Issue 16, March'19

State of the HEART

A monthly cardiology news

INTAS MEDICAL AFFAIRS

Monthly Magazine Issue 16

State of the Heart

Dear Reader,

We are grateful to present you the 16th issue of "**State of the Heart**", which explores the clinical evidence supporting the new understandings and happenings in the field of cardiology.

In India, the epidemiological transition from predominantly infectious disease conditions to non-communicable diseases has occurred over a rather succinct period of time. Despite wide heterogeneity in the prevalence of cardiovascular risk factors across different regions, CVD has emerged as the leading cause of death in all parts of India, including poorer states and rural areas. In this research driven time, management of these disorders is also constantly evolving towards the betterment whether it's pharmacological or non-pharmacological.

Being a healthcare custodian of the society, clinicians are constantly thriving to be abreast with the novel understandings of disease and its management. In this context, this is our initiative to provide you a compiled and to the point information.

Present booklet comprises of recent and latest deeds in the field of cardiovascular diseases like dyslipidemia, coronary artery disease, heart failure and its management. We hope that it will facilitate increased cooperation and innovation, and enthuse commitment to prevent these life-threatening and disabling disorders and providing the best possible care for people who suffer from these conditions.

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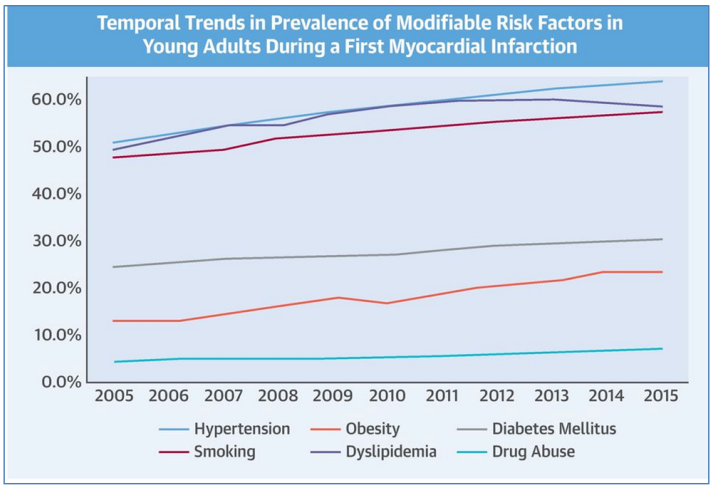
1. Modifiable Risk Factors in Young Adults With First Myocardial Infarction

Modifiable Risk Factors in Young Adults With First Myocardial Infarction

	During a first myocardial infarction in young adults (18-59 years) in the U.S.		
25%	Diabetes Mellitus	>1 in 4	34%
6%	Drug Abuse	>1 in 20	5%
57%	Hypertension	>1 in 2	61%
58%	Dyslipidemia	>1 in 2	52%
16%	Obesity	>1 in 6	23%
54%	Smoking	>1 in 2	50%
92%	Any of these modifiable risk factors	>9 in 10	91%

During a first AMI in young adults in whom preventive measures are more likely to be effective, modifiable RFs were highly prevalent and progressively increased over time. Significant sex and racial disparities were observed for individual RFs.



J Am Coll Cardiol. 2019 Feb 12;73(5):573-584

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Objectives

To study the prevalence rates of modifiable RFs during a first AMI, sex/race differences, and temporal trends in U.S. young adults.

Methods

This was a retrospective cohort analysis of the U.S. National Inpatient Sample years 2005 and 2015 to identify adults 18 to 59 years of age hospitalized for a first AMI. Prevalence rates, race and sex differences, and temporal trends of hypertension, diabetes mellitus, obesity, smoking, dyslipidemia, and drug abuse were analyzed in these patients.

Results

The authors' study included 1,462,168 young adults with a first AMI (mean age 50 ± 7 years, 71.5% men, 58.3% white) of whom 19.2% were 18 to 44 years of age, and 80.8% were 45 to 59 years of age. In the 18- to 44-year group, smoking (56.8%), dyslipidemia (51.7%), and hypertension (49.8%) were most prevalent, and 90.3% of patients had at least 1 RF. In the 45- to 59-year group, hypertension (59.8%), dyslipidemia (57.5%), and smoking (51.9%) were most prevalent, and 92% patients had at least 1 RF. Significant sex and racial disparities were observed in the prevalence of individual RFs. Women **had a higher prevalence of diabetes mellitus, hypertension, and obesity, and men had a higher prevalence of dyslipidemia, drug abuse, and smoking.** The prevalence of all these RFs increased temporally except for the rate of dyslipidemia, which decreased more recently. Trends were generally consistent across sex and racial groups.

"During a first AMI in young adults in whom preventive measures are more likely to be effective, modifiable RFs were highly prevalent and progressively increased over time. ."

2. The Evolving Story of Triglycerides and Coronary Heart Disease Risk

The Evolving Story of Triglycerides and Coronary Heart Disease Risk

JAMA Editorial by Navar AM, MD, Phd

Key Message

- **Hypertriglyceridemia should not be considered as a single entity** but rather multiple conditions that vary in CHD risk based on overall particle number and composition.
- A **simple diagnostic algorithm using total cholesterol level, TG level, and ApoB**, a measure of the number of VLDL and LDL particles in circulation, can be used to categorize phenotypes of hypertriglyceridemia.
- **Elevations in TG levels that are associated with greater particle number are associated with greater CHD risk**, and the relative potential benefits of TG lowering and LDL-C lowering (via genetics at least) are similar when standardized for their effects on ApoB.
- Barring off-target effects, **treatments that lower LDL-C or TG levels should lead to reductions in CHD risk** proportional to their reduction in ApoB.
- Given the growing body of evidence supporting the **importance of ApoB, the guidelines should consider including broader measurement of ApoB as part of routine clinical care**.

The clinical benefit of lower triglyceride levels was similar to the clinical benefit of lower LDL-C levels per unit difference in ApoB and may be related to the absolute reduction in ApoB-containing lipoprotein particles.

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JAMA. 2019;321(4):347-349.

Question

What is the clinical benefit of lowering plasma triglyceride levels compared with lowering low-density lipoprotein cholesterol levels?

Findings

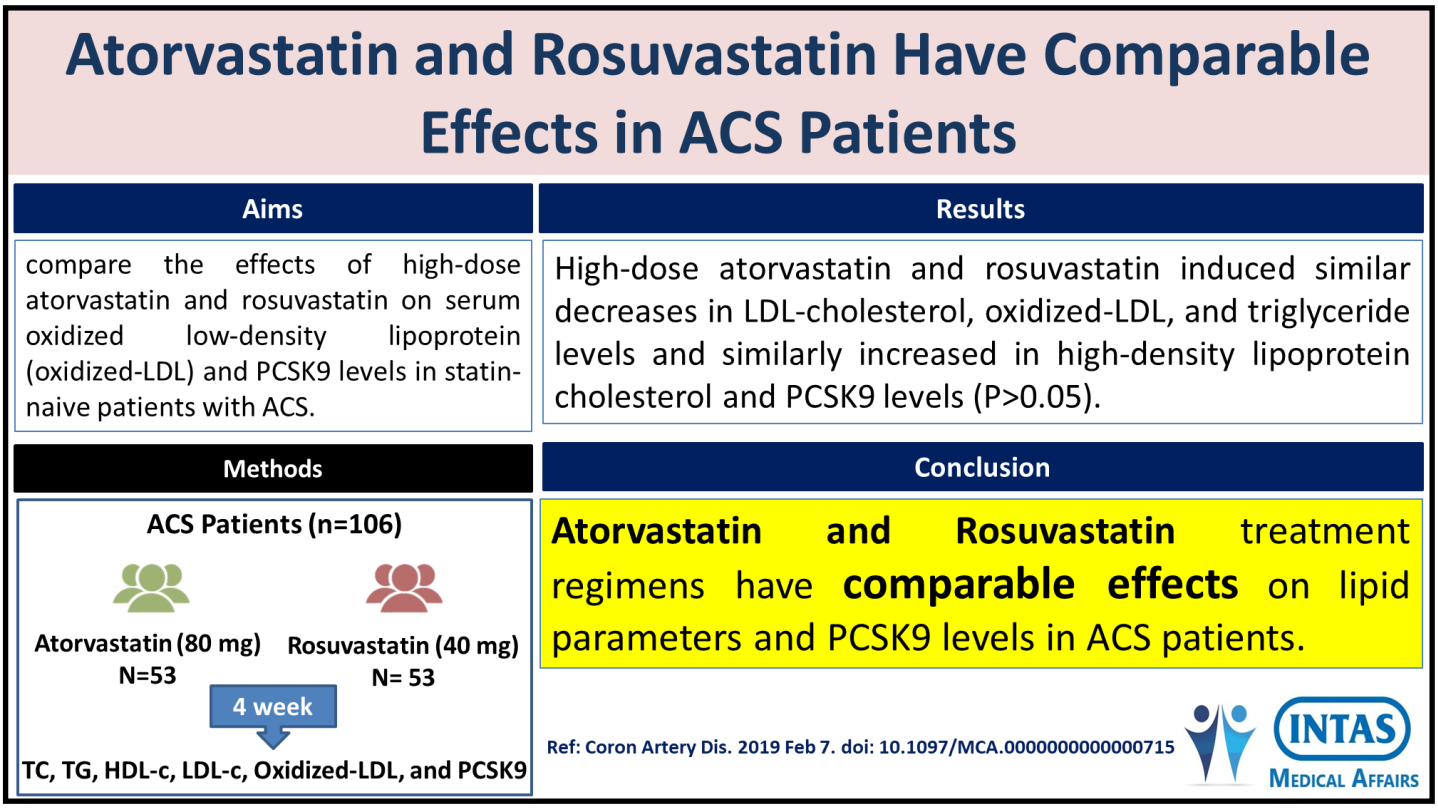
In mendelian randomization analyses involving 654 783 participants, triglyceride-lowering variants in the lipoprotein lipase gene and low-density lipoprotein cholesterol (LDL-C)–lowering variants in the LDL receptor gene were associated with similar lower risk of coronary heart disease per 10-mg/dL lower level of apolipoprotein B (ApoB)–containing lipoproteins (odds ratios of 0.771 and 0.773, respectively).

Meaning

The clinical benefit of lower triglyceride levels was similar to the clinical benefit of lower LDL-C levels per unit difference in ApoB and may be related to the absolute reduction in ApoB-containing lipoprotein particles

" TREATMENTS THAT LOWER LDL-C OR TG LEVELS SHOULD LEAD TO REDUCTIONS IN CHD RISK PROPORTIONAL TO THEIR REDUCTION IN APOB. ."

3. Atorvastatin and Rosuvastatin Have Comparable Effects in ACS Patients



Aim

Current guidelines recommend administration of high-dose statins in acute coronary syndrome (ACS). It has been reported that statins upregulate proprotein convertase subtilisin kexin 9 (PCSK9) mRNA expression and increase circulating PCSK9 levels. Study aimed to compare the effects of high-dose atorvastatin and rosuvastatin on serum oxidized low-density lipoprotein (oxidized-LDL) and PCSK9 levels in statin-naive patients with ACS.

Methods

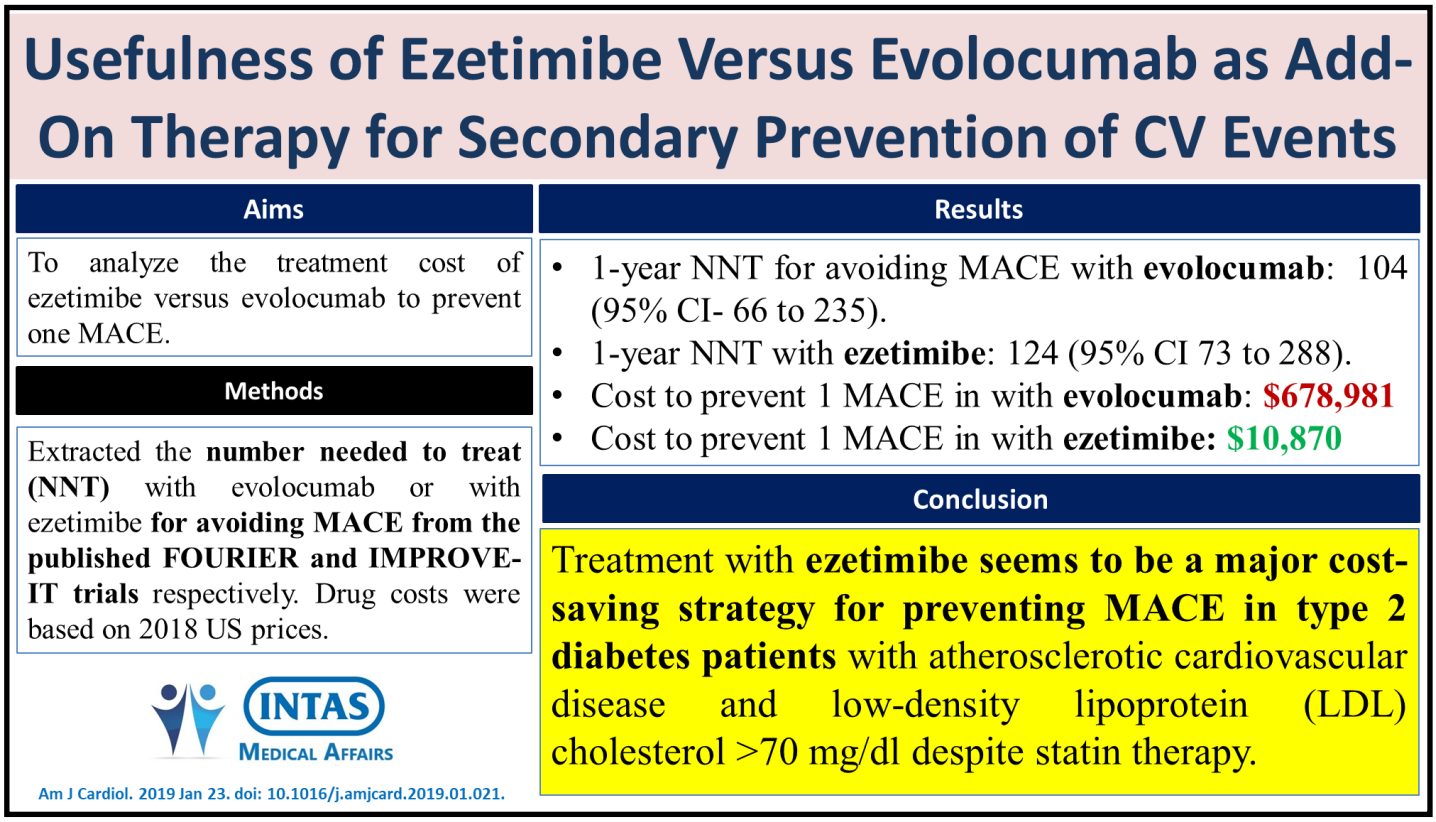
One hundred and six patients with ACS were enrolled in this study. The patients were assigned randomly to receive atorvastatin (80 mg/day) or rosuvastatin (40 mg/day) by using a ratio of 1 : 1 in randomization. The levels of total cholesterol (TC), triglyceride, high-density lipoprotein cholesterol, LDL-cholesterol, oxidized-LDL, and PCSK9 were compared between groups after a 4-week treatment.

Results

Our study population included 53 patients in the atorvastatin group (age: 58.13±11.30 years, 11.32% female) and 53 patients in the rosuvastatin group (age: 59.08±12.44 years, 15.09% female). In both groups, lipid parameters, oxidized-LDL, and PCSK9 values changed significantly according to the baseline following treatment. High-dose atorvastatin and rosuvastatin induced similar decreases in LDL-cholesterol, oxidized-LDL, and triglyceride levels and similarly increased in high-density lipoprotein cholesterol and PCSK9 levels (P>0.05).

"Atorvastatin and Rosuvastatin treatment regimens have comparable effects on lipid parameters and PCSK9 levels in ACS patients."

4. Usefulness of Ezetimibe Versus Evolocumab as Add-On Therapy for Secondary Prevention of CV Events



Background and Aim

Evolocumab and ezetimibe, were both proven to significantly reduce the incidence of major adverse cardiovascular events (MACE), in type 2 diabetes patients with atherosclerotic cardiovascular disease and low-density lipoprotein (LDL) cholesterol >70 mg/dl despite statin therapy. Providing evolocumab for all such patients may be a significant burden on healthcare systems. Study aimed to analyze the treatment cost of ezetimibe versus evolocumab to prevent 1 MACE.

Methods

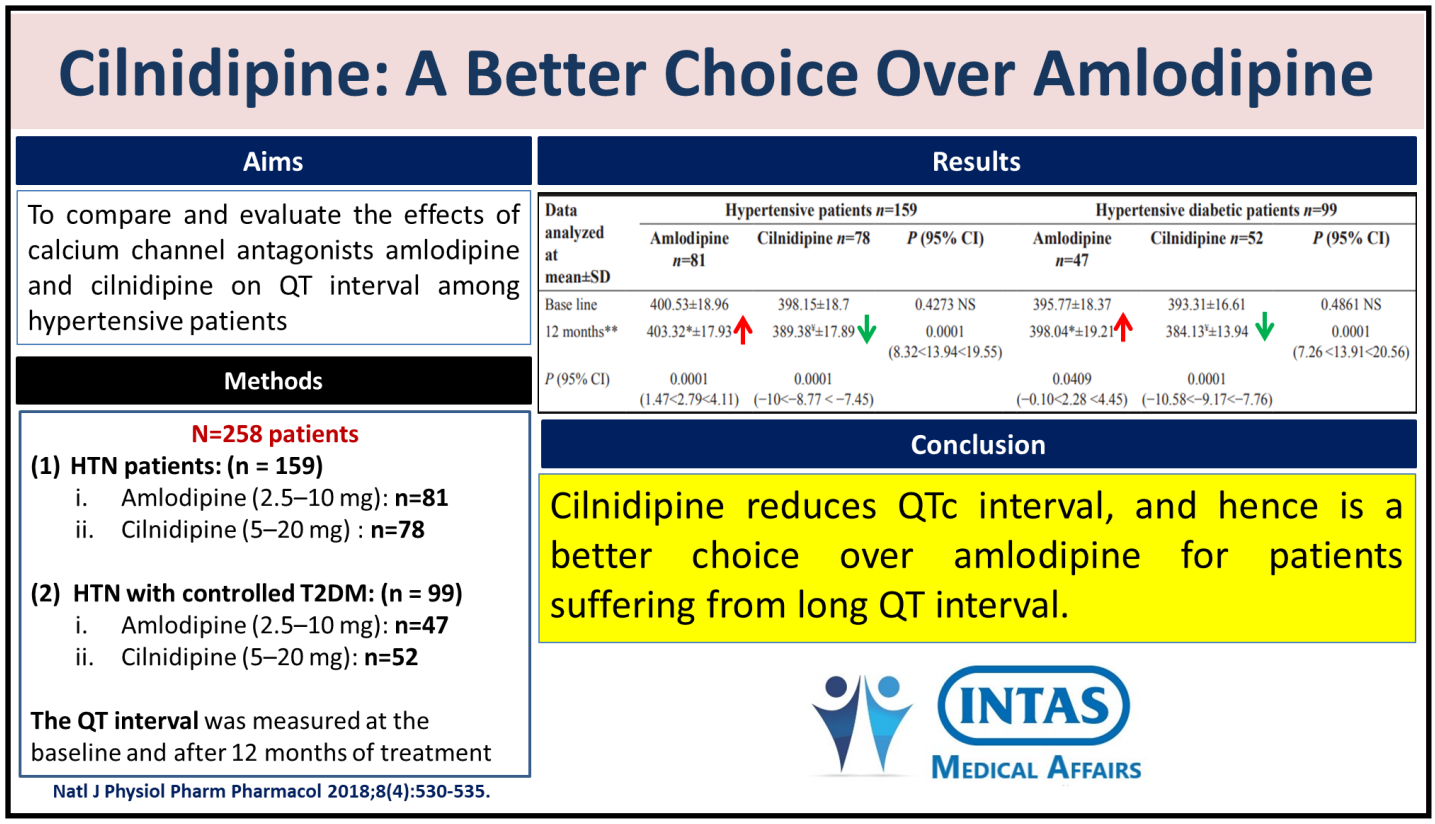
The number needed to treat (NNT) with evolocumab or with ezetimibe for avoiding MACE from the published FOURIER and IMPROVE-IT trials respectively was extracted. Drug costs were based on 2018 US prices. Sensitivity and scenario analyses were performed to overcome variances in terms of population risk, efficacy of therapies, and costs.

Results

In FOURIER, the 1-year NNT for avoiding MACE with evolocumab was 104 (95% confidence intervals [CI] 66 to 235). In IMPROVE-IT, the 1-year NNT with ezetimibe was 124 (95% CI 73 to 288). The annual cost of evolocumab and ezetimibe is $6,540 and $88, respectively. Therefore, the cost to prevent 1 MACE in the FOURIER and IMPROVE-IT trials would have been $678,981 (95% CI $429,810 to $1,537,910,149) and $10,870 (95% CI $6,384 to $25,322), respectively. Ezetimibe was consistently a cost-saving strategy compared with evolocumab, in all analyses performed, except for the case where evolocumab price is significantly reduced and the branded ezetimibe is used.

"Treatment with ezetimibe seems to be a major cost-saving strategy for preventing MACE in T2DM patients with atherosclerotic cardiovascular disease and LDL-C >70 mg/dl despite statin therapy."

5. Cilnidipine: A Better Choice Over Amlodipine



Background

The duration of the QT interval as measured by 12-lead electrocardiography is a measure of myocardial repolarization and is widely used to describe cardiac abnormalities, to determine the presence of cardiac toxicity and to evaluate drug safety.

Aim

To compare and evaluate the effects of calcium channel antagonists amlodipine and cilnidipine on QT interval among hypertensive patients.

Methods

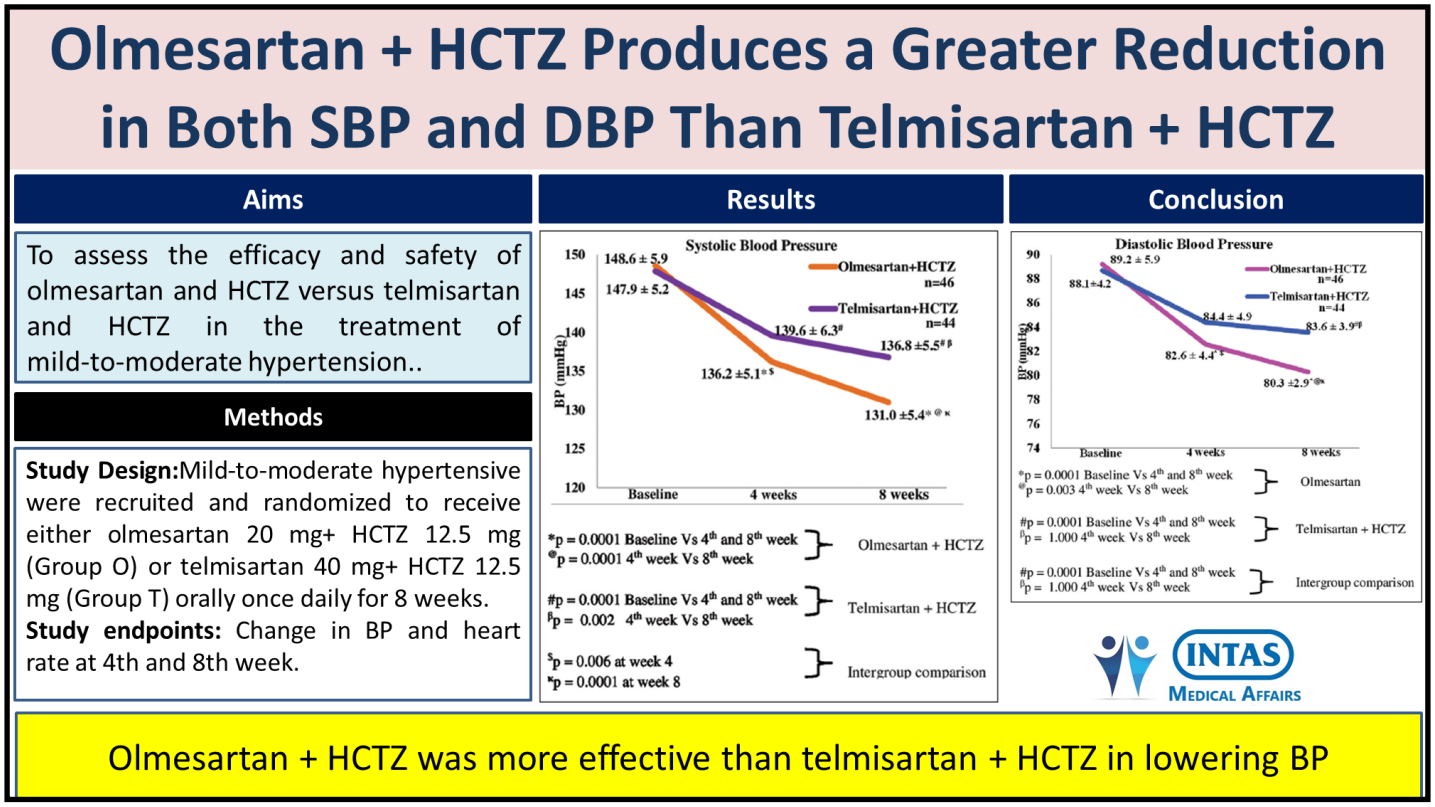
A total of 258 patients were screened, examined, and enrolled as study participants during that period. The enrolled patients were then divided as (1) hypertensive patient (n = 159) - selected patients received either amlodipine (2.5–10 mg) or cilnidipine (5–20 mg) with or without angiotensin receptor blocker (ARB) and (2) hypertensive with controlled diabetic patients (n = 99) - selected patients received either amlodipine (2.5–10 mg) or cilnidipine (5–20 mg) with or without ARB along with antidiabetic medication. Calculated by Bazett's formula (most commonly used) = QT Interval/√ (relative risk [RR] interval) where RR interval = 60/heart rate, normal QTc ≤440 ms. The QT interval was measured at the baseline and after 12 months of treatment for hypertensive patients.

Results

There was extremely significant QTc reduction was seen with cilnidipine therapy and significant elevation seen by amlodipine treatment but without any clinical relevance. While comparing the effect of amlodipine and cilnidipine, extremely significant as well as clinically relevant difference between the two treatments was noted.

"CILNIDIPINE REDUCES QTC INTERVAL, AND HENCE IS A BETTER CHOICE OVER AMLODIPINE FOR PATIENTS SUFFERING FROM LONG QT INTERVAL."

6. Olmesartan + HCTZ Produces a Greater Reduction in Both SBP and DBP Than Telmisartan + HCTZ



Aim

To assess the efficacy and safety of olmesartan and HCTZ versus telmisartan and HCTZ in the treatment of mild to moderate hypertension.

Methods

A total of 120 patients with mild to moderate hypertension were recruited and randomized to receive either olmesartan 20 mg+HCTZ 12.5 mg (Group O) or telmisartan 40 mg+HCTZ 12.5 mg (Group T) orally once daily for 8 weeks. Blood pressure (BP) and heart rate were recorded at baseline and at 4th and 8th weeks, but blood sugar and lipid profile were estimated at baseline and 8th week.

Results

Forty six Group O and 44 Group T patients completed the study. Majority of patients were in the fifth decade of life (72.3%), 56% were males, and 35% had type II diabetes mellitus and received oral antidiabetics. The mean BP was 148.6 ± 5.9/89.2 ± 5.9 and 147.9 ± 5.2/88.1 ± 4.2 mmHg at baseline and decreased significantly at week 8 (131.0 ± 5.4/80.3 ± 2.9 and 136.8 ± 5.5/83.6 ± 3.9 mmHg) in Group O and Group T respectively. Patients in Group O had significant reduction in systolic BP (SBP) (P = 0.0001) and diastolic BP (P = 0.04) than that in Group T. More than 10 mmHg decrease in SBP was observed in 86.9% versus 65.9% of patients in Group O and Group T, respectively, which was statistically significant (P = 0.01). Diabetic patients in both groups had a significant decrease in blood sugar by week 8, but intergroup comparison was insignificant. Change in heart rate and lipid profile was negligible. Common adverse effects were dizziness, abdominal pain, and pedal edema in both groups.

"Olmesartan + HCTZ was more effective than telmisartan + HCTZ in lowering BP."

Abbreviated Prescribing Information

Lipicure

Active Ingredient: Lipicure 10/20/40/80 tablet contains atorvastatin 10mg, 20mg 40mg or 80 mg respectively. **Indication:** To reduce elevated total cholesterol and triglyceride levels in patients with primary hypercholesterolemia and mixed dyslipidemia. **Dosage & Administration:** Once a day or as directed by physician. **Contraindications:** Active liver disease, women who are pregnant or may become pregnant. **Warnings & Precautions:** Skeletal muscle effects (e.g., myopathy and rhabdomyolysis), A higher incidence of hemorrhagic stroke was seen in patients without CHD but with stroke or TIA within the previous 6 months atorvastatin 80 mg. **Pregnancy & Lactation:** Pregnancy Category X. It is contraindicated in women who are or may become pregnant. **Interactions:** It is metabolized by cytochrome P450 3A4. Concomitant administration with strong inhibitors of CYP 3A4 can lead to increases in plasma concentrations of atorvastatin. **Adverse reactions:** The most common adverse reaction in adults was nasopharyngitis, arthralgia, diarrhea, pain in extremity, and urinary tract infection **Overdose:** There is no specific treatment for atorvastatin overdosage. In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required. Due to extensive drug binding to plasma proteins, hemodialysis is not expected to significantly enhance atorvastatin clearance. **Updated on:** Feb 2015

Lipitas

Active ingredient: Lipitas 5/10/20/40 mg tablet contains rosuvastatin 5/10/20/ 40 mg respectively. **Indication:** As an adjunct to diet to reduce elevated total-C, LDL-C, ApoB, non HDL-C, and TG levels to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and on familial) and mixed dyslipidaemia (Fredrickson Type IIa and IIb), elevated serum TG levels (Fredrickson type IV), slow the progression of atherosclerosis in adult patients as part of a treatments strategy to lower Total-C and LDL-C to target levels. **Dosage and administration**: Once a day or as directed by physician. **Contraindication:** Rosuvastatin is contraindicated in patients with a known hypersensitivity to any component of this product. Rosuvastatin is contraindicated in patients with active liver disease or unexplained persistent elevations of serum transaminase. **Warning & precautions:** The incidence of persistent elevations (>3 times the upper limit of normal [ULN] occurring on 2 or more consecutive occasions) in serum transaminases in fixed dose studies was 0.4, 0, 0 and 0.1% patients who received rosuvastatin 5, 10, 20 and 40 mg, respectively. Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with rosuvastatin and with other drugs in the class. **Pregnancy & Lactation:** Category X. Rosuvastatin may cause fatal harm when administered to pregnant women. Rosuvastatin is contraindicated in who are may become pregnant. Safety in pregnant women has not been established. There are no adequate and well controlled studies of rosuvastatin in pregnant women. If this drug is administered to a woman with reproductive potential, the patient should be appraise of the potential hazard to a foetus. **Interactions:** Co-administration of a single rosuvastatin dose to healthy volunteers on gemfibrozil (600mg twice daily) resulted in 2.2 and 1.9 fold, respectively. Increase in mean Cmax and mean AUC of rosuvastatin. Co-administration of rosuvastatin to patients on stable warfarin therapy resulted in clinically significant rises in INR (>4, baseline 2-3). **Adverse reactions:** Adverse experiences reported in 2% patients in placebo controlled clinical studies of rosuvastatin are as follows; pharyngitis, headache, diarrhea, dyspepsia, nausea, myalgia, asthenia, back pain, flu syndrome, urinary tract infection, rhinitis, sinusitis. **Overdose:** There is no specific treatment in the event of overdose. In the event of overdose, the patient should be treated symptomatically and supportive measures instituted as required. Hemodialysis does not significantly enhance clearance of rosuvastatin

SARTEL

Active ingredient: Sartel 20/40/80 tablet contains telmisartan 20/ 40/80 mg respectively. **Indication:** Treatment of hypertension to lower blood pressure. For the prevention of cardiovascular morbidity and mortality in patients 55 years older at high risk of CVD **Dosage and administration**: Once a day or as directed by physician. **Contraindication:** Telmisartan is contraindicated in patients with a known hypersensitivity to any component of this product. **Warning & precautions:** Avoid fetal or neonatal exposure. Correct any volume or salt depletion before initiating therapy and observe for signs and symptoms of hypotension. Monitor carefully in patients with impaired hepatic or renal function. Avoid concomitant use of ACE inhibitor and angiotensin receptor blocker **Pregnancy & Lactation:** Category D. When pregnancy is detected, discontinue telmisartan as soon as possible. Discontinue nursing or drug, taking into account the importance of the drug to the nursing mother **Interactions:** NSAIDs– increased risk of renal impairment and loss of antihypertensive effect. Do not co-administer aliskiren with telmisartan in patients with diabetes **Adverse reactions:** The most common adverse events (> 1%) reported in hypertension trials are back pain, sinusitis and diarrhea. **Overdose:** Hypotension, dizziness and tachycardia can occur. If symptomatic hypotension occur, supportive treatment should be instituted. Telmisartan is not removed by haemodialysis. **Updated on:** Feb 2015

ARVAST

Active ingredient: Arvast 5/10/20/40 mg tablet contains rosuvastatin 5/10/20/ 40 mg respectively. **Indication:** As an adjunct to diet to reduce elevated total-C, LDL-C, ApoB, non HDL-C, and TG levels to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and on familial) and mixed dyslipidaemia (Fredrickson Type IIa and IIb), elevated serum TG levels (Fredrickson type IV), slow the progression of atherosclerosis in adult patients as part of a treatments strategy to lower Total-C and LDL-C to target levels. **Dosage and administration**: Once a day or as directed by physician. **Contraindication:** Rosuvastatin is contraindicated in patients with a known hypersensitivity to any component of this product. Rosuvastatin is contraindicated in patients with active liver disease or unexplained persistent elevations of serum transaminase. **Warning & precautions:** The incidence of persistent elevations (>3 times the upper limit of normal [ULN] occurring on 2 or more consecutive occasions) in serum transaminases in fixed dose studies was 0.4, 0, 0 and 0.1% patients who received rosuvastatin 5, 10, 20 and 40 mg, respectively. Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with rosuvastatin and with other drugs in the class. **Pregnancy & Lactation:** Category X. Rosuvastatin may cause fatal harm when administered to pregnant women. Rosuvastatin is contraindicated in who are may become pregnant. Safety in pregnant women has not been established. There are no adequate and well controlled studies of rosuvastatin in pregnant women. If this drug is administered to a woman with reproductive potential, the patient should be appraise of the potential hazard to a foetus. **Interactions:** Co-administration of a single rosuvastatin dose to healthy volunteers on gemfibrozil (600mg twice daily) resulted in 2.2 and 1.9 fold, respectively. Increase in mean Cmax and mean AUC of rosuvastatin. Co-administration of rosuvastatin to patients on stable warfarin therapy resulted in clinically significant rises in INR (>4, baseline 2-3). **Adverse reactions:** Adverse experiences reported in 2% patients in placebo controlled clinical studies of rosuvastatin are as follows; pharyngitis, headache, diarrhea, dyspepsia, nausea, myalgia, asthenia, back pain, flu syndrome, urinary tract infection, rhinitis, sinusitis. **Overdose:** There is no specific treatment in the event of overdose. In the event of overdose, the patient should be treated symptomatically and supportive measures instituted as required. Hemodialysis does not significantly enhance clearance of rosuvastatin

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