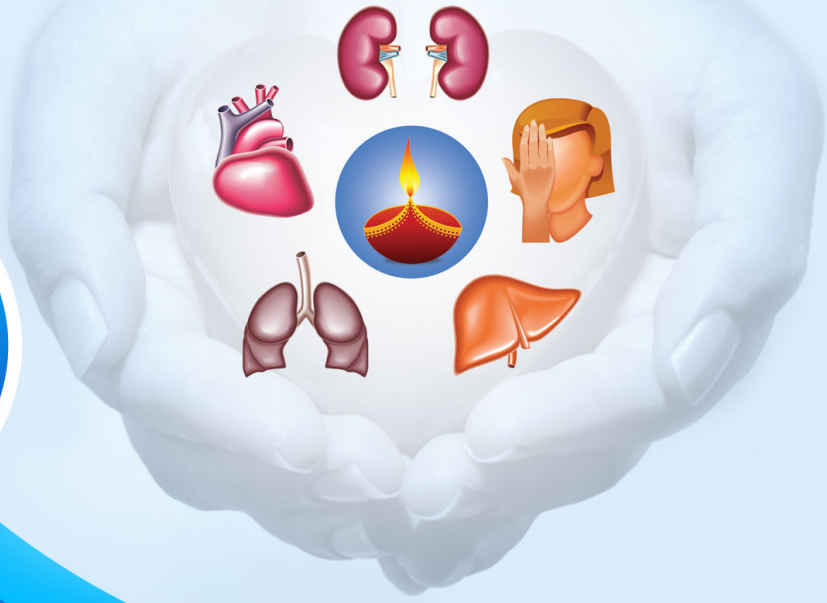
Indian Society of Organ Transplantation

Mid-Term Meeting



24th & 25th June 2016
Bengaluru

STANDARDISING TRANSPLANT CARE
&
MAKING IT AFFORDABLE

NOTTO
सत्यमेव जयते

THE INTEGRATED LIVER CARE foundation

ZCCK

MOHAN FOUNDATION

www.txupdate.co.in

WELCOME MESSAGE

Dear Delegate

It is a pleasure to welcome you to the ISOT Midterm Meeting - Transplant Update 2016. It is the first meeting being held along with a multi-organ retrieval workshop on the theme of 'Standardising Transplant Care and Making it Affordable.'

Over the past 26 years, the society has grown to be the main forum for discussions on transplants and has over 1000 members.

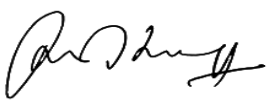
Last year there was a significant increase in deceased organ donations and there were an additional 1,600 organs and a similar number of tissues added to the overall transplantation numbers in the country with Tamil Nadu leading the way.

This year, the number of available organs is likely to double. With this encouraging scenario, it is important to ensure that potential organ donors are well optimised, organs well retrieved and transplanted for good graft outcomes.

Equally important is making transplants more affordable, so that a larger section of the community can benefit from this increase in the organ pool. The issues related to this matrix are still evolving in India and hence this focused meeting has been planned to discuss the subject and evolve standard protocols and templates of costs to standardise our care in this field.

This conference is combined with a Multi organ retrieval Workshop being organised at MS Ramaiah Advanced Learning Centre, Bengaluru.

We hope that you will find the meeting informative and enriching, and also enjoy the delights that the garden city of Bengaluru has to offer.



Dr. Georgi Abraham
Chairman

Dr. Sunil Shroff
Convener

June 2016

AGENDA

Day 1 - 24th June 2016

10:30 AM Registration & coffee

11.15 AM Welcome Dr. R. K. Sharma

11.25 AM - 11.45 AM
TRANSPLANTS, CURRENT SCENARIO & QUALITY INDICATORS IN TRANSPLANTS – Dr. Sunil Shroff

11.45 AM - 1.15 PM
SESSION I (a) - ORGAN DONATION AND TRANSPLANATATION - QUALITY ISSUES
Chair: Dr. A. Olithselvan, Dr. Prashant Marla & Dr N. S. Nagesh

Dr. Shakir Tabrez
Standard Vs expanded deceased donor (15 mins)

Dr. B. Subba Rao
Difficult cadaver donations - our experiences (10 mins)

Dr. Anand Khakhar
Cadaver liver - criteria for selection and contraindications (10 mins)

Dr. Jacob Abraham
Heart donation - selection & dilemmas as we move forward (10 mins)

SESSION I (b) - ORGAN DONATION AND TRANSPLANTATION - QUALITY ISSUES
Chair: Dr. Narayan Prasad, Dr. Gokulnath

Dr. S. Sundar
Induction or no induction for cadaver donor transplantation (10 mins)

Dr. Noble Gracious
Donor sepsis - our experience (10 mins)

Dr. Ravi Mohanka
Perfusion Fluids – types, costs, amounts used in living and cadaver, outcomes of various fluids making it affordable (15 mins)

Dr. Ashish Sharma
Quality of organs from Donation after Circulatory Death - our early results (10 mins)

1.15 PM to 2 PM Lunch

2.00 PM - 3.30 PM

SESSION II (a) - TRANSPORT OF ORGANS

Chair: Dr. Kishore Babu, Dr. Rajendra Pandey & Dr. Jose Chacko Periapuram

Dr. J. Amalorpavanathan
Stretching the boundaries – interstate organ sharing (10 mins)

Dr. D. Ramesh
Creating green corridors - Logistic issues in transport (10 mins)

Mr. L. Satish
Air-transport for patients and organs (10 mins)

SESSION II (b) - BRIDGE TO TRANSPLANTS

Chair: Dr. Rajasekhar Perumalla, Dr. Anil Kumar, Dr. Devanand

Dr. K. R. Balakrishnan
Organ care systems & Bridge to transplants (15 mins)

Dr. Mahesh Gopashetty
Machine perfusion for organs (10 mins)

Discussion

3.30 PM - 4.30 PM

SESSION III - POST OP TRANSPLANT ISSUES – MAKING THE ECONOMICS AFFORDABLE

Chair: Dr. Chittaranjan Kar, Dr. Vishwanath Siddhini & Dr. R. Bagirath

Dr. R. K. Sharma
Introduction to Affordability in transplants (10 mins)

Dr. Rajeevalochana Parthasarathy
Cost comparisons of common immunosuppressive drugs (10 mins)

Dr. Rajasekara Chakravarthi
Drugs used in transplantation & how to keep costs down (10 mins)

Panel Discussion
OPTIMUM TRANSPLANT CARE WITH LOW COSTS (30 mins)
Moderator: Dr. Edwin Fernando
Discussants: Dr. Narayan Prasad, Dr. Jose Chacko Periapuram, Dr. A. Olithselvan, Dr. Raghunadhan, Dr. Thomas Matthew

4.15 PM - 4.30 PM Tea Break

4.30 PM - 5.15 PM

SESSION IV - STANDARDISING EXCHANGE OF INFORMATION AND ORGAN RETRIEVAL

Chair: Dr. Nagamalesh, Dr Sanjay Govil & Dr. Sujata Patwardhan

Dr. Isabel Quiroga
Need for Standardised Exchange of Information & Standardised Organ Retrieval (10 mins)

Dr. Sunil Shroff
Forms for kidney (10 mins)

Dr. Ramdip Ray
Forms for liver (10 mins)

Dr. Jose Chacko Periapuram
Forms for heart (10 mins)

Dr. Gomathy Narasimhan
Can multi- organ retrieval be standardised (10 mins)

Discussion

5.15 PM-6.15 PM

SESSION V - NATIONAL TRANSPLANT PROGRAMME

Chairs: Dr. Vimal Bhandari, Mr. PWC Davidar & Dr. J. Amalorpavanathan

Dr. Vimal Bhandari
Nurturing the programme: Progress made & implementing the programme (10 mins)

Dr. Sujata Patwardhan
Challenges in formation of ROTTO and SOTTO for the west (10 mins)

Dr. Harsha Jauhari
Expectations & Reality (10 mins)

Discussion (30 mins)

6.30 PM to 7.00 PM

KEY NOTE ADDRESS

"ALTRUISM - THE CORNERSTONE OF ORGAN TRANSPLANTATION" - Mr. P.W.C. Davidar, IAS

7.15 PM to 8.00 PM

INAUGURATION

FOLLOWED BY DINNER

Day 2 - 25th June 2016

9.30 AM – 10.55 AM

SESSION I (a) - TRANSPLANT SURGERY AND FINANCIAL CHALLENGES

Chair: Dr. S. Jeswanth, Dr. Ravindra Prabhu & Dr. Julius Punnen

Dr. Nitin Kekre
Health of living kidney donors post donation - current evidence (10 mins)

Mrs. Yegnapriya Bharath
How can IRDA Help - Current policies on kidney and liver transplantation for recipient and donors (15 mins)

Dr. S. Prakash
Health Insurance- Impacting lives beyond business (10 mins)

Ms. Usha Girish
How can transplants get covered – exclusions and inclusions for recipients and donors (10 mins)

SESSION I(b) - TRANSPLANT SURGERY AND FINANCIAL CHALLENGES

Chair: Dr. Renuka Satish & Dr. K.C. Gurudev & Dr. Ravindra Prabhu

Ms. Aneka Paul
Subsidizing Transplant Care - Role of private trusts (10 mins)

Mr. Vasu
Our experiences in supporting transplant patients (10 mins)

10.55 AM - 11.15 AM Tea Break

11.15 AM to 11.45 AM

SESSION II - INVITED TALKS

Chair: Dr. J. Amalorpavanathan & Dr. L. K. Tripathi

Mr. Anoj Vishwanathan
Raising Funds for Transplant surgery - Using Technology (Social Media, Micro-financing) (15 mins)

Dr. R. Surendran
Lessons Learnt - Organising deceased donation transplantation program in government and private hospitals (20 mins)
Discussion

11.45 AM - Noon - **GROUP PHOTO**

Noon - 12.45 PM

SESSION III - SUPPORTING TRANSPLANT PATIENTS - HOW CAN THE INDUSTRY HELP

Moderator – Dr. Anand Khakhar

Discussants – Mr. Rajeev Sindhi, Mr. Yogesh Puri

1.00 PM - 1.30 PM Lunch

1.30 PM - 2.30 PM

SESSION IV COMPUTATION OF COSTS FOR AFFORDABLE TRANSPLANTS - BREAKOUT SESSION

Coordinators: Dr. S. Jeswanth, Dr. D. K. Srinivas & Dr. Sunil Shroff

Mrs. Lalitha Raghuram
Cost computing in transplants – Introduction and exercise (10 mins)

Kidney – Private, Public & non profit
Dr. Ashish Sharma, Dr. Keshavamoorthy, Dr. Girish Namagondlu, Dr. Gokulnath, Dr. Harsha Jauhari, Dr. Sanjeev Nair, Dr. Rajeeva, Dr. Vishwanath Siddhini

Liver – Private, Public & non profit
Dr. Anand Khakhar, Dr. S. Jeswanth & Dr. A. Olithselvan, Dr. Ravi Mohanka, Dr. Mahesh Gopashetty, Dr. Nagesh

Heart – **Private, Public & non profit**
Dr. Jose Chacko Periapuram, Dr. Devanand, Dr. Nagamallesh, Dr. R Bhagirath, Dr. Julius Punnen

Paediatric transplants – Dr. Arpana Iyengar, Dr. Gomathy Narasimhan

Deceased donor – Dr. Vijayanand Palaniswamy, Dr. Jacob Abraham, Dr. Shilpa Rao

2.30PM- 3.00 PM

SESSION IV (CONTD.) - GROUP PRESENTATIONS ON TRANSPLANTS COSTS

(5 mins each group**)**

3.00 PM - 3.10 PM

Subsidizing transplant care using the CSR model (10 mins)

Dr. Sonal Asthana

3.10 PM – 3.40 PM
SESSION V - TRAINING OUR MANPOWER - UPSCALING SKILLS
Chair – Dr. Philip Thomas, Dr. Anand Subrahmanyam & Dr. Nitin Kekre

Dr. Sonal Asthana & Dr. Sunil Shroff
Surgeons (10 mins)

Dr. Vijayanand Palaniswamy
Nurses & Technicians (10 mins)

Dr. Sumana Navin
Social workers – transplant coordinators (10 mins)

3.40 PM – 4.00 PM
VALEDICTORY AND OPEN HOUSE

Content

MAKING TRANSPLANTS AFFORDABLE WITH STANDARDISED CARE

Dr.Sunil Shroff, Convener, Transplant update 2016

An article in the Economic times 14 May 2016 highlighted the wide gap between the number of transplants and the number of patients in need of one. Apart from the non availability of organs the second most important factor that hampers transplantation is the cost. With costs that range in multiples of lakhs, transplants are perceived as a treatment option for only the rich and "well off" patients. Currently only a handful of Government run hospitals have a vibrant program on organ transplants for those who cannot afford the treatment.

The three fold increase in deceased donations in India since 2012 has meant more organs and more patients benefitting with the gift of life that comes with an altruistic tag. The spirit of altruism is the driving force in the deceased donation programme and hence it is mandatory that all sections of the society should derive benefit when such organs that are donated by a family keeping the larger good of community in mind. However the small success of this program has made us think about equitable distribution, the costs of transplants and their outcomes and our professional responsibility to the society.

Transplantation involves costs before, during, and after the actual transplant surgery. Costs starts from the day there is declining function of an organ and it never ends and goes on till the patient dies with either a functioning or non-functioning transplanted graft. Cost include laboratory tests; housing costs if from outstations while waiting for an organ, operating room cost, cost of organ acquisition, rehabilitation costs, medications - including immunosuppressive drugs and many other smaller hidden costs. There are large variations in the costs of transplantation in the different hospitals in India with some hospitals subsidising the care while others making large profits from such transplants.

With insurance being in state of infancy in India, most of the costs are borne by the patients. In a study carried out in 2013 the two main source of raising funds for a transplant was by selling property or homes and using personal savings[1]

Some of the patient who are able to somehow put the money together for transplantation surgery are unable to afford the lifelong post transplant treatment. Noncompliance with medication is a major reason for loss of graft in patients from lower or middle income group.

At present some of the health insurance policy does cover transplantation costs but there are limits to what they will cover. The excess expenditure including those of a living donor may have to be borne by the patient.

Unlike in the USA, support network like "Transplant Living" (that assists patients with information, education and links with philanthropic organization), India has very few NGO/ government agencies where a patient can clarify all their doubts regarding financing the surgery and the post surgery expenses.

Transplant economics is about making **transplants affordable** so that more patients can get access to this life saving surgery. This conference will address some of these common issues and try to find solutions.

Good outcomes require **Standardizations of transplant procedures** and starts from early identification and certification of brain death followed by maintenance, and a standardised organ retrieval and transplantation.

Transplant update 2016 aims to focus in the above two key areas and have a two day conference to deliberate on the above issues.

With the increasing numbers of both live related and deceased donor transplants, its imperative to standardise transplant care in India. This ISOT Midterm 2016 meeting is a step to address this pressing issue.

Reference

1. Ramachandran R, Jha V (2013) Kidney Transplantation Is Associated with Catastrophic Out of Pocket Expenditure in India. PLoS ONE 8(7): e67812. doi:10.1371/journal.pone.0067812

ORGAN DONATION / LIVING DONORS AND HEALTH INSURANCE

Ms. Susmitha Menon, Intern - Database Management, MOHAN Foundation
Dr. Hemal Kanvinde, Quality Assurance Officer, MOHAN Foundation

One of the greatest advancements in healthcare is organ donation. One can still have some hope to live a better life even after a vital organ failure. India has had steady raise in organ donation rate in the past years (2000-2009). However, organ transplantation is a costly procedure and most of the insurance providers do not cover the expenses incurred by an organ donor. There are six types of medical expenses incurred by an organ donor[1:]

- Organ screening for compatibility
- Pre-hospitalization expenses
- Hospitalization charges
- Organ transplant surgery
- Post surgery hospitalization and monitoring charges
- Post hospitalization charges

Kidney donor surgery charges:

The post surgery complication charges are not covered by any insurance policies in India. So an insurance company with *"Organ donor coverage"* (like National insurance, New India insurance, Tata AIG, Religare, etc.) actually covers only the hospitalization charges and nothing apart from that and this is only 10% of the total expense incurred. Even when an organ donor already has a health insurance of their own, there will be no coverage for the expense incurred. The reason, organ donation is a voluntary act and the insurers find it difficult to price for such events[2.]

Thus the recipient ends up with a greater burden in out of pocket costs that are not covered by his/her insurance.

Health insurance after donating kidney/liver:

If a person who has already donated an organ and is healthy applies for a health insurance the probability of rejection is very high because of a missing organ. If the person already has a health insurance there will not be any discrimination provided he continues to pay the premium. This is similar to a person holding life insurance as long as he continues to pay his premium. If the person stops paying his premium then his policy is subject to rejection. But if he applies for a fresh insurance after he has donated his organs his application will be rejected[2.] However there are some insurance companies likeLiberty Videocon General Insurance which provides policy for expenses incurred towards organ donors screening & treatment for harvesting of the organ donated[3.]

CASE STUDY : 1

HEALTH INSURANCE DILEMMA OF KIDNEY DONOR

Dr. Ravi Wankhede

My wife and self were covered for hospitalization expenses with the New India Assurance Company for about two decades. On attaining the age of 65 years, the Insurance policy ended about two years ago. I had not availed any claim for myself during the period. I came to know that the government has extended the Insurance cover for citizens above the age of 65. On my financial consultant's advice, representatives of Religare Health Insurance Company Limited called on me. I gave all my details, including no history of any sickness. I told them that I had donated a kidney to my friend in 2009 and was not having any complaints whatsoever. I asked the representatives, whether donation of kidney will have any negative impact on my proposal. I was told that my medical examination with laboratory tests would be carried out and if any major contraindications were detected the proposal would be rejected. I paid the premium. Within a fortnight I got an email that the proposal *was rejected as per guided by our underwriting policy that endeavours to group individuals who exhibit homogenous risk profiles. It is in no way an indicator of your past, present or future state of health.* I wrote to the Religare Health Insurance Company Limited wanting to know what exactly was the meaning of homogenous risk profile. The RHICL did not elaborate on the condition.

After sometimes I applied online to CignaTTK Health Insurance Company. There were several rounds of telephone conversations which according to the company were recorded for future reference. As earlier, I informed about my kidney donation, including keeping absolutely perfect health. Because of my past experience, I gave a lot of stress and asked whether kidney donation was a deterrent to get the health policy. I was told several times, that my medical examination and investigations would be carried out and if anything abnormal was found, the proposal would be declined. I paid the premium of over lakh rupees. Here again I got an email informing "We regret to inform you that we are unable to provide you with the insurance cover applied in view of personal medical history of organ donation… This decision is purely on the basis of an underwriting risk assessment done by the company and is not a recommendation on your health status."

I wrote to the CignaTTK customer services at all levels to redress my grievance as to why my proposal was accepted if it was known that I was a kidney and in that an altruistic donor. Also no medical examination and investigations were carried out. I wrote to them that one kidney was sufficient to live a normal life and they could check it with the medical advisors of the company. I wrote to them that Insurance pays for kidney donors' hospital expenses. One afternoon, I got a telephonic call from the office of CignaTTK and we spoke at length and exchanged our views. I have not heard anything from their office so far.

The Country Director of MOHAN Foundation Mrs. Lalitha Raghuram took pains to talk to Mrs. Yegnaprabha Bharat the Joint Director of IRDAI and apprised her of the my case. Mrs. Bharat told her that "all live donors ARE given Insurance, and there has been no exception to this". I was asked to make a complaint to the IRDAI, which I have done recently. I have not heard anything from IRDAI as well as CignaTTK.

My dilemma is what happens if ever, I will require hospitalization (unless I die in my sleep) for a major ailment in my senescent years which is unavoidable. Looking of late at the huge hospital expenses, I will have to shell out major part of my savings which is basically meant for OUR old age. People who run the Insurance companies should put themselves in the context scenario anddecide for themselves.

CASE STUDY : 2

Malini Kalyanam

I donated a kidney to my mother 34 years ago. I was healthy and had to go through a battery of medical tests to be certified fit, more than average with tissue typing matching to that of the recipient; else I would not have been allowed to be a living donor. Yes, I am still healthy. So, logically, if I want medical insurance, my health plan should not be affected by organ donation as I am neither at an increased risk of illness or at an increased risk of death. I decided to find out.

My first halt was at the Life Insurance Corporation of India. I was given to understand that although the core business of LIC is Life insurance, they do have a health product, “Jeevan Arogya” which provides fixed amounts against hospitalization and major-minor surgeries.

My meeting with senior officials did not yield substantial information. I gathered that there is no single underwriting principle that fits all. Each person is evaluated based on the results of the medical tests mandated for a certain age and policy value, personal and family history. This will determine whether he/she is a standard life or not. If these tests reveal some adverse medical condition like diabetes or hypertension, then it may have a bearing on the policyholder being a donor. Extra tests may be called for.

So depending on the conclusion, either the term may be restricted or extra premium may be charged or the proposal declined. I realize that in order to understand the implications of organ donation for the purpose of medical insurance in India, I must actually propose insurance for a factual study.

References:

1)http://www.moneycontrol.com/master_your_money/stocks_news_consumption.php?autono=1663741

2)http://www.moneycontrol.com/news/insurance/organ-donationinsurance-cover-at-your-own-risk_3850421.html

3)http://www.business-standard.com/article/finance/insurance-cover-for-organ-transplants-to-ease-donor-costs-114122200071_1.html

RAISING FUNDS FOR TRANSPLANT SURGERIES USING TECHNOLOGY LIKE SOCIAL MEDIA, ETC

Mr. Anubhav A Kediaa, Intern-Marketing & Communication, MOHAN Foundation

The advancement of technology has improved the life expectancy of man but the demand for organs for transplantation is ever increasing. On average 200000 kidneys, 100000 livers, 50000 hearts, 20000 lungs and about 100000 corneas[1] are required for transplanting but only 10% of this estimate is actually achieved. The average cost of having a kidney transplant in a private setup is around Rs 5,00,000 while that of a liver transplant is Rs.25,00,000[2].

When spoken to about the cost of a transplant many people say that most of it is covered by your insurance provider which is not true. Health insurance only covers the hospitalisation costs of the recipient and not the actual cost of surgery which in itself is a whopping amount. Also these insurance firms have varying waiting periods depending on the type of ailment after which only can the recipient claim his insurance. But the bigger question is that "How many people in India have a health insurance?". According to a survey by TOI in September 2015, less than one-fifth of India's population is covered by some form of health insurance. In such a situation we must look for alternative methods for fund generation which can help facilitate transplants and not deny the non affording a chance to a new life.

With the advent of technology the aforementioned alternative fund generation has become possible with it offering us a lot of choices. These range from social media platforms to text donations and from corporate donation portals to crowdfunding platforms. Let us now look at the working and ways to implement these options for our cause. In the following sections the word donor is referred to the patrons contributing funds and recipients are those who receive those funds helping them to pay for their transplants. These should not be confused with organ donors and recipients.

Social Media

Social media platforms are used extensively nowadays to convey messages and express ones views. They form an impressive and interactive network to connect with like minded people and get your message across to not just them but a million other people on this planet. There are many social media platforms available these days but the most widely used are:

- Facebook
- Twitter
- YouTube
- Instagram
- Tumblr

Facebook and Twitter are used to connect with people all around the globe through messaging and following them. They are huge platforms where information can go viral via pages, pictures, videos, messages, etc. Instagram and Tumblr are applications where one uploads pictures of various activities done by him and his friends and followers are free to

view them and know about his whereabouts. Twitter, Instagram and Tumblr use geotagging and hashtags to sort pictures which make it easy to access them in the long run.

Here are some steps using which one can use social media for his nonprofit fundraising campaign's advantage[3]:

1. Consider your campaign

What are your goals? Who is your target audience? Learn where your donors and patrons are and identify the social media platforms they are most active on. Interact with them over there rather than being present everywhere.

2. Customise your message

Customise each post to fit the various platforms. Each platform has a limit and different style of expressing. Don't copy and paste he same message across various platforms.

3. Be engaging, and engaged

Proper follow up must be done. Someone must always be engaged monitoring conversations on these platforms. Every interaction with a donor should receive a response; a small thank you is also enough. Keep sharing your organisations posts and tweets and spread the word asking others to also look at them ad share them.

4. Experiment with different types of content

Try different contents too see what works. Spend more time working on content that has generated more response. Give importance to the feedback received by followers and adjust your posts accordingly. Analyse your content and modify it accordingly to get more viewership.

5. Convey Urgency

Provide real-time updates on the progress of the campaign and state the deadlines and deficits. This can help inspire people to donate more.

6. Focus on impact

Use social media to thank donors and volunteers for their support and let them know specifically how their gift will be used. A thank you video or letter from the recipients should be circulated to the various donors.

7. Include a call to action

Add a call to action in some of the posts asking your followers to take the next step. Have a “Donate now”, “Share this” option in your posts.

8. Turn your network into an army

Encourage your donors to raise money and promote your cause through their own channels. Creating such a network via social media can help a great deal as not only your donors but also their friends and followers will now be aware of your campaign. More exposure more probability of generating more funds.

Some facts and stats on the use of social media for fundraising are as follows:

- Social media platforms are accessible on many devices such as laptops, computers, smartphones, tablets,etc. Responsive designs, which work on every platform like phone, tablet, computer, etc. ; of fundraising pages have increased mobile donations by 96%.[4]
- Peer-to-peer fundraising, which is possible with greater efficiency on social media platforms has resulted in contributing almost one-third of all online donations in 2015.[5]
- Smartphones are responsible for almost 65% of all the social media activity.[6] Thus pages should be made in such a way that the same level of information accessibility is available on all devices.
- 55% of those who engage with nonprofits via social media have been inspired to take further action.[7]
- Nonprofits are a daily average of 1.2 updates on Facebook and 5.3 tweets.[8]
- 30% of nonprofits are experimenting with Instagram. Pictures and videos help spread the essence of the cause in a much more understanding way.[9]

Crowdfunding Websites

Crowdfunding websites are online portals where individuals or organisations can start campaigns in support of a cause. These websites are designed in such a way that any person logging on to their website can choose a campaign which he wants to support and donate to that campaign. The individual can see the status of the campaign and how much money is collected and whats the target. This inspires people to donate more sometimes. Organisations must create their campaigns in a very attractive and informative way. Pictures, videos, infographics, etc must be added to inspire the donor to donate for the campaign. The success of these ventures lies in the way one markets their cause. Social media platforms provide the ideal platform to market such campaigns. Some of the crowdfunding websites are:

- www.ketto.org
- www.bitgiving.com
- www.milaap.org
- www.giveforward.com(USA only. Mostly for health)

These websites charge a small percentage of the funds raised as their fee but are very useful in generating huge sums of money.

Some facts about crowdfunding websites are as follows[10]:

- A nonprofit crowdfunding campaign raises an average of $9,237.55.
- 17% of crowdfunding donations are made on mobile devices.
- There is an average of a 35% increase in giving when there's a crowdfunding thermometer.
- 62% of the donors who give to crowdfunding campaigns are new to it.
- $66 is the average donation size to a crowdfunding campaign.

Crowdfunding is a great way of micro-financing and if done the right way can prove to be a very powerful tool to generate funds.

Text Donations

Text donations are one of the most user friendly ways of micro-financing. It is one of the fastest and easiest methods to generate small amounts of money. Mobile phone users can make donations by texting a keyword to a specific SMS short code. Keywords are determined by the organisation, and usually pertain to the organisation's cause or purpose. Donation amounts are predetermined, and users often have an upper limit of how many micro-donations they can send via SMS to a single campaign in one month. This amount is added to their monthly bill or deducted from their prepaid account. Donations are also possible through a mobile WAP website.

Some facts about text donations are as follows[11]:

- 99%of text messages are opened and read within the first five minutes after they've been sent.
- The average donation size for text-to-donate fundraisers is $107.
- A large fraction of people own smartphones these days.

Donation Portals

Donation portals are online websites where one can register their nonprofit organisation and they help the organisation earn donations through thousands of their corporate donor clients. They partner the corporates in their CSR activities and help them choose from a long list of charities and nonprofit organisations registered with them. The corporates then decide the size of their gifts and donate it to the charity of their choice through these portals. Examples of such portals are:

- Benevity
- Guidestar
- Gift of giving
- Nasscom
- Amazonsmile

Some of these portals have helped raise around $350 million[12] in donations through their corporate clients.

Mobile Applications/ E-Mails/ Website

Other than just maintaining websites it is advisable to launch mobile applications for the same or at least develop a mobile version of the website. This has ease of viewership as a large portion of the society owns smartphones nowadays. Another way of spreading the message and getting donations is by sending e-mails. E-mails which contain details about the cause and links to the donation page can be sent to a long list of people. People do respond to such mails and contribute in some way or the other.

Some facts pertaining to these are as follows[13]:

- Direct fundraising is 245 times more expensive than email.
- For every 1000 mails a firm generates $17.
- Recurring donors end up giving 42% more in a year than one-time donors do.
- Emails with social sharing options increase click-through by almost 158%.
- Custom-branded donate pages nested inside a nonprofits's website raise 6 times more money.

Rich people have the luxury of money and can afford to travel and be on more than one transplant list and thus have an increased chance of getting an organ but its just the opposite for this who are not this strong financially. These methods can thus be employed in raising funds to enhance and save the lives of such needy people. Technology has created wonders and it all depends on how best we exploit these wonders for our cause.

References:

1. FORT
2. http://zeenews.india.com/exclusive/liver-transplant-overall-success-rate-is-more-than-94-says-expert_1562601.html
3. http://www.frontstream.com/8-ways-boost-nonprofit-fundraising-using-social-media/
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AIR AMBULANCE IN INDIA

Mr. Karthikeyan. P, Site Operation Manager, New Fly Air Charter Services Pvt. Ltd

Air medical service is a comprehensive term covering the use of air transportation, airplane or helicopter, to move patients to and from healthcare facilities. Personnel provide comprehensive emergency and critical care to all types of patient during helicopter and propeller aircraft or jet aircraft.

Hospitals to know

Major Air Bases in India with 24 hours Air support - Delhi, Mumbai, Bangalore, Chennai, Kolkatta

Nearest base station

- The nearest airport to the hospital or permanent helipad
- Aircraft availability in that particular station

If no nearest permanent helipad is available we can use a plain ground for landing by getting the District Collector Permission. If no aircraft present in the nearest base the hospital should know about the other nearest base which have aircraft.

Basic air operation time

Fixed wing aircraft - Fixed wing aircraft which can able to land only in airports or airstrips and the fixed wing aircraft can able to fly on any time whether it is a day or night.

Helicopter- As per technical restriction in India, helicopters can be used from sunrise to sunset and some of the technically advanced helicopters can make a night flying also but it should be airport to airport not airport to helipad.

Note: That particular airport also should have the facility to receive the helicopter after sunset

Things to prepare for patient transfer

- Latest medical report of the patient
- Fit to fly certificate from doctors who is treating the patient
- NOC from the parents if the patient is minor
- Hospital Ground ambulance and Ambulance driver details in both the stations i.e. Departure and arrival station.
- Consult with the On board doctor about the patient status
- Passport copy of the patient and co-passenger if it is international

Public and Private Service

Private

- Private services haves a dedicative and special medical and air operation team for this service
- Immediate Response from Private
- Providing 24 hours service On board on ground for patient from the hospital to airport

Public

- There is no aircraft assigned by Indian government specially for air ambulance
- Process of getting naval aircrafts for air ambulance very difficult situation in emergency criteria

TRAINING OUR MANPOWER - TRANSPLANT COORDINATORS' TRAINING PROGRAMME

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INTRODUCTION

Deceased organ donation offers families who have lost a loved one solace and comfort and it gives patients with organ failure a renewed lease of life. Trained personnel who counsel and motivate families of brain dead patients about organ donation play an integral role in effecting this lifesaving act. They are also a vital link in the living organ donation and transplantation programme. The Government of India initially in a 2008 Gazette notification and later in the Transplantation of Human Organs and Tissues Act, 2011 made transplant coordinator nomination mandatory before a hospital is registered as a transplant centre [1]. This means that there is a huge requirement for Transplant coordinators in close to 400 transplant centres across the country.

TRANSPLANT COORDINATOR – DEFINITION, QUALIFICATION & ROLE

Definition - Transplant coordinator means a person appointed by the hospital for coordinating all matters relating to removal or transplantation of human organs or tissues or both and for assisting the authority for removal of human organs as per the Transplantation of Human Organs and Tissues Act, 2011.

Qualification & Role- According to the Transplantation of Human Organs and Tissues Rules, 2014, the transplant coordinator shall be an employee of the registered hospital having qualification such as:

(a) graduate of any recognised system of medicine; or

(b) Nurse; or

(c) Bachelor's degree in any subject and preferably Master's degree in Social work or Psychiatry or Sociology or Social Science or Public Health

The concerned organization or institute shall ensure initial induction training followed by retraining at periodic interval and the transplant coordinator shall counsel and encourage the family members or near relatives of the deceased person to donate the human organ or tissue including eye or cornea and coordinate the process of donation and transplantation.

TRANSPLANT COORDINATORS' TRAINING PROGRAMME

To address the training needs of this cadre of health care professionals, MOHAN Foundation established the **"Transplant Coordinators' Training Programme"** in 2009. This programme is the only one of its kind in the Indian subcontinent and is supported by the Sir

Ratan Tata Trust and the Navajbai Ratan Tata Trust, Mumbai [2]. From December 2009 to December 2015, 34 training programmes have been conducted all over the country (Chennai, Hyderabad, Delhi-NCR, Mumbai, Bengaluru, Nagpur, Pune, Ahmedabad, Chandigarh, Cuttack, Jaipur, Vijayawada, Visakhapatnam) and in Bangladesh. A total of 1019 transplant coordinators have been trained in this period.

Duration & Curriculum of Training programme– One week, one month, and one year. The programme involves training in counselling families of brain dead patients to donate organs and coordinating the entire process of organ donation, retrieval and transplantation. It also imparts knowledge in the theoretical concepts of organ donation and transplantation including medical, legal, ethical, socio-cultural and religious aspects. In addition, workshops, surveys, and project / internship are part of the curriculum. The one year training is a unique blended learning course for working health care professionals. It comprises E-learning and contact sessions at regional learning centres for soft skills, simulations and role play. This is a cost effective method of ensuring a wider reach of the training.

Collaboration with International, National and State Bodies

International

The first ever Transplant Coordinators' Training Programme in Bangladesh was conducted in collaboration with the Society of Organ Transplantation (SOT) and Kidney Foundation, Bangladesh in September 2014 in Dhaka.

Agreements with NHS Blood and Transplant, UK and Gift of Life Institute, Philadelphia, USA have enabled sharing of best practices of both countries in various areas including training.

The International Society of Nephrology - American Nephrologists of Indian Origin (ISN-ANIO) has also supported the training programme.

National

MOHAN Foundation was invited as Steering Committee Member in developing the standardised course curriculum for the Transplant Coordinators' Training Programme by National Organ & Tissue Transplant Organization (NOTTO) - the national level organization set up under the Directorate General of Health Services, Ministry of Health and Family Welfare, Government of India**.** It has conducted two training programmes jointly with NOTTO.

State

MOHAN Foundation has conducted one week Transplant Coordinators' Training Programmes in collaboration with various state bodies – Zonal Transplantation Coordination Centre (ZTCC) – Mumbai, Nagpur and Pune chapters, Zonal Coordination Committee of Karnataka for Transplantation (ZCCK), MFJCF-Rajasthan Network for Organ Sharing, and Armed Forces Hospitals (Army Research & Referral Hospital, Delhi and Command Hospital, Chandimandir). Cadaver Transplant Programme, Govt. of Tamil Nadu and Jeevandan, Govt. of Telengana have also participated in the training programmes.

Annual Transplant Coordinators' Conference

Transplant coordinators are growing to be a strong force in augmenting organ donations in India. They are constantly energising the organ donation movement, and now have their own association called "National Association of Transplant Coordinators (NATCO)", which meets annually and exchanges ideas and innovations in the field. The Annual Conference, which MOHAN Foundation organises in collaboration with NATCO, provides a platform to Transplant coordinators to share both their successes and challenges. It is also a forum where the efforts of those who work tirelessly in the field of Transplant Coordination are recognised through the presentation of the Swamy Narayan Best Transplant Coordinator's Award.

IMPACT OF TRAINED TRANSPLANT COORDINATORS ON ORGAN DONATION

MOHAN Foundation's trained transplant coordinators were placed in Rajiv Gandhi Government General Hospital (RGGGH), Chennai, the largest public sector hospital in Tamil Nadu, which handles a large number of trauma cases. From February 2010 to December 2015, 169 brainstem deaths were identified in RGGGH. The families of 146 brain dead patients were counselled about organ donation. 23 families could not be approached because of extenuating medical/medicolegal reasons. As a result of the counseling, 95 families said 'yes' to organ donation, which resulted in a conversion/consent rate of 65%.

Similar work by MOHAN Foundation's trained transplant coordinators in the country resulted in the retrieval of a total of 3937 organs and tissues from 745 deceased donors from December 2009 to December 2015. In addition, the transplant coordinators facilitated the retrieval of 492 tissues from donation after circulatory death in the same period of time. The impact of the work of MOHAN Foundation's trained transplant coordinators was studied from 2012 to 2015, both in terms of the number of multi-organ donors as well as the number of solid organs retrieved. The study showed that their work resulted in 39% of the total multi-organ donors in the country and 40% of the total organs retrieved from the deceased donors on an average over four years.

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COST COMPARISONS OF COMMON IMMUNOSUPPRESSIVE MEDICATIONS

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Solid organ transplantation is one of the remarkable achievements of modern medicine. Patient and kidney graft survival rates at 1 year exceed 95% after living donor kidney transplantation, and life expectancy is substantially increased compared with those patients who remain on dialysis[1]

Replacement of lost organ function by transplantation clearly increases longevity and improves quality of life, but at the cost of requisite immunosuppression to prevent allograft rejection. Effective immunosuppression has numerous side effects, including nephrotoxicity, diabetes, anemia, cytopenias, hypertension, neuropathy and manifestations of over immunosuppression, such as infection and malignancy. However, one of the most universal complications of immunosuppressive drugs used in current protocols for solid organ transplantation is the economic burden placed on graft recipients.

As a young nephrologist the importance of economics dawns on you when you start following up patients on your own and realize cost of immunosuppressive therapy becomes a major hurdle in the compliance and successful treatment of transplant recipients.

The ideal cost-effective therapy is one where the therapeutic agent produces the desired therapeutic effect with a single dose, has no side effects, is easy to produce, is available in abundance, and can be easily provided to or obtained by the patient without charge. Clearly, few if any treatments in medicine meet the 'ideal.' Consequently, a 'cost-effective' modality is likely to strike a balance between efficacy and cost. The most medically effective treatment, if unobtainable or unaffordable, is not clinically useful, nor is a low-cost ineffective intervention.

On a cost-per-dose basis, antibody induction immunotherapy is the most expensive component of the immunosuppressive regimen. One consideration is to forego antibody induction therapy. Indeed, use of antibody induction immunosuppression is not universal in kidney and pancreas transplantation, and its use for other solid organ transplants, such as liver, is even less common. Potentially life-saving induction agents such as interleukin-2 receptor antibodies and polyclonal antibodies are expensive, and hence the majority of the patients on the recipient list, who are self-paying, cannot afford them. Patients must bring upfront cash for hospitalization and management, as fewer than 15% have full reimbursement or insurance coverage. [2]

In the long term, maintenance immunotherapy accounts for the largest share of post-transplant drug costs and even dwarfs the costs of acute care (e.g., hospitalization and surgery). Pharmacy, organ acquisition and clinical laboratory services account for nearly 80% of hospital charges for the initial transplant hospitalization. Drug costs encompass the majority of expenses for subsequent and outpatient care.

Most solid organ transplant centers employ a combination of antibacterial, antifungal and antiviral agents as part of the immunotherapy regimen. Trimethoprim-sulfamethoxazole , initially used for prophylaxis of urinary tract infections, was later proven to be of value for the prevention of opportunistic infections, including *Pneumocystis* and *Nocardia*. The unique coverage that TMP-SMX provides, along with its relative low cost, makes the drug a particularly cost-effective component of the immunosuppressive protocol. Antiviral prophylaxis accounts for a large fraction of the costs of the immunotherapy regimen in the early months after transplantation, but this cost may be justified based upon the substantial economic impact of CMV infection.[3]

Transplant recipients frequently have comorbid conditions that require pharmaceutical therapy unrelated to the immunosuppressive regimen. In the setting of immunotherapy, these comorbid conditions can be thought of as two often-overlapping groups, those conditions naturally present in the recipient (regardless of the transplanted organ) and those conditions brought on or aggravated by immunotherapy. Hypertension, diabetes, hyperlipidemia, anemia and cytopenias are examples of drug-related effects that frequently require therapy after solid organ transplantation. Although the costs of management of these conditions are generally forgotten in the academic analysis of costs associated with immunotherapy, the additional expenses incurred matters greatly to the patient.

The Indian pharmaceutical industry has shown robust growth in the past decade by manufacturing cheaper immunosuppressive agents that are not inferior in pharmacokinetics and pharmacodynamics to the original brands. A cost comparison of the immunosuppressive agents is given in Table 1. This initiative by the Indian pharmaceutical industry has often forced the multinationals that produce the brands of microemulsion forms of cyclosporine, tacrolimus, mycophenolate mofetil, and sirolimus to bring down their prices to withstand the competition. Immunosuppressive agents of Indian origin, because of their quality and low cost, are widely used in Africa, Latin America, Russia, and Eastern Europe in addition to Asia. Therapeutic drug monitoring is available in the major cities, and the results are provided within 24–48 hours. However, the cost of drug- level monitoring can be prohibitive (US$74.50 for sirolimus, US$15.50 for tacrolimus, US$19.70 for cyclosporine), and hence it is limited in the tailoring of immunosuppressive agents. As a cost-effective measure, CYP3A4 inhibitors, including diltiazem and ketoconazole, are used to increase the blood levels and hence reduce the cost of immunosuppression. Immunosuppressive drugs are given free of cost in the state government run hospitals in some southern states, such as Tamil Nadu which lets the poorest of the poor avail the gift of life.

Improvements in quality of life and longevity attributed to solid organ transplantation stem largely from the efficacy of immunotherapy. However, as with any medical intervention, immunosuppression has limitations and side effects. Of the numerous risks associated with immunotherapy for the prevention of rejection, cost is perhaps the most universal. Standardisation of costs and minimizing the side effects of therapy will go a long way in decreasing the economic burden on the patient. Tolerance the ‘holy grail’ of transplantation and regenerative medicine may be the future in having a immunosuppressive free transplantation.. Only time will tell.

TABLE 1

DRUG	INTRODUCTORY PRICE (US$)	CURRENT PRICE(US$)	GENERIC PRICE IN INDIA(Rs)
RABBIT ANTI THYMOCYTE GLOBULIN, 25 mg	230	187	16500
RITUXIMAB 500MG	1800	1200	16000
TACROLIMUS 1MG	NONE	0.54	410
MYCOPHENOLATE MOFETIL 500MG	2.40	1.12	619.60
BASILIXIMAB 20Mg 2 DOSES	2880	2000	1,52,612
EVEROLIMUS 0.25MG	NONE	1.44	920 / Strip (Novartis)
VALGANCICLOVIR 450MG	15	9.60	490
CYCLOSPORINE MICROEMULSION 100MG	NONE	2.20	111.8

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The Declaration of Istanbul
on Organ Trafficking and Transplant Tourism

Participants in the International Summit on Transplant Tourism and Organ Trafficking convened by The Transplantation Society and International Society of Nephrology in Istanbul, Turkey, April 30–May 2, 2008*

Preamble

Organ transplantation, one of the medical miracles of the twentieth century, has prolonged and improved the lives of hundreds of thousands of patients worldwide. The many great scientific and clinical advances of dedicated health professionals, as well as countless acts of generosity by organ donors and their families, have made transplantation not only a life-saving therapy but a shining symbol of human solidarity. Yet these accomplishments have been tarnished by numerous reports of trafficking in human beings who are used as sources of organs and of patient-tourists from rich countries who travel abroad to purchase organs from poor people. In 2004, the World Health Organization, called on member states "to take measures to protect the poorest and vulnerable groups from transplant tourism and the sale of tissues and organs, including attention to the wider problem of international trafficking in human tissues and organs" (1).

To address the urgent and growing problems of organ sales, transplant tourism and trafficking in organ donors in the context of the global shortage of organs, a Summit Meeting of more than 150 representatives of scientific and medical bodies from around the world, government officials, social scientists, and ethicists, was held in Istanbul from April 30 to May 2, 2008. Preparatory work for the meeting was undertaken by a Steering Committee convened by The Transplantation Society (TTS) and the International Society of Nephrology (ISN) in Dubai in December 2007. That committee's draft declaration was widely circulated and then revised in light of the comments received. At the Summit, the revised draft was reviewed by working groups and finalized in plenary deliberations.

This Declaration represents the consensus of the Summit participants. All countries need a legal and professional framework to govern organ donation and transplantation activities, as well as a transparent regulatory oversight system that ensures donor and recipient safety and the enforcement of standards and prohibitions on unethical practices.

Unethical practices are, in part, an undesirable consequence of the global shortage of organs for transplantation. Thus, each country should strive both to ensure that programs to prevent organ failure are implemented and to provide organs to meet the transplant needs of its residents from donors within its own population or through regional cooperation. The therapeutic potential of deceased organ donation should be maximized not only for kidneys but also for other organs, appropriate to the transplantation needs of each country. Efforts to initiate or enhance deceased donor transplantation are essential to minimize the burden on living donors. Educational programs are useful in addressing the barriers, misconceptions and mistrust that currently impede the development of sufficient deceased donor transplantation; successful transplant programs also depend on the existence of the relevant health system infrastructure.

Access to healthcare is a human right but often not a reality. The provision of care for living donors before, during and after surgery–as described in the reports of the international forums organized by TTS in Amsterdam and Vancouver (2-4)–is no less essential than taking care of the transplant recipient. A positive outcome for a recipient can never justify harm to a live donor; on the contrary, for a transplant with a live donor to be regarded as a success means that both the recipient and the donor have done well.

This Declaration builds on the principles of the Universal Declaration of Human Rights (5). The broad representation at the Istanbul Summit reflects the importance of international collaboration and global consensus to improve donation and transplantation practices. The Declaration will be submitted to relevant professional organizations and to the health authorities of all countries for consideration. The legacy of transplantation must not be the impoverished victims of organ trafficking and transplant tourism but rather a celebration of the gift of health by one individual to another.

Definitions

Organ trafficking is the recruitment, transport, transfer, harboring or receipt of living or deceased persons or their organs by means of the threat or use of force or other forms of coercion, of abduction, of fraud, of deception, of the abuse of power or of a position of vulnerability, or of the giving to, or the receiving by, a third party of payments or benefits to achieve the transfer of control over the potential donor, for the purpose of exploitation by the removal of organs for transplantation (6).

Transplant commercialism is a policy or practice in which an organ is treated as a commodity, including by being bought or sold or used for material gain.

Travel for transplantation is the movement of organs, donors, recipients or transplant professionals across jurisdictional borders for transplantation purposes. Travel for transplantation becomes **transplant tourism** if it involves organ trafficking and/or transplant commercialism or if the resources (organs, professionals and transplant centers) devoted to providing transplants to patients from outside a country undermine the country's ability to provide transplant services for its own population.

Principles

1. National governments, working in collaboration with international and non-governmental organizations, should develop and implement comprehensive programs for the screening, prevention and treatment of organ failure, which include:
   a. The advancement of clinical and basic science research;
   b. Effective programs, based on international guidelines, to treat and maintain patients with end-stage diseases, such as dialysis programs for renal patients, to minimize morbidity and mortality, alongside transplant programs for such diseases;
   c. Organ transplantation as the preferred treatment for organ failure for medically suitable recipients.

2. Legislation should be developed and implemented by each country or jurisdiction to govern the recovery of organs from deceased and living donors and the practice of transplantation, consistent with international standards.
   a. Policies and procedures should be developed and implemented to maximize the number of organs available for transplantation, consistent with these principles;
   b. The practice of donation and transplantation requires oversight and accountability by health authorities in each country to ensure transparency and safety;
   c. Oversight requires a national or regional registry to record deceased and living donor transplants;
   d. Key components of effective programs include public education and awareness, health professional education and training, and defined responsibilities and accountabilities for all stakeholders in the national organ donation and transplant system.

3. Organs for transplantation should be equitably allocated within countries or jurisdictions to suitable recipients without regard to gender, ethnicity, religion, or social or financial status.
   a. Financial considerations or material gain of any party must not influence the application of relevant allocation rules.

4. The primary objective of transplant policies and programs should be optimal short- and long-term medical care to promote the health of both donors and recipients.
   a. Financial considerations or material gain of any party must not override primary consideration for the health and well-being of donors and recipients.

5. Jurisdictions, countries and regions should strive to achieve self-sufficiency in organ donation by providing a sufficient number of organs for residents in need from within the country or through regional cooperation.
   a. Collaboration between countries is not inconsistent with national self- sufficiency as long as the collaboration protects the vulnerable, promotes equality between donor and recipient populations, and does not violate these principles;
   b. Treatment of patients from outside the country or jurisdiction is only acceptable if it does not undermine a country's ability to provide transplant services for its own population.

6. Organ trafficking and transplant tourism violate the principles of equity, justice and respect for human dignity and should be prohibited. Because transplant commercialism targets impoverished and otherwise vulnerable donors, it leads inexorably to inequity and injustice and should be prohibited. In Resolution 44.25, the World Health Assembly called on countries to prevent the purchase and sale of human organs for transplantation.
   a. Prohibitions on these practices should include a ban on all types of advertising (including electronic and print media), soliciting, or brokering for the purpose of transplant commercialism, organ trafficking, or transplant tourism.
   b. Such prohibitions should also include penalties for acts—such as medically screening donors or organs, or transplanting organs—that aid, encourage, or use the products of, organ trafficking or transplant tourism.
   c. Practices that induce vulnerable individuals or groups (such as illiterate and impoverished persons, undocumented immigrants, prisoners, and political or economic refugees) to become living donors are incompatible with the aim of combating organ trafficking, transplant tourism and transplant commercialism.

Proposals

Consistent with these principles, participants in the Istanbul Summit suggest the following strategies to increase the donor pool and to prevent organ trafficking, transplant commercialism and transplant tourism and to encourage legitimate, life-saving transplantation programs:

To respond to the need to increase deceased donation:

1. Governments, in collaboration with health care institutions, professionals, and non-governmental organizations should take appropriate actions to increase deceased organ donation. Measures should be taken to remove obstacles and disincentives to deceased organ donation.
2. In countries without established deceased organ donation or transplantation, national legislation should be enacted that would initiate deceased organ donation and create transplantation infrastructure, so as to fulfill each country's deceased donor potential.
3. In all countries in which deceased organ donation has been initiated, the therapeutic potential of deceased organ donation and transplantation should be maximized.
4. Countries with well established deceased donor transplant programs are encouraged to share information, expertise and technology with countries seeking to improve their organ donation efforts.

To ensure the protection and safety of living donors and appropriate recognition for their heroic act while combating transplant tourism, organ trafficking and transplant commercialism:

1. The act of donation should be regarded as heroic and honored as such by representatives of the government and civil society organizations.

2. The determination of the medical and psychosocial suitability of the living donor should be guided by the recommendations of the Amsterdam and Vancouver Forums (2-4).
    a. Mechanisms for informed consent should incorporate provisions for evaluating the donor's understanding, including assessment of the psychological impact of the process;
    b. All donors should undergo psychosocial evaluation by mental health professionals during screening.

3. The care of organ donors, including those who have been victims of organ trafficking, transplant commercialism, and transplant tourism, is a critical responsibility of all jurisdictions that sanctioned organ transplants utilizing such practices.

4. Systems and structures should ensure standardization, transparency and accountability of support for donation.
    a. Mechanisms for transparency of process and follow-up should be established;
    b. Informed consent should be obtained both for donation and for follow-up processes.

5. Provision of care includes medical and psychosocial care at the time of donation and for any short- and long-term consequences related to organ donation.
    a. In jurisdictions and countries that lack universal health insurance, the provision of disability, life, and health insurance related to the donation event is a necessary requirement in providing care for the donor;
    b. In those jurisdictions that have universal health insurance, governmental services should ensure donors have access to appropriate medical care related to the donation event;
    c. Health and/or life insurance coverage and employment opportunities of persons who donate organs should not be compromised;
    d. All donors should be offered psychosocial services as a standard component of follow-up;
    e. In the event of organ failure in the donor, the donor should receive:
        i. Supportive medical care, including dialysis for those with renal failure, and
        ii. Priority for access to transplantation, integrated into existing allocation rules as they apply to either living or deceased organ transplantation.

6. Comprehensive reimbursement of the actual, documented costs of donating an organ does not constitute a payment for an organ, but is rather part of the legitimate costs of treating the recipient.
    a. Such cost-reimbursement would usually be made by the party responsible for the costs of treating the transplant recipient (such as a government health department or a health insurer);
    b. Relevant costs and expenses should be calculated and administered using transparent methodology, consistent with national norms;
    c. Reimbursement of approved costs should be made directly to the party supplying the service (such as to the hospital that provided the donor's medical care);
    d. Reimbursement of the donor's lost income and out-of-pockets expenses should be administered by the agency handling the transplant rather than paid directly from the recipient to the donor.

7. Legitimate expenses that may be reimbursed when documented include:
    a. the cost of any medical and psychological evaluations of potential living donors who are excluded from donation (*e.g.*, because of medical or immunologic issues discovered during the evaluation process);
    b. costs incurred in arranging and effecting the pre-, peri- and post-operative phases of the donation process (*e.g.*, long-distance telephone calls, travel, accommodation and subsistence expenses);
    c. medical expenses incurred for post-discharge care of the donor;
    d. lost income in relation to donation (consistent with national norms).

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* ***The Participants in the International Summit on Transplant Tourism and Organ Trafficking and the manner in which they were chosen and the meeting was organized were as follows:***

Process and Participant Selection

Steering Committee:

The Steering Committee was selected by an Organizing Committee consisting of Mona Alrukhami, Jeremy Chapman, Francis Delmonico, Mohamed Sayegh, Faissal Shaheen, and Annika Tibell.

The Steering Committee was composed of leadership from The Transplantation Society, including its President-elect and the Chair of its Ethics Committee, and the International Society of Nephrology, including its Vice President and individuals holding Council positions. The Steering Committee had representation from each of the continental regions of the globe with transplantation programs.

The mission of the Steering Committee was to draft a Declaration for consideration by a diverse group of participants at the Istanbul Summit. The Steering Committee also had the responsibility to develop the list of participants to be invited to the Summit meeting.

Istanbul Participant Selection:

Participants at the Istanbul Summit were selected by the Steering Committee according to the following considerations:

- The country liaisons of The Transplantation Society representing virtually all countries with transplantation programs;

- Representatives from international societies and the Vatican;
- Individuals holding leadership positions in nephrology and transplantation;
- Stakeholders in the public policy aspect of organ transplantation; and
- Ethicists, anthropologists, sociologists, and legal scholars well-recognized for their writings regarding transplantation policy and practice.

No person or group was polled with respect to their opinion, practice, or philosophy prior to the Steering Committee selection or the Istanbul Summit.

After the proposed group of participants was prepared and reviewed by the Steering Committee, they were sent an letter of invitation to the Istanbul Summit, which included the following components:

- ❖ the mission of the Steering Committee to draft a Declaration for all Istanbul participants' consideration;
- ❖ the agenda and work group format of the Summit;
- ❖ the procedure for the selection of participants;
- ❖ the work group topics;
- ❖ an invitation to the participants to indicate their work group preferences;
- ❖ the intent to communicate a draft and other materials before the Summit convened;
- ❖ the Summit goals to assemble a final Declaration that could achieve consensus and would address the issues of organ trafficking, transplant tourism and commercialism, and provide principles of practice and recommended alternatives to address the shortage of organs;
- ❖ an acknowledgment of the funding provided by Astellas Pharmaceuticals for the Summit;
- ❖ provision of hotel accommodations and travel for all invited participants.

Of approximately 170 persons invited, 160 agreed to participate and 152 were able to attend the Summit in Istanbul on April 30-May 2, 2008. Because work on the Declaration at the Summit was to be carried out by dividing the draft document into separate parts, Summit invitees were assigned to a work group topic based on their response concerning the particular topics on which they wished to focus their attention before and during the Summit.

Preparation of the Declaration:

The draft Declaration prepared by the Steering Committee was furnished to all participants with ample time for appraisal and response prior to the Summit. The comments and suggestions received in advance were reviewed by the Steering Committee and given to leaders of the appropriate work group at the Summit. (Work group leaders were selected and assigned from the Steering Committee.)

The Summit meeting was formatted so that breakout sessions of the work groups could consider the written responses received from participants prior to the Summit as well as comments from each of the work group participants. The work groups elaborated these ideas as proposed additions to and revisions of the draft. When the Summit reconvened in plenary session, the Chairs of each work group presented the outcome of their breakout session to all Summit participants for discussion. During this process of review, the wording of each section of the Declaration was displayed on a screen before the plenary participants and was modified in light of their comments until consensus was reached on each point.

The content of the Declaration is derived from the consensus that was reached by the participants at the Summit in the plenary sessions which took place on May 1 and 2, 2008. A formatting group was assembled immediately after the Summit to address punctuation, grammatical and related concerns and to record the Declaration in its finished form.

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Nephrology
Dialysis
Transplantation

SECTION II: Evaluation and selection of donors

II.1 Cadaveric heart-beating donors

Guidelines

II.1.1 Selection of donors

A. Any comatose patient with irreversible cerebral damage who appears likely to progress to brain death prior to terminal circulatory failure must be considered as a potential donor, regardless of age.
(Evidence level C)

B. Physicians caring for the potential donors should be encouraged to make early contact with the organ procurement team for assistance in the further management of the donor and the donor's family.
(Evidence level C)

C. Absolute contra-indications against organ donation are based on risk of disease transmission and include a history of cancer other than non-invasive tumours, HIV-positive serology, acute hepatitis, tuberculosis, severe untreated systemic sepsis and viral infection. Persons who have been engaged in activities with a high risk of HIV infection should not be considered as organ donors.
(Evidence level B)

D. Relative contra-indications against organ donation are based on the quality of the potential graft and include suboptimal to non-acceptable renal function or presence of risk factors. It is recommended that each procurement centre formulates its standards and follow up on the effects of their implementation.
(Evidence level C)

E. The aim of the procurement team should be to increase the acceptance rate of potential donors without risking unacceptably poor graft function and survival.
(Evidence level C)

F. At this time and in the absence of a 'gold standard' it is recommended that donors be evaluated on the basis of renal function (calculated creatinine clearance, CrCl), age and vascular disease. Limits may be set as CrCl >60 ml/min as acceptable, 50–60 ml/min as marginal and <50 ml/min as non-acceptable for single kidney transplantation. Non-acceptable kidneys may be considered for dual transplantation. High donor age (70+) and vascular risk factors such as long-term history of hypertension, severe vascular disease, long-term diabetes or proteinuria, or findings of vascular changes or extensive glomerular sclerosis on procurement biopsy may add negatively to the evaluation.
(Evidence level B)

G. Recipients of sub-optimal kidneys or dual kidneys should have given their informed consent prior to transplantation
(Evidence level C)

Commentary on Guideline II.1.1: Selection of donors

Contra-indications

The ideal kidney donor is a previously healthy individual aged 10–55 years, brain dead due to trauma or intracerebral bleeding, with no ongoing infection and with excellent organ function. However, the majority of potential donors do not belong to this category. Increasing age, previous medical history and current medical state of the donor all raise a number of considerations that might contra-indicate donation. It is not uncommon for the transplant centre to accept only 50–75% of the offers of organ donation made by the units caring for the potential donors. There are several absolute and relative contra-indications to donation, the former to avoid transferring intercurrent disease to the recipient and the latter to prevent less than optimal function of the transplanted organ.

Absolute contra-indications include previous or current history of cancer except non-invasive brain tumours, non-melanotic non-metastasizing skin tumours and *in situ* cervical cancer. HIV-positive serology or a history of activities with high risk for HIV infection are contra-indications; also uncontrolled or untreated septicaemia or septicaemia of unknown origin. Hepatitis B-positive antigenaemia is a contra-indication for hepatitis B-negative recipients where negativity is defined as HBsAg negative or hepatitis B antibody-negative. However, hepatitis B-positive antigenaemia is not a contra-indication for HBsAg-positive recipients.

Relative contra-indications may include very elderly donor (>70 years of age), severe vascular disease, long-term insulin-dependent diabetes mellitus (IDDM), hypertension, or other conditions that may have impaired renal function. However, there is no consensus on these limitations between centres or clinicians. In severe cases such as long-standing IDDM, malignant hypertension, or renal and systemic disease such as amyloidosis, the contra-indication is not con-

troversial. It is noteworthy that a potential donor may be excluded from kidney donation but may remain an optimal liver donor.

The lack of kidney donors implies a need for the limits of the relative contra-indications to be widened, to accept kidneys with less than optimal function. In general, the aim of renal transplantation is long-term graft survival for 10–20 years. If the acceptance criteria are widened to include older donors or those with vascular disease, reduced renal function or glomerulosclerosis in a zero biopsy, the prognosis after transplantation may be more limited. These marginal kidney grafts should not be given to young recipients but preferably to elderly patients with a limited life-expectancy who express a preference and provide informed consent for a suboptimal donor kidney as an alternative to prolonged dialysis.

Social history

The donor must not be in a high-risk group for HIV infection. This group includes intravenous drug users and those who engage in unsafe sexual activities. A history of heavy smoking could contra-indicate donation of the heart and lungs, and would also increase the risk of atherosclerosis with impaired renal function. A history of alcohol abuse has less impact on kidneys, heart and lungs but is of great importance when considering donation of liver or pancreas.

Medical history

It is mandatory to rule out previous history of *cancer* in a potential donor. Any malignancy (except those of extremely low risk of metastasis, such as skin cancer) contra-indicates donation even though the potential donor may have been considered healthy for several years and the risk of metastases to the kidney may be extremely low. This is because the recipient is immunosuppressed and is therefore more likely to develop recurrence of the malignancy. With intra-cranial tumours it is vital to know the exact diagnosis, since those that are confined to the brain do not constitute an absolute contra-indication, unlike those that might have metastasized (Table II.1).

In most European countries, age of donor has slowly increased over recent years, as has the proportion of donors with intra-cranial bleeding as the cause of death. Cause of death (cerebral vascular disease or trauma) and ongoing medication are key questions. The most important intercurrent disease in the donor is severe *vascular disease*, with a possible reduction of renal function as a consequence of atherosclerosis and nephrosclerosis.

Cardiovascular disease, such as a previous myocardial infarction, coronary by-pass operation or angina are important factors. History of hypertension and its treatment, number of years on treatment, number and kind of medication, and success of treatment should be noted. In addition, any pathological changes associated with hypertension or vascular disease, such as presence of retinal capillary changes, left ventricular hypertrophy on the electrocardiogram and proteinuria, should be investigated.

The final series of events leading to death of the potential donor may have induced renal (and liver) damage. Factors such as length of intensive care, stability of blood pressure, resuscitation, signs of infection and antibiotic treatment or prophylaxis should all be noted. Current and, if possible, historical laboratory values of renal and liver function should be evaluated.

Renal function

The potential donor's history of plasma creatinine (SCr) and the level at admission indicate the baseline donor renal function. The acute medical situation of hypotension caused by dilatation of the vascular bed as a consequence of brain death may have led to a deterioration in donor renal function. Following admission, the serum creatinine level usually increases and it is important to verify a shift towards normalization after intravenous fluid compensation. Normal or high urine production is early evidence of adequate compensation.

SCr varies with muscular mass as well as with renal function. There is no 'gold standard' test for the evaluation of donor renal function, but CrCl calculated according to the Cockcroft–Gault formula [1] is often used. It is a better estimate of glomerular filtration rate than SCr alone, particularly in elderly and critically ill patients [2]. In a report from Barcelona [3], elderly donors aged 60–87 years were accepted whenever CrCl, calculated from the best admittance SCr, $\geqslant 60$ ml/min, 24-h urine proteinuria was <0.5 g, and renal size and morphology were normal on ultrasound. No biopsies were evaluated. Graft survival at 5 years post-transplantation was similar compared to when donor age was <60 years (81 *vs* 85%), but the mean SCr was significantly higher (205 *vs* 133 μmol/l).

A low CrCl, in the range 50–60 ml/min, would indicate a suboptimal donor with prognosis of an inferior graft function. Donor kidneys with functional levels below this range should not be used or should be transplanted as a pair in the same recipient with the objective of reaching acceptable results. Dual transplantation of kidneys is a novel procedure used to increase the transplanted nephron mass. The Stanford group [4] have suggested that the two kidneys from donors aged 60 years or more with calculated CrCl <90 ml/min should be used for dual kidney transplants. With these standards, their objective is to achieve similar results with expanded donor criteria as those achieved with single renal transplants. However, the use of double kidney transplantation halves the number of potential transplants, and in view of the shortage of donors, some centres prefer the use of single kidneys from older donors.

The use of a procurement renal biopsy to exclude a potential donor is controversial. In a large sample of 200 donors there was no overall correlation between histological findings (i.e. glomerulosclerosis or vascular

changes) and prognosis after transplantation [5]. In another study using a small cohort of eight patients [6] with >20% of the kidney affected by glomerulosclerosis, a high risk of delayed onset of function and early loss of the graft was observed.

In a recent Canadian study [7], the clinical outcome of 57 kidney transplants from 34 donors over 60 years of age, with hypertension and/or vascular disease, was compared with 57 historical recipients of low-risk donor kidneys. Graft survival at 1 year was similar (87 *vs* 85%) but the proportion of patients with SCr >200 μmol/l at 1 year was 46 *vs* 16%, respectively. A combination of CrCl <100 ml/min and a high vessel score in the procurement biopsy evidenced by severe arteriolar narrowing or arterial sclerosis, was predictive of a poorer prognosis. At 1 year, all such patients had SCr >200 μmol/l. The authors therefore suggest that in all high-risk older donors, a CrCl should be calculated and a biopsy taken. If CrCl is >100 ml/min and biopsy changes are minor, conventional renal transplantation should be performed. Donors with CrCl <100 ml/min and >20% glomerulosclerosis or severe vascular changes may be considered for dual transplantation. In contrast to these recommendations, donors with CrCl 50–100 ml/min are at many centres accepted for single kidney transplantation with excellent results, independent of histology.

When the potential donor is younger than 50 years, with a normal SCr at admission, no history of vascular disease or current episode of hypotension, it is seldom needed to calculate CrCl or take a biopsy. In elderly or marginal donors, however, careful evaluation of renal function, possibly including a procurement biopsy, is important. This may be used to determine non-acceptance of the donor or to indicate the possibility of using dual kidney transplantation.

Donor age

Is donor age *per se* a criterion for determining acceptance of a potential donor? Renal function decreases with increasing age. It is therefore not surprising that donor age is one of the strongest factors affecting outcome after renal transplantation [5,8,9]. In the elderly, a major decrease in glomerular filtration rate is uncommon in the absence of disease [10] but the variation is great. Living donor renal transplantation with highly selected older donors aged over 70 years is quite successful. It is therefore difficult to set an absolute age limit without the risk of losing some grafts with good potential.

Nevertheless, donor age is still a widely used criterion. Donors over the age of 60 years are rarely accepted in the United States. With the adoption of expanded criteria, the proportion of donors over 50 years has increased from 12% in 1988 to 25% in 1995. However, the percentage of donors over the age of 60 years has increased to a lesser degree, from 5% in 1991 to only 8% in 1996 [11,12]. In the Scandinavian countries, the median donor age is approaching 60 years and occasionally donors over the age of 70 are accepted. In The Netherlands, donors up to the age of 75 years are acceptable. Within Eurotransplant, donors over the age of 65 may be accepted but the kidneys are generally used locally and not shared.

When evaluating elderly potential donors, especially those aged over 70, it is important that risk factors other than age are absent or minimal. These may include history of severe vascular disease, long-term hypertension or diabetes, findings of retinal vascular changes or proteinuria, and episodes of hypotension or oliguria during the stay in the intensive care unit (ICU). If the elderly donor kidney is considered suitable for transplantation, it is of consequence that the cold ischaemia time is reduced to a minimum.

Eliminating the risk of infection

The potential donor should be tested for HIV, HTLV1, hepatitis B and C, and cytomegalovirus (CMV). During the incubation period before the development of antibodies, these tests may give false negative results. Furthermore, many donors are given large volumes of 'safe' blood as part of the resuscitation process and subsequent serology may then be ambiguous or even negative due to dilution of the donor's blood [13]. In the past, HIV has been transmitted from an infected blood donor via a multi-organ donor to several transplant recipients. These are problems that should be considered carefully in connection with a social history of unsafe sexual activities or drug abuse, and if infection in the preceding 2 months cannot be ruled out, the donor organs should not be used. Tests for hepatitis may give false negative results throughout the incubation period of up to 6 months. Hepatitis B-positive donors may be accepted for transplantation to seropositive recipients. Hepatitis C-positive donors may be accepted for seropositive recipients if the PCR for HCV is also positive [14].

The donor should also be tested for CMV serology. The high probability of transferring CMV *de novo* or inducing CMV recurrence has led to the selection of recipients with CMV compatibility, if possible. With recent improvements in CMV prophylaxis, the importance of CMV compatibility has been reduced. Epstein–Barr virus (EBV) is also tested for since there is a substantial risk of a lymphoproliferative disorder following a primary infection. However, EBV-negative adult recipients are quite rare [15].

Bacterial infections are commonly seen during long periods in the ICU. Appropriate antibiotic treatment should ideally be given before organ retrieval, and then subsequently to the recipient for 3–5 days. This was the practice undertaken in a recent retrospective multicentre study [16] of 212 recipients of organs from 95 bacteraemic donors. There were no cases of transmission of pathogens or possible pathogens, no primary non-function, and a similar patient and graft survival rate when compared with transplants from non-bacteraemic donors. This study does not justify the use of donors with profound systemic signs of sepsis, since these donors would not have been accepted and

were therefore not included in the study. However, the results do suggest that potential donors with positive blood cultures may be acceptable. Finally, there is a need for extra caution in cases of positive *Pseudomonas* cultures because of an increased risk of rupture of arterial anastomoses associated with this micro-organism [17].

Eliminating the risk of cancer

A cancer may be transmitted to a recipient from a donor who has had a malignancy in the past. It may also be transmitted if a malignancy is found during the retrieval operation or when intracranial malignancy is the cause of death.

Careful attention must first be paid to the donor history. Donation is contra-indicated with a past treatment for a diagnosed malignancy.

A recent history of symptoms that might be related to an undiagnosed malignancy should be questioned. Menstrual irregularities following pregnancy or abortion in a female of child-bearing age could indicate a metastatic choriocarcinoma. If suspected, a highly positive pregnancy test would support the diagnosis.

During organ retrieval the surgeon should carefully examine the intra-abdominal and intra-thoracic cavities to exclude neoplastic disease. If a suspicious nodule is found, a biopsy and histopathological examination should be performed before any organs may be transplanted.

If the cause of death is a brain tumour or a suspected brain malignancy without histopathological diagnosis, an autopsy should be performed after the retrieval operation and before transplantation of any of the organs. If it is not possible to determine the histopathological diagnosis, the potential donor should be excluded from donation.

Autopsy should always be encouraged following organ retrieval to account for unsuspected diagnoses of malignancy. In the rare case when an unforeseen malignancy is found, transplantectomy is indicated if at all possible (such as in the renal transplant patients).

The Council of Europe has recently published an international consensus on the prevention of neoplastic disease in transplantation. In this document [18], primary brain tumours were classified according to acceptability for organ donation as shown in Table II.1.

Table II.1. Brain tumors and organ donation

Tumours that do not exclude the donor from organ donation
Benign meningiomas
Pituitary adenomas
Acoustic schwannomas
Craniopharyngiomas
Pilocytic astrocytomas (astrocytomas grade I)
Epidermoid cysts
Colloid cysts of the third ventricle
Choroid-plexus papillomas
Haemangioblastomas (not associated with von Hippel-Lindau syndrome)
Ganglional cell tumours (gangliomas, gangliocytomas)
Pineocytomas
Low-grade oligodendrogliomas (Schmidt A and B)
Ependymomas
Well differentiated teratomas
Tumours where the donor can be considered for organ donation depending on characteristics
Low-grade astrocytoma (grade II)
Gliomatosis cerebri
Tumours where the donor should not be considered for organ donation
Anaplastic astrocytoma (grade III)
Glioblastoma multiforme
Medulloblastoma
Anaplastic oligodendroglioma (Schmidt C and D)
Malignant ependymomas
Pineoblastomas
Anaplastic and malignant meningiomas
Intracranial sarcomas
Germ-cell tumours (except well differentiated teratomas)
Chordomas
Primary cerebral lymphomas

Selection criteria

In summary, a cadaveric donor may be accepted for kidney donation if the following criteria are met:

- *Absence of cancer* other than primary non-invasive brain tumours, non-melanotic non-metastasizing skin tumours and cancer *in situ* of the uterine cervix.
- *Absence of infections* such as HIV, acute hepatitis, tuberculosis, severe untreated systemic sepsis and viral infection. Donors must not have been engaged in activities with a high risk of HIV infection.
- *Absence of renal* disease or impaired renal function (calculated creatinine clearance >60 ml/min and no or minimal proteinuria).
- *Donor age below 70 years.*

Expanded selection criteria

Selection criteria for acceptance of donors may be expanded to include marginal or suboptimal donors as suggested below. However, at present, there is not enough support in the literature for firm recommendations. Centres are advised to define their standards and perform quality control to evaluate their implementation. Suboptimal but acceptable donor criteria may include:

- Donor age >70 years, with presence of minimal or no other risk factors other than age.
- Donor age >60 years, and few or moderate risk factors of impaired renal function including history of severe vascular disease, long-term hypertension or diabetes mellitus, or findings of proteinuria or retinal vascular changes.

- Several indicators of impaired renal function, irrespective of age.
- Donor calculated creatinine clearance of 50–60 ml/min may be considered suboptimal but still suitable for single kidney transplantation. Further impaired donor renal function (<50 ml/min) may imply dual transplantation or non-acceptance for kidney donation.

In cases of dual transplantation to one patient, the necessity of informed consent from the recipient is mandatory. However, informed consent should also routinely be obtained from recipients of single suboptimal donor kidneys. A shorter graft survival after transplantation may be expected and should be balanced against a further period of time on dialysis waiting for an optimal donor kidney. Young and otherwise healthy renal patients would benefit more from waiting for a kidney with a good long-term prognosis. Elderly patients, with a shorter life expectancy, might prefer to have a transplant as soon as possible despite a prognosis of good function for only a few years.

It is important that the transplant centre or the region define the objectives of prognosis after transplantation of kidneys retrieved from marginal donors. Criteria for donor acceptance are expanded to transplant a greater number of patients. This will inevitably be associated with a reduction of the quality of post-transplant results, such as SCr of 200 μmol/l at 1 year and 50–60% graft survival at 5 years. In the US, this does not yet appear to be an accepted policy, and 'expanded criteria' at American centres include donors that are considered normal at most European centres (i.e. hypertension and donor age >50 years) [19].

II.1.2 Determination of brain death

Guideline

A. It is recommended that the procurement centres encourage standardization of the management of the brain-dead donor including easy-to-use forms to assist the responsible physician in the emergency situation, and in line with national (or regional) laws and regulations which determine the criteria and methods for diagnosing terminal and irreversible loss of brain functions, i.e. brain death.
(Evidence level C)

Commentary on Guideline II.1.2: Determination of brain death

Any comatose patient with irreversible cerebral disease who appears to have progressed to brain death should be considered a potential donor and should be adequately assessed. There are two procedures to determine whether a patient with cerebral damage and preserved circulation supported by a ventilator has proceeded to brain death. These procedures are clinical neurological examination and cerebral angiography. The tests should be performed and the diagnosis made by specialist physicians independent of the transplant unit. The use of these tests vary according to laws and regulations in various countries. For instance, in The Netherlands, a cerebral angiogram is forbidden unless the apnoea test is associated with <80 mmHg systolic pressure. In the Czech Republic, brain death is always diagnosed with angiography. In the UK, cerebral angiography is not mandatory, but brain death must be confirmed by areflexia of the brainstem reflexes and persistant apnoea tested by strict criteria. In Sweden, clinical examination is the rule, i.e. angiography is used in cases of hypothermia or intoxication/sedation. The clinical neurological examination is described and discussed in some detail below.

Clinical neurological examination

Certain parts of the clinical neurological examination may be performed with some variation. It is important that the transplant centre ensures that a fixed routine for the examination is used in all units within the region and that all responsible doctors are informed. An example of a check list for the examination (currently being implemented throughout Sweden) is given in Table II.2.

Basic criteria for clinical neurological examination to be used:

- Known cerebral disease that can cause total cerebral infarction.
- Normal body temperature (>33°C).
- Poisoning, sedation, and metabolic, electrolyte or acid/base disturbances are ruled out.

If any of the above factors is absent, or if there is any doubt, cerebral angiography should be performed for the diagnosis of brain death.

Clinical criteria:

- Unconscious. No reaction to speech, touch or pain.
- Spontaneous breathing absent.
- Spontaneous muscular movements in area innervated by cranial nerves absent. Spinal reflexes in trunk or extremities may be seen.
- Defensive movements of head, extremities and trunk on painful stimuli absent. Spinal reflexes may be present.
- Reactions of pupils to light absent.
- Corneal reflexes absent bilaterally.
- Doll's eye movements absent.
- Cardiocerebral reflexes absent (eye bulb pressure).
- Blinking reflexes on sound stimuli absent.
- Laryngeal reflexes absent.
- Apnoea test shows absence of spontaneous breathing.

Supportive criteria:

- Masseter reflexes absent.
- Glabellar and snout reflexes absent.

Table II.2. Clinical neurological determination of brain death

An example of a checklist for the examination. Two examinations should be performed at least 2 h apart.	Exam no. 1	Exam no. 2
Date:		
Time:		
Glasgow Coma Scale = 3	☐	☐
Body temperature $\geqslant 33^{\circ}C$*	☐	☐
No poison or sedation, or serious metabolic, electrolyte or acid/base disturbances*	☐	☐
No reaction to pain within trigeminal innervated area	☐	☐
No spontaneous movements of eyes, jaws, face, tongue or larynx	☐	☐
No pupillary reaction to light	☐	☐
No corneal reflex	☐	☐
No blink reflex	☐	☐
No laryngeal or cough reflex	☐	☐
No reflexive eye movements on turning the head	☐	☐
No heart rate changes associated with pressure on eyes or carotid sinus	☐	☐
No spontaneous breathing	☐	☐
aB-pCO_2 level (should be ~5 kPa before and increased by at least 3 kPa after apnoea test)	———/——— before/after	———/——— before/after
No spontaneous breathing on apnoea test	☐	☐
Examination no. 1 performed by	Dr ————	
Examination no. 2 performed by		Dr ————

***If uncertain, cerebral angiography should be performed.**
When all parts above have been checked, the patient may be declared deceased.

- Progressive poikilothermia present.
- Isolectric electroencephalogram.

Apnoea test:

- Calibrate the ventilator minute volume to reach normocapnia (arterial carbon dioxide pressure [aB-CO_2] at 5 kPa).
- aB-CO_2 before test is registered.
- Ventilate with the above minute volume and 100% oxygen for 5 min.
- Turn off the ventilator but let the oxygen flow down the endotracheal tube or tracheal cannula.
- Continue 5–10 min. Monitor blood pressure and pulse frequency. Stop if signs of hypoxia are seen (e.g. arrhythmia).

In cases of serious pulmonary damage, PaO_2 cannot be elevated above 10–12 kPa, and the apnoea test can only be performed for ~1 min. If the apnoea test cannot be performed for >5 min, cerebral angiography should be carried out.

II.1.3 Support of the potential donor and optimization of organ function

Guidelines

A. Any comatose patient with irreversible cerebral disease should be identified as a potential donor and monitored carefully awaiting determination of brain death, evaluation and consent of organ donation and the final event of retrieval.
(Evidence level C)

B. The management of a potential donor should be basically similar to normal intensive care but with important variations, i.e. the objectives are to support future function of renal, cardiac and/or pulmonary grafts.
(Evidence level C)

C. A simplified goal for management of the donor may be to maintain a central venous pressure of 10 cm H_2O, a systemic blood pressure of 100 mmHg and a urine output of 100 ml/h.
(Evidence level C)

Commentary on Guidelines II.1.3: Support of the potential donor and optimization of organ function

Transplant results depend to a large extent on the quality of the transplanted organ, which in turn depends on age and previous medical history as well as on intensive care management at the time of death. Following identification of the potential donor, full support of intensive care should be given with the objective to optimize organ function although a decision against donation might be made at a later stage.

Most donors die because of herniation of the brain and brainstem leading to cessation of cerebral blood circulation and brain death. This diagnosis is based on the verification of absence of all brain and brainstem functions or absence of cerebral circulation, and may be performed by means of a clinical neurological test or angiography as described above. While the deceased patient is on a ventilator, the blood is sufficiently oxygenated, and circulation is maintained in organs such as the kidneys, liver, pancreas, heart and lungs, which will remain viable for a limited time. During this period retrieval for transplantation may be performed. Metabolic changes occur during and after brain and brainstem herniation, and these changes may impair organ function. The progress of these changes may be modulated to some extent.

The process of herniation has been studied primarily in experimental animals. At the time of herniation there is an increase in blood levels of epinephrine, norepinephrine and dopamine [20,21], the size of the increase depending on how fast intracranial pressure rises. The catecholamines induce an increase in peripheral vascular resistance and an increase in cardiac work load. Despite this increase in cardiac work load, some studies have shown a reduction in cardiac output because of the increased peripheral vascular resistance. The increased cardiac work load is associated with an imbalance between oxygen demand and oxygen supply in the heart. Therefore, there are often signs of ischaemia and arrhythmias on the electrocardiogram (ECG) at the time of herniation.

When peripheral circulatory control has disappeared as a consequence of herniation, blood pressure and heart rate both decrease and reduced amplitudes of the QRS complexes may be seen on the ECG. Autopsy may show small areas of necrosis within the myocardium and the amount of intracellular energy-containing compounds (ATP, glycogen, …) may be reduced. The overall result of these factors is a slightly reduced cardiac function.

A lack of intracellular energy-containing compounds develops following herniation. With normal cerebral function, this deficiency would rapidly be counterbalanced by increased synthesis, but for reasons that are still unclear this does not occur in brain-dead patients. Studies in experimental animals show that supplementation with hormones such as corticosteroids, insulin and triiodthyronine may reverse the condition in the heart [22]. Clinical studies, however, have not been convincing and hormonal substitution is not generally recognized.

After herniation, the release of antidiuretic hormone from the pituitary is interrupted, causing a state of diabetes insipidus and dehydration of the donor. Substitution with common electrolyte solutions will induce disturbances of water and electrolyte balance (oedema and hyperosmolarity; hypernatraemia and hypokalaemia) with deterioration of cell membrane and organ function. Treatment with vasopressin or synthetic analogues to restore normal urine output has been shown to reduce these disturbances. Large volumes (200–1000 ml/h) of sodium-free fluids, preferably sterile water, may be needed to correct the water deficit and hypernatraemia.

In brain death, circulation is characterized by bradycardia and hypotension. The hypotensive state is due primarily to a moderate cardiac insufficiency combined with hypovolaemia. There may also be an absolute hypovolaemia secondary to diabetes insipidus, and a relative hypovolaemia secondary to reduced peripheral vascular resistance and increased vascular capacity. Hypotension may lead to hypoperfusion of various organs. Ischaemia in the kidneys, due to prolonged hypotension, is considered one of the main causes of damage to the kidneys in brain death. Preventing hypotension has been shown to improve renal function after transplantation [23].

Donor management aims to optimize the circulation and oxygenation of the organs that are to be transplanted. There are several excellent overviews on this subject [24,25]. In brief, the guidelines should include the following:

- Increase the blood volume with crystalloids and colloids to a central venous pressure of 10 cm H_2O.
- The goal is a systemic arterial pressure of 100 mmHg. If this cannot be reached using fluids alone, dopamine may be added as an inotropic support. In cases of lung donation, colloids are preferred to crystalloids. Avoid hypothermia by using warmed fluids.
- A reduced urine output at the time of herniation is most often normalized after restoration of the blood volume, then followed by a state of diabetes insipidus. The best treatment for diabetes insipidus is vasopressin or one of its analogues. The goal should be to reduce the urine output to $\sim$100 ml/h. With this treatment, electrolyte disturbances and development of peripheral oedema are to some extent avoided.
- The aim of ventilator therapy should be to achieve normal values of blood gas analysis. To retard the development of atelectasis, a positive end expiratory pressure of 5 cm H_2O is advisable.

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II.2 Cadaveric non-heart beating donors (NHBD)

Guidelines

A. Non-heart beating donors should be considered as a valuable source of kidneys for transplantation, despite shorter graft survival and higher serum creatinine in recipients compared with those transplanted from classical cadaveric donors.
(Evidence level B)

B. Young donors who die from trauma can be safely considered as non-heart beating donors.
(Evidence level B)

C. To optimize this promising alternative, it is recommended that centres start and accumulate experience.
(Evidence level C)

Commentary on Guideline II.2: Cadaveric non-heart beating donors (NHBD)

Guideline A. To expand the number of cadaveric kidneys available for transplantation, several units have used kidneys from donors without a beating heart. Initial experience was performed in Europe, mainly in the Netherlands [1–3], and Japan, where brain death was not recognized. Encouraging results were obtained and this possibility for transplantation has been adopted by groups around the world [4,5].

Kootstra *et al*. established four categories of non-heart beating donor:

1. Death on arrival; mostly victims of an accident outside the hospital.
2. Unsuccessful resuscitation, where resuscitation is taken over by the hospital team.
3. Awaiting cardiac arrest; 'this includes patients who die in the intensive care unit and the family have agreed with organ donation'.
4. Cardiac arrest while brain dead: including 'patients who suffer an unexpected cardiac arrest in the process of being diagnosed of brain death or after the determination of brain death, but before they are taken into the operating room'. [2].
5. Recently, Sanchez-Fructuoso *et al*. added category 5: unexpected cardiac arrest in intensive care unit [6,7].

The principal ethical problem is represented by category 3. Kootstra *et al*. considered a period of 10 min of no intervention very important: 10 min of asystole without blood circulation results in irreversible damage of the brain at room temperature. Kidneys from patients of category 4 can be used when heart function cannot be restored.

Using NHBDs could increase the number of donors by 20% and the number of transplants by 16%. In the centre with most experience in Spain, despite the fact that $\sim$10% of kidneys from NHBDs were discarded due to poor arterial perfusion, NHBD kidneys were used in 32% of all transplants performed in 1999 [7]. Therefore, renal transplantation from NHBDs represents a promising alternative to enlarge the donor pool. In the Netherlands and Spain consensus documents have been finished to improve this method of obtaining organs for transplantation.

Guideline B. Experience from several countries [2–4,7–9] have shown that patients who received an organ from a NHBD had reduced [3,8,9] or similar graft survival [2,4,7] compared with matched patients who received kidneys from heart beating donors (HBD). However, in these studies, donor characteristics were very different and therefore it was difficult to make comparisons. Interestingly, in the largest multicentre series reported by Cho *et al*., survival rate at 1 year was higher for grafts from NHBDs who died of trauma (young people) compared with grafts from HBDs who died of other causes [5]. NHBDs should ideally be under 55 years of age [7].

The largest series in Spain, recently published, showed similar results with 1- and 5-year graft survival among NHBD compared with HBD grafts (85 and 83% *vs* 87 and 84%, respectively). Negative predictive factors for NHBD graft survival were the type of NHBD and the presence of corticosteroid-resistant acute rejection [7]. Results from Japan with CsA or FK506 as basic immunosuppression showed good results: patient survival rates of 97, 95, 93 and 89% at 1, 3, 5 and 10 years, respectively, and graft survival rates of 83, 72, 65 and 49% at 1, 3, 5 and 10 years, respectively [4].

The most important problem is the high incidence of post-transplant acute tubular necrosis requiring dialysis. This was between 50 and 70% in several series, and was associated with a 5.73-fold increase in the incidence of delayed graft function in the Madrid experience [3–7]. Also, primary failure of the graft is

between 4 and 14% compared with the percentage for kidneys from HBDs [2–5]. Delayed graft function in NHBD groups is influenced by the warm ischaemia time, which is directly related to the number of days to achieve a serum creatinine of <300 mmol/l [3]. Also, the number of days of hospitalization after transplantation is higher. In general, renal function is lower in patients who receive kidneys from NHBDs [2–5], although Sanchez-Fructuoso *et al.* reported similar serum creatinine levels at 1 and 5 years after transplantation [7].

Guideline C. Transplantation using kidneys from a NHBD requires: first, an organizational structure to detect and to maintain donors; secondly, technical experience to maintain perfusion of the kidneys; and thirdly, careful local guidelines and consideration of the ethical issues of particular importance in these types of donors [1,3,7]. As discussed previously, the organization of transplant co-ordination is very important to detect all possible NHBD and subtypes. Particularly in type I NHBDs, a relationship with the municipal emergency service should be developed to ensure transfer to hospital of all possible donors who die suddenly on the street and after unsuccessful cardiopulmonary resuscitation. It is necessary to support these donors during transfer with external cardiac massage, mechanical ventilation and intravenous fluids [7].

Cardiopulmonary bypass involving extracorporeal circulation, external oxygenation and intense hypothermia are required to maintain grafts from the moment of cardiac arrest until the procurement of kidneys. It is clear, therefore, that an effective organization and training for the transplant team is mandatory. Data from the Hospital Clinico San Carlos in Spain is an example of this: results with NHBD have clearly improved with experience developed over the years [7].

Great caution should be taken with respect to legal problems in organizing the harvesting of cadaveric NHBDs, depending on the nation and its specific legislation, if any.

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II.3 Living kidney donors

Guidelines

A. Use of kidneys from 'living donors' is recommended for renal transplantation whenever possible and is supported by the especially favourable results obtained after transplantation.
(Evidence level B)

B. Before being selected as a 'living donor', careful information should be provided to the potential donor and he or she should undergo a careful medical and physical evaluation, as listed in Table II.3.
(Evidence level A)

C. After complete evaluation of the donor, formal written consent (often legal) must be obtained from the donor.
(Evidence level A)

D. Special care must be taken to ensure that a potential 'living related donor' does not fulfil any of the exclusion criteria listed in Table II.4.
(Evidence level A)

E. The use of 'living non-related donors' may be justified if the donor is a spouse, an unmarried life-long partner, a step parent or in some occasions a close friend, and if it is ensured that the donation is purely altruistic, and if commercial transactions are excluded.
(Evidence level B)

F. Commercially motivated kidney transplantation is not acceptable and all procedures must comply with existing national (regional) and EU laws.
(Evidence level A)

G. 'Living non-related donors' require the same level of information, consent and evaluation as 'close related living donors'.
(Evidence level B)

H. It is desirable that the 'living donor' should be offered long term follow-up at regular intervals. Steps should be taken to ensure against the rare development of late complications.
(Evidence level B)

I. The 'living donor' should always be left with the best kidney.
(Evidence level B)

Table II.3. Evaluation of the potential living kidney donor

ABO blood typing
HLA-A, -B and -DR tissue typing
Cross-match
Initial medical evaluation:
History and physical examination
Blood pressure
Psychosocial evaluation (optional)
Electrocardiogram, optional echocardiography
Chest radiograph, optional pulmonary function tests
Complete blood count, platelet count, prothrombin time, partial thromboplastin time
Cardiovascular evaluation (including echocardiography and/or scintigraphy) for donors older than 50 years or with a history of heavy smoking or with mild hypertension
Chemistry: blood urea nitrogen, s-creatinine, sodium, potassium, bicarbonate, fasting blood glucose, calcium, phosphorus, albumin, total protein, uric acid, liver enzymes, bilirubin, fasting cholesterol, triglycerides, high- and low-density lipoproteins
Further renal assessment:
Urinanalysis, microscopy of urinary sediment
Urine culture
Twenty-four-hour urine for creatinine clearance or a direct evaluation of the GFR by CrEDTA or iohexol or inulin clearance
Radionuclide determination of glomerular filtration rate, as a separate evaluation of the function of the two kidneys, renography (optional)
Twenty-four-hour urine for total protein
Urine for microalbuminuria (optional)
Ultrasound examination of the kidneys and the abdomen
Intravenous pyelogram (optional)
Renal arteriogram
Additional screening tests
CMV antibodies (Ab) titres, HBsAg, HCV antibody, HIV antibody, EBV Ab titres, herpes simplex virus (HSV) Ab, varicella zoster virus (VZV) Ab, Toxoplasma Ab, and syphilis test
In females: pregnancy test, if relevant, gynaecological examination when older than 40 years
In males: PSA when older than 50 years

Commentary on Guideline II.3: Living kidney donors

Despite the improvement in immunosuppression and better graft and patient survival in cadaver kidney transplantation, the use of living donors for kidney transplantation still results in a slightly superior graft and patient survival, and less morbidity due to fewer rejection episodes, less immunosuppression and better immediate graft function.

Furthermore, the number of cadaver grafts available is far less than is needed in order to transplant the increasing number of uraemic patients on the waiting lists. Therefore, the need for kidneys from other sources than cadaveric donors is ever rising and consequently the use of related donors and unrelated living donors has increased.

In the United States, practice guidelines have been formulated on the basis of consensus and literature reviews [1,2]. The British Renal Association (BRA) has produced EBP Guidelines for treatment of adult patients with renal failure from November 1997 [3]. Their standards of recommendation are that patient survival should be at least 95% 1 year after grafting and that $>90\%$ of the grafts from living kidney donors should be functioning at 1 year. The British Transplant Society (BTS) has in November 1998 published their guidelines: 'Towards standards for organ and tissue transplantation in the United Kingdom' [4]. Their recommendations are at least 99% patient survival at 1 year after grafting and 95% at 5 years. Ninety-five percent of live donated kidney allografts should still be functioning at 1 year and $>80\%$ at 5 years. It should, however, be stated that these recommendations will be difficult to live up to, when doing transplantations between older living donors and older recipients. BTS and BRA new 2000 guidelines have just been released [5].

II.3.1 Related living kidney donors

In general, it is recommended that the first contact between the potential living kidney donor and the transplant team should be initiated by the potential donor. Counselling given to the donor should focus on the risks of donation and not especially on the benefits for the recipient.

Table II.4. Exclusion criteria for a potential living kidney donor

Kidney disease:
Reduced GFR, in comparison to normal range for age
Proteinuria of >300 mg/day
Microhaematuria, except when an urologic evaluation and a possible kidney biopsy are normal
Multiple kidney stones
Multiple cysts
Three or more arteries
Family history of autosomal dominant polycystic kidney disease (ADPKD), unless ultrasound or CT scan is normal and donor age is >30 years
Bilateral fibromuscular arterial dysplasia
Other exclusion criteria:
ABO incompatible
Cross-match positive
Hypertension without good control
Diabetes mellitus
Cardiovascular disease
Pulmonary insufficiency
Abuse of morphine, heroin or cocaine
HIV positive
Hepatitis B antigen-positive to a negative recipient (or unprotected)
Hepatitis C-positive to a negative recipient
Other severe infections
Malignancy
Long-term use of nephrotoxic drugs
Age <18 years
Previous severe abdominal surgery

Information to the donor

The potential kidney donor should be informed of the following:

1. There is no guarantee involved. Although an extensive examination is performed, there is no guarantee of successful outcome of the transplant. Early and late possible complications in renal transplantation should be mentioned.
2. A potential family donor can always withdraw his or her consent.
3. The potential donor will have to undergo a careful medical examination in order to ensure that he or she is healthy, and that surgery can be performed with a minimum risk [6]. Despite such examinations, the mortality risk was estimated to be 0.03% and the risk of morbidity 0.23% in large studies from donor operations performed in the 1980s [7].

The potential, but unlikely risks of kidney donation include:

- Short-term surgical risks.
- Theoretical and extremely unlikely long-term risks of impaired kidney function and hypertension.
- Loss of time and money.
- Psychological risks.

It should be stressed, however, that the long-term risk of kidney donation is very low and that the 'living donor' has a longer life survival than the general population, possibly due to the positive selection.

Consent to donation

Great care should be taken during the information procedure to ensure that the kidney donation is truly voluntary and in no way coerced. The potential kidney donor should receive direct personal information as well as written information. The potential kidney donor should sign a statement allowing the transplant surgeon to perform the nephrectomy and acknowledging the appropriate verbal and written information.

Evaluation of the potential living kidney donor

The aims of the investigations performed to evaluate the potential living kidney donor are:

1. To ensure that the donor decides by him/herself, that he or she really wants to go through the procedure and that the donor is not forced or obliged to do it.
2. To ensure that there will be a minimum of risk for anaesthesia and surgical intervention.
3. To ensure that the donor is healthy and that there is no risk of transmitting disease.
4. To ensure that the unilateral nephrectomy will have no negative effects on the long-term renal function of the donor.
5. To make the decision on alternative surgical procedures; left or right nephrectomy performed by open surgery or laparoscopic technique.

To ensure that the autonomy of the potential donor is protected, the physician carrying out the primary evaluation should ideally be independent of the recipient's team and should not be a member of the transplant team. However, this is not always possible and in that case, the potential donor should be evaluated by the surgeon who will be performing the nephrectomy. Only then should the decision on eventual donation be made. However, in practice many donors refer directly to the transplant physician or transplant surgeon to ask for advice.

The very first test to be performed is often an ABO blood group test. If compatible, a complete medical history and physical examination should be done together with further examinations as presented in Table II.3. The medical history should include presence of any sign of renal disease, such as hypertension, nephrolithiasis, proteinuria, haematuria, oedema and renal parenchymal infections. Furthermore, a thorough investigation should be conducted to detect cardiovascular risk factors, diabetes mellitus, malignancy and systemic diseases. Psychological problems or diseases and medication given should be included. It should be emphasized that this information and the results of the examinations are designed to prevent harm to the donor by detecting possible renal disease, to ensure that the recipient receives a normal kidney, to ensure that the potential donor may retain one normal kidney and to ensure a normal kidney function after the nephrectomy. Finally, angiography is performed to exclude vascular disease and as a basis for the decision on which kidney should be retrieved.

A number of exclusion criteria of live kidney donation are presented in Table II.4. Special emphasis should be made on the possible presence of hereditary renal diseases, as presented in Table II.5. Donors should be offered life-long follow-up with check-up examinations once a year.

II.3.2 Unrelated living kidney donors

Acceptability of donors

A living organ donation programme requires great care to ensure that donation is altruistic, without coercion or reward, that the risk to the donor is minimized, and that the requirements of the Human Organ Transplantation Act from 1989 are met in all respects. Permission from the local ethical committee has to be obtained in some countries, while in other countries it is necessary to obtain permission from the court. Clearly defined protocols of investigation and management are essential, and such transplants should not be carried out in centres where they constitute an occasional event [1].

Table II.5. Screening for familial renal disease:

Diabetes mellitus
Autosomal dominant polycystic kidney disease
Systemic lupus erythematosus
Hereditary nephritis

The use of highly motivated, but unrelated living donors, such as spouses, unmarried life-long partners, step-parents or even close friends is becoming widely accepted, and graft survival rates obtained are comparable to those of living related kidney donors and superior to cadaver kidney grafts [8].

The provisions of the Human Organ Transplants Act 1989 are specifically designed to prevent abuse in this area. Nonetheless, coercion remains a great concern. A particular risk occurs when a potential donor needs a translator in order to understand the questions and issues being put to him or her by clinicians [4].

The arguments for and against the use of emotionally related living kidney donors have been carefully presented in several publications [9–14]. **Commercially motivated renal transplantation must not be accepted**, despite the occurrence in some countries [15], and **the International Society of Transplantation strongly opposes this practice**.

Besides a careful evaluation of the possibility of pressure put on the potential unrelated living kidney donor and a careful attempt to ensure absence of coercion of any kind, the evaluation of this type of kidney donor should follow the scheme presented above in Tables II.3, II.4 and II.5.

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II.4 Immunogenetic work-up of the donor

See section I.6.1: Immunogenetic work-up of the recipient (and donor).

See paragraph III.1.1: Cross-matching donor/recipient: ABO blood group matching.

See paragraph III.1.2: Cross-matching donor/recipient: HLA matching and mismatching.

Care of the Live Kidney Donor: Consensus on the Ultimate Gift

Anthony P. Monaco and Peter J. Morris

The Editors of *Transplantation* are pleased to present to their readers this supplement which records the consensus of an International Forum on the care of the Live Kidney Donor held in Amsterdam, The Netherlands from April 1-4, 2004. The objective of the meeting was to develop an international consensus on the standard of care and a position statement of The Transplantation Society defining and affirming the responsibility of the transplantation community for the live kidney donor. The result was a real international consensus, with over 100 transplant experts from more than 40 countries around the world participating. This Forum was also in part a result of the involvement of The Transplantation Society with the World Health Organization (WHO) and functioned as a continuum of the Madrid WHO conference on organ donation and transplantation held in October 2003. What is presented is a detailed analysis of all relevant aspects of selection and management of live kidney donors. This document should serve as a useful benchmark for living donor programs all over the world.

The Forum analyzed the sentinel events associated with live kidney donation; the data emphasized the extremely low operative mortality rates and the long-term safety of this procedure with, noting the absence of accelerated loss of renal function and lack of appearance of hypertension in normal donors post nephrectomy. Forum participants affirmed the necessity for live donors to receive complete medical and psychosocial evaluation prior to donation (*1*); they elaborated in detail the acceptance limits of donor hypertension, obesity, dyslipidemia, renal function, urine protein and blood, stone disease, and historical malignancy that still permit live kidney donation. A great detail of discussion focused on prevention of transmissible infectious diseases through live kidney transplantation. Specific recommendations for screening of various viral, bacterial, and parasitic diseases are presented. Likewise pre- and postoperative donor issues such as determination of cardiovascular risk in the live donor, the salutary effects of smoking cessation and alcohol abstinence, and the screening for pulmonary risk and thromboembolism are detailed. Readers will find the discussion of risk estimation for donor candidates with isolated medical abnormalities (hypertension, low grade proteinuria, microscopic hematuria, etc.) useful and somewhat reassuring in justifying decisions to include such people as potential living donors in specific instances.

Readers of this supplement will also find interesting and provocative the discussion on how a number of aspects of live kidney donation vary around the world. Thus some of the extremely rigid blood and tissue donation restrictions currently enforced in certain countries should probably not be applied to organ donation where the risk/benefit ratio is so different. Also, restrictions on live unrelated kidney donation (presently prohibited in various countries because of the absence of HLA matches) are certainly not justified. Likewise, live donor exchanges specifically banned in certain countries as valued considerations should be allowed. The high rate of female live kidney donation was acknowledged and the potential role of coercion/discrimination in many countries was discussed and the need to deal with this issue in a culturally sensitive manner emphasized. The high rate of minors donating to adults was also identified and a consensus proposal that minors less than 18 years of age should not be used as living kidney donors was agreed to.

The Editors of *Transplantation* hope that this supplement will be used where appropriate as a benchmark for standard of care in selection and management of live kidney donors. We welcome your thoughts and reactions to the ideas and recommendation contained therein.

Weblinks

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14578768
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12451277

REFERENCE

1. The Consensus Statement of the Amsterdam Forum on the care of the live kidney donor. *Transplantation* 2004; 78: 491-492.

A Report of the Amsterdam Forum On the Care of the Live Kidney Donor: Data and Medical Guidelines

Kidney transplant physicians and surgeons met in Amsterdam, The Netherlands, from April 1–4, 2004 for the International Forum on the Care of the Live Kidney Donor. Forum participants included over 100 experts and leaders in transplantation representing more than 40 countries from around the world, including participants from the following continents: Africa, Asia, Australia, Europe, North America, and South America.

(*Transplantation* 2005;79: S53–S66)

The objective of the Forum was to develop an international standard of care with a position statement of The Transplantation Society regarding the responsibility of the community for the live kidney donor. The position statement was adopted by the Council of The Transplantation Society (*1*).

The Mission of the Amsterdam Forum

Abdallah Daar presented the mission statement of the Amsterdam Forum emphasizing the concern of the participants for the welfare of the live donor. Specific objectives of the Forum included the development of an international standard of care for the live donor; the development of a position statement regarding the responsibility of the transplant community for the live kidney donor; and the forging of an alliance with the World Health Organization (WHO) to implement these standards. The intent of the Forum leaders was for conference participants to become subsequent emissaries of these standards within their geographical sphere of influence around the world.

Alliance with the World Health Organization

Carl Groth and Luc Noël provided a background report regarding the involvement of The Transplantation Society with WHO, and the role of the Amsterdam Forum as a continuum of the Madrid WHO conference on organ donation and transplantation in October 2003.

Preamble

This report of the Amsterdam Forum is derived from an international experience of participants and also from evidence-based recommendations; it is not a document of mandatory regulation. Medical judgment as a reflection of published data and physician experience influences the decision to accept (or not) an individual as a live kidney donor.

What Is Known Regarding the Sentinel Events of Live Kidney Donors

Forum participants were charged with outlining what is known—and not known—about the sentinel events regarding living donors in the current era (death, dialysis, and need for a kidney transplant), and developing recommendations for the collection of data to improve the care of potential and actual living donors.

Ahad Ghods and Nasser Simforoosh presented the Iranian experience with live donor outcomes (*2*). As of 2003, a total of 15,948 renal transplants have been performed in Iran (12,504 living unrelated, 3,049 living related, and 395 deceased donor transplants). With over 15,000 live kidney donors in Iran, the perioperative mortality rate of live kidney donation was 3 in 15,000 (0.02%).

Ingela Fehrman-Ekholm and Jonas Wadström presented data of the Swedish Registry. With more than 20 years of follow-up, 85% of over 400 kidney donors were alive, whereas the expected survival rate was 66% (*3*, *4*). Survival was 29% better in the donor group than in the comparative cohort.

Arthur Matas submitted data from a survey of 171 United States kidney transplant centers to determine current living donor morbidity and mortality for open nephrectomy, hand-assisted laparoscopic nephrectomy (LN), and non-hand-assisted LN (*5*). Between January 1, 1999 and July 1, 2001, these centers carried out 10,828 living donor nephrectomies: 52.3% open, 20.7% hand-assisted LN, and 27% non-hand-assisted LN. Two donors (0.02%) died from surgical complications and one is in a persistent vegetative state (all after LN). Reoperation was necessary in 22 (0.4%) open, 23 (1.0%) hand-assisted LN, and 21 (0.9%) non-hand-assisted LN cases ($P=0.001$). Complications not requiring reoperation were reported for 19 (0.3%) open, 22 (1.0%) hand-assisted LN, and 24 (0.8%) non-hand-assisted LN cases ($P=0.02$). Readmission rate was higher for LN (1.6%) versus open (0.6%) donors ($P<0.001$), almost entirely as a result of an increase in gastrointestinal complications in LN donors.

Long-Term Complications of Donors

Ingela Fehrman-Ekholm and Jonas Wadström reported upon the glomerular filtration rate (GFR) and the prevalence of hypertension as compared with age- and gender-expected values. In their series of over 400 donors, no accelerated loss of kidney function was observed in live donors who had normal renal function at the time of nephrectomy (*4*). However, there was deterioration in the renal function of donors with increasing age, similar to what is seen among normal healthy subjects. The average glomerular filtration rate in donors aged 75 years and over was 48 ml/min/1.73 m2. A GFR $<$ 30 ml/min was found in five donors. However, three donors developed renal disease, and one was on dialysis treatment. In two of these cases, hereditary factors were possibly involved.

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There was no increase in age-specific prevalence of hypertension for female kidney donors. However, one-third of the donors (aged 46–91 years) who had donated more than 20 years ago had hypertension; but the age-adjusted prevalence of hypertension among donors was not higher than in the general population. Significant proteinuria (≥1.0 g/L) was found in 3% and slight proteinuria (<1.0 g/L) in 9% of the donors. Proteinuria was associated with hypertension and a lower GFR.

Pregnancy after Live Kidney Donation

Annika Tibell and Anders Hartmann concluded that donor nephrectomy is not detrimental to the prenatal course or outcome of future pregnancies. There are no data to suggest that hyperfiltration associated with the combination of unilateral nephrectomy and pregnancy leads to significant hypertension, proteinuria, change in glomerular filtration rate, or abnormalities of the urinary sediment (*6*, *7*). It was recommended, however, to delay pregnancy until at least 2 months after nephrectomy to assess renal compensation prior to conception with evaluation including blood pressure, GFR, and assessment for microalbuminuria. The emphasis was to verify that postpartum renal function is normal.

Donors Needing Transplants

A total of 56 previous living donors were identified in the database of the United Network for Organ Sharing (UNOS) as having been subsequently listed for deceased donor kidney transplantation, with more than 50,000 live kidney transplants performed since 1987. Of the previous kidney donors, 43 received transplants and 36 had functioning grafts at the time of the published report (*8*). One patient died after transplantation; two candidates died while waiting on the list. At the time of the donation, the donors ranged in age from 17 to 61, with an average age of 31. The time from donation to listing ranged from 2 to 32 years, with a mean and median of 15 years. At listing, 40% had a diagnosis of hypertensive nephrosclerosis. An additional 17% were listed with focal glomerulosclerosis, and 13% with chronic glomerulonephritis.

Bob Metzger brought to attention a current UNOS policy for live kidney donors that assigns an allocation priority for a deceased donor kidney if the previous live kidney donor subsequently become a candidate for a kidney transplant later in life. However, there was no consensus to develop such a policy internationally. Stephen Munn reported that the New Zealand community has no facility in its cadaver organ allocation system for any such priority provision that was not of medical benefit to the list as a whole. Further, 20% of the live donors in New Zealand are from other countries, some of which have no end-stage renal program. Thus, such an allocation priority for previous donors is not feasible to implement internationally.

Fifty Years of Live Kidney Donation

Fifty years have elapsed since the first successful kidney transplant from a live donor and a substantial body of published evidence indicates that there is little long-term medical risk to a healthy donor after unilateral nephrectomy. Gil Thiel brought to attention, however, the potential of underreporting donor complications because of the hesitation of the transplant physicians to reveal them either to the hospital center, future donors, or insurance carriers.

Eduardo Santiago-Delpín stressed the responsibility of transplant centers to assure donor protection, safety, and welfare. Forum participants agreed that prior to donation, the live kidney donor must receive a complete medical and psychosocial evaluation, receive appropriate informed consent, and be capable of understanding the information presented in that process to make a voluntary decision. All donors should have standard tests performed to assure donor safety (*1*). These include blood and urine screening tests, chest X ray, electrocardiogram, cardiac stress test, radiographic assessment of the kidneys and vessels. A complete listing of tests is appended by Andrew Bradley. Human leukocyte antigen (HLA) typing can be useful to determine an HLA identical sibling; otherwise it is not seemingly vital to a successful outcome (*9*). Forum participants discussed the evaluation of various medical issues in the potential donor, such as donor hypertension, body mass index, dyslipidemia, renal function, malignancy, and a history or current presence of infectious diseases such as tuberculosis or hepatitis.

As in the general population, based upon age and other medical risk factors (e.g., hypertension, proteinuria, hyperlipidemia, impaired glucose tolerance test), kidney donors should undergo regular long-term follow-up of body weight, blood pressure, blood sugar, serum creatinine, and urinalysis. Abnormalities should be treated promptly by either the local medical physician or the transplant nephrologist. Long-term collaborative prospective studies and comprehensive national registries should be established to determine whether the incidence of medical risk factors and renal dysfunction is different from the general population.

Donor Hypertension

Hypertension has been considered to be a contraindication in potential renal transplant donors. However, the precise risk to donors who have borderline elevation in blood pressure (BP) and those with a family history of hypertension has not been conclusively determined. Greg Obrador noted that the threshold values for hypertension are different depending on the technique used to measure BP. Ambulatory blood pressure monitoring (ABPM) was reported by Fatma Nurhan Ozdemir to be more accurate than in-office blood pressure measurement (OBPM) in recording true potential donor BP (*10*, *11*).

Gil Thiel reported 18 donors who were hypertensive at the time of nephrectomy. At 7 years following nephrectomy, 10 of the 18 donors were on antihypertensive treatment (five donors with one medication, three donors with two medications, and two donors with three medications). One-third of these 18 donors (hypertensive at donation) were normotensive at 7 years following nephrectomy without any treatment. Thus, hypertension at the time of nephrectomy may have been due to stress conditions before donation. In contrast, among 73 normotensive donors at the time of nephrectomy, only 15 were on antihypertensive treatment (12 donors on one medication, two donors on two medications, and one donor on three medications) at 7 years after nephrectomy. The outcome (renal function) of the 18 donors determined to be hypertensive at nephrectomy was no different than the 75 normotensive donors. At 7 years, the mean estimated creati-

nine clearance for the hypertensive donor group was 71±19 (median 67) ml/min/1.73 m^2, not statistically different for the initially normotensive group 75±17 (median 73) ml/min/1.73 m^2.

Mark Stegall reported upon the recent Mayo Clinic experience. The GFR (as determined by iothalamate clearance corrected for body weight) of 25 hypertensive donors was not statistically different than 150 normotensive donors prior to nephrectomy or at 1 year postdonation (*12*). Blood pressure was easily controlled in hypertensive donors with an angiotensin receptor blocker and diuretics; none had microalbuminuria.

The following consensus guidelines regarding hypertensive donors were adopted following discussion by Greg Obrador, M.K. Mani and Ian Dittmer:

- Patients with a BP >140/90 by ABPM are generally not acceptable as donors.
- BP should preferably be measured by ABPM, particularly among older donors (>50 years) and/or those with high office BP readings.
- Some patients with easily controlled hypertension who meet other defined criteria (e.g., >50 years of age, GFR >80 ml/min, and urinary albumin excretion <30 mg/day) may represent a low-risk group for development of kidney disease after donation and may be acceptable as kidney donors.
- Donors with hypertension should be regularly followed by a physician.

Obesity

Gabriel Danovitch and Jose Morales led the discussion on live obese kidney donors. Obesity was defined by a body mass index (BMI) of > 30 kg/m^2. All potential donors should have BMI determined at initial evaluation. Evaluation should also include other comorbidities associated with obesity such as microalbuminuria, impaired GTT, hypertension, hyperlipidemia, cardiovascular disease, sleep apnea, and liver disease.

Obesity should be considered an increased risk for renal disease; however, there is no data on the outcome of such individuals. Jose Morales commented upon patients who underwent unilateral nephrectomy for reasons other than donation, noting an increased risk for proteinuria and renal insufficiency on long-term follow-up if the BMI was ≥30 (*13*). However, Mark Stegall reported that renal function of more than 100 obese donors (≥30 BMI) after donation was no different from that of nonobese donors. Further, the corrected GFR of obese donors was greater than that of nonobese donors, and the morphology of biopsied obese donor kidneys (particularly glomerular volume) is no different from nonobese donors. The selection criteria for all donors at the Mayo Clinic were the same by a corrected GFR >80 ml/min/BSA; normal urinary protein and albumin secretion, and fasting blood glucose <126 mg/dl (for fasting glucose 100–125, a 2-hour GTT is recommended). Finally, in the Mayo experience, hand-assisted donor nephrectomy is safe in obese donors.

The following consensus guidelines were adopted regarding obesity:

- Patients with a BMI >35 kg/m^2 should be discouraged from donating, especially when other comorbid conditions are present.
- Obese patients should be encouraged to lose weight prior to kidney donation and should be advised not to donate if they have other associated comorbid conditions.
- Obese patients should be informed of both acute and long-term risks, especially when other comorbid conditions are present.
- Healthy lifestyle education should be available to all living donors.

Dyslipidemia

Arturo Dib-Kuri noted that various types of dyslipidemia have been associated with decreased kidney function in the general population and with faster rates of progression in patients who have chronic kidney disease. Dyslipidemia should be included along with other risk factors in donor risk assessment, but dyslipidemia alone does not exclude kidney donation.

Acceptable Donor Renal Function

Robert Gaston and Mario Abbud-Filho led the discussion on the level of renal function that defines an acceptable living kidney donor. Individuals contemplating donor nephrectomy should demonstrate "normal" renal function as determined by assessment of GFR. The definition of "normal" GFR changes with age, as renal function deteriorates over time (*14–16*). Carl Cardella noted a decrease in GFR of approximately 1 ml/min/1.73 m^2 per year after age 40. There is a documented acute decrease in GFR of approximately 30% after unilateral nephrectomy; however, the impact of unilateral nephrectomy on this rate of decline in GFR is unknown.

All potential kidney donors should have GFR estimated. Creatinine based methods may be used to estimate the GFR; however, creatinine clearance (as calculated from 24-hour urine collections) may under- or overestimate GFR in patients with normal or near normal renal function (*17*). Calculated GFR values (Modification of Diet in Renal Disease [MDRD], Cockcroft-Gault) are not standardized in this population and may overestimate GFR. These methods may be replaced or supplemented by isotopic estimation of GFR (e.g., iothalamate, 99-technetium clearances) in cases of borderline GFR determination.

Jaime Herrera-Acosta noted that some might have difficulty in obtaining ^{125}Iothalamate clearance, for which his center substitutes creatinine clearances obtained during mild water diuresis and short-term urine collections to make sure that urine flows were exact. An excellent correlation of creatinine clearance with simultaneous ^{125}Iothalamate clearance was achieved in 46 kidney donors ($r=0.84$, $P<0.0001$).

Acceptable GFR in a donor is that which can be predicted to provide adequate GFR for both donor and recipient after donor nephrectomy/transplantation. Robert Gaston and Mario Abbud-Filho cited reports of the literature that reveal donors with GFR ≤80 ml/min before nephrectomy cannot be reliably expected to provide or maintain optimal function after nephrectomy, although as many as 20% of U.S. transplant centers would accept a creatinine clearance as low as 60 ml/min (*18*, *19*).

Dan Brennan noted that donors who are thin, small, and female with a creatinine clearance of <80 ml/min and normalized for body surface area (BSA) could alternatively be normalized for height and a more accurate GFR can be determined. An average-sized 60-year-old person (70 kg body weight) with a serum creatinine of 1.0 mg/dl can be presumed to have a GFR of 80 ml/min (*20*).

Bernardo Rodríguez-Iturbe commented that if donors are challenged with a creatinine load, they might not normally increase the tubular secretion of creatinine (revealing an impaired tubular functional reserve) (*21*).

The following consensus guideline was adopted regarding acceptable renal function: a GFR <80 ml/minute or 2 standard deviations below normal (based on age, gender, and BSA corrected to 1.73/m^2) generally preclude donation. Kidneys from live donors with GFR ≤80 ml/min are associated with relative risk of graft loss of 2.28 compared to those with greater prenephrectomy GFR (*22*). However, successful transplantation was noted from some, usually elderly, living donors with GFR as low as 65–70 ml/min, indicating a need for individualization and careful follow-up of donors with GFR of <80 ml/min/1.73/m^2.

Urine Analysis for Protein and Blood

The discussion was initiated by M.K. Mani and Yves Vanrenterghem. Proteinuria is a marker of glomerular pathology and renal disease. Proteinuria should be assessed as a standard part of the donor work up. Dipstick urinalysis for proteinuria and hematuria has been used to screen renal disease, but Gil Thiel suggested that dipstick measurements of proteinuria are not adequate in the assessment of a potential donor. Laboratories vary as to normal values of quantitated urine protein, but a consensus was reached to conclude that a 24-hour urine protein of >300 mg is a contraindication to donation.

The significance of microalbuminuria has been studied mostly in patients with diabetes mellitus. However, even in nondiabetics, it may be the first sign of a glomerular pathology. Gil Thiel suggested that kidney donors merit a screening and follow-up with microalbuminuria measurement (*23*). Albumin and protein concentration in urine should be referenced to either a time-collected specimen or to urinary creatinine concentration. A level of 5 mg (u-albumin/mmol u-creatinine) in a morning urine specimen represents approximately 50 mg albumin/24 h urine. M.K. Mani suggested, however, that the assessment of microalbuminuria is more expensive to perform and has not been well established in all parts of the world. A concern regarding laboratory consistency and accuracy was expressed.

Thus, Forum participants concluded that microalbuminuria determination may be a more reliable marker of renal disease, but its value as an international standard of evaluation for kidney donors has not been determined.

The discussion of hematuria was initiated by Kazuhide Saito and commented upon by Osman Alfurayh. Isolated microscopic hematuria (defined as >3–5 urinary sediment red blood cells (RBCs)/ HPF) may not be a contraindication to donation. RBCs with glomerular origin have a dysmorphic appearance observed by phase-contrast microscopy and automated RBC analysis. Patients with persistent microscopic hematuria should not be considered for kidney donation unless urine cytology and a complete urologic work up are performed. If urological malignancy and stone disease are excluded, a kidney biopsy may be indicated to rule out glomerular pathology such as IgA nephropathy.

Dan Brennan cited a recent report from Japan describing the presence of latent mesangial IgA deposits in approximately 16% of biopsies obtained at the time of transplantation from both living and deceased donors otherwise considered healthy (*24*). In some of the affected individuals, these findings were associated with a mild degree of microhematuria, mesangial proliferation, and glomerular macrophage infiltration, especially with combined IgA and C3 deposition.

Diabetes

The risk of the donor developing diabetic nephropathy following kidney donation was discussed by Connie Davis and Ed Cole. Diabetes is associated with an increased risk of postsurgical complications and future development of renal failure compared to the general population. Data by Silveiro et al. (*25*) were referenced to suggest that a nephrectomy in a patient with Type 2 diabetes might increase the progression of disease. Further, the prevalence of microalbuminuria is increased after nephrectomy.

Individuals who are at risk for developing Type 2 diabetes include those with a familial history, a BMI of >30 kg/m^2, woman with gestational diabetes, and excessive alcohol use. The following guideline was developed: individuals with a history of diabetes or fasting blood glucose ≥126 mg/dl (7.0 mmol/L) on at least two occasions (or 2-hour glucose with OGTT ≥200 mg/dl (11.1 mmol/L)) should not donate.

Stone Disease

Fernando Gabilondo and Mahendra Bhandari led the discussion of stone disease. Patients with lithiasis should be screened for metabolic stone forming abnormalities. Kidneys have been transplanted knowingly containing a renal stone (*26*, *27*).

An asymptomatic potential donor with history of a single stone may be suitable for kidney donation if:

- No hypercalcuria, hyperuricemia, or metabolic acidosis.
- No cystinuria or hyperoxaluria.
- No urinary tract infection.
- Multiple stones or nephrocalcinosis are not evident on computed tomography (CT) scan.

Younger patients have a longer exposure to risk of recurrence. The risk of recurrence after any single stone is difficult to predict in any individual. The younger the donor age (age 25–35), the longer the exposure to the possibility of a recurrence (*28*).

Asymptomatic potential donor with current single stone may be suitable if:

- The donor meets the criteria shown previously for single stone formers, and current stone is <1.5 cm in size or potentially removable during transplant.

Ex vivo ureteroscopy is a technically feasible means of rendering a stone-bearing kidney stone free, without compromising ureteral integrity or renal allograft function (*29*). It is not known whether stone formers who donate a kidney

have worse outcomes with respect to renal function compared to stone formers with two kidneys. However, a recurrent stone may not affect the function of a remaining kidney if it is carefully monitored (*30*).

Stone formers who should not donate are those with: 1) nephrocalcinosis on X ray or bilateral stone disease; and 2) stone types that have high recurrence rates and are difficult to prevent, such as:

- Cystine stones that have a high rate of recurrence and a need for urologic procedures in the donor.
- Struvite stones or infection stones that are difficult to eradicate and thus not feasible to transplant them into an immunosuppressed patient.
- Stones associated with inherited or other systemic disorders, such as primary or enteric hyperoxaluria, distal renal tubular acidosis, and sarcoid, because of the probability of a high rate of recurrence and the risk of renal insufficiency.
- Stones in the setting of inflammatory bowel disease with an increased risk of stones particularly after bowel resection, also increased risk of renal insufficiency.
- Recurrence while on appropriate treatment (i.e., failed therapy).

History of Donor Malignancy

Jeremy Chapman and Domingo Casadei led the discussion of donor malignancy. Living kidney donors should be screened by standard medical guidelines to exclude malignancy, noting that:

- The risk of clinical and subclinical malignancy increases markedly with age, especially over 50 years.
- The risk of different cancers differs between countries.
- Donors with low-grade nonmelanoma skin cancer may be accepted; otherwise the living kidney donor should be free of current or untreated malignancy.

A prior history of the following malignancies usually excludes live kidney donation:

- Melanoma, testicular cancer, renal cell carcinoma, choriocarcinoma, hematological malignancy, bronchial cancer, breast cancer and monoclonal gammopathy (*31–34*).

A prior history of malignancy may only be acceptable for donation if:

- Prior treatment of the malignancy does not decrease renal reserve or place the donor at increased risk for end-stage renal disease (ESRD).
- Prior treatment of malignancy does not increase the operative risk of nephrectomy.

A prior history of malignancy usually excludes live kidney donation but may be acceptable if:

- The specific cancer is curable and the potential transmission of the cancer can reasonably be excluded. Examples include: colon cancer (Dukes A, >5 years ago), nonmelanoma skin cancer, or carcinoma in situ of the cervix.

Consent to receive a renal transplant must include a discussion with the donor and the recipient that transmission of malignant disease cannot be completely excluded.

Screening for Infectious Disease

Essam Elsawy led the discussion of donor screening to prevent transmissible infectious disease through live kidney transplantation.

HIV

The detection of a positive human immunodeficiency virus (HIV-1 and HIV-2) by an ELISA assay for both antigen and antibody in a potential kidney donor should be confirmed by a neutralization test and a western blot analysis. The positive result rules out an individual from being a live kidney donor.

HTLV 1

If human T-lymphotropic virus (HTLV) 1 is transmitted from a live kidney donor, the recipient may be at risk for the development of T cell leukemia and neurological disorders such as a subacute myelopathy or spastic paraparesis (*35*). The ELISA test identifies HTLV 1 and 2, but does not distinguish either. Polymerase chain reaction (PCR) is needed to differentiate. The risk for HTLV 2 infection is unknown; it is detected in intravenous drug users.

HTLV is endemic in the West Indies and Japan. Norio Yoshimura presented his personal experience of a recipient developing T cell leukemia from a donor who was HTLV positive; this complication has also been reported from blood transfusion (*36*). Therefore, HTLV has been included in the routine screening (Table 1) assembled by Dr. Bradley. However, Dan Brennan suggested that the disease is rare in other parts of the world, and testing for its detection in live kidney donors is not routinely done.

CMV and EBV

Essam Elsawy screens for cytomegalovirus (CMV) IgM to evaluate recent infection, because CMV-reactive IgG is detected in more than 90% positive of his donors. If the CMV IgM is positive, a PCR for CMV is performed. If the PCR is positive, Essam Elsawy excludes live kidney donation until PCR becomes negative. If the CMV IgM positive and PCR are negative, they proceed with transplantation.

Bill Harmon suggested that a living donor (e.g., a parent) who is either CMV or Ebstein-Barr virus (EBV) positive is still acceptable for a recipient who is CMV or EBV negative.

Most of the adults are EBV and CMV positive; most of the children are EBV negative and many are CMV negative. Gil Thiel and Peter Morris expressed a concern that the incidence of posttransplantation lymphoproliferative disorder (PTLD) is rising in pediatric recipients. Approximately 5% of infants who receive living donor transplants develop PTLD, in part because of the intensity of immunosuppression, but also in the circumstance of an EBV positive donor transplant to a negative recipient. The possibility of EBV vaccination of the recipient was discussed by Ian Dittmer. Alternatively, another parent or a relative within the family might be evaluated to determine if they are either EBV (or CMV) negative. Despite these efforts, the importance and success of a live donor

TABLE 1. Routine screening for the potential living kidney donor

- Urinalysis
  - Dipstick for protein, blood and glucose
  - Microscopy, culture and sensitivity
  - Measurement of protein excretion rate
- Assessment of renal function
  - Estimation/measurement of GFR
- Blood tests
  - Hematological profile
    - Complete blood count
    - Hemoglobinopathy (where indicated)
    - Coagulation screen (PT and APTT)
    - G6PD deficiency (where indicated)
  - Biochemical profile
    - Creatinine, urea, and electrolytes
    - Liver tests
    - Urate
    - Fasting plasma glucose
    - Bone profile
    - Glucose tolerance test (if fasting plasma glucose >6–7 mmol/l)
    - Blood lipids
    - Thyroid function tests (if indicated)
    - Pregnancy test (if indicated)
    - PSA (if indicated)
  - Virology and infection screen
    - Hepatitis B and C
    - Toxoplasma
    - Syphilis
    - HIV and HTLV 1/2
    - Malaria (where indicated)
    - Cytomegalovirus
    - Trypanozome cruzi (where indicated)
    - Epstein-Barr virus
    - Schistosomiasis (where indicated)
    - HHV8 and HSV (where indicated)
    - Strongyloides (where indicated)
    - Typhoid (where indicated)
    - Brucellosis (where indicated)
- Cardiorespiratory system
  - Chest X-ray
  - Electrocardiogram
  - Stress test
  - Echocardiography (where indicated)
- Assessment of renal anatomy
  - Appropriate imaging investigations should allow confirmation of the presence of two kidneys of normal size and enable abnormalities of the collecting system and calcification or stone disease in the renal tract to be detected. They must also delineate the anatomy of the renal vasculature.

PSA, prostate-specific antigen; HIV, human immunodeficiency virus; HTLV, human T-lymphotropic virus; HHV, human herpes virus; HSV, herpes simplex virus.

parental transplant was sufficient to not prohibit the use of a CMV or EBV positive donor for a recipient who is CMV or EBV negative.

Hepatitis C Virus

If the donor has normal liver function tests and the serology test for hepatitis C virus (HCV) is negative (nonreactive antibody determination by ELISA), there is no contraindication for donation. However, if the serology test is positive for HCV, Essam Elsawy recommended that the recipient HCV status be evaluated. If the potential recipient is negative for HCV, the potential positive HCV donor should be excluded. If the potential recipient is also positive for HCV, the potential donor should be assessed by PCR for HCV. If the potential donor is PCR positive, the potential donor should be excluded because of the risk of HCV transmission to the recipient and because the potential donor may have chronic hepatitis (and is not well). If the potential donor is negative by PCR, the potential donor may not necessarily be excluded because the likelihood of transmission of HCV through the kidney is remote.

Nevertheless, Jose Morales expressed concern regarding HCV superinfection if a different HCV genotype of a positive donor is transmitted to a recipient. The Spanish group has transplanted kidneys from deceased donors with HCV reactivity to HCV positive recipients, but they have not performed live kidney transplantation from HCV positive donors (*37*). Further, Chakko Jacob and Nabil Mohsin questioned the justification of removing a kidney from a patient who in the future may develop an HCV-associated renal disease. However, Stephen Munn suggested that if certain HCV genotypes (genotype 4) are treated and eradicated in the donor, the potential donor could be reconsidered (if no evidence of chronic hepatitis or cirrhosis on biopsy).

Hepatitis B Virus

The detection of hepatitis B surface antigen (HBsAg) in a potential donor generally excludes the individual from live kidney donation (*38*). However, Stephen Munn reported that in New Zealand, some of the live kidney donors have been hepatitis B virus (HBV) core antibody positive. An IgM core positive result indicates a recent exposure to the HBV; in contrast, a surface antibody positive result indicates that months may have elapsed since the hepatitis infection. Even if HBsAg is negative, screening for HBV core total antibody (IgM and IgG) should be done to exclude low-level HBsAg and escape mutants of HBV not detectable by the current screening assays for HBsAg.

The ELISA core antibody test can distinguish between IgM and IgG reactivity. If the core antibody result is positive for IgM, a delay in the consideration of the potential donor was recommended to determine whether HBV infection might be progressing. A PCR quantitation of HBV DNA should be performed as appropriate care of the donor. Otherwise, by the New Zealand practice, if the potential donor is PCR negative for HBV, kidneys may be transplanted safely from either an HBV surface antibody positive donor or a donor who is HBV core antibody (IgG) positive into recipients who either have successfully recovered from hepatitis B infection or been immunized against hepatitis B.

Human Herpes Virus 8

Human Herpes Virus 8 (HHV8) has been shown to induce Kaposi sarcoma and can be transmitted by organ transplantation (*39*). Gil Thiel mentioned an ongoing research project of screening donors and recipients for HHV8 in Switzerland, but there is no world wide routine screening of live donors for HHV8.

TABLE 2. Amsterdam Forum Guidelines

Donor evaluation
- Prior to donation, the live kidney donor must receive a complete medical and psychosocial evaluation, receive appropriate informed consent, and be capable of understanding the information presented in that process to make a voluntary decision. All donors should have standard tests performed to assure donor safety.

Hypertension
- Patients with a BP >140/90 by ABPM are generally not acceptable as donors.
- BP should preferably be measured by ABPM, particularly among older donors (>50 years) and/or those with high office BP readings.
- Some patients with easily controlled hypertension, who meet other defined criteria, e.g. >50 years of age, GFR >80 ml/min, and urinary albumin excretion <30 mg/day may represent a low-risk group for development of kidney disease after donation and may be acceptable as kidney donors.
- Donors with hypertension should be regularly followed by a physician.

Obesity
- Patients with a BMI >35 kg/m^2 should be discouraged from donating, especially when other comorbid conditions are present.
- Obese patients should be encouraged to lose weight prior to kidney donation and should be advised not to donate if they have other associated co-morbid conditions.
- Obese patients should be informed of both acute and long-term risks, especially when other comorbid conditions are present.
- Healthy lifestyle education should be available to all living donors.

Dyslipidemia
- Dyslipidemia should be included along with other risk factors in donor risk assessment, but dyslipidemia alone does not exclude kidney donation.

Acceptable donor renal function
- All potential kidney donors should have GFR estimated.
- Creatinine based methods may be used to estimate the GFR; however, creatinine clearance (as calculated from 24-hour urine collections) may under or overestimate GFR in patients with normal or near normal renal function.
- Calculated GFR values (MDRD and Cockcroft-Gault) are not standardized in this population and may overestimate GFR.
- A GFR <80 ml/min or 2SD below normal (based on age, gender, and BSA corrected to 1.73/m^2) generally precludes donation.

Urine analysis for protein
- A 24-hour urine protein of >300 mg is a contraindication to donation.
- Microalbuminuria determination may be a more reliable marker of renal disease, but its value as an international standard of evaluation for kidney donors has not been determined.

Urine analysis for blood
- Patients with persistent microscopic hematuria should not be considered for kidney donation unless urine cytology and a complete urologic work up are performed. If urological malignancy and stone disease are excluded, a kidney biopsy may be indicated to rule out glomerular pathology, such as IgA nephropathy.

Diabetes
- Individuals with a history of diabetes or fasting blood glucose ≥126 mg/dl (7.0 nmol/l) on at least two occasions (or 2-hr glucose with OGTT ≥200 mg/dl (11.1 mmol/l) should not donate.

Stone Disease
- An asymptomatic potential donor with history of a single stone may be suitable for kidney donation if:
  - No hypercalcuria, hyperuricemia, or metabolic acidosis.
  - No cystinuria, or hyperoxaluria.
  - No urinary tract infection.
  - If multiple stones or nephrocalcinosis are not evident on CT.
- An asymptomatic potential donor with a current single stone may be suitable if:
  - The donor meets the criteria shown previously for single stone formers and current stone <1.5 cm in size, or potentially removable during the transplant.
- Stone formers who should not donate are those with:
  - Nephrocalcinosis on x ray or bilateral stone disease.
  - Stone types with high recurrence rates, and are difficult to prevent (see text).

Malignancy
- A prior history of the following malignancies usually excludes live kidney donation:
  - Melanoma, testicular cancer, renal cell carcinoma, choriocarcinoma, hematological malignancy, bronchial cancer, breast cancer and monoclonal gammopathy.
- A prior history of malignancy may only be acceptable for donation if:
  - Prior treatment of the malignancy does not decrease renal reserve or place the donor at increased risk for ESRD.
  - Prior treatment of malignancy does not increase the operative risk of nephrectomy.
- A prior history of malignancy usually excludes live kidney donation but may be acceptable if:
  - The specific cancer is curable and potential transmission of cancer can reasonably be excluded.

Urinary tract infections
- The donor urine should be sterile prior to donation; asymptomatic bacteria should be treated per donation.
- Pyuria and hematuria at the proposed time of donation is a contraindication to donation.
- Unexplained hematuria or pyuria necessitates evaluation for adenovirus, tuberculosis, and cancer. Urinary tuberculosis or cancer are contraindications to donation.

Live unrelated donors
- The current available data suggest no restriction of live kidney donation based upon the absence of an HLA match. An unrelated donor transplant is equally successful to the outcome achieved by a genetically related family member such as a parent, child, or sibling, who is not HLA identical to the recipient.

Determination of cardiovascular risk
- The clinical predictors of an increased peri operative cardiovascular risk (for non-cardiac surgery) by the American College of Cardiology/American Hospital Association standards fall into 3 categories: major, intermediate, minor.
  - All major predictors: unstable coronary syndromes, decompensated heart failure, significant arrhythmias and severe valvular disease are contraindications to live kidney donation. Most of the intermediate predictors: mild angina, previous myocardial infarction, compensated or prior heart failure, diabetes mellitus are also contraindications to donation; Minor predictors: older age, abnormal ECG, rhythm other than sinus, low cardiac functional capacity, history of stroke or uncontrolled hypertension warrant individual consideration.

Assessment of pulmonary issues
- A careful history and physical examination are the most important parts of assessing risk.
- Routine preoperative pulmonary function testing (PFT) is not warranted for potential live kidney donors unless there is an associated risk factor such as chronic lung disease.
- Increased risk of post operative pulmonary complication is assoc with an FEV1 <70% or FVC <70% of predicted, or a ratio of FEV1/FVC <65%.

Smoking cessation and alcohol abstinence
- Smoking cessation at least 4 weeks prior to donation is advised based on recommendations for patients undergoing elective surgical procedures.
- Cessation of alcohol abuse defined by DSM-3: 60 gm of alcohol/day sustained over ≥6 months should be avoided for a minimum of 4 weeks to decrease the known risk of postoperative morbidity.

BP, blood pressure; ABPM, ambulatory blood pressure monitoring; GFR, glomerular filtration rate; BMI, body mass index; BSA, body surface area; CT, computed tomography; ESRD, end-stage renal disease; HLA, human leukocyte antigen.

Tuberculosis

Essam Elsawy presented the following information regarding tuberculosis. Active *Mycobacterium tuberculosis* infection is a contraindication for donation because tuberculosis has been transmitted from live kidney donors to their recipients (*40*). Further, a past history of pulmonary tuberculosis is relative contraindication to donation. However, there were instances reported by Forum participants where individuals with history of treated pulmonary tuberculosis have donated a kidney.

Enrique Ona presented that many of the Philippine live kidney donor population may have fibrosis of the lung apex, which radiologists read as evidence of a past tuberculous infection by this "primary complex." The radiologist's evaluation is important to determine active infection by a comparative current chest x-ray with a previous one (if available). They are accepted as donors if it is proven that they don't have an active pulmonary infection and after it is shown that they don't have genitourinary tract tuberculosis. If active pulmonary infection is suspected, the donors are treated (as are most of the recipients) with prophylactic isoniazid (INH) for about 4 months. Thus, a potential donor with a past history of pulmonary tuberculosis who has received adequate treatment may still be an acceptable donor if there is no renal infection. Enrique Ona suggested that donors treated for pulmonary tuberculosis require a more specific and extensive examination of the urinary tract and the kidneys prior to donation.

Pyuria or an anatomical defect on renal ultrasound or intravenous pyelogram (IVP) may be indicative of donor urinary tract infection with tuberculosis. Urinary tuberculosis is contraindication for donation. Essam Elsawy suggested that donors previously treated for urinary tuberculosis might have dormant tuberculosis within the kidney, and thus remain unsuitable for donation. Further, tuberculous pyelonephritis usually results in a decreased GFR of the diseased kidney, making it unsuitable for donation.

M.K. Mani presented the following information. Urinary culture for tuberculosis is not done routinely as it is a poor screening tool; however, the potential donor is usually assessed for pyuria and anatomical radiographic abnormalities of the urinary tract and kidneys, despite a normal chest X ray. Mahendra Bhandari concurred to report in his experience that genitourinary tuberculosis might exist without chest X ray evidence. Finally, in some regions of the world (from Fernando Gabilondo and Nasser Simforoosh), a purified protein derivative (PPD) skin test of tuberculosis is still used to screen potential kidney donors, even though some of the donors may have been vaccinated with Bacille Calmette-Guerin (BCG), a genetically-altered tubercular bacteria rendered avirulent. However, in Egypt, Essam Elsawy noted that BCG vaccination is mandatory for all the population from birth. A positive PPD on that basis may not be helpful to screen a potential live kidney donor. In New Zealand, neither Stephen Munn nor Ian Dittmer screens their donors with a PPD.

Syphilis

Donors should be screened for syphilis (*Treponema pallidum*) with the rapid plasma reagin (RPR) or Venereal Disease Research Laboratory (VDRL) slide test. The RPR and the older VDRL test detect reactive antibodies. There are several conditions that may cause a false positive test: HIV, Lyme disease, mycoplasma pneumonia, malaria, and systemic lupus erythematosus. Therefore, these screening tests, if found to be positive, must be confirmed by a more specific test for syphilis such as a fluorescent treponemal antibody (FTA) absorption test. Donors with a positive confirmatory FTA should be treated according to stage and donation should be delayed until successful treatment is accomplished. There may be a risk of syphilis transmission if the donor is untreated (*41*). The recipient could receive treatment following transplantation, if there is an urgent need to perform transplant. Secondary syphilis is associated with reversible renal disease.

Chagas Disease

Chagas disease is endemic in parts of Central and South America and Mexico, where an estimated 16–18 million people are infected with *Trypanosoma cruzi* (*42*). Trypanosomiasis has been transmitted to kidney transplant recipients from an infected donor (*43*). Donors from endemic areas should be screened by serologic tests (there are at least three of them). A complement fixation test (Machado-Guerreiro reaction) becomes positive in the acute stage at one month postinfection and remains positive thereafter. The Machado-Guerreiro has a low sensitivity and specificity that yields high incidence of false positives and negatives. The precipitin test (hemagglutination reaction) is 95% positive in the early stages. The immunofluorescence and ELISA tests are highly sensitive and specific, although false-positive reactions occur with malaria, leprosy, and leishmaniasis. If two of the screening tests are positive, the detection of the trypanosome should be ruled out in the blood by a xenodiagnostic test that entails the following: uninfected laboratory-raised insects are fed on a patient, and then examined 30 days later for metacyclic trypanosomes in their hindgut or feces. If positive, the potential donor must be treated and cannot donate until parasitemia turns negative. Otherwise, Mario Abbud-Filho, José Medina-Pestana, and Domingo Casadei suggested that there is no contraindication to live kidney donation from a serology positive donor. In a referenced report by Sousa, nine recipients of kidneys were obtained from Chagas seropositive donors among 239 kidney transplantations between 1992 and 1997 (*43*). All were treated with benznidazole (5 mg/kg/d) for 14 days. None of them experienced acute Chagas disease or seroconversion even after 10 years follow-up. The Forum participants concluded that donors with positive serology for Chagas disease should not be excluded.

Schistosomiasis

Essam Elsawy suggested that uncomplicated bilharziasis of living kidney donors does not adversely affect either the function or the morphology of the remaining kidney, provided that the donor had functionally and morphologically intact kidneys and bilharzia was treated before donation. There has been no significant difference between bilharzial and nonbilharzial renal transplants in graft function and incidence of graft rejection after 10 years of follow up (*44*). Nabil Mohsin posed a question regarding the routine treatment of schistosomiasis in an asymptomatic donor who resides in an endemic area. Essam Elsawy replied that treatment is not given unless the donor has an active infection. If there is active schistosomiasis in an otherwise healthy donor, the do-

nor is treated at least one month before transplantation by combined antischistosomal drugs (praziquantel and oxamniquine). Cure without impairing renal function has been observed without a negative impact on the transplant outcome.

Strongyloides

Larvae of *Strongyloides stercoralis* penetrate the skin or mucosa from fecally contaminated soil, are carried by the blood stream to the lungs, break into the alveoli, ascend, are swallowed, and then reach the small intestine. The female worms produce larvae parthenogenically (without fertilization), and the larvae are passed in the host's feces. The presence of nematode larvae in a fecal sample is characteristic of strongyloidiasis; however, an ELISA assay is available for serological detection of strongyloides. Potential donors should be screened for strongyloides in endemic areas because strongyloides has been transmitted via a kidney transplant (*45*).

Brucellosis

Brucellosis is derived from the bacteria of the genus *Brucella*, primarily passed among animals and acquired by humans from contact with animals or animal products that are contaminated with these bacteria. Brucellosis has been transmitted to recipients of bone marrow transplants (*46*). Nasser Simforoosh suggested that a patient successfully treated for brucellosis infection may still be a suitable live kidney donor.

Malaria

Malaria has been transmitted from an organ donor to multiple transplant recipients, resulting in the death of a heart transplant recipient (*47*). Potential live kidney donors who either reside or have traveled to endemic areas should be screened for *Plasmodium falciparum*. Automated hematology analyzers have been used to detect malarial parasites in peripheral blood samples.

Urinary Tract Infections

The donor urine should be sterile prior to donation. Pyuria and hematuria at the proposed time of donation is a contraindication to donation. Asymptomatic bacteruria should be treated predonation. Unexplained hematuria or pyuria necessitates evaluation for adenovirus, tuberculosis, and cancer. Urinary tuberculosis and cancer are contraindications to donation.

Essam Elsawy presented the following information. A history of recurrent cystitis is not a contraindication to donation from a healthy young female; however, unexplained recurrent pyelonephritis is a contraindication to donation. Persistent infection (same pathogen recurs after treatment) warrants anatomic evaluation of urinary tract by upper tract study (IVP, CT scan) and cystoscopy. In men, persistent infection may be associated with chronic bacterial prostatitis. There is no association of renal infection with chronic bacterial prostatitis.

Recurrent urinary tract infection from childhood may indicate reflux and potential donors should undergo a voiding cystourethrogram (VCUG) and an upper tract study. Donation is contraindicated until anatomical cause is ruled out.

Blood Donor Regulation and Organ Donor Screening

Stephen Munn and Carl Cardella noted blood donor services in North America, Australia, and New Zealand have precluded individuals from donating blood if they resided in the United Kingdom during the bovine spongiform encephalopathy (BSE) risk period (during the 1980s and early 1990s) and ate meat (*48*). Chris Rudge also reported that the U.K. national blood service has issued an instruction to not permit blood donation from anybody who has received a blood transfusion within the last 24 years. Andrew Bradley suggested that, for live kidney donation, the remote risk could be discussed with a prospective recipient and they could accept that risk or not. In contrast, the donor of a blood transfusion is usually to an anonymous recipient. Chris Rudge agreed that regulations for blood and tissues should not apply to organs because the risk/benefit ratio is different, citing the example of screening for HTLV and variant for Creutzfeld-Jacob disease (v-CJD). The conclusion of the Forum participants was that a center transplanting a kidney from a live donor who falls into at-risk categories for v-CJD (residency in the U.K. or a family history of unexplained neurodegenerative disease) has a responsibility to explain the possibility of transmission to the recipient. Nevertheless, the risk is likely to be extremely low and not prohibit live donor kidney transplantation.

Live Unrelated Donors

In Mexico and some European countries, unrelated kidney transplantation is currently illegal. Enrique Ona posed the following question to participants: "Since live donors are more commonly done in the Philippines, what is a minimum HLA-DR antigen match acceptable for transplantation? Blood relation in our part of the world extends to distant relatives and not just from siblings, parents or children. The same is true with the adoption of incentives, gifts, or gratitudinal reciprocity to the donation process which can easily be misconstrued as 'commercialization' or sale."

Chris Rudge presented data from the U.K. evaluating the degree of HLA match in transplants from different donor types and the influence of HLA match on the outcome of all living donor transplants in the U.K. (*49*). Transplants from unrelated living donors were significantly less well matched. There were two HLA-DR mismatches in 41% of living unrelated donor transplants but less than 5% in living related donor transplants. Nevertheless, there were no significant differences in one-year transplant survival between the two living donor transplant groups.

Francis Delmonico presented current U.S. data that examined whether HLA matching influences the outcome of living donor kidney transplants. Among living unrelated donor transplant recipients, there was no independent effect of DR matching on graft survival, as indicated by 5-year survival rates of 86% (reference group), 85% ($P=0.85$) and 84% ($P=0.64$) for zero, one, and two HLA-DR mismatched grafts, respectively.

Thus, the current available data suggest no restriction of live kidney donation based upon the absence of an HLA match. An unrelated donor transplant is equally successful to the outcome achieved by a genetically related family member such as a parent, child, or sibling who is not HLA identical to the recipient.

Live Donor Exchanges

ABO blood type incompatibility or T cell crossmatch reactivity has generally precluded successful kidney transplantation. A crossmatch performed between the prospective donor and recipient may detect antibodies that would result in an accelerated rejection of the allograft. Natural antibodies to the A or B blood types can also cause immediate allograft loss. These biologic realities have circumvented the intent of a willing kidney donor to provide for needy recipient, until now (*50*). Recently however, protocols have been developed to overcome these barriers by using plasma exchange to remove either the isoagglutinin or HLA antibodies (see below) (*51*). Nevertheless, these "conditioning" regimens are still associated with an unpredictable rate of biological graft loss that could be averted by other innovative methods of live donor transplantation. One such approach is live donor exchange (i.e., exchanging donors incompatible with their intended recipients so that, instead, each donates to a compatible recipient). With donor exchange, the hazard of either blood type or crossmatch incompatibility can be avoided, while both recipients still derive the benefit of a living donor kidney transplant.

Section 301 of the U.S. National Organ Transplant Act of 1984 (NOTA), 42 U.S.C. 274e states: "It shall be unlawful for any person to knowingly acquire, receive, or otherwise transfer any human organ for valuable consideration for use in human transplantation". Valuable consideration under NOTA § 301 has traditionally been considered to be monetary transfer or a transfer of valuable property between donor, recipient, and/or organ broker in a sale transaction.

However, in some regions of the world, the live donor exchange is considered to be valuable consideration; thus, it is not permitted. For example, Jeremy Chapman brought to attention a law in Australia that prohibits such exchanges that have occurred in the United States or Korea (*52*, *53*). These exchanges are considered illegal in Australia because the donor is deemed to receive valuable consideration in return for the donation; therefore, it is not considered to be an altruistic donation. Carl Cardella presented a different interpretation to suggest that receiving a transplanted kidney is not the same as getting a monetary value; and that although it is obviously of value, it is not the same as buying and selling organs.

The Gender Imbalance

Data were presented by Gil Thiel, Mahendra Bhandari, S. Adibul Hasan Rizvi, and Bob Metzger to reveal the following international experience: approximately 65% of live kidney donors have been women and approximately 65% of recipients have been men.

Abdullah Alkhader Al Sayarri observed that among some living kidney transplants, there might be an unethical component of coercion and family/social pressures to bear. Participants agreed that these gender data display an excessive disparity, perhaps reflecting a psychological submission of women or discrimination of woman in many countries, including Western nations. However, there are more males than females with end stage renal disease, which may partly explain why there are more wives than husbands who donate in the case of transplants between spouses (*54*, *55*).

S. Adibul Hasan Rizvi noted a Nobel laureate perspective to say, "the burden of hardship often falls disproportionately on women." In some parts of the world, female gender bias is historically deep rooted. When the live related renal transplantation program was begun at the Sindh Institute of Urology and Transplantation, the factor of coercion was anticipated. In the prevailing culture, it was highly probable that females would have no choice but to donate a kidney. Dr. Rizvi reported that this donor coercion was encountered in the initial period, but it was subsequently overcome by efforts of a dedicated transplant team. Presently, despite existing cultural barriers, the female to male donor ratio at the Sindh Institute of Urology and Transplantation is 0.9:1.

Mahendra Bhandari endorsed the objective of establishing a genuineness of voluntary donation. In India, however, the family elder's domination is a reality of that culture; it is rare to find a prospective donor bold enough to decline. The issue is extremely sensitive and relevant in the case of female spouses as prospective donors.

Sadek Beloucif observed that accepting to donate depends on a number of contradictory considerations: the wish to help a member of one's family, with the family's opinion in the background, and the anticipation of possible loss of body integrity. The role of the doctor, who is the mandatory intermediary in the situation of donor consent, cannot be overlooked.

Data and Perspective Regarding Minors as Donors

A review of the U.S. experience was presented by Bill Harmon. Minor donor kidneys were transplanted more frequently to adults than to pediatric recipients. Only 12% of the recipients from minor donors were identical twins (*56*). In some instances, minors gave their kidney to grandparents.

The use of a minor donor provided no better outcome than that expected from an adult donor. With the excellent outcome of unrelated transplantation from an adult living donor currently achieved, Forum participants agreed with the consensus proposal by Eduardo Santiago-Delpín that minors less than 18 years of age should not be used as living kidney donors.

Risk Estimation for Donor Candidates with Medical Abnormalities

R. Steiner suggested that the ethical position of transplant centers could be best validated if kidney donor candidates were presented a defensible and quantitative estimate of medical risk. This risk assessment applies not only to "normal" donors but also to donors with isolated medical abnormalities (IMAs) such as hematuria, low grade proteinuria, hypertension, stone disease, and borderline normal GFR (*57*). Centers may accept some IMA donors considering the small risk of ESRD developing as result of the IMA (*18*). However, donors may reasonably ask whether their IMA entails an ESRD risk of 1 in 10, 1 in 100, or 1 in 1,000.

Steiner proposed that the risk of ESRD for many IMAs can be estimated semiquantitatively by knowing the prevalence of the IMA in the general population, and the incidence of the kind of ESRD with which that IMA might be associated. For example, suppose an IMA is present in millions of people in a population, but only one person a year in that population develops ESRD from that IMA. The risk is therefore much less

than for an IMA, present in 100 people in a population, that generates 50 new cases of ESRD caused by that IMA each year.

In the year 2000, almost 20,000 new cases of hypertensive ESRD were reported in the United States (*58*). Hypertension is common in the U.S. population, afflicting perhaps 25% of the population (*59*). The U.S. population in 2000 was about 280 million; therefore, there were about 70 million hypertensive patients, who produced almost 20,000 cases of hypertensive ESRD that year. When these data are expressed to "normalize" the yearly incidence of hypertensive ESRD for the prevalence of hypertension in the same population, the fraction has the units "new cases of hypertensive ESRD per hypertensive year." This fraction is the raw yearly risk for hypertensive ESRD for that hypertensive population. The raw yearly risk for hypertension in the United States is therefore 20,000/70,000,000 or 1 case in 3500 patient years. The 20-year risk for ESRD is 20 times the yearly risk, or 20 in 3500 (1 in 175). Based upon these data, the lifetime risk of ESRD that is associated with their isolated mild to moderate hypertension is less than 1 in 100.

The estimate of any IMA risk (hematuria, etc.) can be determined by the formula developed by R. Steiner:

Yearly risk for risk factor A = (Yearly incidence of ESRD A) / (Prevalence of risk factor A)

The risk over the next *n* years is $n \times$ the yearly risk. The yearly risk for ESRD for "medical condition A" that is assumed to be the only cause of "ESRD A" (e.g., hypertension and hypertensive ESRD) is the yearly incidence of "ESRD A" in the general population divided by the prevalence of "condition A."

When this epidemiologic method is used to calculate the baseline lifetime risk for any form of ESRD in the general U.S. population, assuming a population of 275,000,000, a yearly incidence of ESRD of 85,000, and a 70-year life span, the calculated lifetime ESRD risk is strikingly close to the figure determined by more sophisticated methods (2% for whites and 7% for blacks) (*60*). However, the formula above estimates the baseline two-kidney risk for ESRD that is associated with a given IMA, irrespective of donation. Predicting the effect of uninephrectomy on the progression of postdonation ESRD is a separate problem that applies only to the small fraction of donors with IMAs who actually will develop renal disease. Predicting the effect of nephrectomy is also a problem for "normal" donors, as some "normal" donors will develop diabetic nephropathy or other forms of ESRD after donation later in life (*58*). Even though their risks for ESRD are often lower, "normal" donors also need to know their risks, for the same reasons that apply to donors with IMAs.

Determining Equipoise in the Risk-Benefit Analysis

Thomas Gutmann suggested the following: "In developing international standards of care for the live kidney donor and standards of medical suitability, the risk-benefit ratio of any proposed living donor transplant should be determined not only by medical facts, but ultimately by personal value judgments. These judgments should generally be made by the one most affected by the outcome—i.e., the prospective donor him/herself. After appropriate information has been given to the patients, the question of whether it is 'worth it' and the risks [are] 'acceptable' to the particular donor can only be based on the character and values of that person and their actual relationship with the intended recipient."

Pre-, Peri-, and Postoperative Issues

Determination of Cardiovascular Risk

Stephen Munn presented the following information. The clinical predictors of an increased perioperative cardiovascular risk (for noncardiac surgery) by the American College of Cardiology /American Hospital Association standards fall into three categories: major, intermediate, and minor (*61*). All major predictors (unstable coronary syndromes, decompensated heart failure, significant arrhythmias and severe valvular disease) are contraindications to live kidney donation. Most of the intermediate predictors (mild angina, previous myocardial infarction, compensated or prior heart failure, diabetes mellitus) are also contraindications to donation, although a history of a myocardial infarction many years prior to the possible donation may not be an absolute contraindication. Minor predictors (older age, abnormal electrocardiogram, rhythm other than sinus, low cardiac functional capacity, history of stroke, or uncontrolled hypertension) warrant individual consideration.

Most potential donors will need only an electrocardiogram prior to surgery. Few potential donors may need a stress test such as a dobutamine stress echocardiogram (perhaps some >60 years of age), because most individuals with a significant cardiac risk factor should have been excluded from donation.

Smoking Cessation

Mehmet Haberal and Frederic Oppenheimer presented the following information. Pneumonia is the most serious complication following noncardiac surgery. It ranks as the third most common postoperative infection, behind urinary tract and wound infections (*62*). Smokers have a higher risk of pulmonary and wound infections after surgery than nonsmokers (*63*). No current evidence exists to suggest that smoking increases morbidity or mortality of live kidney donors; however, observational evidence suggests a benefit to cessation before surgery (*64*). Cigarette smoking is associated with an increase in tracheobronchial secretions and a decrease in mucociliary clearance. In smokers, the respiratory epithelium is altered, and poor ciliary activity combined with the production of more viscous mucus leads smokers to be more reliant on the cough to clear secretions from their lungs.

Abstinence of smoking for only 12 hours can greatly reduce carboxyhemoglobin concentrations, improve oxygen content and availability, and reverse negative inotropic and arrhythmic effects (*65*, *66*). Smokers' polycythemia and increased blood viscosity take a few days to reverse (*67*). If smoking is stopped, sputum production declines over a 6-week period (*65*).

Alcohol Abstinence

Mehmet Haberal and Frederic Oppenheimer presented the following information. An increase in postoperative morbidity is reported for alcohol abusers who drink at least five drinks (>60 g ethanol) a day (*68*). Specific studies are lacking, but the result from observational evidence in other clinical settings is that alcohol misuse should be included in the pre-

operative assessment of live donors and withdrawal is recommended for at least 1 month before the operation (*69*).

Despite the high risk of complications, it was the experience of some Forum participants that recommendations to stop smoking and alcohol before elective surgery are not often heeded. There is a need for clinical guidelines for smokers and alcohol abusers in living donors undergoing surgery that include up-to-date patient information and four weeks of abstinence before surgery.

Forum Statement on Smoking Cessation and Alcohol Abstinence

- Smoking cessation at least 4 weeks prior to donation is advised, based on recommendations for patients undergoing elective surgical procedures.
- Cessation of alcohol abuse defined by DSM-3: 60 g alcohol/day sustained ≥6 months should be avoided for a minimum of 4 weeks to decrease the known risk of postoperative morbidity.
- All potential donors should have a health-promoting dialogue with the anesthesiologist or another health professional, which focuses on alcohol and smoking cessation in the context of other risk factors.

Assessment of Pulmonary Issues

Abdias Hurtado presented the following information regarding the determination of pulmonary risk in donor surgery. A careful history and physical examination are the most important parts of assessing risk (*70*). Routine preoperative pulmonary function testing (PFT) is not likely warranted for potential live kidney donors unless there is an associated risk factor such as chronic lung disease. Preoperative PFTs can be reserved to these patients. There are no cut-off values in PTFs; however, increased risk of postoperative pulmonary complication is associated with FEV1 <70% or FVC <70% of predicted, or a ratio of FEV1/FVC <65% (*71*). Patients with chronic pulmonary disease, who are at risk of the development end-stage pulmonary disease, should not be candidates for living kidney donation. Patients with asthma who are well controlled, and with a peak flow measurement > 80% predicted, can be considered on an individual basis for live kidney donation (*71*).

Venous Thromboembolism

Factor V-Leiden, a variant of the coagulation protein Factor V, is associated with venous thrombosis, especially in oral contraceptive users. Factor V-Leiden is the most common hereditary blood coagulation disorder, present in 3–8% of the healthy white population (*72*). Marwan Masri has detected Factor V-Leiden mutant genes in 2% of living donors. In Britain, 5% of the population carries one or more genes for Factor V Leiden (far more than the number of people who will actually suffer from thrombosis). However, the odds ratio of a venous thrombolic event is 11 times greater in women taking oral contraceptives who have the Factor V Leiden mutation than for those who do not (*73*). Dan Brennan has also identified such a high rate of Factor V-Leiden in the U.S. population, suggesting that oral contraceptives and hormone replacement therapy be withheld for 3 months prior to an elective surgery.

Jonas Wadström suggested that potential living kidney donors should evaluated by a comprehensive coagulation profile to include PT, PTT, antithrombin 3, protein S, and protein C, Activated protein C (APC) resistance, as well as an PT-prothrombin mutation, cardiolipin antibodies, and lupus anticoagulants. APC resistance is due to an inherited disorder of the Factor V molecule (usually Factor V-Leiden) and is again associated with venous thromboembolism.

However, there was no consensus on this particular issue of screening for a coagulopathy. Mark Stegall recommended that a history of venous thromboembolism be ascertained prior to an in-depth coagulation workup. Unless the history reveals a medical concern that would necessitate a comprehensive coagulation profile, these tests were considered expensive and not likely to yield consequential information.

Vascular Imaging

Sunil Shroff suggested that a noninvasive method of imaging such as magnetic resonance imaging or spiral CT scan (rather than a conventional contrast angiogram) could now be recommended, as these approaches are associated with less morbidity for the donor.

Conclusions

This report of the Amsterdam Forum presents a comprehensive review of the international practice of live kidney donation. Forum participants emphasize concertedly that medical judgment regarding the suitability of the potential donor is derived from a reflection of published data and physician experience. This report is intended to provide a compilation of information upon which appropriate medical judgment can be applied in the medical evaluation of every potential live kidney donor.

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A Paired Survival Analysis Comparing Hemodialysis and Kidney Transplantation From Deceased Elderly Donors Older Than 65 Years

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Background. Kidney transplantation from deceased donors aged 65 years or older is associated with suboptimal patient and graft survival. In large registries, survival is longer after kidney transplantation than when remaining on dialysis. However, whether recipients of these old grafts survive longer than their dialysis counterparts is unknown.
Methods. We retrospectively assessed the outcomes of 5,230 recipients of first deceased donor grafts transplanted during the period of 1990 to 2010 in Catalonia, 915 of whom received grafts from donors 65 years or older. In a match-pair analysis, we aimed to pair each of 915 eligible cases with one control (1:1 ratio). Each pair had the same characteristics at the time of entering dialysis program: age, sex, primary renal disease, period of dialysis onset, and cardiovascular comorbidities. We found 823 pairs.
Results. Patient survival of 823 recipients of elderly donors was significantly higher than that of their 823 matched dialysis waitlisted nontransplanted partners (91.6%, 74.5%, and 55.5% vs. 88.8%, 44.2%, and 18.1%, respectively at 1, 5, and 10 years; $P<0.001$). The probability of death after the first year was similar (8.1% transplant vs 10.3% dialysis; $P=0.137$); however, analyzing the whole period, the adjusted proportional risk of death was 2.66 (95% confidence interval, 2.21–3.20) times higher for patients remaining on dialysis than for transplanted patients ($P<0.001$).
Conclusion. Our study demonstrates that despite the fact that kidney transplantation from elderly deceased donors is associated with reduced graft and patient survival, their paired counterpart patients remaining on dialysis have a risk of death 2.66 times higher.

Keywords: Dialysis, Kidney transplantation, Elderly, Donation, Survival, Paired survival.

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Until the 1990s, deceased donors older than 55 years were usually discarded. It was not until the progressive improvement of the whole process of procurement and better organ assessment (*1, 2*) that it became evident that age itself should not be a limiting parameter (*3, 4*). The need to accept elderly donors was emphasized by the increase in the waiting lists and the decreasing number of young donors (*5*). Currently, older age and stroke as the cause of death predominate among deceased donors (*6, 7*).

The use of elderly donors revealed that the increase in donor age was associated with reduced graft function as well as recipient and graft survival (*6, 8*). To minimize this impact, age matching criteria between donor and recipient were adopted, reasoning that elderly recipients have shorter life expectancy, independent of the extended lifetime provided by the graft (*9*). At the same time, the age of waitlisted patients also rose as a consequence of the increasing age

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TABLE 1. Donor characteristics according to donor age

		<45 yr		45–54 yr		55–64 yr		65–69 yr		70–75 yr		>75 yr		
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	P
Donor sex	Male	1,430	68.6	685	63.9	744	64.9	203	56.9	155	41.3	83	45.6	<0.001
Donor cause of death	Trauma	1,084	54.4	178	16.9	197	17.6	66	18.6	65	17.4	44	24.4	<0.001
	Hemorrhage	527	26.4	666	63.4	715	63.8	255	71.8	275	73.7	126	70.0	
	Anoxia	168	8.4	91	8.7	74	6.6	17	4.8	12	3.2	3	1.7	
	Tumors	20	1.0	14	1.3	7	0.6	0	0.0	3	0.8	0	0.0	
	Other	195	9.8	102	9.7	127	11.3	17	4.8	18	4.8	7	3.9	
Donor eGFR, mL/min[a]	<80	193	24.2	158	32.2	262	46.5	79	43.6	150	63.6	90	78.3	<0.001
	80–90	65	8.1	68	13.8	69	12.2	30	16.6	22	9.3	9	7.8	
	91–99	86	10.8	55	11.2	60	10.6	17	9.4	19	8.1	8	7.0	
	≥100	455	56.9	210	42.8	173	30.7	55	30.4	45	19.1	8	7.0	

[a] 2000–2010 data.
eGFR, estimated glomerular filtration rate.

of incident dialysis patients and their improved survival rates (*6, 10*).

One unresolved question is whether the reduced survival of the recipients of kidneys from elderly donors provides longer survival than maintenance dialysis, as some reports may suggest (*11–13*). However, this has not yet been conclusively demonstrated. We performed and published a systematic review of the results achieved with kidney transplantation using expanded criteria donors (*14*). For the current report, we were only able to find one large observational study assessing a comparison between transplanting a marginal kidney and remaining on dialysis (*13*). No large study compared two matched populations in the way the present study shows.

We carried out a paired analysis, which is the most reliable method when a randomized trial is not feasible. In our study, we first describe the characteristics of a large series of recipients of deceased donors according to donor age and identify the associated variables that influence recipient and graft survival. We subsequently present a comparative survival analysis between recipients of kidneys from deceased donors older than 65 years with that of their paired patients of the same characteristics who remained on maintenance dialysis.

RESULTS

The cohort of recipients of single first kidney transplantation (KT) from deceased donors during the period of 1990 to 2010 comprised 5,230 patients: 3,300 (63.1%) were males and 1,930 (36.9%) females. Recipient and donor mean age (standard deviation was 49.8 (15.2) years and 46.6 (18.6) years, respectively.

Characteristics According to Donor Age

In Table 1, we describe the donor characteristics according to their age: the percentage of males decreases with advancing age, with female predominance in the older groups ($P<0.001$). Cranioencephalic trauma remains the main cause of death younger than 45 years (54.4%) but stroke predominates over 45 years ranging from 63.4% for ages 45 to 54 to over 70% for donors 65 years or older ($P<0.001$). The percentage of donors with high glomerular filtration rate (GFR) is progressively reduced with increasing age and lower GFRs progressively rise with increasing age ($P<0.001$).

In Table 2, we describe the characteristics of the recipients and the KT according to donor age. Mean recipient age correlates with donor age, by recipient age segments (80.1% of the kidneys from donors ≥65 years went to recipients ≥60 years). Male recipients predominate (from 64.3% for donors aged 45 to 54 years to 57.1% for donors ≥75 years). Primary renal disease distribution is statistically different between the donor age groups ($P<0.001$). Mean time on dialysis before KT is significantly shorter for those younger than 45 years ($P<0.001$), although none of the donor age segments exceed a mean time of 3 years. Kidney transplantation recipients of older donors show lower panel reactive antibody (PRA) ($P=0.03$), lower mean human leukocyte antigen (HLA)-A, HLA-B, and HLA-DR matching ($P<0.001$) and shorter mean cold ischemia time ($P=0.046$). Delayed graft function (DGF) rate is lower in recipients of donors younger than 45 years compared to all other age groups ($P<0.001$).

Survival and Associated Variables

Patient survival of the 915 recipients of donors 65 years or older at 1, 5, 10, and 15 years was 91.8%, 74.9%, 54.3%, and 37.6%, respectively, significantly lower than that of the 4,139 recipients of younger donors (96.4%, 89.7%, 77.1% and 64.8%, respectively) ($P<0.001$). Graft survival was also significantly lower (84.4%, 61.0%, 40.1%, and 27.4% vs. 90.1%, 77.6%, 58.9%. and 42.7%) ($P<0.001$).

The results of the proportional risk Cox model applied to the analysis of the variables associated to patient survival, graft survival, and death-censored graft survival are shown in Table 3. Recipients of donors 65 years or older showed an increased risk of death 1.3 times higher than recipients of younger donors. The donor cause of death was also statistically related to recipient survival. In addition, the recipient sex, age, primary renal disease, and hepatitis C virus (HCV) significantly influenced recipient survival. Finally, DGF was also significantly associated with greater recipient mortality. Related to the graft survival multivariate analysis, we observed

TABLE 2. Recipient characteristics according to donor age

		<45 yr		45–54 yr		55–64 yr		65–69 yr		70–75 yr		>75 yr		
		n	%	n	%	n	%	n	%	n	%	n	%	*P*
Recipient age distribution, yr	0–45	1,224	58.5	318	29.6	124	10.8	8	2.2	2	0.5	1	0.5	<0.001
	45–54	488	23.3	400	37.2	322	28.1	54	15.1	10	2.7	2	1.1	
	55–64	315	15.0	267	24.8	521	45.5	166	46.5	130	34.6	34	18.7	
	65–69	53	2.5	71	6.6	116	10.1	92	25.8	127	33.8	45	24.7	
	70–75	14	0.7	19	1.8	61	5.3	34	9.5	99	26.3	81	44.5	
	>75	0	0.0	0	0.0	2	0.2	3	0.8	8	2.1	19	10.4	
Mean recipient age (mean [SD]), yr		40.0 (14.9)		49.4 (11.3)		56.0 (9.5)		61.7 (7.5)		66.0 (5.8)		69.0 (6.4)		<0.001
Recipient sex	Female	1,310	62.6	691	64.3	705	61.5	227	63.6	219	58.2	104	57.1	0.214
Primary renal disease	Unknown	352	16.8	186	17.3	219	19.1	75	21.0	91	24.2	44	24.2	<0.001
	Glomerular	643	30.7	289	26.9	279	24.3	82	23.0	60	16.0	29	15.9	
	Interstitial	374	17.9	149	13.9	135	11.8	31	8.7	40	10.6	30	16.5	
	Polycystic	261	12.5	195	18.1	214	18.7	57	16.0	57	15.2	19	10.4	
	Vascular	160	7.6	123	11.4	137	12.0	47	13.2	54	14.4	32	17.6	
	Diabetes	61	2.9	52	4.8	86	7.5	44	12.3	53	14.1	16	8.8	
	Other	243	11.6	81	7.5	76	6.6	21	5.9	21	5.6	12	6.6	
Time on dialysis before transplant	<1 yr	604	28.8	204	19.0	211	18.4	67	18.8	54	14.4	28	15.4	<0.001
	1–2 yr	543	25.9	304	28.3	293	25.6	91	25.5	120	31.9	53	29.1	
	>2 yr	947	45.2	567	52.7	642	56.0	199	55.7	202	53.7	101	55.5	
Mean time on dialysis before KT (mean[SD]), yr		2.57 (2.67)		2.94 (2.79)		3.04 (2.76)		2.85 (2.37)		2.85 (2.34)		2.95 (2.54)		<0.001
Hepatitis C virus		262	13.0	124	12.0	128	11.6	45	12.9	19	5.2	8	4.5	<0.001
Maximum PRA (%)	0–10	1,751	83.9	869	80.9	937	82.1	312	87.6	321	85.4	155	86.1	0.030
	11–50	246	11.8	158	14.7	166	14.5	30	8.4	43	11.4	21	11.7	
	>50	90	4.3	47	4.4	38	3.3	14	3.8	12	3.2	4	2.2	
Mean HLA-A matches (SD)		0.62 (0.59)		0.68 (0.6)		0.65 (0.59)		0.62 (0.59)		0.59 (0.57)		0.54 (0.6)		0.016
Mean HLA-B matches (SD)		0.56 (0.57)		0.57 (0.58)		0.56 (0.57)		0.49 (0.56)		0.45 (0.53)		0.41 (0.53)		<0.001
Mean HLA-DR matches (SD)		0.98 (0.58)		1.03 (0.56)		1.02 (0.61)		0.85 (0.63)		0.91 (0.62)		0.82 (0.61)		<0.001
Mean cold ischemia time hours (SD)		18.1 (6.7)		18.2 (6.2)		18.0 (6.2)		17.5 (6.10)		17.3 (6.0)		16.8 (7.5)		0.046
Delayed graft function		464	25.1	353	36.2	405	40.1	118	37.1	125	36.8	68	39.8	<0.001

HLA, human leukocyte antigen; KT, kiney transplantation; PRA, panel reactive antibody.

TABLE 3. Patient, graft, and death-censored graft survival analysis

Survival model		Patient	Graft	Graft (censoring death)
		Cox proportional	Parametric (exponential)	Parametric (exponential)
		HR (95% CI)	HR (95% CI)	HR (95% CI)
Donor age >65 yr[a]	Yes	1.30 (1.09–1.55)**	1.34 (1.16–1.55)**	1.77 (1.44–2.16)**
Donor cause of death	Trauma	1	N/S	N/S
	Hemorrhage	1.16 (0.99–1.34)		
	Anoxia	1.03 (0.73–1.45)		
	Tumors	0.92 (0.50–1.69)		
	Other	1.42 (1.11–1.82)*		
Recipient sex[a]	Female	0.79 (0.69–0.91)	N/S	1.22 (1.07–1.39)**
Recipient age, yr	<45	1	1	1
	[45–54]	2.26 (1.79–2.84)**	1.06 (0.92–1.22)	0.79 (0.66–0.94)*
	[55–64]	4.30 (3.47–5.32)**	1.41 (1.23–1.62)**	0.76 (0.64–0.91)**
	[65–69]	5.88 (4.55–7.59)**	1.76 (1.46–2.12)**	0.82 (0.63–1.06)
	[70–75]	7.34 (5.36–10.04)**	2.06 (1.63–2.61)**	0.84 (0.59–1.18)
	>75	14.03 (7.51–26.21)**	4.03 (2.32–7.00)**	1.79 (0.82–3.87)
Primary renal disease	Interstitial	1	1	1
	Glomerular	1.11 (0.89–1.40)	1.10 (0.94–1.29)	1.15 (0.94–1.40)
	Unknown	1.21 (0.95–1.53)	1.04 (0.87–1.25)	1.03 (0.82–1.29)
	Polycystic	1.14 (0.89–1.46)	0.92 (0.76–1.11)	0.81 (0.64–1.04)
	Vascular	1.30 (1.01–1.69)*	1.16 (0.95–1.41)	1.20 (0.93–1.54)
	Diabetes	2.56 (1.93–3.38)**	1.73 (1.38–2.17)**	1.59 (1.17–2.16)**
	Other	1.30 (0.96–1.76)	1.11 (0.89–1.39)	1.00 (0.76–1.32)
Recipient HCV positive[a]	Yes	2.13 (1.83–2.49)**	1.74 (1.53–1.98)**	1.63 (1.38–1.93)**
Maximum PRA, %	0–10		1	1
	11–50	N/S	1.10 (0.96–1.27)	1.21 (1.02–1.44)
	>50		1.43 (1.16–1.78)**	1.46 (1.11–1.91)*
DGF[a]	Yes	1.42 (1.24–1.62)**	1.54 (1.39–1.70)**	1.62 (1.42–1.84)**

[a] These variables take their complement as a reference.

* $P < 0.05$; ** $P < 0.005$.

N/S, not significant; 95% CI, 95% confidence interval; DGF, delayed graft function; HCV, hepatitis C virus; PRA, panel reactive antibody; HR, hazard ratio.

a significant increased risk of graft failure in recipients of donors aged 65 years or older both censoring and non-censoring for death. Lower graft survival was also significantly associated with recipient age, positive HCV, diabetes as primary renal disease, DGF, and high PRA level. The negative impact of advanced donor age was more evident after censoring for death (hazard ratio, 1.34 vs. 1.77, respectively). Contrarily, the negative impact of advanced recipient age disappeared, and female sex appeared as a risk factor for graft loss after censoring for death.

Comparison Between Kidney Transplanted Patients and Patients That Remained on Dialysis

Table 4 shows the characteristics of both cohorts. The distribution of matching variables was homogeneous in both groups. There were no statistically significant differences in cardiovascular comorbidity events (the sum of all comorbidities) or the presence of malignant tumors.

The whole cohort of 1,646 patients (823 KT and 823 dialysis controls) was followed-up for a maximum of 21 years, with a median of 3.2 years. During the whole observation period, there were 270 deaths (33.2%) among the 823 KT and 424 (52.1%) among the 823 controls. The survival of the KT group was significantly higher (P<0.001) than that of the dialysis group: 91.6%, 85,9%, 74.5% and 55.5 and 88.8%, 63,8%, 44.2%, and 18.1% at 1, 3, 5, and 10 years, respectively (P<0.001) (Fig. 1). Figure 1 shows adjusted survival rates taking into account all potential confounding aforementioned variables. For KT patients, uncensored-for-death graft survival at 1, 3, 5, and 10 years were 85.0%, 75.2%, 61.4%, and 40.5%, respectively. The probability of death at the end of the first year did not reach statistically significant differences between the two groups: 8.1% for KT and 10.3% for dialysis (P=0.137). When analyzing the whole period, the proportional risk of death was 2.66 (95% confidence interval [95% CI], 2.21–3.20) times higher for patients remaining on dialysis than that for KT patients. Sensitivity analysis, including stratification for age and first vascular access, yielded similar estimates. In all different age groups, the dialysis group had higher adjusted proportional risk of death, although there was a decreasing trend: 4.14 (95% CI, 2.48–6.90) in patients younger than 50 years; 2.96 (95% CI, 2.27–3.86) aged 51 to 64 years; 2.20 (95% CI, 1.60–3.09) aged 65 to 69 years; 1.86 (95% CI, 1.11–3.11) older than 70 years. The dialysis group had higher and similar adjusted proportional risk of death in both groups of first vascular access: 2.63 (95% CI, 1.79–3.88)

TABLE 4. Characteristics of the paired transplanted and dialysis patients

		Transplant		Dialysis		Total		
		n	%	n	%	n	%	
Age	0–50	70	8.5	70	8.5	140	8.5	1,000[a]
	51–64	429	52.1	429	52.1	858	52.1	
	65–69	202	24.5	202	24.5	404	24.5	
	≥70	122	14.8	122	14.8	244	14.8	
Age (mean [SD]), yr		61.6 (7.8)		61.7 (8.2)		61.7 (8.0)		0.897[b]
Sex	Male	527	64.0	527	64.0	1,054	64.0	1,000[a]
Period	≤2,000	365	44.3	365	44.3	730	44.3	1,000[a]
	2,001–2,010	458	55.7	458	55.7	916	55.7	
Diabetic nephropathy	Yes	105	12.8	105	12.8	210	12.8	1,000[a]
Any cardiovascular comorbidity	Yes	229	31.3	229	31.3	458	31.3	1,000[a]
Ischemic heart disease	Yes	97	13.3	95	13.0	192	13.2	0.885[a]
Cardiomyopathy	Yes	105	14.4	101	14.0	206	14.2	0.796[a]
Cardiac conduction disorders	Yes	46	6.3	59	8.1	105	7.2	0.190[a]
Cerebrovascular disease	Yes	31	4.3	32	4.4	63	4.3	0.884[a]
Vascular disease	Yes	72	9.9	94	13.0	166	11.5	0.065[a]
Number of cardiovascular comorbidity events (mean [SD])		0.47 (0.84)		0.52 (0.91)		0.49 (0.88)		0.314[c]
Malignant tumors	Yes	54	7.4	51	7.0	105	7.2	0.726[a]
Chronic liver disease	Yes	23	3.2	37	5.1	60	4.1%	0.185[a]

[a] Chi-square test.
[b] *t* test.
[c] Mann-Whitney *U* test.

in patients initiating chronic hemodiañysis treatment by catheter, and 2.65 (95% CI, 1.94–3.62) in patients initiating by arteriovenous fistula.

Patient survival of the 92 KT unpaired cases excluded from the study was not significantly lower compared to the 823 KT paired cases (94.2%, 77.9%, and 43.8% vs 91.6%, 74.5%, and 55.5%, respectively, at 1, 5, and 10 years, P=0.607).

DISCUSSION

This study analyzes one of the largest series of renal allograft recipients from deceased donors aged 65 years or older ever reported. It gathers information on the activity of the six adults transplant programs, which serve the 7.5 million Catalan population. One of the values of this registry is the homogeneity of the results among the centers, a consequence of sharing consensus protocols.

In 1980, Catalonia pioneered a procurement model based on a comprehensive approach to the whole process (*15*) which led to world leading figures in 1984 (19.1 deceased donors per million population (pmp) and 36.4 KT pmp) that have been maintained over time (30.1 deceased donors pmp and 54.4 KT pmp in 2012) (*16*). This has been in part because of the increasing acceptance of expanded criteria deceased donors since the early 1990s (*17, 18*). In 2012, deceased donors 60 years or older represented 45% of our total number of effective donors and stroke as cause of death among donors 65 years or older represent 73.2% of the cases (*16*), figures significantly higher than those reported by other registries like United Network for Organ Sharing (UNOS) or Eurotransplant (*19, 20*). Donor kidney discarding (17.9%) (*16*) is also lower in our series than in other reports (*19, 21*). In particular, the kidney discarding rate from donors older than 65 years in the UNOS database is above 60%, a policy that probably does not allow access to KT for a significant number of elderly recipients who remain on dialysis.

We have also been proactive in including older patients on the waiting lists, as some other programs do (*21–23*). We give them priority for the allocation of kidneys from deceased donors older than 65 years so that 80.1% of those kidneys went to recipients older than 60 years. The

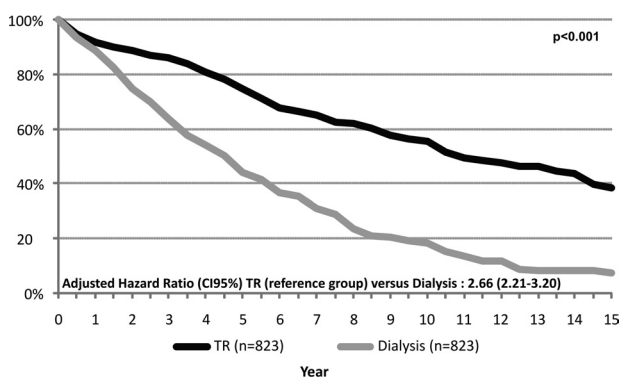

FIGURE 1. Patient survival in renal allograft recipients of kidneys from donors older than 65 years old versus patients remaining on dialysis in a paired analysis.

Eurotransplant Senior Program that is a specific program of strict elderly donor-recipient age (≥65 years) matching allocation, reported a fivefold increase in this activity between 1991 (3.6%) and 2007 (19.7%) (*20, 22*).

As with other reports (*14*), our series confirms that patient and graft survival is reduced with the increasing age of donor and recipient, particularly in those that receive a kidney from a donor aged 65 years or older. However, we also observed, as did others (*24–27*), that elderly recipients of these old kidneys have a reduced risk of death-censored graft failure compared to younger recipients of these grafts. On the other hand, it has been reported that old recipients of young donor kidneys show graft survival exceeding patient survival, which means a significant graft-years loss (*28*).

The second part of our study contains the first report ever that demonstrates a threefold lower death risk for KT patients receiving a graft from a deceased donor older than 65 years compared to their control pairs remaining on dialysis. The analyses of large series have shown that transplantation is the preferred treatment option for end-stage renal disease (*11–13*). According to a seminal report from the UNOS Registry (*11*) and a systematic review, including the meta-analysis of 110 studies (*12*), also concluded that KT is associated with reduced risk of mortality and cardiovascular events as well as with better quality of life than treatment with chronic dialysis. Nonetheless, the information on the benefits of KT using kidneys from deceased donors aged 65 years or older over staying on dialysis is limited. Ojo et al. (*13*), analyzing data from the UNOS registry, reported that recipients older than 65 years who received marginal donor kidneys lived an average of 3.8 years longer than their dialysis wait-listed counterparts. However, the value of their report is quite limited because their "marginal" donors included one of the following circumstances: age older than 55 years (36% were <55 years), hypertension longer than 10 years, diabetes longer than 10 years, cold ischemia time longer than 36 hr, and non–heart-beating donors. The specific and unique value of our study lies in the selection of the KT-dialysis pairs (one dialysis control pair (1:1 ratio) for 100% of the KT cases), patient by patient, with comparable characteristics that prevents any confusing effect. No previous reports are based on paired patients, the most reliable method for comparing groups and validating the results, particularly when true randomization is not feasible. In contrast, all previous reports are based on an intention-to-treat manner using the nonproportional Cox regression technique adjusted for some baseline variables.

We should mention, in agreement with others (*11, 12*), that the probability of death at the end of the first year did not reach statistically significant differences (P=0.137) between KT and dialysis patients. Our survival curves began to significantly separate both populations after the first year, showing that the proportional risk of death was 2.66-fold higher for those that remained on dialysis than for those that received a kidney from a deceased donor older than 65 years.

In conclusion, our study shows that KT from deceased donors older than 65 years provides significantly better survival than chronic dialysis for comparable paired patients. Our findings demonstrate and emphasize the need for the implementation of active policies and strategies addressed to increase the number of elderly patients to be included in the waiting lists who may benefit from KT from elderly donors. To attain this objective, it is necessary to be proactive in accepting deceased donors older than 65 years and to review some current discard policies of potentially viable organs.

MATERIALS AND METHODS

We analyzed the data provided by the Catalan Renal Registry, a mandatory population-based registry that collects information on all patients with end-stage renal disease requiring renal replacement therapy in Catalonia. All Dialysis and KT patients receive permanent full public medical coverage, including all medications.

Patients

A total of 23,923 had started renal replacement therapy until 2010 in Catalonia. For the initial descriptive analysis of recipients, we considered 5,230 patients who received a first KT from a deceased donor in any of the six adult transplant centres of Catalonia between 1990 and 2010. For the paired analysis, we considered 915 (17,4%) of the 5,230, who received a kidney from a deceased donor older than 65 years: 357 (39%) donors were aged 65 to 69 years, 376 (41.1%) between 70 and 75 years, and 182 (19.9%) were older than 75 years.

Variables Analyzed and Statistical Analysis

We first describe donor, recipient, and KT characteristics according to the different donor age groups: 0 to 45 years, 45 to 54 years, 55 to 64 years, 65 to 69 years, 70 to 75 years, and older than 75 years. Donor variables considered were sex, cause of death, and estimated GFR (calculated by the Cockroft-Gault formula). Recipient variables were: sex, age, primary renal disease, HCV serology, and time on dialysis before KT. Transplant variables were: cold ischemia time, DGF defined as need of dialysis the first week after KT, PRA level, and HLA-A, HLA-B and HLA-DR matching.

The differences between each donor age group were assessed using the chi-square test for categorical variables and the analysis of the variance for continuous variables. We identified the variables significantly associated with patient, graft, and graft-censored death survival by means of the Cox proportional hazard model. In the cases where the Cox regression model did not fit, we calculated the multivariate risk by means of a model of generalized parametric survival choosing the exponential distribution after testing the proportional hazard assumptions based on the Schoenfeld residuals. The exponential distribution was tested by plotting the cumulative hazard function at the mean value of the covariates, obtaining a line function Λ (t)=t. The final model was chosen using the Akaike Information Criterion (*29*) which assumes that the lower the values the better the value of the model.

We then studied the 915 KT cases that received a first single kidney graft from deceased donors aged 65 years or older. Controls were defined as those patients that initiated dialysis until 2010 and were included in the waiting list for KT but were not transplanted during the whole study period. We paired each case with one control (1:1 ratio). Each pair had the same characteristics at the time of entering dialysis program: age, sex, primary renal disease, period of dialysis onset, and to have or not have at least one of the five cardiovascular comorbidities. The control patients were included in the waiting list with the same criteria as the transplanted patients, thus the final population of controls and transplant recipients was comparable. Of the 915 KT patients, we excluded 92 because we did not find a paired control. We finally chose 823 KT patients that we were able to pair with 823 patients who remained on dialysis.

The starting point for the calculation of patient survival was the transplant date for KT cases. Calculation of their controls' survival was started at the date on which they had spent the same amount of time on dialysis as their respective KT pairs. The observation period was until death, date of the follow-up loss, or December 31, 2010. Survival time for both groups was calculated and compared by the Kaplan-Meier curve and the log-rank test. The risk for death onset was estimated using the Cox proportional hazard model, making a cluster by pairs and calculating the robust estimation of the variance. Potential confounding baseline variables were included: to have chronic liver and respiratory diseases, malignant tumors and diabetes

not considered as primary kidney disease. Sensitivity analysis included stratification of final models by (i) all different age groups and (ii) first vascular access for hemodialysis. The statistical analysis was carried out by means of the STATA version 11 software.

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Accepting Kidneys from Older Living Donors: Impact on Transplant Recipient Outcomes

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Older living kidney donors are regularly accepted. Better knowledge of recipient outcomes is needed to inform this practice. This retrospective cohort study observed kidney allograft recipients from Ontario, Canada between January 2000 and March 2008. Donors to these recipients were older living (≥60 years), younger living, or standard criteria deceased (SCD). Review of medical records and electronic healthcare data were used to perform survival analysis. Recipients received 73 older living, 1187 younger living and 1400 SCD kidneys. Recipients of older living kidneys were older than recipients of younger living kidneys. Baseline glomerular filtration rate (eGFR) of older kidneys was 13 mL/min per 1.73 m^2 lower than younger kidneys. Median follow-up time was 4 years. The primary outcome of total graft loss was not significantly different between older and younger living kidney recipients [adjusted hazard ratio, HR (95%CI): 1.56 (0.98–2.49)]. This hazard ratio was not proportional and increased with time. Associations were not modified by recipient age or donor eGFR. There was no significant difference in total graft loss comparing older living to SCD kidney recipients [HR: 1.29 (0.80–2.08)]. In light of an observed trend towards potential differences beyond 4 years, uncertainty remains, and extended follow-up of this and other cohorts is warranted.

Key words: Administrative data, cohort study, donor age, kidney transplant, survival analysis

Abbreviations: CAD, Canadian dollars; CCI, Charlson Comorbidity Index; CI, Confidence interval; CIHI-DAD, Canadian Institute for Health Information Discharge Abstract Database; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; DCD, Donation after cardiac death; DONOR, Donor Nephrectomy Outcomes Research Network; ECD, Expanded criteria donor; GFR, Glomerular filtration rate; HR, Hazard ratio; ICES, Institute for Clinical Evaluative Sciences; IKN, ICES Key Number; IQR, Interquartile range; LOESS, Locally weighted scatterplot smooth; MDRD, Modification of diet in renal disease; OHIP, Ontario Health Insurance Plan; PRA, Panel reactive antibody; RPDB, Registered Persons Database; SCD, Standard criteria donor (deceased kidney donor); SD, Standard deviation; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology Statement; TGLN, Trillium Gift of Life Network; Tx, Transplant; UNOS, United Network for Organ Sharing.

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Background

Living donor kidney transplantation provides the best and most flexible option for individuals with end stage renal failure. As more individuals develop renal failure, a larger spectrum of potential donors is being considered. Consequently, the definitions of previously unacceptable living kidney donors are changing. For example, close to a quarter of all living kidney transplants performed in the United States in recent years now involve donors with one or more medical complexities (1). Many transplant programs report that they no longer have an upper age limit for living donors (2,3). Older donors are most often defined by an age ≥60 years old (4). In addition to being driven by the demand for kidneys, their increasing prevalence may be a function of the overall aging population structure (5), or the increasing proportion of older transplant recipients with similarly aged potential donors (e.g. spouse or sibling).

Despite growth in the acceptance of older living donors, knowledge of recipient outcomes in this circumstance is limited. Biologically, an age-related decline in renal function may reduce the duration of recipient graft survival, as may an age-related predisposition to ischemia and drug toxicity, a reduced capacity for repair, and a higher degree of immunogenicity (6). In a recent meta-analysis of 12 clinical studies, 5-year survival was worse for recipients of kidneys from older living donors compared to younger donors (unadjusted relative risk of survival: 0.89, 95% CI 0.83 to 0.95) (7). Notably, studies included in this review were typically from single-centers, with limited numbers of patients, and there was a great deal of between-study heterogeneity. The majority of studies failed to account for confounding variables such as predonation donor renal function, and pretransplant duration of dialysis. While analyses of large U.S. data sets exist (8,9), no multicenter Canadian studies have ever been performed, where practice patterns and patient outcomes have been shown to differ (10).

The objectives of this study were to compare recipients of older living kidney donations (≥60 years) to recipients of younger living and deceased standard criteria donor (SCD) kidneys on outcomes of death and/or graft loss.

Methods

Data sources

This was a retrospective cohort study using Ontario-based electronic healthcare data. Transplant recipient data from January 2000 to March 2008 were obtained from the Trillium Gift of Life Network (TGLN), Ontario's central organ and tissue donation agency. The medical records of each living kidney donor across five transplant centers were also manually reviewed to ensure data accuracy, and to supplement TGLN data. Data were then linked to the Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD) which contains data on in-hospital diagnoses and procedures, the Ontario Health Insurance Plan (OHIP) which records inpatient and outpatient physician and allied health claims, and Ontario's Registered Persons Database (RPDB) which has demographic and vital statistics on all Ontario residents. Personal identifiers were removed from linked data sets. All recipients were followed until March 2009.

This study was conducted and reported according to recommendations from the STROBE Statement (Appendix A) (11). Ethics approval was obtained from the Sunnybrook Health Sciences Centre.

Study participants

The study included adult kidney transplant recipients, whose donors were: (1) living and older (≥60 years of age); (2) living and younger (<60 years of age) and (3) deceased SCD. Recipients of deceased expanded criteria donor (ECD) kidneys, donation after cardiac death kidneys, multiorgan, or dual/en bloc transplants were excluded. Electronic healthcare data codes for criteria meeting the UNOS definition of ECD were used to exclude ECD: previous diagnosis of hypertension, chronic kidney disease (proxy for serum creatinine ≥133 μmol/L), or diagnosis of cerebrovascular accident prior to death (12). The selection criteria for living kidney donors used in the five major transplant programs in Ontario during the period of study were quite conservative. All donors had a glomerular filtration rate ≥80 mL/min per 1.73 m^2 (through direct or indirect measurements). Patients accepted with hypertension on a single agent were relatively uncommon during the study period.

Outcomes

Outcomes were defined using electronic health care and TGLN data. The primary outcome, total graft loss, was a composite of time from transplantation to graft loss (i.e. codes for chronic dialysis over three consecutive months or more, or identified in TGLN as having had another kidney transplant), or all-cause mortality (i.e. death with a functioning graft). Secondary outcomes included recipient death due to all causes (not censored for graft loss), and death-censored graft loss. Recipients were censored at study end (March 31, 2009) or earlier if they emigrated from the province during the study period.

Statistical analysis

Sample size for this study was fixed based on the total number of kidney allograft recipients during the study period (all events captured in electronic healthcare databases). 95% CIs were reported to suggest a plausible range where the true point estimate may lie. Baseline characteristics were compared using t-tests, Mann–Whitney U or chi-square tests as appropriate. For missing predonation GFR and peak-PRA (missing <5%), mean values were imputed. For each comparison, univariable and multivariable Cox proportional hazards regression analyses were performed for each outcome. As recommended in the STROBE statement, age was modeled as both a continuous and dichotomous exposure (11). Departures from linearity were assessed by plotting a locally weighted scatterplot smooth (LOESS) curve through martingale residuals as a function of donor age (13). The proportional hazards assumption was assessed by plotting the log-minus-log transformed Kaplan–Meier estimates of the survival. Time-dependent covariates, which allowed for a change in the hazard ratio over time were considered (14). To account for clustered data (i.e. re-transplants; two kidneys from one deceased donor), sandwich estimators of the standard error of the hazard ratio were used (15).

Recipient age, pretransplant duration of dialysis, transplant year and predonation donor renal function were adjusted for in all models. Additional factors [donor and recipient sex, donor–recipient relationship, recipient race, recipient Charlson Comorbidity Index (CCI), open versus laparoscopic surgery, number of renal arteries on the donated kidney and recipient panel reactive antibody (PRA)] were assessed empirically. A 10% change between crude and adjusted estimates was considered important (16). All models were stratified by transplant center to allow for distinct baseline hazard functions across all five sites. Subgroup analyses by recipient age (≥ or <60 years) and donor eGFR (≥ or <90 mL/min per 1.73 m^2) at the time of donation were tested using interaction terms (17). A two-sided p-value <0.05 was considered statistically significant. Statistical analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, North Carolina, USA).

Results

Baseline characteristics

From January 1, 2000 to March 31, 2008, TGLN collected information on 3511 kidney transplant recipients. Figure 1 shows a flow diagram of applied exclusions. Analyses included recipients of 73 older living donor kidneys (5.8% of living transplants), 1187 younger living kidneys and 1400 deceased SCD kidneys. Nineteen recipients had two kidney transplants over the study period. Deceased kidney allografts were from 828 donors; 572 donated both of their kidneys.

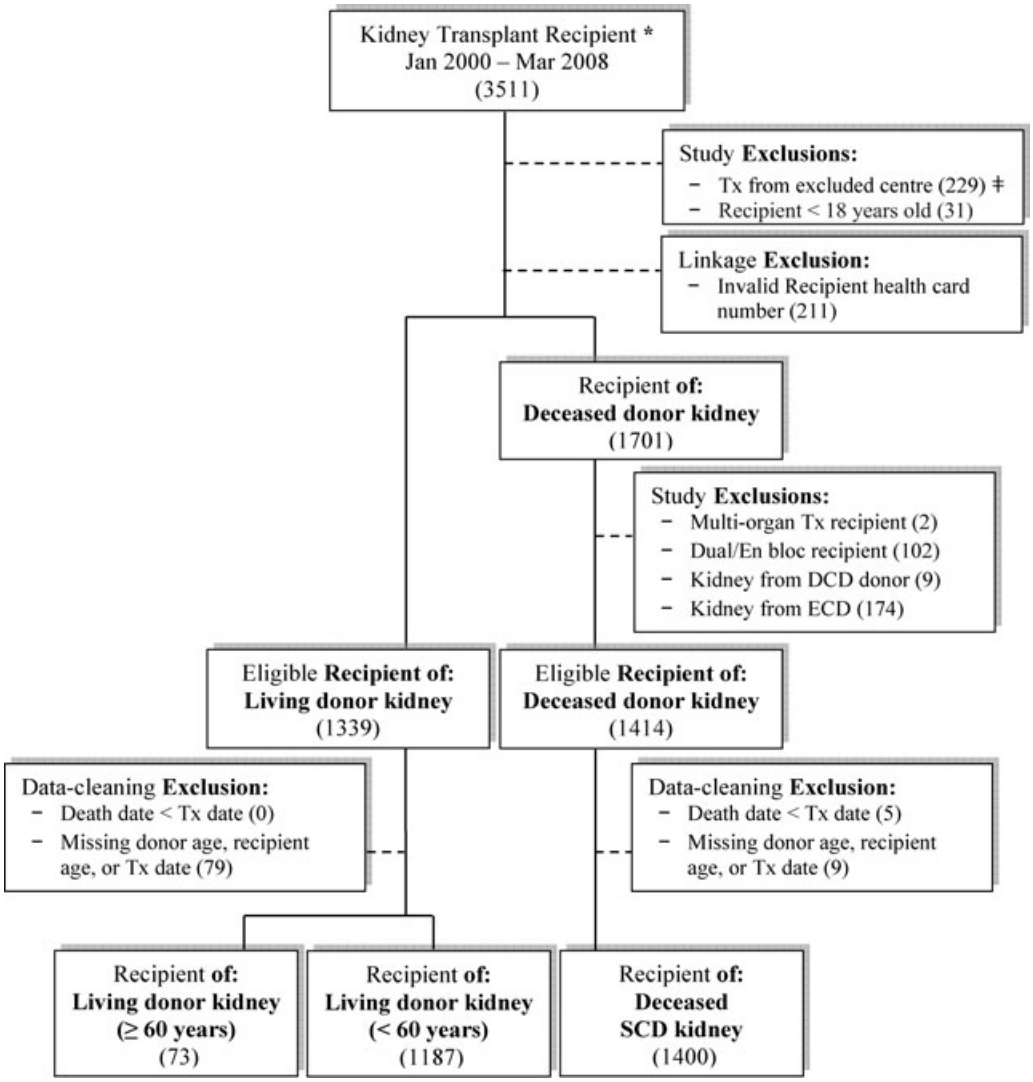

Figure 1. Flow diagram of participation in this study. *Note*: Number included/excluded indicated in (parentheses). (∗) As identified by Trillium Gift of Life Network, Ontario, Canada. (#) Excluded centers were Hospital for Sick Children (exclusively performs pediatric transplants) and Kingston General Hospital (discontinued transplant program during study period). TGLN = Trillium Gift of Life Network; Tx = Transplant; IKN = ICES Key Number; DCD = Donation after cardiac death; ECD = Expanded criteria donor; RPDB = Registered persons database; SCD = Standard criteria donor.

Recipient characteristics at the time of transplant are summarized in Table 1. Recipients of older living kidneys were older than recipients of younger living kidneys [mean age: 49 vs. 45 years ($p = 0.03$), 33% vs. 14% over 60 years]. Both groups of living kidney recipients spent similar times on dialysis prior to transplant ($p = 0.94$), and had similar CCI scores ($p = 0.55$). When comparing recipients of older living kidneys to SCD deceased kidney recipients, their average age did not differ ($p = 0.38$). Recipients of older living kidneys spent significantly less time on dialysis than deceased kidney recipients (23 vs. 49 months, $p < 0.001$), but had a similar distribution of CCI scores ($p = 0.93$).

Donor characteristics at the time of transplant are shown in Table 2. The mean age of older living donors was 63 years, while younger living donors were 42 years and deceased SCDs were 39 years old. As expected, mean predonation eGFR was lower in older living donors compared to younger living donors (Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI]: 83 vs. 96 mL/min per 1.73 m^2, $p < 0.0001$). However, there was no difference in serum creatinine between the two groups (77 vs. 75 μmol/L, $p = 0.27$).

Transplant outcomes

Median (IQR) follow-up time for the cohort was 4 (2 to 6) years. For the primary outcome, total graft loss, there were 269, 5199 and 5810 person-years of follow-up for recipients of older living, younger living and SCD deceased

Table 1: Characteristics of recipients at the time of transplantation

	Living donor recipients			Deceased donor recipients	
	Older Kidney (≥60 years) N = 73	Younger Kidney (<60 years) N = 1187	p-Value[1]	SCD Kidney (<60 years) N = 1400	p-Value[2]
Age (years), mean (SD)	49 (14)	45 (13)	0.03	50 (13)	0.38
18–39 years	26 (36)	408 (34)	< 0.001	317 (23)	0.001
40–49 years	11 (15)	302 (25)		342 (24)	
50–59 years	12 (16)	315 (27)		385 (28)	
60–69 years	23 (32)	141 (12)		274 (20)	
≥70 years	≤5 (≤7)[3]	21 (2)		82 (6)	
Gender (Female)	24 (33)	477 (40)	0.22	511 (37)	0.53
Preemptive transplant (no dialysis history)	19 (26)	228 (19)	0.15	≤5 (≤0.4)[3]	<0.001
Duration of dialysis history, months[4]					
Mean (SD)	23 (22)	23 (24)	0.94	49 (31)	<0.001
Median (IQR)	16 (8–30)	16 (8–29)	0.81	44 (23–71)	<0.001
Charlson Score					
2–3	51 (70)	887 (75)	0.55	976 (70)	0.93
4–5	18 (25)	258 (22)		360 (26)	
≥6	≤5 (≤7)[3]	42 (4)		64 (5)	
Peak PRA					
<20%	60 (82)	980 (83)	0.74	1036 (74)	<0.001
20–50%	≤5 (≤7)[3]	61 (5)		128 (9)	
≥50%	7 (10)	88 (7)		236 (17)	
Missing	≤5 (≤7)[3]	58 (5)		0	

Notes: Values reported as N (%), unless stated otherwise. SCD = Standard criteria donor; PRA = Panel reactive antibody.
[1]Comparing recipients of older living donors to younger living donors.
[2]Comparing recipients of older living donors to standard criteria deceased donors.
[3]Note: Cells with ≤5 observations were suppressed to prevent indirect identification of individuals.
[4]Only applies to patients with a history of dialysis prior to transplant.

kidneys, respectively. Less than 2% were censored due to provincial emigration. Among living kidney transplants, there were 195 events of total graft loss: 17 for recipients of older living kidneys (6.3 per 100 person years) and 178 for recipients of younger living kidneys (3.4 per 100 person years). For SCD deceased recipients, 355 events of total graft loss were observed (6.1 per 100 person years).

Older living kidneys versus younger living kidneys

When donor age was modeled as a continuous predictor, each additional year increase in donor age was not associated with an increase in total graft loss [adjusted hazard ratio (HR): 1.01, 95% confidence interval (CI): 0.98 to 1.03, p = 0.49]. Assessment of the functional form of donor age confirmed no significant departures from linearity.

Donor age was next modeled as a dichotomous exposure using a cut-off of ≥60 years. The results are presented in Table 3. The adjusted hazard of total graft loss was increased by 56% for recipients with older living donors, but this was not statistically significant (95% CI: 0.98 to 2.50, p = 0.06). The hazard of death for recipients of older living donor kidneys was significantly higher (adjusted HR: 2.70, 95% CI: 1.39 to 5.26, p = 0.0004). There was no significant difference for death-censored graft loss (p = 0.72). Visual inspection of the log-minus-log transformed K–M plots revealed possible violations of the proportional hazards assumption. Models with a time-dependent interaction suggested that the HR of total graft loss with older living kidneys compared to younger living kidneys increased with time. Recipient age (≥ or <60 years) and donor eGFR (≥ or <90 mL/min per 1.73 m^2) did not significantly modify the effect of living donor age on transplant outcomes (interaction p ranged from 0.10 to 0.58).

Older living kidneys versus SCD deceased kidneys

A comparison of the outcomes of older living versus SCD deceased kidney recipients is presented in Table 4. The adjusted hazard of total graft loss was not significantly different for recipients of older living kidneys compared to recipients of SCD deceased kidneys (adjusted HR: 1.28, 95% CI: 0.79 to 2.08, p = 0.30). There was also no difference between groups for death or death-censored graft loss. Visual assessment revealed possible violations of the proportional hazards assumption. Time-dependent interaction reached statistical significance for total graft loss (p = 0.01), suggesting that recipients of older donor kidneys had a risk of total graft loss that increased with time. No significant interaction by recipient age was detected for any of the outcomes (p ranged from 0.13 to 0.79).

Discussion

In Ontario, about 6% of living kidney donors may be considered 'older'. Trends suggest that this proportion is

Table 2: Characteristics of kidney donors at the time of transplantation

	Living kidney donors			Deceased kidney donors	
	Older kidney (≥60 years) N = 73	Younger kidney (<60 years) N = 1187	p-Value[1]	SCD Kidney (<60 years) N = 1400	p-Value[2]
Age (years), mean (SD)	63 (3)	42 (10)	–	39 (14)	–
Age (years), median (IQR)	62 (60–64)	42 (34–50)	–	42 (28–50)	–
60–69 years	70 (96)				
≥70 years	≤5 (≤7)[3]				
Gender [Female, n (%)]	36 (49)	731 (62)	0.04	593 (42)	0.24
Relationship to their Recipient					
Parent	24 (33)	103 (9)	<0.0001		
Child	≤5 (≤7)[3]	186 (16)			
Sibling	13 (18)	404 (34)			
Spouse	18 (25)	232 (20)			
Other related	≤5 (≤7)[3]	84 (7)			
Unrelated	11 (15)	178 (15)			
Serum Creatinine (μmol/L)					
Mean (SD)	77 (14)	75 (14)	0.27		
Median (IQR)		77 (67–86)	73 (65–85)	0.23	
CKD-EPI eGFR (mL/min per 1.73 m^2)					
Mean (SD)	83 (10)	96 (15)	<0.0001		
Median (IQR)	84 (74–91)	96 (85–106)	<0.0001		
MDRD eGFR (mL/min per 1.73 m^2)					
Mean (SD)	84 (12)	92 (17)	<0.0001		
Median (IQR)	83 (74–92)	90 (80–101)	<0.0001		
Laparoscopic	43 (60)	587 (50)	0.12		

Notes: Values reported as N (%), unless stated otherwise. SCD = Standard criteria donor; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; MDRD = Modification of diet in renal disease.
[1]Comparing older living donors to younger living donors.
[2]Comparing older living donors to standard criteria deceased donors.
[3]Cells with ≤5 observations were suppressed to prevent indirect identification of individuals.

increasing with time (18). In other countries, older donors are accepted more frequently than ever before. For example, according to the Norwegian Renal Registry, 16% of living kidney donors are now ≥60 years old and 7.7% are ≥65 years of age (19). In the United States, the majority of transplant centers report no upper age limit, which precludes an individual from becoming a living donor (3). Despite these trends in the acceptance of older living kidney donors, knowledge of recipient outcomes from such donors is limited. This disconnect between evidence and practice has been highlighted elsewhere (7).

To better inform current practice, we studied recipient outcomes of all older living kidney donors across five

Table 3: Association of older living versus younger living with transplant outcome

Recipient outcome	Younger donor (<60 years) N = 1187	Older donor (≥60 years) N = 73	p-Value
Total graft loss (n)	178	17	–
Rates (Events per 100 person-years)	3.4	6.3	–
Unadjusted HR (95% CI)	1.0 (reference)	1.78 (1.11–2.87)	0.02
Multivariable adjusted HR (95% CI)	1.0 (reference)	1.56 (0.98–2.49)	0.06
Death (alone), n	74	11	–
Rates (Events per 100 person-years)	1.3	3.8	–
Unadjusted HR (95% CI)	1.0 (reference)	2.97 (1.58–5.56)	0.001
Multivariable Adjusted HR (95% CI)	1.0 (reference)	2.73 (1.39–5.35)	0.004
Death-censored graft loss (n)	114	6	–
Rates (Events per 100 person-years)	2.2	2.2	–
Unadjusted HR (95% CI)	1.0 (reference)	0.96 (0.43–2.14)	0.91
Multivariable Adjusted HR (95% CI)	1.0 (reference)	0.84 (0.34–2.11)	0.72

Notes: All multivariable models adjusted for: Recipient age, dialysis duration, donor GFR and year of transplant. Additional adjustment on the basis of operational confounding criteria depends on outcomes: Total graft loss, No additional covariates added to the model; Death, Donor–recipient relationship; Death-censored graft loss, Recipient race, Charlson score, peak PRA, donor gender, donor–recipient relationship, surgical technique and number of renal arteries.

Table 4: Association of older living versus SCD deceased with transplant outcome

Recipient outcome	SCD deceased (<60 years) N = 1400	Older living (≥60 years) N = 73	p-Value
Total graft loss (n)	355	17	–
Rates (Events per 100 person-years)	6.1	6.3	–
Unadjusted HR (95% CI)	1.0 (ref)	1.03 (0.64–1.64)	0.91
Multivariable adjusted HR (95% CI)	1.0 (ref)	1.29 (0.80–2.08)	0.30
Death (alone), n	201	11	–
Rates (Events per 100 person-years)	3.1	3.8	–
Unadjusted HR (95% CI)	1.0 (ref)	1.27 (0.69–2.32)	0.44
Multivariable adjusted HR (95% CI)	1.0 (ref)	1.83 (0.96–3.48)	0.07
Death-censored graft loss (n)	173	6	–
Rates (Events per 100 person-years)	3.0	2.2	–
Unadjusted HR (95% CI)	1.0 (ref)	0.71 (0.32–1.56)	0.39
Multivariable adjusted HR (95% CI)	1.0 (ref)	0.74 (0.34–1.62)	0.45

Notes: All multivariable models adjusted for: Recipient age, dialysis duration and year of transplant. Additional adjustment on the basis of operational confounding criteria depends on outcomes: Total graft loss, Recipient race, Charlson score and peak PRA; Death, Peak PRA; Peak PRA, Death-censored graft loss.

transplant centers in Ontario, Canada. We found that acceptable 4-year recipient outcomes were achieved when using older living donor kidneys. Initial unadjusted analyses suggested an increased hazard ratio for total graft loss when comparing recipients of older and younger living donor kidneys. After accounting for age differences and other confounding factors, this difference was no longer statistically significant. The risk of death with a functioning graft was observed to be significantly higher for recipients of older living donor kidneys. This may partly be mediated by differences in kidney function in the absence of graft failure, or in recipient case mix. There may also be a role for residual confounding by factors related to health status that were difficult to ascertain. However, there was no difference in death-censored graft loss between older and younger living donors, and no relationship with graft loss when age was modeled as a continuous covariate. Recipient outcomes for older living kidney donors were no different than deceased SCDs.

A systematic review summarizing the results of 31 previous studies suggested that total graft survival in older living kidney recipients was significantly worse at 5 years compared to younger living donors (7). Several factors may explain the discrepancy between the current data and previous studies. First, living donor selection criteria in Canada are quite conservative, which may lead to better outcomes for Canadian kidney transplant recipients. This contrasts to practices in the United States, where almost a quarter of living kidney donors have some preexisting, moderate health condition (4). Such conditions would be most prevalent among older individuals. This is best highlighted in a well-conducted study using data of United States Renal Data System, which showed a progressively higher risk of graft loss in recipients of older living kidneys (55 years and older) (9). In both settings, excellent clinical outcomes for older living donors compared to deceased SCDs were observed. Second, this analysis accounted for potential confounding factors that were not considered in most previous studies, such as pretransplant duration of dialysis in months, transplant year, predonation donor renal function, surgical type (open versus laparoscopic) and recipient PRA. Finally, this study focused on the most recent era of transplants, those performed from the years 2000 to 2008. Results were consistent with the trend highlighted in a meta-regression of previous studies suggesting a less prominent 'period' effect over time (7).

To our knowledge, this is the first study to assess the effect of donor age on transplant outcome in a Canadian setting. It is one of the largest studies to date; only two other studies of US health administrative data have followed a larger group of donors (8,9). Almost all adult-transplant recipients (first and retransplants) from multiple centers in Ontario were considered. Recipient follow-up during the full study period was excellent (<2% was lost due to provincial emigration). It is also the first study to deterministically link transplant recipients to Canadian electronic healthcare data; previous studies relied on a probabilistic linkage, which linked a maximum of 70% of the eligible cohort (20). Our use of electronic healthcare data was also supplemented by manual chart review to ensure accurate and complete information.

A few limitations of this study merit consideration. Data for several potential confounding factors were not well documented in the data sources used, and were often difficult to ascertain from medical records. Thus, some residual confounding may be present. Such factors included various laboratory measures, donor blood pressure, ischemic time, cytomegalovirus mismatch, induction therapy and baseline maintenance immunosuppression. We studied transplants from all older living donors in Ontario during the study period. However, this number was finite. A greater number of donors would have resulted in more precise estimates, and a greater ability to rule out clinically important differences between our study groups.

Implications for clinical care

Using the results from this study, transplant professionals can inform their patients that graft survival from older living kidney donors is not inferior to receiving a kidney from a deceased SCD. This information may be particularly well received given long waiting times for deceased donation in many jurisdictions.

In practice, more than one eligible potential living donor may come forward for a single potential recipient, and these donors may differ in age (e.g. a parent and child). Based on current data, there remains uncertainty as to the comparability of selecting the younger versus the older donor. Practically speaking, 4-year outcomes when using older living donor kidneys may be considered acceptable in some settings. For example, in cases involving young recipients who may need another transplant in their lifetime, transplant professionals may choose to accept an older donor despite shorter graft survival, in order to save the younger donor for a possible future transplant (immunological sensitization notwithstanding). In cases involving older recipients where projected life expectancy is not as high, transplant professionals may feel comfortable selecting the older donor (i.e. old-for-old). Arguments have been proposed suggesting this may be the safer practice in considering donor health as well (21).

A living donor paired exchange registry was recently established in Canada in 2009 (22). Similar registries have been established in other nations. As part of the exchange process, the transplant team is responsible for assessing the 'fairness' of each proposed exchange. When donors involved in an exchange are of markedly different ages, there may be a question of whether the recipient of an older kidney is receiving a kidney of equal quality to another recipient of a younger kidney. These results suggest that a matching algorithm involving similarly aged donors may not be too critical on 4-year recipient outcomes.

Finally, from an economic perspective, every older donor who may have otherwise been precluded from donation contributes a cost savings of about $100 000 Canadian dollars over a 20-year period, compared to the patient who waits on dialysis (23).

In conclusion, this study extends current understanding of the utility of older living kidney donors by observing outcomes among Ontario kidney transplant recipients in the most recent era, with better follow-up and supplementation of electronic health data with more detailed techniques for data ascertainment. Recipients of older living donor kidneys had similar 4-year total graft survival when compared to recipients of SCD deceased donor kidneys. As for outcomes when using older versus younger living donor kidneys, the difference was not statistically significant. In light of an observed trend towards potential differences beyond 4 years, uncertainty remains and extended follow-up of this and other cohorts is warranted.

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Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation.*

Conflict of Interest

None declared.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix A: STROBE Statement checklist for cohort study reports.

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Expanded criteria donor and donation after circulatory death renal allografts in the west of Scotland: Their place in the kidney allocation process

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Standard criteria donor
Expanded criteria donor
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Outcomes
Organ allocation

ABSTRACT

Introduction: Due to the rising disparity between demand and availability, organs from expanded criteria donors (ECD) and donors after determination of circulatory death (DCD) are increasingly used. The purpose of this study was to report outcomes in recipients of ECD and DCD renal allografts from a single centre.

Methods: A retrospective analysis from a single centre for all renal transplants performed between 2001 and 2010 inclusive was undertaken. SCD (standard criteria donor) and ECD organs were compared, as were DCD and DBD (donation after determination of brain stem death) organs. Baseline data and predefined standard transplant outcomes were collected and compared using appropriate statistical tests. $P < 0.05$ was defined as significant.

Results: 729 renal transplants were performed. Comparing ECD to SCD organs, there was a significant difference in graft survival between groups (logrank for trend, $p = 0.032$) with ECD organs doing worse than SCD organs. Short-term outcomes showed a similar disparity with a higher 1-year post-transplant creatinine and delayed graft function (DGF) rate in ECD grafts. Nevertheless, outcomes were still clinically acceptable. When comparing DCD to DBD organs, no such differences were apparent, with DCD organs appearing to perform at least as well as DBD organs. In our cohort, unlike some previous studies, DGF rates were similar in both DCD and DBD groups.

Conclusions: Although ECD organs perform less well than SCD organs, outcomes are still acceptable and our results support their continuing use. When considering DCD organs, our data support the view that they should no longer be necessarily regarded as marginal grafts. Our low DGF rates are perhaps explained by local factors contributing to a short CIT.

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Introduction

Renal transplantation has experienced an exponential growth.[1] Shortage in organ supply has replaced inadequacies in immunosuppression therapy as the limiting factor for this treatment. Donor pool expansion has formed a central part of the UK strategy aimed at reversing this trend and the ambitious target of the organ donor task force, a 50% increase in donor numbers, has been reached.[1] Achieving this has involved acceptance of older donors with significant co-morbidity. This naturally leads to increased numbers of organs from expanded criteria donors (ECD) and donations after circulatory death (DCD). Although outcomes following DCD and ECD transplants are better than those on dialysis, concern remains about the risks associated with these non-traditional sources of deceased donor organs.[1,2,3]

By definition, ECD kidneys have a 70% higher relative risk of graft failure compared to standard criteria donor (SCD) kidneys because they are characterized by worse prognostic factors (relative hazard ratio = 1.70). [4–7]DCD kidney allografts have been associated with a greater risk of delayed graft function (DGF, usually defined as a need for the use of dialysis in the first postoperative week).[4] There are those who have argued that the absence of the neuroendocrine crisis associated with brain stem dead donors (DBD), that itself is associated with a major up regulation of systemic inflammation and stress, may favour the DCD kidney.[4] Until recently, DCD organs have been only allocated locally as it was believed that reducing the cold ischaemic time would be the only way to abrogate the effects of the warm ischaemia associated with circulatory arrest. However, based on published outcomes and statistical modelling of transport and cold ischaemic times, the prevailing opinion has changed.

There is therefore a need for more data on the implications of DCD and ECD kidney transplantation. This information is central to recipient counselling and optimal allocation. The purpose of this study was to compare the outcomes of SCD *versus* ECD and DCD *versus* DBD kidney transplants. By robustly defining the factors that dictate outcomes, patients, healthcare teams and policy makers will be able to make more informed decisions and allocation policies may be appropriately tailored. This will improve the overall utility and equity of kidney transplantation.

Materials and methods

Study population

The study population included all patients that received a deceased-donor renal transplant in a single centre in the West of Scotland from 2001. The scope of the investigation was limited to transplants that occurred between 2001 and 2010 inclusive, as follow-up data for transplants post 2010 were incomplete. Every transplant in the study time window was evaluated and categorised as either a standard or expanded criteria donor organ. ECDs were defined as donors aged >60 years or aged between 50 and 60 years with ≥2 of the following conditions[1]: diagnosed hypertension,[2] terminal serum creatinine >1.5 mg/dL (>133 μmol/L),[3] cause of death is stroke. SCDs were donors that did not fulfil the ECD criteria. The Scottish Electronic Renal Patient Record (SERPR) was used to populate any missing data required to accurately classify the donor–recipient pairs. Exclusion criteria included live donors, dual transplants, and subjects in whom insufficient information on expanded criteria status was available.

Study design

We carried out a retrospective analysis of all renal transplants performed at the West of Scotland Renal Transplant Unit. The study was performed with the approval of the local Clinical Effectiveness Committee and in accordance with the Declaration of Helsinki.

Standard recipient and donor demographic data were collected. This included donor age, sex, cytomegalovirus (CMV) status, cause of death, and recipient age, sex, duration of dialysis, length of hospital stay, number of previous transplants and cause of end-stage renal disease (ESRD). Additionally, the following information was obtained for each donor–recipient pair: donation after brain death (DBD) or donation after circulatory death (DCD) donor, cold ischaemic time (CIT, in hours) and age difference.

The donor–recipient pairs were then stratified according to donor groups, comparing ECD *versus* SCD renal transplantations and DBD *versus* DCD renal transplantations.

Outcomes

Short-term outcomes were defined as 1-year graft and patient survival, biopsy-proven acute rejection (BPAR), 1-year creatinine (μmol/L) and delayed graft function (DGF, defined as a post-transplant need for dialysis). The long-term outcome was 5-year death-censored graft survival.

Statistical analyses

Continuous variables were tested for normality, using the D'Agostino Person Omnibus test. Normal continuous data were expressed as mean ± standard deviation and were compared with the unpaired Student's *t*-test. Non-normal continuous data were presented as median with interquartile range and were compared using the Mann–Whitney *U* test. Categorical data were presented in percentages and were compared using Fisher's exact or X^2 tests.

5-year death-censored graft survival was estimated using the Kaplan–Meier procedure. Curves were compared using the Logrank test for trend.

Statistical analysis was performed with the use of IBM SPSS Statistics version 21 and Graph Pad Prism version 5 (GraphPad Software Inc., California USA). A two-sided $p < 0.05$ was defined as significant.

Results

Data from a total of 729 renal transplants performed between 2001 and 2010 inclusive were available for analysis. After exclusions, data from 510 procedures were analysed (see Fig. 1).

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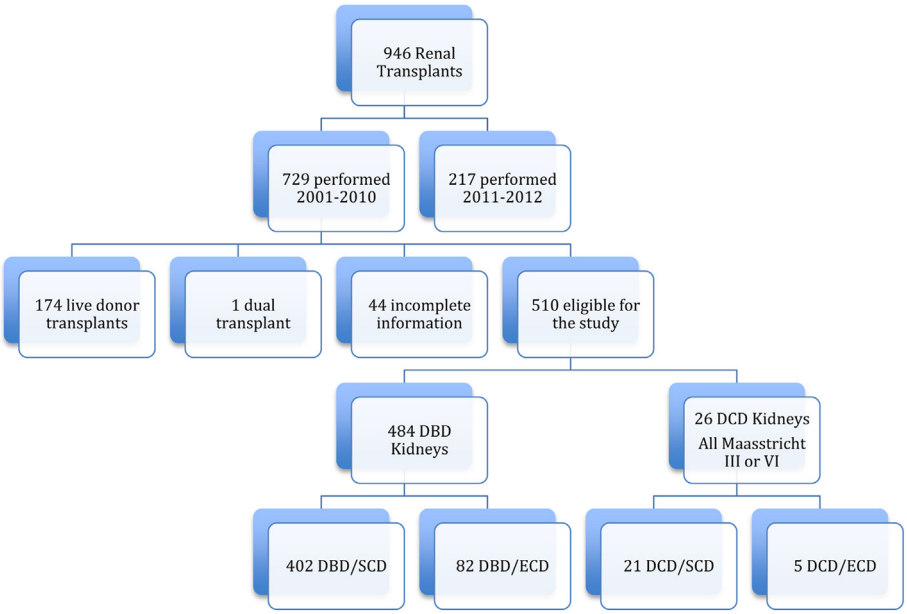

Fig. 1 – Flow chart, illustrating the breakdown of transplant data.

Demographics and baseline characteristics

Baseline donor and recipient characteristics are summarised in Table 1. Key differences between groups that might be expected to influence outcomes were as follows:

Comparing ECD with SCD grafts, as expected, expanded criteria donors were on average 20 years older than standard criteria donors (66.0 and 42.0 years respectively, $p < 0.001$); recipients of ECD kidneys were on average 10 years older than the recipients of SCD kidneys (55.0 and 43.0 years respectively, $p < 0.001$); ECD recipients had been on dialysis for 2 years longer on average than SCD recipients (4.25 and 2.5 years respectively, $p = 0.002$).

Comparing DCD to DBD grafts, the median CIT for DCD organs was 3 h shorter than for DBD organs (13.25 and 16.5 h respectively, $p < 0.001$); CMV positivity in the donor and recipient was significantly higher in the DBD group; there was a trend to a longer duration of dialysis in the DCD group (DCD 3.9 years *versus* DBD 2.5 years, $p = 0.081$).

Outcomes comparing SCD to ECD allografts

As would be expected, ECD transplants performed less well that SCD transplants; median 1-year post-transplant creatinine levels were approximately 40 μmol/L higher (166.0 and 123.0 μmol/L respectively, $p < 0.001$) (Table 2). ECD organs were also subject to higher delayed graft function rates (42.5% *versus* 18.0%, $p < 0.001$) and on Kaplan–Meier analysis (Fig. 2), death-censored 5-year graft survival was significantly worse (logrank test for trend $p = 0.032$).

Outcomes comparing DBD to DCD allografts

When comparing DBD to DCD transplants, short-term outcomes defined as 1-year creatinine, 1-year graft and patient survival, biopsy proven acute rejection or the occurrence of DGF (Table 2) did not differ significantly between groups. The crucial long-term outcome of 5-year death-censored graft survival also did not differ significantly (Fig. 3).

Discussion

Kidney transplantation is the treatment of choice for ESRD, yet to match the 260% increase in the deceased donor waiting list, the transplantation community cannot rely on a declining pool of optimal DBD donors and so must instead look to other sources. This includes expanded criteria donations (ECD) and donations after circulatory death (DCD). [4–7]Studies have shown that ECD kidneys have historically increased the donor pool modestly at the expense of a worse outcome. By contrast, DCD kidneys, particularly controlled DCD allografts, represent a promising partial solution in the context of an ageing and increasingly co-morbid population.[2] Despite this promise, there still remains the need to garner further evidence to prove the comparability of outcomes with DBD transplantation.

SCD versus ECD

Our study shows that ECD allografts perform less well than SCD allografts. This is likely to be due primarily to the adverse donor factors that define ECD organs: donor age and co-morbidity. Nevertheless, whilst showing statistically significant worse outcomes, the important 5-year death-censored graft survival in ECD grafts is certainly clinically acceptable. This is despite our ECD recipient cohort being older and having a greater exposure to dialysis than our SCD recipient cohort.

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Table 1 – Baseline characteristics of the donor–recipient pairs in the two principle comparisons, ECD *vs.* SCD and DCD *vs.* DBD kidney transplantations.

General	SCD ($n = 423$)	ECD ($n = 87$)	p	DBD ($n = 484$)	DCD ($n = 26$)	P
CIT [median (IQR)]	16.5 (3.5)	16.5 (4.1)	0.387	16.5 (3.5)	13.25 (7.4)	<0.001
Donor						
Age [median (IQR)]	42.0 (18.0)	66.0 (6.0)	<0.001	45.0 (21.0)	45.5 (24.5)	0.686
Sex [% (*n*)]						
Male	54.4 (230)	48.3 (42)	0.452	55.0 (266)	23.1 (6)	0.006
Unknown	0.5 (2)	0.0 (0)		0.4 (2)	0.0 (0)	
CMV positive [% (*n*)]	40.7 (172)	48.3 (42)	0.168	49.8 (206)	30.8 (8)	<0.001
Cause of death [% (*n*)]			0.168			<0.001
Traumatic ICH	16.5 (70)	5.7 (5)		15.1 (73)	7.7 (2)	
Spontaneous ICH/SAH	63.1 (267)	82.8 (72)		68.0 (329)	38.5 (10)	
Meningitis/encephalitis	4.0 (17)	2.3 (2)		3.9 (19)	0.0 (0)	
Hypoxic brain injury	9.2 (39)	4.6 (4)		7.9 (38)	19.2 (5)	
Infarction	3.1 (13)	4.6 (4)		3.5 (17)	0.0 (0)	
Respiratory/cardiac arrest	2.4 (10)	0.0 (0)		0.2 (1)	34.6 (9)	
Other	1.7 (7)	0.0 (0)		1.4 (7)	0.0 (0)	
Recipient						
Age [median (IQR)]	43.0 (18.0)	55.0 (18.0)	<0.001	44.5 (19.75)	52.0 (20.5)	0.109
Sex [% (*n*)]						
Male	60.0 (254)	66.7 (58)	0.278	61.4 (297)	57.7 (15)	0.686
Time on dialysis [median (IQR)]	2.5 (3.67)	4.25 (4.65)	0.002	2.5 (4.0)	3.9 (2.75)	0.081
Length of hospital stay [median (IQR)]	8.0 (3.0)	8.0 (3.0)	0.522	8.0 (3.0)	7.5 (3.0)	0.751
No. of previous transplants [% (*n*)]			0.908			0.682
Zero	76.1 (322)	77.0 (67)		75.8 (367)	84.6 (22)	
One	20.6 (87)	19.5 (17)		20.7 (100)	15.4 (4)	
Two	2.8 (12)	3.5 (3)		3.1 (15)	0.0 (0)	
Three	0.5 (2)	0.0 (0)		0.4 (2)	0.0 (0)	
CMV positive [% (*n*)]	23.2 (98)	33.3 (29)	0.004	25.6 (124)	11.5 (3)	0.013
Cause of ESRD [% (*n*)]			0.320			0.062
Diabetic nephropathy	6.9 (29)	4.6 (4)		6.8 (33)	0.0 (0)	
Hypertension	3.8 (16)	6.9 (6)		4.5 (22)	0.0 (0)	
Glomerulonephritis	16.3 (69)	19.5 (17)		17.2 (83)	11.5 (3)	
APKD	12.3 (52)	12.6 (11)		11.8 (57)	23.1 (6)	
Congenital hypoplastic kidneys	7.3 (31)	3.4 (3)		7.0 (34)	0.0 (0)	
FSGS	2.6 (11)	3.4 (3)		2.9 (14)	0.0 (0)	
Obstruction	2.4 (10)	4.6 (4)		2.9 (14)	0.0 (0)	
IgA nephropathy	9.9 (42)	6.9 (6)		9.5 (46)	7.7 (2)	
Pyelonephritis	5.7 (24)	8.0 (7)		5.4 (26)	19.2 (5)	
Reflux nephropathy	6.6 (28)	8.0 (7)		7.0 (34)	3.9 (1)	
Other	13.0 (55)	4.6 (4)		11.2 (54)	19.2 (5)	
Unknown	13.2 (56)	17.2 (15)		13.8 (67)	15.4 (4)	

ECD indicates expanded criteria donor; SCD: standard criteria donor; DCD: donation after circulatory death; DBD: donation after brain death; CIT: cold ischaemic time; CMV: cytomegalovirus; ICD: intracerebral haemorrhage, ICH/SAH: intracerebral haemorrhage/subarachnoid haemorrhage; APKD: adult polycystic kidney disease; FSGS: Focal segmental glomerulosclerosis.

DBD versus *DCD*

In agreement with previous research, our results demonstrate that DCD kidney transplants are comparable to DBD kidney transplants over a 5-year timeframe. However, our short-term results perhaps diverge slightly from previous published research in that our DCD graft DGF rates were not significantly worse than DBD grafts.

Table 2 – Comparison of short-term primary and surrogate outcomes between the donor groups, ECD *vs.* SCD and DCD *vs.* DBD.

Outcomes	SCD ($n = 423$)	ECD ($n = 87$)	p	DBD ($n = 484$)	DCD ($n = 26$)	p
1-year graft survival (%)	92.4	88.5	0.282	91.5	96.2	0.713
1-year patient survival (%)	97.9	97.7	1.00	97.7	100.0	1.00
Biopsy-proven acute rejection (%)	17.3	24.1	0.132	18.4	19.2	1.00
1-year creatinine [median (IQR)]	123.0 (61.0)	166.0 (94.0)	<0.001	130.0 (72.75)	121.5 (66.0)	0.372
Delayed graft function (%)	18.0	42.5	<0.001	22.5	15.4	0.476

ECD indicates expanded criteria donor; SCD: standard criteria donor; DCD: donation after circulatory death; DBD: donation after brain death.

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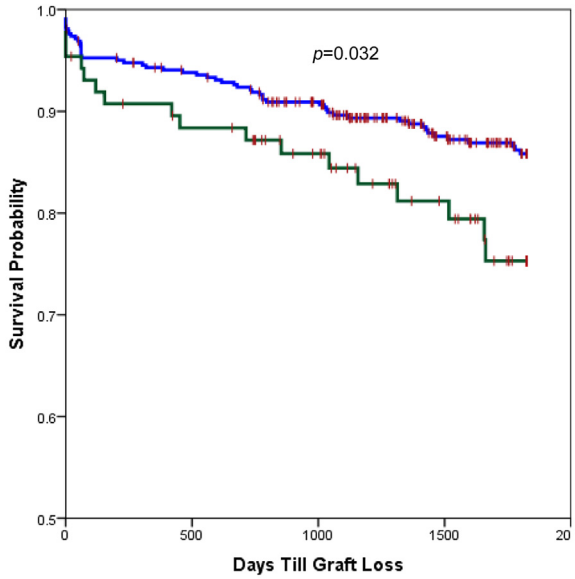
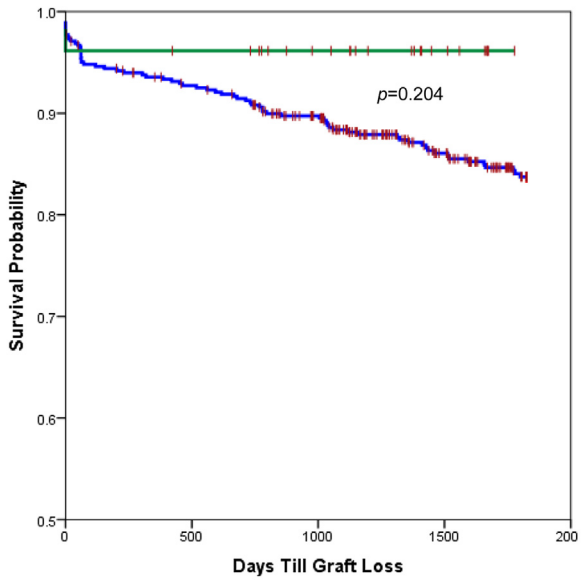


	Donor group	Number of patients	Events	Censored
	SCD	423	55	368
	ECD	87	18	69

Fig. 2 – Kaplan–Meier 5-year death-censored graft survival curves, comparing the donor groups, SCD vs. ECD.

It is thought that DCD organs are associated with a higher DGF rate due to the occurrence of warm ischaemia associated with the agonal phase of the DCD retrieval.[8–10] Nevertheless, on the clinically important outcome of 5-year death-censored graft survival, they appear to compare favourably with the traditionally optimal standard criteria DBD kidneys.[4,6,8–10] Although this discrepancy might at first appear counterintuitive, as DGF is known to predict poor long term outcome in DBD organs,[4,10,11] it is explained by the events that happen at the time of brain stem death. Irreversible brain stem injury is an extremely physiologically disturbing event that entails major haemodynamic, metabolic and immunological changes. These changes render the kidney more vulnerable to the secondary injuries that will occur during retrieval and cold storage. Conversely the DCD kidney is spared the first 'hit' of brain stem death. Although a higher DGF rate was observed in DCD kidneys, Summers D et al. noted that DGF did not affect the long-term outcome of DCD kidneys[9] and furthermore Locke[4] has noted, that when CIT was <12 h DGF rates are significantly abrogated. We speculate that the substantially shorter CIT in our DCD cohort, due to local shared allocation of DCD organs and early uptake of virtual cross matching may explain the similar rates of DGF in DBD and DCD organs.



	Donor group	Number of patients	Events	Censored
	DBD	484	72	412
	DCD	26	1	25

Fig. 3 – Kaplan–Meier 5-year death-censored graft survival curves, comparing the donor groups, DBD vs. DCD.

Implications for allocation and patient decision

DCD and ECD donors are an invaluable source of organs and our data support their expanded use.

Currently, DBD kidneys are allocated nationally, based on HLA tissue match, ABO blood group compatibility, waiting time, difference in age and distance between the donor and recipient. Priority is given to paediatric and highly sensitized patients.[12] In certain allocation systems such as the USA, patients on the waiting list, willing to accept ECD kidneys, are also identified, in order to reduce the allocation time for this category.[4,5,13] However, optimising allocation schemes is a complex balance between equity of access and utility. One weakness of the current UK system is a lack of influence for an individual's expectations and attitude to risk. This has been previously proposed (e.g. the UNOS choice system) and is not entirely impractical.[13,14] The approach of preferentially allocating ECD transplants to younger patients may be appropriate for those patients eager to avoid dialysis, however, the strategy of waiting for a demographically optimal, well matched kidney with improved expectation of long-term outcome may be preferable to others.

DCD kidneys, having been previously excluded from the national kidney allocation scheme, are now beginning to be allocated nationally. When a DCD meets the age criteria for sharing, one kidney will be retained by the local centre and the other kidney will be offered to another transplant patient in one of four predefined regions, allocated in line with the 2006 algorithm for DBD kidney allocations.[15] This would help maintain a low CIT by avoiding the complications of concurrent transplantations in one centre. It would also further improve the equity and utility of donations by offering the second kidney to a greater number of younger, highly sensitised and long waiting patients.

Weaknesses

As with all observational studies, there is always potential for statistical error due to unmeasured or unaccounted confounders (i.e. changes in immunosuppression which we did not include in the analysis). Our study was also retrospective and limited by a small DCD group. Nevertheless, it is still encouraging that the differences observed in larger registries

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are apparent at the level of the single centre with these smaller numbers.

Conclusion

Our results support the use of ECD kidney allografts. Although worse than the outcomes of SCD kidneys, the results of ECD kidney transplantations are acceptable. By placing more value on recipient age and duration on dialysis when offering ECD kidneys, these outcomes could still improve. Furthermore, as our data suggests that DCD allografts are comparable to DBD kidneys, the recent proposal to allocate DCD kidneys from younger donors nationally appears a reasonable approach provided a relatively short CIT can be maintained. In the end, a larger and more defined national allocation scheme may prove the best way to enhance the utility and equity of kidney transplants.

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High-risk donors: extending our criteria in times of organ shortage

Alexander M. Bernhardt and Hermann Reichenspurner

Purpose of review
Increasing waiting lists and declining transplant numbers due to organ shortage are a global problem that needs a multimodal approach to overcome this situation. Extending the criteria for transplantation may be one part of the solution.

Recent findings
There are political efforts to increase the donor rate and change the listing criteria and the allocation process. Recently, the cardiac allocation score was introduced enhancing the factor urgency to the allocation process. Marginal donor organs can be accepted using ex-vivo perfusion strategies. Experimental approaches, such as donation after circulatory death and xenotransplantation, need to be further developed to be applied to humans and increase the pool of available transplant organs.

Summary
Organ shortage needs new approaches to overcome the discrepancy between the number of patients on the wait list and performed heart transplantations, reduce wait list mortality and improve long-term outcomes after transplantation.

Keywords
heart transplantation, organ donation, organ shortage

INTRODUCTION

Orthotopic heart transplantation is still the only curative treatment for patients with terminal heart failure, despite significant improvements in medical or cardiac resynchronization therapy implantable cardioverter defibrillator-cardiac resynchronization therapy, mechanical circulatory support and promising experimental approaches in the field of myocardial regeneration (e.g., stem cells and tissue engineering). But, widespread use of heart transplantation has been increasingly limited by the growing discrepancy between the number of patients on the waiting list and the number of available organs. According to the international foundation Eurotransplant data, 381 patients were on the waiting list for hearts in January 2001 in Germany. In January 2011, however, there were already 952 patients on the list and the number is steadily increasing and is already 1250 in 2013 [1]. In contrast, the number of performed heart transplantations decreased from more than 550 in 1995 to 356 in 2011, and further decreasing in 2013 with only 313 performed heart transplants. In 2012, individual German liver transplant programs supposedly either manipulated the laboratory values of patients on the waiting list or hemodialyses were forged to increase the model for end-stage liver disease score. Bilirubin, creatinine and international normalized ratio levels are used to calculate this score; the higher the score the higher the expected mortality on the waiting list and thus the urgency. These irregularities led to a drop in the trust in transplant medicine, in general, within the German public. In 2012, the number of organ donations dropped by 12.8% throughout Germany compared with the previous year and even further decreased in 2013 by another 15.5% [1]. The waiting time and urgency for a patient on the waiting list has risen accordingly over the past 10 years. In Germany, a

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KEY POINTS

- Changing local transplant laws, implementing transplant coordinators in potential donor hospitals and improving donor management are important steps to increase the number of available donor hearts.
- The CAS was recently introduced and adds the expected posttransplant outcome to the determining factors urgency and waiting time.
- Ex-vivo heart perfusion for organ procurement is already in clinical use and shows promising results, potentially leading to greater utilization of marginal donor hearts.
- Donation after circulatory death and xenotransplantation are interesting approaches that still need further experimental research to be translated into clinical reality.

patient's medium waiting time on the waiting list for a heart transplant is steadily rising and has now, at the status of high urgency, reached a median of more than 60 days, with also noticeably longer waiting times up to 6–8 months for individual patients, especially for those with certain blood groups, size and weight. Whereas most of the patients were able to electively receive transplants at status T (transplantable) and only about 30% at high-urgency status in 2001, the rate of high-urgency patients receiving transplants rose to 88% in 2011 in Germany [1,2].

INCREASING OF AVAILABLE DONOR HEARTS

In 2012, the German transplant law was amended to increase organ donations. The existing 'informed consent' law was extended by an element of structural information on organ transplantation to stimulate the individual decision-making process regarding organ donation. All German citizens should regularly be given the opportunity to inform themselves on the subject of organ donation and make their own decision [2]. However, in 2013, there were only 10.6 donors per million population in Germany, which was the lowest donor rate around Eurotransplant countries [1].

Another approach to increase the number of available donors is the installation of transplant coordinators in potential organ donor hospitals. Transplant coordinators are intensive-care physicians who are specialized in identifying potential donors, caring, informing and consenting of relatives of potential donors, coordinating diagnostics of brain death and teaching transplant and organ donation-related issues within the hospitals.

Brain stem death has a variety of deleterious effects on the heart from catecholamine stress, acute subendocardial ischemia, right ventricular stretch, loss of vascular tone to inflammatory activation. Circulating proinflammatory cytokines, such as tumour necrosis factor-alpha, have a direct myocardial suppressant effect. In addition, management of the severely brain-injured patient, particularly the maintenance of perfusion pressure with noradrenaline, may worsen the situation. Filling pressures may also be affected by vigorous diuresis, and then diabetes insipidus [3]. Improved management of the donor can increase the number of available donor hearts. In a recent paper by Abuanzeh *et al.* [4▪], it was shown that substantial numbers of hearts that initially fall short of requirements can be improved to a state in which they can be used very successfully. The timing of retrieval after brain death has also an important influence on the graft function. The heart has the ability to recover from the insult of brain death, as long as the donor can be stabilized and supported. The later after brain death retrieval is undertaken, the greater the yield of suitable organs [3]. In a study comparing different time points of organ donation after brain death, a rate of only 20% of donors had hearts suitable for transplantation if the retrieval was within 24 h after brain death. This rate could be increased to more than 50% if the time span was 36 h between brain death and donation [5].

ALLOCATION

The classic model of waiting time as the determining factor of allocating hearts was enhanced by the factor urgency in 2000. In Germany, the shortage of donor organs resulted in modifying the allocation criteria to primarily grant high-urgency patients the few available organs. In 2005, these regulations were tightened again so that in the meantime the majority of patients receive a transplant while being listed in high-urgency status as described above. The increasing organ shortage, which entails longer waiting times and the fact that sicker patients are transplanted, is considered an important factor for the declining results. The criteria that account for the high-urgency status are almost the same as the risk factors for 1-year mortality. As a consequence, the expected outcome after transplantation (chances of success) has gained increasing attention both in the transplant community and the general public. Actually, next to the urgency of the transplant the chances of success are explicitly named as the second important allocation principle

in the German transplant law. Recently, allocation based on urgency and outcome is already realized for lung transplantation by the introduction of the lung allocation scores for allocation in 2011. The first experiences with the lung allocation scores are promising; therefore, a cardiac allocation score (CAS) has been developed [6▪▪]. Urgency is measured by the Seattle Heart Failure Score [7]; posttransplant survival is estimated by the index for mortality prediction after cardiac transplantation score [8]. The CAS works well for non-VAD patients; however, for VAD patients, urgency is difficult to predict because waitlist mortality is not based on heart failure-related symptoms rather on complications, such as infections, bleeding and thromboembolic complications during VAD support. Therefore, a VAD-CAS is currently developed and the CAS will be introduced in Germany within the next 12–24 months.

TRIMMING OF THE WAITING LIST

Accompanying the publication of the CAS by Smits *et al.* [6], Stevenson [9▪] wrote an editorial article about the trimming of the waiting list. She emphasized that the allocation calculus will not solve the waiting list problem unless the waiting list is trimmed to the proper size fitting to the number of realized heart transplants. This will be different for every country depending on their listing practices and donor supply. However, a consistent increase in candidate listing without increase in donor supply is unsustainable for any country. Using current data in the USA of the alleged 150 000 patients who could benefit from heart transplantation, only about 3000 are listed annually. The impact of an immediate reduction of 20% in the number of patients listed each year could be projected from 3000 to 2400. On the basis of current event rates on the list, this number would be lower enough than the number of patients removed from the list during the year to initiate a steady reduction in the carryover list size. The removal rate is, of course, primarily due to transplantation, but is also due to patients removed for listed reasons of death, which has been decreasing, or 'too sick to transplant', which has been increasing. This combined rate over the past 5 years has been approximately 8% [10]. There is an additional rate of approximately 6% of listed patients removed due to improvement, patient reluctance or other various causes. If the list additions were reduced soon to 2400, the standing list would be decreased to less than 1000 within 5 years. When there is equilibrium between the patients entering and leaving the list, there will be greater tolerance for the uncertainty around any risk score because there are likely to once again be enough hearts in time for those who need them [9▪].

CIRCULATORY DEATH DONORS

The shortage of suitable organs from brain-dead donors significantly limits cardiac transplantation. This has prompted a renewed interest in donation after circulatory death (DCD) to expand the pool of organs available for transplant. For most organs except the heart, grafts retrieved from controlled donors after DCD are used to increase the graft pools [11,12]. The results of transplantation of controlled DCD livers or kidneys are encouraging [13,14]. However, the hypoxemic cardiac arrest exposes the heart to a significant period of global ischemia prior to organ procurement. Subsequent reperfusion initiates a complex cascade of events that cause intracellular Ca^{2+} overload and propagate myocyte death through the development of hypercontracture, activation of calcium-dependent proteases, generation of reactive oxygen species, activation of the mitochondrial permeability transition pore and initiation of apoptotic pathways [15–17]. Until now, DCD heart transplantation has not reached clinical practice because of concerns regarding the potential deleterious effects of warm ischemia and reperfusion injury occurring during DCD procurement on heart graft functionality and viability [18,19] Therefore, the establishment of evidence-based guidelines for DCD heart resuscitation is essential before clinical application can occur [20] and several concerns, especially about the functionality of such grafts, still need to be addressed [19]. Studies on animal models showed promising results after 30 min of normothermic ischemia [21–24]. A retrospective single-center study from Belgium reviewed their local donor database from 2006 to 2011, and screened the complete controlled DCD donor population for potential heart donors, using the same criteria as for donation after brain death (DBD) heart transplantation. Acceptable donation warm ischemic time was limited to 30 min. During this period, 177 DBD and 70 DCD were performed. From the 177 DBD, a total of 70 (39.5%) hearts were procured and transplanted. Of the 70 DCD, eight (11%) donors fulfilled the criteria for heart procurement with a donation warm ischemic time of under 30 min. Within the same period, 82 patients were newly listed for heart transplantation, of which 53 were transplanted, 20 died or were unlisted and nine were waiting. It could be estimated that 11% of the DCD might be heart donors, representing a 15% increase in heart

transplant activity, as well as potential reduction in the deaths on the waiting list by 40% [19].

EX-VIVO HEART PERFUSION

Historically, conventional cold, static storage is used for heart harvesting. Although numbers of available donors decrease, marginal organs and longer distances tend to be accepted for heart transplantation. However, with older donor age, other donor-specific risk factors and longer cold ischemic times the risk for primary graft failure and 1-year mortality increase [25]. A new technology is currently being evaluated in which normothermic perfusion provides continuous warm blood flow to the beating donor heart during transportation [26,27]. This switch from conventional cold, static storage may not only decrease reperfusion injury and primary graft dysfunction but may also allow greater utilization of available organs [27]. Recently, the results from the PROCEED II trial were presented at the annual meeting of the International Society for Heart and Lung Transplantation (ISHLT) in San Diego, California, USA. The PROCEED II trial is an international United States FDA pivotal trial to assess the clinical efficacy and safety of the organ care system (OCS) heart technology for heart transplantation. It is a prospective, randomized multicenter trial comparing the safety and efficacy of the OCS using warm blood perfusion to cold storage (SOC) of donor hearts. The primary endpoint is the 30-day patient and graft survival. The secondary endpoints were the incidence of cardiac-related adverse events and biopsy-proven rejections. One hundred and twenty-eight patients were enrolled, 62 randomized to the OCS arm and 66 to the SOC arm. Thirty-day patient and graft survival rates were 96% in the SOC arm and 93% in the OCS arm ($P = 0.04$). The incidence of biopsy-proven ISHLT grade 2R and 3R rejection was 14 vs. 18%, respectively ($P = 0.63$). There is an ongoing trial in Germany in which the OCS is compared to SOC for extended criteria donor hearts (e.g., mild-to-moderate hypertrophy, inotrope-dependent donor, coronary artery disease). To date, preliminary results are not available. However, the switch from conventional cold, static storage may not only increase donor organ retrieval distances, but also allow a greater utilization of marginal donor hearts [27].

XENOTRANSPLANTATION

Several alternatives have been suggested to overcome the grave shortage of organs. One possible solution could be clinical xenotransplantation using nonhuman primates as concordant donors and triple drug immunosuppression [28]. However, ethical and logistical considerations preclude this. Apes are highly problematic from an ethical point of view; other nonhuman primates are too small and their growth is too slow. In contrast, discordant species, for example pigs, have been bred for a long time; so ethical objections should be minor. The main disadvantages arise from genetic disparities between pigs and primates resulting from evolutionary divergence, which can affect important protein–protein and other biochemical interactions [29▪]. A few research groups worldwide are focusing on animal research on xenotransplantation. Before this approach can be applied to humans, some hurdles need to be taken and problems need to be solved.

After opening of the aortic clamp primate blood containing preformed antibodies perfuse the porcine coronary arteries in which they activate complement reactions leading to formation of the membrane attack complex and destruction of graft vasculature. Subsequent interstitial hemorrhage and edema lead to graft failure, which is the histological manifestation of hyperacute rejection [29▪].

If this first phase can be circumvented, the next obstacle is to overcome the delayed humoral response developing within 3 weeks after transplantation. During the same time, the effects of protein incompatibilities within the coagulation system also become evident, leading to occlusive thrombotic microangiopathy in transplanted porcine organs within weeks postoperatively. Over the longer term, cellular rejection signs are similar to those observed after allogeneic procedures in humans.

To overcome the early immunologic hurdles, genetically modified pigs were developed to minimize or even abolish hyperacute and delayed humoral rejection reactions. Modifications include genetic knock-out of α-Gal epitopes, a sugar epitope present on the surface of all porcine cells. α-Gal is the most important porcine xeno-antigen and initiates hyperacute rejection. Modifications also include hyperexpression of the complement regulators CD46, CD55 and CD59 to block complement reactions initiated by secondary induced antibodies and expression of human thrombomodulin to overcome the cross-specific protein incompatibility ensuring Protein C activation and anticoagulation.

Xenogeneic heart transplantation will need additional immunosuppressive strategies. A proposed immunosuppressive regime could be that the bone marrow and therefore antibody production is suppressed before transplantation using anti-CD20 to destroy B-cells, bortezomib in combination with cortisone to destroy plasma cells and cyclophosphamide

[29▪,30]. Extracorporeal immunoadsorption is used to remove preexisting antibodies and any antibodies formed postoperatively. Maintenance immunosuppression is provided by tacrolimus, mycophenolate and cortisone as for allogeneic transplants antithymocyte globulin induction therapy is also applied [29▪].

Initial clinic xenogeneic heart transplantations may, therefore, provide a solution for heart failure patients with severe right ventricular dysfunction, coagulation disorders or difficult anatomical preconditions such as small left ventricles or significant aortic incompetence. A high antibody titer against the human leukocyte antigen system will be an early indication as the swine leukocyte antigen system does not cross-react [31,32].

The group from Munich, Germany, has achieved so far 50 days of survival in a genetically modified animal model with the unique thoracic heterotopic heart transplantation technique developed by Barnard and Losman [33,34], using a dedicated immunosuppressive treatment described above [29▪].

Before the step into the clinic can be made, the guidelines of the Xenotransplantation ISHLT Advisory Board [35] need to be followed achieving good graft function for a minimum of 3 months in a life-supporting position in at least 60% of consecutive experiments. To date, this has not been achieved so far. Future results of cardiac xenotransplantation must be compared with recent 6-month 60% patient survival after implantation of biventricular continuous-flow mechanical assist devices and, of course, the near 90% survival of those patients without right ventricle dysfunction, in whom simple left ventricular assists work well [29▪,36].

CONCLUSION

Increasing waiting lists and declining transplant numbers due to organ shortage are a global problem that needs a multimodal approach to overcome this situation. This can be done by increasing the donor rate, changing our listing criteria and allocation process. Marginal donors can be accepted using ex-vivo perfusion strategies. Experimental approaches, such as DCD and xenotransplantation, need to be further developed to be applied to humans and increase the pool of available transplant organs.

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Conflicts of interest

The authors have no conflicts of interest.

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Clinical Transplantation

The policy of placing older donors into older recipients: is it worth the risk?

Tehrani YS, Yu Z, Luu M, Liou F, Rafiei M, Hamilton M, Kobashigawa JA. The policy of placing older donors into older recipients: is it worth the risk?

Abstract: Background: To expand the donor pool, older donors (≥50 yr) are frequently used in older recipients (≥60 yr). Older recipients and those receiving older donor hearts have independently displayed decreased post-transplant survival. However, outcomes in older patients receiving older donor hearts are contentious.
Methods: Eight hundred and seventy-nine heart transplant patients between 2000 and 2010 were analyzed, excluding patients with donor coronary artery disease. From 380 patients ≥60 yr, 327 patients with donors <50 yr old were compared with 53 patients with donors ≥50 yr old for: five-yr actuarial survival, freedom from cardiac allograft vasculopathy (CAV: stenosis ≥30%), non-fatal major adverse cardiac events (NF-MACE: MI, CHF, stroke, need for pacemaker/ICD), one-yr freedom from any treated rejection.
Results: The older vs. younger donor group demonstrated significantly lower five-yr survival (57% vs. 85%, $p < 0.001$) and freedom from CAV (83% vs. 92%, $p = 0.03$). No difference was observed in five-yr freedom from NF-MACE and one-yr freedom from any treated rejection. Multivariate analysis found donor age ≥50 to be an independent risk factor for death (HR 1.8, CI 1.1–2.9, $p = 0.008$) and CAV (HR 1.9, CI 1.2–2.9, $p = 0.004$).
Conclusions: Use of older donors (≥50 yr) in older recipients (≥60 yr) results in lower five-yr survival and freedom from CAV. Caution is required in these cases. Larger studies are warranted to confirm findings.

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Key words: cardiac allograft vasculopathy – cardiac transplantation – older donors – older recipients – outcomes – rejection – survival

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The treatment of advanced heart failure is continuously undergoing improvements, including advances in mechanical support and medical therapies. However, the widely accepted treatment of choice for advanced heart disease remains cardiac transplantation.

Donor availability has been the key limiting factor to heart transplant. According to the statistics of the Organ Procurement and Transplantation Network as of December 6, 2013, there were 3689 heart transplant candidates on the waiting list. However, between 2010 and 2012, the average annual number of heart transplants performed was 2344.

Advanced recipient age is among the various contraindications for cardiac transplantation. The reduced ability to recover from major cardiac surgery, the presence of increasing comorbidities with aging (1), and the impaired capacity to tolerate the complications associated with chronic immunosuppression are some reasons for the hesitance in providing older patients with cardiac transplantation. The ISHLT registry has documented that increasing recipient age is a risk factor for mortality after cardiac transplantation (2).

Undoubtedly, there are not enough donors available to accommodate even younger patients requiring cardiac transplantation (3). As a result, the criteria for potential donors have been expanded, although finding an acceptable heart donor is a more selective process than that of other organs (4–8).

Over the years, the donor pool has been expanded to include older donors. In 1990, the median age of heart donors was 27 yr old. Between 1990 and 1999, the median age of heart donors rose to 31 yr old, due in part to the utilization of an alternate list by many heart transplant programs. This alternate list supported the use of older donors for older recipients (older than 60 yr) (9). Of concern is the observation from the ISHLT registry that increasing donor age is a risk factor

for mortality after cardiac transplantation (2). However, the outcomes of utilizing older donors for older recipients have not been firmly established. This study examines whether older patients receiving hearts from older donors have acceptable outcomes after heart transplantation in the current era.

Methods

Between 2000 and 2010, we evaluated 879 heart transplant patients from a single center, excluding patients with known donor coronary artery disease. Of those 879 patients, there were 380 patients who were ≥60 yr old at the time of heart transplant.

This cohort of patients was stratified into two groups: patients with donors <50 yr of age (n = 327) and patients with donors ≥50 yr of age (n = 53). Both groups of patients were assessed for outcomes including five-yr actuarial survival, five-yr freedom from cardiac allograft vasculopathy (CAV, defined as any epicardial vessel with ≥30% angiographic stenosis), five-yr freedom from non-fatal major adverse cardiac events (NF-MACE, defined as development of myocardial infarction, congestive heart failure, stroke, need for pacemaker/implantable cardioverter-defibrillator, and percutaneous cardiac intervention) and one-yr freedom from any-treated rejection. Treated rejection was defined as any instance where endomyocardial biopsy indicated rejection (of any ISHLT grade) and/or the clinical diagnosis of heart allograft rejection was made, and the patient received high dose corticosteroids (either intravenous or oral), and/or anti-thymocyte globulin, and/or intra-venous immunoglobulin as treatment. The patients had been monitored for rejection in the following ways: In the first month post-transplant, they would undergo twice-weekly visits: one clinic/laboratory visit, consisting of full clinical evaluation and blood work, and one biopsy visit. In the second month, the patient would undergo both clinic/laboratory and biopsy visits every other week. In months three–six, monthly biopsy visits occurred. In months six–12, biopsy visits occurred every two months. If clinically indicated (e.g., clinical signs or symptoms of heart failure), patients would undergo biopsy and evaluation outside of scheduled visits.

Normally distributed continuous variables were compared across two groups using the independent samples *t*-test and were reported as mean ± standard deviation. Categorical variables were summarized by frequency and percent. Outcome measures were compared using a Kaplan–Meier curve with log rank statistics for significant differences. Multivariate analyses were conducted using Cox proportional hazard model to identify the risk factors for worse outcomes. Univariate analyses were conducted in SPSS version 18.0 (SPSS, Chicago, IL, USA). Multivariate analysis was performed using Stata version 8.0 (College Station, TX, USA). A p-value < 0.05 was considered significant. Institutional review board (IRB) approval was obtained prior to commencement of the study.

Results

Baseline data for the two groups are presented in Table 1. The demographics between the two groups were similar except that the mean recipient age for the older donor group was significantly higher than for the younger donor group (67 ± 4 vs. 65 ± 4 yr, $p < 0.001$). Additionally, there were proportionally less patients with Status 1A in the older donor group (28% vs. 40%, $p = 0.07$), although this was not significant. As expected, the mean donor age for donors ≥50 yr old was significantly higher than for donors <50 yr old (55 ± 4 vs. 30 ± 10 yr, $p < 0.001$).

Five-yr actuarial survival was significantly lower in the older donor group compared with the younger donor group (57% vs. 85%, $p < 0.001$; Table 2, Fig. 1). Investigation into cause of death revealed no difference between groups among

Table 1. Baseline demographics between the two groups

Demographic	Donor age <50 (n = 327)	Donor age ≥50 (n = 53)	p-value
Recipient age, mean yr ± SD	65 ± 4	67 ± 4	<0.001
Donor age, mean yr ± SD	30 ± 10	55 ± 4	<0.001
% Female	18	16	0.65
% Status 1 at listing	40	28	0.07
BMI, mean ± SD	25 ± 4	25 ± 4	0.99
Height (in), mean inches ± SD	68 ± 2	68 ± 4	0.99
Weight (lbs), mean lbs ± SD	166 ± 31	164 ± 30	0.63
Ischemic time, mean min ± SD	199 ± 76	205 ± 73	0.56
Primary reason for transplant, coronary artery disease as underlying diagnosis (%)	64	61	0.64
CMV mismatch (%)	22	18	0.55
Diabetes mellitus (%)	28	35	0.31
Treated hypertension (%)	43	44	0.92
Insertion of ventricular assist device (%)	10	9	0.87
Pre-transplant PRA ≥10% (%)	16	18	0.58

CMV, cytomegalovirus; PRA, panel reactive antibody; BMI, body mass index.

Table 2. Post-transplant outcomes

Outcomes	Donor age <50 (n = 327) (%)	Donor age ≥50 (n = 53) (%)	p-value
Five-yr actuarial survival	85	57	<0.001
Five-yr freedom from CAV	92	83	0.03
Five-yr freedom from NF-MACE	90	89	0.80
One-yr freedom from any-treated rejection	90	90	0.96

CAV, cardiac allograft vasculopathy; NF-MACE, non-fatal major adverse cardiac events.

various categories (Table 3). The older donor group compared with the younger donor group endured a significantly lower five-yr freedom from CAV (83% vs. 92%, p = 0.03; Fig. 2).

Cox proportional hazard model revealed that donor age ≥50 to be an independent risk factor for death (HR 1.8, CI 1.1–2.9, p = 0.008) and CAV (HR 1.9, CI 1.2–2.9, p = 0.004) during the five-yr follow up.

The two groups demonstrated no significant difference in five-yr freedom from NF-MACE or in one-yr freedom from any-treated rejection. There was no significant difference between groups by incidence of NF-MACE, or cause of treated rejection. A break-down of the incidences of NF-MACE can be found in Table 4. A break-down of the incidences of heart allograft rejection can be found in Table 5.

Table 3. Causes of death

Causes of death	Donor age <50 (n = 48) (%)	Donor age ≥50 (n = 23) (%)	p-value
Cardiac death	19	9	0.48
Rejection	6	22	0.10
Malignancy	13	0	0.17
Multi-organ failure	6	13	0.38
Infection	21	13	0.60
Stroke	4	9	0.53
Pulmonary embolism	4	0	>0.99
Respiratory failure	2	4	0.55
Liver failure	4	0	>0.99
Kidney failure	6	4	>0.99
Motor vehicle accident	2	0	>0.99
Unknown	13	26	0.18

Discussion

Outcomes regarding the usage of older donor hearts specifically in older recipients are controversial (8, 10). However, in an era of increasing recipient age and marginal heart usage, knowledge of long-term outcomes in this specific cohort is important. The results of this single-center retrospective study indicate that older recipients (≥60 yr) receiving their heart transplants from older donors (≥50 yr) will have overall lower five-yr survival and are at a significantly greater risk for acquiring CAV, defined as ≥30% angiographic stenosis. However, older recipients receiving older donor hearts did not demonstrate a higher rate of

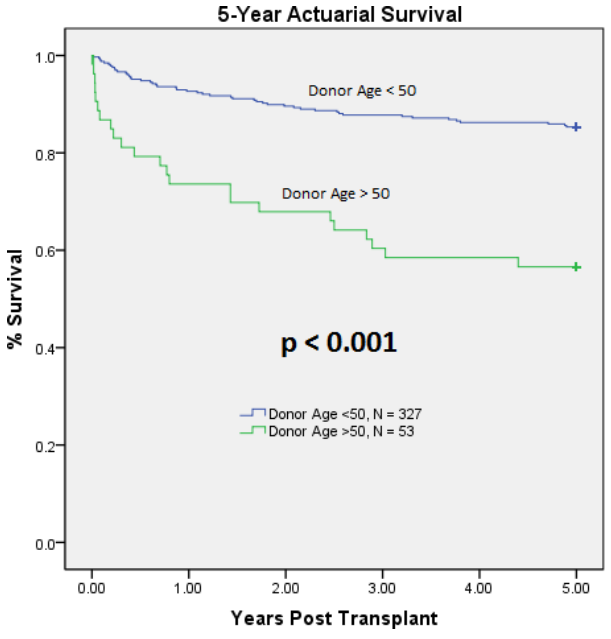

Fig. 1. Comparison of five-yr actuarial survival.

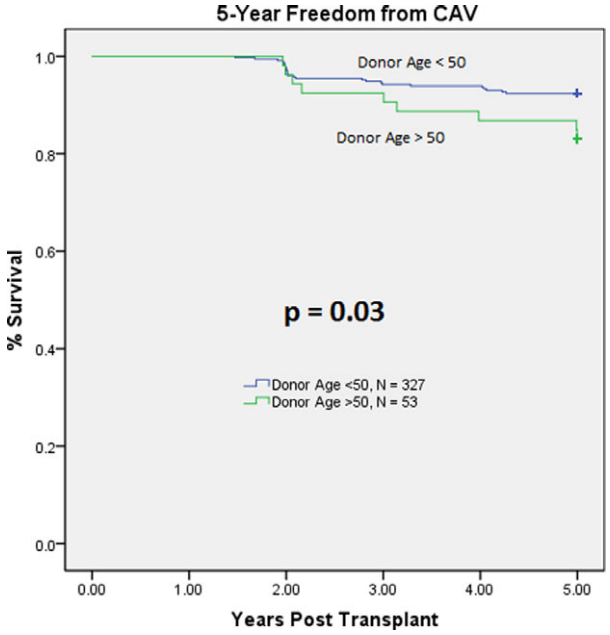

Fig. 2. Comparison of five-yr freedom from cardiac allograft vasculopathy (CAV).

Table 4. Break-down of incidences of NF-MACE

NF-MACE incidence	Donor age <50 (n = 32) (%)	Donor age ≥50 (n = 6) (%)	p-value
Myocardial infarction	2/32 (6)	0	>0.99
New congestive heart failure	13/32 (41)	4/6 (67)	0.38
Percutaneous cardiac intervention	4/32 (13)	2/6 (33)	0.23
Pacemaker/implantable cardioverter-defibrillator	8/32 (25)	0	0.30
Stroke	6/32 (19)	0	0.56

NF-MACE, non-fatal major adverse cardiac events.

Table 5. Break-down of incidences of rejection

Type of allograft rejection	Donor age <50 (n = 32) (%)	Donor age ≥50 (n = 5) (%)	p-value
Treated acute cellular rejection (ACR)[a]	10/32 (31)	1/5 (20)	>0.99
ISHLT 1R	0/32 (0)	0/5 (0)	
ISHLT 2R	7/32 (22)	1/5 (20)	>0.99
ISHLT 3R	3/32 (9)	0/5 (0)	0.46
Treated antibody-mediated rejection (AMR)[b]	18/32 (56)	4/5 (80)	0.63
Treated mixed rejection (ACR[a] and AMR[b])	3/32 (9)	0	0.46
ISHLT 1R with AMR	0/32 (0)		
ISHLT 2R with AMR	2/32 (6)		>0.99
ISHLT 3R with AMR	1/32 (3)		>0.99
Hemodynamic compromise biopsy-negative rejection	1/32 (3)	0	>0.99

[a]Includes diagnoses prior to 2004 according to former 1990 nomenclature, with the following equivalents according to ISHLT guidelines: grade 1R in new 2004 nomenclature = grade 1A, 1B, 2; grade 2R = 3A; grade 3R = 3B, 4.
[b]AMR biopsy diagnosis made prior to pAMR classification in 2011, hence not available.

treated rejection or development of NF-MACE. Importantly, all donor and recipient characteristics (other than donor age) were not significantly different between the two study groups, reducing the potential for bias.

The reduced five-yr actuarial survival seen in our study can be compared with previous work on older donor age and older recipient age as independent factors. In our study, there is a noticeably higher rate of death in the older donor group in the initial three months, after which the rate of death is roughly similar to the younger donor group. This is similar to trends seen in previous work by Gupta et al. and Lietz et al., which analyzed survival in those receiving older donors (using a threshold of ≥50 and ≥40 yr, respectively), although not specifically in older recipients (7, 11). While recipient-related factors cannot be ruled out as a cause, there is little difference in recipient demographics between study groups (age, proportion of status 1A, VAD status, sensitized, etc.) and no predominant cause of death in either group. Thus, one must consider the possibility that older donor hearts possess intrinsic attributes that predispose their recipients to poor early survival; it has been postulated that the increased likelihood of transmitting hypertensive disease and degenerative valvular disease, as well as poor protection against catecholamine release during brain death, may be reasons (12). The notion of poor older donor group survival is also supported by data from the ISHLT registry, including over 80 000 transplant recipients from 1982 to 2011, which demonstrate significantly lower overall survival in patients receiving older donor hearts (>60), compared with donors aged 40–59 and 11–39 ($p < 0.05$) (2). Further multicenter analyses concur: Bourge et al. (13) demonstrated donor age >60 to be a risk factor ($p = 0.001$) for worse one-yr survival, and Pierson et al. (14) of 8925 patients also showed that older donor age (>44) was associated with significantly increased risk of two-yr mortality (odds ratio 2.0, $p < 0.02$). A retrospective single-center analysis by Del Rizzo et al. (15) of 372 patients found the highest risk ratio of lower one-yr survival to be in patients receiving older donor hearts (risk ratio = 2.20; $p = 0.004$); in the context of advanced recipient age, this study also found it to increase the risk of mortality among other factors. However, we accept that not all studies concur on the topic: Several smaller single-center retrospective analyses have found no correlation between increased donor age and reduced survival (16–18); this may be a function of their small numbers.

With regard to the older recipients (≥60 yr) in our study, it is already established that they fare less well than younger ones; ISHLT registry data demonstrate five-yr actuarial survival among a cohort of 18 896 to be significantly lower in recipients 60–69 yr old, compared with those in the 18–39 ($p = 0.02$) and 40–59 ($p = 0.001$) age groups (2). Kilic et al. (8) demonstrated multivariate analysis of 5000 patients that both younger donor age and younger recipient age to be independently associated with improved five-yr survival. Further retrospective analyses by Peraira et al. and Marelli et al., defining older recipients as those older than 60 and 62, respectively, found a significantly lower (albeit acceptable) rate of survival for the older groups (10, 19). However, as all patients in our study are older recipients, we cannot attribute any differences between study groups to this. Indeed, the rate of five-yr survival in the older donor group

in our study (57%) is comparable to that of other retrospective studies which use older donors (≥50 yr) in younger recipient populations, with survival ranging from 48.3% to 55% (11, 16, 17). One might thus infer that when older donors are used, the age of the recipients does not affect survival.

Our study also demonstrated significantly lower five-yr freedom from CAV in the older donor group. Notably, similar findings have been found from previous multicenter analyzes of older donors, regardless of recipient age: ISHLT registry data show a direct positive correlation between the hazard ratio (HR) of developing CAV within 5 yr and increasing donor age ($p < 0.0001$); a HR of 1.5 is seen at donor age 40, compared with 2.6 if the donor age is 60 (2). In addition, an analysis of the United Network for Organ Sharing (UNOS) heart transplant database from August 1987 to May 2008 by Nagji et al. (20) demonstrated that older donor age (>50 yr) independently yielded higher risk of CAV development compared with younger donor age (0–19.9 yr; $p < 0.01$). In part, these results may be due to increased pre-existing atherosclerosis in the older donor heart (12). In addition, while increased rejection has been proposed as a cause for increased CAV (21), there was no difference between our study groups with regards to incidence and frequency of rejection.

It is interesting that despite increased CAV and lower survival in the older donor group, there was no significant difference in NF-MACE and one-yr freedom from treated rejection. There are less data in the literature concerning these endpoints. While multiple analyses have demonstrated a lower risk of rejection in older compared with younger recipients (independent of donor age), possibly due to reduced T-cell immunity in these older patients (10), both groups in our study consisted of older recipients. This may explain the relatively low proportion of acute cellular rejection episodes (and thus high proportion of antibody-mediated rejection) among patients who displayed rejection. As Gupta et al. and Kobashigawa et al. have shown by multivariate analysis, older donor age has also been demonstrated to correlate with a lower risk of rejection (11, 22). Based on these studies, one might expect greater freedom from rejection in the older donor group, although this did not materialize. Again, this is likely due to the small numbers seen in the older donor group, and there are insufficient past data on the topic. With regards to NF-MACE, new congestive heart failure was the predominant incidence in both groups. Unfortunately, there are scant data on NF-MACE incidence and older donor hearts, and it is difficult to place our findings in the context of previous data. Although Blanche et al. (17) demonstrated numerically more coronary interventions in younger donors compared with older donors, their sample size was insufficient to draw conclusions. Regarding older recipients (≥60 yr) and NF-MACE, multivariate analysis of the UNOS database demonstrated that there is no significant increase in post-operative stroke (1). Certainly, more research is needed on the effect of donor age on NF-MACE.

The concept of transplanting an older donor heart into an older recipient is not novel. As mentioned previously, the development of an alternate list strategy in the modern era has facilitated this. Many of these donor hearts would be discarded if not used in these older patients. While survival in the older donor group (57% at five yr) may not be comparable to those who received younger donor hearts (85%), the patients who received older donor hearts have still demonstrated acceptable survival, in contrast to the limited life expectancy in end-stage heart failure waitlist patients. A relative risk analysis performed by Bennett et al. (23) demonstrated that after 64 d, patients receiving donor hearts >50 yr of age possessed a distinct survival advantage compared with those on the waiting list.

The results of the study must be interpreted in the context of various limitations. Notably, the data are heavily skewed toward younger donors, with limited numbers in the older donor group (327 vs. 53). Realistically, this is unavoidable due to current heart transplantation practices, but raises the possibility that our findings reflect a weak power of analysis; a study involving a larger cohort would be essential to confirm our findings. In addition, the study is limited by its retrospective nature, and hence, lacks control of all possible confounders. Of note, the mean recipient age of the younger donor group was statistically lower than in the older donor group ($p < 0.001$), potentially biasing results, as younger patients might reasonably be expected to fare better. However, the difference between a 65 and 67 yr old, while statistically significant due to the large number of patients in the younger donor group, is not felt to be clinically significant.

In conclusion, our study indicates that the use of donor hearts aged 50 yr and older for recipients aged 60 yr and older compared with younger donor hearts in the same older recipients results in lower five-yr survival and lower freedom from CAV. Careful consideration should be utilized when selecting older donors for older recipients. However, accepting an older donor (which would

not be used otherwise) for an older recipient presents them with a second chance at life instead of having limited life expectancy with end-stage heart disease. A study involving a larger cohort is warranted.

Authors' contributions

Yonah S. Tehrani: designed/performed study, analyzed data, wrote the paper; Zhe Yu: wrote the paper, analyzed data; Minh Luu: analyzed data, wrote the paper; Frank Liou: collected/analyzed data; Matthew Rafiei: collected/analyzed data; Michele Hamilton: designed/performed the study; Jon A. Kobashigawa: designed/performed the study, approved the paper.

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Utilization of Advanced-Age Donors in Renal Transplantation

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ABSTRACT

The shortage of organ availability in recent years has made it necessary to use grafts from advanced-aged donors to maintain the rate of renal transplantation in our country. The objective of this study was to evaluate the graft function and patient survival using kidneys from deceased donors of over 65 year of age. From 2005 until 2010, we compared the outcomes of patients who received grafts from donors over 65 years old vs less than 65 years. We observed no significant difference in sex, time on dialysis, or cold ischemia time between the groups. As expected the recipient age was significantly different. For the analysis of survival, we used the Tablecloth-Haenzel test and the Kaplan-Meier survival estimator. Actuarial survivals at 3 years after transplantation showed 84.8% among patients transplanted with kidneys from donors over 65 years old versus 97.5% in the control group. The graft survival was 78.8% among expanded criteria versus 86.85% in the control group. When we analyzed graft survival using an "exitus-censured" analysis, we obtained graft survivals of 89.1% in the expanded criteria kidney group versus 88.6% among the controls. We concluded that the use of kidney from donors over 65 years of age allows us to increase the rate of renal transplantation to about 15 to 20 per million population, with good graft and patient survivals provided that the protocol for expanded criteria organs ensured proper macroscopic and microscopic evaluation of the organ for transplantation.

THE INCREASING SHORTAGE of young donors with greater demand for transplantation has made it necessary to annually increase the number of kidneys from deceased individuals over 65 years of age[1–3] to maintain our current rate of these procedures. In recent years, there has been a change in the profile of donors that can be attributed to alterations in the causes of death. In the 1980s, the main cause was head trauma, especially from traffic accidents. At present, cerebrovascular disease with brain death is the major cause for donation,[4] which occurs mainly in elderly patients with comorbidities.[5] This evolution has led to an inversion, in terms of donor age: in 1986 it was 25 years and in 2010, 60 years. This is also reflected in the percentage of elderly donors that we see today, namely 51% over 65 years old, in 2010 with 42% over 70 years. Another reason that has led to the use of elderly donors is the increasing demand by renal transplant recipients who are currently over 65 years of age. The benefits analysis of a policy of "old for old" has suggested that these patients will gain from expanded criteria organs, reducing their waiting list time.[6] Improved surgical techniques and new immunosuppressants have resulted in inclusion of patients who had been until recently rejected due to age and concomitant diseases.[7] In the early 1990s the our percentage of patients over 60 years of age on the transplant waiting list was 16.2%; in 2001 it rose to 31.2% and since then, due to the use of expanded criteria grafts, it has stabilized at 29.1% in 2010.[8]

The objective of this study was to assess the impact of utilization of kidneys from deceased donors over 65 years of age on graft and recipient survivals and of its impact to increase the transplantation rate.

METHODS

We analyzed all of the patients transplanted in our hospital from 2005 to 2010, comparing the two groups who received a graft from a deceased donor over versus less than 65 years of age. The groups showed no significant difference regarding sex, as well as dialysis and cold ischemia time. The analysis showed statistically significant

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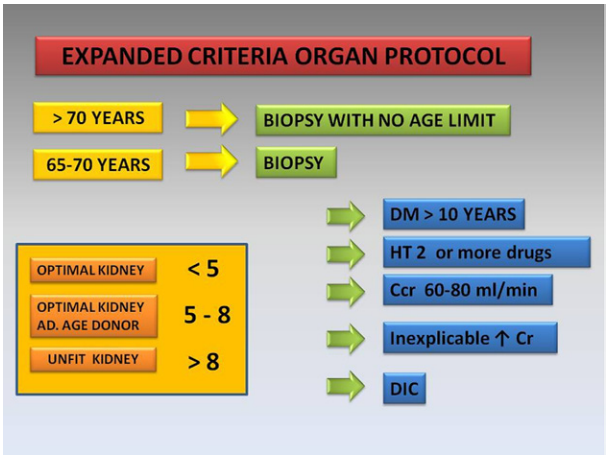

Fig 1. Expanded criteria organ protocol.

differences in the age of the recipients, been significantly higher in the group of patients transplanted with grafts from donors over 65 years of age (age> ± 6.85 65:65.35 vs age> 65: 47.46 ± 15.76). This is explained by the "old to old" policy recommended for expanded criteria organ transplantation, our hospital wherein organs are grafted from donors to recipients of similar ages.

The "expanded donor protocol" employs microscopic and macroscopic assessments of the graft to reject organs. Macroscopic lesions are associated with poor perfusion, and no recovery after perfusions, we discard grafts with severe or irreparable vascular or excretory system lesions. Biopsies are performed on all kidneys from patients over 70 years of age and those between 65 and 70 years with comorbidities such as diabetes mellitus with over 10 years' evolution, hypertension on two or more drugs, creatinine clearances below 60 to 80 mL/min, increased serum creatinine values, or disseminated intravascular coagulation (Fig 1). Paraffin-embedded biopsies use a microwave oven with controlled temperature and power. The biopsy assesses the presence and severity of lesions in the glomerulus, vascular tree, and tubulointerstitium, assigning them a score of 0 to 3 depending on severity. We considered grafts with a score of less than 5 optimal for transplantation; 5 and 8, suitable for an elderly recipient; and greater than 8 for discard as unfit for transplantation.

To analyze differences between survivals in both groups, we used Tablecloth-Haenzel as well as Kaplan-Meier survival estimator tests. We examined actuarial recipient and graft survivals at 3 years after transplantation.

RESULTS

Among 375 kidneys extracted from donors older than 65 years between 2005 and 2010, 37.6% (n = 141) were

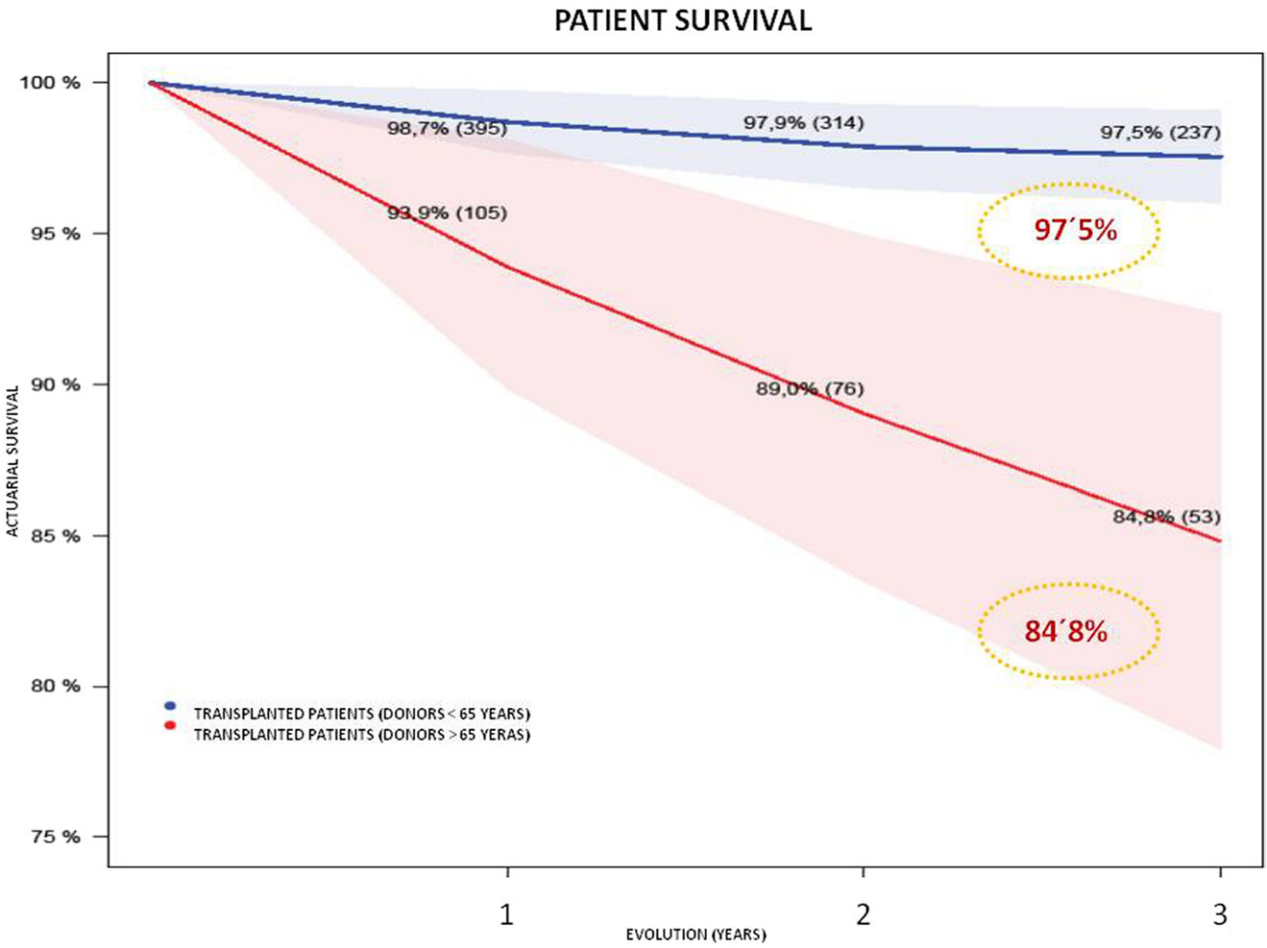

Fig 2. Three-year survival of patients according to donor age.

discarded, due to macroscopic (61.7%; $n = 87$) or microscopic criteria (38.3%; $n = 54$). We transplanted 62.4% ($n = 234$) of them. Biopsies of 156 (41%) organs were performed with a resulting evaluation as "fit" (65%) or not for transplantation thus rejecting 35% of the total kidneys. If we analyze only kidneys from donors older than 70 years ($n = 244$), 47.9%; ($n = 117$) were nonviable including 60.7% due to macroscopic and 39.3%, microscopic criteria. We performed 127 transplantations that represented 52.1% of all kidneys from donors older than 70 years.

Analyzing actuarial patient survival at 3 years posttransplantations, subjects transplanted with a cadaveric graft from a donor less than 65 years old showed a survival rate of 97.5% versus 84.8% for those from a donor over 65 years, a significant difference (Fig 2). The actuarial 3-year graft survival based upon the age of the donor also showed a significant difference: of 86.8% versus 78.8% respectively (Fig 3). The major cause of graft loss among elderly patients was the decease of the recipients for other causes with no direct relation with the transplant or graft function. If we analyze graft survival by donor age but with an "exitus-censored" analysis, that is, ruling out patients who lost the graft for causes independent of the transplantation, there was no significant difference between the groups, namely 89.1% versus 88.6% (Fig 4).

DISCUSSION

The current growing shortage of young donors and increasing supply of elderly grafts is mainly due to a change in the cause of death.[1–3] Stroke is now the major cause of donor death, which mostly occurs among elderly patients with comorbidities. Due to improvements in surgical techniques and better immunosuppressive drugs, there is an increasing demand for kidney transplantation by elderly patients who previously were denied this possibility. The static or even declining donation rates in our country, which we want to maintain above 40 per million population, requires the use of an more kidneys from elderly donors.

We sought to analyze whether these grafts showed worse survival in the short to medium term. We observed that a good protocol for expanded criteria donors can be implemented to identify organs likely to experience worse viability. There was no significant difference in terms of graft survival between grafts from donors older versus younger than 65 years.

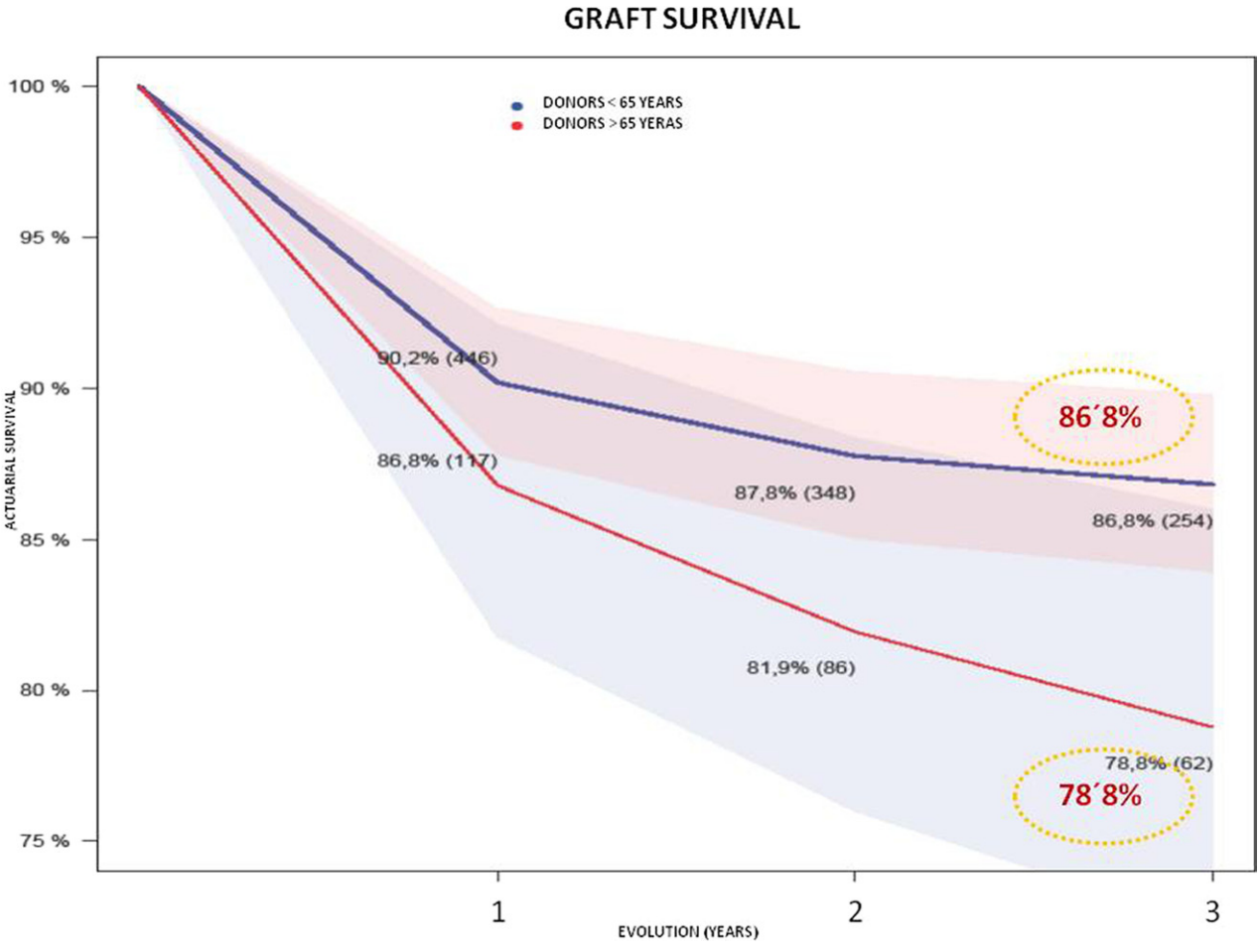

Fig 3. Three-year actuarial survival of grafts according to donor age.

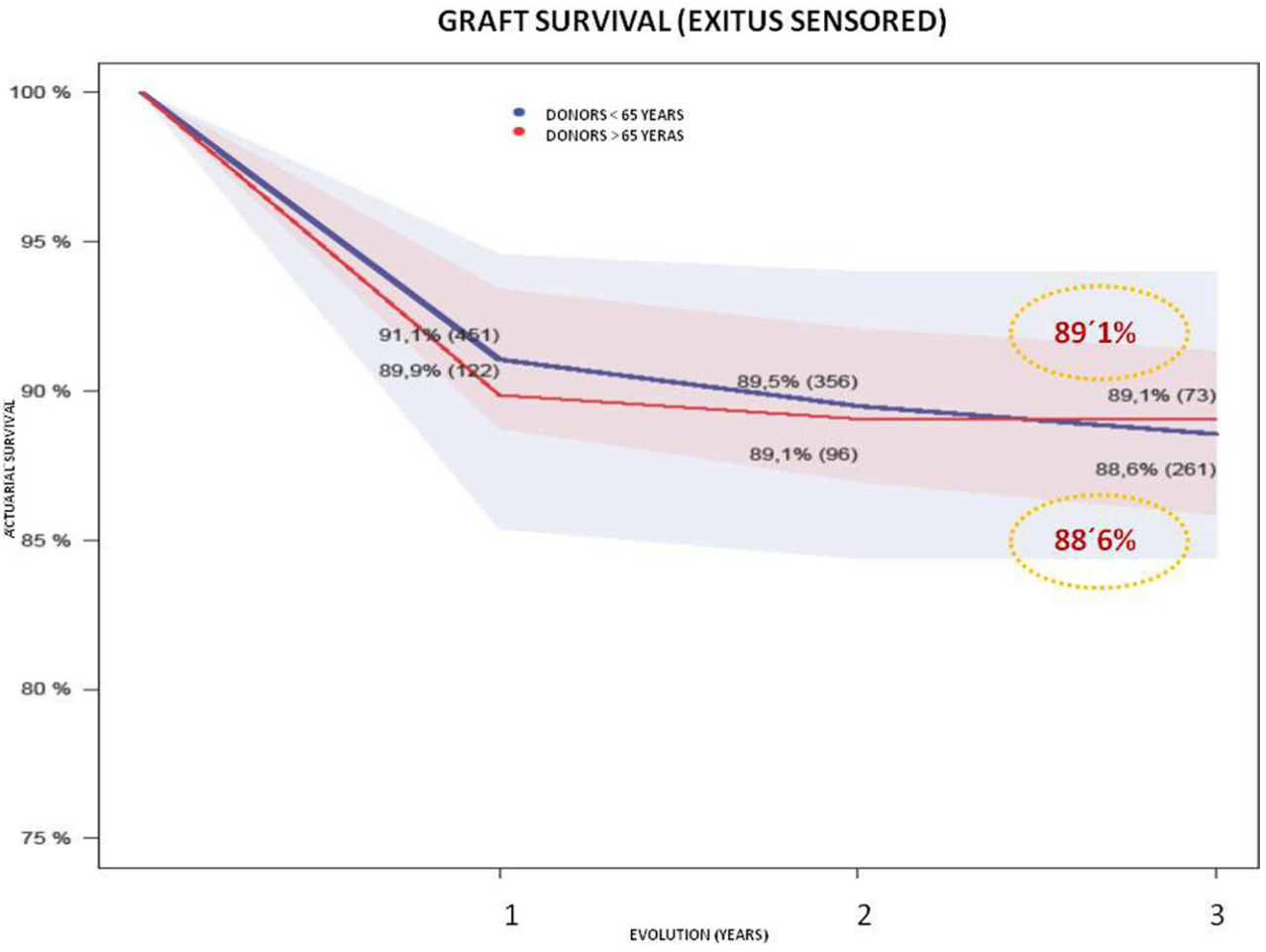

Fig 4. Three-year actuarial survival (exitus censored) of grafts according to donor age.

To use expanded donor grafts from elderly donors requires a protocol to evaluate the micro- and macroscopic features of organs to decide in favor of transplant or discard of the grafts. If we are more flexible with these criteria, we are likely to perform a larger number of transplants but with a worse graft survival in the short to medium term. In contrast, if the protocol is more restrictive the number of grafts will be smaller, rejecting a greater number of grafts, but their survival will presumably be better. Therefore, we must try to balance these considerations to obtain a higher rate of transplantations with acceptable graft function and patient survivals to meet our patients' needs.

In conclusion, we have observed that with the use of expanded donor protocols, we have managed to increase the transplant rate by 15 to 20 per million population, while maintaining acceptable results in terms of graft function and patient survival in the short to medium term.

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Guidelines for Maintenance of Adult Patients With Brain Death and Potential for Multiple Organ Donations: The Task Force of the Brazilian Association of Intensive Medicine the Brazilian Association of Organs Transplantation, and the Transplantation Center of Santa Catarina

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ABSTRACT

Introduction. The organ shortage for transplantation, the principal factor that increases waiting lists, has become a serious public health problem. In this scenario, the intensivist occupies a prominent position as one of the professionals that first has a chance to identify brain death and to be responsible for the maintenance of the potential deceased donor.

Objective. This report attempts to establish guidelines for care and maintenance of adult deceased donor organs guiding and standardizing care provided to patients with brain death.

Method. These guidelines were composed by intensivists, transplant coordinators, professionals from various transplant teams, and used transplant center. The formulated questions were forwarded to all members and recommendations were constructed after an extensive literature review selecting articles with the highest degree of evidence.

Results. Guidelines were developed in the form of questions reflecting frequent experiences in clinical intensive care practices. The main questions were: Is there an optimal interval for keeping organs of deceased donors viable? What actions are considered essential for maintaining deceased donors in this period? What are the limits of body temperature? How should the patient be warmed? Which laboratory tests should be performed? What is the collection interval? What are the limits in the laboratory and the capture scenario? What are the limits of blood pressure? When and how should one use catecholamines?

Conclusions. This pioneer project involved a multidisciplinary team working in organ transplantation seeking to provide treatment guidance to increase the number of viable organs from deceased adult donors.

THE organ shortage has been one factors responsible for the increase in transplant waiting lists. It has been accompanied by an increased mortality of candidates during the waiting period, greater use of marginal donors, and transplantation of more severely ill patients.[1–3] The expansion of donor selection criteria within safe limits helps to increase transplantation numbers, although it is not always accompanied by good results. Maintenance care of deceased donors does not differ significantly from that adopted for critically ill patients. Unfortunately, in most

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intensive care units, this concern is not fully incorporated into clinical protocols. The primary care of individuals with donor potential must provide better quality grafts. This manuscript sought to guide and to standardize the care provided to deceased donors to increase the number and quality of donor organs. These guidelines serve as a practical tool to help intensive care physicians making decisions regarding the maintenance of potential donors and appropriate therapies, with the intention of decreasing the shortage of transplantable organs of the best quality possible.

METHOD

In order to establish the first Brazilian guidelines for maintenance of adult multiple organ donors with brain death, The Brazilian Association of Intensive Medicine (AMIB), the Brazilian Association of Organ Transplants (ABTO), and the Transplantation Center of Santa Catarina (SC-Tx) formed a multidisciplinary task force composed of individuals working in the intensive care unit and in organ transplantation. The articles with the highest levels of evidence were selected after an extensive literature review. Expert members from different transplant specialities and intensivists judged the final document at the plenary session. The recommendation grade and the evidence level of selected articles obeyed the following distribution: **A,** experimental or observational studies of best consistency; B, experimental or observational studies of lower consistency; and C, case reports or uncontrolled studies devoid of critical assessment, as based on consensus, physiologic studies, or animal models. These evidence levels were also considered to establish the recommendation grades of this guideline.

The recommendation classes were: class I, consensus on the indications for the procedure or treatment; class IIa, evidence favoring an indication of procedure or treatment; class IIb, evidence not favoring the indication of procedure or treatment; and class III, procedure or treatment is not indicated.

Considering the paucity of evidence in studies of deceased donors, some of the recommendations described herein were based on analogies with other clinical settings. For this reason, we also used classically accepted physiological considerations as well as epidemiological and experimental studies. These guidelines were developed using practical questions to facilitate the management by intensive care teams. For didactic reasons, it was divided into seven discussion themes: 1, general aspects; 2, hemodynamic support; 3, endocrine and metabolic maintenance; 4, lung maintenance and mechanical ventilation; 5, liver maintenance; 6, kidney maintenance; and 7, heart maintenance.

GENERAL ASPECTS

Is There a Period Considered Optimal for Organ Maintenance of Deceased Donors? How Must the Deceased Donor Be Maintained Viable Until the Removal of the Organs?

Considerations. All efforts should be made to perform transplantations quickly after the diagnosis of brain death and consent for donation, because many organs are lost due to delays before the harvest operation.[1] Unfortunately, few medical teams are able to maintain the deceased donor properly and to ensure organ viability. All supportive measures aim to ensure oxygen supply to maintain organic tissue functions within physiological standards and to reverse dysfunctions in order to increase the utility of donated organs.[4] The adoption of uniform aggressive protocols to maintain potential deceased donors reduces losses resulting from hemodynamic instability in 87%, increasing the total donor number by 19%, actual donors by 82%, and effective donations by 71%.[2] The 12 to 24-hour period has been considered adequate to manage administrative aspects and reverse organ dysfunction.[1,2]

Recommendations. The objective is to maintain body functions, correct organic dysfunctions, and expedite organ removal for transplantation within 12 to 24 hours from the diagnosis of brain death[1,3] (class I–C).

Next, one must prevent and correct all organic dysfunctions aggressively in coordinated and simultaneous fashion. This should be done to ensure hemodynamic stability, correct oxygen deficits, treat bacterial infections, reverse hypothermia and monitor and correct metabolic disorders, especially hypernatremia. One must also correct endocrine, renal, hepatic, coagulation, and any other organic disorders considered reversible[2] (class I–C).

What Are the Limits of Body Temperature to Be Maintained? How Should One Warm the Patient?

Considerations. The regulation of body temperature is an important prerequisite for thermal homeostasis. The afferent and efferent pathways of the hypothalamus circulate continuous information generated by thermal receptors in the hypothalamus itself as well as bone, brain, skin, and deep tissues. The normal temperature ranges from 36.0°C to 37.5°C. The dead brain paralyzes hypothalamic thermoregulatory functions leading to progressive hypothermia with a tendency to equalize with the environmental temperature. Monitoring of temperature which is essential can be obtained at the nasopharynx, esophagus, tympanic membrane, or pulmonary artery. Use of oral cavity, axilla, or rectum is not recommended (C).[5] To ensure viable organs for transplantation, the temperature must be maintained higher than 35°C (ideally between 36°C and 37.5°C) to avoid undesirable effects of hemodynamic instability, acidosis, and coagulopathy (B).[5] Hypothermia must be avoided previously with the use of a thermal blanket or infusion of heated intravenous crystalloid solutions because reversal of hypothermia is harder than maintenance of the temperature (C).[5] Other methods such as immersion in hot water, heat lamps, and infusing warm fluids into the bladder, stomach or pleural or peritoneal cavity should be avoided in organ donors (C).[5]

Recommendations. Maintain the core body temperature higher than 35°C, ideally between 36.0°C and 37.5°C (B).[5] Check core temperature (C)[5] and prophylactically prevent hypothermia (B)[5] with the use of warmed air into the mechanical ventilator (42°C to 46°C), thermal blankets and infusion of the warmed intravenous fluids (43°C). Do not perform warmed irrigation of the peritoneal cavity, thorx, or bladder (B)[5] (class I–C).

What Laboratory Tests Must Be Performed? What Should Be the Collection Interval? What Are the Limits of Laboratory Tests in the Setting of Organ Harvest?

Considerations. The organ donor must be treated always as a critical patient with evaluation of organ function as well as clinical and metabolic control. The following laboratory examinations are important: blood type, blood count, platelets, sodium, potassium, calcium, phosphorus, magnesium, creatinine, urea, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), bilirubin, amylase, creatine kinase-MB (CKMB), troponin, arterial blood gases, and lactate. Blood and urine cultures with antibiogram must be obtained from all potential donors. The serologic evaluation must include hepatitis, acquired immunodeficiency syndrome, syphilis, cytomegalovirus, toxoplasmosis, and Chagas disease (C).

Abnormalities in the levels of sodium, potassium, magnesium, and calcium may be the result of large urinary losses due to diabetes insipidus or inadequate repletion. These ions play important roles in cell physiology; therefore, changes in their serum concentrations must be vigorously treated. The association of hypokalemia, hypothermia, and acidosis is highly deleterious to the heart, predisposing mainly to arrhythmias, and ventricular fibrillation during donor heart harvest. The monitoring of electrolytes and gasoes during the correction should be performed using serial measurements every 6 hours and routinely each 12 hours. However, according to the severity of the hemodynamic instability or water and electrolytic disturbances, the exam schedule may be modified (C).[6,7] Blood count and coagulation monitoring should be performed every 6 hours due to the risk for coagulopathy. The indication and timing of some biochemical tests are organ-specific. For cardiac evaluation, the relevant enzymes (CKMB/troponin) should be repeated every 24 hours. For hepatic evaluation, determinations of SGOT, SGPT, bilirubin, and prothrombin activity should be repeated every 24 hours. For kidney donors, creatinine and urea must be measured every 24 hours. Hyperglycemia or hyperamylasemia alone are not contraindications for pancreas donation, except in the presence of direct pancreatic trauma, pancreatitis, or diabetes. (C).

Recommendations. Perform periodically the basic biochemical examinations with the aim to help physiologic parameter correction (C), including electrolytes and blood gases every 6 hours (C)[7] (class I–C).

Recommendations for laboratory evaluation for specified organ transplantations are as follows: For the heart measure CKMB and troponin every 24 hours (C) (class II–C); for the liver, measure SGOT, SGPT, bilirubin, and prothrombin activity every 24 hours (C) (class II–C); for the kidney, measure urea and creatinine levels every 24 hours (C) (class I–C); for the pancreas; measure amylase and glycemia every 24 hours (C) (class I–C); for all potential donors collect two hemocultures and urine cultures on (C) (class I–C).

HEMODYNAMIC SUPPORT

How Should Blood Pressure Be Measured?

Considerations. Hemodynamic instability is the main challenge in the treatment of potential donors because many patients have experienced prolonged hypoperfusion (C). The methods of noninvasive blood pressure measurement are inaccurate in shock due to the hypotension and filiform pulse characteristics (B). There are significant differences between noninvasive and invasive measurements, especially when there is increased systemic vascular resistance due to vasoconstriction (C). Invasive blood pressure measurements are safe and essential to guide hemodynamic therapy (B), as recommended by several international guidelines for potential donor maintenance. (C).[1,3] In addition, arterial access facilitates the collection of serial blood samples for arterial blood gas analysis as well as determination of arterial pressure.

Recommendations. Invasive arterial blood pressure measurement should be performed on all potential deceased donors (C) (class I–C).

Should Hypertension Related to Increased Intracranial Pressure (Sympathetic Storm) Be Treated? What Are the Limits of Acceptable Blood Pressure? What Are the Drugs of Choice?

Considerations. Brain death produces physiological changes in response to irreversible loss of encephalic trunk function. One of the most significant changes is hemodynamic instability occurs in two phases (C).[8] The initial phase shows adrenergic hyperactivity leading to tachycardia, hypertension, increase systemic vascular resistance, increased myocardial oxygen consumption, and reflex systolic arterial hypertension (C).[8] This "sympathetic storm" phase, lasting approximately 20 to 30 minutes is followed by hypotension (C).[8] The "adrenergic storm" produces systolic arterial hypertension which leads to hypoperfusion due to transitory vasoconstriction (C),[1,8] producing splanchnic ischemia, myocardial hypoperfusion, and arrhythmias (C).[7] Pharmacological treatment is not recommended because this hypertension is transitory and followed by progressive hypotension (C).[8] Only severe, prolonged hypertension should be treated; sodium nitroprusside is the preferred agent due to its short time of action (C).[8] Beta blockers should be used sparingly because they possibly lead to myocardial depression (C).[8]

Recommendations. The systemic arterial hypertension related to "adrenergic storm" of severe degree (systolic $>$ 180 mm Hg; diastolic $>$ 100 mm Hg; or mean $>$ 90 mm Hg) and prolonged ($>$ 30 to 60 minutes) may be treated with sodium nitroprusside (C) 8 or short-acting cardioselective beta-blockers (esmolol) (class I–C).

What Is the Blood Pressure Goal to Be Achieved in Potential Deceased Donors?

Considerations. After the adrenergic storm, there is catecholamine depletion followed by vasodilation and arterial

hypotension (C).[7] The clinical picture becomes more serious in the presence of secondary hypovolemia from polyuria due to diabetes insipidus as well as mannitol administration or hyperglycemia that lead to an osmotic diuresis. The coexistence of ventricular dysfunction as a cause of hypotension should be considered; it may result from myocardial injury, electrolyte abnormalities, pulmonary hypertension, and neurogenic myocardial depression. There is no evidence concerning the optimal blood pressure level for potential multiple organ donors, however, it has been recommended to maintain the mean arterial pressure between 60 mm Hg and 80 mm Hg, which corresponds to a systolic pressure between 90 mm Hg and 100 mm Hg (C).[7] Normalization of mean arterial pressure does not guarantee restoration of tissue flow; its analysis should always be accompanied by markers of tissue perfusion.

Recommendations. Maintain mean arterial pressure higher than 65 mm Hg or systolic higher than 90 mm Hg (C) (class I-C).

What Are the Therapeutic Orientations to Be Used to Achieve Target Arterial Pressure?

Considerations. Hypovolemia is one of the major causes of hemodynamic instability in potential donors. Aggressive fluid resuscitation must be the first measure to improve tissue perfusion, inhibit systemic inflammatory activation, and ensure the organ quality. On the other hand, excessive fluid administration may cause acute pulmonary edema, compromising lung viability for transplantation (C).[9] Thus, either water failure or excess can be detrimental for organs. Adequate hemodynamic monitoring is the best method to control volume repletion and avoid iatrogenic fluid overload (C).[9] Vasopressor and inotropic support should be based on physiological principles because there are no definitive studies about this topic. The vasopressor support in brain death must be started only if the blood pressure is not achieved or maintained after adequate volume repletion. The indiscriminate use of vasopressors may lead to deterioration with arrhythmias, worsening hypotension (in the case of dobutamine), or exaggerated vasoconstriction followed by multiple organ ischemia (C).[1,3,9]

Recommendations. The first step for pressure stabilization is volume repletion with 20 mL/kg to 30 mL/kg of heated crystalloid solution (43°C) over 30 minutes (C)[9] (class I–C). Subsequent aquacon infusions must be guided by oxygenation and metabolic parameters (C)[9] (class I–C).

Start an inotropic agent infusion or vasopressor only after administration of 20 mL/kg to 30 mL/kg of crystalloid solution (C).[9] Start a vasopressor agent before completion of or simultaneously with volume repletion if mean arterial pressure lower than 40 mm Hg or systolic arterial pressure lower than 70 mm Hg (C)[9] (class I–C).

Are Hemodynamic Parameters Useful for Evaluation of Fluid Replacement During Resuscitation of Potential Organ Donors?

Considerations. Aggressive volume resuscitation is the cornerstone in the maintenance of a deceased donor. However, if the patient is normovolemic or has heart dysfunction (C),[7] uncontrolled fluid infusion can result in hypervolemia with organ damage principally to the lungs. Moreover, the simple addition of vasopressors without adequate preload can affect tissue perfusion and organ quality. Therefore, cardiovascular capacity must be analyzed carefully beforehand, to correct arterial hypotension and tissue hypoperfusion. Many guidelines indicate that central venous pressure should be monitored in all deceased donors. However, a study of 805 deceased donors showed that the central venous pressure and other hemodynamic parameters did not influence the effectiveness of organ grafts (C).[10] A recent meta-analysis which reviewed several studies in various populations of critical patients concluded that central venous pressure or pulmonary capillary wedge pressure values between 8 mm Hg and 12 mm Hg did not discriminate responsive individuals versus those nonresponsive to blood volume restoration (sensitivity and specificity, 50%) (B).[11] In contrast, consensus recommendations suggest that low values of central venous pressure or pulmonary capillary wedge pressure (lower than 4 mm Hg) allow fluid infusion with careful monitoring of unstable individuals. Variations in central venous or pulmonary capillary wedge pressure after infusion of 500 mL to 1000 mL of crystalloid solution over 15 minutes to 30 minutes are more reliable than single measures. The crystalloid solution infusion should be discontinued or reduced if there is an increase of $\geq$ 2 mm Hg in the venous or pulmonary capillary wedge pressure (C).[11] Respiratory changes in arterial pulse pressure (ΔPp) reliably assess cardiovascular responses to blood volume restoration during mechanical ventilation (sensitivity and specificity, $\sim$95%) in the absence of cardiac arrhythmias (C).[11] Potential deceased donors who respond to volume (ΔPp $>$ 13%) show higher levels of interlukin-6 when compared to nonresponders (ΔPp $<$ 13%). This inflammatory response was associated with decreased use of organs among individual nonresponders: 1.8 $\pm$ 0.9 versus 3.7 $\pm$ 2.5 (number of organs transplanted per donor) (P = .034). The results suggest that volume expansion guided by parameters of greater accuracy can produce the most effective graft. Variations of pulse plethysmography (ΔPplet) provide a fast, noninvasive alternative to ΔPp, by analysis of waveform amplitudes.

Recommendations. Use preferably hemodynamic parameters to evaluate responsiveness of individuals to volume replacement (C)[11] (class I–B). Infuse 500 mL to 1000 mL of crystalloid solution whenever there are signs of hypovolemia or central venous pressure lower than 4 mm Hg (C)[11] (class I–C). Do not use central venous pressure as an isolated measure to guide fluid replacement (C).[11] Stop the infusion among individuals responsive to volume based on

dynamic parameters, such as an increase in central venous pressure greater than 2 mm Hg after infusion of 500 mL to 1000 mL of crystalloids (C)[11] (class I–C).

Which Vasopressors and Inotropic Agents Should Be Used During Hemodynamic Resuscitation of the Potential Organ Donor? Are There Drugs Preferences? What Are the Maximum Doses?

Considerations. Epinephrine, norepinephrine, or dopamine may be used with infusions adjusted to maintain blood pressure and tissue perfusion within physiological ranges to enable donation of multiple organs. There is no consensus concerning the maximum dose of catecholamine (B).[12,13]

The commonly used catecholamines include noradrenaline, dopamine, and dobutamine. When administered at high dose, they decrease the chances of organ utilization principally of the heart. Beta-agonist therapy (dopamine and dobutamine) may be used particularly in cases of low output cardiac secondary to hypoperfusion. There are no randomized studies to define the best choice of vasopressors. Vasopressin can be used both as a vasopressor and to manage diabetes insipidus. Organ donors who require vasopressors often display depletion of vasopressin (B).[13] In some cases, the use of vasopressin can guarantee the stability of blood pressure and facilitate the discontinuation of catecholamines (B).[13] Hormone replacement therapy include the addition of vasopressin, thyroid hormones, and/or corticosteroids can provide a therapeutic test for organ donors with hemodynamic instability. The best results are obtained when they are administered precociously before or upon the appearance of deleterious effects from prolonged hypotension B.[13]

Recommendations. Start vasopressor drugs (norepinephrine, epinephrine, or dopamine) to maintain blood pressure > 65 mm Hg or systolic blood pressure > 90 mm Hg. There is no dose limit (B)[13] (class I–C).

The indication for vasopressin is similar to the others vasopressors: 1 IU initial bolus followed by continuous infusion from 0.5 IU/h to 2.4 IU/h. Discontinue gradually catecholamine infusion once blood pressure stabilizes after the vasopressin infusion (B)[13] (class I–B).

Start dobutamine if there is any impairment of heart rate or signs of hypoperfusion with no clinical evidence of ventricular dysfunction or an ejection fraction $< 40\%$ or a cardiac index < 2.5 L/min/m^2. The beta-agonist therapy in high doses (> 10 μg/kg/min) or norepinephrine (>1–2 μg/kg/min) for prolonged period can compromise especially the success of heart transplantation (B)[13] (class I–C).

Should The Venous Oxygen Saturation (SvO2) Values Be Used as a Reference Parameter During Hemodynamic Resuscitation of the Potential Organ Donor?

Considerations. Mixed (SvO_2) and central ($ScvO_2$) venous oxygen saturation reflect the balance between oxygen supply and demand showing inverse correlations with cardiac output (CO). Both low and high values are associated with greater mortality when present in a critical patient (C).[14-18] In patients with brain death, venous oxygen saturation measured in the jugular bulb is high, reflecting cerebral oxygen consumption, and contributing to the elevation of $ScvO_2$ measured in the superior vena cava or right atrium (C).[18] No studies have defined the ideal goal for $ScvO_2$ during hemodynamic resuscitation. Furthermore, there is no observational study to evaluate whether abnormal levels are associated with the use or quality of organs for transplantation. There is only one mention in the literature (C),[18] in which the authors claimed that there are no studies showing that values that would be considered "normal" in brain death were due to decreased cerebral oxygen consumption. So, until these values are unidentified, they did not recommend using $ScvO_2$ to assess tissue oxygenation as parameter for resuscitation. In contrast, in sepsis restoration of $ScvO_2$ and lactate to normal values appears to impact beneficial impacts on patient outcomes.

Recommendations. There is no $ScvO_2$ cutoff established for deceased donors (C). Low values of $ScvO_2$ ($< 70\%$) could indicate low cardiac output. In these cases, the $SvcO_2$ may be used as an evolution parameter during hemodynamic resuscitation (C) (class IIb–C). Adopt hemodynamic adjustments precociously guided by well-established protocols, regardless of the target for $ScvO_2$. Early Therapeutic interventions to correct metabolic disorders are more important than the $ScvO_2$ values to determine the success of deceased donation (C) (class I–C).

Should Lactate Values Be Used as a Reference Parameter During Hemodynamic Resuscitation of the Potential Organ Donor?

Considerations. Resuscitation must be guided by organ maintenance and normalization of hemodynamic parameters to improve oxygen delivery to tissues before the development of multiple organ dysfunction (A).[14,15] Blood lactate (venous or arterial) correlates with hemodynamic recovery among the critically ill patients. However, the usefulness of lactate is not totally clear as a guide for hemodynamic resuscitation on seriously ill patients due to few existent studies. However, some observations have shown that the clearance of blood lactate is associated with successed hemodynamic resuscitation among patients with sepsis or trauma (B).[15] In this manner, Two studies have assessed the usefulness of blood lactate clearance as a goal for resuscitation in sepsis (B).[15] The first study comparing hemodynamic resuscitation guided by venous oxygen saturation versus blood lactate did not show any significant benefit. The second study compared resuscitation guided by lactate versus a standard strategy. Multivariate analysis showed decreased mortality associated with greater use of fluid and nitroglycerin. However, no specific studies have evaluated the role of lactate in the resuscitation of organ donors.

Recommendations. Do not use the normalization of lactate as a therapeutic goal. Values greater than 2 mmol/dL may indicate reduced blood flow and might serve to monitor the progress of patients as an additional metabolic parameter (C)[15] (class IIb–C).

What Is the Target Arteriovenous CO_2 Gradient During Hemodynamic Resuscitation of the Potential Organ Donor?

Considerations. The central or mixed arteriovenous CO_2 gradient shows the opposite behavior as cardiac output as well as other parameters that reflect blood perfusion, but the reason for this proportion is not known. Hemodynamic parameters and intramuscular CO_2 tension have been described in brain death, but no prospective studies have demonstrated its success to improve organ retrieval (B).[18] The relevance of central arteriovenous CO_2 gradients in deceased donors is unclear. The jugular-arterial CO_2 gradient is important only as an index for the diagnosis of cerebral hypoperfusion or brain death (C).[18]

Recommendations. Do not use arteriovenous CO_2 gradients to guide therapy on deceased donors. However, they can be used as additional metabolic parameters in clinical monitoring (C)[18-23] (class I–C).

When Is Echocardiography Indicated During Hemodynamic Resuscitation of Potential Organ Donors?

Considerations. Hemodynamic monitoring based on the classical parameters may not be sufficient to evaluate patients with severe hemodynamic instability after expansion with crystalloid or subsequent instollation of increasing doses of vasoactive drugs (C).[24,25,26] Echocardiography may assist in rescue therapy of unstable patients among organ donors, this examination has more utility in the selection of hearts for transplantation (C).[24,27-29] The method is widely used, since it is simple, rapid, and noninvasive, allowing sequential evaluations of pharmacological interventions in the search for correction of cardiovascular changes. Various studies have shown good correlations between the cardiac output as measured by echocardiography or thermodilution techniques; however, there are errors dealing with the extreme limits of low or high cardiac outputs (C).[24]

Recommendations. Echocardiography is indicated to guide basic hemodynamic monitoring for deceased organ donors whenever there is a failure of hemodynamic resuscitation with crystalloid, vasopressors, or inotropic agents (C).[24,30,31] (class IIb–C).

How Does One Prevent and or Treat Cardiac Arrhythmias in Deceased Donors?

Considerations. Various cardiac arrhythmias may occur in deceased donors leading to reduced cardiac output and hemodynamic instability (C).[8] The etiology of arrhythmias is multifactorial hypovolemia, hypotension, hypothermia, sympathetic storm, catecholamine administration, myocardial contusion, as well as acid-base or electrolyte changes (hypo or hyperkalemia) (C).[8] The prevention and treatment of arrhythmias involve correction of the reversible causal factors described above. Pharmacological treatment of an arrhythmia may lead to myocardial depression. In brain death, bradyarrhythmias are resistant to the use of atropine due to the absence of vagal activity; therefore, the use of epinephrine, dopamine, or isoproterenol is recommended (C).[8]

Recommendations. Prevention and treatment of arrhythmia must be initiated by correction of reversible factors such as electrolyte and acid-base disturbances, hypovolemia, hypotension, hypothermia, or excessive inappropriate administration of catecholamines (C)[8] (class I–C). Treat tachyarrhythmia and cardiac arrest according to American Heart Association guidelines (C)[8] (class I–C). Do not use atropine for bradyarrhythmia treatment (C).[8] (class I–C). Treat bradyarrhythmias in the absence of hemodynamic instability with epinephrine (2 mg/min to 10 mg/min) or dopamine (5 mg/kg/min to 10 mg/kg/min) or isoproterenol (2 mg/kg/min to 10 mg/kg/min) (C)[8] (class I–C). Treat bradyarrhythmias or hypotension accompanying low cardiac output with a temporary transcutaneous pacemaker that can be followed with a transvenous pacemaker (C).[8] (class I–C).

After the Occurrence of Cardiac Arrest in the Potential Deceased Donor Should Transfer to the Operating Room Be Considered for Removal of Viable Organs? If the Operating Room or Surgical Team Is Unavailable, Is There any Alternative That Maintains Organ Perfusion?

Considerations. Deceased donors who develop cardiac arrest may be designated for a non–heart-beating organ donation (NHBD) protocol which is gaining acceptance to expand the donor pool. If the donation has not yet implemented, the complex ethical issues associated with NHBD may be a further disincentive. Organ donation only occurs with family consent in Brazil; mechanical perfusion of a deceased potential donor deserves further discussion. If the donation is fully implemented, the deceased donor must be immediately transferred to the operating room with manual or mechanical chest compressions to ensure organ viability. If there are logistical difficulties for the immediate removal of organs, a double-balloon triple-lumen perfusion catheter may be introduced through the femoral artery during the cardiac massage as an alternative to preserve the kidneys. This catheter allows removal of blood and infusion of preservation solution into both kidneys. A second more complex alternative involves the installation of femorofemoral bypass with membrane oxygenation and induction of hypothermia (C).[32]

Recommendations. Initiate immediate cardiovascular resuscitation and move to the operating room for removal of viable organs (C)[32] (class I–C). Consider installing double-balloon triple-lumen perfusion catheter for renal preservation, using cardiopulmonary bypass via the femoral approach, if immediate removal not possible (C)[32] (class IIb–C).

Is There an Indication for High-dose Heparin Administration (500 U/Kg) During Cardiovascular Resuscitation?

Considerations. The administration of high-dose heparin to the organ donor has been recommended in the initial stages of resuscitation manuvers during cardiac arrest (C).[32]

Recommendations. Administer 500 IU/Kg of sodium heparin in the initial stages of resuscitation if immediate organ withdrawal or mechanical perfusion as possible (C)[32] (class I–C).

HEMATOLOGICAL ASPECTS

What Is the Hemoglobin Limit for Transfusion of Red Blood Cells to Potential Deceased Donors? Should the Red Blood Cell Transfusion be Liberal or Restrictive?

Considerations. Oxygen delivery (DO_2) to tissues in brain death is still unknown. Oxygen consumption (VO_2) decreases after brain death, similar to general anesthesia, in which VO_2 decreases to 25% (C).[30] Hemodynamic instability alters the normal distribution of blood flow promoting changes in regional DO_2/VO_2 which may produce organs ischemia even in the presence of an adequate systemic DO_2. Therefore, the DO_2 does not reflect the effectiveness of tissue perfusion. Blood transfusions are administered in the liberal strategy when the hemoglobin level (Hb) is less than 10 g/dL and in a restrictive one at Hb $<$ 7 g/dL (C).[30] For deceased donors, it is recommended to maintain the Hb between 9 g/dL and 10 g/dL, with a minimum value of 7 g/dL.

Recommendations. Do not transfuse red blood cells if Hb $\geq$ 10 g/dL. Do not transfuse red blood cells if Hb between 7 g/dL and 10 g/dL in potential donors with hemodynamic stability and adequate tissue perfusion (C).[30] Transfuse red blood cells if Hb $\leq$ 7 g/dL. Transfuse red blood cells if Hb $<$ 10 g/dL in potential donors, only if there is hemodynamic instability associated with failed resuscitation (C)[30] (class I–C).

CONCLUSIONS

This pioneer project involved a multidisciplinary team working in organ transplantation. The aim of the study is to provide guidance for treatment of deceased potential adult donors, seeking to increase the number of viable organs for transplant.

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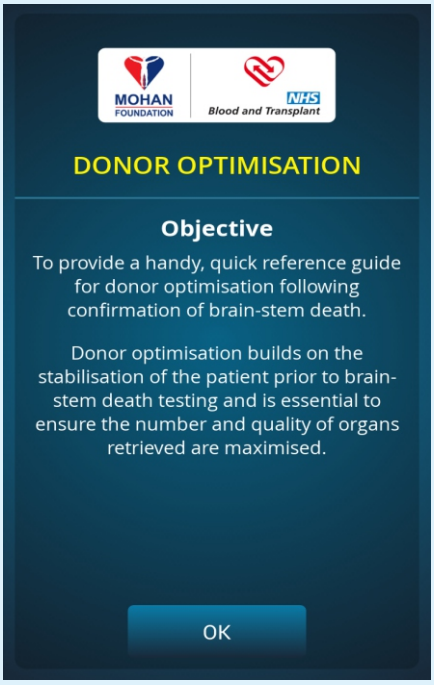

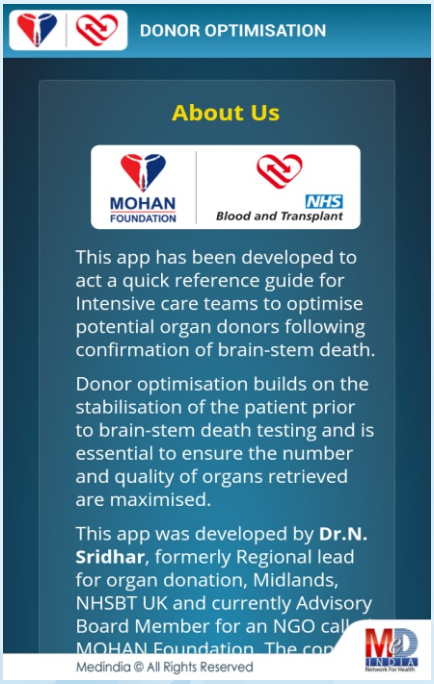

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B.J.J.M. Haase-Kromwijk, director

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