CEYLON COLLEGE OF PHYSICIANS

MEDICINE UPDATE

2017

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2.1 What are the risks for second cancers after radiotherapy for prostatic CA?.

Risk for 2nd cancers in patients who receive therapeutic radiation for Hodgkin's lymphoma, breast cancer and testicular cancer is well recognized. What about prostate cancer?.

Investigators conducted a meta analysis of 21 studies of radiotherapy – mostly conformal external beam radiotherapy (lesser number had brachytherapy) – vs surgery or vs no radiotherapy (3 groups). The primary outcome was the development of secondary bladder, colorectal, lung or haematologic cancer. The hazard ratio for radiotherapy vs no radiotherapy was as follows.

a) Secondary bladder cancer = 1.67.
b) Colorectal cancer = 1.79.
c) Rectal cancer = 1.79.
d) Lung and haematologic malignancies = 1.0 (no excess).

Risk for 2nd cancers were much higher for external beam radiotherapy than with brachytherapy.

Ref:Wallis C.J.D et al BMJ 2016 March 2; 352: i 851.

2.2 A new treatment for Giant Cell Arteritis (GCA) – Tocilizumab.

GCA is also referred to as "temporal arteritis". The standard of care has hitherto been steroid therapy. However, prolonged courses of steroid are required, leading to substantial steroid induced complications. Up to now, steroid sparing immunosuppressive therapies have not been convincingly effective. Recently case series have suggested that the Interleukin -6 receptor antagonist – Tocilizumab effectively treats patients with GCA.

In an Industry sponsored study, 30 patients with GCA were randomized in a 2:1 ratio to receive **monthly infusions** of the drug or placebo for 1 year. All patients received daily oral Prednisolone – starting at 1.0mg/Kg and tapering to 0.1mg/Kg by week 12. By 12 weeks, 85% in the active drug group and 40% in the placebo group attained complete remission (no symptoms of GCA, normal ESR and CRP at a daily prednisolone dose of 0.1mg/Kg). After 52 weeks, the respective values of remission were 85% vs 20% (P = 0.0005, very significant difference). Patients in the Tocilizumab were able to wean off steroids (38 weeks vs 50 weeks), and their median cumulative steroid dose was lower.

Comment: This study although very small, offers a potential option for treating GCA patients. A larger study should elucidate the role of this drug in the initial treatment of GCA or whether it should be added to GCA patients who do not tolerate a steroid taper.

Ref:Viliger P.M. et al Lancet 2016 March 4: e pub.

2.3 Incretin based diabetic drugs and heart failure.

These include DPP4 inhibitors and GLP – 1 receptor agonists. In the SAVOR – TIMI 53 trial, the DPP 4 inhibitor Saxagliptin was associated with excess incidence of hospitalization for heart failure. In contrast, risk for heart failure was not elevated in randomized trials of 2 other DPP 4 inhibitors – Alogliptin and Sitagliptin. Now, researchers have addressed this inconsistency in an observational study that involved 1.5 million patients with Type 2 DM in the US, Canada and the UK. The researchers also examined heart failure risk who received GLP 1 receptor agonists (Exenatide and Liraglutide).

After adjustment for confounders, use of incretin based drugs, compared with use of other anti diabetic drug combinations was **not associated** with excess risk for heart failure related hospitalization. This was true for both DPP 4 inhibitors and for GLP 1R agonists, whether they had or did not have prior heart failure.

Comment: These findings are reassuring. However, whether the excess risk for heart failure with Saxagliptin in the SAVOR – TIMI 53 was a chance finding or a side effect that is unique to Saxagliptin alone – is not certain.

Ref:Filion K.B. et al NEJ Med 2016 March 24; 374: 1145.

2.4 Prevention of HIV by vaccination (passive immunization) – is it possible?.

Active immunization against HIV has not yet produced a viable vaccine. The discovery of **Broadly neutralizing antibodies** against HIV has generated more enthusiasm for passive immunization.

An International team led by NIH, created a cocktail of 4 broadly neutralizing antibodies against HIV and tested its efficacy in monkeys. Repeated low doses of simian HIV to mimic repeated low dose exposures typical of human infection were used to challenge the effect of the vaccination. Control animals all became infected after 2-6 challenges. The treated animals remained virus free after as many as 23 weekly challenges.

Comment: A single injection of multiple broadly neutralizing antibodies offered protection for many weeks against acquiring HIV in monkeys. If this is replicated in humans, passive immunization may be a reality in the future.

Ref:Gautam R. et al Nature 2016 May 5; 533: 105.

2.5Oral Fluoroquinolones (FQ) – are they effective in community acquired pneumonia (CAP)?.

FQs are fully bio available in patients who can take them orally. 36,405 patients with CAP admitted to 304 hospitals were analysed retrospectively. Outcomes between those treated initially with FQs orally vs FQs taken intravenously were compared. After adjustment for confounding factors, the 2 routes were found to be equivalent in hospital mortality, length of stay, hospital costs, late intensive care unit admissions or late vasopressor use.

Comment: Oral FQ therapy for patients at low risk for severe pneumonia is adequate. The Infectious Disease Society of America however recommends iv therapy for higher risk CAP.

Ref:Belforti R.K. et al Clin.Infect. Dis. 2016 July 1st; 63: 1.

2.6 Bed side water swallowing test for Dysphagia

The gold standard for assessing oropharyngeal dysphagia is by video fluoroscopy or fibreoptic nasopharyngoscopy. However, initial bed side swallowing evaluation by the primary physician, is often appropriate. Researchers undertook a meta analysis of studies in which adults were given a thin liquid and observed for coughing, choking, throat clearing or change in voice. This procedure was compared with video fluoroscopy or naso endoscopy in the same patients. 22 studies with 4,617 patients with dysphagia due to both neurological and non-neurological causes were identified. Results were as follows:

a) Single sips of <20ml – sensitivity 67%, specificity 90%.

b) Consecutive sips, drinking as much as 100ml without stopping – sensitivity 91% but specificity 53%.

c) Progressively increasing swallowing volumes – sensitivity 86% specificity 65%.

Comment: Increasing the volume and number of swallows increases the sensitivity, ie detects more dysphagia cases, but is less specific than single sips (identifies non dysphagic patients as having dysphagia).

Ref:Brodsky M.B. et al Chest 2016 July; 150 : 148.

2.7 Potential therapy for Vasovagal syncope (VVS) – Fludrocortisone (FC).

VVS is mediated through decreased preload and reduced cardiac output in association with the vasovagal reflex which decreases the heart rate. A multicenter trial was undertaken to assess the value of FC in VVS. 210 patients with recurrent VVS were randomized to receive FC starting with 50mcg daily and increasing to 200mcg daily over 2 weeks or placebo. The trial lasted 12 months. Syncope recurred in 44% of FC patients vs 60% in placebo patients (hazard ratio 0.69, P = 0.07, non significant). However, in an analysis of 61 % of patients who achieved stabilized dosing of **200mcg daily**, syncope recurred less frequently in FC treated patients (HR 0.51, P= 0.02, significant).

Comment: This population had a mean age of only 30yrs. Elderly patients with more co morbidities and VVS had greater risk of adverse events such as falls, fractures, head injury etc. Even in this young population, a substantial minority did not achieve the target of 200 mcg/day. In those who tolerated this dose, FC was an effective therapy for VVS.

Ref:Sheldon R. et al J.Am.Coll.Cardiol 2016 July 5; 68:1.
Brignole M IBID:10.

2.8 What do we know of the "Postdrome Phase" (PDP) of migraine?.

PDP is the exhibition of symptoms during the time between headache resolution and feeling completely back to normal. 97 patients with migraine were analysed. PDP was seen in 89%. The following were seen.

a) Tired and weariness – 88%.
b) Difficulty concentrating – 56%
c) Stiff neck – 42%.
d) Duration of PDP – average 6 hours (7% lasted >24 hrs).

Comment: PDP is common in migraine sufferers. They are unable to perform optimally at work, school or other activities for several hours after an attack.

Ref:Giffin N.J. et al Neurology 2016 July 19; 87:309.

2.9 An impending breakthrough in the treatment of Type 2DM! – FGF1.

The brain can profoundly influence metabolic and inflammatory diseases in other organs. The latest example – a multi Institutional team injected a molecule – Fibroblast Growth Factor 1(FGF1) into the cerebral ventricles of a mouse model of Type 2DM which led to remarkable results. The FGF1 acted on hypothalamic neurones that controlled metabolic rate and appetite. Surprisingly the glucose levels normalized during the next 7 days and remained normal for the next 17 weeks. None of the animals developed hypoglycaemia. No other complications were seen. FGF1 reduced food intake and body weight only temporarily but the effect on blood sugar was durable. The low blood sugar levels appeared to be due to increased glucose uptake by the liver and by the conversion of glucose to glycogen. When the same treatment was given to normoglycaemic healthy mice, no substantial effect on blood sugar levels was noted.

Comment: Intracerebral injections are not feasible in humans. These same researchers have already shown that a **nasal spray of FGF1** confers similar physiological effects in rodents. If these results are duplicated in humans, we would have a truly new method of treating diabetes Type2.

Ref:Scarlett J.M. et al Nat. Med. 2016July; 22:800.

2.10 Hand, Foot and Mouth disease (HFMD) in adults.

HFMD is a febrile illness that often includes a papular vesicular rash that occurs in children seasonally. It is caused most commonly by an enterovirus, Coxsackie A 16. Sometimes they may be seen in adults. The rash occurs on the extensor surfaces of the upper and lower extremities. Prodromes of malaise and fever were reported. Dermal involvement of palms and soles as well as stomatitis were often present. The differential diagnosis includes Henoch – Schonlein purpura, Parvo virus B19 infection and Tick borne Typhus, when the oromucosal rash is not seen Diagnosis was by nasopharyngeal swabs tested by rt- PCR which identifies the Coxsackie virus. Spontaneous resolution occurred in all patients. In adults, the disease occurs in clusters.

Ref:Banta J et al MMWR Morb. Mortal Wkly Rep2016 July 8; 65:678.

2.11 For how long should we treat Community Acquired Pneumonia (CAP) patients?.

The Infectious Disease Society of America (IDSA) treatment guidelines recommend a 5 day antibiotic course. This was tested in 4 hospitals in the US where patients were randomized to an intervention group – only 5 days of antibiotics if they had been afebrile and clinically stable for 48 hours or control group where the duration was determined by the treating physicians. In this group, the average duration was 10 days. At day 10 and day 30, pneumonia related signs and symptoms were comparable in both groups. The results were similar at all levels of CAP severity but readmission within 30 days was more common among control patients.

Comment: These findings clearly support **a 5 day antibiotic course** for hospitalized patients provided they are afebrile and clinically stable, who have a prompt response to treatment. Important caveats are that patients who require intensive care were excluded and 80% of patients received Quinolones, so applicability to other antibiotic regimens is uncertain.

Ref:Uranga A. et al JAMA Intern.Med 2016 July 25; e pub.

2.12 Vasopressin (V) vs Norepinephrine (N) in septic shock.

The VASST trial showed no benefit of adding V to N in septic shock, but smaller studies have suggested improved renal function with early use of V.

UK investigators randomized 409 patients with septic shock to either V (titrated up to 0.06u/mt) or N (titrated upto 12mcg/mt) as a 1st vasopressor + hydrocortisone or placebo as a 2nd intervention. Radomization occurred within 6 hours of developing shock and the mean arterial pressure was maintained between 65 – 75 mmHg. At 28 days after randomization, no differences in kidney failure free days were found between the 2 groups, although fewer patients in the V group received renal replacement therapy.

Comment: Although clinicians normally initiate N in patients in septic shock, this study indicates that initiation with V is not inferior to any patient on N. Adding steroids for persistent hypotension despite use of 2 vasopressors is reasonable.

Ref:Gordon A.C. et al – The VANISH randomized clinical trial JAMA 2016 Aug 2; 316: 509.

2.13 A new treatment for Clostridium difficile (CD) infection – Faecal Microbiota Transplantation(FMT).

A number of case series have demonstrated that faecal microbiota transplantation (FMT) is effective in the treatment of recurrent CD infection. 2 US centres undertook the 1st randomized, blinded, controlled trial of FMT for recurrent CD infections.

46 patients who had >3 recurrences and had received > 1 full course of Vancomycin for their most recent acute episode, received donor FMT or autologous FMT administered via colonoscopy. All donors underwent infection screening before donation.

Cure rates were 91% with donor FMT and 63% with autologous FMT (P = 0.04, significant).

Comment: This study provides proof of the efficacy of **healthy donor FMT** in the treatment of recurrent CD infection.

Ref:Kelly C.R. et al Ann.Intern.Med. 2016 Aug 23; e pub.

2.14 Should low dose aspirin be continued after a lower GI bleed in patients with high CV risk?.

When aspirin treated patients with high CV risk develop GI bleeding, should aspirin be continued or stopped?. For **upper GI bleeding,** researchers in HongKong addressed this question previously in a small randomized trial where the bleeding was from peptic ulcers. They found that the benefits of continuing aspirin after the bleeding stopped outweighed the risk. Now the same team has conducted a retrospective study in patients with **lower GI bleeding.**

295 patients with high CV risk, who were hospitalized with non fatal lower GI bleeding while taking low dose aspirin were studied. 59% had continued taking aspirin and 41% discontinued it. During an average follow up of about 2 years, hospitalization for recurrent lower GI bleeding occurred in 7 % of the "no aspirin" patients and in 18% of "aspirin patients". However, serious adverse CV events occurred in 33% of the "no aspirin group" and in 21 % of the "aspirin group". After multivariate analysis, aspirin continuers had significantly **higher probability of recurrent lower GI bleeding** (HR = 2.76) but significantly **lower probability of serious adverse CV events** (HR = 0.59) and significantly **lower overall mortality**.

Comment: The benefits of continuing aspirin outweighed the harms in patients with high CV risk who developed lower GI bleeding.

Ref:Chan F.K.L et al Gastroeneterology 2016 Aug; 151: 271.

2.15 Beta blockers (BBs) in cirrhosis.

Non selective BBs reduced portal pressures and are used in the primary and secondary prevention of variceal haemorrhage. However, various studies cautioned the use of BBs in situations such as

a) Decompensated cirrhosis with refractory ascites.
b) Spontaneous bacterial peritonitis.
c) Severe alcoholic hepatitis.

In patients who have **early** cirrhosis **without moderate to large varices,** BBs do not prevent the development of varices. BBs are mainly indicated when the varices are moderate to large. BBs are also ineffective in

a) Refractory ascites.
b) Hypotension.
c) Hepatorenal syndrome.
d) Spontaneous bacterial peritonitis.
e) Sepsis.
f) Severe alcoholic hepatitis.

If patients are already on BBs, they should be discontinued if

a) The BP is < 100/73mmHg.
b) Serum sodium is < 120mmol/l

Ref:Ge P.S. and Runyon B.A. NEJ Med 2016 Aug 25; 375: 767 – 777.

2.16 What is triple rule out CT (TRCT) and what is it used for?.

TRCT views the coronary artery, thoracic aorta and pulmonary arteries in one sitting. CT coronary angiography (CTCA) is used to evaluate whether chest pain symptoms could be caused by coronary artery disease (CAD). TRCT provides greater anatomic coverage than CTCA and thus can demonstrate non coronary artery disease such as aortic dissection, pulmonary embolism, pneumonia etc which could cause chest pain and be missed in a CTCA.

1,192 patients with chest pain were studied. 81% were shown to have no significant pathology. 12% had >50% coronary artery stenosis (significant) while 9% exhibited non coronary findings – pulmonary embolism, aortic aneurysm and pneumonia. These would have been missed on CTCA alone.

Comment: This is the largest longitudinal evaluation of TRCT in an emergency department chest pain population. CTCA alone will miss important " chest pain mimics" .

Ref:Wnorowski A.M. and Halpern E.J. AJR Am. J. Roentgenol 2016 Aug ; 207 : 295.

2.17 Does Colchicine (CC) prevent adverse CV events in patients with gout?.

Both gout and hyperuricaemia are known cardiovascular risk factors. CC has been known to be effective in treating patients with pericarditis. This may be due to its anti inflammatory action. It has also been found to prevent adverse coronary events in one randomized secondary prevention trial (J. Am.Coll. Cardiol 2013; 61:404). Researchers now conducted a retrospective study of 501 patients with gout who used either CC or an equal number of age and sex matched non CC therapeutic agents. Follow up was 1.3 years. This was a primary prevention study.

Prevalence of hypertension and use of statins, Allopurinol, NSAIDs and steroids were higher in the CC group. After adjustment for confounders, CC use was associated with **49% lower relative risk for the primary CV outcome (**MI , stroke or TIA). All cause mortality was also significantly lower with CC.

Comment: This retrospective study suggest that CC use is associated with lower CV risk. However it must be remembered that CC users were more likely than controls to take other medications that can lower CV risk (statins and antihypertensives) or increase CV risk (NSAIDs and steroids). Prospective randomized trials would be desirable.

Ref:Solomon D.H. et al Ann.Rheum. Dis.2016 Sept; 75: 167.

2.18 Which is better for localizing acute lower GI bleeding - Technetium labelled red cell scintigraphy or CT angiography?.

These two procedures are options for evaluation of acute lower GI bleeding. These are done if flexible sigmoidoscopy and colonoscopy are negative. In a single centre with 135 patients with lower GI bleed, 45 CT angiography and 90 red cells scintigrams were done. Only 9 patients underwent both studies. The presumed bleeding site was identified significantly more often in patients who underwent CT angiography (53%) vs red cell scintigraphy (30%). The commonest cause of bleeding identified was diverticulosis.

Comment: In this study, the diagnostic yield was better with CT angiography. This is also the more available round the clock procedure. Lower GI bleeding often stops spontaneously and the source thereafter is difficult to identify.

Ref:Feuerstein J.D. et al A.J.R Am.Roentgenol 2016 Sept; 207: 578.

2.19 An antidote for the newer anticoagulants – Andaxanet (ADX).

The newer anticoagulants - Rivaroxaban, Dabigatram, Apixaban and Edoxaban are being increasingly used for the prevention of pulmonary embolism after DVT and for the prevention of embolism in atrial fibrillation. They have been shown to be as effective as warfarin but have less intracerebral haemorrhage than warfarin and may have a relative increase of GIT haemorrhage. The advantage of these new anticoagulants is that they do not require regular monitoring with prothrombin time etc. However the disadvantage compared to warfarin has hitherto been the absence of an antidote to reverse their effects, whereas warfarin has an antidote in Vitamin K. A new antidote has now been developed – ADX. This is a recombinant decoy protein that binds tightly to the active site of antifactorXa anticoagulants. These have been shown to reverse the anticoagulant effects of Rivaroxaban and Apixaban. A new study was undertaken to determine the efficacy and safety of ADX.

67 older patients – mean age 77, with major GIT bleeding (33 patients), intracranial bleeding (28 patients) and other bleeding (6 patients) on either Rivaroxaban, Apixaban or Enoxaparin were enrolled. ADX was given as a bolus dose and a 2 hour iv infusion. Results were as follows:

a) Median antifactorXa levels fell dramatically and haemostatic efficiency was rated as excellent or good in 80% of Rivaroxaban and Apixaban patients.

b) Bleeding was controlled in patients on Enoxaparin in only 1 patient.

c) Thrombotic events (over activity of the antidote) occurred in 12 patients.

d) 19 % died of mostly cardiovascular causes.

Comment: Anticoagulants often accumulate and cause bleeding in older patients with impaired renal function. ADX rapidly reduced elevated anti Xa factor levels and controlled bleeding in most patients. FDA has withheld approval of ADX pending further studies.

Ref:Connolly S.J. et al NEJ Med 2016 Aug 30 : e pub.

2.20 A new treatment for primary biliary cirrhosis (PBC) – Obeticholic acid (OBCA).

PBC is now called Primary biliary cholangitis. It is an autoimmune liver disease characterized by elevated alkaline phosphatise (AP), gamma glutamyltransferase (GGT) and later on in the disease – serum bilirubin. The only approved treatment at present is ursodeoxycholic acid (UDCA). However, the abnormally elevated AP may persist in many patients even with UD, and mortality is significantly higher.

OBCA is a selective Farnesoid X receptor (FXR) agonist. It is derived from the bile acid Chenodeoxycholic acid (CDCA) which is the endogenous FXR ligand. OBCA has 100 times greater potency in activating FXR than CDCA. FXR signalling protects hepatocytes against bile acid toxicity by decreasing bile acid synthesis and stimulating choleresis by means of up regulation of bile acid transporters. In addition, FXR regulates other pathways with direct anti inflammatory and anti fibrotic effects.

216 patients were randomized in a double blind, placebo controlled, phase 3 trial, (for 1 year with a follow up for 2 years) who had an inadequate response to UD or intolerant to UD. There were 3 groups:

a) OBCA 10mg daily.

b) OBCA 5 mg daily and adjusted to 10mg daily.

c) Placebo.

The primary end point was a normal total bilirubin level + an AP level < 1.67 X upper limit of normal. UD was continued in most patients. The results of the primary end point was reached in 47% , 46% and 10% in groups A,B and C resp. Non invasive measures of liver fibrosis did not differ. Pruritus was more common with OBCA. Serious adverse events were about 13% with OBCA vs 4% in the control group. Levels of IgM , IgA, IgG, IL -12, TNF Alpha and hsCRP were decreased with OBCA. There was also a reduction in the HDLC and TG levels.

Comment: 12 months of OBCA administered as mono therapy or combined with UD in patients with PBC resulted in improvements in AP, total bilirubin and other biochemical markers. These effects were sustained for 2 years. OBCA increased the incidence of pruritus which tended to obfuscate the normal improvement in pruritus which follows treatment of PBC with UD.

Ref:Nevens F. et al for the POISE study group. NEJ Med 2016 Aug 18; 375: 631 – 643.

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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*

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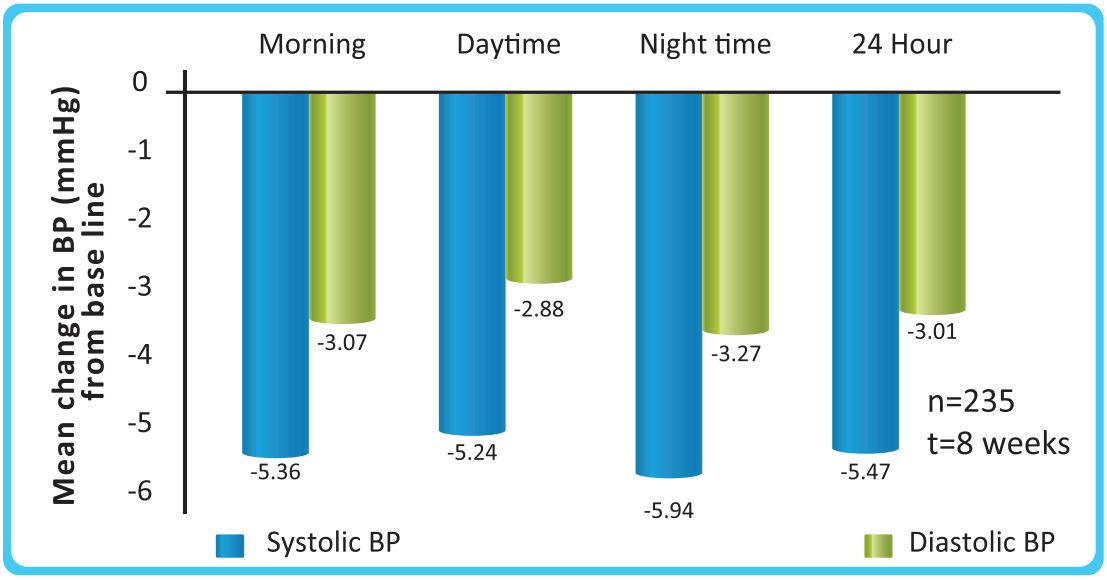

Telmisartan has shown significant reductions in morning, daytime, night time and 24 hour in systolic and diastolic blood pressure of all previously treated patients.

Hypertension Research (2012): 1-6.

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