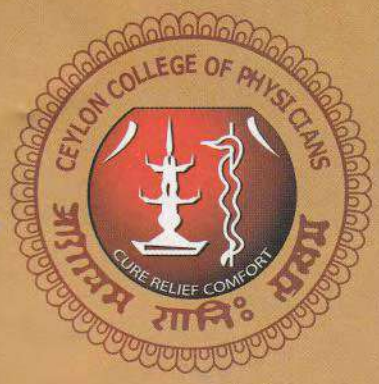

CEYLON COLLEGE OF PHYSICIANS

MEDICINE UPDATE

2016

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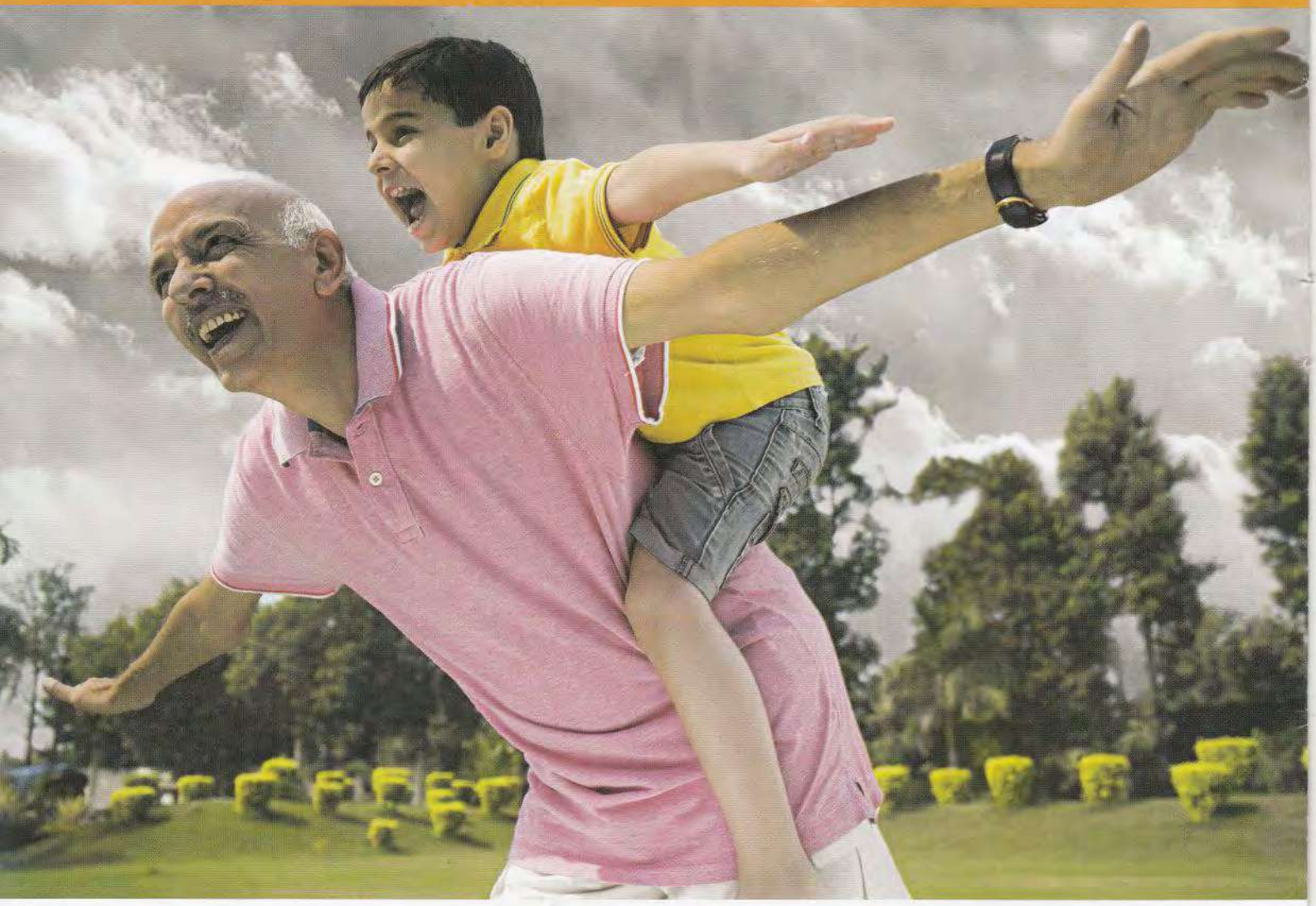

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- Safest DPP-4 inhibitor for Type 2 Diabetes management
- Attenuates progression of Carotid Intima Thickening in Insulin treated patients

4.1 What is the long term prognosis of elderly patients who survive an attack of sepsis?.

960 patients >65yrs who survived an attack of sepsis in hospital were followed up for a period of 31 days to 2 years. This was compared with 777 adults of similar age admitted to hospital without sepsis. In this observational cohort study, sepsis patients had a significant absolute increased mortality of 22% compared with the controls. This excess risk for late death was constant across most sub groups such as sepsis source, age, sex, comorbidities, pre morbid functional limitations and self rated health. These findings suggest that sepsis has long term detrimental effects on human physiology that confer additional risk for late death.

Ref: Prescott H.C. et al BMJ 2016 May 17; 353:I 2375.

4.2 Are antidepressants overprescribed?.

Antidepressant use has increased substantially in recent years. Frequently these are for non depressive indications. A study was undertaken in Quebec, Canada between 2006 and 2015 to examine the indications for antidepressant prescriptions by primary care Physicians. Only 55% were for depressive disorders. 23% were indicated for anxiety or panic disorders. The balance 22% were distributed between insomnia (10%), non specific pain (6%), fibromyalgia (1.5%) and migraine (1.5%). The balance were for either menopause, nicotine dependence, sexual dysfunction or digestive disorders.

Ref: Wong.J. et al JAMA 2016 May 24/31; 315: 2230.

4.3 Does the loss of smell sensation predict a higher mortality?.

The olfactory nerve is the only cranial nerve directly exposed to the environment. Olfactory dysfunction can be an early manifestation of neuro degenerative disease in humans. To determine whether olfactory dysfunction is associated with mortality, researchers prospectively studied 3005 older US adults (age range 50 – 75) for 5 years. Olfactory function for odours was tested with rose, leather, orange, fish and peppermint.

After controlling for confounding variables – anosmic and hyposmic people were approximately 3.4 times and 1.5times resp, more likely to die during the study than normosmic individuals.

Comment: This study identified olfactory function as a powerful predictor of 5 year mortality in the 50 – 75 year group. It is not contended that olfactory dysfunction itself causes the mortality but is only a marker for increased mortality. The mortality may reflect the effect of cumulative toxic environmental exposures which have direct access to the olfactory nerve via the nostrils.

Ref: Pinto J.M. et al PLoSone 2014 Oct 1st; 9:

4.4 Treating Gonococcal (GC) infection in Cephalosporin resistant or Cephalosporin allergic patients.

Cephalosporins have been the only CDC recommended agents for treating patients with GC infection in the US since 2007. 600 patients, mostly men with uncomplicated urogenital or pharyngeal GC infection were evaluated with two combination regimens. The 1st regimen consisted of **Azithromycin** 2 G orally + 240 mg of **gentamycin** i.m. The 2nd regimen consisted of Azithromycin 2G orally + 320mg of **Gemifloxacin**. A microbiologic cure was achieved by all patients who received Azithro + Genta and by all (except 1) who received Azithro + Gemi combination. Both regimes carried a sizable risk for GIT side effects such as nausea and diarrhoea.

Comment: Although both combination regimens were effective, the frequency of side effects is disturbing. They may serve as stop gap measures until better alternatives are available.

Ref: Kirkcaldy R.D. et al Clin.Infect.Dis. 2014 Oct 15; 59: 1083.

4.5 What is best for MRSA infections?.

1) **Vancomycin** – requires iv administration in hospital.

2) **Linezolid** – oral preparation, well absorbed, high anti MRSA activity, but high cost, drug interactions and adverse events.

3) **Cotrimoxazole** – oral preparation, absorbed well, good anti MRSA activity and can be given in combination with or without Rifampicin.

In a non inferiority trial, 150 patients with MRSA infection were randomized to Linezolid 600mg b.i.d or Cotrimoxazole 960mg t.i.d + Rifampicin 600mg once daily for 7 days. 75% of the former and 79% of the latter group achieved clinical cure. 4 adverse drug reactions occurred in the Linezolid group (thrombocytopaenia and hepatotoxicity) vs 9 for the Cotrim (haemato and nephro toxicity) + Rifampicin group (hepato toxicity + drug interactions).

Comment: Cotrim + Rifampicin appears to be equally efficacious, equally well tolerated and cheaper alternative to Linezolid for oral treatment of MRSA infections. Patients on oral regimes should be monitored closely for adverse events.

Ref: Harbarth S. et al J.Antimicrob.Chemother. 2014 Sept 10; e pub.

4.6 Polyneuropathy with fluroquinolones.

The FDA recently required a warning on sale leaflets about the risk of polyneuropathy associated with these drugs. To quantify this risk, researchers identified 6,226 patients with incident polyneuropathy and 24,904 (1:4) age and diseased duration matched controls. They compared fluroquinolone use in each group. Any peripheral neuropathy within 14 days was labelled as "current users" and between 14 days and one year as "past users". After adjustment for potential confounders, the relative risk for polyneuropathy for current users was 1.83.

Comment: Since fluroquinolones are used widely, the almost two fold higher risk for polyneuropathy may be an important and often unrecognized cause for polyneuropathy. This drug induced neuropathy is usually acute, affects sensory fibres more than motor fibres and might not be fully reversible after drug discontinuation.

Ref: Etminan M. et al Neurology 2014 Sept 30; 83: 1261.

4.7 Orthostatic hypotension – some aspects.

When old people fall, the cause may be balance related (trips or slips) or unexplained falls. These are usually preceded by dizziness or feeling faint or by no warning symptoms. Orthostatic hypotension is defined as a drop of **>20mmHg of systolic BP or >10mmHg in diastolic BP** during the first 3 minutes of a 70 degrees tilt test.

In a study of 529 community dwelling Australians, 85% of fallers had balance related falls and 15% unexplained falls. On multivariate analysis, the only baseline variables that predicted unexplained falling were

1) Orthostatic hypotension.

2) Depressive symptoms.

Comment: Orthostatic hypotension should be suspected when there are unexplained falls in the elderly. Seated / supine and standing BPs should be recorded – the latter immediately on standing, at 30 seconds and 180 seconds later. The onset at 180 seconds explains some of the so called cases of "delayed" orthostatic hypotension. The link between depression and orthostatic hypotension is unexplained.

Ref: Menant J.C. et al J.Am.Geriatr. Soc. 2016 May ; 64: 1073.

4.8 New Antibiotics.

The Infectious Disease Society of America (IDSA) sponsored an initiative in 2010 calling for the release of 10 new antibiotics by the year 2020 (10 by 20). Since 2010, 8 new antibiotics have been approved by FDA.

a) For skin infections – Ceftaroline, Dalmavancin, Tedizolid and Oritavancin.

b) For complicated intra abdominal and urinary tract infections – Ceftolozane – Tazodactam and Ceftazidime – Avibactam.

c) For Clostridium difficile infections – Fidaxomicin.

d) For drug resistant TB – Bedaquiline.

e) Community acquired pneumonia – Ceftaroline.

Almost all the drug approvals were based on **non inferiority trials** ("me too drugs") in fewer than 1,000 patients. Prices for seven of the new agents are considerably higher than their comparator drugs, ranging from prices twice as high to almost 6,000 times higher. The only exception is **Tedizolid** which costs about the same as its comparator Linezolid.

Comment: It would be preferable to have **Superiority trials** against standard antibiotics to obtain value for money.

Ref: Deak D. et al Ann.Intern.Med. 2016 May 31; e pub.

4.9 Does increased leisure time physical activity decrease the incidence of cancer?.

Risk for **colon, breast and endometrial cancer** are reduced with physical activity. Researchers pooled the results of 12 prospective cohort studies that involved 1.44 million participants (median age 59yrs). It was found that there was a significant relative reduction for 13 cancers. These values were:

Oesophageal adeno CA – 42%.

Renal CA - 23%.

Myeloid leukaemia – 20%.

Overall risk reduction for **any CA** – 7%.

There was an increased relative risk for malignant melanoma (27%) and prostate cancer 5%.

Comment: These findings do not prove cause and effect. Nevertheless increase in leisure time physical activity is recommended although sunlight exposure may explain the findings of excess malignant melanoma. Suitable head covering is recommended for white Caucasians when involved in outdoor physical activity during summer.

Ref: Moore S.C. et al JAMA Intern Med. 2016 June 1; 176: 816.

4.10 TNF α inhibitors vs Rituximab for rheumatoid arthritis – Which is better?.

Biologic agents are used to treat patients with rheumatoid arthritis who do not respond completely to standard disease modifying agents (DMAs) such as Sulphasalazine, Hydroxychloroquine, Methotrexate and Leflunomide or combinations of these.

Rituximab and TNF inhibitors such as Etanercept and Adalimumab were compared in 295 patients with sero positive RA who had not responded to DMAs.

At 1 year, Rituximab therapy was non inferior to anti TNF therapy. 32% on TNF inhibitors crossed over to Rituximab while only 19% on Rituximab crossed over to TNF inhibitors. The health related costs for Rituximab was 20% less than for TNF inhibitors.

Comment: Rituximab was as effective as a TNF inhibitor and was more cost effective. It must be remembered however that there is a black box warning about progressive multifocal encephalopathy with Rituximab. At present, Rituximab is reserved for RA patients who have not improved with TNF inhibitors.

Ref: Porter D. et al Lancet 2016 May 16; e pub.

4.11 Which is better for osteoarthritis (OA) of the knees – Intra articular steroid (IAS) or intra articular Hyaluronic acid (IAHA)?.

A recent meta analysis suggested that the efficacy of IAHA for knee OA is marginal at best. Many patients report improvement but placebo effects account for much of that improvement.

In a DBR trial, 110 patients with painful knee OA each received a single injection of HA or Triamcinolone acetonide. Compared with baseline, symptoms improved in both groups through 6 months of follow up. At 2 weeks, (early follow up), the extent of improvement in pain and function was significantly greater with Triamcinolone than with IAHA, but differences between the 2 groups was not significant for the rest of the follow up period.

Comment: Usually IAHA is given repeatedly at weekly intervals for 3 weeks. However the cost is extraordinary, varying from Rs.30,000 to Rs. 140,000 per dose, compared with Rs. 400 for IAS. The American Academy of Orthopaedic Surgeons advises against the use of IAHA for knee OA.

Ref: Tammachote N. et al J.Bone.Joint. Surg Am.2016 June 1st; 98:885.

4.12 Prevention of obesity – new research.

In humans, fat cells are mainly white and **store fat** and brown fat which is found in smaller amounts **burn fat** (consume more energy).If white fat can be converted to brown fat, this would result in increased energy expenditure which will result in loss of weight. It has now been found that in vitro stimulation of white fat by either **Rosiglitazone** or a **Prostaglandin E2 analogue** can convert white fat to brown fat. These two agents can also stimulate angiogenesis and attract the new blood supplies that the newly created brown fat cells need.

A multi Institutional team created nano particles with two properties. The 1st contained either Rosiglitazone or the Prostaglandin E2 analogue. The 2nd - was that they adhered selectively to the endothelium of the vasculature within white fat, which in obese mice helped to convert white fat into brown fat. This led to decrease of cholesterol, Triglycerides and insulin levels. They also inhibited weight gain. These results in mice, if duplicated in humans, could result in decrease of the risk factors which constitute the metabolic syndrome. The caveat is that Rosiglitazone and its family members are known to increase weight. Do humans and mice act differently to glitazones?.

Ref: Xue Y. et al Proc.Natl.Acad.Sci.USA 2016 May 17; 113: 5552.

4.13 Can oral therapy be initiated for new onset Type 2DM patients with blood glucose levels above 300mg/dl?.

ADA recommends insulin therapy for such patients, but these high blood sugar levels may have been due to a temporary rise, secondary to intake of high sugar content liquids induced by thirst. If these liquids are not taken, the blood sugar could fall to more moderate levels.

Researchers enrolled 100 adults with newly diagnosed Type 2DM with blood glucose levels of 300 to 450mg/dl and **no evidence of ketoacidosis or hyperosmolar symptoms.** The regimen used was either glipizide ER 10mg once daily or a combination of Saxagliptin 5mg + Metformin 2,000mg once daily. At initiation, the mean glucose level was 342mg/dl and the mean A1C was 11%. At 12 weeks, glycaemic control improved substantially in nearly all patients in both groups. The mean blood glucose level was 130mg/dl and the mean A1C 7%. Prevalence of hypoglycaemia (RBS <70mg/dl) was greater with Glipizide than with the combination of Saxa + Met (24% vs 8%). Severe hypoglycaemia (<50mg/dl) did not occur in either group.

Comment: Oral therapy is an acceptable option for clinically stable, newly diagnosed Type 2DM patients with blood glucose levels between 300 and 450mg/dl - provided they are not ketoacidotic or exhibit hyperosmolar symptoms. All these patients were on standard diabetic diets and supervised physical activity. Glipizide is cheap and readily available while the combination of Saxa + Met (Kombiglyze XR) which is available in the USA costs about US$5,000 (Rs.700,000/=) annually.

Ref: Amblee A. et al JCEM 2016 June; 101: 2528.

4.14 Is Empagliflozin (E) safe in renal disease?.

A recent placebo controlled randomized trial involving 7,000 patients with long standing Type 2DM and documented cardiovascular disease, were given E – a SGLT2 inhibitor (secondary cardiovascular disease prevention trial). It was found that it lowered the incidence of MI, stroke and CV related death by 1.6 percentage points during 3 years (NEJ Med 2015;373:2117). Now, the researchers present the renal outcomes.

The composite renal outcome of incident or worsening nephropathy occurred in significantly fewer E patients than placebo (13% vs 19%). The 4 components of the renal outcomes were progression to macroalbuminuria, doubling of serum creatinine levels + eGFR <45ml/mt, initiation of renal replacement therapy and death from renal disease. All these components were improved by E. E however did not prevent the onset of microalbuminuria in patients who were normoalbuminuric at the beginning of the trial. The most benefit was seen in the progression to macroalbuminuria.

Comment: These were all high risk patients who had been previously diagnosed with cardiovascular disease. Surprisingly, retinopathy which is also a microvascular disease did not benefit although it improved

renal outcomes.

Ref: Wanner C. et al NEJ Med 2016 June 14; e pub.

4.15 Does Liraglutide decrease cardiovascular events (CVEs) in long standing Type 2DM?.

In a randomized trial, researchers enrolled 9,340 Type 2 DM patients who fell into one of 2groups.

1. 50 or older who had known CV disease (81%) – secondary Prevention Trial.
2. 60 or older with at least 1 CV risk factor (19%) – Primary Prevention Trial.

Patients received either Liraglutide 1.8mg/d sc or placebo in addition to their previous diabetes drugs – either Metformin, Sulphonylurea or insulin alone or in combination. Mean age was 64, mean duration of diabetes 13 years and mean A1C 8.1%. Median follow up was 3.8 years. The primary composite outcome was CV related death + non fatal MI + non fatal stroke. This occurred significantly less often in the Lira group vs placebo (8.2% vs 9.6%). Severe hypoglycaemia was higher in the placebo group probably because insulin or Sulphonylurea had to be added during the trial. However, acute gall stone disease was more common with Liraglutide. A broadly defined renal end point was new onset macroalbuminuria + double serum creatinine level + end stage renal disease. This occurred less commonly with Lira (5.7% vs 7.2%). A retinopathy end point was similar in the 2 groups. By the end of the trial, the Lira group had an A1C 0.4% less than the control group.

Comment: Older patients with long standing diabetes with add on Liraglutide had a 2% reduction in a composite CV end point during about 4 years of treatment. This difference may be due to a beneficial effect of Lira or detrimental effects of added drugs in the placebo group. Liraglutide 1.8mg/d is three times the starting dose of 0.6mg/d. It is prohibitively expensive, and could be used only in the small coterie who can afford and withstand the GIT side effects. Also this study was Industry sponsored and included 11 Academic Investigators and 4 employees of the sponsor.

Ref: Marso S.P. et al NEJ Med. 2016 June 13; e pub

Ingelfinger J.R. and Rosen C.J. IBID ; e pub.

4.16 Does the microbiome promote the metabolic syndrome and obesity?.

Certain phyla of gut bacteria are more common in patients with metabolic syndrome and obesity. Large numbers of Firmicutes and small numbers of Bacteroidetes lead to glucose intolerance and obesity in rats. This bacterial milieu is associated with a high concentration of the short chain fatty acid, **acetate**, in the gut. High fat diets promote this bacterial milieu and increases the production of acetate. The acetate reaches the brain via the blood stream and stimulates the parasympathetic nervous system to increase Beta cell production of insulin and also increases the production of Ghrelin – the "appetite hormone" in the stomach. This in combination with the increased insulin levels led to weight gain. Eliminating gut bacteria with antibiotics or interrupting parasympathetic signals to the gut either by vagotomy or atropine, eliminated glucose intolerance and weight gain.

Comment: If these results from rat's studies are replicated in humans, 3 new targets for preventing metabolic syndrome and obesity have been identified.

1.Modification of the gut microbiome.

2.Lowering acetate production in the gut.

3.Parasympathetic blockade.

Ref: Perry R.J. et al Nature 2016 June 9; 534: 213.

Trajkovski M. and Wolheim C.B. IBID : 185.

4.17 In non valvular atrial fibrillation (AF), which is better – Warfarin or Apixaban?.

Warfarin exhibits a huge number of drug interactions. What about Apixaban - which is a new anticoagulant drug, similar in action to Rivoroxaban and Dabigatran?. The ARISTOTLE trial was a randomized study in which 18,000 people with AF received Apixaban or Warfarin. Apixaban was found to be superior in preventing stroke and systemic embolism and had less major bleeding and a lowered 2 year all cause mortality. In a post hoc analyses of the ARISTOTLE data, researchers determined whether the treatment effects of Warfarin vs Apixaban differed with increasing numbers of concurrent drug treatments. Participants were grouped according to the number of concurrent drugs used at baseline viz 0 – 5, 6 – 8 and >9. The risk for stroke, systemic embolism, major bleeding and death was found to be increased significantly with higher number of concurrent drugs used. Apixaban conferred larger risk reduction for stroke or systemic embolism and all cause death than with Warfarin – regardless of the number of concurrent drugs used. Bleeding risk was also less with Apixaban, regardless of the number of concurrent drugs used.

Comment: Apixaban was superior to Warfarin in preventing stroke or systemic embolism and all cause death – regardless of the number of concurrent drugs used, and it was at least as safe as Warfarin in regard to major bleeding.

Ref: Focks J.J. et al BMJ 2016 June 15; 353: I 2868.

4.18 A new treatment for rheumatoid arthritis (RA) – Vagus nerve stimulation (VNS).

VNS is an established therapy for epilepsy. It is also known to diminish inflammatory cytokine production such as TNF, IL -6 and IL – 1β. Can it benefit patients with RA?.

Researchers implanted VNS devices in 2 cohorts of RA patients.

1. 7 patients with active disease despite methotrexate therapy and no past treatment with biologics.

2. 10 patients with severe RA who had not responded to combination methotrexate + biologics.

On day 42 (6 weeks), 57% of patients in the 1st cohort and 30% of patients in the 2nd cohort had achieved a 50% response by the American College of Rheumatology criteria. No serious adverse effects were reported.

Comment: These findings should promote a study of the mechanism by which VNS improves RA. Hopefully this will lead to less invasive treatments that can achieve the same results. The understanding of the communication between the nervous and immune systems can point to the discovery of novel therapies in the future.

Ref: Koopman F.A. et al Proc.Natl.Acad.Sci.USA 2016 July 19; 113:8284.

4.19 Spondyloarthropathy – some aspects.

Spondyloarthritis includes a broad group of inflammatory conditions, with ankylosing spondylitis being the most common.They may be divided into 2 groups.

1. Spondyloarthritis without radiographic changes but with either the HLA B27 haplotype + more than two defined clinical features of inflammatory back disease **(clinical arm criteria).**
2. Spondyloarthritis with radiographic changes on radiographs or MRI which show sacroiliitis + at least one clinical feature **(imaging arm criteria)**.

How many patients with the 1st type go on to Type 2 and how long does it take to develop stage 2?.

Out of 1,142 patients who had pelvic MRIs for various reasons, 18 (1.5%)were identified as meeting the image arm criteria for active sacroiliitis. Of 1009 patients with HLA B27 positivity, 65 (6.4%) met the clinical arm criteria. Mean follow up was 11 years. Patients in the clinical arm progressed more slowly to ankylosing spondylitis (median time 6.8 years) than with patients with pre existing MRI abnormalities (median time 4.8 years). Progression to ankylosing spondylitis was also more common in the imaging arm vs the clinical arm (28% vs 17%).

Comment: Patients with non radiographic spondyloarthritis are less likely than patients with radiographic sacroiliitis to progress to ankylosing spondylitis and those who do will progress slower.

Ref: Wang R. et al Arthritis Rheumatol 2016 June ; 68:1415.

4.20 Can primary unexplained infertility be due to a viral infection?.

Italian investigators studied 30 women with unexplained primary infertility and a control group of 36 age matched women with at least one successful pregnancy.

Half of women with primary infertility (but no controls) harboured **Human Herpes Virus 6A** (HHV6A) in endometrial cells obtained on curettage. The concentrations of the virus were also substantial and HHV6A proteins were also detected by immunohistochemistry. Different types of natural killer lymphocytes were also found as well as different immune mediators. Finally, infertile women had higher levels of circulating oestradiol than did controls.

Comment: This study showed that women with unexplained infertility with HHV6A was found in almost 50%. This virus may have been accrued during childhood or early adulthood. However, because some antivirals can successfully eradicate HHV6A, we might have a new approach to treating some women with primary unexplained infertility.

Ref: Marci R. et al PLoS one 2016 July 1st; 11: e 0158304.

Compiled by: *- Dr Henry N. Rajaratnam*

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LDL-C	≥ 50% Reduction achieved	30% to < 50% Reduction achieved
Clinical ASCVD*	Age ≤ 75	Age > 75 or If not candidate for HIS**
Diabetes type I or II Age 40-75 years	Yes (10 year ASCVD risk ≥ 7.5%***)	Yes

* Atherosclerotic cardiovascular disease.
** High Intensity Statin.
*** ASCVD 10 year risk calculator.

This approach supports the use of statins to prevent both nonfatal and fatal ASCVD events.[1]

1. *Adapted from: Stone NJ, et al. 2013 ACC/AHA Blood Cholesterol Guideline*

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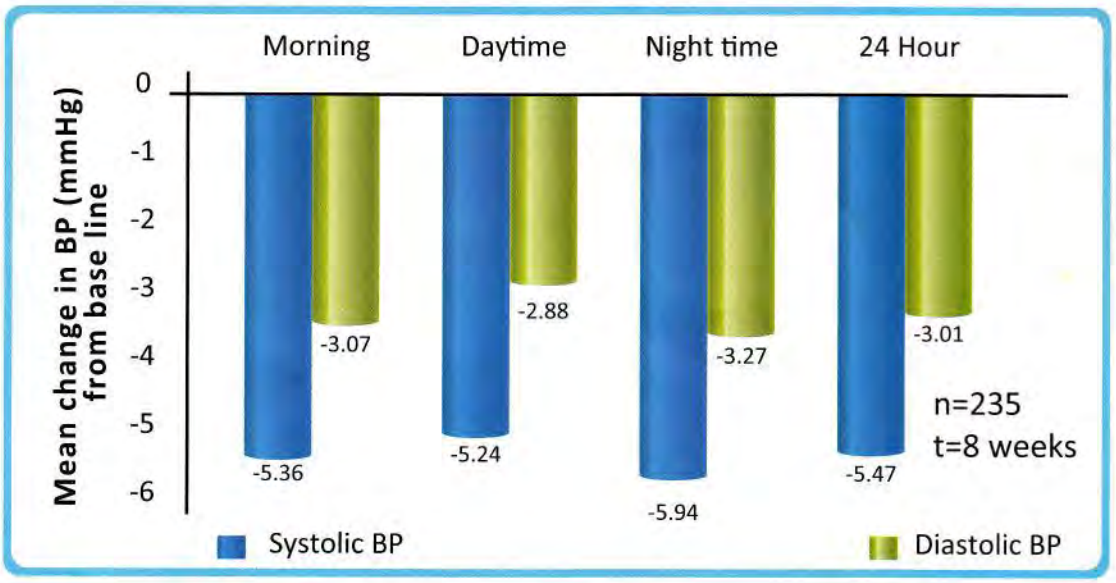

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Hypertension Research (2012): 1-6.

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