

# JournalScan

Iqbal Malik, Editor



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## ISCHAEMIC HEART DISEASE

**High dose statins better than low dose** ▶ Statins are known to reduce atherogenic lipoproteins and hence cardiovascular morbidity and mortality. However, the impact of their varying efficacies on clinical outcome is unknown. Hence the REVERSAL (reversal of atherosclerosis with aggressive lipid lowering) study recruited 654 patients with low density lipoprotein (LDL) cholesterol concentrations between 3.24–5.44 mmol/l and an angiographically proven narrowing of 20% or more. Participants were randomised to 18 months of intensive treatment with atorvastatin 80 mg or moderate treatment with pravastatin 40 mg. Those in the intensive treatment group showed significantly reduced progression of coronary artery stenosis as assessed by intravascular ultrasound, with some actually showing disease regression. These differences may be due to the greater reduction in atherogenic lipoproteins and C reactive protein caused by atorvastatin.

▲ **Nissen SE**, Murat Tuzcu E, Schoenhagen P, *et al*. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis. *JAMA* 2004;291:1071–80.

**Simvastatin lowers the risk of stroke** ▶ A total of 3280 adults with cerebrovascular disease, and an additional 17 256 with other occlusive arterial disease or diabetes, were randomly allocated 40 mg simvastatin daily or matching placebo. Overall, there was a highly significant 25% (95% confidence interval (CI) 15% to 34%) proportional reduction in the first event rate for stroke (4.3% simvastatin v 5.7% placebo;  $p < 0.0001$ ), reflecting a definite 28% (95% CI 19% to 37%) reduction in presumed ischaemic strokes ( $p < 0.0001$ ) and no apparent difference in strokes attributed to haemorrhage (51 (0.5%) v 53 (0.5%); rate ratio 0.95, 95% CI 0.65 to 1.40;  $p = 0.8$ ). In addition, simvastatin reduced the numbers having transient cerebral ischaemic attacks alone (2.0% v 2.4%;  $p = 0.02$ ) or requiring carotid endarterectomy or angioplasty (0.4% v 0.8%;  $p = 0.0003$ ). The reduction in stroke was not significant during the first year, but was already significant ( $p = 0.0004$ ) by the end of the second year. Among patients with pre-existing cerebrovascular disease there was no apparent reduction in the stroke rate, but there was a highly significant 20% (95% CI 8% to 29%) reduction in the rate of any major vascular event (24.7% v 29.8%;  $p = 0.001$ ). The proportional reductions in stroke were about a quarter in each of the other subcategories of participant studied, including: those with coronary disease or diabetes; those aged under or over 70 years at entry; and those presenting with different levels of blood pressure or lipids (even when the pre-treatment LDL cholesterol was below 3.0 mmol/l).

▲ **Heart Protection Study Collaborative Group**. Effects of cholesterol-lowering with simvastatin on stroke and other major vascular events in 20 536 people with cerebrovascular disease or other high-risk conditions. *Lancet* 2004;363:757–67.

**Dietary fibre reduces CHD risk** ▶ Increased fibre intake is recommended to reduce the risk of colon cancer, and as part of the DASH diet to control hypertension. In an analysis of prospective cohort studies from the USA and Europe, an estimate of the association between dietary fibre intake and the risk of coronary heart disease (CHD) was made. Over 6–10 years of follow up, 5249 incident total coronary cases and 2011 coronary deaths occurred among 91 058 men and 245 186 women. After adjustment for demographics, body mass index, and lifestyle factors, each 10 g/day increment of energy adjusted and measurement error corrected total dietary fibre was associated with a 14% (relative risk (RR) 0.86, 95% CI 0.78 to 0.96) decrease in risk of all coronary events and a 27% (RR 0.73, 95% CI 0.61 to

0.87) decrease in risk of coronary death. Results were similar for men and women.

▲ **Pereira MA**, O'Reilly E, Augustsson K, Fraser GE, Goldbourt U, Heitmann BL, Hallmans G, Knekt P, Liu S, Pietinen P, Spiegelman D, Stevens J, Virtamo J, Willett WC, Ascherio A. Dietary fiber and risk of coronary heart disease: a pooled analysis of cohort studies. *Arch Intern Med* 2004;164:370–6.

**CRP is less impressive than standard risk factors as a marker of CHD risk** ▶ Apart from standard risk factors, C reactive protein (CRP) has received the most attention, with a call for it to be included in modern risk assessment tools. This large study and meta-analysis suggests that it has some value, but questions how much there is to gain by adding this test. After adjustment for baseline values for established risk factors, the odds ratio (OR) for CHD was 1.45 (95% CI 1.25 to 1.68) in a comparison of participants in the top third of the group with respect to baseline CRP values with those in the bottom third. Equivalent figures for total cholesterol concentration (OR 2.35, 95% CI 2.03 to 2.74) and cigarette smoking (OR 1.87, 95% CI 1.62 to 2.16) were higher.

▲ **Danesh J**, Wheeler JG, Hirschfield GM, Eda S, Eiriksdottir G, Rumley A, Lowe GDO, Pepys MB, Gudnason V. C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. *N Engl J Med* 2004;350:1387–97.

## HEART FAILURE

**BNP is not very sensitive in detecting LV dysfunction in patients with CHD** ▶ In a cross sectional study of 293 outpatients who had stable coronary disease and no history of heart failure, plasma BNP (brain natriuretic peptide) concentrations were compared with echocardiography for the diagnosis of systolic dysfunction (ejection fraction  $< 55\%$ ) and diastolic dysfunction (diastolic dominant pulmonary vein flow with ejection fraction  $\geq 55\%$ ). A total of 48 patients (16%) had systolic dysfunction, and among the remaining 245 with preserved systolic function, 31 (13%) had diastolic dysfunction. At the standard cut off point of  $> 100$  pg/ml, an elevated BNP value was 38% sensitive (80% specific) for systolic dysfunction and 55% sensitive (85% specific) for diastolic dysfunction. Previous studies in unselected patients and in those with symptoms of heart failure suggest BNP is a useful screening test, but in patients with CHD it is not.

▲ **Bibbins-Domingo K**, Ansari M, Schiller NB, Massie B, Whooley MA. Is b-type natriuretic peptide a useful screening test for systolic or diastolic dysfunction in patients with coronary disease? Data from the heart and soul study. *Am J Med* 2004;116:509–16.

## Natriuretic peptides do not predict coronary stenoses

▶ Plasma concentrations of ANP (atrial natriuretic peptide), N-terminal proANP, and BNP were higher in patients with ( $n = 65$ ) than in those without ( $n = 39$ ) coronary artery stenosis, defined as angiographic stenosis  $> 75\%$ . Patients who had coronary artery stenosis with only distal lesions ( $n = 36$ ) had higher levels of all three natriuretic peptides than did patients with no coronary artery stenosis. Multiple logistic regression analysis revealed that N-terminal proANP, but not ANP or BNP, was independently associated with coronary artery stenosis after adjusting for clinical and demographic variables. However, the sensitivity, specificity, and positive and negative predictive values of each peptide were not sufficiently high to be used for prediction. Further studies in only patients with cardiac sounding chest pain, and with diastolic dysfunction excluded, may reveal more information.

▲ **Nishikimi T**, Mori Y, Ishimura K, Tadokoro K, Yagi H, Yabe A, Horinaka S, Matsuoka H. Association of plasma atrial natriuretic peptide, n-terminal proatriuretic peptide, and brain natriuretic peptide levels with coronary artery stenosis in patients with normal left ventricular systolic function. *Am J Med* 2004;116:517–23.

**BUN is a good marker of risk in HF** ▶ Hospitalisation for acutely decompensated heart failure is associated with a high mortality after discharge. Circulating concentrations of neurohormones increase with the severity of heart failure, and deterioration of renal function is common. However, the prognostic importance of

renal function in patients with decompensated heart failure is not known. The prognostic importance of four measures of renal function—blood urea nitrogen, serum creatinine, blood urea nitrogen/creatinine ratio, and estimated creatinine clearance—was evaluated in 541 patients (mean (SD) age, 63 (14) years; 377 men (70%)) with a previous diagnosis of heart failure (96% with New York Heart Association functional class III or IV symptoms) who were admitted for clinical decompensation. During a mean follow up of 343 (185) days, 177 patients (33%) died. In multivariable Cox regression models, the risk of all cause mortality increased with each quartile of blood urea nitrogen (BUN), with an adjusted relative risk of 2.3 in patients in the upper compared with the lower quartiles (95% CI 1.3 to 4.1;  $p = 0.005$ ). Creatinine and estimated creatinine clearance were not significant predictors of mortality after adjustment for other covariates.

▲ **Aronson D**, Mittleman MA, Burger AJ. Elevated blood urea nitrogen level as a predictor of mortality in patients admitted for decompensated heart failure. *Am J Med* 2004;116:466-73.

**Measure BNP in pleural effusions in cases of diagnostic doubt** ► The diagnosis of pleural effusions caused by heart failure is usually made clinically, supported by finding of a transudate when pleural fluid is examined. However, about a quarter of pleural fluids from patients with a sole diagnosis of heart failure are misclassified as exudates by standard Light's criteria, particularly when patients have been treated with diuretics. A series of 117 samples were collected over six years. Older age, bilateral pleural effusions of small size, and the typical biochemical profile of a transudate were associated with heart failure. Median concentrations of proBNP in pleural fluid among patients with heart failure were significantly higher (6931 pg/ml; 3342 to 17 764 pg/ml) than in patients with other conditions (all  $p < 0.001$  for comparisons with heart failure). Using a cutoff value  $\geq 1500$  pg/ml, pleural proBNP concentration was an accurate predictor that a patient met clinical criteria for heart failure, with a sensitivity of 91% and a specificity of 93%.

▲ **Porcel JM**, Vives M, Cao G, Esquerda A, Rubio M, Rivas MC. Measurement of pro-brain natriuretic peptide in pleural fluid for the diagnosis of pleural effusions due to heart failure. *Am J Med* 2004;116:417-20.

**Viagra (sildenafil) in heart failure patients** ► Erectile dysfunction (ED) is common in patients with congestive heart failure (CHF) and is often associated with symptoms of depression. Although sildenafil citrate, a phosphodiesterase 5 inhibitor, is effective in treating ED, its use is considered a relative contraindication in CHF. In 35 patients with a history of chronic ED and absence of ischaemia (negative results from exercise stress test or nuclear perfusion scan) or nitrate use, sildenafil caused a mean (SEM) asymptomatic decrease in blood pressure of 6 (3) mm Hg. No patient experienced symptomatic hypotension or other significant adverse effects. Sildenafil improved the international index for erectile function ( $p < 0.001$ ) and depression scores. The living with heart failure questionnaire index also improved with sildenafil ( $p = 0.02$ ).

▲ **Webster LJ**, Michelakis ED, Davis T, Archer SL. Use of sildenafil for safe improvement of erectile function and quality of life in men with New York Heart Association classes II and III congestive heart failure: a prospective, placebo-controlled, double-blind crossover trial. *Arch Intern Med* 2004;164:514-20.

## HYPERTENSION

**Home BP may be a better guide than office BP** ► The relation between high blood pressure (BP) and cardiovascular risk is well known when BP is measured with a mercury sphygmomanometer. Home BP monitoring is known to improve the precision and reproducibility of readings, but its prognostic value in western populations has not previously been proven. The SHEAF (self-measurement of blood pressure at home in the elderly: assessment and follow-up) trial looked at 4939 treated hypertensive patients over 60 and allowed their general practitioners to use home BP readings to guide hypertensive treatment as they felt appropriate. Over a three year period they were then followed up primarily for cardiovascular mortality, and a number of secondary end points indicative of vascular disease. Using home BP measuring, each 10 mm Hg increase in systolic BP increased the risk of a cardiovascular event by 17.2%, while a 5 mm Hg increase in diastolic BP increased the risk by 11.7%. Conversely, the same

increase in BP using office measurement showed no significant increase in the risk of cardiovascular events. In particular, a subgroup of 9% of patients with a poorer prognosis was identified who had poor control of their hypertension at home yet appeared normal in the office. Whether this can be used to improve cardiovascular prevention remains to be shown.

▲ **Bobrie G**, Chatellier G, Genes N, et al. Cardiovascular prognosis of "masked hypertension" detected by blood pressure self-measurement in elderly treated hypertensive patients. *JAMA* 2004;291:1342-9.

## GENERAL CARDIOLOGY

**Benefits of carotid artery treatment after stroke are time dependant** ► Carotid endarterectomy reduces the risk of stroke in patients with recently symptomatic stenosis. Benefit depends on the degree of stenosis, but is affected by timing and the age and sex of the patient. In pooled data from the European carotid surgery trial and the North American symptomatic carotid endarterectomy trial, 5893 patients with 33 000 patient-years of follow up were analysed. Sex ( $p = 0.003$ ), age ( $p = 0.03$ ), and time from the last symptomatic event to randomisation ( $p = 0.009$ ) modified the effectiveness of surgery. Benefit from surgery was greatest in men, patients aged 75 years or older, and those randomised within two weeks after their last ischaemic event, and fell rapidly with increasing delay. For patients with 50% or higher stenosis, the number of patients needed to undergo surgery (that is, number needed to treat) to prevent one ipsilateral stroke in five years was nine for men versus 36 for women, five for age 75 years or older versus 18 for younger than 65 years, and five for those randomised within two weeks after their last ischaemic event versus 125 for patients randomised after more than 12 weeks. Urgent treatment appears of greatest benefit.

▲ **Rothwell PM**, Eliasziw M, Gutnikov SA, Warlow CP, Barnett HJ, for the Carotid Endarterectomy Trialists Collaboration. Endarterectomy for symptomatic carotid stenosis in relation to clinical subgroups and timing of surgery. *Lancet* 2004;363:915-24.

**No need to rush for stem cell transplant to treat myocardial damage** ► A group in South Korea prospectively randomised 27 patients with myocardial infarction who underwent coronary stenting for the culprit lesion of infarction into three groups; cell infusion ( $n = 10$ ), granulocyte-colony stimulating factor (G-CSF) alone ( $n = 10$ ), and control group ( $n = 7$ ). Changes in left ventricular systolic function and perfusion were assessed after six months. By December 2003, seven patients from the cell infusion group, three from the G-CSF group, and one from the control group had been assessed. Exercise capacity (mean (SD) treadmill exercise time: 450 (178) s at baseline v 578 (168) s at six months' follow up,  $p = 0.004$ ), myocardial perfusion (perfusion defect 11.6 (9.6)% v 5.3 (5.0)%,  $p = 0.020$ ), and systolic function (left ventricular ejection fraction 48.7 (8.3)% v 55.1 (7.4)%,  $p = 0.005$ ) improved significantly in patients who received cell infusion (beyond that expected for revascularisation). However, there was an unexpectedly high rate of in-stent restenosis at culprit lesion in patients who received G-CSF, and therefore enrolment was stopped. Further data are needed. Importantly, no electrical instability was seen in these patients.

▲ **Kang H-J**, Kim H-S, Zhang S-Y, et al. Effects of intracoronary infusion of peripheral blood stem-cells mobilised with granulocyte-colony stimulating factor on left ventricular systolic function and restenosis after coronary stenting in myocardial infarction: the MAGIC cell randomised clinical trial. *Lancet* 2004;363:751-6.

### Journals scanned

American Journal of Medicine; American Journal of Physiology; Heart and Circulatory Physiology; Annals of Emergency Medicine; Annals of Thoracic Surgery; Archives of Internal Medicine; BMJ; Chest; European Journal of Cardiothoracic Surgery; Lancet; JAMA; Journal of Clinical Investigation; Journal of Diabetes and its Complications; Journal of Immunology; Journal of Thoracic and Cardiovascular Surgery; Nature Medicine; New England Journal of Medicine; Pharmacoeconomics; Thorax

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