Mild cognitive impairment more prevalent in men

The Mayo Clinic Study of Aging evaluated an age- and sex-stratified random sample of Olmsted County residents aged 70–89 years, using the Clinical Dementia Rating Scale, a neurological evaluation, and neuropsychological testing to assess four cognitive domains: memory, executive function, language and visuospatial skills.

Information for each participant was reviewed by an adjudication panel and a diagnosis of normal cognition, mild cognitive impairment or dementia was made using published criteria.

Of 1969 subjects without dementia, 329 had mild cognitive impairment, with a prevalence of 16.0% (95% confidence interval 14.4–17.5) for any mild cognitive impairment, 11.1% (95% confidence interval 9.8–12.3) for amnestic mild cognitive impairment, and 4.9% (95% confidence interval 4.0–5.8) for non-amnestic mild cognitive impairment.

The prevalence of mild cognitive impairment increased with age and was higher in men. The prevalence odds ratio in men was 1.54 (95% confidence interval 1.21–1.96; adjusted for age, education, and non-participation). The prevalence was also higher in subjects who never married and in subjects with an APOE ε3ε4 or ε4ε4 genotype. Mild cognitive impairment prevalence decreased with increasing number of years of education (*P* for linear trend <0.0001).

The study suggests that approximately 16% of elderly subjects who are free of dementia are affected by mild cognitive impairment, and amnestic mild cognitive impairment is the most common type. The higher prevalence of mild cognitive impairment in men may suggest that women transition from normal cognition directly to dementia at a later age but more abruptly.

Petersen RC, Roberts RO, Knopman DS et al (2010) Prevalence of mild cognitive impairment is higher in men. The Mayo Clinic Study of Aging. *Neurology* **75**(10): 889–97

Deaths from liver disease up 60% in last decade

Huge variations in hepatitis C services in hospitals across the country are revealed in a new report by the All-Party Parliamentary Hepatology Group and the Hepatitis C Trust.

The MPs' report is based on the findings of a national audit of hepatitis C hospital services conducted by the All-Party Parliamentary Hepatology Group and the Hepatitis C Trust. It presents data from 69 hospitals delivering hepatitis C services in England.

The report uncovers alarming national and regional liver mortality statistics: deaths from liver disease and liver cancer increased from 6058 to 9719 per year between 1997 and 2008 (a 60% increase). The East Midlands saw the highest rate of increase (87%) over this period – from 440 to 824, and London saw the lowest rate of increase (23%) from 968 to 1190. This is in stark contrast to the rest of Western Europe where deaths from liver disease have been falling for years.

The All-Party Parliamentary Hepatology Group (2010) *In The Dark. An audit of hospital hepatitis C services across England.* www.hepctrust.org.uk/treatment/hcv+reports (accessed 28 September 2010)

Significant geographical variation in hip fracture care

A report from the world's largest and fastest-growing national hip fracture audit (www.nhfd.co.uk/) reveals that NHS hip fracture patients – often some of the most elderly and vulnerable patients in the NHS – are now getting far greater access to specialist care by geriatricians, as well as osteoporosis screening, assessment for the likelihood of future falls and bone protection drugs – which alone can reduce fracture incidence by up to 50%, potentially saving the NHS millions of pounds.

However, the report also flags up significant variations in care quality provision between hospitals, with some patients not being assessed by appropriate doctors, having unacceptable delays before surgery, and missing out on osteoporosis care and falls prevention.

The National Hip Fracture Database National Report 2010 covers more than 36 000 hip fracture patients treated in hospitals in England, Wales, Northern Ireland and the Channel Islands. The findings include:

- 68% of patients assessed for, and 57% discharged on bone protection medicine. A further 7% awaiting a bone scan or bone clinic appointment: total 75% (up 15% from 2009). In 2007 the total figure was less than 15%
- 60% of patients now receive an assessment to determine the likelihood of future falls, with 3% awaiting appointment: total 63% (up 19% from 2009)
- 31% assessed preoperatively by a geriatrician with 32% having other forms of medical assessment: total 63% (up 22% from 2009)
- 80% of patients receive surgery within 48 hours (up 5% from 2009)
- 57% of patients are admitted to an orthopaedic ward within 4 hours.

Rob Wakeman, the National Hip Fracture Database's lead clinician in orthopaedic surgery and a consultant orthopaedic surgeon in Basildon, said: 'Hip fractures are threatening to overwhelm trauma and orthopaedic units, and it is the responsibility of clinicians and managers to work together to come up with solutions to improve patient care in their hospital.'

He continued: 'We are seeing lots of evidence from around the UK that big improvements in the quality of hip fracture care can be achieved in a short space of time. It is vital that those few units that are still underperforming use this guidance and the examples of best practice to improve services in line with the rest of the UK.'

Europe-specific atrial fibrillation guidelines

New Europe-specific guidelines on the management of atrial fibrillation were released at the European Society of Cardiology Congress in Stockholm.

'We needed to create up-to-date guidelines because of new drug therapies available, and also because accumulated evidence continuously refines the advice on treatment regimens that give the best outcomes,' said Professor John Camm, chairman of the European Society of Cardiology Task Force who developed the guidelines.

The guidelines, he added, are the first to be prepared solely by the European Society of Cardiology on the topic of atrial fibrillation, in recognition of key differences between Europe and the USA in practice, drug treatments and regulator issues.

Key features in the new atrial fibrillation guidelines included:

- The addition of long standing persistent atrial fibrillation, defined as atrial fibrillation that lasts for more than 1 year to the four other clinically distinguishable types of atrial fibrillation – first diagnosed, paroxysmal, persistent, and permanent atrial fibrillation
- The adoption of a more sensitive system for CHADS2 scoring, known as CHA2DS2-VASc, to allow identification of the patients who will benefit most from new anticoagulants – both the direct thrombin inhibitors (dabigatran) and the factor Xa inhibitors (apixaban and rivaroxaban) – to prevent stroke
- Advice on how to use the anti-arrhythmic drug dronedarone, with the guidelines specifically stating that dronedarone is not recommended for treatment of atrial fibrillation in patients in New York Heart Association classes III and IV, or with recently unstable New York Heart Association class II heart failure
- That catheter ablation for paroxysmal atrial fibrillation should be considered in symptomatic patients who have previously failed a trial of antiarrhythmic medication
- Updated advice on 'upstream' therapy that may be prescribed to prevent deterioration of atrial fibrillation, including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and statins.

Gregory Lip, professor of cardiovascular medicine at the University of Birmingham Centre for Cardiovascular Sciences, who presented the new guidelines at the Congress, commented: 'The updated guidelines reflect the high need for novel treatments in the prevention of atrial fibrillation related stroke. Both the personal and economic burden of atrial fibrillation-related stroke is high. Consideration of new prevention therapies will improve the overall standard of care.'

Janet Fricker

Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC) (2010) Guidelines for the management of atrial fibrillation of the European Society of Cardiology. *Eur Heart J* Sep 25 [Epub ahead of print]

Online resource for laparoscopic surgeons

A new website (www.lapco.nhs.uk) has been launched to support the National Training Programme in Laparoscopic Colorectal Surgery, known as Lapco.

The site pairs established surgeons with trainees and allows them to undertake colorectal procedures together at a convenient centre. The trainee's performance is assessed and logged on the site, ultimately leading to an assessment of competence to carry out the procedures.

Lapco is funded by the Cancer Action Team at the Department of Health to provide laparoscopic colorectal surgery training for colorectal consultants in England.

It was devised in 2007 to implement the 2006 National Institute for Health and Clinical Excellence guidelines which state that laparoscopic (including laparoscopically assisted) resection is recommended as an alternative to open resection for individuals with colorectal cancer in whom both laparoscopic and open surgery are considered suitable.

National Institute for Health and Clinical Excellence (2006) *Laparoscopic surgery for colorectal cancer.* National Institute for Health and Clinical Excellence, London

Low grade non-Hodgkin's lymphoma gets new treatment

Bendamustine (Levact) has been approved for use in patients with indolent non-Hodgkin's lymphoma whose cancer has progressed during or within 6 months of treatment with rituximab. In two clinical studies 77% and 75% of patients responded to treatment, a quarter of whom achieved a complete response.

Quetiapine approved for major depressive disorder and bipolar disorder

Quetiapine prolonged release (Seroquel) has been approved as an add-on treatment for patients with major depressive disorder who have had sub-optimal response to antidepressant monotherapy, and as monotherapy for acute bipolar disorder.

Transcatheter heart valve implantation

Results of the PARTNER trial, the first randomized, controlled trial of a transcatheter aortic heart valve, were published in the *New England Journal of Medicine*. Transcatheter aortic valve implantation significantly reduced the rates of death in patients who have severe aortic stenosis and are not suitable candidates for surgery compared with standard therapy.

EUROPEAN SOCIETY OF CARDIOLOGY CONGRESS
STOCKHOLM, 28 AUGUST–1 SEPTEMBER

RE-LY: dabigatran superior to warfarin irrespective of INR

Dabigatran – the new direct thrombin inhibitor – is superior to warfarin at preventing strokes in patients with atrial fibrillation irrespective of the time warfarin was in the therapeutic range, concluded the latest sub-analysis of the RE-LY study presented at the European Society of Cardiology Congress.

Although the RE-LY study reported that dabigatran 150 mg twice daily was more effective in preventing strokes in high risk atrial fibrillation patients than warfarin while the lower dose 110 mg was comparable, questions remained over whether dabigatran's advantage would persist when warfarin was controlled to the best possible level.

In the latest analysis, published simultaneously in the *Lancet* (Wallentin et al, 2010), investigators assessed dabigatran 150 mg, dabigatran 110 mg and warfarin according to each centre's mean time for warfarin in the therapeutic range.

The centres were divided into quartiles, with the lowest quartile representing centres where patients were in the therapeutic range less than 57.1% of the time, the second where patients were in the therapeutic range between 57.1% and 65.5% of the time, the third between 65.5 and 72.6% of the time, and the fourth more than 72.6% of the time.

The investigators, led by Lars Wallentin, from Uppsala Clinical Research Centre, Sweden, found that the benefits of dabigatran 150 mg at reducing stroke, dabigatran 110 mg at reducing bleeding, and both doses at reducing intracranial bleeding *vs* warfarin were consistent irrespective of centres' quality of internal normalized ratio (INR). Furthermore, for all vascular events, non-haemorrhagic events and mortality, advantages of dabigatran were greater at sites with poor INR control for warfarin than at those with good INR control.

'This reinforces the original findings from the RE-LY study that dabigatran offers greater protection against haemorrhagic stroke, while offering the same or even greater protection against ischemic stroke compared with optimum warfarin,' said Adrian Brady, a cardiologist at Glasgow Royal Infirmary.

Country-wide comparisons of mean time for warfarin in the therapeutic range showed that the UK came fifth out of 44 countries with a score of 72%. Scores ranged from a low of 44% for Taiwan to a high of 77% for Sweden.

Janet Fricker

Wallentin L, Yusuf S, Ezekowitz MD et al on behalf of the RE-LY investigators (2010) Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. *Lancet* **376**(9745): 975–83

Heart-rate lowering agent benefits heart failure patients

Ivabradine reduced cardiovascular death and heart failure hospitalization by 18% when added to standard treatment in patients with chronic heart failure and elevated heart rates, reported the SHIfT trial at the European Society of Cardiology Congress.

The study, published simultaneously in *The Lancet* (Swedberg et al, 2010), showed that the number of patients needed to treat for 1 year to prevent one primary end point event was just 26.

'The SHIfT trial has demonstrated for the first time that reducing heart rate alone is beneficial for patients with heart failure,' said principal investigator Professor Michel Komajda, from the Pitié-Salpêtrière Hospital in Paris.

Heart failure patients with higher heart rates appear to have a significantly greater risk of death or hospitalization. Ivabradine slows the heart rate by binding to I_f channels in the sinus node, and was chosen for the study since it lowers heart rate without affecting blood pressure.

The Systolic Heart Failure Treatment with the If inhibitor Ivabradine Trial (SHIfT), conducted at 677 centres in 37 countries, randomized 6505 people with New York Heart Association II–IV heart failure, and left ventricular ejection fraction < 35% to receive either placebo (n=3264) or ivabradine (initial 5 mg twice daily up to a maximum of 7.5 mg twice daily, n=3241). All patients were receiving currently recommended heart failure medication, had heart rates of at least 70 beats per minute and had been hospitalized for heart failure within the last year. Patients were followed up for an average of 22.9 months.

The primary end point of cardiovascular death or heart failure hospitalization occurred in 24% of patients receiving ivabradine *vs* 29% receiving placebo (hazard ratio 0.82, confidence interval 0.75–0.90, P<0.0001). Furthermore 3% of patients in the ivabradine group died of heart failure compared to 5% in the placebo group (hazard ratio 0.74, confidence interval 0.58–0.94, P=0.014).

The benefit of ivabradine was consistent across all the subgroups including age and gender, use or not of beta blockers, aetiology of heart failure (ischaemic or non-ischaemic), functional severity, and presence or absence of diabetes or hypertension. 'The only noticeable exception was that patients with higher heart rates at baseline, above the median value of 77 beats per minute, showed greater benefits,' Professor Komajda added.

Ivabradine was overall safe and well tolerated, with fewer adverse events occurring among patients taking ivabradine than those in the placebo group.

'This is very good news for patients and doctors that, even when using the best current drug treatment available, ivabradine further reduces the risk of death or hospitalization,' said Professor Komajda.

Janet Fricker

Swedberg K, Komajda M, Böhm M et al (2010) Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet* **376**(9744): 875–85

European Respiratory Society
Barcelona, 18–22 September

Beta2-agonist treatment of chronic obstructive pulmonary disease

The new ultra-long acting beta2-agonist, indacaterol, provides faster onset and superior bronchodilation compared with salmeterol in patients with moderate to severe chronic obstructive pulmonary disease according to data presented at the European Respiratory Society.

The findings from the INSIST study were presented by principal investigator Dr Stephanie Korn from Mainz University Hospital, Germany.

Patients were randomized to receive once daily indacaterol 150 µg (*n*=559) or salmeterol 50 µg given twice daily (*n*=562). Concurrent treatments were allowed for inhaled corticosteroids either alone or as fixed combination with a long-acting beta2-agonist and salbutamol was taken as required.

The primary efficacy variable was time-standardized area under the curve of forced expiratory volume in 1 minute (FEV_1) between 5 minutes and 11 hours 45 minutes after the morning dose at week 12. Indacaterol was statistically superior to salmeterol with an adjusted mean difference of 60 ml (95% confidence interval=40–80; *P*<0.001).

Indacaterol was also statistically superior to salmeterol for the secondary efficacy variable of trough FEV_1 at week 12, with an adjusted mean difference of 60 ml (95% confidence interval 40–80; *P*<0.001). Indacaterol also increased the proportion of patients with a clinically relevant reduction in breathlessness compared to salmeterol (69.4% *vs* 62.7%) and the number of days on which patients did not require rescue medication. Overall and serious adverse events were similar in both treatment groups.

Professor Peter Barnes, Professor of Thoracic Medicine and Head of Airway Disease at the National Heart and Lung Institute, and Honorary Consultant Physician at the Royal Brompton Hospital, commented: 'Indacaterol is more convenient for patients than salmeterol. This study and others show it is a very promising treatment.'

Dr Dermot Ryan, GP in Loughborough and Respiratory Lead for East Midlands Strategic Health Authority, said: 'It appears that indacaterol has superior powers of bronchodilation. Patients with chronic obstructive pulmonary disease need a range of effective treatments and indacaterol is now an option for maintenance treatment.'

Rhonda Siddall

Combination therapy for patients with persistent asthma

A new fixed-dose combination therapy of fluticasone and formoterol (FP/FORM) was as effective as fluticasone combined with salmeterol (FP/SAL) but with a more rapid onset of action in patients who had persistent asthma for at least 6 months, according to data from a phase III study presented at the European Respiratory Society.

The multicentre, randomized, open-label, active controlled, parallel group study found that the mean pre-dose forced expiratory volume in 1 minute (FEV_1) at week 12 was about 2.4 litres for both treatments. Non-inferiority for FP/FORM delivered via a pressurized metered dose inhaler *vs* FP/SAL was shown: -0.161 litre (*P*=0.007) exceeded the non-inferiority acceptance limit (-0.20 litre).

FP/FORM was at least as effective as FP/SAL for least-squares mean changes in pre-dose FEV_1 from baseline to week 12 (-0.061; *P*=0.007) and pre-dose FEV_1 at baseline to 2 hours post-dose FEV_1 at week 12 (-0.013; *P*=0.002). Discontinuations as a result of lack of efficacy were similar.

Professor David Price, Professor of Primary Care Respiratory Medicine at the University of Aberdeen, said: 'There are still many challenges with achieving optimal control in asthma patients. These data show the FP/FORM combination has good efficacy and reinforces its potential to become an alternative treatment option for people with asthma.'

The study, presented by Dr Anna Bodzenta-Lukaszyk from the Medical University of Bialystok in Poland, randomized 202 patients to FP/FORM or FP/SAL twice daily over 12 weeks. Two dose options of each treatment were available based on pre-study medication: FP/FORM 100/10 µg (27.7%) or 250/10 µg (72.3%), and FP/SAL 100/50 µg (24.8%) or 250/50 µg (75.2%).

Dr Bodzenta-Lukaszyk said: 'Formoterol has a rapid onset of action in the treatment of asthma which is very important for the patient.'

The overall rate of adverse events was 23.8% for both treatments, most of which were mild or moderate. The most common adverse events in the FP/FORM and FP/SAL arms were infections (13.9% *vs* 12.9% respectively). Two patients had severe adverse events, one patient taking FP/FORM had a haemorrhagic stroke and died and another patient on FP/SAL had an episode of pneumococcal pneumonia. Both events were not considered treatment related, said Dr Bodzenta-Lukaszyk.

Professor David Price, Professor of Primary Care, University of Aberdeen

In a separate study presented by Professor Price at the meeting, retrospective data from the General Practice Research Database suggests that the type of asthma device influences treatment outcomes in asthma patients. Professor Price added: 'This research shows that it is important to consider the right device, for the right patient.'

Rhonda Siddall