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Effectiveness and safety assessment of calcium channel blockers compared to beta blockers in patients with angina: An observational study

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Abstract: Beta blockers (BB) and calcium channel blockers (CCB) are highly effective to suppress angina attacks. Current observational study is designed to investigate the effectiveness of BB, CCB, and its combination in angina patients. Angina patients from different tertiary care hospital cardiology OPDs were recruited from June 2022 to June 2023. Patient's history and suspected adverse drug effects (ADE) observed by manual chart review. Results showed baseline demographics and comorbidities were similar. Medication assessment revealed that most patients were on CCB (54.4%) and BB (36.36%) than combination (9.8%). Compared with BB, CCB and combination drugs taking patients represented stable heart rate and blood pressure ($P<0.05$). There were insignificant differences were observed in electrolytes and lipid profile in each groups. In addition, the Seattle questionnaire for angina (SQA) showed improved symptoms in 83 patients out of 110 ($P<0.05$). Further ADE were observed by using Naranjo scale that represented BB taking patients were found to have more ADRs than CCB and combination therapy. In conclusion, patients using BB, CCB or a combination of CCB+BB had improved angina symptoms and represented same efficacy however CCB exhibited lesser number of ADRs that shows CCB is more effective than BB in prolong use of angina control

Keywords: Angina, beta-blockers, calcium channel blockers, seattle score, Naranjo Scale, adverse drug effects

INTRODUCTION

Angina pectoris is a prevalent sign of myocardial ischemia in people who have obstructive coronary artery disease. This condition is characterized by discomfort in the substernal chest that can be provoked by physical activity or mental stress and can be alleviated by taking rest or nitro-glycerine (AlBadri *et al.*, 2017). Ischemia of the myocardium happens when the blood supply to the coronary arteries is inadequate to supply the required amount of oxygen to the heart muscle. The most common cause of myocardial ischemia is atherosclerotic obstruction of one or more of the coronary arteries (Radico *et al*., 2014). However, any significant imbalance between myocardial oxygen supply and demand can lead to myocardial ischemia and angina (Sabidó *et al*., 2019). The prevalence of angina varies between countries, it appears to be about 2%–7% among middle-aged individuals in developed countries (Haq., 2021). Angina causes 25% of the total deaths in developed and 80% in middle and low income countries. The prevalence of angina in Pakistan is 26.9% and it is one of the leading causes of death (Zuhaid *et al*., 2014). However females are more vulnerable for precipitating angina as Zubair *et al.*, 2018 reported angina is more common in females than males (18.30% women and 16.60% men) in Pakistan.

To combat the rising prevalence of ischemic heart disease and related problems in changing socioeconomic situations in Pakistan requires comprehensive public health policies that include preventive interventions and conveniently accessible healthcare facilities. European and US guidelines recommend that stable angina should be routinely treated with either a β-blocker (BB) or calcium channel blocker (CCB) (Kloner & Chaitman., 2017). BB and CCB are essential drugs to treat angina and related cardiac disorders (Jain *et al*., 2017). These drugs can be used alone or with nitrates if necessary. Recent research suggests beta-blockers may be useful in treating abrupt cardiac episodes (Mehta *et al*., 2021). Randomized clinical trials have shown BB and CCB are effective in chronic heart failure with left ventricular systolic dysfunction (Wu *et al*., 2023; Kim *et al*., 2023). Verapamil, diltiazem, and amlodipine have each been shown to be effective antianginal agents in patients with chronic stable angina. Multiple clinical trials have indicated that these drugs reduce episodes of angina, diminish nitroglycerin consumption, improve exercise

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performance, and lessen ischemic electrocardiographic changes during exercise (Pascual *et al*., 2016; Cruz Rodriguez & Alkhateeb, 2020). Similarly, BB like bisoprolol, atenolol, and carvedilol alone and in combination with long-acting nitrates, had been used as standard medical therapy in most of the angina patients (Shu *et al.*, 2012). Now, with the broader use of CCB for ischemic chest pain, it is useful to consider the potential beneficial interactions between CCB, BB and its combination, as well as possible adverse drug-related effects.

Current literature suggests a significant number of angina patients in Pakistan are taking BB and CCB, however the effectiveness of these drugs have still not been evaluated in our population. CCB and BB's treatment in angina patients associated with different symptoms and adverse drug reactions (ADRs), such as tiredness, sleep disturbances, dry mouth, edema, GI discomfort, electrolyte imbalance and impotence (Tuchinda *et al*., 2014; Rajak *et al.*, 2022). In the treatment of angina ADRs and the patient's perceptions of them play an important role to gain success in the therapeutic regimen. However ADR monitoring and reporting activity is in its preliminary stage in Pakistan as DRAP (Drug Regulatory Authority of Pakistan) has been working recently on collecting the ADR data (Hussain *et al*., 2022).

The lack of well-structured and effective ADR reporting and monitoring programs is a major problem in Pakistan. Studies from various literature revealed that review and monitoring of prescribed medicines by pharmacists may help to improve the clinical condition of the patients and may reduce the incidence of adverse events and also the cost of treatment (Arredondo *et al.*, 2021). Thus current study was designed to evaluate the effectiveness of BB, CCB, and its combination in Angina patients. This study will help clinicians to choose more appropriate medication selection with the least ADRs.

MATERIALS AND METHODS

This study was performed in two tertiary care hospitals that provide cardiac care to approximately 50-100 patients in a month, the age ranges from 20-75 years. The study was approved by the Institutional Bio-ethical Research Committee of University of Karachi, with reference No. (IBC KU-317/2023) of Informed consent was taken prior from all enrolled patients since the study did not involve any intervention.

Eligibility

110 patients of 25-75 years were enrolled during 1 year study period from June 2022 to June 2023. Both males and females' genders were included after appropriate consent.

Inclusion criteria

All newly diagnosed angina patients (1month-2year) were recruited randomly who were receiving beta-blockers/calcium channel blockers medications.

Exclusion criteria

Patients who were not prescribed CCB and BB therapy, All mentally compromised or unconscious patients; Patients with other comorbidities including myocardial Infarction, Hyperthyroidism, congestive heart failure, and any congenital abnormality; Patients unable to respond to verbal questions and females who are pregnant or breastfeeding or on the oral contraceptive pill.

Sample size

The determination of sample size was done based on data from past studies (Jafar *et al*., 2005) and calculated from a formula on SPSS with a sample size of angina 26.90%, precision 8% and 95% confidence Interval. 110 participants were newly diagnosed with angina and undergoing treatment for at least 1.5 years were recruited.

Study design procedure

All newly diagnosed patients who visited cardiology OPD were recruited by the physician according to AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR 2021 Guideline (Writing committee members, *et al*., 2021). After recruitment pharmacist had taken demographics and performed therapeutic drug monitoring of all medications prescribed with beta-blockers and calcium channel blockers. The effectiveness and safety profile of these drugs was evaluated by assessing Seattle angina questionnaire - 7 test that measures patient-reported symptoms, function and quality of life for patients with angina (Jones *et al*., 2013).

A subjective assessment of symptoms was also taken, with the following grading system: 1) angina relieved (patient asymptomatic); 2) angina improved; 3) angina unchanged; 4) angina worsened. Based on symptoms, clinical profile and results of non-invasive testing (exercise stress test and stress imaging test). Further blood pressure and heart rate were also measured to assess the patient's condition.

Anthropometric measurements were measured following a standardized protocol (Huqi *et al*., 2016). Weight was measured without shoes with an electronic scale to the nearest 0.1 kg; height was measured and BMI was calculated for each participant respectively. SBP, DBP, and heart rate were measured by OMRON®M6 (HEM 70001). Participants were seated in a separate room for 10 min with their backs supported and feet on the ground. Two SPB readings were taken at 10-minute intervals, and the lowest measure was used. Finally, the blood samples were collected by venipuncture in heparinized tubes and stored at -80°C until assayed (Orsini *et al.*, 2022). TG,

TC, HDL, urea and creatinine were measured using enzymatic methods while electrolytes were measured from frozen serum using an Immulite 2000 analyzer (DPC Bierman GmbH, Bad Nauheim, Germany).

Data collection

The data was collected on a structured performa filled by the participation of clinical pharmacists in daily rounds at cardiac OPD. Structured performa was finalized in a review of published literature by the research team. It comprised numbered items, and these items were shortlisted after consultation with the senior cardiologist and pharmacist practicing within the hospital.

Moreover, any other information that was considered essential during data collection was noted regardless of the presence of this item in the performa. The data recorded includes the demographics of patients i.e., weight, gender and age, co-morbidity, past medication history, vital signs, laboratory values,and the treatment plans. Angina symptoms and quality of life were evaluated by the Seattle Angina Questionnaire shortened version (SAQ-7) (Jones *et al.*, 2013).

Adverse drug reactions determination

Medication chart review and direct observation method were used to detect adverse drug reactions and the probability that a drug caused ADRs, was determined by using the Naranjo algorithm. According to the Naranjo scale, the possibility that the adverse reaction is related to drug therapy is expressed as definite, probable, possible, and precise which are based on a simple questionnaire (Naranjo., 1981). The algorithm comprises 10 questions each with distinct marks score of ≥9 considered "definite", 5 to 8 "probable", 1 to 4 "possible" and those ≤0 "doubtful" likelihood of the drug causing the ADR.

STATISTICAL ANALYSIS

The data were analyzed using one way ANOVA, the chi-square test and t test on SPSS version 26.0. The results were presented as percentages and numerically coded for the ease of descriptive statistics. Graph Pad Prism software version 9.0 were used to plot the graph. Final p values less than 0.05 were considered significant.

RESULTS

Patient's Demographical Characteristics

A total of 110 patients completed all study assessments. The baseline demographical characteristics of the sample population are listed in table 1. This table showed no statistically significant differences among all patients using sex, age, weight, BMI, duration of angina, SBP, DBP, heart rate, comorbidity, lifestyle, triglycerides, HDL, LDL, electrolytes, urea and creatinine. table 1 shows that 110 patients were enrolled (61 male, 49 female) with a median age of 54.12 years, median BMI was 27.22 kg/m^2 and duration of angina was 1.7 years. 61(55.45%) patients were living with sedentary life style while 49 (%) patients were lived healthy active life.

Among 110 patients 68 (61.81%) patients were with hypertension history, 18 (16.36%) were with diabetes, 5 (4.54%) were with renal impairment and 19 (17.27%) patients were with dyslipidemia comorbidity. All patients showed slightly raised mean SBP 139.75 mmHg while the mean DBP were up to normal 85.89 mmHg. Among all angina patients, the mean heart rate was normal as values are within the range (83.45) beats/min. Out of 61 male 16 (14.54%) male patients were smokers and 94 (85.45%) were nonsmokers.

All participants showed mild hyperlipidemia as mean triglycerides levels were 168.87mg/dl, HDL 41.15 and LDL levels were 82.66mg/dl. Similarly, Urea and creatinine levels were found to be raised in angina patients 44.25mg/dl and mean creatinine levels were 1.5mg/dl. The mean electrolyte values were found to be normal sodium (135.98), potassium (4.25) and chloride levels were within the range 97.34mEq/L respectively.

Comparison of past medication history among angina patients

Table 2 showed a comparison of past medication history among angina patient data analyzed by chi-square test that represented significant differences among beta blocker and calcium channel blocker use among male and female patients $P<0.05$. while the use of combination therapy BB+CCB was found to be insignificant $P>0.05$ among both genders. All of the patients were treated according to ACCA Angina guidelines, majority of the participants were receiving four frequently prescribed drugs anti-anginal drugs BB (45.45%), CCB (40.9%), CCB+BB (13.63%), Hypolipidemic agents (statins 100%), anti-thrombotic agents (clopidogrel/Aspirin 73.63%) and diuretics (16.36%).

All participants were taking statins especially Rosuvastatin as 33 (54.1%) male patients and 28 (57.1%) female patients were taking Rosuvastatin. Atorvastatin was taken by 20 (32.8%) male and 15 (30.6%) female patients, while use of simvastatin was lesser as 8 (13.1%) male and 6(12.2%) female were taking simvastatin.

The use of the antithrombotic agents among both genders was insignificant $P>0.05$ as both genders were taking aspirin, females were taking clopidogril significantly as compared to males (6 (9.83%), 14 (28.57%) female). Diuretics were used by most of the male angina patients 15 (24.5%) while females 3 (6.12%) were observed with significantly a smaller number of diuretics users $P<0.05$.

Table 1: Represents demographics of angina patients, data analyzed by one Way ANOVA and by cross tab (chi-square), significant ≤0.05, highly significant ≤0.01

Demographics (N=110)	
Age (years)	54.12±9.18
Gender Male	55.45% (61)
Female	44.54% (49)
Weight (kg)	65.0±9.59
BMI(kg/m^2)	27.22±4.8
Duration of Angina (years)	1.73±0.58
Life style Sedentry	61(55.45%)
Non-sedentry	49(44.54%)
Comorbidity	
Hypertension	68 (61.81%)
Diabetes	18(16.36%)
Renal impairment	5 (4.54%)
Dyslipidemia	19 (17.27%)
SBP mmHg	139.75±15.7
DBP mmHg	85.98±5.84
Heart rate beats/min	83.45±9.1
Smoking History Yes	16 (14.54%)
No	94 (85.45%)
Tryglycerides (mg/dl)	168.87±94.59
HDL (mg/dl)	41.15±4.64
LDL (mg/dl)	82.66±30.76
Urea (mg/dl)	44.25±22.08
Creatinine (mg/dl)	1.5±0.94
Sodium (mEq/L)	135.98±14.06
Potassium (mEq/L)	4.25±0.89
Chloride (mEq/L)	97.34±2.17

Table 2: Comparison of past medication history among angina patients, data analyzed by cross tab (chi-square), significant ≤0.05, highly significant ≤0.01

Medications	Male (N-61) %	Female(N-9) %	P value
Beta Blockers	22 (36.1%)	28(57.1%)*	<0.05
Calcium Channel Blockers	33 (54.4%)*	12 (24.5%)	<0.05
Combo (BB+CCB)	6 (9.8%)	9 (18%)	>0.05
Statins Rosuvastatin	33 (54.1%)	28 (57.1%)	>0.05
Atorvastatin	20 (32.8%)	15 (30.6%)	>0.05
Simvastatin	8 (13.1%)	6 (12.2%)	>0.05
Antithrombotic agents yes	41 (67.2%)	40 (83.3%)	>0.05
No	20 (71.4%)*	8 (28.6%)	<0.05
Aspirin	35 (57.37%)	26 (53.06%)	>0.05
Clopidogril	6 (9.83%)	14 (28.57%)*	<0.05
Diuretics Yes	15 (24.5%)*	3 (6.12%)	<0.05
No	46 (75.4%)	46 (93.87%)	>0.05

Table 3: represents percentage of beta blockers use among participants, data analyzed by cross tab (Chi square), significant ≤0.05, highly significant ≤0.01

Beta blocker therapy	Bisoprolol	Propranolol	Nebivolol	Carvedilol	Atenolol	Metoprolol
Patients (n=110)	40(36.36%)	3(2.7%)	7(6.36%)	10(9.09%)	2(1.8%)	4(3.63%)
Daily dose (mg/day)	16.01±2.58	166.7±21.33	5.0±2.11	25.56±10.98	50.2±13.25	96.2±34.87

Table 4: Represents percentage of CCB and combination of BB+CCB therapy use among participants, Data analyzed by one Way ANOVA and cross tab (chi-square), significant ≤0.05, highly significant ≤0.01

CCB therapy	Amlodipine	Diltiazem	CCB+BB
Patients (n=110)	13 (11.81%)	12 (10.9%)	20 (18.18%)
Daily dose (mg/day)	10.0±4.24	250.6±56.8	82.5+5.0

Table 5: Comparison of self-assessment angina scale and SQA score among angina patients

Self-Assessment Scale	Male (N-61) %	Female (N-49) %	P value
Angina relieved	4 (6.55%)	4 (8.16%)	>0.05
Angina improved	45 (73.77%)	38 (77.55%)	>0.05
Angina unchanged	10 (16.39%)*	5 (10.20%)	<0.05
Angina worsened	2 (3.27%)	2 (4.08%)	>0.05
Seattle Questionnaire for Angina (SQA) score	85.75 ± 16.3	84.98±15.92	>0.05

Data analyzed by by cross tab (Chi square) and One Way Anova, significant ≤0.05, highly significant ≤0.01

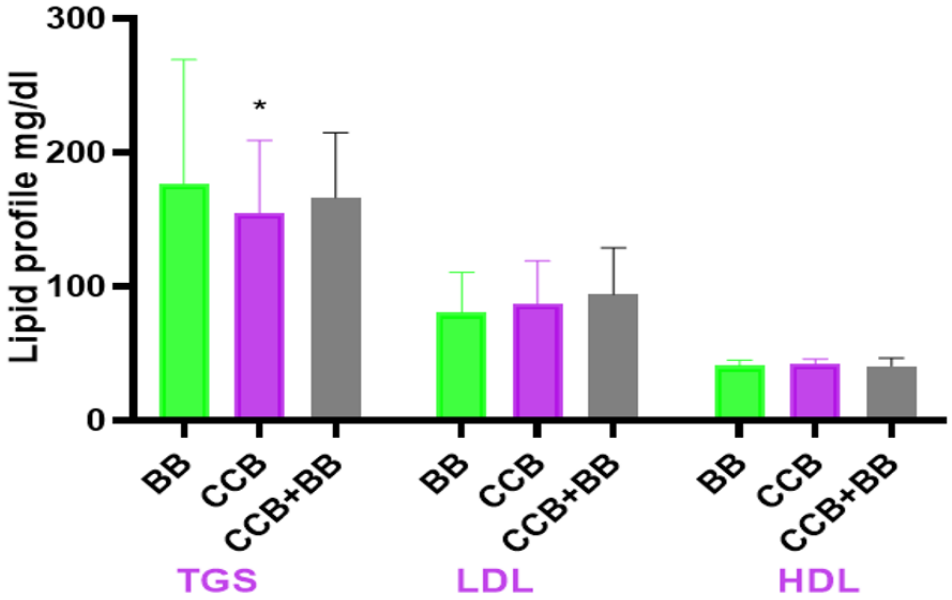

Fig. 1: Represents Mean and SD of lipid profile mg/dl in patients using beta blockers, calcium channel blockers and combination of beta blockers and calcium channel blockers, data analyzed by One Way Anova, significant ≤0.05, highly significant ≤0.01.

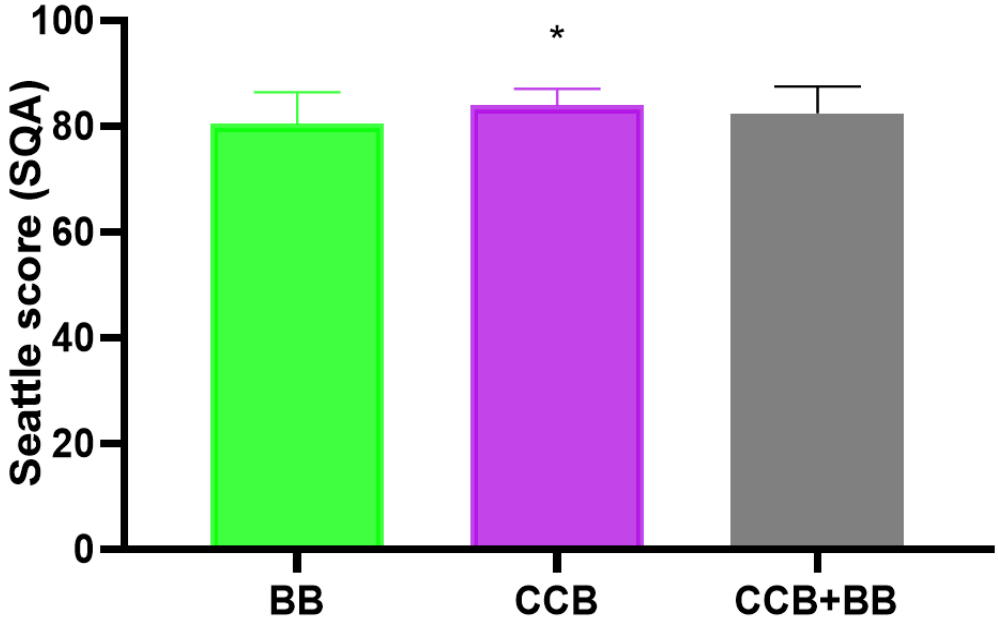

Fig. 2: Represents Mean and SD of Seattle score in patients using beta blockers, calcium channel blockers and combination of beta-blockers and calcium channel blockers data analyzed by one way ANOVA, significant ≤0.05, highly significant ≤0.01

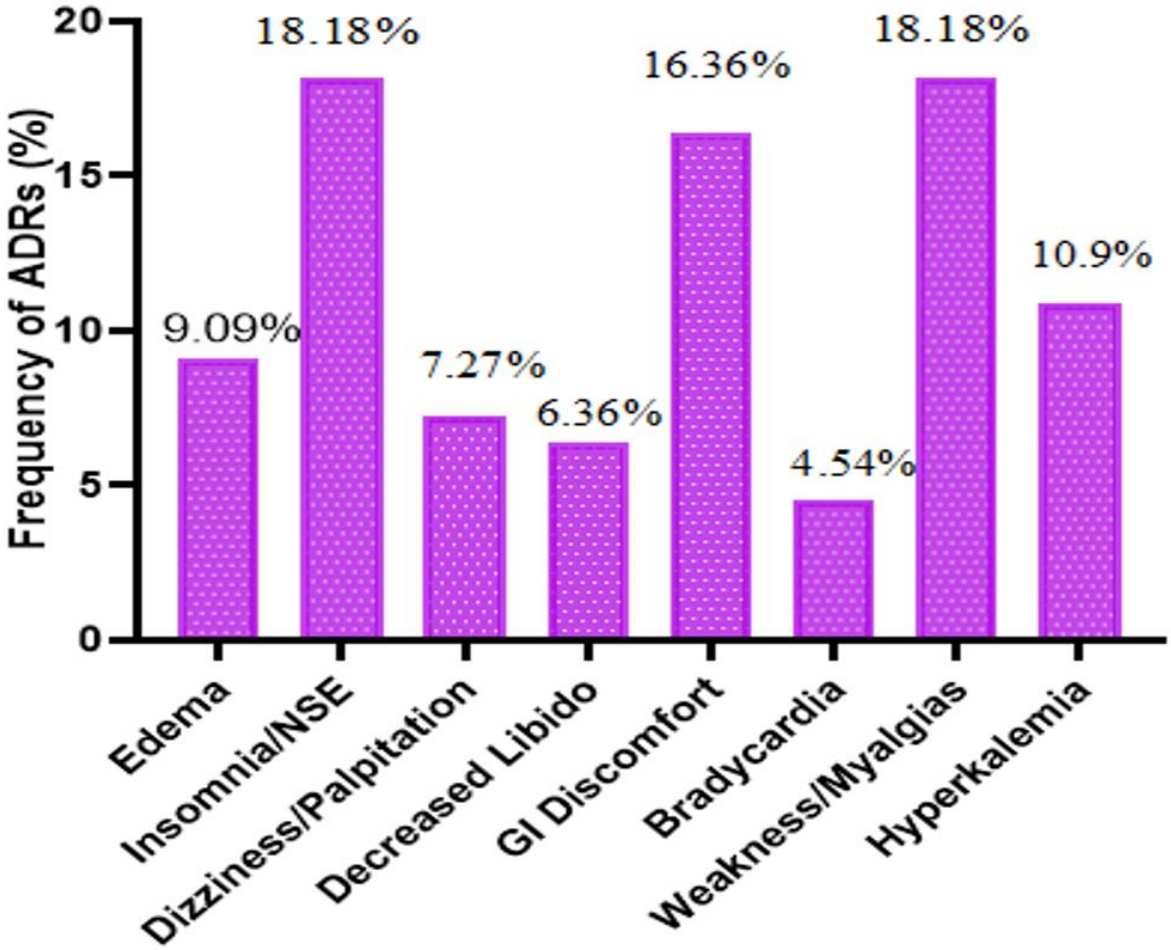

Fig. 3: Represents the percentage of adverse drug reactions in patients using beta blockers, calcium channel blockers, and a combination of beta-blockers and calcium channel blockers Data analyzed by cross tab (Chi square), significant ≤0.05, highly significant ≤0.01.

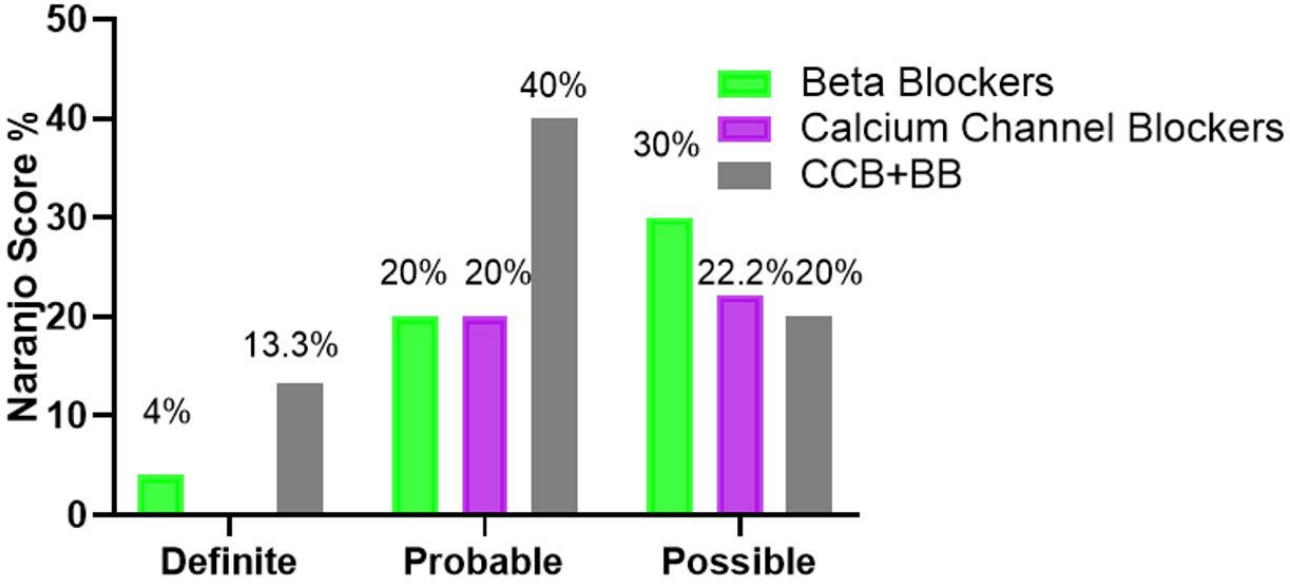

Fig. 4: Correlation of beta-blockers, calcium channel blockers, and combination therapy with Naranjo score. Data analyzed by cross tab (Chi square), significant ≤0.05, highly significant ≤0.01.

Beta-blocker and calcium channel blocker therapy of the study cohort

Table 3 and 4 represented the percentage use and prescribed daily dose pattern of BB, CCB and its combination among angina patients. At enrolment the majority of the patients were taking BB, among them the most used was by far bisoprolol [36.36%; mean dose (6.01±2.58)], followed by carvedilol [9.09%; mean dose (27.56±10.98)], nabivolol [6.36%; mean dose (5.1±2.11)], propranolol [2.7%; mean dose (166.7±21.33)], atenolol [1.8%; mean dose (55.2±13.25)] and metoprolol (3.63%; mean dose (96.2±34.87)]. Similarly the most prescribed CCB were amlodipine [11.81%; mean dose (10.1±4.24)] followed by dilitiazem [10.9%; mean dose (250.6±56.8)].

Comparison of Self-assessment angina scale and SQA score among Angina Patients

Table 5 Represented impact of BB and CCB therapy on angina patients, data showed anginal symptoms were significantly improved (P<0.05) in both genders however male patients were either asymptomatic with unchanged angina as compared to female.

Majority of the participants were asymptomatic except 4 (2 male+ 2 female) who reported angina symptoms in a month having Seattle score 71.2±45.2. Total 8 patients 4 (6.55%) male and 4 (8.16%) female were reported that they have relieved their angina after taking their medications with Seattle score 89.31±29.61 indicating a progressive improvement of the patient's functional status. Conversely, 15 patients 10 (16.39%) male and 5 (10.20%) female presented persistently symptomatic condition (with angina unchanged) having Seattle score 80.72±26.57 however out of 110 patients 83 were presented improved symptoms after 1.5±0.54 years treatment, 45 (73.77%) male and 38 (77.55%) females with Seattle score 85.93±32.41.

Correlation of beta blockers, calcium channel blockers and combination therapy with dyslipidemia

Fig. 1 represented the correlation of BB, CCB and their combination with TGS, LDL and HDL among angina patients, data analyzed by one way ANOVA and post hoc LSD that represented significant differences (P<0.05) in TGs levels among all treated groups. BB group showed raised TGs levels 76.6±92.8, followed by CCB 154.82±54.33 and combination group exhibited 166.46±113.1mg/dl respectively. LDL levels of BB, CCB and combination therapy were found to be insignificant P>0.05 among BB, CCB and combination group (80.58±29.97; 87.27±31.92 and 94.06±34.94 respectively). Similarly, HDL levels were found to be insignificant P>0.05 among BB, CCB and combination group (4.76±4.43, 42.31±3.48 and 40.0±5.91 respectively).

Correlation of beta blockers, calcium channel blockers and combination therapy with Seattle score

Fig. 2 represented the correlation of BB, CCB and their combination with seattle score among angina patients, data analyzed by one way ANOVA and post hoc LSD that represented significant differences among seattle score P<0.05 in all patient groups. BB group score was 80.46±5.99, followed by CCB 83.97±3.18 and combination therapy were also found to be significant better scores than BB 82.64±5.12. Results suggest comparatively improved quality of life and angina symptoms in CCB and combination group.

Frequency of adverse drug reactions observed in angina patients

Fig. 3 represents the frequency of adverse drug reaction observed in angina patients. Out of 110 patients, overall 57 patients reported minor to moderate ADRs that showed most of the patients treated with CCB's, reported weakness/myalgias and edema (P<0.05). However hyperkalemia, libido, palpitation and insomnia were the most reported ADRs of BB (P<0.05). In addition, BB+CCB combination patients also reported edema, palpitation/dizziness and GI discomfort (P<0.05).

Correlation of beta-Beta blockers, calcium channel blockers and combination therapy with Naranjo Scale

Fig. 4 represented the correlation of Naranjo score with treatment groups. Fig. showed four patients reported definite Naranjo score, among them, two patients were taking BB and the remaining two were taking a combination of BB+CCB. The observed ADRs by patients taking BB were insomnia and hypokalemia. While in patients taking combination therapy BB+CCB was reported nervous system effects/Insomnia and weakness / myalgia.

Among 25 patients with probable score BB taking patients were found to have more frequent ADRs, among them three patients reported insomnia, three patients reported dizziness, one patient reported hyperkalemia, two patients reported decreased libido and the remaining one reported GI discomfort/constipation. Similarly the CCB taking patients reported probable ADRs like weakness /myalgia, dizziness and one patient reported bradycardia. Probable scoring was found for six patients taking combination therapy BB & CCB, among them two patients reported GI discomfort, one patient reported weakness and myalgia, two patients reported bradycardia, palpitation and one patient reported edema.

Possible ADRs were detected in 28 patients among them five BB using patients reported dizziness, five patients reported GI discomfort, three patients reported palpitation and two patients reported bradycardia. Among patients taking CCB ten patients reported ADRs, five patients reported edema, three patients reported GI discomfort and

two patients reported bradycardia. Three patients who were taking combination therapy BB+CCB reported possible ADR scores. Among them one patient reported edema, one patient reported GI discomfort and one patient reported bradycardia.

DISCUSSION

Antianginal medication for the treatment of angina requires careful evaluation of several parameters. The presence of concomitant illnesses, the patient's reaction and tolerance to the initial treatment, and the patient's overall cardiovascular risk profile may have an impact on the decision. According to ACCA guidelines, the first line treatment for angina is BB (Writing Committee Members *et al*., 2021). However, in some cases combining a beta blocker with a long-acting nitrate or a calcium channel blocker can have a similar impact that addresses the enhancement of coronary blood flow as well as the decrease in myocardial oxygen demand. Moreover, to lower blood pressure and heart rate stability, BB are essential in lowering the total amount of oxygen that the heart uses. Conversely, CCB causes vasodilation, which improves coronary blood flow, by preventing calcium from entering vascular smooth muscle cells (Thadani, 2016).

In the current study, we found most of the angina patients' average age was 54.12 years which reflects a population within a middle-aged range, with a fairly equal distribution between males (55.45%) and females (44.54%). In Pakistan, these findings are in accordance with (Haq., 2021) who reported the same incidence age of angina in Pakistani population. Similar findings were also reported by Pimple *et al.* who found a significantly higher ratio of male angina participants than females in clinical study (Pimple *et al*., 2018). According to western societies, majority of ischemic heart disease occurs 7-10 times higher in men than women. Men are more likely, around 3-4 times than women to suffer from stable and unstable angina (Suman *et al*., 2023).

Body measurements, such as weight (65.0 kg) and BMI (27.22 kg/m2), highlight factors relevant to cardiovascular health and potential risk factors for angina as represented in table 1. We have enrolled newly diagnosed patients who represented 1.73 years duration of angina, Among them half of the patients were living with a sedentary lifestyle (55.45%), It is a factor known to impact cardiovascular health. Similar findings were also reported by Orsini *et al.* Who found newly diagnosed angina patients with sedentary lifestyle (Orsini *et al*., 2022). Different comorbidities were reported in angina patients like most of the participants reported diabetes (16.36%), renal impairment (4.54%), and dyslipidemia (17.27%). Gazzaz *et al* (2020) observed that the major comorbidities associated with angina patients were hypertension, diabetes, and dyslipidemia. A subset of patients with a history of smoking (14.54%) adds another layer to the cardiovascular risk profile. Mei *et al*., 2021 also studied that smoking is also a major contributing risk factor in coronary heart disease.

We have found insignificant differences among all patients in terms of sex, age, weight, BMI, duration of angina, SBP, DBP, heart rate, comorbidity, lifestyle, triglycerides, HDL, LDL, electrolytes, urea and creatinine. The average blood pressure (139.75/85.98 mmHg) and heart rate (83.45 beats/min) provide insights into the cardiovascular status of the cohort and all were stable on their medications. The lipid profile, including triglycerides (168.87 mg/dl), HDL (41.15 mg/dl), and LDL (82.66 mg/dl) revealed beta-blocker-taking patients represented elevated TG levels. Majid *et al*., 2020 reported BB especially atenolol has a great impact on metabolic profile and is responsible for significantly raising lipid profile in angina patients. Statins are the lipid-lowering agents commonly used in patients with angina for the prevention of atheromatous plaque development and complications, to reduce the risk of cardiac death and infraction (Manfrini *et al.*, 2020). All participants taking statins, especially rosuvastatin and atorvastatin were taken by a majority of the patients, while the use of simvastatin was less. These results were in accordance with Laks *et al.* (2008) who found that most of the angina patients take rosuvastatin and atorvastatin as rosuvastatin 10mg achieved good control on cholesterol compared with the simvastatin 20 mg group. Moreover, the use of the antithrombotic agents among both genders was insignificant $P>0.05$ as both genders were taking aspirin and clopidogrel.

Among BB the most frequently prescribed medicine was bisoprolol, carvedilol, nabivilol, and metorpolol while among CCB amlodipine and diltiazem were mostly prescribed medications. 20 patients were taking both BB and CCB as at present, published reports exploring the potential benefits of combination diltiazem along with BB in patients with chronic stable angina. Current guidelines recommend that a beta-blocker with CCB should be considered a part of the treatment of hypertension if rate control is required (Williams *et al*., 2018).

We had used the SAQ scale to understand the relationship between BB, CCB, and its combination on angina (Kobalava *et al*., 2014). A patient's overall quality of life and the variety of experiences related to angina are significantly affected by the drug they select. Recognizing the influence of distinct SAQ domains may provide substantial knowledge of how particular antianginal medications influence multiple aspects of patients' lives. Improvements in angina stability may show how effectively a given treatment works to improve the standard of living and decrease the effect of angina symptoms on patients' activities (Jespersen *et al*., 2013).

The study results indicate that there was a statistically significant difference in the Seattle score between the three treatment groups. The CCB and combination group significantly improved P<0.05 seattle score and improved angina symptoms just like of BB group. This observation is in accordance with Ford and Berry (2020), reported that in vasospastic angina CCB are more effective in treating over 90% of patients by improving angina symptoms. Studies reported a significantly lower incidence of Angina in patients with abnormal epicardial vasoconstriction treated with dihydropyridine calcium channel blocker (Balla *et al*., 2018). These results support that CCB are highly effective in reducing ischemic episodes in patients with abnormal vasoconstriction and are currently recommended for these patients as first-line agents for the treatment and prevention of anginal symptoms (Nishigaki *et al.*, 2010; Boerhout *et al.*, 2023).

Pharmacovigilance in cardiology is a crucial aspect of ensuring patient safety and monitoring the long-term effects of cardiovascular medications. Given the prevalence of cardiovascular diseases and the widespread use of medications such as anticoagulants, antiplatelets, beta-blockers, and statins, rigorous surveillance is essential to detect and assess adverse drug reactions (ADRs) of these drugs (Ribeiro-Vaz *et al*., 2016). Among 110 patients, a significant frequency of insomnia and nervous system symptoms was noted in the BB-treated group (18.18%). Similarly, 18.18% of patients felt weakness/myalgias, and 16.36% reported GI pain, indicating the effect on the musculoskeletal and gastrointestinal systems. Most of the CCB-treated patients showed edema (9.09%), hyperkalemia (10.9%), and palpitations/dizziness (7.27%).

The correlation of beta-blockers, calcium channel blockers (CCB), and combination therapy with the Naranjo score, a tool assessing the probability of adverse drug reactions (ADRs), reveals insights into the likelihood of a causal relationship between these medications and observed adverse events. In the beta blockers group, two cases were categorized as "definite," indicating a high probability of the ADR being associated with the medication. Solanki and colleagues reported that patients are more prone to ADRs with BB than CCB. Their study explored that calcium channel blockers have better efficacy compared to other classes of drugs for long-term treatment and even in combination (Solanki et al., 2021).

Moreover in the CCB group, we haven't found any case classified as "definite." However, in the combination therapy group, two cases were categorized as "definite." reported insomnia, dizziness and myalgia. Additionally beta blockers and calcium channel blockers both showed considerable number of "probable" cases, suggesting a strong likelihood of the mild ADRs being related to these medications. Datta, 2016 also discussed that BB and CCB have shown ADRs on angina patients on long-term use. These results underscore the importance of monitoring and managing potential ADRs, especially in cases where the probability is higher, providing valuable insights for clinical decision-making.

CONCLUSION

We concluded that CCB by decreasing afterload produces suppressant effects on the sinoatrial node and myocardium that contributes to antianginal effects. Whereby BB reduces ischemia by decreasing myocardial oxygen demand thus heart rate and myocardial contractility would be reduced. Based on these beneficial mechanisms, combinations (CCB+BB) are more effective in angina treatment as BB and CCB alone. However, the ADRs related to CCB are less frequent over long-term use than BB.

The study has some limitations. The first limitation is it was an observational design, suggesting caution when making comparisons in randomized controlled trials. Secondly, the sample size of this study is limited and we didn't take follow-up. Besides this, patients were newly diagnosed that couldn't show definite impact on drug-related ADRS. Treatment duration is too short to assess the long-term impact on the angina outcomes. Further observational studies to explore long-term medication use may help to identify accurate BB, CCB and combination related problems. The original plan was to enroll a larger population and to follow patients. Unfortunately, newly diagnosed patients did not have severe symptoms and they didn't want to follow the clinics for their regular checkups. One of the major reasons was the socioeconomic conditions of patients, as Pakistan is a third-world country and most of the people belong to underprivileged groups. So, we opted to stop the study, as we couldn't find patients who were managing angina with consistent with standard practice.

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