Panic attacks linked to higher risk of heart disease

People who have been diagnosed with panic attacks or panic disorder have a greater risk of subsequently developing heart disease or suffering a heart attack than the normal population, with higher rates occurring in younger people (Walters et al, 2008).

People who were younger than 50 years of age when first diagnosed had a significantly higher risk of subsequent myocardial infarctions, but this was not the case in older people. A significantly higher incidence of subsequent coronary heart disease was found in people diagnosed with panic attacks or disorder at all ages, but was more marked in the under 50s.

However, the research also showed that the risk of dying from coronary heart disease was actually reduced among people of all ages who had been diagnosed with panic attacks/disorder.

The study looked at a large sample of the UK population of all ages (404 654 people) from a primary care population that can be broadly generalized to countries with a similar socio-demographic structure.

Dr Kate Walters, a senior lecturer in primary care at University College London, who led the research, said: 'Not much is known about the relationship between panic disorder and cardiac disease. The symptoms of panic attacks can closely mimic those of a heart attack or acute cardiac disease, and it seems that there may be a complex relationship between them.

'Our findings have significant implications for clinicians. Panic attacks were associated with a significant increased risk of a subsequent diagnosis of coronary heart disease and acute myocardial infarctions in those aged younger than 50 years. This may be a result of initial misdiagnosis of coronary heart disease as panic attacks, or a true underlying increased risk of coronary heart disease with panic attacks.'

Dr Walters speculated about possible reasons for the reduced risk of death. 'This might be because the higher risk of coronary heart disease and heart attacks occurred among younger people who have fewer heart-related deaths generally; or it might be because people with panic disorders go to their doctors earlier and more frequently and, therefore, are more likely to have their heart disease identified and treated early, thus reducing the likelihood of dying from it.'

Walters K, Rait G, Petersen I, Williams R, Nazareth I (2008) Panic disorder and risk of new onset coronary heart disease, acute myocardial infarction, and cardiac mortality: cohort study using the general practice research database. *Eur Heart J* **29**(24): 2981–8

Step forward in management of atopic dermatitis

The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency has issued a positive opinion, recommending the approval of a twice-weekly application regimen of Protopic ointment (tacrolimus monohydrate) for the prevention of flares and prolongation of flare-free periods.

This regimen is indicated for appropriate adults and children 2 years of age and above, with moderate to severe atopic dermatitis who have had an initial response to a maximum of 6 weeks treatment of twice daily tacrolimus ointment (lesions cleared, almost cleared or mildly affected).

The standard approach to managing atopic dermatitis has been to treat flares as and when they occur with topical anti-inflammatory agents, such as topical corticosteroids or topical calcineurin inhibitors. However, a deeper understanding of the pathology of this disease has revealed that subclinical inflammation persists, even after the clinical signs of flare have resolved.

This twice-weekly treatment regimen with tacrolimus ointment would allow physicians to actively manage the subclinical inflammation between flares in appropriate patients with moderate or severe disease to prevent flare recurrence and prolong the time that patients are free from flares.

Tacrolimus has been available for the treatment of moderate to severe atopic dermatitis in appropriate adults and children 2 years of age and above since 1999. This new indication is for the prevention of flares and the prolongation of flare-free intervals in patients experiencing a high frequency of disease exacerbations (i.e. occurring 4 or more times per year) who have had an initial response to a maximum of 6 weeks' treatment with twice daily tacrolimus ointment (lesions cleared, almost cleared or mildly affected).

The positive opinion is now referred for final action to the European Commission, which grants approval in the European Union, to evaluate this recommendation and issue final authorization. The Commission usually makes a decision within 2–3 months of the CHMP issuing its recommendation.

Lowest human blood oxygen levels on record

The lowest ever levels of oxygen in humans have been reported in climbers. The world-first measurements of blood oxygen levels in climbers near the top of Mount Everest could eventually help critical care doctors to re-evaluate treatment strategies in some long-term patients with similarly low levels of blood oxygen.

The Caudwell Xtreme Everest team made the measurements by taking blood from leg arteries while they were close to the summit of Mount Everest at 8400 m above sea level. The team climbed with oxygen tanks, then removed their masks 20 minutes before testing to equilibrate their lungs with the low-oxygen atmosphere. The team were unable to make the measurement on the summit as conditions were too severe, with temperatures at -25°C and winds above 20 knots.

Having descended a short distance from the summit, the doctors drew blood from the femoral artery. Blood collected from four team members was then carried back down the mountain to be analysed within 2 hours at a science laboratory set up at the team's camp at 6400 m on Everest.

Grocott MP, Martin DS, Levett DZ, McMorrow R, Windsor J, Montgomery HE; Caudwell Xtreme Everest Research Group (2009) Arterial blood gases and oxygen content in climbers on Mount Everest. *N Engl J Med* **360**(2): 140–9

Etanercept in children with severe psoriasis

Enbrel (etanercept), a tumour necrosis factor (TNF) blocker, has been approved for the treatment of children with severe plaque psoriasis. Etanercept is the only biologic treatment approved for chronic severe plaque psoriasis in children and adolescents aged 8 years and above. Paediatric patients who have taken etanercept experienced significant improvement in their signs and symptoms of psoriasis (Paller et al, 2008).

Psoriasis is one of the most debilitating skin conditions and its impact on children's lives is similar to that of asthma and epilepsy. Psoriasis in adults is often associated with other conditions such as obesity, type 2 diabetes, hypertension and clinical depression. Its effective management in children is a significant challenge as many existing treatments are not licensed or have limited use as a result of their low tolerability and adverse reactions.

'The efficacy and safety profile of etanercept is supported by extensive clinical evidence and its availability for children represents a significant milestone in the treatment of childhood psoriasis,' said Dr Ruth Murphy, Consultant Dermatologist at Queen's Medical Centre, Nottingham.

Etanercept is an effective treatment for children with severe plaque psoriasis according to the results of a 48-week study that involved 211 patients with moderate-to-severe psoriasis between the ages of 4 and 17 years.

Paediatric patients treated with etanercept experienced a significant improvement in their psoriasis compared with those treated with placebo. At week 12, almost two thirds of patients (57%) achieved a 75% improvement in the psoriasis area and severity index, compared with 11% of patients receiving placebo.

Within the 48-week study, four serious adverse events occurred in three patients. All occurred in patients receiving open-label treatment and all resolved without sequelae. No serious adverse events were reported during the 12-week placebo-controlled period.

Paller AS, Siegfried EC, Langley RG et al (2008) Etanercept treatment for children and adolescents with plaque psoriasis. *N Engl J Med* **358**: 241–51

Mouth rinse prevents and treats oral mucositis

Caphosol, a new mouth rinse, has been launched for the prevention and treatment of oral mucositis. Oral mucositis is one of the most common and debilitating side effects of cancer treatment caused by radiotherapy or chemotherapy and affects approximately 115 000 people a year in the UK.

In a double-blind, prospective, randomized clinical trial of 95 patients undergoing bone marrow transplantation following radiotherapy or chemotherapy, more than twice as many patients in the Caphosol treatment group avoided oral mucositis altogether and the duration of symptoms was halved. In the Caphosol group patients used 72% less morphine for the pain and nearly 75% needed no morphine at all.

'It is extremely frustrating having to watch my cancer patients go through the pain and discomfort of oral mucositis, particularly as it is a predictable complication,' said Professor Charlie Craddock, Consultant Haematologist, University Hospitals Birmingham NHS Foundation Trust. 'Preventing its development in the first place would allow us to avoid treatment interruptions that can lengthen inpatient stay and may compromise delivery of treatment in a timely fashion'.

Oral mucositis affects virtually all patients receiving radiation therapy for head and neck cancer, more than 70% of patients undergoing bone marrow transplantation and 40% of patients who receive conventional chemotherapy. The economic impact of mucositis can be significant. In severe cases, the costs of cancer care for oral mucositis patients can more than double.

Oral mucositis symptoms range from redness to severe ulceration of mucosal tissues. It can limit patients' ability to eat or swallow as well as causing severe pain that can require the use of opioid analgesics and may ultimately require hospitalization.

Oral mucositis can necessitate reductions in dose and/or duration of radiotherapy, cause treatment delays and is associated with a higher risk of infection in patients that are already immunocompromised.

Caphosol consists of a supersaturated calcium and phosphate solution. Calcium has an important role in tissue repair while phosphate is a key building block of the mucosal lining, helps maintain the pH balance, reducing the risk of bacterial overgrowth and helps maintain dental structure. Caphosol is convenient and easy to use and can be used at home, without medical supervision.

Tibolone off limits for breast cancer patients

A double-blind, randomized trial was conducted in patients with a history of breast cancer who experience vasomotor symptoms to see if tibolone affects disease recurrence. The trial was stopped early as a result of the findings, so tibolone remains contraindicated for women with past or suspected breast cancer.

Adjunctive lacosamide for partial-onset seizures

Lacosamide is now an option as adjunctive treatment in patients with uncontrolled partial-onset seizures. A double-blind, placebo-controlled trial looked at its efficacy and safety when added to concomitant antiepileptic drugs in patients with uncontrolled partial-onset seizures.

Treating progressive neurological manifestations of Niemann–Pick type C

Miglustat (Zavesca) has been approved in the EU for the treatment of progressive neurological manifestations in patients with Niemann–Pick type C disease. It is already indicated for treatment of adult patients with mild to moderate type 1 Gaucher disease for whom enzyme replacement therapy is unsuitable.

AMERICAN SOCIETY OF HEMATOLOGY
SAN FRANCISCO, CALIFORNIA, 6–9 DECEMBER

Deferasirox reduces cardiac iron in beta-thalassaemia patients

New data from the largest prospective trial in iron chelation demonstrate the efficacy and safety of Exjade (deferasirox) in treating chronic transfusional iron overload. This is a potentially life-threatening condition for patients who have had multiple blood transfusions to treat underlying anaemias such as beta-thalassaemia.

Data from this landmark trial, known as EPIC, were presented at the American Society of Hematology meeting.

The EPIC cardiac substudy showed that deferasirox removed iron from the heart in beta-thalassaemia patients, based on a statistically significant improvement (P<0.0001) in T2*(i) magnetic resonance imaging (a validated technique to assess cardiac iron content). The 2-year substudy included 114 beta-thalassaemia patients with cardiac iron overload, the leading cause of death in these patients.

'These data clearly demonstrate that deferasirox significantly reduces cardiac iron in beta-thalassaemia patients with iron overload, which is a critical goal of treatment for these patients,' said Dudley Pennell, Professor of Cardiology, Royal Brompton and Harefield NHS Trust and Imperial College, London. 'Cardiac complications caused by the buildup of toxic iron in the heart can be life-threatening for people living with thalassaemia.'

Regular blood transfusion therapy is essential for patients with chronic anaemias such as beta-thalassaemia, and may be necessary in diseases such as sickle cell disease and myelodysplastic syndromes, in order to improve quality of life and survival. However, the consequence of these blood transfusions may be iron overload as the body has no physiological means to remove iron. This iron overload is life-threatening and if left untreated causes significant tissue damage to the heart, other organs such as the liver and endocrine glands, and can ultimately lead to death.

Dudley Pennell, Professor of Cardiology, Royal Brompton and Harefield NHS Trust

Chronic lymphocytic leukaemia: rituximab 'will change clinical practice'

Data from a new multinational phase III clinical trial suggest that immunochemotherapy – resulting from a combination of chemotherapy with a new biologic agent – may become the new standard first-line therapy for the treatment of advanced chronic lymphocytic leukaemia.

Dr Michael Hallek (Department of Internal Medicine, University of Cologne, Germany) reported that in the CLL8 study (thought to be the largest of its kind in untreated chronic lymphocytic leukaemia), more than 44% of patients achieved complete remission on immunochemotherapy with rituximab – nearly double that for those on chemotherapy alone. In addition, progression-free survival was significantly improved at 2 years.

'With a median age of onset of 70 years, chronic lymphocytic leukaemia is a classic haematological malignancy of the elderly,' he said. 'Until now, chemotherapy with a combination of fludarabine and cyclophosphamide was considered to be the standard first-line therapeutic option for physically fit patients with chronic lymphocytic leukaemia.'

A total of 817 patients with previously untreated chronic lymphocytic leukaemia (median age 61 years) were randomized to receive six 28-day cycles of fludarabine and cyclophosphamide alone (FC) or in combination with rituximab (FCR).

After an average follow-up of 25.5 months, the end-of-treatment response rate was significantly higher in the FCR arm compared to the FC arm (84.1% *vs* 73.3 P<0.01), with most of the benefit seen in terms of complete responders (44.5% *vs* 22.9%, P<0.01).

At 2 years, progression-free survival was highly significantly improved in 76.6% of patients in the FCR arm compared to 62.3% for FC alone. Median progression-free survival was 42.8 months *vs* 32.3 months favouring FCR (P≤0.0001).

'Of course, safety is just as important as efficacy,' insisted Dr Hallek. He reported that while FCR was found to cause more neutropaenia (33.6% *vs* 20.9%, P=0.0001) and leukocytopaenia (24% *vs* 12.1%, P<0.0001), it did not increase the incidence of severe infections (18.8% *vs* 14.8%, P=0.68) compared to FC.'

'Importantly,' he added, 'increasing age made no difference on the impact of the FCR regimen in terms of grade 3/4 adverse events (75.6% *vs* 83.7% for ages <70 years and >70 years respectively, non-significant). This was not the case for FC, however, where total grade 3/4 adverse events significantly increased in older patients (61.0% *vs* 78.4% for those aged <70 and >70 years, P=0.04).'

Dr Hallek concluded: 'These results suggest that FCR immunochemotherapy might become the new standard first-line treatment for physically fit chronic lymphocytic leukaemia patients.'

Predicting that the FCR regimen would soon become the new global standard for the first-line treatment of physically fit chronic lymphocytic leukaemia patients – even for those aged 70 years and beyond – he concluded: 'This will undoubtedly change clinical practice in the management of this difficult-to-treat haematological cancer'.

Stephen Pinn

This conference report is published online by Doctors.net.uk. For further articles and video interviews, visit www.doctors.net.uk/ch1

AMERICAN SOCIETY OF HEMATOLOGY
SAN FRANCISCO, CALIFORNIA, 6–9 DECEMBER

Erythropoietin increases risk of death in cancer

Erythropoietin-stimulating agents significantly increase the risk of death in cancer patients, concluded a meta-analysis presented in the late-breaking session at ASH.

The industry-independent study, undertaken by investigators from the University of Bern, Switzerland, and the University of Cologne, Germany, reviewed data on 13 933 cancer patients, taken from 53 clinical trials, comparing those receiving erythropoietin-stimulating agents with those not.

Results show that for all patients in the study, the on study mortality had a hazard ratio of 1.17 (1.06–1.30) for use of erythropoietin-stimulating agent (P=0.002), and overall survival had a hazard ratio of 1.06 (1.00–1.12) for erythropoietin-stimulating agent use (P=0.05). For the 10 441 patients who were also receiving chemotherapy, on study mortality had a hazard ratio of 1.10 for erythropoietin-stimulating agent use (0.98–1.24) (P=0.12), and overall survival had a hazard ratio of 1.04 (0.97–1.11) (P=0.26) for erythropoietin-stimulating agent use.

'The increased risk of death must be balanced against the benefits of erythropoietin-stimulating agents, taking into account each patient's clinical circumstances and preferences,' commented Dr Julia Bohlius from the University of Bern, who presented the data.

Speculating on possible explanations for these findings, Andreas Engert, the lead author from the University of Cologne, said there were data showing erythropoietin receptors were found on tumours, suggesting that erythropoietin-stimulating agents might stimulate and promote tumour growth. An alternative explanation, he added, was that the mortality resulted from an increase in thromboembolic events.

Future studies, suggested Dr Bohlius, should include evaluation of the impact of haemoglobin baseline levels on mortality, and the impact of erythropoietin-stimulating agents on thromboembolic events and tumour progression.

Janet Fricker

Improving outcomes in thrombocytopaenia

Significant advances in treatment and survival outcomes for patients with thrombocytopaenia were highlighted in a landmark study – profiling a low-dose platelet transfusion strategy for patients with hypoproliferative thrombocytopaenia.

Dr Sherrill Slichter (Puget Sound Blood Center, Seattle, Washington) reported data from the Effects of Prophylactic Platelet Dose on Transfusion Outcomes (PLADO) study, which showed that patients with hypoproliferative thrombocytopaenia can be safely and effectively transfused with low doses of platelets.

A total of 1272 patients with hypoproliferative thrombocytopenia (caused by failure of the marrow to produce platelets) who were expected to be hospitalized with platelet counts of ≤10 000 µl for more than 5 days were enrolled in the study and received at least one platelet transfusion.

Patients were randomized to receive one of three platelet-transfusion dosing regimens: a low dose ($1.1x10^{11}$ platelets/m^2), a medium dose ($2.2x10^{11}$ platelets/m^2), or a high dose ($4.4x10^{11}$ platelets/m^2). An acceptable dose of platelets could be within 25% (lower or higher) of the target dose. About 85% of patients in this cohort were transfused prophylactically, and 15% therapeutically.

The number of platelets transfused was significantly lower in the low-dose arm – a median of $9x10^{11}$ compared to $11x10^{11}$ for the medium dose and $20x10^{11}$ for the high dose (P=0.002 for low dose *vs* medium dose, P<0.001 for medium *vs* high-dose, and P<0.001 for low *vs* high-dose).

Dr Slichter concluded: 'The cost of platelet transfusion is prohibitively expensive, so anything we can do to reduce that cost is of benefit to the medical community. This study has shown that use of a low-dose prophylactic platelet transfusion strategy would be expected to reduce costs of platelet therapy as well as helping to prevent shortages in platelet supply.'

Stephen Pinn

This conference report is published online by Doctors.net.uk. For further articles and video interviews, visit www.doctors.net.uk/ch1

Imatinib gives impressive long-term survival in CML patients

Nearly nine out of ten patients (86%) with a life-threatening leukaemia are still alive 7 years after diagnosis when treated with Glivec (imatinib). Data from the largest clinical trial of over 1100 newly diagnosed patients with Philadelphia chromosome positive (Ph+) chronic myeloid leukaemia (CML) demonstrate the longest overall survival observed to date in this disease area.

Data presented at ASH from the 7-year update of the landmark International Randomized Interferon versus STI571 (IRIS) study also demonstrate an extremely low rate of disease progression. Between years six and seven, only one patient progressed to a more advanced stage of the disease.

Dr Stephen O'Brien, Senior Lecturer in Experimental Haematology, University of Newcastle, and investigator on the IRIS trial said: 'Chronic myeloid leukaemia patients treated with imatinib continue to demonstrate impressive long-term survival. Long-term analyses are offering important new insights and, encouragingly, we're seeing that patients' clinical responses are durable over time.'