Ageism in prostate cancer management 'must end'

Clinical decisions on how to treat men with prostate cancer should be influenced by their general health status rather than their age, experts involved in preparation of new guidelines for managing advanced prostate cancer in senior adults stressed.

Calling for an end to age bias in management, they said many elderly but otherwise fit men with prostate cancer are currently being denied survival-extending treatments such as radical prostatectomy and standard chemotherapy, purely on grounds of age.

The proposed new guidelines, produced by the International Society of Geriatric Oncology (SIOG) and launched at the European Association of Urology meeting in Milan (26–29 March), call for senior adults (over age 70) to be managed in the same way as younger patients.

'All patients should be assessed for treatment suitability according to their co-morbidities, independence in activities of daily living, nutritional and cognitive status.' said the Society's President Jean-Pierre Droz, Professor of Medical Oncology at Lyon. 'Senior adult patients considered fit or healthy should get the same treatment as fit and healthy younger men.'

Where patients are considered 'vulnerable' on account of a reversible condition, this should be addressed first, allowing patients to receive standard chemotherapy subsequently, he noted.

Those considered 'frail' with non-reversible co-morbid conditions should receive adapted treatment given weekly and only those considered 'too sick' to tolerate therapy should be restricted to symptomatic treatment alone.

Others experts included John Fitzpatrick, Professor of Surgery at University College, Dublin and Louis Denis, Director of the Oncology Centre, Antwerp and Secretary of Europa Huomo, The European Coalition against Prostate Cancer.

'Traditionally, we have not offered older people the same range of treatments as younger people because we're afraid the treatment will cause them more harm than the disease itself,' said Professor Fitzpatrick. 'But studies show complications are related more to co-morbidity than age.'

The Mayo Clinic series of patients over 70 years of age who underwent radical prostatectomy show good rates of 10-year survival, he noted.

Chemotherapy with docetaxel is the standard treatment after failure of androgen deprivation and clinical trials show there is no difference in treatment effect between senior and younger adults. Both derive equal benefits in survival and quality of life improvement.

Professor Denis said 'Patients want treatment based on their personal and individual circumstances rather than on group outcomes.'

Olwen Glynn Owen

Don't delay schizophrenia treatment, says professor

While it is reasonably easy to treat an acute episode of schizophrenia, trying to persuade patients to comply with treatment schedules over 10 years or more is much more difficult.

So said Professor Wolfgang Fleischhacker of the Department of Psychiatry, University of Innsbruck, Austria, as he introduced some new strategies to improve outcomes in schizophrenia at the 16th European Congress of Psychiatry in Nice, France.

'What is clear,' he commented, 'is that we cannot afford to delay treatment in our patients once schizophrenia is first diagnosed – not only from a psychiatric perspective, but from a neurobiological perspective. Successful intervention in first-episode schizophrenia is critical.'

He reported recent data from the EUFEST trial (Kahn et al, 2008), which demonstrated that clinically-meaningful antipsychotic treatment of first-episode schizophrenia is a realistic goal.

A total of 498 patients were randomized to haloperidol (1–4 mg/day), or to one of four second generation antipsychotic agents – amisulpride (200–800 mg/day), olanzapine (5–20 mg/day), quetiapine (200–750 mg/day) or ziprasidone (40–160 mg/day).

At 1-year follow up, the number of patients who had discontinued treatment for any reason was significantly less for all of the second generation agents than for haloperidol – olanzapine 72% lower (hazard ratio (HR) 0.28), amisulpride 63% lower (HR 0.37), quetiapine 48% lower (HR 0.52), and ziprasidone 49% lower (HR 0.51).

The authors emphasized, however, that discontinuation rates are not necessarily consistent with symptomatic improvement.

Stephen Pinn

Kahn RS, Fleischhacker WW, Boter H et al (2008) Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomized clinical trial. *Lancet* **371**: 1085–97

HRT 'raises' breast cancer recurrence

Hormone replacement therapy (HRT) not only increases the risk of first-time breast cancer, but may increase the risk of its recurrence in breast cancer survivors, according to new research (Holmberg et al, 2008).

The findings arise from follow up of patients who took part in the HABITS (Hormone replacement therapy After Breast cancer diagnosis – is IT Safe?) study, a randomized trial comparing HRT to best management without hormones in treating menopausal symptoms in women with previously treated breast cancer.

The trial was stopped early in December 2003 after two large studies linked HRT to an increased risk of new breast cancer events.

In this 4-year follow-up, 39 of the 221 women who were treated with HRT had a recurrence of breast cancer, compared to 17 of 221 controls (hazard ratio 2.4, 95% confidence interval 1.3–4.2).

The cumulative incidence of a new breast cancer event at 5 years was 22.2% for the HRT arm and 8.0% for controls. After 4 years, there had been six deaths as a result of breast cancer and six cases of metastatic disease in the HRT group, compared to five cases and four cases respectively in the control group.

Stephen Pinn

Holmberg L, Iversen O-E, Rudenstam CM et al (2008) Increased risk of recurrence after hormone replacement therapy in breast cancer survivors. *J Natl Cancer Inst* **100**: 475–82

Trial demonstrates positive effect of pioglitazone

New data suggest that treatment with pioglitazone in patients with type 2 diabetes and coronary artery disease results in a statistically significantly lower rate of progression of coronary atherosclerosis compared with glimepiride.

Researchers investigated the effects of pioglitazone compared with glimepiride on the progression of coronary atherosclerosis in patients with type 2 diabetes.

The PERISCOPE trial (Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation) was a prospective, randomized, multicentre, double-blind clinical trial involving 543 patients with coronary disease and type 2 diabetes (Nissen et al, 2008).

Patients were randomized to receive glimepiride (1–4 mg) or pioglitazone (15–45 mg) for 18 months with titration to maximum dosage.

The researchers reported the following results for 360 patients who completed the study:

- Mean per cent atheroma volume scores increased 0.73% with glimepiride and decreased 0.16% with pioglitazone (P=0.002)
- Mean HbA_{1c} levels decreased 0.55% with pioglitazone and 0.36% with glimepiride (P=0.03)
- In the pioglitazone group, high-density lipoprotein levels increased 5.7 mg/dl (16.0%) *vs* 0.9 mg/dl (4.1%) with glimepiride, while triglyceride levels decreased 16.3 mg/dl (5.3%) *vs* an increase of 3.3 mg/dl (0.6%) (P<0.001 for both)
- Median fasting insulin levels decreased with pioglitazone and increased with glimepiride (P<0.001)
- Hypoglycaemia was more common in the glimepiride group, while oedema, fractures and decreased haemoglobin levels occurred more frequently in the pioglitazone group.

In a related editorial, the authors point out that the clinical relevance of the data favouring pioglitazone over glimepiride is unclear. The differences appear to be minimal (<1% change in atheroma volume), although this effect is within the range of what has been demonstrated with beneficial cardiovascular outcomes associated with high-dose statins.

Stephen Pinn

Nissen SE, Nicholls SJ, Wolski K et al (2008) Comparison of pioglitazone *vs* glimepiride on progression of coronary atherosclerosis in patients with type 2 diabetes. *JAMA* **299**(13): 1561–73

HPV vaccine reduces early cervical lesions

Vaccination with a quadrivalent human papillomavirus (HPV) vaccine achieves sustained protection against early cervical lesions, in addition to vaginal and vulval lesions and genital warts.

This is according to 48-month study follow-up data reported at the European Congress of Obstetrics and Gynaecology (5–7 March, 2008; Lisbon, Portugal).

The study combined data for 18 150 women (aged 16 to 26 years) in three clinical trials which randomized them to quadrivalent HPV vaccine (against HPV types 6,11,16 and 18; Gardasil) or placebo at day one, month two and month six.

They were followed up with genital examination, Pap testing and collection of cervicovaginal specimens, for 4 years. Results for the study included women who received all three doses of vaccine, had no major protocol violations, and who tested negative for the four HPV types in the vaccine at day 1 and after the vaccination schedule was completed at 7 months.

Results showed that the efficacy of the vaccine against HPV6/11/16/18-related early cervical lesions (CIN1 or worse) was 96.0% (95% confidence interval (CI) 92.3–98.2).

The vaccine also achieved 99% protection against genital warts (95% CI 96.2–99.9) and 100% protection against early and precancerous vulvar (vulvar intraepithelial neoplasia grade 1 and 2/3) and vaginal (vaginal intraepithelial neoplasia grade 1 and 2/3) lesions caused by the virus types targeted by the vaccine.

Professor Charles Lacey, Professor of Genitourinary Medicine, University of York, and lead author of the study, said: 'The new data confirm the very significant benefit, both for women's health and for health authorities, that quadrivalent vaccination can provide in addition to prevention of cervical cancer.'

He added: 'Gardasil offers a wide spectrum of protection against genital diseases caused by HPV and both early and sustained protection that translates into rapid individual and long-lasting socioeconomic benefit.'

The sustained efficacy of the vaccine – with very high rates of protection out to 4 years in follow-up so far – was also very reassuring, he said.

Susan Mayor

Susan Mayor's attendance at the 20th European Congress of Obstetrics and Gynaecology was sponsored by Sanofi Pasteur MSD

Tuberculosis has come back

'Tuberculosis was believed to be almost eradicated, but we have observed a dramatic re-emergence', said Professor Robert Read of Sheffield University.

He was speaking at the European Congress of Clinical Microbiology and Infectious Diseases in Barcelona.

'In Europe and worldwide, there is more tuberculosis nowadays than 20 years ago; no country has eliminated it or come close to eliminating it', he remarked.

Depressed people 'too tired' to work

A new report, published by Depression Alliance and funded by Servier Laboratories Limited, reveals the majority (83%) of people diagnosed with depression in the UK feel their work is adversely affected by poor quality of sleep.

The report highlights that people with depression still find it difficult to remain in employment.

Treating secondary hyperparathyroidism

Abbott UK have launched an oral formulation of Zemplar (paricalcitol) for the treatment and prevention of secondary hyperparathyroidism, a common complication of chronic kidney disease.

AMERICAN COLLEGE OF CARDIOLOGY
CHICAGO, 29 MARCH–1 APRIL

Lowering blood pressure reduces all-cause mortality in the very elderly

HYVET (Hypertension in the Very Elderly Trial), the largest-ever clinical study to examine the effects of blood-pressure lowering in people aged ≥80 years, demonstrates that treatment with a diuretic, with or without an angiotensin-converting enzyme (ACE) inhibitor, can reduce total mortality by one-fifth and risk of cardiovascular events by one-third in very elderly hypertensive patients.

Results were presented for the first time in Chicago, and published simultaneously in the *New England Journal of Medicine* (Beckett et al, 2008).

The study, which was coordinated by scientists at Imperial College London, randomized 8345 patients to either placebo or the diuretic indapamide SR 1.5 mg, plus the ACE inhibitor perindopril 2 or 4 mg if needed to achieve target blood pressure of 150/80 mmHg.

At entry, 90% of patients were hypertensive, but otherwise relatively healthy since exclusion criteria included recent haemorrhagic stroke, heart failure, chronic kidney disease, gout, dementia and requirement for nursing home care. Patients could also only enter the study if their systolic blood pressure on standing was 140 mmHg.

Lead investigator Emeritus Professor Christopher Bulpitt said: 'One message to doctors treating very elderly hypertensive people is that you must monitor standing blood pressure to avoid over-treatment.'

At baseline, mean blood pressure was 173/91 mmHg, and after 2 years 48.0% of the active treatment group had reached target blood pressure compared with 19.9% of the placebo group (P<0.001). Active treatment reduced death from stroke by 39% (P=0.05), all-cause mortality by 21% (P=0.02), cardiovascular mortality by 23% (P=0.06), and heart failure by 64% (P<0.001). Fatal or non-fatal stroke fell by a non-significant 30% (P=0.06). There were significantly fewer serious adverse events among actively treated patients (358 *vs* 448 for placebo; P=0.001).

Professor Christopher Bulpitt, Imperial College London

The fall in all-cause mortality was a surprise to investigators, since previous smaller studies had suggested that, while lowering blood pressure in the over-80s reduced the number of strokes, it did not lower, and might even increase, total mortality. HYVET was stopped early in June 2007 on the recommendation of the independent data monitoring committee, and an extension using active treatment is under way to assess longer-term outcomes.

Sue Lyon

Beckett NS, Peters R, Fletcher AE et al (2008) Treatment of hypertension in patients 80 years of age or older. *N Engl J Med* Mar 31 [Epub ahead of print]

Telmisartan is 'non-inferior' in cardiac treatment

The angiotensin receptor blocker (ARB) telmisartan (Micardis) was found to be 'non-inferior' to the angiotensin-converting enzyme (ACE) inhibitor ramipril in preventing cardiovascular events in a high-risk population. It also produces fewer side effects, reported the ONTARGET study. Combining the two drugs, however, produced no additional benefits.

Previously, in 2000, the HOPE trial showed that cardiovascular risk for a similar group of patients treated with ramipril was reduced by 20% in comparison with placebo.

The ONTARGET study set out to determine if an ARB would give the same benefit as an ACE inhibitor and if combination treatment would result in any additional benefits.

'The good news is that telmisartan is a bit better tolerated than ramipril and we now know that we can use it with confidence. We have a new choice,' said Salim Yusuf, the principal investigator from McMaster University, Hamilton, ON, Canada.

In ONTARGET investigators from 733 centres in 40 countries enrolled 25 620 patients over the age of 55 years with coronary heart disease or diabetes plus additional risk factors, but without evidence of heart failure.

Patients were randomly assigned to receive ramipril 10 mg per day (n=8576), telmisartan 80 mg per day (n=8542) or combination therapy (n=8502). The composite primary end point was death from cardiovascular causes, myocardial infarction, stroke or hospitalization for heart failure.

At a median follow up of 56 months the primary outcome had occurred in 1412 patients in the ramipril group (16.5%), compared with 1423 patients in the telmisartan group (16.7%) and with 1386 (16.3%) in the combination therapy group.

As compared with the ramipril arm, patients receiving telmisartan had lower rates of cough (1.1% *vs* 4.2%; P<0.001), and angiooedema (0.1% *vs* 0.3%, P=0.01) and a higher rate of hypotensive symptoms (2.6% *vs* 1.7%, P<0.001).

As compared to the ramipril group, patients receiving combined treatment showed an increased risk of hypotension, syncope and renal dysfunction.

'From a clinical perspective the ARB telmisartan now moves alongside ACE inhibition as a treatment for patients with high cardiovascular risk,' said Professor Bryan Williams from the University of Leicester School of Medicine. He added that in future telmisartan could be considered as having additional value because of its better tolerability. 'If you have a patient with an asymptomatic condition who is taking medication for the long term, then tolerability will be a real issue,' he said.

Janet Fricker

AMERICAN COLLEGE OF CARDIOLOGY
CHICAGO, 29 MARCH–1 APRIL

Study: no ENHANCE-ment of changes to intima media thickness

Compared with simvastatin alone, the combination of ezetimibe and simvastatin does not result in a significantly different change in arterial intima media thickness on digitized, single-frame ultrasound. This is the result of the ENHANCE (Simvastatin With or Without Ezetimibe in Familial Hypercholesterolemia) study. Results were released in January 2008, but were presented for the first time at the ACC meeting with simultaneous publication (Kastelein et al, 2008).

ENHANCE was a double-blind, 2-year study that randomized 720 patients with heterozygous familial hypercholesterolaemia to daily treatment with simvastatin 80 mg plus either ezetimibe 10 mg or placebo. Ezetimibe–simvastatin resulted in significantly greater reductions in low-density lipoprotein cholesterol (16.5%), triglycerides (25.7%) and C-reactive protein (6.6%) than simvastatin alone ($P<0.01$).

However, there was no significant difference between study groups on the primary end point of change in mean carotid artery intima media thickness, a surrogate marker of atherosclerosis progression.

There were also no differences between groups in the rate of cardiovascular events, although the study was not powered to assess clinical outcomes.

Speaking in Chicago, lead investigator Dr John Kastelein from the Netherlands, rejected suggestions that lowering low-density lipoprotein cholesterol with ezetimibe might not produce additional vascular benefits beyond those of statins or that the ultrasound technique did not accurately reflect changes in atherosclerosis.

He suggested that the results might be caused by improved treatment of familial hypercholesterolaemia. 'In the last 10–15 years, we have shifted intima media thickness distribution from very abnormal to less abnormal, and therefore it has become more difficult to show an effect of the addition of any other therapy,' he said.

The debate over ezetimibe will only be resolved by the results of large outcome studies such as IMPROVE-IT, which is unlikely to report until 2012 or later.

These findings are likely to reinforce National Institute for Health and Clinical Excellence guidance: that ezetimibe should be reserved for patients who cannot tolerate or do not reach target cholesterol with the highest-dose statin.

Sue Lyon

Kastelein JJ, Akdim F, Stroes ES et al (2008) Simvastatin with or without ezetimibe in familial hypercholesterolemia. *N Engl J Med* **358**(14): 1431–43

ACCOMPLISH trial results show fewer cardiovascular events

An angiotensin-converting enzyme (ACE) inhibitor–calcium-channel blocker combination (ACE–CCB) was more effective than an ACE inhibitor–diuretic combination (ACE–D) in preventing cardiovascular events and hospitalization.

This result emerged from ACCOMPLISH (Avoiding Cardiovascular Events Through Combination Therapy in Patients Living with Systolic Hypertension), the first study to compare single-tablet, fixed-dose combination therapies as initial treatment in high-risk hypertensive patients.

ACCOMPLISH randomized 11 508 high-risk patients aged ≥55 years to either amlodipine-benazepril (ACE–CCB) or benazepril-hydrochlorothiazide (ACE–D), titrated to a target (blood pressure <140/90 mmHg or <130/80 mmHg in patients with diabetes or chronic kidney disease), with other agents added only if targets were not achieved at the highest dose of study drugs. ACCOMPLISH was terminated early in October 2007 on the data safety monitoring board's recommendation. Results presented in Chicago were an interim analysis with 95.3% of end points adjudicated.

On the primary end point of cardiovascular morbidity and mortality – defined as cardiovascular death, fatal or non-fatal myocardial infarction, fatal or non-fatal stroke, hospitalization for unstable angina or coronary revascularization – ACE–CCB reduced cardiovascular morbidity and mortality by 20% compared with ACE–D ($P<0.0001$).

Lead investigator Dr Kenneth Jamerson, from the USA, added: 'Both fixed-dose combinations provided exceptional blood pressure control, with 79.9% in the ACE–CCB group and 76.2% in the ACE–D group achieving a blood pressure <140/80 mmHg, and over half of patients achieving this with a single tablet.' At entry to ACCOMPLISH, 74% of patients were receiving two or more antihypertensive agents, but only 37% were controlled to <140/80 mmHg.

Sue Lyon

Rosuvastatin regresses coronary atherosclerosis

Two years' treatment with rosuvastatin regresses coronary atherosclerosis on intravascular ultrasound, according to ASTEROID (A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden).

In the prospective, open-label study, 507 patients with a clinical indication for coronary catheterization received rosuvastatin 40 mg/day. After 24 months, mean per cent diameter stenosis decreased from 37.3% to 36.0% ($P<0.001$) and minimum mean lumen diameter increased from 1.65 mm to 1.68 mm ($P<0.001$), measured on quantitative coronary angiographic ultrasound. Rosuvastatin also reduced low-density lipoprotein cholesterol by 53.3% and increased high-density lipoprotein cholesterol by 13.8%.

The JUPITER study has been stopped early because of rosuvastatin's superiority to placebo in reducing cardiovascular morbidity and mortality.

Sue Lyon