Kidneys from cardiac death donors comparable quality and survival

Donor kidneys from individuals who have recently died from cardiac arrest perform just as well in recipients as kidneys from traditional 'brain-dead' donors, scientists have found.

Researchers hope their findings, published in *The Lancet* (Summers et al, 2010), will increase the use of kidneys from cardiac death donors (kidneys which were previously viewed by some as inferior) and possibly reform how these kidneys are allocated – thereby increasing the fairness of kidney distribution as well as the likelihood of a successful transplant.

There are currently over 7000 patients waiting for a kidney transplant, but because of the dire lack of donation organs, almost 10% of these patients die every year while waiting for a healthy kidney.

The scientists examined data from 9134 kidneys transplants conducted in 23 centres; 8289 of the kidneys were donated after brain death and 845 after controlled cardiac death. They found no difference in survival rates or kidney function of recipients for up to 5 years after transplantation. (The researchers did not have the data to explore the success rates beyond 5 years but indicate that there is no reason to suspect longer-term transplant outcomes would be different.)

Factors which decreased the success rate of cardiac death transplantations included increasing age of donor and recipient, repeat transplantation, and organs kept cold but without blood supply for longer than 12 hours.

Lead author of the paper, Professor Andrew Bradley of the Department of Surgery, University of Cambridge, said: 'Cardiac death donors represent an extremely important and overlooked source of high-quality donor kidneys and have the potential to increase markedly the number of kidney transplants performed in the UK.'

Dr Dominic Summers added: 'What we have shown, for the first time, is that cardiac death donor kidneys last as long and work as well as brain-death donor kidneys, and should be regarded as comparable. In view of our findings, we recommend that cardiac death kidneys be allocated in a similar way as brain death kidneys, ensuring better tissue matches and favouring those who have waited longest.

'Hopefully this paper will provide the evidence and impetus to greatly expand the national programme, and improve the national organ donation rates,' concluded Dr Summers.

Summers DM, Johnson RJ, Allen J, Fuggle SV, Collett D, Watson CJ, Bradley JA (2010) Analysis of factors that affect outcome after transplantation of kidneys donated after cardiac death in the UK: a cohort study. *The Lancet* (epub before print 19 August 2010)

Effect of EWTR 'getting worse'

European law brought in to improve patient safety and the working lives of doctors has 'failed spectacularly' say surgeons a year after its implementation.

Results of a survey by the Royal College of Surgeons of England (www.rcseng.ac.uk/media) show that since the restrictions of the European Working Time Regulations (EWTR) limiting doctors to 48 hours a week, patients in NHS hospitals are less safe than they were a year ago, and the situation is getting worse.

The survey of 980 surgeons and surgical trainees covered all nine surgical specialties and all strategic health authorities in England as well as surgeons based in Scotland, Northern Ireland and Wales, and compared responses to a similar survey undertaken last year.

The survey found that 80% of consultant surgeons and two thirds of surgical trainees (66%) say that patient care has deteriorated under the directive, compared with 72% of consultants and 59% of trainees consulted in 2009.

Two thirds of trainees (65%) say their training time has decreased – a quarter more than in 2009 (41%). More than a quarter of senior surgeons are no longer able to be involved in all the key stages of a patient's care.

Almost three quarters of trainees (72%) of trainees and two thirds of consultants (61%) consistently work more than the permitted hours. Over half of trainees say they cover rota gaps which result in them working in excess of their contracted hours.

The lack of exposure to vital hands-on training alongside experienced colleagues is eroding NHS care and will cause a critical shortage of capable, skilled surgeons in the future.

Use of paracetamol increases risk of asthma and eczema

Two written questionnaires and one video questionnaire were administered to more than 300 000 13- and 14-year-old children in 113 centres throughout 50 countries, asking them to quantify their use of acetaminophen (paracetamol) (none, 'medium' – at least once in the last year, or 'high' – at least once in the last month) and their asthma, eczema and allergy symptoms.

There was a significant association between acetaminophen use and risk of asthma and eczema. For medium users the risk of asthma 43% higher than non-users; high users had 2.51 times the risk of non-users.

Similarly, the risk of rhinoconjunctivitis (allergic nasal congestion) was 38% higher for medium users and 2.39 times as great for high users compared to non-users. For eczema, the relative risks were 31% and 99% respectively.

'This study has identified that the reported use of acetaminophen in 13- and 14 year old adolescent children was associated with an exposure-dependent increased risk of asthma symptoms,' said first author Richard Beasley, professor of medicine, at the Medical Research Institute of New Zealand.

As this was a cross-sectional study, causality could not be determined. However, there is mounting evidence that suggests a causal link.

Beasley RW, Clayton TO, Crane J, Lai CKW, Montefort SR, von Mutius E, Stewart AW, and the ISAAC Phase Three Study Group (2010) Acetaminophen Use and Risk of Asthma, Rhinoconjunctivitis and Eczema in Adolescents: ISAAC Phase Three. *Am J Respir Crit Care Med* (epub ahead of print 13 August 2010)

Guidelines for complications of cirrhosis

The European Association for the Study of the Liver (2010) has published guidelines for the management of ascites, the most common complication of cirrhosis. They also provide recommendations for the management of spontaneous bacterial peritonitis and hepatorenal syndrome, which often affect patients with cirrhosis.

An estimated 75% of patients presenting with ascites in Western Europe and the USA have cirrhosis as the underlying cause. Development of ascites is an extremely common yet debilitating complication for cirrhotic patients and has a huge impact on their life expectancy and quality of life.

Spontaneous bacterial peritonitis and hepatorenal syndrome are ominous complications of which patients with ascites are at risk. They carry a high mortality and prophylactic measures, early diagnosis and appropriate treatments are crucial, especially to bridge eligible patients to liver transplantation.

'It is estimated that almost 60% of cirrhotic patients develop ascites within 10 years of their disease, which is a huge proportion of patients. These guidelines provide clinicians with the latest recommendations from a panel of experts on the management of ascites, spontaneous bacterial peritonitis and hepatorenal syndrome. It is hoped that the guidelines will improve and facilitate best practice and ultimately improve disease outcomes and symptoms for cirrhotic patients in the future,' stated Pere Ginès, lead contributor of the guidelines.

European Association for the Study of the Liver, Ginès P, Angeli P, Lenz K et al (2010) EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. *J Hepatol* **53**(3): 397–417

Most deaths in England in 65–84-year-olds

The first comprehensive overview for England of variations in place of death by geography, demography and main cause of death have been published, taken from the first tranche of national End of Life Care Profiles (National End of Life Care Intelligence Network, 2010).

In 2007, there were 471 092 deaths in England, 52% of which (246 412) were in females. This equates to about 1300 deaths per day in England or about one death per minute.

While the highest crude mortality rates are in males and females aged 85 years and over at 16 759 and 14 731 per 100 000 respectively, the greatest number of deaths are in 65–84-year-olds. In 2007, there were 225 531 (48%) deaths in 65–84-year-olds compared with 81 353 (17%) deaths in under 65-year-olds and 164 208 (35%) deaths in the 85 years and over age group.

Between 1998 and 2007 there was a 19% decrease in the number of deaths in 65–84-year-olds, a 7% decrease in deaths in the under 65-year-olds but a 7% increase in deaths in people aged 85 years and over.

Females tend to die at an older age than males – 43% of females were aged 85 years and older at death compared with 24% of males. Females aged 85 years and over account for 23% of all deaths.

The highest proportion of deaths in under-65-year-olds is in the London Government Office Region (21%); the north east Government Office Region has the highest proportion of deaths in 65–84-year-olds (53%), and the highest proportion of deaths in people aged 85 years and over is in the south west (38%).

Over half of people die in hospital (58%), with only 19% dying in their own residence.

When deaths are analysed by the principal groups of main 'underlying' causes, cardiovascular disease accounts for the greatest number. There were an average of 150 034 (31.6%) deaths from cardiovascular disease per year in 2005–7, compared with 130 181 (27.4%) deaths from cancer, 128 649 (27.1%) deaths from other causes and 65 854 (13.9%) deaths from respiratory causes.

The proportion of deaths with cancer as the underlying cause is higher in the least deprived quintile (29%) compared with the most deprived (26%) ($P<0.05$), whereas the proportion of deaths in which respiratory disease is the underlying cause is higher in the most deprived quintile (15%) than the least (12%) ($P<0.05$).

National End of Life Care Intelligence Network (2010) *Variations in Place of Death in England.* www.endoflifecare-intelligence.org.uk (accessed 23 August 2010)

Combination therapy recommended for patients co-infected with HIV and HCV

New guidance from the National Institute for Health and Clinical Excellence recommends combination therapy with peginterferon alfa and ribavirin as an option for patients who are co-infected with HIV or patients with hepatitis C who require re-treatment (as they either did not respond to previous treatment or peginterferon alfa monotherapy, or responded initially but subsequently relapsed).

Antiseptic dressing may reduce surgical site infections

A new bio-cellulose dressing, Suprasorb X+PHMB, can donate polyhexamethylene biguanide to any wound type. It is hoped that this effective antiseptic, which acts quickly and has no known bacterial resistance, will help to prevent surgical site infections.

Spirometry e-learning course

Education and research charity Education for Health has launched a new interactive eLearning resource on spirometry. The courses incorporate the latest changes in technology and clinical guidance. A taster session can be accessed at elearning.educationforhealth.org

ERA-EDTA Congress
Munich, 25–28 June

No advantage for early *vs* late start to dialysis, says IDEAL trial

Starting dialysis early neither improves survival nor reduces complications in patients with end-stage renal disease. This was the message of Initiating Dialysis Early and Late (IDEAL), a large, prospective, randomized clinical trial presented at the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) congress and published online in the *New England Journal of Medicine* (Cooper et al, 2010).

According to lead investigator Dr Bruce Cooper: 'Our results demonstrate that in a closely managed setting – all patients received nephrological follow up for about 30 months before computer randomization – start of dialysis can be delayed. There is now level A evidence for European guideline recommendations that chronic kidney disease stage 4–5 patients should receive close clinical follow up and that dialysis can be started on the basis of symptoms alone.'

Between July 2000 and November 2008, 828 adults (aged ≥18 years) from Australia and New Zealand with progressive chronic kidney disease and an estimated glomerular filtration rate (eGFR) of 10–15 ml/min/1.73m^2 were randomized to planned start of dialysis when eGFR was either 10–14 (early start) or 5–7 (late start) ml/min/1.73m^2.

After a median follow-up of 3.59 years, there was no difference between the two groups on the primary end point of death from any cause (37.6% early start *vs* 36.5% late start). There was also no significant difference in the frequency of cardiovascular events, infections or dialysis complications. The findings applied to all subgroups in the study, stratified at baseline by renal function, age, sex, body mass index, and the presence of cardiovascular disease, diabetes or albuminuria.

Median time to start of dialysis was 1.80 months in the early-start group and 7.40 months in the late-start group. In the late-start group, however, 76% of patients started dialysis before eGFR was >5–7 ml/min/1.73m^2 because of uraemic symptoms and fluid overload. As a result, their mean eGFR at the start of dialysis was well above target, at 9.8 ml/min/1.73m^2.

In a separate analysis of IDEAL data, Professor David Harris reported that median dialysis costs were significantly higher for early-start compared to late-start dialysis (AU$117 000 *vs* AU$96 000), although there was no difference in total costs (AU$215 368 *vs* AU$205 767).

'Planned early start did not result in an improvement in patient quality of life. Indeed, when adjusted for baseline quality of life, there was a small but non-significant reduction in quality of life in the early-start group,' he added.

About 12–25% of patients die each year on dialysis so it was an attractive concept that early-start dialysis might avoid complications of advanced uraemia. Conversely, there were concerns that earlier treatment might reduce quality of life and increase costs. In the UK, indicative costs for hospital haemodialysis are £35 000 per patient per year.

Sue Lyon

Cooper BA, Branley P, Bulfone L et al (2010) A randomized controlled trial of early versus late initiation of dialysis. *N Engl J Med* [epub before print June 27]

Role of FGF-23 in mineral metabolism in chronic kidney disease

A paradigm shift is underway in understanding the central regulatory role of fibroblast growth factor (FGF)-23 in mineral and bone disorders in chronic kidney disease (CKD), according to Dr Myles Wolf, University of Miami, USA.

Mineral and bone disorder in CKD is a systemic disorder of mineral and bone homeostasis that manifests in abnormalities in calcium, phosphorus, parathyroid hormone and vitamin D levels, leading to skeletal abnormalities and calcification of the vasculature or other soft tissues.

Speaking during the ERA-EDTA congress, Dr Wolf commented: 'The role of FGF-23 in mineral metabolism was first discovered in connection with rare diseases such autosomal dominant hypophosphataemic rickets, but its primary use in clinical practice appears to lie in the management of CKD.'

Serum FGF-23 levels are significantly elevated in CKD patients, and rise as estimated glomerular function rate falls. In contrast, FGF-23 remains stable in healthy volunteers despite variations in phosphate intake.

'It is also notable that FGF-23 is three times the normal range in CKD stage 3b, even when serum phosphorus and parathyroid hormone are normal. It increasingly looks like FGF-23 excess is the primary mechanism [in CKD],' said Dr Wolf.

Serum levels of FGF-23 independently predict progression of CKD. There is also an independent association between FGF-23 levels and the risk of mortality in patients starting haemodialysis.

In the future, FGF-23 might be a useful surrogate marker to identify high-risk CKD patients who might benefit from early treatment. According to Dr Wolf, intervention might involve treatment of disordered phosphorus metabolism, using phosphate binders, before the phosphate levels are overtly elevated.

'There is evidence, at least with sevelamer, that it is possible to use a phosphate binder to lower FGF-23 levels in CKD patients with normal serum phosphate (Oliveira et al, 2010). This sets the stage for larger clinical trials targeting this group of patients,' he concluded.

Sue Lyon

Oliveira RB, Cancel AL, Graciolli FG et al (2010) Early control of PTH and FGF23 in normophosphatemic CKD patients: a new target in CKD-MBD therapy? *Clin J Am Soc Nephrol* **5**: 286–91

European League against Rheumatism
Rome, 16–19 June

Modified-release prednisone improves rheumatoid arthritis symptoms

A modified-release formulation of low-dose prednisone improves rheumatoid arthritis symptoms and morning stiffness, according to new results presented at EULAR.

The single-pulse night-time release tablet formulation of low dose prednisone (Lodotra) was approved in the EU for the treatment of rheumatoid arthritis and associated morning stiffness last year.

Once ingested, prednisone is not released until 4 hours later and maximum plasma levels are reached 6 hours after intake. This enables a dose to be taken at 10 pm, with the dose of prednisone not being released until 2 am, reaching maximum plasma levels at 4 am – regarded as the optimal timing to relieve stiffness and pain on waking.

A phase III study (CAPRA-1) in 288 patients reported in the *Lancet* 2 years ago showed that modified-release prednisone provided an improvement over the immediate release formulation in reducing morning stiffness.

New results from the Phase III CAPRA-2 (Circadian Administration of Prednisone in Rheumatoid Arthritis-2) study show that ACR20 was achieved by nearly twice as many patients treated with Lodotra (48.5%) as in those given placebo in addition to their disease-modifying anti-rheumatic drug (28.6%) after 12 weeks' treatment. CAPRA-2 randomized 350 patients with active rheumatoid arthritis to modified-release prednisone chronotherapy (5 mg once daily) or placebo, in addition to their pre-existing disease-modifying anti-rheumatic drug.

Rhonda Siddall

Certolizumab pegol maintains quality of life over 3 years

The efficacy of certolizumab pegol, a novel PEGylated anti-tumour necrosis factor drug, is sustained over 3 years, according to data from an open label extension study presented at EULAR.

The study included 96% of patients (342) with active rheumatoid arthritis in spite of methotrexate treatment who completed the 24-week Rheumatoid Arthritis Prevention of Structural Damage (RAPID 2) study. RAPID 2 showed that certolizumab combined with methotrexate was effective in improving the signs and symptoms of rheumatoid arthritis and inhibited joint damage progression.

Patients taking certolizumab pegol 200 mg or 400 mg plus methotrexate who completed RAPID 2 initially received certolizumab pegol 400 mg plus methotrexate every other week in the open label extension. The dose was decreased to 200 mg every other week after about 6 months.

Improvements in symptoms and inhibition of progression of joint damage were sustained for 3 years and 2.5 years respectively. No new safety signals were identified.

Lead investigator Professor Josef Smolen from the University of Vienna said: 'It is critical that patients and physicians are confident new treatments can deliver a rapid response and are effective in the longer term to help maintain overall quality of life.'

Rhonda Siddall

COX-2 selective treatment reduces gastrointestinal side effects

The cyclo-oxygenase-2 (COX-2) selective non-steroidal anti-inflammatory drug (NSAID) celecoxib is less likely to cause gastrointestinal damage than the combination of a non-selective NSAID and a proton pump inhibitor, new data presented at EULAR and published in the *Lancet* shows.

Adverse upper and lower gastrointestinal outcomes were four times more likely in patients receiving non-COX-2-selective pain relief than those treated with a selective NSAID and a proton pump inhibitor.

The Celecoxib *vs* Omeprazole and Diclofenac in Patients With Osteoarthritis and Rheumatoid Arthritis (CONDOR) trial was a 6-month, double-blind trial which randomized 4484 osteoarthritis or rheumatoid arthritis patients at increased gastrointestinal risk to either celecoxib 200 mg twice a day or diclofenac slow release 75 mg twice a day plus omeprazole 20 mg once a day. The primary end point was a composite of clinically significant upper or lower gastrointestinal events (Chan et al, 2010).

Other studies have shown that COX-2 selective NSAIDs plus a proton pump inhibitor have similar side effects in the upper gastrointestinal tract but that adverse effects in the entire gastrointestinal tract might be less frequent with selective drugs than with non-selective drugs.

CONDOR lead investigators Professor Francis Chan from the Prince of Wales Hospital in China and Professor Jay Goldstein from the University of Illinois have suggested that patients who are not at increased risk of cardiovascular disease but at higher risk of gastrointestinal problems might benefit from a selective strategy for pain relief and suggested that guidelines should be reviewed in light of these findings.

In an accompanying editorial, Drs Rahme and Bernatsky (2010) from McGill University in Montreal question these conclusions, writing that this advice might be premature.

Rhonda Siddall

Chan FKL, Lanas A, Scheiman J, Berger MF, Nguyen H, Goldstein JL (2010) Celecoxib versus omeprazole and diclofenac in patients with osteoarthritis and rheumatoid arthritis (CONDOR): a randomised trial. *The Lancet* **376**(9736): 173–9

Rahme E, Bernatsky S (2010) NSAIDs and risk of lower gastrointestinal bleeding. *The Lancet* **376**(9736): 146–8