The final results of the HYpertension in the Very Elderly Trial (HYVET) have been announced at the American College of Cardiology Annual Scientific session, held in Chicago, IL, USA

Reduction of stroke and all-cause mortality in the very elderly using antihypertensive treatment: results from the HYVET trial

A new trial has studied the treatment of elderly patients with low-dose indapamide, with or without perindopril, and claims to significantly reduce stroke and all-cause mortality in hypertensive patients aged 80 years and older. Evidence that treating people aged 80 years or more to lower blood pressure is beneficial has until now been inconclusive.

"It is never too late to start antihypertensive medication."

They trial was lead by Nigel Beckett from the University College London, UK. He indicated that the findings demonstrated that, "it is never too late to start antihypertensive medication."

Beckett explained that previous results had been inconclusive, owing to the under-representation of those 80 years of age or above in clinical trials. Epidemiologic data have even suggested that higher blood pressure (BP) levels may be protective in the very elderly, although this could reflect risks from therapy or conditions associated with BP reduction.

The Hypertension in the Very Elderly Trial (HYVET) included 3485 patients over the age of 80 years with systolic (S)BP 160–199 mmHg and diastolic (D)BP of 95–109 mmHg, no severe postural hypotension, and standing SBP greater than or equal to 140 mmHg. Individuals with standing SBP less than 140 mmHg, stroke in the last 6 months, dementia or daily nursing care were excluded. The patients were enrolled in an international, open-label study and randomly assigned to treatment with indapamide, with or without additional perindopril, or placebo.

The average age of patients was 84 years at baseline with a mean entry BP level of 173/91 mmHg; around 8.5% of the patients were diagnosed with orthostatic hypotension; a third had isolated systolic hypertension; and 65% were currently or had previously taken antihypertensive medication.

Those assigned to active treatment received the sustained-release formulation of indapamide at 1.5 mg daily, with addition of perindopril, if needed, first at 0.2 mg, and then 0.4 mg daily to achieve the target BP of 150/80 mmHg.

"...anyone who deals with elderly individuals knows that what they fear most is heart failure events, being breathless, and the loss of independence that comes with a stroke."

After 2 years, SBP had dropped approximately 15 mmHg and DBP 6 mmHg further in patients taking indapamide with or without perindopril than in the placebo group. A total of 48% of the participants in the non-placebo treatment groups achieved their goal BP, with only 19% in the placebo group achieving the same.

At the median follow-up of 1.8 years there was evidence of a 30% relative reduction in the primary end point of all stroke in the indapamide with or without perindopril group compared with the placebo group, but these results could not be proved as significant.

Total mortality was reduced by 21% in the non-placebo groups, but this could be owing to offset by an increase in total mortality in this age group. A total of 57% of strokes were fatal in HYVET, but there was also a significant 39% reduction in fatal stroke.

The trial was halted prematurely in July 2007, when a planned interim analysis showed a significant reduction in the primary end point and total mortality.

Beckett also acknowledged that there was a highly significant 64% reduction in heart failure in patients in the non-placebo group and substantially less serious adverse events.

'The USA and European bodies should provide stronger guidelines recommendations for the management of hypertension in elderly patients.'

"Hopefully we've squashed the idea that it's a balance between risk and benefit, because it was all benefit ... anyone who deals with elderly individuals knows that what they fear most is heart failure events, being breathless and the loss of independence that comes with a stroke", added Beckett.

He recommended that doctors monitor their very elderly patients' BP levels regularly and offer antihypertensive medication to those with elevated BP. Beckett also suggested that the USA and European bodies should provide stronger guidelines recommendations for the management of hypertension in elderly patients.

Source: www.acc.org/media/acc_scientific_session_08/press/monday/10am_ACC_beckett.pdf (press release).

in brief...

An interval >7 weeks between neoadjuvant therapy and surgery improves pathologic complete response and disease-free survival in patients with locally advanced rectal cancer.

Tulchinsky H, Shmueli E, Figer A, Klausner JM, Rabau M: *Ann. Surg. Oncol*. (2008) (Epub ahead of print).

This study uses the pathologic complete response (pCR) rate to assess whether the time interval between neoadjuvant therapy and surgery affects the operative and postoperative morbidity and mortality of patients with locally advanced low- and mid-rectal cancer. The study enrolled 132 pateinets who underwent radical resection preceded by neoadjuvant chemoradiation. Each patient was assessed for neoadjuvant-surgery interval, final pathology, type of operation, operative time, intraoperative blood transfusions, postoperative complications, length of hospital stay, disease recurrence and mortality. The median interval between chemotherapy and surgery was 56 days. Results indicated that 28% of patients had pCR. It was demonstrated that pCR and near pCR rates were higher with longer interval.

Effect of rimonabant on progression of atherosclerosis in patients with abdominal obesity and coronary artery disease: the STRADIVARIUS randomized controlled trial.

Nissen SE, Nicholls SJ, Wolski K *et al.*: *JAMA* 299(13), 1547–1560 (2008).

Abdominal obesity has been associated with metabolic abnormalities and an increased risk of atherosclerotic cardiovascular disease, yet no obesity management strategy has demonstrated an ability to slow progression of coronary disease. This study assesses whether weight loss and metabolic effects of the selective cannabinoid type 1 receptor antagonist rimonabant reduces progression of coronary disease in obese patients. A multi-center randomized, double-blinded, placebo-controlled study compared rimonabant with placebo in 839 patients. The main outcome measures was change in percent atheroma volume (PAV); the secondary efficacy parameter was change in normalized total atheroma volume (TAV). After 18 months of treatment, the study failed to show an effect for rimonabant on disease progression for the primary end point, PAV, but showed a favorable effect on the secondary end point, TAV.

Psoriatic arthritis symptoms may be relieved with long-term infliximab therapy

New research has indicated that patients with treatment-refractory psoriatic arthritis could benefit from long-term infliximab therapy. The therapy was investigated in a total of 104 patients with active psoriatic arthritis who had failed to respond to treatment with at least one disease modifying antirheumatic drug.

Each patient was randomly assigned to receive infliximab 5 mg/kg or placebo infusions at weeks 0, 2, 6, and 14. All patients received infliximab 5 mg/kg every 8 weeks at week 16 until week 46. A total of 78 patients were able to complete the first year of treatment and continued in an extension phase which involved an open-label study, with patients receiving infliximab 5 mg/kg at weeks 54, 62, 70, 78, 86, and 94.

The results showed that 62% of the patients achieved an improvement in American College of Rheumatology (ACR) response criteria of at least 20% at week 98m, with 35% achieving an improvement of at least 70% in ACR scores.

"Findings from the present evaluation of infliximab in psoriatic arthritis indicated that a majority of patients experienced improvement in their disease after 2 years," the team says. "The challenge for the future will be to identify patents most likely to be responders."

Source: Antoni CE, Kavanaugh A, van der Heijde D: Two-year efficacy and safety of infliximab treatment in patients with active psoriatic arthritis: findings of the infliximab multinational psoriatic arthritis controlled trial (IMPACT). *J. Rheumatol.* (2008) (Epub ahead of print).

Oral mini-pulse therapy shows potential in treatment of oral lichen planus

Researchers have demonstrated that betamethasone oral mini-pulse (OMP) is as equally effective for treating oral lichen planus (OLP) as the current recommendation – topical triamcinolone acetonide. The research has also suggested that OMP is associated with an earlier response time. The study enrolled 49 patients with moderate-to-severe OLP to receive either oral betamethasone on 2 consecutive days each week or topical triamcinolone acetonide application three-times a week for a total of 3 months, with reducing amounts being applied for a further 3 months.

Results demonstrated that 68% of OMP-treated patients and 66% of topical triamcinolone acetonide-treated patients achieved a good-to-excellent response, indicated by a 50–75% reduction in clinical score.

The median response seen with OMP was 15.5 weeks, compared with 19 weeks in triamcinolone acetonide-treated patients. Adverse events were reported in 56 and 25% of patients in the betamethasone- and triamcinolone acetonide-treated patients, respectively.

The authors concluded, "We believe that combination therapy or sequential therapy with topical corticosteroids should be evaluated to achieve longer remissions and less frequent relapses."

Source: Malhotra AK, Khaitan BK, Sethuraman G, Sharma VK: Betamethasone oral mini-pulse therapy compared with topical triamcinolone acetonide (0.1%) paste in oral lichen planus: A randomized comparative study. *J. Am. Acad. Dermatol.* 58, 596–602 (2008).

Individualized patient management for breast cancer

The development of a new breast cancer prognostic tool could pave the way for improved therapeutic treatment strategies. The novel tool incorporates gene-expression signatures with clinical and pathological risk factors, which may improve outcome for women in early stages of the disease.

The authors of the study commented, "We envision that the genomic information from an individual patient could easily be incorporated within the context of the clinicopathological prognostic model, to provide a basis for more refined prognosis."

The model is said to provide a more practical solution than current gene predictor models and could easily be incorporated into current clinical practice.

Tumor samples from 964 women with early-stage breast cancer were analyzed with over 11 years follow-up of each patient. Each patient was placed in either a low-risk, intermediate-risk, or a high-risk category for relapse using the novel risk tool that assesses age, comorbidities, estrogen receptor status, tumor grade, tumor size and lymph node status as covariates to assess each patient.

This information was incorporated with several validated gene-expression signatures generated by gene microarray analysis. These signatures are based on genes known to be involved in various malignant processes such as wound healing, invasiveness, epigenetic stem cell specification and tumor necrosis factor activation. This allowed each patient to be assigned to a cluster group that would reflect their relapse-free survival time and sensitivity to various chemotherapy agents.

The authors speculated that, "In an attempt to tailor risk estimation, these investigators shy away from pure metagene predictors but instead focus on genes with mechanistic implication in breast cancer … because these genes represent potential targets for specific molecular therapy, this approach represents an advance in the changing landscape of oncology toward individualized patient management."

Source: Acharya CR, Hsu DS, Anders CK: Gene expression signatures, clinicopathological features,and individualized therapy in breast cancer. *JAMA* 299, 1574–1587 (2008).

Treatment of bipolar I disorder with tamoxifen offers hope in the treatment of mania symptoms

The well-known breast cancer drug, tamoxifen has shown efficacy in treating patients with bipolar disorder. The drug, with an effect similar to that of lithium, was demonstrated to be well tolerated in patients with bipolar I disorder of both sexes.

It is speculated that tamoxifen, a selective estrogen-receptor modulator, works by correcting abnormal protein kinase C (PKC) activity in the brain. Excess PKC activation is known to disrupt regulation of behavior in certain parts of the brain, which could be responsible for some of the symptoms of bipolar disorder, especially those experienced during the mania phase.

The study is reported to be the first proof-of-concept study on the role of PKC activity in the brain. The 3-week randomized, double-blind trial involved 18–60 year olds in a manic or mixed episode state. Those admitted had initial Young Mania Rating Scale (YMRS) scores averaging 38, with some as high as 49, out of a maximum possible rating of 60.

> "With such rapidly acting treatments, patients may have the chance of preventing the emergence of full-blown mania once they sense a manic episode coming on."

A total of 66 patents were enrolled and randomly assigned to tamoxifen or placebo. Initial symptom rates and clinical characteristics were a match for both groups. As well as the YMRS, researchers utilized the Clinical Global Impressions–Mania (CGI–Mania) scale, Positive and Negative Syndrome Scale (PANSS) for psychotic symptoms, depression rating scales, and adverse-effects questionnaires as assessment tools. After 3 weeks, a 50% or greater reduction in YMRS scores from baselines was 48 and 5% in the treated and the placebo group, respectively.

"Tamoxifen resulted in an 18.3 point mean improvement (47.4% improvement relative to the baseline score) in a mania rating scale, in contrast to a 2.9 point worsening (7.8% worsening relative to the baseline score) with placebo," added Yildiz, lead author of the study.

PANNS total scores showed greater improvement with tamoxifen than with placebo, and changes in depression scores also tended to be greater with tamoxifen. There were low rates of adverse events in both groups.

"With such rapidly acting treatments, patients may have the chance of preventing the emergence of full-blown mania once they sense a manic episode coming on", concluded Yildiz.

Source: Tohen M: Clinical trials in bipolar mania: implications in study design and drug development. *Arch. Gen. Psychiatry* 65(3), 255–263 (2008).