JournalScan

Iqbal Malik, Editor

Please visit the Heart website (www.heartjnl.com) for links to these articles – many to full text.

ISCHAEMIC HEART DISEASE

Clopidogrel is useful in addition to aspirin in AMI ▶ In > 45 000 patients, the addition of 75 mg clopidogrel < 24 hours after ST elevation myocardial infarction (STEMI), in addition to aspirin and reperfusion, was assessed. Treatment was to continue until discharge or up to four weeks in hospital (mean 15 days in survivors) and 93% of patients completed it. The two prespecified co-primary outcomes were: (1) the composite of death, reinfarction, or stroke; and (2) death from any cause during the scheduled treatment period. Comparisons were by intention to treat, and used the log rank method. Allocation to clopidogrel produced a highly significant 9% (95% confidence interval (CI) 3% to 14%) proportional reduction in death, reinfarction, or stroke (2121 (9.2%) clopidogrel *v* 2310 (10.1%) placebo; p = 0.002), corresponding to 9 (SE 3) fewer events per 1000 patients treated for about two weeks. There was also a significant 7% (95% CI 1% to 13%) proportional reduction in any death (1726 (7.5%) *v* 1845 (8.1%); p = 0.03). Considering all fatal, transfused, or cerebral bleeds together, no significant excess risk was noted with clopidogrel, either overall (134 (0.58%) *v* 125 (0.55%); p = 0.59), or in patients aged older than 70 years or in those given fibrinolytic treatment.

▲ COMMIT (Clopidogrel and Metoprolol in Myocardial Infarction Trial) Collaborative Group. Addition of clopidogrel to aspirin in 45852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet* 2005;**366**:1607–21.

Intravenous metoprolol < 24 hours after STEMI does not improve prognosis ▶ Using the same population as for the COMMIT study, the use of early intravenous β blocker treatment was also assessed. For death, reinfarction, or cardiac arrest, 2166 (9.4%) patients allocated metoprolol had at least one such event compared with 2261 (9.9%) allocated placebo (odds ratio (OR) 0.96, 95% CI 0.90 to 1.01; p = 0.1). For death alone, there were 1774 (7.7%) deaths in the metoprolol group versus 1797 (7.8%) in the placebo group (OR 0.99, 95% CI 0.92 to 1.05; p = 0.69). Any benefit in terms of reinfarction and arrhythmias was balanced by an increase in cardiogenic shock in the β blocker group.

▲ COMMIT (Clopidogrel and Metoprolol in Myocardial Infarction Trial) Collaborative Group. Early intravenous then oral metoprolol in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet* 2005;**366**:1622–32.

Marked out at risk at birth by your (low) weight ▶ Childhood growth was recorded in 8760 people born in Helsinki from 1934 through 1944. A total of 357 men and 87 women had been admitted to the hospital with coronary heart disease or had died from the disease. Coronary risk factors were measured in a subset of 2003 people. The mean body size of children who had coronary events as adults was below average at birth. At 2 years of age the children were thin; subsequently, their body mass index (BMI) increased relative to that of other children and had reached average values by 11 years of age. In simultaneous regressions, the hazard ratios (HR) associated with a 1 SD increase in BMI were 0.76 (95% CI 0.66 to 0.87; p < 0.001) at 2 years and 1.14 (95% CI 1.00 to 1.31; p = 0.05) at 11 years among the boys. The corresponding figures for the girls were 0.62 (95% CI 0.46 to 0.82; p = 0.001) and 1.35 (95% CI 1.02 to 1.78; p = 0.04). Low BMI at 2 years of age and increased BMI from 2–11 years of age were also associated with raised fasting insulin concentrations (p < 0.001 for both). The risk of coronary events was more strongly related to the tempo of childhood gain in BMI than to the BMI attained at any particular age.

▲ Barker JP, Osmond C, Forsén TJ *et al*. Trajectories of growth among children who have coronary events as adults. *N Engl J Med* 2005;**353**:1802–9.

HEART FAILURE

ARBs are ''ACE inhibitors without a cough'' but may have added benefit ▶ Angiotensin converting enzyme (ACE) inhibitors reduce the risk of myocardial infarction (MI), but do angiotensin receptor blockers (ARBs) have the same effect? Data from the CHARM (candesartan in heart failure: assessment of reduction in mortality and morbidity) programme suggests they do. A total of 7599 patients with New York Heart Association class II–IV heart failure symptoms were enrolled over a period of two years. At baseline 53% had experienced a previous MI, and 24% had angina at the time; 41% were receiving an ACE inhibitor, 55% a β blocker, 42% a lipid lowering agent, 56% aspirin, and 83% were on a diuretic. Primary outcome was a composite end point of death or MI in patients with heart failure receiving candesartan or placebo. During an average follow up of 37.7 months, this primary outcome occurred in 20.4% of those receiving candesartan, compared to 22.9% of those receiving placebo (p = 0.004; number needed to treat, 40). Non-fatal MI alone was also significantly reduced in the candesartan group (3.1%) versus the placebo group (3.9%) (p = 0.03). The secondary outcome of fatal MI, sudden death, or non-fatal MI was significantly reduced with candesartan (12.1%) versus placebo (13.8%) (p = 0.02). Therefore angiotensin II receptor blockade seems to confer an advantage even in patients otherwise optimally treated for heart failure. How much non-ACE angiotensin II generation might be contributing to the continuing risk of MI in patients treated with an ACE inhibitor may be answered by two large prospective trials currently under way: ONTARGET (ongoing telmisartan alone and in combination with ramipril global endpoint trial) and TRANSCEND (telmisartan randomized assessment study in ACE intolerant subjects with cardiovascular disease).

▲ Demers C, McMurray JJV, Swedberg K, *et al*. Impact of candesartan on nonfatal myocardial infarction and cardiovascular death in patients with heart failure. *JAMA* 2005;**294**:1794–8.

CPAP does not improve mortality in heart failure ▶ After medical treatment was optimised, 258 patients who had heart failure (mean (SD) age 63 (10) years; ejection fraction 24.5 (7.7)%) and central sleep apnoea (number of episodes of apnoea and hypopnoea per hour of sleep, 40 (16)) were randomly assigned to receive continuous positive airways pressure (CPAP) (128 patients) or no CPAP (130 patients) and were followed for a mean of two years. During follow up, sleep studies were conducted and measurements of the ejection fraction, exercise capacity, quality of life, and neurohormones were obtained. Three months after undergoing randomisation, the CPAP group, as compared with the control group, had greater reductions in the frequency of episodes of apnoea and hypopnoea (−21 (16) *v* −2 (18) per hour, p < 0.001) and in noradrenaline (norepinephrine) values (−1.03 (1.84) nmol/l *v* 0.02 (0.99) nmol/l, p = 0.009), and greater increases in the mean nocturnal oxygen saturation (1.6 (2.8)% *v* 0.4 (2.5)%, p < 0.001), ejection fraction (2.2 (5.4)% *v* 0.4 (5.3)%, p = 0.02), and the distance walked in six minutes (20.0 (55) m *v* −0.8 (64.8) m, p = 0.016). There were no differences between the control group and the CPAP group in the number of hospitalisations, quality of life, or atrial natriuretic peptide values. The overall event rates (death and heart transplantation) did not differ (32 *v* 32 events, respectively; p = 0.54).

▲ Bradley D, Logan AG, Kimoff JR, *et al*, for the CANPAP Investigators. Continuous positive airway pressure for central sleep apnea and heart failure. *N Engl J Med* 2005;**353**:2025–33.

ESCAPE from routine PA catheterisation ▶ The ESCAPE (evaluation study of congestive heart failure and pulmonary artery catheterisation effectiveness) trial was a multicentre randomised controlled trial designed to assess the safety and efficacy of pulmonary artery catheterisation (PAC) in the treatment of patients with heart failure. A total of 433 patients from 26 centres were

enrolled over a three year period. Patients were assigned to receive treatment guided by clinical assessment and PAC, or by clinical assessment alone. The target in both groups was resolution of the clinical symptoms and signs of cardiac failure (orthopnoea, oedema, jugular venous pressure elevation), with additional PAC targets of pulmonary capillary wedge pressure of 15 mm Hg and a right atrial pressure of 8 mm Hg. No specific pharmacological treatment agents were specified, although inotrope use was discouraged. Treatment in both groups led to a substantial reduction in symptoms, jugular venous pressure, and oedema. However, the trial was terminated early (at enrolment of 433, rather than the planned 500) when a significant number of excess adverse events were noted in the PAC group (47 *v* 25 in hospital adverse events), and it was determined that any benefit of PAC on the primary end point of days alive out of hospital at six months was not likely to be observed (133 *v* 135 days; HR 1.00). Furthermore no significant differences were seen in mortality (43 *v* 38 patients; OR 1.26; p = 0.35), or the number of days hospitalised (8.7 *v* 8.3; HR 1.04; p = 0.67). There were no deaths related to PAC use, and no difference noted for in hospital plus 30 day mortality (10 *v* 11 patients; OR 0.97; p = 0.97) improvement with the PAC. An accompanying meta-analysis in the same issue of *JAMA* reviews data from 5051 patients in 13 randomised controlled trials over the last 20 years. The combined odds ratio for mortality in those treated with a PAC was 1.04 (95% CI 0.9 to 0.12; p = 0.59). The difference in the mean number of days hospitalised was 0.11 (95% CI −0.51 to 0.74; p = 0.73). Use of the PAC was associated with a higher use of inotropes and intravenous vasodilators.

▲ The ESCAPE Investigators and ESCAPE Study Coordinators. Evaluation study of congestive heart failure and pulmonary artery catheterization effectiveness. The ESCAPE trial. *JAMA* 2005;**294**:1625–33.

▲ Shah MR, Hasselblad V, Stevenson LW. Impact of pulmonary artery catheter in critically ill patients. Meta-analysis of randomized clinical trials. *JAMA* 2005;**294**:1664–70.

HYPERTENSION

After all the debate, β blockers are not first line in hypertension ► In 13 trials of > 100 000 patients with hypertension comparing β blockers to other agents, and in trials totalling >20 000 patients comparing β blockers to placebo, the relative risk of stroke was 16% higher for β blockers (95% CI 4% to 30%) than for other drugs. There was no difference for MI. When the effect of β blockers was compared with that of placebo or no treatment, the relative risk of stroke was reduced by 19% for all β blockers (7–29%), about half that expected from previous hypertension trials. There was no difference for MI or mortality.

▲ Lindholm LH, Carlberg B, Samuelsson O. Should β blockers remain first choice in the treatment of primary hypertension? A meta-analysis. *Lancet* 2005;**366**:1545–53.

GENERAL CARDIOLOGY

Vasodilators appear not to prevent progression of aortic regurgitation ► Scognamiglio and colleagues used clinical end points rather than surrogate variables alone, such as the function or size of the left ventricle (LV), to assess the value of vasodilators in severe aortic regurgitation. In that study, a mean of 34 (6)% of the patients in the digoxin group required aortic valve replacement (AVR) at six years, as compared with 15 (3)% of the patients in the nifedipine group. The present study randomised 95 patients with asymptomatic severe aortic regurgitation and normal LV function to receive open label nifedipine (20 mg every 12 hours), open label enalapril (20 mg per day), or no treatment (control group) to identify the benefits of vasodilator treatment on LV function and the need for AVR. After a mean of seven years of follow up, the rate of AVR was similar among the groups: 39% in the control group, 50% in the enalapril group, and 41% in the nifedipine group (p = 0.62). In addition, there were no significant differences among the groups in aortic regurgitant volume, LV size, LV mass, mean wall stress, or ejection fraction. Thus, the benefits of vasodilators may have been overestimated by the previous study.

▲ Scognamiglio R, Rahimtoola SH, Fasoli G, *et al*. Nifedipine in asymptomatic patients with severe aortic regurgitation and normal left ventricular function. *N Engl J Med* 1994;**331**:689–94.

▲ Evangelista A, Tornos P, Sambola A, *et al*. Long-term vasodilator therapy in patients with severe aortic regurgitation. *N Engl J Med* 2005;**353**:1342–9.

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

Reviewers ► Dr Diana Gorog, Dr Akhil Kapur, Dr Masood Khan, Dr Alistair Lindsay, Dr Andrew Sharp

FROM BMJ JOURNALS

Epidemiological modelling of routine use of low dose aspirin for the primary prevention of coronary heart disease and stroke in those aged ⩾70

Mark R Nelson, Danny Liew, Melanie Bertram, Theo Vos

Please visit the *Heart* website [www.heartjnl.com] for a link to the full text of this article.

Objective: To investigate the routine use of low dose aspirin in people aged ⩾70 without overt cardiovascular disease.

Design: Epidemiological modelling in a hypothetical population.

Setting: Reference populations of men and women in the year 2000 from the state of Victoria, Australia.

Subjects: 10 000 men and 10 000 women aged 70–74 with no cardiovascular disease.

Main outcome measures: First ever myocardial infarction or unstable angina, ischaemic or haemorrhagic stroke, and major gastrointestinal haemorrhage. Health adjusted years of life lived.

Results: The proportional benefit gained from the use of low dose aspirin by the prevention of myocardial infarctions (−389 in men, −321 in women) and ischaemic stroke (−19 in men and −35 in women) is offset by excess gastrointestinal (499 in men, 572 in women) and intracranial (76 in men, 54 in women) bleeding. The results in health adjusted years of life lived (which take into account length and quality of life) are equivocal for aspirin causing net harm or net benefit.

Conclusion: Epidemiological modelling suggests that any benefits of low dose aspirin on risk of cardiovascular disease in people aged ⩾70 are offset by adverse events. These findings are tempered by wide confidence intervals, indicating that the overall outcome could be beneficial or adverse.

▲ *BMJ* 2005;**330**:1306–1308.