involving consecutive NDD donors. For each donor, we determined last available measures of organ injury and number of organs transplanted, and compared these variables for different causes of NDD. Comparative national Canadian data were obtained.

Results: Between 2003 and 2014, there were 226 NDD donors. The relative proportion with traumatic brain injury (TBI) decreased over time (2003-2005: >30% vs. 2012-2014: 6-23%; p=0.004), while that with anoxic brain injury (ABI) increased (2003-2005: 14-37% vs. 2012-2014: 46-80%; p=0.0002). Among 4290 NDD donors across Canada 2000-2013, the annual number with TBI decreased from >4 to ≈3 per million population, while that with ABI increased from ≈1 to >3 per million. Donors with ABI had higher concentrations of creatinine, ALT and troponin T, and lower P_aO_2/F_IO_2 and urine output than donors with TBI or stroke. Organs transplanted per donor averaged 3.6 with ABI versus 4.5 with TBI or stroke (p=0.002), and decreased over time from 3.7-4.5 (2003-2005) to 3.4-3.8 (2012-2014). Nationally, this figure remained stagnant despite increments for each individual cause of death. There was a significant association between duration of donor cardiac arrest and delayed kidney graft function.

Interpretation: ABI has become a more common source of NDD organ donation than TBI in Canada. Fewer organs are procured from ABI donors. Strategies to maximize organ usage should be pursued.

Introduction:

Despite the emergence of donation after cardiocirculatory determination of death (DCD), donation after neurological determination of death (NDD) remains the most common source of organ transplantation across the world. Several studies, performed in various countries, have reported that the proportion of brain-injured patients that progresses to NDD has decreased over time[1-7]. This temporal trend may be most pronounced among patients with traumatic brain injury (TBI)[1, 6-7]. Advances in injury prevention, resuscitation, and supportive care are likely to be contributing factors[1, 8-11].

In contrast, the proportion of patients with cardiac arrests where bystander cardiopulmonary resuscitation, automated external defibrillation and advanced cardiac life support leads to return of spontaneous circulation is increasing, such that more patients with anoxic brain injury (ABI) are admitted to intensive care units[12-15]. In some cardiac arrest victims, ischemic injury to the brain is sufficiently severe to cause progression to NDD[16]. Apart from causing ABI, cardiac arrests may also induce ischemic injury to other organs. In patients that progress to NDD, this may reduce the number of organs available for donation and transplantation. When "marginal" organs are transplanted, graft function in recipients may be delayed or permanently impaired.

We performed a cohort study among consecutive NDD donors in Southern Alberta to determine whether the distribution of causes responsible for NDD has changed, and if so, whether this has had an impact on organ quality, transplantation rates and recipient outcomes. Using administrative data, we also assessed national trends across Canada.

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Materials and Methods:

The Conjoint Health Research Ethics Board at the University of Calgary approved this

research.

A comprehensive clinical information system (AltraBase) is used to manage all organ

donation referrals in Southern Alberta, and enables linkage of donor and recipient data.

Donor management is in accordance with national guidelines, which are incorporated directly

into a region-wide electronic order set[17]. In every donor, solid organs are routinely offered to

transplant programs across the country and to the United Network for Organ Sharing (UNOS)

when no suitable recipient is found in Canada. Kidney and pancreas transplantation are

performed locally. Liver, lung, heart and small bowel allografts are transported to other

centers.

Using prospectively collected data, we identified consecutive patients that progressed to NDD

between 2003 (earliest reliable data) and 2014, for whom surrogate decision makers

consented to organ donation. The cause of NDD was categorized as TBI, ABI, stroke

(subarachnoid hemorrhage, spontaneous intracerebral hemorrhage, ischemic stroke or

cerebral venous thrombosis), or other causes. This determination was made by a specialist

in neurocritical care (AK) based on review of medical records and neuroimaging, without

coinciding knowledge regarding organs procured and transplanted. Patients were classified

as having ABI if there was documentation of a preceding cardiac arrest in the medical record.

Patients with cardiac arrest in the context of another type of brain injury were categorized as

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having ABI if the arrest lasted longer than five minutes. The rationale was twofold: First, five

minutes is the approximate time frame after which permanent ischemic injury to the brain

becomes possible[18]. Second, although the original etiology of brain injury might have been

an equally or more important factor causing progression to NDD, the concomitant cardiac

arrest had the potential to perpetuate organ injury. Significant sustained organ dysfunction is

unusual simply from prolonged hypoxemia or a brief cardiac arrest.

For each donor, the following measures of organ injury were determined: last available

concentration of creatinine, urea, alanine aminotransferase (ALT), and bilirubin; average urine

output over the three hours preceding organ procurement; international normalized ratio

(INR); peak troponin T (TnT); ejection fraction by echocardiography; and the last ratio relating

the partial pressure of oxygen to the inhaled fraction of oxygen (P_aO_2/F_IO_2), performed in a

standardized fashion, with F_IO_2 100% and PEEP 5 mmHg.

A secondary outcome was whether organ function was impaired among recipients of grafts

from donors with ABI in relation to other etiologies. For recipients of kidney transplants from

NDD donors in 2009-2014, we evaluated the following outcomes: patient and graft survival,

delayed graft function (DGF), and creatinine concentration at discharge and after one year.

DGF was defined in two ways: (1) As the temporary need for intermittent hemodialysis in the

week following transplantation; and (2) "Functional" DGF, namely failure of the creatinine

concentration to decrease by $\geq$ 10% on $\geq$ 3 consecutive days during the week following

transplantation[19]. Because liver, lung and heart transplantation are not performed at our

center, outcomes in recipients could not be determined. The time frame was chosen because

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2009 was when a provincial electronic health record system became available in Alberta, enabling detailed follow-up of recipient and kidney graft function.

To examine national trends in the etiology of NDD and number of organs transplanted per donor, we obtained data from the Canadian Institute of Health Information (CIHI) from 2000-2013. Data from the province of Quebec, as well as national data from the year 2014 were not yet available. Diagnostic codes in the CIHI database for patients with NDD were clustered into the following categories to match, as much as possible, our local data: TBI ("trauma", "motor vehicle collision", "gunshot"); ABI ("anoxic", "CO poisoning", "asthma"), stroke ("stroke", "ruptured cerebral aneurysm", "spontaneous intracranial haemorrhage"), and "other" ("primary CNS tumour", "CNS infection", "intracranial event", "SIDS", "unknown", "other", "cerebral edema"). CIHI data only assigns one code per donor. It was therefore impossible to know whether patients with TBI, stroke or "other" causes of NDD may have also had a cardiac arrest. We therefore anticipated that the proportion categorized as having ABI would be smaller in the CIHI database than in our local data set. Furthermore, some patients with TBI, ABI or stroke could have been categorized in a less specific fashion simply as having "cerebral edema". It was therefore to be expected that there would be more patients with "other" causes of NDD in the CIHI dataset. For privacy protection, CIHI regulations preclude release of data when there are fewer than five patients per data cell. Data were therefore clustered into epochs of three years.

Chi-square analysis or Fisher's exact test, as appropriate, were used to compare categorical variables. Analysis of Variance (ANOVA) and Mann-Whitney U tests were used to compare continuous variables, with adjustments for multiple comparisons using Tukey's test[20]. The

Cochrane-Armitage test was used to assess the significance of temporal trends[21]. In

assessing the association between cause of NDD and number of organs transplanted per

donor, we used multivariable linear regression to adjust for confounders, including donor age,

sex, body mass index, presence of pre-existing hypertension or diabetes, use of

methylprednisolone and levothyroxine, and presence of positive viral serology (HIV or

hepatitis).

Results:

Temporal Trends In Cause of NDD

Over 12 years, there were 226 NDD organ donors in Southern Alberta. Of these, there were

100 with ABI (44%), 63 with stroke (28%), and 51 with TBI (23%). Of those with ABI, 16 had

another co-existing form of brain injury, with seven cardiac arrests occurring in the setting of

stroke and nine with TBI. Twelve donors (5%) developed NDD due to other causes. The

consent rate for organ donation among patients identified as having progressed to NDD was

72%, 73% and 84% with ABI, TBI, and stroke, respectively (p=0.42), and did not change over

time. The relative proportion of NDD donors with ABI increased over time, from as low as

14% in 2004 to as high as 80% in 2013 (Figure 1; p=0.0002). In contrast, the proportion with

TBI gradually decreased, from about 30% in 2003-2005 to 6-7% in 2013-2014 (p=0.004).

The proportion with stroke remained relatively unchanged. Cause of the cardiac arrest was

classified as follows: overdose 24%; respiratory 20%; traumatic 15%; primary cardiac 13%;

neurological 10%; suicide by hanging 6%; carbon monoxide poisoning 3%; drowning 3%;

pulmonary embolism 3%; anaphylaxis 1%; sepsis 1%; and unknown 1%.

Organ Injury

Table 1 compares characteristics of donors with ABI, TBI and stroke. At least one kidney was transplanted from 84%, 96% and 86% of donors with ABI, TBI, and stroke, respectively (p=0.10).   Donors with ABI had higher creatinine and urea concentrations, as well as lower urine output, compared with donors with TBI or stroke. Among ABI donors, there was a significant association between the duration of cardiac arrest and last available creatinine concentration (p=0.03).

The liver was transplanted from 81%, 92% and 86% of donors with ABI, TBI, and stroke, respectively (p=0.19). The median ALT concentration was significantly higher in donors with ABI than in those with other diagnoses. The INR was higher in donors with ABI than in those with stroke.

At least one lung was transplanted from 22%, 41% and 54% of donors with ABI, TBI and stroke, respectively (p=0.0001). The last available P_aO_2/FIO2 was significantly lower in donors with ABI than in those with TBI or stroke. The heart was transplanted in 30%, 37% and 37% of donors with ABI, TBI, and stroke, respectively (p=0.57). Troponin T concentrations were higher among donors with ABI, but ejection fraction did not differ.

Organs Per Donor

A mean of 3.6 organs were transplanted from donors with ABI, compared with 4.5 from those with TBI or stroke (p=0.002). In multivariable analysis, ABI remained an independent predictor of fewer organs transplanted per donor (p=0.003). Corresponding with the emergence of ABI as the predominant cause of NDD in our region, there was a reduction in the number of organs transplanted per donor, from a peak of 4.5-4.6 in 2005-2006 to 3.4-3.8 in 2012-2014.

When the analysis was restricted to donors with ABI, there was an inverse relationship between duration of cardiac arrest and number of organs procured per donor. The mean number of organs transplanted was 4.0 when the cardiac arrest was less than 30 minutes, compared with 3.2 (p=0.08) and 2.6 (p=0.04) when it was longer than 30 and 60 minutes, respectively.

Kidney Recipient Outcomes

Over six years, 145 patients received kidney transplants from local NDD donors. The cause of NDD was ABI, TBI or stroke in 143 cases (99%). The rate of DGF was lowest among recipients of kidneys from donors with TBI and highest with stroke, although these differences were not statistically significant (Table 2; p=0.20). Creatinine concentrations throughout the post-transplant week, at the time of hospital discharge, and after one year were consistently lowest among recipients of kidneys from TBI donors.

In recipients of kidneys from donors with ABI, the median donor cardiac arrest duration was 45 minutes (IQR 21-69) when DGF occurred, compared with 30 minutes (IQR 20-43) without

DGF (p=0.06). The incidence of DGF was 22% (p=0.73), 38% (p=0.01), and 50% (p=0.005)

when cardiac arrest duration in donors was longer than 30, 45 and 60 minutes, respectively.

At one year post-transplantation, six patients (4%) had died or were receiving dialysis.

National Data

Across Canada, the number of NDD organ donors changed minimally over 14 years,

remaining in the range of 12-13 donors per million population (DPMP). The number of NDD

donors with TBI decreased from a maximum of 4.4 DPMP in 2000-2002 to fewer than 3

DPMP in 2009-2013. This decrement was offset by a threefold rise in NDD ABI donors (0.7-

1.1 DPMP in 2000-2005 to 3.1 DPMP in 2012-2013) (Figure 2).

The number of organs transplanted was higher in donors with TBI in comparison to those with

ABI or stroke (Figure 3). This was true for each individual organ system (Table 3). Within

each diagnostic category, the number of organs transplanted per donor increased over time.

However, with the relative decline in TBI donors and increment in ABI donors, the national

average of organs transplanted following NDD remained stagnant at 3.3-3.5 per donor.

Interpretation:

Over the past decade, ABI has replaced TBI and various forms of stroke as the most common

cause of NDD among organ donors in our region. Across Canada, the annual rate of NDD

organ donation following TBI has decreased by about 25%, while the rate of NDD organ

donation following ABI has tripled. A reduction in donors with TBI is likely due to a declining

incidence of severe TBI, as well as a smaller proportion of patients that progress to NDD[1, 22].

These observations, in turn, are likely due to advances in injury prevention and care of TBI

patients. Severe cerebral edema following TBI is sometimes managed with decompressive

surgery, after which progression to NDD becomes uncommon [8]. Conversely, the proportion

of cardiac arrest victims that achieve return of spontaneous circulation has increased over

time, a trend that has been attributed, in part, to greater provision of bystander

cardiopulmonary resuscitation and availability of automated external defibrillators[12-15].

Donors with ABI had, on average, a greater degree of organ injury than those with other

conditions. Accordingly, the number of organs transplanted per donor was lower with ABI

than with other causes of NDD, even after adjustment for potentially confounding donor

characteristics. With an increment in the proportion of donors with ABI in our region, there

was a corresponding decline in the number of organs procured per donor.

Measures of organ injury are not recorded by CIHI and could not be assessed using national

data. The number of organs transplanted per donor across Canada was highest with TBI, but

was similar between ABI and stroke. Despite the relative decline in TBI, and increase in ABI

donors, the average number of organs transplanted per NDD donor did not change, largely

because of an increment within each individual diagnostic category. It is possible that

transplantation programs have become more willing to accept marginal organs, including

those from post-cardiac arrest donors.

DGF was uncommon in recipients of kidneys from TBI donors. In contrast, there was a high

incidence among recipients of kidneys from donors who had sustained cardiac arrests

exceeding 45-60 minutes. DGF is associated with a higher incidence of acute rejection, eventual graft failure, and long-term mortality, as well as higher cost [23-24]. Interventions aimed at reducing DGF, such as systemic hypothermia in donors, pulsatile machine perfusion, or adjustment to immunosuppressive regimens in recipients may be particularly important when kidneys are procured from donors at high risk of DGF, such as those with prolonged cardiac arrests[24-26].

Previous small studies have assessed organ injury in cardiac arrest victims that progressed to NDD[27-30]. ABI donors were generally reported to have greater hemodynamic instability, higher liver enzymes, and fewer organs procured. However, outcomes in recipients of organs from ABI donors were not necessarily worse than with other diagnoses[31-37]. Despite the high rate of DGF with prolonged cardiac arrests, few patients required dialysis after one year. Nevertheless, there was a consistent trend towards improved early and long-term kidney function in recipients of allografts from donors with TBI compared with ABI or stroke.

Achievement of certain "donor management goals" (DMGs) prior to organ procurement has been associated with a larger number of organs transplanted[38-39]. Based on our observations, consistent achievement of DMGs may be less realistic for donors with ABI, especially those sustaining prolonged cardiac arrests.   Professional groups have formulated guidelines for donor management[17, 40]. Adoption of Canadian recommendations may be one reason why the number of organs transplanted per donor has increased nationally for each individual cause of NDD[17].

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In summary, the epidemiology of NDD in Canada has changed, with a relative decline in the

proportion of donors with TBI, and an increment in those with ABI. Because fewer organs are

procured and transplanted from ABI donors, this epidemiologic shift has contributed to

stagnancy in the total number of organs available for transplantation. Outcomes are

favourable when organs from well-selected NDD donors with ABI are transplanted, although

prolonged cardiac arrests in the donor are associated with more DGF, which may impact

longer-term outcomes. Future research should develop additional strategies aimed at

optimizing organ usage in NDD donors.

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Figure Legends:

Figure 1. Temporal trends in the relative distribution of causes of brain death in deceased

organ donors in Southern Alberta, 2003-2014.

Figure 2. Temporal trends in the relative distribution of causes of brain death among organ

donors in Canada (minus Quebec), 2000-2013.

Figure 3. Temporal trends in the number of organs transplanted per brain dead organ donor

by diagnosis in Canada (minus Quebec), 2000-2013.

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Table 1. Comparison of organ donor characteristics based on the cause of brain death.

	Anoxic Brain Injury (n=100)	Traumatic Brain Injury (n=51)	Stroke[a] (n=63)
Age (years)	35 (23-52)	25 (20-42)[b]	53 (39-59)[b]
Sex (female / male)	47 (47%) / 53 (53%)	20 (39%) / 31 (61%)	32 (51%) / 31 (49%)
Body Mass Index	35 (25-47)	30 (25-35)	34 (24-43)
Expanded Criteria Donors[c]	12 (12%)[d]	6 (12%)[d]	24 (38%)
Positive viral serology (HIV, hepatitis B or C)	6 (6%)	3 (6%)	6 (10%)
Kidneys			
Creatinine (μmol/L)	86 (64-140)	75 (52-96)[b]	66 (50-83)[b]
Urea (mmol/L)	6.6 (4.8-9.9)	4.8 (3.6-6.3)[b]	4.2 (3.2-7.3)
Urine Output (mL/hr)	65 (30-125)	125 (63-200)[b]	100 (45-175)[b]
$\geq$ 1 transplanted	84 (84%)	49 (96%)	53 (86%)
Liver			
ALT (units/L)	107 (59-283)	34 (21-54)[b]	23 (14-42)[b]
INR	1.3 (1.2-1.4)	1.2 (1.1-1.3)	1.2 (1.1-1.3)[b]
Bilirubin (μmol/L)	8 (5-13)	10 (7-16)	8 (6-12)
Transplanted	81 (81%)	47 (92%)	54 (86%)
Lungs			
P_aO_2/F_IO_2 (Last O_2 challenge)	251 (120-370)	328 (218-407)[b]	316 (227-394)[b]
$\geq$ 1 transplanted	22 (22%)	21 (41%)[e]	34 (54%)[e]
Heart			
Low sens troponin T (ng/mL; pre 2011)	0.30 (0.04-0.83)	0.15 (0.03-0.40)[b]	0.07 (0.03-0.32)[b]
High sens troponin T (ng/L; post 2011)	311 (65-1121)	33 (9-62)	14 (5-116)
Ejection Fraction (%)[f]	55 (40-60)	54 (40-60)	60 (54-64)
Transplanted	30 (30%)	19 (37%)	23 (37%)
Pancreas			
Whole transplanted	20 (20%)	17 (33%)	14 (22%)
Islet cells transplanted	20 (20%)	6 (12%)	20 (32%)
Total Organs Transplanted (median, IQR)	4 (2.5-5)	4 (3-6)[b]	5 (3-6)[b]
Total Organs Transplanted (mean, SD)	3.6 (1.9)	4.5 (1.8)[b]	4.5 (2.2)[b]

[a] Defined as subarachnoid hemorrhage, intracerebral hemorrhage, or ischemic stroke

[b] $P < 0.05$ compared with anoxic brain injury using ANOVA with adjustment for multiple comparisons

[c] Defined as age $\geq$ 60 or age $\geq$ 50 with at least two of hypertension, creatinine > 132 μmol/L or cause of death cerebrovascular accident

[d] $P < 0.05$ compared with stroke using chi-square analysis

[e] $P < 0.05$ compared with anoxic brain injury using chi-square analysis

[f] Available for only 66% of donors

Table 2. Characteristics and Outcomes in Recipients of Kidney Allografts Based on Etiology of Brain Death (2009-2014)

	Anoxic Brain Injury (n=80)	Traumatic Brain Injury (n=23)	Stroke[a] (n=40)
Donor Age (years)	35 (21-52)	34 (25-52)	55 (37-59)[b]
Recipient Age (years)	50 (37-59)	60 (49-71)	48 (35-61)
Delayed Graft Function (Need for Dialysis)	16 (20%)	2 (9%)	11 (28%)
Functional Delayed Graft Function[c]	24 (30%)	3 (13%)	12 (30%)
Length of Stay (Days)	11 (8-14)	8 (7-10)	11 (8-21)
Creatinine (µmol/L)			
Day 3	360 (205-476)	232 (129-358)	457 (222-536)[d]
Day 5	205 (125-407)	121 (85-231)	254 (135-421)[d]
Day 7	146 (105-288)	108 (79-161)	210 (125-347)
Hospital Discharge	124 (93-186)	94 (80-137)	145 (92-170)
One Year	105 (87-140)	98 (73-111)	124 (98-169)
Hospital Mortality	2 (3%)	0	0
Dialysis at One Year	1 (1%)	1 (4%)	2 (5%)

[a] Defined as subarachnoid hemorrhage, intracerebral hemorrhage, or ischemic stroke
[b] $P < 0.05$ compared with other categories using ANOVA with adjustment for multiple comparison
[c] Defined as $\leq$ 10% reduction in the serum creatinine concentration on $\geq$ 3 consecutive days during the first post-transplantation week
[d] $P < 0.05$ compared with TBI with adjustment for multiple comparisons

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Table 3. Proportion of brain dead organ donors that transplanted specific organs in Canada (Quebec excluded) from 2000-2013

Cause of Death	Kidney	Liver	Lung	Heart	Pancreas[*]
Traumatic Brain Injury	94%	86%	37%	48%	36%
Anoxic Brain Injury	84%	83%	26%	28%	26%
Stroke	86%	82%	34%	23%	23%
Other	85%	80%	40%	37%	26%

[*]Whole pancreas or islet cells

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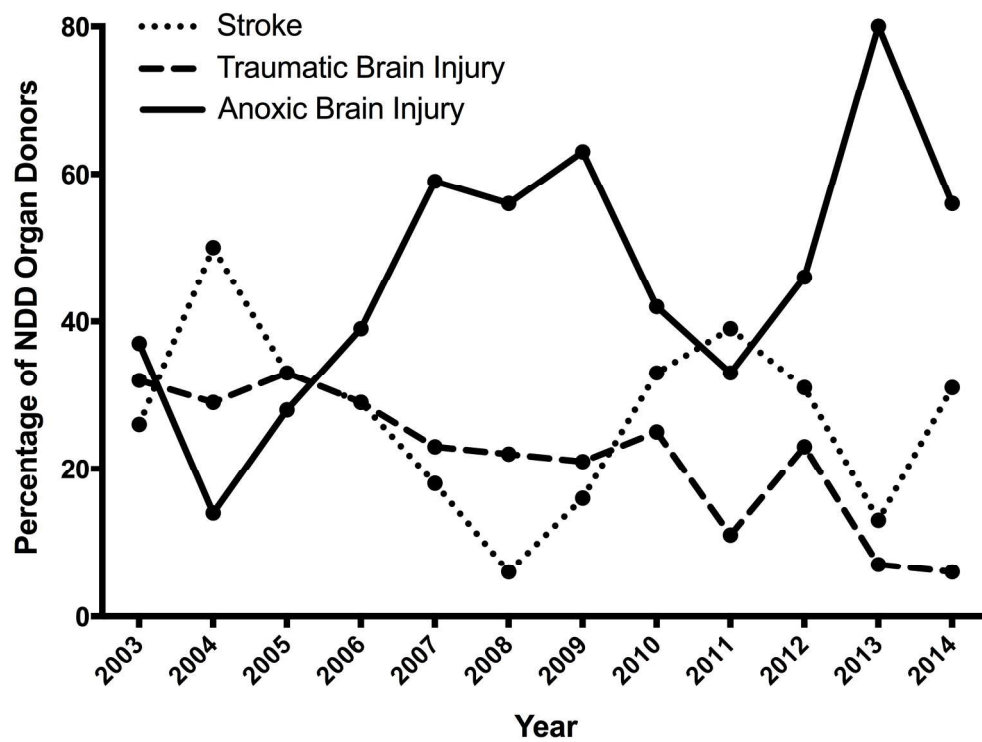
Figure 1
197x150mm (300 x 300 DPI)

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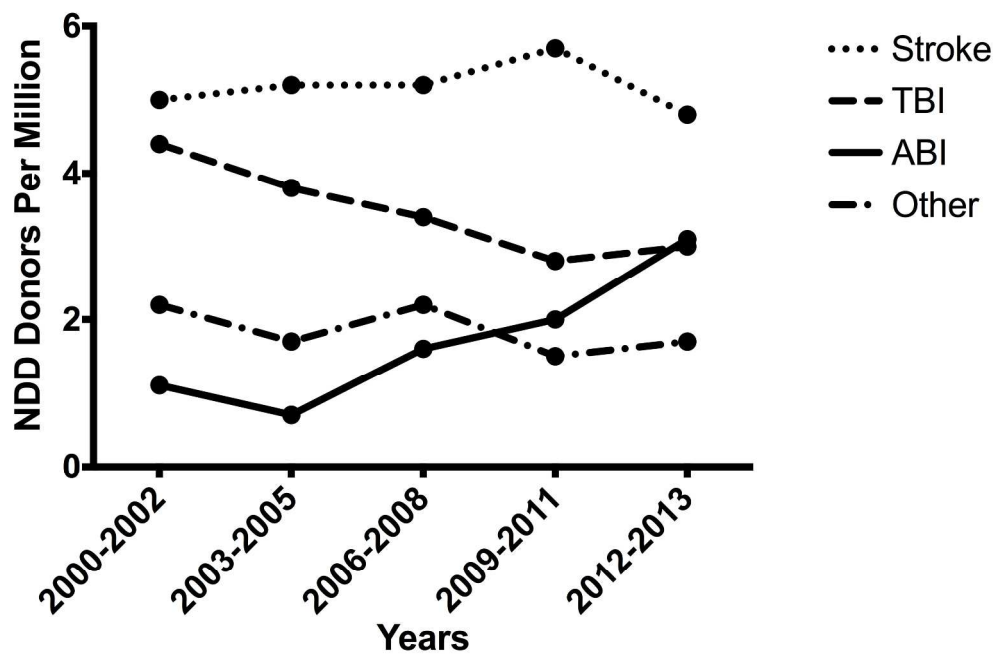
Figure 2
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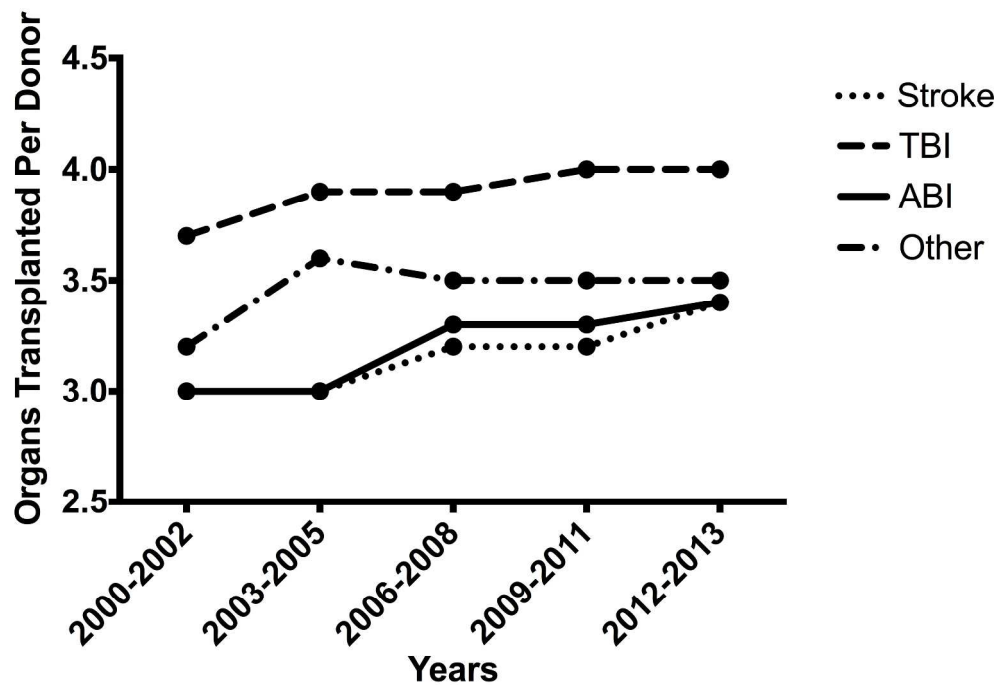31
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Figure 3
255x177mm (300 x 300 DPI)