CEYLON COLLEGE OF PHYSICIANS

MEDICINE UPDATE

2014

VOL-25 NO : 01

Synergistic Antioxidants, Vitamins & Minerals

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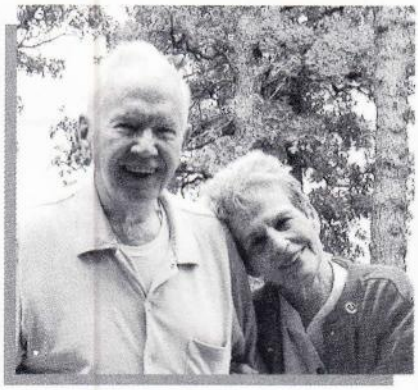

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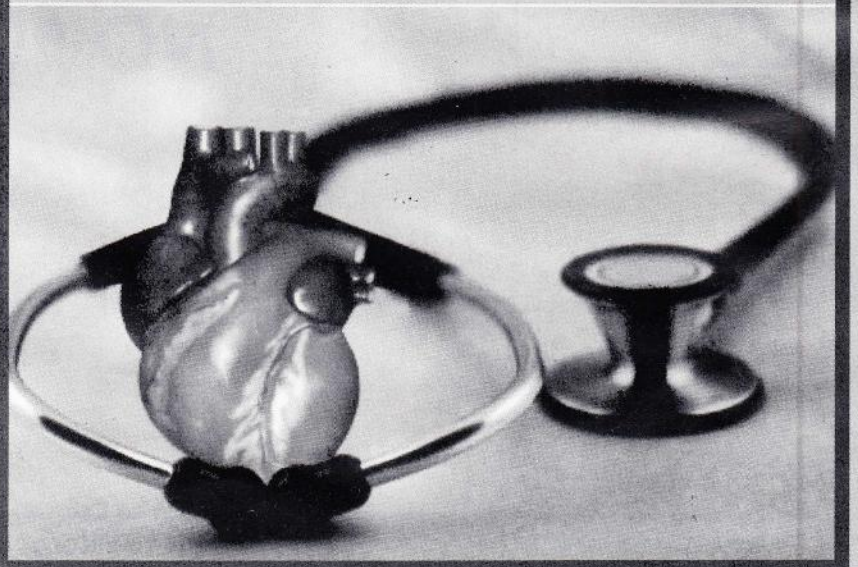

1.1 A new treatment for resistant hypertension – Renal Sympathetic Denervation (RSD).

RSD is achieved via a catheter mediated ablation of the renal sympathetic nerves. It has already been shown to lower BP in resistant hypertension. The duration of this effect and the long term safety was evaluated in an uncontrolled, manufacturer funded, proof of concept study published in 2009.

150 patients with treatment resistant hypertension (Systolic BP > 160mmHg despite optimized treatment with > 3 antihypertensive agents) experienced rapid and persistant reductions in BP from a mean of 175/98 mmHg at baseline to 149/84mmHg at one year after RSD. 88 of these patients were followed up for 3 years and the mean BP continued to decline reaching 143/82mmHg at 3 years. No major renal or vascular adverse events occurred but patients were unable to reduce the number of antihypertensive medications.

Comment: This report dispels concerns that BP reductions after RSD may be shortlived due to regrowth of the ablated sympathetic nerves or that important adverse events such as renal artery stenosis might emerge. Larger and longer studies would be required to discern the effects on cardiovascular events and to identify subgroups who would benefit most from this procedure.

Ref: Krum H et al Lancet 2013 Nov 7 (e pub ahead of print).

1.2 A new alternative for warfarin in atrial fibrillation (AF) – Edoxaban (E).

E is an oral factor Xa inhibitor not yet FDA approved. 21,000 patients with AF were randomized in an industry sponsored, International trial comparing E 30mg or 60mg/d vs placebo. During a median follow up of 2.8 yrs, annualized rates of various outcomes were as follows.

1. Primary efficacy end point of stroke or systemic embolism was 1.50% for warfarin vs 1.61% for low dose E and 1.18% for high dose E. The low dose regime was non inferior to warfarin and the high dose E was superior to warfarin.
2. Major bleeding was 3.43% vs 1.61% and 2.75% for warfarin, low dose E and high dose E resp. These rates with both E doses were significantly lower than warfarin.
3. All cause mortality was 4.35%, 3.80% and 3.99% for the same regims resp.
4. Several net clinical outcome end points - combined stroke, major bleeding and death – favoured E over Warfarin, with little difference between the 2 E doses.

Comment: In this study, high dose E appeared to be more effective than warfarin with respect to stroke prevention while the low dose E appeared to be safer than warfarin with respect to bleeding. 3 warfarin alternatives namely Dabigatran (thrombin inhibitor), Rivaroxaban and Apixaban (both factor Xa inhibitors) are FDA approved for atrial fibrillation. E may soon join them.

Ref: Giugliano R.P et al NEJ Med 2013 Nov 28; 369: 2093.

1.3 Does the Human Microbiome (HM) play a major role in health?.

Humans are colonized by bacteria and a few species benefit human health by synthesizing important vitamins and amino acids, degrading toxins and helping digest plant material. We have assumed hitherto that most species that live on or within us do not affect our health. However, an explosion of research is changing this view radically. We now know that our 13 trillion human cells coexist with 130 trillion

bacterial cells. Our 20,000 human genes coexist with 5 – 8 million bacterial genes – what is called the "microbiome" or the "2nd Human Genome".

The microbiome has now been linked to **obesity, inflammatory bowel disease, psoriasis, non alcoholic fatty liver disease, asthma** and even **autism**. Further the gut bug Fusobacterium nucleatum has been linked to **colorectal cancer**. These bacteria contain a unique receptor that binds to colorectal cells, stimulating both inflammation and carcinogenesis. When this bacterium was placed in the guts of colorectal cancer susceptible mice, they developed excess numbers of colorectal carcinomas. In 2013, several groups identified a "microbiome signature" that did a better job of predicting which people would develop **Type 2 DM** than any human gene or behavior which has been linked to that disease. Finally gut bugs that transform dietary lecithin and L- carnitine into a proatherogenic molecule, trimethylamine – N – oxide (TMAO) resulting in high blood levels of TMAO have been found to have excess risk for **adverse cardiovascular events**. This excess risk could be abolished by both probiotic or antibiotic interventions.

Comment: None of the evidence suggest a definitive aetiological role for the microbiome in major human diseases. But we might be witnessing the birth of a revolution in our understanding of human health and disease.

Ref: Komaroff A.L. N.E.J.M. Journal Watch 2014 Jan 15; 34(2): 17.

1.4 A new combination treatment for early Rheumatoid Arthritis (RA) – Adalimumab (ALM)+ Methotrexate (MTX).

The present combination treatment for early RA is hydroxyl chloroquine + Sulphasalazine + MTX. This has been shown to be non inferior to the more expensive combination of Etanercept + MTX after 2 years of treatment (Arthritis Rheum 2012; 64: 2824). Researchers now consider whether the biologic agent ALM is more effective than MTX monotherapy in early RA.

1,000 patients with early RA were randomized to either MTX only or ALM + MTX for 26 weeks. At 26 weeks, non responders in either group were switched to open label combination therapy while MTX responders continued the blinded regime. 207 patients who responded to combination therapy were randomized further to continue combination therapy or to de escalate to MTX + placebo. At 78 weeks, significantly more patients who received initial combination therapy achieved low disease activity than did those who received MTX alone (70% vs 54%). Most patients who de escalated from ALM + MTX to MTX alone maintained good responses at 78 weeks.

Comment: Combination therapy with ALM + MTX was better than MTX alone. Those who responded to combination therapy can be de escalated to MTX monotherapy without adverse effects on disease activity.

Ref: Smolen J.S. et al Lancet 2013 Oct 26 – OPTIMA trial.
Kirwan J.R. and Boers M IBID.

1.5 Is sustaining a hip fracture a risk factor for new onset diabetes or acute MI in non diabetic patients?.

Hip fracture is the main complication of osteoporosis among aged patients, and prevention of hip fracture related complications has become increasingly important, mainly focusing on diagnosis and therapy of

pulmonary embolism and bronchopneumonia. Adverse CV events have been recognized as one of the main reasons for an increased mortality risk after hip fracture. Hip fractures lead to injuries of the musculoskeletal system and induce a stress state simultaneously, thereby stimulating the release of stress hormones and reducing insulin sensitivity through neuro endocrine changes.

A study was undertaken to investigate the risk of acute myocardial infarction (AMI) following stress hyperglycaemia after hip fracture. A prospective observational study of 1,257 consecutive patients with no history of diabetes who suffered hip fractures was undertaken. Stress hyperglytcaemia was seen in 48% and AMI occurred in 9%. The occurrence of AMI in the stress hyperglycaemia group was higher than in the nonhyperglycaemia group (12% vs 6% , $p < 0.05$). In the stress hyperglycaemia group, the FPG reached maximum levels at 2 – 3 days after hip fractures and then decreased gradually. The AMI incidence was highest in the initial 3 days in the stress hyperglycaemia group, significantly coinciding with the FPG peak time. In the patients with AMI, the non STEMI occurred more often than STEMI (62% vs 38%).

Comment: This study suggest that stress induced hyperglycaemia is not uncommon after hip fracture and it increases the risk for AMI. Some investigators have reported that the increased incidence of AMI after hip fracture was related to osteoporosis. Osteoporosis and CVD share common risk factors like poor general health status, life style, nutrition, hormone secretion, Vitamin D deficiency, systemic inflammation (elevated CRP, IL – 6 or TNF alpha) and medications - through different mechanisms both in bone and arteries. Acute fractures induced stress hormones to be secreted viz glucocorticoid, glucagons, adrenaline, thyroxine, somatotropin and others, which constitute the so called "stress response". These hormones induce insulin resistance, resulting in hyperglycaemia and other associated risk factors. The stress hyperglycaemia which results is associated with oxidative stress and inflammatory responses which damage the coronary artery endothelium and ADP induced platelet aggregation. The increase in plasma catecholamine is known to be associated with vulnerable plaque evolution and thrombogenesis. These facts make the detection of hyperglycaemia within the first 3 days after the hip fracture to be important with prompt treatment for all risk factors to prevent AMIs. In patients without previous diabetes, FPGs and ECGs should be monitored for atleast 7 days after the fracture.

Ref: Chen .Y. et al Diabertes Care 2013 Oct; 36: 3328 – 3332.

1.6 Should you wash your stethoscope?.

Health care worker's hands clearly can transmit organisms from one patient to another and washing hands between patients clearly limits nosocomial out breaks. Should we be decontaminating our stethoscopes and reflex hammers as assiduously as we do our hands?. Swiss researchers wearing sterile gloves and using sterilized stethoscopes, performed standardized brief physical exams on 33 patients. Standard microbiology techniques were used to quantify bacterial contamination of examiners hands and stethoscopes.

Stethoscope diaphragms picked up significantly fewer total aerobic bacteria than did the examiner's gloved finger tips, but significantly more than did the palms or backs of examiner's hands. Stethoscope tubing cultured about 3 inches from stethoscope heads acquired about as many bacteria as did the palms of examiner's hands. Finger tips and stethoscope diaphragms picked up similar quantities of MRSA.

Comment: These data confirm a link between the microbial flora of the stethoscope and nosocomial infections. Stethoscope heads become as contaminated as Physician's finger tip during brief physical exams. It appears logical that we should wash not only our hands but also the heads and adjoining tubing

of our stethoscopes to prevent spreading nosocomial infection. This is specially important in the ICU. Dedicated stethoscopes should be assigned to each and every patient in ICU. In the general ward round, these recommendations may not be practicable.

Ref: Longtin Y et al MAYO Clin. Proc 2014 Mar; 89: 291.

1.7 What is the period when women are hypercoagulable post partum, is it 6 weeks, or 3 months?.

In a study of all California women who had delivered babies between 2005 and 2010, the incidence of a 1st thrombotic event (ischaemic stroke, acute MI or DVT) 7 – 12 weeks after delivery was found to be twice that at 1 year post partum. This thrombotic risk leveled off after 12 weeks post partum.

Comment: Offering thrombotic prophylaxis to high risk women throughout the first 12 weeks after delivery appears reasonable. The CDC states that women without risk factors for thromboembolism generally can initiate oestragen containing contraception 21 days after delivery whereas women with Caesarean deliveries or previous thrombosis should wait 42 days post partum. To wait 12 weeks post partum before using oestragen containing contraception appears rational from this study. For those who want immediate post partum contraception, intra uterine devices and implants of a highly effective reversible contraception without increasing clot risk are options.

Ref: Kamel H. et al NEJMed 2014Feb 13. e pub.

1.8 Radiofrequency ablation (RFA) for Atrial Fibrillation(AF).

RFA for AF is relatively new but already carries a class 1 guideline recommendation for patients who have failed to respond to antiarrhythmic drugs (AADs). 127 patients were randomized to treatment with either AADs (Flecainide, Propafenone) or RFA. The rates of the primary end point (Atrial flutter or Atrial tachycardia of >30 sec duration during 2 year follow up) were 55% in the RFA group and 72% in the AAD group (p=0.02). 4 patients in the ablation group experienced pericardial tamponade. Quality of life scores were equal.

Comment: RFA was more effective than AADs for the primary treatment of AF. However the efficacy was modest and came at the cost of excess risk for complications. Patient preference and clinical circumstances should continue to drive individual decision making.

Ref: Morillo C.A. et al JAMA 2014 Feb 19; 311: 692.
Calkins H. IBID : 679.

1.9 Is dual antiplatelet therapy beneficial in patients who suffer lacunar strokes while receiving Aspirin therapy?.

In the previously published SPS3 trial, 3,000 patients who experienced lacunar strokes during the previous 6 months were randomized to receive Aspirin alone or Aspirin (A)+ Clopidogrel (C). During several years of follow up, dual antiplatelet therapy did not prevent recurrent stroke and increased risk for major haemorrhage and death (NEJM 2012;367:817). Now, in a post hoc analysis from this study, researchers present data on 838 patients who already have been taking prophylactic Aspirin at the time of the lacunar stroke that qualified them for the trial.

Outcomes in this sub group mirrored those of the larger study. During mean follow up of 3.5 years , the annual stroke rate was 3% in both the Aspirin mono therapy and dual antiplatelet therapy treatment

groups. However annual mortality was higher with dual therapy than with Aspirin alone (2.9% vs 1.4%, p = 0.004). Further, GIT bleeding was more common with dual therapy.

Comment: A + C dual therapy was not more effective than A alone for preventing subsequent strokes in patients with previous lacular strokes that occurred during A therapy. Note that SPS3 patients were randomized an **average of 2.5 months after their index lacunar strokes**. In contrast, in the recently published CHANCE trial (NEJMed 2013 ; 369: 11) short term dual therapy was more effective than A alone in patients with **transient ischaemic attack or minor stroke who were randomized within 24 hours**. In that study, no distinction was made between lacunar strokes and other stroke sub types.

Ref: Cote R. et al Neurology 2014 Ferb 4; 82: 382.

1.10 Is Citalopram (C) useful in reducing agitation in Alzheimer disease (AD)patients?.

Agitation in patients with AD causes substantial patient and care giver distress. 186 older adults (mean age 78) with AD and clinical agitation were randomized to C 30mg/d or placebo. At 9 weeks, C patients had significantly lower scores on standardized measures of agitation than did controls. Care givers in the C group reported lower stress levels. Improvement in agitation was 40% in the C group vs 26 % in controls (NNT =7). C patients experienced more frequent worsening of cogtnitive function, anorexia, diarrhea and falls. Prolonged QTc intervals were more frequently prolonged in C patients.

Comment: C appears to reduce agitation in AD patients with additional benefits to care givers. However its side effects could detract substantially from overall quality of life and even cause cardiac complications or death. Cautious use of C in selected patients might be warranted.

Ref: Porsteinsson A.P. et al JAMA 2014 Feb 19; 311: 682.
Small G.W. IBID : 677.

1.11 Can prolonged gastric acid suppression lead to Vitamin B12 deficiency?.

Gastric acidity promotes extraction of B12 from food, allowing it to be absorbed after binding to intrinsic factor. Prolonged suppression of gastric acid production by Omeprazole or its derivatives could predispose patients to Vitamin B12 deficiency. A study from the Kaiser system in California showed that those who received more than 2 years of recent PPI therapy were more likely to have B12 deficiency than for controls (OR 1.65). The association with more than 2 years of H2 receptor antagonist such as Ranitidine was much weaker (OR 1.25).

Comment: Add Vitamin B 12 deficiency to the list of possible adverse effects associated with prolonged PPI therapy. These include diminished absorption of iron, Calcium and Thyroxine. To this should be added the greater tendency for C difficile infection and spontaneous bacterial peritonitis in cirrhosis patients.

Ref: Lam J.R. et al JAMA 2013 Dec 11; 310: 2435.

1.12 Should all patients with COPD exacerbations be treated with antibiotics?.

Patients with severe COPD exacerbations are treated with antibiotics. Do patients with mild to moderate COPD exacerbations (FEV1 > 50% of predicted) require antibiotics?. A recent study in this category of patients who received either Coamoxyclav or placebo, 80% of placebo patients had satisfactory outcomes in the absence of antibiotic therapy. The only symptom that predicted potential benefit from antibiotics was increased purulence of sputum. Patients with dyspnoea , increased sputum volume without increased

purulence or both did well without receiving antibiotics. The 2 best predictors of potential benefit from antibiotics were

1. Purulent sputum.
2. CRP >40mg/l.

Comment: This study supports foregoing antibiotics in patients who have mild to moderate COPD exacerbations without purulent sputum.

Ref: Miravitlles M et al Chest 2013 Nov; 144: 1571.

1.13 Should unruptured brain AV malformations (AVM) be subject to intervention treatment?.

Unruptured AVMs may be found incidentally on brain imaging. Should these be subjected to interventions?. The 1st randomized trial of intervention vs conservative therapy for unruptured AVMs was undertaken. The specific interventions to obliterate AVMs included neurosurgery, radiotherapy, embolization or a combination. After 226 patients were enrolled, the study was halted because the primary outcome of death or symptomatic stroke occurred significantly more often in the intervention group than in the control group. during a mean follow up of 33 months (31 % vs 10%). Excess stroke accounted for difference between groups and rates of neurological disability were much higher in the intervention group than in the control group.

Comment: Some people might argue that benefits of obliterating unruptured AVMs will accrue over time and outweigh the short term harms seen here. Long term follow up is certainly needed but imagining a realistic long term benefit that could outweigh this much excess short and intermediate term risk for stroke and disability is difficult.

Ref: Mohr J.P. et al Lancet 2013 Nov 20; e pub. Ahead of print.

1.14 Can breast cancer be prevented?.

Women with excess risk for breast cancer can be treated with Tamoxifen (T) or Raloxifene (R) which are the only agents presently approved for preventing breast cancer in women at high risk. What about aromatase inhibitors which prevent the conversion of testosterone to oestrogen and therefore theoretically have the potential of preventing oestrogen receptor positive breast cancer?. The efficacy and safety of the aromatase inhibitor Anastrozole (A) vs placebo was investigated in 3,864 post menopausal women (median age 60) with excess risk for breast cancer.

During 5 years of follow up, overall incidence of breast cancer was significantly lower in the A group than in the placebo group (2% vs 4%) but as expected A did not significantly lower the incidence of oestrogen receptor negative breast cancer. Arthralgias, carpal tunnel syndrome, vasomotor symptoms, vaginal dryness, hypertension and dry eyes were significantly more common with A.

Comment: The reduction in risk for breast cancer with A is similar to that seen with another aromatase inhibitor Exemestane (E) but greater than that reported for SERMs such as T or R. Both E and A may soon be approved by FDA for prevention of breast cancer. However, a clear mortality benefit has not been shown and toxicity with long term oestrogen deprivation is of concern.

Ref: Cuzick J et al Lancet 2013 Dec 12; e Pub ahead of print.

Cameron D.A. Lancet 2013 Dec 12 e Pub.

1.15 Should patients with benign prostatic hyperplasia (BPH) be treated with Alpha blockers only or by a combination of Alpha blockers + anticholinergics?.

In patients with BPH, Alpha blockers such as Tamsulosin (T) and Doxazocin (D) work primarily by relieving obstructive symptoms such as incomplete emptying and weak stream. However, many BPH patients also have " storage symptoms" such as frequency, urgency and nocturia for which anticholinergic drugs such as Oxybutynin (O) and Tolterodine (T) might be helpful. A meta analysis of 7 studies (N= 3,600) was undertaken, in which an Alpha blocker monotherapy was compared with combination therapy.

Combination therapy compared with monotherapy improved symptoms on a storage score. However, add on anticholinergic therapy had a predisposition for acute urinary retention in the 12 week trial (1.4% vs 0.4%). Combination therapy however did not improve the total symptom scores or quality of life scores.

Comment: The one additional case of acute urinary retention per 100 treated patients (1%) is of concern in a 3 month study. What might happen over 1-2 years of treatment?. The authors also do not discuss the non urinary side effects of anticholinergic drugs in older people. Although combined therapy might be worthwhile for selected individuals, potential benefits do not outweigh potential harms.

Ref: Filson C.P. et al J . Urol. 2013 Dec; 190: 2153.

1.16 Combination of Clarithromycin (C) + Calcium channel blockers (CCBs) may cause acute Kidney Injury (AKI).

CYP 3A4 inhibition by C can lead to excessive plasma levels of CCBs which may cause hypotensive episodes leading to AKI. C vs Azithromycin (A) was compared in 95,000 older adults (mean age 76) who were chronic users of CCBs. Within 30 days of antibiotic initiation, the risk for AKI was 0.44% for C vs 0.22% for A. The risk for hypotension was 0.12% vs 0.07% and for all cause mortality was 1.02% vs 0.59% resp. The risk was greatest among patients who received C + the CCB – Nifedipine.

Comment: 464 patients would have to be coprescribed a CCB + C for one patient to be harmed. Frequent coprescribing of this combination could result in unnecessary hospitalization and excessw mortality. If a macrolide is indicated A seems to be a safer alternative for coprescription with CCBs.

Ref: Gandhi S. et al JAMA 2013 Dec 18; 310: 2544.

1.17 A new imaging technique for non alcoholic fatty liver disease (NAFLD) - Shear wave velocity (SWV).

NAFLD enhances an individual's risk of CVD independent of the components of the metabolic syndrome including adiposity. There is a genetic susceptibility to predispose the fatty liver to secondary hits that include oxidative stress, mitochondrial dysfunction, proinflammatory cytokine imbalance and stellate cell activation. NAFLD is usually diagnosed by an abdominal ultrasound scan which estimates fat content, liver enzyme estimation and liver biopsy (at least 5% of hepatocytes containing macrovesicular fat). The fibrotic component can be measured by acoustic radiation post impulse imaging which measures SWV as a continuous measure of liver stiffness. The stiffer the tissue, the faster is the SWV. Thus the speed of the SWV increases with the severity of the liver fibrosis in any chronic liver disease.

Comments: Paediatric guidelines state that overweight or obese children age 10 yrs or more should be screened for NAFLD using AST and ALT. It now appears that not only ultra sound scan for the detection of fatty liver but also USS based estimation of liver stiffness should be considered as valuable 1st line screening in overweight / obese adolescents. In fact, USS and SWV may work better than liver enzymes as 1st line screening before liver biopsy. SWV is a non invasive, user friendly technique that is a surrogate to quantify the degree of fibrosis with good sensitivity and specificity.

Ref: Manco M JCEM 2014 Mar; 99 (3) : 774 -776.

1.18 Which is better for faecal occult blood testing – Immunochemical method or Guaiac testing?.

Faecal immunochemical testing (FIT) for haemoglobin is more specific than stool Guaiac testing because FITs returned positive results only when globins are present. FITs do not react with foods that have peroxidase activity and are not positive in patients with upper GI bleeding because the globin component from upper GI bleeds has been digested. These characteristics negate the need to alter patient's diet, abstain from iron tablets and a single sample usually is sufficient. FITs is therefore useful to diagnose GIT bleeding from beyond the pylorus especially for detecting colorectal cancer.

In a meta analysis of 19 studies, the pooled sensitivity, specificity, positive likelihood ratio and negative likelihood ratio were 0.79, 0.94, 13.10 and 0.23 resp. Performance characteristics did not change significantly when 1, 2, or 3 stool samples were used.

Comment: This meta analysis confirms previous findings in which FIT was reported to be highly accurate for detecting lower GI cancer. Given that only a single stool sample was needed and diet and drug modification is not necessary, FIT might prove to be more cost effective than stool Guaiac testing in most settings. Comparison of FIT vs colonoscopy in the diagnosis and mortality of colorectal cancer is being carried out in the CONFIRM trial, but the results will not be available for many years.

Ref: Lee J.K. et al Ann.Intern. Med. 2014 Feb 4; 160: 171.
Maki D IBID : 277.

1.19 Can warfarin (W) be used for atrial fibrillation (AF) in the presence of chronic kidney disease (CKD)?.

AF that requires anticoagulation often coexist with CKD, raising concerns about the risk for bleeding with W. 24,317 consecutive survivors of MI with AF who had creatinine levels <60ml/mt were analysed.

At 1 year after discharge, the risk for a composite end point of death + readmission for MI + ischaemic stroke was lower in W recipients than in non recipients in every stratum of kidney dysfunction. In patients with eGFR <15ml/mt , the hazard ratio with W was 0.57 – a significant difference. In contrast W was not associated with significantly higher bleeding risk at any level of kidney dysfunction.

Comment: These data suggest that anticoagulation with W is safe and is associated with improved clinical outcomes in post MI patients with AF and CKD. These findings are not necessarily generalizable to populations other than patients hospitalized for MI. To what extent these results apply to patients on dialysis is unclear.

Ref: Carrero J.J. et al JAMA 2014 Mar 5; 311: 919.

Winkelmayer W.C and Turakhia M.P. IBID : 913.

1.20 Is partner bereavement associated with excess risk for MI and stroke?.

Many Physicians know of cases in which a patient dies, and then the patient's spouse or partner dies shortly thereafter. 31,000 older adults (mean age 76) whose partners died and were on a UK National primary care data base were compared with 84,000 age and sex matched controls whose partners were alive.

During the **first 30 days** after the loss of a partner, 50 participants in the bereavement group (0.16%) vs 67 in the control group (0.08%) had fatal or non fatal MI or strokes. The relative risk adjusted for CV disease and risk factors was 2.2 in the bereavement group. The risk was lower during the following 60 days (RR 1.35) and was no different during the remainder of the year.

Comment: An elevated risk for death or adverse CV events exist in the first 3 months after the death of a partner.

Ref: Carey I.M. et al JAMA Intern Med 2014 Feb 24; e pub.

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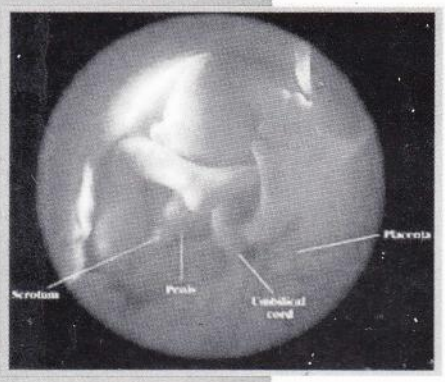

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