CEYLON COLLEGE OF PHYSICIANS

MEDICINE UPDATE

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Inosita®

Sitagliptin 50 mg & 100 mg

- Unique Glucose Regulation Dual Mode of Action
- Recommended by ADA Guidelines 2017 as monotherapy or combination therapy
- Initial combination of Sitagliptin with Metformin provides substantial & additive glycaemic improvement
- Global HbA1c Initiative for Type 2 Diabetes management
- Attenuates progression of Carotid Intima Thickening in insulin treated patients

2.1 Do DPP4 inhibitors (DPP4Is) cause acute pancreatitis (AP)?.

DPP4Is include Sitagliptin, Vildagliptin, Saxagliptin ,Alogliptin and Linagliptin. In the February 2017 issue of Diabetes Care, two teams conducted meta analysis of 3 large randomized PCTs involving the DPP4Is Sita, Saxa and Alogliptins. Each of the trials individually showed a **non significant numerical trend** toward more pancreatitis cases compared to placebo. However, in the 3 trials taken together, 52 cases of acute pancreatitis occurred among roughly 18,000 recipients compared to 29 cases in placebo recipients during 1.5 - 3 years of treatment. This was **a significant difference (**Relative Risk 1.8; P = 0.01).

Comment: These analyses suggest that DPP4Is related pancreatitis is a real phenomenon. However the **absolute excess risk** is small – about 1.3 cases per 1,000 patients. One should be on the lookout for pancreatitis in all patients on DPP4Is. Serum amylase and Lipase should be done in patients with abdominal pain while on DPP4Is. Elevation of these enzymes without abdominal pain may not be due to pancreatitis as these drugs stimulate the Acinar cells to increase the exocrine enzymes which may not result in clinical acute pancreatitis. DPP4Is should not be prescribed for those with prior history of pancreatitis.

Ref:Buse J.B. et al Diabetes Care 2017 Feb; 40: 164.

Tkac I and Raz I IBID : 284.

De Vries J.H. and Rosenstock J IBID : 161.

2.2 Does pioglitazone (Pio) increase fracture risk in non diabetics?.

In a recently published placebo controlled randomized trial that involved nearly 4,000 insulin resistant (but not frankly diabetic) patients with recent stroke or transient ischaemic attack, Pio lowered risk for cardiovascular events (NEJ Med 2016; 374: 1371). However, fracture incidence was significantly higher in Pio recipients than for placebo. The following additional details on fractures were:

a) The estimated 5 year overall incidence of fractures was 13.6% with Piovs 8.8% with placebo.

b) Pio was associated with significantly higher fall related fractures, hospitalization, surgery or other procedures.

c) Fracture sites were lower extremity, upper extremity, spine, ribs and other sites in descending order of frequency.

d) Excess fracture risk was somewhat more evident in men than in women.

Comment: Fractures, weight gain and oedema are adverse effects of Pio. Regular exercise and prudent eating habits can modify weight gain. Oedema can be lessened with the use of Spiranolactone. The adverse effect on bone could be related to the presence of PPAR Gamma receptors in bone in addition to those in the liver, muscle and adipocytes. The primitive mesenchymal cell can differentiate into either the osteoblast or to the pre adipocyte. Pio directs the differentiation to the pre adipocyte series and away from the osteoblast series. The advantages of Pio is not only in diabetes where it decreases insulin resistance but also in the prevention of cardiovascular disease such as MI, ischaemic stroke and T.I.As.

Ref:Viscoli C.M. et al J.C.E.M. 2017 March; 102: 914.

2.3 Do 5Alpha reductase inhibitors (ARIs) affect mental health?.

ARIs include Finasteride and Dutaseride. They are used for the treatment of benign hypertrophy of the prostate and for androgenic alopecia. This benefit is due to the prevention of the conversion of testosterone to Di hydro testosterone (DHT). DHT is a growth factor for prostate, seminal vesicles and the penis. Since these drugs affect neuropeptides, testosterone and other neuro transmitters, it is biologically plausible that they may affect mental health and increase the risk for depression and suicide.

In a retrospective Canadian study, of 93,000 older men (mean age 75) who were prescribed Finasteride or Dutaseride, it was found that during continuous medication for 18 months, suicide rates were similar for those on ARIs vs non ARI users. However, the risk for **self harm** was modestly but significantly elevated and the risk for **depression** was also increased. After 18 months of use, the risk for self harm faded but the risk for depression also faded but remained significant compared to non users.

Comment: This is only a retrospective cohort study with a potential for unidentified confounders. The risk is quite small although statistically significant. These side effects are unlikely to discourage patients from using and Physicians prescribing ARIs.

Ref:Welk .B. et al JAMA Intern Med 2017 March 20; e pub.

2.4 Do PCSK inhibitors improve cardiovascular outcomes?.

Evolocumab is a PCSK9 inhibitor which is FDA approved and can lower LDL cholesterol by 50 – 60%. The normal target of LDLC is 100mg/dl for those who have not had CVD (primary prevention) and 70mg /dl for those with prior cerebrovascular disease. Statins are the 1st line treatment for elevated LDLC, but escalation of statin dose sometimes does not result in LDLC levels <70mg/dl. This may also occur if side effects of statins preclude use of a adequate statin dose or if the patient refuses statins. In such cases a PCSK inhibitor may be used alone or in addition to statins.

27,554 statin treated patients with atherosclerotic CVD (secondary prevention trial) whose LDLC exceeded 70mg/dl were treated with Evolocumab subcutaneously. At 48 weeks, the drug had lowered LDLC to a median 30mg/dl. The median reduction in LDLC levels was 59% less than placebo. During a median follow up of 2.2years, the incidence of the primary composite end point – CV related death, MI, stroke, hospitalization for unstable angina was significantly lower with Evolocumab than placebo (9.8% vs 11.3%, RR 0.80). The main secondary end point of CV related death, MI or stroke was 5.9% for the active drug vs 7.4% for placebo (RR 0.75). No prominent safety concerns emerged. All cause mortality did not differ between the groups.

Comment: Statin treated patients having additional Evolocumab suffered significantly fewer adverse CV events. Evolocumab is expensive and has to be given by injection. These should be factored when using this PCSK9 inhibitor. Safety and effectiveness in the long term will need to be monitored.

Ref:Sabatine M.S. et al NEJ Med 2017 March 17; e pub.

2.5 Is measurement of coronary artery Calcium (CAC)valuable in assessing risk for future coronary artery disease (CAD) and premature death?.

CAC estimation in older adults is a strong predictor of future CAD. Does this apply to younger adults age 32 – 46?.

3,000 adults underwent CAC scanning in the CARDIA study. The CAC severity is assessed by the Agatston score. Over a median follow up of 12.5 years, the incidence of CAD correlated with the CAC scores as follows.

a) 5% had scores between 1–19.
b) 11% had scores between 20 – 99.
c) 26% had scores above 100.

The event rate ranged from about 2% in those with CAC scores of 0 and 20% in those with CAC scores over 100.

Comment: Among the risk prediction tools are measurement of CRP, Carotid intima media thickness, coronary artery Calcium score and Framingham risk scores. Of the first three of these, CAC is the strongest predictor of CAD events. The CAC score improved risk prediction when added to the Framingham risk scores. The presence of CAC in younger adults should trigger an aggressive review of preventive measures.

Ref:Carr J.J. et al JAMA Cardiol 2017 Feb 8; e pub.

2.6 A new preventive treatment for hereditary angio oedema (HAE).

In HAE, there is a deficient level or function of the C1 esterase inhibitor protein causing swelling of the extremities, gut mucosa and upper airways. Acute events are frequent and sometimes life threatening. Standard preventive therapy is a twice weekly **C1 esterase inhibitor infusions.** But this has to be given intravenously and some patients have breakthrough swelling.

A new Industry sponsored Phase 3 cross over trial of 79 patients with frequent HAE attacks (>4 during 2 months) was undertaken. Two doses of **subcutaneous** human plasma derived C1 inhibitor or placebo was given twice weekly for 16 weeks and then crossed over to the other regimen for 16 weeks. This preparation lowered the rate of HAE attacks from 4 to 0.5 monthly.

Comment: This preparation which can be given subcutaneously is welcome news as it can be self administered.Further more physiological levels of C1 inhibitor with fewer peaks and troughs are attained. The price of this new drug may be even more than the current IV preparation (Cinryze) which costs more than US$ 300,000/= annually.

Ref:Longhurst H. et al NEJ Med 2017 March 23; 376: 1131.

2.7 Endocarditis trends 2002 – 2017.

Prior to 2002, the commonest cause of endocarditis was rheumatic valvular heart disease. Congenital heart disease was the next commonest cause. A study of 76,000 patients hospitalized with 1st episodes of endocarditis in the combined California and New York states were undertaken. Streptococal endocarditis incidence did not change during this period. However, 3 aetiologies were noted.

a) Prosthetic valve endocarditis increased.

b) Cardiac device related endocarditis also increased.

c) Native valve endocarditis decreased.

d) 50% of all endocarditis cases were "health care associated endocarditis" throughout the study. These patients had a mortality of about 50%.

e) Drug injection endocarditis was seen increasingly in young people who inject drugs.

Ref:Toyoda N. et al JAMA 2017 Apr 25; 317: 1652.

2.8 Does the combination of Vancomycin (V) and Piperacillin – Tazobactam (PT) result in excess of nephrotoxicity?.

Combination V + PT is an often used empirical antibiotic regimen for severe infections in hospitalized patients. Both drugs can be nephrotoxic. What about the combination?.

Acute kidney injury was defined by the RIFLE criteria.

R - Risk of renal dysfunction

I – Injury to the kidney.

F – Failure of kidney function.

L – Loss of kidney function.

E – End stage kidney disease.

11,650 patients without baseline r4enal disease who received at least 48 hours of V or PT or both were studied. RIFLE defined acute kidney injury occurred in 8% of patients who received V , 8% of patients who received PT and 21% of patients who received both V and PT. Combination patients were significantly more likely to develop hypotension, longer treatment duration and longer lengths of stay. Each of these was associated independently with higher risk for acute kidney injury.

Comment: This study involves the largest cohort today of use of these antibiotics. Its findings suggest an additive detrimental renal effect of the combination. Clinicians should monitor renal function carefully when using this antibiotic combination.

Ref:Rutter W.C. et al J.Hosp.Med.2017 Feb; 12: 77.

2.9 Should all patients with TSH values above the upper limit of normal be treated promptly with Thyroxine?.

Patients with decreased free T4 and raisedTSH are diagnosed as **Hypothyroid.** When the free T4 is normal and TSH elevated, then the diagnosis is **subclinical hypothyroidism (SCT).** Very often patients with SCT when retested with free T4 and TSH may have levels of these in the normal range. Therefore, retesting after a period of time is recommended for SCT patients before thyroxine replacement is initiated. This is often so in elderly patients over the age of 65 yrs.

The indications for prompt treatment with thyroxine are

1) Pregnancy.
2) Thyroid peroxidase antibody positive patients.
3) Fine needle aspiration patients with diagnosis of autoimmune thyroiditis.
4) Recurrent pregnancy loss.
5) Women expecting to become pregnant with a TSH value above 2.5miu/ml.

Repeat TSH testing and thyroxine therapy may be given for

1) Hyperlipidaemia.
2) Heart failure (cautiously).
3) Entrapment neuropathies such as Carpal tunnel syndrome (median nerve), neuralgia paraesthetica (lateral cutaneous nerve of thigh).
4) Dementia.

In these cases, clinical assessment after about 3 months is recommended and thyroxine continued if signs and symptoms have improved.

Ref:Stott D.J. et al NEJ Med 2017 Apr3; (e pub).

2.10 Can recurrent venous thrombo embolism (VTE) be predicted?.

When VTE is unprovoked, then recurrent VTE within one year is likely in 10%. When VTE is provoked by surgery, post operatively, post pregnancy and bedridden patients, the chances of recurrence is much less likely after the treatment with anticoagulants for about 3-6 months.

The risk in unprovoked cases **in women** can be predicted using the pnemonic **HERD002.**

H – Hyperpigmentation.

E – Edema.

R – Redness.

D – D dimer value > 250mcg/l.

O – Obesity (BMI>30).

O - Older age (>65 yrs).

Each risk factor is counted as 1. If only 1 risk factor is present, the risk for recurrent VTE is 1.8% if anticoagulation is continued and only 3% annually if anticoagulation is stopped after 6 months. When women had 2 or more criteria, the risk was 7.4% for those who stopped anticoagulation and 2.5% in those who continued it.

Men with unprovoked VTE are all considered to be at **high risk.**

Comment: In unprovoked VTE, women with only 1 risk factor may stop anticoagulation after 6 months. If they have 2 or more risk factors, they should continue anticoagulation indefinitely. All men with unprovoked VTE should have indefinite anticoagulation.

Ref: Rodger M.A. et al BMJ 2017 March 17; 356: j1065.

2.11 Preservation of fertility in women undergoing chemotherapy.

Chemotherapy for cancers damages primordial ovarian follicles (POF)and prevent them from activating and ovulating later in life. If these POFs can be protected from development prior to chemotherapy, then ovarian reserve remains stable and contraception is induced if the damage can be prevented. This is now possible by exposure to **Mullerian inhibiting substance (MIS).**When mice are given this, and then challenged with oncological agents such as carboplatin, Doxorubicin or Cyclophosphomide – serious ovarian damage is prevented. After completion of chemotherapy, if the MIS is withdrawn, then the POFs resume normal activation resulting in ovarian follicles.

Comment: This work in mice if confirmed in humans who are facing chemotherapy may result in the following:

- **a)** Better odds of conceiving following the completion of chemotherapy.
- **b)** Provide a new and potent type of female contraceptive.
- **c)** Controlled chronic levels of MIS might allow extension of women's reproductive life span, although the quality of oocytes who undergo this therapy might still be low.

Ref:Kano M. et al Proc.Natl.Acad.Sci.USA 2017 Feb 28; 114: E 1688.

Woodruff T.K. IBID : 2101.

2.12 Are steroid injections for knee osteoarthritis harmful?.

Osteoarthritis (OA) is not only a degenerative process but also has an inflammatory component. This can lead to progressive cartilage loss. Hitherto, steroid intra articular injections have been considered safe, if they are not more frequent than every 3 months.

140 patients with symptomatic knee OA and ultra sound positive for effusion and synovitis were randomized to intra articular injections of Triamcinolone or placebo every 3 months. At 2 years, Triamcinolone patients exhibited significantly greater loss in cartilage thickness and no significant difference in pain. Triamcinolone was not associated with faster progression of other OA features, structurally or clinically. The patients were permitted to continue NSAIDs.

Comment: This study raises concerns about repetitive intra articular steroid injections. Occasional injections are reasonable for patient with severe pain who cannot take NSAIDs or who do not respond to them. Loss in cartilage thickness without faster progression of OA is of uncertain significance. However, a 2014 study exhibited that faster rates of cartllage loss were associated with higher incidence of arthroplasties.

Ref:McAlindon T.E. et al JAMA 2017 May 16; 317: 1967.

Osteoarthritis Cartillage 2014; 22: 1542.

2.13 Are muscle symptoms truly seen in Statin users?.

In observational studies, 20% of statin users report muscle pain or weakness. However in randomized blinded clinical trials, myopathy with muscle pain, weakness and substantially elevated creatine kinase levels are only seen in < 0.2% (1 in 500) patients per year of treatment.

To better understand this discrepancy, researchers reanalysed data from the ASCOT lipid lowering arm trials, in which more than 10,000 adults with hypertension were randomized to daily Atorvastatin 10mg or placebo. The lipid arm was stopped after a mean 3.3 years because of significantly better CV outcomes in the Atorvastatin arm. All patients thereafter were offered open label Atorvastatin and followed up for a further 2.3 years (5.6 years in all). In the blinded phase, muscle symptoms were reported in 2% annually of both the lipid and non lipid arms (similar rates). However, in the unblinded phase, muscle symptoms were reported more often among the statin users (1.26% vs 1.0% annually).

Comment: The experience of similarity of adverse events during the blinded phase but a difference in the unblended observational phase is referred to as the "Nocebo" effect. Nevertheless, drug literature recommends reduction of dose or withdrawal if CPK levels increase more than 10 times the upper limit of normal.

Ref: Gupta A. et al Lancet 2017 May 2; (e pub).

2.14 In end stage renal disease (ESRD) what are the predictors of short term mortality?.

Older patients with ESRD are more likely than younger patients to develop complications during haemodialysis. 2,200 older adults, age >65 on maintenance haemodialysis were studied for a 6 month mortality prediction tool. The following factors predicted short term (6 months) mortality.

1. Age >80 yrs.
2. EGFR< 10ml/mt at dialysis initiation.
3. Atrial fibrillation.
4. Congestive heart failure.
5. Metastatic cancer.
6. Lymphoma.
7. Hospitalization during the past 6 months.

Ref:Wick J.P. et al Am.J.Kidney. Dis. 2017 May; 69:568.

2.15 What are the Haemoglobin thresholds for transfusion in patients with cancer?.

Convincing evidence supports a restrictive transfusion threshold of **Hb 7.0g/dl** in most **critical ill patients**. In the case of patients with solid cancers, the threshold has been found to be best when the **Hb is < 9.0g/dl**. The mortality at 28 days in 300 patients with **solid organ malignancies** was 45% and 59% in the 9.0g/dl vs 7.0g/dl groups respectively.

Ref:Bergamin F.S et al Crit.Care.Med 2017 May; 45: 766.

2.16 Treatment of cellulitis.

Uncomplicated cellulitis is usually due to infection with Beta haemolytic streptococci. Treatment is with a Cephalosporin (oral Cephalexin) or a Macrolide (Clarithromycin) for 7 days. If response is unsatisfactory, Cotrimoxazole may be added.

Purulent cellulitis is usually due to Staph aureus. A swab for culture is useful to differentiate Methicillin sensitive Staph aureus (MSSA) and Methicillin resistant Staph aureus (MRSA). MSSA can be treated with Cloxacillin, Flucloxacillin or Cefazolin. MRSA infection will require either Vancomycin, Cotrimoxazole or Linezolid.

Immunodeficientpatients like diabetes may have polymicrobial infections. Combination of Betalactams + Cloxacillin may be in order. Presence of bullae in the vicinity of the cellulitis indicates the possibility of **anaerobic infection.** Metronidazole or Clindamycin are appropriate.

In severe infection, medications need to be given parenterally. Incision, drainage and desloughing may be required for localized abscess or necrotic tissue.

Underlying cause such as diabetes may require insulin.

Ref:Moran G.J. et al JAMA 2017 May 23; 317:2088.

Shuman E.K. and Malani P.N. IBID : 2070.

1.17 What is the optimum duration of dual antiplatelet therapy (DAPT) after insertion of drug eluting stents for coronary artery disease?.

Researchers examined 12 randomized trials in which shorter (<12 months) and longer (>12 months) duration of dual antiplatelet therapy after drug eluting coronary artery stenting, were administered.

Short duration DAPT was associated with significantly lower rates of bleeding (HR 0.66), bleeding related death (HR 0.65) but a higher rate of myocardial infarction (HR 1.33) when compared with longer duration therapy. There was also **a trend** towards lower all cause mortality (HR 0.85).

Comment: Higher mortality observed after long term DAPT was due to more bleeding relateddeaths. However, there were less MI events. Approaches that weigh the competing risks for bleeding against those for ischaemia seems sensible.

Ref:Palmerini T et al J.Am.Coll.Cardiol 2017 April25; 69:2011.

Rao S.V. and Harrington R.A. IBID : 2023.

2.18 Is anticoagulation for portal vein thrombosis in patients with cirrhosis safe?.

Anticoagulation of patients with cirrhosis and portal vein thrombosis (PVT) leads to thrombosis regression and even resolution. However, bleeding risk is a concern.

8 studies (5 retrospective and 3 prospective) comprising 563 patients were subjected to a systematic review and metaanalysis. They had been treated with no anticoagulation or anticoagulation with low molecular weight heparin or warfarin.

Any PVT recanalization (complete or partial) occurred more frequently in the anti coagulated group (71% vs 42%) and complete recanalization (53% vs 33%). Incidence of bleeding was similar among groups (11% in each), but **variceal bleeding** occurred at a **lower rate** in the anticoagulated group (2% vs 12%).

Comment: This systematic review and meta analysis demonstrates that anticoagulation is more effective than no treatment in achieving recanalization of the portal vein, without imparting risk for bleeding.

Ref:Loffredo L. et al Gastroenterology 2017 May 4; e pub.

1.19 **What is the prognosis of non malignant pleural effusions?.**

Malignant pleural effusions are a sign of advanced disease and have a poor prognosis. 356 patients with non malignant pleural effusions were followed up over 7 years. Transudative effusions were caused by congestive cardiac failure, renal failure or hepatic failure. Surprisingly, 35% of heart failure patients had exudative effusions. The 1 year mortality of patients with heart failure with effusions was 50%. Patients with bilateral transudative effusions were more likely to die by 1 year than those with unilateral exudative effusions.

Ref:Walker S.P. et al Chest 2017 May; 151: 1099.

2.20 Is intradiscalgluco corticoid injection (IGCI) for chronic low back pain efficacious?.

French researchers evaluated IGCI in a sub group of 135 patients whose chronic low back pain was associated with active discopathy (MRI identified vertebral end plate bone oedema adjacent to a degenerated disc). Patients were randomized to receive either a single IGCI during discography (injection of contrast into the disc) or discography alone. At 1 month, improvement in low back pain occurred in a significantly higher proportion of patients in the IGCI group than in the discography alone group (55% vs 33%).However, at 3 months, the mean pain scores were higher in the IGCI group. At 12 months, pain intensity did not differ significantly among the groups.

Comment: IGCI did not result in sustained reduction in pain. The initial improvement might have been due to the glucocorticoid and the increase in pain at 3 months may have been due to a rebound effect following IGCI.

Ref: Nguyen C. et al Ann.Intern.Med. 2017 Apr 18; 166:547.

Kennedy D.J. and Schneider B.J. IBID: 601.

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