

A Cross-sectional Analysis of the Role of Amlodipine Plus Metoprolol in the Management of Coronary Artery Disease and Hypertension

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ABSTRACT

Introduction: Hypertension affects all the organ systems of the body is one of the leading causes of morbidity and is a major cause of coronary artery disease (CAD) worldwide. The disease is affecting the working age population to a greater extent and developing countries' manpower is significantly affected. This has caused a large financial burden on the national health sector budget and the productivity of the nation is affected. Despite a number of blood pressure (BP) lowering medicines, the choice of the antihypertensive should be individualized considering the associated comorbid condition, age, pattern, and the severity of the BP. The advantage of combining calcium channel blocker (CCB) with a β adrenoceptor blocker is that though the modes of action of the two drugs are different but their action on BP is complementary. **Materials and Methods:** After applying the selection criteria, a total of 440 completed and properly filled questionnaires were selected and the data were statistically analyzed. **Observation and Results:** CAD was the most common complication of hypertension seen by the physicians and it was seen in 67.9% and is more common among males. The most preferred antihypertensive among the clinicians for patients of hypertension with CAD was beta blockers among 39.5% and the reason for the same was that beta blockers have many advantages in controlling BP in patients with CAD. The combination of CCB with beta blockers was most commonly used by clinicians; it was used by 78.8% of the clinicians. **Conclusion:** The combination of CCBs with beta blockers was most commonly used for the treatment of patients of hypertension with CAD and stable angina along with the incorporation of lifestyle modification. A longtime gap is there for the development of coronary artery disease after the onset of hypertension. Heart failure is seen as the most common complication of it.

Key words: Beta blockers, calcium channel blockers, coronary artery disease, hypertension

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INTRODUCTION

Hypertension affects all the organ systems of the body is one of the leading causes of morbidity and is a major cause of coronary artery disease (CAD) worldwide.^[1] CAD in India is on the increase as the country harbors maximum cases of hypertension and diabetes mellitus and together the figure is greatly increased. Apart

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from CAD, it is also a major cause of cerebrovascular accidents, and cardiac and renal failure.

It has been projected that cardiovascular-related mortality in developed countries has increased and is estimated up to 6 million in 2020, the same trend is seen in under-developed and developing nations also where it has reached 19 million.^[2,3] The disease is affecting the working age population to a greater extent and developing countries' manpower is significantly affected. This has caused a large financial burden on the national health sector budget and the productivity of the nation is affected. The statistics clearly reflect the importance of controlling blood pressure (BP) so that its sequelae can be prevented. Despite lots of effort by the physician, BP is difficult to control and the major issue is fluctuation in the BP which further leads to end organ damage and thereby increases morbidity.

Despite a number of BP lowering medicines, there is difficulty in achieving the target BP, and the cause of the same is multifactorial. The choice of the antihypertensive should be individualized considering the associated comorbid condition, age, pattern, and the severity of the BP. The antihypertensive and lipid lowering to prevent heart attack trial supported the combination therapy for BP and reported that irrespective of the initial antihypertensive agents; more than 40% of hypertensive patients require two or more drugs at the end of 4 years of treatment.^[4]

The clinical practice has shown that there is difficulty in treating the BP with monotherapy as the causation is multifactorial and multiple parameters need to be addressed and monitored during the course of follow-up. Hence, many studies have proven the role of a combination of antihypertensives in the treatment of hypertension. The rationale in the combination is that the mode of action should be different of the two drugs and also the side effects should be minimum.

The various antihypertensive agents in various classes which are frequently combined in fixed dose combinations are diuretics, calcium channel blockers (CCBs), angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and β adrenoceptor blockers. The combined use of two antihypertensives may provide enhanced efficacy and similar tolerability to the same dosages of the individual drugs administered as monotherapy and by combining drugs each agent must also be able to neutralize counter-regulatory mechanisms triggered by the other.

The advantage of combining CCB with a β adrenoceptor blocker is that though the mode of action of the two drugs are different but their action on BP

is complementary. The β adrenoceptor blocker might regulate any CCB-induced acute reflex increase in sympathetic activity and conversely, the CCB might compensate for the peripheral vasospasm and drop in cardiac output caused by the β adrenoceptor blocker; thus, reducing the overall burden of side effects. These properties of the two drugs are the key to ensuring effective control of the BP as well as better long-term compliance with the therapy.

Metoprolol is a selective β_1 blocker and is devoid of sympathomimetic activity and possesses a weak membrane stabilizing activity, its Controlled release/extended release (CR/ER) formulation has been designed to provide relatively constant metoprolol concentration in the plasma whereas, Amlodipine is a dihydropyridine CCB causing vasodilatation as well as the reduction in peripheral vascular resistance, thereby reducing the BP. In the combined analysis of clinical trials, amlodipine was found to have protection against stroke and myocardial infarction.^[5,6]

The present survey has been conducted among clinicians who are regularly seeing hypertensive patients to assess the role of combination therapy of metoprolol and amlodipine in the prevention and control of CAD and their opinion on prescribing different antihypertensives.

MATERIALS AND METHODS

The present cross-sectional study is a questionnaire-based survey. The validated questionnaire consisted of 25 structured questions. The study was approved by the institutional ethical committee of After the approval from the ethical committee, the questionnaire was distributed among clinicians in different parts of the country. The clinicians included were cardiologists and general physicians dedicated in the practice of hypertension. The survey was conducted over a period of 6 months. All the completed forms were included in the study whereas incomplete forms were excluded from the study. After applying the selection criteria as mentioned above, a total of 440 completed and properly filled questionnaires were selected and the data was entered in the Microsoft Excel sheet. The data were statistically analyzed and presented.

OBSERVATION AND RESULTS

The following were the observations and results obtained after the data were analyzed.

The minimum qualification of the clinicians included in the study was post-graduation in Medicine and many were super-specialized in cardiology.

CAD was the most common complication of hypertension seen by the physicians and it was seen in 67.9%, renal dysfunction was seen in 16.4%, hypertensive emergency in 13.4%, and ocular complication in only 2% of the survey [Figure 1]. It is more common among males as compared to females.

About 45.6% of the clinicians are of the opinion that about 21–30% of their hypertensive patients develops CAD over a period of time [Figure 2].

The most preferred antihypertensive among the clinicians for patients of hypertension with CAD was beta blockers among 39.5%. It was 27% and 25% for CCB and ARBs respectively. However, many clinicians also prefer combination therapy initially and many reserve the combination therapy of antihypertensives working by different modes of action in cases where monotherapy does not provide effective control of BP.

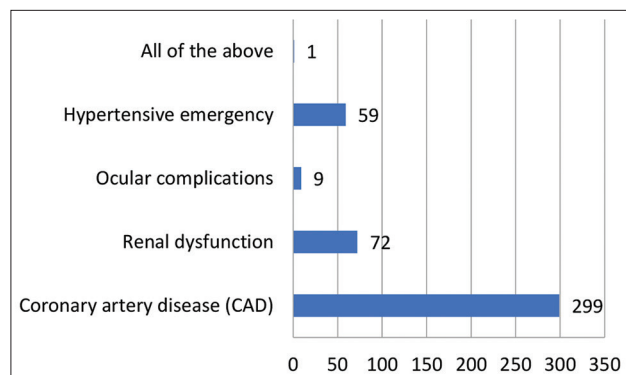


Figure 1: Common complication of hypertension

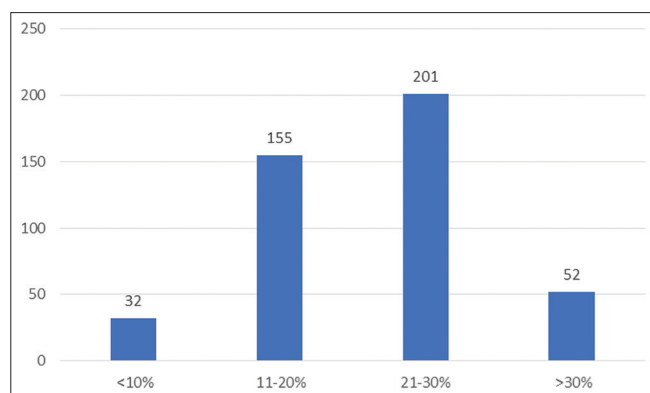


Figure 2: Opinion on the number of patients with hypertension seen to develop coronary artery disease over time

Most of the clinicians (42.3%) are of the opinion that beta blockers have many advantages in controlling BP in patients with CAD [Figure 3].

The most preferred antihypertensive among the clinicians for patients of hypertension with CAD was beta blockers among 39.5%. It was 27% and 25% for CCB and ARBs, respectively. However, many clinicians also prefer combination therapy initially and many reserve the combination therapy of antihypertensives working by different modes of action in cases where monotherapy does not provide an effective control of BP.

The most common reason why CCBs are preferred in patients with hypertension with a risk of CAD was antiatherosclerotic properties and the same was felt by 36.6% of clinicians in the survey. It has lesser side effects; first dose hypertension and a favorable dosing regimen were the other reasons quoted for its preference [Figure 4].

Fifty percent of the clinicians are of the opinion that they see heart failure as the most common complication

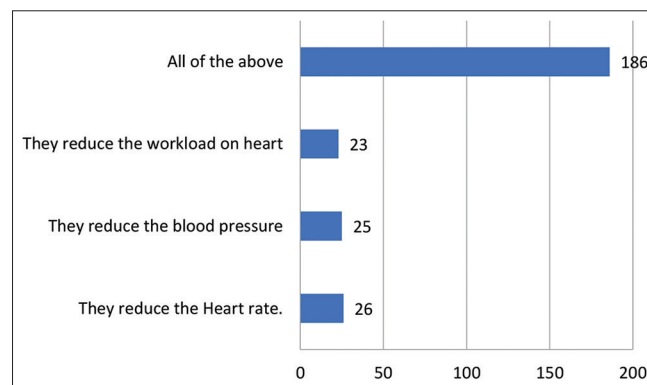


Figure 3: Reason for preferring beta blockers in patients with coronary artery disease

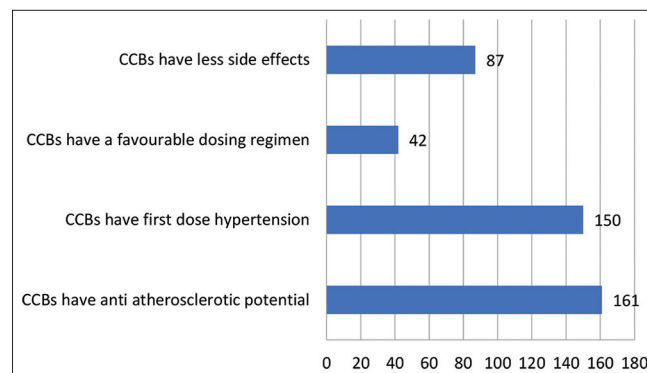


Figure 4: Reasons why calcium channel blockers are preferred in patients with hypertension with a risk of coronary artery disease

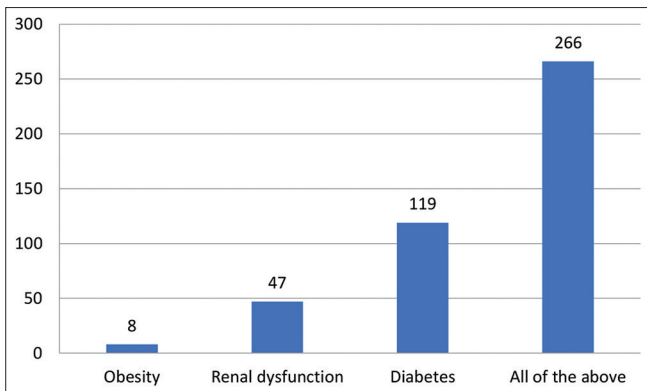


Figure 5: Common comorbid conditions associated with coronary artery disease

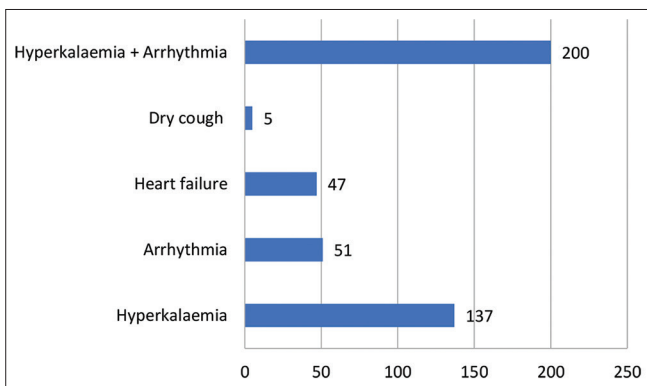


Figure 6: Disadvantage of angiotensin-converting enzyme inhibitors in patients with recent coronary artery disease

seen in patients with CAD and hypertension. Another complication is uncontrolled hypertension (28.4%), recurrent heart attacks (17.5%), and cerebrovascular accidents (3.8%).

It takes 1-5 years to develop CAD in cases with uncontrolled hypertension as per 51% of the clinicians out of their experience whereas 34.7% of clinicians say the duration is between 6 and 10 years and 7% believe it takes more than 10 years to develop CAD in cases of uncontrolled hypertension.

Physicians are of the opinion that the most common comorbid conditions associated with CAD apart from hypertension are diabetes mellitus, renal dysfunction, and obesity. However, 51.4% of patients had all three conditions, and 27% of clinicians think that diabetes is the most common comorbid condition. The study indicates that diabetes is the most common comorbid condition that directly and indirectly affects renal function.

The combination of CCBs with beta-blockers was most commonly used by clinicians, it was used by

78.8% of the clinicians and this was followed by CCBs with diuretics by only 8% of the clinicians [Figure 5].

The present study has found that the disadvantage of using ACE inhibitors in patients with recent CAD was the precipitation of heart failure, hyperkalemia, arrhythmia, and dry cough. The maximum reported side effects were both hyperkalemia and arrhythmia, which is reported by 200 (45.54%) clinicians in their patients [Figure 6].

The most common antihypertensives used for hypertensive emergencies by clinicians in their practice were CCBs (45.6%) and beta-blockers (22.5%). It was followed by ARBs and ACE inhibitors, very few clinicians used various combinations of nitro-glycerine, beta-blocker, and nitroprusside.

The most common causes of coronary stenting in cases of CAD are multiple vessel block, recurrent episodes of CAD, and failure of antithrombotic therapy.

Most of the clinicians (41.5%) usually monthly diagnose at least 20 cases of hypertension with CAD, and 10% of clinicians diagnose more than 40 cases of the same in a month. The most common age group affected by CAD with hypertension is the 40-50-year-old age group and 75% of the disease usually affects patients with an age >40 years.

Clinicians are of the opinion that patients should be encouraged to be strict with their medication along with certain lifestyle modifications such as regular exercise, cessation of smoking, and reduction in salt intake in a regular diet.

The opinion of clinicians on the combination of CCB and beta blockers in the treatment of CAD with hypertension is cost effective with less side effects, and effective control of BP. The combination helps in cardiac remodeling and works well in patients of stable angina. It also prevents endothelial dysfunction and reduces heart rate so less blood supply to the kidney. Therefore, it has got end organ protection.

Nitrates and beta-blockers are the most common drugs in the management of angina followed by CCBs and a combination of the drugs.

A combination of Amlodipine with metoprolol is preferred by clinicians in the age group of 40-50 years in 62.7% of patients with angina, 24% in the 50-60 years age group whereas clinicians prescribe the combination in <11% in age <40 years [Figure 7].

In the management of angina, most of the clinicians (69.77%) prefer a combination of amlodipine and metoprolol, beta blocker plus trimetazidine and amlodipine plus nitrates were preferred by 17.27%, and 12.95% of clinicians [Figure 8]. Amlodipine plus

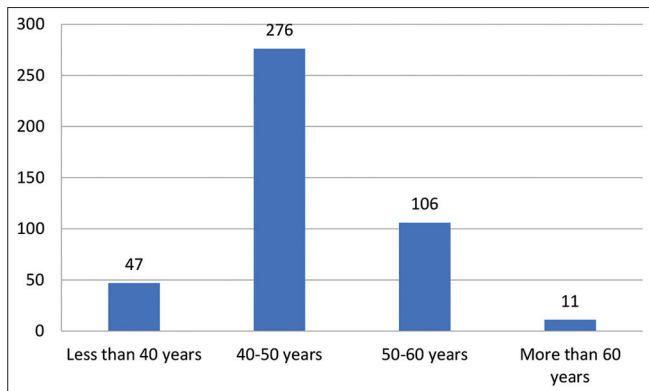


Figure 7: The age group of patients with angina in which amlodipine + metoprolol is preferred

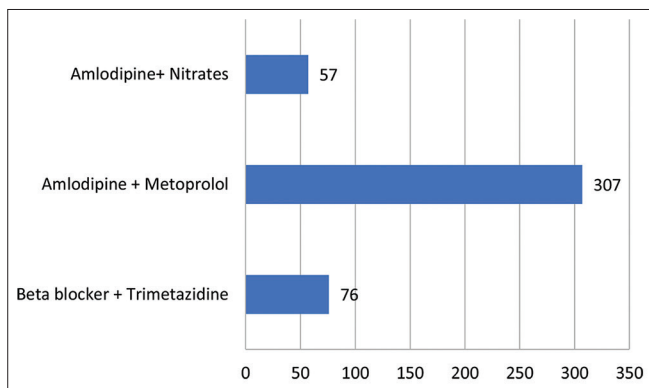


Figure 8: Preference of the clinicians in the management of angina

metoprolol was also the combination mostly preferred by clinicians in the treatment of hypertension associated with CAD.

Amlodipine + metoprolol was the most preferred combination by 53.6% of the clinicians for the management of hypertension co-morbid angina, rest of the clinicians seldom prescribe it for the management of the same.

The main parameter considered by clinicians for selecting the brand of antihypertensives for their patient is always the quality of the drug first and also a reasonable and affordable price is another criteria that are taken into account.

DISCUSSION

In a review done by Fuchs and Whelton^[7] found that high BP has the strongest association with the causation of CAD. A study done by Chen *et al.*^[8] has found an increase in the incidence of CAD attributed to hypertension.

Many studies such as those done by Fuchs and Whelton^[7] and Tilea *et al.*^[9] have established a strong correlation between hypertension and CAD but could not establish concrete data in terms of the probability of developing CAD.

The reason for preferring beta-blockers over others was multiple beneficial properties of it, as beta blockers reduce the workload on the heart apart from reducing the BP and heart rate. Khan *et al.*^[10] advocated the beneficial role of beta blockers in acute myocardial infarction. Ray *et al.*^[11] also advocated the role of beta blockers particularly β_1 selective blockers for the entire spectrum of cardiovascular diseases.

The CCBs provide multiple benefits in reducing BP in patients who also had the risk for CAD as seen in the study done by Fares *et al.*^[12] such as anti-atherosclerotic, cardio, and renal protective properties.

The present study has found combination therapy of CCB with beta blocker as the most preferred regimen. Studies shown by Pareek *et al.*^[6] has also found the beneficial effect in combining CCB and beta-blocker in hypertensive patients with CAD.

The high incidence of hyperkalemia has been reported by ACE inhibitors and this is attributable to the causation of arrhythmia also. Ko *et al.*^[13] has found in their study found lower rates of adverse clinical cardiovascular outcomes among older patients presenting with myocardial infarction with ARBs in comparison to ACEIs.

A review done by Arnold^[14] has found that coronary stenting has a clear benefit in cases of ST elevation myocardial infarction

The higher percentage of clinicians diagnosing hypertension with CAD (73.9%) in a month clearly indicates the severity of the disease in society and is a point of concern. Another point of concern is 75% of the patients are above 40 years and this clearly points out that as the duration of the disease increases so does the chances of CAD. The measure to improve the outcome of patients with CAD includes compliance to the treatment with modification of lifestyle which includes cessation of smoking as it accelerates atherosclerosis. Limited use of salt improves BP and less salt in diet should be strictly followed, exercise increases the metabolism of fat and decreases peripheral insulin resistance and this add on in decreasing the insulin resistance and rate of atherosclerosis.

Glazer^[15] in their study on Trimetazidine-bisoprolol combination in the treatment of angina in symptomatic patients found it to be effective in reducing the frequency of angina attacks, the benefits

of the same were found to be observed within 2 weeks of the treatment and well tolerated.

CONCLUSION

A long-time gap is there for the development of CAD after the onset of hypertension and the gap can even be reduced to within 5 years in cases where the hypertension gets uncontrolled. Heart failure is seen as the most common complication of it. Other comorbid conditions associated with CAD apart from hypertension are diabetes mellitus, renal dysfunction, and obesity. The combination of CCBs with beta-blockers was most commonly used for the treatment of patients of hypertension with CAD and stable angina along with the incorporation of lifestyle modification including cessation of smoking.

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