JournalScan

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Ischaemic heart disease

C reactive protein predicts death but not restenosis ▶ There is a lot of information about the role of C reactive protein (CRP) in predicting death/myocardial infarction (MI) in patients at risk of ischaemic heart disease. Data on its role in patients undergoing percutaneous coronary intervention is less clear. These studies of 1458 and 1152 patients suggested that CRP concentrations > 3 mg/dl and > 5 mg/dl, respectively, predicted death/MI as expected, but the occurrence of restenosis was not linked to CRP values. This confirms that the pathological process in a restenotic lesion is different to native atherosclerosis.

▲ **de Winter RJ**, Koch KT, van Straalen JP, Heyde G, Bax M, Schotborgh CE, Mulder KJ, Snaders GT, Fischer J, Tijssen JGP, Piek JJ. C-reactive protein and coronary events following percutaneous coronary angioplasty. *Am J Med* 2003;115:85–90.

▲ **Dibra A**, Mehillie J, Braun S, Hadamitzky M, Baum H, Dirschinger J, Schühlen H, Schömig A, Kastrati A. Association between C-reactive protein levels and subsequent cardiac events among patients with stable angina treated with coronary artery stenting. *Am J Med* 2003;114:715–22.

α2 Adrenergic agonists to reduce perioperative risk ▶ Approximately 4.5% of patients undergoing cardiac surgery will have a perioperative MI. The benefits of perioperative β blockade in patients at risk of coronary heart disease (CHD) is well proven. This study assessed a less used class of drugs that includes clonidine, dexmedetomidine, and mizaverol. A total of 23 trials comprising 3395 patients were included in the meta-analysis. Overall, α2 agonists reduced mortality (relative risk (RR) 0.64, 95% confidence interval (CI) 0.42 to 0.99, $p = 0.05$) and ischaemia (RR 0.76, 95% CI 0.63 to 0.91, $p = 0.003$) significantly. The same was true for vascular surgery. Although dominated by one large study, and unable to fully control for the effect of β blockers, this study at least suggests that α2 agonists may help if β blockers are contraindicated.

▲ **Wijesundera DN**, Naik JS, Beattie S. Alpha-2 adrenergic agonists to prevent perioperative cardiovascular complications: a meta-analysis. *Am J Med* 2003;114:742–52.

Merely reducing smoking may not prevent myocardial infarction ▶ A Danish pooled cohort study has followed more than 19 000 adults for a mean of nearly 14 years, with full information on smoking habits at five year intervals. During the course of the study, 2179 were diagnosed as having a myocardial infarction. As expected, heavy smokers (more than 15 a day) were at greater risk. However, contrary to previous assumptions, those who reported having reduced the amount of tobacco they smoked did not reduce their risk, whereas fewer myocardial infarctions than expected occurred among those who had quit. This is a new finding and implies that persuading people who are unable or unwilling to quit smoking that they should reduce their habit is not likely to be a useful strategy, at least as far as cardiovascular protection is concerned.

▲ **Godtfredsen NS**, Osler M, Vestbo J, Andersen I, Prescott E. Smoking reduction, smoking cessation, and incidence of fatal and non-fatal myocardial infarction in Denmark 1976–1998: a pooled cohort study. *J Epidemiol Community Health* 2003;57:412–6.

Treating diabetes before it occurs ▶ There is no such thing as primary prevention in diabetes mellitus—risk levels are high once the disease is established. How about treating at the stage of impaired glucose tolerance (IGT) instead? A total of 1429 patients with IGT were randomised to acarbose or placebo, with 61

patients (4%) excluded because they did not have IGT or had no post-randomisation data. These patients were followed up for a mean (SD) of 3.3 (1.2) years. Nearly a quarter of patients discontinued their participation prematurely, 211 in the acarbose treated group and 130 in the placebo group. Even after adjusting for major risk factors, the reduction in the risk of cardiovascular events (hazard ratio (HR) 0.47, 95% CI 0.24 to 0.90; $p = 0.02$) and hypertension (HR 0.62, 95% CI 0.45 to 0.86; $p = 0.004$) associated with acarbose treatment was still significant.

▲ **Chiasson J-L**, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M, for the STOP-NIDDM Trial Research Group. Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM trial. *JAMA* 2003;290:486–94.

Raised troponin may identify haemodialysis patients with severe angiographic coronary disease even without obvious ACS ▶ Cardiac troponin T (cTnT) and CRP are prognostic markers in acute coronary syndromes. However, for patients with end stage renal disease (ESRD) the ability of combinations of these markers to predict outcomes, and their association with cardiac pathology, are unclear. A prospective cohort study enrolled 224 patients with ESRD. Concentrations of cTnT and CRP were analysed at study entry in patients without ischaemic symptoms.

The combination of cTnT and CRP results provided prognostic information when patients were divided into groups at or above and below the biomarker medians (high cTnT/high CRP concentrations v low cTnT/low CRP concentrations for risk of death: HR 2.5, 95% CI 1.5 to 4.0). Raised concentrations of cTnT, but not CRP, were strongly associated with diffuse coronary artery disease (CAD) ($n = 67$; 0%, 25%, 50%, and 62% prevalence of multivessel CAD across progressive cTnT quartiles, $p < 0.001$).

▲ **deFilippi C**, Wasserman S, Rosanio S, Tiblier E, Sperger H, Tocchi M, Christenson R, Uretsky B, Smiley M, Gold J, Muniz H, Badalamenti J, Herzog C, Henrich W. Cardiac troponin T and C reactive protein for predicting prognosis, coronary atherosclerosis, and cardiomyopathy in patients undergoing long-term hemodialysis. *JAMA* 2003;290:353–9.

Heart failure

Comparing systolic and diastolic heart failure ▶ Studies have found that 30–50% of all patients with chronic heart failure have preserved left ventricular systolic function. Despite this, the natural course of the condition in these patients is controversial, and their pathophysiological characterisation poor. As a result, optimum treatment strategies are unclear. In all, 522 patients had adequate measurements of ejection fraction, of whom 163 (31%) had values $\geq 50\%$ and 359 (69%) $< 50\%$. Information on deaths was recorded to April 2000, allowing five year survival status to be determined for all patients. Five year mortality was substantial in both groups but significantly greater in patients with impaired left ventricular systolic function (41.5% v 25.2%, $p < 0.001$). Twenty five per cent of patients with preserved function had non-sustained ventricular tachycardia.

▲ **MacCarthy PA**, Kearney MT, Nolan J, Lee AJ, Prescott RJ, Shah AM, Brooksby WP, Fox KAA. Prognosis in heart failure with preserved left ventricular systolic function: prospective cohort study. *BMJ* 2003;327:78–9.

Carvedilol is superior to metoprolol in heart failure

▶ β Blockers reduce mortality in patients who have chronic heart failure and systolic dysfunction. A total of 1511 patients with chronic heart failure were given carvedilol (target dose 25 mg twice daily) and 1518 metoprolol (metoprolol tartrate, target dose 50 mg twice daily). Patients were required to have chronic heart failure (New York Heart Association II–IV), previous admission for a cardiovascular reason, an ejection fraction of less than 0.35, and to have been treated optimally with diuretics and angiotensin converting enzyme (ACE) inhibitors unless not tolerated. The mean

(SD) study duration was 58 (6) months. The mean ejection fraction was 0.26 (0.07) and the mean age 62 (11) years. The all cause mortality was 34% (512 of 1511) for carvedilol and 40% (600 of 1518) for metoprolol (HR 0.83, 95% CI 0.74 to 0.93; $p = 0.0017$). The reduction of all cause mortality was consistent across predefined subgroups. The composite end point of mortality or all cause admission occurred in 1116 (74%) of 1511 patients on carvedilol and in 1160 (76%) of 1518 on metoprolol (HR 0.94, 95% CI 0.86 to 1.02; $p = 0.122$). Incidence of side effects and drug withdrawals did not differ by much between the two study groups.

▲ **Poole-Wilson PA**, Swedberg K, Cleland JGF, Di Lenarda A, Hanrath P, Komajda M, Lubsen J, Lutiger B, Metra M, Remme WJ, Torp-Pedersen C, Scherhag A, Skene A, for the COMET investigators. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the carvedilol or metoprolol European trial (COMET): randomised controlled trial. *Lancet* 2003;**362**:7–13.

Watch out for anti-TNF treatment ► Tumour necrosis factor (TNF) concentrations rise in advanced heart failure, and a causal relation has been postulated but not proven. A trial of etanercept (TNF blocker) for heart failure (class III and IV) was stopped early after patients had worse outcomes with TNF blockade (101 TNF blockade, 50 placebo, with worse death (7 v 0) and hospitalisation results in the treated group). This studies the US Food and Drug Administration database for adverse events and analyses young people reported to have heart failure while on either etanercept or infliximab for other reasons (Crohn's disease/ rheumatoid arthritis/psoriatic arthritis/ juvenile arthritis) and found 38 cases of new onset heart failure, with 19 of those having no obvious cause other than the drug (mean age 62 years). What is worth noting, however, is that the majority had rheumatoid arthritis, and this is of course a risk factor for heart failure. The counter argument is that most improved upon stopping the medication and receiving heart failure treatment.

▲ **Kwon HJ**, Coté TR, Cuffe MS, Kramer JM, Braun MM. Case reports of heart failure after therapy with a tumor necrosis factor antagonist. *Ann Intern Med* 2003;**138**:807–11.

Hypertension

β Blockers may be less effective than other agents in reducing LVH ► Eighty trials with 146 active treatment arms ($n = 3767$ patients) and 17 placebo arms ($n = 346$ patients) were included in the meta-analysis. Adjusted for treatment duration and change in diastolic blood pressure, there was a significant difference ($p = 0.004$) among medication classes: left ventricular mass index decreased by 13% with angiotensin II receptor antagonists (95% CI 8% to 18%), by 11% with calcium antagonists (95% CI 9% to 13%), by 10% with ACE inhibitors (95% CI 8% to 12%), by 8% with diuretics (95% CI 5% to 10%), and by 6% with β blockers (95% CI 3% to 8%). With paired comparisons, β blockers were worse at reducing left ventricular mass than the other classes. The question of whether this translates into clinical benefit was open to debate, but the LIFE study suggests that the angiotensin II receptor blocker losartan may reduce CHD events in patients with hypertension and left ventricular hypertrophy (LVH) more than atenolol in patients without vascular disease. Blood pressure was reduced similarly by losartan and atenolol, but the primary composite end point of death/MI/cerebrovascular accident occurred in 282 losartan treated patients (17.5 per 1000 patient-years) and 355 atenolol treated patients (21.8 per 1000 patient-years) (RR 0.81, 95% CI 0.69 to 0.95; $p = 0.008$).

▲ **Klingbeil AU**, Schneider M, Martus P, Messerli FH, Schmieder RE. A meta-analysis of the effects of treatment on left ventricular mass in essential hypertension. *Am J Med* 2003;**115**:41–6.

▲ **Devereux RB**, Dahlöf B, Kjeldsen SE, *et al* for the LIFE Study Group. Effects of losartan or atenolol in hypertensive patients without clinically evident vascular disease: a substudy of the LIFE randomized trial. *Ann Intern Med* 2003;**139**:169–77.

General cardiology

Aortic stenosis and bleeding ► Bleeding can occur in patients with aortic stenosis due to an association with angiodysplasia and the altered coagulability resulting from blood passing through a narrow orifice. In 50 patients with severe aortic stenosis, skin or mucosal bleeding occurred in 21% of the patients. Platelet function abnormalities under conditions of high shear stress, decreased von Willebrand factor collagen binding activity, and the loss of the largest multimers, or a combination of these was present in 67–92% of patients with severe aortic stenosis and correlated significantly with the severity of valve stenosis. Primary haemostatic abnormalities were completely corrected on the first day after surgery but tended to recur at six months, especially when there was a mismatch between patient and prosthesis (with an effective orifice area of less than 0.8 cm² per square metre of body surface area).

▲ **Vincentelli A**, Susen S, Le Tourneau T, Six I, Fabre O, Juthier F, Bauters A, Decoene C, Goudemand J, Prat A, Jude B. Acquired von Willebrand syndrome in aortic stenosis. *N Engl J Med* 2003;**349**:343–9.

Basic science

Pneumococcal vaccine to reduce atherosclerosis ► Growing evidence suggests that both adaptive and innate immune mechanisms can modulate the progression of atherosclerosis. Among the antigens identified in atherosclerotic lesions, oxidised low density lipoprotein (oxLDL) has a prominent role. Pneumococcal immunisation reduced atherogenesis in LDL receptor deficient mice. Plasma from these mice blocked oxLDL uptake by macrophages. In addition, IgM antibodies in sera from humans with pneumococcal pneumonia reacted significantly with both pneumococcal polysaccharides and oxLDL. These experiments establish for the first time a surprising connection between naturally occurring autoantibodies, microbial antigens, and atherogenesis. Before making a vaccine against atherosclerosis, it should be borne in mind that some antibodies to oxLDL do the exact opposite: they enhance LDL uptake and accelerate atherosclerosis. More work is therefore needed.

▲ **Binder CJ**, Hörkö S, Dewan A, Chang M-K, Kieu EP, Goodyear CS, Shaw PX, Palinski W, Witztum JL, Silverman GJ. Pneumococcal vaccination decreases atherosclerotic lesion formation: molecular mimicry between *Streptococcus pneumoniae* and oxidized LDL. *Nature Med* 2003;**9**:736–43.

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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