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Ischaemic heart disease

Only about 6% of episodes of cocaine induced chest pain are caused by MI ► Chest pain may be caused by ischaemia without infarction, or it may be extracardiac (for example, pleuritic) in nature. Weber and associates report on a prospective study in which they validated the hypothesis that such an approach is safe. They evaluated 344 patients with cocaine related chest discomfort. Forty two of these patients (12%) were admitted to the hospital with acute myocardial infarction (MI), unstable angina, or another cardiac condition. Among the remaining 302 patients, those who had no new electrocardiographic changes indicative of ischaemia, as well as normal concentrations of cardiac troponin I, a negative exercise test, and no cardiovascular complications during a 9–12 hour period in an observation unit, were discharged. Thirty day follow up in this cohort revealed that none of the patients died of a cardiovascular event. Four patients sustained a non-fatal MI; however, these patients had continued to use cocaine. So, many patients can be sent home from the emergency room, if all the standard tests are available all night.

▲ **Weber JE**, Shofer FS, Larkin L, Kalaria AS, Hollander JE. Validation of a brief observation period for patients with cocaine-associated chest pain. *N Engl J Med* 2003;**348**:510–17.

Fish oils enhance plaque stability ► One hundred and eighty eight patients awaiting carotid endarterectomy were enrolled and randomised to sunflower oil, placebo, n-3 PUFA (polyunsaturated fatty acid) or n-6 PUFA; 18 withdrew and eight were excluded. Duration of oil treatment was 7–189 days (median 42 days) and did not differ between groups. Sunflower oil had little effect on the fatty acid composition of lipid fractions. Fewer carotid plaques from patients being treated with fish oil had thin fibrous caps and signs of inflammation and more plaques had thick fibrous caps and no signs of inflammation, compared with plaques in patients in the control and sunflower oil groups (odds ratio (OR) 0.52, 95% confidence interval (CI) 0.24 to 0.89, and OR 1.19, 95% CI 1.02 to 1.57, *v* control; OR 0.49, 95% CI 0.23 to 0.90, and OR 1.16, 95% CI 1.01 to 1.53, *vs* sunflower oil). The number of macrophages in plaques from patients receiving fish oil was lower than in the other two groups. Carotid plaque morphology and infiltration by macrophages did not differ between control and sunflower oil groups. Thus, atherosclerotic plaques readily incorporate n-3 PUFAs from fish oil supplementation, inducing changes that can enhance stability of atherosclerotic plaques. By contrast, increased consumption of n-6 PUFAs does not affect carotid plaque fatty acid composition or stability over the time course studied here. Stability of plaques could explain reductions in non-fatal and fatal cardiovascular events associated with increased n-3 PUFA intake.

▲ **Thies F**, Garry JMC, Yaqoob P, Rerkasem K, Williams J, Shearman CP, Gallagher PJ, Calder PC, Grimble RF. Association of n-3 polyunsaturated fatty acids (PUFA) with stability of atherosclerotic plaques: a randomised controlled trial. *Lancet* 2003;**361**:477–85.

Cost effectiveness of population measures to reduce CHD risk ► Systolic blood pressure above 115 mm Hg accounts for two thirds of strokes and almost half of ischaemic heart disease cases, and cholesterol concentrations exceeding 3.8 mmol/l for 18% and 55%, respectively. Non-personal health interventions, including government action to stimulate a reduction in the salt content of processed foods, are cost effective ways to limit cardiovascular disease. Targeting patients at highest 10 year risk of coronary heart disease (CHD) is also cost effective and could be combined with population measures for added benefit.

▲ **Murray CJL**, Lauer JA, Hutubessy RCW, Niessen L, Tomijima N, Rodgers A, Lawes CMM, Evans DB. Effectiveness and costs of interventions to lower systolic blood pressure and cholesterol: a global and regional analysis on reduction of cardiovascular-disease risk. *Lancet* 2003;**361**:717–25.

Use of iso-osmolar contrast agents reduces nephropathy risk ► Nephropathy induced by contrast medium remains one of the most clinically important complications of the use of iodinated contrast medium. Most commonly, it is defined as an acute impairment of renal function manifested by an absolute increase in the serum creatinine concentration of at least 0.5 mg/dl (44.2 µmol/l) or by a relative increase of at least 25% from the baseline value. The serum creatinine concentration typically peaks on the second or third day after exposure to contrast medium and usually returns to the baseline value within two weeks. In a study the nephrotoxic effects of an iso-osmolar, dimeric, non-ionic contrast medium, iodixanol, was compared with low osmolar, non-ionic, monomeric contrast medium, iohexol, in 129 patients with diabetes with serum creatinine concentrations of 135–315 µmol/l who underwent coronary or aortofemoral angiography. The primary end point was the peak increase from baseline in the creatinine concentration during the three days after angiography. Two of the 64 patients in the iodixanol group (3%) had an increase in the creatinine concentration of > 45 µmol/l, as compared with 17 of the 65 patients in the iohexol group (26%) (p = 0.002; odds ratio for such an increase in the iodixanol group = 0.09, 95 CI 0.02 to 0.41).

▲ **Aubrey P**, Fransson S-G, Strasser R, Willenbrock R, Berg KJ, for the NEPHRIC Study Investigators. Nephrotoxic effects in high-risk patients undergoing angiography. *N Engl J Med* 2003;**348**:491–9.

Acetylcysteine is useful in preventing contrast nephropathy ► Participants with impaired renal function were randomly assigned to receive oral acetylcysteine (600 mg twice per day; n = 102) or matching placebo tablets (n = 98) on the day before and the day of angiography. All patients received low osmolality contrast agent. Twelve control patients (12%) and four acetylcysteine patients (4%) developed a more than 25% increase in serum creatinine concentration within 48 hours after contrast administration (relative risk 0.32, 95% CI 0.10 to 0.96; p = 0.03). Serum creatinine was lower in the acetylcysteine group (107.8 µmol/l *v* 122.9 µmol/l; p = 0.006) during the first 48 hours after angiography. Acetylcysteine treatment significantly increased creatinine clearance from 44.8 ml/min (0.75 ml/s) (95% CI 42.7 to 47.6 ml/min) to 58.9 ml/min (0.98 ml/s) (95% CI 55.6 to 62.3 ml/min) two days after the contrast administration (p < 0.001).The increase was not significant in the control group (from 42.1 to 44.1 ml/min (0.70 to 0.74 ml/s); p = 0.15). The benefit of acetylcysteine was consistent among various patient subgroups and persistent for at least seven days. There were no major treatment related adverse events.

▲ **Kay J**, Chow WH, Chan TM, Lo SK, Kwok OH, Yip A, Fan K, Lee CH, Lam WF. Acetylcysteine for prevention of acute deterioration of renal function following elective coronary angiography and intervention: a randomized controlled trial. *JAMA* 2003;**289**:553–8.

Treatment with ibuprofen limits the cardioprotective effects of aspirin ► In a study of 7107 patients who survived for at least one month and who were prescribed low dose aspirin (< 325 mg/day), compared with those who used aspirin alone, patients taking aspirin plus ibuprofen had an increased risk of all cause mortality (adjusted hazard ratio (HR) 1.93, 95% CI 1.30 to 2.87; p = 0.0011) and cardiovascular mortality (HR 1.73, 95% CI 1.05 to 2.84; p = 0.0305). In all, 6285 received aspirin alone, 187 aspirin plus ibuprofen, 206 aspirin plus diclofenac, and 429 aspirin plus other NSAIDs. All patients had vascular disease, but ibuprofen was not given randomly, only if needed for

another reason. The detrimental effect of ibuprofen was not seen with diclofenac or paracetemol.

▲ **MacDonald TM**, Wei L. Effect of ibuprofen on cardioprotective effect of aspirin. *Lancet* 2003;**361**:573–4.

Heart failure

Anaemia is a marker of poor prognosis in heart failure ► In 2281 consecutive patients > 65 years old with a principal discharge diagnosis of heart failure, haematocrit was categorised into subgroups: < 27%—severe anaemia, > 27–32%, >32–37%, > 37–42%—normal value, > 42%. Anaemia was present in 48%, and was associated with renal insufficiency, hypertension, a low ejection fraction, and a low sodium concentration. Haematocrit was an independent predictor for one year mortality, with a 2% greater mortality per 1% lower haematocrit (HR 1.02, 95% CI 1.01 to 1.04; p = 0.007) and was not affected by use of pre-admission ACE inhibitors. Those with a haematocrit < 27% had a 40% higher mortality than those > 42% (HR 1.4, CI 1.02 to 1.92; p = 0.04) and this increased risk was similar to mortality in those with ejection fraction < 20% compared to those with an ejection fraction > 40%. But importantly, it is not clear whether anaemia is a marker of how ill these patients are or is actually causally linked through its effects on myocardial blood flow, peripheral vasodilatation, and reduced renal perfusion; there is some evidence that correcting anaemia with erythropoietin and iron can improve left ventricular ejection fraction and functional status.

▲ **Kosiborod M**, Smith GL, Radford MJ, Foody JM, Krumholz H. The prognostic importance of anaemia in patients with heart failure. *Am J Med* 2003;**114**:112–19.

Hypertension

ANBP-2 study wins ground back for ACE inhibitors ► Treatment of hypertension with diuretics, β blockers, or both leads to improved outcomes. It has been postulated that agents that inhibit the renin–angiotensin system confer benefit beyond the reduction of blood pressure alone. The ALLHAT study suggested that diuretics were at least as good as angiotension converting enzyme (ACE) inhibitors. Older subjects with hypertension who were treated with an ACE inhibitor (enalapril) were compared to those treated with a diuretic (hydrochlorothiazide) in the ANBP-2 study. In the 6083 subjects (65–84 years of age) follow up was for a median of 4.1 years. By the end of the study, blood pressure had decreased to a similar extent in both groups (a decrease of 26/12 mm Hg). There were 695 cardiovascular events or deaths from any cause in the ACE inhibitor group (56.1 per 1000 patient-years) and 736 cardiovascular events or deaths from any cause in the diuretic group (59.8 per 1000 patient-years). The hazard ratio for a cardiovascular event or death with ACE inhibitor treatment was 0.89 (95% CI 0.79 to 1.00; p = 0.05). The rates of non-fatal cardiovascular events and myocardial infarctions decreased with ACE inhibitor treatment, whereas a similar number of strokes occurred in each group (although there were more fatal strokes in the ACE inhibitor group). Why the results of ALLHAT and ANBP-2 are at odds is not clear.

▲ **Wing LMH**, Reid CM, Ryan P, *et al*, for the Second Australian National Blood Pressure Study Group. A comparison of outcomes with angiotensin-converting–enzyme inhibitors and diuretics for hypertension in the elderly. *N Engl J Med* 2003;**348**:583–92.

▲ **The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group**. 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.

General cardiology

The ECG is predictive of poor left ventricular recovery post MI ► This study examined the baseline and discharge ECGs of 272 patients with anterior MI enrolled in the Healing and Early Afterload Reducing Therapy (HEART) trial. A total of 87% of patients received reperfusion therapy. ST segment elevation post-MI is a marker for increased left ventricular size. The sum of ST segment elevation (OR 0.78), maximum ST segment elevation (OR 0.25), and the number of leads with ST segment elevation > 1 mm (OR 0.58) were independently associated with a lower likelihood of recovery of function at 90 days (all highly significant). Each lead with ST segment elevation > 1 mm was associated with 3.5 ml of ventricular enlargement (p < 0.0001).

▲ **Manes C**, Pfeffer MA, Rutherford JD, Greaves S, Rouleau J, Arnold MO, Menapace F, Solomon SD. Value of the electrocardiogram in predicting left ventricular enlargement and dysfunction after myocardial infarction. *Am J Med* 2003;**114**:99–105.

Exercise induced ventricular ectopy predicts an increased risk of death ► In 29 244 patients (mean (SD) age 56 (11) years; 70% men) who had been referred for symptom limited exercise testing without a history of heart failure, valve disease, or arrhythmia, frequent ventricular ectopy was defined by the presence of seven or more ventricular premature beats per minute, ventricular bigeminy or trigeminy, ventricular couplets or triplets, ventricular tachycardia, ventricular flutter, torsade de pointes, or ventricular fibrillation. Frequent ventricular ectopy occurred only during exercise in 945 patients (3%), only during recovery in 589 (2%), and during both exercise and recovery in 491 (2%). There were 1862 deaths during a mean of 5.3 years of follow up. Frequent ventricular ectopy during exercise predicted an increased risk of death (five year death rate, 9% *v* 5% among patients without frequent ventricular ectopy during exercise; hazard ratio 1.8, 95% CI 1.5 to 2.1; p < 0.001), but frequent ventricular ectopy during recovery was a stronger predictor (11% *v* 5%; hazard ratio 2.4, 95% CI 2.0 to 2.9; p < 0.001). After matching for confounding variables, frequent ventricular ectopy during recovery predicted an increased risk of death (adjusted hazard ratio 1.5, 95% CI 1.1 to 1.9; p = 0.003), but frequent ventricular ectopy during exercise did not (adjusted hazard ratio 1.1, 95% CI 0.9 to 1.3; p = 0.53). More severe frequent ventricular ectopy was associated with a greater risk (adjusted hazard ratio 2.1, 95 % CI 1.4 to 3.3; p < 0.001).

▲ **Frolkis JP**, Pothier CE, Blackstone EH, Lauer MS. Frequent ventricular ectopy after exercise as a predictor of death. *N Engl J Med* 2003;**348**:781–90.

HIV survival on triple therapy has not caused a cardiovascular disease epidemic yet ► Metabolic abnormalities associated with human immunodeficiency virus (HIV) infection, including dysglycaemia and hyperlipidaemia, are increasingly prevalent, and there is concern about the possibility of an association with accelerated cardiovascular and cerebrovascular disease. A retrospective study of the risk of cardiovascular and cerebrovascular disease among 36 766 HIV positive patients showed that between 1995 and 2001, the rate of admissions for cardiovascular or cerebrovascular disease decreased from 1.7 to 0.9 per 100 patient-years, and the rate of death from any cause decreased from 21.3 to 5.0 deaths per 100 patient-years. Regression analyses indicated that there was no relation between the use of nucleoside analogues, protease inhibitors, or non-nucleoside reverse transcriptase inhibitors and the hazard of cardiovascular or cerebrovascular events, but the use of antiretroviral drugs was associated with a decreased hazard of death from any cause.

▲ **Bozzette SA**, Ake CF, Tam HK, Chang SW, Louis TA. Cardiovascular and cerebrovascular events in patients treated for human immunodeficiency virus infection. *N Engl J Med* 2003;**348**:702–10.

Cardiac resynchronisation works: biventricular pacing has "arrived" ► Of the 6883 potentially relevant reports initially identified, 11 reports of four randomised trials with 1634 total patients were included in a meta-analysis. Follow up in the included trials ranged from 3–6 months. Pooled data from the four selected studies showed that cardiac resynchronisation reduced death from progressive heart failure by 51% relative to controls (OR 0.49, 95% CI 0.25 to 0.93). Progressive heart failure mortality was 1.7% for cardiac resynchronisation patients and 3.5% for controls. Cardiac resynchronisation also reduced heart failure hospitalisation by 29% (OR 0.71, 95% CI 0.53 to 0.96) and showed a trend toward reducing all cause mortality (OR 0.77, 95% CI 0.51 to 1.18). Cardiac resynchronisation was not associated with a significant effect on non-heart failure mortality (OR 1.15, 95% CI 0.65 to 2.02). Among patients with

implantable cardioverter-defibrillators, cardiac resynchronisation had no clear impact on ventricular tachycardia or ventricular fibrillation (OR 0.92, 95% CI 0.67 to 1.27).

▲ **Bradley DJ**, Bradley EA, Baughman KL, Berger RD, Calkins H, Goodman SN, Kass DA, Powe NR. Cardiac resynchronization and death from progressive heart failure: a meta-analysis of randomized controlled trials. *JAMA* 2003;**289**:730–40.

Higher digoxin concentrations are associated with worse prognosis ► The Digitalis Investigation Group (DIG) trial reported that digoxin provided no overall mortality benefit and only a modest reduction in hospitalisations among patients with heart failure and depressed left ventricular systolic function. Patients randomly assigned to receive digoxin were divided into three groups based on serum digoxin concentrations (SDCs) at one month (0.5–0.8 ng/ml, n = 572; 0.9–1.1 ng/ml, n = 322; and ⩾ 1.2 ng/ml, n = 277) and compared with patients randomly assigned to receive placebo (n = 2611). Higher SDCs were associated with increased crude all cause mortality rates (0.5–0.8 ng/ml, 29.9%; 0.9–1.1 ng/ml, 38.8%; and 1.2 ng/ml, 48.0%; p = 0.006 for trend). Patients with SDCs of 0.5–0.8 ng/ml had a 6.3% (95% CI 2.1% to 10.5%) lower mortality rate compared with patients receiving placebo. Digoxin was not associated with a reduction in mortality among patients with SDCs of 0.9–1.1 ng/ml (2.6% increase, 95% CI –3.0% to 8.3%), whereas patients with SDCs of 1.2 ng/ml and higher had an 11.8% (95% CI 5.7% to 18.0%) higher absolute mortality rate than patients receiving placebo. The association between SDC and mortality persisted after multivariable adjustment.

▲ **Rathore SS**, Curtis JP, Wang Y, Bristow MR, Krumholz HM. Association of serum digoxin concentration and outcomes in patients with heart failure. *JAMA* 2003;**289**:871–8.

Basic science

Use of carbon monoxide to prevent restenosis after PTCA ► Carbon monoxide (CO) blocks development of arteriosclerotic lesions associated with chronic graft rejection and balloon angioplasty induced vessel injury. Exposure to a low concentration of CO (250 parts per million) for one hour before injury is sufficient to suppress intimal hyperplasia arising from balloon injury in rats. The data indicate that the protective effect of CO relies on its ability to block leucocyte infiltration/activation as well as smooth muscle cell proliferation, the latter occurring through a mechanism dependent on activation/expression of signalling molecules including guanylate cyclase, generation of cGMP, activation of cGMP-dependent protein kinase, and p38 mitogen activated protein kinase. These findings demonstrate a protective role for CO in vascular injury and support its use as a therapeutic agent.

▲ **Otterbein LE**, Zuckerbraun BS, Haga M, Liu F, Song R, Usheva A, Stachulak C, Bodyak N, Smith RN, Csizmadia E, Tyagi S, Akamatsu Y, Flavell RJ, Billiar TR, Tzeng E, Bach FH, Choi AMK, Soares MP. Carbon monoxide suppresses arteriosclerotic lesions associated with chronic graft rejection and with balloon injury. *Nature Med* 2003;**9**:183–90.

The importance of platelets in the inflammatory disease "atherosclerosis" ► Atherogenesis is a chronic inflammatory process in which monocytes and T cells interact with structurally intact but dysfunctional endothelium of arteries. This inflammation hypothesis of atherosclerosis has led to questions regarding the involvement of platelets in the development of spontaneous atherosclerotic lesions. These are present in the circulating blood of patients with unstable atherosclerosis, stable coronary disease, and hypercholesterolaemia. The present investigation found circulating activated platelets bound to leucocytes, preferentially monocytes, to form platelet–monocyte/leucocyte aggregates. The interactions of activated platelets with monocytes and atherosclerotic arteries led to delivery of the platelet derived chemokines CCL5 and CXCL4 to the monocyte surface and endothelium of atherosclerotic arteries. The presence of activated platelets promoted leucocyte binding of vascular cell adhesion molecule-1 and increased their adhesiveness to inflamed or atherosclerotic endothelium. Injection of activated wild-type, but not P-selectin deficient, platelets increased monocyte arrest on the surface of atherosclerotic lesions and the size of atherosclerotic lesions in *Apoe*$^{-/-}$ mice. This role of activated platelets in atherosclerosis is attributed to platelet P-selectin mediated delivery of platelet derived proinflammatory factors to monocytes/leucocytes and the vessel wall.

▲ **Huo Y**, Schober A, Forlow SB, Smith DF, Hyman MC, Jung S, Littman DR, Weber C, Ley K. Circulating activated platelets exacerbate atherosclerosis in mice deficient in apolipoprotein E. *Nature Med* 2003;**9**:61–7.

Myoblast transplants survive long term in human hearts ► Autologous skeletal myoblast transplantation might improve postinfarction ventricular function, but graft viability and differentiation (that is, proof of concept) has not been shown. A 72 year old man had autologous cultured myoblasts from his vastus lateralis injected into an area of transmural inferior myocardial infarction in non-reperfused scar tissue. He showed improvement in symptoms and left ventricular ejection fraction. When he died 17.5 months after the procedure, the grafted postinfarction scar showed well developed skeletal myotubes with a preserved contractile apparatus. By staining, 65% of myotubes expressed the slow myosin isoform and 33% co-expressed the slow and fast isoforms (*v* 44% and 0.6%, respectively, in skeletal muscle). Myoblast grafts can survive and show a switch to slow twitch fibres, which might allow sustained improvement in cardiac function.

▲ **Hagège AA**, Carrion C, Menasché P, Vilquin J-T, Duboc D, Marolleau J-P, Desnos M, Bruneval P. Viability and differentiation of autologous skeletal myoblast grafts in ischaemic cardiomyopathy. *Lancet* 2003;**361**:491–2.

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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