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ISCHAEMIC HEART DISEASE

Get LDL below 2.0 mmol/l in patients with stable coronary disease? ► Previous trials (for example, PROVE-IT) have demonstrated that lowering low density lipoprotein (LDL) cholesterol below currently recommended values is beneficial in patients with acute coronary syndromes. In the TNT (treating to new targets) study, a total of 10 001 patients with clinically evident coronary heart disease (CHD) and LDL cholesterol < 130 mg/dl (< 3.4 mmol/l) were randomly assigned to double blind treatment and received either 10 mg or 80 mg of atorvastatin per day. Patients were followed for a median of 4.9 years. The primary end point was the occurrence of a first major cardiovascular event, defined as death from CHD, non-fatal myocardial infarction, resuscitation after cardiac arrest, or fatal or non-fatal stroke. The mean LDL cholesterol concentrations were 77 mg/dl (2.0 mmol/l) during treatment with 80 mg of atorvastatin and 101 mg/dl (2.6 mmol/l) during treatment with 10 mg of atorvastatin. The incidence of persistent elevations in liver aminotransferase concentrations (> 3× normal) was 0.2% in the group given 10 mg of atorvastatin and 1.2% in the group given 80 mg of atorvastatin ($p < 0.001$). In all, 7% of the 80 mg group versus 5% of the 10 mg group stopped treatment ($p < 0.001$). A primary event occurred in 8.7% receiving 80 mg of atorvastatin, as compared with 10.9% receiving 10 mg of atorvastatin, representing an absolute reduction in the rate of major cardiovascular events of 2.2% and a 22% relative reduction in risk (hazard ratio 0.78, 95% confidence interval (CI) 0.69 to 0.89; $p < 0.001$). There was no difference between the two treatment groups in overall mortality. So at present, it is worth trying to see if 80 mg atorvastatin is tolerated, since it does no harm, and may do some good. Whether this is cost effective remains to be shown.

▲ LaRosa JC, Grundy SM, Waters DD, *et al*, for the Treating to New Targets (TNT) Investigators. Intensive lipid lowering with atorvastatin in patients with stable coronary disease (TNT). *N Engl J Med* 2005;**352**:1425–35.

▲ Cannon CP, Braunwald E, McCabe CH, *et al*. Intensive versus moderate lipid lowering with statins after acute coronary syndromes (PROVE-IT). *N Engl J Med* 2004;**350**:1495–504.

Speciality hospitals: cherry picking easy patients? ► There is evidence for having procedures done in institutions that do a lot of them, and by high volume surgeons. This has sometimes led to the production of speciality hospitals. Although perhaps reasonable for minor procedures, is this good for the heart? Outcomes were compared in a retrospective cohort study of 42 737 Medicare beneficiaries who underwent percutaneous coronary intervention (PCI) and 26 274 who underwent coronary artery bypass grafting (CABG) during 2000 and 2001 in specialty cardiac hospitals and general hospitals in the same markets. Patients undergoing PCI or CABG in specialty hospitals were less likely to have coexisting conditions and were less likely to have had an acute myocardial infarction ($p < 0.001$). Mean volumes of PCI and CABG procedures in 2000 and 2001 were higher in specialty hospitals than in general hospitals (799 *v* 375 PCI procedures, $p < 0.001$; and 571 *v* 236 CABG procedures, $p < 0.001$). The unadjusted rate of death during the index hospitalisation or within 30 days after admission was lower in specialty hospitals than in general hospitals (2.1% *v* 3.2% for PCI, and 4.7% *v* 6.0% for CABG; $p < 0.001$ for both comparisons). In multivariate analyses adjusted for patients' characteristics, the odds ratio for death after PCI in specialty hospitals and general hospitals was similar (OR 0.89, 95% CI 0.69 to 1.15; $p = 0.39$), but the odds ratio for death after CABG was lower in specialty hospitals than in general hospitals (OR 0.84, 95% CI 0.72 to 0.99; $p = 0.05$). In stratified analyses comparing specialty and general hospitals with similar volumes, differences in mortality were not significant. By cherry picking healthy patients (who use fewer resources) the formation of specialist hospitals could disadvantage general hospitals which will have to treat more costly, sicker patients.

▲ Cram P, Rosenthal GE, Vaughan-Sarrazin MS. Cardiac revascularization in specialty and general hospitals. *N Engl J Med* 2005;**352**:1454–62.

Primary prevention with aspirin in women works in those over 65 ► To date, five randomised trials involving 55 580 participants have evaluated aspirin in the primary prevention of cardiovascular disease. In this large, placebo controlled, primary prevention trial (women's health study) involving 39 876 initially healthy women, prophylactic aspirin at a dose of 100 mg every other day was associated with a non-significant reduction in the risk of major cardiovascular events, a reduced risk of total stroke and of ischaemic stroke, a non-significant increase in the risk of haemorrhagic stroke, and no significant effect on the risk of myocardial infarction or death from cardiovascular causes. However, there was benefit in women of 65 years of age or older. The authors performed a meta-analysis that included current data from the women's health study, as well as data from five prior trials involving 55 580 participants with no history of heart disease. In women, aspirin treatment was associated with a significant 19% reduction in the risk of stroke (relative risk (RR) 0.81, 95% CI 0.69 to 0.96; $p = 0.01$), with no reduction in the risk of myocardial infarction (RR 0.99, 95% CI 0.83 to 1.19; $p = 0.95$). By contrast, the aggregate data on men indicate that aspirin treatment was associated with a significant 32% reduction in the risk of myocardial infarction (RR 0.68, 95% CI 0.54 to 0.86; $p = 0.001$) and a non-significant increase in the risk of stroke (RR 1.13, 95% CI 0.96 to 1.33; $p = 0.15$). The differences between men and women were significant at the $p = 0.01$ level for myocardial infarction and at the $p = 0.005$ level for stroke. Thus, aspirin for all women over 45 is not justified, but treating those over 65 would result in 44 fewer cardiovascular events at a cost of 16 more gastrointestinal bleeds.

▲ Eidelman RS, Hebert PR, Weisman SE, *et al*. An update on aspirin in the primary prevention of cardiovascular disease. *Arch Intern Med* 2003;**163**:2006–10.

▲ Ridker PM, Cook NR, Lee I-M, *et al*. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. *N Engl J Med* 2005;**352**:1293–304.

Aspirin plus clopidogrel plus thrombolysis is the new standard for STEMI (if primary angioplasty is not available) ► Aspirin plus thrombolysis has proven benefits in ST elevation myocardial infarction (STEMI). Clopidogrel is an ADP receptor blocker, and a potent antiplatelet agent also. In this study, patients with myocardial infarction with ST segment elevation who were treated with fibrinolytic therapy and aspirin derived further benefit if clopidogrel was administered concomitantly, in that their coronary arterial patency improved. At the same time, the addition of clopidogrel to full dose fibrinolytic therapy, aspirin, and heparin did not appear to increase the incidence of bleeding complications—a finding in clear contrast to those of the previously mentioned studies of combination treatment with reduced dose fibrinolytic therapy, aspirin, and a glycoprotein IIb/IIIa inhibitor. However, some of the difference may be due to the fact that angiography was performed at 3–4 days after acute myocardial infarction, at which time the clopidogrel arm had in effect been pre-treated with clopidogrel as is current practice in all PCI, while the placebo arm had not. The rate of the composite end point of death, recurrent myocardial ischaemia, or recurrent myocardial infarction was similar in the clopidogrel and placebo groups before angiography (8.3% and 9.3%, respectively; $p = 0.27$), but favoured clopidogrel treatment after percutaneous intervention at the 30 day follow up. In addition, the overall mortality in this study was surprisingly low at < 5% at 30 days, and in a higher risk group, bleeding with clopidogrel may have been

more of an issue. Finally, the results certainly do not suggest that primary PCI should be shelved as the best treatment option.

▲ Sabatine MS, Cannon CP, Gibson MC, *et al* for the CLARITY–TIMI 28 Investigators. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *N Engl J Med* 2005;**352**:1179–89.

No HOPE for vitamin E ► Initial studies suggested a possible benefit for vitamin E in reducing CHD risk and cancer rates. Now data suggest that this is not the case. In the HOPE study, and the extension to include > 7000 patients, patients were given a daily dose of natural source vitamin E (400 IU) or matching placebo. Patients in the vitamin E group had a higher risk of heart failure (RR 1.13, 95% CI 1.01 to 1.26; p = 0.03) and hospitalisation for heart failure (RR 1.21, 95% CI 1.00 to 1.47; p = 0.045). Similarly, among patients enrolled at the centres participating in the HOPE-TOO trial, there were no differences in cancer incidence, cancer deaths, and major cardiovascular events, but higher rates of heart failure and hospitalisations for heart failure.

▲ The HOPE and HOPE-TOO Trial Investigators. Effects of long-term vitamin E supplementation on cardiovascular events and cancer: a randomized controlled trial. *JAMA* 2005;**293**:1338–47.

HYPERTENSION

ALLHAT says use diuretics first in hypertension ► The main ALLHAT study suggested diuretics as first line agents in hypertension. What about in groups at higher cardiovascular risk? ALLHAT was a randomised, double blind, active controlled, clinical outcome trial conducted between February 1994 and March 2002 in 33 357 hypertensive US and Canadian patients aged 55 years or older (35% black), with at least one other cardiovascular risk factor. Pre-specified subgroup analysis suggested that in black and non-black subgroups, rates were no lower in the amlodipine or lisinopril groups than in the chlorthalidone group for either the primary CHD or any other pre-specified clinical outcome. In addition, diuretic based treatment resulted in the lowest risk of heart failure.

▲ Wright JT, Dunn KJ, Cutler JA, *et al* for the ALLHAT Collaborative Research Group. Outcomes in hypertensive black and non-black patients treated with chlorthalidone, amlodipine, and lisinopril. *JAMA* 2005;**293**:1595–608.

GENERAL CARDIOLOGY

Symptomatic intracranial stenosis is a marker for high risk ► The WASID trial was an intention to treat, comparison trial of the administration of aspirin at a dose of 1300 mg per day and warfarin with a target international normalised ratio (INR) of 2.0–3.0 in patients with > 50% intracranial vascular stenosis and recent symptoms. Ischaemic stroke, brain haemorrhage, or death from vascular causes other than stroke occurred within two years in approximately 22% of the patients in both groups. The target INR turned out to be not so easy to achieve. In this study, the patients receiving warfarin were within their INR goal only about 63% of the time, and approximately 28% of the patients dropped out of the warfarin treated group. As compared with published data, 63% as a percentage of time in the target range is not bad. Even considering only the patients who received treatment, the rate of ischaemic stroke was 25 per 100 patient-years with a subtherapeutic INR—a rate that was reduced to 5 per 100 patient-years with a therapeutic INR. The rate of major cardiac events was 10.8 per 100 patient-years with a subtherapeutic INR and was reduced to 0.4 per 100 patient-years with a therapeutic INR. These data suggest that anticoagulation within the therapeutic range is associated with a striking reduction in the risk of cerebrovascular and cardiovascular events. Unfortunately, it is extremely difficult, if not impossible, to achieve a consistent therapeutic INR with warfarin in a population study or in routine practice. Aspirin as an alternative is no better, but clopidogrel and also angioplasty need to be tested.

▲ Chimowitz MI, Lynn MJ, Howlett-Smith H, *et al*. Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis. *N Engl J Med* 2005;**352**:1305–16.

The end of COX-2 inhibitors in those at cardiovascular risk ► These three trials all say the same thing: COX-2 inhibitors may have fewer gastrointestinal side effects, but they appear to increase cardiovascular risk. This is probably due to selective inhibition of prostacyclin production without blockade of thromboxane A2 production. In one of the studies, the adverse effects were seen as early as 10 days after initiation of the drug.

▲ Solomon SD, McMurray JJV, Pfeffer MA, *et al*. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. *N Engl J Med* 2005;**352**:1071–80.

▲ Nussmeier NA, Whelton AA, Brown MT, *et al*. Complications of the COX-2 inhibitors parecoxib and valdecoxib after cardiac surgery. *N Engl J Med* 2005;**352**:1081–91.

▲ Bresalier RS, Sandler RS, Quan H, *et al*. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. *N Engl J Med* 2005;**352**:1092–102.

Sleep apnoea: treatment reduces the cardiovascular risk ► Participants were followed up at least once per year for a mean (SD) of 10.1 (1.6) years and continuous positive airways pressure (CPAP) ventilation compliance was checked with the built-in meter. End points were fatal cardiovascular events (death from myocardial infarction or stroke) and non-fatal cardiovascular events (non-fatal myocardial infarction, non-fatal stroke, coronary artery bypass surgery, and percutaneous transluminal coronary angiography). A total of 264 healthy men, 377 simple snorers, 403 with untreated mild–moderate obstructive sleep apnoea–hypopnoea, 235 with untreated severe disease, and 372 with the disease and treated with CPAP were included in the analysis. Patients with untreated severe disease had a higher incidence of fatal cardiovascular events (1.06 per 100 person-years) and non-fatal cardiovascular events (2.13 per 100 person-years) than did untreated patients with mild–moderate disease (0.55, p = 0.02, and 0.89, p < 0.0001), simple snorers (0.34, p = 0.0006, and 0.58, p < 0.0001), patients treated with CPAP (0.35, p = 0.0008, and 0.64, p < 0.0001), and healthy participants (0.3, p = 0.0012, and 0.45, p < 0.0001). Multivariate analysis, adjusted for potential confounders, showed that untreated severe obstructive sleep apnoea–hypopnoea significantly increased the risk of fatal (OR 2.87, 95% CI 1.17 to 7.51) and non-fatal (OR 3.17, 95% CI 1.12 to 7.51) cardiovascular events compared with healthy participants.

▲ Marin JM, Carrizo SJ, Vicente E, *et al*. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. *Lancet* 2005;**365**:1046–53.

Nurse led clinics for CHD are cost effective ► This study aimed to establish the cost effectiveness of nurse led secondary prevention clinics for CHD based on four years' follow up of a randomised controlled trial. A total of 1343 patients (673 in the intervention group and 670 in the control group, as originally randomised) aged under 80 years with a diagnosis of CHD but without terminal illness or dementia and not housebound were included in the trial. Nurse led clinics promoted medical and lifestyle components of secondary prevention. The cost of the intervention (clinics and drugs) was £136 ($254, €195) per patient higher (1998–9 prices) in the intervention group, but the difference in other National Health Service costs, although lower for the intervention group, was not significant. Overall, 28 fewer deaths occurred in the intervention group leading to a gain in mean life years per patient of 0.110 and of 0.124 quality adjusted life-years (QALYs). The incremental cost per life year saved was £1236 and that per QALY was £1097, well below the £30 000 considered adequate.

▲ Raftery JP, Yao GL, Murchie P, *et al*. Cost effectiveness of nurse led secondary prevention clinics for coronary heart disease in primary care: follow up of a randomised controlled trial. *BMJ* 2005;**330**:707.

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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