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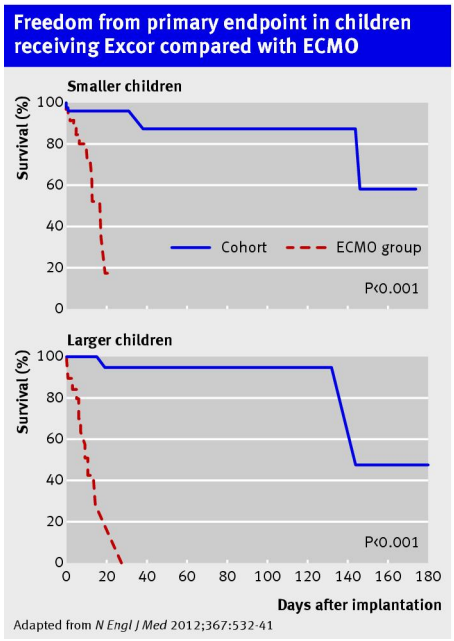
RESEARCH NEWS

All you need to read in the other general journals

Heart pumps improve children's survival to transplantation

N Engl J Med 2012;367:532-41



Compared with adults, children with severe heart failure wait longer for a transplant. Also, fewer and less successful options are available, in terms of mechanical heart support, to prolong survival until a donor heart is available. Extracorporeal membrane oxygenation (ECMO) is most commonly used for this purpose, but previous research indicated that a ventricular assist device called the Berlin Heart Excor might offer additional survival benefit.

Direct comparison of the two approaches was considered unethical. Thus, propensity score matched registry data for children who previously received ECMO were used as a comparison. Even the primary outcomes differed: for Excor, this was time to death or weaning from the device owing to an unacceptable neurological outcome (coma or severe impairment after stroke); for ECMO, neurological outcomes were unavailable so only time to death was assessed.

Forty eight children 16 years or younger awaiting transplantation because of severe heart failure, despite state of the art medical treatment, were recruited in 17 centres across the US and Canada. All children were implanted with Excor devices. Among the 24 smaller children (body surface area <0.7 m^2; median age 1 year), more than half were free of the primary outcome at 174 days—the longest any child was on the pump; 21 children underwent transplantation, whereas two children had died and one was taken off the pump because of severe stroke. In contrast, more than half of the smaller children who had received ECMO died by day 13. A similar survival benefit with Excor, compared with ECMO, was seen in larger children (body surface area 0.7-1.5 m^2; median age 9 years).

However, serious adverse events such as major bleeding or infection occurred in about half of the children implanted with the device, and nearly one in three had a stroke. Pumps often needed to be exchanged, usually because of clotting inside the pump.

The editorialist (p 567) expects that devices still being developed will offer even greater benefits for small patients.

How best to treat elderly people with mantle cell lymphoma

N Engl J Med 2012;367:520-31

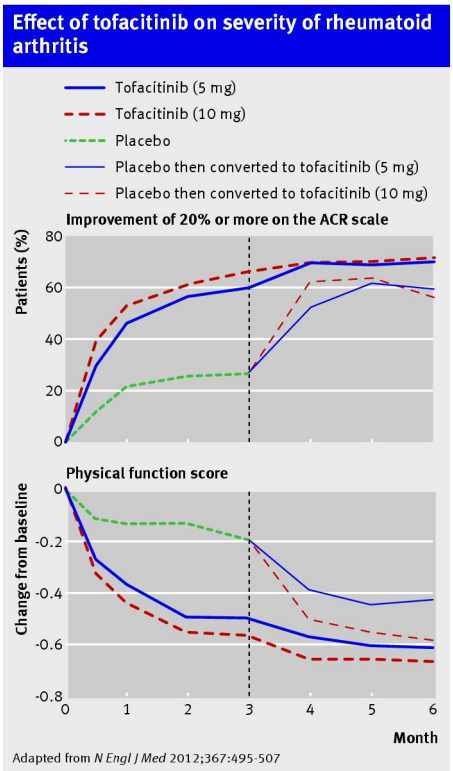
A trial compared two regimens and, if the regimen was successful, two types of maintenance treatment in people with mantle cell lymphoma, a rare form of non-Hodgkin's lymphoma with a poor prognosis. The R-CHOP regimen was better than the R-FC one, and maintenance treatment with rituximab was better than maintenance with interferon alfa. All participants were 60 years or older, and half were 70 or older at baseline.

R-CHOP comprises the anti-CD20 monoclonal antibody rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. It was given in eight cycles every 21 days. R-FC contains rituximab, fludarabine, and cyclophosphamide and was given in six cycles every 28 days.

No difference was seen for the primary outcome—complete remission—between the two regimens (40% (98/246) with R-FC *v* 34% (81/239) with R-CHOP). However, progression was more common with R-FC (14% *v* 5%). Higher grade toxicity against all types of blood cells was also more common with this regimen, although rates of serious infections were comparable between the groups (17% with R-FC *v* 14% with R-CHOP).

At four years, fewer than half of those who received R-FC were still alive, compared with nearly two thirds of those who were allocated R-CHOP (47% *v* 62%). In addition, 87% of patients randomised to rituximab versus 63% of those who received interferon alfa were still alive at four years.

A new antirheumatic may soon become available, but its safety needs further study



N Engl J Med 2012;367:495-507

N Engl J Med 2012;367:508-19

Tofacitinib—a Janus kinase inhibitor that is taken orally—showed promise as a new agent against rheumatoid arthritis in two phase III trials. The trials tested people with an inadequate response to treatment with methotrexate or other available agents.

In both trials, only about a quarter of patients receiving placebo had an improvement of 20% or more on the American College of Rheumatology (ACR) scale between baseline and three or six months. With tofacitinib, such improvements were seen for half to two thirds of patients. The score reflected the number of tender and swollen joints, as well as pain, disability, inflammation, and patient's and doctor's global assessment of the disease.

Improvements in physical function, measured by the Health Assessment Questionnaire Disability Index, were also greater with tofacitinib than with placebo. However, tofacitinib reduced disease activity—as assessed by a score that takes into account 28 joints, general patient's assessment of the disease, and the erythrocyte sedimentation rate—in only one of the trials. This trial also included adalimumab, a tumour necrosis factor inhibitor, which seems to be similar to tofacitinib in its effectiveness against rheumatoid arthritis.

If the new drug is approved, it is not yet clear who should take it and when (p 565). This will largely depend on the safety profile, which is not well documented. Tofacitinib seems to be toxic for neutrophils and the liver. Serious infections were seen in the one year trial, including two cases of pulmonary tuberculosis among the 201 patients who received tofacitinib at a dose of 10 mg twice a day.

Weighing cardiovascular benefits of statins against increased risk of diabetes

Lancet 2012;380:565-71

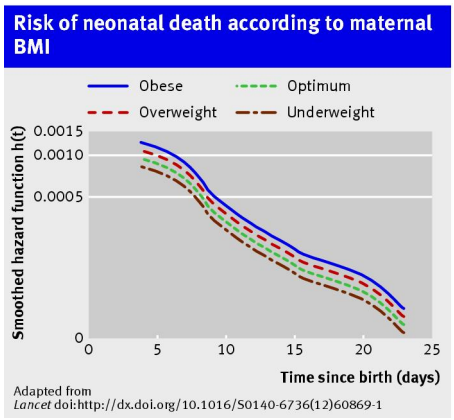
Concerns had been raised that statins increase the risk of diabetes, especially in people without previous cardiovascular disease. A trial of 17 603 people, which tested rosuvastatin 20 mg daily against placebo, provided data to help researchers weigh risks against benefits. All participants were free of cardiovascular disease or diabetes at baseline but had plasma C reactive protein at or above 2 mg/L, putting them at increased risk of both. Participants were followed up for up to five years, with a median of two years, but the study did not evaluate all participants for development of new diabetes. Instead, it relied on treating physicians to report newly diagnosed cases.

Participants had at least one major risk factor for diabetes—metabolic syndrome, fasting glucose 5.55-6.99 mmol/L, body mass index of 30 or more, or glycated haemoglobin >6% (42 mmol/mol). Rosuvastatin reduced the occurrence of the primary outcome—a composite of myocardial infarction, stroke, admission to hospital for unstable angina, arterial revascularisation, or cardiovascular death—by 39% compared with placebo (hazard ratio 0.61, 95% CI 0.47 to 0.79). Rosuvastatin also non-significantly reduced the occurrence of venous thromboembolism (0.64, 0.39 to 1.06) and total mortality (0.83, 0.64 to 1.07). However, the statin increased the incidence of diabetes by 28% (1.28, 1.07 to 1.54).

In other words, in people with at least one major risk factor for diabetes, 134 cardiovascular events or deaths were avoided with rosuvastatin for every 54 new cases of diabetes diagnosed. In people without major risk factors for diabetes at baseline, 86 cardiovascular events or deaths were avoided, without increased risk of diabetes (0.99, 0.45 to 2.21). The primary outcome was reduced by 52% (0.48, 0.33 to 0.68), although in these people the reductions in venous thromboembolism and total mortality did not reach statistical significance (0.47, 0.21 to 1.03 and 0.78, 0.59 to 1.03, respectively).

The editorialists (p 541) conclude that benefits do seem to outweigh the risks. But doctors need to inform patients of the risks, monitor their blood glucose, and advise them to exercise and lose weight to help prevent diabetes.

Maternal obesity is linked with newborn deaths in sub-Saharan Africa



Lancet 2012; http://dx.doi.org/10.1016/S0140-6736(12)60869-1

In high income settings, maternal obesity is a known risk factor for newborn deaths. This has also been shown for sub-Saharan Africa, where data are hard to come by. In the absence of longitudinal studies, the researchers relied on self reported survey data collected from more than 80 000 women across 27 countries. The response rate was over 90%.

Women's body mass index (BMI), calculated from weight and height measured at the time of the survey, was found to be associated with the risk of death in their newborn offspring in the five preceding years. Only births closest to the survey date were taken into account.

Although two out of three women were in the normal range of BMI (18.5-24.9), 13.7% (11 252/81 126) were overweight and 5.3% (4266) were obese (BMI 25-29.9 and 30 or over, respectively). On the day of delivery and the next day, the odds of neonatal death were increased 1.32-fold for mothers who were overweight and 1.62-fold for those who were obese. No excess risk was seen in underweight women (BMI <18.5) or in overweight or obese women in the rest of the neonatal period, up to the 28th day of life.

The study could not pinpoint the mechanisms that may be at play. Potential candidates are prematurity, intrapartum events, or infections. The odds of neonatal death were 2.69-fold higher if the baby was born by caesarean section rather than vaginally.

Exercise improves quality of life for people with cancer

Cochrane Database Syst Rev 2012;8:CD007566

Cochrane Database Syst Rev 2012;8:CD008465

Two Cochrane reviews analysed dozens of trials involving thousands of participants that assessed potential benefits of exercise to ameliorate adverse effects of disease as well as treatment in people with cancer. One review focused on people who were still being treated and the other covered survivors of cancer. Trials performed in people who were terminally ill or in hospice care were excluded.

Beneficial effects of exercise were seen on overall quality of life, as well as specific domains such as concerns about cancer, self esteem, emotional wellbeing, sexuality, and sleep. Improvements were also seen in physical, emotional, and social functioning. In addition, exercise reduced depression, anxiety, fatigue, and pain.

Various types of exercise—such as strength or resistance training, walking, cycling, yoga, Qigong, tai chi, or some combination of these—were tested against usual care or other non-exercise interventions. Medium to high intensity rather than low intensity exercise seemed to be of most benefit, but more research is needed to pinpoint exactly when to start, in what way, for how long, and how hard. Few adverse events were reported with exercise.

Garlic, drugs, or cocoa for hypertension?

Cochrane Database Syst Rev 2012;8:CD006742

Cochrane Database Syst Rev 2012;8: CD007653

Cochrane Database Syst Rev 2012;8:CD008893

One review of four trials that comprised nearly 9000 participants looked at how well antihypertensive drugs prevent cardiovascular events and death in people with mild hypertension, defined as systolic blood pressure of 140-159 mm Hg or diastolic pressure 90-99 mm Hg (or both). All participants were free of cardiovascular disease at baseline.

No effects were seen over four to five years, compared with placebo, for overall mortality (relative risk 0.85, 95% CI 0.63 to 1.15), coronary heart disease (1.12, 0.80 to 1.57), stroke (0.51, 0.24 to 1.08), or total cardiovascular events (0.97, 0.72 to 1.32). One in 10 people stopped taking antihypertensives because of adverse effects, a fivefold increase over placebo. The review did not report effects of drugs on blood pressure, if any.

Another review found two small trials that compared garlic powder with placebo in people with mild hypertension. Garlic might help reduce blood pressure—possibly by about 10 mm Hg for systolic blood pressure and a little less for diastolic blood pressure. However, the confidence intervals were wide, and no data were available on which to assess the potency of garlic to prevent cardiovascular events.

Cocoa is rich in flavanols, which cause blood vessel dilatation and are thought to reduce blood pressure. Most of the 20 trials (about 850 participants) tested a daily dose of 500-750 mg of flavanols ingested through chocolate or cocoa products. Most participants were healthy and normotensive at baseline, and most trials lasted only about a month.

Small reductions in blood pressure were seen with cocoa, compared with placebo: −2.77 (−4.72 to −0.82) mm Hg for systolic pressure and −2.20 (−3.46 to −0.93) mm Hg for diastolic blood pressure. One in 20 people allocated cocoa had adverse effects, compared with one in 100 of those receiving placebo. Gastrointestinal effects and a dislike of the product's taste were the most common problems.

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