

**CEYLON COLLEGE OF
PHYSICIANS**

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2.1 Does resting heart rate predict adverse coronary events in women?

Resting heart rate independently predicts adverse coronary events in men. Does this association apply to women also?.

In a prospective observational study that involved nearly 130,000 post menopausal women enrolled in the Women's Health Initiative (WHI) and followed up for a mean 7.8 years, it was found that higher the resting heart rate higher the incidence of MI or coronary death. Women with resting heart rates > 76 beats per minute were 26 % more likely to have experienced adverse coronary events compared to those with rates < 62. The association between higher resting heart rate and coronary events was stronger in younger women (age 50 – 64) than in older women (age 65 -79). The resting heart rate was not associated with stroke Incidence.

Comment: Resting heart rate is a measure of autonomic tone and independently predicts MI or coronary death in women.

Ref: Hsia J. et al BMJ 2009 Feb 3; 308: b 219.

2.2 Is stenting for totally occluded coronary arteries, three days and more after an MI of any use?.

The open artery hypothesis holds that stenting might be beneficial for a patient with MI and total occluded coronary arteries even several days after an MI. However, in a randomized trial published in 2006, stenting performed 3-28 days after MI did not lower 4 year incidence of death, recurrent MI or severe heart failure. The investigators now in 2009, report outcomes related to quality of life.

At 4 months, the mean score on QOL was modestly but significantly higher in the stenting group than in the medical therapy group. However, differences between groups disappeared by 12 and 24 months. Angina was lower after stenting (10 vs 16% at 4 months and 7 vs 12% at 24 months). Higher cumulative 2 year cost in the stenting group did not translate into better 2 year quality adjusted survival.

Comment: These results, taken together with the previously published findings from this trial, argue against routine stenting of persistently occluded infarct related arteries following MI. A modest early benefit in physical function is not associated with longer survival, and the strategy is not cost effective.

Ref: Mark D.B. et al NEJ Med 2009 feb 19; 360: 774.

2.3 Intermittent claudication (IC) – which is better – exercise or revascularization?.

150 patients with IC were randomized to receive either supervised exercise training or angioplasty (with stenting in some cases) of femoral or iliac stenoses. During the first weeks of the study, patients in the revascularising group improved much more rapidly than those in the exercise group. But at 6 and 12 months, maximum walking distances and quality of life scores had

improved similarly in the two groups. Only 11 % of exercise patients crossed over to revascularization during the one year follow up.

Comment: Revascularization provides a quicker fix than exercise training in IC but within a few months the exercise group catches up. Complications can occur with revascularization procedures whereas exercise confers a variety of benefits. This study strengthens the case for structured exercise as the initial approach to managing IC.

Ref: Spronk S et al Radiology 2009 Feb; 250: 586.

2.4 Chondroitin Sulphate (CS) for knee osteoarthritis (OA).

In the large NIH funded GAIT study of knee OA, glucosamine, CS or both was found to be no better than placebo in relieving pain or slowing the progression of joint space narrowing. A new manufacturer funded study from Europe has been presented recently.

622 knee OA patients were randomized to receive daily CS (800mg) or placebo. During 2 years of follow up, narrowing of medial tibio femoral joint space was significantly less in the CS group than in the placebo group. The difference between groups became even greater during the 2nd year of the study. Pain scores were significantly lower with CS than with placebo during the 1st year, but pain scores did not differ between groups in the 2nd year.

Comment: Studies of glucosamine and CS continue to generate conflicting findings. Whether CS provides clinically meaningful benefits for patients with OA remains unclear. Clinicians continue to prescribe them even though the benefits have not been validated uniformly in all trials. It is also an expensive drug.

Ref: Kahan A et al Arthritis Rheum 2009 Feb; 60: 524.

2.5 NIH consensus statement on management of hepatitis B infection.

The goals of treatment are to prevent cirrhosis, liver failure, hepatoma and death. No RCTs have so far demonstrated that treatment was associated with beneficial effects on these outcomes. However some positive effects were reported for surrogate clinical outcomes, such as normalization of ALT, improvement in histologic appearance, and clearance of HBV DNA and surface and e antigens. These findings were based on 16 RCTs of HBV drug treatments involving 4,431 patients. About 50% experienced adverse events.

Despite these findings, the panel recommended therapy for patients with decompensated cirrhosis, for patients with cirrhosis or advanced fibrosis and detectable HBV DNA and for patients with HBV reactivation after chemotherapy or immunosuppression. They also recommended vaccination and immunoglobulin administration for infants born to women who were positive for HBV surface antigen. The panel recognized that therapy might be indicated for patients in the immune active phase.

Ref: Sorrell M.F. et al Ann. Intern. Med 2009 Jan 20; 150: 104.
Shamliyan T.A. et al IBID : 111.

2.6 Vitamin K for warfarin induced elevated INR

Excessive response to warfarin is often treated with Vitamin K, which often quickly lowers the INR. Would low dose oral Vitamin K (1.25mg) reduce bleeding events when the INR is between 4.5 and 10.0 while on warfarin.

724 patients were randomized to Vitamin K or placebo. 90 days after enrollment, 15.8% of vit K recipients and 16.3 % on placebo had a bleeding event. These occurred within 7 days in 7.9% and 9.2% of patients resp. Major bleeding occurred in 9 VitK and 4 placebo recipients. Thromboembolism occurred in 1.1% and 0.8% resp. INR decreased more rapidly in the Vit K group. The average reduction in INR was 2.8 units in Vit K and 1.4 units in the placebo group.

Comment: In this multicenter randomized trial, Vit K lowered INR more and faster than placebo, but these effects did not lead to fewer major bleeding events. These results suggest that simply stopping warfarin may suffice to treat patients with elevated INR.

Ref: Crowther M.A. et al Ann.Intern. Med 2009 March 3; 150: 293.

2.7 Herpes Zoster (HZ) risk in arthritis patients on anti TNF Alpha agents (ATA)

ATA use (infliximab, adalimumab, etanercept) is associated with increased risk for bacterial infections. 5,040 patients with rheumatoid arthritis (RA) treated with either ATAs or standard disease modifying anti rheumatic drugs were followed up prospectively for three years. In an analysis adjusted for age, RA, glucocorticoid use – patients who received infliximab or adalimumab had significantly elevated risk for HZ (hazard ratio 1.82) while those who received etanercept did not (HR 1.36).

Comment: There is an elevated risk for HZ among RA patients who received ATA agents infliximab and adalimumab. More aggressive use of HZ vaccine would be appropriate in patients for whom these two drugs are being considered. However, because it contains live virus, HZ vaccine is contraindicated during ATA therapy. Therefore vaccination should occur several weeks before initiation of therapy.

Ref: Strangfeld A et al JAMA 2009 Feb 18; 301: 737.

Whitley R.J. and Gnann J.W. Jr IBID : 774.

2.8 Oral thrombopoietin receptor agonist (OTRA) in Immune thrombocytopaenic purpura (ITP)

Traditional therapies for ITP include steroids, immunoglobulins, immunosuppressives and splenectomy. These primarily act by inhibiting platelet destruction and can have serious side effects. Last year, the FDA approved the first two TRAs viz injectable romiplostim and oral eltrombopag (E). Both stimulate platelet production.

110 patients with ITP of 6 months duration or more with platelet counts less than 30,000 and at least one previous treatment for ITP were randomized to daily E 50mg or placebo for 6 weeks. The E dose could be increased if platelets remained below 50,000 after 3 weeks. At the end of treatment, 59% of E recipients and 16% of placebo recipients had platelet counts more than 50,000. Fewer E recipients had bleeding symptoms (39 vs 60%). Both these results were

statistically significant. Platelet counts generally return to baseline within 2 weeks after stopping treatment. Side effects included nausea, vomiting and minor transaminase increases.

Comment: E has now been approved for patients with ITP who have failed at least one standard therapy. Whether further dose escalation would improve response rates or how the drug will perform over longer periods is not known. Platelet counts return to baseline when the drug is stopped indicating that its main use would be to tide over a difficult period as before surgery or splenectomy. Could it be used when platelet counts are plunging in Dengue haemorrhagic fever?

Ref: Bussel J.B. et al Lancet 2009 Feb 21; 373: 641.

2.9 Should every middle aged and older adult take statins?

In the recently published JUPITER trial, Rosuvastatin lowered a risk for CV events among men above 50 and women above 60, who had high sensitivity CRP levels exceeding 2.0mg/l and LDLC < 130mg/dl. If the JUPITER selection criteria were applied to middle aged or older Americans, how many would become “eligible” for statin therapy?. From the NHANES published in 2005, more than half of middle aged or older Americans – 59%, 64%, and 65% of adults in their 50s, 60s, and 70s, resp – had hsCRP levels >2.0mg/l. Now in a new analysis of these data, researchers estimate that 19% of middle aged or older adults would become eligible for statin therapy solely based on their hsCRP levels. An additional 58% are already eligible for statins, based on traditional NCEP guidelines. Thus about 77% of middle aged or older Americans would be candidates for statins.

Comment: The benefits of Rosuva in JUPITER were statistically significant, although small in absolute terms. The JUPITER trial was stopped at 2 years. We therefore are uncertain whether the favourable balance of benefits and harms persist during many years of statin therapy.

Ref: Spatz E.S. et al Circ. Cardiovasc. Qual. Outcomes 2009 Jan; 2: 41.

2.10 Clopidogrel (C) and Proton pump inhibitors (PPIs)

PPIs are known to reduce the inhibitory effect of C on platelet aggregation. In a Veterans Affairs Data base studied retrospectively, 8,205 patients discharged with acute coronary syndromes (ACS), it was found that 64% were taking both C and a PPI and 36% were taking C alone.

At a mean follow up of roughly 18 months, death or re hospitalization for ACS had occurred in 30% taking both medications and in 21% of patients taking only C. The risk for death or re hospitalization was roughly 25% higher in patients taking both medications (86% higher for recurrent ACS, 49% higher for revascularization procedures, but no difference for death alone).

Comment: This is a retrospective analysis and therefore prospective clinical trials are needed to confirm this result. The plausible biological mechanism is that the PPIs may inhibit the cytochrome P 450 enzyme system responsible for the production of the active metabolite of C. Clinicians should therefore be more parsimonious in their use of PPIs for specific indications, rather than using them for routine prophylaxis, as is often done. If PPIs are indeed necessary, it may be required to increase the dose of C.

Ref: Ho P.M. et al JAMA 2009 March 4; 301: 937.

2.11 CABG vs stenting for severe coronary disease – The SYNTAX trial

CABG has been the standard of care for patients with left main or three vessel coronary disease who require revascularization. Stenting is also an option in such cases. These 2 interventions were compared in the SYNTAX trial. The stent used was the Taxus drug eluting stent. The trial was sponsored by the manufacturer of the Taxus stent.

1,800 patients with untreated left main or 3 vessel disease were randomized to CABG or stenting. At one year, the incidence of the primary composite end point (death, stroke, MI, or repeat revascularization) was significantly lower with CABG than with stenting (12.4% vs 17.8%).

Comment: CABG was superior to stenting for a pre defined composite end point. The difference was largely driven by less need for repeat revascularization in the CABG group. The CABG group had a small but significantly higher rate of stroke. Choosing CABG over stenting implies a roughly 8 per 100 lower probability of needing another procedure during the ensuing year, at the expense of a roughly 2 per 100 higher risk for stroke. Other issues include longer recuperation time after CABG and need for prolonged dual antiplatelet therapy with drug eluting stents.

Ref: Serruys P.W. et al NEJ Med 2009 March 5; 360: 961.

2.12 Salt restriction and the metabolic syndrome (MS)

Salt restriction reduces blood pressure in those with or without elevated BP. Small studies have suggested that sodium restriction is more effective in people with metabolic syndrome than in those without.

1,881 adults without diabetes were recruited from rural China. 15% had baseline metabolic syndrome. It was found that the main BP decline with sodium restriction was significantly greater with the group in MS than in the group without. Mean BP also rose more in subjects with MS during high sodium intervention. A significant trend was noted towards greater salt sensitivity as the number of metabolic risk factors increased.

Comment: Sodium restriction is an effective way to lower BP and it could be particularly effective in patients with multiple metabolic risk factors.

Ref: Chen J et al Lancet March 7 2009; 373: 829.

2.13 Which is more important for decreasing coronary heart disease (CHD) risk – LDLC reduction or HDLC elevation?

HDLC is associated independently and inversely with CHD risk. However treatment mediated increases in HDLC has not been shown to decrease CHD risk. An analysis of 108 randomized trials was undertaken to determine whether treatment induced changes in HDLC were associated with all cause death, CHD related death and adverse CHD events. After adjustment for other risk factors, no association was found between CHD risk and treatment mediated changes of HDLC. However changes in LDLC levels were associated with significant outcomes. A 10mg/dl reduction in LDLC lowered the relative risk for all cause death by 4.4%, for CHD related death by 7.2% and for adverse CHD events by 7.1%.

Comment: Lowering LDLC should be the primary goal of lipid modifying treatments.

Ref: Driel M et al BMJ 2009 Feb 16; 338: B92.

2.14 Preventing recurrent Calcium stones – use Potassium citrate (PC)

PC is used to prevent recurrent calcium kidney stones. It works by increasing urinary pH. This enhances urinary citrate excretion which increases the solubility of stone forming salts. A retrospective cohort study of 503 patients who experienced recurrent kidney stones and who received PC therapy for at least 6 months was undertaken. The mean urinary citrate levels rose from 470 – 700 mg and mean urinary pH rose from 5.9 to 6.5. Mean duration of treatment was 41 months. Stone forming rate dropped from a baseline of 1.89 stones annually to 0.46 stones annually.

Comment: PC prevents recurrent calcium stone formation. Long term PC therapy is an effective intervention to prevent recurrent stone formation.

Ref: Robinson M.R et al J. Urol. 2009 Mar; 181: 1154.

2.15 Snippets.

1. What is “radiologically isolated syndrome of multiple sclerosis (MS)” ?.

This is the finding of incidental MS lesions on MRI in the absence of clinical features. When 44 such young and middle aged patients were followed up for a median 2.7 years, 33% progressed to a clinically isolated syndrome or clinically definite MS.

Ref: Neurology 2009 March 3; 72:800.

2. Do statins prevent CV events in haemodialysis patients?

Patients on haemodialysis often have increased LDLC levels. 2,773 patients age range 50 – 80 yrs who had received haemodialysis for more than 3 months, were randomized to rosuvastatin 10mg daily or placebo. At 3 months, LDL and CRP levels decreased by 43 and 12% resp. Average follow up was 3.2 years. The time for first major CV event was similar in both groups. No benefit was noted among patients with raised LDLC or raised CRP levels.

Ref: NEJ Med 2009 April 2; 360: 1395.

3. Does BP lowering in dialysis patients decrease CV events?

A meta analysis of 8 RPC trials involving 1,679 adult dialysis patients, with or without hypertension, was undertaken to assess the effect of BP lowering on CV outcomes. ACEIs , ARBs, Beta blockers and CCBs were compared with placebo or usual treatment. Follow up was 12 – 36 months. Mean BP reductions in the active treatment group was 4.5mm Hg systolic and 2.3mm Hg diastolic. Active treatment patients experienced significantly fewer CV events (RR 0.80), CV deaths (RR0.71) and all cause deaths (RR 0.80). Thus unlike the routine use of statins which produced no benefit, use of antihypertensives in both normal BP and raised BP dialysis patients produced benefit.

Ref: Lancet 2009 March 21; 373: 1009.

2.16 Do statins prevent venous thromboembolic disease (VTE) - JUPITER Trial substudy ?

The JUPITER trial looked at the effect of Rosuvastatin 20mg daily in preventing coronary disease in 17,802 healthy men and women with LDLC < 130mg/dl and elevated hS CRP. During a median follow up of 1.9years of the same cohort, the rates of symptomatic VTE were 0.18 and 0.32 events per 100 person years in the rosuva vs placebo groups (P= 0.007).

Comment: In apparently healthy individuals, rosuvastatin was associated with lessening of symptomatic VTE. This benefit was independent of rosuva's benefit on adverse cardiac events which were seen in the main trial. However whether statins can prevent recurrent VTE in patients with previous DVT or pulmonary embolism, which is the important clinical problem has not yet been studied.

Ref: Glynn NEJ Med 2009 Apr 30; 360: 1851.

2.17 Approaches to dyspepsia.

Initial approaches to dyspepsia vary considerably among clinicians. In a UK trial, 762 patients (28% over 50 yrs) with dyspepsia were randomized to 4 treatment strategies. Patients with symptoms suggesting malignancy and those previously diagnosed as oesophagitis or peptic ulcer by endoscopy were excluded. The 4 randomized treatment groups were

1. **Early endoscopy** – endoscopy was associated with urease testing for Helicobacter pylori (HP) infection. HP positive patients with ulcers or erosions received treatment to eradicate HP. All others received proton pump inhibitors (PPIs) for 1 month.
2. **Test and Refer.**- Patients underwent serologic testing for HP. HP +ve patients underwent endoscopy and were treated similarly to those in the early endoscopy group (Gp 1). HP negative patients received PPIs for 1 month.
3. **Test and Treat** - Patients underwent serological HP testing. HP +ve patients received eradication therapy. HP negative patients received PPIs for 1 month.
4. **Empirical treatment** – Patients received PPIs for 1 month.

Results: 1/3rd of patients who did not undergo initial endoscopy eventually underwent the procedure because of persistent symptoms. At 1 yr, about half the patients in each group were asymptomatic and patient satisfaction and overall use of dyspepsia medications were similar in the 4 groups. The early endoscopy group (Gp 1) had the fewest subsequent office visits for dyspepsia. The test and treat (Gp 3) was the most cost effective strategy. 37% of the whole group were HP positive.

Comment: The 1 yr outcomes with the 4 approaches to dyspepsia were similar. The Authors conclude that early endoscopy is appropriate for older populations and the test and treat or empirical therapy is appropriate in younger populations.

Ref: Duggan A.E. et al . Aliment Pharmacol Ther 2009 Jan; 29 : 55.

2.18 A new option for atrial fibrillation (AF) – Dronedarone (D).

D is similar to amiodarone but has been engineered to reduce accumulation in tissues and does not contain iodine. Thyroid and pulmonary adverse effects are not seen unlike amiodarone.

4,628 patients with AF and high risk features were randomized to D or placebo. After a mean follow up of 21 months, the incidence of the primary combined outcome of death or first hospitalization due to adverse CV events was significantly lower in the D group than in the placebo group (32% vs 39%). The rate of CV death was also significantly lower. Bradycardia, QT prolongation, nausea, diarrhea, rash and elevated creatinine levels were observed side effects.

Comment: D was associated with lower rates of adverse CV events and death. Long term follow up for safety and efficacy are now required.

Ref: Holmloser S.H. et al NEJ Med 2009 Feb 12; 360:668.

2.19 Antiepileptic drugs (AED) during pregnancy.

Cognitive deficits have been noticed in animals exposed in utero to AED. Is it the same with humans?. 309 offspring of women with epilepsy who received monotherapy with carbamazepine, lamotrigine, phenytoin or valproate during pregnancy were studied. At age 3, the cognitive function was assessed. The mean IQ was significantly lower in children exposed to valproate in utero than in children exposed to other AEDs. A median dose of valproate < 1000mg/d was not associated with excess risk.

Comment: Unless valproate is the only drug that will control a patient's seizures, it should be avoided in women who might become pregnant.

Ref: Meador K.J. et al NEJ Med 2009 Apr 16; 360: 1597.
Tomson T. IBID: 1667.

2.20 Do aspirin and NSAIDs affect immunochemical faecal occult blood tests (FOBT)?.

FOBT can be tested by either Guaiac based tests or by immunochemical methods. When the guaiac based tests are used, it is advised to discontinue aspirin and other NSAIDs for 1 week before testing. Does this restriction also apply to the newer immunochemical FOBTs?.

Among 980 patients not using aspirin or NSAIDs , the immunochemical FOBT was 51% sensitive and 91% specific for colonic neoplasia screening. Among 212 patients who were on aspirin or NSAIDs, the sensitivity was higher (67%) whereas the specificity was similar (90%).

Comment: These findings suggest that use of aspirin and NSAIDs increase immunochemical FOBT sensitivity without compromising specificity. Thus these drugs **need not be discontinued** before immunochemical FOBT screening.

Ref: Levi Z et al Am.J.Gastroenterol 2009 Apr; 104: 933.

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