

Cardiovascular prevention in an older adult population

Dr Eamon Dolan, Research Registrar, ADAPT Centre, Beaumont Hospital, Dublin
Dr Joe Duggan, Consultant Physician in Medicine for the Elderly, Mater Misericordiae Hospital and St Mary's Hospital, Dublin

Introduction

While cardiovascular disease remains the most common cause of death and disability in older adults, proven preventive strategies are now available which show significant reductions in both morbidity and mortality. Advancing age is one of the strongest risk factors for cardiovascular events in our population.

In addition, other risk factors such as hypertension, hyperlipidaemia, diabetes, obesity and sedentary lifestyle are more common in older age groups. Hence, older populations have a higher incidence of stroke and coronary events and warrant appropriate management of their global cardiovascular risk.

Blood pressure management

An increase in blood pressure was once considered a part of the normal ageing process. It is now recognised that elevations in blood pressure, particularly systolic and pulse pressure, are associated with an increase in cardiovascular event rates. Numerous studies of both primary and secondary prevention demonstrate that cardiovascular protection can be achieved by treatment based on a variety of different antihypertensive drug classes, i.e. diuretics, beta-blockers, calcium antagonists, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II antagonists. This would suggest that the protection is largely due to blood pressure lowering as opposed to drug class.

Treatment of isolated systolic hypertension with a diuretic led to reductions in cardiovascular events in the Systolic Hypertension in the Elderly Program (SHEP) Cooperative Research Group. Data from the Systolic Hypertension in Europe study (Syst-Eur) provided evidence that blood pressure control with a calcium antagonist reduced the incidence of dementia. The ALLHAT study involved hypertensive patients with at least one other cardiovascular risk factor. When the primary outcome was considered, diuretic-based therapy was of similar efficacy to either therapy with a calcium channel blocker or an ACE inhibitor. The SCOPE study, which compared treatment regimes with and

without the angiotensin receptor antagonist candesartan, showed a reduction in non-fatal strokes in hypertensive patients aged 70 years or older.

The PROGRESS study looked at secondary prevention. Patients with a previous history of stroke or transient ischaemic attack (TIA) were randomly allocated to perindopril 4mg ± indapamide 2.5mg versus placebo, regardless of whether there was a history of hypertension or not. When given together, this combination reduced the risk of fatal and non-fatal stroke in both normotensive and hypertensive patients. There was also a significant reduction in major coronary events (26%) and the development of heart failure (26%) in these patients.

To date, the majority of blood pressure studies have used clinic blood pressure measurement (CBPM) to guide management. There is considerable evidence that ambulatory blood pressure monitoring (ABPM) may be a better predictor of outcome and correlate closer to target organ damage than CBPM. In particular, it seems that night-time blood pressure is the strongest predictor of cardiovascular outcome. Abnormal circadian blood pressure profiles such as reduced nocturnal fall, also referred to as 'non-dipping', are now accepted to increase cardiovascular risk. Recently, a Japanese group showed the association of stroke risk and greater early morning blood pressure surge in elderly hypertensive individuals. For these reasons, ABPM is useful in the risk stratification of high risk patients. Furthermore, the prevalence of 'white coat' hypertension increases with age, with ABPM being the only reliable means for its detection. It would seem that ABPM is particularly useful in the older person where there is sometimes understandable concern with regard to commencing and up-titrating antihypertensive medication.

The target blood pressure in older adults is the same as for younger adults and should follow the recently published hypertension guidelines. There is, in fact, a greater benefit with regards to event reduction in treating older individuals with hypertension compared to younger age groups. Doses of

medications may need to be adjusted for reduced renal function and postural symptoms, both of which increase with age. Concerns that lowering diastolic pressure below 80mmHg might provoke myocardial infarction (MI) in elderly patients have not been substantiated by data from trials. At present, there are no data showing that treatment decreases cardiovascular mortality above the age of 80 years; however, studies are ongoing. Diagnosis and treatment of raised blood pressure in older individuals require special consideration of the presence and extent of other risk factors, end-organ damage, co-existing diseases and their treatment, general health and frailty, as well as the presence and impact of cognitive impairment.

Hyperlipidaemia

In older people, the relative risk of coronary heart disease (CHD) conferred by raised cholesterol is only moderate or mild; however, the attributable risk is high. This is because the prevalence of CHD is much higher in the older compared to younger groups. A high cholesterol level leads to more cardiovascular events in older people and therefore the need to treat also exists in this age group. However, evidence in primary prevention is limited. It is important to consider biological age rather than chronological age when considering treatment and the target lipid levels in the elderly are currently those used for the general adult population.

The principal secondary prevention trials — 4S, CARE and LIPID — enrolled patients to a maximum age of 75 years. Patients aged >65 years had similar benefits compared to younger patients. The Heart Protection Study (HPS) enrolled patients aged 40-80 years with vascular disease and/or diabetes and a total cholesterol (TC) >3.5mmol/l in whom there was uncertainty whether cholesterol lowering was indicated. Patients were randomised to treatment with simvastatin 40mg daily or placebo and followed for five years. Simvastatin reduced cardiovascular mortality by 17%. The benefits were similar for patients aged <65, 65-70 and >70 years. The 1,263 patients aged 75-80 years at entry and hence aged 80-85 years at the end of the study derived an equivalent reduction in major vascular events of about 25% relative risk reduction. HPS suggests that all patients with a history of coronary disease, other occlusive arterial disease or diabetes benefit from statin therapy with simvastatin 40mg regardless of age, gender or baseline lipid parameters.

The PROSPER trial was designed to examine the hypothesis that pravastatin would reduce cardiovascular and cerebrovascular events in older subjects with existing vascular disease or at high risk of developing the condition. A total of 5,804 elderly men (n=2,804) and women (n=3,000) aged 70-82 years with total plasma cholesterol of 4.0-9.0mmol/l, triglycerides <6mmol/l and good cognitive function were recruited by community screening in the environs of Glasgow, Leiden and Cork. Participants were randomised to receive pravastatin 40mg/day or matching placebo, with an average

follow up of 3.2 years. The primary outcome measure, which was the combined endpoint of CHD death, non-fatal MI and fatal plus non-fatal stroke, was reduced by 15% (hazard ratio 0.85, 95% confidence interval [CI] 0.74-0.97, p=0.014). Stroke risk was unaffected (1.03, 0.81-1.31, p=0.8), but the hazard ratio for TIA was 0.75 (0.55-1.00, p=0.051). New cancer diagnoses were more frequent on pravastatin than on placebo (1.25, 1.04-1.51, p=0.020). However, incorporation of this finding in a meta-analysis of all pravastatin and all statin trials showed no overall increase in cancer risk. Mortality from coronary disease fell by 24% (p=0.043) in the pravastatin group. Pravastatin had no significant effect on cognitive function or disability.

The ALLHAT-LLT, a sub-study of ALLHAT, randomised 10,355 people aged 55 years or older with low-density lipoprotein (LDL) cholesterol 3-4.725mmol/l (or 2.5-3.25mmol/l if known cardiovascular disease) to pravastatin 40mg/day (n=5,170) or usual care (n=5,185). Mean age was 66 years and mean follow up was 4.8 years. There was no significant difference in the primary outcome of all-cause mortality or the secondary outcomes of non-fatal MI or fatal CHD events, cause-specific mortality including CHD and stroke, or cancer. TC levels were reduced by 17% with pravastatin and by 8% with usual care. During the trial, 32% of the usual care participants and 29% without CHD started taking lipid-lowering drugs. The modest TC reductions between the study groups and the high use of non-study statin in the usual care group probably accounts for the negative results of the trial.

In summary, therefore, a growing body of clinical trials evidence supports the use of statins for lipid lowering in elderly patients to age 80-85 years, with either clinical vascular disease (coronary, cerebrovascular or peripheral arterial) or with diabetes. In light of the HPS, statin therapy should be considered in these higher risk patients regardless of their LDL cholesterol level provided the patients do not have significant co-morbidities that would be expected to limit their lifespan to less than the expected window of benefit.

Smoking cessation

Advanced age does not diminish the benefits of smoking cessation. In those with cardiovascular disease who quit smoking, there is a 25-50% mortality reduction. Almost 50% of this benefit accrues in the first year of cessation. Smoking cessation benefits blood pressure control and lipid profile. Both nicotine replacement therapy and other pharmacological agents are safe in patients with cardiovascular disease, including older people. Stopping smoking also has beneficial effects on non-cardiovascular morbidity and mortality.

Diabetes mellitus

Diabetes confers a significant risk for cardiovascular disease and the prevalence of diabetes rises in older people. A seven-year follow up of 2,432 patients aged 45-64 years, hence with

follow up to age 71 years, highlighted the high risk that type 2 diabetes imparts for the development of macrovascular disease: CHD, cerebrovascular disease and peripheral vascular disease. Prevention of macrovascular complications requires aggressive control of risk factors, particularly hypertension and dyslipidaemia. The evidence of benefit in the older patient is well supported by published data. Prevention of microvascular complications such as nephropathy, retinopathy and neuropathy may be achieved not only from blood pressure control but also from tight glycaemic control.

The evidence for benefit in the older person beyond age 75 years is limited. The hazards of hypoglycaemia in the older patients merit a cautious approach with regard to tight control in those with advanced diabetes, life-limiting co-morbid illness and cognitive or functional impairment.

Antiplatelet therapy

Aspirin (75-150mg/day) has been shown to have significant benefit for patients at high risk of cardiovascular disease, particularly in secondary prevention, although blood pressure should be tightly controlled to minimise the risk of haemorrhagic stroke. It must be recognised, however, that the benefits of aspirin are not clear in older patients (>70 years) with no previous cardiovascular events who, due to age, remain at risk of cardiovascular disease. The risks associated with gastrointestinal and cerebral bleeding in older patients may offset any cardiovascular protection benefits.

Alternative or additional antithrombotic therapies such as clopidogrel or dipyridamole (stroke or TIA only) may be required if aspirin is not tolerated or if the patient experiences recurrent cardiovascular events while taking aspirin.

Conclusion

In the older person, because of lack of evidence, polypharmacy-induced drug interactions and side effects, in addition to concerns regarding compliance, there is sometimes a reluctance to use preventive treatments. There is sufficient evidence to justify therapy in those between 65 and 75 years. In addition, evidence may exist or be extrapolated for individuals aged between 75 and 80 years. In treating patients aged >80 years, there is little or no evidence, and prudence and common sense must prevail. Most of the clinical trials of statins, beta-blockers, calcium blockers and ACE inhibitors in the prevention of cardiovascular disease have focused on those aged <80 years.

There has been a failure to deliver proven cardiovascular preventive therapies in older patients and a more aggressive approach to risk reduction is essential to avert the rising tide of cardiovascular events in this population. Failure to apply the evidence in these patient populations represents a huge lost opportunity to prevent cardiovascular disease and reduce attendant morbidity. Heart disease, heart failure and stroke are the main causes of morbidity and death in older people and it should not be forgotten that non-fatal events often have the

effect of preventing older people from living independently. Preventing these major human and financial burdens for families and for society is the goal of cardiovascular prevention in the older person.

Bibliography

- Rosenson RS, Stamos TD. *Treatment of dyslipidaemia in the elderly*. In: Up-To-Date (Rose BD Ed), Up-To-Date, Wellesley, MA, 2002.
- Yusuf S. Two decades of progress in preventing vascular disease. *Lancet* 2002; 360: 2-3.
- Fries JF Reducing disability in older age. *JAMA* 2002; 288: 3164.
- Xhignesse M, Laplante P, Grant AM et al. Anti-platelet and lipid lowering therapies for the secondary prevention of cardiovascular disease: are we doing enough? *Can J Cardiol* 1999; 15 (2): 185-9.
- UK Prospective Diabetes Study (UKPDS) Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes. *BMJ* 1998; 317 (7160): 703-13.
- Benner JS, Glynn RJ, Mogun H et al. Long-term persistence in use of statin therapy in elderly patients. *JAMA* 2002; 288 (4): 455-61.
- Mendelson G, Aronow WS. Underutilization of angiotensin-converting enzyme inhibitors in older patients with Q-wave anterior myocardial infarction in an academic hospital-based geriatrics practice. *JAGS* 1998; 46 (6): 751-2.
- Shepherd J, Cobbe SM, Ford I et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med* 1995; 333: 1301.
- Downs JR, Clearfield M, Weis S et al for the AFCAPS/TexCAPS Research Group. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. *JAMA* 1998; 279: 1615.
- Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994; 344: 1383.
- Sacks FM, Pfeffer MA, Moye LA et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. *N Engl J Med* 1996; 335: 1001.
- Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group [see comments]. *N Engl J Med* 1998; 339: 1349.
- Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high risk individuals: a randomized placebo-controlled trial. *Lancet* 2002; 360: 7-22.
- Shepherd J, Blauw GJ, Murphy MB et al on behalf of the PROSPER study group. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet*, 19 November 2002.
- Major Outcomes in Moderately Hypercholesterolemic, Hypertensive Patients Randomized to Pravastatin vs Usual Care: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). *JAMA* 2002; 288: 2998-3007.
- Amery A, Birkenhager W, Brixho P et al. Mortality and morbidity results from the European Working Party in High Blood Pressure in the Elderly Trial. *Lancet* 1985; 1: 1349-54.
- Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the

- Elderly Program (SHEP). SHEP Cooperative Research Group. *JAMA* 1991; 265: 3255.
- Dahlöf B, Lindholm LH, Hansson L et al. Morbidity and mortality in the Swedish Trial in Old Patients with Hypertension (STOP-Hypertension). *Lancet* 1991; 338: 1281.
- Staessen JA, Fagard R, Thijs L et al. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. *Lancet* 1997; 350 (9080): 757-64.
- Hansson L, Zanchetti A, Carruthers SG et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomized trial. *Lancet* 1998; 351: 1755.
- Hansson L, Lindholm LH, Niskanen L et al for the Captopril Prevention Project (CAPPP) study group. Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomised trial. *Lancet* 1999; 353: 611.
- Hansson L, Lindholm LH, Ekblom T et al. Randomised trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity the Swedish Trial in Old Patients with Hypertension-2 study. *Lancet* 1999; 354: 1751.
- Hansson L, Hedner T, Lung-Johansen P et al for the NORDIL Study Group. Randomised trial of effects of calcium antagonists compared with diuretics and beta-blockers on cardiovascular morbidity and mortality in hypertension: the Nordic Diltiazem (NORDIL) study. *Lancet* 2000; 356: 359.
- Brown MJ, Palmer CR, Castaigne A et al. Morbidity and mortality in patients randomised to double-blind treatment with a long-acting calcium-channel blocker or diuretic in the International Nifedipine GITS study: Intervention as a Goal in Hypertension Treatment (INSIGHT). *Lancet* 2000; 356: 366.
- Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack. PROGRESS Collaborative Group. *Lancet* 2001; 358: 1033.
- Dahlöf B, Devereux RB, Kjeldsen SE et al. Cardiovascular morbidity and mortality in the Losartan Intervention for Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 2002; 359: 995.
- Hansson L, Lithell H, Skoog I et al. Study on COgnition and Prognosis in the Elderly (SCOPE). *Blood Press* 1999; 8: 177-83.
- Bulpitt C, Fletcher A, Beckett N et al. Hypertension in the Very Elderly Trial (HYVET). Protocol for the main trial. *Drugs Aging* 2001; 18: 151-64.
- Major outcomes in high risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002; 288: 2981-97.
- MRC trial of treatment of mild hypertension: principal results. Medical Research Council Working Party. *BMJ* 1985; 291: 97.
- Staessen J, Thijs L, Fagard R et al for the Systolic Hypertension in Europe Trial Investigators. Predicting cardiovascular risk using conventional vs ambulatory blood pressure in older patients with systolic hypertension. *JAMA* 1999; 282: 539-46.
- Ohkubo T, Imai Y, Tsuji I et al. Prediction of mortality by ABPM blood pressure monitoring versus screening blood pressure measurements: a pilot study in Ohasama. *J Hypertens* 1997; 15: 357-64.
- Ohkubo T, Hozawa A, Nagai K et al. Prediction of stroke by mortality by ambulatory blood pressure monitoring versus screening blood pressure measurements in a general population: the Ohasama study. *J Hypertens* 2000; 18: 847-54.
- Clement DL, De Buyzere M, De Bacquer DA et al for the Office versus Ambulatory Blood Pressure (OvA) Study Investigators. Prognostic value of ambulatory blood-pressure recordings in patients with treated hypertension. *N Engl J Med* 2003; 348: 207-15.
- Verdecchia P, Schillaci G, Borgioni C et al. ABPM pulse pressure: a potent predictor of total cardiovascular risk in hypertension. *Hypertension* 1998; 32: 983-8.
- Pickering TG, James GD. ABPM blood pressure and prognosis. *J Hypertens* 1994; 12 (Suppl 8): S29-S33.
- Khattar RS, Senior R, Lahiri A. Cardiovascular outcome in white-coat versus sustained mild hypertension: a 10-year follow-up study. *Circulation* 1998; 98: 1982-7.
- O'Brien E, Sheridan J, O'Malley K. Dippers and non-dippers. *Lancet* 1988; ii: 397.
- Verdecchia P, Schillaci G, Gatteschi C et al. Blunted nocturnal fall in blood pressure in hypertensive women with future cardiovascular morbid events. *Circulation* 1993; 88: 986-92.
- Yamamoto Y, Akiguchi I, Oiwa K et al. Adverse effect of night-time blood pressure on the outcome of lacunar infarct patients. *Stroke* 1998; 29: 570-6.
- Stolarz K, Staessen JA, O'Brien E. Night-time blood pressure – dipping into the future? *J Hypertens* 2002; 20: 2131-3.
- Cuspidi C, Meani S, Salerno M et al. Cardiovascular target organ damage in essential hypertensives with or without reproducible nocturnal fall in blood pressure. *J Hypertens* 2004; 22: 273-80.
- Verdecchia P, Porcellati C, Schillaci G et al. Ambulatory blood pressure: an independent predictor of prognosis in essential hypertension. *Hypertension* 1994; 24: 793-801.
- Kario K, Pickering TG, Matsuo T et al. Stroke prognosis and abnormal nocturnal blood pressure falls in older hypertensives. *Hypertension* 2001; 38: 852-7.
- Ohkubo T, Hozawa A, Yamaguchi J et al. Prognostic significance of the nocturnal decline in blood pressure in individuals with and without high 24-h blood pressure: the Ohasama study. *J Hypertens* 2002; 20: 2183-9.
- Williams M, Fleg J, Ades P et al. Secondary prevention of coronary heart disease in the elderly (with emphasis on patients >75 years of age). *Circulation* 2002; 105: 1735-43.
- Ockene I, Houston-Miller N for the American Heart Association Task Force on Risk Reduction. Cigarette Smoking, Cardiovascular Disease, and Stroke; A Statement for Healthcare Professionals From the American Heart Association. *Circulation* 1997; 96: 3243-7.
- Kjeldsen SE, Stevo J, Hedner T et al. Stroke is more common than myocardial infarction in hypertension: analysis based on 11 major randomized intervention trials. *Blood Pressure* 2001; 10: 190-2.
- Bucher H, Griffith L, Guyatt G. Systematic review on the risk and benefit of different cholesterol-lowering interventions. *Arterioscler Thromb Vasc Biol* 1999; 19: 187-95.
- Standards of medical care for patients with diabetes mellitus. *Diabetes Care* 2002; 25 (Suppl 1): S33-49.
- Update Consensus Panel Guide to Comprehensive Risk Reduction for Adult Patients Without Coronary or Other Atherosclerotic Vascular Diseases. *Circulation* 2002; 106: 388-91.
- Gorelick PB, Sacco RL, Smith DB et al. A Review of Guidelines and a Multidisciplinary Consensus Statement From the National Stroke Association. *JAMA* 1999; 281 (12): 24-31.