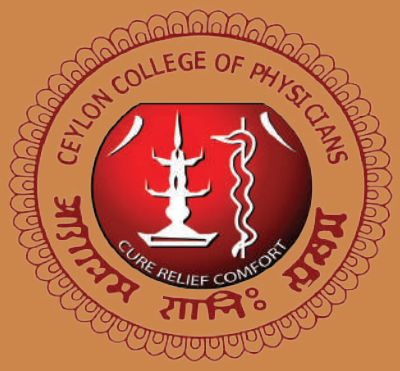

CEYLON COLLEGE OF PHYSICIANS

MEDICINE UPDATE

2020

Vol :31 No : 02

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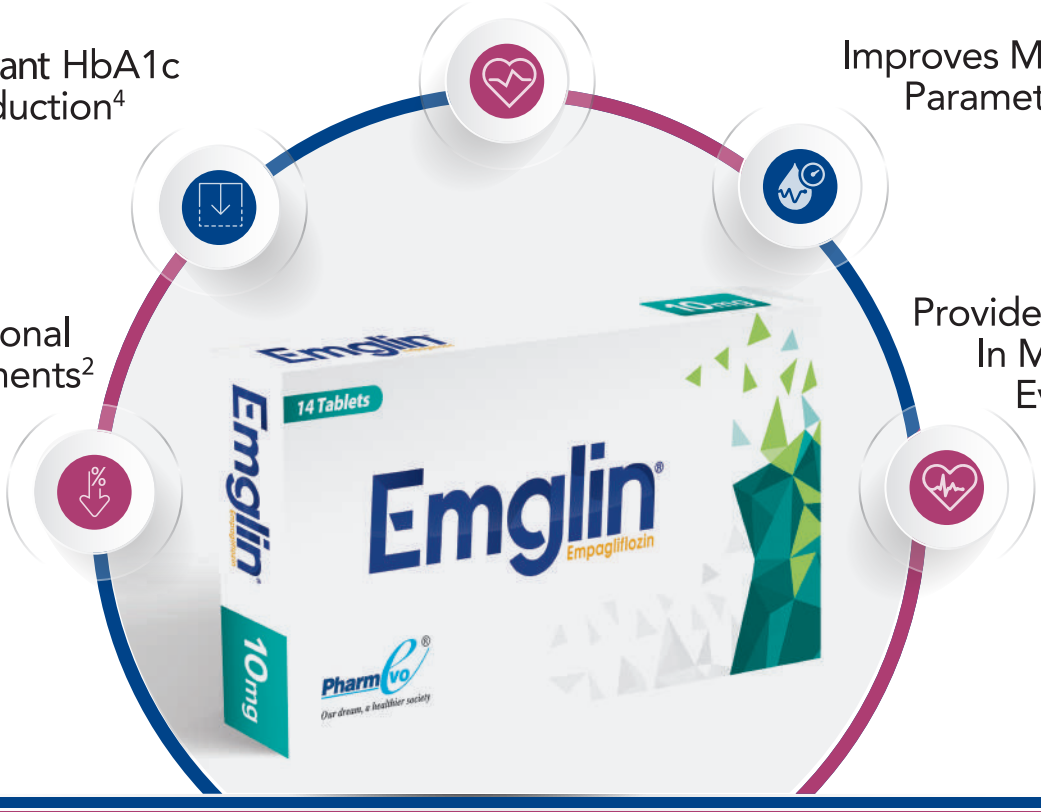
Effective In Achieving Significant Cardiovascular Outcomes[3]

Significant HbA1c Reduction[4]

Improves Metabolic Parameters[3]

Key International Endorsements[2]

Provides Reduction In Major CV Events[5]



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(4.) Diabetes Res Clin Pract. 2019;151:65-73
(5.) Circulation Journal. 2017;81(2):227-34

2.1 Chronic Spontaneous Urticaria (CSU) – a new treatment – Ligelizumab.

CSU is defined as the presence of urticarial and /or angio oedema lasting for more than 6 weeks with no apparent cause. Half of these patients have autoantibodies directed against immunoglobulin E receptors on mast cells. Ligelizumab is a new anti IGE monoclonal antibody in addition to currently approved Omalizumab. 382 adult patients whose CSU was uncontrolled with antihistamines were randomized to either of these given **subcutaneously monthly** or placebo. All patients also received H1 anti histamines, H2 anti histamines and Leukotriene receptor blockers. At 12 weeks, about 50% of those on Ligelizumab and 26% on Omalizumab had complete control of their CSU.

Comment: CSU unlike anaphylaxis is not life threatening but has an enormous effect on quality of life and typically takes years to resolve. About half of these patients only respond to combination high dose anti histamines
(eg: Cetirizine 20mg b.i.d) + Ranitidine + Monteleukast. Many end up receiving long term steroids. A recent study indicates that Dapsone may be useful. Ligelizumab may be more effective than the accepted Omalizumab. The monoclonal antibody are presently marketed at astronomical prices which are beyond the common patient.

Ref: Maurer .M. et al NEJ Med 2019 Oct 3rd; 381: 1321.

2.2 A new treatment for Heart failure – Diabetic and non diabetic - SGLT2 Inhibitors (SGLT2Is).

Evidence has grown that SGLT2Is can lower risk for heart failure in patients with Type 2 Diabetes. What about those without Diabetes?.

4,744 patients (mean age 66) with New York Heart Association Class 2 or higher heart failure and ejection fraction < 40% were studied. 45% of these had Type 2 Diabetes and 55 % no diabetes. Mean ejection fraction was 31%. Dapagliflozin in a dose of 10mg daily was given in addition to standard treatment and patients followed up for 18 months while the placebo group was given standard treatment only. In a median follow up of 18 months, the primary combined outcome for hospitalization or urgent IV therapy or CV death occurred significantly less often in the Dapa group (16.3% vs 21.2%). The benefit was consistent across sub groups including patients without Diabetes. Individually, worsening heart failure was 9.7% vs 13.4% , CV death 9.6% vs 11.5% and all cause death 11.6% vs 13.9%. All symptoms were improved. No important safety issues were seen.

Comment: This is a game changing discovery for the treatment of heart failure with reduced ejection fraction. It is effective in both Diabetics and Non Diabetics. It improved symptoms , all cause mortality, CV mortality and worsening heart failure. The mechanism is probably due to its osmotic diuretic action, removal of Sodium and increase in haematocrit which follows its administration. A word of caution- that aggressive diuresis may cause a fall of blood pressure and syncope. Some studies have also shown that patients with preserved ejection fraction and heart failure may also benefit from the use of SGLT2Is.

Ref: Murray J.J.V et al NEJ Med 2019 Nov 21; 381: 1995.
Fang J.C IBID : 2063.

2.3 Do medications for Hepatorenal syndrome (HRS) work?.

In patients with cirrhosis and HRS, guidelines continue to recommend splanchnic vaso constrictor medications such as Midodrine, Octreotide, Vasopressin or analogues in combination with albumin (Hepatology 2013; 57:1651). A network meta analysis of 25 RCTs with more than 1,200 patients with HRS Type 1, Type 2 or both was undertaken. The investigators compared the effect of albumin + various vasoactive medications – Noradrenaline, Terlipressin, Octreotide, Midodrine + Octreotide and Midodrine + Octereotide + Pentoxyfylline. The vasoactive medications were compared with each other and with albumin alone. Follow up period varied from 1 week to 6 months.

Overall mortality was high(59%) and recovery from HRS was low (35%). Patients treated with **albumin + Terlipressin** had the highest rate of HRS recovery. However, all therapeutic strategies including albumin alone yielded similar mortality and rates of liver transplantation.

Comment: Terlipressin an analogue of Vasopressin is the agent most likely to offer improvement in HRS. However at present, there is absence of survival benefit.The dose of Terlipressin was 2mg iv every 6 hours up to 72 hours.

Ref: Best L.M.J et al Cochrane Database Syst Rev 2019 Sept 2nd; 9: cv013103.

2.4 A new treatment for gout and pseudo gout - Anakinra.

Gout is a disorder associated with increased serum Uric acid while pseudo gout is commonly due to deposition of Calcium Pyrophosphate. The acute phase of these diseases are usually managed with Colchicine, NSAIDs, steroids or joint injections. In patients with chronic kidney disease, Heart failure, Diabetes or hypertension, these standard therapies are often avoided.

Anakinra is a IL- 1 receptor antagonist which is sometimes used off label in patients with acute crystal disease which cannot be managed with traditional therapy. A retrospective US study of 100

medically complex hospitalised patients, mean age 60, with acute gout or pseudo gout were given Anakinra. Renal disease was present in 45%, 14% had prior organ transplants, 29 episodes occurred peri operatively and concurrent infection was present in 34 patients. 115 episodes of crystal associated arthritis occurred and 86 responded partially or completely to Anakinra within 4 days. 66 responded partially or completely within 1 day. The drug was well tolerated.

Comment: This is the largest observational study of the use of Anakinra for treatment of acute gout or pseudo gout. 75% of patients improved within 4 days. Anakinra is a safe (but very expensive) treatment for patients with acute crystal disease with substantial co morbidities.The dose of anakinra was 100 mg s/c once daily

Ref: Liew J.W and Gardner G.C. J.Rheumatol 2019 Oct; 46: 1345.

2.5 Treatments for refractory Heart burn (RHB).

The US Veterans Affairs conducted a randomized trial to compare the success in refractory cases of Heartburn. Refractory patients had persistent Heartburn after a two weeks trial of Omeprazole 20mg b.i.d. The following modalities of therapy were compared:

1. Laparoscopic Nissen fundoplication (Surgical).
2. Omeprazole + Baclofen.
3. Desipramine.
4. Combination Desipramine + Omeprazole + Baclofen.
5. Omeprazole + placebo (control group).

All patients had positive symptoms and abnormal acid exposure as shown by ambulatory pH/ Impedance testing. At 1 year, treatment success according to a standardized scoring system revealed that 67% of Surgical patients, 28% of active medical patients and 12% of control patients had treatment success.

Comment: In this study, refractory heart burn was best treated surgically. However, since surgery in invasive, it might be prudent to first try medical therapy and then resort to surgery. It is important to note that all these patients had ambulatory pH or impedance testing. Those who did not undergo this procedure were excluded from the trial. Usually in refractory cases of dyspepsia, it would be prudent to do Upper GI endoscopy, and if there is no ulceration, to exclude hyperparathyroidism and Zolinger –Ellison syndrome. In patients where ambulatory pH testing or impedance testing is feasible, refractory cases may be referred for fundoplication after a course of medical therapy.

Ref: Spechler S.J. et al NEJ Med 2019 Oct 17; 381: 1513.
Talley N.J "Think first, cut last" IBID 1580.

2.6 Non Alcoholic Fatty Liver Disease (NAFLD) – could it be due to gut bacteria producing alcohol?.

A man with known NAFLD walked into a Doctor's office and the Doctor obtained a blood alcohol level even though the patient denied drinking. Lo and behold, the blood alcohol level was 40mg/dl – a level at which people can be mildly intoxicated. The legal limit for driving is usually 80mg/dl. The Doctor then placed the man on an alcohol free diet for several days and his blood alcohol remained high.

Alcohol producing strains of Klebsiella pneumoniae were remarkably present in the man's stool. A similar result was found in 60% of stools of 43 other people with NAFLD. To evaluate the potential of these bacteria to cause disease, human faeces rich in these bacteria were transplanted by oral gavage into germ free mice. The mice developed NAFLD with typical elevated transaminases and triglycerides and a typical histology picture on biopsy. When the faecal material was treated with agents that selectively killed the alcohol producing K.pneumoniae prior to oral faecal transplant, no NAFLD resulted.

Comment:
This fantastic study suggests that alcohol producing strains of gut bacteria might be a common cause of NAFLD. Bacterially produced gut alcohol travels through the enterohepatic circulation to the liver causing toxicity. This means that alcohol but not "alcoholism" , might be one cause of NAFLD. This Chinese study needs to be replicated.

Ref: Yuan J. et al Cell Metab 2019 Oct 1; 30: 675.

2.7 Weaning off a ventilator.

Shorter duration of mechanical ventilation has many benefits such as lowering risk for ventilator associated pneumonia and delirium. To prevent reintubation after extubation 2 strategies are employed.

1. Immediate support with non invasive ventilation (NIV).
2. High flow nasal cannula Oxygen (HFNC).

What about combination 1 and 2?.

641 patients at high risk for extubation failure (age over 65 , underlying cardiac or pulmonary disease) were randomized to either 48 hours of HFNC alone or NIV + HNFC during breaks from NIV. Patients who received HFNC alone were significantly more likely to be reintubated within 7 days after extubation. Similar results were found between 24 and 48 hours after extubation. The difference between the 2 groups was most pronounced in the patients who had **PaCO2 > 45mmHg at extubation**.

Comment: Many patients do not tolerate NIV well after extubation. NIV with support during breaks with HFNC is definitely worth trying.

Ref: Thille A.W. et al JAMA 2019 Oct 2; 322: 1465.
Telias I and Fergusan N.D IBID: 1455.

2.8 Orthostatic Hypotension (OH) in Parkinson's Disease (PD).

How frequently does OH occur in PD?. 185 patients with PD who had not received Dopaminergic drugs and 172 age and sex matched controls without PD were studied. Significant OH was defined as a mean arterial pressure of < 75 mmHg in the standing position.

During a mean 7 years of follow up, OH was more common in PD than controls. The relative risk was 3.0 at baseline and 4.9 at 7 years. OH was independent of older age. Levodopa use was associated with clinically significant OH.

Comment: All patients with PD should have their BP measured seated and standing at every visit.

Those with OH could be treated with

a) Hydration.
b) Increased salt intake.
c) Compression stockings.
d) Abdominal binders.
e) Raising the head of the bed.
f) Alteration of Dopaminergic drug doses.
g) Reduction or stopping of antihypertensive drugs.

Ref: Hiorth Y.H. et al Neurology 2019 Oct 15; 93: e 1526.

2.9 Triglycerides (TG) and CV outcomes in Statin treated patients at high risk for CVD.

Do statin treated patients with diabetes, CVD or both + elevated TG levels have worse outcomes than patients with normal TG levels?. 50,000 patients treated with statins and aged >45 with diabetes or CVD and elevated TG > 150mg/dl were compared with patients whose TG levels were < 150mg/dl and whose HDLC levels were more than 40mg/dl. Mean follow up was 3.5 years.

Adjusted for multiple variables including LDLC levels, the elevated TG cohort had significantly higher risk than the comparator cohort for major adverse CV events overall (HR 1.26). Specifically for coronary revascularization HR was 1.46, non fatal MI HR 1.32 and Non fatal stroke HR 1.14 but not for CV related death.

Comment: Statin treated patients with diabetes or CVD + elevated TG levels above 150mg/dl but HDLC levels <40mg/dl had worse outcomes than with patients with optimal TG levels. These results suggest that increased TG levels might be an independent risk factor for adverse outcomes. Clincians should consider lowering TG levels through diet, weight loss or exercise. Studies on add on fibrates have been negative but recently Icosapentyl Ethyl was superior to placebo (NEJ Med 2019; 380: 11). However this study was funded by th maker of Icosapentyl Ethyl and the lead author is a consultant for and two other authors are employees of that company. Verification with other studies is therefore of paramount importance before Icosapentyl Ethyl is officially approved.

Ref: Tots P.P. et al Mayo Clin. Proc. 2019 Sept ; 94: 1670.

2.10 Does adding Fenofibrate (FF) to statins in patients with metabolic syndrome (MS)have benefits?.

Randomized trials have shown that FF does not lower risk for adverse CV events in people with **Diabetes.** However, evidence suggest that FF might lower CV risk in people with MS. MS is defined as the presence of any 3 of the following.

1. Large waist circumference.
2. Elevated triglycerides.
3. Low HDL.
4. Elevated blood sugar in the pre diabetic or diabetic range.
5. Elevated BP or on antihypertensive treatment.
6. Obesity.

2,200 Korean patients who received combined statins and FF were matched with 8,500 patients who received statins only. The primary outcome was a composite of incident coronary artery disease, stroke or CV related death. During 6 years of follow up, the primary outcome was significantly lower in the combination group (17.7 vs 22.0 per 1,000 person years).

Comment: The participants were propensity matched. Adding FF **might benefit** patients with MS in whom life style modification and statin therapy have not achieved treatment goals. This should be confirmed by randomized trials.

Ref: Kim N.H. et al BMJ 2019 Sept 27; 366: l5125.

2.11 Are Direct Acting Oral Anticoagulants (DAOAs) superior to Vitamin K antagonists in the treatment of Antiphospholipid Syndrome (APLS)?,

Rivaroxaban an oral DAOA was compared with Warfarin in patients with APLS to prevent arterial and venous thrombosis. Investigators conducted a 3 year randomized non inferiority trial in 190 adults who had thrombotic events with APLS.

Recurrent thrombosis (the primary end point) occurred in more Rivaroxaban than Warfarin recipients (11 vs 6). These figures with Rivaroxaban failed to meet non inferiority criteria. 9 of the thrombotic events in the Rivaroxaban group were arterial in nature (mainly stroke). Rates of major bleeding were similar.

Comment: Rivaroxaban, which is useful in the treatment and prevention of venous thromboembolism in non APLS patients appears to be **less effective** than Warfarin. Whether other DAOAs such as Apixaban also behave like Rivaroxaban in APLS needs to be studied.

***Ref**:* Ordi – Ros J. et al Ann.Intern. Med 2019 Oct 15; e pub.
Wahl D. and Dufrost V. IBID: 2815.

2.12 A new drug to treat Bacterial pneumonia - Lefamulin.

Lefamulin is the 1st of the broad spectrum group called the **Pleuromutilins.** 738 patients , mean age 57, with community acquired pneumonia (CAP) were randomized to either oral Lefamulin twice daily for 5 days or Moxifloxacin daily for 7 days. Patients were recruited from 19 countries, 40% were smokers and most had comorbidities.

Both drugs performed equally well with about 90% of each group being clinically improved after 4 days and also after treatment cessation. Responses were equally good for the sub group where a bacterial pathogen was identified, including the very few patients with drug resistant pneumococcus or MRSA (S.aureus). GIT side effects were more frequent with Lefamulin (18% vs 8%) most often with diarrhoea and vomiting.

Comment: Pleuromutilins inhibit bacterial protein synthesis. This means induction of resistance will be relatively slow. They should be reserved for managing infections that fail to respond to older drugs or treating patients who cannot tolerate older drugs. However, this new drug will be more expensive than older alternatives.

Ref: Alexander E. et al JAMA 2019 Sept 27; e pub.
Malani P.N. IBID: 16215.

2.13 Are Ultrasound guided Thoracentesis safe in patients on oral anticoagulant or antiplatelet drugs?.

A British guideline recommends correction of bleeding risk factors, including the cessation of anticoagulant or antiplatelet agents. This opinion relies heavily on expert opinion. However, recent series have shown minimal complication when patients with thrombocytopaenia or mild coagulation abnormality undergo thoracentesis.

103 patients from a single Mayo clinic institution underwent 115 ultra sound guided thoracentesis while receiving direct acting anticoagulants (43 patients) or Clopidogrel (59 patients). Most patients had additional risk factors for bleeding, including renal insufficiency for elevated INRs.

No patient developed a chest wall haematoma or required intervention (eg: chest tube placement) or haemothorax. 6 patients received packed red cells within 48 hours of their procedures although none had decreases in haemoglobin > 2g/dl. Overall the drop in Hb was 0.24g/dl.

Comment: This study suggests that the procedure can be done safely even in those who are on direct acting anticoagulants or antiplatelet agents. Other studies have shown that spinal anaesthesia and joint aspirations are also safe in similar patients. However, ultrasound guided or CT guided biopsies of solid organs are not safe with these agents.

Ref: Patel P.P et al Mayo Clin. Proc. 2019 Aug ; 94: 1535.

2.14 Should adults with normal Calcium and Vitamin D levels take more than 1,000 units of Vitamin D daily ?.

311 Canadian adults in the category above, were given 3 levels of Vitamin D supplementation – 400 iu, 4,000 iu or 10,000 iu daily. At base line the mean serum Vitamin D level was 32ng/ml = 79 nmol/l. The serum Vitamin D levels increased significantly for participants who received 4,000 iu or 10,000 iu daily but not in those who received 400 iu daily. At 3 years, declines in BMD at the radius was significantly steeper in the 4,000 and 10,000 iu groups.
(-2.4 and – 3.5% respectively) than in the 400 iu group (- 1.2%). A similar pattern was noted in the Tibia. Bone strength estimates declined in all 3 groups, with non significant trends towards lower strength in the high dose Vitamin D groups than in the 400 iu group. Patients who had prior high dose Vitamin D or disorders of Vitamin D metabolism or high 10 year risk for osteoporotic fractures were excluded.

Comment: This small study suggests that there is no benefit for bone integrity – and even potential harm – with high dose Vitamin D supplementation in patients whose Vitamin D levels are adequate. The mechanism may be due to increased bone resorption secondary to parathyroid hormone suppression.

Ref: Burt L.A. et al JAMA 2019 Aug27; 322: 736.

2.15 Is the use of proton pump inhibitors (PPIs) safe with long term use?.
In recent years, observational studies have suggested associations between use of PPIs and multiple adverse outcomes. These include, pneumonia, hip fracture, dementia, enteric infections (including Clostridium difficile) , CV events, CKD, Diabetes, COPD and mortality. As these

observational studies are subject to residual confounding and other biases – a large prospective study of antithrombotic therapy of patients with stable coronary or peripheral artery disease was undertaken. They compared the safety of PPI use (Pantoprazole 40mg/d) with that of placebo in 17,600 older patients (age over 65, 78% men, 23 % smokers). During a median follow up of 3 years, results were as follows:

1. NO significant differences were noted in rates of pneumonia, fracture, new onset diabetes, chronic kidney disease, dementia, COPD, gastric atrophy, overall cancer and site specific cancers.
2. Enteric infection other than C.difficile were more common in patients who took Pantoprazole (1.4% vs 1.0% P = 0.04 – significant)..
3. C. difficile infections were twice as common with Pantoprazole use (non significant).

Comment: This is the 1st large scale prospective randomized trial on long term safety of PPIs. This study substantiates the excellent safety profile of PPIs, except for a small excess of enteric infection.

Ref: Moayyedi P et al Gastroenterology 2019 Sept; 157: 682.

2.16 Is Acupuncture of any value for chronic stable angina?.

A Chinese study recruited 404 patients, mean age 62, with chronic stable angina for atleast 3 months for the largest randomized trial to date. Patients with prior MI, severe heart failure, unstable angina or other chronic diseases were excluded. They were assigned to 4 groups.

1. Mechanical and electrical acupuncture at acupoints based on expert consensus.
2. Acupuncture at non therapeutic acupoints.
3. Acupuncture using non stimulating sham procedure.
4. Patients put on a waiting list.

Intervention procedures (1, 2 and 3) were done 3 times weekly for 4 weeks. All patients continued concordant medical therapy. Angina diaries were maintained individually.

At 16 weeks, angina episodes were on average 8 per week in those on the waiting list and 2-4 per week lower in the other 3 groups. The difference was statistically significant. Anginal severity was also significantly less in the interventional group. Adverse effects of intervention were minor and self limited.

Comment: Acupuncture may be an adjunctive measure for patients with chronic stable angina. The lack of difference between procedures 1 and 2 vs the sham procedure 3 is perplexing. This study is also dependent on a specific (Chinese) population where knowledgeable, experienced acupuncturists are available.

2.20 Can the gut microbiome enhance athletic performance?.

Gut microbes produce many molecules that affect human physiology. Can the gut microbiome affect athletic performance?. To determine this, investigators obtained daily stool samples from 15 runners for 1 week before and 1 week after the Boston Marathon and compared the microbiome findings of those of a group of 10 sedentary controls. They then confirmed their findings in a 2nd group of athletes and controls.

Athletes had a higher abundance of one bacterial species –
Veillonella.atypica than controls. It was also found that the bacterial genes that convert lactate to propionate were activated by the exercise. The blood lactate generated by exercise spilled into the gut lumen, where it was metabolized to propionate by V.atypica. It was then reabsorbed in the colon and entered the circulation. Even mice who were given V.atypica orally or given intra rectally propionate could exercise longer.

Comment: This study of human athletes and mice indicate that atleast one bacterial species in the gut might enhance atheletic performance by promoting conversion of the lactate produced during exercise into propionate. The obvious question is now whether the athlete's native microbiome make them top Marathon runners or does Marathon training programme change the microbiome in a beneficial way or both?.

Ref: Scheiman J. et al Nat. Med. 2019 July; 25: 1104.

Compiled By;

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Consultant Physician and Endocrinologist.

Ref: Zhao L. et al JAMA Intern Med 2019 July 29: e pub.

2.17 What is the protocol for the treatment of unprovoked Venous Thrombo Embolism (VTE)?.

Clinicians are faced with a dilemma whether to continue anticoagulation indefinitely in patients with unprovoked VTE. To help Physicians in this decision, a meta analyses of pooled data from 18 Randomized trials or prospective cohort studies was undertaken. The long term rates of recurrent VTE in 7,500 such patients whose anticoagulation was stopped after **atleast 3 months** was estimated. The key findings were as follows:

1) Cumulative incidence of recurrent VTE was 10%, 16%, 25% and 36% at 1,2,5 and 10 years respectively.
2) The cumulative incidence was lower in women than in men (29% vs 41%).
3) The cumulative 2 year rate of recurrent VTE was slightly higher in patients whose initial event was **proximal DVT,** than in those whose initial event was isolated pulmonary embolism or isolated distal vein thrombosis.
4) Cumulative incidence of **fatal pulmonary embolism** was 0.4%, 0.7%, 1.0% , and 1.5% at 1,2,5,and 10 years.

Comment: These data are important for Physician's and patient's decisions regarding duration of anticoagulation. Those with proximal DVT may be considered for indefinite anticoagulation. A via media could be to initially give a 3-6 months period of anticoagulation and then withdraw them for about 2 weeks - at which time, a plasma D dimer estimation is performed. If it is elevated, then indefinite anticoagulation is advisable. In those in whom anticoagulation is stopped, regular estimation at increasing intervals of time may detect those who are prone for recurrent VTE.

Ref: Khan F et al BMJ 2019 July 24; 366: l4363.

2.18 What is the significance of " non obstructive " coronary artery disease(CAD)?.

CAD is classified on coronary arteriography or CT coronary angiography as "normal", "non obstructive" and "obstructive" . In "obstructive" CAD, there is > 50% in the left main coronary artery or >70% in the other major coronary arteries. "Non obstructive" CAD, exhibits < 50% obstruction in the left main coronary artery or <70% in the other major coronary arteries. "Normal" coronary arteries have normal coronary angiograms.12,814 Canadian patients with heart failure and reduced ejection fraction were studied. 21%, 18% and 61% had normal, non obstructive and obstructive coronary arteries respectively.

Compared with those with non obstructive or obstructive arteries - having "normal" coronary arteries were associated with significantly lower for a composite of cardiovascular death, non fatal

MI, non fatal stroke or hospitalization for heart failure. As expected, obstructive CAD conferred the highest risk for the composite outcome.

Comment: The presence of non obstructive CAD increases the mortality risk and considering medical therapy for these patients seem reasonable.

Ref: Braga J.R et al JACC Heart Fail 2019 June; 7: 493.

2.19 A new drug for prevention both primary and secondary cardiovascular disease in diabetics – Dulaglutide.

Both GLP1 receptor agonists and SGLT2 inhibitors prevent some adverse CV events in middle aged patients with prior CVD (secondary prevention). They may also prevent some chronic renal outcomes.

A manufacturer sponsored randomized study of 9,900 patients with Type 2DM (mean age 66; mean A1C 7.2%) and known CV disease
(secondary prevention) and with CV risk factors (primary prevention) was undertaken. The patients received weekly Dulaglutide, ("Trulicity") 1.5mg sc or placebo. Median follow up was for 5.4 years. The following outcomes were seen.

1. Dulaglutide caused a reduction in the composite CV end points (Non fatal MI, non fatal stroke, CV related death and all cause mortality of 12.0% vs 13.4% for placebo. NNT for 1 event prevention was 70. The main difference was in the reduction of **non fatal stroke.** The reduction for the composite CV events was the same for both primary and secondary prevention groups.
2. A composite of **microvascular events (**retinal and renal) also occurred significantly less frequently in the Dulaglutide group.
3. Renal outcome – a composite of new macro albuminuria, sustained decline of >30% from baseline in eGFR or renal replacement therapy- occurred significantly less frequently in the Dulaglutide group. (3.5 vs 4.1 per 100 patient years). This was driven primarily by the lower incidence of macroalbuminuria.

Comment: The patients in this trial generally were healthier than those in comparable studies of other GLP1R agonists, suggesting that Dulaglutide might be effective for primary as well as secondary prevention of adverse CV outcomes.

Ref: Gerstein H.C et al REWIND trial Lancet 2019 July 13; 394: 121.
Gerstein H.C. et al IBID : 131.
Verma S. et al IBID : 95.

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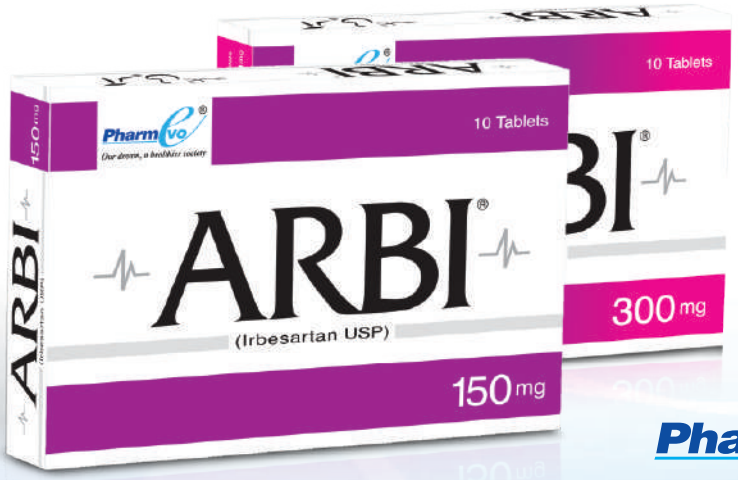

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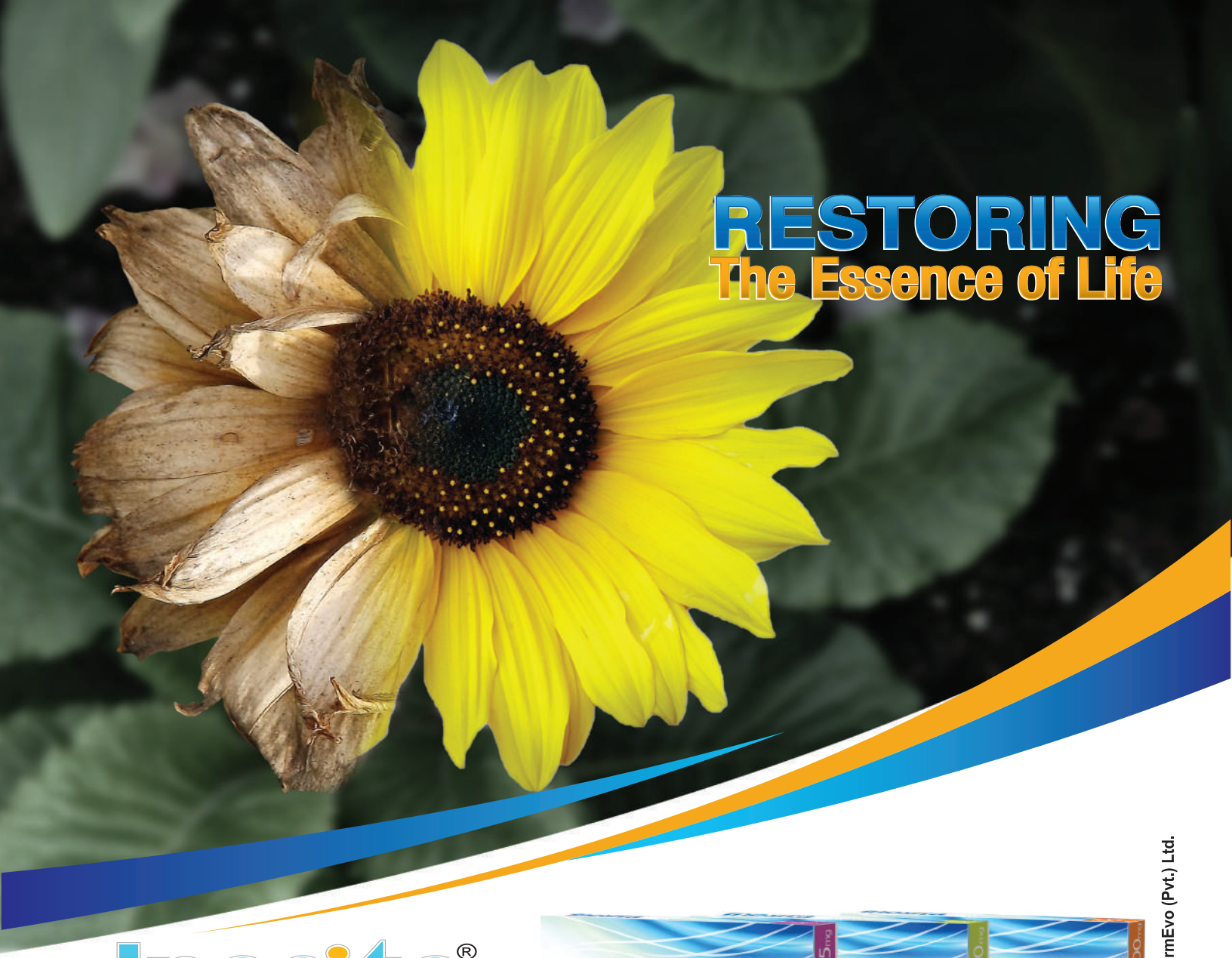

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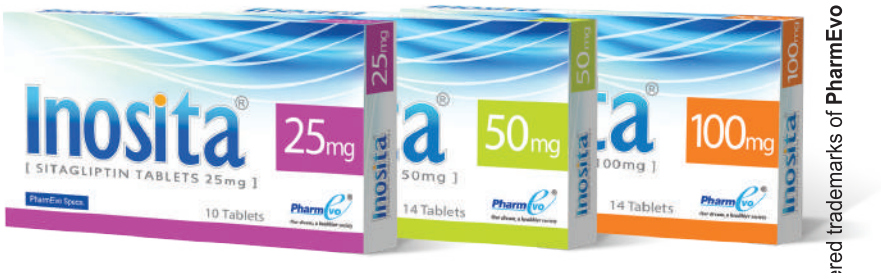

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