

1.1 White matter changes in MRI of the brain – Are they significant?

Age related white matter changes on MRI of the brain are noted commonly. This imaging finding has been associated with incontinence, difficulty in walking and cognitive impairment. Do they also predict functional decline?. In a multicenter longitudinal European study, 639 elders – mean age 74 who underwent MRI and who showed white matter changes were followed up for a mean 2.4 years. The rates of transition from independence in activities of daily living to moderate or severe disability or death were 10.5 in mild, 15.1 in moderate and 29.5 in severe cases of white matter changes per hundred person years.

Comment: These results suggest that white matter changes especially severe changes predict functional decline. Whether aggressive treatment of risk factors will make a difference is not known.

Ref: Inzitari D. et al BMJ 2009 July 6; 339: 2477.

1.2 Does stopping Protein Pump Inhibitors (PPIs) cause rebound symptoms?

PPIs cause rebound hypersecretion of acid. The presumed mechanism is a PPI induced increase in serum gastrin, which exerts trophic effects on acid producing gastric cells. When a PPI is withdrawn, these cells are poised to hypersecrete acid.

120 healthy volunteers with no heart burn or dyspepsia received 12 weeks of placebo or 8 weeks of esomeprazole 40 mg /d followed by 4 weeks of placebo. Scores for heart burn, regurgitation and dyspepsia became modestly higher in the original esomeprazole group than in the placebo group during weeks 9 – 12.

Comment: Patients on PPIs should be warned about possible rebound when the drug is stopped. When dyspepsia occurs on rebound it is perhaps best managed with antacids as rebound has been reported not only with PPIs but also with H2 blocker therapy.

Ref: Reimer C. et al Gastroenterology 2009 July; 137: 80.
McColl K.E.L. et al IBID: 20.

1.3 Are PPIs safe in pregnancy?

1,530 women who were exposed to PPIs in their first trimester were compared to 133,000 unexposed controls. PPIs was not associated with elevated risk for major congenital malformations, spontaneous abortions or pre term delivery. This was specially so for omeprazole.

Ref: Gill S.A. et al Am. J. Gastroenterol 2009 June; 104: 1541.

1.4 Lower heart rate leads to better survival in heart failure.

Beta blockade in patients with heart failure has been shown to result in mortality benefit. Researchers conducted a systematic review of 23 randomized trials in which the heart rate in patients on Beta blockade with heart failure at baseline and at the end of dose titration were recorded. During a follow up of 3-24 months, Beta blocker treatment was associated with lower mortality (RR 24%) compared to placebo. A median reduction of 15 beats per minute was associated with lower mortality than was a median reduction of 8 beats per minute (RR 0.64 vs 0.91). Risk for death was 18% lower for every 5 beats per minute reduction with Beta blocker treatment. The Beta blocker dose itself was not associated significantly with mortality.

Comment: Titrating a Beta blocker dosage in a heart failure patient to achieve a reduction in heart rate seems to be a reasonable practice. However, the optimal magnitude of heart rate reduction remains uncertain. Most clinicians aim for a lower limit of heart rate to 60 beats per minute.

Ref: McAlister F.A. et al *Ann.Intern.Med* 2009 June 2; 150:784.

1.5 A prolonged PR interval (first degree heart block) – What is its prognostic significance?

A PR interval exceeding 200 milli seconds is called first degree heart block. In the Framingham Heart Study, 7,575 adults, (mean age 47) had first degree heart block. They were followed up for a mean 36 years. The hazard ratio for atrial fibrillation was 2.1, for pace maker placement 2.9 and all cause mortality was 1.4 compared to those without first degree block. All these risks were statistically significant.

Comment: First degree heart block is not entirely benign.

Ref: Cheng S. et al *JAMA* 2009 June 24; 301: 2571.

1.6 Are statins useful in the primary prevention of cardiovascular disease in those with CV risk factors?

A meta analysis of 10 randomized controlled trials involving 70,000 patients who had no CV disease but had CV risk factors was conducted.

Participants were followed for an average 4.1 years. Death was 5.1% vs 5.7% for statin users vs non users (OR 0.88). Major adverse coronary events were 4.1% vs 5.4% (OR 0.70). Major adverse CV events were 1.9% vs 2.3% (OR 0.81). No significant differences in treatment benefit were noted between men and women, younger and older participants and those with or without diabetes. Notably statin use was not associated with excess risk for cancer.

Comment: Statins significantly lowered risk for death, major adverse coronary events and major adverse cerebrovascular events in patients without established CV disease but with CV risk factors. The relative risk reductions are impressive but the absolute risk reductions are small. The absolute treatment benefit would certainly be less than 1% and the NNT would be in excess of 100 for 4 years to prevent one adverse CV event. Statins have been validated for secondary prevention of CV disease. This is in contrast to the use of fenofibrate which in the FIELD study was found to be useful only in those without prior CV disease and those under 65.

Ref: Brughts J.F. *BMJ* 2009 June 30; 338: 2376.

1.7 Is Aspirin useful in the primary prevention of CV disease in non diabetics?.

Aspirin has been validated for the secondary prevention of CV disease. A meta analysis was undertaken to determine whether it was useful in primary prevention and whether the net benefit outweighs the risk. 6 large prospective primary prevention trials of aspirin involving 95,000 patients without diabetes and without history of vascular disease who were randomized to receive aspirin or no aspirin for more than 2 years - were analysed.

Compared to the no aspirin group, aspirin recipients had a statistically significant but a very small absolute reduction of 0.51 vs 0.57 annually in serious vascular events. Patients who received aspirin had significantly fewer ischaemic strokes but significantly more haemorrhagic strokes. Aspirin users also had more major extracranial bleeds (0.10% vs 0.07%) annually.

Comment: These data suggest a possible small net benefit for aspirin in primary prevention of CVD. The authors point out that few of these patients had the benefits of statins and other modern, low risk, primary prevention interventions, and they suggest that the benefits of adding aspirin to these newer therapies no longer outweighs the risk.

Ref: ATT Collaboration Lancet 2009 May 30th; 373:1849.

1.8 Do Beta blockers reduce perioperative cardiovascular events in non cardiovascular surgery?

The DECREASE IV study included 1,066 intermediate risk patients for adverse cardiovascular events, scheduled for elective non cardiovascular surgery. They were randomized to receive the cardioselective Beta blocker Bisoprolol, starting at 2.5mg daily or no Bisoprolol and to receive Fluvastatin 80mg/d or no Fluvastatin. Medications were started **one month** before surgery and Bisoprolol dose was titrated to achieve a pulse of 50 – 70 beats/mt and systolic BP > 100mmHg.

The 30 day incidence of the primary end point – cardiac death + non fatal MI, was significantly lower in Bisoprolol recipients (2.1% vs 6.0%, P=0.002). Nearly all these events were non fatal MIs. Fluvastatin had no effect.

Comment: In last year's land mark POISE trial of 8,300 patients, perioperative Metoprolol lowered the incidence of MI but raised mortality. In DECREASE IV, low dose Bisoprolol was started one month before surgery and was titrated, whereas in POISE, median dose Metoprolol was started only several hours before surgery. POISE was placebo controlled but DECREASE IV was not. It appears therefore that Beta blockade use should be started several weeks before surgery – a practice that is not feasible in many settings, to make sure it is well tolerated.

Ref: Dunkelgrun M. et al Ann.Surg. 2009 Jun; 249: 921.

1.9 Angina with normal coronary angiograms (CA) in women – Is it an innocent condition?

About 50% of all women who undergo CA have normal coronary arteries (below 50% stenosis). These women were compared with asymptomatic women free of known CAD. 540 symptomatic women were followed up for 5 years and compared with 1,000 age and race matched asymptomatic controls. The mean age of the study population was 56.

The 5 year annualized rate for cardiovascular events (MI + stroke + heart failure + CV death) was significantly higher among the symptomatic women compared with the asymptomatic women. This higher incidence was mainly due to increased heart failure and stroke.

Comment: Symptomatic women with non obstructed (<50%) or normal CAs had higher rates of CV events. Aggressive management of such women for CV risk factors is warranted. Endothelial dysfunction may be the mechanism explaining these findings.

Ref: Gulati M. et al Arch. Intern Med 2009 May 11; 169: 843.

1.10 What is the significance of the ultra sound findings of small gall bladder polyps?

Retrospective data suggest that polyps > 1cm can undergo malignant transformation but smaller polyps are generally considered to be benign. 56 consecutive patients with small polyps < 1cm on USS were followed up in a single center Italian study. 32 had multiple polyps. Those who had concomitant gall stones were excluded. During a 5 year follow up, no patient reported biliary pain or required cholecystectomy. Also none developed gall bladder cancer.

Comment: Small gall bladder polyps have a benign course with enlargement only in a minority. They are also unlikely to develop asymptomatic gall stones. “Wait and see” without preemptive cholecystectomy is the best policy.

Ref: Colecchia A et al Am.J.Gastroenterol 2009 Mar ; 104:624.

1.11 Do cancer patients with anaemia benefit from Erythropoietin (E) or Darbopoietin (D)?

E is associated with excess mortality when patients with chronic renal failure are treated to achieve near normal target Hb levels. What about cancer patients?. A meta analysis of 52 randomized trials involving 12,000 patients with cancer related anaemia was undertaken. E or D were compared with no treatment. During a median follow up of one year, all cause mortality was significantly higher in the treatment groups. This elevated mortality was not related to the Erythropoietic agent (E or D used). It was also not related to the type of cancer (solid or haematologic) and whether the target Hb level achieved was < 12g/dl or > 12g/dl. Serious adverse events also occurred more commonly with either E or D. Benefits of treatment included fewer blood transfusions and improved quality of life.

Comment: Use of Erythropoietic agents for cancer related anaemia is associated with improved quality of life but elevated mortality. The authors suggest that Erythropoietic agents should not be used routinely as an alternative to blood transfusions in anaemia related to cancer.

Ref: Tonelli M. et al CMAJ 2009 May 26; 180: E62.

1.12 Can patients with acute gout present with normal serum uric acid (SUA) levels (<8mg/dl)?

Normal SUA does not exclude gout as the cause of an acute inflammatory arthritis. How common is this phenomenon?.

339 patients were analysed and 14% had SUA < 6mg/dl and 18% had SUA between 6 and 8 Mg/dl - total 32%. The mean SUA level was 8.3mg/dl. Patients taking allopurinol earlier had a mean SUA of 7.2mg/dl and those not taking allopurinol was 8.5mg/dl.

Comment: This study suggest that about 1/3rd of patients with acute gouty arthritis had SUA levels below 8mg/dl. Those already on allopurinol are more likely to have normal SUA levels with acute gout.

Ref: Schlesinger N et al J.Rheumatol 2009 June; 36: 1287.

1.13 Combined antiplatelet and anticoagulant drugs – Do they increase the bleeding risk?.

40,000 Danish adults within 90 days of their first acute MI and who were on one or more of 3 drugs viz aspirin, clopidogrel and Vit K antagonist were analysed. During a mean follow up of about 16 months, 115 fatal bleeding events and 1,852 non fatal bleeding events occurred. With aspirin monotherapy as a reference, the adjusted relative risks for fatal and non fatal bleeding were 1.23 for a Vit K antagonist alone, 1.33 for clopidogrel alone, 1.47 for aspirin + clopidogrel, 1.84 for aspirin + Vit K antagonist, 3.52 for clopidogrel + Vit K antagonist and 4.05 for all three. Only aspirin vs Vit K antagonist alone was a non significant difference.

Comment: These findings suggest that dual and triple combinations of antithrombotic agents should be prescribed only after careful, individualized risk benefit evaluations have been done.

Ref: Sorensen R et al Lancet 2009 Dec 12; 374: 1967.

1.14 Are ACEIs, ARBs or their combination beneficial in Ischaemic heart disease (IHD) with preserved ventricular function?

ACEIs and ARBs benefit patients with MI + depressed LV ejection fraction after MI. Is it beneficial when the LV ejection fraction is preserved?

A systematic review identified 9 randomized trials, 2 non randomized controlled studies and 6 systematic reviews (N > 30,000). They analysed the effect of ACEIs and or ARBs when added to standard therapy with antiplatelet and anti lipid therapy in patients with IHD and preserved LV function.

Compared with placebo, ACEIs were associated with lower CV mortality in 6 trials and total mortality in 7 trials, fewer non fatal MIs in 6 trials and strokes in 7 trials. ARBs on the other hand lowered the incidence of a composite end point of stroke, non fatal MI and cardiovascular death only in a single study. ARBs and ACEIs in combination were associated with similar outcomes as ACEIs alone but the combination was associated with more adverse events such as hypotension, hyperkalaemia and deterioration of renal function.

Comment: ACEIs added to standard medical therapy for patients with IHD with normal LV function is beneficial. ARBs alone or combined ARBs + ACEIs are not recommended in this category of IHD patients.

Ref: Baker W.L. et al Ann.Intern Med 2009 Dec 15; 151: 861.

1.15 Are adult survivors of childhood cancer at greater risk for heart disease?

Advances in paediatric oncology have enabled children with cancer to survive into adulthood. What are the long term adverse outcomes?

1. Secondary cancers.
2. Cardiac effects attributable to cancer treatment such as chemotherapy and radiation viz heart failure (HR 5.9), MI (HR 5.0), pericardial disease (HR 6.3), and heart valve abnormalities (HR 4.8) compared with their non affected siblings.

Comment: Clinicians treating adults should be aware that adult survivors of childhood cancers are at elevated risk for heart disease as well as for secondary cancers.

Ref: Mulrooney D.A. et al BMJ 2009 Dec 8; 339: 4606.

1.16 Can patients with peptic ulcer bleeding continue low dose aspirin?.

Patients who take aspirin daily and who present with peptic ulcer bleeding typically discontinue aspirin to lower risk for recurrent bleeding. However, does that risk actually outweigh aspirin's cardiovascular benefits?.

Researchers in Hong Kong looked at 156 consecutive patients who had upper GI bleeding while on low dose aspirin (<325mg/d) taken for secondary prevention of cardio and cerebrovascular disease. They were first treated with endoscopy and PPIs and then randomized to either daily aspirin 80mg/d or placebo for 8 weeks while being on daily oral PPI therapy. The 30 day cumulative incidence of recurrent ulcer bleeding was 10% in the aspirin group and 5% in the placebo group – a non significant difference. Within 30 days one aspirin recipient and 10 placebo recipients died. 5 deaths in the placebo group were from vascular complications. All cause mortality at 8 weeks was significantly lower in the aspirin group than in the placebo group (1.3% vs 12.9%).

Comment: In this small short term trial, involving patients with bleeding peptic ulcers, those who continued low dose aspirin had a higher rate of recurrent bleeding than those who stopped taking aspirin although the difference was not significant. More importantly, mortality was significantly lower when aspirin therapy was continued. Larger confirmatory trials are needed but we can reasonably allow patients with peptic ulcer bleeding who had high risk for CV events to continue taking aspirin therapy when indicated along with PPI therapy.

Ref: Sung J.J.Y Ann.Intern.Med 2010 Jan 5; 152: 1.

1.17 What is the value of bone marrow biopsy (BMB) in diagnosing pyrexia of unknown origin (PUO)?.

BMB can be useful in diagnosing the cause of fever in patients with HIV. Whether it is useful in PUO immunocompetent patients was evaluated in a retrospective French study of 130 consecutive patients. PUO was defined as an illness of > 3 weeks duration with repeated documented temperature of > 38.3 C.

In 31 cases (24%) a specific diagnosis was achieved by bone marrow biopsy. Haematologic malignant disease (mainly lymphomas and Leukaemias) were by far the most commonly diagnosed disorders (25 cases). TB and systemic mastocytosis each were diagnosed in 2 patients.

Comment: Among immunocompetent patients with PUO, BMB might provide clinically important information in a sizable proportion and should be considered when other studies are negative.

Ref: Hot A. et al Arch. Intern. Med 2009 Nov 23; 169: 2018.

1.18 A new treatment for venous thromboembolism (VTE) – Dabigatran (D).

D is a direct oral thrombin inhibitor. It can be given in a fixed dose and requires no lab monitoring. Recently it was found to compare favourably with warfarin in patients with atrial fibrillation.

2,500 patients with acute VTE (69% with DVT only, 21% with pulmonary embolism only and 10 % with both) were randomized to either warfarin or D after initial heparin therapy. At 6 months, no significant differences were found between D and the warfarin groups in recurrent VTE or major bleeding. A combined end point of major bleeding + clinically relevant non major bleeding occurred less often with D. One side effect viz dyspepsia occurred more commonly with D.

Comment: D is comparable to warfarin in both efficacy and safety in patients with VTE. Ximelagatran also a direct oral thrombin inhibitor failed to gain FDA approval because of hepato toxicity. But this has not been found with D. D is not yet FDA approved but both D and an oral direct inhibitor of factor Xa (Rivaroxaban) already have been approved in Canada and some European countries for DVT prophylaxis following total hip or knee arthroplasty but not yet for treatment of DVT or atrial fibrillation.

Ref: Schulman S et al NEJ Med 2009 Dec 10; 361: 2342.

1.19 How long does the protective effect of HPV vaccine last?.

Vaccine against two oncogenic human papilloma viruses (HPV types 16 and 18) are highly immunogenic and markedly lowered cervical HPV 16/18 infections and cervical pathology. In a recent study of 1,100 women, age 15 – 25, randomized to receive either 3 doses of the bivalent vaccine or placebo, it was found that after 6.4 years of follow up, there was a 95% protection against incident HPV infection and 100% protection for preventing persistent HPV infection. There was also 97% protection against developing any HPV related cytopathology and 100% protection for HPV related cervical intraepithelial neoplasia.

Comment: The prolonged preventive efficacy for 6.4 years encourages a growing confidence in the efficacy and safety of HPV vaccines.

Ref: Romanowski B et al Lancet 2009 Dec 12; 374: 1975.
Clifford G.M. IBID: 1948.

1.20 Losartan high dose vs low dose in congestive heart failure (CHF).

In several studies, high dose ARBs, either alone or in combination with ACEIs, have lowered CV morbidity and mortality in patients with CHF and reduced LV ejection fraction. The effects of different ARB dosing regimens are unknown.

3,846 patients with NYHA class II –IV CHF, LVEF <40% and **intolerance to ACEIs** were randomized to receive Losartan up titrated to either 50mg or **150mg**. Most patients also received Beta blockers. After a median 4.7 years of follow up, high dose recipients were significantly less likely to reach the composite primary end point (hospitalization for heart failure or death) than were those in the low dose group (11.1 vs 12.4 events per 100 patients years). High dose recipients also had significantly fewer CV and heart failure admissions but differences in all cause and CV mortality were not significant. More hyperkalaemia, hypotension, renal impairment and angioedema occurred in high dose recipients.

Comment: High dose ARBs in CHF patients incrementally inhibit angiotensin receptor activity, with potentially improved clinical outcomes with more adverse effects. These conclusions cannot be extended to patients who tolerate ACEIs or who are taking them concomitantly nor does it suggest that ARBs are better than ACEIs in this setting.

Ref: Constam M.A. et al Lancet 2009 Nov 28; 374: 1840.