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A COMPARATIVE STUDY OF THE EFFECTS OF THE ANGIOTENSIN CONVERTING ENZYME INHIBITORS AND CALCIUM CHANNEL BLOCKERS ON THE CARDIOVASCULAR OUTCOME IN HYPERTENSIVE PATIENTS WITH TYPE-2 DIABETES MELLITUS

U K Chandelkar*[1], P V Rataboli[1], S A Bhounsule[1], J S C Pereira, F S Vaz[2], M S Kulkarni[2]

1. Department of Pharmacology, Goa Medical College, Bambolim-Goa, India.
2. Department of Preventive and Social Medicine, Goa Medical College, Bambolim-Goa, India.

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Angotensin converting enzyme inhibitors, Calcium channel blockers, Blood pressure, Type 2 diabetes mellitus, Cardiovascular events

For Correspondence:

Dr. U K Chandelkar

Department of Pharmacology, Goa Medical College, Bambolim-Goa, India.

E-mail:

starulhas@gmail.com

ABSTRACT

Introduction: Hypertension often coexists with insulin resistance which can lead to diabetes mellitus (DM). Hypertension together with DM can increase the risk of cardiovascular mortality and morbidity two to three fold. Reduction of high blood pressure (BP) in high risk patients with diabetes reduces cardiovascular morbidity and mortality, and delays the progression to end stage renal disease. **Methods:** The 24 months follow up study was conducted at the Urban Health Centre at Santa Cruz, Goa, India. Hypertensive patients with type-2 diabetes mellitus (T2DM) of either sex aged between 40-75 years constituted the study participants. Two groups of 35 patients each receiving either an angiotensin converting enzyme inhibitor (ACEI) or a calcium channel blocker (CCB) were studied. **Results**: BP lowering effect was more marked in the ACEI group. Incidence of myocardial infarction (MI) and angina was 11.42% and 2.86% respectively in ACEI group while in CCB group the incidence of MI was 25.71% and angina was 8.57%. Incidence of stroke was 2.86% in both groups. Around 30.2% of participants in ACEI group had dry cough, where as 25.2% of patients in CCB group reported ankle edema. ACEI group showed significant fall in serum creatinine and blood urea. **Conclusion:** With the aim of preventing the cardiovascular and renal complications in mind, while treating hypertensive patients with T2DM, antihypertensive drugs like ACEI, with the least adverse effect on glucose level can be selected. In patients where ACEI or angiotensin receptor blockers (ARB) are contraindicated or not tolerated, CCB should be the second option.

INTRODUCTION

Hypertension is a growing epidemic affecting an important percentage of the population and is a major contributor to the development and progression of cardiovascular disease.[1-2] It is strongly associated with risk factors that impair glucose homeostasis and is often presented as a component of the metabolic syndrome. It is related with obesity, insulin resistance as well as DM and also play a major role in the development and progression of micro- and macrovascular disease.[2, 3-4] Hypertension is defined conventionally as a sustained increase in BP more than 140/90 mm Hg, a criterion that characterizes a group of patients whose risk of hypertension-related cardiovascular disease is high enough to merit medical attention.[5]

Increased BP often coexists with insulin resistance.[2] Thus hypertensive patients have a 2.5-fold higher risk of T2DM onset compared with normotensive subjects.[6] In persons with hypertension, concomitant DM is known to increase the risk of cardiovascular mortality and morbidity two to three fold. [7-8] Diabetes is a rapidly growing health problem worldwide, related in part to improved living conditions and increasing rate of obesity[9]. It is estimated that approximately 5% of people in the general population of most industrialized societies have diabetes mellitus and that an additional 3%–5% have either undiagnosed diabetes or impaired glucose tolerance.

According to the World Health Organization (WHO), worldwide, the number of people living with diabetes is projected to increase from 172 million in 2000 (prevalence: 2.8%) to 366 million (prevalence: 4.4%) in 2030[10]. Prevalence of hypertension in the diabetic population is 1.5–3 times higher than in the age- and weight-adjusted non-diabetic group.[11-12] Reduction of high BP reduces cardiovascular morbidity and mortality and delays the progression to end stage renal disease (ESRD). Indeed, various studies has shown that lowering BP in high risk patients with diabetes reduces overall mortality[13-15] , death from stroke[16] and cardiovascular events [13,17] and slows the progression of renal disease in patients with T2DM[18-20].

The various antihypertensive drugs have different effects on glucose metabolism. ARB as well as ACEIs have been associated with beneficial effects on glucose homeostasis. CCB are considered to have neutral metabolic effects. As a result, the metabolic effects of the various BP lowering drugs should be taken into account when selecting an antihypertensive treatment.[2] Therefore effective antihypertensive is quite mandatory to reduce the cardiovascular risks in hypertensive patients with concomitant DM [21]. However some of the antihypertensives could themselves be responsible for complications like myocardial infarction (MI) or unstable angina.[22-23] The use of anti-hypertensives in diabetic patients should therefore be considered in the context of preventing the development of complications.[24]

Hence this study was undertaken to assess the effects of two commonly prescribed groups of antihypertensive agents i.e. ACEI and CCB on cardiovascular outcomes in patients with hypertension and concomitant DM.

MATERIALS AND METHODS

i) Study design and setting: The 24 months follow up study was conducted at the Urban Health Centre (UHC) at Santa Cruz, Goa, India.

ii) Study participants: The study involved hypertensive patients with associated T2DM. Those patients who were stabilized on a single antihypertensive medication like ACEI or CCB for two years or more were studied. Seventy patients formed the study sample. There were 35 patients in each group i.e. ACEI group and CCB group. The outpatient department (OPD) patients at the UHC at Santa-Cruz, Goa, India were included in this study.

iii) Inclusion criteria: Hypertensive patients of either sex aged between 40-75 years and diagnosed as T2DM were included in the study.

iv) Exclusion criteria: Patients with evidence of acute ischemia or myocardial ischemia (MI), unstable angina or cerebrovascular accident (CVA) in last six months, patients with known allergy to dihydropyridine (DHP) CCB or ACEI, patients who underwent coronary artery bypass surgery within last three months, patients with abnormal renal function, patients with congestive heart failure (CHF) and patients on other medication affecting BP were excluded from the study.

v) Study instruments: A pretested structured interview schedule was used to collect information from the study participants. Information collected included baseline demographic details, adverse events, cardiovascular events etc. BP was measured in the supine position after five minutes of rest using a mercury sphygmomanometer.

vi) Follow up processes: After the initial dose titration period, BP measurement was recorded at end of one week, two weeks, 4 weeks, eight weeks, four months, five months six months and every month thereafter for a total period of twenty four months. Laboratory tests and electrocardiography (ECG) were done routinely during follow up.

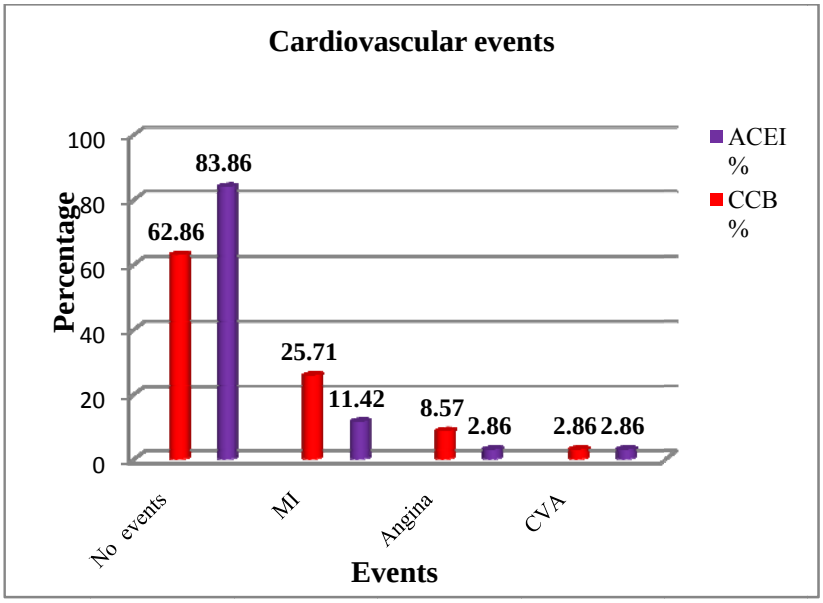
vii) Ethics and statistical analysis: The study was approved by the ethics committee of the institute. SPSS software package was used for the statistical analysis. Analysis of variance for repeated measure was the statistical test used.

RESULTS

A total of 70 patients with hypertension with associated T2DM were studied. Each study group i.e. ACEI group and CCB group consisted of 35 study participants. As far as cardiovascular events were concerned, ACEI treated group reported lower incidence of cardiovascular events

compared to CCB group. Incidence of MI and angina was 11.42% and 2.86% respectively in ACEI group as compared to CCB wherein incidence of MI was 25.71% and incidence of angina was 8.57%.Incidence of cerebrovascular accidents was similar in both groups(2.86%)(Fig 1).

Fig 1: CARDIOVASCULAR EVENTS WITH ACEI AND CCB GROUPS



The mean BP recordings over 24 months follow up period showed significant reduction of systolic blood pressure (SBP) as well as diastolic blood pressure (DBP) in the ACEI group compared to CCB group (Table 1).

Table 1: MONTHLY MEAN SBP AND DBP RECORDINGS IN VARIOUS STAGES OF HYPERTENSION.

Stages	Pre-hypertension				Stage 1 hypertension				Stage 2 hypertension			
No. of patients	11		11		12		12		12		12	
Months	Systolic BP		Diastolic BP		Systolic BP		Diastolic BP		Systolic BP		Diastolic BP	
	ACEI	CCB	ACEI	CCB	ACEI	CCB	ACEI	CCB	ACEI	CCB	ACEI	CCB
1	126	131	80	81	150	146	90	91	170	177	105	102
2	123	129	77	80	140	137	90	84	151	161	94	93
3	124	128	76	78	134	137	82	83	138	151	85	89
4	124	128	77	79	130	130	84	85	132	144	85	89
5	124	126	74	79	126	131	83	85	133	143	84	89
6	122	121	74	78	128	129	81	84	134	140	85	89
7	122	122	77	78	122	127	82	84	131	134	81	87
8	121	122	73	80	125	128	82	83	133	133	82	88
9	120	121	73	79	124	128	83	84	132	134	85	85
10	121	123	72	76	122	129	82	84	130	135	82	88
11	118	124	71	78	124	128	80	83	126	133	81	88
12	120	121	73	77	123	129	83	83	123	137	83	87
13	120	122	72	79	122	129	82	84	123	136	81	90
14	120	123	70	80	122	128	80	84	122	137	81	88
15	119	124	71	80	120	130	79	83	123	138	79	87

16	118	126	71	79	122	129	77	83	122	138	79	88
17	118	122	72	80	123	128	75	84	120	133	79	89
18	118	120	72	75	122	126	78	83	120	133	79	89
19	118	124	72	75	120	127	77	83	119	134	77	86
20	118	121	71	75	122	126	76	83	118	133	78	88
21	118	121	71	78	123	127	77	83	118	133	76	86
22	117	122	70	76	120	127	78	80	117	132	77	86
23	119	121	71	77	121	126	76	82	118	133	77	83
24	118	123	70	79	118	126	76	83	118	132	77	86

As compared to CCB, the percentage of reduction of BP was more in the ACEI group. Further when BP reduction in different stages were compared, there was significant reduction of BP observed in stage 2 hypertension (Table 2).

Table 2: PERCENTAGE (%) OF REDUCTION OF MEAN SBP AND DBP WITH ACEI AND CCB

Stages	**Pre-hypertension**				**Stage 1 hypertension**				**Stage 2 hypertension**			
No. of patients	**11**		**11**		**12**		**12**		**12**		**12**	
Months	**Systolic BP**		**Diastolic Bl**		**Systolic BP**		**Diastolic Bl**		**Systolic BP**		**Diastolic Bl**	
	ACEI	**CCB**	**ACEI**	**CCB**	**ACEI**	**CCB**	**ACEI**	**CCB**	**ACEI**	**CCB**	**ACEI**	**CCB**
6	3.17	7.63	7.5	3.7	14.66	11.64	10.0	7.69	21.17	20.90	19.04	12.74
12	4.7	7.63	8.75	4.93	18.0	11.64	7.77	8.79	27.64	22.59	20.95	14.7
18	6.34	8.46	10.0	7.4	18.66	13.69	13.33	8.79	29.41	24.85	24.76	12.74
24	6.34	6.10	12.5	2.46	21.33	13.69	15.55	8.79	30.58	25.42	26.66	15.68

The Analysis of Variance (ANOVA) showed that there was a significant difference in mean SBP ($P<0.0001$) during the 24 months study period between the ACEI and CCB group (Table 3).

Table 3: ANALYSIS OF VARIANCE (ANOVA) SHOWING SBP AND GROUPS

Source of variation	**D f**	**Sum of square**	**Mean sum of square**	**F ratio**	**Significance**
SBP	2.801	46720.205	16681.1740	207.105	P<0.0001
SBP Group*	14.004	26253.521	1874.7330	23.276	P<0.0001
Error (SBP)	179.25	4437.593	80.5450		

* Various stages of hypertension have been divided into groups for statistical calculation.

ANOVA showed a significant difference in mean DBP ($P<0.0001$) between the two groups during the 24 months study period (Table 4).

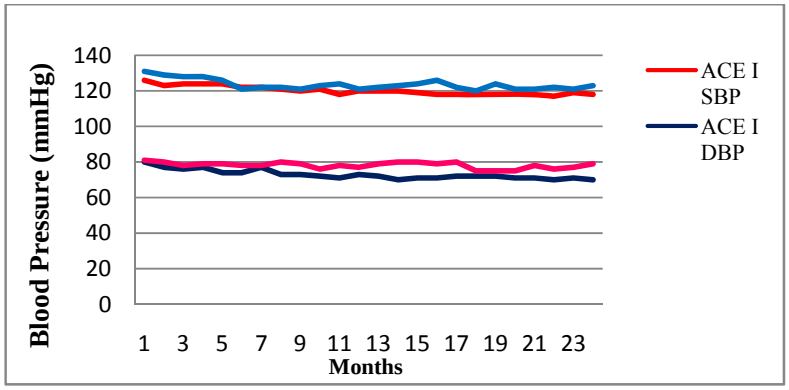
Table 4: ANOVA SHOWING DBP AND GROUPS

Source of variation	**D f**	**Sum of square**	**Mean sum of square**	**F ratio**	**Significance**
DBP	7.881	927.922	006.0110	67.593	P<0.0001
DBP Group*	39.403	4959.767	125.8740	8.457	P<0.0001
Error (DBP)	504.355	506.524	4.8830		

*Various stages of hypertension have been considered as groups for statistical calculation.

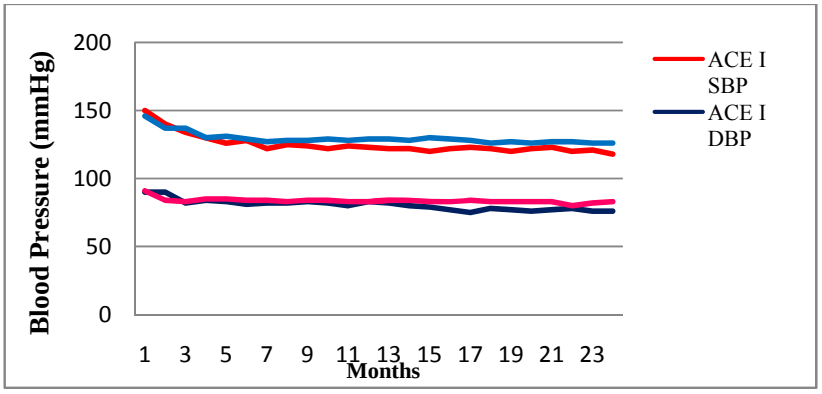
SBP in pre-hypertension reduced from 126 to 118 mm Hg in the ACEI group where as in CCB group it reduced from 131 to 123 mm Hg. DBP in ACEI and CCB group reduced from 80 to 70 mm Hg and 81 to 79 mm Hg respectively (Fig 2).

Fig 2: COMPARATIVE EFFECTS OF ACEI AND CCB ON SYSTOLIC AND DIASTOLIC BLOOD PRESSURE IN PRE-HYPERTENSION



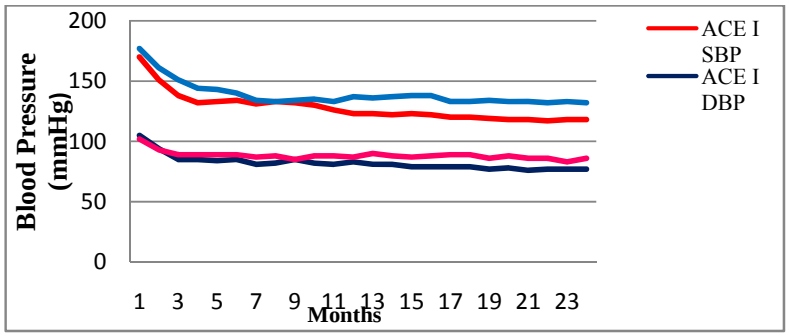
In stage 1 hypertension SBP in ACEI group reduced from 150 to 118 mm Hg while in CCB group it reduced from 146 to 126 mm Hg. DBP was reduced from 90 to 76 mm Hg and 91 to 83mm Hg in ACEI and CCB group respectively (Fig 3).

Fig 3: **COMPARATIVE EFFECTS OF ACEI AND CCB ON SYSTOLIC AND DIASTOLIC BLOOD PRESSURE IN STAGE 1 HYPERTENSION.**



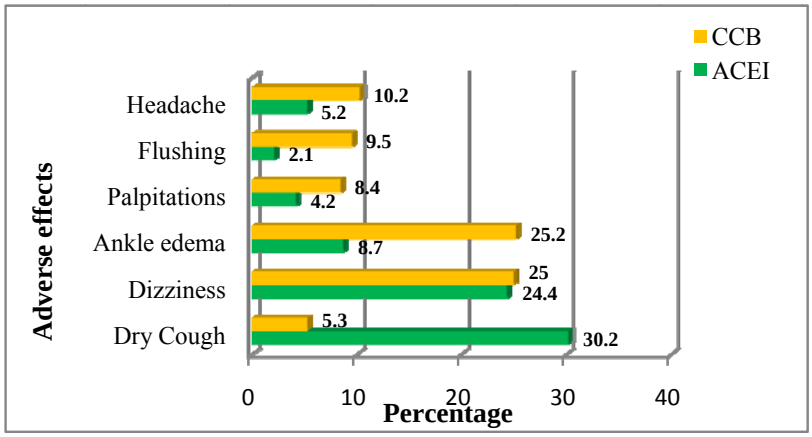
When compared with pre-hypertension and stage 1 hypertension, SBP as well as DBP in patients from both the groups in stage 2 hypertension have shown significant reduction. However there was more marked reduction in SBP and DBP in ACEI group than in CCB group (Fig 4).

Fig 4: **COMPARATIVE EFFECTS OF ACEI AND CCB ON SYSTOLIC AND DIASTOLIC BLOOD PRESSURE IN STAGE 2 HYPERTENSION.**



Proportion of adverse effects was higher in CCB group compared to ACEI group. Around 30% of participants in ACEI group had dry cough compared to only 5.3% in CCB group while 25.2% of those in CCB reported ankle edema compared to 8.7% in ACEI group (Fig 5).

Fig 5: PERCENTAGE OF THE MOST COMMON ADVERSE EFFECTS WITH THE TWO GROUPS.



ACEI group showed significant fall in serum creatinine and blood urea as compared to CCB group (Table 5).

Table 5: LEVELS OF CREATININE AND UREA IN ACEI AND CCB GROUP

Months	ACEI		CCB	
	Urea (mg %)	Creatinine (mg %)	Urea (mg %)	Creatinine (mg %)
Jan	47	1.1	49	1.6
Apr	38	1	47	1.48
July	36	1	48	1.5
Oct	36	1	45	1.4
Jan	34	1	44	1.4
Apr	34	0.9	46	1.5
July	33	0.9	43	1.5
Oct	32	0.85	47	1.5

DISCUSSION

Hypertension is strongly associated with risk factors that impair glucose homeostasis.[2] In our study cardiovascular events were found to be markedly lower in ACEI group compared to CCB group. Besides having beneficial effects on glucose homeostasis, ACEI is also associated with lower incidence of new onset diabetes as compared to CCB[25], but, azelnidipine and manidipine some new members of the CCBs have been shown to have advantageous effects on glucose homeostasis and this finding coincides with recent reanalysis data from NAVIGATOR trial which showed that CCBs were not associated with new onset diabetes[26]. Indeed, a recent meta-analysis of 10 randomized clinical trials evaluated the effects of CCB treatment on new onset T2DM.[27]

Interestingly in contrast to our study, New JP et al[28] found ACEIs having a neutral effect on glucose metabolism, wherein patients with T2DM and hypertension (***n*** = 24) resulted no change

in insulin sensitivity after ACEI-trandolapril treatment. However, Bosch J et al during their 3 years study period noted that, though ACEIs (ramipril) treatment did not reduce the incidence of diabetes, but it increased regression to normoglycemia.[29] According to Landmark K et al[30] conventional therapy induces a small increase of blood glucose without increasing cardiovascular events but newer antihypertensive drugs (ACEI/ARB and CCB) do not have this effect. However in our study we found 25.71% (n=9) and 8.57 % (n=3) patients suffering from MI and angina respectively on CCB where as among the ACEI group incidence of MI was 11.42% (n=4) and angina was 2.86% (n=1).

In a study by Nosadini R et al, out of 141 patients who received amlodipine, a CCB, the incidence of patients experiencing acute MI and angina was 9.2% (n=13) and 2.8% (n=4) respectively as compared to 7 patients (5.34%) suffering from MI, out of 131 who received ACEI. There were no reports of angina among the ACEI group.[31] In contrast to this study, the incidence of MI and angina in both the groups in our study is on the higher side. However, overall incidence of cardiovascular events in CCB group in our study is in line with the findings reported by Chen N. et al and Grossman et al[32-33] which reveal that CCB were less effective than renin-angiotensin-system (RAS) blockers (ACEI and ARB) in preventing cardiovascular events.

There were no reports of deaths in both the groups during 24 months follow up study. This finding correlates well with findings of Chalmers J et al.[34] where active treatment with CCB reduced the relative risk of death by 28% as compared to 5% among those not on CCB and 14 % for whole population (n=3427); further the relative risk reduction for major cardiovascular events was 12% versus 6% for those with and without CCB at baseline but as far as overall advantages are concerned ACEIs are more beneficial in patients with T2DM and hypertension. Though left ventricular hypertrophy (LVH) was not found during our study, ACEI are most effective in reducing LVH in T2DM as reported by Derosa et al.[35] The American Heart Association/American Stroke Association stated that although an absolute target of BP level has not been clearly defined, a reduction in recurrent stroke has been associated with an average lowering of 10/5 mm Hg,[36] because as diabetes epidemic continues to grow unabated, concomitant hypertension doubles total mortality and stroke risks.[37] According to Chen at al[34] and Grossman et al[35] CCB reduces the stroke as compared to ACEI and conventional therapy. These findings do not match with our study, as we found same incidence of stroke in both the groups. Further, Nosadini R et al reported 7.09% (n=10) and 2.29% (n=3) of patients experiencing CVA with CCB and ACEI respectively. These findings resemble our results in ACEIs group i.e 2.86% (n=1) but, incidence of stroke with CCB group (2.86%) in our study was less as compared to their findings.[31]

There is convincing evidence that CCB have stroke preventing potential (syst EUR, ALLHAT studies) and they are preferred in the elderly hypertensives.[38] That could be the reason why CCB are prescribed more commonly to treat hypertensive patients with T2DM in Hospital University Sains Malaysia as found in study by Abougalambou AS et al.[39] Besides this, data from several large studies has shown that effective use of antihypertensive drugs reduces occurrence of stroke by 30-50%, heart failure by 40-50% and coronary artery disease (CAD) by approximately 15%.[40] The use of antihypertensive in T2DM patients should be considered in the context of preventing the development of complications. CCB bring down the BP by causing relaxation of vascular smooth muscles especially in arterial beds. These drugs also may produce negative inotropic and chronotropic effects in the heart.[41]RAS plays a major role in the pathogenesis of hypertension as well as glucose homeostasis, and maintaining a constant set point for long-term levels of arterial BP despite extreme changes in dietary Na^+ intake.

The glucose transporter type 4 (GLUT-4), the principal glucose transporter protein that mediates insulin-stimulated glucose transport into muscle and adipose tissues play a key role in the regulation of glucose homeostasis.[42] Moreover, ACEIs have been associated with increase of GLUT-4 protein expression in skeletal muscle and myocardium in insulin-resistant animal models.[43] Angiotensin II decreases GLUT-4 translocation to the cell membrane.[44-45] As a result the RAS inhibition could promote insulin sensitivity. Furthermore, angiotensin II can promote the production of inflammatory cytokines[46] which promote oxidative stress thus also leading to increased insulin resistance. Inhibition of angiotensin II production by ACEI will lower BP, decrease insulin resistance and enhance natriuresis. Besides these, ACEI increase bradykinin levels and bradykinin in turn stimulates prostaglandin (PG) biosynthesis; both may contribute to the pharmacological effects of ACEI.[47] In addition, endothelial dysfunction is also associated with insulin resistance[48] ACEI have also been shown to improve vascular function, insulin-mediated vascular responses and reduce cardiovascular complications more than other antihypertensives by improving endothelial function[49-50] and improve the state of target organs in hypertensive patients with T2DM.[51]Furthermore, ACEI may also have direct beneficial effects on pancreatic β cells.[52] In addition, vasodilation of blood vessels by ACEI increases total perfusion,[53] which results in increased glucose uptake and insulin sensitivity.[54-55] As compared to CCB group, ACEI group has reported less cardiovascular events in our study. This is also reported by Gianpaolo R et[37] who opine that BP reduction is a major priority in preventing clinical events in patients with T2DM and hypertension, who are at very high risk of cardiovascular and renal outcomes and this seems to be true because, as compared to CCB group there is marked reduction of BP in ACEI group

and similar finding can be considered responsible for lower incidence of cardiovascular events in our study.[37] In contrast to Swedish Trial in Old Patients with hypertension-2 (STOP-2) trial, wherein BP lowering effect were similar in CCB, ACEI and conventional (diuretics or beta blockers) treatment group,[56] we found more marked fall in systolic as well as DBP with ACEI in our study. In another study Fogari R et al reported significant greater reduction in both SBP and DBP in small crossover trial in[37] patients with T2DM and hypertension, when ACEI was combined with amlodipine (CCB) as compared to amlodipine alone.[57] This finding proves that ACEI reduce BP more than CCB which is in line with our findings. But in contrast, Tabur et al did not find any significant difference in SBP and DBP reduction.[58]

In our study around 31.42% of participants in ACEI group had dry cough, which matches with the study by Lv J et al[59] wherein they too found significantly increased risk of cough with ACEI (which is more than the reported value of 5 to 20% in standard literature). Interestingly, our study revealed cough in a significant 5.71% patients in CCB group. Thromboxane antagonism, aspirin and iron supplements can decrease cough induce by ACEI.[60] A significant number of patients (22.86%) on CCB reported ankle edema compared to 8.57% receiving ACEI. Edema with CCB is not due to fluid retention: it mostly likely results from increased hydrostatic pressure in the lower extremities owing to precapillary dilatation and reflex postcapillary constriction.[61] Headache was reported by 8.57% of patients on CCB as compared to 5.72% in ACEI group which is almost similar to findings by Lv J et al.[59] According to Chalmers J et al there was no detectable increase in adverse effects in those receiving CCB in contrast to our study.[34]

It has been demonstrated that strict BP control with ACEI or beta blockers below 130/80 mm Hg, attenuates the deterioration of renal function. By decreasing creatinine and blood urea ACEI may slow progression of kidney failure and cardiovascular mortality in patients with DM and hypertension.[62-63] This effect may be correlated to our study as serum creatinine was reduced from 1.1 to 0.85 mg (22.73%) in ACEI group as compared to 1.6 to 1.5 mg (6.25%) in CCB group. This is in line with the finding reported by Tabur et al.[58] Finding by Kloke et al[62] in their study may be significant where they opine that DHP CCB do not lower proteinuria despite reduction of BP. Blood urea levels were reduced from 47 to 32 mg% (31.91%) in ACEI group in our study as compared to 49 to 47 mg% (4.08%) in CCB group which is consistent with findings by Tabur S et al.[58] In conclusion, CCB have stroke preventing potential and are preferred in the elderly hypertensives with T2DM. ACEI enhance natriuresis and increase bradykinin levels. Vasodilation of blood vessels by ACEI increases total perfusion which in turn results in increase glucose uptake and insulin sensitivity. ACEI also improve vascular function, insulin-mediated vascular

responses and reduce cardiovascular complications more than other antihypertensives by improving endothelial function. In patients where ARB and ACEI are contraindicated or not tolerated, CCB can be the second option. As more than 75% of hypertensive patients with T2DM will require a combination therapy to adequately control BP, ACEIs /CCB combination may be used in high-risk patients that may provide both reno-and cardioprotection at the same time.

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Conflict of interest: none

Ethical approval: Approval was obtained from the Institutional Ethics Committee, Goa Medical College, Bambolim-Goa, India.

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