CEYLON COLLEGE OF PHYSICIANS

MEDICINE UPDATE

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Effective In Achieving Significant Cardiovascular Outcomes[3]

Significant HbA1c Reduction[4]

Improves Metabolic Parameters[3]

Key International Endorsements[2]

Provides Reduction In Major CV Events[5]

References:
(1.) IDF Diabetes Atlas 9th edition 2019.
(2.) Endocrine practice. 2019;25(1):69-100.
(3.) New England Journal of Medicine . 2015;373 (22) :2117 -28
(4.) Diabetes Res Clin Pract. 2019;151:65-73
(5.) Circulation Journal. 2017;81(2):227-34

1.1 A new treatment for primary biliary cirrhosis (Primary Biliary Cholangitis – PBC) – Combined Ursodeoxycholic acid (UDCA) and Bezafibrate.

UDCA has been established for the treatment of PBC since 1980. It decreases the biochemical markers of cholestasis and extends the time to liver transplantation. A combination of Obeticholic acid (OBCA) – a selective agonist of the Farnesoid X receptor with UDCA has recently been shown to decrease the levels of biochemical markers in PBC, although there were higher rates of severe pruritus with OBCA.

A 24 month DB, PC phase 3 trial with 100 patients who had inadequate response to UDCA were randomized to receive either additional fibrate at a daily dose of 400mg or placebo in addition to UDCA. The primary outcome was a complete biochemical response which was defined as normal levels of total bilirubin, alkaline phosphatase, aminotransfererases and albumin as well as a normal prothrombin index at 24 months.

The primary outcome was 31% less in that assigned to Bezafibrate vs placebo. Normal alkaline phosphatase levels were 67% in the Bezafibrate group vs 2% in the placebo group. Appropriate improvements in pruritus, fatigue, non invasive measures of liver fibrosis, including liver thickness and liver fibrosis score were consistent with the primary outcome results. Two patients in each group had end stage liver disease. The creatinine level increased 5% from baseline in the Bezafibrate group and decreased 3% in the placebo group (a difference of 8%). Myalgia scores were 20% for the Beza group and 10% for the placebo group. Patients with portal hypertension and high levels of alkaline phosphatase at initiation had lesser benefits with Bezafibrates.

Comment: Bezafibrate acts by decreasing bile acid synthesis and the immune response seen in PBC. Presently, UDCA, Bezafibrate and OBCA are available for treatment of PBC. Bezafibrate is the first drug to show improvement in biochemical liver measures and measures of fibrosis. However, hepatotoxicity, Rhabdomyolysis and an increase in serum creatinine are known adverse events. It is however inexpensive and readily available. Combination of UDCA and Bezafibrate is efficacious for PBC according to this study. Combination UDCA + OBCA has been found to be effective in an earlier study. The combination of all 3 agents is a possibility in the future. All patients on medical therapy should have follow up of liver function tests, serum creatinine and liver fibrosis estimation. Levels of FGF 23 and Galectin3 are recent additions as markers of the levels of liver fibrosis.

Ref: Corpechot C. et al NEJ Med 7th June 2018; 378: 2171 – 2181 and 2234.
Hirschfield G.M. et al Gastroenterology 2015; 148: 751 – 761.

1.2 Is Systemic Lupus Erythematosus (SLE) caused by changes in the gut microbiome?.

The bacteria in our intestine are essential to life both in humans and animals. They not only dispose of waste, but also educate the immune system, regulate levels of neurotransmitters and synthesize essential nutrients such as Vitamin K. Recently, Manfredo Vieira reported that the gram positive bacterium **Enterococcus gallinarum** has a causative role in the mouse model of SLE. They found that **Vancomycin and Ampicillin** improved survival in the mice with SLE and had lower serum titres of antibodies to autoantigens such as double standard DNA compared to untreated mice. Increased permeability of the bowel has been reported in irritable bowel disease as well as in diabetes, rheumatoid arthritis and ankylosing spondylitis. SLE mice had increased bowel permeability and reduced levels of protein that make up tight junctions (intercellular adhesions) in the gut epithelium. Antibiotics such as Vancomycin, which reduce gallinarum titres, diminish the permeability of the bowel. This prevents translocation of bacterial products from the bowel into the circulation which is normally facilitated by bacterial endotoxin and peptidoglycans. E.gallinarum increases levels of interferon alpha and Beta 2 glycoprotein 1 which is the target of antibodies in the antiphospholipid syndrome. SLE is one of the known causes of the antiphospholipid syndrome. Further, DNA from E.gallinarum has been found in the livers of patients with both SLE and autoimmune hepatitis. Mice immunized against E gallinarum and those treated with antibiotics had a prolonged survival. This opens the possibility of modification of the enterobiome in the treatment of SLE.

Ref: Rosenbaum J.T and Silverman G.J NEJ Med June 7 2018; 378: 2236 – 2237.

1.3 What is the best time to administer antihypertensive medications?.

Blood pressure during sleep predicts cardiovascular outcomes better than day time blood pressure. The peak activity of the Renin angiotensin system is greatest during sleep. A Spanish team randomized more than 19,000 primary care patients with hypertension to take their medication either at bed time or on awakening. The patients were followed up for a median duration of 6.3 years.

Day time and night time BPs were significantly lower in the bed time group than in the awakening group. Incidence of the primary outcome (composite of CV related death, MI, revascularization, heart failure and stroke) was significantly lower in the bed time group than in the awakening group (6.5% vs 11.9%) – a nearly 50% relative reduction. No excess risk for adverse events eg: fainting, falling on awakening was seen in the bed time group.

Comment: Hypertensive patients will have better CV outcomes if they take their medications at bed time. When once daily preparations are used, using them in the evening seems reasonable. When preparations are taken twice a day, a higher dose at bedtime is recommended.

Ref: Hermida R.C. et al Eur.Heart J 2019 Oct 22; e pub.

1.4 Should patients with dyslipidaemia and no cardiovascular disease and who are over the age of 75 be treated with statins?.

The degree of association between LDL cholesterol levels and risk for a 1st adverse CV event in older populations is uncertain. 4 prospective cohort studies with 2,700 participants above the age of 75 without CVD were examined. After adjustment, no significant association between LDL cholesterol levels and 5 year incidence of adverse CV events was noted. Even those who smoked, had hypertension or diabetes when examined separately had no benefit from statin therapy.

Comment: Statin therapy would not, on average, benefit older patients with no history of CVD (primary prevention).

Ref: Nanna M.G. et al J.Am. Geriatr.Soc 2019 Dec; 67: 2560.

1.5 Should patients presenting with syncope be investigated with a

D-dimer evaluation?.

Patients with pulmonary embolism (PE) may present with syncope but with no symptoms of chest pain or dyspnoea. Evidence of a deep vein thrombosis may be absent. A prospective study of 400 such patients seen in 7 French Emergency Departments underwent serum D-dimer testing. An elevated, age adjusted D-dimer level was seen in 1/3rd of patients. Imaging studies for pulmonary embolism confirmed PE in 6.6% of patients with positive D-dimer (1/16), and in 2.2% of the overall cohort (1/49).

Comment: Serum D=-dimer evaluation can be a part of evaluation for syncope and might detect more patients with pulmonary embolism.

Ref: Raynal P.A et al Eur.J.Emerg.Med 2019Dec; 26: 458.

1.6 Management strategies in uninvestigated dyspepsia.

Guidelines recommend Endoscopy as the 1st line strategy for affected patients older than 60 and also in those of any age with alarm features such as dysphagia, weight loss or anaemia. What about those below 60 years without alarm features?.

6,200 adults under 60 years were followed up for 12 months. 5 strategies were evaluated.

1. Prompt Endoscopy. (Best satisfaction).
2. Testing for H.pylori and performing endoscopy in those who tested positive (test and scope).
3. Testing for H.pylori and eradicating H.pylori in positive cases (test and treat).
4. Emperical acid suppression only.

5. Symptom based management only.

It was found that the “test and treat” strategy was ranked as most effective followed by prompt endoscopy, “ test and scope” , empirical acid suppression and symptom based management in descending order. 20 cancers were detected (1 case per 310 patients).

Comment: Test and treat strategy in this meta analysis effectively resolved symptoms and resulted in fewer endoscopies than in other strategies. The US and Canadian guidelines also recommend test and treat as the 1st line strategy in affected younger patients less than 60 years of age. In this cohort, about 40% of patients were positive for H.pylori. H.pylori can be detected by measurement of H.pylori antibody in the serum, H.pylori antigen in the stool, urea breath test or endoscopic biopsy.

Ref: Eusebi L.H. et al BMJ 2019 Dec 11; 367: l 6483.

1.7 New Endoscopic surgical treatments for benign prostatic hyperplasia (BPH).

For decades, monopolar transurethral resection of prostate (TURP) has been the main stay of surgical treatment for BPH. During this procedure, the prostate adenoma is removed piece by piece with a monopolar electrode. 8 newer endoscopic surgical modalities for BPH was assessed in a meta analyses of 109 RCTs in about 14,000 men, mean age 68. The modalities assessed were

1. Monopolar TURP.
2. Bipolar TURP.
3. Bipolar and laser enucleation, during which the adenoma is peeled from the prostate capsule, pushed into the bladder, broken into pieces and removed.
4. Bipolar vapourization using 4 types of laser.

Overall, the new enucleation methods resulted in superior peak urinary flow and better prostate symptoms scores at 12 months. Compared with TURP, all new methods were safer than monopolar TURP in that there were fewer blood transfusions, less haemoglobin decline and shorter urinary catheterization duration.

Comment: The newer methods are superior to the usual TURP. The choice of method depends on the patient’s characteristics – enucleation for large prostates and vaporization for small prostates or when bleeding risks is elevated.

Ref: Huang S.W. et al BMJ 2019 Nov 14; 367: l 5919

1.8 A new treatment for diabetic foot osteomyelitis (DFO) - Rifampicin.

Rifampicin has the ability to penetrate biofilms and achieve intracellular concentration within osteoblasts. These properties make it an attractive option for treatment of DFOs.

6,174 patients with DFO of which 130 received Rifampicin in addition to other treatments were studied.Those who did not receive Rifampicin were treated as controls. The amputation free survival rate in those who received more than 14 days of Rifampicin – was significantly higher

than controls (27% vs 37%). Other factors associated with amputation free survivals were younger age, fewer comorbidities, HbA1C < 7.5% and lower serum creatinine levels.

Comment: These findings support the concept that Rifampicin therapy improves the out come of patients with DFO. This concept now needs to be studied in a prospective randomized trial.

Ref: Wilson B.M. et al JAMA Netw.Open 2019 Nov 1st; 2: e 1916003.

1.9 Does testosterone therapy confer risk for Venous thromboembolism (VTE)?.

Testosterone therapy can induce haematological abnormalities such as Erythrocythaemia and Dyslipidaemia, which are associated with hypercoagulability. Would this increase a risk for VTE?.

40,000 patients with Deep vein thrombosis (DVT) or pulmonary embolism (PE) in a US database were analysed. Patients with cancer were excluded. 4% of these men had received testosterone therapy during the year preceding their VTE events. The design of the study was " Case cross over" in which patients served as their own controls. When use of testosterone during the 6 months immediately preceding VTE (Case period) was compared with use of testosterone during months 6 – 12 prior to VTE (control Period) – it was found that recent testosterone therapy was associated significantly with VTE in a ratio of 2:1.

Comment: This study suggests that testosterone therapy is associated with increased VTE in the first 6 months after initiation.

Ref: Walker R.F. et al JAMA Intern.Med 2019 Nov 11: e pub.

1.10 What's new in the Guidelines for Bacterial Pneumonia – an Update ?.

1. The Centre for Disease Control (CDC) no longer supports routine administration of the 13 valent conjugate pneumococcal vaccine for adults over the age of 65.
2. Patients over the age of 65 should take the above vaccine only if they are immunocompromized, have CSF leaks or Cochlear implants.
3. Patients over the age of 65 may routinely take the 23 valent (pneumovax) vaccine.
4. The single greatest risk for community acquired pneumonia (CAP) with MRSA or P. aeruginosa is having had a previous episode.
5. Recommends against using steroids without refractory septic shock.
6. Recommends against using procalcitonin as a marker of illness severity.
7. Recommends against routine post treatment chest imaging.
8. Moderates enthusiasm for macrolides because of increasing resistance and auto toxicity. Amoxyclav or Cephalosporin with a macrolide or a respiratory quinolone is recommended.
9. A minimum treatment period of 5 days is recommended for all patients.

Ref: Zuger A. Journal Watch General Medicine, 2020 Jan 1; Volume 40: (1) 4.

1.11 Is there an increased risk for atrial fibrillation (AF) with intake of alcohol?.

Epidemiological studies show a dose dependent association between alcohol consumption and risk for AF and even for AF recurrence after AF ablation. Australian investigators randomized 140 patients (mean age 62) in sinus rhythm who routinely consumed **> 10 alcoholic drinks weekly,** who previously had more than 2 AF episodes, to undergo alcohol abstinence or continue consuming alcohol as usual. They were on rhythm control strategies. The abstinence group took on average 2 drinks weekly while the control group took 13 drinks weekly. 61% achieved complete abstinence. The following results were seen:

1. Recurrence of AF lasting more than 30 seconds occurred in 53% of the abstinence group and in 73% of the control group during the first 6 months. Those with abstinence had a significantly longer time to recurrence.
2. Median time in atrial fibrillation was significantly lower in the abstinence group.
3. Hospital admission for AF occurred in 9% and 20% of the two groups respectively.

Comment: This fine study, although small, shows a big effect of an abstinence strategy on AF. This is strong evidence for a alcohol withdrawal recommendation in all patients with AF.

Ref: Voskoboinik A. et al NEJ Med 2020 Jan2; 382: 20
Gillis A.M. IBID : 83.

1.12 Concomitant use of NSAIDs and anticoagulants – Is it dangerous?.

Physicians are appropriately concerned about risk for bleeding in patients who take both anticoagulants and NSAIDs. In the ARISTOTLE trial, about 18,000 patients with AF were randomized to Apixaban or Warfarin. At randomization, 5% were taking NSAIDs. During median follow up of 1.8 years, an additional 13% reported NSAID use. Nearly 1/3rd of patients taking NSAIDs also took Aspirin or Clopidogrel.

Using NSAIDs overall (either at baseline or started during the study), was not associated significantly with excess risk for clinically relevant non major bleeding (HR 1.3) , major bleeding (HR 1.2) or GIT bleeding (HR 1.1). However, initiation of NSAIDs **during the trial** was associated with significantly major bleeding (HR 1.6) and clinically non major bleeding (HR 1.7) but not with GIT bleeding. NSAID use did not appear to alter the efficacy of Apixaban or Warfarin which were used in this trial.

Comment: Relatively high use of NSAIDs in this cohort was probably due to frequency of arthritis and other painful conditions in this age group of patients. Why only the patient who began NSAIDs during the trial and not those who were on it prior to the trial – had excess bleeding is not clear. Duration of NSAID use which is an important variable was not mentioned in the article.

Ref: Dalgaard F. et al Circulation 2020 Jan 7; 141: 10.

1.13 Is it worth performing a MRI study for relatively low risk neurological presentations?.

1,028 patients with relatively low risk neurological presentations either non motor/ non speech neurological events of any duration or motor or speech symptoms lasting less than 5 minutes completed MRI examination within 8 days of symptom onset. Key findings were as follows:

1. MRI showed acute stroke (diffusion weighted imaging positive lesions) in 14% of cases.
2. A DWI positive lesion was noted more frequently when neurological examination suggested acute stroke than when neurological examination was normal.
3. Older age, male sex, motor or speech symptoms, abnormal initial neurological examination were risk factors for DWI positive MRI findings.
4. MRI findings changed the neurologist's provisional diagnosis in 30% of cases.

Comment: In this study, 14% of patients with recent so called "minor neurological events" had evidence of acute ischaemia on MRI.

Ref: Coutts S.B. et al JAMA Neurol. 2019 Dec ; 76: 1439.

1.14 Are DPP4 inhibitors associated with pancreatitis or pancreatic cancer?.

Some studies have suggested that DPP4 I s are associated with excess risk for pancreatitis and pancreatic cancer. A population based cohort study from Korea compared risks for these disorders in 10,000 new users of DPP4I and 23,000 new users of other diabetic drugs (excluding GLP1RAs).

The overall incidence rates were roughly 10 cases for pancreatitis and 2 cases for pancreatic cancer per 1,000 patient years. The Hazard Ratios were 1.27 for pancreatitis and 1.81 for pancreatic cancer, after a 6 months lag period. P values were significant for both conditions.

Comment: Although this is an observational study and not a randomized controlled trial, the evidence suggests that DPP4I's may occasionally cause pancreatitis or pancreatic cancer. It would be advisable to desist from use of DPP4I's in patients who already have one of these two conditions.

Ref: Lee M et al Diabetes Care 2019 Nov; 42: 2057

1.15 What is the optimal cholesterol level after stroke or transient Ischaemic attack(TIA)?.

Some epidemiologic studies have raised the issue of whether excessive LDLC lowering confers risk for brain haemorrhage. Investigators enrolled 2,860 patients (mean age 67; 86% with ischaemic strokes within 3 months and 14% with TIAs within 15 days). They were randomized

either to a lower target of LDLC < 70mg/dl or a higher targets of 90 – 110mg/dl. The Physicians could prescribe any statin with or without Ezetimibe.

Mean LDLC levels achieved were 65mg/dl in the lower target group and 96 mg/dl in the higher target group. Median follow up was for 3.5 years. The primary end point of combination stroke + MI + carotid or coronary revascularization + CV death occurred in 8.5% of the lower target group and 10.9% in the higher target group. These results were statistically significant.
P = 0.04. Rates of intra cranial haemorrhage or new onset diabetes did not differ between the two groups.

Comment: Following ischaemic stroke or TIA – the LDLC target should be < 70mg/dl.

Ref: Amarenco P et al NEJ Med 2019 Nov 18; e pub.

1.16 What is the target Blood pressure goal after stroke – a randomized trial?.

In a large randomized trial in which Researchers compared target BP of < 130mmHg vs 130 – 149mmHg, recurrent stroke was not significantly lower with more intensive treatment (Lancet 2013; 382: 507). Now a new Japanese study of 1,300 patients with recent stroke (85% ischaemic, 15% haemorrhagic) were randomized to a long term target of < 120/80mmHg or < 140/90mmHg.

During a mean follow up of 4 years, average systolic BP was 126.7 vs 133.2mmHg and diastolic BP 77mmHg in both groups. However, there was a difference in the incidence of recurrent stroke (6.2% vs 8.2% P = 0.15) but not statistically significant. In sub group analysis the incidence of ischaemic stroke was not statistically significantly different but incidence of intra cerebral haemorrhage was lower in the more intensively treated group P = 0.02.

Comment: In this trial, lowering systolic BP to < 130mmHg did not reduce the overall incidence of recurrent stroke. However, when these results are pooled with results from the other large trial mentioned before, there was a small reduction in recurrent stroke of 1.5% points during 4 years and this reaches statistical significance. Maintaining systolic BP at about 120mmHg in patients with previous stroke is reasonable, provided that there are no adverse effects.

Ref: Kitagawa K. et al JAMA Neurol 2019 Nov; 76: 1309.

1.17 A new treatment after MI – Colchicine.

Inflammation can increase the risk for adverse cardiovascular events. Colchicine is a potent, inexpensive, orally administered anti inflammatory medication. Would its use result in improved outcome after a recent MI?.

4,745 patients, mean age 61 with recent MI were studied. 93% underwent PCI and almost all took statins, dual antiplatelet agents and Beta blockers. Colchicine was dosed at 0.5mg/day. At a median of 23 months, incidence of the primary composite end point of CV death, resuscitated cardiac arrest, MI, stroke, unstable angina and coronary revascularization was significantly lower with Colchicine than in the placebo group (5.5% vs 7.1%). The end points that showed the greatest advantage for Colchicine were stroke (HR 0.26) and urgent hospitalization for angina (HR 0.50). Adverse events were similar in the two groups and CRP declined equally.

Comment: This study suggest that Colchicine in a small dose after MI lowers risk for adverse CV events after MI. Its safety profile is reasonable. Since the hs CRP had no group differences, the mechanism of benefit may not be its anti inflammatory action. However, its is an effective, oral, inexpensive medication to lower CV risk.

Ref: Tardif J.C. et al NEJ Med 2019 Nov 16; e pub.
Newby L.K. IBID: e pub.

1.18 Should Aspirin be used for primary prevention of Cardiovascular disease (CVD)?

Recently, negative studies have been published which has decreased the enthusiasm of using Aspirin to primarily prevent CVD. Aspirin is definitely indicated in secondary prevention of CVD (those who have experienced any type of CVDs). Now, Researchers in New Zealand have attempted to identify sub groups of patients for whom benefits of Aspirin might outweigh harms. They observed 5 year rates of CVD and bleeding according to individualized risk predictors in a large adult primary care cohort without Aspirin use. They then estimated the extent to which Aspirin might lower CVD risk and confer bleeding risk in 250,000 patients in their Database. The estimates were based on previously published meta analyses. They found that Aspirin confers a 11% relative reduction in CVD risk and a relative 43% increase in risk for major bleeding. Only patients with very high CVD risk and low bleeding risk would gain a net benefit from Aspirin therapy. In this cohort, only 1 in 40 women and 1 in 8 men fell into this category.

Comment: This study confirms that for primary prevention, most patients **do not benefit** from Aspirin therapy. A small minority of patients with high CVD risk and low bleeding risk might still benefit but the probability of benefit is small.

Ref: Selak V. et al Ann.Intern. Med 2019 Oct 15; 171: 529.
Kostis J.B. IBID: 583.

1.19 For how long should dual antiplatelet therapy be used after Percutaneous Coronary Intervention (PCI) ?.

A Multicentre trial was undertaken comparing one year out comes with 2 treatment regimens after PCI using drug eluting stents. The 1st group had 3 months of dual antiplatelet therapy (Ticagrelor + Aspirin) and continued same for another 9 months. The 2nd group had dual antiplatelet therapy for the first 3 months and Ticagrelor alone for the balance 9 months. The primary end point of major bleeding was 7% for the 1st group and 4% for the 2nd group. This was a significant difference. Incidence of ischaemic events or stent thrombosis were not significantly different between the groups.

Comment: Ticagrelor combined with Aspirin for 3 months followed by Ticagrelor alone appears to be the superior regimen. Stopping Aspirin after 3 months in patients with dual blockade seems reasonable.

Ref: Mehran R. et al NEJ Med 2019 Sept 26; e pub.

1.20 If you desire longevity - be optimistic.

Longevity is influenced by genetic, socio demographic and life style factors. Does an optimistic attitude influence longevity?. 70,000 participants from the Nurses Health Study and the Veteran's Affairs Aging Study completed validated instruments that measure optimism.

In both sexes, higher optimism levels correlated with increased longevity after adjustment for socio demographic, life style and co existing health condition factors. Study participants with the highest levels of optimism had (50% for women and 70% for men) higher likelihood of surviving to age 85.

Comment: Optimism is associated independently with longevity, after adjustment for potentially confounding factors. The results raise the "Chicken or egg" question – does good health breed optimism or optimism improve longevity?. The authors favour the latter theory.

Ref: Lee L.O. et al Proc.Natl. Acad.Sci. USA 2019 Sept 10; 116: 18357.

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