CEYLON COLLEGE OF PHYSICIANS

MEDICINE UPDATE

2018

Vol : 29 No : 01

Performs...

When needed most!

- Enhanced BP reductions with combination therapy.
- Better Metabolic Control

1.1 Do patients on cancer immunotherapy agents develop new onset rheumatic symptoms?.

Immune check point inhibitors (ICIs) such as Ipilimumab, Nivolumab and Pembrolizumab are increasingly being used to treat advanced cancers. Immune related adverse events include

a) Life threatening pneumonitis.
b) Colitis.
c) Autoimmune thyroiditis.
d) Hypophysitis.
e) Vitiligo.
f) Inflammatory arthritis.
g) Sicca symptoms.
h) Interstitial nephritis.
i) Myositis.
j) Polymyalgia rheumatica.

None of the inflammatory arthritis patients had positive rheumatoid factors or anti CCP antibodies. Of these arthritis patients, many required high dose steroids and some had continuing synovitis after stopping ICI therapy. Sudden onset sicca syndrome patients had severe dry mouth with salivary hypofunction. The colitis, pneumonitis and interstitial nephritis resolved with steroid therapy.

Ref:Cappelli L.C. et al Ann. Rheum. Dis. 2017 Jan; 76: 43.

1.2 Gestational Diabetes Mellitus (GDM) – some aspects.

a) **Terminology** - The WHO in 2014 changed the terminology as follows:

1. Hyperglycaemia in pregnancy (HIP) – all women with an abnormal blood sugar level at any stage of pregnancy.

2. Diabetes in Pregnancy (DIP) – Hyperglycaemia during 1st 24 weeks.

3. Gestational Diabetes Mellitus (GDM) – Hyperglycaemia from week 24 to end of pregnancy.

b) **Diet**: Low carbohydrate diet with higher intake of protein and fat from animal sources increase the risk of developing GDM. Similarly, high consumption of cholesterol (>300mg/d), Haem iron (>1.1mg/d) red and processed meat (>1 serving per day) and eggs (>7 per week) have a higher risk of GDM. On the other hand, a dietary pattern rich in fruit, vegetables, whole grains and fish (while low in red and processed meat, refined grains and high fat dairy products) were found to be beneficial.

c) **Effects on the next generation**: Children of mothers with GDM have an increased risk for childhood obesity, early onset Type 2DM and female offspring of mothers with GDM may have increased risk of GDM themselves.

Ref:Moses R.G. and Cefalu W.T Diabetes Care 2016 Jan; 39 (1): 13 – 16.

Shoenaker D.A.J.M et al Diabetes Care 2016 Jan ; 39(1): 16 – 23.

1.3 Life style intervention for Gestational Diabetes Mellitus (GDM).

Mothers at risk for GDM include those with :

a) BMI >30.
b) Past history of GDM.
c) Family history of diabetes.
d) Past history of macrosomia(baby>3.5Kg).

These mothers should be supervised individually and in groups atleast 3 times during the pregnancy regards diet and exercise. The diet is focussed on optimizing consumption of vegetables, fruits and berries, whole grain products rich in fiber, low fat dairy products, vegetablefats high in unsaturated fatty acids, fish, low fat meat products and lower intake of sugar rich foods.

Exercise – a minimum of 150 mts of moderate intensity of physical activity per week is the goal. Individualization of possible exercises and duration, sometimes broken up twice or thrice a day is to be encouraged. These life style modifications can reduce GDM by about 39%. Exercise is begun as early as possible in gestation and continued throughout till delivery. If antenatal contractions or if the physical state precludes exercise, then focus must be on dietary modification.

Ref:Koivusalo S.B. et al Diabetes Care 2016 Jan ; 39 (1): 24 – 30.

1.4 Glucokinase (GCK) Maturity onset Diabetes of the Young (MODY) presenting as GDM.

MODY is a form of diabetes which is transmitted as an autosomal dominant disorder. This disorder should be suspected when diabetes presents in an individual below 25 years, with 3 generations of diabetes and a BMI < 25.

GCK –MODY is a mild form of diabetes, usually subclinical and may be 1st detected during routine screening for gestational diabetes. It constitutes between 0.5 – 1.0% of all cases of GDM. It does not require intensive glycaemic control during pregnancy – in fact this effort may adversely affect the foetus. It should be suspected if the fasting glucose pre pregnancy is between 5.5 – 8.0 mmol/l (99 – 144mg/dl). Also if the increment between the fasting and the 2 hour glucose in a GTT is less than 4.6mmol = 80mg/dl. During pregnancy, the pregnancy specific screening criteria is a fasting plasma glucose > 99mg/dl = 5.5mmol/l on antepartum OGTT and a pre pregnancy BMI <25. If these criteria are met, then a gene testing for a GCK –MODY is warranted.

Ref:Rudland V.L. et al Diabetes Care 2016 Jan ; 39 (1): 50 – 52.

1.5 Should ACE inhibitors or ARBs be withheld just before non cardiac surgery?.

In 2014, The American College of Cardiology and the American Heart Association guidelines recommended continuation of ACEIs or ARBs perioperatively (Circulation 2014; 130:e278). Researchers addressed this problem by looking at 4,802 who use ACEIs and ARBs routinely. Patients were > 45 yrs of age. 74% took the drug during the 24 hours before surgery. The balance 26% withheld the drug before surgery.

The primary composite outcome was death + stroke or myocardial injury indicated by a perioperative rise in troponin levels. This outcome occurred in 12% who with-held the drugs and in 12.9% of those who continued the drugs. The relative risk for this outcome was significantly lower in the drug with-held group(RR = 0.82; P = 0.01). The incidence of intraoperative hypotension was also lower in the drug withheld group (23.3% vs 28.6%) (RR =0.80 ; P < 0.001).

Comment: With-holding ACEIs and ARBs before non cardiacsurgery appears reasonable. The findings may be explained by the fact that anaesthesia blunts the sympathetic vascular tone , thereby increasing the reliance on the renin- angiotensin system in maintaining the blood pressure intraoperatively. Giving ACEIs or ARBs would compromise this effect.

Ref:Roshanov P.S. et al Anaesthesiology 2017 Jan; 126:16.

1.6 Incidental interstitial lung disease – does it require investigation?.

Sometimes a CT scan of the chest is done to evaluate pulmonary symptoms or for other reasons. This may reveal interstitial lung abnormalities. To shed light on the natural history and possible significance of such findings, researchers analysed paired chest CT scans done about 6 years apart, in 1867 mostly middle aged participants in the Framingham Heart study.

155 of these participants (8%) had interstitial lung abnormalities – 53 on the 1st CT scan and 102 on the 2nd CT scan. Among the 53 who had disease on the 1st CT scan, 16 had radiographic progression on the 2ndscan(30%). Disease progression was associated with older age and with a geno type **MUC5B promoter polymorphism,** which is known to be associated with idiopathic pulmonary fibrosis. Those who had progression of disease also had a decline in forced vital capacity and excess mortality over 4 years of follow up.

Comment: Incidental findings of interstitial lung abnormalities are not rare when CT scans of the chest are performed. These radiographic abnormalities might be an early manifestation of interstitial pulmonary fibrosis.

Ref:Araki T et al Am.J.Respir.Crit.Care Med. 2016 Dec 15; 194:1514.

Wells A.U. and Kokosi M.A. IBID : 1445.

1.7 Is medical treatment effective for large ureteral stones?.

Alpha blockers such as Tamsulosin, Doxazosin and Terazosin have been used to promote passage of ureteral stones (kidney stones that have migrated into the ureters). A meta analysis of 55 randomized controlled trials to determine the efficacy and safety of Alpha blockers, in treating 6,000 people (mean age 40) with ureteral stones (mean size 5.7mm) was undertaken.

Tamsulosin was the commonest Alpha blocker used. Control groups received no specific treatment to promote stone passage. The following results were seen after a follow up of 1 – 6 weeks.

a) Stone passage was successful in **75 %** with Alpha blockers and 50% in control groups.
b) Benefit with Alpha blockers wasw more evident for large stones.
c) Mean time for stone passage was shorter with Alpha blockers – **9** vs 13 days.
d) Fewer pain episodes were seen with Alpha blockers.
e) Surgical intervention and hospitalization was lower with Alpha blockers.
f) The effect of Alpha blockers was independent of stone location.

Comment: Alpha blocker therapy (also known as Medical expulsive therapy) was effective in patients with large ureteral stones. 4 patients would need to be treated with Alpha blockers for 1 patient to benefit.

Ref:Hollingsworth J.M. et al BMJ 2016 Dec1; 355: i 6112.

1.8 Is continuous infusion of Beta – Lactams (BLs) more effective than bolus doses in septic patients?.

Maximum bactericidal activity of BLs is dependent on maintaining drug concentrations above the minimum inhibitory concentration of the targeted organisms. Continuous infusion of antibiotics could theoretically offer superior outcomes compared with intermittent dosing. Is this true during medical treatment of sepsis?.

A meta analysis of 632 patients from 3 randomized trials in which continuous infusion (CI) was compared with intermittent dosing (ID) strategy in critically ill patients with sepsis or shock was undertaken. CI significantly lowered 30 day mortality (RR 0.73). Also it improved clinical cure rates. Number needed to treat for mortality was 15 and for clinical cure was 11. Piperacillin – Tazobactam specifically was superior with CI compared to ID for lowering mortality (RR 0.63, NNT 11) and improved clinical cure rate (32% , NNT 8) compared to ID.

Comment: This meta analysis provides convincing evidence that CI of Beta – Lactams especially Piperacillin – Tazobactam improves outcomes for septic patients.

Ref:Roberts J.A. et al Am.J.Respir, Crit. Care.Med 2016 Sept 15; 194: 681.

1.9 Can Marijuana be used for medical purposes?.

Many States in the US have approved Marijuana (Cannabis) for medical purposes. Marijuana has analgesic effects. Could there be more harmful long term effects when used for treatment of chronic pain?.

"Medicalization" is often a gambit to legalize recreational use to take the edge off non medical distress. Adverse effects with regular marijuana use which have been reported are

a) Harm to the adolescent brain.

b) Less cortical grey matter in adults.

c) Diminished cognitive function.

d) Increased risk for psychosis.

e) Increased risk for vehicular accidents.

Chronic users had

1. Higher rates of anxiety disorder.
2. Higher rates of perceived poor health and disability.
3. Lower use of alcohol, non medical use of stimulants and analgesics.
4. Greater rates of connective tissue and skeletal disease.
5. Greater incidence of cancer.

Rational use of marijuana can be canvassed for

a) Cancer sufferers with nausea and pain.

b) Chronic pain sufferers unable to wean themselves from prescription opioids.

c) For acute anxiety states.

Comment: Solid research is needed to clearly identify to what extent marijuana has medical benefits. Standard medical approaches must be pursued before considering medical use of marijuana. The long term effects are unpredictable.

Ref:Roy – Byrne P NEJM Journal Watch Psychiatry.

1.10 Are very low LDL cholesterol levels safe?.

Recently new drugs have been introduced for the treatment of resistant hyperlipidaemias ie resistant to either statins on maximum dose or fibrates alone or in combination. These are **Evolocumab**and **Alirocumab .**These are called the PCSK -9 inhibitors and are given by injection. Their use can result in very low LDLC levels.

14 trials in an Industry sponsored pooled analysis with Alirocumab was undertaken. Treatment duration ranged from 8 – 104 weeks. Number treated was 3,340. 25% of these achieved a LDLC levels of <25mg/dl. 9% achieved levels less than 15mg/dl. The normal target for patients without prior Cerebro vascular disease (CVD) is 100mg/dl and for those with prior CVD is 70mg/dl. The rates of adverse events were similar for both 25mg/dl and 15mg/dl. Specific adverse events such as diabetes, neurological or neurocognitive defects were not different between those with <25mg/dl and those with higher levels. However, **rates of incident cataracts** were significantly higher in those with LDLC levels <25mg/dl.

A 2nd meta analyses of studies with atleast 6 months of follow up also showed no significant difference in serious adverse events. However, sub group analysis of the larger outcome studies suggested excess incidence of **neurocognitive adverse events** in the very low cholesterol group. The overall incidence was very low – less than 1%.

Comment: In the 1st analysis, very low LDLC levels were not associated with excess adverse events, except for a higher incidence of cataracts. This finding has biological plausibility, since the lens synthesises cholesterol for structure and clarity.

In the 2nd analysis, neurocognitive adverse events in sub group analysis only was noted. However, the low incidence overall (<1%) and the unknown type and severity of these adverse events are unknown. These results are generally reassuring. However, long term monitoring and assessment of neurocognitive adverse events will be needed before the safety of very low LDLC by PCSK9 inhibitors are fully assessed. These very low levels are usually not observed during statin use. Therefore "lower the better" for LDLC levels with statins is permissible.

Ref:Robinson J.G. et al J.Am.Coll. Cardiol. 2017 Feb 07; 69:471.

Everett B.M. IBID : 483.

Khan A.R. et al Circ. Cardiovasc. Qual. Outcomes 2017 Jan; 10:e 003153.

1.11 Can Cancer be diagnosed without a tissue biopsy but by blood examination alone?.

Cancers shed cells into the blood stream, often at an early stage. If these cells are detected in the blood, it would be possible to identify primary tumours even when they are very small. This may be called a

"liquid biopsy". However the number of circulating tumour cells signal may be dwarfed by the signals of the huge number of blood cells. This is called "the noise".

Recently, a technology for identifying circulating hepatocellular carcinoma (HCC) cells has been developed. A set of 10 mRNAs for genes expressed in HCC cells and a technique by digital PCR helps to detect lower levels of signals. The "noise" may be reduced without altering the mRNA within circulating tumour cells by depleting the leucocytes. This technology was more accurate than Alpha foeto protein estimation, which is presently the standard investigation for detection of HCC apart from biopsy.

Ref:Kalinich M. et al Proc.Natl.Acad.Sci.USA 2017Jan 31; 114: 1123.

1.13 How should Epinephrine be given for anaphylaxis in patients older than 70 – intramuscular or intravenous?.

Epinephrine (Adrenalin) is given **intramuscularly** and rapidly reverses the effects of allergy and anaphylaxis. It can be life saving. Because of its vasoconstrictive effects, its use in elders may be withheld on the basis that it may lead to cardiac complications. Is this true ?

492 patients with anaphylaxis were given Epinephrine. Of these 16% were older than 70 years. 5 patients had cardiac complications which were minor and included asymptomatic ST depression, spontaneously resolving ventricular tachycardia, atrial fibrillation and chest discomfort. Complications were more likely with **iv than im** (43% vs 1%).

Comment: The normal dose of 0.3 to 0.5 mg **im**of **1/1,000** Epinephrine should be given to a patient with anaphylaxis, regardless of age ieim Epinephrine is 1st line treatment. **IV** Epinephrine in a dilution of **1/10,000** is reserved for refractory hypotension in anaphylaxis.

Ref:Kawano T et al Resuscitation 2017 March; 112: 53.

1.14. Antibiotics for acne.

Current guidelines recommend that a course of oral antibiotic therapy for patients with acne should be limited to **3 - 6 months** especially if they are moderate or severe. **Doxycycline** 100 mg b.i.d is a common prescription. Concomitant topical retinoid therapy in the form of **Tretinoin, Adapalene and Tazarotene** are also recommended. These are not given if the patient is pregnant or if desiring a pregnancy, because of teratogenic effects. Other topical therapies include **Benzoylperoxide** and topical antibiotics such as **Erythromycin cream**. Topical retinoids (unlike other agents) target the primary lesion of acne – Comedones.

Ref:Barbieri J.S. et al J.Am.Acad. Dermatol 2016 Dec; 75:1142.

1.15 Are ACE inhibitors (ACEIs) or Angiotensin Receptor Blockers (ARBs) of any value in treating stable coronary artery disease (CAD)?.

Current guidelines recommend ACEIs or ARBs for all patients with stable CAD and any one of the following conditions viz hypertension, diabetes, LV ejection fraction <40% or chronic kidney disease. To evaluate this recommendation, researchers conducted a metaanalysis of 24 randomized trials (62,000 patients, average follow up 3.2 years) in which these drugs were used compared with placebo or active controls. These patients had stable CAD without heart failure. The active controls used were calcium channel blockers, thiazide diuretics or "conventional treatment".

ACEIs or ARBs significantly lowered risk for the individual end points viz

a)All cause mortality.

b) CV mortality.

c) MI.

d) Stroke.

e) Heart failure.

This was true when they were compared with placebo but not when compared with active controls. The benefits seen against placebo were independent of baseline systolic BP. Compared with active control drugs, the benefit was not seen regardless of the systolic BP.

Comment: This meta analysis does not support the recommendation for routine use of ACEIs or ARBs in stable CAD. However, these results do not apply to patients with low LV ejection fractions <40% or those with chronic kidney disease.

Ref: Bangalore S. et al BMJ 2017 Jan 19; 356: j4.

1.16 Does Chondroitin Sulphate (CS) and Glucosamine Sulphate (GS) benefit patients with osteoarthritis (OA)?.

Physicians and GPs continue to use CS and GS for the treatment of knee OA in spite of lack of compelling evidence of benefit. A previous trial (GAIT) failed to demonstrate improvement in joint pain significantly with the use of these drugs in the entire cohort. However, sub analysis of patients with moderate to severe knee OA showed some benefit

(NEJM 2006; 354: 795).

In a new trial, once daily combination of CS/GS in a dose of 1,200mg/1,500 mg was compared with placebo in 164 patients with moderate to severe OA. After 6 months of treatment, mean pain scores decreased from baseline by 33% in the placebo group compared with 19% in the CS/GS group. This was a significant difference in favour of placebo.

Comment: In this study, patients with moderate to severe knee OA who received CS/GS had **inferior** outcomes to patients who received placebo. CS and GS are relatively expensive drugs and even though side effects are negligible, prescription of these drugs for knee OA cannot be recommended.

Ref:Roman – Blas J.A. et al ArthitisRheumatol 2017 Jan; 69: 77.

1.17 Managing stings by insects.

Stinging byHymenoptera order insects such as hornets, wasps, yellow jackets, honey bees and fire ants can cause systemic reactions in about 3% of people bitten. In patients with severe systemic reactions, 50% will experience anaphylaxis after future stings. Administration of **venom immunotherapy (VIT)**can reduce this risk to <5%.

The American Academy of Allergy and American College of Allergy, Asthma and Immunology recommend the following:

a) Large **local reactions** can be treated symptomatically and possibly with a short course of oral steroids. VIT is not indicated.

b) Reaction with urticarial and peripheral angioedema need only oral therapy and do not need VIT.

c) Measuring baseline **serum tryptase** can identify patients at high risk for anaphylaxis (VIT indicated).

d) Patients with **mastocytosis** also have high risk for anaphylaxis (VIT indicated).

e) VIT should be continued for 5 years when indicated.

f) Epinephrine injection and medical identification should be readily available for patients at high risk.

g) **Beta blockers and ACE inhibitors** heighten risk for serious adverse events from stings or VIT and should be avoided.

h) Those requiring VIT should be referred to an immunologist.

Ref:Golden D.B.K et al Ann.Allergy.AsthmaImmunol 2017 Jan; 118: 28.

1.18 In obese diabetic patients, which is better – Medical therapy or bariatric surgery?.

150 obese or over weight adults with **BMI >27** with long standing Type 2DM were randomized to receive intensive medical therapy alone or intensive medical therapy + either Roux – en – Y gastric bypass or sleeve gastrectomy. This was a trial conducted by the Cleveland clinic. **5 Year** follow up data for 134 patients with mean HbA1C of 9.2% at base line are available.

The primary outcome of HbA1C level <6.0% was achieved by 29% of Roux – en – Y, 23% of sleeve gastrectomy and 5% of medical therapy only groups. Quality of life outcomes on a standardized survey also favoured the surgical groups. The favourable effect of surgery was seen in both <35 and >35 Kg /m2 BMI patients. 5 Surgical patients required reoperation for complications in the 1st 5 years.

Comment: Glycaemic control and quality of life benefits were seen after both types of surgery compared to medical treatment only, and was durable for at least 5 years. Gastric sleeve operation is a simpler procedure than bypass, but bypass has the superior effect on diabetic remission after 5 years. The Swedish Obesity Study (SOS) which has been followed up for more than 10 years have revealed that microvascular and macrovascular adverse event are significantly less in those who underwent surgery.

Ref:Schauer P.R. et al NEJ Med 2017 Feb 16; 376: 641.

1.19 Are E – cigarettes safe?.

Electronic cigarettes (E cigarettes) function by heating nicotine containing solvents to produce an inhaled aerosol. Early data demonstrate that E cigarettes have lower levels of carcinogens compared to combustible cigarettes. A cross sectional study was undertaken to compare nicotine levels and tobacco related carcinogens between these 2 groups over a period of 6 months at least. Analysis was performed on breath, saliva and urine samples. No significant difference was found in nicotine levels across the group. E cigarette had substantially lower levels of measured carcinogen and toxins compared to combustible cigarettes. Nicotine replacement therapy patients also had substantially lower levels of measured carcinogens and toxins.

Comment: Long term use of E cigarettes only or nicotine replacement therapy are associated with substantially lower levels of measured carcinogens and toxins compared to combustible smoking. Since nicotine replacement therapy can lead to abstinence from cigarette smoking, this type of therapy may be the most preferable treatment for chronic smokers. Use of E cigarettes is certainly better than using the traditional combustible cigarettes.

Ref: Shahab L et al Ann. Intern. Med 2017 Feb 7; e pub.

1.20 How should we follow up a patient with ischaemic stroke for possible embolism from atrial fibrillation (AF)?.

It is traditional to perform an ECG, ECHO study and bilateral carotid Doppler studies to exclude AF and embolic stroke. But does performing an ECG once only adequate to exclude AF, as it may be only episodic. Intermittent AF is seen in 5 – 20% of patients with AF.

400 German patients with ischaemic stroke were randomized to either traditional 24 hour Holter or Telemetry monitoring and compared with 3 time point examination (base line, 3 months and 6 months monitoring). At 6 months, AF was detected in 14% of extended monitoring patients and 5% in the traditional 24 hour group. This difference was statistically significant.

Comment: Extended monitoring over 6 months at 3 time points detects more cases with AF in cases of ischaemic stroke and allows long term prevention of embolic stroke with the use of Vitamin K antagonists (warfarin) or direct acting anticoagulants such as Epixaban, Rivaroxaban and Dabigatran. **Congestive heart failure** or **Left atrial enlargement** on ECHO studies may be added risk factors for AF.

Ref: Wachter R et al Lancet Neurol 2017 Apr; 16: 282.

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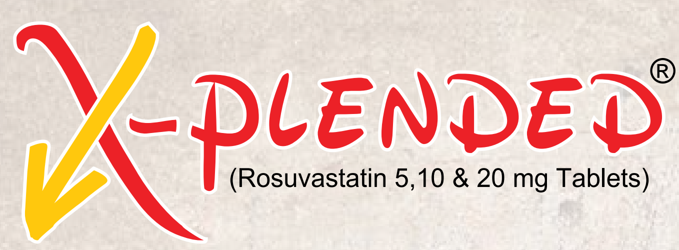


The Super Statin

Evidence based ASCVD management

2013 ACC/AHA Blood Cholesterol Guideline

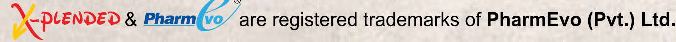
	High Intensity Statin	Moderate Intensity Statin
Daily Dose Statin	Rosuvastatin 20 *(40) mg*	Rosuvastatin 10 *(5) mg*
LDL-C	≥ 50% Reduction achieved	30% to < 50% Reduction achieved
Clinical ASCVD*	Age ≤ 75	Age > 75 or If not candidate for HIS**
Diabetes type I or II Age 40-75 years	Yes (10 year ASCVD 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

- Evidence based ASCVD management
- A better option than other statins
- Superior pharmacokinetic Profile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The Essence of Life

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- Recommended by AACE Guidelines 2017 as monotherapy or combination therapy
- Initial combination of Sitagliptin with Metformin provide substantial & additive glycemic improvement
- Safest DPP-4 inhibitor for Type 2 Diabetes management
- Attenuates progression of Carotid Intima Thickening in Insulin treated patients

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